SPONSOR: SOLTI

TITLE: Targeting non-Luminal disease by PAM50 with pembrolizumab + paclitaxel in Hormone Receptor-positive/HER2-negative advanced/metastatic breast cancer, who have progressed on or after CDK 4/6 inhibitor treatment (TATEN trial)

IND NUMBER: *SOLTI-1716*

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Contact Addresses

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Pharmacovigilance:	PPD

Traslational Research:	PPD
Statistician Data management:	PPD

PROTOCOL APPROVAL SIGNATURES

Title: **Targeting non-Luminal disease by PAM50 with pembrolizumab + paclitaxel in Hormone Receptor-positive/HER2-negative advanced/metastatic breast cancer, who have progressed on or after CDK 4/6 inhibitor treatment (TATEN trial)**

Approval:

PPD

PI Signature (Name and Title) *Date*

PPD

PI Signature (Name and Title) *Date*

PPD

Chief Scientific Officer Signature (Name and Title) *Date*

PROTOCOL AGREEMENT - SITE PRINCIPAL INVESTIGATOR

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing SOLTI with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: SOLTI-1716

Protocol Date: 10-May 2021

PPD

Investigator Signature *Date*

Print Name and Title

Site #

Site Name

Address

Phone Number

PPD

INDEX

1. TRIAL SUMMARY

Abbreviated Title	**Targeting non-Luminal disease by PAM50 with pembrolizumab + paclitaxel in Hormone Receptor-positive/HER2-negative advanced/metastatic breast cancer**
Trial Phase	*Phase II*
Clinical Indication	Pre and post-menopausal women with locally advanced or metastatic HR+/HER2-negative endocrine resistant breast cancer
Trial Type	Single arm
Type of control	-
Route of administration	I.V.
Trial Blinding	No
Treatment Groups	Pembrolizumab in combination with paclitaxel
Number of trial participants	46 evaluable patients (Approximately 184 screened)
Estimated enrollment period	Approximately 18 months
Estimated duration of trial	Approximately 56 months
Duration of Participation	Approximately 2 years or PD or discontinuation for any other reason whichever occurs first
Estimated average length of treatment per patient	Approximately 10 months

2. TRIAL DESIGN

Trial design

This is an open-label, single arm, multicenter phase II study evaluating treatment with pembrolizumab in combination with paclitaxel in patients with locally advanced or metastatic non-luminal Hormone receptor-positive, HER2-negative (hereafter referred to as HR+/HER2-) breast cancer who had recurrence or progression while receiving previous therapy with a CDK inhibitor in the adjuvant setting or to treat advanced disease (or both).

The study will utilize the optimal Simon's two-stage design[1] with one interim and a final analysis. The interim analysis will be conducted when 15 patients are evaluable for ORR as determined locally by the investigator through the use of RECIST v.1.1. If 5 or fewer responses are observed in up to 15 patients of evaluable population (EP), the trial will be terminated in favor of the null for futility. Otherwise, up to a further 31 patients may be evaluated, for a maximum

total of 46 evaluable patients. If a total of 19 or more responses are seen at the end of the second stage, then the null will have been rejected in favor of the alternative; and further investigation of the combination is warranted.

Recruitment will not be halted during the interim analysis period. Therefore, no interruption in the accrual will be done during the interim analysis in order to maintain the dynamic of accrual in the trial.

Before signing the main study informed consent form, patients who meet all clinical selection criteria will sign the pre-screening study informed consent form which will allow the patient to be pre-screened under SOLTI's biomarker program. Estrogen Receptor (ER), Progesterone Receptor (PR) and epidermal growth factor receptor 2 (HER2) immunohistochemistry (IHC)/fluorescence in situ hybridization (FISH) will be determined locally and PAM50 standardized subtyping will be centrally determined to confirm the non-luminal status prior to starting the study treatment. If non-luminal disease (i.e. HER2-enriched [HER2-E] or basal-like) is identified, patients will be eligible for the trial and screening procedures will start (i.e. blood test, imaging…). Imaging will be performed prior to Day 1 of treatment and target lesions will be identified. Remaining tissue will be kept for future biomarker studies at the Central Laboratory. The study population consists of male or female patients age ≥ 18 years with advanced HR+/HER2- breast cancer who have received a CDK4/6 inhibitor containing regimen for locally recurrent and/or metastatic disease or in the adjuvant setting. Patients have to be CDK4/6 refractory, defined as progression while on, or within 6 months of ending CDK4/6 inhibition for locally advanced or metastatic breast cancer, or relapse during or after adjuvant with CDK4/6 inhibitors. Previous PI3K-pathway-targeted therapies (including PI3K, mTOR and AKT inhibitors) are permitted.

After confirmation of all eligibility criteria, eligible patients will receive pembrolizumab 200 mg every 3 weeks (on D1 of each 21-day cycle, beginning in Cycle 1) in combination with paclitaxel 80 mg/m^2 administered at days 1, 8, 15 of each 21-day cycle beginning at cycle 2. Treatment will continue until disease progression, the development of unacceptable toxicity, withdrawal of consent, 24 months from the date of the first dose of pembrolizumab or end of study, whichever occurs first.

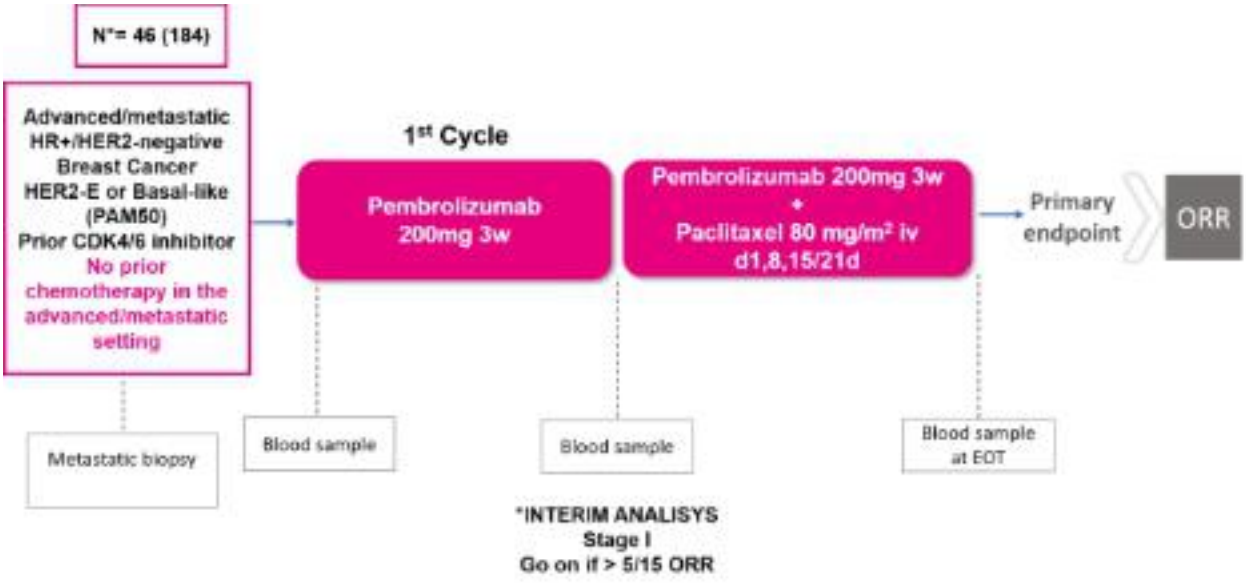
Tumor assessments per Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 (see **Appendix 5**) and Immune-Related Response Evaluation Criteria In Solid Tumors (iRECIST) (see **Appendix 4**) will be performed every 9 weeks (63 days ± 5 days) until disease progression, treatment discontinuation, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. Tumor assessments will be performed on the specified schedule regardless of treatment delays.

For estimation of overall response rate (ORR), clinical benefit rate (CBR), duration of response (DoR) and progression-free survival (PFS), tumor response will be based on RECIST v.1.1 (see **Appendix 5**). In patients who continue treatment beyond radiographic disease progression per RECIST v.1.1, tumor response (ORR and PFS) may continue to be assessed using iRECIST criteria (see **Appendix 4**) until study treatment discontinuation.

All patients will be followed for survival from screening until the last patient recruited has been followed for 12 months, has progressed or has died, whichever occurs first. The patient will be followed for survival approximately every 3 months (± 21 days) until death, withdrawal of consent, loss to follow-up, or study termination by SOLTI. In addition, information regarding use of subsequent anti-cancer agents for metastatic HR+/HER2- during the survival follow-up period will be collected.

Safety assessments will include the incidence, nature, and severity of adverse events (AEs) and laboratory abnormalities graded per the NCI CTCAE v.5. Laboratory safety assessments will include the regular monitoring of hematology, blood chemistry and pregnancy test. A schedule of assessments is provided in **section 6.1**.

Trial diagram



3. OBJECTIVE(S) & HYPOTHESIS(ES)

Primary objective(s) & hypothesis(es)

Primary objective	Primary endpoint
To assess the efficacy of pembrolizumab in combination with paclitaxel in HR+/HER2- non-luminal subtype advanced breast cancer defined by the PAM50 assay.	Overall Response rate (ORR) defined as the proportion of patients with best overall response of complete response (CR) or partial response (PR), as per local investigator´s assessment and according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria (see **Appendix 5**).

Secondary objective(s) & hypothesis(es)

Secondary objectives	Secondary endpoints
1. To determine the clinical benefit of pembrolizumab and paclitaxel in terms of:	1.1. Clinical Benefit Rate (CBR) defined as the proportion of patients with a best overall response of CR, PR or an overall lesion response of Stable Disease (SD) or Non-PR/Non-progression disease (PD) lasting ≥ 24 weeks, based on local investigator´s assessment according to RECIST v1.1. 1.2. Progression free survival (PFS) defined as the time from allocation to the first occurrence of disease progression, as determined locally by the investigator through the use of RECIST v.1.1, or death from any cause, whichever occurs first. 1.3. Duration of response (DoR) defined as the time from the first occurrence of a documented objective response to disease progression, as determined locally by the investigator through use of RECIST v.1.1, or death from any cause, whichever occurs first 1.4. Time to response (TtR) defined as the time from allocation to the first objective tumor response (tumor shrinkage of ≥30%) observed for patients who achieved a CR or PR. 1.5. Overall survival (OS) defined as the time from allocation to death from any cause (OS will be determined at the end of the study).

	1.6. PFS on study treatment compared to PFS on prior line of therapy (pre-PFS). 1.7. ORR according to PD1 mRNA expression. 1.8. ORR according to early dynamic changes in ctDNA between baseline and after 1 cycle of pembrolizumab. 1.9. PFS according to early dynamic changes in ctDNA between baseline and after 1 cycle of pembrolizumab.
2. To assess the safety and tolerability of the combination of pembrolizumab with paclitaxel:	2.1. Incidence, duration and severity of Adverse Events (AEs) assessed by the NCI Common Terminology for Classification of Adverse Events (CTCAE) version 5, including dose reductions, delays and treatment discontinuations.

Exploratory objective

- To determine the ORR based on iRECIST.
- To determine the PFS, DoR, TtR based on iRECIST.
- To determine ORR according to PD-L1 protein expression by IHC.
- To evaluate ORR according to stromal TILs.
- To identify a new gene signature predictive of pembrolizumab and paclitaxel therapy benefit.

Mandatory tumor samples collected during the pre-screening phase of the study will be used to investigate potential value of current and future RNA- and DNA-based biomarkers to predict response to the study drug(s). The following correlative science studies are planned:

- Evaluation of gene expression

  To identify new biomarkers of response to the combination treatment, we aim to further evaluate the expression of 752 genes that encompass important genomic signatures and individual genes. The nCounter® Breast Cancer 360 Panel includes 752 genes that cover established breast cancer diagnostic and research signatures as well as key pathways at the interface of the tumor, tumor microenvironment and immune response. Special attention will be given to innate immune response genes as well as markers of antigen presentation, which are expected to be determinant for this combination treatment. The following genes/signatures will be evaluated among others: PAM50 genes and signatures, risk of recurrence (ROR) score, ER signaling biology, immune cell marker (e.g. BCL2;

CD163; CD68; CD84; CD8A; CD8B; CHIT1), chemo-endocrine score (CES), immune infiltration (e.g. CCL5; CD27; CD274; CD276; CD8A; CMKLR1; CXCL9) or proliferation.

4. BACKGROUND & RATIONALE

[redacted] Background

4.1.1 Breast cancer

Breast cancer is a life-threatening disease and is the second leading cause of cancer death among women. Although metastatic breast cancer is diagnosed in only 5% of cases at presentation, nearly one third of breast cancer patients with non-metastatic tumors will eventually develop metastases[2].

Breast cancer is considered a genetically heterogeneous and biologically diverse disease. Endocrine therapies that target estrogen receptor (ER) signaling pathways for ER-positive disease and human epidermal growth factor receptor 2 (HER2)-targeted therapies for HER2-positive disease play a critical role in the treatment of most patients with breast cancer[3–5], but not every breast tumor responds equally to a specific agent.

Hormone receptor-positive, HER2-negative breast cancer (hereafter referred to as HR+/HER2-) accounts for approximately 60-70% of all early stage breast cancer cases[6]. For this type of cancer, all patients are recommended for adjuvant endocrine therapy (ET) for 5-10 years. In the case of patients with intermediate/high risk, a chemotherapy regimen that generally contains anthracyclines and taxanes is also recommended[7]. However, in spite of this combination, these patients have a substantial relapse risk as shown by the large adjuvant studies GEICAM/9906 and CALGB/9741[8–10]. A similar situation occurs in locally recurrent/metastatic HR+/HER2- disease, with a median overall survival not exceeding 30-35 months in the post-aromatase inhibitors setting[11,12]. Therefore, new therapies and treatment strategies to improve the prognosis of patients with HR+/HER2- breast cancer are of great importance.

4.1.2 Background on HR+/HER2- metastatic breast cancer and treatment

Patients with metastatic HR+/HER2- breast cancer are treated with endocrine therapy; premenopausal patients often undergo additional ovarian ablation/suppression. Chemotherapy is indicated in patients with symptomatic visceral disease (visceral crisis) or in patients with disease progression after demonstration of endocrine resistance[13,14].

In the last 5 years, incorporation of novel drugs in combination with endocrine therapy is improving patient outcomes in HR+/HER2- advanced disease. The first success is exemplified by the 2012 approval of the mTOR inhibitor everolimus in combination with exemestane based on the BOLERO-2 study, setting a new standard for the second-line treatment of patients with

advanced HR+/HER2- breast cancer. Everolimus plus exemestane showed a median progression-free survival (PFS) of 11 months versus 4.1 months for exemestane alone. In addition, 3 CDK4/6 inhibitors are currently in late-stage commercialized for metastatic HR+/HER2- breast cancer: palbociclib, abemaciclib and ribociclib. All 3 of them are orally bioavailable and have similar mechanisms of action **(Table 1)**. Palbociclib and ribociclib recently received FDA/EMA approval for the treatment of postmenopausal women with ER+/HER2- advanced breast cancer in combination with letrozole/fulvestrant as endocrine-based therapy for their metastatic disease.

Table 1: Summary of recent trials using combination of CDK 4/6 inhibitors plus endocrine therapy in HR+/HER2- metastatic breast cancer.

	PALOMA 2[15]	**MONALEESA 2**[16]	**MONALEESA 7**[17]	**MONARCH 3**[18]	**PALOMA 3**[19]	**MONARCH 2**[20]	**MONALEESA 3**[21]
Study design	LTZ/Pbo vs LTZ/Palbo	LTZ/Pbo vs LTZ/Ribo	LTZ/ GnRh/Pbo Vs LTZ/GnRh/Ribo	LTZ/Pbo Vs LTZ/Abema	FVT/Pbo vs FVT/palbo	FVT/Pbo vs FVT/ abema	FVT/Pbo vs FVT/ Ribo
No. of pts	666	668	672	493	521	699	726
Setting	*No progression on AIs*	*No progression on AIs*	*No progression on AIs (allow 1L prior CT)*	*No progression on AIs*	*Progression on AIs (allow 1L prior CT)*	*Progression on AIs*	*No or progression on AIs*
PFS	14.5 vs 24.8 mo HR 0.58	16 vs 25.3 mo HR 0.556	13 vs 23.8mo HR 0.55	NR vs 14.7 HR 0.54	4.6 vs 11.2 mo HR 0.5	9.3 vs 16.4 mo HR 0.55	12.8 vs 20.5 mo HR 0.59

Pbo: Placebo; LTZ: letrozole; FVT: Fulvestrant Palbo: plabociclib; Ribo: ribociclib; Abema: abemaciclib; AIs: Aromatase inhibitors; mo: months; HR: hazard ratio.

4.1.3 The importance of intrinsic subtyping in HR+/HER2- breast cancer

Breast cancer is a clinically and biologically heterogeneous disease. In terms of global gene expression, 4 main molecular subtypes (Luminal A, Luminal B, HER2-enriched [HER2-E] and Basal-like) have been identified and intensively studied in the last 15 years[22–25]. Known as the 'intrinsic subtypes of breast cancer, these groups of tumors have revealed critical differences in incidence[26,27], survival[28–30], and response to treatment[31,32]. Importantly, the information provided by the intrinsic subtypes complements and expands the information provided by classical clinical parameters (e.g. age, node status, tumor size, histological grade) and pathological markers (estrogen receptor [ER], progesterone receptor [PR] and HER2)[8,30], all of which are routinely used today in the clinic to stratify patients for prognostic predictions and to select treatments. Although once thought that HR+/HER2- breast cancer was composed of Luminal disease, recent studies have shown that 5-20% of HR+/HER2- primary tumors do not fall into the Luminal A or B subtypes but rather fall into the HER2-E or Basal-like phenotype[8,33,34](section 4.1.5)

The importance of intrinsic subtyping in breast cancer has been highlighted in one of the most complete molecular characterization studies that have ever been performed in breast cancer[22]. In this study, led by The Cancer Genome Atlas Project (TCGA), more than 500 primary breast cancer were extensively profiled at the DNA (i.e. methylation, chromosomal copy-number changes and somatic and germline mutations), RNA (i.e. miRNA and mRNA expression) and protein (i.e. protein and phosphor-protein expression) levels using the most recent technologies[22]. In a particular analysis of over 300 primary tumors (i.e. shown in **Fig. 2** of that publication https://www.nature.com/articles/nature11412[22], 5 different data-types (i.e. all except DNA mutations) were combined together in a cluster of clusters in order to identify how many biological homogenous groups of tumors one can identify in breast cancer. The consensus clustering results showed the presence of 4 main entities of breast cancer but, more importantly, these 4 entities were found to be very well recapitulated by the 4 main intrinsic subtypes (Luminal A, Luminal B, HER2-E and Basal-like) as defined by mRNA expression only[35]. Overall, these results suggest that intrinsic subtyping captures the vast majority of the biological diversity occurring in breast cancer.

4.1.4 The main molecular features of the HER2-enriched and Basal-like subtypes

The HER2-E is characterized by high expression of growth factor receptor-related genes, such as HER2 and/or FGFR4, and of cell cycle-related genes, and low expression of estrogen-related genes such as estrogen and progesterone receptors, as well as low expression of basal-related genes (e.g. keratin 5 and FOXC1)[22]. At the DNA level, these tumors show the highest number of mutations across the genome, and 72% and 39% of HER2-E tumors are TP53 and PIK3CA mutated, respectively. Interestingly, the HER2-E subtype has been found uniquely enriched for tumors with high frequency of APOBEC3B-associated mutations[36]. APOBEC3B is subclass of APOBEC cytidine deaminases, which convert cytosine to uracil and has been implicated as a source of mutations in many cancer types[37].

The Basal-like is characterized by high expression of EGFR and cell cycle-related genes, and very low expression of estrogen-related genes such as estrogen and progesterone receptors, as well as ERBB2/HER2. At the DNA level, these tumors show high number of mutations across the genome, and 80% of Basal-like tumors are TP53 mutated[22].

4.1.5 Identification of non-luminal subtypes within HR+/HER2- disease

For many years, it has been thought that Basal-like tumors are always triple-negative by immunohistochemistry (IHC) and that HER2-E tumors have always ERBB2/HER2 overexpression and/or amplification and do not express ER and PR by IHC. However, we now know this is not entirely correct. For example, HER2-E tumors are identified in 6.6-11.0% HR+/HER2-, 18.7% HR+/HER2+ and 9.1% triple-negative breast cancer (**Table 2)**. In a previous study, we showed that, from a biological perspective, HER2-E tumors that are HER2+ are practically the same as HER2-E tumors that are HER2-negative, except for the amplification/overexpression of the ERBB2 DNA amplicon[29]. Thus, although HER2-E tumors might express HER2, ER or PR, the main biological features are maintained within this subtype.

Table 2. Distribution of the PAM50 intrinsic subtypes within the pathology-based groups in primary tumors*.

			PAM50 Intrinsic Subtype Distribution			
IHC-based group	**References**	**N**	**Luminal A**	**Luminal B**	**HER2-enriched**	**Basal-like**
HR+/HER2-	(10, 12, 15, 20-25)	**4,295**	**60.3%**	**31.9%**	**6.6%**	**1.2%**
Luminal A	(10, 15, 21, 25)	**637**	**62.2%**	**27.0%**	**10.2%**	**0.6%**
Luminal B	(10, 15, 21, 25)	**317**	**34.1%**	**51.1%**	**11.0%**	**3.8%**
HER2+	(4, 11, 13, 26, 27)	**831**	**17.6%**	**26.8%**	**44.6%**	**11.0%**
HER2+/HR+	(13, 27)	**182**	**33.0%**	**46.2%**	**18.7%**	**2.2%**
HER2+/HR-	(13, 27)	**168**	**19.0%**	**4.2%**	**66.1%**	**10.7%**
TNBC	(10, 11, 28, 29)	**868**	**1.6%**	**3.2%**	**9.1%**	**86.1%**

*The table has been published previously[38] and has been obtained from different publications. Several studies have performed a standardized version of the PAM50 assay (RT-qPCR-based or nCounter-based) from formalin-fixed paraffin-embedded tumor tissues[8,28,30,39,40], while others have performed the microarray-based version of the PAM50 assay[22,29,31,41–44].

Based on the molecular features of the HER2-E and Basal-like subtypes, it is expected to identify these 2 subtypes in tumors that express low levels of ER by IHC. In fact, intrinsic subtyping in 25 tumor samples with 1-9% ER-positive tumor cells found that 48% and 32% were Basal-like and HER2-E[45], respectively. Moreover, a combined analysis of 48 borderline cases (1-10% ER+ tumor cells) from the MA.5, MA.12 and GEICAM9906 phase III clinical trials revealed that 31% and 18% were identified as HER2-E and Basal-like[33,46], respectively. However, the HER2-E and Basal-like subtypes can also be identified in tumors that have very high expression of ER by IHC (i.e. Allred Score of 6-8) as exemplified by the identification of 6 HER2-E tumors and 1 Basal-like tumor in the Z1031 phase III trial (representing 2.9% of the entire cohort of HR+/HER2-). Thus, current IHC-based biomarkers cannot identify this biomarker.

4.1.6 Non-luminal subtypes in HR+/HER2- advanced/metastatic disease

Although the incidence of the Basal-like and HER2-E subtypes in primary tumors is below 10%, current evidence suggest that this frequency is much larger in the advanced/metastatic setting, specially following endocrine treatment. This increase in the HER2-E subtype in the metastatic setting may be due to setting selection, a change in the biology of the tumor due to the inherent evolution of the tumor or the effects of the treatment, or a combination of both. Current evidence supports this latter possibility. On the one hand, patients with early RH+/HER2-/HER2-E breast cancer have a higher probability of relapse than luminal disease. Therefore, it is likely that a given population of patients with metastatic disease is more enriched for the HER2-E

subtype compared to patients with early breast cancer. On the other hand, Cejalvo and colleagues[47] showed using 123 pairs of primary vs. metastatic tumor samples (70% being HR+/HER2-) that the HER2-E signature and HER2-E subtype are enriched in the metastatic samples compared to primary tumors. For example, 13% of primary Luminal A and B tumors were identified as HER2-E in the relapsed tumor sample. Overall, the proportion of HER2-E tumors in primary vs. metastatic was 11.4% vs. 22%, respectively. Moreover, in a retrospective analysis of tumor samples from the BOLERO-2 study, where patients with HR+/HER2- advanced disease resistant to an aromatase inhibitor, the proportion of HER2-E in primary vs. metastatic tumors was 19% vs. 32%[48].

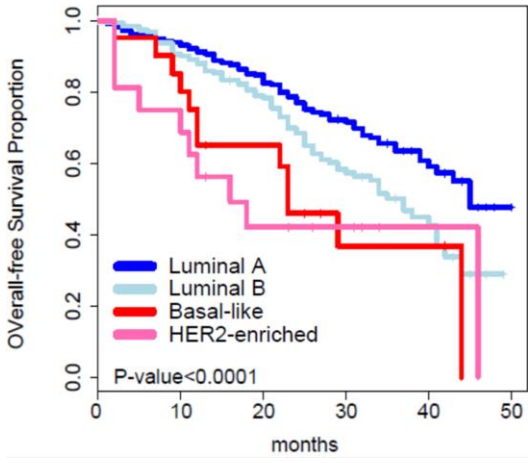
Recently, data from the gene expression in the PALOMA 2 study have been presented in SABCS 2017[15]. In this retrospective analysis, which included 68% (445/666) of the tumors (both primary and metastatic samples) of the clinical trial population, the HER2-E population represented 19% and the Basal-like population represented 1%.

4.1.7 Prognostic value of non-luminal subtypes in HR+/HER2-

The prognostic value of the Basal-like and HER2-E intrinsic subtypes has been evaluated in various studies and cohorts. For example, intrinsic subtyping was performed in a cohort of 1,380 patients with ER+ early breast cancer treated with 5 years of adjuvant tamoxifen-only[28]. Patients with HER2-E and Basal-like disease, which represented ~7% of the entire cohort, showed a statistically significant worse outcome compared to Luminal A subtype.

Moreover, the prognostic value of the HER2-E intrinsic subtype has been evaluated retrospectively in 3 studies of HR+/HER2-metastatic disease[28,33,49]. In the first one, intrinsic subtyping was performed in a cohort of 821 patients with HR-positive disease (644 HER2-negative and 157 HER2+) treated in the first-line metastatic setting with letrozole or letrozole plus lapatinib in the EGF30008 Phase III clinical trial[49]. Patients with HER2-E and Basal-like disease showed worse PFS and overall survival (OS) compared to Luminal A disease regardless of the HER2 status and treatment (**Fig. 1**). Median PFS with letrozole-only was 4-5 months in both subtypes.

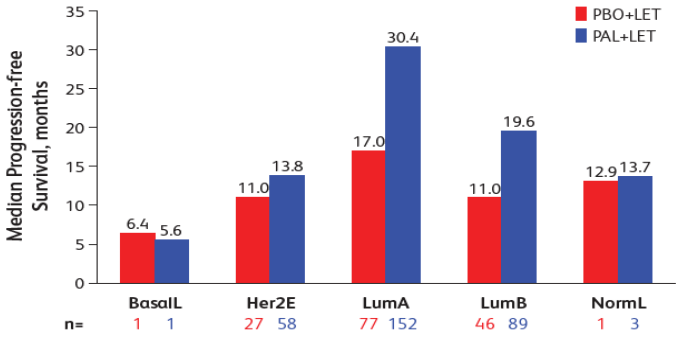
Figure 1. Overall survival based on intrinsic subtype in HR+/HER2-neg metastatic disease[50].



In the second study, PAM50 was performed in 261 tumor samples from the BOLERO-2 phase III trial[48]. The subtype distribution was: 46.7% Luminal A, 21.5% HER2-E, 15.7% Luminal B, 14.2% Normal-like and 1.9% Basal-like. Non-luminal disease was independently associated with poor PFS and OS compared to the rest of the subtypes.

In the third study, PAM50 was performed in 465 tumor samples from the PALOMA-2 phase III trial[15]. Both non-luminal subtypes were associated with worse PFS compared to Luminal A subtype (**Fig. 2**). Thus, non-luminal HR+/HER2- tumors are aggressive and require novel therapeutic approaches.

Figure 2. Median PFS based on intrinsic subtypes in PALOMA-2 study.



4.1.8 Anti-estrogen sensitivity of the HER2-E subtype

The ability of the Basal-like and HER2-E subtype to predict benefit from anti-estrogen therapy has been evaluated in the neoadjuvant setting. In the Z1031 neoadjuvant trial[42] within ER+/HER2- negative disease, patients with HER2-E or Basal-like disease had persistently high surgical Ki67 levels (20%) after 4-6 months of treatment with an aromatase inhibitor, consistent with high-level estrogen-independent growth. In another retrospective study[41] of 112 postmenopausal women with stages I–IIIB ER+ early breast cancer before and after 2-weeks' anastrozole treatment in a neoadjuvant trial, patients with HER2-E subtype (n=9 [8.0%]) or Basal-like subtype (n=3 [2.7%]) showed a poorer Ki67 response (mean Ki-67 change of -50.7% and +15.3%) compared to Luminal A or B subtypes (mean Ki-67 change of -75%)[41]. Interestingly, this study also profiled post-treatment samples. As expected, the vast majority of Luminal A samples (31/32, 97%) continued being Luminal A[41]. However, although the majority of Luminal B tumors became Luminal A (9/17, 53%), 12% (2/17) became HER2-E[41]. Overall, this data, together with the poor PFS of the HER2-E subtype following endocrine therapy in EGF30008[50], BOLERO-2[48] and PALOMA 2 trials[15], suggest that both non-luminal subtypes within HR-positive disease might not benefit substantially from anti-estrogen therapy.

4.1.9 Anti-CDK4/6 sensitivity of the non-luminal subtypes within HR+ disease

The ability of the Basal-like and HER2-E subtype to predict benefit from palbociclib has been recently evaluated in 465 samples of the PALOMA-2 study[15]. As shown in **Fig. 2**, the increase in median PFS in the HER2-E subtype was modest (2.8 months), compared to the increase in median PFS of 13.4 and 8.6 months in Luminal A and B subtypes, respectively. Regarding Basal-like, only 1 patient was identified and progressed at 6.4 months following letrozole + palbociclib. This data suggest that non-luminal subtypes do not benefit much from CDK4/6 inhibition. Further confirming this hypothesis, Ma and colleagues conducted the NEOPALANA neoadjuvant trial with anastrozole and palbociclib and identified by PAM50 analysis 2 patients with non-luminal disease (1 HER2-E and 1 Basal-like)[51]. Interestingly, none of the 2 patients responded to the combined treatment[51].

4.1.10 Chemotherapy sensitivity of the non-luminal subtypes within HR+ disease

The ability of the Basal-like and HER2-E subtype to predict chemotherapy sensitivity within HR+/HER2- disease has been evaluated in the neoadjuvant setting. In one study, P and colleagues evaluated the pathological complete response (pCR) rated in 451 patients with HR+/HER2- disease treated with standard multi-agent neoadjuvant chemotherapy[52]. The pCR rates in the non-luminal subtype was 23.2% compared to 15% in Luminal B and 5% in Luminal A tumors. In another neoadjuvant study, PP and colleagues evaluated the residual cancer burden (RCB) 0/1 rates of the intrinsic subtypes in 180 patients with HR+/HER2- disease treated with anthracycline/taxane-based chemotherapy[53]. Concordant with the first study, the RCB0/1 rates were higher in the non-luminal subtypes (38.1%) compared to Luminal B (20.0%) and Luminal A (9.3%). Overall, this data suggests that within HR+/HER2- disease, non-luminal tumors are highly chemo-sensitive.

4.1.11 Immune infiltration of non-luminal subtypes within HR+/HER2- disease

Previous studies of the intrinsic subtypes have shown that Basal-like and HER2-E are associated with higher expression of immune-related genes or higher infiltration of stromal tumor infiltrating lymphocytes compared to the luminal subtypes[54–56]. However, this has not been specifically evaluated in HR+/HER2- disease until recently. For example, in a SOLTI cohort of 101 patients with HR+/HER2- disease, the PAM50 intrinsic subtype was performed. As shown in **Fig. 3 (unpublished)**, both non-luminal subtypes showed higher stromal TILs than luminal subtypes. Similar data has been observed using gene expression of PD1 (PDCD1), PD-L1 (CD274), CD8A and CD4 in another cohort of 261 tumor samples from PPD laboratory (**Fig. 4**; **unpublished**).

Figure 3. Stromal TILs across the intrinsic subtypes in HR+/HER2- disease.

Figure 4. Expression of immune-related genes in 261 tumor samples.

[redacted] Pharmaceutical and therapeutic background

4.2.1 Paclitaxel

Taxane-based regimens are considered a standard of care (SoC) option in first-line therapy for patients with metastatic breast cancer[13]. No standard approach exists for second- or further-line

treatment, and options for HR+/HER2- patients of cytotoxic chemotherapy are the same as those for other subtypes. Single-agent cytotoxic chemotherapeutic agents are generally regarded as the primary option for patients with metastatic breast cancer, although combination chemotherapy may be used when there is aggressive disease and visceral involvement.

The role of paclitaxel in the treatment of breast cancer is well established. The response rates for paclitaxel administered as a single agent to patients with metastatic breast cancer are approximately 25% in first-line treatment[57–60].

Weekly paclitaxel (80–90 mg/m^2) is currently considered the most effective schedule for delivering paclitaxel, and was found to be associated with higher overall survival (OS) and lower incidence of serious adverse events (AEs), neutropenia, neutropenic fever, and peripheral neuropathy compared with the three-weekly taxane schedules in advanced breast cancer[58,61].

4.2.2 Immunoncology

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades[62]. The modern era of cancer immunology has focused on using immunotherapy to "boost" the immune system through vaccination, adoptive cellular immunotherapy or inhibiting immune checkpoints[63]. All these strategies aim to enable the patient's immune system to specifically recognize and kill cancer cells.

Cancer is characterized by the accumulation of different genetic and epigenetic alterations which lead to the expression of different tumor antigens, which are displayed on the surface of cancer cells. At the same time, cancer cells have developed sophisticated ways of escaping from immune attack, which has been a major limitation of cancer immunotherapy[64,65]. To date, many immune escape mechanisms have been identified, including expression of endogenous "immune checkpoints" that normally terminate immune responses after antigen activation[64,66,67]. These observations have resulted in the development of immune checkpoint-pathway inhibitors such as anti-programmed death 1 (PD1) or anti-CTL antigen-4 (CTLA4).

Durable monotherapy responses are currently consistently being reported for a broad range of human cancers with several different agents[68–70]; providing a compelling argument that cancer immunotherapy is active in a range of indications beyond melanoma, a disease often thought to be atypically immunogenic[71]. Many of this studies are now demonstrating long-terms events as increases in OS in particularly immunotherapy, that use monoclonal antibodies that block inhibitory immune checkpoint molecules[72–75]. As a consequence, several immunotherapies have been approved by the US Food and Drug Administration (FDA) and other regulatory agencies worldwide for the treatment of various tumors.

4.2.3 Immunotherapy in breast cancer

PD1 receptor/ PD1 ligand (PD-L1) interaction is a key immune checkpoint that is overridden by malignant tumors to escape from the immune surveillance[76]. PD1 receptors are normally expressed during the initial activation of T-cell to suppress the unnecessary or excessive immune response that can precipitate autoimmune reactions. The PD1/PD-L1 pathway is engaged by

cancer cells to undergo immune evasion. PD1 receptors suppress T-cell activation upon the interaction of PD1 with PD-L1 ligand proteins. PD1 is expressed on activated T lymphocytes and myeloid cells, while PD-L1 is mostly expressed on antigen-presenting cells together with other hematopoietic, non-hematopoietic cells and some epithelial cells[77]. Tumor immune evasion occurs because of the upregulated expression of PD-L1 on tumor cells and on other components of tumor microenvironment[78].

The PD1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD1 (encoded by the gene *PDCD1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2)[79,80].

The structure of murine PD1 has been resolved[81]. PD1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade[80,82–84]. The mechanism by which PD1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins[82,85]. As a consequence, the PD1/PD-L1 pathway is an attractive target for therapeutic intervention in several malignancies.

Monoclonal antibodies targeting PD1/PD-L1 immune checkpoints are an evolving approach for the management of cancer. These immune checkpoint inhibitors include PD1 antibodies such as pembrolizumab and nivolumab or PD-L1 antibodies as durvalumab, avelumab and atezolizumab[86]. The favorable clinical outcomes in patients receiving PD1/PD-L1 immune checkpoint inhibitors are mostly associated with upregulated expression of PD-L1. Nonetheless, some studies reported clinical outcomes in patients with tumors that lack PD-L1 expression[87]. Tumor infiltrating lymphocytes (TILs) enriched tumor microenvironment is a feature associated with higher response rates to immune checkpoint inhibitors[88]. Such tumors are called hot or inflamed tumors. Accumulating evidence shows a correlation between TILs in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. TILs can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma[89,90].

It is noteworthy that breast tumors, which exhibit poor prognostic criteria such as ER-negative or PR-negative status and lymph node positivity were shown to have higher levels of TILs[91,92]. Outcomes from clinical trials highlighted that a higher percentage of CD8+ TILs is a feature associated with higher response rates to immune check point inhibitors in TNBC patients[87,93]. Thus, immunotherapy is considered a promising therapeutic option for TNBC which has poor response to conventional therapies and does not have any specific targeted therapy options. The response of TNBC to immunotherapy is higher than the response rate of ER- positive breast cancer[94,95]. Several studies have characterized the immune landscape of ER-positive/HER2-negative breast cancer. ER-positive/HER2-negative breast cancer is associated with lower rate of lymphocytic infiltration[96], especially by CD8+ T cells[97]. In a study that included 2009 samples, the median infiltration by lymphocytes was 10 in ER-positive/HER2-negative breast cancer as compared to 20 in TNBC. In a pooled analysis of four studies, ER-positive/HER2-negative breast cancer presented a lower rate of infiltration by CD8+ T cells. Interestingly, while associated with lower infiltration of T cell, 71% of ER- positive/HER2-negative breast cancer presented expression of PD-L1[98]. Although the presence of TILs and PD-L1 expression is less common in the HR+/HER2- subtype than in TNBC, patients with ER-positive/HER2-negative tumors represent a considerable proportion of PD-L1-positive tumors given their high prevalence.

Since advanced TNBC is among the tumors that exhibit high recurrence rate and resistance to the common chemotherapies, clinical trials are in process to evaluate the potential merit of immune checkpoint inhibitors in an effort to find a successful approach for treatment of such hard to treat tumors Four phase I studies have evaluated the antitumor activity of pembrolizumab (anti-PD1), atezolizumab (anti-PD-L1) (alone or in combination with chemotherapy), and avelumab (anti-PD-L1) in patients with advanced TNBC. Some of these trials included HR+/HER2- patients. **(Table 3).**

Table 3. Targeting the PD1/PD-L1 pathway in breast cancer.

Antibody	Trial	Study type	Target	Subtype	n	ORR (%)
Avelu	JAVELIN[94]	Phase 1 stratified for PD-L1 solid tumor	PD-L1	All	168	4.8
				PD-L1+ All	12	33.3
				TNBC	58	8.6
				PD-L1+ TNBC	9	44.4
Pembro	KEYNOTE-012[99]	Phase 1b for PD-L1 positive solid tumors	PD1	PD-L1+ TNBC	27	18.5
	KEYNOTE-028[100]	Phase 1b for PD-L1 positive solid tumors		PD-L1+ HR+/HER2-	25	12
	KEYNOTE-086[101]	Phase 2 for TNBC		TNBC	170	4.7

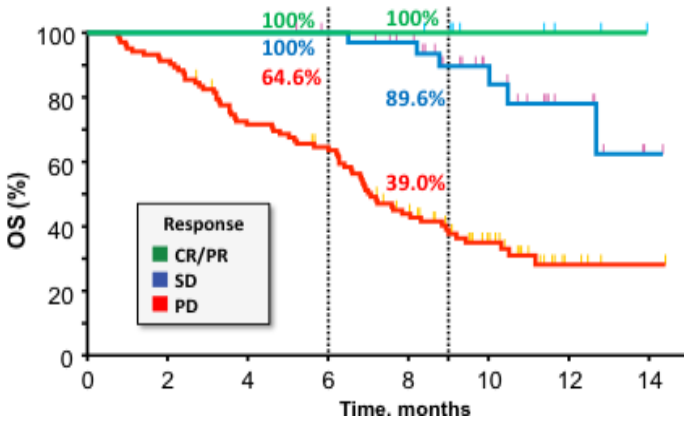
				PD-L1+ TNBC	105	4.8
Atezo	NCT01375842[102]	Phase 1 stratified PD-L1 for solid tumors	PD-L1	TNBC	112	10
				PD-L1+ TNBC	71	13

While the response was relatively low, it is still promising because of the observation that the patients who respond to treatment with immune checkpoint blockade have favorable prognosis and often show a significant increase in the overall survival with extended anti-tumor immunity (**Fig. 5**). Therefore, the main challenge is to find ways to enhance the tumor response to such therapy and to convert the non-responders to responders, and more important to further select the patients who are more likely to benefit. This will consequently help to decrease deaths tolls and open new hopes for patients with advanced stage/metastatic breast cancer.

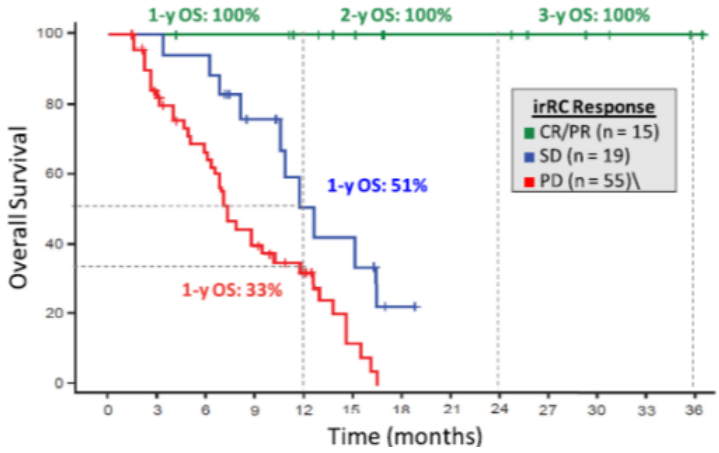
Immune checkpoint inhibitors have been studied in the neoadjuvant and adjuvant space in combination with chemotherapy as well. Currently 13 clinical trials with pembrolizumab are being studied in early breast cancer in all the subtypes (9 in TNBC and 4 HER2-negative), all setting (9 neoadjuvant and 4 adjuvant) and in combination with different SoC agents.

Figure 5. Kaplan-Meier overall survival analysis based on clinical response in TNBC patients treated with pembrolizumab in (A) KEYNOTE-086 and in (B) NCT01375842.

(A)



(B)



4.2.4 Combination of PD1/PD-L1 inhibition and chemotherapy in breast cancer

In early breast cancer, preliminary results from KEYNOTE-173 evaluating pembrolizumab in combination with chemotherapy as neoadjuvant treatment for TNBC were presented at ASCO 2017[103]. Data on 10 patients treated in cohort A and B, respectively, were reported. Treatment in cohort A consisted of 4 cycles of pembrolizumab + nab-paclitaxel followed by four cycles of pembrolizumab + doxorubicin + cyclophosphamide; treatment in cohort B was the same as in A but with carboplatin added to pembrolizumab and nab-paclitaxel. ORR in cohort A and B was 80% and 100%, respectively [42]. The ypT0/Tis ypN0 (noninvasive cancer and non in-situ cancer in the breast) pCR rate was 60% in cohort A and 90% in B. Using a Bayesian design, Nanda et al[104] used the I-SPY platform to compare preoperative pembrolizumab in combination with standard treatment with paclitaxel followed by doxorubicin + cyclophosphamide with standard treatment in HER2-negative early breast cancer. Addition of pembrolizumab increased pCR in HR+/HER2- patients from 14.8% to 28% and in TNBC patients from 19.3% to 71.4%.

In metastatic breast cancer, a phase Ib study of atezolizumab in combination with nab-paclitaxel in 32 pretreated patients with TNBC, of whom 24 were evaluable, have shown a confirmed ORR of 42% and an ORR of 71% with 4% CR. Notably, responses occurred both in tumors with high and little to no PD-L1 expression. The DoR was not reported[105].

Recently, the results of IMpassion130 have been reported. The Phase III IMpassion130 study met its co-primary endpoint of PFS. Results demonstrated that the combination of atezolizumab plus *nab*-paclitaxel, as a first-line treatment, significantly reduced the risk of disease worsening or death (PFS) in the intention-to treat and PD-L1 positive population with metastatic or unresectable locally advanced TNBC.

Treatment with the combination of pembrolizumab and eribulin demonstrated a 26.4% ORR for patients with metastatic (TNBC, according to updated findings from the ENHANCE1/KEYNOTE-150 phase Ib/II study presented at the 2017 San Antonio Breast Cancer

Symposium).

A range of studies have been initiated including several phase II/III studies evaluating in particular pembrolizumab and atezolizumab in combination with different chemotherapeutic compounds routinely used in breast cancer.

4.2.5 Pembrolizumab

4.2.5.1 Preclinical and clinical trial data

Although breast cancer has historically been considered immunologically silent, several preclinical and clinical studies suggest that immunotherapy has the potential to improve clinical outcomes for patients with breast cancer[106,107]. Breast cancer is one of the most commonly studied tumors for the presence of immune system cells in the lesion and scores of ongoing clinical trials are evaluating the role of immunotherapy in breast cancer treatment and prevention.

4.2.5.2 Preclinical studies with PD1 immune checkpoint inhibitors

Preclinical data from mouse models have shown that administration of antibodies blocking PD1/PD-L1 interaction increases infiltration of tumor-specific CD8-positive T cells and finally guides to tumor rejection, either as a monotherapy or in combination with other treatment modalities[108,109].

Pembrolizumab potently blocks binding to both ligands, PD-L1 and PD-L2, with IC50 values below 1 nM. Pembrolizumab binds to human and Cynomolgus monkey PD1 with comparable affinity and blocks the binding of human and Cynomolgus monkey PD1 to PD-L1 and PD-L2 with comparable potency. Pembrolizumab does not cross-react with dog, rat, or mouse PD1.

Pembrolizumab enhances T-cell responses in human donor blood cell cultures, with a half-maximal effective concentration of approximately 0.1 to 0.3 nM. Pembrolizumab strongly enhances T-lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and Cynomolgus monkeys. The antibody potentiates existing immune responses only in the presence of antigen-receptor stimulation and does not nonspecifically activate all T-cells.

Pembrolizumab does not bind Ig superfamily members CD28, CTLA-4, or ICOS. In in vitro PBMC and whole blood cytokine release assays, the cytokine levels induced by pembrolizumab were low, and comparable to those induced by trastuzumab. Pembrolizumab does not induce ADCC or CDC.

Safety pharmacology evaluations conducted as part of the 1- and 6-month toxicity and TK studies in Cynomolgus monkeys showed no pembrolizumab–related effects on any parameter evaluated (ECGs, general veterinary and physical examinations with body temperature and blood pressure, clinical observations, and histopathology of tissues from the cardiovascular, respiratory, renal, and nervous systems).

4.2.5.3 Clinical studies with pembrolizumab in various cancer types.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody of the IgG4/kappa isotype designed to directly block the interaction between PD1 and its ligands, PD-L1 and PD-L2. Many clinical studies have been conducted to evaluate the efficacy of pembrolizumab to treat various cancers. Pembrolizumab has demonstrated robust, substantial, and clinically meaningful benefit in the treatment of melanoma, non-small cell lung cancer (NSCLC), head and neck squamous cell cancer (HNSCC), urothelial carcinoma (UC), microsatellite instability-high (MSI-H) tumors, and gastric or esophagogastric junction adenocarcinoma based on RECIST 1.1 criteria and iRECIST recommendation. For classical Hodgkin lymphoma (cHL), demonstration of clinically meaningful benefit was based on Revised Response Criteria for Malignant Lymphoma (2007) from the IWG (For study details please refer to the pembrolizumab Investigator's Brochure.).

Pembrolizumab is indicated in Europe for the treatment of:

- In combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic **NSCLC** in adults whose tumors have no EGFR or ALK positive mutations.

- As monotherapy is indicated for the treatment of recurrent or metastatic **HNSCC** in adults whose tumors express PD-L1 with a ≥50% tumor proportion score (TPS) and progressing on or after platinum-containing chemotherapy.

- As monotherapy is indicated for the treatment of advanced (unresectable or metastatic) **melanoma** in adults.

- As monotherapy is indicated for the first-line treatment of metastatic **NSCLC** in adults whose tumors express PD-L1 with a ≥50% TPS with no EGFR or ALK positive tumour mutations.

- In combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous **NSCLC** in adults whose tumors have no EGFR or ALK positive mutations.

- As monotherapy is indicated for the treatment of locally advanced or metastatic **NSCLC** in adults whose tumors express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumor mutations should also have received targeted therapy before receiving Pembrolizumab.

- As monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical **cHL** who have failed autologous stem cell transplant and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV.

- As monotherapy is indicated for the treatment of locally advanced or metastatic **UC** in adults who have received prior platinum-containing chemotherapy.

- As monotherapy is indicated for the treatment of locally advanced or metastatic **UC** in adults who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 with a combined positive score ≥10

4.2.5.4 PD-L1PD-L1Clinical studies of pembrolizumab inhibitor in HR+/HER2 disease

Pembrolizumab has been evaluated in patients with HR+/HER2- metastatic breast cancer and in triple-negative disease[99,100]. Of the 248 patients with ER+/HER2-negative breast cancer who had evaluable tumor samples screened for PD-L1 expression, 48 (19%) had PD-L1-positive tumors. Of these, 25 patients were enrolled[100]. The overall response rate (ORR) observed was 14% and responses seemed to be long-lived. Overall tolerance was acceptable and no new concerns regarding auto-immune toxicity have emerged. In the triple-negative phase IB study (KEYNOTE-012), 111 heavily pre-treated patients with PD-L1-positive (defined as >1% expression in tumor or stromal cells) disease were included and received 10 mg/kg of pembrolizumab every 2 weeks as monotherapy[99]. Twenty-seven patients were evaluable for response and had an ORR of 18.5% with duration of 15 weeks to more than 47 weeks. Grade 3 or higher toxicity was observed in 15.6% of patients and there was one treatment-related death from disseminated intravascular coagulation in a patient with rapidly progressive disease not responding to three previous lines of therapy[99]. Findings presented during the 2017 San Antonio Breast Cancer Symposium (SABCS) showed the combination of eribulin and pembrolizumab resulted in an objective response rate (ORR) of 26.4% (95% CI: 18.3 – 35.9), the primary efficacy endpoint of the study. Three complete responses were observed; one of which was in a patient with a PD-L1-negative tumor (ENHANCE1/KEYNOTE-150).

4.3 Rationale

4.3.1 Rationale for the trial and selected population

Breast cancer is a clinically and biologically heterogeneous disease. In terms of global gene expression, 4 main molecular subtypes (Luminal A, Luminal B, HER2-E and Basal-like) have been identified and intensively studied in the last 15 years[22–25]. Known as the 'intrinsic subtypes of breast cancer', these groups of tumors have revealed critical differences in incidence[26,27], survival[28–30], and response to treatment[31,32]. Although the incidence of the non-luminal subtypes (i,e. Basal-like and HER2-E) in primary tumors is below 10%, current evidence suggest that this frequency is much larger in the advanced/metastatic setting, specially following endocrine treatment, 15-25% approximately[15,47,110].

The rationale to assess the anti-tumor effect (efficacy) of pembrolizumab and paclitaxel in PAM50 non-luminal disease within HR+/HER2- advanced breast cancer is as follows:

1. The prognostic value of the Basal-like and HER2-E intrinsic subtypes in metastatic breast cancer has been evaluated in four studies and cohorts. In all these studies[15,50,111] both non-

luminal subtypes were associated with worse PFS compared to Luminal subtypes. Thus, non-luminal HR+/HER2- tumors are aggressive and require novel therapeutic approaches.
2. Several studies[15,50] suggest that both non-luminal subtypes within HR-positive disease might not benefit substantially neither from anti-estrogen therapy and CDK4/6 or mTOR inhibitors. On the other hand, some studies[52,53] had shown that within HR+/HER2- disease, non-luminal tumors are highly chemo-sensitive.
3. Previous studies of the intrinsic subtypes have shown that Basal-like and HER2-E are associated with higher expression of immune-related genes or higher infiltration of stromal tumor infiltrating lymphocytes compared to the luminal subtypes[54–56]. Immune infiltration in breast cancer is associated with chemo-responsiveness and potentially benefit from anti-PD1/PD-L1 inhibitors[101,102,112–114].
4. In addition, one emerging biomarker of response to anti-PD1 therapy is the tumor mutational burden (I.e. the total number of mutations per coding area of a tumor genome). The HER2-E and Basal-like profiles have been associated with high mutational burden[112].
5. Immune checkpoint inhibitors given in monotherapy in advanced breast cancer have shown modest benefit in first-line, and very limited efficacy in later lines. However, response following anti-PD1/PD-L1 monotherapy is associated with large survival benefit in the advanced setting. Thus combination therapies are needed[101,102,114].
6. A range of studies have been initiated including several phase II/III studies evaluating in particular pembrolizumab in combination with different chemotherapeutic compounds routinely used in breast cancer, but none with predefined biomarker.

4.3.2 Justification for dose

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships

across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD1 saturation over a wide range of tumor penetration and PD1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.3.3 Rationale for endpoints

4.3.3.1 Efficacy endpoint

ORR is based on criteria related to changes in tumor size (e.g., RECIST) and is generally defined as the sum of partial and complete responses. ORR is a robust indicator of antitumor activity in many agents including anti-PD1 and is considered to be an established surrogate marker for clinical benefit. Significant antitumor activity of anti-PD1 agent in combination with chemotherapy, has been reported in patients with advanced TNBC[101]. Preliminary data with pembrolizumab in refractory ER-positive/HER2-negative metastatic breast cancer patients have shown promising antitumor activity, resulting in response rates practically similar to those observed with the best chemotherapy agents used in this setting[100]. However, no data are available so far with anti-PD1 and anti-PD-L1 agents in combination with chemotherapy in this non-luminal subtype.

The patients who respond to treatment with immune checkpoint blockade have favorable prognosis and often show a significant increase in the overall survival with extended anti-tumor immunity (**Fig. 5**) and also acceptable safety profile in early phase trials in metastatic setting.

4.3.3.2 Biomarker research

4.3.3.2.1 Biomarkers to predict benefit of anti-PD1

Anti-PD1 drugs such as pembrolizumab have demonstrated unprecedented clinical efficacy in more than 15 cancer-types[115]. Patients responding to these therapies usually gain a large survival benefit, leading to impressive outcomes. Thus, pre-selecting patients most likely to respond to anti-PD1 is necessary.

Recent studies support the role of PD-L1 expression by immunohistochemistry (IHC) as a potential biomarker for pembrolizumab in non-small cell lung cancer (NSCLC)[116]. However, its predictive value in other cancer-types is controversial. Moreover, IHC-based detection of PD-L1 has important limitations, such as different sensitivities of the antibodies used, its subjectivity in scoring and cut-off determination, and varying tissue sources assayed for expression (archived or fresh, primary or metastatic tumor)[116]. Therefore, identification of reproducible biomarkers that can be applied to predict benefit of anti-PD1 might be of clinical value.

It is abundantly clear that robust biomarkers are needed to determine which breast cancer patients may or may not respond to checkpoint blockade. Response to checkpoint blockade has been associated with several biomarkers, including PD-L1 expression on tumor cells and/or associated immune cells, tumor-infiltrating lymphocytes (TILs), tumor mutational burden (TMB), and PD1 mRNA expression. All these biomarkers will be detected in the TATEN study samples. In addition, the first cycle is given without paclitaxel to be able to analyze the early dynamics changes of ctDNA after 1 cycle of pembrolizumab and the relationship with efficacy of the treatment.

5. METHODOLOGY

[redacted] Study population

5.1.1 Participant inclusion criteria

Patient eligibility will be reviewed and documented by a suitable member of the Investigator's study team before the patients are enrolled in the study (section 7.1.1.2)

Any asterisked* are also applicable as an exclusion criterion prior to perform the prescreening PAM50 testing. To perform the PAM50 assay, investigator judgement of patient's potential eligibility to the study should be assessed as per TRIAL FLOW CHART (section 6).

Participants are eligible to be included in the study only if all of the following criteria apply:

1. *Male/female participants who are at least 18 years of age on the day of signing informed consent with histologically confirmed diagnosis of locally advanced or metastatic, histologically documented hormone receptor positive (ER and/or PR expression >1%) and

HER2- breast cancer by local testing, not amenable to surgical therapy will be enrolled in this study.

a) HER2 negativity is defined as either of the following by local laboratory assessment: IHC 0, IHC 1+ or IHC2+/*in situ* hybridisation (ISH) negative as per American Society of Clinical Oncology (ASCO)-College of American Pathologists Guideline (CAP) guideline (ISH negative is defined as a ratio of HER2 to CEP17 <2.0)[117].
b) ER and/or PR positivity are defined as >1% of cells expressing HR via IHC analysis as per ASCO-CAP guideline[118]

2. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.

3. * Eligible for taxane therapy.

4. * No prior chemotherapy for inoperable locally advanced or metastatic breast cancer.

5. Prior radiation therapy for metastatic disease is permitted. Subjects who were treated with radiation therapy may participate as long as at least 2 weeks have elapsed since the last dose of radiation therapy or have recovered from the effects of radiation before allocation whichever is the latest.

6. Disease refractory to CDK4/6 inhibitors, defined as recurrence during or within 12 months after the end of adjuvant treatment or progression during or within 6 months after the end of treatment for advanced/metastatic disease.

   Notes: CDK4/6 inhibitors do not have to be the last treatment prior to randomization. Other prior anticancer endocrine therapy, e.g. aromatase inhibitors, fulvestrant or tamoxifen, are also allowed.

7. * Previous chemotherapy with a taxane for early breast cancer (neoadjuvant or adjuvant setting) is permitted.

8. * Availability of formalin-fixed paraffin-embedded (FFPE) tumor block, collected during advanced/metastatic disease, with an associated pathology report. The tumor tissue should be of good quality based on total and viable tumor content and must be evaluated centrally for PAM50 analysis prior to enrollment. Patients whose tumor tissue is not evaluable for central testing are not eligible. If PAM50 analysis of tumor sample has alredy been performed at central lab (i.e analysis from other SOLTI clinical trial) PAM50 result can be valid for this study.

   a) Acceptable samples include core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions or biopsies from bone metastases.

   b) Fine needle aspiration, brushing, cell pellet from pleural effusion and lavage samples are not acceptable.

9. Non-Luminal subtype as per PAM50 analysis (i.e. HER2-enriched or Basal-like).

10. * Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Evaluation of ECOG is to be performed within 10 days prior to the date of allocation/randomization.

11. * Life expectancy ≥ 12 weeks

12. * Measurable disease, as defined by RECIST v1.1. (Note: Previously irradiated lesions can be considered as measurable disease only if disease progression has been unequivocally documented at that site since radiation.)

13. Adequate hematologic and end-organ function, defined by the following laboratory results (**Table 4**) obtained within 10 days prior to the first study treatment (Cycle 1, Day 1):

Table 4. Adequate organ function laboratory values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL[a]
Platelets	≥100 000/µL[b]
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[c]
Renal	
Creatinine OR Measured or calculated [d] creatinine clearance (MDRD GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or a PTT is within therapeutic range of intended use of anticoagulants
ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.	

[a] Criteria must be met without granulocyte colony stimulating factor [G-CSF] support within 2 weeks prior to Cycle 1, Day 1.

[b] Criteria must be met without transfusion within 2 weeks prior to Cycle 1, Day 1.

[c] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within 2 weeks prior to Cycle 1, Day 1.

[d] Creatinine clearance (CrCl) should be calculated per institutional standard.

Male participants:

14. A male participant must agree to use contraception as detailed in Appendix 3 of this protocol during the treatment period and for at least 180 days after the last dose of paclitaxel and 120 days form the last doses of pembrolizumab and refrain from donating sperm during this period.

Female participants:

15. A female participant is eligible to participate if she is not pregnant (see Appendix 3), not breastfeeding, and at least one of the following conditions applies:
    a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix 3
    OR
    b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 180 days after the last dose of paclitaxel and 120 days from the last dose of pembrolizumab.

5.1.2 Participant exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

1. A WOCBP who has a positive urine pregnancy test within 72 hours prior to C1D1 (see Appendix 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

2. * Has received prior therapy with an anti-PD1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).

3. * History of hypersensitivity reactions to paclitaxel or other drugs formulated in the same solvent as paclitaxel (polyoxyethylated castor oil).

4. Resolution of all acute toxic effects of prior anti-cancer therapy or major surgical procedures to NCI CTCAE version 5.0 Grade ≤ 1 (except alopecia or other toxicities not considered a safety risk for the patient at investigator´s discretion).
    Note: Placement of central venous access catheter(s) (e.g., port or similar) is not considered a major surgical procedure and is therefore permitted.

5. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

   Note: It is not recommended the use of live or attenuated COVID-19 vaccines within 30 days of initiation or during study treatment. However, if vaccination with these vaccines is required, please ask for advice on how to proceed the Medical Monitor.

6. Uncontrolled pleural effusion, pericardial effusion, or ascites (Note: patients with indwelling catheters, such as PleurX® are allowed).

7. Uncontrolled hypercalcemia (>1.5 mmol/L [>6 mg/dL] ionized calcium or serum calcium [uncorrected for albumin] >3 mmol/L [>12 mg/dL] or corrected serum calcium >ULN) or clinically significant (symptomatic) hypercalcemia

8. * Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

9. * Has a known additional malignancy that is progressing or has required active treatment within the past 3 years. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin or carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

10. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e. without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.

11. * Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

12. * Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

13. * Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.

14. * Prior allogeneic stem cell or solid organ transplantation

15. Has an active infection requiring systemic therapy.

16. * Has a known history of Human Immunodeficiency Virus (HIV).

17. * Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Note: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

18. * Has a known history of active TB (Bacillus Tuberculosis).

19. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

20. * Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

21. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of pembrolizumab or 180 days after the last dose of paclitaxel.

5.1.3 Lifestyle restrictions

5.1.3.1 Meals and dietary restrictions

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

5.1.3.2 Contraception

Pembrolizumab and paclitaxel may have adverse effects on a fetus in utero. Refer to Appendix 3 for approved methods of contraception.

For this study, male participants will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

5.1.4 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab or paclitaxel, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy

has been completed or terminated. The outcome of the pregnancy will be reported to Merck within 2 working days if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to Merck and followed as described in Section 7.2.2.

5.1.5 Use in nursing women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breast-feeding are not eligible for enrollment.

[redacted] Trial treatments

The treatment to be used in this trial is outlined below in **Table 5**

Table 5. Trial treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
Paclitaxel	80 mg/m^2	Q1W	IV infusion	Day 1,8,15 of each 3 week cycle (beginning in cycle 2)	Standard of care

Trial treatment should begin on the day of inclusion or up to 3 days after the scheduled Day 1.

5.2.1 Timing of dose administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.1). Trial treatment may be administered up to 3 days after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as 30 minutes IV infusion every 3 weeks beginning in Cycle 1. 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 of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

For the first infusion of pembrolizumab, no premedication will be administered. However, should the patient experience infusion-related reaction(s) during any infusion, premedication with

antihistamines will be administered for subsequent infusions at the discretion of the treating physician.

Administration of pembrolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. Pembrolizumab infusions will be administered per the instructions outlined in **Table 6**.

On day 1 cycle 2 (C2D1) when paclitaxel and pembrolizumab are given, pembrolizumab will be given first and patients will be observed for 1 hour for infusion and other AEs. Paclitaxel may then be administered.

Paclitaxel will be administered at the 80 mg/m2 dose via 1-hour IV infusion on Days 1, 8, and 15 of every 21-day cycle (beginning in Cycle 2). On days of scheduled infusions of pembrolizumab and paclitaxel (i.e., Day 1 of every cycle), paclitaxel is to be administered after infusion of pembrolizumab. Doses of paclitaxel should not be administered more frequently than every 7 days.

To reduce the risk of severe hypersensitivity reactions, all patients should be premedicated prior to paclitaxel administration. Prior to receiving the first two study infusions of paclitaxel, all patients will receive corticosteroids (8-10 mg dexamethasone or equivalent) as part of either the institutional SoC or the following premedication:

- Dexamethasone 8-10 mg (or equivalent) administered orally approximately 12 and 6 hours prior to the paclitaxel infusion. Patients may be treated with dexamethasone ≤10 mg IV within 1 hour prior to the paclitaxel infusion if the patient did not take the oral dexamethasone.

- Diphenhydramine 50 mg IV (or equivalent) 30-60 minutes prior to the paclitaxel infusion

- Cimetidine 300 mg IV or ranitidine 50 mg IV (or equivalent) 30-60 minutes prior to paclitaxel infusion.

Because the effects of corticosteroids on T-cell proliferation have the potential to ablate early pembrolizumab-mediated anti-tumor immune activity, it is recommended that the dose of dexamethasone (or equivalent) is minimized to the extent that is clinically feasible. For example, if paclitaxel is well tolerated during the first two weekly infusions without apparent hypersensitivity reaction, a reduction in the dose of dexamethasone premedication (or equivalent) should be considered for subsequent cycles if permitted by institutional SoC. This approach has been reported to be successful in the literature[119].

In the absence of unacceptable toxicity, paclitaxel will be administered until PD or until the end of the study, whichever occurs earlier. Paclitaxel and pembrolizumab may be discontinued for toxicity independently of each other in the absence of disease progression.

Any overdose or incorrect administration of paclitaxel should be noted on the Paclitaxel Administration eCRF. AEs associated with an overdose or incorrect administration of paclitaxel should be recorded on the AE eCRF.

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

5.2.2 Dose modification and toxicity management: general considerations

Reasons for dose modifications or delays, the supportive measures taken, and the outcomes will be documented in the patient's chart and recorded on the eCRF.

When several toxicities with different grades of severity occur at the same time, the dose interruptions or modifications should be according to the highest grade observed. If, in the opinion of the investigator, a toxicity is considered to be due solely to one component of the study treatment (i.e., pembrolizumab or paclitaxel) and the dose of that component is delayed or modified in accordance with the guidelines below, the other component may be administered if there is no contraindication.

When treatment is temporarily interrupted because of toxicity caused by pembrolizumab or paclitaxel, the treatment cycles will be restarted such that the pembrolizumab and paclitaxel infusions remain synchronized.

If it is anticipated that paclitaxel will be delayed by $\geq$1 week, then pembrolizumab should be given without the chemotherapy, as long as there is no contraindication.

In general, the start of a cycle may be delayed allowing recovery from toxicities, but there should be no delays within cycles. Cycle length is fixed at 21 days, and dosing on days 8 and 15 of a cycle may be skipped but should not be delayed outside of the +1 days window.

The treating physician may use discretion in accelerating the dose modification guidelines described below depending on the severity of toxicity and an assessment of the risk versus benefit for the patient.

5.2.3 Dose modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in **Table 6**.

Table 6. Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv5.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus).

	Recurrent Grade 3 or Grade 4	Permanently discontinue		• Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with 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.
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.

Nephritis grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. **NOTE:** For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in **Table 7**.

Table 7. Pembrolizumab infusion reaction dose modification and treatment guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 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 participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with SOLTI. The reason for interruption should be documented in the patient's study record.

5.2.4 Dose modification and toxicity management for AEs associated with paclitaxel

Paclitaxel infusion should be discontinued immediately in case of severe hypersensitivity reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria; these events should be treated with aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with paclitaxel. In addition, paclitaxel should be permanently discontinued upon ruling out infectious etiology (using routine microbiological and/or immunologic methods) and making a diagnosis of pneumonitis. Consideration may be given to performing pulse oximetry and pulmonary function tests to confirm respiratory and ventilation compromise in patients with suspected pneumonitis.

Other events that required discontinuation of paclitaxel in clinical trials include cases of severe neurotoxicity, such as peripheral neuropathies (1% of all patients). Occasionally paclitaxel infusions must be interrupted or discontinued because of initial or recurrent hypertension. Frequent vital sign monitoring, particularly during the first hour of paclitaxel infusion, is recommended.

Refer to the local paclitaxel prescribing information for further details

Hematologic Toxicities

Absolute neutrophil count (ANC) must be ≥1500/μL (≥1500 cells/mm3) and platelet count must be ≥100,000/μL (≥100,000 cells/mm3) for the patient to receive paclitaxel 80mg/m^2 on any treatment day (Day 1, 8, 15 of any 21-day cycle).

Dose modifications should be made according to the following **Table 8**:

Table 8. Hematological dose modifications

ANC		Platelets	Paclitaxel Dose
≥1,500/µL (≥1,500 cells/mm3)	and	≥100,000/µL (≥100,000 cells/mm3)	80 mg/m^2
1,000-1,499/µL (1,000-1,499 cells/mm3)	or	75,000-99,999/µL (75,000-99,999 cells/mm3)	65mg/m^2
<1,000/µL (<1,000 cells/mm3)	or	<75,000/µL (<75,000 cells/mm3)	Hold(1)

(1) If treatment is held, the CBC should be repeated until ANC ≥1500/µL (≥1500 cells/mm3) and platelets ≥100,000/µL (≥100,000 cells/mm3). If paclitaxel therapy must be held for > 3 weeks to allow for resolution of haematologic toxicity, the patient will discontinue paclitaxel treatment but may continue receiving pembrolizumab.

For any patient experiencing any of the following haematologic toxicities, the paclitaxel dose should be reduced to 65 mg/m² for all subsequent cycles:

- Fever (>38.5°C) associated with ANC <1,000/µL (<1,000 cells/mm3)
- Absolute granulocyte count <500/µL (<500 cells/mm3) for > 5 days
- Significant bleeding associated with a platelet count <40,000/µL (<40,000 cells/mm3)
- Any platelet count <20,000/µL (<20,000 cells/mm3).

If these severe hematologic toxicities recur in subsequent cycles despite dose reduction, paclitaxel should be discontinued, however the patient may continue receiving pembrolizumab.

If the start of a cycle is delayed (i.e. both pembrolizumab and paclitaxel are held) for low counts, Day 1 will be postponed**,** and dosing resumed when ANC recovers to ≥1500/µl (≥1500 cells/mm3) and platelet count returns to ≥100,000/µl (≥100,000 cells/mm3).

In certain situations, a cycle may begin with the administration of pembrolizumab alone (without paclitaxel on Day 1). If paclitaxel cannot be administered on Day 8 of the cycle, it may be administered on Day 15 if counts have recovered to permissible levels. If paclitaxel cannot be administered on Day 15 of the cycle, the next dose of paclitaxel should be

administered on Day 1 of the following cycle when ANC and platelets counts have recovered to permissible levels.

Hepatic Toxicities

In case of hepatic toxicities, dose modifications should be made according to the following **Table 9**:

Table 9: Hepatic dose modifications

AST		**Bilirubin**	**Paclitaxel dose**
≤ 5 x ULN	And	≤ 1.5 mg/dL (≤ 25.65 µmol/L)	80mg/m2
> 5 but ≤ 10 x ULN	Or	1.6 - 2.5 mg/dL (27.36 - 42.75 µmol/L)	65mg/m2
> 10 x ULN	Or	≥ 2.6 mg/dL (≥ 44.46 µmol/L)	Hold(1)

AST: aspartate aminotransferase; ULN: upper limit of normal

(1) Hold therapy until AST < 10 x ULN and bilirubin < 2.5 mg/dL. If paclitaxel must be held for > 3 weeks to allow for resolution of hepatic toxicity, the patient will discontinue paclitaxel treatment but may continue receiving pembrolizumab.

Patients requiring a delay in paclitaxel therapy due to hepatic toxicity should be evaluated for possible progressive hepatic metastases.

Peripheral Neuropathy

If grade 3 toxicity develops, paclitaxel treatment should be withheld until the neuropathy recovers to < grade 1 (pembrolizumab treatment should continue as scheduled). When treatment is resumed, the paclitaxel dose should be reduced permanently to 65 mg/m². If grade 3 neuropathy persists for > 3 weeks or recurs after dose reduction, the patient will discontinue paclitaxel treatment but may continue receiving pembrolizumab.

Gastrointestinal Toxicity

Nausea and/or vomiting should be controlled with standard antiemetics and will not result in dose modification.

Anaphylaxis/Hypersensitivity

- Mild symptoms (e.g., mild flushing, rash pruritus): No treatment needed. Supervise at bedside and complete paclitaxel infusion.

- Moderate symptoms (moderate flushing, rash, mild dyspnea, chest discomfort): Stop paclitaxel infusion. Administer diphenhydramine 25 mg (or equivalent) and dexamethasone 10 mg IV (or equivalent). After recovery of symptoms, resume infusion at half the previous rate for 15 minutes. If no further symptoms occur, complete the infusion at the full dose rate. If symptoms recur, the reaction should be reported as an AE and the patient will discontinue paclitaxel treatment but may continue pembrolizumab.

- Severe life-threatening symptoms (e.g., hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilators, generalized urticaria): Stop the infusion and administer diphenhydramine 25 mg (or equivalent) and dexamethasone 10 mg IV (or equivalent). Add epinephrine or bronchodilators if needed. The reaction should be reported as an AE and the patient will discontinue paclitaxel treatment but may continue pembrolizumab.

Other Toxicity

If the patient develops any other grade 3 or 4 toxicity considered related to paclitaxel, paclitaxel should be held until symptoms resolve to grade 1 or less (pembrolizumab treatment should continue as scheduled). When treatment is resumed, the paclitaxel dose should be reduced permanently to 65 mg/m^2. If grade 3 toxicity persists for >3 weeks or recurs after dose reduction, the patient will discontinue paclitaxel treatment but may continue pembrolizumab.

Refer to the local paclitaxel prescribing information for further details.

[redacted] Concomitant medications/vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participants's primary physician.

5.3.1 Acceptable concomitant medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.3.2 Prohibited concomitant medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with SOLTI.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, SOLTI and the participant.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.3.3 Rescue medications & supportive care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.2, [**Table 6**]. Where appropriate, these guidelines include the use of oral or IV 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 of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to [**Table 6**] in Section 5.2.2 for guidelines regarding dose modification and supportive care.

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

[redacted] Participant withdrawal/discontinuation criteria

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or SOLTI if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A participant must be discontinued

from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment.
- Confirmed radiographic disease progression outlined in Section 7.1.2.6.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.
- Unacceptable adverse experiences as described in Section 5.2.2.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.

- The participant has a confirmed positive serum pregnancy test.
- Noncompliance with study treatment or procedure requirements.
- Recurrent Grade 2 pneumonitis.
- Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving 2 cycles of the combination including 2 doses of pembrolizumab and at least 80% of the planned doses of paclitaxel beyond the date when the initial CR was declared.
- The participant is lost to follow-up.
- Completion of 35 treatments (approximately 2 years) with pembrolizumab.

Note: The number of treatments is calculated starting with the first dose.

- Administrative reasons

5.5 Participant replacement strategy

Patients will be replaced if they are considered to be non-evaluable. An evaluable patient is one that has received at least one combination dose, has measurable disease according to the Investigator site assessment and has at least one postbaseline tumor assessment.

Patients who have failed screening (usually because they have failed one or more of the inclusion or exclusion criteria) will not receive study treatments and are considered not to be evaluable

5.6 Clinical criteria for early trial termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to participants

4. Plans to modify or discontinue the development of the study drug

SOLTI, as Sponsor, may decide to put an end to the study at any time for safety reasons, due to slow patient recruitment or due to the emergence of new data that could alter the relevance of the study objectives. The steering committee (SC) will provide their counsel. Ethics committees and health authorities will be informed about all decisions in this respect. The decision to terminate the study early will be binding for all investigators at all study sites.

In the event of early termination, all investigators must inform their patients as soon as possible and they will be responsible for the follow-up and subsequent therapeutic management as appropriate and in accordance with recommended standard practice. Investigators may be informed of additional procedures to be performed to ensure the safety and better care of their patients.

6. TRIAL FLOW CHART

[redacted] Study flow chart

Trial Period:	**Screening Phase**		**Treatment Cycles[b]**									**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening[a] (Visit 2)	1			2			All Cycles			Discon	Safety Follow-up[c]	Follow-Up	Survival Follow-Up
Scheduling Window (Days):		-28 to -1	1+ 3	8± 1	15± 1	1+3	8± 1	15± 1	1+ 3	8± 1	15± 1	At time of Discon	30 days post discon	Every 9 weeks post discon	Every 12 weeks[t] (±21 days)
Administrative Procedures															
Pre-screening Consent	X														
Informed Consent		X													
Inclusion/Exclusion Criteria	X	X													
Demographics and Medical History[d]		X													
Prior and Concomitant Medication Review[e]		X	X			X			X			X	X		
Pembrolizumab Administration			X			X			X						
Paclitaxel[f]						X	X	X	X	X	X				
Post-study anticancer therapy status														X	X
Survival Status															X
Clinical Procedures/Assessments															
Review Adverse Events			X			X			X			X	X	X	
Full Physical Examination[g]		X													
Directed Physical Examination[h]			X			X			X			X			
Height		X													

Trial Period:	**Screening Phase**		**Treatment Cycles[b]**									**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening[a] (Visit 2)	1			2			All Cycles			Discon	Safety Follow-up[c]	Follow-Up	Survival Follow-Up
Scheduling Window (Days):		-28 to -1	1+ 3	8± 1	15± 1	1+3	8± 1	15± 1	1+ 3	8± 1	15± 1	At time of Discon	30 days post discon	Every 9 weeks post discon	Every 12 weeks[t] (±21 days)
Vital Signs and Weight[i]		X	X			X			X						
ECOG Performance Status[j]		X	X			X			X			X	X	X	
12- Lead Electrocardiogram (Locally performed)		X													
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory															
Pregnancy Test – Urine or Serum β-HCG[k]		X	X			X			X						
PT/INR and aPTT		X													
CBC with Differential[l]		X	X	X	X	X	X	X	X	X	X		X		
Comprehensive Serum Chemistry Panel[m]		X	X			X			X				X		
Urinalysis[n]		X	X			X			X				X		
T3 (free or total), Free T4 and TSH			Every 2 cycles										X		
Efficacy Measurements															
Tumor Imaging[o]			Every 9 weeks (63 ± 5 days)									X[p]		X[q]	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood															
Archival or Newly Obtained Tissue Collection[r]	X														
Blood Collection[s]			X			X						X			
Confirmation of *PAM50* eligibility & inclusion criteria															
Medical monitor eligibity confirmation		X													

a) Written informed consent is required before performing any study-specific tests or procedures. Signing of the Informed Consent Form can occur outside the 28-day screening period. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study entry (except where otherwise specified) may be used for screening assessments rather than repeating such tests. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

b) Assessment window of + 3 days for Cycles ≥2, Day 1. If scheduled dosing is precluded because of a holiday, then dosing may be postponed to the soonest following date, with subsequent dosing continuing on the specified schedule. If treatment was postponed for fewer than 2 days, the patient can resume the original schedule. If scheduled study assessments cannot be obtained because of a holiday, these assessments should then be obtained at the soonest following date, provided that the soonest following date is not within 2 days of other regularly scheduled study assessments. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed prior to study treatment infusion unless otherwise noted.

c) Patients will be asked to return to the clinic not more than 30 days after the decision to discontinue treatment for a treatment discontinuation visit. The visit at which the decision is made to discontinue treatment (e.g., disease progression is determined or confirmed) may be used as the treatment discontinuation visit. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy.

d) Cancer history includes stage, date of diagnosis, and prior anti-tumor treatment. Demographic information includes age and self-reported race/ethnicity. Reproductive status and smoking history should also be captured.

e) Concomitant medications include any prescription medications or over-the-counter medications. At screening, any medications the patient has used within the 28 days prior to Cycle 1, Day 1. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded.

f) Weekly paclitaxel beginning in Cycle 2.

g) A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems as well as weight (in kilograms) and height (in centimeters; height is measured at the screening visit only). Symptom-directed physical exam after baseline assessment.

h) Directed physical examination should include, symptom-directed examination or as clinically indicated. Limited physical examination will be performed monthly every treatment cycle, with additional examinations as clinically indicated at baseline.

i) Vital signs include heart rate, blood pressure, and temperature.

j) Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, as assessed within 10 days prior to the start of study treatment

k) Serum/urine pregnancy test within 72 hours before Cycle 1, Day 1. Afterward, perform every cycle. A positive urine test must be confirmed with a serum test

l) Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated. Local laboratory assessments from each cycle must be reviewed prior to study treatment administration for each cycle. Laboratory tests for screening should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing.

m) Serum chemistry includes creatinine, sodium, potassium, magnesium, calcium, glucose, total bilirubin, ALT, AST, alkaline phosphatase, Lactate dehydrogenase (LDH). Local laboratory assessments from each cycle must be reviewed prior to study treatment administration for each cycle. Screening results may be valid for Cycle 1, Day 1 if performed within 10 days prior to Week 1, Day 1.

n) Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood). Screening results may be valid for Week 1, Day 1 if performed within 10 days prior to Week 1, Day 1.

Trial Period:	**Screening Phase**		**Treatment Cycles[b]**									**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening[a] (Visit 2)	1			2			All Cycles			Discon	Safety Follow-up[c]	Follow-Up	Survival Follow-Up
Scheduling Window (Days):		-28 to -1	1+ 3	8± 1	15± 1	1+3	8± 1	15± 1	1+ 3	8± 1	15± 1	At time of Discon	30 days post discon	Every 9 weeks post discon	Every 12 weeks[t] (±21 days)

o) Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to Cycle 1, Day 1 may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at the screening visit. Radiologic imaging performed during the screening period should consist of 1) CT and/or MRI of the chest/abdomen/pelvis 2) Bone scan or PET scan should be performed to evaluate for bone metastases and 3) any other imaging studies (CT neck, plain films, bone scan etc.) as clinically indicated by the treating physician. The same radiographic procedures and technique must be used throughout the study for each patient (e.g., if the patient had CT chest/abdomen/pelvis performed during screening, then she should subsequently undergo CT performed using the same radiologic protocol throughout the remainder of the study). Results must be reviewed by the investigator before dosing at the next cycle. Tumor assessments will be performed at baseline, every 9 weeks (63 days ± 5 days). All known sites of disease documented at screening should be re-assessed at each subsequent tumor evaluation. Tumor assessments performed after the screening period should consist of 1) CT and/or MRI of the chest/abdomen/pelvis, 2) bone scan or PET scan if there were osseous sites of disease identified or if these studies are felt to be clinically indicated by the treating physician, and 3) any other imaging studies felt to be clinically indicated by the treating physician. Tumor response will be evaluated using both RECIST v1.1 and immune-modified RECIST criteria. In the absence of disease progression, tumor assessments should continue regardless of whether patients discontinue study treatment, unless they withdraw consent or the study is terminated by SOLTI, whichever occurs first.

p) If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. In participants who discontinue study treatment due to documented disease progression and the Investigator elects not to implement iRECIST, this is the final required tumor imaging.

q) In subject who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 9 weeks (± 5 days) until (1) the star of new anti-cancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs the first.

r) Tumor tissue should be of good quality based on total and viable tumor. An FFPE block should be provided. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Retrieval of archival tumor sample can occur outside the 28-day screening period (centrally perform PAM50 test). Tumor sample from metastatic disease period is mandatory.

s) Plasma from 30 ml of blood will be collected and banked at C1D1 (samples may be extracted within the ten previous days to Week 1 Day1), C2D1 and at progression.

t) Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 21 days) until death, loss to follow-up, withdrawal of consent or until study termination by SOLTI. All patients will be followed for survival and new anti-cancer therapy (including targeted therapy and immunotherapy) information unless the patient requests to be withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

7. TRIAL PROCEDURES

[redacted] Trial procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by SOLTI and/or Merck for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative procedures

7.1.1.1 Informed consent

The Investigator must obtain documented consent from each potential participant prior to participating in a clinical trial.

7.1.1.1.1 Molecular pre-screening

After signing the molecular pre-screening consent, tumor tissue (archival or newly obtained or excisional biopsy of a tumor lesion not previously irradiated) will be sent to a central laboratory to analyze non-luminal subtype by PAM50 test. This will be conducted during a pre-screening phase prior to enrolling into the trial (≥ Day 1). For eligibility into the study, patients **must** be non-luminal by PAM50 test analyzed in the designated laboratory. Tumor tissue sample obtained during the advanced/metastatic setting is mandatory, it is recommended to provide a tumor sample collected after the most recent progression or recurrence. Tumor tissue requirements, along with shipping requirements, will be detailed in the sample management plan provided by SOLTI.

To perform the PAM50 test, investigator judgement of patient's potential eligibility to the study should be assessed as per inclusion/exclusion criteria (section 5.1) and TRIAL FLOW CHART (section 6.1).

7.1.1.1.2 General informed consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB/ERC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.3 Consent and collection of specimens for future biomedical research

The investigator or qualified designee will explain the Future Biomedical Research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research subtrial. A copy of the informed consent will be given to the participant.

7.1.1.2 Inclusion/exclusion criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the trial. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before allocation. Results from evaluation will be sent together with a completed study-specific Patient Enrollment Form to the medical monitor for evaluation. Decision will be available within 24 hours, confirming whether patient might be allocated. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

7.1.1.3 Medical history

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and concomitant medications review

7.1.1.4.1 Prior medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the trial. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.1.4.2 Concomitant medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Disease details and treatments

7.1.1.5.1 Disease details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.5.2 Prior treatment details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.5.3 Subsequent anti-cancer therapy status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up.

7.1.1.6 Assignment of screening number

All consented participants will be given a unique screening number and will be done centrally through the eCRF that will be used to identify the participant for all procedures that occur prior to randomization. Each participant will be assigned only one screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit.

7.1.1.7 Assignment of randomization number

Not applicable

7.1.1.8 Trial compliance (medication/diet/activity/other)

Administration of trial medication(s) will be witnessed by the investigator and/or trial staff. The total volume of trial medication infused will be compared with the total volume prepared to determine compliance with each dose administered.

Interruptions from the protocol specified treatment plan for greater than 3 weeks between pembrolizumab or paclitaxel doses for nondrug-related or administrative reasons require consultation between the investigator and SOLTI and written documentation of the collaborative decision on participant management.

7.1.2 Clinical procedures/assessments

7.1.2.1 Adverse event (AE) monitoring

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0 (see Appendix 2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full physical exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening.

Complete physical examination: must include evaluation of the head, mouth, eyes, ears, nose and throat, neck (including thyroid), abdomen, back, extremities, lymph nodes, and cardiovascular systems, dermatological, locomotor, respiratory, digestive, genitourinary and neurological systems, weight (Kg) and height (cm). If no abnormal data are observed during selection, the full physical examination may be based on concurrent signs and / or symptoms.

7.1.2.3 Directed physical exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.1.2.4 Vital signs

The investigator or qualified designee will take vital signs at screening, at Day 1 of each cycle of treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.1). Vital signs should include temperature, pulse, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) performance scale

The investigator or qualified designee will assess ECOG status (see Appendix 1) at screening, at Day 1 of each cycle of treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor imaging and assessment of disease

Tumor imaging is strongly preferred to be acquired by computed tomography (CT). For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when local practice mandates it. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

Expedited confirmation of measurable disease based on RECIST 1.1 at screening should be used to determine participant eligibility. Confirmation that the participant's imaging shows at least 1 lesion that is appropriate for selection as a target lesion per RECIST 1.1 is highly recommended prior to participant allocation.

7.1.2.6.1 Initial tumor imaging

Initial tumor imaging at Screening must be performed within 28 days prior to the date of allocation. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1.

Radiologic imaging performed during the screening period should consist of the following:

1) Initial screening assessments must include computerized tomography (CT) scans (with oral/IV contrast unless contraindicated) and/or magnetic resonance imaging (MRI) of the chest/abdomen/pelvis. A spiral CT scan of the chest may be obtained but is not a requirement.

MRIs of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest may be used in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance). If a CT scan for tumor assessment is performed using a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full contrast diagnostic CT scan.

2) Bone scan or PET scan should be performed to evaluate for bone metastases;

3) CT scans of the neck should also be performed if clinically indicated during the screening period;

4) At the investigator's discretion, other methods of assessment of measurable disease per RECIST v1.1 may be used.

5) Brain imaging, if performed to document the stability of existing metastases, should be by MRI if possible. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

7.1.2.6.2 Tumor imaging during the study

The first on-study imaging assessment should be performed at 9 weeks (63 days ± 5 days]) from the date of allocation. Subsequent tumor imaging should be performed every 9 weeks (63 days ±5 days) or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator.

For each patient, the same radiographic procedures and technique used to assess disease sites at screening must be used throughout the study (e.g., the same contrast protocol for CT scans and/or magnetic resonance imaging [MRI]), and results must be reviewed by the investigator before dosing at the next cycle. All known sites of disease documented at screening/baseline should be re-assessed at each subsequent tumor evaluation. To the extent feasible, assessments should be performed by the same evaluator to ensure internal consistency across visits

At the investigator's discretion, CT or other clinically appropriate scans may be repeated at any time if progressive disease is suspected. If the initial screening bone scan or PET scan does not show evidence of bone metastases, then these procedures do not need to be repeated unless clinically indicated or at the treating physician's discretion.

Per iRECIST (Section 7.1.2.6.5), disease progression should be confirmed by the site 4 to 8 weeks after first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the Investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 7.1.2.6.5 Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may

resume at the subsequent scheduled imaging time point, if clinically stable. Participants who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment. Exceptions are detailed in Section 7.1.2.6.5.

7.1.2.6.3 End of treatment and follow-up tumor imaging

In participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (every 9 weeks (± 5 days)). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. In participants who discontinue study treatment due to documented disease progression and the Investigator elects not to implement iRECIST, this is the final required tumor imaging.

In participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every 9 weeks(63 ± 5 days)) to monitor disease status until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.2.6.4 RECIST 1.1 assessment of disease

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study treatment). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, SOLTI allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

7.1.2.6.5 iRECIST assessment of disease

iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs. When clinically stable, participants should not be discontinued until progression is confirmed by the Investigator, working with local radiology, according to the rules below. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response.

Evaluation of response will also be performed using iRECIST guidelines as an exploratory assessment. Additional details and definitions of iRECIST are found in Appendix 4, with additional detail in the iRECIST publication[120].

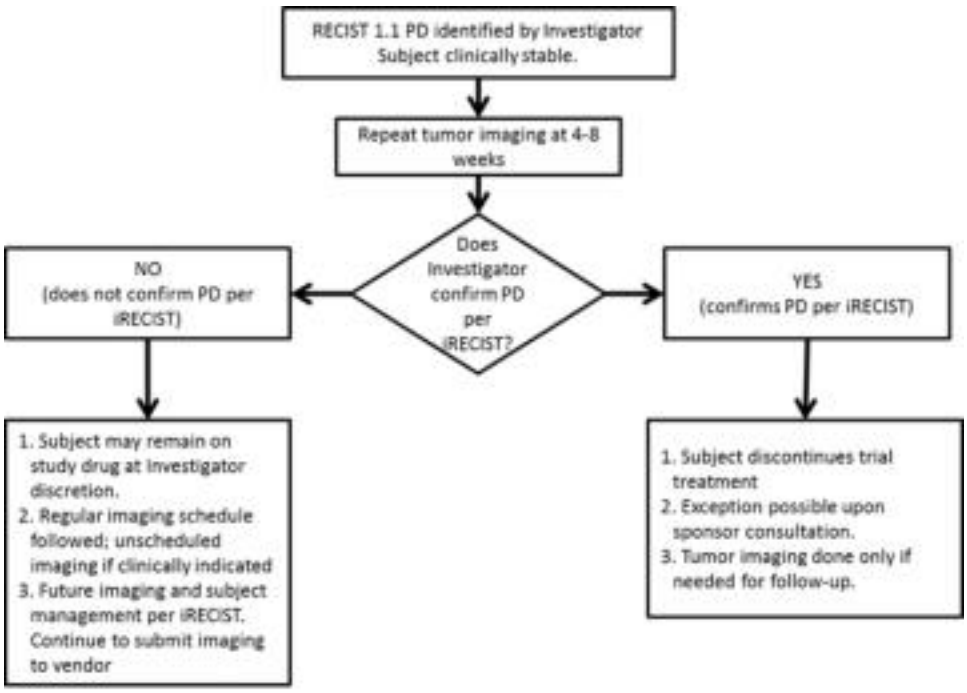
Table 10. Imaging and treatment after first radiologic evidence of progressive disease.

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per Investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per Investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the Investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per Investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the Investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor image should occur according to the regular imaging schedule.

iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1.

For this study in which ORR is the primary endpoint use the following figure:

Figure 6. Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the Investigator



7.1.2.7 Tumor tissue collection

Tissue for PAM50 analysis should be obtained from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. An archival tumor tissue sample must be obtained during the advanced/metastatic setting. Informed consent for the study must be taken prior to collection of a new biopsy. If the participant signs the Future Biomedical Research consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for Future Biomedical Research. Include a copy of the local pathology report with the tissue for PAM50 analysis. For a tumor biopsy to be considered newly obtained (fresh biopsy) the sample from a core or excisional biopsy must be obtained from the subject during the screening period.

Plasma sampling will be obtained from all participants. All baseline plasma samples should be drawn in screening period, at Cycles 2 and at EOT.

Sample collection, storage, and shipment instructions for serum samples will be provided in the study sample management plan.

7.1.3 Laboratory procedures/assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in **Table 11**.

Table 11. Laboratory tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Alkaline phosphatase	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alanine aminotransferase (ALT)	Glucose	(β-hCG)†
Platelet count	Aspartate aminotransferase (AST)	Protein	PT (INR)
WBC (total and differential)	Lactate dehydrogenase (LDH)	Specific gravity	aPTT
Red Blood Cell Count	Calcium	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3) or T3 free
Absolute Neutrophil Count	Glucose	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	Potassium	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Sodium		Blood for correlative studies
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnanc y test will be required.			

Laboratory tests for screening (hematology and serum chemistry) should be performed within 10 days prior to the first dose of treatment. Pregnancy test must be performed within 72 hours before Cycle 1 Day1. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.4 Other procedures

7.1.4.1 Withdrawal/discontinuation

When a participant discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Participants who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 5.2.3. After discontinuing treatment following assessment of CR, these participants should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.4.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4.2). Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn.

Patients will be replaced if they are considered to be non-evaluable. An evaluable patient is one that has received at least one combination dose, has measurable disease according to the Investigator site assessment and has at least one postbaseline tumor assessment.

7.1.4.2 Blinding/unblinding

This is an open-label trial; therefore, SOLTI, investigator and participant will know the treatment administered.

7.1.5 Visit requirements

Visit requirements are outlined in Section 6.1 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7 - Trial Procedures.

7.1.5.1 Pre-screening

After signing the molecular pre-screening consent, tumor tissue (archival or newly obtained or excisional biopsy of a tumor lesion not previously irradiated) will be sent to a central laboratory to analyze non-luminal subtype by PAM50 test. This will be conducted during a pre-screening phase prior to enrolling into the trial. For eligibility into the study, patients must be non-luminal/ by PAM50 test analyzed in the central laboratory. Tumor tissue sample obtained during the advanced/metastatic setting is mandatory, it is recommended to provide a tumor sample collected after the most recent progression or recurrence. Tumor tissue requirements, along with shipping requirements, will be detailed in the sample manual provided by the central laboratory.

To perform PAM50 test, investigator judgement of patient's potential eligibility to the study should be assessed as per inclusion/exclusion criteria (section 5.1) and TRIAL FLOW CHART (section 6).

7.1.5.2 Screening

Within 28 days prior to treatment allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 6.1 Visit requirements are outlined in the Schedule of Activities (Flow Chart).

Participants may be rescreened after consultation with SOLTI. Rescreening should include all screening procedures listed in the protocol Flow Chart, including consent review. Rescreen procedures cannot be conducted the day prior to treatment allocation if there are Day -1 procedures planned per protocol.

Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the allocation for the following:

- Evaluation of ECOG is to be performed within 10 days prior to the first dose of trial treatment.

- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local trial site laboratory).

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. Participants who are rescreened will retain their original screening number.

7.1.5.3 Treatment period

Visit requirements are outlined in the Section 6 – Schedule of Activities. Specific procedure related details are provided in Section 7

7.1.5.4 Post-treatment visits

7.1.5.4.1 Safety follow-up visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be

recorded. Participants with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Participants who are eligible for retreatment/crossover with pembrolizumab (as described in Section 5.2.3) may have up to two safety follow-up visits, one after the Initial Treatment Period and one after the Second Course Treatment.

7.1.5.4.2 Follow-up visits

Discontinuation of study treatment does not represent withdrawal from the study. Participants who discontinue study treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 9 weeks (63 ± 5 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of the study or if the participant begins retreatment with pembrolizumab as detailed in Section 5.2.3. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 5.2.3 will move from the follow-up phase to the Second Course Phase when they experience disease progression.

7.1.5.4.3 Survival follow-up

Participants who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-Up Phase and should be contacted by telephone every 3 months (± 21 days) to assess for survival status until death, withdrawal of consent, loss to follow-up, or study termination by SOLTI , whichever occurs first. In addition, information regarding use of subsequent anti-cancer agents for metastatic breast cancer during the survival follow-up period will be collected.

[redacted] Assessing and recording adverse events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the pembrolizumab, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples

of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if the participant is receiving treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator.

- All AEs meeting serious criteria, from the time of treatment allocation through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.

- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.

- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately by the investigator if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify Merck.

7.2.1 Definition of an overdose for this protocol and reporting of overdose to SOLTI and to Merck

For purposes of this study, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the

treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to SOLTI and within 2 working days hours to Merck Global Safety. PPD PPD PPD

7.2.2 Reporting of pregnancy and lactation to SOLTI and to Merck

Although pregnancy and infant exposure during breast feeding are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a participant (spontaneously reported to them) that occurs during the study.

Pregnancies and infant exposures during breastfeeding that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the participant to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and infant exposures during breastfeeding that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to PPD within 24 hours of learning of its occurrence within 2 working days to SOLTI Project Manager and to Merck Global Safety. PPD PPD

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and send by email to PPD

.

In case of any problem, please contact under following phone number: PPD

Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

7.2.3 SOLTI immediate reporting of adverse events to SOLTI and to Merck

7.2.3.1 Serious adverse events

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event

- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Refer to **Table 12** for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any participant must be reported within 24 hours of learning of its occurrence. within 2 working days to SOLTI Project Manager and to Merck Global Safety. PPD PPD

SOLTI if it causes the participant 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 through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious

adverse event, including death due to any cause whether or not related to the Merck product, must be reported within 24 hours of learning of its occurrence. within 2 working days to SOLTI Project Manager and to Merck Global Safety. PPD PPD PPD

SOLTI Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to Merck Global Safety.

All participants with serious adverse events must be followed up for outcome.

SAE reports and any other relevant safety information are to be forwarded to within 24 hours of learning of its occurrence within 2 working days to SOLTI Project Manager and to Merck Global Safety. PPD

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. PPD at the time of submission to FDA.

7.2.3.2 Events of clinical interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours of learning of its occurrence. within 2 working days to SOLTI Project Manager and to Merck Global Safety. PPD PPD

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 participant must be reported within within 24 hours of learning of its occurrence. within 2 working days to SOLTI Project Manager and to Merck Global Safety. PPD PP PPD if it causes the participant 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 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 2 working days to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to SOLTI, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 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.

7.2.4 Evaluating adverse events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 12. Evaluating adverse events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V5.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the participant, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of participant taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to SOLTI within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to SOLTI and to Merck within 2 working days..	

	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause Merck product to be discontinued?	
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the participant was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of SOLTI's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the participant re-exposed to Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY SOLTI AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).**	
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.	
No, there is not a reasonable possibility of Merck product relationship	Participant did not receive the Merck product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a participant with overdose without an associated AE.)	

7.2.5 Sponsor responsibility for reporting adverse events

Prompt notification (within 24 hours) by the investigator to SOLTI of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

- SOLTI has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. All AEs will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R2) Guidelines for GCP.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from SOLTI will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8. STATISTICAL ANALYSIS PLAN

Statistical and analysis plan summary

This is an open-label, single arm, multicenter phase II study evaluating treatment with paclitaxel in combination with pembrolizumab in patients with locally advanced or metastatic non-luminal HR+/HER2- breast cancer refractory to CDK inhibitors. This study will utilize a Simon's two-stage design, single arm, with one interim and a final analysis. The interim analysis will be conducted when 15 patients are evaluable for Objective Response Rate (ORR) as determined locally by the investigator through the use of RECIST v.1.1. Recruitment will not be halted during the interim analysis period. Therefore, no interruption in the accrual will be done during the interim analysis in order to maintain the dynamic of accrual in the trial.

Detailed statistical analysis information will be provided separately in the Statistical Analysis Plan (SAP). The SAP will be approved before the final close of database and will detail all data analyses and deviation to the final version of Protocol study.

8.1.1 Analysis populations

All patients included into the study will be considered in the statistical report.

Intent-to-Treat (ITT) population: includes all patients that are enrolled in the study. This population will be used for the efficacy analysis, with the exception of overall response rate and clinical benefit rate, which used the evaluable population.

Evaluable population (EP): includes all patients who have received at least one combination dose of pembrolizumab and paclitaxel who had measurable disease according to the Investigator site assessment at baseline and who had at least one postbaseline tumor assessment . This population will be used for overall response rate and cinical benefit rate analysis.

Safety population (SP): includes the set of patients who received at least one (even incomplete) part of the study treatments. This population will be analyzed for the secondary endpoint of safety.

8.1.2 Statistical analysis

The statistical analysis will be conducted following the principles as specified in International Conference on Harmonization (ICH) Topic E9 (CPMP/ICH/363/96). The significance level will be α=0.05 for all tests. As an exploratory study, multiple testing without adjustment of the significance level is considered acceptable.

A summary of the general approach to statistical analysis is given below. A detailed statistical plan will be issued and approved prior to declaration of clean database.

Quantitative variables will be summarized using descriptive statistics, including number of missing values, number of valid values and their observed range, median, mean, standard deviation and 95% confidence interval for the mean. The Kaplan-Meier method will be used to estimate the time to event function the median of time to event and the 95% confidence interval of the same will be calculated. These confidence intervals will be calculated based on the Greenwood method.

Qualitative variables will be summarized presenting frequency and percentage of each level of the variable. In case of dichotomous variables, as ORR, estimation of proportions will be done by 95% confidence interval using the Wilson's method. Ordinal variables will be described as both quantitative and qualitative variables.

All safety analyses will be performed on the Safety Population. All AEs will be graded according to the NCI CTCAE v.5.0. Appropriate summary statistics will be provided for the analyses of vital signs (i.e., weight, blood pressure, heart rate, and body temperature), ECOG performance status, and ECGs.

[redacted] Sample size calculations

The primary endpoint, objective response rate (ORR) as determined locally by the investigator through the use of RECIST v.1.1. The rationale for a null hypothesis of $p \leq 0.30$ is based on previously published analysis from a clinical trial with paclitaxel (BELLE-4) in 209 patients with metastatic disease with no prior chemotherapy for advanced disease, where an ORR of 27.1% has been observed for paclitaxel monotherapy 121. The ORR of pembrolizumab in combination with paclitaxel is expected to be at least as high as this in patients unselected for PD-L1 positive disease. Supposing a minimum increase of 20% in the ORR to be considered

the study successful, the ORR at the end of stage 2 should be ≥ 50%, to warrant further research of this treatment combination in this patient population.

This study will utilize the optimal two-stage Simon's design (1989)[1]. The null hypothesis that the true response rate is not more than 30% ($p \leq 0.3$) versus the alternative hypothesis that the true response rate is at least 50% ($p \geq 0.50$) will be tested. The first stage, will be conducted with 15 evaluable patients. If there are 5 or fewer responses in these 15 patients, the study will be stopped. Otherwise, 31 additional patients will be accrued for a total of 46. The null hypothesis will be rejected if 19 or more responses are observed in 46 patients of EP. This design yields a one-sided type I error rate of 0.05 (alpha) and power of 80%.

Up to 46 evaluable patients of EP may therefore be enrolled to this clinical trial. It is expected that approximately 184 patients will be screened in order to identify 51 patients who meet all the inclusion and exclusion criteria. Assuming a dropout rate of 10%, the study will aim to recruit 51 patients in total in order to have at least 46 evaluable patients of EP to attain 80% power at nominal level of one-sided alpha of 0.05.

[redacted] Primary objective

The primary objective of the study is to assess the proportion of patients with best overall response of CR or PR, as per local investigator's assessment and according to RECIST v1.1 (see Appendix 5 for details) with paclitaxel and pembrolizumab among patients with HR+/HER2-, non-luminal metastatic breast cancer who have progressed on or after CDK 4/6 inhibitor. To be consistent with the sample size calculation, the primary hypothesis will be tested at 0.05 level of significance (one-sided) and a 90% confidence intervals will be reported. Additionally, the ORR will be reported along with associated 95% confidence interval.

8.4 Secondary objectives

The secondary objectives in this study are to evaluate the progression free survival (PFS), clinical benefit rate (CBR) and duration of response (DOR), Time to response (TtR), Pre-PFS, overall survival (OS) and safety. In addition of the calculation of 90% confidence intervals for efficacy secondary objectives, 95% confidence intervals may also be provided as needed.

Progression free survival

PFS is defined as the time from the date of allocation to the date of the first documented progression or death due to any cause occurring in the study. PFS will be assessed based on local investigator's assessment according to RECIST v1.1 (see Appendix 5 for further details).

PFS will be censored if no PFS event is observed before the cut-off date. The censoring date will be the date of last adequate tumor assessment before the cut-off date. If a PFS event is observed after two or more missing or non-adequate tumor assessments, then PFS will be censored at the last adequate tumor assessment. If a PFS event is observed after a single missing or non-adequate tumor assessment, the actual date of event will be used (see Appendix

5). It is not intended to censor patients for new anticancer therapy prior to documented disease progression in the primary analysis.

The Kaplan-Meier estimate of the PFS survival function will be estimated and displayed. The resulting median PFS time will be given for each cohort with 95% confidence intervals, as well as 25th and 75th percentiles will be reported.

Clinical benefit rate

Clinical Benefit Rate is defined as the proportion of patients with a best overall response of CR or PR or an overall lesion response of stable disease (SD) or Non-CR or PR/ Non-PD lasting ≥ 24 weeks based on local investigator's assessment according to RECIST v1.1. CBR will be calculated based on the mFAS. The CBR and its exact 90% confidence interval.

Duration of response

DOR is the time from the date of first documented response (confirmed CR or PR) to the date of first documented progression or death due to underlying cancer. DOR only applies to patients whose best overall response is CR or PR according to RECIST v1.1 based on tumor response data per local investigator's assessment. The start date is the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death due to underlying cancer. Patients continuing without progression or death due to underlying cancer will be censored at the date of their last adequate tumor assessment.

Time to response

TtR is defined as the time from the allocation to the first objective tumor response (tumor shrinkage of ≥30%) observed for patients who achieved a CR or PR. TtR only applies to patients whose best overall response is CR or PR according to RECIST v1.1 based on tumor response data per local investigator's assessment.

Overall Survival

OS is defined as the time from the date of allocation to the date of death due to any cause. Data for patients who are alive at the time of the analysis data cutoff will be censored at the last date they were known to be alive. Data from patients without post-baseline information will be censored at the date of allocation.

The results from log-rank test will be provided. The OS curve will be estimated by the Kaplan-Meier methodology, and the 95% CI will be estimated by the Cox proportional-hazards models.

PFS on study treatment compared to PFS on prior line of therapy (pre-PFS).

PFS is defined as the time from the date of allocation to the date of the first documented progression or death due to any cause occurring in the study. PFS will be assessed based on local investigator's assessment according to RECIST v1.1 (see Appendix 5 for further details).

Pre-PFS is defined as the time from the date of first dose of the previous medication to the date of the first documented progression in the previously metastatic line. Pre-PFS only applies to patients whose received have previous treatment for metastatic disease

ORR according to PD1 mRNA expression

To evaluate the direct association of PD1 FFPE-based mRNA expression with ORR we evaluate the PD1 mRNA pre-established cutoff (median or tertiles) and as a continuous variable.

Median: Cutoff points are calculated according to the median value for the mRNA expression. Samples with mRNA expression above or equal to the median were considered as samples with high expression, while those with value below the median as samples with low expression.

Tertiles: Cutoff points are calculated according to the tertiles value for the mRNA expression. Samples with mRNA expression above or equal to the tertile-1 (PD1-high) were considered as samples with high expression, samples with mRNA expression above or equal to the tertile-2 (PD1-high) were considered as samples with intermediate expression, while those with value below the tertile-2 as samples with low expression.

To compare distribution of variables between two groups, we used Fisher's exact test. Proportions and 95% CI were also provided. Univariate and multivariable logistic regression analyses are done to investigate the association of each variable with ORR. Odds ratios (ORs) and 95% CIs are calculated for each variable. All the laboratory analyses are performed blinding to the clinical data.

ORR and PFS according to early dynamic changes in ctDNA between before the treatment and cycle 2 after one dose of pembrolizumab.

The "circulating tumor DNA response" is defined as the ratio of mutant copies/ml of plasma at day 1 cycle 2 and day 1 cycle 1, subsequently denoted as CDR_{21}. Aggregate totals of genes mutation copies/ml will be used where a sample exhibited polyclonality for these mutations. Paired day 1 cycle 2 and day 1 cycle 1 copies/ml and allele fractions will be compared using Wilcoxon signed-rank test. The distribution of copies/ml between selected genes will be compared using the Mann–Whitney test. Comparisons of CDR_{15} distributions will be treated similarly. Harrell's c-index will be used to optimize the CDR_{21} cut-off. The test for an association between undetectable mutation at day 1 cycle 2 and end of treatment will be conducted with Fisher's exact test. Proportions of patients with undetectable mutations at the end of treatment for selected genes will be compared with a two-sample test of proportions. For all analyses, a p value of <0.05 will be considered statistically significant.

For analyses of PFS, Kaplan–Meier curves will be plotted, and groups compared using the log-rank test. Hazard ratios and associated 95% CIs will be obtained from Cox proportional hazards regression models. In order to determine the optimal cut-point for CDR_{21} in relation to PFS, the maximally selected log-rank statistics will be used to selected the cut-off that better separate patients according CDR_{21} .

9. TRANSLATIONAL RESEARCH

Translational research data will be collected outside the clinical database; correlations with relevant clinical features will be performed by specialized scientists of PPD and reported in a separate ad-hoc report, which will integrate the results and findings described in the clinical study report.

All the data analyses of the study will be under the responsibility of SOLTI and they will be based on a statistical plan according to the protocol specifications.

Biological specimens

The tissue samples collected will be used to identify biomarkers that may be predictive of response or toxicity to the proposed treatments and/or prognostic for breast cancer. Since the knowledge of new markers that may correlate with disease activity and the efficacy or safety of the treatment is evolving, the analytes may change during the course of the study and may include determination of additional markers of tumorigenesis pathways and mechanisms of treatment response. The collected tumor tissue samples may also be used to develop and validate diagnostic assays and allow the generation of statistically meaningful biomarker data.

Remaining sample materials after the completion of the initial biomarker assessments (e.g., aliquots of tumor RNA or DNA) may be used for further assessment of expanded marker panels.

Samples will be stored at the PPD for up to 15 years after database closure, with the additional option of further long-term storage. They will be stored under the responsibility of the Dr PPD.

All patients will be consented for the collection and use of research blood and tissue samples. All samples will be linked anonymized and only identified by the trial ID and unique sample number allocated by the SOLTI SAMPLE TRACKER SYSTEM coordinating team.

For sampling procedures and shipment see instructions in the appropriate sections of the study sample management manual

9.1.1 Tumor tissue samples

Collection of tumor biopsies is an essential part of this study. Paraffin-embedded and formalin-fixed tumor samples will be obtained from all patients. Quality of tumor samples even for pre-screening sample will be evaluated upon arrival to central laboratory. Pathological analysis includes hematoxylin and eosin (H&E) staining, identification of areas with greater amount of tumor cells and determination of their tumor cell percentage. Confirmation of eligibility criteria requires central assessment of an adequate quantity and quality of pre-screening sample. If not available, the patient must agree to re-biopsy.

9.2 Gene expression signatures

The study foresees the identification of the molecular intrinsic subtypes (Luminal A, Luminal B, HER2-E, basal-like) and the normal breast-like group using the PAM50 panel (non-commercial version). This panel measures the expression of 50 classifier genes and 5 control genes, which classify the tumors into 5 intrinsic subtypes (luminal A, luminal B, HER2-enriched and basal-like) and the normal breast-like group.

Besides of PAM50 gene expression analysis at baseline and in order to identify new biomarkers of response to the combination treatment, we aim to further evaluate the expression of 702 additional genes that encompass important genomic signatures and individual genes of importance for breast cancer: The nCounter®Breast Cancer 360 Panel includes 752 genes across 23 key breast cancer pathways and processes (**Table 13**) as well as established breast cancer diagnostic and research signatures, tumor microenvironment, and immune response. Special attention will be given to innate immune response genes as well as markers of antigen presentation, which are expected to be determinant for this combination treatment. The following genes/signatures will be evaluated among others:

- Intrinsic PAM50 subtypes (Basal-like, HER2-enriched, Luminal A, Luminal B, and Normal-like): 50 genes including probes for ER, PgR and HER2.
- ROR score: Validated score for predicting risk of relapse in a cohort of node-negative patients with OR- and OR+ tumors who did not receive adjuvant systemic treatment. ROR-S (with subtype information) and ROR-P (using proliferation data separately)
- EGFR-related genes: ERBB2, EGFR, ERBB4, GRB7, CRYAB
- PI3K pathway genes: PIK3CA, PTEN.
- Claudin-low subtype: Recently described subtype, enriched for stem cell and/or tumor initiating features, as well as metaplastic features, containing genes coding for of Vimentin, Claudins 3, 4 and 7, ZEB1.
- VEFG signature: containing VEGF, adrenomedulin (ADM), angiopoietin 4-type (ANGPTL4) and likely indicative of hypoxia.
- Proliferation: Multi-gene signature indicative of cell proliferation rate, containing genes such as MKI67, MYC, TOP2A, CCNB1, CCNE1, RB1 and p16.
- Estrogen-responsive signature: ESR1, PGR, NAT1, FOXA1, BCL2, BAG1 and GATA3
- Basal-luminal differentiation: keratin 5, 19, 14, 8 and 17
- DNA replication genes: TYMS, CDC6, RRM2, ORC6L, CENPF, RAD51.

- Stroma-related genes: vimentin, CAV1, SFRP1
- Immune Infiltration: CD27, CD274, CD276, CD8A, LAG3
- Other genes: MLPH, CD24, EPCAM, DDR1, BIRC5, CDH3

Table 13: Type of immune genes to be assayed.

Pathway	# Genes
Adhesion and Migration	83
Angiogenesis	34
Antigen Presentation	21
Apoptosis	9
Cytokine and Chemokine Signaling	50
DNA Damage Repair	140
EMT	85
ER Signaling	27
Epigenetic Regulation	18
Hedgehog	20
Immune Infiltration	33
Internal Reference Gene	18
JAK-STAT	47
MAPK	100
Notch	22
PI3K	96
Proliferation	142
Stromal Markers	6
Subtypes	70
TGF-beta	57
Transcriptional Misregulation	63
Triple Negative Biology	50
Tumor Metabolism	15
Wnt	51

9.2.1 The nCounter platform

The NanoString nCounter Analysis System (http://www.nanostring.com/) delivers direct, multiplexed measurements of gene expression through digital readouts of the relative abundance of hundreds of mRNA transcripts. It uses gene-specific probe pairs that hybridize directly to the mRNA sample in solution eliminating any enzymatic reactions that

might introduce bias in the results. After hybridization, all of the sample processing steps are automated.

9.2.2 RNA extraction

The PAM50 assay uses RNA from FFPE breast tumor tissue. A section of the FFPE breast tissue will first be examined with a hematoxylin and eosin (H&E) staining to determine percent tumor nuclei, percent normal nuclei, and percent necrosis per standard pathology processing. The slide will then be reviewed by a pathologist, who will identify and mark the region of the tissue that contains an adequate percentage of tumor for the gene expression test on the slide. RNA will be extracted from the FFPE tissue sample using an RNA isolation kit. Additional general-purpose laboratory reagents are required for deparaffinization. The extraction process includes a step for removing genomic DNA from the sample. Following extraction of total RNA and removal of genomic DNA, the optical density is measured at wavelengths of 260 nm and 280 nm to determine both yield and purity using a low volume spectrophotometer. RNA will be stored at –80ºC until time of testing.

9.2.3 Technical procedures and data analysis

For each set of up to 10 RNA samples isolated from breast cancer tissue, the user will pipette a defined amount of RNA into separate tubes within a 12-reaction strip tube and add the CodeSet and hybridization buffer as specified within the assay protocol. A set concentration of reference sample is pipetted into the remaining two tubes with CodeSet and hybridization buffer. The CodeSet consists of probes for each gene that is targeted, additional probes for endogenous “housekeeping” normalization genes and positive and negative controls that are spiked into the assay. The reference sample consists of in vitro transcribed RNA for the targeted genes and housekeeping genes. Once the hybridization reagents are added to the respective tubes, the user transfers the strip tube into a specified heated-lid heat block and incubates for a defined period of time at a set temperature of 65ºC.

Upon completing hybridization, the user will then transfer the strip tube containing the set of 10 assays and two reference samples into the nCounter Prep Station. An automated purification process then removes excess capture and reporter probe through two successive hybridization-driven magnetic bead capture steps. The nCounter Prep Station then transfers the purified target/probe complexes into an nCounter cartridge for capture to a glass slide. Following completion of the run, the user removes the cartridge from the Prep Station and seals it with an adhesive film.

The cartridge is then sealed and inserted into the nCounter Digital Analyzer. The analyzer counts the number of probes captured on the slide for each gene, which corresponds to the amount of target in solution. The signals of each sample will be normalized using the housekeeping genes to control for input sample quality. The signals are then normalized to the reference sample within each run to control for run-to-run variations. The resulting normalized data is input into the breast cancer-subtyping algorithm or gene signatures score algorithm.

9.2.4 Immunohistochemistry

Immunohistochemistry at a central laboratory will be used to measure the number of stromal tumor-infiltrating lymphocytes (TILs) and PD-L1 staining in immune cells and tumor cells.

9.3 Circulant tumor DNA

Plasma samples will be collected at day 1 cycle 1, day 1 cycle 2, and end of treatment in EDTA blood collection tubes. Samples will be processed within 30 min of collection by centrifugation at 1500–2000 × *g* for 10 min. Plasma will be then separated and stored at −70 to −80 °C. Prior to DNA extraction plasma samples will be thawed and subjected to further centrifugation at 3000 × *g* for 10 min.

[redacted] Sample repository

All residual samples after protocol-defined studies are completed will be stored in a central sample repository as a collection. The samples in the study repository might be used for future biomarker research towards further understanding of treatment with study drugs, of breast cancer, related diseases, and adverse events, and for the development of potential, associated diagnostic assays, in accordance with the recommendations and approval of the Study Steering Committee. Samples will be stored up to 15 years or until they are exhausted, whatever happens first, in accordance with applicable local regulations (Law 14/2007 on Biomedical Research and the Royal Decree 1716/2011).

A separate, specific signature will be required to document a patient's agreement to allow future biomarker research and storage in repository of any remaining samples. Labels of biological samples will not contain any clinical information of patients.

Samples will be stored in the biorepository of the PPD. Responsible for the samples custody is PPD PPD of the Hospital Clínic of Barcelona and head of the research group PPD. The repository is located in the PPD PPD Barcelona (Spain); Phone: PPD

Samples will be stored as a collection and registered in the National Registry of Biobanks, in agreement with article 37 of the Royal Decree 1716/2011.

Results derived from the analysis of biological samples of a patient will not be provided to the Site Investigators, unless patient explicitly requests this information, in compliance with local and national law. Patient must be informed that those results are for investigational use only and should not be used for treatment decision. The final results deriving from investigation with these biological samples will be published in accordance with the Steering Committee charter of this study.

10. LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

10.1 Investigational product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Pembrolizumab will be provided by Merck as summarized in **Table 14.**

Table 14. Product Descriptions

Product Name & Potency	**Dosage Form**
Pembrolizumab 100 mg/ 4mL	Solution for Infusion

Paclitaxel is considered as SoC Treatment and will be supplied locally, and packaged, stored and administered according to their label.

10.2 Packaging and labeling information

Supplies will be labeled in accordance with regulatory requirements.

Pembrolizumab will supplied by Merck or its designee. Storage conditions are described in the medication label. All prescribed and dispensed dosages must be recorded.

Paclitaxel will be supplied locally, and packaged, stored and administered according to their label. All prescribed and dispensed dosages must be recorded.

[redacted] Clinical supplies disclosure

This trial is open-label; therefore, the participant, the trial site personnel, SOLTI and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

[redacted] Storage and handling requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

[redacted] Returns and reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and the amount remaining at the conclusion of the trial. Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

11. ADMINISTRATIVE AND REGULATORY DETAILS

[redacted] Ethical and regulatory standards

11.1.1 Independent Ethics Committee

This protocol and any amendments will be submitted to a properly constituted Independent Ethics Committee (IEC), in accordance with the International Conference on Harmonization (ICH) guidelines, the applicable European Directives and local legal requirements, for approval of the study. Approval must be obtained in writing before the first subject can be recruited.

During the Clinical Trial, any amendment or modification to the Protocol should be submitted to the Ethics Committee (IRB/IEC) before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the Clinical Trial, in particular any change in safety.

Principal Investigator will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and SOLTI. Before study start, the investigator must sign the Protocol signature page to confirm that he/she agrees to conduct the study in compliance with these documents and with all instructions and procedures described in the Protocol and to permit access to all relevant data and records to the study monitors, SOLTI auditors, representatives of SOLTI's clinical quality assurance department, designated SOLTI agents, IECs and health authorities upon request.

A progress report is sent to the Ethics Committee (IRB/IEC) at least annually DSUR and a summary of the Clinical Trial's outcome at the end of the Clinical Trial.

11.1.2 Ethical conduct of the study

The Clinical Trial will be conducted in compliance with the Protocol, regulatory

requirements, the ICH guidelines for Good Clinical Practice (GCP) and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association.

This Clinical Trial will be recorded in the public registry website clinicaltrials.gov and Registro Español de Ensayos Clinicos before the enrollment of the first patient. The registry will contain basic information about the trial sufficient to inform interested patients and their healthcare practitioners on how to enroll in the trial.

11.1.3 Subject information and consent

All potential participants will receive verbal and written information on the study in a previous interview with the study doctor in their hospital. In this information, special emphasis will be placed on the fact that participation in the study is voluntary and that the patient may withdraw herself from the study at any time and for any reason, without this affecting her medical care. All patients will have the opportunity to ask questions about the study and they will be given sufficient time to decide if they wish to participate.

The ICF must mention the specific data that will be recorded, collected, processed and that can be sent to countries pertaining to and outside of the European Economic Area (EEA). In accordance with the in accordance with the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 and LOPD, the individuals participating in the study shall not be identified.

Personal data will be managed in accordance with the applicable legislation in force at the time, and in particular, in accordance with Regulation (EU) No 2016/679 of 27 April 2016 on the protection of individuals with regard to the processing of their personal data (hereinafter, "GDPR").

The patient will be given a copy of the Patient Information Sheet, including the signed ICF.

Eligible patients can only be included after granting their written informed consent (before witnesses, when required by laws or standards). The signature of the ICF must be obtained before performing any study-specific procedures (that is, any of the procedures described in the Protocol). The date on which the ICF is signed must be recorded in the eCRF.

The investigators will be given an ICF approved by the IEC that is considered to be appropriate for the study and that satisfies the ICH GCP standards and legal requirements. Any modification to this ICF proposed by the investigator must be accepted by SOLTI and approved by the local IEC. A copy of the approved version must be provided to the trial monitor after IEC approval is obtained.

[redacted] Subject records and source data

A current copy of the Curriculum Vitae describing the experience, qualification, and training of each Investigator and Sub-investigator will be signed, dated and provided to SOLTI

prior to the beginning of the Clinical Trial.

It is the responsibility of the Investigator to record essential information in the medical records in accordance with national regulations and requirements. The following information should be included as a minimum:

- A statement that the subject is in a clinical study
- The identity of the study, e.g., Study code
- Subject screening number and/or subject number
- That IC was obtained and the date
- Diagnosis
- Dates of all visits during the study period
- Any information relating to AEs
- All treatments and medications prescribed/administered (including dosage)
- Date of study termination
- Subject health service identification number

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data recorded on the e-CRFs. Data reported on the e-CRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. Signed sections of CRFs will be monitored on a regular basis.

11.2.1 Study documentation and storage of records

The investigator or the site must store the essential documents (as defined in Standard E6 of the ICH GCP, section 8) as required by the applicable administrative requirements. The investigator or the site will have to take measures to prevent the accidental or early destruction of said documents.

After the study is closed, the investigator or the designated individual from the site must store all study records in a secure, protected area of the site, except where, according to local legislation, they must be stored by another person or institution. The records must be stored to enable their easy, timely recovery as needed (for example, audit or inspection) and, whenever possible, to allow any subsequent analysis of the data together with the site's assessment, the support systems and the personnel. When so permitted by local standards or legislation or the institution's policy, some or all of these records can be stored in a format other than hard copy (for example, microfile, scanned or electronic support); however, precaution must be exercised before adopting these measures. The investigator must make certain that all reproductions are legible, a true and exact copy of the original and that they comply with the standards for accessibility and recovery, including that of re-generating a printed copy if necessary. Moreover, the investigator must make certain that there is an acceptable backup copy of these reproductions and an acceptable quality control process for making said reproductions.

SOLTI will inform the investigator of the period for storing these records for the purposes of complying with all current administrative requirements. The minimum storage period must

comply with the strictest standard applicable to the study at this site, as dictated by the institutional requirements, laws or local standards or SOLTI's procedures and standards; otherwise, the default storage period shall be at least 25 years after the finalization of the study.

The investigator must notify SOLTI of any change in the availability of the files, for example: archived in an off-site facility or transfer of the ownership of the records in the event the investigator leaves the site.

[redacted] Access to source data and documentation

For the purpose of ensuring compliance with the Clinical Trial Protocol, GCP, and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of SOLTI and by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and, as such, will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents. As soon as the Investigator is notified of a planned inspection by the authorities, he/she will inform SOLTI and authorize SOLTI to participate in this inspection. The confidentiality of the data verified and the protection of the patients should be respected during these inspections. Any results and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to SOLTI.

The Investigator must take appropriate measures required by the SOLTI to take corrective actions for all problems found during the audit or inspections.

[redacted] Study monitoring

11.4.1 Responsibilities of the investigators

The Investigators and delegated investigator staff undertakes to perform the Clinical Trial in accordance with this Clinical Trial Protocol, ICH guidelines for GCP, and the applicable regulatory requirements.

The Investigator is required to ensure compliance with all procedures required by the Clinical Trial Protocol and with all study procedures provided by SOLTI (including security rules). The Investigator agrees to provide reliable data and all information requested by the Clinical Trial Protocol (with the help of the e-CRF, Discrepancy Resolution Form [DRF], or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by SOLTI representatives.

If any circuit includes transfer of data, particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint other individuals, as he/she may deem appropriate, as Sub-investigators to assist in the conduct of the Clinical Trial in accordance with the Clinical Trial Protocol. All Sub-investigators must be appointed and listed in a timely manner. The Sub-investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the Clinical Trial Protocol and all necessary information.

11.4.2 Responsibilities of SOLTI and monitoring

The Sponsor of this Clinical Trial, SOLTI, is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the Clinical Trial Protocol as regards ethics, Clinical Trial Protocol compliance, and integrity and validity of the data recorded on the e-CRFs. Thus, the main duty of the Monitoring Team is to help the Investigator and SOLTI maintain a high level of ethical, scientific, technical, and regulatory quality in all aspects of the Clinical Trial.

At regular intervals during the Clinical Trial the site will be contacted through monitoring visits, letters, or telephone calls by a representative of the Monitoring Team to review study progress, Investigator and patient compliance with Clinical Trial Protocol requirements, and any emergent problems.

The Monitor will visit the study site on a regular basis to ensure that the study is conducted and documented in accordance with this protocol, ICH GCP guidelines, regulatory requirements, and any study specific documents such as e-CRF completion guidelines.

Monitoring visits will be conducted to confirm that:

- The investigational team is adhering to the study protocol.
- IC has been obtained from all participants.
- AEs have been reported as required.
- Data are being accurately recorded on the e-CRFs.
- IMP is being stored correctly and drug accountability is being performed on an on-going basis.
- Facilities are, and remain, acceptable throughout the study.
- The Investigator and the site are receiving sufficient information and support throughout the study.

Moreover, during monitoring visits, the data recorded on the e-CRFs, source documents, and other study-related records will be compared against each other in order to ensure accurate data that reflect the actual existence of the subject in the study, i.e., source data verification.

Detailed monitoring visit information will be provided separately in the Monitoring Plan (MP). The MP will be approved before the first patient is included.

11.4.3 Source document requirements

According to the ICH guidelines for GCP, the Monitoring Team must check the e-CRF entries against the source documents, except for the pre-identified source data directly recorded on the e-CRF. The IC Form will include a statement by which the patient allows SOLTI´s duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records, which support the data on the e-CRFs (e.g., patient's medical file, appointment books, original laboratory records, etc.).

These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

11.4.4 Use and completion of case report forms and additional requests

It is the responsibility of the Investigator to maintain adequate and accurate Case Report Forms, which for this trial will be of electronic nature. The electronic Case Report Form (e-CRF) is designed by SOLTI to record, according to SOLTI instructions, all observations and other data pertinent to the Study. All e-CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data. Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available to SOLTI as soon as they are entered in the e-CRF system. The computerized handling of the data by SOLTI when available in the e-CRF may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests along with their responses will be managed through the e-CRF.

11.4.5 Use of computerized systems

Procedures shall be employed and controls designed to ensure the confidentiality of electronic records. Such procedures and controls must include validation of systems to ensure accuracy and reliability, ability to generate accurate and complete copies of records, protection of records to enable retrieval, use of secure, computer-generated, time-stamped entries, use of operational system checks, use of device checks to determine validity of source data input, determination that those who develop, maintain, or use such systems have adequate education and training, the establishment and adherence of written policies to deter record falsification, the use of appropriate controls over systems documentation including the distribution or use of documentation for system operation and maintenance, and revision and change control procedures, which document time-sequenced development and modifications of systems documentation. For data management activities, the e-CRF will be built using e-Clinical SQL Server.

[redacted] Data management

Data management and handling will be conducted according to the study specific Data Management Plan in accordance with ICH guidelines and SAIL standard operating procedures (SOPs), which will be prepared and approved before the first patient is included.

Data entry, validation, and data queries will be handled by the SAIL The data will be subjected to validation according to SAIL SOPs in order to ensure accuracy in the collected e-CRF data.

Before database closure, reconciliation will be performed between the SAEs entered in the safety database and the study database. After database closure, the database will be exported as SAS® data sets.

Any deviations, i.e., discrepancies and additions from the process defined in the Data Management Plan, will be described in a study-specific Data Management Report.

[redacted] Confidentiality

11.6.1 Patient records

The investigator shall ensure that the anonymity of the patients and protection of her identity from unauthorized individuals are maintained. In the eCRFs or other documents sent to the data management department, patients shall not be identified by name, but by an identification code. The investigator must keep a patient inclusion log with their codes and full names. The investigator will have to store the documents that are not going to be sent to the data processing center, for example, original patient ICFs, in a strictly confidential manner.

11.6.2 Study documentation and related data

All information disclosed or provided by SOLTI (or any company/institution acting on its behalf), or produced during the Clinical Trial, including, but not limited to, the Clinical Trial Protocol, the e-CRFs, the Summary of Product Characteristics and the results obtained during the course of the Clinical Trial, is confidential prior to the publication of the Clinical Trial results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of SOLTI. However, the submission of this Clinical Trial Protocol and other necessary documentation to the Ethics Committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Sub-investigators are bound by the same obligations as the Investigator. The Investigator must inform the Sub-investigators of the confidential nature of the Clinical Trial. The Investigator and the Sub-investigators should use the information solely for the purposes of the Clinical Trial, to the exclusion of any use for their own or for a third party's account. Furthermore, the Investigator and SOLTI agree to adhere to the principles of

personal data confidentiality in relation to the patients, the Investigator, and the collaborators involved in the study.

[redacted] Property rights

All information supplied by SOLTI in connection with this study will remain the sole property of SOLTI and is to be considered confidential information. No confidential information will be disclosed to others without obtaining prior written consent from SOLTI and will not be used except in the performance of this Study. SOLTI will retain ownership of all data.

All information, documents, and intellectual property (IP) provided by Merck are and remain the sole property of Merck. The Investigator shall not mention any information or the Product in any application for a patent or for any other intellectual property rights.

In terms of the results generated by the study, SOLTI will maintain ownership of all data and will allow Merck to make scientific and commercial use of it, if it considers it pertinent. Any reports, documents, publications and inventions directly or indirectly arising from this study shall be the immediate and exclusive property of SOLTI. SOLTI, as Sponsor, may use and exploit all the study results at its full discretion.

As the case may be, the Investigator and/or the Sub-investigators should provide all assistance required by SOLTI, at SOLTI's expense, for obtaining and defending any patent, including signature of legal documents.

11.8 Clinical trial protocol amendments

All appendices attached hereto and referred to herein are made part of this Clinical Trial Protocol.

The Investigator should not implement any deviation from, or changes to the Clinical Trial Protocol without agreement by SOLTI and prior review and documented approval/favorable opinion from the IRB/IEC of an substantial amendment, except where necessary to eliminate immediate hazard(s) to patients enrolled in the trial, or when the change(s) involves only logistical or administrative aspects of the trial (i.e. non substantial amendments). Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by SOLTI, and the signed amendment will be filed with this Clinical Trial Protocol.

Any substantial amendment to the Clinical Trial Protocol requires written approval/favorable opinion by the Ethics Committee (IRB/IEC) prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the IC Form. In cases of substantial amendments the Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised IC form prior to implementation of the change and patient signature should be recollected if necessary.

[redacted] Protocol deviations

Deviations to the study protocol will be documented in a Protocol Deviation Log.

The classification of subjects into protocol violators will be made during a meeting before database lock. Listings will indicate the allocation of subjects by analysis set and the number of subjects per analysis set will be recorded in the Clinical Study Report.

[redacted] Insurance

SOLTI should provide insurance or should indemnify (legal and financial coverage) the Investigator/the institution against claims arising from the study, except for claims that arise from malpractice, negligence, or non-compliance with the protocol.

11.11 Study committees

11.11.1 Steering Committee

A SC will be created comprising SOLTI investigators associated with the design or conduct of the study, as well as non-SOLTI investigators, provided the Principal Investigator of the study deems it appropriate. They will review the main safety and efficacy data after the first 15 patients are evaluable for Objective Response Rate (ORR) at the time of primary analysis.

The SC shall ensure that the management of the study is carried out in line with the Protocol and GCP guidelines. The SC may propose and must review and approve any necessary amendment to the Protocol. It will also make decisions regarding the publications generated from the study data. Information on members, responsibilities and frequency of steering committee meetings are specified in the SC statutes.

The SC may be consulted for advice when needed, either in face-to-face meetings or via teleconference.

[redacted] Premature discontinuation of the study or close- out of a site

Decided by SOLTI in the following cases:

- If new information on the product leads to doubt as to the benefit/risk ratio.
- If the Investigator has received from SOLTI all IP, means, and information necessary to perform the Clinical Trial and has not included any patient after a reasonable period of time mutually agreed upon.
- In the event of breach by the Investigator of a fundamental obligation under this agreement, including, but not limited to, breach of the Clinical Trial Protocol, breach of the applicable laws and regulations, or breach of the ICH guidelines for GCP.

- If the total number of patients are included earlier than expected.

In any case, SOLTI will notify the Investigator of its decision by written notice.

Decided by the Investigator

The Investigator must notify (30 days' prior notice) SOLTI of his/her decision and give the reason in writing. In all cases (decided by SOLTI or by the Investigator), the appropriate Ethics Committee(s) (IRB/IEC) and Health Authorities should be informed according to applicable regulatory requirements.

[redacted] Report and publication

All publications and presentations of the study results must comply with the approved scientific practice and academic standards and comply with SOLTI's publication policy. This policy is available to all investigators and groups participating in the study. Every investigator who wishes to publish or present the study data must obtain the permission of the study SC. SOLTI must review and approve any article prior to it being submitted to journals, congresses or conferences. The authorship of the publications will be decided by the SC, which will follow the standard guidelines of peer-reviewed journals and will observe SOLTI's publication policy.

Key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov prior to enrolment of the first patient.

Once the study has been completed, SOLTI will prepare a Clinical Study Report (CSR) in line with the ICH guidelines on the structure and content of clinical study reports (ICH E3). All publications and presentations must be based on the CSR.

SOLTI agrees to communicate the results of the study, regardless of if they are positive or negative, in public access media, and shall particularly respect the dissemination of the results in scientific publications, assuming an active role in the preparation of articles or summaries, in line with the SC, and participating in its submission to the corresponding authors. All study communications must mention Merck's economic support and supply of the drugs. In order to guarantee the protection of the industrial property arising from the study, Merck will have the right to review all articles prior to submission.

SOLTI will have the right to use the results in internal presentations and for the external promotion of its interests.

If an Investigator wishes to publish results from this clinical study, written permission to publish must be obtained from SOLTI in advance.

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13. APPENDICES

Appendix 1: ECOG performance status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. 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	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. 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.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix 2: Common Terminology Criteria for Adverse Events V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

Appendix 3: Contraceptive guidance and pregnancy testing

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception requirements

Male participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in section 5.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in **Table 15** when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception that has a low user dependency consistently and correctly as described in **Table 15** during the protocol-defined time frame in Section 5.1.

Table 15. Highly Effective Contraceptive Methods That Have Low User Dependency

Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant [a, b] • Intrauterine hormone-releasing system (IUS) [b] • Intrauterine device (IUD) • Bilateral tubal occlusion
• **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least [X days, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment.

Pregnancy testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test and in accordance with local requirements. When applicable this test should be repeated a maximum of 24-hours before the first dose/vaccination.

Following initiation of treatment additional pregnancy testing will be performed at monthly intervals during the treatment period.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

Appendix 4: Description of the iRECIST process for assessment of disease progression

Assessment at screening and prior to RECIST 1.1 progression

Until radiographic progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and decision at RECIST 1.1 progression

In participants who show evidence of radiological PD by RECIST 1.1 the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management (see **Table 10** and **Fig. 6**). This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed clinically unstable should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment. I

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥ 20% and ≥ 5 mm from nadir
    - Please note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the confirmatory imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥ 5 mm, compared to any prior iUPD time point
  - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
  - For new lesions, worsening is any of these:
    - An increase in the new lesion sum of diameters by ≥ 5 mm from a prior iUPD time point
    - Visible growth of new non-target lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the scan on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation scan proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management following the confirmatory imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 6.

Detection of progression at visits after pseudo-progression resolves

After resolution of pseudo-progression (ie, achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
    - Sum of diameters reaches the PD threshold ($\geq$ 20% and $\geq$ 5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions

  - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If non-target lesions had shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.

- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, except in one respect. If new lesions occurred at a prior instance of iUPD, and at the confirmatory scan the burden of new lesions has increased from its smallest value (for new target lesions, their sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication[120] .

Appendix 5: Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria for evaluating response in solid tumors

RECIST v.1.1[122] will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST v.1.1, CT is the preferred imaging technique in this study.

Patient eligibility

Only patients with measurable disease at baseline should be included in this study. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v 1.1.

Note: Lesions are either measurable or nonmeasurable using the criteria provided below. The term "evaluable" in reference to measurability provides neither additional meaning nor accuracy and will not be used.

Measurable disease

Tumor 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)
- 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.

Nonmeasurable disease

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.

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). 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. Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor.

Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥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 tumor. 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, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 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. All other pathological nodes (those with short axis ≥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 characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions

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 nontarget lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Guidelines for evaluation of measurable disease

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 28 days before the beginning of the treatment.

Method of assessment

The same method of assessment and the same technique should be used to characterize 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 (eg, skin nodules). For the case of skin lesions, documentation by color 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.

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. 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 (eg, for body scans).

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. 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 utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in studies where recurrence following CR or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in CR. Because tumor 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. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line studies in ovarian cancer.

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 tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, 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 tumor has met criteria for response or SD in order to differentiate between response (or SD) and PD.

Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumor response for 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.

Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor 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 normalization of tumor 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 tumor marker level above the normal limits.

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

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

Abbreviations: CR: complete response; NE: not evaluated; PD: progressive disease; PR: partial response; SD: stable disease.

Note: Patients with a global deterioration of health status requiring discontinuation of investigational product without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of investigational product. In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the CR status.

Confirmatory measurement/duration of response

Confirmation

In non-randomized studies 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 studies. However, in all other circumstances, ie, in randomized studies (phase 2 or 3) or studies where SD or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of study 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.

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

Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized studies, from date of randomization) 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 SD varies in different studies and diseases. If the proportion of patients achieving SD for a minimum period of time is an endpoint of importance in a particular study, the protocol should specify the minimal time interval required between two measurements for determination of SD. Note: The DoR and SD as well as the PFS 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 studies are to be made.