# PROTOCOL

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| **TITLE:** | **R**andomized Phase 2 Trial of **A**CP-196 and **P**embrolizumab **I**mmunotherapy **D**ual **CHECK**point Inhibition In Platinum Resistant Metastatic Urothelial Carcinoma (RAPID CHECK study) |
| **PROTOCOL NUMBER:** | ACE-ST-005 |
| **STUDY DRUG:** | Acalabrutinib (ACP-196) and KEYTRUDA® (pembrolizumab) |
| **IND NUMBER:** | 124755 |
| **MEDICAL MONITOR:** | [redacted] |
| **DCRI COORDINATING CENTER CONTACT:** | [redacted] |
| **SPONSOR:** | Acerta Pharma BV<br>Kloosterstraat 9<br>5349 AB Oss<br>The Netherlands |
| **PROTOCOL DATE:** | Version 0.1 – 03 January 2015 |
| **AMENDMENT 1:** | Version 1.0 – 27 April 2015 |
| **AMENDMENT 2:** | Version 2.0 – 22 July 2015 |
| **AMENDMENT 3:** | Version 3.0 – 13 January 2016 |
| **AMENDMENT 4:** | Version 4.0 – 23 May 2016 |

**Confidentiality Statement**

This document contains proprietary and confidential information of Acerta Pharma BV that must not be disclosed to anyone other than the recipient study staff and members of the institutional review board (IRB)/independent ethics committee (IEC). This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Acerta Pharma BV.

## PROTOCOL APPROVAL PAGE

I have carefully read Protocol ACE-ST-005 entitled "Randomized Phase 2 Trial of ACP-196 and Pembrolizumab Immunotherapy Dual Checkpoint Inhibition in Platinum Resistant Metastatic Urothelial Carcinoma". I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements. Furthermore, I understand that the sponsor, Acerta Pharma, and the IRB/ IEC must approve any changes to the protocol in writing before implementation.

I agree not to divulge to anyone, either during or after the termination of the study, any confidential information acquired regarding the investigational product and processes or methods of Acerta Pharma. All data pertaining to this study will be provided to Acerta Pharma. The policy of Acerta Pharma requires that any presentation or publication of study data by clinical investigators be reviewed by Acerta Pharma, before release, as specified in the protocol.

Principal Investigator's Signature Date

Print Name

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## IN–TEXT TABLES



## IN–TEXT FIGURES

## SUMMARY OF AMENDMENT 4

This protocol is being amended to include findings from aggregate analyses from the acalabrutinib (ACP-196) clinical program of observed increases in frequency and severity of serum transaminase elevations in subjects exposed to the combination of acalabrutinib and pembrolizumab, as compared with subjects exposed to pembrolizumab monotherapy and subjects exposed to acalabrutinib monotherapy.

Additional changes in this protocol amendment include updated background information on acalabrutinib and changes made to align this protocol with other Acerta Pharma protocols.

Clarifying edits and typographical changes have been made throughout the protocol. In addition, the following substantive changes were made as part of this amendment:

| Change | Rationale |
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| Title Page<br><br>Changed medical monitor to Tianling Chen, MD, MSc.<br><br>Revised text as shown (**bold** indicates new text):<br><br>**DCRI** COORDINATING CENTER **CONTACT** ~~PRINCIPAL INVESTIGATOR~~ | Acerta Pharma medical monitor change.<br><br>Updated contact information. |
| Protocol Approval Page: Removed Acerta approver. | Acerta Pharma process change. |
| Synopsis | Updated to reflect changes made throughout the protocol. |
| Section 1.6.3 Drug-drug Interaction Potential<br><br>Replaced text with reference to the Acalabrutinib Investigator Brochure. | The Investigator Brochure is the primary source for detailed information on acalabrutinib drug-drug interaction potential. |
| Section 1.8.2 Acalabrutinib in CLL<br><br>Updated summary of data from the ACE-CL-001 study.<br><br>Deleted Tables 1-1, 1-2, and 1-3. | The summary of data from the ACE-CL-001 study was updated based on the most recent data cut (October 2015) per the Acalabrutinib Investigator Brochure. |
| Section 1.9 KEYTRUDA (Pembrolizumab)<br><br>Revised text as shown (**bold** indicates new text):<br><br>Pembrolizumab **(Keytruda [United States]),** ~~is~~ a ~~potent and highly selective~~ humanized monoclonal antibody **against the programmed death receptor-1 (PD-1) protein, has been developed by Merck & Co for the treatment of patients** | Updated text to reflect currently approved indications in the KEYTRUDA US prescribing information. |

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| **with cancer** ~~of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2~~. Pembrolizumab is approved for treatment of **patients with melanoma in several countries; in the United States and European Union it is approved for the treatment of adult** patients with **advanced (**unresectable or metastatic**)** melanoma. Pembrolizumab has also been ~~granted approval~~ **approved for treatment of patients with non-small cell lung cancer (NSCLC) in several countries;** in the United States **it is indicated** for the treatment of patients with metastatic ~~non-small cell lung cancer (~~NSCLC~~)~~ whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. **Patients with NSCLC and EGFR or ALK genomic tumor aberrations should also have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab.** | |
| Section 1.10 Benefit/Risk<br>Revised text as shown (**bold** indicates new text):<br><br>In the Phase 1/2 study of acalabrutinib in subjects with CLL, **an ORR of 95% has been observed with a median follow-up of 14.3 months**~~. no DLTs have been identified and no SAEs related to study drug have occurred at dosages of ≤ 400 mg QD or 100 to 200 mg BID. The ORR in the evaluable subjects for this study is currently 94% with some subjects obtaining PRs after only 2 cycles of therapy~~. | Revised text to match updates made in Section 1.8.2. |
| Section 3.0 Study Design<br>Revised text as shown (**bold** indicates new text):<br><br>Subjects who progress on the combination of pembrolizumab and acalabrutinib will discontinue study treatment while those with progression of disease in the pembrolizumab monotherapy arm will continue on pembrolizumab with the addition of acalabrutinib until a second disease progression. **For subjects who cross over to receive combination treatment, acalabrutinib treatment will begin at the next visit at which subjects are scheduled to receive pembrolizumab.**<br><br>Refer to Appendix 4 **and Appendix 5** for ~~a~~ comprehensive list**s** of study assessments and their timing.<br><br>Section 3.8 Dosing Delays and Modifications<br>Revised text as shown (**bold** indicates new text):<br>For treatment-emergent hepatotoxicity in the combination arm ~~only~~ **or for subjects who cross over to receive combination therapy**: Important guidelines for treatment-emergent hepatotoxicity are provided in Section 3.8.2 for pembrolizumab. In the combination arm **or for** | Given the new findings of observed increases in frequency and severity of serum transaminase elevations in subjects exposed to acalabrutinib and pembrolizumab in combination as compared with subjects exposed to pembrolizumab monotherapy and subjects exposed to acalabrutinib monotherapy, additional assessments have been added for subjects who cross over to receive acalabrutinib and pembrolizumab to allow for more frequent monitoring. |

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| **subjects who cross over to receive combination therapy**, treatment with acalabrutinib should be withheld for Grade 3 or 4 hepatitis.<br><br>Added **Appendix 5 Schedule of Assessments - Crossover** | |
| Section 3.3.2 Exclusion Criteria<br>Revised text as shown (**bold** indicates new text):<br>6. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab, **tremelimumab,** nivolumab, pembrolizumab, MPDL3280A or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways). | Added tremilumumab as an example therapy. |
| Section 3.4.2 Formulation, Packaging, and Storage<br>Revised text as shown:<br>If a drug shipment arrives damaged, or if there are any other drug complaints, a ~~SAE/~~Product Complaint Form should be completed and emailed or faxed to the sponsor or the sponsor's representative.<br>Section 6.2 Documenting and Reporting of Adverse and Serious Adverse Events<br>Revised text as shown:<br>All SAEs must be reported on the SAE~~/Product Complaint~~ form or clinical database.<br>Section 6.2.4 Expedited Reporting Requirements for Serious Adverse Events<br>Revised text as shown (**bold** is new text):<br>If electronic SAE reporting is not available, paper SAE~~/Product Complaint~~ forms must be emailed or faxed to Acerta Pharma Drug Safety, or designee. | Revised for consistency with other acalabrutinib protocols. |
| Section 3.4.4 Assuring Subject Compliance<br>Added the following text:<br>**Missed doses of pembrolizumab should not be made up, with the next dose occurring in agreement with the original schedule for this agent (every 3 weeks).**<br>Section 3.8 Dosing Delays and Modifications<br>**In cases where pembrolizumab is held, pembrolizumab should be restarted in agreement with its original dosing schedule (every 3 weeks).** | Text added to clarify that missed doses of pembrolizumab should not be made up. |
| Added **Section 3.10.1 Transaminase Elevations for Acalabrutinib in Combination with Pembrolizumab** | Section has been added based on findings from aggregate data analyses from the acalabrutinib |

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| **Serum transaminase elevations (including elevations of AST and/or ALT) may be increased in severity and frequency in subjects exposed to the combination of acalabrutinib and pembrolizumab, as compared with subjects exposed to pembrolizumab monotherapy and subjects exposed to acalabrutinib monotherapy. Routine monitoring for serum transaminase elevations must follow the Schedule of Assessments (serum chemistry lab assessments in Appendix 4 and Appendix 5). Dosing delays and modifications for subjects with serum transaminase elevations must follow guidance provided in Section 3.8.** | clinical program of observed increases in frequency and severity of serum transaminase elevations in subjects exposed to the combination of acalabrutinib and pembrolizumab, as compared with subjects exposed to pembrolizumab monotherapy and subjects exposed to acalabrutinib monotherapy. |
| Section 3.14 Data and Safety Monitoring<br>Revised text as shown (**bold** is new text):<br>This trial will be monitored in accordance with the sponsor's ~~Pharmacovigilance Committee~~ **pharmacovigilance** procedures. | Revised for consistency with other acalabrutinib protocols. |
| Section 4.1.1 Informed Consent<br>Revised text as shown (**bold** is new text):<br>The subject must read, understand and sign the ICF approved by the institutional review board or independent ethics committee (IRB/IEC), confirming his or her willingness to participate in this study before initiating any screening activity that is not **considered** standard of care **by institutional standards**. Subjects must also grant permission to use protected health information **if required by local regulations**. | Revised text to align with language in other acalabrutinib protocols. |
| Section 4.1.15 Hepatitis B and C Testing<br>Revised text as shown (**bold** is new text):<br>Hepatitis serology testing must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (**anti-**HBs~~Ab~~), **hepatitis B core antibody (**anti-HBc**)**, and **hepatitis C (**HCV**)** antibody. In addition, any subjects testing positive for any hepatitis serology, must have PCR testing **during screening and on study** (see Appendix 4 and exclusion criterion #16). Testing will be done by local or central laboratory.<br>**Subjects who are anti-HBc positive should have quantitative PCR testing for HBV DNA performed during screening and monthly thereafter. Monitoring should continue every 4 weeks (± 7 days) until 12 months after last dose of study drug(s). Any subject with a rising viral load (above lower limit of detection) should discontinue study drug and have antiviral therapy instituted and a** | Clarified on-study testing criteria for subjects who test positive for any hepatitis serology during screening. Added HCV PCR testing at Weeks 13 and 25 to ensure that subjects maintain a sustained virologic response, based on 2015 guidelines from the American Association for the Study of Liver Diseases. |

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| **consultation with a physician with expertise in managing hepatitis B.**<br><br>**Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should have quantitative PCR testing for HCV DNA performed during screening and at Weeks 13 and 25. No further testing beyond Week 25 is necessary if PCR results are negative.**<br><br>Refer to Section 3.10.2 and Appendix 4 regarding monitoring of subjects who are anti-HBc positive **or hepatitis C antibody positive** or **who** have a known history of HBV **or HCV infection**.<br><br>Appendix 4 Schedule of Assessments – Treatment Arms 1 and 2<br><br>Added HBV PCR testing at screening; revised text to clarify that in Week ≥ 10, HBV PCR is conducted at Week 12, then every 4 weeks.<br><br>Added row for HCV PCR, with HCV PCR testing at screening, Week 13, and Week 25.<br><br>Revised footnotes as shown (**bold** is new text):<br><br>u. Subjects who are hepatitis B core antibody positive (or have a known history of HBV infection) should ~~be monitored monthly with~~ **have** a quantitative PCR test for HBV DNA **during screening and monthly thereafter**. ~~Monthly~~ **M~~m~~onitoring should continue **Q4W (± 7 days)** until 12 months after last dose of study drug(s). Any subject with a rising viral load (above lower limit of detection) should discontinue study drug(s) and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B.<br><br>**v. Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should have quantitative PCR testing for HCV DNA performed during screening and at Weeks 13 and 25. No further testing beyond Week 25 is necessary if, PCR results are negative.** | |
| Section 4.3 Safety Follow-up Visit<br><br>Revised text as shown (**bold** is new text):<br><br>Each subject should be followed for 30 (+ 7) days after his or her last dose of study drug (ie, the "safety follow-up visit") to monitor for resolution or progression of AEs (see Section 6.2.6) and to document the occurrence of any new events~~; unless, the subject receives a new anticancer therapy within this timeframe~~**, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe**. | Revised for consistency with other acalabrutinib protocols. |
| Section 5.2 Definition of Analysis **Populations** ~~Sets~~<br><br>Revised text as shown (**bold** is new text): | Revised for consistency with other acalabrutinib protocols. |

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| The following definitions will be used for the efficacy and safety analysis **populations** ~~sets~~.<br><br>**All-treated population** ~~Safety analysis set~~: All enrolled subjects who receive ≥ 1 dose of **any** study drug **(either acalabrutinib or pembrolizumab). The safety and primary efficacy analyses will be performed on the All-treated population.**<br><br>**Efficacy-evaluable population** ~~Per-protocol (PP) analysis set~~: All ~~enrolled~~ subjects **in the All-treated population who have ≥ 1 evaluable response assessment after the first dose of study drug (either acalabrutinib or pembrolizumab)** ~~who receive ≥ 1 dose of study drug, have sufficient baseline measurements, and undergo ≥ 1 assessment for the endpoint of interest (eg, response and PD parameters) after treatment~~. **Sensitivity analyses for efficacy will be carried out on the Efficacy-evaluable population.**<br><br>~~The safety analysis set will be used for evaluating the safety and efficacy parameters in this study (with the exception of assessment of duration of response). The PP analysis sets will be analyzed for efficacy and PD parameters in this study..~~ | |
| Section 5.5 Futility and Toxicity Monitoring<br><br>Revised text as shown (**bold** is new text):<br><br>Enrollment in the combination arm will be stopped early if there is > 95% probability that the irDCR is < 20% or there is > 90% probability that the toxicity rate is higher than 30% in that arm. Where $\theta_E$ denotes the marginal response rate, assuming that $\theta_E$ follows a prior distribution of beta (a, b), where a and b represent ~~non~~response and **non**response rates (0.2, 0.8), and $T_E$ denotes the marginal toxicity rate, assuming that $T_E$ has a prior distribution of beta (a, b), where a and b represent toxicity and no toxicity (0.3, 0.7). | Correction to text. |
| Section 6.1.1 Adverse Events<br><br>Revised text as shown (**bold** is new text):<br><br>An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product ~~or other protocol-imposed intervention~~, regardless of attribution.<br><br>This includes the following:<br><br>• AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with bladder cancer that were not present before the AE reporting period (see Section 6.2.1).<br><br>• ~~Complications that occur as a result of protocol-~~ | Revised text to be consistent with ICH and FDA guidelines. |

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| ~~mandated interventions (eg, invasive procedures such as biopsies).~~<br>• Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.<br>Abnormal laboratory values ~~should not be reported as AEs; however, any~~ **considered** clinically significant ~~laboratory values (eg, causing withdrawal from study or any type of intervetions)~~**by the investigator** should be reported as AEs. | |
| Section 6.2.1 Adverse Event Reporting Period<br>Revised text as shown (**bold** is new text):<br>**After the signing of the ICF, all SAEs must be reported. After the first dose of study drug, all AEs, irrespective of seriousness, must be reported.**<br>**For acalabrutinib, AE reporting, irrespective of seriousness, ends 30 days after the last dose of study drug(s). For pembrolizumab, all AEs must be reported through 30 days after the last dose of pembrolizumab; any SAEs, or follow-up to a SAE, including death due to any cause other than progression of the cancer under study, must be reported through 90 days after the last dose or 30 days after the last dose of pembrolizumab if the subject initiates a new anticancer therapy within the 90-day posttreatment timeframe.**<br>**SAEs considered related to study drug(s) occurring after the end of the AE reporting period (as defined above) must be reported.**<br>**If an SAE is present at the last study visit, the SAE should be followed to resolution or until the investigator assesses the subject as stable, or the subject is lost to follow-up or withdraws consent. Resolution/stable means the subject has returned to baseline state of health or the investigator does not expect any further improvement or worsening of the event.**<br>~~The AE reporting period for this study begins when the subject receives the first dose of study drug and ends with the safety follow-up visit unless a subject received a new anticancer therapy before the safety follow-up visit. An exception to this reporting period is any AE occurring due to a protocol-defined screening procedure. If a fatal AE occurs beyond 30 days after the last dose of acalabrutinib and/or pembrolizumab *AND* it is assessed by the investigator as related to acalabrutinib and/or pembrolizumab it must be reported as an SAE.~~ | Revised to match recent language from Merck Sharp & Dohme Corp and for consistency with other acalabrutinib protocols. |

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| Section 6.2.2 Assessment of Adverse Events<br>Revised text as shown (**bold** is new text):<br>All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, or other means**, that occur to any subject from the time of first dose through 30 days following the cessation of study drug(s), and all SAEs that occur to any subject receiving pembrolizumab from the time of first dose through 90 days following cessation of pembrolizumab, or 30 days following cessation of pembrolizumab if the subject initiates new anticancer therapy (whichever is earlier)** will be recorded in the subject's medical record and on the AE CRF. | Revised guidance for documenting AEs and SAEs to match recent language from Merck Sharp & Dohme Corp and for consistency with other acalabrutinib protocols. |
| Section 6.2.3 Pregnancy<br>Revised text as shown (**bold** is new text):<br>All pregnancies and partner pregnancies that are identified during or after this study, wherein the estimated date of conception is determined to have occurred from the time of consent to 90 days after the last dose of acalabrutinib, 120 days after the last dose of pembrolizumab, or 30 days after the last dose **of** either treatment if the subject initiates a new anticancer threapy (whichever is earlier) will be reported, followed to conclusion, and the outcome reported**, as long as the subject or partner is willing to participate in follow-up**.<br>Added the following text:<br>**Upon completion of the pregnancy, additional information on the mother, pregnancy, and baby will be collected and sent to DrugSafety@acerta-pharma.com.** | Revised for consistency with other acalabrutinib protocols. |
| Section 6.2.4 Expedited Reporting Requirements for Serious Adverse Events<br>Revised text as shown (**bold** indicates new text):<br>Whenever possible, **AEs/**SAEs should be reported by diagnosis term, not as a constellation of symptoms.<br>**Death due to disease progression should be recorded on the appropriate form in the electronic data capture system. If the primary cause of death is disease progression, the death due to disease progression should not be reported as an SAE. If the primary cause of death is something other than disease progression, then the death** ~~All deaths~~ should be reported **as an SAE** with the primary cause of death as the **event** ~~AE~~ term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to Acerta Pharma Drug Safety, or designee, as | Greater detail has been added to aid sites with reporting of deaths due to disease progression and to encourage sites to report causality of SAEs on the initial report. |

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| outlined above. If study drug is discontinued because of an SAE, this information must be included in the SAE report.<br><br>An SAE may qualify for mandatory expedited reporting to regulatory authorities if the SAE is attributable to the investigational product **(or if a causality assessment is not provided for the SAE, in which case the default of 'related' must be used for expedited reporting purposes)** and **the SAE** is not listed in the current Investigator~~'s~~ Brochure (ie, an unexpected event). | |
| Added **Section 6.2.7 Other Safety Issues Requiring Expedited Reporting**<br><br>**For studies being conducted in Europe expedited reporting is required for safety issues that might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. For a detailed description of safety issues that may qualify for expedited reporting please refer to the European Commission guidance titled, "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use – April 2006" available at http://ec.europa.eu/health/files/eudralex/vol-10/21_susar_rev2_2006_04_11_en.pdf.** | Added new section and text that is standard across all Acerta Pharma protocols |
| Section 7.6 Investigational Study Drug Accountability<br><br>Revised text as shown (**bold** is new text):<br><br>Acalabrutinib **and pembrolizumab** ~~capsules~~ must be kept in a locked limited access cabinet or space**, under appropriate storage conditions**. | Revised to correct omission of pembrolizumab. |
| Section 8.0 References | Revised as needed to reflect changes in the protocol. |
| Appendix 4. Schedule of Assessments **– Treatment Arms 1 and 2**<br><br>Thyroid panel, ≥ 10 Weeks: Revised text to clarify than thyroid panel is conducted at Week 13, then every 6 weeks.<br><br>Removed study window from Week 1 visit. | <br><br>Clarifying edits.<br><br>Correction, as the study window does not apply to the Week 1 visit. |

## ABBREVIATIONS

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| $\lambda_z$ | terminal elimination rate constant |
| ACP-196 | acalabrutinib |
| AE | adverse event |
| AKT | protein kinase b |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| anti-HBc | hepatitis B core antibody |
| anti-HBs | hepatitis B surface antibody |
| aPTT | activated partial thromboplastin time |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| AV | atrioventricular |
| BCG | Bacillus Calmette Guerin |
| BCRP | breast cancer resistance protein |
| BID | twice per day (dosing) |
| BOR | best overall response |
| BTK | Bruton tyrosine kinase |
| BUN | blood urea nitrogen |
| CBC | complete blood count |
| CD | cluster of differentiation (cell surface marker) |
| CFR | Code of Federal Regulations |
| cGMP | current Good Manufacturing Practice |
| CI | confidence interval |
| CL/F | oral clearance |
| CLL | chronic lymphocytic leukemia |
| $C_{max}$ | maximum concentration |
| CR | complete response (remission) |
| CRF | case report form |
| CSSF | Clinical Supplies Shipping Receipt Form |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria For Adverse Events |
| CTLA-4 | cytotoxic t-lymphocyte-associated protein 4 |
| CYP | cytochrome p450 |
| DCR | disease control rate |
| DLT | dose-limiting toxicity |
| DOR | duration of response |
| ECG | electrocardiogram |
| ECI | Events of Clinical Interest |
| ECOG | Eastern Cooperative Oncology Group |

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| EGFR | epidermal growth factor receptor |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| hERG | human ether-à-go-go-related gene |
| HIV | human immunodeficiency virus |
| HNSTD | highest non-severely toxic dose |
| $IC_{50}$ | half-maximal inhibitory concentration |
| ICF | informed consent form |
| IEC | independent ethics committee |
| Ig | immunoglobulin |
| IRB | institutional review board |
| ir | immune-related |
| irAE | immune-related adverse event |
| irRECIST | immune-related response criteria |
| IUD | intrauterine device |
| IV | intravenous or intravenously |
| JAK | Janus kinase |
| LDH | lactate dehydrogenase |
| MDSC | myeloid suppressive monocyte |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRP | multidrug-resistance-associated protein |
| MTD | maximum tolerated dose |
| mTOR | mammalian target of rapamycin |
| NE | nonevaluable |
| NK | natural killer (cells) |
| NOAEL | no observed adverse effect level |
| NSCLC | non-small cell lung cancer |
| NTCP | sodium taurochlorate co-transporting polypeptide |
| ORR | overall response rate |
| OS | overall survival |
| PCR | polymerase chain reaction |
| PBMC | peripheral blood mononuclear cells |
| PFS | progression-free survival |
| PD | pharmacodynamic, pharmacodynamics, or progressive disease |
| PD-1 | programmed death-1 (receptor) |

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| PD-L1 | programmed death ligand-1 |
| PD-L2 | programmed death ligand-2 |
| P-gp | p-glycoprotein 1 (transporter) |
| PI3K | phosphatidylinositol-3 kinase |
| PK | pharmacokinetic or pharmacokinetics |
| PR | partial response (remission) |
| PSA | prostate-specific antigen |
| PT | prothrombin time |
| Q3M | every 3 months |
| Q3W | every 3 weeks |
| Q12W | every 12 weeks |
| QD | once per day (dosing) |
| QM | every month |
| $QT_c$ | corrected QT interval |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | stable disease |
| SUSAR | suspected unexpected serious adverse reaction |
| SYK | spleen tyrosine kinase |
| $t_{½}$ | terminal elimination half-life |
| T3 | triiodothyronine |
| T4 | thyroxine |
| TAM | tumor-associated macrophage |
| TGF-β | transforming growth factor-β |
| $T_{max}$ | time to maximum concentration |
| TSH | thyroid-stimulating hormone (thyrotropin) |
| $T_{reg}$ | regulatory T cells |
| TURBT | transurethral resection of bladder tumor |
| ULN | upper limit of normal |
| $V_z$ | volume of distribution |
| $V_z/F$ | oral volume of distribution |
| WHODRUG | World Health Organization Drug Dictionary |

**STUDY SYNOPSIS**

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| **Protocol Number:** | ACE-ST-005 |
| **Study Drugs:** | Acalabrutinib (also known as ACP-196)<br>KEYTRUDA® (pembrolizumab) |
| **Protocol Title:** | Randomized Phase 2 Trial of ACP-196 and Pembrolizumab Immunotherapy Dual Checkpoint Inhibition in Platinum Resistant Metastatic Urothelial Carcinoma |
| **Phase:** | Phase 2 |
| **Comparator:** | KEYTRUDA® (pembrolizumab) |
| **Study Centers:** | Up to 30 centers in the United States will participate on this protocol. |
| **Background and Rationale for Study** | Urothelial carcinoma is common in the US, and metastatic urothelial carcinoma is an aggressive disease with high mortality. The checkpoint ligand, programmed death-1 ligand (PD-L1) expression in urothelial carcinoma was found to correlate with increased stage, grade, and tissue-infiltrating mononuclear cells in urothelial carcinoma (Inman 2007). The checkpoint interaction of PD-L1 on urothelial carcinoma cells and PD-1 receptor on infiltrating T cells may have an important role in dampening cytotoxic T-cell response to urothelial carcinoma. Targeting immune infiltrates and disrupting PD-1 ligand-receptor interactions may impair stromal support and enhance immune cell destruction of tumors that could offer therapeutic benefits to patients with urothelial carcinoma. Indeed, a monoclonal antibody directed at PD-L1 was shown recently to have a 26% response rate in unselected patients with metastatic urothelial carcinoma after disease progression with cisplatin-based chemotherapy (Powles 2014). A Phase 2 study of pembrolizumab (Keytruda®), a monoclonal antibody against PD-1, in 33 patients with PD-L1 positive urothelial carcinoma showed an overall response rate of 24.1% and complete response rate of 10.3% (Plimack 2014).<br>Myeloid derived suppressor cells (MDSCs) are important in promoting tumor growth and metastases by inducing epithelial-mesenchymal transition, allowing tumor invasion, and promoting angiogenesis (Condamine 2014). Therefore, MDSCs can be a mechanism of resistance to anti-PD-1 therapy. When used in combination with checkpoint inhibitors, agents that inhibit MDSCs can improve outcomes in murine models of metastatic disease (Kim 2014).<br>Bruton tyrosine kinase (BTK) is a non-receptor enzyme of the Tec kinase family that is expressed in B cells, myeloid cells, and mast cells, where it regulates cellular proliferation, differentiation, apoptosis, and cell migration. BTK inhibition leads to preferential |

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| | differentiation of macrophages into M1 instead of immunosuppressive M2 macrophages; BTK inhibition thus decreases the tumor-associated macrophages that promote tumor invasion and metastasis.<br>Acerta Pharma BV is developing acalabrutinib, an orally administered, small-molecule inhibitor of BTK. A Phase 1 study of acalabrutinib in [redacted] with relapsed/refractory chronic lymphocytic leukemia showed an overall response rate of 95%. Acalabrutinib monotherapy has shown robust antitumor activity in murine solid tumor models. The antitumor effect observed with acalabrutinib correlates with biomarkers of response similar to those reported for other immunomodulating agents such as inhibitors of CTLA-4, PD-1 and PD-L1.<br>To determine whether there is potential synergy between BTK inhibition and PD-1 blockade, Acerta has conducted a nonclinical study of acalabrutinib in combination with an anti-PD ligand 1 (anti-PD-L1) antibody in an orthotopic colon cancer murine model. Treatment with anti-PD-L1 as a single agent reduced tumor growth, but tumor regression was not observed. However, combined anti-PD-L1 and acalabrutinib treatment showed a further reduction in tumor growth. Specifically, 6 of 9 animals displayed tumor regression compared with no animals treated with anti-PD-L1 alone (Figure 1-6). These results suggest the combination therapy of BTK inhibition and PD-1 blockade leads to greater benefit compared with PD-1 blockade alone.<br>This proof-of-concept study will assess the clinical potential of a targeted dual inhibition approach by evaluating the safety, pharmacodynamics (PD), and efficacy of acalabrutinib and pembrolizumab in subjects with metastatic urothelial carcinoma who have progressed after treatment with cisplatin-based chemotherapy. |
| **Study Design:** | This clinical trial is a Phase 2, multicenter, open-label, randomized study evaluating pembrolizumab monotherapy and the combination of acalabrutinib and pembrolizumab in subjects who have metastatic bladder cancer with disease progression on or after platinum-based chemotherapy.<br>Subjects meeting the eligibility criteria for the study will be randomized 1:1 to one of the following arms:<br>Arm 1: Pembrolizumab 200 mg administered as an intravenous (IV) infusion every 3 weeks (Q3W)<br>Arm 2: Acalabrutinib 100 mg administered orally (PO) twice per day (BID) plus pembrolizumab 200 mg IV Q3W<br>Although acalabrutinib has not demonstrated any dose-limiting toxicities (DLTs) to date, the safety of acalabrutinib in combination with pembrolizumab in this patient population needs to be assessed. Thus, standard DLT criteria will be applied to Arm 2 of the study. Therefore an interim safety analysis will occur once [redacted] have been successfully randomized to the combination arm (Arm 2) and have been treated a minimum of 4 weeks. |

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| | Enrollment will be paused while the interim safety analysis occurs. If a DLT rate of < 33% is observed in Arm 2 (ie, DLT review is cleared), then randomization will continue to evaluate the objective response rates of pembrolizumb monotherapy and the combination of pembrolizumab and acalabrutinib (ie, up to [redacted] per arm). If a DLT rate of ≥ 33% is observed in Arm 2, then enrollment (1:1) will continue until an additional [redacted] are randomized to Arm 2, and consideration will be given to reducing the dose of acalabrutinib (Level -1), taking into account the nature of the DLTs and the DLT rate in the single-agent arm. In addition, analyses for continuous futility and toxicity monitoring will also be done as outlined in Section 5.5.<br><br>Acalabrutinib treatment can continue for subjects who are tolerating therapy and not progressing. Pembrolizumab treatment is for 24 months from the date of first dose for subjects who are tolerating therapy and not progressing. Subjects who have confirmed progressive disease on the combination of pembrolizumab and acalabrutinib will discontinue study treatment while those with confirmed progressive disease in the pembrolizumab monotherapy arm will continue on pembrolizumab with the addition of acalabrutinib until a second disease progression. For subjects who cross over to receive combination treatment, acalabrutinib treatment will begin at the next visit at which subjects are scheduled to receive pembrolizumab. The immune-related response criteria (irRECIST; Appendix 8 and Section 3.11) will be used to determine progression on this study.<br><br>Pembrolizumab treatment can end for subjects with confirmed complete response (CR) if treatment has been administered for at least 24 weeks and 2 doses of pembrolizumab have been administered after confirmation of CR. The end of study is defined as 12 months after the last subject is randomized.<br><br>Refer to Appendix 4 and Appendix 5 for comprehensive lists of study assessments and their timing. A study schema is provided in Figure 3-1. |
| **Definition of Dose-limiting Toxicity:** | A DLT will be defined as the occurrence of any of the following study drug-related adverse events (note: Adverse events [AEs] clearly related to disease progression or the subject's current medical history and associated comorbidities will not be considered DLTs):<br><br>1. Grade 4 vomiting or diarrhea<br>2. Grade 3 nausea, vomiting, or diarrhea lasting for > 72 hours<br>3. Other Grade ≥ 3 toxicites (Note: Transient Grade 3-4 laboratory abnormalities that are not clinically significant will not be considered DLTs)<br>4. Dosing delay due to toxicity for > 21 consecutive days |
| **Study Objectives:** | **Primary Objectives:** |

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| | • To characterize the safety profile of acalabrutinib and pembrolizumab in subjects with metastatic, platinum-refractory bladder cancer<br>• To determine the best overall response rate (BOR) and overall response rate (ORR) of pembrolizumab monotherapy and the combination of acalabrutinib and pembrolizumab in subjects with metastatic, platinum-refractory bladder cancer<br>**Secondary Objectives:**<br>• To determine progression-free survival (PFS) in subjects treated with pembrolizumab monotherapy and the combination of acalabrutinib and pembrolizumab<br>• To evaluate the overall survival (OS) in subjects treated with pembrolizumab monotherapy and the combination of acalabrutinib and pembrolizumab<br>**Exploratory Objectives:**<br>• Determine the effects of acalabrutinib plus pembrolizumab on peripheral blood T cells and myeloid-derived suppressor cells (MDSCs)<br>• Determine the PK of acalabrutinib alone and in combination with pembrolizumab<br>• Determine if any characteristics of peripheral blood T cells and/or MDSCs correlate with immune-mediated toxicities<br>• Determine if any characteristics of peripheral blood T cells and/or MDSCs correlate with response to acalabrutinib and pembrolizumab<br>• Determine if any baseline tumor characteristics correlate with response to acalabrutinib and pembrolizumab<br>• To evaluate the efficacy of adding acalabrutinib to pembrolizumab in subjects who progress on pembrolizumab monotherapy |
| **Safety Endpoints:** | Type, frequency, severity, timing of onset, duration, and relationship to study drug of any treatment-emergent AEs or abnormalities of laboratory tests; serious adverse events (SAEs); DLTs or AEs leading to discontinuation of study treatment. |
| **Pharmacodynamic, Pharmacokinetic and Biomarker Parameters:** | The occupancy of BTK by acalabrutinib will be measured in peripheral blood mononuclear cells (PBMCs) with the aid of a biotin-tagged acalabrutinib analogue probe. The effect of acalabrutinib and pembrolizumab on B cells, T cells, and MDSCs will also be evaluated. Tumor tissue, when available, will be evaluated for PD-L1 expression. Acalabrutinib will be measured in blood plasma. |

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| **Efficacy Endpoints:** | • BOR<br>• ORR, defined as partial response (PR) and complete response (CR), based on modified RECIST 1.1 criteria (Appendix 7)<br>• Disease control rate (DCR), defined as CR, PR, and stable disease (SD) based on modified RECIST 1.1 criteria<br>• Duration of response (DOR)<br>• Progression-free survival (PFS)<br>• Overall survival (OS)<br>Exploratory endpoints for efficacy based on immune-related response criteria (irRECIST) (Appendix 8):<br>• Immune-related BOR (irBOR)<br>• irORR, defined as immune-related partial response (irPR) and immune-related complete response (irCR)<br>• irDCR<br>• irDOR<br>• irPFS |
| **Sample Size:** | An interim safety analysis will occur once [redacted] have been successfully randomized to the combination arm (Arm 2) and have been treated a minimum of 4 weeks. Provided the DLT period is cleared in the combination arm, the study will proceed to full enrollment of [redacted] per arm for a total enrollment of [redacted]. |
| **Inclusion Criteria:** | 1. Men and women ≥ 18 years of age.<br>2. Histologically or cytologically confirmed urothelial (transitional cell) carcinoma of the bladder or mixed histology bladder cancer (with transitional cell components).<br>3. Presence of metastic bladder cancer that has either progressed during or after platinum-based chemotherapy administered for metastatic disease or has recurred during or within 1 year after the completion of platinum-based neoadjuvant or adjuvant therapy.<br>4. Any primary site of urothelial carcinoma including upper tract, renal pelvis, bladder, and ureters.<br>5. Prior therapy with ≥ 1 systemic chemotherapy regimens for urothelial carcinoma<br>6. Presence of radiographically measurable disease as defined by RECIST 1.1.<br>7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.<br>8. Completion of all therapy (including surgery, radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for |

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| | the treatment of cancer ≥ 2 weeks before the start of study therapy and recovered (ie, Grade ≤ 1 or baseline) from AEs associated with prior cancer therapy. Note: Subjects with Grade ≤ 2 neuropathy or Grade ≤ 2 alopecia are an exception to the latter criterion and may qualify for the study.<br>9. Women who are sexually active and can bear children must agree to use acceptable forms of contraception during the study and for 90 days after the last dose of acalabrutinib or 120 days after the last dose of pembrolizumab, whichever is longer. Note: Acceptable forms of contraception are defined in Section 3.10.6.<br>10. Men who are sexually active and can beget children must agree to use acceptable forms of contraception during the study and for 90 days after the last dose of acalabrutinib or 120 days after the last dose of pembrolizumab, whichever is longer.<br>11. Men must agree to refrain from sperm donation during the study and for 90 days after the last dose of acalabrutinib or 120 days after the last dose of pembrolizumab, whichever is longer.<br>12. Able to provide tissue for biomarker analysis from either an archived tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated.<br>13. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.<br>14. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations). |
| **Exclusion Criteria:** | 1. Prior malignancy (other than bladder cancer), except for treatment-naive prostate cancer (defined as Stage T1/T2a, Gleason score ≤ 6, and prostate-specific antigen [PSA] < 10 ng/mL) undergoing active surveillance; or localized, very low to intermediate risk prostate cancer treated with curative intent and absence of PSA relapse; or adequately treated basal cell or squamous cell skin cancer, in situ cancer, or other cancer from which the subject has been disease free for ≥ 2 years.<br>2. Known central nervous system metastases and/or carcinomatous meningitis. Note: Imaging studies of the central nervous system are not required as a condition of study enrollment<br>3. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification and corrected QT interval (QTc) > 480 msec. |

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| | 4. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.<br>5. Prior therapy with any inhibitor of BTK, protein kinase B (AKT), Janus kinase (JAK), mammalian target of rapamycin (mTOR), phosphatidylinositol-3 kinase (PI3K), or spleen tyrosine kinase (SYK).<br>6. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD ligand 2 (anti-PD-L2), anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab, tremelimumab, nivolumab, pembrolizumab, MPDL3280A or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways)<br>7. Receiving ongoing immunosuppressive therapy, including systemic or enteric corticosteroids except for minimally systemically absorbed treatments (such as inhaled or topical steroid therapy for asthma, chronic obstructive pulmonary disease, or allergic rhinitis) within 7 days before the first dose of pembrolizumab.<br>8. Active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Note: Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.<br>9. Has history of interstitial lung disease or evidence of active non-infectious pneumonitis.<br>10. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.<br>11. History of bleeding diathesis (eg, hemophilia or von Willebrand disease).<br>12. Requires treatment with a strong cytochrome P450 3A (CYP3A) inhibitor/inducer.<br>13. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 7 days of first dose of study drug.<br>14. Requires treatment with proton-pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole).<br>15. Has received a live vaccine within 30 days of planned start of study therapy.<br>16. Known history of human immunodeficiency virus (HIV) or serologic status indicating active hepatitis C virus (HCV) or hepatitis B virus (HBV) infection or any uncontrolled active systemic infection. Subjects with hepatitis B core antibody positive who are surface antigen negative or who are hepatitis |

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| | C antibody positive will need to have a negative polymerase chain reaction (PCR) result before enrollment. Those who are hepatitis B surface antigen positive or hepatitis B PCR positive and those who are hepatitis C PCR positive will be excluded.<br>17. History of stroke or intracranial hemorrhage within 6 months before the first dose of study drug.<br>18. Major surgical procedure within 28 days of first dose of study drug. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug.<br>19. Absolute neutrophil count (ANC) < 1.5 x $10^9$/L or platelet count < 100 x $10^9$/L or hemoglobin < 8.0 g/dL.<br>20. Total bilirubin > 1.5 x ULN; or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3.0 x ULN.<br>21. Estimated creatinine clearance of < 30 mL/min, calculated using the formula of Cockroft and Gault [(140-Age) • Mass (kg)/(72 • creatinine mg/dL); multiply by 0.85 if female].<br>22. Breastfeeding or pregnant or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.<br>23. Is currently participating in a clinical trial and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.<br>24. Immediate family members of the sponsor personnel or site staff directly involved with the conduct of this protocol are excluded from participating on this study.<br>25. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months prior to screening. |
| **Dose Regimen/Route of Administration:** | Acalabrutinib is provided as hard gelatin capsules for oral administration.<br>KEYTRUDA® (pembrolizumab) for injection is provided as a 100 mg/4 mL (25 mg/mL) solution in a single-use vial or as a lyophilized powder for reconstitution (50 mg/vial). It is administered as an IV infusion over 30 minutes.<br>**Arm 1:**<br>Pembrolizumab 200 mg every 3 weeks (Q3W)<br>**Arm 2:** |

| Dose Level | Acalabrutinib | Pembrolizumab |
|---|---|---|
| Starting Dose | 100 mg BID PO | 200 mg Q3W IV |
| Level -1 | 100 mg QD PO | 200 mg Q3W IV |

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| | Level -2 50 mg BID PO 200 mg Q3W IV<br>Abbreviations: BID = twice per day; IV = intravenous, PO = oral; Q3W = every 3 weeks |
| **Concomitant Medications:** | The concomitant use of strong inhibitors/inducers of CYP3A or P-gp with acalabrutinib should be avoided when possible. The effect of agents that reduce gastric acidity (eg, proton-pump inhibitors, H2-receptor antagonists or antacids) on acalabrutinib absorption was evaluated in a healthy volunteer study (ACE-HV-004). Results from this study indicate that subjects should avoid the use of calcium carbonate-containing drugs or supplements and short-acting H2-receptor antagonists for a period of at least 2 hours before and after taking acalabrutinib. Use of omeprazole or esomeprazole or any other proton-pump inhibitors while taking acalabrutinib is not recommended due to a potential decrease in study drug exposure. |
| **Statistical Methods:** | Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions and confidence intervals [CIs] for discrete variables) will be used to summarize data as appropriate.<br>**Statistical Basis for the Sample Size**<br>For the interim safety analysis (DLT review), enrollment of 6 subjects in the combination arm for DLT review is consistent with sample sizes used in oncology studies for determination of maximum tolerated dose (MTD). The trial employs the standard National Cancer Institute definition of MTD (dose associated with DLT in ≤ 17% of subjects). Provided the DLT period is cleared in the combination arm, and this arm is not stopped early due to futility or toxicity, then up to 31 subjects will be added per arm.<br>The sample size for this 2-arm trial was determined by a Z-test for normal approximation of binomial distribution, based on one-sided $\alpha = 0.10$, 80% power, with projected response rates of 40% in pembrolizumab/acalabrutinib arm and 18% in pembrolizumab arm. The final sample size is 37 in each arm. |

# 1.0 BACKGROUND INFORMATION

## 1.1 UROTHELIAL CARCINOMA

In 2014, approximately 141,610 people in the United States will be diagnosed with urothelial carcinoma of the bladder, renal pelvis, or ureter (Siegel 2014). Although many newly diagnosed patients have localized disease, urothelial carcinoma is often fatal for those diagnosed with metastatic disease. Approximately 30,350 people are anticipated to die from this disease in 2014. In most patients with localized disease, treatment includes localized excision with transurethral resection of bladder tumor (TURBT) and intravesicular Bacillus Calmette Guerin (BCG) infusions (Martyn-Hemphill 2013). In the ~30% of patients who develop metastatic disease, chemotherapy with a platinum-based regimen is the primary treatment (Gartrell 2013). Current standard of care first-line therapy includes combination chemotherapy with cisplatin or carboplatin with gemcitabine, or the combination of methotrexate, vinblastine, adriamycin, and cisplatin (MVAC). However, because of the inherent chemoresistance of bladder cancer, median progression-free survival (PFS) with these chemotherapy regimens is approximately 7.4 months (von der Maase 2000). The addition of paclitaxel to gemcitabine/cisplatin has improved PFS to 8.3 months (Bellmunt 2012). Currently, second-line therapies are limited, and no therapies have been approved by the United States Food and Drug Administration (FDA) for patients who survive to undergo second-line treatment. Survival at 2 years is therefore < 20% (Bellmunt 2012). Thus, while antitumor benefit has been observed with such regimens, toxicity is substantial and therapeutic options are limited. Novel, less toxic approaches are needed for metastatic, platinum-refractory urothelial carcinoma.

## 1.2 THE ROLE OF STROMA IN UROTHELIAL CARCINOMA

The importance of the stroma in urothelial carcinoma has been increasingly recognized (van der Horst 2012), particularly in its role in tumor progression and formation of metastases. Several stromal-changing growth factors, such as FGF2, VEGF, PDGF, EGFR ligands, and TGF-β are important in mediating tumor progression, supporting tumor associated fibroblasts in urinary bladder tumor specimens (Enkelmann 2011). Tumor-associated fibroblasts have also shown increased populations in invasive bladder tumors and not in superficial bladder tumors, thus associating with muscle invasion and formation of metastases (Alexa 2009). Furthermore, tumor-associated macrophages have been shown to mediate hypoxia-driven angiogenesis, contributing to tumor progression in bladder

cancer (Onita 2002). The TGF-β mediator is also known to shift macrophages from an M1 antitumor phenotype to an M2 protumor phenotype, leading to remodeling of the microenvironment, angiogenesis, and epithelial plasticity (Fuxe 2012). In summary, urothelial carcinoma exists in a complex desmoplastic microenvironment providing stromal support for tumor growth, resembling wound healing, thus increasing motility, invasion, and angiogenesis.

## 1.3 PROGRAMMED DEATH LIGAND/RECEPTOR INTERACTIONS IN UROTHELIAL CARCINOMA

Several negative regulatory checkpoint molecules function to check overstimulation of immune responses and contribute to the maintenance of immune tolerance to self-antigens (McDermott 2013). These molecules include cytotoxic T-lymphocyte antigen-4 (CTLA-4) as well as the programmed death (PD)-1 receptor and its ligands (PD-L1 and PD-L2). CTLA-4 acts as a signal dampener that acts largely within the lymph nodes to regulate the magnitude of early activation of naive and memory T cells. By contrast, PD-1 is induced on T cells after activation in response to inflammatory signals and limits T-cell function at sites of infection or tumor in peripheral tissues. As the T-cell response increases, these negative regulatory molecules are induced, limiting the magnitude and duration of the response to prevent healthy tissue damage. Tumors are capable of exploiting the homeostatic mechanisms regulated by these checkpoint molecules, thus limiting immune destruction.

Such checkpoint pathways appear to be operative in urothelial carcinoma. Immunohistochemistry analyses have shown PD-L1 positivity is associated with increased staging, high-grade tumors, and tissue-infiltrating mononuclear cells in urothelial carcinoma (Inman 2007). In a series of 318 patients with urothelial carcinoma, PD-L1 and PD-1 expression were associated with advanced disease, and PD-L1 expression independently predicted for mortality (Boorjian 2008). PD-L1 expression may protect cancer cells from immune-mediated destruction. In a clinical study of subjects with urothelial carcinoma evaluating the efficacy of an anti-PD-L1 antibody, high expression of PD-L1 in tumor-infiltrating immune cells correlated with a higher overall response rate (ORR, 40% to 50%) compared with an ORR of 13% and 8% for low PD-L1 or no PD-L1 expression (Powles 2014). In a clinical study of the anti-PD-1 monoclonal antibody, pembrolizumab, in subjects with recurrent or metastatic urothelial carcinoma, a 24% ORR, including 10% CR rate, was observed

across the 33 subjects treated. Analysis of the relationship between PD-L1 expression and pembrolizumab efficacy was pending at the time of publication (Plimack 2014).

## 1.4 BRUTON TYROSINE KINASE INHIBITION IN CANCER

Bruton tyrosine kinase (BTK) is a non-receptor enzyme in the Tec kinase family that is expressed among cells of hematopoietic origin, including B cells, myeloid cells, mast cells and platelets, where it regulates multiple cellular processes including proliferation, differentiation, apoptosis, and cell migration (Khan 2001, Mohamed 2009, Bradshaw 2010). In addition, BTK-dependent activation of mast cells, myeloid cells, and other immunocytes in peritumoral inflammatory stroma has been shown to sustain the complex microenvironment needed for lymphoid and solid tumor maintenance (Soucek 2011, Ponader 2012, de Rooij 2012). Taken together, these findings suggest inhibition of BTK may offer an attractive strategy for treating B-cell neoplasms, other hematologic malignancies, and solid tumors.

In model systems, ex vivo analyses demonstrated BTK inhibition results in macrophages that polarize into M1 macrophages, instead of showing enhanced induction of immunosuppressive M2 macrophages (Ni Gabhann 2014, Lannutti personal communication). These data suggest inhibition of BTK may impair the capacity of tumor-associated macrophages critical for promotion of tumor invasion and metastasis (Mouchemore 2013). Several lines of evidence demonstrate BTK inhibition interferes with cross-talk between malignant cells and their microenvironment, suggesting disruption of intrinsic and extrinsic survival signals may be a critical mechanism for the clinical activity of BTK inhibitors (Ponader 2012, Herman 2013). Furthermore, epithelial derived tumors contain large numbers of tumor-associated macrophages (TAMs), which are the dominant innate immune cell in mammary cancers of humans (Pollard 2009). Therefore, the clinical usefulness of BTK inhibitors may extend to the treatment of invasive solid tumors.

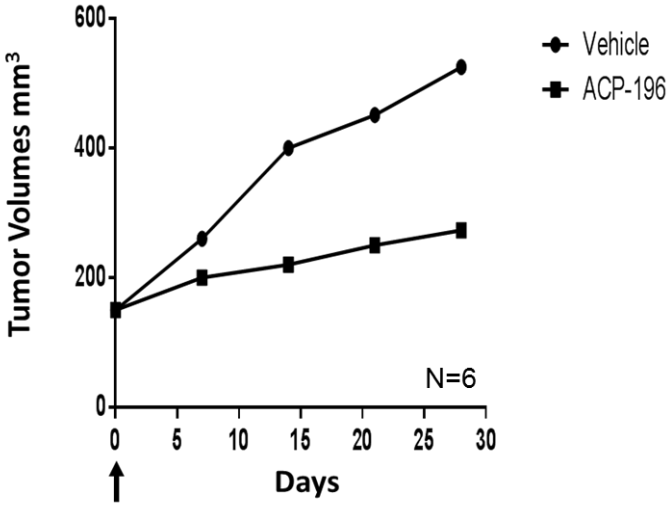
BTK is also a signaling hub in immature myeloid cells known as myeloid derived suppressor cells (MDSCs) (Schmidt 2004). Recent evidence suggests MDSC play an important part in suppression of host immune responses through several mechanisms such as production of arginase 1, release of reactive oxygen species, nitric oxide and secretion of immune-suppressive cytokines. This leads to an immunosuppressive

environment necessary for the growth of malignant cells (Condamine 2014, Wesolowski 2013).

Immune evasion is one of the multiple characteristics of cancer. Monoclonal antibodies that block negative regulators of T cells, such as PD-1, amplify immune responses. Antibodies against PD-1 are showing impressive results in advanced hematologic and solid malignancies (Hamid 2013, Westin 2014, Berger 2008, Topalian 2014). nterestingly, studies examining circulating MDSCs in anti-CTL4 and anti-PD-1/PD-L1-treated patients have shown alterations in the myeloid cell compartment correlate with clinical outcome. Specifically, solid tumor progressors had proportionally higher circulating MDSC levels and a high myeloid gene signature (Powles 2014, Heery 2014, Weide 2014, Meyer 2014). Recent preclinical results show elevated MDSC levels are responsible for this lack of response and elimination of MDSCs may lead to increased efficacy with immune checkpoint blockade (Highfill 2014, Kim 2014).

Given the potential for BTK inhibition to affect TAMs and MDSCs, single-agent acalabrutinib was evaluated in mice with advanced pancreatic cancer arising as the result of genetic modifications of oncogenes KRAS and p53, and the pancreatic differentiation promoter PDX-1 (KPC mice). The KPC mouse model recapitulates many of the molecular, histopathologic, and clinical features of human disease (Westphalen 2012). Mice were enrolled after identification of spontaneously appearing tumors in the pancreas that were ≥100 $mm^3$ (as assessed by high-resolution ultrasonography). Mice were treated with vehicle (N=6) or acalabrutinib administered orally at a dosage of 15 mg/kg/dose twice per day (BID) (N=6). As shown in Figure 1-1, treatment with single-agent acalabrutinib substantially slowed pancreatic cancer growth and increased animal survival.

**Figure 1-1. Efficacy of Acalabrutinib Monotherapy in a Genetic Model of Pancreatic Cancer**




**Tumor volumes**

| | Predose | Day 28 |
|---|---|---|
| Control | 152 $mm^3$ | 525 $mm^3$ |
| ACP-196 | 165 $mm^3$ | 272 $mm^3$ |

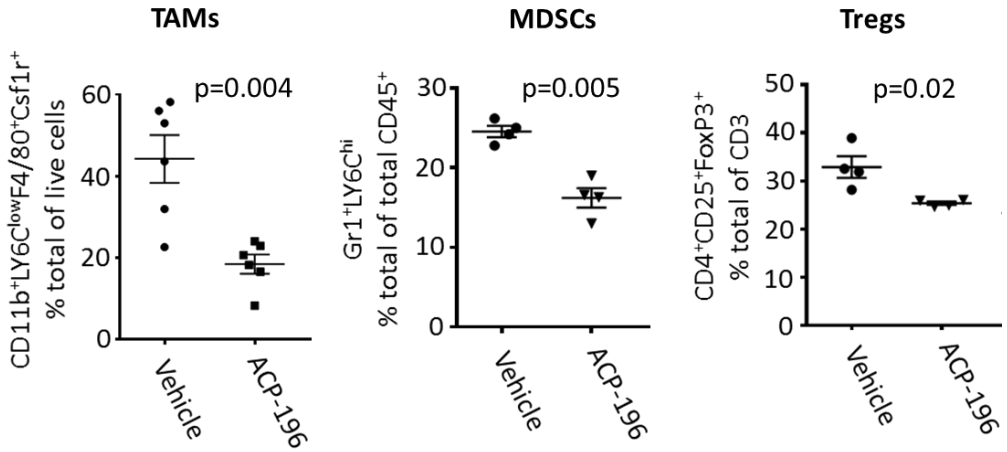
**Survival**

| | Day 14 | Day 28 |
|---|---|---|
| Control | 5/6 | 0/6 |
| ACP-196 | 6/6 | 5/6 |

Abbreviation: ACP-196 = acalabrutinib.

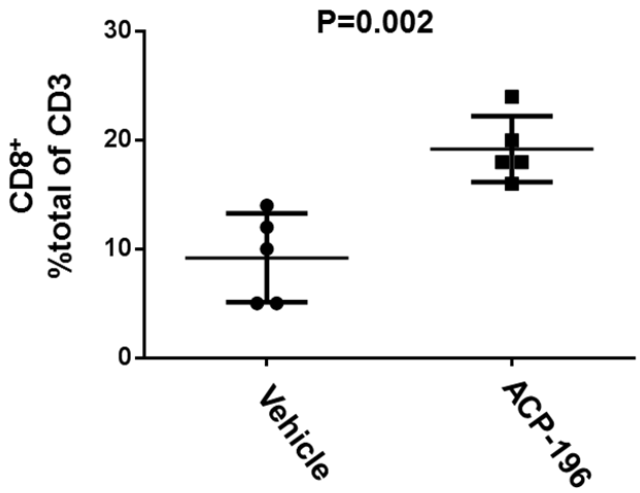
Analysis of tumor tissues showed that immunosuppressive TAMs ($CD11b^+Ly6C^{low}F4/80^+Csf1r^+$), MDSCs ($Gr1^+Ly6C^{Hi}$), and $T_{reg}$ ($CD4^+CD25^+FoxP3^+$) were significantly reduced with acalabrutinib treatment by 47%, 30%, and 20%, respectively (Figure 1-2). As expected the decrease in these immunosuppressive cell subsets correlated with a significant increase in $CD8^+$ cells (Figure 1-3).

**Figure 1-2. Effects of Acalabrutinib on Tumor-Associated Immunosuppressive Cells in a Genetic Model of Pancreatic Cancer**




Abbreviations: ACP-196 = acalabrutinib; MDSC = myeloid-derived suppressor cell; TAM = tumor-associated macrophage; $T_{reg}$ = regulatory T cell.

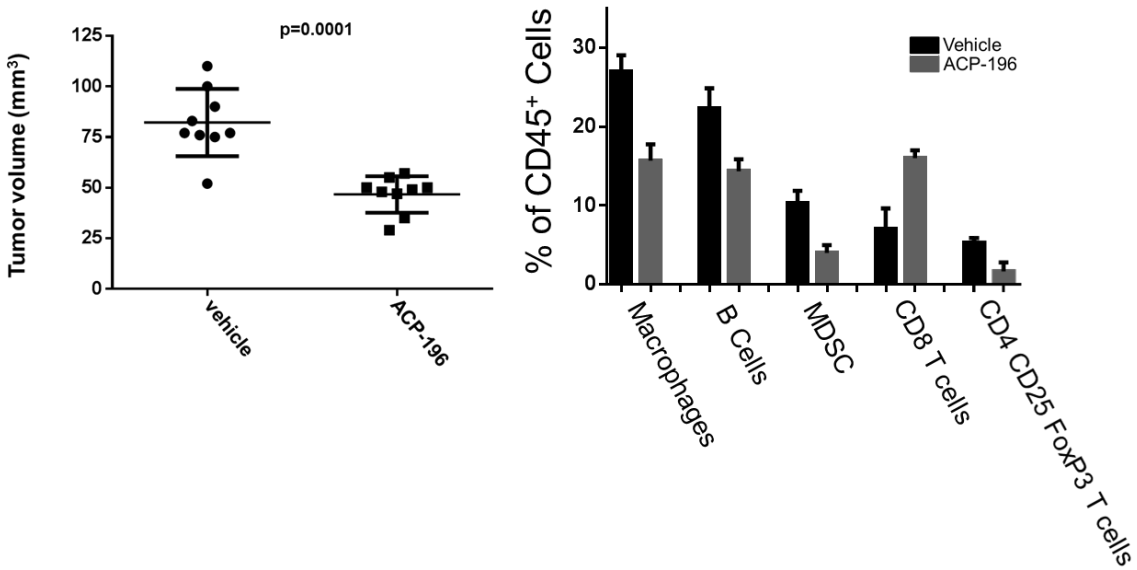
**Figure 1-3. Effects of Acalabrutinib on Cytolytic T Cells in a Genetic Model of Pancreatic Cancer**




Abbreviation: ACP-196 = acalabrutinib.

Similar single-agent activity was also observed with acalabrutinib (15 mg/kg BID) in the ID8 syngeneic orthotopic ovarian model. Figure 1-4 shows a substantial decrease of tumor growth in this model with acalabrutinib monotherapy compared with vehicle. This antitumor effect correlated with a significant decrease in immunosuppressor cells and an increase in cytolytic T cells similar to the KPC pancreatic model.

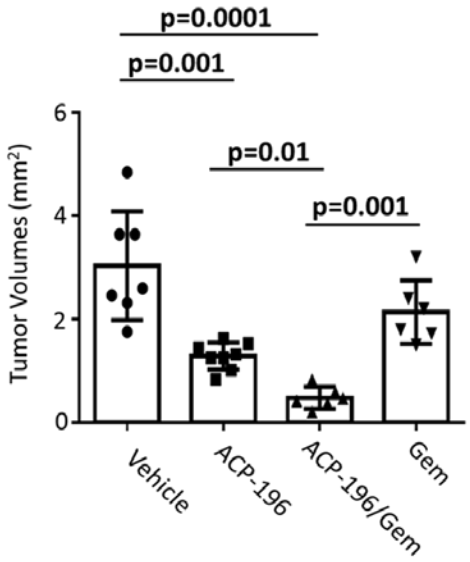
**Figure 1-4. Acalabrutinib Impairs ID8 Ovarian Cancer Growth and Decreased Immunosuppressive Cellular Subsets in Syngeneic Murine Model**




Abbreviations: ACP-196 = acalabrutinib; MDSC=myeloid-derived suppressor cell.

Lastly, the activity of acalabrutinib was confirmed in an orthotopic mouse model evaluating both single-agent and combination efficacy. In this study, 10,000 KPC mouse pancreatic cancer cells were injected into the pancreases of 24 female mice. After one week of expansion, drug treatment was started in mice developing pancreatic tumors. Animals were treated with vehicle (N=6); acalabrutinib, 15 mg/kg/BID given orally (N=6); gemcitabine 50 mg/kg intravenous (IV) administered every 4 days for 3 injections (N=6); or acalabrutinib, 15 mg/kg/BID given orally together with gemcitabine, 50 mg/kg IV administered every 4 days for 3 injections (N=6). At 2 weeks after initiation of treatment, mice in the vehicle group showed signs of deteriorating health and all groups were euthanized. Tumors were collected and measured (Figure 1-5); relative to the vehicle treatment, acalabrutinib monotherapy resulted in a 2-fold reduction in tumor growth, results which compared favorably with gemcitabine alone. The combination of acalabrutinib and gemcitabine resulted in a further reduction in tumor growth when compared to each single agent.

**Figure 1-5. Efficacy of Acalabrutinib Monotherapy and Combination Therapy with Gemcitabine in an Orthotopic Model of Pancreatic Cancer**



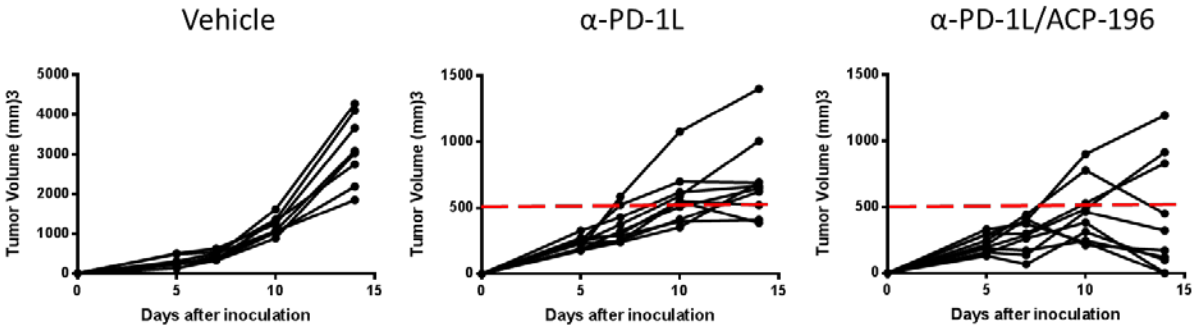

Abbreviations: ACP-196 = acalabrutinib; Gem = gemcitabine.

In summary, acalabrutinib alone and in combination with gemcitabine produces robust antitumor effects in established solid tumor models. The antitumor effect observed with acalabrutinib correlates with biomarkers of response similar to those reported for other immunomodulating agents such as inhibitors of CTLA-4, PD-1 and PD-L1.

## 1.5 A CASE FOR COMBINATION BTK AND CHECKPOINT BLOCKADE

To determine whether there is potential synergy between BTK inhibition and PD-1 blockade, Acerta has conducted a nonclinical study of acalabrutinib in combination with an anti-PD-L1 antibody in an orthotopic colon cancer murine model. Mice were inoculated with syngeneic CT26 colorectal cancer cells on Day 0; Anti-PD-L1 (150 µg on Day 6, 9, 12, 15) and acalabrutinib (15 mg/kg BID) treatment was begun on Day 6, when the tumor was well established. Treatment with anti-PD-L1 as a single agent reduced tumor growth, but tumor regression was not observed (Figure 1-6). However, combined anti-PD-L1 and acalabrutinib treatment showed a further reduction in tumor growth (anti-PD-L1, 820 $mm^3$ vs anti-PD-L1/acalabrutinib, 411 $mm^3$). Most strikingly, 6 of 9 animals displayed tumor regression (Figure 1-6). These results suggest the combination therapy of BTK inhibition and PD-1 blockade leads to greater benefit compared with PD-1 blockade alone.

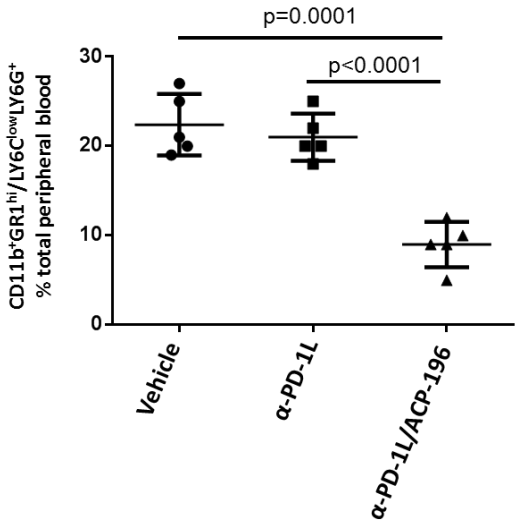
**Figure 1-6. Acalabrutinib Enhances the Antitumor Effects of α-PD-L1 in the Orthotopic CT26 Colon Cancer Model**




Abbreviation: ACP-196 = acalabrutinib.

In the tumor microenvironment, we observed a significant reduction in the number of MDSCs within the tumor in mice treated with the anti-PD-L1/acalabrutinib combination when compared with anti-PD-L1 treatment alone (Figure 1-7). The decrease of MDSCs is directly related to BTK inhibition. This effect has been observed in monotherapy studies of acalabrutinib in murine pancreatic and ovarian cancer models (as described in Section 1.4). Together, these data implicate tumor-associated MDSCs in preventing the full benefit of immune checkpoint blockade and offer a translatable, therapeutic option by targeting the MDSCs population with acalabrutinib to improve the efficacy of checkpoint blockade.

**Figure 1-7. BTK Inhibition Leads to Modulation of Infiltrating Immature Myeloid Cells Which Can Limit the Activity of Anti-PD-L1 Antibodies**




Abbreviation: ACP-196 = acalabrutinib.

This proof-of-concept study will assess the clinical potential of combined BTK inhibition and checkpoint blockade by evaluating the safety, PD, and efficacy of acalabrutinib and pembrolizumab in subjects with previously treated metastatic urothelial carcinoma.

Summaries of preclinical and clinical studies for acalabrutinib are provided below. For more detailed information please refer to the investigator brochure for acalabrutinib. For detailed information on pembrolizumab refer to the KEYTRUDA package insert provided in Appendix 6 or to the investigator brochure for pembrolizumab.

## 1.6 ACALABRUTINIB

Acalabrutinib is an imidazopyrazine analogue with a molecular weight of 465.5 g/mol. The compound has 1 stereogenic center and acalabrutinib is the S-enantiomer. Acalabrutinib is orally administered in animals and is suitable for formulating in capsules. For clinical testing, acalabrutinib has been manufactured and formulated according to current Good Manufacturing Practices (cGMP).

Acalabrutinib is an investigational product and has not been approved for marketing in any country.

### 1.6.1 Mechanism of Action

Acalabrutinib was specifically designed to be a more potent and selective inhibitor of BTK to avoid off-target side effects as seen with ibrutinib. When profiled against 395 human kinases, acalabrutinib is more selective than ibrutinib (Covey 2015). For additional details, refer to the Acalabrutinib Investigator Brochure.

### 1.6.2 Safety Pharmacology

In vitro and in vivo safety pharmacology studies with acalabrutinib have demonstrated a favorable nonclinical safety profile.

When screened at 10 μM in binding assays evaluating interactions with 80 known pharmacologic targets such as G-protein-coupled receptors, nuclear receptors, proteases, and ion channels, acalabrutinib shows significant activity only against the A3 adenosine receptor; follow-up dose-response experiments indicated an $IC_{50}$ of 2.7 μM, suggesting a low clinical risk of off-target effects.

The in vitro effect of acalabrutinib on human ether-à-go-go-related gene (hERG) channel activity was investigated in vitro in human embryonic kidney cells stably transfected with hERG. Acalabrutinib inhibited hERG channel activity by 25% at 10 μM, suggesting a low clinical risk that acalabrutinib would induce clinical QT prolongation as predicted by this assay.

Acalabrutinib was well tolerated in standard in vivo Good Laboratory Practices (GLP) studies of pharmacologic safety. A functional observation battery in rats at doses through 300 mg/kg (the highest dose level) revealed no adverse effects on neurobehavioral effects or body temperature. A study of respiratory function in rats also indicated no treatment-related adverse effects at doses through 300 mg/kg (the highest dose level). In a cardiovascular function study in awake telemeterized male Beagle dogs, single doses of acalabrutinib at dose levels through 30 mg/kg (the highest dose level) induced no meaningful changes in body temperature, cardiovascular, or electrocardiographic (including QT interval) parameters. The results suggest that acalabrutinib is unlikely to cause serious off-target effects or adverse effects on critical organ systems.

### 1.6.3 Drug-drug Interaction Potential

For more detailed information on drug-drug interaction potential for acalabrutinib, refer to the Investigator Brochure.

Please refer to Section 3.10.4 for guidance on drugs that may cause drug-drug interactions.

## 1.7 IN VIVO GENERAL TOXICOLOGY – ACALABRUTINIB

The systemic toxicity of acalabrutinib has been investigated in six repeat-dose general toxicology studies, three with recovery periods, in the rat and the dog. The pivotal GLP studies were two 28-day repeat dose studies in Sprague Dawley rats with 32- and 28-day recovery periods, and a 28-day study in Beagle dogs with a 28-day recovery period.

The no observed adverse effect level (NOAEL) in the dog was 30 mg/kg/day, which was the highest dose evaluated. In rats, 30 mg/kg/day resulted in minimal inflammation of the pancreas in some animals, with reversal, indicating the rat to be the more sensitive preclinical species. The pancreatic effects were minimally increased at 100 mg/kg/day in the rat though there was no clinical evidence of toxicity. Hence, 100 mg/kg/day was selected to conservatively represent the highest non-severely toxic dose (HNSTD). The pancreatic findings were investigated in subsequent rat toxicology studies and found to be treatment related, non-adverse at lower doses, and not associated with systemic toxicity or changes in biomarkers of pancreatic function. The islet cell changes resemble a spontaneous pancreatic lesion that is described as an age-related finding in male rats of this strain. In dogs at 30 mg/kg/day, there were no microscopic findings in the pancreas, and all clinical biomarkers of pancreatic function were normal.

In rats and dogs, no adverse ECG or histopathologic cardiovascular effects were noted at the planned conclusion of the 28-day toxicology studies. However, in 5 of 6 rats from the 300-mg/kg dose group that died early in the study, slight to moderate necrosis of the myocardium and/or white blood cell infiltration/inflammation of the myocardium were noted on microscopic examination of the hearts. These findings were most likely incidental postmortem changes.

## 1.8 CLINICAL EXPERIENCE – ACALABRUTINIB

For more detailed information on the clinical experience for acalabrutinib please refer to the Investigator Brochure.

### 1.8.1 Pharmacokinetics and Pharmacodynamics of Acalabrutinib

ACE-HV-001 was a PK/pharmacodynamic (PD), dose-ranging, food-effect, and drug-drug interaction study evaluating BID and QD dosing for 1 or 2 days in healthy volunteers. This study evaluated the PK/PD of acalabrutinib at various dose levels and regimens. The starting dose for acalabrutinib was 2.5 mg BID. This study has been completed and no adverse laboratory, vital signs, or ECG findings were observed (2.5 to 50 mg BID; 50 to 100 mg QD). Three adverse events (AEs) related to study drug were reported. Each AE was Grade 1 and resolved without treatment. The AEs were constipation (2.5 mg BID), feeling cold (75 mg QD), and somnolence (75 mg QD).

In Part 1, PK properties of acalabrutinib were evaluated after oral administration of 2 daily divided doses of 2.5 to 50 mg and a single dose of 100 mg. Of the 30 subjects evaluated, all had observed systemic concentrations of acalabrutinib. Acalabrutinib plasma time to maximum concentration ($T_{max}$) values were between 0.5 and 1.0 hour for all dose cohorts and were independent of dose level. The increase in mean $C_{max}$ values was greater than dose proportional based on the increases of $C_{max}$ from the first dose administered. When evaluating $AUC_{0-12}$, $AUC_{0-24}$ or $AUC_{0-inf}$, the mean values increased in a dose-proportional manner based on the increases of the total dose administered. Mean half-life ($t_{1/2}$) values ranged from 0.97 to 2.1 hours, and appeared to decrease as the dose increased. The mean calculated oral clearance (CL/F: 165 to 219 L/h) and volume of distribution values (Vz/F: 233 to 612 L) appeared to be independent of the dose administered.

Acalabrutinib was not detected in the urine of subjects receiving the 2.5- or 5.0-mg BID doses of acalabrutinib. Acalabrutinib was detected in urine of other subjects (0.4% to 0.6% of dose) and amounts increased in a dose-dependent manner.

In Part 2, the effect of food on the PK of acalabrutinib (75 mg) after a single oral administration was evaluated in 6 men and 6 women. Median time to maximum plasma acalabrutinib ($T_{max}$) values were increased in the fed state (2.5 hours) relative to the fasted state (0.5 hour). The mean plasma acalabrutinib $C_{max}$ fed values decreased to 27.3% of the $C_{max}$ values observed in the fasted state. In contrast, the relative AUC exposure of acalabrutinib remained mostly unchanged in both states.

In Part 3, the effect of itraconazole on the PK of acalabrutinib (50 mg) after a single oral administration was evaluated in 17 subjects. No difference in acalabrutinib $T_{max}$ values was observed in the presence or absence of itraconazole.

Mean acalabrutinib exposures (as assessed by $C_{max}$, $AUC_{0\text{-last}}$, $AUC_{0\text{-}24}$, and $AUC_{0\text{-inf}}$) increased in the presence of itraconazole. The mean plasma acalabrutinib $C_{max}$ values increased 3.7-fold in the presence of itraconazole. The mean plasma $AUC_{0\text{-last}}$, $AUC_{0\text{-}24}$, and $AUC_{0\text{-inf}}$ values also increased between 4.9- to 5.1-fold in the presence of itraconazole. Mean CL/F and Vz/F values decreased in the presence of itraconazole (CL/F: 217 vs 44 L/h; Vz/F: 1190 vs 184 L). No differences in half-life values were observed (3.3 vs 2.5 hours).

The PD of acalabrutinib was evaluated using a BTK occupancy assay and correlated with a functional assay that determines the level of BTK inhibition by measuring expression of CD69 and CD86 on B cells. A dose-dependent increase in BTK occupancy and corresponding decrease in CD69/86 expression was observed in this study. Full BTK occupancy (≥ 90%) and complete CD86 and CD69 inhibition (≥ 90%) occurred at the 75- and 100-mg single dosed cohorts 1 to 3 hours after administration. However, only the 100-mg cohort maintained high BTK occupancy (91.5%) and high BCR functional inhibition (CD86: 86 ± 3% and CD69: 78 ± 8%) at 24 hours. For subjects receiving a second dose of acalabrutinib 12 hours after the first administration, full BTK target occupancy was observed 3 hours after the second dose for the 50-mg dosed cohort (BTK occupancy 97 ± 4%).

### 1.8.2 Acalabrutinib in CLL

As of 01 October 2015, acalabrutinib has been administered to > 800 participants in clinical studies, including subjects with hematologic malignancies, solid tumors, or rheumatoid arthritis, and participants who are healthy volunteers or with mild to moderate hepatic impairment. No SAEs have been reported in the hepatic impairment study or in the healthy volunteer studies. For more detailed information on the clinical experience for acalabrutinib, please refer to the Investigator Brochure.

This section briefly summarizes data from ACE-CL-001 (NCT02029443), an ongoing non-randomized, sequential group, dose-escalation Phase 1/2 study in subjects with relapsed/refractory or previously untreated CLL, Richter's syndrome, or prolymphocytic leukemia.

As of 01 October 2015, 60 subjects with relapsed CLL have been evaluated for tumor response based on International Working Group response criteria (Hallek 2008) as recently updated (Cheson 2012) to include PR with treatment-induced lymphocytosis (PRL). With a median follow up of 14.3 months, an ORR of 95% has been observed (Byrd 2016). Few subjects have had disease progression and no Richter's transformation has been observed in these subjects.

## 1.9 KEYTRUDA (PEMBROLIZUMAB)

Pembrolizumab (Keytruda [United States]), a humanized monoclonal antibody against the programmed death receptor-1 (PD-1) protein, has been developed by Merck & Co for the treatment of patients with cancer. Pembrolizumab is approved for treatment of patients with melanoma in several countries; in the United States and European Union it is approved for the treatment of adult patients with advanced (unresectable or metastatic) melanoma. Pembrolizumab has also been approved for treatment of patients with non-small cell lung cancer (NSCLC) in several countries; in the United States it is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with NSCLC and EGFR or ALK genomic tumor aberrations should also have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab. For complete information on pembrolizumab refer to the KEYTRUDA package insert (Appendix 6) or the Pembrolizumab Investigator Brochure.

Serious adverse reactions associated with pembrolizumab are described in the package insert (Appendix 6) and also Section 3.8.1 of this protocol.

## 1.10 BENEFIT/RISK

Acalabrutinib is a potent, orally administered small-molecule inhibitor of BTK. A PK/PD study has been completed with acalabrutinib in healthy volunteers (ACE-HV-001; Section 1.8.1). The safety results showed no safety risk was identified in healthy subjects receiving 1 or 2 days of acalabrutinib ≤ 100 mg. In the Phase 1/2 study of acalabrutinib in subjects with CLL, an ORR of 95% has been observed with a median follow-up of 14.3 months. In summary, the preliminary data suggest that acalabrutinib is well tolerated and has robust activity as a single agent in the treatment of subjects with CLL including those with 17p del.

The nonclinical and toxicology results of acalabrutinib suggest it may have an improved therapeutic window relative to ibrutinib; it may be more readily combined with other agents for the treatment of cancer. Based on the currently known toxicity profiles of acalabrutinib and pembrolizumab overlapping toxicities are not anticipated. Preliminary results in preclinical cancer models suggests a synergistic antitumor effect of BTK inhibition in combination with PD-1 blockade, which support evaluating the combination in clinical trials.

## 2.0 STUDY OBJECTIVES

### 2.1 PRIMARY OBJECTIVES:

- To characterize the safety profile of acalabrutinib and pembrolizumab in subjects with metastatic, platinum-refractory bladder cancer
- To determine the BOR and ORR of pembrolizumab monotherapy and the combination of acalabrutinib and pembrolizumab in subjects with metastatic, platinum-refractory bladder cancer

### 2.2 SECONDARY OBJECTIVES:

- To determine PFS in subjects treated with pembrolizumab monotherapy and the combination of acalabrutinib and pembrolizumab
- To evaluate the OS in subjects treated with pembrolizumab monotherapy and the combination of acalabrutinib and pembrolizumab

### 2.3 EXPLORATORY OBJECTIVES

- Determine the effects of acalabrutinib plus pembrolizumab on peripheral blood T cells and MDSCs
- Determine the PK of acalabrutinib alone and in combination with pembrolizumab
- Determine if any characteristics of peripheral blood T cells and/or MDSCs correlate with immune-mediated toxicities
- Determine if any characteristics of peripheral blood T cells and/or MDSCs correlate with response to acalabrutinib and pembrolizumab
- Determine if any baseline tumor characteristics correlate with response to acalabrutinib and pembrolizumab
- Evaluate the efficacy of adding acalabrutinib to pembrolizumab in subjects who progress on pembrolizumab monotherapy

## 3.0 STUDY DESIGN

This clinical trial is a Phase 2, multicenter, open-label, randomized study evaluating pembrolizumab monotherapy and the combination of acalabrutinib and

pembrolizumab in subjects who have metastatic bladder cancer with disease progression on or after platinum-based chemotherapy.

Subjects meeting the eligibility criteria for the study will be randomized 1:1 to one of the following arms:

Arm 1: Pembrolizumab 200 mg administered as an IV infusion every 3 weeks (Q3W)

Arm 2: Acalabrutinib 100 mg administered PO BID plus pembrolizumab 200 mg IV Q3W

Although acalabrutinib has not demonstrated any DLTs to date the safety of acalabrutinib in combination with pembrolizumab in this patient population needs to be assessed and standard DLT criteria will be applied to Arm 2 of the study. Therefore an interim safety analysis will occur once 6 subjects have been successfully randomized to the combination arm (Arm 2) and have been treated a minimum of 4 weeks. Enrollment will be paused while the interim safety analysis occurs. If a DLT rate of < 33% is observed in Arm 2 (ie, DLT review is cleared), then randomization will continue to evaluate the objective response rates of pembrolizumab monotherapy and the combination of pembrolizumab and acalabrutinib (ie, up to 37 total subjects per arm). If a DLT rate of ≥ 33% is observed in Arm 2, then enrollment (1:1) will continue until an additional 6 subjects are randomized to Arm 2 and consideration will be given to reducing the dose of acalabrutinib (Level -1), taking into account the nature of the DLTs and the DLT rate in the single-agent arm. In addition, analyses for continuous futility and toxicity monitoring will also be done as outlined in Section 5.5.

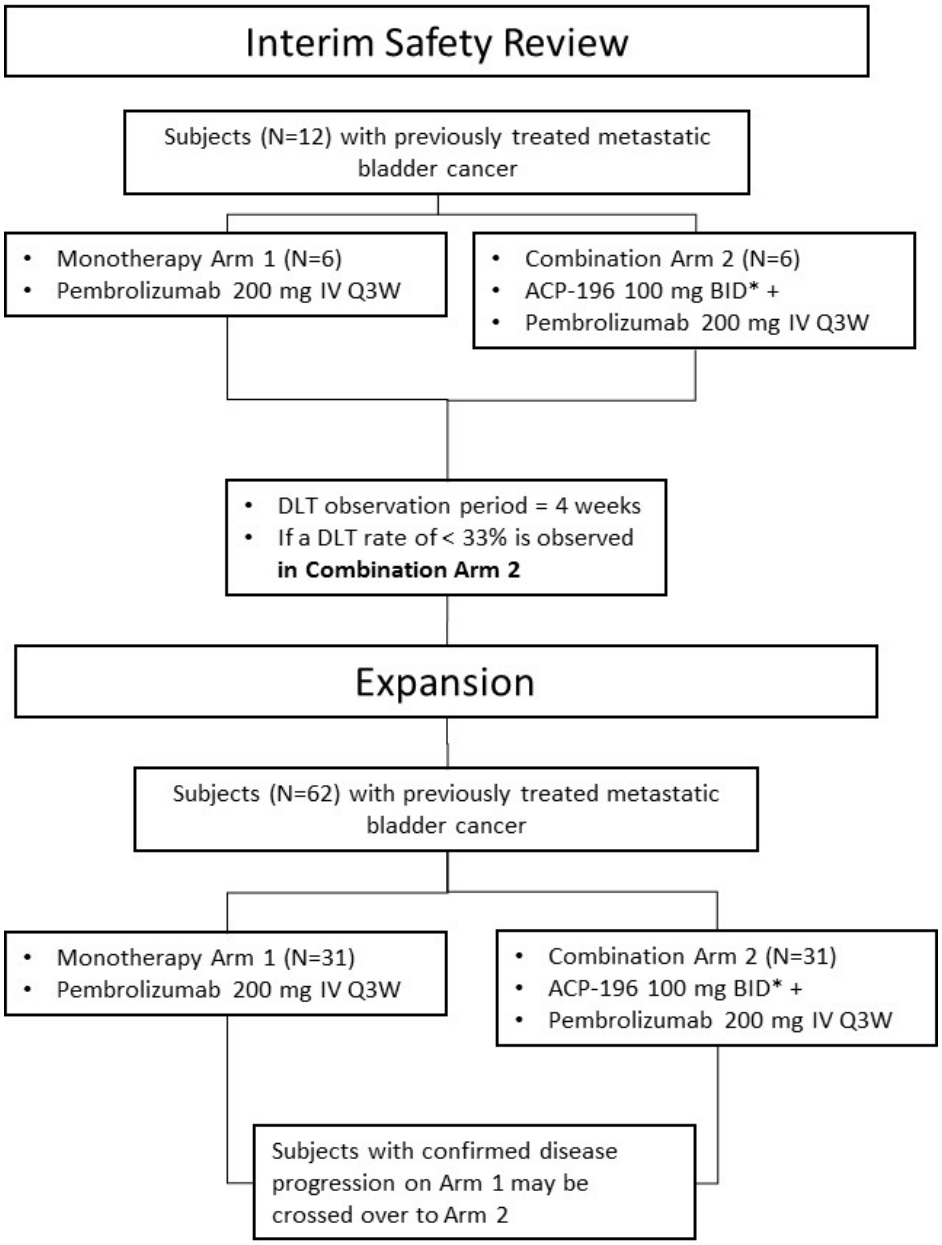
Acalabrutinib treatment can continue for subjects who are tolerating therapy and not progressing. Pembrolizumab treatment is for 24 months from the date of first dose for subjects who are tolerating therapy and not progressing. Subjects who progress on the combination of pembrolizumab and acalabrutinib will discontinue study treatment while those with progression of disease in the pembrolizumab monotherapy arm will continue on pembrolizumab with the addition of acalabrutinib until a second disease progression. For subjects who cross over to receive combination treatment, acalabrutinib treatment will begin at the next visit at which subjects are scheduled to receive pembrolizumab. The dose of acalabrutinib for these subjects will be determined based on the DLT review of Arm 2. Disease progression will be determined based on irRECIST guidelines (Appendix 8 and detailed in Section 3.11).

Also pembrolizumab treatment can end for subjects with confirmed CR if treatment has been administered for at least 24 weeks and 2 doses of pembrolizumab have been administered after confirmation of CR. The end of study is defined as 12 months after the last subject is randomized.

All subjects will have hematology, chemistry, and urinalysis safety panels performed at screening. Once dosing commences (Day 1), all subjects will be evaluated for safety, including serum chemistry, serum amylase and lipase, and hematology. Pharmacodynamic and PK testing will be performed during the first few months of treatment. Radiologic tumor assessments will be completed at baseline and at ~6-week intervals during the trial. Subjects who discontinue study drug for any reason other than disease progression, death, lost to follow-up, or withdrawal of consent will be followed for tumor assessment until disease progression or initiation of any other anticancer therapies, whichever comes first.

Refer to Appendix 4 and Appendix 5 for comprehensive lists of study assessments and their timing. The study schema is provided below (Figure 3-1).

**Figure 3-1. Study Schema**




Abbreviations: ACP-196 = acalabrutinib; BID = twice per day; IV = intravenous; Q3W = every 3 weeks.
*Acalabrutinib and pembrolizumab administration begin on the same day except for the first 6 subjects enrolled due to pharmacokinetic sampling. In the first 6 subjects, acalabrutinib will be administered on Day 1 of Week 1. On Day 2 of Week 1, the first pembrolizumab infusion will occur. When both are administered on the same day, acalabrutinib is administered first followed by the pembrolizumab infusion.

## 3.1 STUDY PARAMETERS

### 3.1.1 Safety Parameters

The safety of acalabrutinib and pembrolizumab will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to study drug(s) of any

treatment-emergent AEs or abnormalities of laboratory tests; SAEs; DLTs or AEs leading to discontinuation of study treatment.

### 3.1.2 Pharmacodynamic and Biomarker Parameters

The occupancy of BTK by acalabrutinib will be measured in peripheral blood mononuclear cells (PBMCs) with the aid of a biotin-tagged acalabrutinib analogue probe. The effect of acalabrutinib and pembrolizumab on B cells, T cells and MDSCs will also be evaluated. Tumor tissue, when available, will be evaluated for PD-L1 expression. Additional exploratory correlative studies of tumor tissue, when available, may include characterization of tumor subtypes by immunohistochemistry, gene expression or mutation analysis.

The following PK parameters will be calculated, whenever possible, from plasma concentrations of acalabrutinib:

- $AUC_{0\text{-}last}$: Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time last, where "last" is the time of the last measurable concentration.
- $AUC_{0\text{-}12}$: Area under the plasma concentration-time curve from 0 to 12 hours, calculated using linear trapezoidal summation.
- $AUC_{0\text{-}inf}$: Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{0\text{-}inf} = AUC_{0\text{-}last} + C_{last} / \lambda_z$, where $\lambda_z$ is the apparent terminal elimination rate constant.
- $AUC_{0\text{-}24calc}$: Area under the plasma concentration-time curve from 0 to 24 hours, calculated by doubling the value for $AUC_{0\text{-}12}$
- $C_{max}$: Maximum observed plasma concentration
- $T_{max}$: Time of the maximum plasma concentration (obtained without interpolation)
- $t_{½}$: Terminal elimination half-life (whenever possible)
- $\lambda_z$: Terminal elimination rate constant (whenever possible)
- CL/F: Oral clearance
- Vz/F: Oral volume of distribution

### 3.1.3 Efficacy Parameters

Efficacy will be evaluated based on assessments of tumor response and progression using the standardized Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 (Eisenhauer 2009; Appendix 7).

Efficacy endpoints will include:

- Best overall response rate (BOR)
- Overall response rate (ORR)
- Disease control rate (DCR)
- Duration of response (DOR)
- Progression-free survival (PFS)
- Overall survival (OS)

Exploratory efficacy endpoints in this study will use the immune-related response criteria (irRECIST) to take into account the clinical finding that some study subjects receiving immunotherapies can experience transient increases in lesion size or new lesions ("pseudoprogression") before immunotherapy-induced tumor regression (Wolchok 2009, Hamid 2013, Nishino 2013, Bohnsack 2014). Guidelines on the irRECIST are provided in Appendix 8.

Efficacy endpoints will include:

- irBOR
- irORR (irCR + irPR)
- irDCR (irCR + irPR + irSD)
- irDOR
- irPFS

## 3.2 RATIONALE FOR STUDY DESIGN AND DOSING REGIMEN

As described in Section 1.8, acalabrutinib is currently being evaluated in a Phase 1/2 study in subjects with CLL (ACE-CL-001). In this study, subjects have received oral dosages of 100 to 400 mg QD and 100 to 200 mg BID of acalabrutinib. All tested dose levels have been well tolerated and, to date, no drug-related toxicities have been observed. Robust clinical responses have been observed with dosages as low as 100 mg QD. Preliminary PK data from ACE-CL-001 suggests a plateauing of exposure after 250 mg QD. Pharmcodynamic results from this study also show 100 and 200 mg BID have the highest BTK occupancy at 24 hours of all the regimens evaluated.

The dose of pembrolizumab planned to be studied in this trial is 200 mg Q3W. The dose recently approved in the United States and several other countries for treatment

of melanoma subjects is 2 mg/kg Q3W. Information on the rationale for selecting 200 mg Q3W is summarized below.

KEYNOTE-001 was an open-label Phase 1 study conducted to evaluate the safety, tolerability, PK and PD, and anti-tumor activity of pembrolizumab when administered as monotherapy. The dose escalation portion of this trial evaluated 3 dose levels, 1 mg/kg, 3 mg/kg and 10 mg/kg, administered every 2 weeks (Q2W) and dose expansion cohorts evaluated 2 mg/kg Q3W and 10 mg/kg Q3W in subjects with advanced solid tumors. All dose levels were well tolerated and no DLTs were observed. This first-in-human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. No MTD has been identified. In addition, 2 randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, and 1 randomized cohort evaluating 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of important differences in efficacy or safety profile across doses.

An integrated body of evidence suggests that 200 mg Q3W is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in subjects with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with 2 mg/kg Q3W dose.

A population pharmacokinetic (PK) model, which characterized the influence of body weight and other patient covariates on exposure, has been developed. The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. Pharmacokinetic properties of pembrolizumab, and specifically the weight-dependency in clearance and volume of distribution are consistent with no meaningful advantage to weight-based dosing relative to fixed dosing.

In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at tested doses among tumor types. Thus the 200 mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as well.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. The existing data suggest 200 mg Q3W as the appropriate dose for pembrolizumab.

As described in Section 1.5, Acerta Pharma has conducted a nonclinical study to evaluate the potential synergy of BTK inhibition with PD-1 blockade and has seen encouraging results which warrant testing the hypothesis in a clinical trial.

## 3.3 SELECTION OF STUDY POPULATION

### 3.3.1 Inclusion Criteria

Eligible subjects will be considered for inclusion in this study if they meet **all** of the following criteria:

1. Men and women ≥ 18 years of age.
2. Histologically or cytologically confirmed urothelial carcinoma of the bladder or mixed histology bladder cancer.
3. Presence of metastic bladder cancer that has either progressed during or after platinum-based chemotherapy administered for metastatic disease or has recurred during or within 1 year after the completion of platinum-based neoadjuvant or adjuvant therapy.
4. Any primary site of urothelial carcinoma including upper tract, renal pelvis, bladder, and ureters.
5. Prior therapy with ≥ 1 chemotherapy regimens for urothelial carcinoma
6. Presence of radiographically measurable disease as defined by RECIST 1.1.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
8. Completion of all therapy (including surgery, radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for the treatment of cancer ≥ 2 weeks before the start of study therapy and recovered (ie, Grade ≤ 1 or baseline) from AEs associated with prior cancer therapy. Note: Subjects with Grade ≤ 2

neuropathy or Grade ≤ 2 alopecia are an exception to the latter criterion and may qualify for the study.

9. Women who are sexually active and can bear children must agree to use acceptable forms of contraception during the study and for 90 days after the last dose of acalabrutinib or 120 days after the last dose of pembrolizumab, whichever is longer. Note: Acceptable forms of contraception are defined in Section 3.10.6.
10. Men who are sexually active and can beget children must agree to use acceptable forms of contraception during the study and for 90 days after the last dose of acalabrutinib or 120 days after the last dose of pembrolizumab, whichever is longer.
11. Men must agree to refrain from sperm donation during the study and for 90 days after the last dose of acalabrutinib or 120 days after the last dose of pembrolizumab, whichever is longer.
12. Able to provide tissue for biomarker analysis from either an archived tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated.
13. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.
14. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations).

### 3.3.2 Exclusion Criteria

Subjects will be ineligible for this study if they meet **any** of the following criteria:

1. Prior malignancy (other than bladder cancer), except for treatment-naive prostate cancer (defined as Stage T1/T2a, Gleason score < 6, and prostate-specific antigen [PSA] < 10 ng/mL) undergoing active surveillance; or localized, very low to intermediate risk prostate cancer treated with curative intent and absence of PSA relapse; or adequately treated basal cell or squamous cell skin cancer, in situ cancer, or other cancer from which the subject has been disease free for ≥ 2 years.
2. Known central nervous system metastases and/or carcinomatous meningitis. Note: Imaging studies of the central nervous symptom are not required as a condition of study enrollment
3. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification or corrected QT interval (QTc) > 480 msec at screening.
4. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.
5. Prior therapy with any inhibitor of BTK, protein kinase B (AKT), Janus kinase (JAK), mammalian target of rapamycin (mTOR), phosphatidylinositol-3 kinase (PI3K), or spleen tyrosine kinase (SYK).
6. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD ligand 2 (anti-PD-L2), anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4)

antibody (including ipilimumab, tremelimumab, nivolumab, pembrolizumab, MPDL3280A or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways)

7. Receiving ongoing immunosuppressive therapy, including systemic or enteric corticosteroids except for minimally systemically absorbed treatments (such as inhaled or topical steroid therapy for asthma, chronic obstructive pulmonary disease or allergic rhinitis) within 7 days before the first dose of pembrolizumab.
8. Active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Note: Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
9. Has history of interstitial lung disease or evidence of active non-infectious pneumonitis.
10. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
11. History of bleeding diathesis (eg, hemophilia or von Willebrand disease).
12. Requires treatment with a strong CYP3A inhibitor/inducer.
13. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 7 days of first dose of study drug.
14. Requires treatment with proton-pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole).
15. Has received a live vaccine within 30 days of planned start of study therapy.
16. Known history of human immunodeficiency virus (HIV) or serologic status indicating active hepatitis C virus (HCV) or hepatitis B virus (HBV) infection or any uncontrolled active systemic infection. Subjects with hepatitis B core antibody positive who are surface antigen negative or who are hepatitis C antibody positive will need to have a negative PCR result before enrollment. Those who are hepatitis B surface antigen positive or hepatitis B PCR positive and those who are hepatitis C PCR positive will be excluded.
17. History of stroke or intracranial hemorrhage within 6 months before the first dose of study drug.
18. Major surgical procedure within 28 days of first dose of study drug. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug.
19. ANC < 1.5 x $10^9$/L or platelet count < 100 x $10^9$/L or hemoglobin < 8.0 g/dL.
20. Total bilirubin > 1.5 x ULN; and AST or ALT > 3.0 x ULN.
21. Estimated creatinine clearance of < 30 mL/min, calculated using the formula of Cockroft and Gault [(140-Age) • Mass (kg)/(72 • creatinine mg/dL); multiply by 0.85 if female].
22. Breastfeeding or pregnant or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
23. Is currently participating in a clinical trial and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.

24. Immediate family members of the sponsor personnel or site staff directly involved with the conduct of this protocol are excluded from participating on this study.
25. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months prior to screening.

### 3.3.3 Replacement of Subjects

Subjects will not be replaced on this study except if needed to complete the DLT assessment (N=6). However, subjects who discontinue from the study due to a DLT during the DLT assessment period will not be replaced.

### 3.3.4 Enrollment and Randomization Procedures

Enrollment of a subject into the study will be performed according to the following procedure:

The study center will notify the sponsor when a clinically eligible subject is identified and is ready to screen, to ensure enrollment availability on the study.

After the subject has signed and dated the Informed Consent Form (ICF), all screening procedures have been completed, and eligibility has been confirmed, the subject can be officially enrolled into the study.

To enroll a subject, the study center will fax/email a completed Enrollment Confirmation Form to the sponsor. The enrollment date will be the date that the sponsor confirms enrollment. The sponsor will aim to fax/email a completed Enrollment Confirmation Form to the study center within 24 hours.

The Enrollment Confirmation Form will contain treatment allocation. The treatment assignment is based on the randomization list generated by the sponsor before study enrollment begins.

Treatment must begin within the screening window (Section 4.1.5) and after the site has received the treatment allocation from the sponsor.

## 3.4 STUDY DRUGS

### 3.4.1 Premedications

No specific premedications or supporting medications are required in conjunction with acalabrutinib or pembrolizumab administration.

### 3.4.2 Formulation, Packaging, and Storage

**Acalabrutinib**

Acalabrutinib is manufactured according to cGMP regulations and will be provided to the investigational site by Acerta Pharma or designee. Acalabrutinib should be stored according to the instructions on the label that is affixed to the package of the drug product. Acalabrutinib will be provided in white, high-density polyethylene bottles.

If a drug shipment arrives damaged, or if there are any other drug complaints, a Product Complaint Form should be completed and emailed or faxed to the sponsor or the sponsor's representative. Refer to the Acalabrutinib Investigator Brochure for additional information regarding the drug product to be used in this trial.

**Pembrolizumab**

Commercially available pembrolizumab (KEYTRUDA) will be provided by the sponsor for use on this study (Table 3-1). Pembrolizumab (100 mg/4 mL) is provided as 25-mg/mL solution in single-use vials or as a lyophilized powder for reconstitution (50 mg/vial).

**Table 3-1 Pembrolizumab Product Descriptions**

| Product Name & Potency | Dosage Form |
|---|---|
| MK-3475 50 mg | Lyophilized Powder for Injection |
| MK-3475 100 mg/ 4mL | Solution for Injection |

Information on the formulation, packaging and storage of pembrolizumab is provided in the package insert (Appendix 6).

### 3.4.3 Administration of Study Drug

Investigators are prohibited from supplying acalabrutinib to any subjects not properly enrolled in this study. The investigator must ensure that subjects receive acalabrutinib or pembrolizumab only from personnel who fully understand the procedures for administering the drugs.

Acalabrutinib 100 mg is intended to be administered orally twice daily with 8 ounces (approximately 240 mL) of water (avoid grapefruit juice or Seville orange juice due to potential inhibition of CYP3A). Doses should be administered 12 hours apart (a window of ± 1 hour is allowed). The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water.

If a dose is missed, it can be taken up to 3 hours after the scheduled time with a return to the normal schedule the same or following day. If it has been > 3 hours, the

dose should not be taken and the subject should take the next dose at the scheduled time the next day. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

Refer to Section 3.10.4 for guidance on concomitant dosing of acalabrutinib with agents that affect gastric pH.

Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes -5 min/+10 min). Detailed information on preparation of pembrolizumab for infusion is provided in Appendix 6.

When acalabrutinib and pembrolizumab are administered on the same day, acalabrutinib should be administered first, followed by pembrolizumab. When PK sampling is done, the pembrolizumab infusion should begin within 10 minutes of ingesting acalabrutinib.

### 3.4.4 Assuring Subject Compliance

For treatments that are taken in the clinic, subjects should take the dose from the drug dispensed for them for that particular time period. All other acalabrutinib treatments will be taken at home. Subjects will receive a drug diary to record the specific time each dose was taken and to record reasons for any missed doses.

Pembrolizumab infusions will be administered only at the clinics per the study schedule. Missed doses of pembrolizumab should not be made up, with the next dose occurring in agreement with the original schedule for this agent (every 3 weeks).

Subject compliance with acalabrutinib dosing will be assessed at every visit. The subject will be instructed to bring the diary and any remaining capsules to the clinic at their next visit. The study staff will review the diary and ask the subject if all of the capsules were administered. Any remaining or returned capsules will be counted and recorded as described in Section 7.6. Returned capsules must not be redispensed to another subject.

## 3.5 STUDY TREATMENT SCHEDULE

### 3.5.1 Arm 1 – Pembrolizumab Monotherapy

Pembrolizumab 200 mg will be administered every 3 weeks by IV infusion.

### 3.5.2 Arm 2 – Combination Treatment

The dose of acalabrutinib is 100 mg BID PO. The doses may be modified for DLTs as summarized in Table 3-2.

Pembrolizumab 200 mg will be administered every 3 weeks by IV infusion.

Acalabrutinib and pembrolizumab dosing will begin on the same day on Week 1 except for the first 6 subjects enrolled due to PK sampling. The first 6 subjects enrolled will receive acalabrutinib on Day 1 of Week 1. Then on Day 2 of Week 1 the first pembrolizumab infusion will be administered.

**Table 3-2. Dose Reduction for Acalabrutinib**

| Dose Level | Acalabrutinib | Pembrolizumab |
|---|---|---|
| Starting Dose | 100 mg BID PO | 200 mg Q3W IV |
| Level -1 | 100 mg QD PO | 200 mg Q3W IV |
| Level -2 | 50 mg BID PO | 200 mg Q3W IV |

Abbreviations: BID = twice per day; IV = intravenous, PO = oral; Q3W = every 3 weeks; QD = once per day

## 3.6 DURATION OF THERAPY

Acalabrutinib treatment can continue for subjects who are tolerating therapy and not progressing. Pembrolizumab treatment is for 24 months from the date of first dose for subjects who are tolerating therapy and not progressing. Pembrolizumab treatment can end for subjects with confirmed CR if treatment has been administered for at least 24 weeks and 2 doses of pembrolizumab have been administered after confirmation of CR.

## 3.7 ASSESSMENT OF DOSE-LIMITING TOXICITY (DLT)

As outlined in Section 3.0, DLT review will be applied to Arm 2 as the combination of acalabrutinib plus pembrolizumab has not been evaluated before, therefore an interim safety analysis will occur once 6 subjects have been successfully randomized to the combination arm (Arm 2) and have been treated a minimum of 4 weeks. Enrollment will be paused while the interim safety analysis occurs.

A DLT will be defined as the occurrence of any of the following study-drug-related AEs (note: AEs clearly related to disease progression or the subject's current medical history and associated comorbidities will not be considered DLTs):

1. Grade 4 vomiting or diarrhea
2. Grade 3 nausea, vomiting, or diarrhea lasting for > 72 hours
3. Other Grade ≥ 3 toxicities (Note: transient Grade 3-4 laboratory abnormalities that are not clinically significant will not be considered DLTs)
4. Dosing delay due to toxicity for > 21 consecutive days.

## 3.8 DOSING DELAYS AND MODIFICATIONS

Subjects should be followed closely for AEs or laboratory abnormalities that might indicate acalabrutinib- or pembrolizumab-related toxicity. If a subject experiences a treatment-related DLT or other intolerable AE during the course of therapy, then acalabrutinib, pembrolizumab, or both drugs should be held, as necessary, until the AE resolves or stabilizes to an acceptable degree. In cases where pembrolizumab is held, pembrolizumab should be restarted in agreement with its original dosing schedule (every 3 weeks). As appropriate, certain laboratory abnormalities may warrant more frequent monitoring (eg, once per week) until abnormalities have recovered to Grade ≤ 1. Dose reductions for acalabrutinib are provided in Table 3-2. If acalabrutinib is reduced for apparent treatment-related toxicity, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates a reduced dose of acalabrutinib for ≥ 4 weeks then the dose may be increased to the next higher dose level, at the discretion of the investigator. Such re-escalation may be particularly warranted if further evaluation reveals that the AE that led to the dose reduction was not treatment-related. However, the maximum dose of acalabrutinib is 100 mg BID for this protocol.

**For treatment-emergent hepatotoxicity in the combination arm or for subjects who cross over to receive combination therapy**: Important guidelines for treatment-emergent hepatotoxicity are provided in Section 3.8.2 for pembrolizumab. In the combination arm or for subjects who cross over to receive combination therapy, treatment with acalabrutinib should be withheld for Grade 3 or 4 hepatitis. For Grade 4 events, acalabrutinib may be restarted only after discussion with the medical monitor. For Grade 3 events, treatment with acalabrutinib can be considered after the LFT laboratory values have returned to Grade ≤ 1 or to baseline.

Note: Temporary withholding of study drug for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Refer to Section 3.11 for more information on assessing disease progression under these circumstances.

### 3.8.1 Dose Modifications for Pembrolizumab

Adverse events (nonserious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3-3 below. See Section 3.8.2 for supportive care guidelines, including use of corticosteroids.

**Table 3-3. Dose Modification Guidelines for Drug-Related Adverse Events**

| Toxicity | Hold Treatment For Grade | Timing for Restarting Treatment | Treatment Discontinuation |
|---|---|---|---|
| Diarrhea/Colitis | 2-3 | Toxicity resolves to Grade 0-1. | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks. |
| | 4 | Permanently discontinue | Permanently discontinue |
| AST, ALT, or Increased Bilirubin | 2 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose. |
| | 3-4 | Permanently discontinue (see exception below)[a] | Permanently discontinue |
| Type 1 diabetes mellitus (if new onset) or Hyperglycemia | T1DM or 3-4 | Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure. | Resume pembrolizumab when patients are clinically and metabolically stable. |
| Hypophysitis | 2-4 | Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks. |
| Hyperthyroidism | 3 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks. |
| | 4 | Permanently discontinue | Permanently discontinue |
| Hypothyroidism | | Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted | Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted. |
| Infusion Reaction | 2[b] | Toxicity resolves to Grade 0-1 | Permanently discontinue if toxicity develops despite adequate premedication. |
| | 3-4 | Permanently discontinue | Permanently discontinue |

| Toxicity | Hold Treatment For Grade | Timing for Restarting Treatment | Treatment Discontinuation |
|---|---|---|---|
| Pneumonitis | 2 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks. |
| | 3-4 | Permanently discontinue | Permanently discontinue |
| Renal Failure or Nephritis | 2 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks. |
| | 3-4 | Permanently discontinue | Permanently discontinue |
| All Other Drug-Related Toxicity[c] | 3 or Severe | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks. |
| | 4 | Permanently discontinue | Permanently discontinue |

**Note: Permanently discontinue for any severe or Grade 3 (Grade 2 for pneumonitis) drug-related AE that recurs or any life-threatening event.**

a For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued

b. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to Table 3-4 for further management details.

c. Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

### 3.8.2 Supportive Care Guidelines for Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 3.8.1 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- **Diarrhea/Colitis**:

  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 2 diarrhea/colitis**, administer oral corticosteroids.
    - For **Grade 3 or 4 diarrhea/colitis**, treat with intravenous steroids followed by high dose oral steroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
    - For **T1DM** or **Grade 3-4** Hyperglycemia
        - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
        - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **Hypophysitis**:
    - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
    - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (eg, propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**:
  - For **Grade 2** events, treatment with pembrolizumab should be withheld. Administer corticosteroids (initial dose of 0.5 to 1 mg/kg/day prednisone or equivalent) (Appendix 6). When LFT laboratory values resolve to baseline or return to Grade ≤ 1, then taper the corticosteroids over no fewer than 4 weeks while continuing to monitor LFTs at least weekly. Further treatment with pembrolizumab can be considered after the LFT laboratory values have returned to Grade ≤ 1 or to baseline either during the steroid taper or after stopping corticosteroids.
  - For **Grade 3-4** events, permanently discontinue pembrolizumab. Treat with corticosteroids initial dose 1 to 2 mg/kg/day prednisone or equivalent) (Appendix 6) until LFT laboratory values resolve to baseline or return to Grade ≤ 1, and then taper the corticosteroids over no fewer than 4 weeks while continuing to monitor LFTs at least weekly.

- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Management of Infusion Reactions:**
  - Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.
  - Table 3-4 shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

**Table 3-4. Infusion Reaction Treatment Guidelines**

| NCI CTCAE Grade | Treatment | Premedication at subsequent dosing |
|---|---|---|
| Grade 1<br>Mild reaction; infusion interruption not indicated; intervention not indicated | Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. | None |
| Grade 2<br>Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs | **Stop Infusion and monitor symptoms.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids<br>Antihistamines<br>NSAIDS<br>Acetaminophen<br>Narcotics<br>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.<br>If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.<br>**Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.** | Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with:<br><br>Diphenhydramine 50 mg po (or equivalent dose of antihistamine).<br><br>Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic). |
| Grades 3 or 4<br><br>Grade 3:<br>Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates)<br><br>Grade 4:<br>Life-threatening; pressor or ventilatory support indicated | **Stop Infusion.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids<br>Antihistamines<br>NSAIDS<br>Acetaminophen<br>Narcotics<br>Oxygen<br>Pressors<br>Corticosteroids<br>Epinephrine<br><br>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.<br>Hospitalization may be indicated.<br>**Subject is permanently discontinued from further trial treatment administration.** | No subsequent dosing |
| Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. | | |

## 3.9 CONCOMITANT THERAPY

### 3.9.1 Permitted Concomitant Therapy

Antiemetics are permitted if clinically indicated. Standard supportive care medications are permitted as per institutional standards.

### 3.9.2 Prohibited or Restricted Concomitant Therapy

Any chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy for treating urothelial carcinoma are prohibited.

Warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) are prohibited.

At study entry, subjects may be using topical or inhaled corticosteroids as therapy for comorbid conditions but use of corticosteroids as therapy of the cancer is not permitted. During study participation, subjects may also receive systemic or enteric corticosteroids at any required dosage as needed for treatment emergent immune-mediated adverse reactions associated with pembrolizumab therapy (see Section 3.8), but use of corticosteroids (at dosages equivalent to prednisone > 20 mg/day for longer than 2 weeks) as therapy for cancer is not permitted.

Live vaccines within 30 days before the first dose of trial treatment and while participating in the trial are prohibited. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, Flu - Mist®) are live attenuated vaccines and are not allowed.

Use of calcium carbonate containing drugs or supplements and short-acting H2-receptor antagonists should be avoided for at least 2 hours before or after acalabrutinib administration (see Section 3.10.4).

## 3.10 PRECAUTIONS

### 3.10.1 Transaminase Elevations for Acalabrutinib in Combination with Pembrolizumab

Serum transaminase elevations (including elevations of AST and/or ALT) may be increased in severity and frequency in subjects exposed to the combination of acalabrutinib and pembrolizumab, as compared with subjects exposed to pembrolizumab monotherapy and subjects exposed to acalabrutinib monotherapy. Routine monitoring for serum transaminase elevations must follow the Schedule of Assessments (serum chemistry lab assessments in Appendix 4 and Appendix 5). Dosing delays and modifications for subjects with serum transaminase elevations must follow guidance provided in Section 3.8.

### 3.10.2 Hepatitis B Reactivation

Serious or life-threatening reactivation of viral hepatitis may occur in subjects treated with acalabrutinib. Therefore, subjects who are hepatitis B core antibody (anti-HBc) positive, or have a known history of HBV infection, should be monitored monthly with a quantitative PCR test for HBV DNA. Monthly monitoring should continue until 12 months after last dose of acalabrutinib. Any subject with a rising viral load (above lower limit of detection) should discontinue study drug and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. Insufficient data exist regarding the safety of resuming acalabrutinib in subjects who develop HBV reactivation.

### 3.10.3 Dietary Restrictions

Acalabrutinib can be taken with or without food. Because acalabrutinib is metabolized by CYP3A, subjects should be strongly cautioned against excessive consumption of grapefruit, grapefruit juice, or Seville orange juice (which contain potent CYP3A inhibitors) or using herbal remedies or dietary supplements (in particular, St John's wort, which is a potent CYP3A inducer).

Otherwise subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

### 3.10.4 Drug-drug Interactions

At the systemic exposure levels expected in this study, acalabrutinib inhibition of CYP metabolism is not anticipated. However, concomitant administration of acalabrutinib with a strong CYP3A and P-gp inhibitor increased exposure by approximately 5-fold. Consequently, the concomitant use of strong inhibitors/inducers of CYP3A (see Appendix 2) should be avoided when possible.

Based on these considerations, subjects who require therapy with drugs listed in Appendix 2 should not be enrolled into the study. If medically justified, subjects may be enrolled if such inhibitors or inducers can be discontinued or alternative drugs that do not affect these enzymes can be substituted within 7 days before first dose of study drug. If a subject requires a strong CYP3A inhibitor while on study, monitor the subject closely for potential drug-related toxicities.

The effect of agents that reduce gastric acidity (eg, proton-pump inhibitors, H2-receptor antagonists or antacids) on acalabrutinib absorption was evaluated in a

healthy volunteer study (ACE-HV-004). Results from this study indicate that subjects should avoid the use of calcium carbonate-containing drugs or supplements (eg, antacids and calcium supplements) and short-acting H2-receptor antagonists for a period of at least 2 hours before and after taking acalabrutinib. Use of omeprazole, esomeprazole, lansoprazole or any other proton-pump inhibitors while taking acalabrutinib is not recommended due to a potential decrease in study drug exposure.

No formal PK drug interaction studies have been conducted with pembrolizumab.

### 3.10.5 Surgery

Susceptibility to bleeding has been observed with the first generation BTK inhibitor, ibrutinib [IMBRUVICA package insert]. As a precaution, it is suggested that acalabrutinib be held for 3 days before and after any major surgical procedure.

### 3.10.6 Reproductive Toxicity

**Acalabrutinib**

Note for subjects receiving only acalabrutinib, the information below applies.

Pilot reproductive toxicity studies have been performed that evaluate the effects of acalabrutinib on embyrofetal development. Definitive studies of acalabrutinib on embryofetal development are pending. Women who are sexually active and can bear children (see definition below) must agree to use acceptable forms of contraception during the study and for 90 days after the last dose of acalabrutinib as defined below.

**Pembrolizumab**

Note for subjects receiving acalabrutinib plus pembrolizumab the information below applies.

Pembrolizumab may have adverse effects on a fetus in utero.

Women will be considered of non-reproductive potential if they are either:

1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Men and women of reproductive potential must agree to avoid impregnating a partner or becoming pregnant, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence† from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

Single method (1 of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of 2 of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual

lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (eg, calendar, ovulation, sympto-thermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Men must refrain from sperm donation during the study and for 90 days after the last dose of acalabrutinib or 120 days after the last dose of pembrolizumab, whichever is longer.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. To participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Subjects should promptly notify the investigator if they, or their partner, become pregnant during this period. If a female subject becomes pregnant during the treatment period, she must discontinue acalabrutinib and pembrolizumab immediately. Pregnancy in a female subject or a male subject's partner must be reported as outlined in Section 6.2.3.

### 3.10.7 Overdose Instructions

For any subject experiencing an acalabrutinib or pembrolizumab overdose (administration of a dose ≥ 1000 mg of acalabrutinib or ≥ 1000 mg of pembrolizumab at once), observation for any symptomatic side effects should be instituted, and vital signs, biochemical and hematologic parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. If the overdose ingestion is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered.

The medical monitor must be contacted if a study drug overdose occurs (Section 6.2.5).

## 3.11 TREATMENT AFTER INITIAL RADIOLOGIC PROGRESSION

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Therefore, RECIST 1.1 will be used with the following adaptations:

- If radiologic imaging verifies initial disease progression, tumor assessment should be repeated ≥4 weeks later to confirm disease progression with the option of continuing treatment per below.
- If repeat imaging shows < 20% tumor burden compared to nadir, stable or improved previous new lesion (if identified as cause for initial disease progression), and stable/improved non-target disease (if identified as cause for initial disease progression), treatment may be continued / resumed.
- If repeat imaging confirms disease progression due to any of the scenarios listed below, subjects will be discontinued from study therapy (except subjects who cross over to receive acalabrutinib in addition to pembrolizumab; they would be discontinued upon a second confirmed disease progression event on the combination therapy).

In determining whether or not the tumor burden has increased or decreased, site study team should consider all target lesions as well as non-target lesions (if needed, the tip sheet provided in the study binder can be used as a reference to assess lesions).

Scenarios where disease progression is confirmed at repeat imaging:

- Tumor burden remains ≥ 20% and at least 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial disease progression is worse (qualitative)

- New lesion resulting in initial disease progression is worse (qualitative)
- Additional new lesion(s) since last evaluation

In subjects who have initial evidence of radiological disease progression, it is at the discretion of the treating physician whether to continue a subject on study treatment until repeat imaging is obtained. This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive study treatment while waiting for confirmation of disease progression if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

When feasible, subjects should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation of progressive disease. The decision to continue study treatment after the first evidence of disease progression is at the Investigator's discretion based on the clinical status of the subject as described in Table 3-5 below.

**Table 3-5. Imaging and Treatment After 1st Radiologic Evidence of Disease Progression**

| | Clinically Stable | | Clinically Unstable | |
|---|---|---|---|---|
| | Tumor Imaging | Treatment | Tumor Imaging | Treatment |
| First radiologic evidence of PD | Repeat imaging at ≥ 4 weeks at site to confirm PD | May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging by site | Repeat tumor imaging at ≥ 4 weeks to confirm PD per physician discretion only | Discontinue treatment |
| Repeat tumor imaging confirms PD | No additional tumor imaging required | Discontinue treatment | No additional tumor imaging required | N/A |
| Repeat tumor imaging shows SD, PR or CR | Continue regularly scheduled tumor imaging assessments | Continue study treatment at the Investigator's discretion | Continue regularly scheduled tumor imaging assessments | May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion |

Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

NOTE: If a subject has confirmed radiographic progression (ie, 2 scans at least 4 weeks apart demonstrating progressive disease) per irRECIST, but the subject is achieving a clinically meaningful benefit, an exception to continue treatment may be considered following consultation with the sponsor.

irRECIST data will be collected in the clinical database.

## 3.12 WITHDRAWAL OF SUBJECTS FROM STUDY TREATMENT

Any subject has the right to withdraw from the study at any time.

- Study treatment should be discontinued in the event of a toxicity lasting > 28 consecutive days, unless reviewed and approved by the medical monitor.
- Any subject who has **confirmed** objective evidence of cancer progression while receiving acalabrutinib and pembrolizumab should discontinue study treatment. Note: Study subjects receiving immunotherapies can experience transient immunotherapy-related increases in lesion size ("pseudoprogression") preceding tumor regression (Hodi 2010). If there is uncertainty regarding whether there is true cancer progression, the subject may continue study treatment and remain under close observation (eg, evaluated at 4-week intervals) pending confirmation of progression. In particular, transient worsening of disease early in therapy or during temporary

interruption of study therapy (eg, for drug-related toxicity, surgery, or intercurrent illness) may not indicate cancer progression (Section 3.11). In such circumstances, and if medically appropriate, subjects may resume therapy and relevant clinical, laboratory, and/or radiographic assessment can be attempted to document whether tumor control can be maintained or whether cancer progression has occurred.

- Any subject whose medical condition substantially changes after entering the study should be carefully evaluated by the investigator in consultation with the medical monitor. Such subjects should be withdrawn from study treatment if continuing would place them at risk.
- Any subject who becomes pregnant should be removed from study treatment.
- Any subject who becomes significantly noncompliant with study drug administration, study procedures, or study requirements should be withdrawn from study treatment in circumstances that increase risk or substantially compromise the interpretation of study results.
- The investigator, in consultation with the medical monitor, may withdraw any subject from study treatment, if, in the investigator's opinion, it is not in the subject's best interest to continue.

Subjects who discontinue study therapy will continue to be followed on study for follow-up of safety (Section 4.3) and survival unless they withdraw consent for further follow-up. Thus, all subjects receiving ≥ 1 dose of study drug will be followed during the immediate post-therapy and long-term follow-up assessments unless the subject withdraws consent for such follow-up to be conducted. The date the subject is withdrawn from study treatment or from the study (including long-term follow-up) and the reason for discontinuation will be recorded and also should be described on the appropriate case report form (CRF).

## 3.13 REASONS FOR STUDY EXIT

Reasons for study exit are:

- Subject's withdrawal of consent from study
- Decision by sponsor to terminate the study
- Subject lost to follow-up
- Death

## 3.14 DATA AND SAFETY MONITORING

This trial will be monitored in accordance with the sponsor's pharmacovigilance procedures. Adverse events and SAEs will be reviewed internally on an ongoing basis to identify safety concerns. Quarterly conference calls with the investigators and applicable site staff will be conducted to discuss study progress, obtain investigator feedback and exchange, and discuss "significant safety events" (ie, AEs leading to dose reductions, related SAEs, and deaths). In addition, for the interim safety analysis, a mandatory safety teleconference will occur before the expansion phase of the protocol can open.

# 4.0 STUDY ACTIVITIES AND ASSESSMENTS

The schedule of events is provided in Appendix 4 and Appendix 5. Descriptions of the scheduled evaluations are outlined below and complete information on study drug and dosing is provided in Section 3.4.

Before study entry, throughout the study, and at the follow-up evaluation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. This study will primarily use central laboratory testing for safety laboratory evaluations. Samples from sites' local laboratories will be used if central laboratory testing is unavailable.

## 4.1 DESCRIPTION OF PROCEDURES

### 4.1.1 Informed Consent

The subject must read, understand and sign the ICF approved by the institutional review board or independent ethics committee (IRB/IEC), confirming his or her willingness to participate in this study before initiating any screening activity that is not considered standard of care by institutional standards. Subjects must also grant permission to use protected health information if required by local regulations.

### 4.1.2 Medical History

Collect and record the subject's complete history through review of medical records and by interview. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of initial diagnosis

and list of all prior anticancer treatments, and responses and duration of response to these treatments, also will be recorded.

### 4.1.3 Adverse Events

The accepted regulatory definition for an AE is provided in Section 6.1. All medical occurrences from the time of first dose that meet this definition must be recorded. Important additional requirements for reporting SAEs are explained in Section 6.2.

### 4.1.4 Concomitant Medications and Therapy

Document all concomitant medications and procedures from within 28 days before the start of study drug administration through 30 days after the last dose of study drug.

### 4.1.5 Confirmation of Eligibility

Subject eligibility for enrollment will be assessed per Section 3.3. All screening procedures, unless otherwise indicated, should be completed within 28 days of the first dose of study drug.

### 4.1.6 ECOG Performance Status

The ECOG performance index is provided in Appendix 1.

### 4.1.7 Physical Examination, Vital Signs, Height & Weight

The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system.

Symptom-directed physical exams will be done during the treatment period and at the safety follow-up visits.

Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) will be assessed after the subject has rested in the sitting position.

### 4.1.8 Electrocardiogram

Subjects should be in supine position and resting for at least 10 minutes before any study related ECGs. Before first dose of study drug on Day 1, Week 1, 3 ECGs will be done at least 1 minute apart. These ECGs and the screening ECG will be considered the baseline ECGs. If an unscheduled ECG is done at any time, then an

electrolyte panel (ie, calcium, magnesium, and potassium) must be done to coincide with the ECG testing.

Single on-treatment ECGs will be done at any time during the following visits:

- Week 2
- Week 4
- Week 7 and every 6 weeks thereafter
- Early termination and/or safety follow-up visit

### 4.1.9 Urine or Serum Pregnancy Test

Pregnancy tests will be required only for women of childbearing potential. Women of childbearing potential must have a negative urine or serum pregnancy testing within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test is required. Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

### 4.1.10 Hematology

Hematology studies must include complete blood count (CBC) with differential and platelet and reticulocyte counts. Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

### 4.1.11 Coagulation

Coagulation studies must include prothrombin time (PT) and activated partial thromboplastin time (aPTT). Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

### 4.1.12 Serum Chemistry

Chemistry will include albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), bone-specific alkaline phosphatase, calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid. If an unscheduled ECG is done at any time, then an electrolyte panel (ie, calcium, magnesium, and potassium) must be done to coincide with the ECG testing. Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

### 4.1.13 Amylase and Lipase

Serum amylase and serum lipase testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

### 4.1.14 Thyroid Panel

The thyroid panel will include total triiodothyronine (T3), free thyroxine (T4), and thyroid stimulating hormone (TSH). Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

### 4.1.15 Hepatitis B and C Testing

Hepatitis serology testing must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis core antibody (anti-HBc), and hepatitis C (HCV) antibody. In addition, any subjects testing positive for any hepatitis serology, must have PCR testing during screening and on study (see Appendix 4 and exclusion criterion #16). Testing will be done by local or central laboratory.

Subjects who are anti-HBc positive should have quantitative PCR testing for HBV DNA performed during screening and monthly thereafter. Monitoring should continue every 4 weeks (± 7 days) until 12 months after last dose of study drug(s). Any subject with a rising viral load (above lower limit of detection) should discontinue study drug and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B.

Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should have quantitative PCR testing for HCV DNA performed during screening and at Weeks 13 and 25. No further testing beyond Week 25 is necessary if PCR results are negative.

Refer to Section 3.10.2 and Appendix 4 regarding monitoring of subjects who are anti-HBc positive or hepatitis C antibody positive or who have a known history of HBV or HCV infection.

### 4.1.16 Urinalysis

Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

### 4.1.17 T/B/NK Cell Count

Flow cytometry testing will include $CD3^+$, $CD4^+$, $CD8^+$, $CD14^+$, $CD19^+$, and $CD16/56^+$ cells. Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

### 4.1.18 Serum Immunoglobulin

Testing for IgG, IgM, and IgA will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

### 4.1.19 Pharmacodynamics/Pharmacokinetics and Biomarker Studies

Blood samples will be used for PD testing (including, but not limited to, BTK occupancy, B-cell activation, MDSCs, and T-cell activation), cytokine analysis, and for further characterization of circulating tumor cells, lymphocyte and myeloid cell subsets.

Tissue sections from archival tumor biopsies and/or any newly obtained biopsies performed during the study will be used for exploratory biomarker studies (including, but not limited to, expression of PD-L1, characterization of disease subtype, and evaluations of MDSCs and activated $CD8^+$ cells). Additional exploratory studies may include, but are not necessarily limited to, characterization of BTK pathway activation status, identification disease subtype, specific genetic markers with prognostic significance and evaluation of tumor microenvironment components and cell cycle proteins in malignant cells. If available, de-identified pathology reports from the most recent diagnostic work-up, including immunohistochemistry and cytogenetic analyses of tumor tissue, may be requested by the sponsor.

Refer to the laboratory manual for instructions on collection and shipment of the PD and biomarker samples. All testing will be done by the sponsor or designee. Leftover blood and tumor samples may also be used for genomic analyses to study mechanisms of action.

Blood sampling for PK analysis of acalabrutinib will be done on all subjects in the combination arm only and intensive PK will be on the first 6 subjects enrolled in the combination arm. For these first 6 subjects, acalabrutinib will be administered alone on Day 1/Week 1. Then on Day 2/Week 1 the first pembrolizumab infusion will be administered. When PK sampling is done at Week 3 and Week 7, the pembrolizumab

infusion should begin within 10 minutes of ingesting acalabrutinib. The PK sampling timepoints for these 6 subjects is as follows:

| Visit | PK Sample Timepoints Relative to Acalabrutinib Administration |
|---|---|
| Day 1, Week 1 | predose and 0.5, 1, 2, and 4 hours |
| Day 2, Week 1 | predose |
| Week 3 | predose and 0.5, 1, 2, and 4 hours postdose |
| Week 7 | predose and 0.5, 1, 2, and 4 hours postdose |

For all other subjects enrolled in the combination arm, PK sampling will be done pre- and 1 hour postdose on Week 3.

The predose sample can be taken up to 30 minutes before dosing. The window for all other timepoints is ± 5 minutes. Testing will be done by a central lab. Refer to the laboratory manual for instructions on collection and shipment of PK samples.

### 4.1.20 Tumor Assessments

A pretreatment computerized tomography (CT) scan with contrast (unless contraindicated) is required of the chest, abdomen, and pelvis and any other disease sites (eg, neck) within 30 days before the first dose of study drug.

On-treatment CT scans with contrast (unless contraindicated) of the chest, abdomen, and pelvis and any other disease sites (eg, neck) will be done for tumor assessments at Week 7, 13, 19 (± 7 days) then every 3 months (± 10 days) thereafter or more frequently at investigator discretion. At all other visits, tumor assessments will be done by physical exam and laboratory results.

RECIST 1.1 guidelines (Eisenhauer 2009) will be followed for selection of measurable and nonmeasurable lesions and also with regard to the number of lesions to be assessed (refer to Appendix 7 for more details on RECIST 1.1). Response will also be assessed by irRECIST (refer to Appendix 8 for more details).

De-identified copies of all radiology results may be requested by the sponsor.

### 4.1.21 Early Termination Visit

An early termination visit is required for safety assessments as outlined in the Schedule of Assessments (Appendix 4). The early termination visit is not required for subjects who discontinue from the study within 10 days of a scheduled study visit.

### 4.1.22 Study Drug Accountability

See Section 7.6.

## 4.2 INVESTIGATOR'S ASSESSMENT OF RESPONSE TO TREATMENT

Responses will be categorized as CR, PR, SD, or PD. The definitions of response in target lesions are provided in Table 4-1. The definitions of response in nontarget lesions are provided in Table 4-2.

**Table 4-1. Evaluation of Target Lesions (RECIST)**

| Response Category | Definition |
|---|---|
| CR | Disappearance of all target and nontarget lesions including normalization of an elevated tumor marker level. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm. |
| PR | A ≥ 30% decrease in the sum of the diameters of target lesions taking as a reference the baseline sum of the diameters. |
| SD | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum diameters while on study. |
| PD[a] | At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: The appearance of one or more new lesions is also considered progression). |

Abbreviations: CR=complete response, PD=progressive disease, PR=partial response, SD=stable disease.

a. Transient apparent worsening of disease early in therapy or during temporary interruption of study therapy (eg, for drug-related toxicity or intercurrent illness) may not indicate true cancer progression. Refer to Section 3.11 for more detailed information.

Evaluation of nontarget lesions: While some nontarget lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the Schedule of Assessments.

**Table 4-2. Evaluation of Nontarget Lesions (RECIST)**

| Response Category | Definition |
|---|---|
| CR | Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10mm short axis). |
| Non-CR/Non-PD | Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits. |
| PD[a] | Unequivocal progression[b] of existing non-target lesions. (Note: The appearance of one or more new lesions is also considered progression). |

Abbreviations: CR=complete response, PD=progressive disease.

a. Transient apparent worsening of disease early in therapy or during temporary interruption of study therapy (eg, for drug-related toxicity or intercurrent illness) may not indicate true cancer progression. Refer to Section 3.11 for more detailed information.

b. Refer to RECIST 1.1 criteria for detailed explanation of "unequivocal progression".

### 4.2.1 Determination of Response at Each Timepoint (RECIST)

The tumor response at each timepoint will be determined. Table 4-3 provides a summary of the overall response status calculation at each timepoint.

**Table 4-3. Timepoint Response (RECIST)**

| Target Lesions | Nontarget Lesions | New Lesions | Overall Response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/non-PD | No | PR |
| CR | Not evaluated | No | PR |
| PR | Non-PD or not all evaluated | No | PR |
| SD | Non-PD or not all evaluated | No | SD |
| Not all evaluated | Non-PD | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

Abbreviations: CR=complete response, PD=progressive disease, PR=partial response, SD=stable disease, NE=nonevaluable.

### 4.2.2 Confirmation of Tumor Status and Determination of Best Overall Response (RECIST)

The best overall response (BOR) recorded from the start of treatment until tumor progression will be determined. Adjudication of BOR is based on evaluation of each successive set of 2 scans as indicated in Table 4-4.

**Table 4-4. Best Overall Response Assessment and Requirements for Confirmation (RECIST)**

| Response Category at First Timepoint | Response Category at Subsequent Timepoint | Best Overall Response |
|---|---|---|
| CR | CR | CR |
| CR | PR | SD, PD, or PR[a] |
| CR | SD | SD provided minimum criteria for SD duration met otherwise PD |
| CR | PD | SD provided minimum criteria for SD duration met otherwise PD |
| CR | NE | SD provided minimum criteria for SD duration met otherwise NE |
| PR | CR | PR |
| PR | PR | PR |
| PR | SD | SD |
| PR | PD | SD provided minimum criteria for SD duration met otherwise PD |
| PR | NE | SD provided minimum criteria for SD duration met otherwise NE |
| NE | NE | NE |

**Abbreviations**: BOR=best overall response, CR=complete response, PD=progressive disease, PR=partial response, SD=stable disease, NE=nonevaluable

a. If a CR is truly met at first timepoint, then any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

### 4.2.3 Immune-related Response Criteria (irRECIST)

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Therefore, RECIST 1.1 will be used with the adaptations described for irRECIST (Appendix 8).

### 4.3 SAFETY FOLLOW-UP VISIT

Each subject should be followed for 30 (+ 7) days after his or her last dose of study drug (ie, the "safety follow-up visit") to monitor for resolution or progression of AEs (see Section 6.2.6) and to document the occurrence of any new events, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe. Subjects who withdraw consent for study treatment should still be encouraged to complete the safety follow-up assessments, but these assessments cannot be mandated if subject consent for further study participation is withdrawn. The Schedule of Assessments (Appendix 4) describes the procedures required for safety follow-up.

### 4.4 SURVIVAL

After discontinuing study therapy, subjects will be contacted approximately every 12 weeks until death, withdrawal by subject, lost to follow-up, or study terminated by the sponsor, whichever comes first.

### 4.5 MISSED EVALUATIONS

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

## 5.0 STATISTICAL METHODS OF ANALYSIS

### 5.1 GENERAL CONSIDERATIONS

Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions and confidence intervals [CIs] for discrete variables) will be used to summarize data as appropriate.

For the interim safety analysis (DLT review), enrollment of [redacted] in the combination arm for DLT review is consistent with sample sizes used in oncology studies for determination of MTD. The trial employs the standard National Cancer Institute definition of MTD (dose associated with DLT in ≤ [redacted]). Provided the DLT period is cleared in the combination treatment arm, and this arm is not stopped early due to futility or toxicity, [redacted]

[redacted] in pembrolizumab arm. The final sample size is 37 in each arm.

## 5.2 DEFINITION OF ANALYSIS POPULATIONS

The following definitions will be used for the efficacy and safety analysis populations.

**All-treated population:** All enrolled subjects who receive ≥ 1 dose of any study drug (either acalabrutinib or pembrolizumab). The safety and primary efficacy analyses will be performed on the All-treated population.

**Efficacy-evaluable population:** All subjects in the All-treated population who have ≥ 1 evaluable response assessment after the first dose of study drug (either acalabrutinib or pembrolizumab). Sensitivity analyses for efficacy will be carried out on the Efficacy-evaluable population.

## 5.3 MISSING DATA HANDLING

No imputation of values for missing data will be performed except that missing or partial start and end dates for AEs and concomitant medication will be imputed according to prespecified, conservative imputation rules. Subjects lost to follow-up (or drop out) will be included in statistical analyses to the point of their last evaluation.

## 5.4 ENDPOINT DATA ANALYSIS

### 5.4.1 Safety Endpoint

Safety summaries will include summaries in the form of tables and listings. The frequency (number and percentage) of treatment-emergent AEs and events of clinical interest will be reported in each treatment group by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Summaries will also be presented by the severity of the AE (per Common Terminology Criteria For Adverse Events [CTCAE], v4.03 or higher) and by relationship to study drug (eg, either acalabrutinib, pembrolizumab, or both).

Laboratory shift tables containing counts and percentages will be prepared by treatment assignment, laboratory parameter, and time. Summary tables will be prepared for each laboratory parameter. Figures of changes in laboratory parameters over time will be generated.

Results of vital sign assessments and physical exams will be tabulated and summarized.

### 5.4.2 Demographics and Baseline Characteristics

Additional analyses will include summaries of subject demographics, baseline characteristics, compliance, and concurrent treatments. Concomitant medications will be coded and tabulated according to the World Health Organization Drug Dictionary (WHODRUG).

### 5.4.3 Study Treatment Administration and Compliance

Descriptive information will be provided regarding the number of acalabrutinib and pembrolizumab doses prescribed, the total number of doses taken, the number of days of treatment, and the number and timing of prescribed dose reductions and interruptions.

For each subject, acalabrutinib and pembrolizumab compliance will be described in terms of the proportion of study drug actually taken.

### 5.4.4 Analysis of Efficacy Parameters

**Disease Control and Response Rate**

The individual and composite endpoints of response and progression will be determined. Tumor control will be documented at each assessment by response category (see Section 4.2) as defined for each response parameter, date that response is first documented, and date of disease progression. DCR will be defined as the proportion of subjects who achieve a SD, PR or CR. ORR will be defined as the proportion of subjects who achieve a CR or PR (see Section 4.2).

DCR and ORR will be calculated and the corresponding 2-sided 95% CI will be derived.

In addition to evaluation of DCR and ORR by RECIST 1.1 criteria (Eisenhauer 2009), ORR will also be evaluated by irRECIST criteria (Appendix 8), though the ORR by RECIST will be considered the primary endpoint.

**Duration of Response**

The duration of response (DOR) is defined as the interval from the first documentation of response to the earlier of the first documentation of definitive disease progression or death from any cause. Kaplan-Meier methods will be used to estimate event-free

curves and corresponding quartiles (including the median). Data from surviving, non-progressing subjects will be censored and detailed censoring rules will be specified in the statistical analysis plan (SAP).

**Progression-free Survival**

Progression-free survival (PFS) is defined as the interval from the date of first dose of study drug to the earlier of the first documentation of objective disease progression or death whichever is earlier. Kaplan-Meier methods will be used to estimate the event-free curves and corresponding quartiles (including the median). Data from surviving, non-progressing subjects will be censored and detailed censoring rules will be specified in the statistical analysis plan.

**Overall Survival**

OS is defined as the time from date of first dose of study drug until date of death due to any cause. Subjects who are known to be alive or whose survival status is unknown will be censored at the date last known to be alive. The analysis methods for overall survival will be similar to those described for progression-free survival.

### 5.4.5 PD or Biomarker Analyses

Additional pharmacodynamic, pharmacokinetic and biomarker analyses may be performed, as deemed appropriate.

Correlations between subject characteristics and outcome measures and correlations among outcomes measures will be explored using regression models or other appropriate techniques.

## 5.5 FUTILITY AND TOXICITY MONITORING

The futility and toxicity monitoring will be analyzed in the combination arm (Arm 2) only as data become available. Futility will be monitored by irDCR, which is defined as irCR, irPR, and irSD by irRECIST (Appendix 8). irDCR of at least 20% is clinically meaningful in this population. The response outcome within the 12 weeks will be used in the futility analyses. A Bayesian method (Thall 1995) will be used for futility and toxicity monitoring for the combination arm (Arm 2). The stopping rules are:

- $Pr(\theta_E < 0.20 \mid data) > 0.95$
- Or
- $Pr(T_E > 0.30 \mid data) > 0.90$

Enrollment in the combination arm will be stopped early if there is > 95% probability that the irDCR is < 20% or there is > 90% probability that the toxicity rate is higher than 30% in that arm. Where $\theta_E$ denotes the marginal response rate, assuming that $\theta_E$ follows a prior distribution of beta (a, b), where a and b represent response and nonresponse rates (0.2, 0.8), and $T_E$ denotes the marginal toxicity rate, assuming that $T_E$ has a prior distribution of beta (a, b), where a and b represent toxicity and no toxicity (0.3, 0.7). The definition of toxicity will follow the same definition used for assessing DLTs (see Section 3.7) including the DLT assessment window.

The above futility and toxicity monitoring rules will be implemented once the first 10 subjects have been evaluated in the combination arm and will use safety data as they become available. The corresponding stopping boundaries for the futility monitoring are: Enrollment will be stopped early due to futility if (number of subjects with irDCR/number subjects evaluated) ≤ 0/(10-15), 1/(16-23), 2/(24-30) and 3/(31-36). The corresponding stopping boundaries for toxicity monitoring are listed in Table 5-1.

The operating characteristics of the design are presented in Table 5-2. Multc Lean software V2.1 was used for the design.

**Table 5-1. Stopping Boundaries for Toxicity Monitoring**

| | Stop enrolling if there are this many DLTs total: |
|---|---|
| No. Subjects (inclusive) | # Toxicities (inclusive) |
| 1-9 | Never stop with this many subjects |
| 10-12 | 6-12 |
| 13-14 | 7-14 |
| 15-17 | 8-17 |
| 18-20 | 9-20 |
| 21-23 | 10-23 |
| 24-25 | 11-25 |
| 26-28 | 12-28 |
| 29-31 | 13-31 |
| 32-34 | 14-34 |
| 35-36 | 15-36 |
| 37 | Always stop due to maximum sample size |

**Table 5-2. Operating Characteristics of the Design**

| irDCR | Toxicity rate | Probability of early stop | Average # of subjects treated |
|---|---|---|---|
| 0.2 | 0.1 | 0.23 | 32.1 |
| 0.2 | 0.3 | 0.41 | 28.2 |
| 0.2 | 0.5 | 0.95 | 14.8 |
| 0.3 | 0.1 | 0.05 | 35.9 |
| 0.3 | 0.3 | 0.28 | 31.3 |
| 0.3 | 0.5 | 0.94 | 15.5 |

# 6.0 ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and recording DLTs, AEs and SAEs; measurements of protocol-specified hematology, clinical chemistry, urinalysis, and other laboratory variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

## 6.1 DEFINITIONS

### 6.1.1 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with bladder cancer that were not present before the AE reporting period (see Section 6.2.1).
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Abnormal laboratory values considered clinically significant laboratory values by the investigator should be reported as AEs.

### 6.1.2 Serious Adverse Event

The terms “severe” and “serious” are not synonymous. Severity (or intensity) refers to the grade of an AE (see below). “Serious” is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a

threat to a subject's life or functioning. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities.

An AE should be classified as an SAE if it meets any 1 of the following criteria:

- It results in death (ie, the AE actually causes or leads to death).
- It is life-threatening (ie, the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- It is considered a significant medical event by the investigator based on medical judgment (eg, may jeopardize the subject or may require medical/surgical intervention to prevent 1 of the outcomes listed above).

### 6.1.3 Severity

Definitions found in the CTCAE version 4.03 or higher will be used for grading the severity (intensity) of AEs. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

## 6.2 DOCUMENTING AND REPORTING OF ADVERSE AND SERIOUS ADVERSE EVENTS

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the CRF. All SAEs must be reported on the SAE form or clinical database.

### 6.2.1 Adverse Event Reporting Period

After the signing of the ICF, all SAEs must be reported. After the first dose of study drug, all AEs, irrespective of seriousness, must be reported.

For acalabrutinib, AE reporting, irrespective of seriousness, ends 30 days after the last dose of study drug(s). For pembrolizumab, all AEs must be reported through 30 days after the last dose of pembrolizumab; any SAEs, or follow-up to a SAE, including death due to any cause other than progression of the cancer under study, must be reported through 90 days after the last dose or 30 days after the last dose of pembrolizumab if the subject initiates a new anticancer therapy within the 90 day posttreatment timeframe.

SAEs considered related to study drug(s) occurring after the end of the AE reporting period (as defined above) must be reported.

If an SAE is present at the last study visit, the SAE should be followed to resolution or until the investigator assesses the subject as stable, or the subject is lost to follow-up or withdraws consent. Resolution/stable means the subject has returned to baseline state of health or the investigator does not expect any further improvement or worsening of the event.

### 6.2.2 Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation timepoints during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, or other means, that occur to any subject from the time of first dose through 30 days following the cessation of study drug(s), and all SAEs that occur to any subject receiving pembrolizumab from the time of first dose through 90 days following cessation of pembrolizumab, or 30 days following cessation of pembrolizumab if the subject initiates new anticancer therapy (whichever is earlier) will be recorded in the subject's medical record and on the AE CRF.

Disease progression itself is not considered an AE; however, signs and symptoms of disease progression may be recorded as AEs or SAEs.

Each recorded AE or SAE will be described by its diagnostic term, duration (eg, start and end dates), severity, regulatory seriousness criteria, if applicable, suspected relationship to the study drugs (see following guidance), and any actions taken. The causality of AEs to the study drugs will be assessed by means of the question: 'Is there a reasonable possibility that the event may have been caused by the study drugs?' per FDA guidance on safety reporting requirements (FDA Guidance 2012).

See Appendix 3 for more detail on assessing causality.

### 6.2.3 Pregnancy

The investigator should report all pregnancies and pregnancies in the partners of subjects within 24 hours using the Pregnancy Report Form. This form should be faxed or emailed to Acerta Pharma Drug Safety. Any pregnancy-associated SAE must be reported to Acerta Pharma, according to the usual timelines and directions for SAE reporting (Section 6.2.4).

Any uncomplicated pregnancy that occurs with the subject or with the partner of a treated subject during this study will be reported. All pregnancies and partner pregnancies that are identified during or after this study, wherein the estimated date of conception is determined to have occurred from the time of consent to 90 days after the last dose of acalabrutinib, 120 days after the last dose of pembrolizumab, or 30 days after the last dose of either treatment if the subject initiates a new anticancer threapy (whichever is earlier) will be reported, followed to conclusion, and the outcome reported, as long as the subject or partner is willing to participate in follow-up.

A pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (eg, congenital abnormalities/birth defects/spontaneous miscarriage or any other serious events) must additionally be reported as such using the SAE report form.

Subjects should be instructed to immediately notify the investigator of any pregnancies. Any female subjects receiving study drug who become pregnant must

immediately discontinue study drug. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Upon completion of the pregnancy, additional information on the mother, pregnancy, and baby will be collected and sent to DrugSafety@acerta-pharma.com.

### 6.2.4 Expedited Reporting Requirements for Serious Adverse Events

All SAEs must be reported within 24 hours of discovery. All initial SAE reports and follow-up information will be reported using the protocol-specific electronic data capture system. If electronic SAE reporting is not available, paper SAE forms must be emailed or faxed to Acerta Pharma Drug Safety, or designee. Acerta Pharma may request follow-up and other additional information from the investigator (eg, hospital admission/discharge notes and laboratory results).

Whenever possible, AEs/SAEs should be reported by diagnosis term not as a constellation of symptoms.

Death due to disease progression should be recorded on the appropriate form in the electronic data capture system. If the primary cause of death is disease progression, the death due to disease progression should not be reported as an SAE. If the primary cause of death is something other than disease progression, then the death should be reported as an SAE with the primary cause of death as the event term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to Acerta Pharma Drug Safety, or designee, as outlined above.

If study drug is discontinued because of an SAE, this information must be included in the SAE report.

An SAE may qualify for mandatory expedited reporting to regulatory authorities if the SAE is attributable to the investigational product (or if a causality assessment is not provided for the SAE, in which case the default of ‘related’ must be used for expedited reporting purposes) and the SAE is not listed in the current Investigator Brochure (ie, an unexpected event). In this case, Acerta Pharma Drug Safety/Designee will forward a formal notification describing the suspected unexpected adverse reaction

(SUSAR) to all investigators. Each investigator must then notify his or her IRB/IEC of the SUSAR.

| Drug Safety Contact Information | |
|---|---|
| Fax: | +1 866 467 0304 (United States)<br>or +1 650 935 4996 (for outside United States) |
| Email: | DrugSafety@acerta-pharma.com |

### 6.2.5 Reporting Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to study drug must be reported within 24 hours to the sponsor either by electronic media or paper as described in Section 6.2.4.

Events of Clinical Interest for this trial include:

1. An overdose of study drug (overdose is defined in Section 3.10.7) that is not associated with clinical symptoms or abnormal laboratory results.

2. An elevated AST or ALT lab value that is ≥ 3 times the ULN and an elevated total bilirubin value that is ≥ 2 times ULN and, at the same time, an alkaline phosphatase value that is < 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The guidance for

assessment and follow up of these criteria can be found in the study binder provided separately from this protocol.

### 6.2.6 Type and Duration of Follow-up of Subjects after Adverse Events

All AEs and SAEs that are encountered during the protocol-specified AE reporting period should be followed to resolution, or until the investigator assesses the subject as stable, a new anticancer therapy is initiated, or the subject is lost to follow-up or withdraws consent.

### 6.2.7 Other Safety Issues Requiring Expedited Reporting

For studies being conducted in Europe expedited reporting is required for safety issues that might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. For a detailed description of safety issues that may qualify for expedited reporting please refer to the European Commission guidance titled, “Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use – April 2006” available at http://ec.europa.eu/health/files/eudralex/vol-10/21_susar_rev2_2006_04_11_en.pdf.

## 7.0 STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

Acerta Pharma retains the right to terminate the study and remove all study materials from a study site at any time. Specific circumstances that may precipitate such termination are:

- Unsatisfactory subject enrollment with regard to quality or quantity
- Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on subjects and maintain adequate study records
- Inaccurate, incomplete and/or late data recording on a recurrent basis
- The incidence and/or severity of AEs in this or other studies indicating a potential health hazard caused by the study treatment

### 7.1 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

The investigator will submit this protocol, the informed consent, Investigator’s Brochure, and any other relevant supporting information (eg, all advertising materials) to the appropriate IRB/IEC for review and approval before study initiation. A signed

protocol approval page; a letter confirming IRB/IEC approval of the protocol and informed consent; and a statement that the IRB/IEC is organized and operates according to Good Clinical Practice (GCP) guidelines and the applicable laws and regulations; **must** be forwarded to Acerta Pharma **before** screening subjects for the study. Additionally, sites must forward a signed Form FDA 1572 (Statement of Investigator) to Acerta Pharma before screening subjects for study enrollment. Amendments to the protocol must also be approved by the IRB/IEC and local regulatory agency, as appropriate, before the implementation of changes in this study.

## 7.2 INFORMED CONSENT AND PROTECTED SUBJECT HEALTH INFORMATION AUTHORIZATION

A copy of the IRB/IEC-approved informed consent must be forwarded to Acerta Pharma for regulatory purposes. The investigator, or designee (designee must be listed on the Study Personnel Responsibility/Signature Log, see Section 7.11), **must** explain to each subject the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as defined in § 21CFR Part 50, and other applicable national and local regulations governing informed consent form. Each subject must provide a signed and dated informed consent before enrollment into this study. In the case of a subject who is incapable of providing informed consent, the investigator (or designee) must obtain a signed and dated informed consent form from the subject's legal guardian. Signed consent forms must remain in each subject's study file and be available for verification by study monitors at any time.

In accordance to individual local and national patient privacy regulations, the investigator or designee **must** explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Acerta Pharma and its designees, regulatory agencies, and IRBs/IECs. As the study sponsor, Acerta Pharma will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the investigator's or designee's responsibility to obtain written permission to use protected health information from each subject, or if appropriate, the subject's legal guardian. If a subject or subject's legal guardian withdraws permission to use protected health information, it is the investigator's responsibility to obtain the withdrawal request in writing from the subject or subject's legal guardian **and** to

ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

## 7.3 SUBJECT SCREENING LOG

The investigator **must** keep a record that lists **all** subjects considered for enrollment (including those who did not undergo screening) in the study. For those subjects subsequently excluded from enrollment, record the reason(s) for exclusion.

## 7.4 CASE REPORT FORMS

Authorized study site personnel (see Section 7.11) will complete CRFs designed for this study according to the completion guidelines that will be provided within the clinical database. The investigator will ensure that the CRFs are accurate, complete, legible, and completed promptly. The investigator will ensure that source documents that are required to verify the validity and completeness of data transcribed on the CRFs are never obliterated or destroyed.

## 7.5 STUDY MONITORING REQUIREMENTS

Representatives of Acerta Pharma or its designee will monitor this study until completion. Monitoring will be conducted through personal visits with the investigator and site staff as well as any appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure compliance with the protocol and the quality and integrity of the data. This study is also subject to reviews or audits.

Every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the investigator agrees to allow the IRB/IEC, representatives of Acerta Pharma, its designated agents, and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. This includes providing by fax, email, or regular mail de-identified copies of radiology, pathology, and/or laboratory results when requested by the sponsor. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

## 7.6 INVESTIGATIONAL STUDY DRUG ACCOUNTABILITY

Acalabrutinib and pembrolizumab must be kept in a locked limited access cabinet or space, under appropriate storage conditions. The study drug must not be used outside the context of the protocol.

Study drug accountability records must be maintained and readily available for inspection by representatives of Acerta Pharma and are open to inspections by regulatory authorities at any time.

Each shipment of study drug will contain a Clinical Supplies Shipping Receipt Form (CSSF) that must be appended to the site's drug accountability records. Additionally a Drug Re-order Form for requesting more study drug is provided in the pharmacy binder. If it is used, then the Drug Re-order Form must also be included in the site's drug accountability records.

Contents of each shipment must be visually inspected to verify the quantity and document the condition of study drug capsules. The designated recipient completes and signs the CSSF. A copy of the signed CSSF must be faxed or emailed to Acerta Pharma at the fax number/email address listed on the form.

An Investigational Drug Accountability Log must be used for drug accountability. For accurate accountability, the following information must be noted when drug supplies are used during the study:

1. study identification number (ACE-ST-005)
2. subject identification number
3. lot number(s) of acalabrutinib dispensed for that subject
4. date and quantity of drug dispensed
5. any unused drug returned by the subject

At study initiation, the monitor will evaluate and approve the site's procedure for investigational product disposal/destruction to ensure that it complies with Acerta Pharma's requirements. If the site cannot meet Acerta Pharma's requirements for disposal/destruction, arrangements will be made between the site and Acerta Pharma or its designee, for return of unused investigational product. Before disposal/destruction, final drug accountability and reconciliation must be performed by the monitor.

All study supplies and associated documentation will be regularly reviewed and verified by the monitor.

## 7.7 RECORD RETENTION

The investigator and other appropriate study staff are responsible for maintaining all documentation relevant to the study. Mandatory documentation includes copies of study protocols and amendments, each Form FDA 1572, IRB/IEC approval letters, signed ICFs, drug accountability records, SAE information transmitted to Acerta Pharma, subject files (source documentation) that substantiate entries in CRFs, all relevant correspondence and other documents pertaining to the conduct of the study.

An investigator shall retain records for a period of at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. The investigator must notify Acerta Pharma and obtain written approval from Acerta Pharma before destroying any clinical study records at any time. Acerta Pharma will inform the investigator of the date that study records may be destroyed or returned to Acerta Pharma.

Acerta Pharma must be notified in advance of, and Acerta Pharma must provide express written approval of, any change in the maintenance of the foregoing documents if the investigator wishes to move study records to another location or assign responsibility for record retention to another party. If the investigator cannot guarantee the archiving requirements set forth herein at his or her study site for all such documents, special arrangements must be made between the investigator and Acerta Pharma to store such documents in sealed containers away from the study site so that they can be returned sealed to the investigator for audit purposes.

## 7.8 PROTOCOL AMENDMENTS

Acerta Pharma will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB/IEC together with, if applicable, a revised model ICF. If the change in any way increases the risk to the subject or changes the scope of the study, then written documentation of IRB/IEC approval must be received by Acerta Pharma before the amendment may take effect. Additionally under this circumstance, information on the increased risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand, and sign any revised ICF confirming willingness to remain in the trial.

## 7.9 PUBLICATION OF STUDY RESULTS

Authorship, in general, will follow the recommendations of the International Committee of Medical Journal Editors (International Committee of Medical Journal Editors 2014).

## 7.10 CLINICAL TRIAL INSURANCE

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

## 7.11 GENERAL INVESTIGATOR RESPONSIBILITIES

The principal investigator must ensure that:

1. He or she will conduct or supervise the study.
2. His or her staff and all persons who assist in the conduct of the study clearly understand their responsibilities and have their names included in the Study Personnel Responsibility/Signature Log.
3. The study is conducted according to the protocol and all applicable regulations.
4. The protection of each subject's rights and welfare is maintained.
5. Signed and dated informed consent and, when applicable, permission to use protected health information are obtained from each subject before conducting nonstandard of care study procedures. If a subject or subject's legal guardian withdraws permission to use protected health information, the investigator will obtain a written request from the subject or subject's legal guardian and will ensure that no further data be collected from the subject.
6. The consent process is conducted in compliance with all applicable regulations and privacy acts.
7. The IRB/IEC complies with applicable regulations and conducts initial and ongoing reviews and approvals of the study.
8. Any amendment to the protocol is submitted promptly to the IRB/IEC.
9. Any significant protocol deviations are reported to Acerta Pharma and the IRB/IEC according to the guidelines at each study site.
10. CRF pages are completed promptly.
11. All IND Safety Reports/SUSAR Reports are submitted promptly to the IRB/IEC.
12. All SAEs are reported to Acerta Pharma Drug Safety/Designee within 24 hours of knowledge via the clinical database and to the IRB/IEC per their requirements.

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# 9.0 APPENDICES

## Appendix 1. Performance Status Scores

| Grade | ECOG |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair |
| 5 | Dead |

As published in Am J Clin Oncol:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Credit: Eastern Cooperative Oncology Group Chair: Robert Comis, MD

Available at: http://www.ecog.org/general/perf_stat.html. Accessed 23 August 2013.

## Appendix 2. Known Strong in Vivo Inhibitors or Inducers of CYP3A

| Strong Inhibitors of CYP3A[a] | Strong Inducers of CYP3A[e] |
|---|---|
| boceprevir | carbamazepine[f] |
| clarithromycin[b] | phenytoin[f] |
| conivaptin[b] | rifampin[f] |
| grapefruit juice[c] | St John's wort[f] |
| indinavir | |
| itraconazole[b] | |
| ketoconazole[b] | |
| lopinavir/ritonavir[b] (combination drug) | |
| mibefradil[d] | |
| nefazodone | |
| nelfinavir | |
| posaconazole | |
| ritonavir[b] | |
| saquinavir | |
| telaprevir | |
| telithromycin | |
| voriconazole | |

Source:

FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers . Web link Accessed 21 January 2015: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo

Note: The list of drugs in these tables is not exhaustive. Any questions about drugs not on this list should be addressed to the medical monitor of the protocol.

a. A strong inhibitor for CYP3A is defined as an inhibitor that increases the AUC of a substrate for CYP3A by ≥ 5-fold.
b. In vivo inhibitor of P-glycoprotein.
c. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (eg, high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (eg, low dose, single strength).
d. Withdrawn from the United States market because of safety reasons.
e. A strong inducer for CYP3A is defined as an inducer that results in ≥ 80% decrease in the AUC of a substrate for CYP3A.
f. In vivo inducer of P-glycoprotein.

## Appendix 3. Adverse Event Assessment of Causality

Is there a reasonable possibility that the event may have been caused by study drugs? No___ Yes___

The descriptions provided below will help guide the principal investigator in making the decision to choose either “yes” or “no”:

No = There is no reasonable possibility that the event may have been caused by study drugs.

The adverse event:

- may be judged to be due to extraneous causes such as disease or environment or toxic factors
- may be judged to be due to the subject’s clinical state or other therapy being administered
- is not biologically plausible
- does not reappear or worsen when study drug is re-administered
- does not follow a temporal sequence from administration of study drug

Yes = There is a reasonable possibility that the event may have been caused by study drugs.

The adverse event:

- follows a temporal sequence from administration of study drug
- is a known response to the study drug based on clinical or preclinical data
- could not be explained by the known characteristics of the subject’s clinical state, environmental or toxic factors, or other therapy administered to the subject
- disappears or decreases upon cessation or reduction of dose of study drug
- reappears or worsens when study drug is re-administered

## Appendix 4. Schedule of Assessments – Treatment Arms 1 and 2

| | | | Treatment Phase (Weeks)[b] | | | | | | | | | | Safety Follow Visit[c] | Follow-up Phase[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Weeks** | | **Screening[a]** | **1** | **2** | **3** | **4** | **5[s]** | **6** | **7** | **8** | **≥ 10 (Q3W)** | **ET** | **+30 days after last dose** | **Q12W** |
| **Study Window** | | **-28 days** | | **± 3 days** | | | | | | | **± 3 days** | **+ 3 days** | **+ 7 days** | **± 10 days** |
| Informed consent | | x | | | | | | | | | | | | |
| Confirm eligibility | | x | | | | | | | | | | | | |
| Medical history | | x | | | | | | | | | | | | |
| PE[e]/Vital signs[f]/Weight | | x | x | x | x | x | x | | x | | x | x | x | |
| ECOG status | | x | x | x | x | x | x | | x | | x | | | |
| ECG[g] | | x | x | x | | x | x | | x | | Q6W | x | x | |
| Lab assessments: | | | | | | | | | | | | | | |
| Pregnancy test[h] | | x | x[q] | | | x | | | x | | x | x | x | |
| Hematology[i] | | x | x[q] | x | x | x | x | | x | | x | x | x | |
| Coagulation | | x | | | | | | | x | | | | | |
| Serum chemistry[j] | | x | x[q] | x | x | x | x | | x | | x | x | x | |
| Serum lipase/amylase | | x | x[q] | | | x | x | | x | | x | x | x | |
| Thyroid panel[k] | | x | x[q] | | | | | | x | | Week 13 then Q6W | x | x | |
| Urinalysis[l] | | x | | | | | | | | | | | | |
| T/B/NK cell count[m] | | x | x[q] | | | | | | x[q] | | Week 10 then Q3M | | | |
| Serum Ig[n] | | | x[q] | | | | | | x[q] | | Week 10 then Q3M | | | |
| Hepatitis serology[t] | | x | | | | | | | | | | | | |
| HBV PCR[u] | | x | | | | x | | | | x | Week 12 then Q4W | | | Q4W |
| HCV PCR[v] | | x | | | | | | | | | Week 13 and 25 | | | |
| Pharmacokinetics[r] | | | x | | x | | | | x | | | | | |
| PD/Biomarkers | | Tumor sample[o] | x[q] | x[q] | x[q] | x[q] | | | x[q] | | Week 10 and 13 only[q] | | | |
| **Arm 1** | Pembrolizumab 200 mg Q3W | | x | | | x | | | x | | x | | | |
| | Acalabrutinib 100 mg BID | | x | x | x | x | x | x | x | x | x | | | |
| **Arm 2** | Pembrolizumab 200 mg Q3W | | x | | | x | | | x | | x | | | |
| Study drug compliance | | | x | x | x | x | x | | x | | x | | | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tumor assessment[p] | x | | | | | | | x | | Week 13 and 19 then every 12 weeks | | | |
| Concomitant medications | x | x | x | x | x | x | | x | | x | x | x | |
| Adverse events | | x | x | x | x | x | | x | | x | x | x | |
| Survival | | | | | | | | | | | | x | x |

Abbreviations: BID = twice per day; ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, ET = early termination; HBV = hepatitis B virus; Ig = immunoglobulin; PCR = polymerase chain reaction; PE = physical exam; Q3M = every 3 months; Q12W = every 12 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; Q6W = every 6 weeks.

Note: Visits to the sites are not required on Week 6 and 8, but subjects will continue to take acalabrutinib 100 mg BID during those weeks.

**Footnotes for ACE-ST-005 Schedule of Study Activities:**

a. Screening tests should be performed within 28 days before the first administration of study drug, unless otherwise indicated.
b. Treatment may be stopped earlier for confirmed CR as described in the protocol.
c. A 30-day (+ 7 days) safety follow-up visit is required when subjects discontinue study drug unless they start another anticancer therapy within that timeframe.
d. Subjects who discontinue study therapy will be followed for survival unless they withdraw consent or are lost to follow-up or the sponsor ends the study. Subjects who discontinue study drug for any reason other than disease progression, death, lost to follow-up, or withdrawal of consent will be followed for tumor assessment until disease progression or initiation of any other anticancer therapies, whichever comes first.
e. The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Symptom-directed physical exams, including tumor assessments by palpation, are done thereafter.
f. Vital signs (blood pressure, pulse, respiratory rate, and temperature) will be assessed after the subject has rested in the sitting position.
g. Subjects should be in supine position and resting for ≥ 10 minutes before study-related ECGs. On Day 1, Week 1 ECGs will be done in triplicate ≥ 1 minute apart. At all other visits the single ECGs will be done at any time during the visit.
h. Women of childbearing potential must have a negative urine or serum pregnancy testing within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test is required.
i. Hematology includes complete blood count with differential and platelet and reticulocyte counts. Week 1 hematology does not need to be repeated if screening hematology was done within 7 days.
j. Serum chemistry: albumin, alkaline phosphatase, alanine transaminase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), bone-specific alkaline phosphatase, calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid. Week 1 serum chemistry does not need to be repeated if screening serum chemistry was within 7 days.
k. Thyroid panel: total triiodothyronine (T3), free thyroxine (T4), and thyroid stimulating hormone (TSH). Week 1 thyroid panel does not need to be repeated if screening thyroid panel was within 7 days.
l. Urinalysis: pH, ketones, specific gravity, bilirubin, blood, and glucose.
m. T/B/NK cell count (ie, CD3, CD4, CD8, CD14, CD19, CD16/56). Week 1 cell count does not need to be repeated if screening cell count was within 7 days.
n. Serum immunoglobulin: IgG, IgM, IgA.
o. Provide tissue sections from either an archived or newly obtained tumor sample (most recent biopsy) for biomarker analysis
p. A pretreatment computed tomography (CT) scan with contrast (unless contraindicated) is required of the chest, abdomen, and pelvis and any other disease sites (eg, neck) within 30 days before the first dose of study drug. CT scans will be done for tumor assessments at Week 7, 13, 19 (± 7 days) and then every 12 weeks (± 10 days) or more frequently at the investigator's discretion.
q. The indicated samples at this timepoint must be drawn predose.
r. Only subjects in Arm 2 will have PK sampling. The first 6 subjects in Arm 2 will have PK samples drawn at Week 1 (Day 1 and Day 2), Week 3 and Week 7. All other subjects in Arm 2 will only have PK samples drawn at Week 3. Refer to Section 4.1.19 complete instructions on the PK sampling timepoints.
s. The Week 5 visit is only required for subjects who will contribute to the DLT assessment.
t. Hepatitis serology must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), and hepatitis C (HCV) antibody. In addition, any subjects testing positive for any hepatitis serology, must have PCR testing (see exclusion criterion #16).

u. Subjects who are hepatitis B core antibody positive (or have a known history of HBV infection) should have a quantitative PCR test for HBV DNA during screening and monthly thereafter. Monitoring should continue Q4W (± 7 days) until 12 months after last dose of study drug(s). Any subject with a rising viral load (above lower limit of detection) should discontinue study drug(s) and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B.
v. Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should have quantitative PCR testing for HCV DNA performed during screening and at Weeks 13 and 25. No further testing beyond Week 25 is necessary if, PCR results are negative.

## Appendix 5. Schedule of Assessments – Crossover

| Treatment Phase (Weeks) | | | | | |
|---|---|---|---|---|---|
| **Weeks After Crossover[a,b]** | **0** | **1** | **2** | **3** | **≥ 4** |
| **Study Window** | **± 3 days** | | | | |
| Vital signs | Refer to Schedule of Assessments in Appendix 4 | x | x | Refer to Schedule of Assessments in Appendix 4 | Refer to Schedule of Assessments in Appendix 4 |
| Lab assessments: | | | | | |
| Hematology[c] | | x | x | | |
| Serum chemistry[d] | | x | x | | |
| Study drug compliance | | x | x | | |
| Concomitant medications | | x | x | | |
| Adverse events | | x | x | | |
| Acalabrutinib 100 mg BID[b] | x | x | x | x | |
| Pembrolizumab 200 mg Q3W | x | | | x | |

Abbreviations: BID = twice per day; Q3W = every 3 weeks.

Footnotes for ACE-ST-005 Schedule of Study Activities - Crossover:

a. Subjects are to complete assessments as shown in the 2 weeks following crossover. (Eg, if a subject crosses over to receive acalabrutinib and pembrolizumab at Week 10, assessments will be performed as listed for Week 10 in Appendix 4. During Weeks 11 and 12, assessments will be performed as listed above for Weeks 1 and 2 after Crossover. During Week 13, assessments will be performed as listed in Week 13 in Appendix 4; assessments will be performed as listed in Appendix 4 for all subsequent weeks).
b. Subjects who cross over to receive acalabrutinib in addition to pembrolizumab should start acalabrutinib treatment at the next visit in which they are scheduled to receive pembrolizumab.
c. Hematology includes complete blood count with differential and platelet and reticulocyte counts.
d. Serum chemistry: albumin, alkaline phosphatase, alanine transaminase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), bone-specific alkaline phosphatase, calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid.

## Appendix 6. KEYTRUDA Package Insert

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use KEYTRUDA safely and effectively. See full prescribing information for KEYTRUDA.**

**KEYTRUDA® (pembrolizumab) for injection, for intravenous use**
**KEYTRUDA® (pembrolizumab) injection, for intravenous use**
**Initial U.S. Approval: 2014**

**----------RECENT MAJOR CHANGES----------**

| | |
|---|---|
| Indications and Usage (1.1) | 12/2015 |
| Indications and Usage (1.2) | 10/2015 |
| Dosage and Administration (2.1, 2.3) | 10/2015 |
| Dosage and Administration (2.4) | 01/2015 |
| Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7) | 12/2015 |

**----------INDICATIONS AND USAGE----------**

KEYTRUDA is a programmed death receptor-1 (PD-1)-blocking antibody indicated for the treatment of:

- patients with unresectable or metastatic melanoma. (1.1)
- patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA.
  This indication is approved under accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.2)

**----------DOSAGE AND ADMINISTRATION----------**

- Administer 2 mg/kg as an intravenous infusion over 30 minutes every 3 weeks. (2.2)
- Dilute prior to intravenous infusion. (2.4)

**----------DOSAGE FORMS AND STRENGTHS----------**

- For injection: 50 mg lyophilized powder in single-use vial for reconstitution (3)
- Injection: 100 mg/4 mL (25 mg/mL) solution in a single-use vial (3)

**----------CONTRAINDICATIONS----------**

None. (4)

**----------WARNINGS AND PRECAUTIONS----------**

- Immune-mediated Pneumonitis: Withhold for moderate, and permanently discontinue for severe, life-threatening or recurrent moderate pneumonitis. (5.1)
- Immune-mediated Colitis: Withhold for moderate or severe, and permanently discontinue for life-threatening colitis. (5.2)
- Immune-mediated Hepatitis: Monitor for changes in hepatic function. Based on severity of liver enzyme elevations, withhold or discontinue. (5.3)
- Immune-mediated Endocrinopathies (5.4):
  - Hypophysitis: Withhold for moderate and withhold or permanently discontinue for severe or life-threatening hypophysitis.
  - Thyroid disorders: Monitor for changes in thyroid function. Withhold or permanently discontinue for severe or life-threatening hyperthyroidism.
  - Type 1 diabetes mellitus: Monitor for hyperglycemia. Withhold KEYTRUDA in cases of severe hyperglycemia.
- Immune-mediated nephritis: Monitor for changes in renal function. Withhold for moderate, and permanently discontinue for severe or life-threatening nephritis. (5.5)
- Infusion-related reactions: Stop infusion and permanently discontinue KEYTRUDA for severe or life-threatening infusion reactions. (5.7)
- Embryofetal toxicity: KEYTRUDA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus. (5.8)

**---------- ADVERSE REACTIONS ----------**

Most common adverse reactions (reported in ≥20% of patients) with:

- melanoma included fatigue, pruritus, rash, constipation, diarrhea, nausea, and decreased appetite. (6.1)
- NSCLC included fatigue, decreased appetite, dyspnea and cough. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**---------- USE IN SPECIFIC POPULATIONS ----------**

Lactation: Discontinue nursing or discontinue KEYTRUDA. (8.2)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

**Revised: 12/2015**

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**FULL PRESCRIBING INFORMATION: CONTENTS***



*Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

### 1.1 Melanoma

KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma *[see Clinical Studies (14.1)]*.

### 1.2 Non-Small Cell Lung Cancer

KEYTRUDA is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 as determined by an FDA-approved test with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA *[see Clinical Studies (14.2)]*.

This indication is approved under accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Patient Selection

Select patients for second line or greater treatment of metastatic NSCLC with KEYTRUDA based on the presence of positive PD-L1 expression *[see Clinical Studies (14.2)]*. Information on FDA-approved tests for the detection of PD-L1 expression in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.

### 2.2 Recommended Dosing

The recommended dose of KEYTRUDA is 2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

### 2.3 Dose Modifications

Withhold KEYTRUDA for any of the following:

- Grade 2 pneumonitis *[see Warnings and Precautions (5.1)]*
- Grade 2 or 3 colitis *[see Warnings and Precautions (5.2)]*
- Grade 3 or 4 endocrinopathies *[see Warnings and Precautions (5.4)]*
- Grade 2 nephritis *[see Warnings and Precautions (5.5)]*
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN
- Any other severe or Grade 3 treatment-related adverse reaction *[see Warnings and Precautions (5.6)]*

Resume KEYTRUDA in patients whose adverse reactions recover to Grade 0-1.

Permanently discontinue KEYTRUDA for any of the following:

- Any life-threatening adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy)
- Grade 3 or 4 pneumonitis or recurrent pneumonitis of Grade 2 severity *[see Warnings and Precautions (5.1)]*
- Grade 3 or 4 nephritis *[see Warnings and Precautions (5.5)]*
- AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN
  - For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week
- Grade 3 or 4 infusion-related reactions *[see Warnings and Precautions (5.7)]*

- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade 0-1 within 12 weeks after last dose of KEYTRUDA
- Any severe or Grade 3 treatment-related adverse reaction that recurs *[see Warnings and Precautions (5.6)]*

### 2.4 Preparation and Administration

**Reconstitution of KEYTRUDA for Injection (Lyophilized Powder)**

- Add 2.3 mL of Sterile Water for Injection, USP by injecting the water along the walls of the vial and not directly on the lyophilized powder (resulting concentration 25 mg/mL).
- Slowly swirl the vial. Allow up to 5 minutes for the bubbles to clear. Do not shake the vial.

**Preparation for Intravenous Infusion**

- Visually inspect the solution for particulate matter and discoloration prior to administration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.
- Dilute KEYTRUDA injection (solution) or reconstituted lyophilized powder prior to intravenous administration.
- Withdraw the required volume from the vial(s) of KEYTRUDA and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.
- Discard any unused portion left in the vial.

**Storage of Reconstituted and Diluted Solutions**

The product does not contain a preservative.

Store the reconstituted and diluted solution from the KEYTRUDA 50 mg vial either:

- At room temperature for no more than 6 hours from the time of reconstitution. This includes room temperature storage of reconstituted vials, storage of the infusion solution in the IV bag, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of reconstitution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Store the diluted solution from the KEYTRUDA 100 mg/4 mL vial either:

- At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the infusion solution in the IV bag, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Do not freeze.

**Administration**

- Administer infusion solution intravenously over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter.
- Do not co-administer other drugs through the same infusion line.

## 3 DOSAGE FORMS AND STRENGTHS

- For injection: 50 mg lyophilized powder in a single-use vial for reconstitution
- Injection: 100 mg/4 mL (25 mg/mL) solution in a single-use vial

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Immune-Mediated Pneumonitis

Immune-mediated pneumonitis, including fatal cases, occurred in patients receiving KEYTRUDA. Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater pneumonitis. Withhold KEYTRUDA for moderate (Grade 2) pneumonitis, and permanently discontinue KEYTRUDA for severe (Grade 3), life-threatening (Grade 4), or recurrent moderate (Grade 2) pneumonitis *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)].*

Melanoma

Pneumonitis occurred in 32 (2.0%) of 1567 patients receiving KEYTRUDA in Trials 1, 2, and 6, including Grade 1 (0.8%), Grade 2 (0.8%), and Grade 3 (0.4%) pneumonitis. The median time to development of pneumonitis was 4.3 months (range: 2 days to 19.3 months). The median duration was 2.6 months (range: 2 days to 15.1 months). Twelve (38%) of the 32 patients received corticosteroids, with 9 of the 12 receiving high-dose systemic corticosteroids for a median duration of 8 days (range: 1 day to 1.1 months) followed by a corticosteroid taper. Pneumonitis led to discontinuation of KEYTRUDA in 9 (0.6%) patients. Pneumonitis completely resolved in 21 (66%) of the 32 patients.

NSCLC

Pneumonitis occurred in 19 (3.5%) of 550 patients with NSCLC, including Grade 2 (1.1%), Grade 3 (1.3%), Grade 4 (0.4%), or Grade 5 (0.2%) pneumonitis in patients receiving KEYTRUDA in Trial 1. The median time to development of pneumonitis was 1.7 months (range: 4 days to 12.9 months). In patients receiving KEYTRUDA 10 mg/kg every 14 days, the median time to development of pneumonitis was shorter (1.5 months) compared with patients receiving 10 mg/kg every 21 days (3.5 months). Sixteen of the 19 patients (84%) received corticosteroids, with 14 of the 19 (74%) requiring high-dose systemic corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day). The median starting dose of high-dose corticosteroid treatment for these fourteen patients was 60 mg/day with a median duration of treatment of 8 days (range: 1 day to 4.2 months). The median duration of pneumonitis was 1.2 months (range: 5 days to 12.4 months). Pneumonitis occurred more frequently in patients with a history of asthma/chronic obstructive pulmonary disease (5.4%) than in patients without a history of these diseases (3.1%). Pneumonitis occurred more frequently in patients with a history of prior thoracic radiation (6.0%) than in patients who did not receive prior thoracic radiation (2.6%). Pneumonitis led to discontinuation of KEYTRUDA in 12 (2.2%) patients. Pneumonitis completely resolved in 9 patients. Pneumonitis was reported as ongoing in 9 patients and one patient with ongoing pneumonitis died within 30 days of the last dose of KEYTRUDA.

### 5.2 Immune-Mediated Colitis

Immune-mediated colitis occurred in patients receiving KEYTRUDA. Monitor patients for signs and symptoms of colitis. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater colitis. Withhold KEYTRUDA for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue KEYTRUDA for life-threatening (Grade 4) colitis *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)].*

Melanoma

Colitis occurred in 31 (2.0%) of 1567 patients receiving KEYTRUDA in Trials 1, 2, and 6, including Grade 2 (0.5%), Grade 3 (1.1%), and Grade 4 (0.1%) colitis. The median time to onset of colitis was 3.4 months (range: 10 days to 9.7 months). The median duration of colitis was 1.4 months (range: 1 day to 7.2 months). Twenty-one (68%) of the 31 patients received corticosteroids, all of whom required high-dose systemic corticosteroids for a median duration of 6 days (range: 1 day to 5.3 months) followed by a

corticosteroid taper. Colitis led to discontinuation of KEYTRUDA in 14 (0.9%) patients. Colitis resolved in 27 (87%) of the 31 patients.

NSCLC
Colitis occurred in 4 (0.7%) of 550 patients, including Grade 2 (0.2%) or Grade 3 (0.4%) colitis in patients receiving KEYTRUDA in Trial 1. The median time to onset of colitis was 1.6 months (range: 28 days to 2.2 months) and the median duration was 16 days (range: 7 days to 1.3 months). Two patients were started on high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) and two patients were started on low dose corticosteroids. One patient (0.2%) discontinued KEYTRUDA due to colitis. Three patients with colitis experienced complete resolution of the event.

### 5.3 Immune-Mediated Hepatitis
Immune-mediated hepatitis occurred in patients receiving KEYTRUDA. Monitor patients for changes in liver function. Administer corticosteroids (initial dose of 0.5 to 1 mg/kg/day [for Grade 2 hepatitis] and 1 to 2 mg/kg/day [for Grade 3 or greater hepatitis] prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)].*

Melanoma
Hepatitis occurred in 16 (1.0%) of 1567 patients receiving KEYTRUDA in Trials 1, 2, and 6, including Grade 2 (0.1%), Grade 3 (0.7%), and Grade 4 (0.1%) hepatitis. The time to onset was 26 days (range: 8 days to 21.4 months). The median duration was 1.2 months (range: 8 days to 4.7 months). Eleven (69%) of the 16 patients received corticosteroids, with 10 of the 11 receiving high-dose systemic corticosteroids for a median duration of 5 days (range: 1 to 14 days) followed by a corticosteroid taper. Hepatitis led to discontinuation of KEYTRUDA in 6 (0.4%) patients. Hepatitis resolved in 14 (88%) of the 16 patients.

### 5.4 Immune-Mediated Endocrinopathies
*Hypophysitis*
Hypophysitis occurred in patients receiving KEYTRUDA. Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). Administer corticosteroids and hormone replacement as clinically indicated. Withhold KEYTRUDA for moderate (Grade 2) hypophysitis and withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hypophysitis *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)].*

Melanoma
Hypophysitis occurred in 13 (0.8%) of 1567 patients receiving KEYTRUDA in Trials 1, 2, and 6 including Grade 2 (0.3%), Grade 3 (0.3%), and Grade 4 (0.1%) hypophysitis. The time to onset was 3.3 months (range: 1 day to 7.2 months). The median duration was 2.7 months (range: 12 days to 12.7 months). Twelve (92%) of the 13 patients received corticosteroids, with 4 of the 12 patients receiving high-dose systemic corticosteroids. Hypophysitis led to discontinuation of KEYTRUDA in 4 (0.3%) patients. Hypophysitis resolved in 7 (54%) of the 13 patients.

NSCLC
In Trial 1, hypophysitis occurred in 1 (0.2%) of 550 patients, which was Grade 3 in severity. The time to onset was 3.7 months. The patient was treated with systemic corticosteroids and physiologic hormone replacement therapy. The patient did not discontinue KEYTRUDA due to hypophysitis.

*Thyroid Disorders*
Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

Administer replacement hormones for hypothyroidism and manage hyperthyroidism with thionamides and beta-blockers as appropriate. Withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hyperthyroidism *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)].*

Melanoma
Hyperthyroidism occurred in 51 (3.3%) of 1567 patients receiving KEYTRUDA in Trials 1, 2, or 6, including Grade 2 (0.6%) and Grade 3 (0.1%) hyperthyroidism. The median time to onset was 1.4 months (range: 1 day to 21.9 months). The median duration was 1.7 months (range: 1 day to 12.8 months). Hyperthyroidism led to discontinuation of KEYTRUDA in 2 (0.1%) patients. Hyperthyroidism resolved in 36 (71%) of the 51 patients.

Hypothyroidism occurred in 127 (8.1%) of 1567 patients receiving KEYTRUDA in Trials 1, 2, and 6 including Grade 3 (0.1%) hypothyroidism. The median time to onset of hypothyroidism was 3.3 months (range: 5 days to 18.9 months). The median duration was 5.4 months (range: 6 days to 24.3 months). No patients discontinued KEYTRUDA due to hypothyroidism. Hypothyroidism resolved in 24 (19%) of the 127 patients.

NSCLC
Hyperthyroidism occurred in 10 (1.8%) of 550 patients receiving KEYTRUDA in Trial 1, including Grade 2 (0.7%) or Grade 3 (0.3%) hyperthyroidism. The median time to onset was 1.8 months (range: 2 days to 3.4 months), and the median duration was 4.5 months (range: 4 weeks to 7.5 months). No patients discontinued KEYTRUDA due to hyperthyroidism.

Hypothyroidism occurred in 38 (6.9%) of 550 patients receiving KEYTRUDA in Trial 1, including Grade 2 (5.5%) or Grade 3 (0.2%) hypothyroidism. The median time to onset was 4.2 months (range: 20 days to 11.2 months), and the median duration was 5.8 months (range: 11 days to 22.8 months). No patients discontinued KEYTRUDA due to hypothyroidism.

*Type 1 Diabetes mellitus*
Type 1 diabetes mellitus, including diabetic ketoacidosis, occurred in 3 (0.1%) of 2117 patients with melanoma or NSCLC receiving KEYTRUDA in Trials 1, 2, and 6. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes, and withhold KEYTRUDA and administer anti-hyperglycemics in patients with severe hyperglycemia *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)].*

### 5.5 Immune-Mediated Nephritis and Renal Dysfunction
Immune-mediated nephritis occurred in patients receiving KEYTRUDA. Monitor patients for changes in renal function. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater nephritis. Withhold KEYTRUDA for moderate (Grade 2), and permanently discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) nephritis *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)].*

Melanoma
Nephritis occurred in 7 (0.4%) of 1567 patients receiving KEYTRUDA in Trials 1, 2, and 6, including Grade 2 (0.2%), Grade 3 (0.2%), and Grade 4 (0.1%) nephritis. The median time to onset of nephritis was 5.1 months (range: 12 days to 12.8 months). The median duration was 1.1 months (range: 3 days to 3.3 months). Six (86%) of the 7 patients received corticosteroids, with 5 of the 6 receiving high-dose systemic corticosteroids for a median duration of 15 days (range: 3 days to 1.6 months) followed by a corticosteroid taper. Nephritis led to discontinuation of KEYTRUDA in 2 (0.1%) patients. Nephritis resolved in 4 (57%) of the 7 patients.

### 5.6 Other Immune-Mediated Adverse Reactions
Other clinically important immune-mediated adverse reactions can occur.

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and administer corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Resume KEYTRUDA when the immune-mediated adverse reaction remains at Grade 1 or less following corticosteroid taper. Permanently discontinue KEYTRUDA for any Grade 3 immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)].*

Melanoma
The following clinically significant, immune-mediated adverse reactions occurred in less than 1% (unless otherwise indicated) of 1567 patients with melanoma treated with KEYTRUDA in Trials 1, 2, and 6: arthritis (1.6%), exfoliative dermatitis, bullous pemphigoid, uveitis, myositis, Guillain-Barré syndrome, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, and partial seizures arising in a patient with inflammatory foci in brain parenchyma.

NSCLC
The following clinically significant, immune-mediated adverse reactions occurred in less than 1% of 550 patients with NSCLC treated with KEYTRUDA in Trial 1: rash, vasculitis, hemolytic anemia, serum sickness, and myasthenia gravis.

### 5.7 Infusion-Related Reactions
Severe and life-threatening infusion-related reactions have been reported in 3 (0.1%) of 2117 patients receiving KEYTRUDA in Trials 1, 2, and 6. Monitor patients for signs and symptoms of infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue KEYTRUDA *[see Dosage and Administration (2.3)].*

### 5.8 Embryofetal Toxicity
Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus. Advise females of reproductive potential to use highly effective contraception during treatment with KEYTRUDA and for 4 months after the last dose of KEYTRUDA *[see Use in Specific Populations (8.1, 8.3)].*

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.
- Immune-mediated pneumonitis *[see Warnings and Precautions (5.1)].*
- Immune-mediated colitis *[see Warnings and Precautions (5.2)].*
- Immune-mediated hepatitis *[see Warnings and Precautions (5.3)].*
- Immune-mediated endocrinopathies *[see Warnings and Precautions (5.4)].*
- Immune-mediated nephritis and renal dysfunction *[see Warnings and Precautions (5.5)].*
- Other immune-mediated adverse reactions *[see Warnings and Precautions (5.6)].*
- Infusion-related reactions *[see Warnings and Precautions (5.7)].*

### 6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in the WARNINGS AND PRECAUTIONS section reflect exposure to KEYTRUDA in 2117 patients in two randomized, open-label, active-controlled clinical trials, which enrolled 912 patients with unresectable or metastatic melanoma and one single-arm trial which enrolled 655 patients with metastatic melanoma and 550 patients with NSCLC. Across all studies, KEYTRUDA was administered at doses of 2 mg/kg intravenously every 3 weeks (19%), 10 mg/kg intravenously every 2 weeks (31%), or 10 mg/kg intravenously every 3 weeks (50%). Among these 2117, 43% of the patients were exposed for 6 months or more and 10% of the patients were exposed for 12 months or more.

The data described below were obtained in two randomized, open-label, active-controlled clinical trials (Trials 2 and 6), which enrolled 912 patients with unresectable or metastatic melanoma or in a single-arm trial (Trial 1), which enrolled 550 patients with metastatic non-small cell lung cancer (NSCLC). In these trials, KEYTRUDA was administered at 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks.

*Unresectable or Metastatic Melanoma*

*Ipilimumab-Naive Melanoma (Trial 6)*
The safety of KEYTRUDA for the treatment of patients with unresectable or metastatic melanoma who had not received prior ipilimumab and who had received no more than one prior systemic therapy was investigated in Trial 6. Trial 6 was a multicenter, open-label, active-controlled trial where patients were randomized (1:1:1) and received KEYTRUDA 10 mg/kg every 2 weeks (n=278) or KEYTRUDA 10 mg/kg every 3 weeks (n=277) until disease progression or unacceptable toxicity or ipilimumab 3 mg/kg every 3 weeks for 4 doses unless discontinued earlier for disease progression or unacceptable toxicity (n=256) *[see Clinical Studies (14.1)]*. Patients with autoimmune disease, a medical condition that required systemic corticosteroids or other immunosuppressive medication; a history of interstitial lung disease; or active infection requiring therapy, including HIV or hepatitis B or C, were ineligible.

The median duration of exposure was 5.6 months (range: 1 day to 11.0 months) for KEYTRUDA and similar in both treatment arms. Fifty-one and 46% of patients received KEYTRUDA 10 mg/kg every 2 or 3 weeks, respectively, for ≥6 months. No patients in either arm received treatment for more than one year.

The study population characteristics were: median age of 62 years (range: 18 to 89 years), 60% male, 98% White, 32% had an elevated lactate dehydrogenase (LDH) value at baseline, 65% had M1c stage disease, 9% with history of brain metastasis, and approximately 36% had been previously treated with one or more lines of systemic therapy which included a BRAF inhibitor (15%), chemotherapy (13%), and immunotherapy (6%).

In Trial 6, the adverse reaction profile was similar for the every 2 week and every 3 week schedule, therefore summary safety results are provided in a pooled analysis (n=555) of both KEYTRUDA arms. Adverse reactions leading to permanent discontinuation of KEYTRUDA occurred in 9% of patients. Adverse reactions leading to discontinuation of KEYTRUDA in more than one patient were colitis (1.4%), autoimmune hepatitis (0.7%), allergic reaction (0.4%), polyneuropathy (0.4%), and cardiac failure (0.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 21% of patients; the most common (≥1%) was diarrhea (2.5%). The most common adverse reactions (reported in at least 20% of patients) were fatigue and diarrhea. Table 1 and Table 2 summarize the incidence of selected adverse reactions and laboratory abnormalities, respectively, that occurred in at least 10% of patients receiving KEYTRUDA.

**Table 1: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA (Trial 6)**

| | KEYTRUDA 10 mg/kg every 2 or 3 weeks n=555 | | Ipilimumab n=256 | |
|---|---|---|---|---|
| **Adverse Reaction** | **All Grades† (%)** | **Grade 3-4 (%)** | **All Grades (%)** | **Grade 3-4 (%)** |
| **General Disorders and Administration Site Conditions** | | | | |
| Fatigue | 28 | 0.9 | 28 | 3.1 |
| **Skin and Subcutaneous Tissue Disorders** | | | | |
| Rash‡ | 24 | 0.2 | 23 | 1.2 |
| Vitiligo§ | 13 | 0 | 2 | 0 |
| **Musculoskeletal and Connective Tissue Disorders** | | | | |
| Arthralgia | 18 | 0.4 | 10 | 1.2 |
| Back pain | 12 | 0.9 | 7 | 0.8 |
| **Respiratory, Thoracic and Mediastinal Disorders** | | | | |
| Cough | 17 | 0 | 7 | 0.4 |
| Dyspnea | 11 | 0.9 | 7 | 0.8 |
| **Metabolism and Nutrition Disorders** | | | | |
| Decreased appetite | 16 | 0.5 | 14 | 0.8 |
| **Nervous System Disorders** | | | | |
| Headache | 14 | 0.2 | 14 | 0.8 |

* Adverse reactions occurring at same or higher incidence than in the ipilimumab arm
† Graded per NCI CTCAE v4.0
‡ Includes rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, and exfoliative rash.
§ Includes skin hypopigmentation

Other clinically important adverse reactions occurring in ≥10% of patients receiving KEYTRUDA were diarrhea (26%), nausea (21%), and pruritus (17%).

**Table 2: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA (Trial 6)**

| | KEYTRUDA 10 mg/kg every 2 or 3 weeks | | Ipilimumab | |
|---|---|---|---|---|
| **Laboratory Test†** | **All Grades‡ %** | **Grades 3-4 %** | **All Grades %** | **Grades 3-4 %** |
| **Chemistry** | | | | |
| Hyperglycemia | 45 | 4.2 | 45 | 3.8 |
| Hypertriglyceridemia | 43 | 2.6 | 31 | 1.1 |
| Hyponatremia | 28 | 4.6 | 26 | 7 |
| Increased AST | 27 | 2.6 | 25 | 2.5 |
| Hypercholesterolemia | 20 | 1.2 | 13 | 0 |
| **Hematology** | | | | |
| Anemia | 35 | 3.8 | 33 | 4.0 |
| Lymphopenia | 33 | 7 | 25 | 6 |

* Laboratory abnormalities occurring at same or higher incidence than in ipilimumab arm
† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (520 to 546 patients) and ipilimumab (237 to 247 patients); hypertriglyceridemia: KEYTRUDA n=429 and ipilimumab n=183; hypercholesterolemia: KEYTRUDA n=484 and ipilimumab n=205).
‡ Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥20% of patients receiving KEYTRUDA were increased hypoalbuminemia (27% all Grades; 2.4% Grades 3-4), increased ALT (23% all Grades; 3.1% Grades 3-4), and increased alkaline phosphatase (21% all Grades, 2.0% Grades 3-4).

*Ipilimumab-Refractory Melanoma (Trial 2)*
The safety of KEYTRUDA in patients with unresectable or metastatic melanoma with disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor, was evaluated in Trial 2. Trial 2 was a multicenter, partially blinded (KEYTRUDA dose), randomized (1:1:1), active-controlled trial in which 528 patients received KEYTRUDA 2 mg/kg (n=178) or 10 mg/kg (n=179) every 3 weeks or investigator's choice of chemotherapy (n=171), consisting of dacarbazine (26%), temozolomide (25%), paclitaxel and carboplatin (25%), paclitaxel (16%), or carboplatin (8%) *[see Clinical Studies (14.1)]*. The trial excluded patients with autoimmune disease, severe immune-related toxicity related to ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks; medical conditions that required systemic corticosteroids or other immunosuppressive medication; a history of interstitial lung disease; or an active infection requiring therapy, including HIV or hepatitis B or C.

The median duration of exposure to KEYTRUDA 2 mg/kg every 3 weeks was 3.7 months (range: 1 day to 16.6 months) and to KEYTRUDA 10 mg/kg every 3 weeks was 4.8 months (range: 1 day to 16.8 months). The data described below reflect exposure to KEYTRUDA 2 mg/kg in 36% of patients exposed to KEYTRUDA for ≥6 months and in 4% of patients exposed for ≥12 months. In the KEYTRUDA 10 mg/kg arm, 41% of patients were exposed to KEYTRUDA for ≥6 months and 6% of patients were exposed to KEYTRUDA for ≥12 months.

The study population characteristics were: median age of 62 years (range: 15 to 89 years), 61% male, 98% White, 41% with an elevated LDH value at baseline, 83% with M1c stage disease, 73% received two or more prior therapies for advanced or metastatic disease (100% received ipilimumab and 25% a BRAF inhibitor), and 15% with history of brain metastasis.

In Trial 2, the adverse reaction profile was similar for the 2 mg/kg dose and 10 mg/kg dose, therefore summary safety results are provided in a pooled analysis (n=357) of both KEYTRUDA arms. Adverse reactions resulting in permanent discontinuation occurred in 12% of patients receiving KEYTRUDA; the most common (≥1%) were general physical health deterioration (1%), asthenia (1%), dyspnea (1%), pneumonitis (1%), and generalized edema (1%). Adverse reactions leading to interruption of KEYTRUDA occurred in 14% of patients; the most common (≥1%) were dyspnea (1%), diarrhea (1%), and maculo-papular rash (1%). The most common adverse reactions (reported in at least 20% of patients) of KEYTRUDA were fatigue, pruritus, rash, constipation, nausea, diarrhea, and decreased appetite.

Table 3 summarizes the incidence of adverse reactions occurring in at least 10% of patients receiving KEYTRUDA.

**Table 3: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA (Trial 2)**

| | KEYTRUDA 2 mg/kg or 10 mg/kg every 3 weeks n=357 | | Chemotherapy† n=171 | |
|---|---|---|---|---|
| **Adverse Reaction** | **All Grades‡ (%)** | **Grade 3-4 (%)** | **All Grades (%)** | **Grade 3-4 (%)** |
| **General Disorders and Administration Site Conditions** | | | | |
| Pyrexia | 14 | 0.3 | 9 | 0.6 |
| Asthenia | 10 | 2.0 | 9 | 1.8 |
| **Skin and Subcutaneous Tissue Disorders** | | | | |
| Pruritus | 28 | 0 | 8 | 0 |
| Rash§ | 24 | 0.6 | 8 | 0 |
| **Gastrointestinal Disorders** | | | | |
| Constipation | 22 | 0.3 | 20 | 2.3 |
| Diarrhea | 20 | 0.8 | 20 | 2.3 |
| Abdominal pain | 13 | 1.7 | 8 | 1.2 |
| **Respiratory, Thoracic and Mediastinal Disorders** | | | | |
| Cough | 18 | 0 | 16 | 0 |
| **Musculoskeletal and Connective Tissue Disorders** | | | | |
| Arthralgia | 14 | 0.6 | 10 | 1.2 |

* Adverse reactions occurring at same or higher incidence than in chemotherapy arm
† Chemotherapy : dacarbazine, temozolomide, carboplatin plus paclitaxel, paclitaxel, or carboplatin
‡ Graded per NCI CTCAE v4.0
§ Includes rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, and rash pruritic

Other clinically important adverse reactions occurring in patients receiving KEYTRUDA were fatigue (43%), nausea (22%), decreased appetite (20%), vomiting (13%), and peripheral neuropathy (1.7%).

**Table 4: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA (Trial 2)**

| | KEYTRUDA 2 mg/kg or 10 mg/kg every 3 weeks | | Chemotherapy | |
|---|---|---|---|---|
| **Laboratory Test†** | **All Grades‡ %** | **Grades 3-4 %** | **All Grades %** | **Grades 3-4 %** |
| **Chemistry** | | | | |
| Hyperglycemia | 49 | 6 | 44 | 6 |
| Hypoalbuminemia | 37 | 1.9 | 33 | 0.6 |
| Hyponatremia | 37 | 7 | 24 | 3.8 |
| Hypertriglyceridemia | 33 | 0 | 32 | 0.9 |
| Increased Alkaline Phosphatase | 26 | 3.1 | 18 | 1.9 |
| Increased AST | 24 | 2.2 | 16 | 0.6 |
| Bicarbonate Decreased | 22 | 0.4 | 13 | 0 |
| Hypocalcemia | 21 | 0.3 | 18 | 1.9 |
| Increased ALT | 21 | 1.8 | 16 | 0.6 |

* Laboratory abnormalities occurring at same or higher incidence than in chemotherapy arm.
† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 320 to 325 patients) and chemotherapy (range: 154 to 161 patients); hypertriglyceridemia: KEYTRUDA n=247 and chemotherapy n=116; bicarbonate decreased: KEYTRUDA n=263 and chemotherapy n=123).
‡ Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥20% of patients receiving KEYTRUDA were anemia (44% all Grades; 10% Grades 3-4) and lymphopenia (40% all Grades; 9% Grades 3-4).

NSCLC

Among the 550 patients with metastatic NSCLC enrolled in Trial 1, the median duration of therapy was 2.8 months (range: 1 day to 25.6 months). Patients with NSCLC and autoimmune disease, a medical condition that required immunosuppression, or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible for Trial 1. The median age of patients was 64 years (range: 28 to 93), 47% were age 65 years or older, 53% were male, 83% were White, and 67% received two or more prior systemic treatments. Disease characteristics were Stage III (4%), Stage IV (96%), and brain metastases (11%). Baseline ECOG performance status (PS) was 0 (35%) or 1 (65%).

KEYTRUDA was discontinued due to adverse reactions in 14% of patients. Serious adverse reactions occurred in 38% of patients receiving KEYTRUDA. The most frequent serious adverse reactions reported in at least 2% of patients were pleural effusion, pneumonia, dyspnea, pulmonary embolism, and pneumonitis. The incidence of adverse reactions, including serious adverse reactions, was similar between the two 10 mg/kg dosing schedules; therefore, these data were pooled. The majority of patients treated with KEYTRUDA 2 mg/kg every three weeks had shorter follow-up compared with patients treated with the 10 mg/kg schedules; therefore, comparisons of adverse reactions between doses were not appropriate.

Table 5 summarizes adverse reactions that occurred in at least 10% of patients. The most common adverse reactions (reported in at least 20% of patients) were fatigue, decreased appetite, dyspnea, and cough.

**Table 5: Adverse Reactions in ≥10% of Patients with NSCLC (Trial 1)**

| | KEYTRUDA 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks n=550 | |
|---|---|---|
| **Adverse Reaction** | All Grades (%) | Grade 3* (%) |
| **General Disorders and Administration Site Conditions** | | |
| Fatigue† | 44 | 4 |
| Pyrexia | 12 | 1 |
| Peripheral Edema | 10 | 0 |
| **Metabolism and Nutrition Disorders** | | |
| Decreased appetite | 25 | 1 |
| **Respiratory, Thoracic and Mediastinal Disorders** | | |
| Dyspnea | 23 | 4 |
| Cough‡ | 29 | <1 |
| **Gastrointestinal Disorders** | | |
| Nausea | 18 | 1 |
| Diarrhea | 15 | 1 |
| Constipation | 15 | <1 |
| Vomiting | 12 | 1 |
| **Musculoskeletal and Connective Tissue Disorders** | | |
| Arthralgia | 15 | 1 |
| Back pain | 10 | 2 |
| **Blood and Lymphatic System Disorders** | | |
| Anemia | 12 | 2 |
| **Skin and Subcutaneous Tissue Disorders** | | |
| Pruritus | 12 | 0 |
| Rash§ | 18 | <1 |

* Of the ≥10% adverse reactions, none was reported as Grade 4 or 5.
† Includes the terms fatigue and asthenia
‡ Includes the terms cough, productive cough and hemoptysis
§ Includes the terms dermatitis, dermatitis acneiform, erythema multiforme, drug eruption, rash, rash generalized, rash pruritic, rash macular/maculo-papular, papular

**Table 6: Laboratory Abnormalities Worsened from Baseline in ≥20% of Patients with NSCLC (Trial 1)**

| | KEYTRUDA n=550 | |
|---|---|---|
| **Laboratory Test** | **All Grades %** | **Grades 3-4 %** |
| **Chemistry** | | |
| Hyperglycemia | 48 | 3* |
| Hyponatremia | 38 | 6 |
| Hypoalbuminemia | 32 | 1 |
| Increased alkaline phosphatase | 26 | 1 |
| Hypertriglyceridemia | 23 | 0 |
| Increased aspartate aminotransferase | 20 | 1 |
| Hypercholesterolemia | 20 | 1* |
| **Hematology** | | |
| Anemia | 36 | 2* |

* Grade 4 abnormalities in this table limited to hyperglycemia (n=4), hypercholesterolemia (n=3), and anemia (n=1).

### 6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. Trough levels of pembrolizumab interfere with the electrochemiluminescent (ECL) assay results; therefore, a subset analysis was performed in the patients with a concentration of pembrolizumab below the drug tolerance level of the anti-product antibody assay. In clinical studies in patients treated with pembrolizumab at a dose of 2 mg/kg every 3 weeks or 10 mg/kg every two or three weeks, 1 (0.3%) of 392 evaluable patients tested positive for treatment-emergent anti-pembrolizumab antibodies and confirmed positive in the neutralizing assay.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to KEYTRUDA with the incidences of antibodies to other products may be misleading.

## 7 DRUG INTERACTIONS

No formal pharmacokinetic drug interaction studies have been conducted with KEYTRUDA.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. In animal models, the PD-1/PD-L1 signaling pathway is important in the maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue *[see Data]*. Human IgG4 (immunoglobulins) are known to cross the placenta; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. There are no available human data informing the risk of embryo-fetal toxicity. Apprise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

*Animal Data*

Animal reproduction studies have not been conducted with KEYTRUDA to evaluate its effect on reproduction and fetal development, but an assessment of the effects on reproduction was provided. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering KEYTRUDA during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 knockout mice. Based on its mechanism of action, fetal exposure to pembrolizumab may increase the risk of developing immune-mediated disorders or of altering the normal immune response.

### 8.2 Lactation

Risk Summary

It is not known whether KEYTRUDA is excreted in human milk. No studies have been conducted to assess the impact of KEYTRUDA on milk production or its presence in breast milk. Because many drugs are excreted in human milk, instruct women to discontinue nursing during treatment with KEYTRUDA and for 4 months after the final dose.

### 8.3 Females and Males of Reproductive Potential

Contraception

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.1)].* Advise females of reproductive potential to use effective contraception during treatment with KEYTRUDA and for at least 4 months following the final dose.

### 8.4 Pediatric Use
Safety and effectiveness of KEYTRUDA have not been established in pediatric patients.

### 8.5 Geriatric Use
Of the 2117 patients with melanoma or NSCLC treated with KEYTRUDA, 43% were 65 years and over. No overall differences in safety or efficacy were reported between elderly patients and younger patients.

### 8.6 Renal Impairment
Based on a population pharmacokinetic analysis, no dose adjustment is needed for patients with renal impairment *[see Clinical Pharmacology (12.3)].*

### 8.7 Hepatic Impairment
Based on a population pharmacokinetic analysis, no dose adjustment is needed for patients with mild hepatic impairment [total bilirubin (TB) less than or equal to ULN and AST greater than ULN or TB greater than 1 to 1.5 times ULN and any AST]. KEYTRUDA has not been studied in patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe (TB greater than 3 times ULN and any AST) hepatic impairment *[see Clinical Pharmacology (12.3)].*

## 10 OVERDOSAGE

There is no information on overdosage with KEYTRUDA.

## 11 DESCRIPTION

Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

KEYTRUDA for injection is a sterile, preservative-free, white to off-white lyophilized powder in single-use vials. Each vial is reconstituted and diluted for intravenous infusion. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab and is formulated in L-histidine (3.1 mg), polysorbate 80 (0.4 mg), and sucrose (140 mg). May contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5.

KEYTRUDA injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action
Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

### 12.3 Pharmacokinetics
The pharmacokinetics of pembrolizumab was studied in 2195 patients who received doses of 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks. Based on population pharmacokinetic analyses

in patients with solid tumors, the geometric mean [% coefficient of variation (CV%)] for clearance, steady-state volume of distribution, and terminal half-life were 202 mL/day (37%), 7.38 L (19%) and 27 days (38%), respectively.

Steady-state concentrations of pembrolizumab were reached by 19 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.2-fold. The peak concentration ($C_{max}$), trough concentration ($C_{min}$), and area under the plasma concentration versus time curve at steady state ($AUC_{ss}$) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

*Specific Populations*: The effects of various covariates on the pharmacokinetics of pembrolizumab were assessed in population pharmacokinetic analyses. The CL of pembrolizumab increased with increasing body weight; the resulting exposure differences were adequately addressed by the administration of a weight-based dose. The following factors had no clinically important effect on the CL of pembrolizumab: age (range: 15 to 94 years), gender, race, renal impairment, mild hepatic impairment, or tumor burden.

*Renal Impairment*: The effect of renal impairment on the CL of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with various solid tumors and mild (eGFR 60 to 89 mL/min/1.73 $m^2$; n=937), moderate (eGFR 30 to 59 mL/min/1.73 $m^2$; n=201), or severe (eGFR 15 to 29 mL/min/1.73 $m^2$; n=4) renal impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1.73 $m^2$; n=1027) renal function. No clinically important differences in the CL of pembrolizumab were found between patients with renal impairment and patients with normal renal function *[see Use in Specific Populations (8.6)].*

*Hepatic Impairment*: The effect of hepatic impairment on the CL of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with various solid tumors and mild hepatic impairment (TB less than or equal to ULN and AST greater than ULN or TB between 1 and 1.5 times ULN and any AST; n=269) compared to patients with normal hepatic function (TB and AST less than or equal to ULN; n=1871). No clinically important differences in the CL of pembrolizumab were found between patients with mild hepatic impairment and normal hepatic function. There is insufficient information to determine whether there are clinically important differences in the CL of pembrolizumab in patients with moderate or severe hepatic impairment *[see Use in Specific Populations (8.7)].*

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to test the potential of pembrolizumab for carcinogenicity or genotoxicity.

Fertility studies have not been conducted with pembrolizumab. In 1-month and 6-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

### 13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-1 signaling resulted in an increased severity of some infections and enhanced inflammatory responses. M. tuberculosis-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus (LCMV). Administration of pembrolizumab in chimpanzees with naturally occurring chronic hepatitis B infection resulted in two out of four animals with significantly increased levels of serum ALT, AST, and GGT, which persisted for at least 1 month after discontinuation of pembrolizumab.

## 14 CLINICAL STUDIES

### 14.1 Melanoma

*Ipilimumab-Naive Melanoma (Trial 6)*
The safety and efficacy of KEYTRUDA were evaluated in Trial 6, a randomized (1:1:1), open-label, multicenter, active-controlled trial. Patients were randomized to receive KEYTRUDA at a dose of 10 mg/kg every 2 weeks or 10mg/kg every 3 weeks as an intravenous infusion until disease progression or unacceptable toxicity or to ipilimumab 3 mg/kg every 3 weeks as an intravenous infusion for 4 doses unless discontinued earlier for disease progression or unacceptable toxicity. Patients with disease progression could receive additional doses of treatment unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging. Randomization was stratified by line of therapy (0 vs. 1), ECOG PS (0 vs. 1), and PD-L1 expression (≥1% of tumor cells [positive] vs. <1% of tumor cells [negative]) according to an investigational use only (IUO) assay. Key eligibility criteria were unresectable or metastatic melanoma with progression of disease; no prior ipilimumab; and no more than one prior systemic treatment for metastatic melanoma. Patients with BRAF V600E mutation-positive melanoma were not required to have received prior BRAF inhibitor therapy. Patients with autoimmune disease; a medical condition that required immunosuppression; previous severe hypersensitivity to other monoclonal antibodies; and HIV, hepatitis B or hepatitis C infection, were ineligible. Assessment of tumor status was performed at 12 weeks, then every 6 weeks through Week 48, followed by every 12 weeks thereafter. The major efficacy outcome measures were overall survival (OS) and progression-free survival (PFS; as assessed by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors [RECIST v1.1]). Additional efficacy outcome measures were overall response rate (ORR) and response duration.

A total of 834 patients were randomized: 277 patients to the KEYTRUDA 10 mg/kg every 3 weeks arm, 279 to the KEYTRUDA 10 mg/kg every 2 weeks arm, and 278 to the ipilimumab arm. The study population characteristics were: median age of 62 years (range: 18 to 89 years), 60% male, 98% White, 66% had no prior systemic therapy for metastatic disease , 69% ECOG PS of 0, 80% had PD-L1 positive melanoma, 18% had PD-L1 negative melanoma, and 2% had unknown PD-L1 status using the IUO assay, 65% had M1c stage disease, 68% with normal LDH, 36% with reported BRAF mutation-positive melanoma, and 9% with a history of brain metastases. Among patients with BRAF mutation-positive melanoma, 139 (46%) were previously treated with a BRAF inhibitor.

The study demonstrated statistically significant improvements in OS and PFS for patients randomized to KEYTRUDA as compared to ipilimumab (Table 7 and Figure 1).

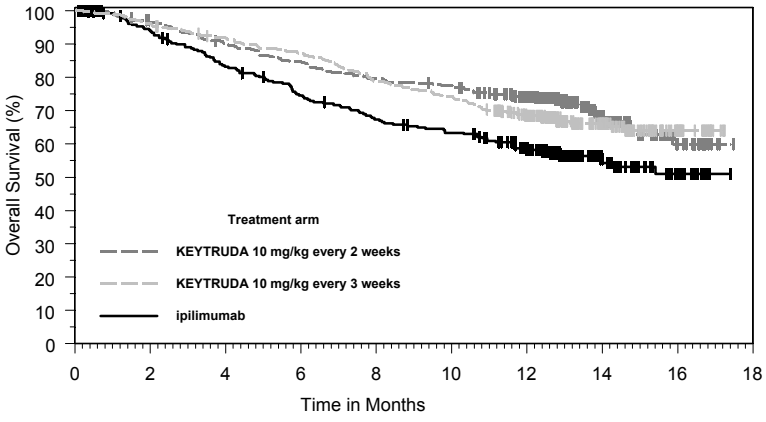
**Table 7: Efficacy Results in Trial 6**

| | KEYTRUDA 10 mg/kg every 3 weeks n=277 | KEYTRUDA 10 mg/kg every 2 weeks n=279 | Ipilimumab 3 mg/kg every 3 weeks n=278 |
|---|---|---|---|
| **OS** | | | |
| Deaths (%) | 92 (33%) | 85 (30%) | 112 (40%) |
| Hazard ratio* (95% CI) | 0.69 (0.52, 0.90) | 0.63 (0.47, 0.83) | --- |
| p-Value (stratified log-rank) | 0.004 | <0.001 | --- |
| **PFS by BICR** | | | |
| Events (%) | 157 (57%) | 157 (56%) | 188 (68%) |
| Median in months (95% CI) | 4.1 (2.9, 6.9) | 5.5 (3.4, 6.9) | 2.8 (2.8, 2.9) |
| Hazard ratio* (95% CI) | 0.58 (0.47, 0.72) | 0.58 (0.46, 0.72) | --- |
| p-Value (stratified log-rank) | <0.001 | <0.001 | --- |
| **Best overall response by BICR** | | | |
| ORR % (95% CI) | 33% (27, 39) | 34% (28, 40) | 12% (8, 16) |
| Complete response % | 6% | 5% | 1% |
| Partial response % | 27% | 29% | 10% |

* Hazard ratio (KEYTRUDA compared to ipilimumab) based on the stratified Cox proportional hazard model

Among the 91 patients randomized to KEYTRUDA 10 mg/kg every 3 weeks with an objective response, response durations ranged from 1.4+ to 8.1+ months. Among the 94 patients randomized to KEYTRUDA 10 mg/kg every 2 weeks with an objective response, response durations ranged from 1.4+ to 8.2 months.

**Figure 1: Kaplan-Meier Curve for Overall Survival in Trial 6**




| Number at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| KEYTRUDA 10 mg/kg every 2 weeks: | 279 | 266 | 248 | 233 | 219 | 212 | 177 | 67 | 19 | 0 |
| KEYTRUDA 10 mg/kg every 3 weeks: | 277 | 266 | 251 | 238 | 215 | 202 | 158 | 71 | 18 | 0 |
| ipilimumab: | 278 | 242 | 212 | 188 | 169 | 157 | 117 | 51 | 17 | 0 |

*Ipilimumab-Refractory Melanoma (Trial 2)*

The safety and efficacy of KEYTRUDA were evaluated in Trial 2, a multicenter, randomized (1:1:1), active-controlled trial. Patients were randomized to receive one of two doses of KEYTRUDA in a blinded fashion or investigator's choice chemotherapy. The treatment arms consisted of KEYTRUDA 2 mg/kg or 10 mg/kg intravenously every 3 weeks or investigator's choice of any of the following chemotherapy regimens: dacarbazine 1000 mg/m$^2$ intravenously every 3 weeks (26%), temozolomide 200 mg/m$^2$ orally once daily for 5 days every 28 days (25%), carboplatin AUC 6 intravenously plus paclitaxel 225 mg/m$^2$ intravenously every 3 weeks for four cycles then carboplatin AUC of 5 plus paclitaxel 175 mg/m$^2$ every 3 weeks (25%), paclitaxel 175 mg/m$^2$ intravenously every 3 weeks (16%), or carboplatin AUC 5 or 6 intravenously every 3 weeks (8%). Randomization was stratified by ECOG performance status (0 vs. 1), LDH levels (normal vs. elevated [≥110% ULN]) and BRAF V600 mutation status (wild-type [WT] or

V600E). The trial included patients with unresectable or metastatic melanoma with progression of disease; refractory to two or more doses of ipilimumab (3 mg/kg or higher) and, if BRAF V600 mutation-positive, a BRAF or MEK inhibitor; and disease progression within 24 weeks following the last dose of ipilimumab. The trial excluded patients with uveal melanoma and active brain metastasis. Patients received KEYTRUDA until unacceptable toxicity; disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging; withdrawal of consent; or physician's decision to stop therapy for the patient. Assessment of tumor status was performed at 12 weeks after randomization, then every 6 weeks through week 48, followed by every 12 weeks thereafter. Patients on chemotherapy who experienced progression of disease were offered KEYTRUDA. The major efficacy outcomes were progression-free survival (PFS) as assessed by BICR per RECIST v1.1 and overall survival (OS). Additional efficacy outcome measures were confirmed overall response rate (ORR) as assessed by BICR per RECIST v1.1 and duration of response.

The treatment arms consisted of KEYTRUDA 2 mg/kg (n=180) or 10 mg/kg (n=181) every 3 weeks or investigator's choice chemotherapy (n=179). Among the 540 randomized patients, the median age was 62 years (range: 15 to 89 years), with 43% age 65 or older; 61% male; 98% White; and ECOG performance score was 0 (55%) and 1 (45%). Twenty-three percent of patients were BRAF V600 mutation positive, 40% had elevated LDH at baseline, 82% had M1c disease, and 73% had two or more prior therapies for advanced or metastatic disease.

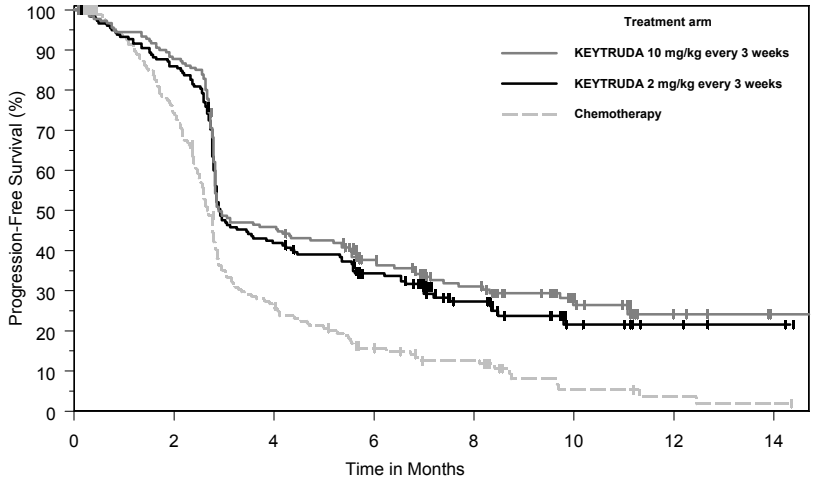
The study demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA as compared to control arm (Table 8). There was no statistically significant difference between KEYTRUDA 2 mg/kg and chemotherapy or between KEYTRUDA 10 mg/kg and chemotherapy in the interim OS analysis with 220 deaths (59% of required events for the final analysis).

**Table 8: Efficacy Results in Trial 2**

| | KEYTRUDA 2 mg/kg every 3 weeks n=180 | KEYTRUDA 10 mg/kg every 3 weeks n=181 | Chemotherapy n=179 |
|---|---|---|---|
| **Progression-Free Survival** | | | |
| Number of Events, n (%) | 129 (72%) | 126 (70%) | 155 (87%) |
| Progression, n (%) | 105 (58%) | 107 (59%) | 134 (75%) |
| Death, n (%) | 24 (13%) | 19 (10%) | 21 (12%) |
| Median in months (95% CI) | 2.9 (2.8, 3.8) | 2.9 (2.8, 4.7) | 2.7 (2.5, 2.8) |
| P Value (stratified log-rank) | <0.001 | <0.001 | --- |
| Hazard ratio* (95% CI) | 0.57 (0.45, 0.73) | 0.50 (0.39, 0.64) | --- |
| **Objective Response Rate** | | | |
| ORR, n% (95% CI) | 21% (15, 28) | 25% (19, 32) | 4% (2, 9) |
| Complete response % | 2% | 3% | 0% |
| Partial response % | 19% | 23% | 4% |

* Hazard ratio (KEYTRUDA compared to chemotherapy) based on the stratified Cox proportional hazard model

**Figure 2: Kaplan-Meier Curve for Progression-Free Survival in Trial 2**




Number at Risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| KEYTRUDA 10 mg/kg: | 181 | 158 | 82 | 55 | 39 | 15 | 5 | 1 |
| KEYTRUDA 2 mg/kg: | 180 | 153 | 74 | 53 | 26 | 9 | 4 | 2 |
| Chemotherapy: | 179 | 128 | 43 | 22 | 15 | 4 | 2 | 1 |

Among the 38 patients randomized to KEYTRUDA 2 mg/kg with an objective response, response durations ranged from 1.3+ to 11.5+ months. Among the 46 patients randomized to KEYTRUDA 10 mg/kg with an objective response, response durations ranged from 1.1+ to 11.1+ months.

### 14.2 Non-Small Cell Lung Cancer

The efficacy of KEYTRUDA was investigated in a sub-group of a cohort of 280 patients enrolled in a multicenter, open-label multi-cohort, activity-estimating study (Trial 1). The cohort consisted of patients with metastatic NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for ALK or EGFR mutations and any evidence of PD-L1 expression by a clinical trial immunohistochemistry assay. Patients with autoimmune disease; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible.

A prospectively defined sub-group was retrospectively analyzed using an analytically validated test for PD-L1 expression tumor proportion score (TPS). This retrospectively identified sub-group of 61 patients accounts for 22% of the 280 patients in the cohort. Patients included in this sub-group had a PD-L1

expression TPS of greater than or equal to 50% tumor cells as determined by the PD-L1 IHC 22C3 pharmDx Kit. Patients received KEYTRUDA 10 mg/kg every 2 (n=27) or 3 (n=34) weeks until unacceptable toxicity or disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging. Assessment of tumor status was performed every 9 weeks. The major efficacy outcome measures were ORR according to RECIST 1.1 as assessed by BICR and duration of response.

Among the 61 patients with a TPS greater than or equal to 50%, the baseline characteristics were: median age 60 years (34% age 65 or older); 61% male; 79% White; and 34% and 64% with an ECOG PS 0 and 1, respectively. Disease characteristics were squamous (21%) and non-squamous (75%); M1 (98%); brain metastases (11%); one (26%), two (30%), or three or more (44%) prior therapies; and the incidence of genomic aberrations was EGFR (10%) or ALK (0%).

Efficacy results are summarized in Table 9. The ORR and duration of response were similar regardless of schedule (every 2 weeks or every 3 weeks) and thus the data below are pooled.

**Table 9: Efficacy Results**

| **Endpoint** | n=61 |
|---|---|
| **Overall Response Rate** | |
| ORR %, (95% CI) | 41% (29, 54) |
| Complete Response | 0% |
| Partial Response | 41% |

Among the 25 responding patients, 21 (84%) patients had ongoing responses at the final analysis of ORR; 11 (44%) patients had ongoing responses of 6 months or longer.

In a separate subgroup of 25 patients with limited follow-up with PD-L1 expression TPS greater than or equal to 50% receiving KEYTRUDA at a dose of 2 mg/kg every 3 weeks in Trial 1, activity was also observed.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

KEYTRUDA for injection (lyophilized powder): carton containing one 50 mg single-use vial (NDC 0006-3029-02).

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F).

KEYTRUDA injection (solution): carton containing one 100 mg/4 mL (25 mg/mL), single-use vial (NDC 0006-3026-02)

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

- Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA, including:
  - Pneumonitis: Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.
  - Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (5.2)]*.
  - Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding *[see Warnings and Precautions (5.3)]*.

- Hypophysitis: Advise patients to contact their healthcare provider immediately for persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes *[see Warnings and Precautions (5.4)]*.
- Hyperthyroidism and Hypothyroidism: Advise patients to contact their healthcare provider immediately for signs or symptoms of hyperthyroidism and hypothyroidism *[see Warnings and Precautions (5.4)]*.
- Type 1 Diabetes Mellitus: Advise patients to contact their healthcare provider immediately for signs or symptoms of type 1 diabetes *[see Warnings and Precautions (5.4)]*.
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis *[see Warnings and Precautions (5.5)]*.

- Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.7)]*.
- Advise patients of the importance of keeping scheduled appointments for blood work or other laboratory tests *[see Warnings and Precautions (5.3, 5.4, 5.5)]*.
- Advise women that KEYTRUDA can cause fetal harm. Instruct women of reproductive potential to use highly effective contraception during and for 4 months after the last dose of KEYTRUDA *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.1, 8.3)]*.
- Advise nursing mothers not to breastfeed while taking KEYTRUDA and for 4 months after the final dose *[see Use in Specific Populations (8.2)]*.

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U.S. License No. 0002

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For KEYTRUDA injection, at:
MSD Ireland (Carlow)
County Carlow, Ireland

For patent information: www.merck.com/product/patent/home.html

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## Appendix 7. RECIST 1.1 Guidelines

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# New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)

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ABSTRACT

*Background:* Assessment of the change in tumour burden is an important feature of the clinical evaluation of cancer therapeutics: both tumour shrinkage (objective response) and disease progression are useful endpoints in clinical trials. Since RECIST was published in 2000, many investigators, cooperative groups, industry and government authorities have adopted these criteria in the assessment of treatment outcomes. However, a number of questions and issues have arisen which have led to the development of a revised RECIST guideline (version 1.1). Evidence for changes, summarised in separate papers in this special issue, has come from assessment of a large data warehouse (>6500 patients), simulation studies and literature reviews.

*Highlights of revised RECIST 1.1:* Major changes include: *Number of lesions to be assessed*: based on evidence from numerous trial databases merged into a data warehouse for analysis purposes, the number of lesions required to assess tumour burden for response determination has been reduced from a maximum of 10 to a maximum of five total (and from five to two per organ, maximum). *Assessment of pathological lymph* nodes is now incorporated: nodes with a *short* axis of $\geqslant$15 mm are considered measurable and assessable as target lesions. The short axis measurement should be included in the sum of lesions in calculation of tumour response. Nodes that shrink to <10 mm short axis are considered normal. *Confirmation of response* is required for trials with response primary endpoint but is no longer required in randomised studies since the control arm serves as appropriate means of interpretation of data. *Disease progression* is clarified in several aspects: in addition to the previous definition of progression in target disease of 20% increase in sum, a 5 mm absolute increase is now required as well to guard against over calling PD when the total sum is very

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small. Furthermore, there is guidance offered on what constitutes 'unequivocal progression' of non-measurable/non-target disease, a source of confusion in the original RECIST guideline. Finally, a section on detection of new lesions, including the interpretation of FDG-PET scan assessment is included. *Imaging guidance*: the revised RECIST includes a new imaging appendix with updated recommendations on the optimal anatomical assessment of lesions.

*Future work:* A key question considered by the RECIST Working Group in developing RECIST 1.1 was whether it was appropriate to move from anatomic unidimensional assessment of tumour burden to either volumetric anatomical assessment or to functional assessment with PET or MRI. It was concluded that, at present, there is not sufficient standardisation or evidence to abandon anatomical assessment of tumour burden. The only exception to this is in the use of FDG-PET imaging as an adjunct to determination of progression. As is detailed in the final paper in this special issue, the use of these promising newer approaches requires appropriate clinical validation studies.

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## 1. Background

### 1.1. History of RECIST criteria

Assessment of the change in tumour burden is an important feature of the clinical evaluation of cancer therapeutics. Both tumour shrinkage (objective response) and time to the development of disease progression are important endpoints in cancer clinical trials. The use of tumour regression as the endpoint for phase II trials screening new agents for evidence of anti-tumour effect is supported by years of evidence suggesting that, for many solid tumours, agents which produce tumour shrinkage in a proportion of patients have a reasonable (albeit imperfect) chance of subsequently demonstrating an improvement in overall survival or other time to event measures in randomised phase III studies (reviewed in [1–4]). At the current time objective response carries with it a body of evidence greater than for any other biomarker supporting its utility as a measure of promising treatment effect in phase II screening trials. Furthermore, at both the phase II and phase III stage of drug development, clinical trials in advanced disease settings are increasingly utilising time to progression (or progression-free survival) as an endpoint upon which efficacy conclusions are drawn, which is also based on anatomical measurement of tumour size.

However, both of these tumour endpoints, objective response and time to disease progression, are useful only if based on widely accepted and readily applied standard criteria based on anatomical tumour burden. In 1981 the World Health Organisation (WHO) first published tumour response criteria, mainly for use in trials where tumour response was the primary endpoint. The WHO criteria introduced the concept of an overall assessment of tumour burden by summing the products of bidimensional lesion measurements and determined response to therapy by evaluation of change from baseline while on treatment.[5] However, in the decades that followed their publication, cooperative groups and pharmaceutical companies that used the WHO criteria often 'modified' them to accommodate new technologies or to address areas that were unclear in the original document. This led to confusion in interpretation of trial results[6] and in fact, the application of varying response criteria was shown to lead to very different conclusions about the efficacy of the same regimen.[7] In response to these problems, an International Working Party was formed in the mid 1990s to standardise and simplify response criteria. New criteria, known as RECIST (Response Evaluation Criteria in Solid Tumours), were published in 2000.[8] Key features of the original RECIST include definitions of minimum size of measurable lesions, instructions on how many lesions to follow (up to 10; a maximum five per organ site), and the use of unidimensional, rather than bidimensional, measures for overall evaluation of tumour burden. These criteria have subsequently been widely adopted by academic institutions, cooperative groups, and industry for trials where the primary endpoints are objective response or progression. In addition, regulatory authorities accept RECIST as an appropriate guideline for these assessments.

### 1.2. Why update RECIST?

Since RECIST was published in 2000, many investigators have confirmed in prospective analyses the validity of substituting unidimensional for bidimensional (and even three-dimensional)-based criteria (reviewed in [9]). With rare exceptions (e.g. mesothelioma), the use of unidimensional criteria seems to perform well in solid tumour phase II studies.

However, a number of questions and issues have arisen which merit answers and further clarity. Amongst these are whether fewer than 10 lesions can be assessed without affecting the overall assigned response for patients (or the conclusion about activity in trials); how to apply RECIST in randomised phase III trials where progression, not response, is the primary endpoint particularly if not all patients have measurable disease; whether or how to utilise newer imaging technologies such as FDG-PET and MRI; how to handle assessment of lymph nodes; whether response confirmation is truly needed; and, not least, the applicability of RECIST in trials of targeted non-cytotoxic drugs. This revision of the RECIST guidelines includes updates that touch on all these points.

### 1.3. *Process of RECIST 1.1 development*

The RECIST Working Group, consisting of clinicians with expertise in early drug development from academic research organisations, government and industry, together with imaging specialists and statisticians, has met regularly to set the agenda for an update to RECIST, determine the evidence needed to justify the various changes made, and to review emerging evidence. A critical aspect of the revision process was to create a database of prospectively documented solid tumour measurement data obtained from industry and academic group trials. This database, assembled at the EORTC Data Centre under the leadership of Jan Bogaerts and Patrick Therasse (co-authors of this guideline), consists of >6500 patients with >18,000 target lesions and was utilised to investigate the impact of a variety of questions (e.g. number of target lesions required, the need for response confirmation, and lymph node measurement rules) on response and progression-free survival outcomes. The results of this work, which after evaluation by the RECIST Working Group led to most of the changes in this revised guideline, are reported in detail in a separate paper in this special issue.[10] Larry Schwartz and Robert Ford (also co-authors of this guideline) also provided key databases from which inferences have been made that inform these revisions.[11]

The publication of this revised guideline is believed to be timely since it incorporates changes to simplify, optimise and standardise the assessment of tumour burden in clinical trials. A summary of key changes is found in Appendix I. Because the fundamental approach to assessment remains grounded in the anatomical, rather than functional, assessment of disease, we have elected to name this version RECIST 1.1, rather than 2.0.

### 1.4. *What about volumetric or functional assessment?*

This raises the question, frequently posed, about whether it is 'time' to move from anatomic unidimensional assessment of tumour burden to either volumetric anatomical assessment *or* to functional assessment (e.g. dynamic contrast enhanced MRI or CT or (18)F-fluorodeoxyglucose positron emission tomographic (FDG-PET) techniques assessing tumour metabolism). As can be seen, the Working Group and particularly those involved in imaging research, did not believe that there is at present sufficient standardisation and widespread availability to recommend adoption of these alternative assessment methods. The only exception to this is in the use of FDG-PET imaging as an adjunct to determination of progression, as described later in this guideline. As detailed in paper in this special issue[12], we believe that the use of these promising newer approaches (which could either *add to* or *substitute for* anatomical assessment as described in RECIST) requires appropriate and rigorous clinical validation studies. This paper by Sargent et al. illustrates the type of data that will be needed to be able to define 'endpoints' for these modalities and how to determine where and when such criteria/modalities can be used to improve the reliability with which truly active new agents are identified and truly inactive new agents are discarded in comparison to RECIST criteria in phase II screening trials. The RECIST Working Group looks forward to such data emerging in the next few years to allow the appropriate changes to the next iteration of the RECIST criteria.

## 2. Purpose of this guideline

This guideline describes a standard approach to solid tumour measurement and definitions for objective assessment of change in tumour size for use in adult and paediatric cancer clinical trials. It is expected these criteria will be useful in all trials where objective response is the primary study endpoint, as well as in trials where assessment of stable disease, tumour progression or time to progression analyses are undertaken, since all of these outcome measures are based on an assessment of anatomical tumour burden and its change on study. There are no assumptions in this paper about the proportion of patients meeting the criteria for any of these endpoints which will signal that an agent or treatment regimen is active: those definitions are dependent on type of cancer in which a trial is being undertaken and the specific agent(s) under study. Protocols must include appropriate statistical sections which define the efficacy parameters upon which the trial sample size and decision criteria are based. In addition to providing definitions and criteria for assessment of tumour response, this guideline also makes recommendations regarding standard reporting of the results of trials that utilise tumour response as an endpoint.

While these guidelines may be applied in malignant brain tumour studies, there are also separate criteria published for response assessment in that setting.[13] This guideline is *not* intended for use for studies of malignant lymphoma since international guidelines for response assessment in lymphoma are published separately.[14]

Finally, many oncologists in their daily clinical practice follow their patients' malignant disease by means of repeated imaging studies and make decisions about continued therapy on the basis of both objective and symptomatic criteria. It is not intended that these RECIST guidelines play a role in that decision making, except if determined appropriate by the treating oncologist.

## 3. Measurability of tumour at baseline

### 3.1. *Definitions*

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows:

#### 3.1.1. *Measurable*

*Tumour lesions*: Must be accurately measured in at least one dimension (*longest* diameter in the plane of measurement is to be recorded) with a *minimum* size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; see Appendix II on imaging guidance).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

*Malignant lymph nodes*: To be considered pathologically enlarged *and* measurable, a lymph node must be ⩾15 mm in *short* axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the *short* axis will be measured and followed (see Schwartz et al. in this Special Issue[15]). See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

#### 3.1.2. *Non-measurable*

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ⩾10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

#### 3.1.3. *Special considerations regarding lesion measurability*

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

*Bone lesions:*.

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

*Cystic lesions:*.

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

*Lesions with prior local treatment:*

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

### 3.2. *Specifications by methods of measurements*

#### 3.2.1. *Measurement of lesions*

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

#### 3.2.2. *Method of assessment*

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

*Clinical lesions:* Clinical lesions will only be considered measurable when they are superficial and ⩾10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

*Chest X-ray:* Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung. See Appendix II for more details.

*CT, MRI:* CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. As is described in Appendix II, when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). More details concerning the use of both CT and MRI for assessment of objective tumour response evaluation are provided in Appendix II.

*Ultrasound:* Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next (described in greater detail in Appendix II). If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

*Endoscopy, laparoscopy:* The utilisation of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

*Tumour markers:* Tumour markers *alone* cannot be used to assess *objective* tumour response. If markers are initially above

the upper normal limit, however, they must normalise for a patient to be considered in complete response. Because tumour markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published.[16–18] In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumour assessment for use in first-line trials in ovarian cancer.[19]

*Cytology, histology:* These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

## 4. Tumour response evaluation

### 4.1. *Assessment of overall tumour burden and measurable disease*

To assess objective response or future progression, it is necessary to estimate the *overall tumour burden at baseline* and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 3). In studies where the primary endpoint is tumour progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

### 4.2. *Baseline documentation of 'target' and 'non-target' lesions*

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a *maximum* of two and four lesions respectively will be recorded). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the article by Bogaerts et al.[10].

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. To illustrate this point see the example in Fig. 3 of Appendix II.

*Lymph nodes* merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. As noted in Section 3, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geqslant$15 mm by CT scan. Only the *short* axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement (See also the example in Fig. 4 in Appendix II). All other pathological nodes (those with short axis $\geqslant$10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*. If lymph nodes are to be included in the sum, then as noted above, only the *short* axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

### 4.3. *Response criteria*

This section provides the definitions of the criteria used to determine objective tumour response for target lesions.

#### 4.3.1. *Evaluation of target lesions*

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (*Note:* the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

#### 4.3.2. *Special notes on the assessment of target lesions*

*Lymph nodes*. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

*Target lesions that become 'too small to measure'*. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (*Note:* It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist *is* able to provide an actual measure, that should be recorded, even if it is below 5 mm.

*Lesions that split or coalesce on treatment*. As noted in Appendix II, when non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

#### 4.3.3. *Evaluation of non-target lesions*

This section provides the definitions of the criteria used to determine the tumour response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only *qualitatively* at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.

Progressive Disease (PD): *Unequivocal progression* (see comments below) of existing non-target lesions. (*Note:* the appearance of one or more new lesions is also considered progression).

#### 4.3.4. *Special notes on assessment of progression of non-target disease*

The concept of progression of non-target disease requires additional explanation as follows:

*When the patient also has measurable disease*. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy (see examples in Appendix II and further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression *solely* on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

*When the patient has only non-measurable disease*. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic

disease from localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. Some illustrative examples are shown in Figs. 5 and 6 in Appendix II. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

#### 4.3.5. *New lesions*

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive[1] FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up:
   If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
   If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
   If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

[1] A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

### 4.4. *Evaluation of best overall response*

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement (see Section 4.6). Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

#### 4.4.1. *Time point response*

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 on the next page provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

#### 4.4.2. *Missing assessments and inevaluable designation*

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

#### 4.4.3. *Best overall response: all time points*

The *best overall response* is determined once all the data for the patient is known.

*Best response determination in trials where confirmation of complete or partial response IS NOT required*: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

**Table 1 – Time point response: patients with target (+/– non-target) disease.**

| Target lesions | Non-target lesions | New lesions | Overall response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/non-PD | No | PR |
| CR | Not evaluated | No | PR |
| PR | Non-PD or not all evaluated | No | PR |
| SD | Non-PD or not all evaluated | No | SD |
| Not all evaluated | Non-PD | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

**Table 2 – Time point response: patients with non-target disease only.**

| Non-target lesions | New lesions | Overall response |
|---|---|---|
| CR | No | CR |
| Non-CR/non-PD | No | Non-CR/non-PD[a] |
| Not all evaluated | No | NE |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

*Best response determination in trials where confirmation of complete or partial response IS required*: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

#### 4.4.4. *Special notes on response assessment*

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is *not* a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine

**Table 3 – Best overall response when confirmation of CR and PR required.**

| Overall response First time point | Overall response Subsequent time point | BEST overall response |
|---|---|---|
| CR | CR | CR |
| CR | PR | SD, PD or PR[a] |
| CR | SD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | NE | SD provided minimum criteria for SD duration met, otherwise NE |
| PR | CR | PR |
| PR | PR | PR |
| PR | SD | SD |
| PR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| PR | NE | SD provided minimum criteria for SD duration met, otherwise NE |
| NE | NE | NE |

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

a If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

### 4.5. *Frequency of tumour re-evaluation*

Frequency of tumour re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumour type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumour evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (e.g. time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomised comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

### 4.6. *Confirmatory measurement/duration of response*

#### 4.6.1. *Confirmation*

In non-randomised trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials (see the paper by Bogaerts et al. in this Special Issue[10]). However, in all other circumstances, i.e. in randomised trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

#### 4.6.2. *Duration of overall response*

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

#### 4.6.3. *Duration of stable disease*

Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the criteria for progression are met, taking as reference the *smallest sum on study* (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

*Note*: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

### 4.7. *Progression-free survival/proportion progression-free*

#### 4.7.1. *Phase II trials*

This guideline is focused primarily on the use of objective response endpoints for phase II trials. In some circumstances, 'response rate' may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases 'progression-free survival' (PFS) or the 'proportion progression-free' at landmark time points, might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled trial, these measures are subject to criticism since an apparently promising observation may be related to biological factors such as patient selection and not the impact of the intervention. Thus, phase II screening trials utilising these endpoints are best designed with a randomised control. Exceptions may exist

where the behaviour patterns of certain cancers are so consistent (and usually consistently poor), that a non-randomised trial is justifiable (see for example van Glabbeke et al.[20]). However, in these cases it will be essential to document with care the basis for estimating the expected PFS or proportion progression-free in the absence of a treatment effect.

#### 4.7.2. *Phase III trials*

Phase III trials in advanced cancers are increasingly designed to evaluate progression-free survival or time to progression as the primary outcome of interest. Assessment of progression is relatively straightforward if the protocol requires all patients to have measurable disease. However, restricting entry to this subset of patients is subject to criticism: it may result in a trial where the results are less likely to be generalisable if, in the disease under study, a substantial proportion of patients would be excluded. Moreover, the restriction to entry will slow recruitment to the study. Increasingly, therefore, trials allow entry of both patients with measurable disease as well as those with non-measurable disease only. In this circumstance, care must be taken to explicitly describe the findings which would qualify for progressive disease for those patients *without* measurable lesions. Furthermore, in this setting, protocols must indicate if the maximum number of recorded target lesions for those patients with measurable disease may be relaxed from five to three (based on the data found in Bogaerts et al.[10] and Moskowitz et al.[11]). As found in the 'special notes on assessment of progression', these guidelines offer recommendations for assessment of progression in this setting. Furthermore, if available, validated tumour marker measures of progression (as has been proposed for ovarian cancer) may be useful to integrate into the definition of progression. Centralised blinded review of imaging studies or of source imaging reports to verify 'unequivocal progression' may be needed if important drug development or drug approval decisions are to be based on the study outcome. Finally, as noted earlier, because the date of progression is subject to ascertainment bias, timing of investigations in study arms should be the same. The article by Dancey et al. in this special issue[21] provides a more detailed discussion of the assessment of progression in randomised trials.

### 4.8. *Independent review of response and progression*

For trials where *objective response* (CR + PR) is the primary endpoint, and in particular where key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomised trial, ideally reviewers should be blinded to treatment assignment. Simultaneous review of the patients' files and radiological images is the best approach.

Independent review of progression presents some more complex issues: for example, there are statistical problems with the use of central-review-based progression time in place of investigator-based progression time due to the potential introduction of informative censoring when the former precedes the latter. An overview of these factors and other lessons learned from independent review is provided in an article by Ford et al. in this special issue.[22]

### 4.9. *Reporting best response results*

#### 4.9.1. *Phase II trials*

When response is the primary endpoint, and thus all patients must have measurable disease to enter the trial, all patients included in the study must be accounted for in the report of the results, even if there are major protocol treatment deviations or if they are not evaluable. Each patient will be assigned one of the following categories:

1. Complete response
2. Partial response
3. Stable disease
4. Progression
5. Inevaluable for response: specify reasons (for example: early death, malignant disease; early death, toxicity; tumour assessments not repeated/incomplete; other (specify)).

Normally, all *eligible* patients should be included in the denominator for the calculation of the response rate for phase II trials (in some protocols it will be appropriate to include all treated patients). It is generally preferred that 95% two-sided confidence limits are given for the calculated response rate. Trial conclusions should be based on the response rate for all eligible (or all treated) patients and should *not* be based on a selected 'evaluable' subset.

#### 4.9.2. *Phase III trials*

Response evaluation in phase III trials may be an indicator of the relative anti-tumour activity of the treatments evaluated and is almost always a secondary endpoint. Observed differences in response rate may not predict the clinically relevant therapeutic benefit for the population studied. If objective response is selected as a primary endpoint for a phase III study (only in circumstances where a direct relationship between objective tumour response and a clinically relevant therapeutic benefit can be unambiguously demonstrated for the population studied), the same criteria as those applying to phase II trials should be used and all patients entered should have at least one measurable lesion.

In those many cases where response is a secondary endpoint and not all trial patients have measurable disease, the method for reporting overall best response rates must be pre-specified in the protocol. In practice, response rate may be reported using either an 'intent to treat' analysis (all randomised patients in the denominator) or an analysis where only the subset of patients with measurable disease at baseline are included. The protocol should clearly specify how response results will be reported, including any subset analyses that are planned.

The original version of RECIST suggested that in phase III trials one could write protocols using a 'relaxed' interpretation of the RECIST guidelines (for example, reducing the number of lesions measured) but this should no longer be done since these revised guidelines have been amended in such a way that it is clear how these criteria should be applied for all trials in which anatomical assessment of tumour response or progression are endpoints.

## Appendix I. Summary of major changes RECIST 1.0 to RECIST 1.1

| | RECIST 1.0 | RECIST 1.1 | Rationale | Reference in special issue (if applicable) |
|---|---|---|---|---|
| Minimum size measurable lesions | CT: 10 mm spiral<br>20 mm non-spiral | CT 10 mm; delete reference to spiral scan | Most scans used have 5 mm or less slice thickness Clearer to give instruction based on slice interval if it is greater than 5 mm | |
| | Clinical: 20 mm | Clinical: 10 mm (must be measurable with calipers) | Caliper measurement will make this reliable | |
| | Lymph node: not mentioned | CT:<br>⩾15 mm short axis for target<br>⩾10–<15 mm for non-target<br><10 mm is non-pathological | Since nodes are normal structure need to define pathological enlargement. Short axis is most sensitive | Schwartz et al.[15] |
| Special considerations on lesion measurability | – | Notes included on bone lesions, cystic lesions | Clarify frequently asked questions | |
| Overall tumour burden | 10 lesions (5 per organ) | 5 lesions (2 per organ) | Data warehouse analysis shows no loss of information if lesion number reduced from 10 to 5. A maximum of 2 lesions per organ yields sufficient representation per disease site | Bogaerts et al.[10] |
| Response criteria target disease | CR lymph node not mentioned | CR lymph nodes must be <10 mm short axis | In keeping with normal size of nodes | Schwartz et al.[15] |
| | PD 20% increase over smallest sum on study or new lesions | PD 20% increase over smallest sum on study (including baseline if that is smallest) and at least 5 mm increase or new lesions | Clarification that if baseline measurement is smaller than any on study measurement, it is reference against which PD is assessed<br>5 mm absolute increase to guard against over calling PD when total sum is very small and 20% increase is within measurement error | |
| Response criteria non-target disease | 'unequivocal progression' considered as PD | More detailed description of 'unequivocal progression' to indicate that it should not normally trump target disease status. It must be representative of overall disease status change, not a single lesion increase | Confusion with RECIST 1.0 where some were considering PD if 'increase' in any non-target lesion, even when target disease is stable or responding | |
| New lesions | – | New section on New lesions | To provide guidance on when a lesion is considered new (and thus PD) | |
| Overall response | Table integrated target and non-target lesions | Two tables: one integrating target and non-target and the other of non-target only | To account for the fact that RECIST criteria are now being used in trials where PFS is the endpoint and not all patients have measurable (target) disease at baseline | Dancey et al.[21] |

| | | | | |
|---|---|---|---|---|
| | | Special notes:<br>How to assess and measure lymph nodes<br>CR in face of residual tissue<br>Discussion of 'equivocal' progression | Frequently asked questions on these topics | |
| Confirmatory measure | For CR and PR: criteria must be met again 4 weeks after initial documentation | Retain this requirement ONLY for non-randomised trials with primary endpoint of response | Data warehouse shows that response rates rise when confirmation is eliminated, but the only circumstance where this is important is in trials where there is no concurrent comparative control and where this measure is the primary endpoint | Bogaerts et al.[10] |
| Progression-free survival | General comments only | More specific comments on use of PFS (or proportion progression-free) as phase II endpoint<br>Greater detail on PFS assessment in phase III trials | Increasing use of PFS in phase III trials requires guidance on assessment of PD in patients with non-measurable disease | Dancey et al.[21] |
| Reporting of response results | 9 categories suggested for reporting phase II results | Divided into phase II and phase III<br>9 categories collapsed into 5<br>In phase III, guidance given about reporting response | Simplifies reporting and clarifies how to report phase II and III data consistently | |
| Response in phase III trials | More relaxed guidelines possible if protocol specified | This section removed and referenced in section above: no need to have different criteria for phase II and III | Simplification of response assessment by reducing number of lesions and eliminating need for confirmation in randomised studies where response is not the primary endpoint makes separate 'rules' unnecessary | |
| Imaging appendix | Appendix I | Appendix II: updated with detailed guidance on use of MRI, PET/CT<br>Other practical guidance included | Evolving use of newer modalities addressed. Enhanced guidance in response to frequent questions and from radiology review experience | |
| New appendices | | Appendix I: comparison of RECIST 1.0 and 1.1<br>Appendix III: frequently asked questions | | |

## Conflict of interest statement

None declared.

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## Appendix II. Specifications for standard anatomical radiological imaging

These protocols for image acquisition of computed tomography (CT) and magnetic resonance imaging (MRI) are recommendations intended for patients on clinical trials where RECIST assessment will be performed. Standardisation of imaging requirements and image acquisition parameters is ideal to allow for optimal comparability of subjects within a study and results between studies. These recommendations are designed to balance optimised image acquisition protocols with techniques that should be feasible to perform globally at imaging facilities in all types of radiology practices. These guidelines are not applicable to functional imaging techniques or volumetric assessment of tumour size.

Scanner quality control is highly recommended and should follow standard manufacturer and facility maintenance schedules using commercial phantoms. It is likely that for RECIST unidimensional measurements this will be adequate to produce reproducible measurements. Imaging quality control for CT includes an analysis of image noise and uniformity and CT number as well as spatial resolution. The frequency of quality control analysis is also variable and should focus on clinically relevant scanning parameters. Dose analysis is always important and the use of imaging should follow the ALARA principle, 'As Low As Reasonably Achievable', which refers to making every reasonable effort to maintain radiation exposures as far below the dose limits as possible.

### *Specific notes*

*Chest X-ray* measurement of lesions surrounded by pulmonary parenchyma is feasible, but not preferable as the measurement represents a summation of densities. Furthermore, there is poor identification of new lesions within the chest on X-ray as compared with CT. Therefore, measurements of pulmonary parenchymal lesions as well as mediastinal disease are optimally performed with CT of the chest. MRI of the chest should only be performed in extenuating circumstances. Even if IV contrast cannot be administered (for example, in the situation of allergy to contrast), a non-contrast CT of the chest is still preferred over MRI or chest X-ray.

*CT scans:* CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomic region of interest. As a general rule, the minimum size of a measurable lesion at baseline should be no less than double the slice thickness and also have a minimum size of 10 mm (see below for minimum size when scanners have a slice thickness more than 5 mm). While the precise physics of lesion size and partial volume averaging is complex, lesions smaller than 10 mm may be difficult to accurately and reproducibly measure. While this rule is applicable to baseline scans, as lesions potentially decrease in size at follow-up CT studies, they should still be measured. Lesions which are reported as 'too small to measure' should be assigned a default measurement of 5 mm if they are still visible.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST are *anatomic coverage, contrast administration, slice thickness, and reconstruction interval*.

a. *Anatomic coverage*: Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and

should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

b. *IV contrast administration*: Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination (see Fig. 1 for impact of different phase of IV contrast on lesion measurement). Most solid tumours may be scanned with a single phase after administration of contrast. While triphasic CT scans are sometimes performed on other types of vascular tumours to improve lesion conspicuity, for consistency and uniformity, we would recommend triphasic CT for hepatocellular and neuroendocrine tumours for which this scanning protocol is generally standard of care, and the improved temporal resolution of the triphasic scan will enhance the radiologists' ability to consistently and reproducibly measure these lesions. The precise dose and rate of IV contrast is dependent upon the CT scanning equipment, CT acquisition protocol, the type of contrast used, the available venous access and the medical condition of the patient. Therefore, the method of administration of intravenous contrast agents is variable. Rather than try to institute rigid rules regarding methods for administering contrast agents and the volume injected, it is appropriate to suggest that an adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a *consistent method* is used on subsequent examinations for any given patient (ideally, this would be specified in the protocol or for an institution). It is very important that the same technique be used at baseline and on follow-up examinations for a given patient. This will greatly enhance the reproducibility of the tumour measurements. If prior to enrolment it is known a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the subject at baseline and follow-up should be guided by the tumour type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality (see Fig. 2 for a comparison of CT and MRI of the same lesion). Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

c. *Slice thickness and reconstruction interval*: RECIST measurements may be performed at most clinically obtained slice thicknesses. It is recommended that CT scans be performed at 5 mm contiguous slice thickness or less and indeed this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Indeed, variations in slice thickness can have an impact on lesion measurement and on detection of new lesions. However, consideration should also be given for minimising radiation exposure. With these parameters, a minimum 10 mm lesion is considered measurable at baseline. Occasionally, institutions may perform medically acceptable scans at slice thicknesses *greater than* 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be *twice the slice*

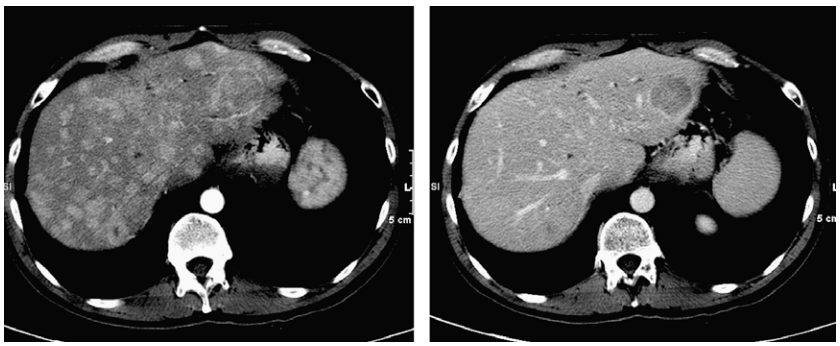

**Fig. 1 – Difference in measurement/visualisation with different phases of IV contrast administration. Hypervascular metastases imaged in the arterial phase (left) and the portal venous phase (right). Note that the number of lesions visible differs greatly between the two phases of contrast administration as does any potential lesion measurement. Consistent CT scan acquisition, including phase of contrast administration, is important for optimal and reproducible tumour**

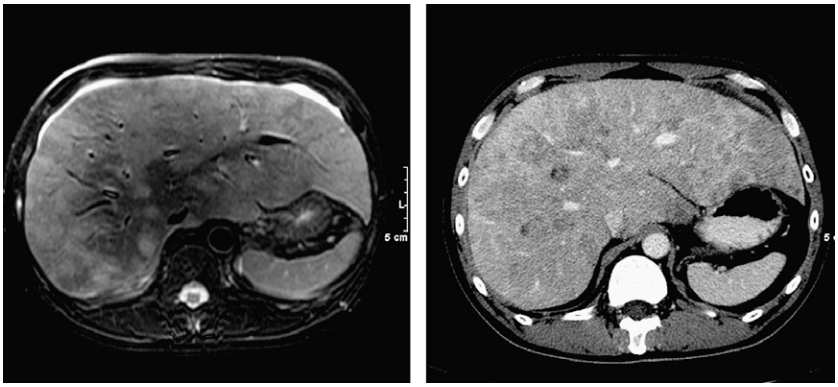

**Fig. 2 – CT versus MRI of same lesions showing apparent 'progression' due only to differing method of measurement.**

*thickness* of the baseline scans. Most contemporary CT scanners are multidetector which have many imaging options for these acquisition parameters.[23] The equipment vendor and scanning manual should be reviewed if there are any specific system questions.

d. *Alternative contrast agents*: There are a number of other, new contrast agents, some organ specific.[24] They may be used as part of patient care for instance, in liver lesion assessment, or lymph node characterisation[25], but *should not as yet be used in clinical trials*.

*FDG-PET* has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. Criteria for incorporating (or substituting) FDG-PET into anatomical assessment of tumour response in phase II trials are not yet available, though much research is ongoing. Nevertheless, FDG-PET is being used in many drug development trials both as a tool to assess therapeutic efficacy and also in assessment of progression. If FDG-PET scans are included in a protocol, by consensus, an FDG uptake period of 60 min prior to imaging has been decided as the most appropriate for imaging of patients with malignancy.[26] Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

*PET/CT scans*: Combined modality scanning such as with PET–CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations in this paper may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based RECIST measurements. However, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

*Ultrasound examinations* should not be used in clinical trials to measure tumour regression or progression of lesions because the examination is necessarily subjective and operator dependent. The reasons for this are several: Entire examinations cannot be reproduced for independent review at a later date, and it must be assumed, whether or not it is the case, that the hard-copy films available represent a true and accurate reflection of events. Furthermore, if, for example, the only measurable lesion is in the para-aortic region of the abdomen and if gas in the bowel overlies the lesion, the lesion will not be detected because the ultrasound beam cannot penetrate the gas. Accordingly, the disease staging (or restaging for treatment evaluation) for this patient will not be accurate.

While evaluation of lesions by *physical examination* is also of limited reproducibility, it is permitted when lesions are superficial, at least 10 mm size, and can be assessed using calipers. In general, it is preferred if patients on clinical trials have at least one lesion that is measurable by CT. Other skin or palpable lesions may be measured on physical examination and be considered target lesions.

Use of *MRI* remains a complex issue. MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimised for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the spe-

cific body part being imaged as well as the scanner utilised. It is beyond the scope of this document or appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

*Selection of target lesions*: In general, the *largest* lesions representative of involved organs (up to a maximum of two per organ and five total) are selected to follow as target lesions. However, in some cases, the largest lesions may not be easily measured and are not suitable for follow-up because of their configuration. In these cases, identification of the largest *most reproducible* lesions is advised. Fig. 3 provides an illustrative example where the largest lesion is not the most reproducible and another lesion is better to select and follow:

### *Measurement of lesions*

The longest diameter of selected lesions should be measured in the plane in which the images were acquired. For body CT, this is the axial plane. In the event isotropic reconstructions are performed, measurements can be made on these reconstructed images; however, it should be cautioned that not all radiology sites are capable of producing isotropic reconstructions. This could lead to the undesirable situation of measurements in the axial plane at one assessment point and in a different plane at a subsequent assessment. There are some tumours, for instance paraspinal lesions, which are better measured in the coronal or sagittal plane. It would be acceptable to measure these lesions in these planes if the reconstructions in those planes were isotropic or the images were acquired with MRI in those planes. Using the same plane of evaluation, the maximal diameter of each target lesion should always be measured at subsequent follow-up time points even if this results in measuring the lesion at a different slice level or in a different orientation or vector compared with the baseline study. Software tools that calculate the maximal diameter for a perimeter of a tumour may be employed and may even reduce variability.

The only exception to the longest diameter rule is lymph node measurement. Because malignant nodes are identified by the length of their short axis, this is the guide used to determine not only whether they are pathological but is also the dimension measured for adding into the sum of target lesions. Fig. 4 illustrates this point: the large arrow identifies a malignant node: the shorter perpendicular axis is $\geqslant$15 mm and will be recorded. Close by (small arrow) there is a normal node: note here the long axis is greater than 10 mm but the short axis is well below 10 mm. This node should be considered non-pathological.

If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient's tumour had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumour status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently 'disappeared' single lesion amongst many which remain is not in itself en-

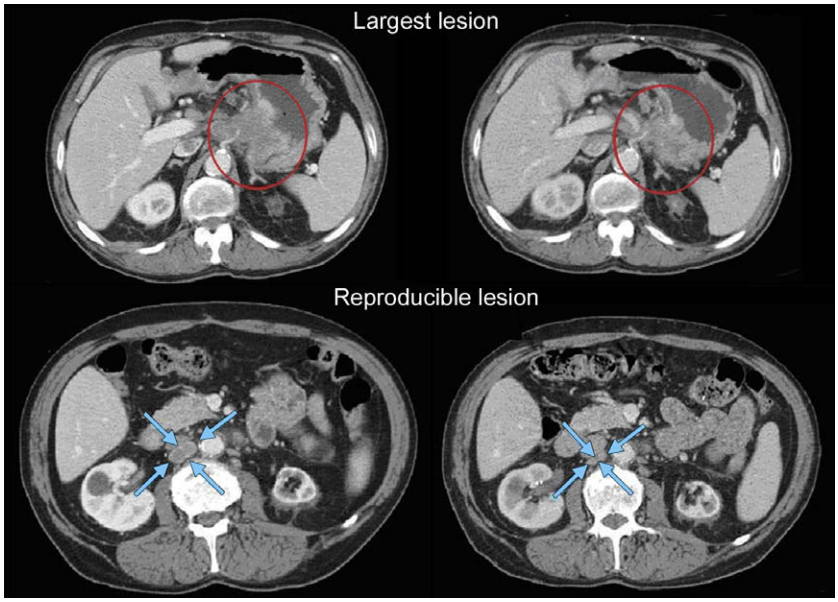


**Fig. 3 – Largest lesion may not be most reproducible: most reproducible should be selected as target. In this example, the primary gastric lesion (circled at baseline and at follow-up in the top two images) may be able to be measured with thin section volumetric CT with the same degree of gastric distention at baseline and follow-up. However, this is potentially challenging to reproduce in a multicentre trial and if attempted should be done with careful imaging input and analysis. The most reproducible lesion is a lymph node (circled at baseline and at follow-up in the bottom two images).**

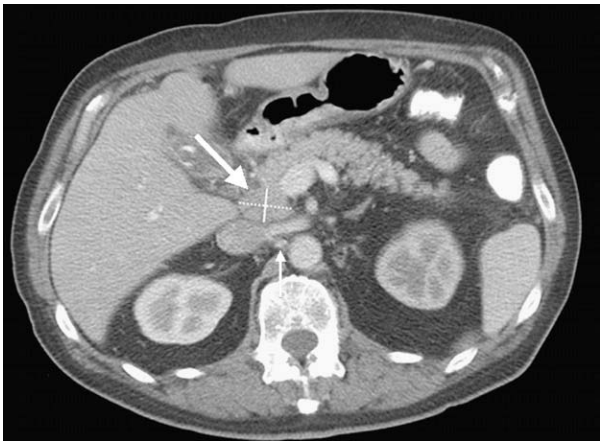

**Fig. 4 – Lymph node assessment: large arrow illustrates a pathological node with the short axis shown as a solid line which should be measured and followed. Small arrow illustrates a non-pathological node which has a short axis <10 mm.**

ough to qualify for PD: that requires the sum of all lesions to meet the PD criteria. The rationale for such a categorisation is based upon the realisation that most lesions do not actually 'disappear' but are not visualised because they are beyond the resolving power of the imaging modality employed.

The identification of the precise boundary definition of a lesion may be difficult especially when the lesion is embedded in an organ with a similar contrast such as the liver, pancreas, kidney, adrenal or spleen. Additionally, peritumoural oedema may surround a lesion and may be difficult to distinguish on certain modalities between this oedema and actual tumour. In fact, pathologically, the presence of tumour cells within the oedema region is variable. Therefore, it is most critical that the measurements be obtained in a reproducible manner from baseline and all subsequent follow-up time-points. This is also a strong reason to consistently utilise the same imaging modality.

When lesions 'fragment', the individual lesion diameters should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'merged lesion'.

### *Progression of non-target lesions*

To achieve 'unequivocal progression' there must be an *overall* level of substantial worsening in non-target disease that is of a magnitude that, even in the presence of SD or PR in target disease, the treating physician would feel it important to change therapy. Examples of unequivocal progression are shown in Figs. 5 and 6.

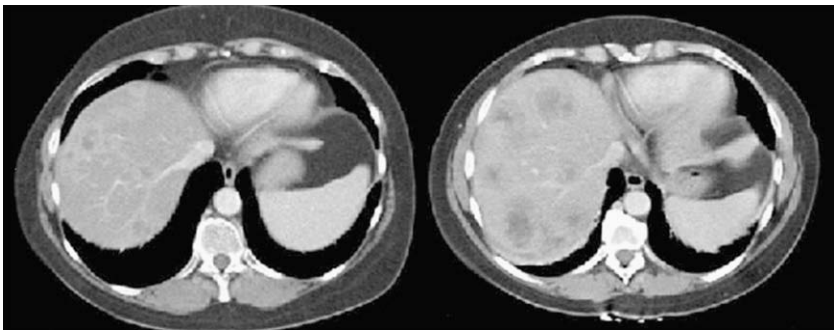

**Fig. 5 – Example of unequivocal progression in non-target lesions in liver.**

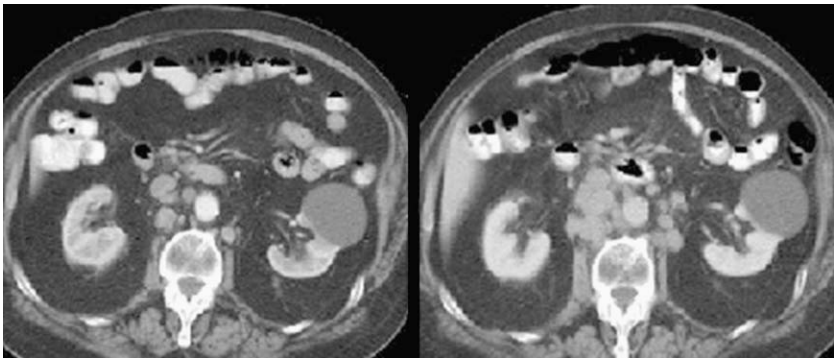

**Fig. 6 – Example of unequivocal progression in non-target lesion (nodes).**

## Appendix III. Frequently asked questions

| Question | Answer |
|---|---|
| What should be done if several unique lesions at baseline become confluent at a follow-up evaluation? | Measure the longest diameter of the confluent mass and record to add into the sum of the longest diameters |
| How large does a new lesion have to be to count as progression? Does any small subcentimetre lesion qualify, or should the lesion be at least measurable? | New lesions do not need to meet 'measurability criteria' to be considered valid. If it is clear on previous images (with the same technique) that a lesion was absent then its definitive appearance implies progression. If there is any doubt (because of the techniques or conditions) then it is suggested that treatment continue until next scheduled assessment when, generally, all should be clear. Either it gets bigger and the date of progression is the date of the first suspicion, or it disappears and one may then consider it an artefact with the support of the radiologists |
| How should one lesion be measured if on subsequent exams it is split into two? | Measure the longest diameter of each lesion and add this into the sum |
| Does the definition of progression depend on the status of all target lesions or only one? | As per the RECIST 1.1 guideline, progression requires a 20% increase in the sum of diameters of all target lesions AND a minimum absolute increase of 5 mm in the sum |
| Are RECIST criteria accepted by regulatory agencies? | Many cooperative groups and members of pharma were involved in preparing RECIST 1.0 and have adopted them. The FDA was consulted in their development and supports their use, though they don't require it. The European and Canadian regulatory authorities also participated and the RECIST criteria are now integrated in the European note for guidance for the development of anticancer agents. Many pharmaceutical companies are also using them. RECIST 1.1 was similarly widely distributed before publication |
| What is the criterion for a measurable lesion if the CT slice thickness is >5 mm? | RECIST 1.1 recommends that CT scans have a maximum slice thickness of 5 mm and the minimum size for a measurable lesion is twice that: 10 mm (even if slice thickness is <5 mm). If scanners with slice thickness >5 mm are used, the minimum lesion size must have a longest diameter twice the actual slice thickness |
| What should we record when target lesions become so small they are below the 10 mm 'measurable' size? | Target lesion measurability is defined at baseline. Thereafter, actual measurements, even if <10 mm, should be recorded. If lesions become very small, some radiologists indicate they are 'too small to measure'. This guideline advises that when this occurs, if the lesion is actually still present, a default measurement of 5 mm should be applied. If in fact the radiologist believes the lesion has gone, a default measurement of 0 mm should be recorded |
| If a patient has several lesions which have decreased in size to meet PR criteria and one has actually disappeared, does that patient have PD if the 'disappeared' lesion reappears? | Unless the sum meets the PD criteria, the reappearance of a lesion in the setting of PR (or SD) is not PD. The lesion should simply be added into the sum.<br>If the patients had had a CR, clearly reappearance of an absent lesion would qualify for PD |
| When measuring the longest diameter of target lesions in response to treatment, is the same axis that was used initially used subsequently, even if there is a shape change to the lesion that may have produced a new longest diameter? | The longest diameter of the lesion should always be measured even if the actual axis is different from the one used to measure the lesion initially (or at different time point during follow-up)<br>The only exception to this is lymph nodes: as per RECIST 1.1 the short axis should always be followed and as in the case of target lesions, the vector of the short axis may change on follow-up |
| Target lesions have been selected at baseline and followed but then one of these target lesions then becomes non-evaluable (i.e. different technique used)<br>What is the effect this has on the other target lesions and the overall response? | What may be done in such cases is one of the following:<br>(a) If the patient is still being treated, call the centre to be sure that future evaluations are done with the baseline technique so at least SOME courses are fully evaluable<br>(b) If that is not possible, check if there IS a baseline exam by the same technique which was used to follow patients…in which case if you retrieve the baseline measures from that technique you retrieve the lesion evaluability<br>(c) If neither (a) nor (b) is possible then it is a judgement call about whether you delete the lesion from all forms or consider the impact of the lesion overall is so important that its being non-evaluable makes the overall response interpretation inevaluable without it. Such a decision should be discussed in a review panel<br>It is NOT recommended that the lesion be included in baseline sums and then excluded from follow-up sums since this biases in favour of a response |

(*continued on next page*)

**Appendix III – *continued***

| Question | Answer |
|---|---|
| What if a single non-target lesion cannot be reviewed, for whatever reason; does this negate the overall assessment? | Sometimes the major contribution of a single non-target lesion may be in the setting of CR having otherwise been achieved: failure to examine one non-target in that setting will leave you unable to claim CR. It is also possible that the non-target lesion has undergone such substantial progression that it would override the target disease and render patient PD. However, this is very unlikely, especially if the rest of the measurable disease is stable or responding |
| A patient has a 32% decrease in sum cycle 2, a 28% decrease cycle 4 and a 33% decrease cycle 6. Does confirmation of PR have to take place in sequential scans or is a case like this confirmed PR? | It is not infrequent that tumour shrinkage hovers around the 30% mark. In this case, most would consider PR to have been confirmed looking at this overall case. Had there been two or three non-PR observations between the two time point PR responses, the most conservative approach would be to consider this case SD |
| In the setting of a breast cancer neoadjuvant study, would mammography not be used to assess lesions? Is CT preferred in this setting? | Neither CT nor mammography are optimal in this setting. MRI is the preferred modality to follow breast lesions in a neoadjuvant setting |
| A patient has a lesion measurable by clinical exam and by CT scan. Which should be followed? | CT scan. Always follow by imaging if that option exists since it can be reviewed and verified |
| A lesion which was solid at baseline has become necrotic in the centre. How should this be measured? | The longest diameter of the entire lesion should be followed. Eventually, necrotic lesions which are responding to treatment decrease in size. In reporting the results of trials, you may wish to report on this phenomenon if it is seen frequently since some agents (e.g. angiogenesis inhibitors) may produce this effect |
| If I am going to use MRI to follow disease, what is minimum size for measurability? | MRI may be substituted for contrast enhanced CT for some sites, but not lung. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. In the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be two times the slice thickness. In the event there are inter-slice gaps, this also needs to be considered in determining the size of measurable lesions at baseline |
| Can PET–CT be used with RECIST? | At present, the low dose or attenuation correction CT portion of a combined PET–CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if your site has documented that the CT performed as part of a PET–CT is of the same diagnostic quality as a diagnostic CT (with IV and oral contrast) then the PET–CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed |

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## Appendix 8. irRECIST Guidelines

ESMO 2014 ABSTRACT 4958

# *ADAPTATION OF THE IMMUNE-RELATED RESPONSE CRITERIA: irRECIST*

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# AIM

RECIST 1.1 has its shortcomings for targeted immunotherapy in oncology. Using RECIST 1.1 in immunotherapy trials would lead to declaration of progressive disease (PD) too early, when the treatment effect is not yet fully evident. RECIST also neglects the importance of the 'flare effect' - pseudo-progression effect within the so-called flare time window.

Immune related Response Criteria (irRC) based on WHO criteria were published with an aim to provide better assessment of the effect of immunotherapeutic agents. With this poster we introduce irRECIST based on RECIST 1.1, irRC and Nishino et al., 2013 findings. Our aim is to define criteria that better capture antitumor activity and reduce irRC criteria ambiguity.

Consistent implementation of irRECIST by both investigators and blinded independent readers will help reduce site: central discordance.

| Original irRC, Including WHO Criteria References | irRECIST Modifications and Clarifications | Rationale for Modification |
|---|---|---|
| At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated. | **1. 0 Baseline: Measurable Lesion Definitions and Target Lesion Selection**<br>Follow the definitions from RECIST 1.1.<br>Measurable lesions must be accurately measured in at least one dimension with a minimum size of:<br>• 10 mm in the longest diameter by CT or MRI scan (or no less than double the slice thickness) for non-nodal lesions and ⩾15 mm in short axis for nodal lesions<br>• 10 mm caliper measurement by clinical exam<br>• 20 mm by chest X-ray | Up to 5 target lesions may be selected at baseline. Lesions will be measured unidimensionally. The minimum target lesion size at baseline in irRECIST is aligned with RECIST 1.1, as outlined in Nishino et al., 2013. |
| WHO 5.1.2<br>Unmeasurable Disease<br>There are many forms of unmeasurable disease, and only a few are mentioned as examples:<br>Lymphangitic pulmonary metastases.<br>Skin involvement in breast cancer.<br>Abdominal masses that can be palpated but not measured. | **1.1. Baseline: Non-measurable Lesion Definitions**<br>Follow the definitions from RECIST 1.1<br>Non-target lesions will include:<br>• Measurable lesions not selected as target lesions<br>• All sites of non-measurable disease, such as neoplastic masses that are too small to measure because their longest uninterrupted diameter is < 10 mm (or < two times the axial slice thickness), ie. the longest per-pendicular diameter is ⩾10 and < 15 mm.<br>• Other types of lesions that are confidently felt to represent neoplastic tissue, but are difficult to measure in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural or pericardial effusions, ascites, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, skin lesions, etc. | Although irRC does not specifically define non-target lesions, irRC is derived from WHO criteria and indicates accordance with the same for the purposes of definitions of non-target lesions. Further clarifications in alignment with RECIST 1.1 are provided. |
| **Not specified.** | **1.2 Baseline: Target and Non-Target Lymph Node Lesion Definitions**<br>Follow the definitions from RECIST 1.1 | No change in definition of target and non-target lymph nodes from RECIST 1.1. |
| **Not specified.** | **1.3 Baseline: Non-Target Lesion Selection**<br>All lesions or sites of disease not recorded as target lesions should be recorded as non-target lesions at baseline. There is no limit to the number of non-target lesions that can be recorded at baseline. | In alignment with RECIST 1.1, all malignant lesions have to be selected at baseline. The excess of measurable lesions and all true non-measurable lesions will be selected as non-target lesions at baseline and followed at subsequent timepoints. |
| **Not specified.** | **1.4 Baseline: Bone Lesions**<br>Follow the definitions from RECIST 1.1.<br>Regardless of the imaging modality blastic bone lesions will not be select-ed as target lesions. Lytic or mixed lytic-blastic lesions with a measurable soft tissue component ⩾10 mm can be selected as target lesions. | Bone lesions are to be handled the same as in RECIST 1.1. |
| **Not specified.** | **1.5 Baseline: Brain Lesions** detected on brain scans can be considered as both target or non-target lesions. | Brain lesions can be selected as target or non-target lesions at baseline, depending on the protocol definition, indication, and study design. |

# METHODS

| Original irRC, Including WHO Criteria References | irRECIST Modifications and Clarifications | Rationale for Modification |
|---|---|---|
| **Not specified.** | **1.6 Baseline: Cystic and Necrotic Lesions as Target Lesions**<br>Lesions that are partially cystic or necrotic can be selected as target lesions. The longest diameter of such a lesion will be added to the Total Measured Tumor Burden (TMTB) of all target lesions at baseline. If other lesions with a non-liquid/non-necrotic component are present, those should be preferred. | RECIST 1.1 does not integrate viability of tumor tissue into the assessment, and that is carried over into irRECIST. |
| **Not specified.** | **1.7 Baseline: Lesions With Prior Local Treatment**<br>During target lesion selection the radiologist will consider information on the anatomical sites of previous intervention (e.g. previous irradiation, RF-ablation, TACE, surgery, etc.). Lesions undergoing prior intervention will not be selected as target lesions unless there has been a demonstration of progress in the lesion. | In order to minimize site vs. central discrepancy information about prior intervention needs to be available to both the investigators and independent reviewers. |
| **Not specified.** | **1.8 Baseline: No Disease at Baseline**<br>If a patient has no measurable and no non-measurable disease at baseline the radiologist will assign 'No Disease' (irND) as the overall tumor assessment for any available follow-up timepoints unless new measurable lesions are identified and contribute to the TMTB. | irND is a valid assessment in studies with adjuvant setting where the protocol and study design allow to include patients with no visible disease. This had not been addressed at all in any prior immune-response related criteria but needs to be included to also allow for these patients to be assessed accurately. |
| At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥5×5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden:<br>**SPDindex lesions + SPDnew measured lesion** | **2.0 Follow-up: Recording of Target and New Measureable Lesion Measurements**<br>The longest diameters of non-nodal target and new non-nodal measurable lesions, and short axes of nodal target and new nodal measurable lesions will be recorded. Together they determine the Total Measured Tumor Burden (TMTB) at follow-up. | In alignment with Nishino et al., 2013, unidimensional measurements are used. Measurements of all measured lesions (baseline-selected target lesions and new measurble lesions) are combined into TMTB at follow-up. |
| | **2.1 Follow-up: Definition of Measurable New Lesions**<br>In order to be selected as new measurable lesions (≤ 2 lesions per organ, ≤ 5 lesions total, per timepoint), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions. | Proposed selection of up to 5 new measurable lesions of at least 10 mm each verus 10 new measurable lesions as suggested in the irRC criteria is due to the following: 5 new measurable lesions add up at least 50 mm to the TMTB. Since PD is determined by at least a 20% increase in TMTB compared to nadir, this would mean that for irPD assessment the nadir TMTB had to be 25 cm, or 10 cm for 2 lesions in one organ, which is a significant tumor burden already for any cancer patient. That is why measuring up to 5 new lesions in total is sufficient and will not obstruct an irPD assessment. Measuring more than 5 new lesons is not needed.<br>Larger lesions must be preferred as new measurable over smaller lesions, because there will be a greater impact of the TMTB %-increase by these larger lesions for irPD, to support a most conservative approach. |

The adaptations from irRC and WHO criteria, as applicable in immunotherapy clinical studies, are documented in the "irRECIST Modifications and Clarifications" column in a comparative table format within our Blinded Independent Central Review (BICR) Charter.

The modifications we introduce represent adaptations of published criteria based on radiology practice and clinical trial experience, and they provide more objective and reproducible response assessments for investigators and for the central independent image review.

# RESULTS

irRECIST criteria are based on irRC criteria adapted for unidimensional measurements, as outlined in Nishino et al., 2013. To further align the criteria with RECIST 1.1 we outline the approach for the assessment of baseline-selected non-target lesions and new non-measurable lesions, and discuss the impact of those lesions on the overall tumor response assessment.

Guidelines for the evaluation of patients with non-target disease only and patients in adjuvant setting is provided.

| Original irRC, Including WHO Criteria References | irRECIST Modifications and Clarifications | Rationale for Modification |
|---|---|---|
| Non-index lesions at follow-up timepoints contribute to defining irCR (complete disappearance required). | **2.2 Follow-up: Non-Target Lesion Assessment**<br>The RECIST 1.1 definitions for the assessment of non-target lesions apply.<br>The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN). Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD. | Non-target lesions have a subordinate function. In the event that non-target lesions massively progress one cannot ignore such worsening and in these rare cases irPD based only on non-target lesions will be a valid assessment option. |
| New, non-measurable lesions at follow-up timepoints do not define progression, they only preclude irCR. | **2.3 Follow-up: New Non-Measurable Lesions Definition and Assessment**<br>All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively. Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the timepoint. Persisting new non-measurable lesions prevent irCR. | When new non-measurable lesions substantially worsen in these rare cases irPD based only on new non-measurable lesions will be an assessment option. |
| **irRC Overall Tumor Assessments**<br>**irCR**, complete disappearance of all lesions (whether measurable or not, and no new lesions)<br>• Confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented<br>**irPR**, decrease in tumor burden ≥50% relative to baseline<br>• Confirmed by a consecutive assessment at least 4 weeks after first documentation<br>**irSD**, not meeting criteria for irCR or irPR, in absence of irPD<br>**irPD**, increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden)<br>• Confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented | **2.4 irRC Overall Tumor Assessments**<br>**irCR,** complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis. Confirmation of response is not mandatory.<br>**irPR**, decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions.<br>**irSD**, failure to meet criteria for irCR or irPR in the absence of irPD.<br>**irNN**, no target disease was identified at baseline and at follow-up the patient fails to meet criteria for irCR or irPD.<br>**irPD**, minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment.<br>**irNE**, used in exceptional cases where insufficient data exists.<br>**irND**, in adjuvant setting when no disease is detected. | The irRECIST overall tumor assessment is based on TMTB of measured target and new lesions, non-target lesion assessment and new non-measurable lesions.<br>The thresholds for irPR and irPD assessment are aligned with RECIST 1.1, and confirmation of response is not required.<br>An irPD confirmation scan may be recommended for patients with a minimal TMTB %-increase over 20% and especially during the flare time-window of the first 12 weeks of treatment, depending on the compound efficacy expectations, to account for expected delayed response. |

# CONCLUSIONS

irRECIST criteria as outlined here introduce the needed clarifications and adjustments to irRC criteria and Nishino et al., 2013 publication to allow for treatment evaluations that better meet both investigators' and patients' needs and with that better reflect sponsors' demands for more reliable and reproducible study data in targeted immunotherapy in oncology studies. The main adaptation of the existing immune-response criteira lies in the assessment of all detected lesions. Unequivocal and substantial increase of non-target and new non-measurable lesions prevents irCR and may also lead to irPD. Reduction of the tumor burden in patients in an adjuvant setting may lead to irPR and such patients may therefore be enrolled in studies with response endpoints.

Clinical relevance of these adaptations needs to be confirmed.

# SUMMARY AND ADDITIONAL GUIDANCE

1. TMTB: Baseline-selected target lesions and new measurable lesions should NOT be assessed separately. Measurements of those lesions should be combined into the Total Measured Tumor Burden (TMTB), and one combined assessment provided.

2. New Measurable Lesions: According to irRC a measurable new lesion has to be at least 5 mm x 5 mm to be selected as an index lesion. For bidimensional measurements this threshold was acceptable. In irRECIST, criteria for unidimensional lesion measurment apply to both target and new measurable lesions: a minimum 10 mm in the longest diameter for non-nodal lesions, and a minimum 15 mm in short axis for lymph nodes. Smaller lesions contribute to the non-target or new non-measurable tumor burden, but do not get measured.

3. irPR if no Target Lesions: If new measurable lesions appear in patients with no target lesions at baseline, irPD will be assessed. That irPD timepoint will be considered a new baseline, and all subsequent timepoints will be compared to it for response assessment. irPR is possible if the TMTB of new measurable lesions decreases by ≥ 30% compared to the first irPD documentation.

4. irPR in Adjuvant Studies: irRECIST can be used in the adjuvant setting, in patients with no visible disease on CT/MRI scans. The appearance of new measurable lesion(s) automatically leads to an increase in TMTB by 100% and leads to irPD. These patients can achieve a response if the TMTB decreases at follow-up, as a sign of delayed response.

   *Considering 3 and 4, sponsors may consider enrolling patients with no measurable disease and/or patients with no visible disease at all in studies with response related endpoints.*

5. Non-Target Lesions: In alignment with RECIST 1.1, baseline selected non-target lesions can never convert to measurable lesions, not even if they increase in size at subsequent timepoints and become measurable. Only true new lesions can be measured and contribute to the TMTB.

6. Example: A patient has multiple lung metastases, all smaller than 10 mm and selected as non-target lesions at baseline. If, at a subsequent timepoint some of these non-target lesions increase and become > 10 mm, and one new lesion >10 mm appears, only the new measurable lesion will contribute to the TMTB, and not the baseline selected non-target lesion that increased in size. Otherwise such an increase would make persisting non-target lesions switch into the new measurable lesion category which would be inaccurate, as the lesion existed at baseline.

7. irPD Based on Non-Target Lesions: Unlike irRC that neglect non-target lesions for the assessment of irPD, in irRECIST a substantial and unequivocal increase of non-target lesions is indicative of progression.

8. irPD Based on New Non-Measurable Lesions: According to irRC, a patient with multiple new lesions of 9 mm would be considered non-PD, whereas a patient with just one new lesion of 10 mm may be assessed as irPD if the TMTB of such a patient increases ≥ 20% compared to nadir. According to irRECIST, the reviewer may assign irPD for the patient with multiple new lesions of 9 mm if they are considered to be a sign of unequivocal, massive worsening (see 2.3)

9. irPD Confirmation: Progression confirmation no less than 4 weeks after the initial irPD assessment is recommended especially in case of marginal disease growth and if the first irPD assessment is within the compound-specific tumor flare window.

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