Stage III NSCLC: New immunotherapy agents in development

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Disclosures

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- Advisory role or speaker's bureau: Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, F. Hoffman-La Roche, GlaxoSmithKline, Ipsen, Janssen, Medscape, Merck KGaA, MSD, Novartis, Peptomyc, PeerVoice, Pfizer, Regeneron, Sanofi, Seattle Genetics, Takeda and Turning Point Therapeutics
- Independent board member: Grifols
- Research funding: Fundación Merck Salud, Grant for Oncology Innovation

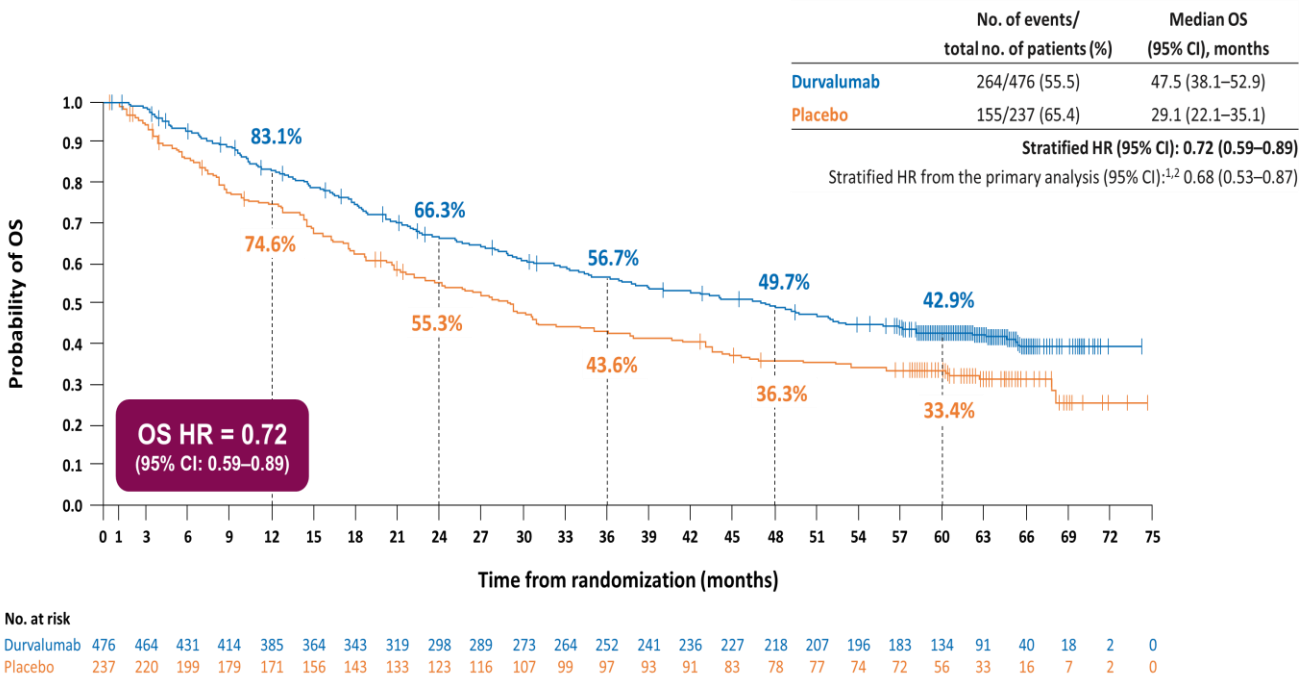
Stage III NSCLC: new immunotherapy agents in development

Good results with the standard treatment (PACIFIC), SoC

Selected patient population

PACIFIC

Updated OS (ITT population)[1]



Data cutoff: 11 January 2021 (median follow-up: all patients, 34.2 months [range, 0.2–74.7]; censored patients, 61.6 months [range, 0.4–74.7]).
1. Antonia SJ, et al. New Engl J Med 2018;379:2342–50; 2. European Medicines Agency. Durvalumab (Imfinzi). Summary of product characteristics 2020. Available from: https://www.ema.europa.eu/en/documents/product-information/imfinzi-epar-product-information_en.pdf 5. [Accessed April 2021]

Spiegel J Clin Oncol 2022

Clinical Trial > Lancet Oncol. 2022 Feb;23(2):220-233. doi: 10.1016/S1470-2045(21)00650-1. Epub 2022 Jan 14.

Sugemalimab versus placebo, in combination with platinum-based chemotherapy, as first-line treatment of metastatic non-small-cell lung cancer (GEMSTONE-302): interim and final analyses of a double-blind, randomised, phase 3 clinical trial

Caicun Zhou [1], Ziping Wang [2], Yuping Sun [3], Lejie Cao [4], Zhiyong Ma [5], Rong Wu [6], Yan Yu [7], Wenxiu Yao [8], Jianhua Chang [9], Jianhua Chen [10], Wu Zhuang [11], Jiuwei Cui [12], Xueqin Chen [13], You Lu [14], Hong Shen [15], Jingru Wang [16], Peiqi Li [16], Mengmeng Qin [16], Dongmei Lu [16], Jason Yang [16]

Anti-PDL1

Methods

GEMSTONE-301 is a randomised, double-blind, placebo-controlled, phase 3 trial in patients with locally advanced, unresectable, stage III NSCLC, done at 50 hospitals or academic research centres in China. Eligible patients were aged 18 years or older with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 who had not progressed after concurrent or sequential chemoradiotherapy. We randomly assigned patients (2:1, using an interactive voice–web response system) to receive sugemalimab 1200 mg or matching placebo, intravenously every 3 weeks for up to 24 months. Stratification factors were ECOG performance status, previous chemoradiotherapy, and total radiotherapy dose. The investigators, trial coordination staff, patients, and study sponsor were masked to treatment allocation. The primary endpoint was progression-free survival as assessed by blinded independent central review (BICR) in the intention-to-treat population. Safety was assessed in all participants who received at least one dose of assigned study treatment. The study has completed enrolment and the results of a preplanned analysis of the primary endpoint are reported here. The trial is registered with ClinicalTrials.gov, NCT03728556.

Findings

Between Aug 30, 2018 and Dec 30, 2020, we screened 564 patients of whom 381 were eligible. Study treatment was received by all patients randomly assigned to sugemalimab (n=255) and to placebo (n=126). At data cutoff (March 8, 2021), median follow-up was 14·3 months (IQR 6·4–19·4) for patients in the sugemalimab group and 13·7 months (7·1–18·4) for patients in the placebo group. Progression-free survival assessed by BICR was significantly longer with sugemalimab than with placebo (median 9·0 months [95% CI 8·1–14·1] *vs* 5·8 months [95% CI 4·2–6·6]; stratified hazard ratio 0·64 [95% CI 0·48–0·85], p=0·0026). Grade 3 or 4 treatment-related adverse events occurred in 22 (9%) of 255 patients in the sugemalimab group versus seven (6%) of 126 patients in the placebo group, the most common being pneumonitis or immune-mediated pneumonitis (seven [3%] of 255 patients in the sugemalimab group *vs* one [<1%] of 126 in the placebo group). Treatment-related serious adverse events occurred in 38 (15%) patients in the sugemalimab group and 12 (10%) in the placebo group. Treatment-related deaths were reported in four (2%) of 255 patients (pneumonia in two patients, pneumonia with immune-mediated pneumonitis in one patient, and acute hepatic failure in one patient) in the sugemalimab group and none in the placebo group.

Stage III NSCLC: new immunotherapy agents in development

PACIFIC 2 (NCT03519971)

Phase III, randomized, double-blind, placebo-controlled, multicenter, global study[1,2]

Patients with Stage III, locally advanced, unresectable NSCLC

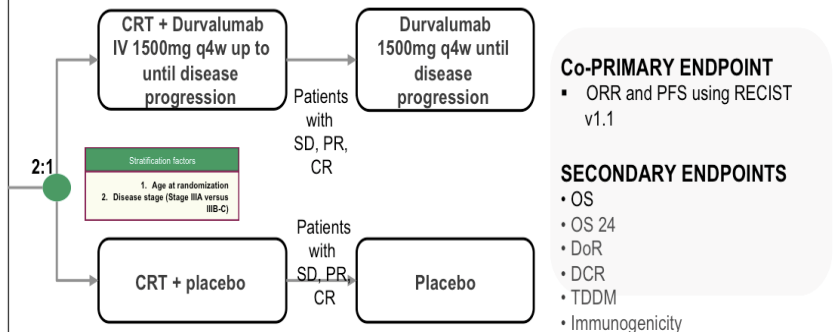
18 years or older

ECOG PS score 0 or 1

Estimated life expectancy of ≥12 weeks

At least 1 lesion, not previously irradiated, that qualifies as a Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 target lesion at baseline.

All-comers population



Co-PRIMARY ENDPOINT
- ORR and PFS using RECIST v1.1

SECONDARY ENDPOINTS
- OS
- OS 24
- DoR
- DCR
- TDDM
- Immunogenicity
- Safety/tolerability

1. In House Data, AstraZeneca Pharmaceuticals LP. CSP D933KC00001

CR = complete response; CRT = chemoradiation therapy; DCR = disease control rate; DoR = duration of response; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; PS = performance status; q4w = every 4 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; TTDM = time to death or distant metastasis; WHO = World Health Organization.

PUBLISHED
14 November 2023

Update on PACIFIC-2 Phase III trial of Imfinzi concurrently administered with platinum-based chemoradiotherapy in unresectable, Stage III non-small cell lung cancer

The PACIFIC-2 Phase III trial for *Imfinzi* (durvalumab) concurrently administered with chemoradiotherapy (CRT) did not achieve statistical significance for the primary endpoint of progression-free survival (PFS) versus CRT alone for the treatment of patients with unresectable, Stage III non-small cell lung cancer (NSCLC).

Bintrafusp Alfa With CCRT Followed by Bintrafusp Alfa Versus Placebo With CCRT Followed by Durvalumab in Patients With Unresectable Stage III NSCLC: A Phase 2 Randomized Study

Everett E. Vokes, MD,[a] Francoise Mornex, MD, PhD,[b] Ahmet Sezer, MD, PhD,[c]

A bifunctional fusion protein targeting TGF-β and PD-L1

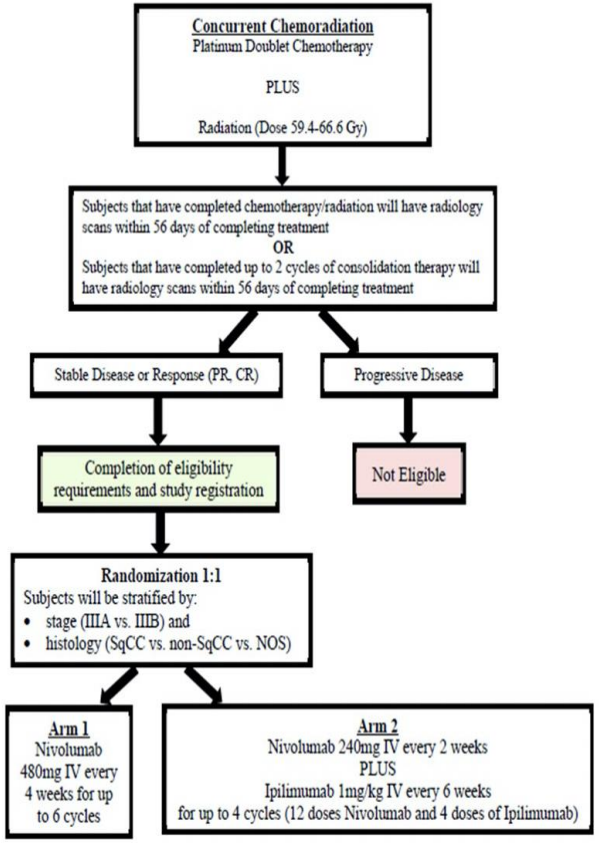
Methods: This multicenter, double-blind, controlled phase 2 study (NCT03840902) evaluated the safety and efficacy of BA with concurrent chemoradiotherapy (cCRT) followed by BA (BA group) versus placebo with cCRT followed by durvalumab (durvalumab group) in patients with unresectable stage III NSCLC. The primary end point was progression-free survival according to Response Evaluation Criteria in Solid Tumors version 1.1 as assessed by the investigator. On the basis of the recommendation of an independent data monitoring committee, the study was discontinued before the maturity of overall survival data (secondary end point).

Results: A total of 153 patients were randomized to either BA (n = 75) or durvalumab groups (n = 78). The median progression-free survival was 12.8 months versus 14.6 months (stratified hazard ratio = 1.48 [95% confidence interval: 0.69–3.17]), in the BA and durvalumab groups, respectively. Trends for overall response rate (29.3% versus 32.1%) and disease control rate (66.7% versus 70.5%) were similar between the two groups. Any-grade treatment-emergent adverse events occurred in 94.6% versus 96.1% of patients in the BA versus durvalumab groups, respectively. Bleeding events in the BA group were mostly grade 1 (21.6%) or 2 (9.5%).

BIG-Ten Lung Trial

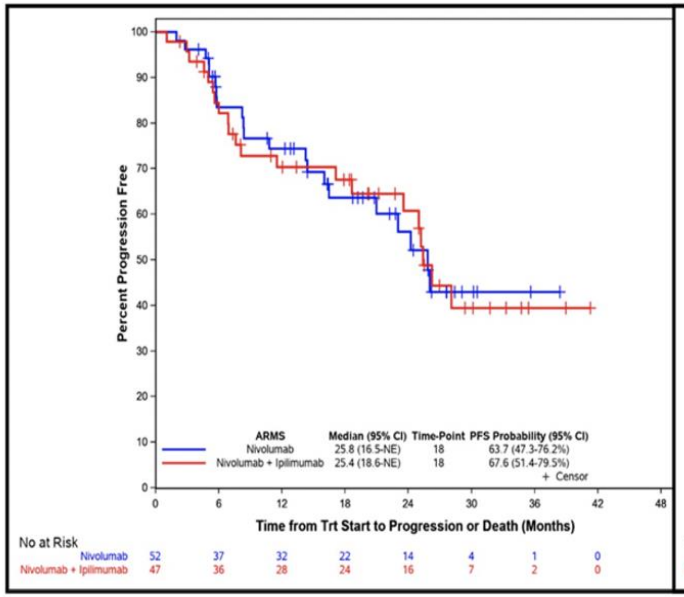
Durm ASCO 2022

Study Design

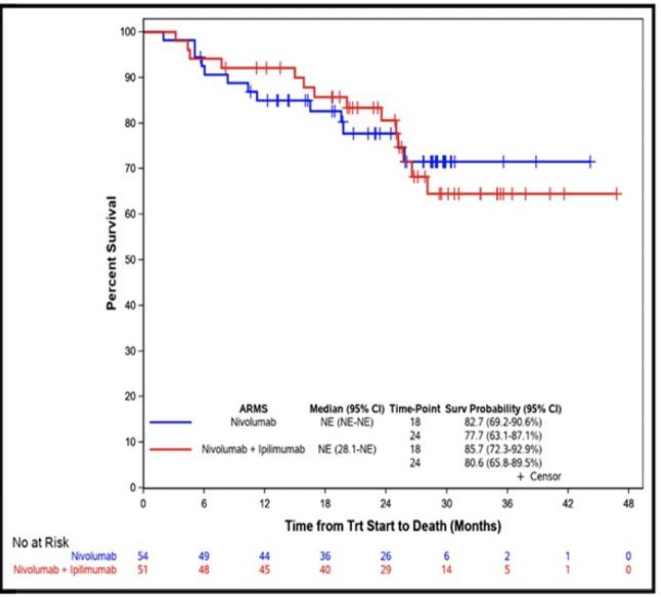


- This was an open-label, multi-site, randomized phase II trial run through the Big Ten Cancer Research Consortium
- It is an investigator-initiated trial funded by Bristol-Myers Squibb
- Pts all received concurrent chemoradiation prior to enrollment
- If repeat imaging showed SD/PR/CR, they were enrolled and randomized 1:1 to:
  - Nivo alone 480mg IV q4 weeks
  - Nivo 240mg IV q2 weeks and Ipilimumab 1/mg/kg q6 weeks
- Both arms got 6 months of treatment

	Nivolumab Alone (N=54)	Nivolumab/Ipilimumab (N=51)
Any Treatment-Related AE (TRAE), n (%)	39 (72.2)	41 (80.4)
Any Grade ≥3 AE, n (%)*	21 (38.9)	27 (52.9)
Any Grade ≥3 TRAE, n (%)	10 (18.5)	14 (27.5)
TRAE Occurring in ≥ 10% Pts, n (%)		
Fatigue	17 (31.5)	16 (31.4)
Dyspnea	8 (14.8)	10 (19.6)
Rash	9 (16.7)	8 (15.7)
Hypothyroidism	7 (13)	8 (15.7)
Diarrhea	4 (7.4)	10 (19.6)
Pruritus	5 (9.3)	9 (17.7)
Arthralgia	2 (3.7)	6 (11.8)
Nausea	2 (3.7)	6 (11.8)
Pneumonitis		
Grade ≥2	12 (22.2)	16 (31.4)
Grade 3 (no Gr 4/5 pneumonitis)	5 (9.3)	9 (17.6)
Median time to Gr ≥2 Pneum, mo. (range)	11.9 (4.1-36.6)	7.3 (1.3-36.9)



Progression free survival



Overall Survival

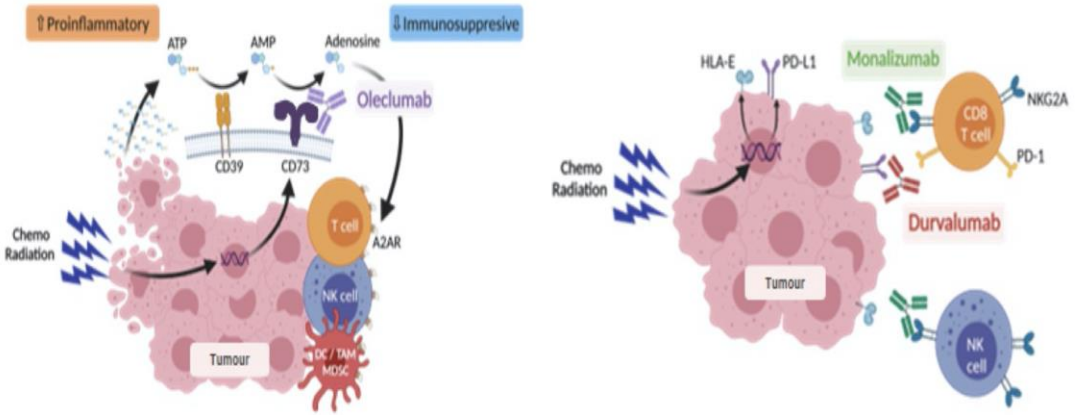
15th CONGRESS on Lung CANCER 23&24 november 2023

2021 ESMO congress

COAST: an open-label, Phase 2, multidrug platform study of durvalumab alone or in combination with novel agents in patients with locally advanced, unresectable, Stage III NSCLC

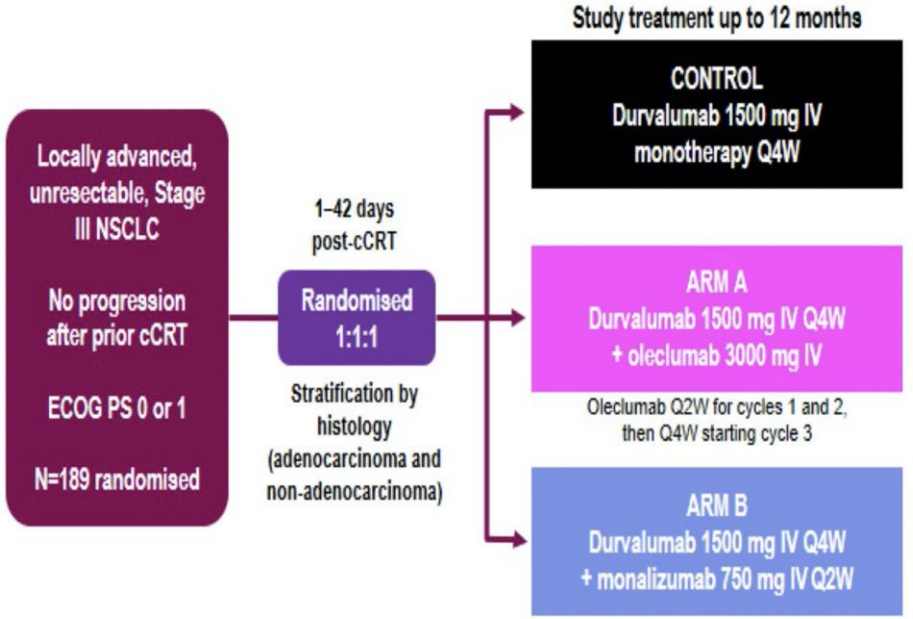
Alex Martinez-Marti[1], Margarita Majem[2], Fabrice Barlesi[3], Enric Carcereny[4],

Rationale for combining durvalumab with oleclumab (anti-CD73) or monalizumab (anti-NKG2A)



- RT induces expression of CD73 and HLA-E (NKG2A ligand), which inhibit antitumour immune response[1-4]
- Oleclumab inhibits CD73 to reduce extracellular adenosine production, thereby promoting antitumour immunity.[5] Oleclumab combined with durvalumab produced durable responses with manageable safety in a Ph I study of advanced *EGFR*m NSCLC[6]
- Monalizumab blocks NKG2A to reduce inhibition of NK and CD8+ T cells.[7] Monalizumab combined with cetuximab had promising activity with manageable safety in a Ph I/II trial of patients with R/M HNSCC[8]
- Combinations of RT and anti-CD73/NKG2A ± anti-PD-(X) show increased antitumour activity in preclinical models[1,2,4]

COAST: Phase 2, randomised open-label study



Primary Endpoint
- ORR by investigator assessment (RECIST v1.1)

Secondary Endpoints
- Safety
- DoR
- DCR
- PFS by investigator assessment (RECIST v1.1)
- OS
- PK
- Immunogenicity

Antitumour activity	D (N=67)	D+O (N=60)	D+M (N=62)
Confirmed ORR (95% CI),[b] %	**17.9 (9.6, 29.2)**	**30.0 (18.8, 43.2)**	**35.5 (23.7, 48.7)**
[n]	[12]	[18]	[22]
Confirmed + unconfirmed ORR (95% CI),[b] %	**25.4 (15.5, 37.5)**	**38.3 (26.1, 51.8)**	**37.1 (25.2, 50.3)**
[n]	[17]	[23]	[23]
ORR odds ratio (95% CI)[a,b]	–	**1.83 (0.80, 4.20)**	**1.77 (0.77, 4.11)**
Objective responses by RECIST,[a] n (%)			
CR	2 (3.0)	1 (1.7)	3 (4.8)
PR	15 (22.4)	22 (36.7)	20 (32.3)
SD	27 (40.3)	25 (41.7)	27 (43.5)
PD	15 (22.4)	7 (11.7)	7 (11.3)
NE	8 (11.9)	5 (8.3)	4 (6.5)
DCR at 16 weeks (95% CI),[a,c] %	**58.2 (45.5, 70.2)**	**81.7 (69.6, 90.5)**	**77.4 (65.0, 87.1)**
[n]	[39]	[49]	[48]
Median DoR (95% CI),[a] months	**NR (2.3, NA)**	**12.9 (6.7, NA)**	**NR (9.0, NA)**
Range	0.0+, 17.5+	0.0+, 16.9+	1.9+, 18.4+

2021 ESMO congress

COAST: an open-label, Phase 2, multidrug platform study of durvalumab alone or in combination with novel agents in patients with locally advanced, unresectable, Stage III NSCLC

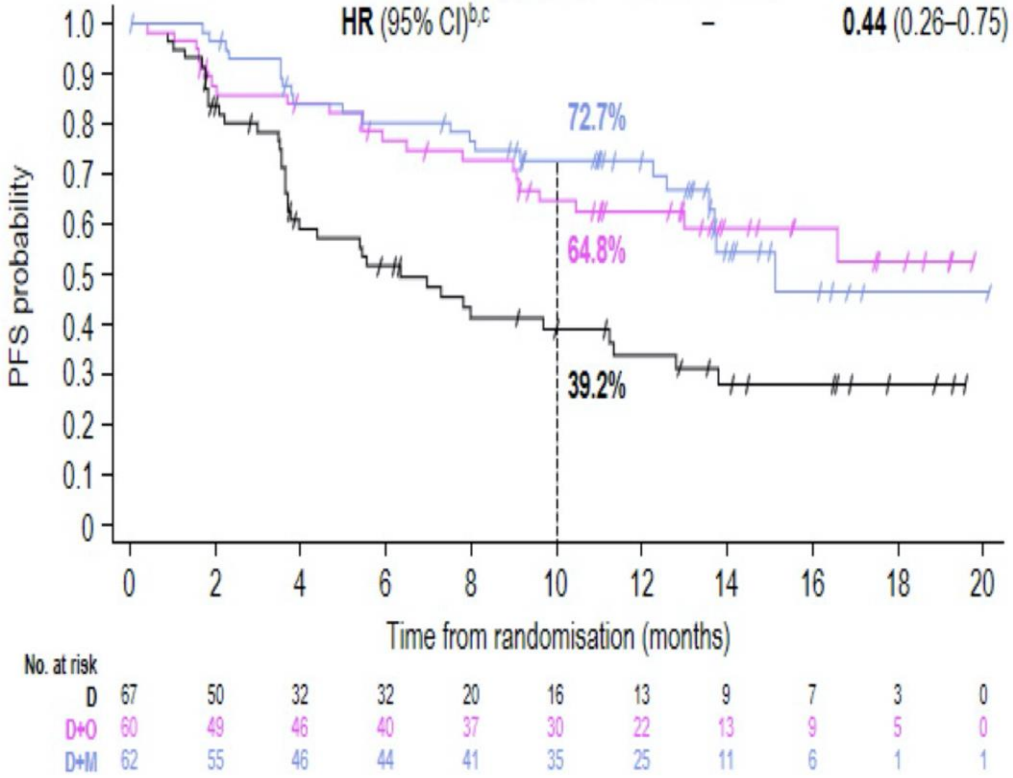
Alex Martinez-Marti[1], Margarita Majem[2], Fabrice Barlesi[3], Enric Carcereny[4],

TEAEs occurring in >15% of patients in any arm
(all causality; as-treated population)

Preferred term, n (%)	D (N=66)		D+O (N=59)		D+M (N=61)	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Patients with ≥1 TEAE	65 (98.5)	23 (34.8)	57 (96.6)	21 (35.6)	61 (100)	16 (26.2)
Cough	12 (18.2)	0	18 (30.5)	1 (1.7)	27 (44.3)	0
Dyspnoea	17 (25.8)	2 (3.0)	15 (25.4)	1 (1.7)	14 (23.0)	1 (1.6)
Pruritus	7 (10.6)	0	10 (16.9)	0	15 (24.6)	0
Asthenia	10 (15.2)	0	10 (16.9)	0	14 (23.0)	0
Hypothyroidism	10 (15.2)	0	9 (15.3)	0	12 (19.7)	0
Diarrhoea	7 (10.6)	1 (1.5)	7 (11.9)	0	12 (19.7)	0
Pneumonitis[a]	11 (16.7)	0	11 (18.6)	0	10 (16.4)	1 (1.6)
Arthralgia	11 (16.7)	0	9 (15.3)	0	10 (16.4)	0
Pyrexia	6 (9.1)	0	8 (13.6)	0	10 (16.4)	0
Rash	6 (9.1)	0	9 (15.3)	0	8 (13.1)	0
Constipation	10 (15.2)	0	4 (6.8)	0	2 (3.3)	0

PFS by investigator assessment
(interim analysis; ITT population)

	D	D+O	D+M
Events/patients, n	38/67	22/60	21/62
mPFS, months (95% CI)[a]	**6.3** (3.7–11.2)	**NR** (10.4–NE)	**15.1** (13.6–NE)
HR (95% CI)[b,c]	–	**0.44** (0.26–0.75)	**0.65** (0.49–0.85)

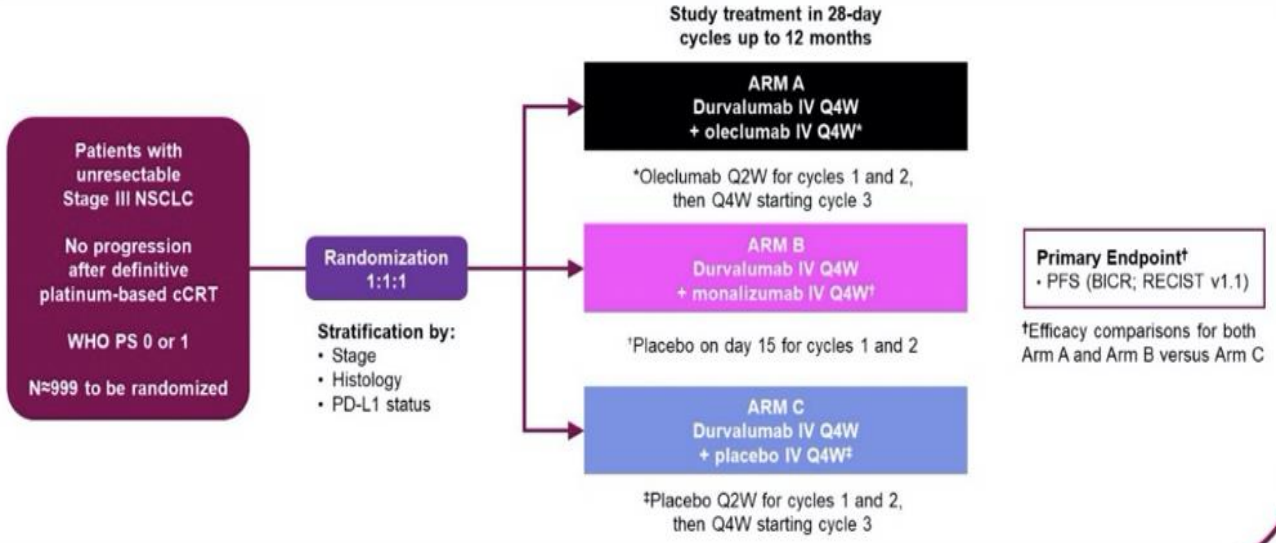


Phase 3 study of durvalumab combined with oleclumab or monalizumab in patients with unresectable Stage III NSCLC (PACIFIC-9)

ASCO 2023

Fabrice Barlesi,[1] Sarah B. Goldberg,[2] Helen Mann,[3] Aarthi Gopinathan,[3] Michael Newton,[4] Charu Aggarwal[5]

PACIFIC-9 (NCT05221840): A phase 3, double-blind, placebo-controlled, randomized, multicenter, international study



Study endpoints

1°
- PFS (BICR per RECIST v1.1).

2°
- OS and 24-month OS rate.
- 6-, 12-, 18-, and 24-month PFS rates (BICR per RECIST v1.1).
- PFS (investigator assessment).
- ORR and DoR (BICR per RECIST v1.1).
- PFS2.
- TTDM (RECIST v1.1) and TFST.
- IHC analysis of PD-L1 TC expression relative to efficacy outcomes (OS, PFS, and ORR).
- Time to first confirmed deterioration of cough, dyspnea, and chest pain.
- Pharmacokinetics and immunogenicity of durvalumab, oleclumab, and monalizumab.
- Safety and tolerability.

Key inclusion criteria

- Patients must be aged ≥18 years at the time of screening.
- Patients must have histologically- or cytologically-documented NSCLC (per the IASLC Staging Manual in Thoracic Oncology 8th ed.) and have been treated with definitive, platinum-based cCRT for unresectable Stage III NSCLC.
  - At least 2 cycles of chemotherapy (cisplatin- or carboplatin-based) concurrent with radiotherapy (total dose, 60 Gy ±10%).
- Patients must not have progressed following cCRT.
- Tumor sample requirements:
  - Documented tumor PD-L1 status by a central laboratory
  - Documented EGFR and ALK wild-type status.
- WHO performance status of 0 or 1.
- Patients must have adequate organ and marrow function.

Key exclusion criteria

- History of another primary malignancy, except for:
  - malignancies treated with curative intent with no known active disease ≥5 years before the first dose of study intervention and of low potential risk for recurrence
  - adequately resected non-melanoma skin cancer and curatively treated in situ disease
  - adequately treated carcinoma in situ or Ta tumors treated with curative intent and without evidence of disease.
- Mixed small-cell and non-small-cell lung cancer histology.
- Patients who receive sequential CRT for unresectable Stage III NSCLC or who have progressed during platinum-based cCRT.
- Patients with unresolved CTCAE grade >2 toxicity or grade ≥2 pneumonitis from prior cCRT.
- History of idiopathic pulmonary fibrosis, drug-induced pneumonitis, or idiopathic pneumonitis – regardless of time of onset prior to randomization. Evidence of active non-CRT-induced pneumonitis (grade ≥2), active pneumonia, active ILD, active or recently treated pleural effusion, or current pulmonary fibrosis – diagnosed in the past 6 months prior to randomization.
- Patients with a history of MI, TIA, stroke, or PE diagnosed in the past 6 months or venous thrombosis diagnosed in the past 3 months prior to the scheduled first dose of study treatment.
- Active or prior documented autoimmune or inflammatory disorders (with exceptions).
- Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab.

Study status

- Study enrollment began in February 2022 and primary completion is anticipated in May 2026.
- PACIFIC-9 is currently active and plans to recruit at 199 sites across 20 countries:
  - Sites open: Australia, Brazil, Canada, China, Colombia, France, Germany, Italy, Japan, Poland, Republic of Korea, Spain, Taiwan, Thailand, Turkey, United Kingdom, United States of America, and Vietnam
  - Sites planned but not yet active: Portugal and Peru.

Phase 3 trial of durvalumab combined with domvanalimab following concurrent chemoradiotherapy (cCRT) in patients with unresectable stage III NSCLC (PACIFIC-8).

Domvanalimab is a Fc-silent humanized IgG1 monoclonal antibody that blocks interaction of the T cell immunoreceptor with Ig and ITIM domains (TIGIT; upregulated by immune cells) with CD112 and CD155 (expressed by tumor and antigen-presenting cells), reducing inhibition of T cells and natural killer cells and, thereby, promoting antitumor activity

Trial design

PACIFIC-8 is a phase 3, double-blind, placebo (pbo)-controlled randomised global trial. Eligible pts (≥18 years) must have PD-L1 positive, unresectable Stage III NSCLC (TC expression ≥1% by central lab; VENTANA SP263 IHC assay), WHO performance status 0/1, documented *EGFR/ALK* wild-type tumour status and not have progressed following definitive platinum-based cCRT (≥2 cycles). Pts (N~860) will be randomised (1:1) to receive SoC durvalumab (1500 mg IV) combined with either domvanalimab (20 mg/kg IV) or pbo, every 4 weeks for up to 12 months. The primary endpoint is progression-free survival (PFS; RECIST v1.1; BICR) in pts with PD-L1 TC ≥50%. Secondary endpoints include PFS (RECIST v1.1; BICR) in pts with PD-L1 TC ≥1%, overall survival, objective response rate and duration of response (RECIST v1.1; BICR), safety/tolerability, and pt-reported outcomes. Enrolment is ongoing.

Clinical trial identification

NCT05211895, release date: January 27, 2022.

SKYSCRAPER-03: Phase III, open-label randomised study of atezolizumab + tiragolumab *vs* durvalumab in patients with locally advanced, unresectable, stage III NSCLC who have not progressed after platinum-based concurrent cRT

Purpose/Objective(s)

Until recently, the standard of care for patients (pts) with locally advanced, unresectable, stage III non-small cell lung cancer (NSCLC) has been platinum-based concurrent chemoradiation (cCRT); however, the 5-year OS rates are poor (13–36%; Goldstraw et al. J Thorac Oncol 2015). Durvalumab (anti-PD-L1) monotherapy was recently approved for pts without progressive disease (PD) after cCRT. However, long-term OS data are not yet available and further evaluation of novel cancer immunotherapy combinations should be explored. Targeted inhibition of a novel checkpoint TIGIT/PVR, by the anti-TIGIT antibody tiragolumab, may amplify the anti-cancer activity of anti-PD-L1/PD-1 antibodies. In the phase II CITYSCAPE study (NCT03563716), tiragolumab plus atezolizumab (anti-PD-L1) was well tolerated and improved ORR compared with atezolizumab alone (31.3 vs 16.2%) in 1L pts with PD-L1+ (TPS ≥1%) metastatic NSCLC; with greater benefit in the PD-L1-high (TPS ≥50%) subset. We hypothesize that tiragolumab plus atezolizumab may provide greater clinical benefit vs single-agent anti-PD-L1 as maintenance therapy in pts with unresectable, stage III NSCLC who have not progressed after platinum-based cCRT. SKYSCRAPER-03 (NCT04513925) will determine if tiragolumab plus atezolizumab provides superior clinical benefit to durvalumab in this setting. Current data suggests that cCRT upregulates PD-L1 expression, potentially enabling PD-L1 low or negative tumors to derive benefit, so outcomes will be evaluated in all-comer (ITT) and PD-L1+ sub-populations.

ACTIVE, NOT RECRUITING

A Study of Atezolizumab and Tiragolumab Compared With Durvalumab in Participants With Locally Advanced, Unresectable Stage III Non-Small Cell Lung Cancer (NSCLC) (SKYSCRAPER-03)

ClinicalTrials.gov ID NCT04513925

Materials/Methods

Eligible pts (≥18 years) must have unresectable, stage III NSCLC without PD after ≥2 cycles of platinum-based cCRT per NCCN/ESMO guidelines, and without an EGFR mutation or ALK rearrangement; known PD-L1 status; ECOG PS 0–1. Approximately 800 pts will be randomized 1:1 to receive tiragolumab 840mg IV plus atezolizumab 1680mg IV Q4W or durvalumab 10mg/kg IV Q2W / 1500mg IV Q4W. Treatment will continue for up to 13 cycles of 28 days, or until unacceptable toxicity or symptomatic deterioration due to PD; in pts with radiographic PD (per RECIST v1.1) treatment may continue if evidence of ongoing clinical benefit. Stratification factors include PD-L1 status, histology (squamous vs non-squamous), staging (IIIA vs IIIB or IIIC) and ECOG PS (0 vs 1). Primary endpoint is independent review facility-assessed PFS in the ITT and PD-L1+ (TC ≥1%) populations. Secondary endpoints include investigator-assessed PFS, OS, ORR and DoR. Safety and biomarker analyses will be performed. Recruitment is ongoing.

ACTIVE, NOT RECRUITING

A Study to Compare Ociperlimab Plus Tislelizumab Versus Durvalumab Following Concurrent Chemoradiotherapy (cCRT) in Patients With Stage III Unresectable Non-Small Cell Lung Cancer

ClinicalTrials.gov ID NCT04866017

Sponsor BeiGene

Information provided by BeiGene (Responsible Party)

Last Update Posted 2023-09-11

Ociperlimab (BGB-A1217) is an investigational humanized monoclonal antibody designed to bind to TIGIT with high specificity and affinity

Study Overview

Brief Summary

The primary objective of this study is to compare progression-free survival (PFS) between Arm A (ociperlimab in combination with tislelizumab) and Arm C (Durvalumab) as assessed by the Independent Review Committee (IRC) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) in participants with stage III unresectable PD-L1-selected non-small cell lung cancer whose disease has not progressed after cCRT.

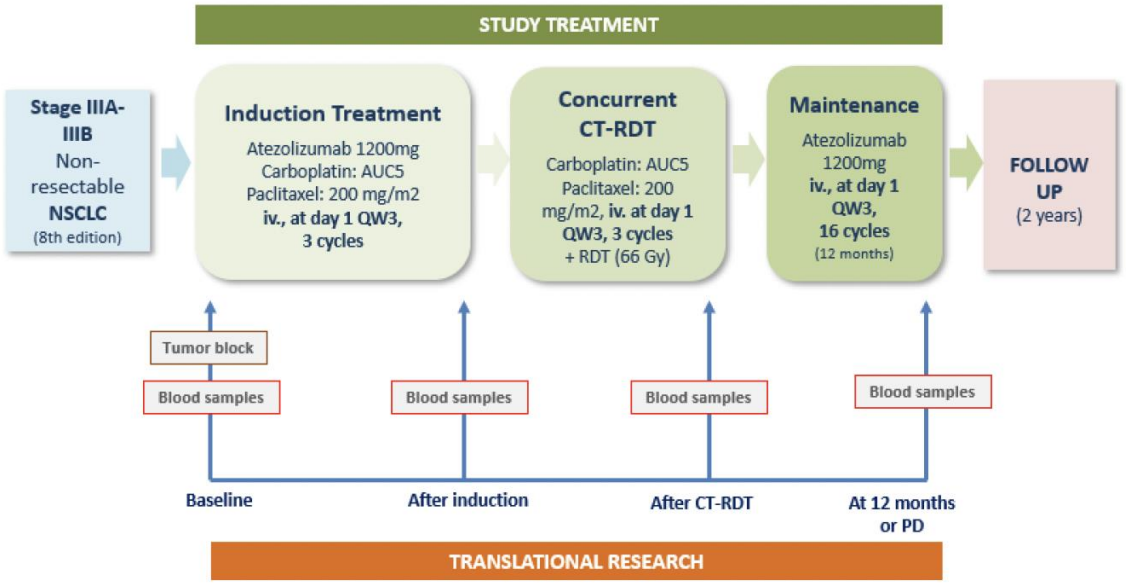
Estadio localmente avanzado

APOLO

A phase II trial of Atezolizumab plus induction chemotherapy (CT) plus chemo-radiotherapy and Atezolizumab maintenance therapy in non-resectable stage IIIA-IIIB non-small cell lung cancer (NSCLC) patients

Promotor: Fundación GECP
Coordinador: Dr. Mariano Provencio

Esquema del estudio



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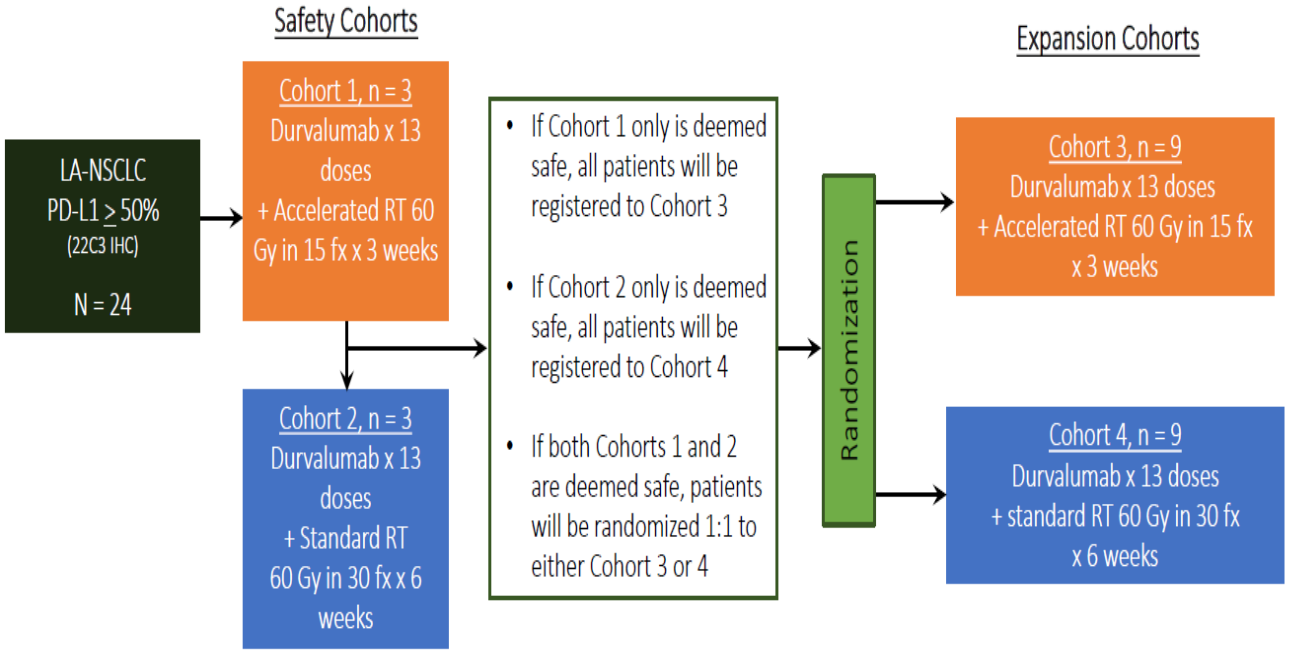
NRG-LU004: Phase I Trial of Accelerated or Conventionally Fractionated Radiotherapy Combined With MEDI4736 (durvalumab) in PD-L1 High Locally Advanced Non-Small Cell Lung Cancer (NSCLC) (ARCHON-1)



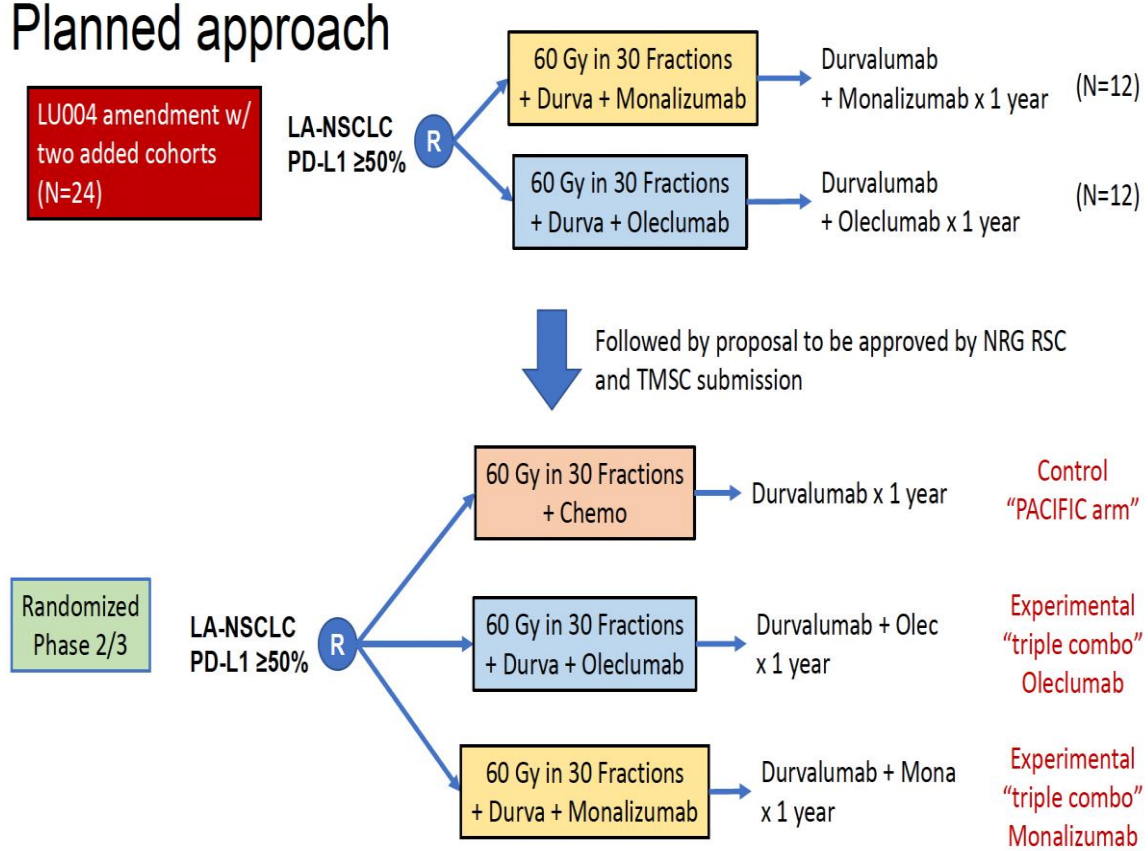
Primary: safety of adding durvalumab to 2 schedules of RT (60 Gy in 30 fx or 15 fx)
Secondary: feasibility, toxicities, PFS
Exploratory: tumor tissue/blood biomarkers, microbiome, TMB, PD-L1 IHC

- Durvalumab begins 2 weeks (day -14) before RT (+/- 48 hours) and is given 1500 mg IV Q4 weeks.
- ClinicalTrials.gov. NCT03801902.

- 24 patients enrolled
- CT-free thoracic RT are safe, when given with concurrent durvalumab in patients with PD-L1 high
  Lin ASCO 2022

clinicaltrial.gov: SUSPENDED
Other - amendment Required

Planned approach

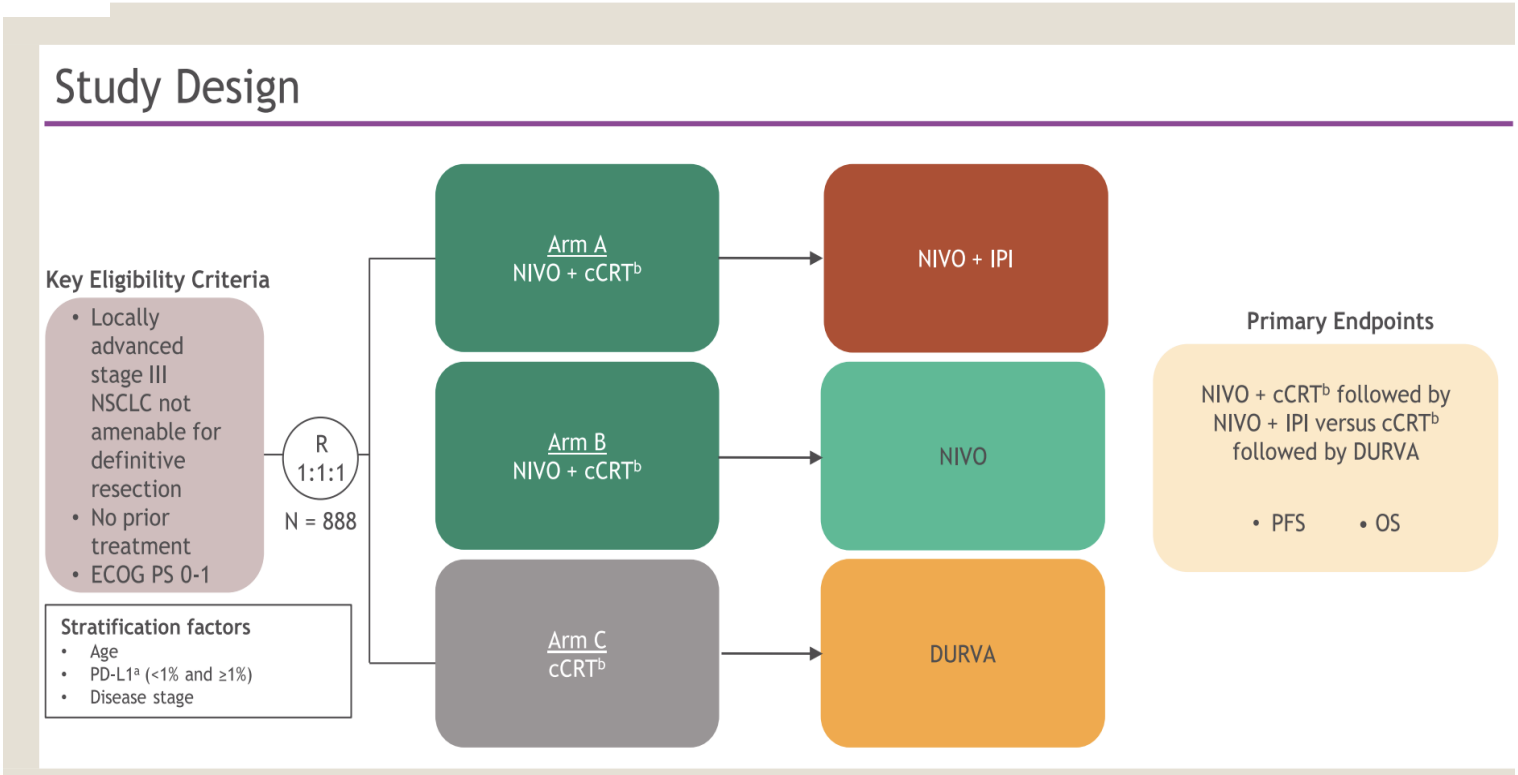


CheckMate 73L: A Phase 3 Study Comparing Nivolumab Plus Concurrent Chemoradiotherapy Followed by Nivolumab With or Without Ipilimumab Versus Concurrent Chemoradiotherapy Followed by Durvalumab fo Previously Untreated, Locally Advanced Stage III Non-Small-Cell Lung Cancer

Dirk De Ruysscher,[1] Suresh Ramalingam,[2] James Urbanic,[3] David E Gerber,[4] Daniel S.W. Tan,[5] Junliang Cai,[6] Ang Li,[6] Solange Peters[7]

Clin Lung Cancer 2022

Study design of CheckMate 73L Study (NCT04026412).
[a]PD-L1 testing will be performed using the validated Agilent/Dako PD-L1 IHC 28-8 pharmDx assay. [b]Patients with tumors of squamous histology will receive etoposide/cisplatin or paclitaxel/carboplatin. Patients with tumors of non-squamous histology will receive either etoposide/cisplatin, paclitaxel/carboplatin, or pemetrexed/cisplatin. If cisplatin cannot be tolerated, cisplatin may be replaced with carboplatin. If pemetrexed cannot be tolerated, pemetrexed may be replaced with etoposide.
Abbreviations: cCRT = concurrent chemoradiotherapy (histologically based platinum-doublet chemotherapy plus radiotherapy); DURVA = durvalumab; ECOG PS = Eastern Cooperative Oncology Group performance status; IPI = ipilimumab; NIVO = nivolumab; NSCLC = non-small-cell lung cancer; OS = overall survival; PD-L1 = programmed cell death ligand-1; PFS = progression-free survival; R = randomization.

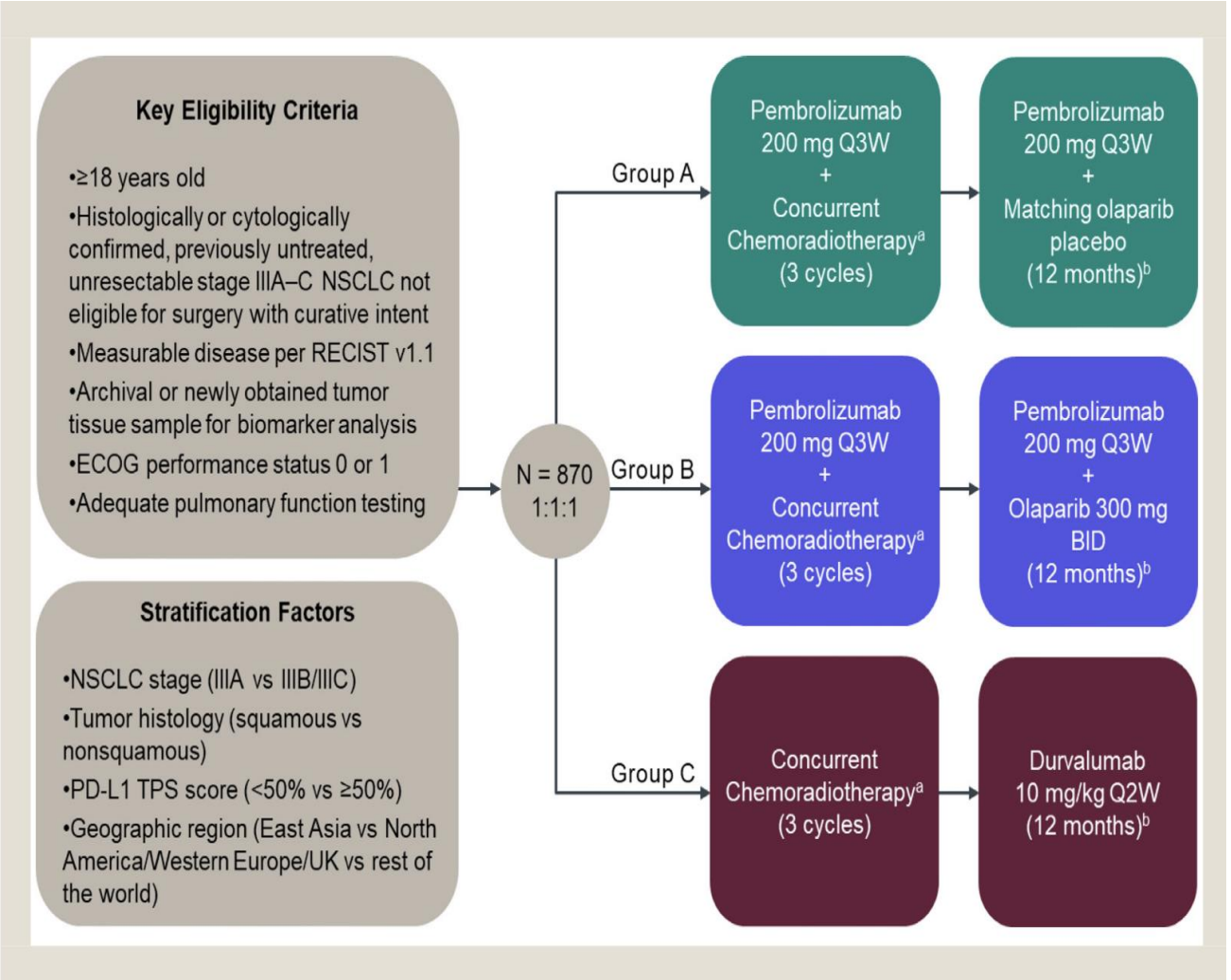


Rationale and Design of the Phase III KEYLYNK-012 Study of Pembrolizumab and Concurrent Chemoradiotherapy Followed by Pembrolizumab With or Without Olaparib for Stage III Non-Small-Cell Lung Cancer

Salma K. Jabbour,[1] Byoung Chul Cho,[2] Emilio Bria,[3] Terufumi Kato,[4] Jaishree Bhosle,[5] Justin F. Gainor,[6] Noemi Reguart,[7] Luhua Wang,[8] Daniel Morgensztern,[9] Yue Shentu,[10] Sung Jin Kim,[10] Fabricio Souza,[10] Martin Reck[11]

Abstract

Background: Concurrent chemoradiotherapy is a standard therapy for patients with stage III non-small-cell lung cancer (NSCLC). Durvalumab is an approved treatment option following concurrent chemoradiotherapy in the absence of disease progression. The multicenter, phase III, randomized, placebo- and active-controlled, double-blind KEYLYNK-012 study evaluates whether initiation of immunotherapy with pembrolizumab concurrently with chemoradiotherapy, followed by post-chemoradiotherapy pembrolizumab with or without olaparib improves outcomes for participants with stage III NSCLC. (ClinicalTrials.gov: NCT04380636) **Methods:** Eligible participants are aged ≥18 years with previously untreated, pathologically confirmed, stages IIIA-C, squamous or nonsquamous NSCLC not suitable for surgery with curative intent. Participants will be randomized 1:1:1 to platinum-doublet chemotherapy plus radiotherapy with pembrolizumab (Groups A and B) or concurrent chemoradiotherapy alone (Group C) for 3 cycles. In the absence of disease progression, participants will receive pembrolizumab plus olaparib placebo (Group A), pembrolizumab plus olaparib (Group B), or durvalumab monotherapy (Group C). Dual primary endpoints are progression-free survival per RECIST version 1.1 by independent central review and overall survival. **Results:** Enrollment began on July 6, 2020, and is ongoing at approximately 190 sites. **Conclusion:** KEYLYNK-012 will provide important information on the efficacy and safety of pembrolizumab combined with concurrent chemoradiotherapy and subsequent pembrolizumab with or without olaparib in participants with unresectable stage III NSCLC.



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Study of Pembrolizumab/Vibostolimab (MK-7684A) in Combination With Concurrent cCRT Followed by Pembrolizumab/Vibostolimab vs Concurrent cCRT Followed by Durvalumab in Participants With Stage III NSCLC (KEYVIBE-006)

Vibostolimab (MK-7684) is a humanized monoclonal antibody that binds to TIGIT, blocking the interaction between TIGIT and its ligands, CD112 and CD155

ClinicalTrials.gov Identifier: NCT05298423

Recruitment Status : Recruiting
First Posted : March 28, 2022
Last Update Posted : November 13, 2023

Study Overview

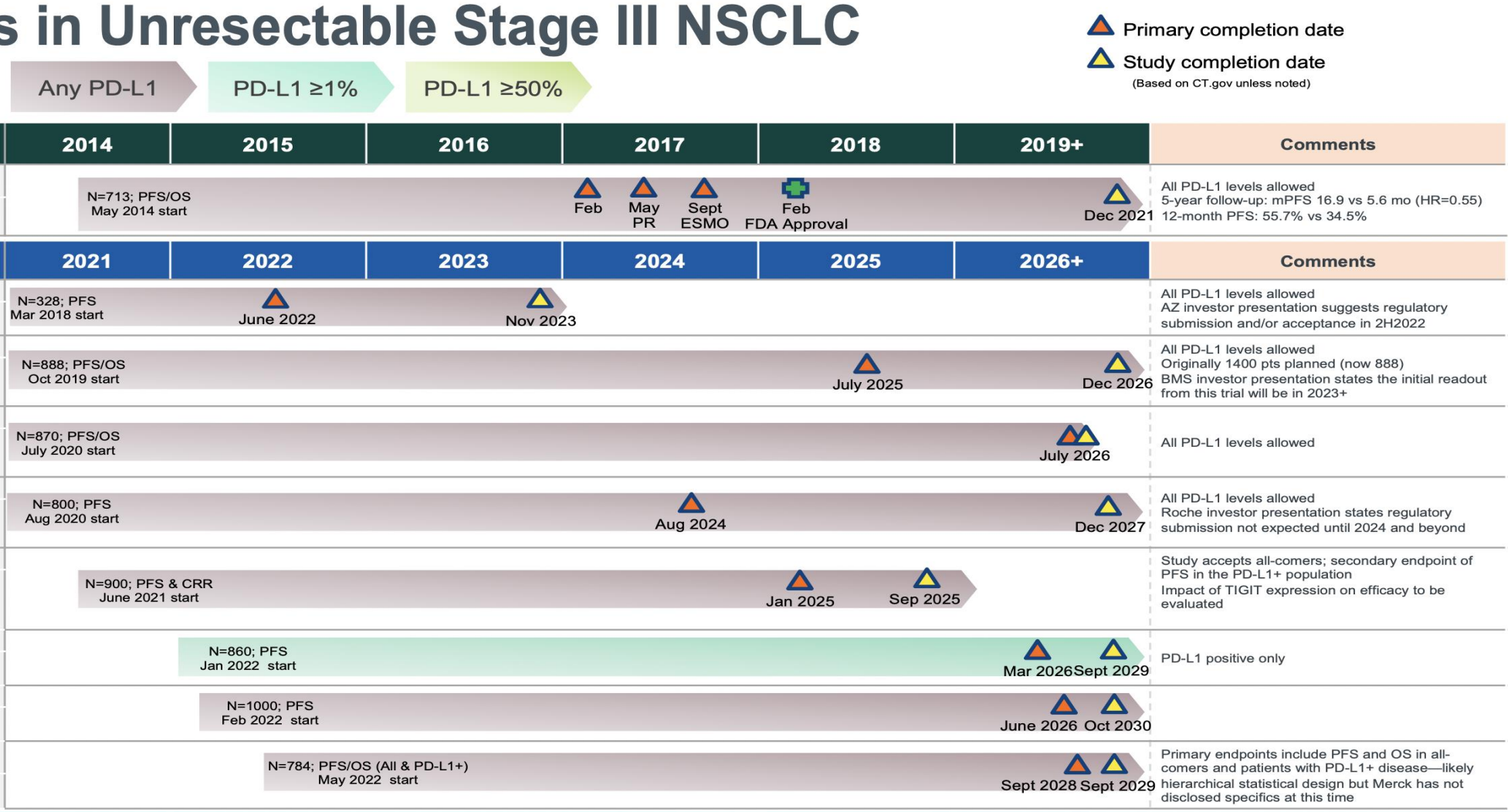
Brief Summary

This study is to evaluate the safety and efficacy of pembrolizumab/vibostolimab (MK-7684A) in combination with concurrent chemoradiotherapy (cCRT) followed by pembrolizumab/vibostolimab versus cCRT followed by durvalumab in participants with unresectable, locally advanced, stage III Non-small Cell Lung Cancer (NSCLC). The primary hypotheses are that pembrolizumab/vibostolimab with cCRT followed by pembrolizumab/vibostolimab is superior to cCRT followed by durvalumab with respect to the following:

- progression free survival (PFS) per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 by blinded independent central review (BICR) in participants with programmed cell death ligand 1 (PD-L1) tumor proportion score (TPS) ≥1% and PD-L1 all comer participants.
- overall survival (OS) in participants with PD-L1 TPS ≥1% and PD-L1 all comer participants.

PACIFIC trial remains the SoC

Pivotal Trials in Unresectable Stage III NSCLC

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