Title: A Phase III Randomized Controlled Trial Comparing Low Dose Immunotherapy (Nivolumab) Combined with Standard Chemotherapy vs. Standard Chemotherapy as First-line Treatment in Patients with Locally Advanced or Metastatic Non-Small-Cell Lung Carcinoma (NSCLC)

Proposal No.: IIT-LEDANG2023001, version 4.0 dated 5 March 2025

Sponsor:

Ministry of Health, Malaysia (MOH)

Co-Sponsor:

Institute for Clinical Research-National Institutes of Health (ICR-NIH)

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MOH Research Grant Management:	
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SYNOPSIS

Study title	A Phase III Randomized Controlled Trial Comparing Low Dose Immunotherapy (Nivolumab) Combined with Standard Chemotherapy vs. Standard Chemotherapy as First-line Treatment in Patients with Locally Advanced or Metastatic Non-Small-Cell Lung Carcinoma (NSCLC)
Sponsor	Ministry of Health, Malaysia (MOH)
Co-Sponsor	Institute for Clinical Research-National Institutes of Health (ICR-NIH)
Clinical Phase	Phase III
Investigators (MOH Sites)	Hospital Sultanah Bahiyah: Dr. Arvindran a/l Alaga (Respiratory physician) Hospital Tengku Ampuan Afzan: Prof. Dr. How Soon Hin (Respiratory physician) Hospital Sultanah Nur Zahirah: Dr. Nor Azlina Samsudin (Respiratory physician) Hospital Raja Perempuan Zainab II: Dr. Azza Omar (Respiratory physician) Hospital Raja Permaisuri Bainun: Dr. Lam Yoke Fong (Respiratory physician) Institut Kanser Negara: Dr. Suhana Yusak (Oncologist) Hospital Sultan Ismail: Dr. Kumutha Chalaya (Oncologist)
Investigators (non-MOH sites)	University Malaya Medical Centre: Prof Pang Yong Kek (Respiratory Physician) Beacon Hospital: Dr Tho Lye Mun (Oncologist)
Study sites	MOH tertiary hospitals, University Hospitals and Private Hospitals with respiratory physicians and/or oncologists
Study period	Trial duration: 48 - 60 months (18 months enrollment; treatment duration up to 24 months

Objectives	Primary Objective • To determine the progression-free survival (PFS) of six-weekly Nivolumab 40mg combined with standard chemotherapy versus standard chemotherapy alone in NSCLC. Secondary Objectives • To evaluate the overall survival (OS) of six-weekly Nivolumab 40mg combined with standard chemotherapy in NSCLC. • To evaluate Patient-Reported Outcome Measure (PROM) for six-weekly Nivolumab 40mg combined with standard chemotherapy in NSCLC. • To assess the safety and tolerability profile of study regimens measured by the incidence of treatment-emergent adverse events (TEAEs), treatment-related discontinuation, treatment-related death and serious adverse events (SAEs) using CTCAE 5.0. • To evaluate the overall response rate (ORR) per RECIST 1.1 of six-weekly Nivolumab 40mg combined with standard chemotherapy in NSCLC
Methodology	This is a multicentre, two-arm randomized, parallel group design trial to evaluate superiority and safety of low dose Nivolumab (40mg) combined with standard chemotherapy versus standard chemotherapy alone in patients with non-small cell lung cancer. Eligible subjects who satisfy the inclusion and exclusion criteria will be randomized 2:1 into 2 arms (Low dose nivolumab arm consisting of six-weekly 40mg Nivolumab plus 4-6* cycles of Cisplatin or Carboplatin plus Pemetrexed or Gemcitabine or Docetaxel or Paclitaxel per local practice, versus standard chemotherapy alone, consisting 4-6* cycles of Cisplatin or Carboplatin plus Pemetrexed or Gemcitabine or Docetaxel or Paclitaxel per local practice.
Study outcomes	Primary efficacy endpoint • PFS Secondary efficacy endpoints • OS • Patient-Reported Outcome Measure (PROM) • Incidence of adverse events and treatment-emergent adverse events (TEAEs), and treatment-related death using CTCAE 5.0.
Sample size	The study aims to recruit about 123 patients (with 2:1 allocation in favour of nivolumab), to detect an PFS differences equivalent to hazard ratio of 0.55

	(15% rate in chemotherapy alone to 35% in chemo plus nivolumab) with 80% power and two-sided significance test at 5%. The interim analysis sample size is 21 patients in nivolumab arm to detect ORR of 45% again null of 20% at 80% power and one-sided significance test at 5%.
Study Population	Participants with Locally Advanced or Metastatic Non-Small-Cell Lung Carcinoma (NSCLC) who meet all the inclusion/exclusion criteria. The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all participants who: • Receive at least one dose of study treatment, and • Have a baseline scan with measurable disease per RECIST 1.1. Inclusion Criteria: 1. Male/female participants who are at least 18 years of age on the day of signing informed consent. 2. Histologically confirmed, treatment naïve, locally advanced, or metastatic (stage IIIB – IV (per AJCC version 8), squamous or non-squamous NSCLC with documented PD-L1 expression and not eligible for definitive chemo-radiation curative therapy and surgery. 3. Patients must be treatment naïve with respect to locally advanced or metastatic disease. Patients who received prior treatment with curative intent for early stage disease and develop recurrent advanced/ metastatic disease must have completed treatment at least 6 months prior to first dose of IP. 4. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Evaluation of ECOG is to be performed within 7 days prior to the first dose of study intervention. 5. At least 1 measurable lesion by RECIST 1.1 in solid tumors criteria. 6. Participants must have adequate organ function including the following laboratory values at the screening visit as per Table 2 7. If a participant has brain or meningeal metastases, the participant must meet the following criteria: a) Metastatic brain lesions do not require immediate intervention. Note: Asymptomatic, treated and stable as well

as not requiring steroids for at least 2 weeks prior to start study treatment. b) Carcinomatous meningitis is excluded regardless of clinical stability.

8. A male participant must agree to use a contraception starting with the first dose of study treatment through the treatment period and for at least 90 days after the last dose of study treatment and refrain from donating sperm during this period.
9. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies: a) Not a woman of childbearing potential (WOCBP), OR, b) A WOCBP who agrees to follow the contraceptive guidance during the treatment period and for at least 180 days after the last dose of study treatment.
10. Can provide evaluable archival tumor tissue sample or willing to provide tissue from newly obtained core or excisional biopsy or fine needle aspirate (FNA) cell block form of tumor lesion not previously irradiated. Note: Formalin fixed, paraffin embedded (FFPE) tissue blocks or slides allowed.

Exclusion Criteria:

1. Presence of EGFR, ALK or ROS1 mutation(s).
2. Patients with locally advanced disease who can receive other potentially curative therapies, such as patients who can afford to pay for or can otherwise access clinically approved doses of immunotherapy.
3. Prior treatment with any anti-PD-1, anti-PD-L1 or any other antibody targeting an immune checkpoint.
4. Use of any live vaccines against infectious diseases within 28 days of first dose of IP(s).
5. Underlying medical conditions that, in the Investigator's or Sponsor-PI's opinion, will make the administration of IP(s) hazardous, including but not limited to interstitial lung disease, including history of interstitial lung disease or non-infectious pneumonitis (lymphangitic spread of NSCLC is not disqualifying), or active viral, bacterial, or fungal infections requiring parenteral treatment within 14 days of the initiation of the IP.
6. Concurrent medical condition requiring the use of supra-physiologic doses of corticosteroids (> 10 mg/day of oral prednisone or equivalent) or immunosuppressive medications (absorbable topical corticosteroids are not excluded).

	7. Active hepatitis B and C infection or human immunodeficiency virus antibody (HIV-1 and/or HIV-2) positive at screening. 8. Known hypersensitivity to recombinant proteins, or any excipient contained in the IP formulations. 9. Known history of autoimmune disease currently on immunosuppressive medications. 10. Known history of second malignancy within two years prior enrolment. 11. Prognosis of three months or less. 12. A WOCBP who has a positive urine pregnancy test within 72 hours prior to treatment allocation. If the urine test positive or cannot be confirmed as negative, a serum pregnancy test will be required.	
Test treatment, dose, and mode of administration	Drug:	Nivolumab
	Dose/Potency:	40 mg
	Dose Frequency:	Every six weeks
	Route of Administration:	IV infusion
	Regimen/ Treatment Period:	Day 1 of each cycle (6-week cycle)
Duration of treatment with study medication	up to 24 months	

GANTT CHART

Activity	**Q3 2024**	**Q4 2024**	**Q1 2025**	**Q2 2025**	**Q3 2025**	**Q4 2025**	**H1 2026**	**H2 2026**	**H1 2027**	**H2 2027**	**H1 2028**	**H2 2028**
Proposal defence, MREC submission, KPK approval, “sebut harga” process, contracts drafting and execution												
Study set up (IP purchase, investigator site file preparation, trial insurance, site initiation)												
Recruitment of patient 1-31 (Arm 1: 21; Arm 2: 10)												
Completion of treatment patient 1-21 in Arm 1												

Interim Analysis (n=21 patients in Arm 1)												
Recruitment of patient 32-123												
Completion of treatment patient 32-123												
Data lock and analysis												

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ABBREVIATION

AE	Adverse Event
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	activated Partial Thromboplastin Time
AST	Aspartate Transaminase
BUN	Blood Urea Nitrogen
CNB	Core Needle Biopsy
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Response
CrCI	Creatinine Clearance
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CT TAP	Computed Tomography of Thorax, Abdomen and Pelvis
DOR	Duration of Response
DOT	Duration of Treatment
EB	Excisional Biopsy
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
ECI	Event of Clinical Interest
EGFR	Estimated Glomerular Filtration Rate
FAS	Full Analysis Set
FBR	Future Biomedical Research
FNAC	Fine Needle Aspirate Cell
GFR	Glomerular Filtration Rate
ICF	Informed Consent Form
IEC	Independent Ethics Committee
INR	International Normalized Ratio

IP	Investigational Product
IRB	Institutional Review Board
irAE	Immune related Adverse Event
ITT	Intention to Treat
LA/M	Locally Advanced/ Metastatic
LDH	Lactate Dehydrogenase
MTI	Maximally Tolerated Imbalance
NSCLC	Non Small Cell Lung Carcinoma
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-L1	Programmed Death-Ligand 1
PFS	Progression Free Survival
PR	Partial Response
PROM	Patient Reported Outcome Measures
PT	Prothrombin Time
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
ROS1	Repressor of Silencing 1
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
T3	Triiodothyronine
T4	Thyroxine
TEAE	Treatment-Emergent Adverse Events
TPS	Tumor Proportion Score
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WBC	White Blood Cell

WOCBP	Woman of Childbearing Potential

GENERAL INFORMATION

Sponsor:

Ministry of Health, Malaysia (MOH)

Roles and Responsibilities

Role	Investigator's Name	Institution
Sponsor/Principal Investigator	Dr. Arvindran a/l Alaga	Hospital Sultanah Bahiyah (HSB)
PI at the Site	Prof. Dr. How Soon Hin	Hospital Tengku Ampuan Afzan (HTAA)
PI at the Site	Dr. Nor Azlina Samsudin	Hospital Sultanah Nur Zahirah (HSNZ)
PI at the Site	Dr. Azza Omar	Hospital Raja Perempuan Zainab II (HRPZ II)
PI at the Site	Dr. Lam Yoke Fong	Hospital Raja Permaisuri Bainun (HRPB)
PI at the Site	Dr. Suhana Yusof	Institut Kanser Negara (IKN)
PI at the Site	Dr. Kumutha Chalaya	Hospital Sultan Ismail (HSI)
PI at the Site	Dr. Tho Lye Mun	Beacon Hospital (BH)
PI at the Site	Prof. Dr. Pang Yong Kek	University Malaya Medical Centre (UMMC)

Funding for this trial is being sought through the Medical Research Grant via Institute of Clinical Research (ICR) for the Ministry of Health sites and charitable donations from Cancer Research Malaysia for the non-Ministry of Health sites. The MRG will be managed centrally by Dr. Mohd Azri Mohd Suan at Clinical Research Centre of Hospital Sultanah Bahiyah (CRC HSB).

The recruitment for this Investigator-Initiated Trial (IIT) will take place at 9 investigator sites, 7 Ministry of Health hospitals, 1 private hospital and 1 public university. All investigators have completed and satisfied the feasibility assessment in terms of their facilities, expertise, patient populations, and resources to support implementation of this IIT.

CRMY plays the following role in this trial:

- As the co-developer of the Study Design and Protocol
- As co-funder of the Study (by providing funds required for additional non-KKM sites)
- As the Central Laboratory to facilitate PD-L1 TPS staining and reporting; molecular testing and reporting; to process biospecimens collected for biomarker research including PD-1 receptor occupancy tests.
- As Trial Coordinators and Data Managers to support Sponsor-PI on the study management, data management, identification of investigator sites, preparation of site readiness, study monitoring, budget coordination and etc.
- As point of contact on administrative matters (e.g. submission of protocol/ amendment to ethics committee, trial progress update and etc.)

Conflict of Interest Declaration

All investigators to be requested to declare they have no conflict of interest.

1. BACKGROUND AND RATIONALE

Lung cancer is one of the most common cancers in Malaysia, accounting for about 10% of all cancer cases (Malaysian National Cancer Registry Report, 2007-2011) and it is the most common cause of cancer-related deaths, accounting for almost 20% of all cancer deaths (International Agency for Research on Cancer in Malaysia, National Cancer Registry). The survival rate of lung cancer is the lowest amongst all cancers, at only 9% 5 year survival (Malaysian Study on Cancer Survival MySCAN 2018). Notably, there have been significant advances in the development of treatments for lung cancer, but these are largely unavailable to patients because of cost: ***this then is the area of greatest medical need – to find ways to improve access to these treatments and to improve survival for lung cancer patients in Malaysia.***

1.1. Checkpoint inhibitors for the treatment of NSCLC

Cancer largely develops as a result of the accumulation of somatic mutation and other genetic alterations that impair cell division, checkpoints, etc., which results in abnormal cell proliferation and eventually tumorigenesis – such mutations are called "driver mutations". Lung cancer is a heterogeneous disease, characterized by different molecular drivers. Patients with non-small cell lung cancer with driver mutations in EGFR or alteration of ALK achieve better survival when treated with EGFR inhibitors and ALK inhibitors respectively, and patients without driver mutations can achieve better survival when treated with checkpoint inhibitor immunotherapy (a form of therapy that releases a natural brake on the immune system so that immune cells called T cells can recognize and attack cancer cells) (Duma et al., 2019; Ia et al., 2019). Such checkpoint immunotherapies include Pembrolizumab, Nivolumab, Atezolizumab and Cemiplimab (Malhotra et al., 2017; Pelosci, A., 2022).

The response of patients to immunotherapy depends in part on whether treatment is given alone or in combination with chemotherapy, and on the patient population. In a first line setting, Pembrolizumab prolonged median overall survival (OS) of patients with NSCLC with PDL1>50% from 14.2 months with chemotherapy to 30 months with immunotherapy (Reck et al., 2019, KEYNOTE 024). When used in combination with chemotherapy, Pembrolizumab in a first line setting prolonged median overall survival from 10.7 months to 22 months in patients with advanced NSCLC without driver mutation regardless of PDL1 status (Gadgeel & Rodr, J Clin Oncol 2020; Gandhi et al., NEJM 2018, KEYNOTE 189), and patients with PDL>50% had the best OS (27.7 months). Notably, the PFS at 1 year was 34.1% (95% CI 28.8 to 39.5) in the

Pembrolizumab-combination group and 17.3% (95% CI, 120 to 23.5) in the placebo-combination group (Gandhi et al., NEJM 2018).

Similarly, in a first line setting, another checkpoint immunotherapy, Atezolizumab, prolonged median overall survival of patients with NSCLC with PDL1>1% from 13.1 to 20.2 months (Herbst et al., 2020; IMpower110 study), and improved overall survival of patients ineligible for platinum based chemotherapy from 9.2 months to 10.3 months (Lee et al., Lancet 2023; IPSOS study).

Similarly, in the first line setting in mNSCLC patients with tumor PD-L1 <1%, addition of nivolumab to chemotherapy improved duration of response from 4.8 to 8.3 months and 5-year estimated OS rates were 19%, 10%, and 7% with nivolumab plus ipilimumab, nivolumab plus chemotherapy and chemotherapy, respectively (HR 0.8, 0.64-1.0 comparing nivolumab-chemotherapy combination and chemotherapy) (Brahmer J Clin Oncol 2023, CHECKMATE 227). Similar clinical benefit patterns were observed with PFS, ORR, and DOR in both the PD-L1>1% and <1% populations. In patients who responded with tumor PD-L1<1%, responses lasting >5 years occurred in an estimated 21% and 13% in the nivolumab plus ipilimumab and nivolumab plus chemotherapy arms; no patients remained in response in the chemotherapy arm at 5 years (HR0.73, 0.58-0.93) (Brahmer J Clin Oncol 2023, CHECKMATE 227).

Finally, in the EMPOWER Lung 3 trial, median progression free survival with cemiplimab plus chemotherapy was 8.2 months (95% CI 6.4-9.3) versus 5.0 months (95% CI 4.3-6.2) for the placebo plus chemotherapy arm (HR = 0.56, 95% CI, 0.44-0.70, p<0.0001). The estimated proportion of patients receiving cemiplimab plus chemotherapy who were alive and had no disease progression at 12 months was 38.1% (95% CI, 32.4-32.8) versus 16.4% (05% CI, 10.5-23.4) for the placebo plus chemotherapy arm (Gogishvili et al., Nat Med 2022). PFS benefits also consistently favoured cemiplimab plus chemotherapy in all predefined subgroups.

Taken together, these results show that checkpoint immunotherapy, especially when used in combination with chemotherapy, significantly improves the survival of lung cancer patients with no driver mutations and these treatments are now the standard of care in the majority of high income countries.

1.2. Poor access to curative checkpoint inhibitors because of cost

Unfortunately, although some studies have shown that Pembrolizumab may be cost effective in first line treatment of advanced PDL1-high NSCLC in high income countries (Ding et al., 2020;

Huang et al., 2019), the use of checkpoint inhibitors remains restricted in developing countries due to its high cost (Bou et al., 2020). In Malaysia, checkpoint inhibitors are not provided for free in government hospitals and an evaluation conducted by the Ministry of Health Health Technology Assessment unit concluded that immunotherapy was not cost-effective in both the 1st and 2nd line setting for the treatment of NSCLC (ICER of MYR142,000 to 264,000 per QALY gained when compared to conventional platinum-based chemotherapy) (Ramli et al., 2022). Excluding the cost of hospital admission, investigation, and medical consultations, the cost of checkpoint inhibitors is between RM300,000 to RM600,000 for 35 doses. As this is unaffordable to the majority of patients, the majority of patients do not receive checkpoint immunotherapies, leading to missed opportunities to save lives (Rajadurai et al., 2020).

1.3. Clinical evidence of efficacy of low dose checkpoint inhibitor treatment

Intriguingly, there is suggestive evidence that a lower and more affordable dosing schedule of checkpoint inhibitors may still have therapeutic effect, and this may provide an opportunity to improve survival of lung cancer patients in low and middle income countries. A prospective trial (Checkmate 153) showed that although progression free survival was better in patients receiving 2 years of checkpoint immunotherapy compared to those receiving 1 year of treatment (65% compared to 40%, HR=0.42), there was no difference in overall survival (Waterhouse et al., JCO 2020). Several case reports and case series have demonstrated patients whose checkpoint inhibitor therapy was discontinued due to severe side effects or cost issues can experience prolonged responses without the need of further treatment. Specifically, 22 patients with advanced NSCLC who were treated with less than 6 months of checkpoint inhibitors in the second line setting or more, had a median OS of 11 months (95% CI:7.1,12.9) which was similar to 9-12 months seen in clinical trials in which checkpoint inhibitors were given for 35 doses or till disease progression (Iivanainen et al., Oncology 2019). Significantly, a retrospective analysis of patients who received either standard dose of 3mg/kg every 2 weeks (n=29) or low dose nivolumab (20 or 100 mg fixed dose every 3 weeks, n=18) because of inability to pay for full dose, observed that there was no statistical difference in objective response of 13.8% in the standard dose group and 16.7% in the low dose group (p=0.788, Yee et al., ESMO Open 2018).

There is also suggestive evidence that a lower dose of checkpoint inhibitors may achieve a similar treatment response as the approved dose. First, Phase 1 studies using Nivolumab showed that there was significant inhibition of PD1 at 2 months following infusion, suggesting that extending the treatment interval from the current recommended interval of 3 weeks to up to 12

weeks could still retain clinical benefit to patients (Brahmer et al, J Clin Oncol 2010). Second, in the phase 1 dose-escalation study of Nivolumab, where six-patient cohorts were treated at 0.3, 1, 3, or 10 mg/kg, followed by a 15-patient expansion cohort at 10 mg/kg (Brahmer et al, J Clin Oncol 2010), pharmacodynamics tests indicated a sustained mean occupancy of 70% of PD-1 molecules on circulating T cells was similar at 0.3mg/kg and 1mg/kg dose, suggesting that even if the plasma levels may be different, the effectiveness of the therapy may be achieved at a lower dose. Finally, dose escalation studies suggest that whilst the clinically recommended dose is 10mg/kg, patients receiving the lowest dose of 0.1 mg/kg still showed high response. For 107 patients with advanced melanoma who were treated with Nivolumab at doses ranging from 0.1 to 10 mg/kg, there was no dose-efficacy relationship for ORR, varying from 20.0% (95% CI: 5.7,43.7) in 10 mg/kg to 41.2% (95% CI: 18.4, 67.1) in 3 mg/kg, whereas the lowest dose of 0.1 mg/kg still showed high activity, with an ORR of 35.3% (95 % CI: 14.2, 16.7) (Topalian et al, NEJM 2014).

Recently, a Phase 3 randomized controlled trial in head and neck cancer has shown that patients receiving 20mg Nivolumab (instead of 120mg-360mg) every 3 weeks in combination with chemotherapy has better overall survival than those receiving chemotherapy alone (10.1 months compared to 6.7 months; Patil et al., J Clin Oncol 2023). The median PFS in the Nivolumab-combination arm was 6.6 months (95% CI 4.4 to 8.9) compared to 4.6 months (95% CI 4.2 to 5.3) in the chemotherapy arm.

Taken together, there is compelling evidence from dose escalation studies, case series, retrospective analyses and one randomized controlled trial in head and neck cancers, that a shorter duration (early cessation), extended treatment interval (from 3 weeks to 6 weeks or longer), or lower dose of checkpoint immunotherapy may result in improved survival for lung cancer patients. Several ongoing randomised trials are evaluating dose optimisation, broadly testing early cessation, extended interval administration or reduced doses (reviewed in Hirsch et al., Nat Med 2022).

Type	Trial (indication)	Design	Planned n	Country	Registration number
Early cessation	SAVE (NSCLC)	Full dose immune checkpoint therapy after chemotherapy randomized to stop at 1 year vs continuation	216	Japan	JCOG1701
	DIAL (NSCLC)	Randomized between 6 months and 2 years of full dose pembrolizumab after chemotherapy	114	France	NCT05255302

Extended interval	NCT04295863 (Any)	1x vs 2x Standard of care interval for full dose immune checkpoint therapy	264	USA	NCT04295863
	REFINE-Lung (NSCLC)	MAMS initially full dose pembrolizumab every 6 vs 12 weeks	1,750	UK	NCT05085028
	NCT04032418 (NSCLC)	Pembrolizumab full dose at 3 vs 12 weeks intervals after combination chemotherapy	152	USA	NCT04032418
	PULSE (NSCLC)	Pembrolizumab full dose at 3 vs 6 weeks intervals after combination chemotherapy	1,100	France	TBC
Low dose	NVALT-30 Dedication NSCLC	Randomized between pembrolizumab and pembrolizumab 25% dose reduction	750	The Netherlands	EudraCT 2020-000493-15
	CTRI-DELLI HNSCC	Low-dose nivolumab (20 mg twice weekly) vs chemotherapy	TBC	India	CTRI/2020/ 02/023441

1.4. Rationale for the LEDANG Study

Notably, as the early cessation and extended regimens are testing full dose and the pembrolizumab dose reduction trial is testing only a 25% reduction, these regimens will still be unaffordable in a low income setting. One low dose nivolumab trial is planned in Head and Neck cancer (CTR1-DELLI) but to the best of our knowledge, none have been planned in lung cancer. ***This then is the area of greatest medical need: to determine the efficacy of a lower (and more affordable) dosing schedule of checkpoint immunotherapy in the lung cancer – the most common cause of cancer-related deaths in Malaysia.*** In this proposal, we aim to investigate that the effectiveness of lower dose of immunotherapy in improving lung cancer survival.

1. **Why Nivolumab?** As the mechanism of action and the data (where available) appear broadly similar across different checkpoint inhibitors, we have chosen to evaluate low dose nivolumab as the smallest vial strength of nivolumab is 40mg vial (compared to 100mg for other checkpoint inhibitors). By choosing nivolumab, we will be able to avoid vial sharing between patients.

2. **Why 6 weekly?** Given that there PD1 receptor occupancy was >80% for up to 12 weeks, we aim is to evaluate a dosing schedule that is affordable to patients.

3. **Why first line setting?** There are 2 reasons for conducting a trial in a first line setting:

a. The therapeutic benefit of checkpoint immunotherapy is greater in a first line setting and it is already approved as standard of care in high income settings. Conducting a trial in a second line setting now would mean that a first line trial would need to be conducted later and this would further delay the potential benefit of treatment to low income patients.

b. The therapeutic benefit of checkpoint immunotherapy in a 2nd line setting is lower, which means that a larger and more expensive study will be required.

	CHECKMATE 057	**CHECKMATE 227**
Setting	2nd line and above, PDL1 all	1st line, PDL1<1%
Comparators	Nivo 360 mg vs docetaxel	Nivo 360 mg-chemo combination vs chemo
OS	12.2 months vs 9.4 months (HR0.73 95% CI 0.59-0.89 p=0.002)	18.8 vs 15.6 months (NSQ NSCLC) (n.s.) 18.3 vs 12.0 months (SQ NSCLC) (sig) 18.3 vs 14.7 months (all) (sig) (HR0.81 95% CI 0.67-0.97)
OS (1 year)	51% vs 39%	67.3% vs 59.2% (NSQ NSCLC) 66.1% vs 48.5% (SQ NSCLC) 66.9% vs 56.2% (all NSCLC)
PFS	2.3 months vs 4.2 months	8.7 vs 5.8 months (NSQ NSCLC) (sig) 7.1 vs 4.4 months (SQ NSCLC) (sig) 8.4 vs 5.5 months (all) (sig)
PFS (1 year)	19% vs 8%	39.5% vs 25.7% (NSQ NSCLC) 31.7% vs 9.3% (SQ NSCLC) 37.3% vs 21.3% (all NSCLC)
ORR	19% vs 12% (p=0.02)	51.5% vs 30.2% (Paz Ares Annals Oncol) 37.3% vs 23.1% (Brahmer JCO 2023)
Reference	Borghaei NEJM 2015	Paz-Ares Ann Oncol 2019

4. **Why is the primary outcome PFS?** In the CHECKMATE 227 full dose Nivo+chemo combination vs chemotherapy trial, an improvement in OS and PFS were observed in the all patient analysis (Paz-Ares et al., Ann Oncol 2019). The number of patients needed in an OS analysis is >1,000 and the Study team has proposed to evaluate PFS as the sample size required is 123.

5. **Why is this an investigator-initiated study?** Although the data from dose escalation studies, case series, retrospective analyses and other cancers (eg. Head and neck cancer) are compelling in suggesting potential patient benefit at an affordable cost in a LMIC setting, a well-designed prospective study, such as the proposed superiority Phase 3 trial with sufficient sample size is needed to confirm the efficacy of low-dose nivolumab. Notably, pharmaceutical companies may consider non-inferiority trials, however, the

samples sizes required are typically significantly larger, and hence academic investigator-initiated studies such as LEDANG is necessary to evaluate potential efficacy at a dose affordable in LMIC settings.

With this data, we hope to enable health policies that address the cancer health equity gaps, specifically access to lifesaving cancer treatments.

2. OBJECTIVES

2.1. Primary Objective

- To determine the progression-free survival (PFS) of six-weekly Nivolumab 40mg combined with standard chemotherapy versus standard chemotherapy alone in NSCLC.

2.2. Secondary objective

- To evaluate the overall survival (OS) of six-weekly Nivolumab 40mg combined with standard chemotherapy in NSCLC.
- To evaluate Patient-Reported Outcome Measure (PROM) for six-weekly Nivolumab 40mg combined with standard chemotherapy in NSCLC
- To assess the safety and tolerability profile of study regimens measured by the incidence of treatment-emergent adverse events (TEAEs), treatment-related discontinuation, treatment-related death and serious adverse events (SAEs) using CTCAE 5.0.
- To evaluate the overall response rate (ORR) per RECIST 1.1 of six-weekly Nivolumab 40mg combined with standard chemotherapy in NSCLC

2.3. Exploratory objectives

- To analyze pre-planned subgroup analysis based on age, gender, ethnicity, histology, PD-L1, and ECOG.
- To assess if variation in checkpoint inhibitor binding to the receptor impact treatment response through PD1 receptor occupancy studies.

2.4. Future Biomedical Research (FBR)

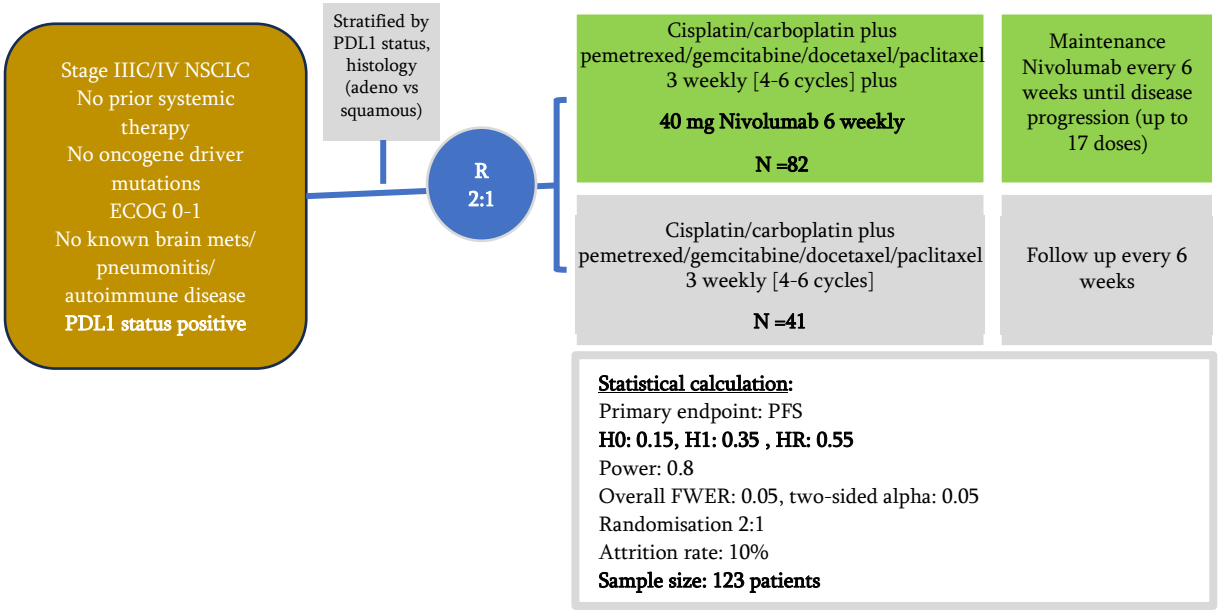
The specimens collected during clinical trial will be analysed to further investigate the association of response to the checkpoint immunotherapy through multiple scientific disciplinary, this includes:

- To identify other factors predictive of clinical response (e.g. immune repertoire, other biomarkers) through techniques including immunohistochemistry, proteomics, gene and transcriptional analyses
- To explore correlation between genetic variation and clinical response
- To conduct on-treatment microbiome profiling and determine the correlation with clinical response

To monitor the changes in circulatory immune cells throughout the treatment period

3. TRIAL DESIGN

This is a randomised controlled phase III trial. An interim efficacy analysis is planned after 21 patients have been recruited to the nivolumab arm, to check that the overall tumor response rate (ORR) is consistent with the expected rate of 45%. If the ORR is noticeably lower, the trial may stop early as this indicates that the efficacy of nivolumab is insufficient.



3.1 Primary Efficacy Endpoint(s):

Progression-Free Survival (PFS). PFS is defined as the time from randomisation to either the date of progression or death from any cause (whichever comes first); and those who are alive and progression-free are censored at the date they were last known to be alive.

3.2 Secondary Efficacy and Safety Endpoint(s)

1. Overall Survival (OS) - OS will be measured from the date of treatment commencement to the date death from any cause. Participants without documented death at the time of the final analysis will be censored at the date of the last follow-up.

2. Patient-Reported Outcome Measure [Time Frame: up to 2 years]: Measurement will be performed at baseline, and every 6 weeks thereafter for both arms for the first 6 months. After that, measurement will be performed every 3 months until the end of treatment follow up or the last study follow up related to adverse event for study discontinuation that is due to the AE.

3. Number of participants experiencing an Adverse Event (AE) [Time Frame: from first dose to last dose of treatment plus follow-up – up to 27 months]. AE will be graded according to NCI-CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) version 5.0. Frequency and intensity of adverse events (CTCAE v.5) as measured at each visit and during safety follow up (90 days after discontinuation of treatment).

3.3 Randomization

Maximally-Tolerated-Imbalance (MTI) Randomization method will be used in this trial to conduct the randomization. This method is designed to prevent selection bias which can impact the effectiveness of the trial and data integrity. The National Cancer Institute provides an easy-to-use tool called Clinical Trial Randomization Tool to generate randomized clinical trial arms. The participants randomization will be controlled centrally by CRMY. Participant must be consented and confirmed on the eligibility prior to randomization. Site investigator or study coordinator to send email clintrial@cancerresearch.my on the eligibility confirmation to receive information on the participant enrolment arm.

3.4 Stratification

Treatment allocation/randomization will be stratified according to the following factors:

a. PD-L1 status: TPS ≥ 50%, and TPS < 50%.

b. Histology: Adenocarcinoma versus squamous

3.5 Assignment of Allocation Number

All consented participants will be given a unique allocation number, Screen ID which will be automatically generated when the first data entered in the REDCap eCRF. It will be used to identify the participants for all the procedures and assessments that occur prior to enrolment. If the participants pass the screening and fulfill the eligibility criteria, then the enrolment ID will be centrally assigned by CRMY along with the randomization arm details. The enrolment ID must not be re-used for different participants.

A single participant cannot be assigned more than one allocation number.

3.6 Trial Interventions

Table 1: Trial Interventions

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Nivolumab	40 mg	Every six weeks	IV infusion	Day 1 of each cycle (6-week cycle)	Experimental Regimen
Cisplatin, Carboplatin, Pemetrexed, Docetaxel, Paclitaxel	As per local practice	Every three weeks	IV infusion	Day 1 of each cycle (3-week cycle) for 4-6 cycles	
Gemcitabine	As per local practice	Every three weeks	IV infusion	Day 1 and 8 of each cycle (3-week cycle) for 4-6 cycles	
Note: Any variation from the standard regimen outlined in the protocol will need to have prior approval from the medical monitor/ trial committee.					

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

3.7 Timing of Dose Administration

Trial interventions should be administered according to the regimen schedule each cycle after all procedures/assessments have been completed. Trial interventions may be administered up to 3 days before or after the scheduled day of each cycle due to administrative reasons per the investigator's judgement. All trial interventions will be administered on an outpatient basis.

Participants may receive a maximum of 6 cycles of Cisplatin or Carboplatin plus Pemetrexed or Gemcitabine or Docetaxel or Paclitaxel. Maintenance dose of Pemetrexed is allowed for patients with adenocarcinoma who showed response to the initial 4 to 6 cycles of chemotherapy.

Dosing interruptions are permitted in the case of medical/ surgical events or logistical reasons (e.g., elective surgery, unrelated medical events, patient vacation, and holidays) not related to study therapy. Patients should be placed back on study therapy within 3 weeks of the scheduled interruption. The reason for the interruption should be documented in the participant's study record.

3.8 Study Visits

3.8.1 Screening Visit

Within 28 days prior to treatment allocation, potential participants will be evaluated to determine that they fulfill the entry requirements. Screening procedures may be repeated.

Participant may be rescreened after initially failing to meet the inclusion/exclusion criteria.

Participants who are rescreened will retain their original allocation number. 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 and the inclusion/exclusion criteria is met. Screening procedures are to be completed within 28 days prior to the first dose trial treatment except for the following:

- Laboratory tests and ECOG PS are to be performed within 7 to 10 days prior to the first dose of trial treatment.
- For women of reproductive potential, a serum pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. A urine test may be considered if serum test is not appropriate.

3.8.2 Treatment Visit

Detailed visit requirements are outlined in Appendix 1.

3.8.3 End of Treatment Visit

End of Treatment Visit will be performed at the time of discontinuation study intervention.

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as per Schedule of Activities.

All participants who have received at least one dose of Nivolumab in arm 1 will be evaluable for safety analysis. All participants who are registered into the study but fail to receive the first dose of study drug and those who are lost to follow up before disease evaluation will be replaced.

The primary reason for discontinuation will be clearly documented in the participant's medical record and recorded in the CRF.

3.8.4 Post Treatment Visits

3.8.4.1 Safety Follow Up Visits

The mandatory Safety Follow-Up Visit should be conducted approximately 90 days after the last dose of study intervention or before the initiation of a new anti-cancer treatment, whichever comes first. The safety follow-up plan for grade 3 and above AEs and SAEs should be performed periodically until resolution to grade 1.

3.8.4.2 Efficacy Follow Up Visits

Participants who complete the protocol-required cycles of study intervention of who discontinue study intervention for a reason other than disease progression will begin the Efficacy Follow-Up Phase and should be assessed every 6 weeks (42 ± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 9 weeks (± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, or end of the study. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter the Survival Follow-up Phase.

3.8.4.3 Survival Follow Up Calls

Participant survival follow-up status will be assessed approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. The first survival follow-up assessment should be scheduled as described below:

- For participants who discontinue treatment intervention and who will not enter the Efficacy Follow-up Phase, the first survival follow-up contact will be scheduled 12 weeks after the discontinuation visit and/or safety follow-up visit (whichever is last).

- For participants who completed assessments in the Efficacy Follow-up Phase, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

3.9 Biospecimen Collection, Storage and Use

3.9.1 Tumor Tissue Collection

At screening, all subjects will submit newly obtained core needle or excisional biopsy or fine needle aspirate (in cell block form) to central lab for characterization of PD-L1 status and molecular and biomarker testing. Next generation sequencing is preferred but depending on sample availability or quantity, other molecular tests (e.g. RT-PCR, PCR), IHC or FISH will be accepted. To determine eligibility, positivity for only three genes (EGFR, ALK or ROS1) will be used. Existing reports with EGFR, ALK and ROS1 will be accepted. Existing PD-L1 reports (28-8, 22C3, SP263) will be accepted based on the high concordance on the Blueprint Harmonization Projects (Hirsch 2017 J Thorac Oncol; Tsao 2018, J Thorac Oncol).

Specimens can be obtained from primary lung tumor or metastatic sites. These specimens may be the diagnostic sample for patients with a new diagnosis of metastatic NSCLC.

Note: Tumor lesions used for newly obtained biopsies should not be the same lesions used as RECIST target lesions unless there are no other lesions suitable for biopsy.

Alternatively, archival formalin-fixed, paraffin embedded (FFPE) slides of up to 3 years prior to trial enrolment are acceptable (i.e., 20-25 unstained FFPE slides and 1 H&E slide, each with 5 microns in thickness) if newly obtained biopsy samples cannot be obtained. A newly obtained biopsy is preferrable over archival tumor samples. It is highly recommended if patients can provide both FFPE samples and tumor biopsy. Any excess tissue surplus for diagnostic requirements will be stored for FBR. Tissue in all forms are acceptable except for PD-L1 testing, which requires specifically unstained tissue slides.

Biospecimens surplus to diagnostic requirements from patients treated in Ministry of Health hospitals will be stored at a location to be determined by the Institute of Clinical Research, for biomarker research to identify factors associated with response to therapy, and may only be used with the explicit approval of the Sponsor-PI and Co-PI (CRMY) of the study. Biospecimens from patients treated in non-Ministry of Health hospitals will be stored at CRMY, for biomarker research to identify factors associated with response to therapy, and may only be used with the explicit approval of the Sponsor-PI and Co-PI (CRMY) of the study.

3.9.2 Correlative Blood and Stool Sampling

All enrolled patients must provide ~24ml of blood at screening, every 6 weekly before (Nivolumab/Chemotherapy) dosing until radiographic confirmed disease progression and up to 3 consecutive imaging timepoints or post discontinuation of treatment or end of treatment (EOT). For treatment arm 1, blood (~24mL) will be used for evaluation of PD1 receptor occupancy, while for treatment arm 2, it will be stored for FBR with patient consent. Additionally, an extra ~16mL of blood will be collected from treatment arm 1 patient who consent to FBR. FBR consented patient may provide stool with collection window -5+3 days following the correlative blood sampling. If the screening imaging was performed as a routine scan prior to giving consent in participation of this trial, the blood and stool samples for FBR will be taken within 28 days prior to treatment allocation.

The collected blood and stool samples from patients treated in Ministry of Health hospitals will be stored at a location to be determined by the Institute of Clinical Research for future disease-related research and may only be used with the explicit approval of the Sponsor-PI and Co-PI (CRMY) of the study. The blood and stool samples from patients treated in non-Ministry of Health hospitals will be stored at CRMY and may only be used with the explicit approval of the Sponsor-PI and Co-PI (CRMY) of the study. Detailed blood and stool samples collection, processing and shipment are provided in the Biospecimen Guideline by CRMY central laboratory.

3.10 Clinical Criteria for Early Trial Termination

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

a. The minimum criterion of 18 responders for the first 40 patients in the intervention arm is not achieved during Phase 2 analysis.
b. The quality or quantity of data recording is inaccurate or incomplete.
c. Poor adherence to protocol and regulatory requirements.
d. Incidence or severity of adverse drug reaction in this study indicates a potential health hazard to participants.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Study Population

Participants with Locally Advanced or Metastatic Non-Small-Cell Lung Carcinoma (NSCLC) who meet all the inclusion/exclusion criteria listed below.

4.1.1 Analysis Population

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all participants who:

a. Receive at least one dose of study treatment, and
b. Have a baseline scan with measurable disease per RECIST 1.1.

4.1.2 Inclusion Criteria:

1. Male/female participants who are at least 18 years of age on the day of signing informed consent.
2. Histologically confirmed, treatment naïve, locally advanced, or metastatic (stage IIIB – IV (per AJCC version 8), squamous or non-squamous NSCLC with documented PD-L1 expression and is not eligible for definitive chemo-radiation curative therapy and surgery.
3. Patients must be treatment naïve with respect to locally advanced or metastatic disease. Patients who received prior treatment with curative intent for early stage disease and develop recurrent advanced/ metastatic disease must have completed treatment at least 6 months prior to first dose of IP.
4. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Evaluation of ECOG is to be performed within 7 days prior to the first dose of study intervention.
5. At least 1 measurable lesion by RECIST 1.1 in solid tumors criteria.
6. Participants must have adequate organ function including the following laboratory values at the screening visit as per Table 2:

Table 2. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (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 Note: Pemetrexed is not recommended to be used if <45ml/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 aPTT 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 erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

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

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

7. If a participant has brain or meningeal metastases, the participant must meet the following criteria:
   a. Metastatic brain lesions do not require immediate intervention.

      Note: Asymptomatic, treated and stable as well as not requiring steroids for at least 2 weeks prior to start study treatment.

   b. Carcinomatous meningitis is excluded regardless of clinical stability.

8. A male participant must agree to use a contraception starting with the first dose of study treatment through the treatment period and for at least 90 days after the last dose of study treatment and refrain from donating sperm during this period.

9. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
    a. Not a woman of childbearing potential (WOCBP) **OR**
    b. A WOCBP who agrees to follow the contraceptive guidance during the treatment period and for at least 180 days after the last dose of study treatment.
10. Can provide evaluable archival tumor tissue sample or willing to provide tissue from newly obtained core or excisional biopsy or fine needle aspirate (FNA) cell block form of tumor lesion not previously irradiated. Note: Formalin fixed, paraffin embedded (FFPE) tissue blocks or slides allowed.

4.1.3 Exclusion Criteria:

1. Presence of EGFR, ALK , ROS1 mutation(s).
2. Patients with locally advanced disease who can receive other potentially curative therapies, such as patients who can afford to pay for or can otherwise access clinically approved doses of immunotherapy.
3. Prior treatment with any anti-PD-1, anti-PD-L1 or any other antibody targeting an immune checkpoint.
4. Use of any live vaccines against infectious diseases within 28 days of first dose of IP(s).
5. Underlying medical conditions that, in the Investigator's or Sponsor-PI's opinion, will make the administration of IP(s) hazardous, including but not limited to a. Interstitial lung disease, including history of interstitial lung disease or non-infectious pneumonitis (lymphangitic spread of NSCLC is not disqualifying), Active viral, bacterial, or fungal infections requiring parenteral treatment within 14 days of the initiation of the IP.
6. Concurrent medical condition requiring the use of supra-physiologic doses of corticosteroids (> 10 mg/day of oral prednisone or equivalent) or immunosuppressive medications (absorbable topical corticosteroids are not excluded).
7. Active hepatitis B and C infection or human immunodeficiency virus antibody (HIV-1 and/or HIV-2) positive at screening.
8. Known hypersensitivity to recombinant proteins, or any excipient contained in the IP formulations.
9. Known history of autoimmune disease currently on immunosuppressive medications.
10. Known history of second malignancy within two years prior enrolment.

11. Prognosis of three months or less.
12. A WOCBP who has a positive urine pregnancy test within 72 hours prior to treatment allocation. If the urine test positive or cannot be confirmed as negative, a serum pregnancy test will be required.

4.2 Subject Informed Consent

The Investigator must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research (FBR). Signing the informed consent for FBR samples is optional. If there are changes to a participant's status during the study (e.g., health requirements) the investigator must ensure appropriate consent is in place.

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.

If the investigator recommends continuation of study intervention beyond disease progression (Appendix 4), the consent by participant or his/her legally acceptable representative will be recorded in patient's study note.

4.3 Subject Withdrawal

A participant must be withdrawn from the study if the participant or the participant's legally acceptable representative withdraws consent from the study. If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

4.4 Subject Discontinuation Criteria

Discontinuation of study intervention does not represent withdrawal from the study. As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will continue to be monitored in this study and participate in the study visits and procedures unless the participant has withdrawn from the study.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor-PI if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study treatment for any of the following reasons:

a. The participant or participant's legally acceptable representative requests to discontinue study intervention.
b. After prolonged study intervention interruption that prohibits restarting study intervention if agreed upon with the Sponsor-PI.
c. Radiographic disease progression.
d. Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.
e. Any study intervention-related toxicity specified as a reason for permanent discontinuation.
f. The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor-PI, places the participant at unnecessary risk from continued administration of study treatment.
g. The participant has a confirmed positive serum pregnancy test.

h. Investigator's decision to withdraw the participant.
i. Non-compliance with trial treatment or procedure requirements.
j. The participant is lost to follow-up.
k. Administrative reasons.
l. Completed 35 treatments (approximately 2 years) with Nivolumab.

5. TREATMENT AND PROCEDURES

5.1. Allowed 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 prior to the first dose of trial intervention and up to 30 days after the last dose of trial intervention should be recorded. If participants experience an SAE or ECI, concomitant medications administered 30 days after the last dose of trial intervention are to be recorded.

5.2. Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

a. Antineoplastic systemic chemotherapy or biological therapy
b. Immunotherapy not specified in this protocol
c. Chemotherapy not specified in this protocol
d. Investigational agents other than Nivolumab
e. Radiation therapy

   Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion. The participant must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.
f. 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.

g. 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 the Sponsor-PI. Additionally, a short, limited course of steroids may be used to treat medical conditions and/or AEs during the study after Sponsor-PI notification and consultation.

   Note: Inhaled steroids are allowed for management of asthma/ COPD.

   Note: Use of prophylactic corticosteroids to avoid allergic reactions (e.g., to IV contract dye) or use of corticosteroids as pre-medication for chemotherapeutic agents specified in the protocol is permitted.

h. Herbal and natural remedies that may affect PK of anti-cancer medicines.

Participants who, in the assessment by the investigator, require the use of any of the 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.

5.3. Rescue Medications & Supportive Care

5.3.1. Supportive Care Guidelines for Nivolumab

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 Table 3. 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 Nivolumab.

5.3.2. Supportive Care Guidelines for Cisplatin/ Carboplatin

Please refer to the product label or local standards of care for cisplatin/ carboplatin supportive measures.

5.3.3. Supportive Care Guidelines for Pemetrexed/ Gemcitabine/ Docetaxel/ Paclitaxel

Please refer to the product label or local standards of care for pemetrexed/ gemcitabine/ docetaxel/ paclitaxel supportive measures.

Table 3. Dose Modification and Toxicity Management Guidelines For Immune-Related AEs Associated With Nivolumab Monotherapy And IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks to avoid relapses of irAE.
4. If study intervention has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Nivolumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 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) • Participants with ≥Grade 2 diarrhea suspecting colitis should
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Nivolumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
				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 or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 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 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper. Second immunosuppressive needs to be added if AST/ALT does not improve in 48 hours. Consultation with hepatologist would then be recommended +/- consideration for liver biopsy.	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM	· Monitor participants for hyperglycemia or other signs and symptoms of diabetes

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Nivolumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
			· Administer antihyperglycemic in participants with hyperglycemia	
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 [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) 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 to 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		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Nivolumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
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 irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue Nivolumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, Nivolumab may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

6. ASSESSMENT OF EFFICACY

6.1. Primary Efficacy Analysis

The primary efficacy analysis is the PFS. This study intends to prove the superiority based on the comparison between the 2 arms. PFS will be analyzed where the PFS will be compared between the two treatment arms by using log-rank test and stratified log-rank test by stratification factors (PD-L1 level) at the overall significance level of 5%. Survival curves are estimated using the Kaplan-Meier estimator. The median PFS time, 95% confidence interval are presented for each arm. The final PFS analysis ends when the last patient randomized follow up for 24 months.

The confirmed 1-year PFS by treatment group will be calculated along with the two-sided CI using the Clopper-Pearson method (exact CI for a binomial proportion computed using GenBinomApps package in R). The alpha value is specified to 0.05. The hypothesis will be tested using a two-sample binomial proportions test. The test statistic z is assumed to have a standard Normal distribution. The significance level for this test will be set at 2 sided alpha = 0.05 with 95% confidence interval for the difference in proportions will be presented.

Using the intent-to-treat cohort, relative risk estimates will be obtained from a Cox proportional hazards model for discrete time observations. Significance test and relative risk (hazard ratio) estimates for the treatment will be obtained adjusted for potential confounder and effect modifier in the multivariable Cox regression.

6.2. Secondary Efficacy Analysis

Sample size calculations have not been made for the secondary objectives as the secondary analyses are exploratory, nonetheless hypothetical testing will be conducted as the findings of this study may guide future research. The secondary efficacy analysis is analyzed in the same way for overall survival (OS), ORR and AE. The ORR will be analyzed using two-sample binomial proportion test while OS will be analyzed using Kaplan Meier estimator, log-rank test, and Cox regression. All statistical tests for the secondary analysis are exploratory and two-sided.

6.3. Summaries of Baseline Characteristics, Demographics and Others

Baseline characteristics will be assessed using tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, allocated, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age, gender, ethnicity, etc), baseline characteristics (e.g., number and percentage of subjects who developed locally advanced disease, number and percentage of subjects who developed metastatic disease, sites of recurrent metastatic, etc.) and prior and concomitant therapies will be summarized by treatment either by descriptive statistics of categorical or continuous variables. Two-sided Fisher's exact tests and chi-square tests for categorical variables and independent-samples Student's t-tests for continuous variables will be used to test for the differences between the two arms. Safety data (i.e., AEs, serious adverse events (SAEs) and events of clinical interest (ECIs)) will be summarized by descriptive statistics.

6.4.Exploratory Analysis

The specimens collected during clinical trial will be analysed to further investigate the association of response to the checkpoint immunotherapy:

- Receptor occupancy studies to determine whether variation in binding of the checkpoint inhibitor to the receptor may be associated with response to treatment. Both nivolumab binding and Ki-67 in T cells has been reported to predict patient response to nivolumab (Osa 2018). Recent study also demonstrated patient with low receptor occupancy but not high receptor occupancy will benefit from nivolumab re-challenge at recurrence (Nose 2022). In this study, we propose to study live PBMCs (isolated 24-48 hours from collection) for the following: (1) dosing frequency that saturate the receptor (2) sustainability of the receptor occupancy and (3) correlate receptor occupancy with treatment response.

6.5. Future Biomedical Research

- Microbial compositions in the lung (via bronchoalveolar lavage fluid) and gut have been shown to differ in responders versus non-responders in nivolumab-treated NSCLC (Hakozaki 2020, Masuhiro 2022). Dysbiosis may affect response to immune checkpoint inhibitors (Jin 2019) with one possible mechanism being the reduction of chemokines (such as CXCL9) (Masuhiro 2022). As there are limited studies in respiratory and gut microbiota in association with ICI efficacy, even more so in low-dose settings, we would like to investigate this in the tumor, stool and pleural effusion samples (where available).

7. ASSESSMENT OF SAFETY

The safety analysis set includes all subjects who received at least one dose of any trial treatment. Analyses performed on the safety analyses set will consider subjects as treated. The safety analyses set will be used for safety analyses.

7.1. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

Progression of the cancer under study is not considered an adverse event unless it is considered drug related by the investigator.

Adverse events, SAEs, and other reportable safety events will be reported by the participant or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

7.1.1. Time Period and Frequency for Collecting AE, SAE and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before treatment allocation must be reported by the investigator if the participant is receiving placebo run-in or other run-in 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 through 90 days following cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment allocation through 90 days following cessation of study intervention or 30 days following cessation of study intervention 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 through 120 days following cessation of study intervention, or 30 days following cessation of study intervention 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 period specified above must be reported immediately to Sponsor-PI and medical monitors if the event is considered drug-related.

Investigators are not obligated to actively seek AEs or SAEs 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 intervention or study participation, the investigator must promptly notify Sponsor-PI and medical monitors.

All initial and follow up AEs, SAEs and other reportable safety events will be recorded and reported to Sponsor-PI and medical monitors within 1 business day and to IRB/IECs in accordance with applicable specific ethics requirements.

7.1.2. Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

7.1.3. Follow-Up of AE, SAE and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up. In addition, the investigator will make every attempt to follow all nonserious AEs that occur in allocated participants for outcome.

7.1.4. Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to Sponsor-PI and medical monitors.

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.

7.1.5. Events of Clinical Interest (ECIs)

Selected non-serious and SAEs are also known as ECIs and must be reported to Sponsor-PI and medical monitors.

Events of clinical interest for this study include:

a. 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.*

8. STATISTICAL ANALYSIS PLAN

8.1. Hypothesis

The null hypothesis is that there is no significant differences of 1-year PFS rate between the two arms. Alternative hypothesis is that there is a 20% differences of 1-year PFS rate between the two arms.

8.2. Study Size

Efficacy data associated with both nivolumab and chemotherapy come from several clinical trials, as follows. (a) KEYNOTE-189 where the PFS at 1-year was 34.1% (95% CI 28.8 to 39.5) in the Pembrolizumab-combination group and 17.3% (95% CI, 120 to 23.5) in the placebo-combination group (Gandhi et al., 2018); (b) the EMPOWER Lung 3 trial, where the PFS at 1-year was 38.1% (95% CI, 32.4-32.8) in the Cemiplimumab-chemotherapy combination group versus 16.4% (05% CI, 10.5-23.4) for the placebo plus chemotherapy arm (Gogishvili et al., Nat Med 2022). Notably, the proportion of patients who had PDL1 >50%, 1-49% and <1% in both the KEYNOTE-189 and EMPOWER Lung 3 trials was appropriately equally distributed, whereas we plan to recruit at least 50% of patients with PDL1>50%, and therefore anticipate that the PFS in the Nivolumab-combination group is likely to be similar or greater than that of KEYNOTE-189 and EMPOWER Lung 3 Trials.

	KEYNOTE 189	**EMPOWER Lung3**	**CHECKMATE 227**
Setting	1st line, stratified for PDL1 [~1/3 each PDL1>50%, 1-49% and <1%]	1st line, stratified for PDL1 [~1/3 each PDL1>50%, 1-49% and <1%]	1st line, PDL1<1%

Comparators	Pembrolizumab-chemo combination vs chemo	Cemiplimumab-chemo combination vs chemo	Nivo 360 mg-chemo combination vs chemo
OS	(median not reached) vs 11.3 months (HR0.45)	21.9 vs 13.0 months (HR0.71)	18.3 vs 14.7 months (HR0.81)
OS (1 year)	69.2% vs 49.4%	65.7% vs 56.1%	66.9 vs 56.2% (n.s.)
PFS	8.8 vs 4.9 months [HR 0.52 (0.43–0.64)]	8.2 vs 5.0 months [HR 0.56 (0.44–0.70)]	8.4 vs 5.5 months [HR 0.62 (0.52–0.73)]
PFS (1 year)	34.1% vs 17.3%	38.1% vs 16.4%	37.3% vs 21.3% (p=ns)
ORR	47.6% vs 18.9% (p=0.02) [difference 28.7%]	43.3% vs 22.7% (p=0.02) [difference 20.6%]	37% vs 23% (p=0.02) [difference 21.3%]
Reference	Gandhi NEJM 2018	Gogishvili Nat Med 2022	Paz-Ares Ann Oncol 2019; Brahmer JCO 2023

We assume the 1-year PFS rate in the chemotherapy alone group to be 15% and we aim to detect a rate of 35% with nivolumab; both consistent with other trials. We specify a 35% rate for nivolumab because it is towards the lower end of the range of the results seen in the prior trials and so reflects a slight loss of efficacy when using a lower dose. This effect (15 vs 35%) is equivalent to a hazard ratio of 0.55. Using a logrank test for time-to-event data, 80% power, 5% two-sided statistical significance, 2:1 allocation ratio in favour of the nivolumab group, 24 months of recruitment then 12 months of follow up we require a total trial size of 111 patients (37 in the control group and 74 given nivolumab). To allow for ~10% loss to follow up, we will aim for about 123 patients.

There will be an interim analysis when 21 patients were recruited in the intervention arm to check that efficacy in the nivolumab group is consistent with what is expected. For this, we will use ORR because it is an accepted measure of treatment response and it can be assessed early. The ORR should be about 45% using nivolumab plus chemotherapy (pembro-chemo 47.6% Gandhi et al., NEJM 2018; cemiplimumab-chemo 43.3% Gogishvilli et al., Nat Med 2022; nivo-chemo (in patients with PDL1<1%) 37% Brahmer al., JCO 2023), and it is about 20% using chemotherapy alone (KEYNOTE 189 18.9% Gandhi et al., NEJM 2018; EMPOWER Lung3 22.7% Gogishvilli et al., Nat Med 2022; CHECKMATE 227 23% Brahmer al., JCO 2023),. Using methods for a single arm trial (with 80% power and 5% one-sided statistical significance), we will assess ORR in the first 21 patients recruited to the nivolumab group (who start treatment), of which at least 8 need to have an ORR to indicate sufficiently high response, because this means that the true ORR is higher than the lowest acceptable rate of 20% using chemotherapy alone (KEYNOTE 189 18.9% Gandhi et al.,, NEJM 2018: EMPOWER Lung3 22.7% Gogishvilli et al., Nat Med 2022; CHECKMATE 227 23% Brahmer al., JCO 2023). Although this analysis is based on the

nivolumab group only, we will also confirm that the ORR rate in the controls is materially lower. The Independent Data Monitoring Committee will examine the interim analysis, along with other efficacy and safety outcomes, and make a decision whether the trial continues to recruit the target of 123 patients or stop early.

Sample size calculation for the main objective was calculated using two arm survival calculator and the interim analysis using one arm binomial calculator from CRAB SWOG Statistical Tools Calculators (https://stattools.crab.org) (Appendix 2 and 3).

8.3.Software

All statistical analyses will be performed using R software version 4.3.1 or higher when available.

8.4. Data Handling for Cut-Off Date

There will be interim lock and final database lock. Interim lock will be done after the first 21 patients enrolled in the intervention arm for the 3 months ORR analysis. The final database lock will be done after the last randomized patient followed up at 1-year. Data after cut-off do not undergo cleaning process. To provide overall estimates of the treatment effect, data will be pooled across the center, but the center factor will not be considered in statistical models or for subgroup analyses. The variable for the treatment allocation will be coded unknown to statistician to ensure blinding.

8.5. Handling of Missing Data

Unless others wise specified, missing data will not be replaced. Missing statistics when cannot be calculated will be presented as “nd”. In all subject data listing imputed value will be presented. Overall, no imputation for missing data will be made. The following will be conducted:

a. Categorical data: When calculating proportion for categorical variable, subject with missing data will be excluded from the denominator.
b. Continuous data: Observed data are based on the analysis and summary of continuous variables and the number of subjects with missing data will be presented.
c. Time to-event data: Censoring rule shall be followed.

8.6. Intention-to-Treat Analysis Set

This will be an intention-to-treat analysis, where all eligible patients that initiated treatment analyzed according to randomized study arm. The reason for the exclusion of those that did not initiate treatment will be captured.

8.7. Per Protocol Analysis Set

The per protocol analysis set includes all ITT subjects who does not meet one or more of the following criteria:

a. Deviations from the inclusion and exclusion criteria
b. Randomization error
c. Use of prohibited medication
d. No availability of primary endpoint measurement

8.8. Significance Level

The overall significance level is 5% two sided. The confirmatory statistical test for the primary and secondary endpoint will be described later. All other statistical analyses performed on the secondary and other endpoints defined in this are to be exploratory in nature. The statistical test performed on the primary and secondary endpoints in comparing treatment arm and control arm will be two-sided and the statistical test for exploratory and safety analyses will be two-sided. The confidence interval will be two-sided with a confidence level of 95%.

8.9. Presentation of Continuous and Qualitative Variables

Continuous variables will be summarized using descriptive statistics i.e., number of non-missing values and number of missing values, [i.e., n (missing)], mean, median, standard deviation (StDev), minimum, maximum and first and third quartile (Q1 and Q3). Qualitative variables will be summarized by counts and percentages. Unless otherwise stated the calculation of proportions will include the missing category. Therefore, counts of missing observations will be included in the denominator and presented as a separate category. In case the analysis refers only to certain visits percentages will be based on the number of subjects still present in the study at that visit, unless otherwise specified.

9. ADMINISTRATIVE, ETHICS, AND REGULATORY DETAILS

9.1. Quality Control and Quality Assurance

During study conduct, the Principal Investigator will be responsible in ensuring that periodic monitoring visits are conducted to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The study monitors may review source documents to confirm that the data recorded on CRFs is accurate.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to inspection by appropriate regulatory authorities. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

9.2. Ethics

9.2.1. Medical Research and Ethics Committee (MREC)/ Local Ethics Committee (LEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, e.g., recruitment advertisements, if applicable, from the MREC/LEC. All correspondence with the MREC/LEC should be retained in the ISF.

The only circumstance in which an amendment may be initiated prior to MREC/LEC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the MREC/LEC and Sponsor-PI immediately after implementation. Otherwise, any amendments submitted to the MREC/LEC shall await approval before implementation.

9.2.2. Data Privacy and Confidentiality

All information obtained in this study will be kept and handled in a confidential manner, in accordance with applicable laws and/or regulations. When publishing or presenting the study results, the patient identity will not be revealed without expressed consent by the patient.

Instead of the study subject's name, patient clinical or medical record number at the hospital will be used and will be coded with a unique study identification number for the clinical trial. The study identification number instead of patient personal identifiers will be used on subject data sheets. Only the study investigator and limited study staff will have access to the coded list of study identification numbers.

9.2.3. Record Retention

To enable evaluations and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g. CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g. letters, meeting minutes, telephone

calls reports). The records should be retained by the investigator according to the International Conference on Harmonization (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

On completion of study, all data entered in the EDC will be exported to a password protected computer and will be copied to CDs. Once copied, the data in the computer will be erased. CDs and all other hardcopy records should be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations. The data will be destroyed after that period of storage. Subjects will not be allowed to view their personal study data, as the data will be consolidated into a database.

9.3. Study Insurance

Trial insurance will be purchased by Sponsor-PI from a reliable insurance company using CRMY funds for the entire duration of the trial to support any approved expenses, claims and events related to the clinical trial protocol and product.

9.4. Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor-PI will work with the authors to submit a manuscript describing trial results within 12 months after the last data becomes available, which may take up to several months after the last subject visit in some cases.

Authorship credit should be based on 1) substantial contributions to conception and design or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be considered to determine authorship if contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor-PI must have the opportunity to review all proposed abstracts, manuscripts, or presentations regarding this trial 45 days prior to submission for publication/presentation. When

publishing or presenting the study results, the patient identity will not be revealed without expressed consent by the patient. Any information identified by the Sponsor-PI as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Permission for any type of publication/presentation will be first obtained from the Director General of Health.

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11.0 APPENDIX

Appendix 1: Schedule of Activities

Study Period	**Screening/ Baseline**[a]		**Treatment Period (6-Weekly Cycles)**													**End of Treatment**	**Post-Treatment**		
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		**Safety Follow Up**	**Follow Up Visits**[u]	**Survival Follow Up**[v]
Treatment Cycle			**C1**		**C2**		**C3**		**C4**		**C5**		**C6**		**C7 onwards**	**Discontinuation**	**90 Days Post Discontinuation**	**Every 6 Weeks Post Discontinuation**	**Every 12 Weeks**
			D1	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**At time of Discontinuation**			
Treatment Day	**-28 to -1**	**-7 to -1**	**1**	**8**	**21**	**28**	**42**	**49**	**63**	**70**	**84**	**91**	**105**	**112**	**126**				
Visit Window (Days)[e]			0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3			±7	
Administrative Procedures[b]																			
Informed Consent[f]	X																		
Inclusion/ Exclusion Criteria	X																		
Demography and Baseline Characteristics	X																		
Medical/ Surgical History	X																		

Prior and Concomitant Medication Review[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Prior Treatment for NSCLC	X																		
Post-Study Anticancer Therapy Status																		X	X
Chemotherapy[d]			X	X	X	X	X	X	X	X	X	X	X	X	[X]				
Trial Treatment Administration[c]			X				X				X				X				
Clinical Procedures/ Assessments[b]																			
Adverse Event/ Serious Adverse Event Review[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs (heart rate, blood pressure), Weight and Height[i]	X	[X][a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Full Physical Examination	X															X			

Directed Physical Examination		[X][a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Laboratory Procedures/ Assessments[b]																			
Hematology[j]	X	[X][a]	[X]	X	X	X	X	X	X	X	X	X	X	X	X	X			
Serum Chemistry[k]	X	[X][a]	[X]	X	X	X	X	X	X	X	X	X	X	X	X	X			
Coagulation/ Urinalysis[l]		X																	
Calculated Creatinine Clearance[m]	X																		
Serum Pregnancy Test[n]	X		[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]			
Urine Pregnancy Test[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
T3, FT4, TSH[o]	X		X								X				X	X			
12-Lead ECG[p]		X														[X]			
Efficacy Assessment[b]																			
CT TAP[q]	X						X				X				X	X		X	
CT Brain[r]	X						[X]				[X]				[X]	[X]		[X]	
Central Laboratory[b]																			

Archival or New Obtained Tissue or FNAC Sample for EGFR, ALK, ROS1 and PDL1[s]	X														[X]				
Blood for PD1 Receptor Occupancy (Arm1)[t]	X						X				X				X	X			
Blood and Stool Sample for Future Biomarker Research (Arm1 & Arm2)[t]	X						X				X				X	X			
Tissue Collection and Pleural Effusion Fluid[w] for Future Biomarker Research	X															X[x]			

[X] denotes as an optional test

Abbreviations: NSCLC, non-small cell lung carcinoma; ECOG, Eastern Cooperative Oncology Group; T3, triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; ECG, electrocardiogram; CT, computed tomography; TAP, thorax, abdomen, pelvis; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; ROS1, proto-oncogene 1 receptor tyrosine kinase; PDL1, programmed cell death ligand 1

[a] The Screening visit must occur within 28 days before treatment allocation, and the baseline visit must occur within 7 days before treatment allocation. If Screening is performed within 7 days before treatment allocation, physical examination, vital signs, and clinical laboratory assessments do not need to be repeated at baseline. Screening and baseline procedures may be performed on the same day as long as it is within 7 days before treatment allocation.

[b] All assessments/ procedures will be performed on Day 1 before dosing except as indicated.

[c] For patients enrolled in arm 1, 40mg Nivolumab will be administered on day 1 of every 6-weekly cycle up to 35 cycles (C1D1, C3D1, C5D1, C7D1, C9D1, C11D1, C13D1, C15D1, C17D1, C19D1, C21D1, C23D1, C25D1, C27D1, C29D1, C31D1, C33D1, C35D1). Dose interruption is permitted due to toxicity or other reasons not related to study therapy, but no dose reduction is allowed. If there is dose interruption, all assessments/ procedures except imaging should be performed based on new dosing schedule.

[d] For both patients in arm 1 and 2, chemotherapy (Cisplatin or Carboplatin AND Pemetrexed or Gemcitabine or Docetaxel or Paclitaxel) will be administered as per local practice. Administration will be 3-weekly basis, up to 4 to 6 cycles based on investigator's discretion. The use of Pemetrexed in patients with adenocarcinoma who showed response to the initial 4 to 6 cycles of chemotherapy can be continued as maintenance dose.

[e] In general, the window for each visit is ± 3 days unless otherwise noted.

[f] Written consent must be obtained prior to performing any protocol specified procedures. 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 (e.g., within 28 days prior to the first dose of trial treatment). Screening number will be assigned when the study informed consent is signed. Signing the informed consent for future biomedical research (FBR) sample is optional.

[g] All concomitant medications or therapies, including herbal supplements, taken from 28 days before treatment allocation to 30 days after the last dose will be recorded.

[h] After written informed consent but before study drug initiation, only SAEs associated with protocol-imposed interventions will be recorded. After the first dose of study drug, all SAEs and AEs will be recorded until 90 days after the last dose of study drug or before initiation of a new antineoplastic therapy, whichever occurs first. SAEs, AEs and pregnancies ongoing at the End of Treatment visit will be followed until resolution or until the condition is considered stable by the Investigator.

[i] Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. If ≥10% change in body weight occurs, weight-based therapy should be adjusted. Height is to be measured at screening/baseline visit only.

[j] **Hematology:** hemoglobin, hematocrit, platelet count, red blood cell (RBC), white blood cell (WBC) count, absolute neutrophil count (ANC), and WBC differential (absolute and/or percent). Hematology assessments scheduled for the day of the dosing must be available and assessed for abnormalities before dosing. The sampling for the hematology assessment can be drawn within 72 hours prior to dosing. If the screening/ baseline hematology assessment is performed 72 hours prior to enrolment, then the assessment need not to be repeated during Day 1 of Cycle 1.

[k] **Serum chemistry:** total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase (LDH), total protein, albumin, sodium, potassium, chloride, carbon dioxide (or bicarbonate), calcium, phosphorus, magnesium, blood urea nitrogen (BUN; also called urea), creatinine, uric acid, glucose. Serum Chemistry assessments scheduled for the day of the dosing must be available and assessed for abnormalities before dosing. The sampling for the hematology assessment can be drawn within 72 hours prior to dosing. If the screening/ baseline hematology assessment is performed 72 hours prior to enrolment, then the assessment need not to be repeated during Day 1 of Cycle 1.

[l] **Coagulation:** activated partial thromboplastin time (aPTT) and prothrombin time (PT)/international normalized ratio
(INR); Urinalysis will be assessed only at baseline.

[m] Calculated creatinine clearance to be performed at screening. Use local laboratory results or calculate by Cockcroft-Gault formula.

[n] For women of child-bearing potential, urine or serum (as per local regulations/ practice) pregnancy test should be performed at Day 1 of each cycle, prior to administration of study medication; if a urine pregnancy test is positive, study drug must be interrupted and a serum pregnancy test performed. Additional pregnancy testing may be performed throughout the study as clinically indicated. A serum pregnancy test should be performed within 72 hours prior to first dose of trial treatment.

[o] T3, FT4 and TSH tests will be at screening and every 12-weekly (± 7 days) until End of Treatment.

[p] Baseline 12–lead ECG; End of Treatment, if clinically indicated.

[q] CT TAP to be performed at screening and every 6-weekly (± 7 days) for the first three months (C3D1, C5D1) from the date of treatment assigned. Subsequent imaging to be performed at 9-weekly (± 7 days) intervals for the first year (C8D1, C11D1, C14D1, C17D1) and 12-weekly (± 7 days) thereafter (C21D1, C25D1, C29D1, C33D1), regardless of any dose interruptions or dose delays. Tumor assessments can occur as clinically indicated anytime during the study, and at the time of clinical suspicion of disease progression. Clinical disease progression should be verified by radiographic imaging; study treatment should continue until radiographic progression has occurred. In participants who discontinue study therapy without confirmed disease progression, a radiologic evaluation should be performed at the time of treatment discontinuation (i.e., date of discontinue ± 4-week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation isn't mandatory. If treatment discontinuation is due to documented disease progression as per investigator's discretion, this is the final required tumor imaging.

[r] Brain CT to be performed at screening and if clinically indicated.

[s] Tumor tissue from an archival tissue sample or newly obtained core or excisional biopsy (EB) or fine needle aspirate cell (FNAC) block from participants is required for EGFR, ALK, ROS1 and PDL1 biomarker analysis. A newly obtained tissue from a core or excisional biopsy or FNAC is preferred, but an archival sample of up to 3 years is also acceptable. If the participant signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR.

[t] For treatment 1, ~24mL of blood will be used to evaluate PD1 receptor occupancy, while for treatment arm 2, it will be stored for FBR with patient consent. An additional ~16mL of blood will be collected from treatment arm 1 patients who consent to FBR. Blood and stool collection will occur at screening, every 6 weekly before dosing until radiographic confirmed disease progression and up to 3 consecutive imaging timepoints or post discontinuation of the treatment or end of treatment (EOT). If the screening imaging was performed as a routine scan prior to giving consent in participation of this trial, the blood and stool samples for FBR will be taken within 28 days prior to treatment allocation.

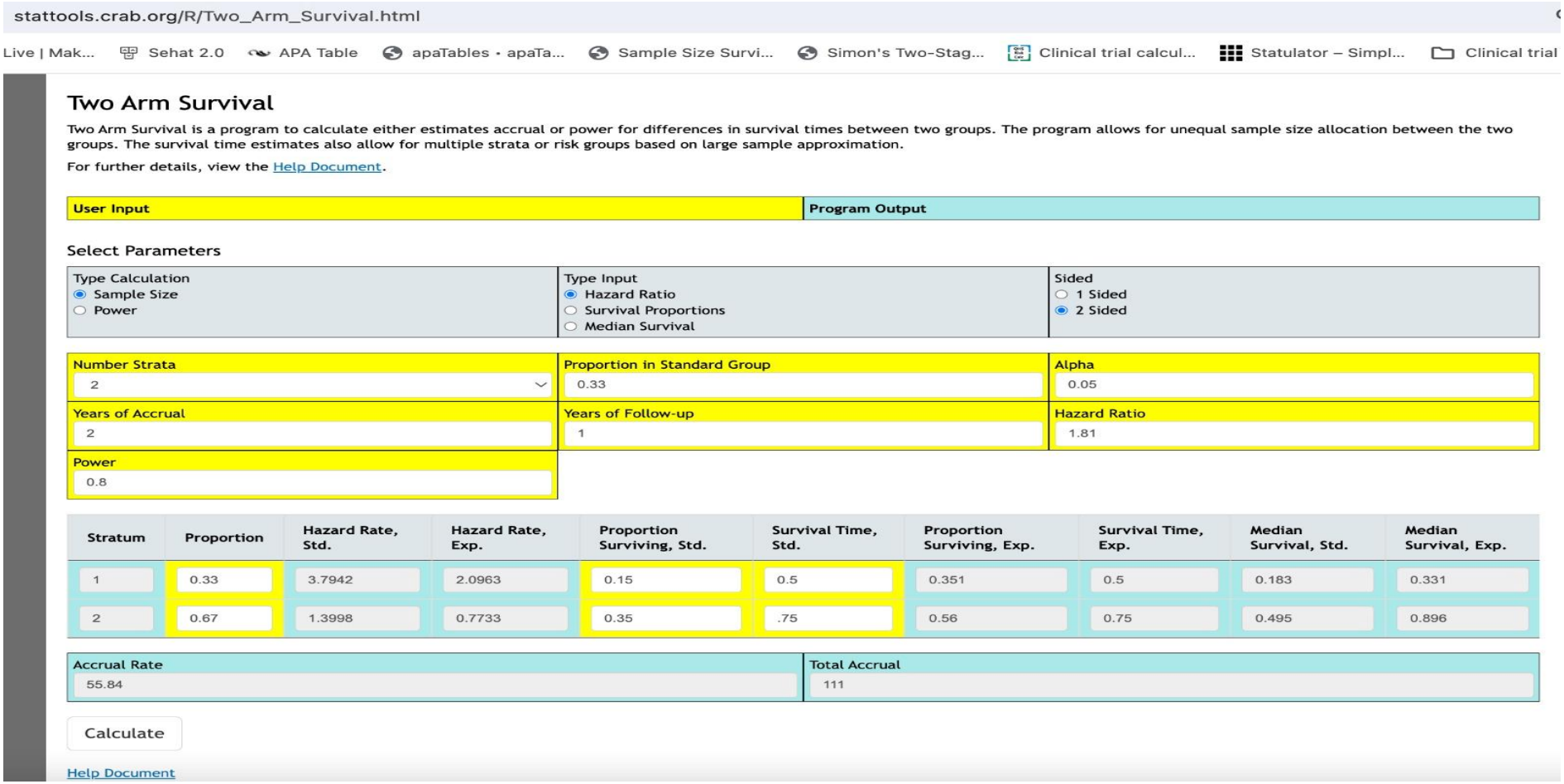
[u] In participants who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 6 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs first.

[v] After the start of new anti-cancer treatment or documented disease progression, the participant should be contacted by telephone every 12 weeks to assess for survival status.

[w] If a FBR-consented patient has any pleural effusion fluid drained throughout the study, the fluid may be collected and stored for FBR.

[x] If a FBR-consented patient has any tissue collected post-progressive disease confirmation, the tissue may be archived for FBR.

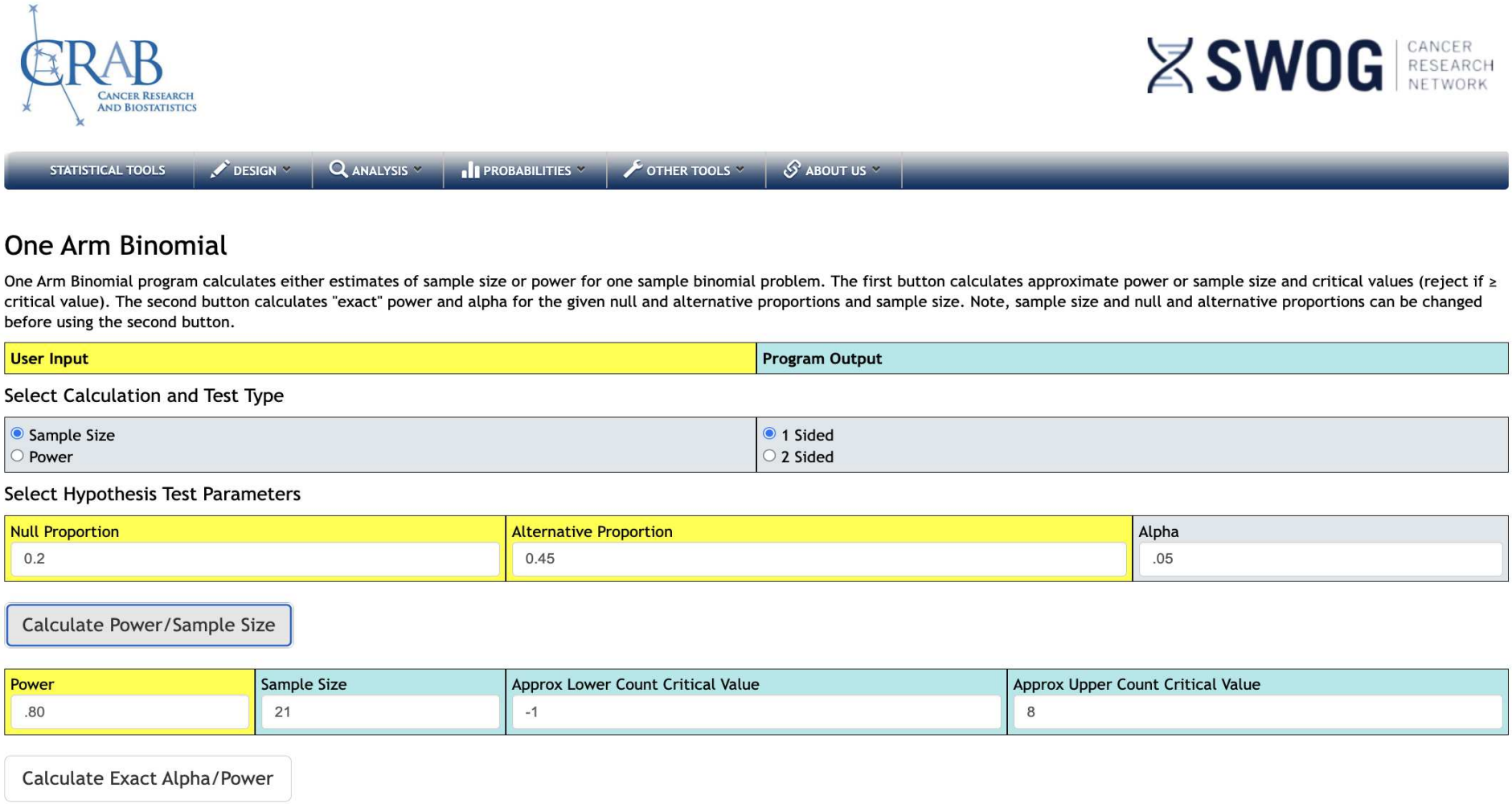
Appendix 2: Sample Size Calculation Method for Complete Analysis



By Schoenfeld - Schoenfeld D. Sample-Size Formula for the Proportional-Hazards Regression-Model. Biometrics. 1983;39(2):499-503

111 with 10% attrition = 111/0.9 = 123

Appendix 3: Sample Size Calculation Method for Interim Analysis



Appendix 4: Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
First radiologic evidence of disease progression by RECIST 1.1 per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm disease progression	May continue study treatment at the assessment of the investigator and after the participant's consent	Repeat imaging at 4 to 8 weeks to confirm disease progression per investigator's discretion only.	Discontinue treatment
First radiologic evidence of disease progression by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm disease progression.	May continue study intervention at the investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm disease progression per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms disease progression (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 disease progression. May occur at next regularly scheduled imaging visit.	Continue study intervention at the investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm disease progression 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 intervention at the investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study intervention if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging 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; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1; VOP=verification of progression				