ESMO 2020 (Virtual) Congress Report

Lung cancer:
PD-1/PD-L1 inhibition and PARP inhibition in NSCLC

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Contents

PD-1: Programmed cell death protein-1. PD-L1: Programmed death ligand 1. NSCLC: Non-small cell lung cancer. 1L: First line. OS: Overall survival.

Introduction to PD-1/PD-L1 and PARP inhibition in NSCLC

- Global estimation of over 2 million new lung cancer cases and 1.8 million deaths occurring annually of which around 90% of all cases are NSCLC
- Recently, PD-1 inhibitor in combination with chemotherapy have been approved in some countries as first-line treatment for advanced NSCLC
- Platinum-based regimens remain standard first-line therapy for patients who have no access
- to checkpoint inhibitors
- Overall survival remains low for patients with advanced NSCLC treated with platinum-based therapies, leaving considerable room for improvement of patient outcomes
- •Combination of PARP inhibition with PD-1/PD-L1 inhibition may enhance antitumour activity of immune checkpoint inhibitors

PD-1: Programmed cell death protein-1. PD-L1: Programmed death ligand 1. PARP: Poly (ADP-ribose) polymerase. NSCLC: Non-small cell lung cancer. OS: Overall survival.
1. Lu, S. et al. 2020. Poster 1263P presented at ESMO 2020. 2. Wang et al, 2020. Poster presented at ESMO 2020

KEYNOTE-033

PD-1 inhibitor pembrolizumab vs docetaxel in patients with previously treated NSCLC with PD-L1 tumor proportion score (TPS) ≥1%

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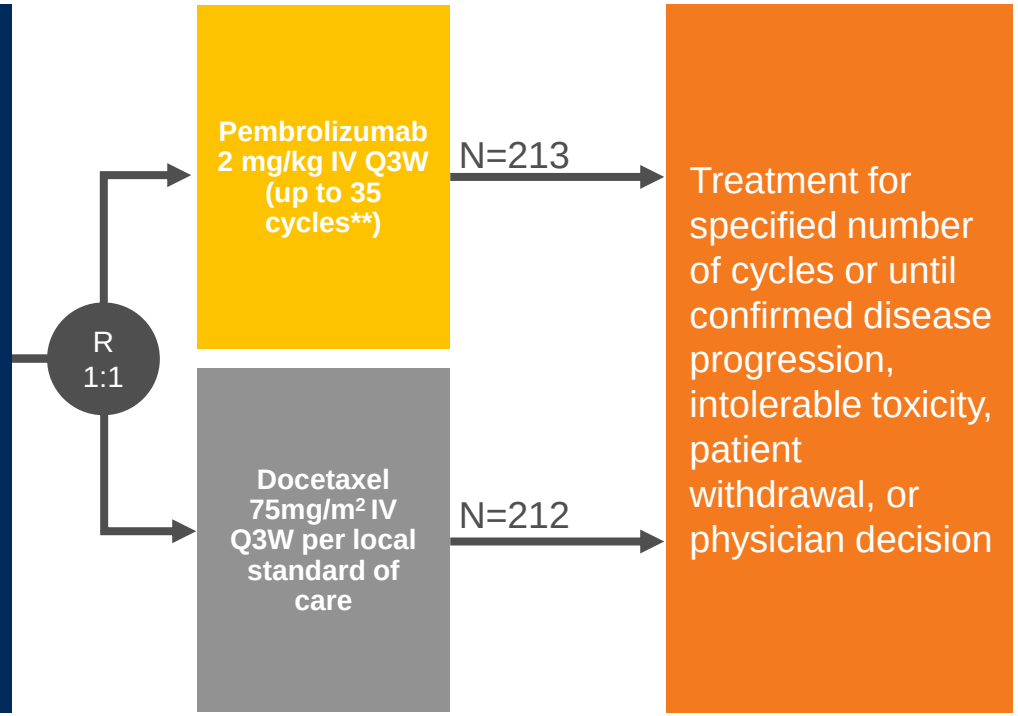
KEYNOTE-033 Study design and objectives

Multi-country, randomized, open-label phase 3 study of pembrolizumab vs docetaxel in patients with previously treated NSCLC with PD-L1 tumor proportion score (TPS) ≥1%

Key eligibility criteria

- Advanced NSCLC (histologically or cytologically confirmed stage 3b/4 or recurrent NSCLC; ≥1 measurable lesion by RECIST 1.1)
- Confirmed PD after ≥1 line of platinum-containing chemotherapy*
- ECOG PS 0-1
- PD-L1 TPS ≥1%
- No active CNS metastases or autoimmune disease
- No pneumonitis requiring systemic steroids



Total of 425 patients enrolled, with the majority (73.2%) from mainland China

Objectives

- Compare OS, progression-free survival (PFS), objective response rate (ORR), and duration of response (DOR) of pembrolizumab vs docetaxel for patients with previously treated, PD-L1-expressing advanced NSCLC
- Evaluate the safety and tolerability profiles of pembrolizumab and docetaxel for patients with previously treated, PD-L1-expressing advanced NSCLC

*Prior therapy must have included ≥2 cycles of platinum-doublet chemotherapy. An ALK-directed tyrosine kinase inhibitor was required for patients whose tumors had an ALK translocation.
**Some patients may be eligible to enter a Second Course Phase of the trial for up to 17 cycles of treatment with pembrolizumab.

NSCLC: Non small cell lung cancer. CNS: Central nervous system. ECOG PS: Eastern Cooperative Oncology Group Performance Status. ICR: Independent central review. IV: Intravenous. PD: Progressive disease. Q3W: every 3 weeks. RECIST: Response Evaluation Criteria in Solid Tumors. TPS: Tumor proportion score. OS: Overall survival. PFS: Progression free survival. DOR: Duration of response.
Zhou, C. et al, 2020. Poster 1262P presented at ESMO 2020.

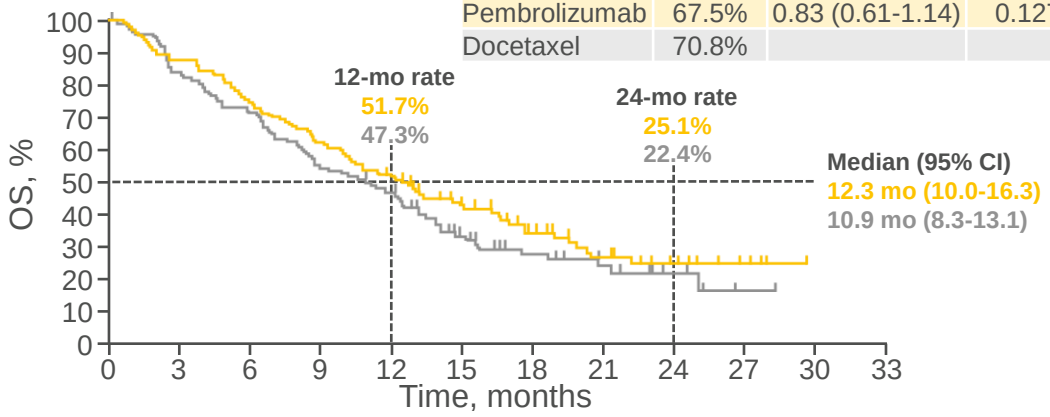
KEYNOTE-033 Results – efficacy in total population

Kaplan-Meier estimates of OS

PD-L1 TPS ≥50%

Because statistical significance for the TPS ≥50% population was not achieved, all sequential testing ceased

	Events	HR (95% CI)	p[a]
Pembrolizumab	67.5%	0.83 (0.61-1.14)	0.1276
Docetaxel	70.8%		



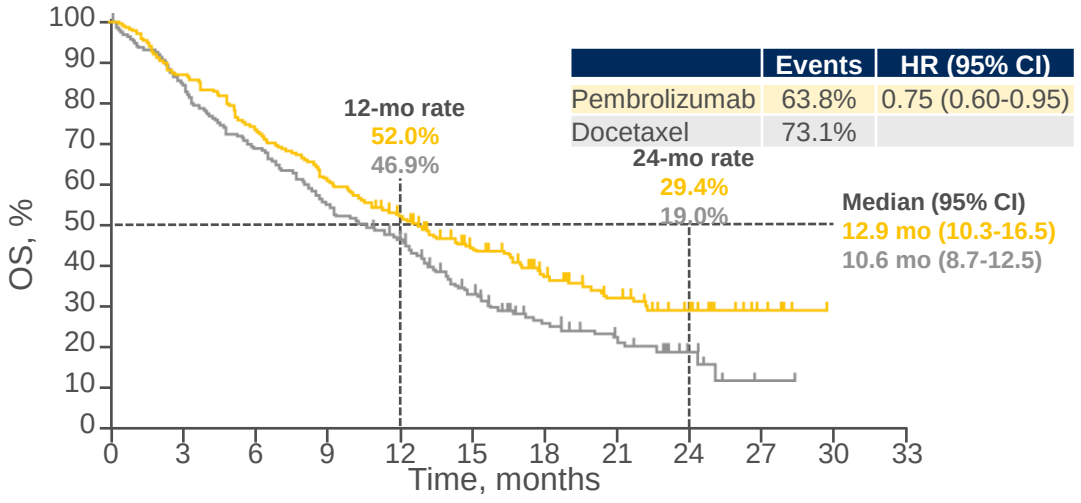
No. at risk												
114	100	86	71	57	39	25	17	10	5	0	0
113	94	80	61	51	27	18	12	5	1	0	0

Pembrolizumab vs docetaxel

- 1.4 month improvement in median OS
- 12-month OS 51.7% vs 47.3%
- 24-month OS 25.1% vs 22.4%

PD-L1 TPS ≥1%

	Events	HR (95% CI)
Pembrolizumab	63.8%	0.75 (0.60-0.95)
Docetaxel	73.1%	



No. at risk												
213	186	159	131	105	76	50	34	16	6	0	0
212	180	146	117	94	51	33	19	7	1	0	0

Pembrolizumab vs docetaxel

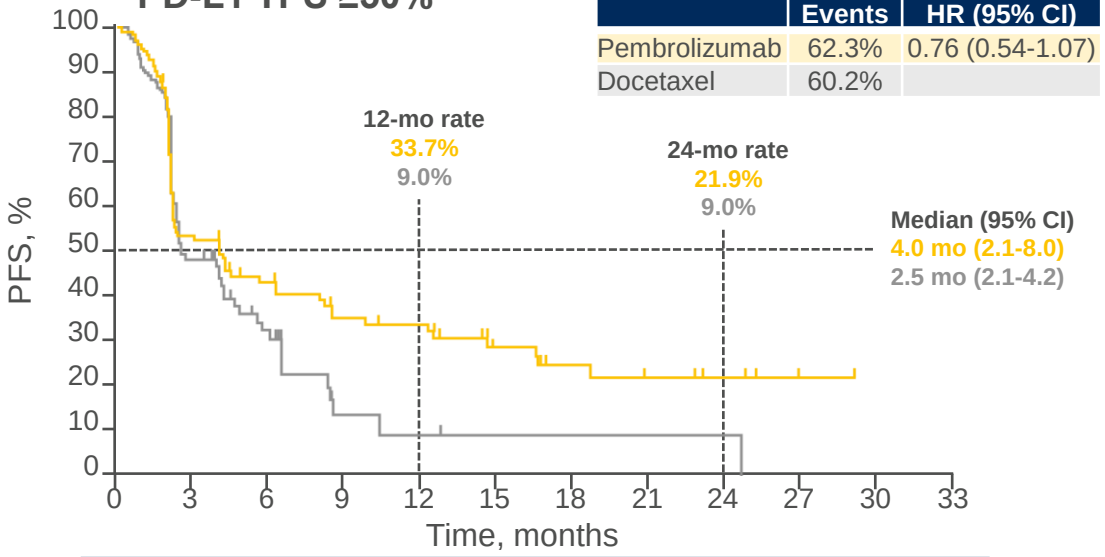
- 2.3 month improvement in median OS
- 12-month OS 52.0% vs 46.9%
- 24-month OS 29.4% vs 19.0%

[a]One-sided P value based on log-rank test. CI, confidence interval. HR, hazard ratio. OS: Overall survival. TPS: Tumor proportion score.
Zhou, C. et al, 2020. Poster 1262P presented at ESMO 2020.

KEYNOTE-033 Results - efficacy in total population

Kaplan-Meier estimates of PFS per RECIST v1.1 by BICR

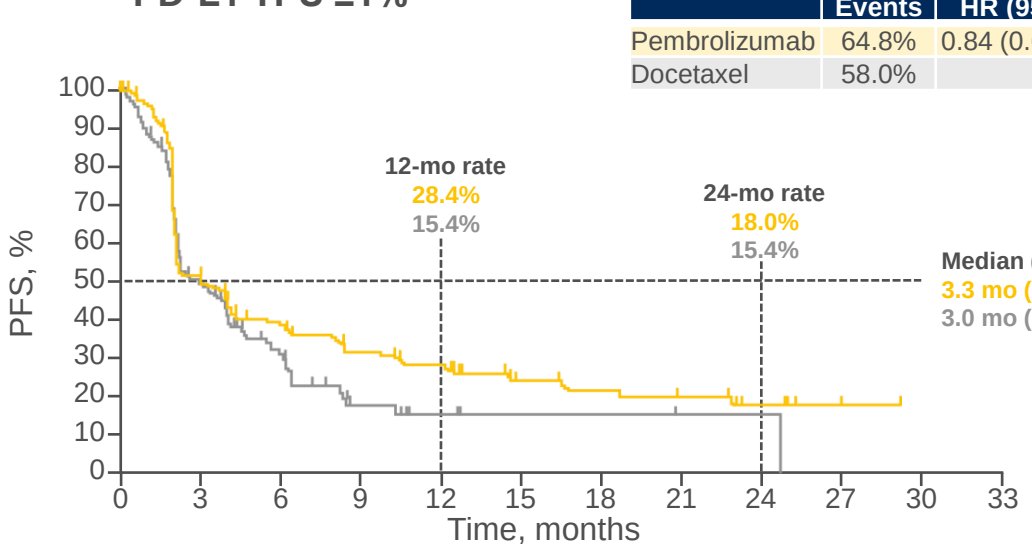
PD-L1 TPS ≥50%



	Events	HR (95% CI)
Pembrolizumab	62.3%	0.76 (0.54-1.07)
Docetaxel	60.2%	

No. at risk												
114	49	34	25	23	14	9	7	4	1	0	0
113	38	18	3	2	1	1	1	1	0	0	0

PD-L1 TPS ≥1%



	Events	HR (95% CI)
Pembrolizumab	64.8%	0.84 (0.66-1.08)
Docetaxel	58.0%	

No. at risk												
213	86	58	42	36	22	13	11	6	1	0	0
212	72	32	8	4	2	2	1	1	0	0	0

Pembrolizumab vs docetaxel

- 12-month PFS 33.7% vs. 9.0%
- 24-month PFS 21.9% vs 9.0%
- 1.5 month improvement in median PFS

Pembrolizumab vs docetaxel

- 12-month PFS 28.4% vs 15.4%
- 24-month PFS 18.0% vs 15.4%
- 0.3 month improvement in median PFS

BICR: Blinded independent central review. CI, confidence interval. HR, hazard ratio. PFS: Progression free survival. RECIST: Response Evaluation Criteria in Solid Tumors. TPS: Tumor proportion score.

Zhou, C. et al, 2020. Poster 1262P presented at ESMO 2020.

KEYNOTE-033 Results – efficacy in total population

Confirmed ORR and DOR per RECIST v1.1 by BICR

	Pembrolizumab	Docetaxel
TPS ≥50%	**N=114**	**N=113**
ORR (95% CI), %	28.1 (20.1-37.3)	7.1 (3.1-13.5)
Ongoing responses*, N (%)	16 (50.0)	1 (12.5)
Median DOR (range)**, months	16.6 (1.1+-24.9+)	6.4 (1.4+-22.3)
TPS ≥1%	**N=213**	**N=212**
ORR (95% CI), %	20.7 (15.4-26.7)	5.7 (3.0-9.7)
Ongoing responses*, N (%)	21 (47.7)	1 (8.3)
Median DOR (range)**, months	16.6 (1.1+-24.9+)	6.3 (1.4+-22.3)

Pembrolizumab vs docetaxel

ORR

- 21% improvement in TPS ≥50% population
- 15% improvement in TPS ≥1% population

Median DOR

- 10.2 months improvement in TPS ≥50% population
- 10.3 months improvement in TPS ≥1% population

*Includes patients who were alive, had not progressed, had not initiated new anticancer treatment, were not lost to follow-up, and whose last disease assessment was <5 months prior to data cutoff date. **Includes patients with confirmed complete response or partial response. From product-limit (Kaplan-Meier) method for censored data.

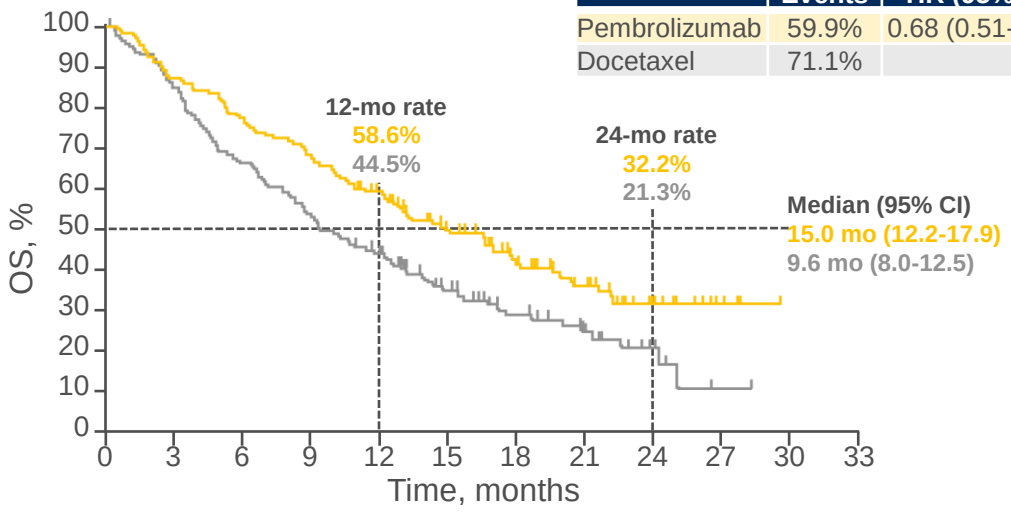
ORR: Objective response rate. DOR: Duration of response. RECIST: Response Evaluation Criteria in Solid Tumors. BICR: Blinded independent central review. TPS: Tumor proportion score. CI: Confidence interval.

Zhou, C. et al, 2020. Poster 1262P presented at ESMO 2020.

KEYNOTE-033 Results – efficacy in mainland China population

Kaplan-Meier estimates of OS in patients with PD-L1 TPS ≥1%

	Events	HR (95% CI)
Pembrolizumab	59.9%	0.68 (0.51-0.89)
Docetaxel	71.1%	



No. at risk											
162	142	126	110	89	66	43	29	12	4	0	0
149	126	99	79	61	39	26	14	5	1	0	0

Pembrolizumab vs docetaxel

- 12-month OS 58.6% vs 44.5%
- 24-month OS 32.2% vs 21.3%
- 5.4 months improvement in median OS

OS, PFS, and ORR in Patients From Mainland China

		Pembrolizumab	Docetaxel
TPS ≥1%		**N=162**	**N=149**
OS	Median (95% CI), months	15.0 (12.2-17.9)	9.6 (8.0-12.5)
	HR (95% CI)	0.68 (0.51-0.89)	
PFS	Median (95% CI), months	4.0 (2.2-8.0)	2.3 (2.1-3.4)
	HR (95% CI)	0.74 (0.55 – 0.99)	
ORR	% (95% CI)	23.5 (17.2-30.7)	6.0 (2.8-11.2)
TPS ≥50%		**N=86**	**N=82**
OS	Median (95% CI), months	13.2 (10.2-17.0)	10.6 (7.1-13.1)
	HR (95% CI)	0.79 (0.55-1.13)	
PFS	Median (95% CI), months	4.2 (2.1-8.4)	2.3 (2.1-4.0)
	HR (95% CI)	0.74 (0.49-1.10)	
ORR	% (95% CI)	31.0 (21.5 – 41.9)	8.5 (3.5-16.8)

Pembrolizumab vs docetaxel

OS
- 5.4 months improvement in TPS ≥1% population
- 2.6 months improvement in TPS ≥50% population

PFS
- 1.7 months improvement in TPS ≥1% population
- 1.9 months improvement in TPS ≥50% population

ORR
- 23.5% vs 6.0% in TPS ≥1% population
- 31.0% vs 8.5% in TPS ≥50% population

Ci, confiidence interval. HR, hazard ratio. PFS: Progression-free survival. ORR: Objective response rate. OS: Overall survival. TPS: Tumor proportion score.
Zhou, C. et al, 2020. Poster 1262P presented at ESMO 2020.

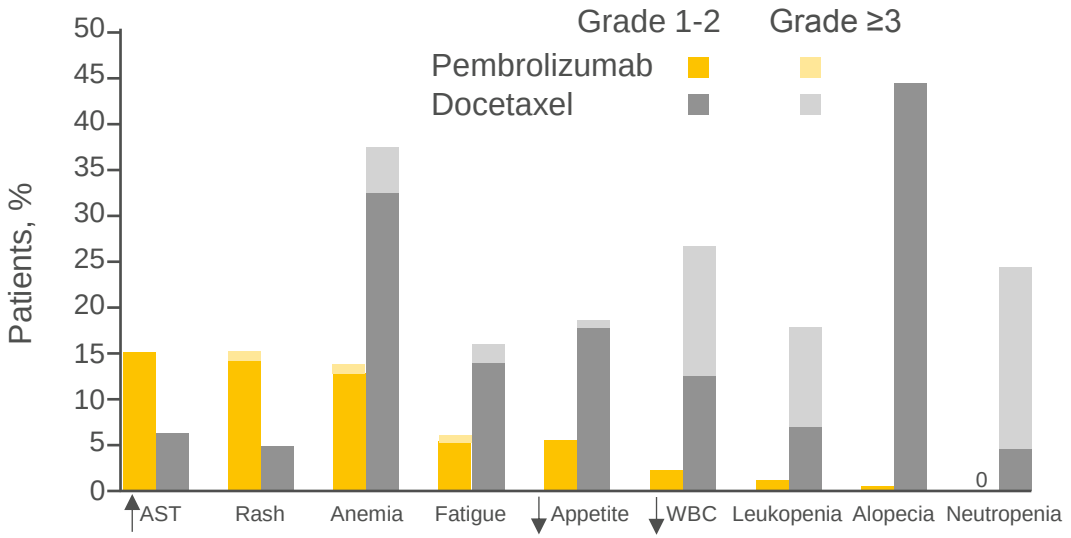
KEYNOTE-033 Results – safety and tolerability

Summary of treatment-related adverse events (TRAEs*) in all treated patients

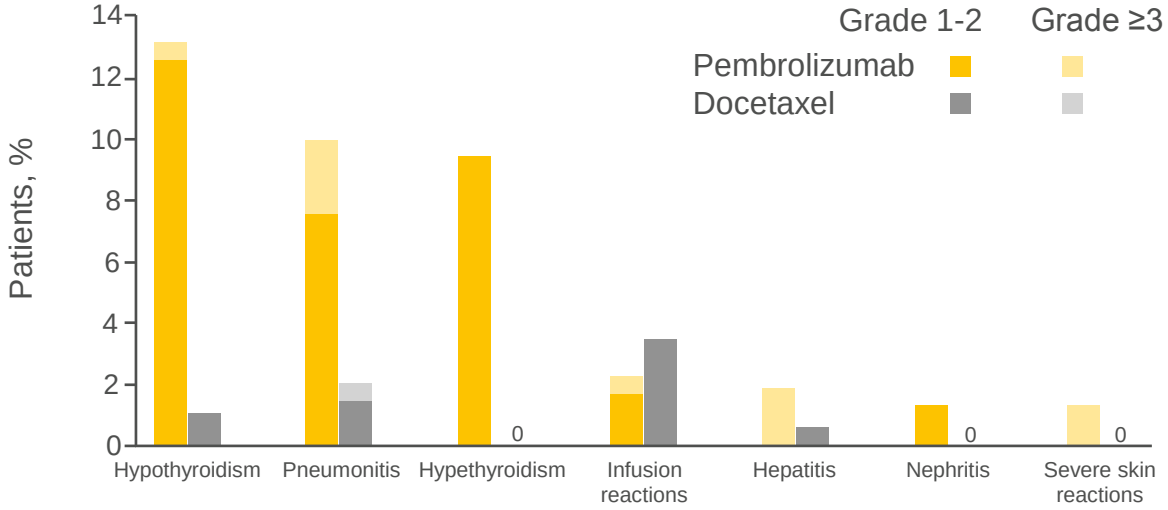
N (%)	Any grade**	Grade 3-5	Led to discontinuation	Led to death
Pembrolizumab (N=213)	149 (70.0)	24 (11.3)	21 (9.9)	4 (1.9)
Docetaxel (N=198)	174 (87.9)	94 (47.5)	15 (7.6)	4 (2.0)

*AEs were followed 30 days after the last dose of study treatment.
**Grades were based on National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.03.

TRAEs with incidence ≥15% in any arm, PD-L1 TPS ≥1%



Incidence of immune-mediated AEs and infusion reactions observed in ≥2 patients in the pembrolizumab arm in the PD-L1 TPS ≥1% population



TRAE: Treatment related adverse event. TPS: Tumor proportion score. AST: Aspartate aminotransferase. WBC: white blood cell count. AE: Adverse event.
Zhou, C. et al, 2020. Poster 1262P presented at ESMO 2020.

KEYNOTE-033 Conclusions

- In this population of patients with previously treated advanced NSCLC, pembrolizumab did not significantly prolong OS in the PD-L1 TPS ≥50% population
    - **HRs for OS and PFS numerically favored pembrolizumab** in both the TPS ≥50% and TPS ≥1% populations
    - **Pembrolizumab was associated with higher ORR and longer DOR** in both TPS populations
    - Similar efficacy benefits were also observed in patients from mainland China
- Safety/tolerability was consistent with the established pembrolizumab safety profile
    - Despite longer follow-up and longer treatment exposure with pembrolizumab, rates of any-grade and grade 3-5 treatment-related AEs, especially hematological AEs, remained lower with pembrolizumab vs docetaxel
    - **Pembrolizumab was well tolerated** in the patient population with NSCLC predominantly from mainland China
- **These data support the use of pembrolizumab for patients with previously treated advanced NSCLC in China**

NSCLC: Non small cell lung cancer. OS: Overall survival. HR: Harzard ratio. PFS: Progression free survival. TPS: Tumor proportion score. DOR: Duration of response. AE: adverse event.
Zhou, C. et al, 2020. Poster 1262P presented at ESMO 2020

KEYNOTE-024

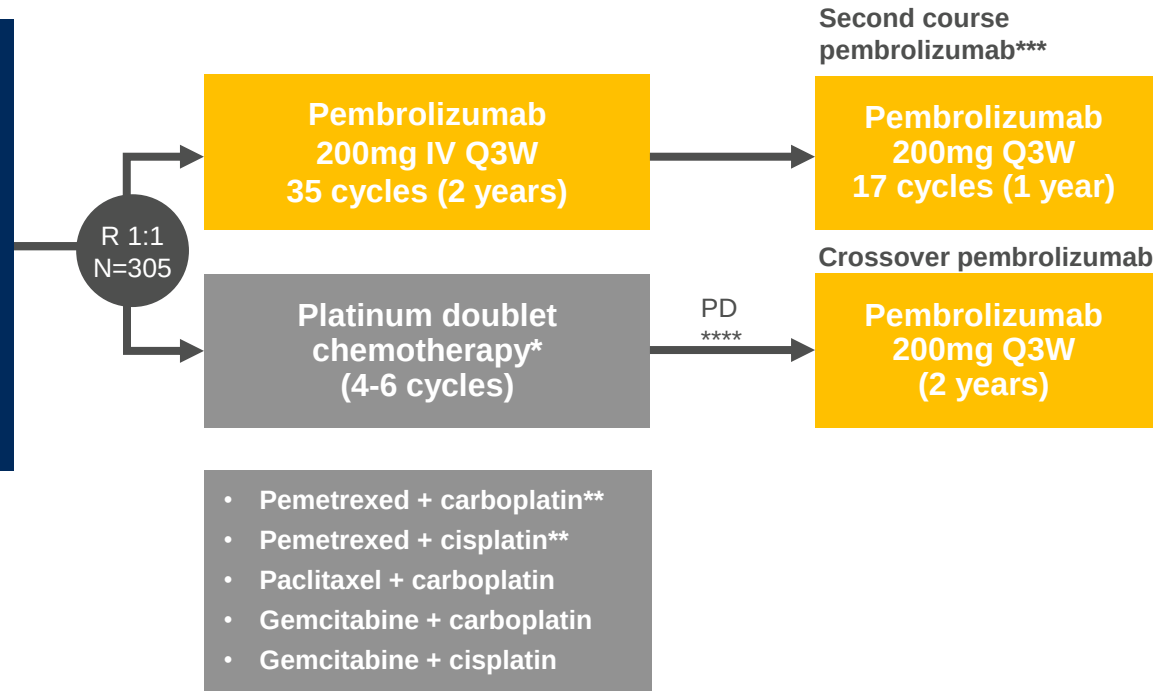
PD-1 inhibitor pembrolizumab (1L) vs platinum based chemotherapy in metastatic NSCLC with PD-L1 tumor proportion score (TPS) ≥50%: 5-Year OS update

KEYNOTE-024 Study design

First-line (1L) pembrolizumab vs platinum-based chemotherapy in patients with metastatic NSCLC and PD-L1 tumour proportion score (TPS) ≥50%: 5-year overall survival (OS) update

Key eligibility criteria

- Untreated stage IV NSCLC
- PD-L1 TPS ≥50%
- ECOG performance status 0-1
- No activating *EGFR* mutations or *ALK* translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy



Primary endpoint: PFS (RECIST v1.1 per BICR)

Key secondary endpoint: OS

Other secondary endpoints: ORR, safety, PFS (RECIST v1.1, per investigator review)

Exploratory endpoint: DOR

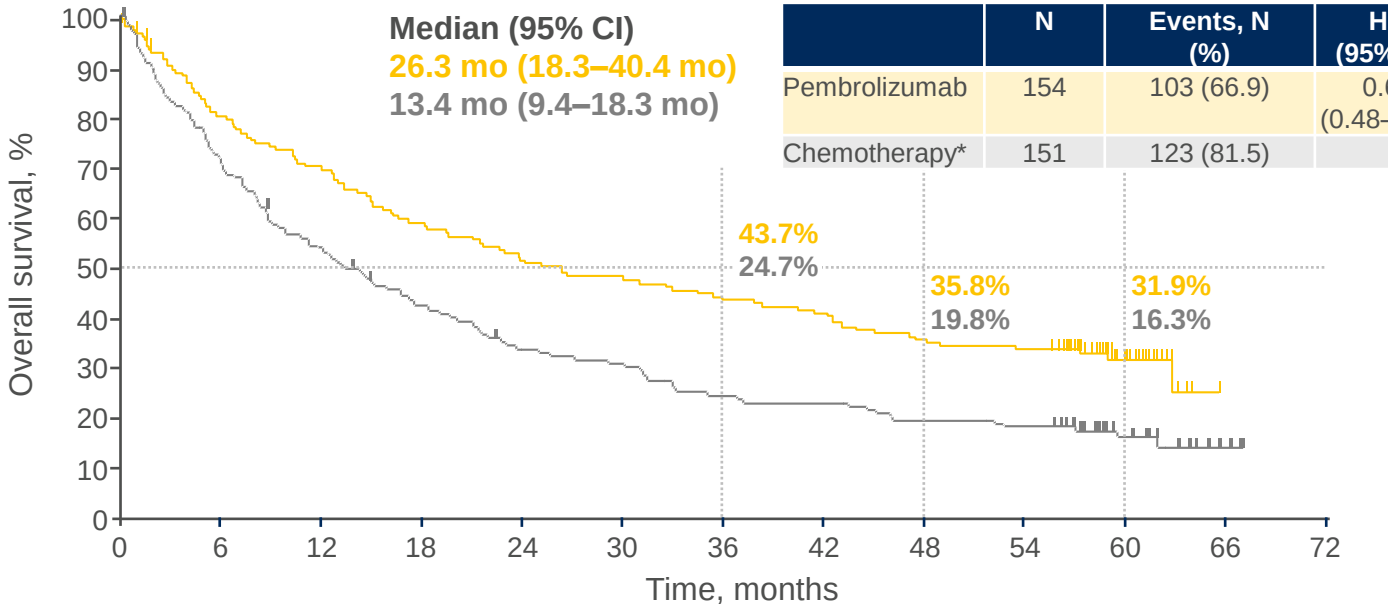
*Optional pemetrexed maintainance therapy for nonsquamous disease. **Permitted for nonsqaumous disease only. ***Patients randomized to pembrolizumab who completed 2 years of therapy or who stopped pembrolizumab after achieving CR and then had PD were eligible for a second course of Pembrolizumab monotherapy. ****Before the DMC recommendadtion and amendment 8, which permitted those in the chemotherapy arm to be offered pembrolizumab (based on interim analysis of phase 2 data) patients were eligible for crossover when PD was confirmed by BICR.

NSCLC: Non small cell lung cancer. OS: Overall survival. ECOG: Eastern Cooperative Oncology Group . PFS: Progression free survival. ORR: Objective response rate. RECIST: Response Evaluation Criteria in Solid Tumors. Q3W: Every 3 weeks. R: Randomization. IV: Intravenous. BICR: Blinded independent central review. CR: Complete reponse. PD: Progressive disease. DOR: Duration of response

Brahmer, J. et al, 2020. Abstract LBA51 presented at ESMO 2020

KEYNOTE-024 Results - efficacy

Overall survival (ITT population)



	N	Events, N (%)	HR (95% CI)
Pembrolizumab	154	103 (66.9)	0.62 (0.48–0.81)
Chemotherapy*	151	123 (81.5)	

No. at risk												
154	121	106	89	78	73	66	62	54	51	20	0	0
151	108	80	61	48	44	35	33	28	26	13	3	0

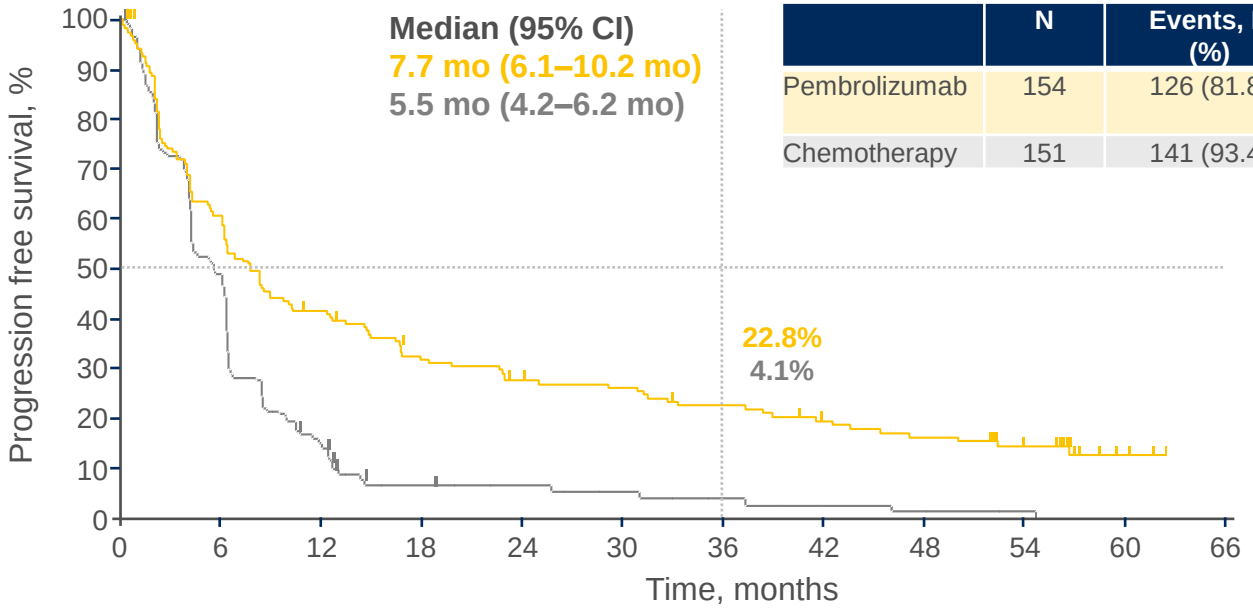
- **Median OS almost double in pembrolizumab arm vs chemotherapy arm** (26.3 months vs 13.4 months, HR 0.62)
- Benefit seen despite 66% crossover rate from chemotherapy to pembrolizumab
- **5-year OS almost double in pembrolizumab arm vs chemotherapy arm** (31.9% vs 16.3%)

*Effective crossover rate from chemotherapy to aniti-PD-(L)1 therapy, 66.0% (99 patients in total crossed over to anti-PD-(L)1 therapy: 83 patients crossed over to pembrolizumab during the study, and 16 patients received subsequent anti-PD-(L)1 therapy outside of crossover; pateints may have received >1 subsequent anti-PD-(L)1 therapy). Data cutoff: 1st June 2020.

ITT: Intention to treat. OS: Overall survival. HR: Hazard ratio. CI: Confidence interval.
Brahmer, J. et al, 2020. Abstract LBA51 presented at ESMO 2020

KEYNOTE-024 Results - efficacy

Progression-free survival (ITT population) by RECIST v1.1 per investigator review*



	N	Events, N (%)	HR (95% CI)
Pembrolizumab	154	126 (81.8)	0.50 (0.39–0.65)
Chemotherapy	151	141 (93.4)	

No. at risk											
154	92	62	46	38	36	30	24	20	15	3	0
151	73	20	6	5	4	3	2	1	1	0	0

- **Median PFS improvemet 2.2 months in pembrolizumab arm vs chemotherapy arm** (7.7 months vs 5.5 months, HR 0.50)
- **3-year PFS 18.7% higher in pembrolizumab arm vs chemotherapy arm** (22.8% vs 4.1%)

*Secondary endpoint; primary endpoint was PFS assessed per BICR.Data cutoff: 1st June 2020.

ITT: Intention to treat. PFS: Progression free survival. BICR: Blinded independent central review. HR: Hazard ratio. CI: Confidence interval. RECIST: Response Evaluation Criteria in Solid Tumors

Brahmer, J. et al, 2020. Abstract LBA51 presented at ESMO 2020

KEYNOTE-024 Results - efficacy

Objective response rate (ITT population) by RECIST v1.1 per investigator review

	Pembrolizumab (N=154)	Chemotherapy (N=151)
Objective response, N (%)	71 (46.1)	47 (31.1)
Best objective response, N (%) CR PR SD PD NE NA	 7 (4.5) 64 (41.6) 37 (22.7) 35 (22.7) 0 (0) 11 (7.1)	 0 47 (31.1) 60 (39.7) 25 (16.6) 1 (0.7) 18 (11.9)
Time to response, median (range), months	2.1 (1.4-14.6)	2.1 (1.1-12.2)
DOR, median (range), months	29.1 (2.2-60.8+)	6.3 (3.1-52.4)

+Indicates response duration is censored

- **Median ORR 15% higher in pembrolizumab arm vs chemotherapy arm** (46.1% vs 31.1%)
- **7 complete responses (CRs) in pembrolizumab arm vs 0 in chemotherapy arm**
- Median time to response 2.1 months for both arms
- **Median DOR 22.8 months longer in pembrolizumab arm vs chemotherapy arm** (29.1 months vs 6.3 months)

ORR: Objective reposonse rate. ITT: Intention to treat. RECIST: Response evaluation criteria in solid tumors. CR: Complete response. PR: Progressive disease. SD: Stable disease. PD: Progressive disease. NE: Not evaluable. NA: No assessment. DOR: Duration of response.

Brahmer, J. et al, 2020. Abstract LBA51 presented at ESMO 2020

KEYNOTE-024 Results - safety and tolerability

Summary of adverse events

	Pembrolizumab* (N=154)	Chemotherapy* (N=151)	35 Cycles (2 years) of Pembrolizumab* (N=39)
TRAEs, N (%)	**118 (76.6)**	**135 (90.0)**	34 (87.2)
Grade 3-5**	48 (31.2)	80 (53.3)	6 (15.4)
Serious	35 (22.7)	31 (20.7)	4 (10.3)
Led to discontinuation	21 (13.6)	16 (10.7)	0
Led to death	2 (1.3)	3 (2.0)	0
Immune-mediated AEs and infusion reactions, N (%)* **	**53 (34.4)**	**8 (5.3)**	**12 (30.8)**
Grade 3-5	21 (13.6)	1 (0.7)	3 (7.7)
Led to death	1 (0.6)	0	0

- Exposure-adjusted AE rates in the ITT population decreased over time in both treatment groups

*During treatment with the initially assigned thearpy. **7 additional patients in the pembrolizumab arm and no additional patients in the chemotherapy arm had treatment related grade 3-5 AEs since the initial publication of KEYNOTE-024 (Reck, M. et al. *NEJM*. 2016;375:1823-1833). There was no change since the updated analysis at 25.2 months median follow up (Reck, M. et al. J Clin Oncol. 2019;37:537-546). ***Irrespective of attribution to treatment by the investigator. Data cutoff: 1st June 2020.

TRAE: Treatment related adverse event. AE: Adverse event. ITT: Intention to treat.
Brahmer, J. et al, 2020. Abstract LBA51 presented at ESMO 2020

KEYNOTE-024 Conclusions

- With 5 years follow-up, pembrolizumab continues to show meaningful improvements in OS and durable responses versus chemotherapy in KEYNOTE-024
  - Despite 66% effective crossover rate, the 5-year OS rate was approximately doubled in pembrolizumab arm vs chemotherapy arm (31.9% vs 16.3%) with median DOR of 29.1 months in pembrolizumab arm
- Patients who completed 35 cycles (2 years) of pembrolizumab experienced long-term OS
  - Second-course pembrolizumab at the time of disease progression was feasible and associated with antitumor activity
- Incidence of any-grade and grade 3-5 TRAEs was lower with pembrolizumab versus chemotherapy
  - Long term treatment with pembrolizumab did not identify new safety signals

- **KEYNOTE-024 is the first phase 3 study to demonstrate 5-year efficacy for 1L immunotherapy and demonstrates that pembrolizumab monotherapy is an effective 1L treatment regimen in patients with metastatic NSCLC and PD-L1 TPS ≥50%**
  - These data confirm 5-year OS outcomes among previously untreated patients in the single-arm KEYNOTE-001 study*

*Garon EB et al. J Clin Oncol 2019;37:2518-2527.
OS: Overall survival. TRAE: Treatment related adverse events. 1L: First line. NSCLC: Non small cell lung cancer. TPS: Tumor proportion score.
Brahmer, J. et al, 2020. Abstract LBA51 presented at ESMO 2020

JASPER

PARPi inhibitor niraparib + PD-1 inhibitor pembrolizumab in NSCLC

JASPER Study design

Multicenter, 2 cohort , open-label, proof-of-concept Phase 2 study of the combination of niraparib and PD-1i in chemotherapy-naïve and PD-(L)1i-naïve patients with metastatic or locally advanced NSCLC

Metastatic or locally advanced NSCLC

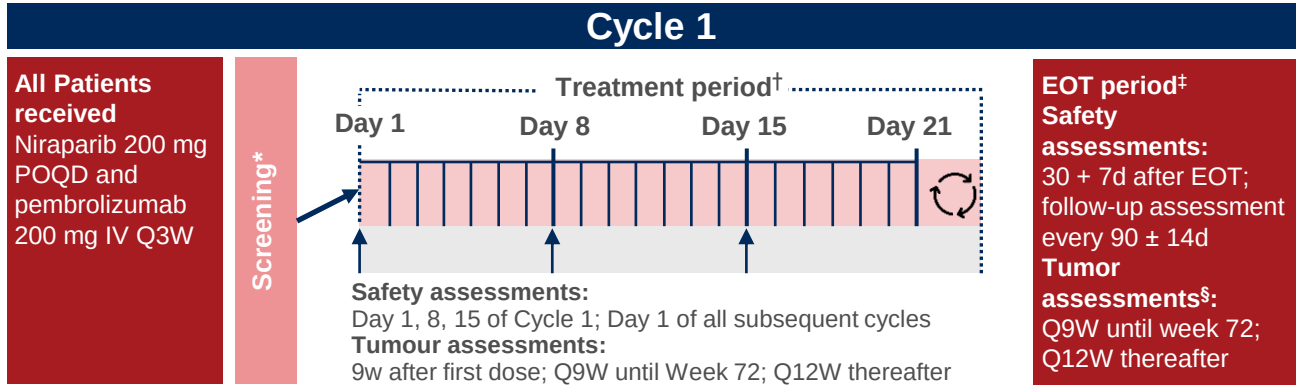
- ≥18 years of age
- Chemotherapy naïve
- PD-(L)1 inhibitor naïve
- Measurable disease per RECIST v1.1
- Stage IIIB/IV NSCLC
- No known EGFR-sensitizing mutations, *ALK* or *ROS1* translocations
- ECOG PS 0-1
- PD-L1 expression (TPS) available

Cohort 1
(niraparib + pembrolizumab)
PD-L1
TPS ≥50

Cohort 2
(niraparib + pembrolizumab)
PD-L1
TPS 1-49

Primary endpoint
ORR, investigator assessed per RECIST v1.1

Secondary endpoints
DOR, PFS, OS, safety



Efficacy analysis
mITT population: Received any study drug and did not withdraw consent prior to having ≥1 post-baseline tumor assessment**

Safety analysis
Received ≥1 dose of study treatment

Statistical analysis
Sample size calculated for each cohort based on primary endpoint of ORR; SAS software v9.4

Objective: To report interim data on the efficacy and safety of the combination of niraparib and pembrolizumab in patients with PD-L1 TPS ≥50% (Cohort 1) and PD-L1 TPS 1–49% (Cohort 2)

*Includes initial safety monitoring and baseline tumor assessment; scans performed as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and performed within 28 days prior to first dose date;†until discontinuation due to death, progressive disease, unacceptable toxicity, severe noncompliance with the protocol, withdrawal of consent, pregnancy, confirmed CR in patient who has >24w of treatment and 2 cycles after CR confirmed, or study termination; ‡until death or end of study data collection (minimum 6 months after enrolment of the last patient); §if patient discontinues treatment for a reason other than progression, death, withdrawal of consent, or loss to follow-up; **mITT population included treated patients who died prior to the first scan.

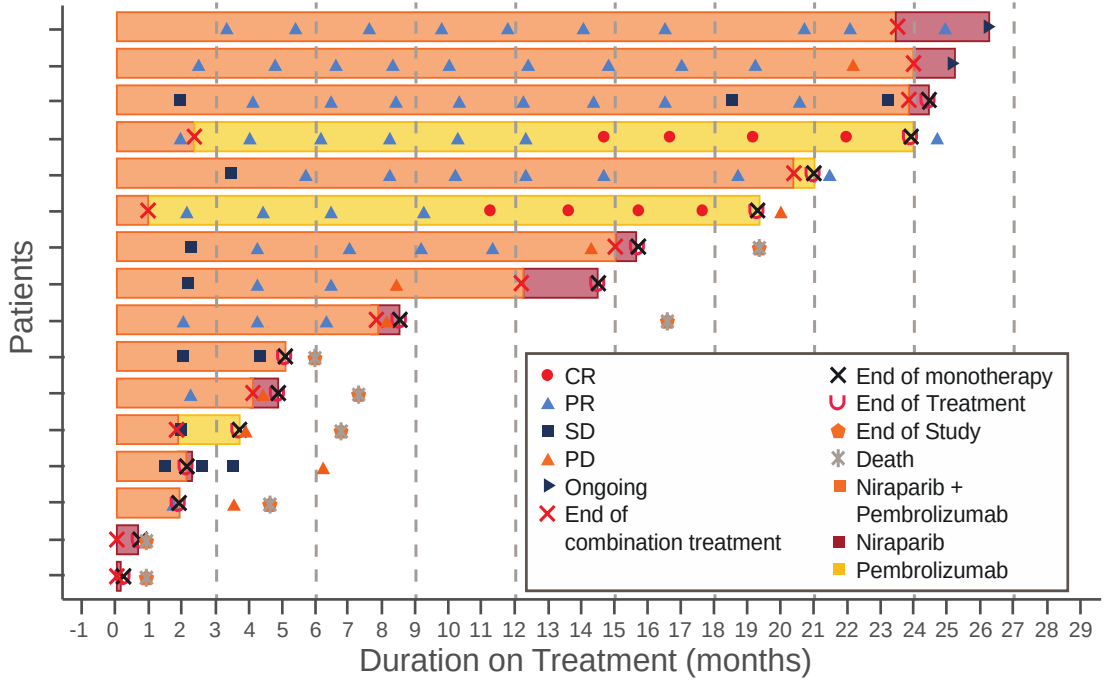
NSCLC: Non small cell lung cancer. IV: Intavenous. DOR: Duration of response. PFS: Progression free survival. OS: Overall survival. RECIST: Response Evaluation Criteria in Solid Tumors. ECOG:Eastern Cooperative Oncology Group. TPS: Tumor proportion score. PD1i: PD1 inhibition.

Ramalingam, S. et al. Poster 1268P presented at ESMO 2020.

JASPER Results – efficacy

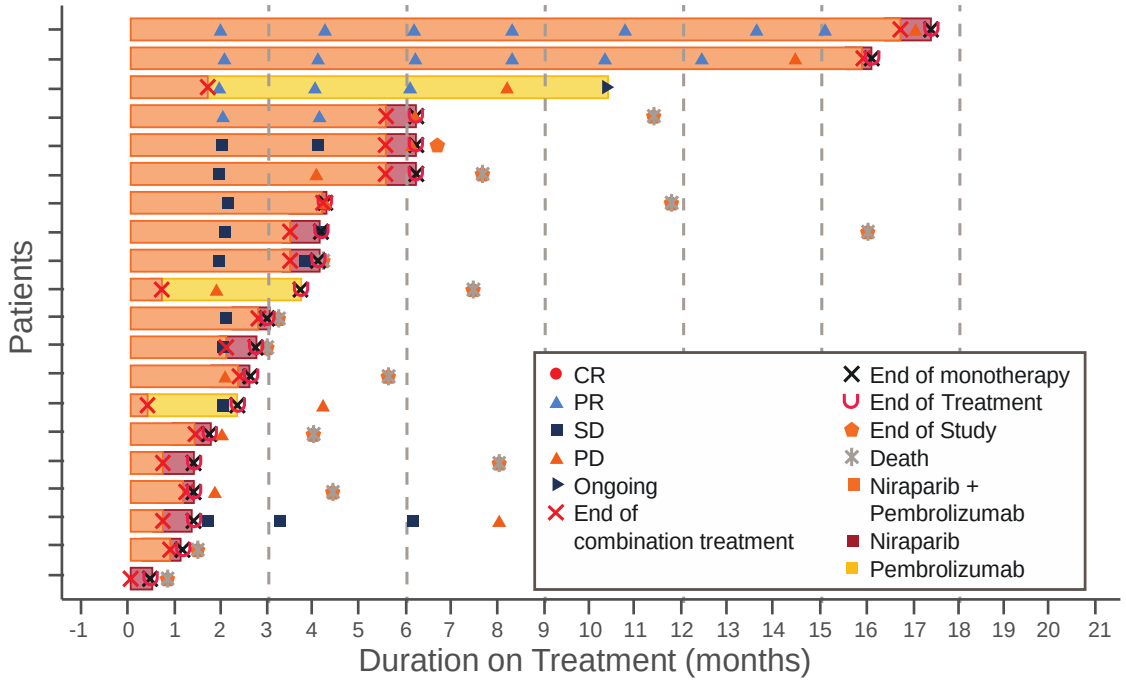
Cohort 1 (PD-L1 TPS: ≥50%)*

- 2 complete responses (CRs) reported
- Objective response rate (ORR) 56% (9/16 patients) (95% CI 30-80)



Cohort 2 (PD-L1 TPS: 1–49%)**

- ORR*** 20% (4/20 patients) (95% CI: 6–44)

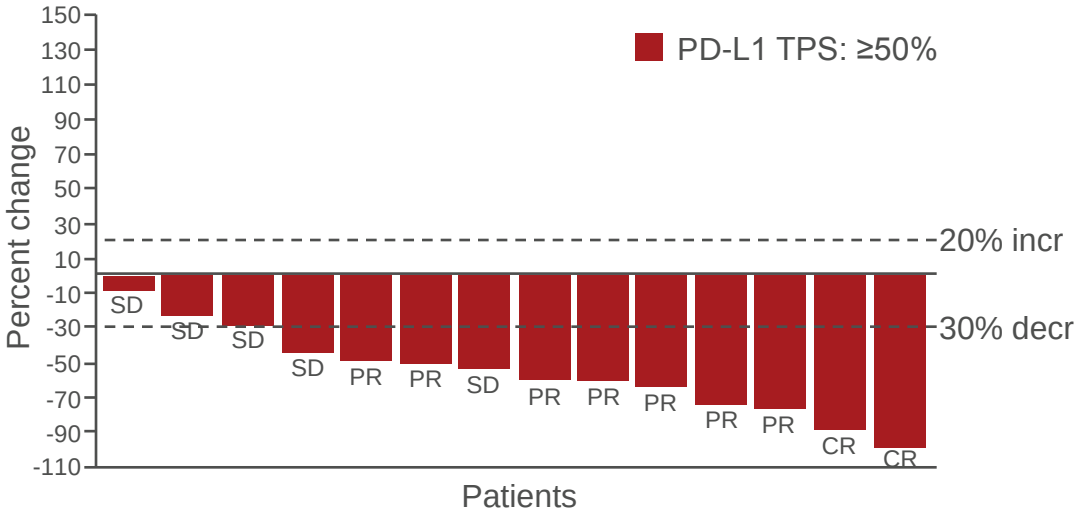


*Cohort 1 enrolled 17 patients; 1 patient withdrew consent prior to the first dose; mITT N=16. **Cohort 2 enrolled 21 patients; 1 patient withdrew consent prior to the first dose; mITT n=20.
***mITT population; confirmed ORR includes patients with CR and PR. mITT includes all patients who received any study drug and did not withdraw consent prior to having at least one post-baseline tumor assessment.

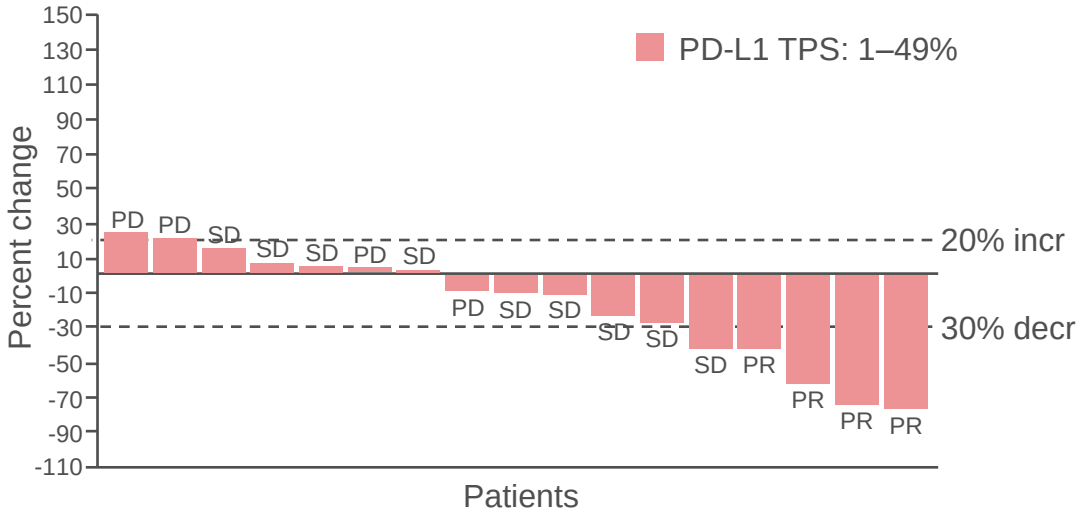
TPS: Tumor proportion score. CR: complete response. ORR: Objective response rate. PR: Partial response. PD: Progressive disease. SD: Stable disease
Ramalingam, S. et al. Poster 1268P presented at ESMO 2020.

JASPER Results – efficacy

In Cohort 1, patients had 8–100% reduction in target lesion size



In Cohort 2, patients had 9–78% reduction in target lesion size



Median DoR and PFS were higher in Cohort 1 compared with Cohort 2

	Cohort 1 (PD-L1 TPS ≥50%)	Cohort 1 (PD-L1 TPS 1–49%)
Median DOR,* months (95% CI)	19.7 (4.2–NE) N=9	9.4 (4.2–15.1) N=4
Median PFS,† months (95% CI)	8.4 (3.9–22.1) N=16	4.2 (2.0–6.2) N=20

2 patients died in Cohort 1 and 3 patients in Cohrot 2 prior to tumor assessment scan
TPS: Tumor proportion score. SD: Stable disease. PR: Partial response. CR: Complete response. DOR: Duration of response. PFS: Progression-free disease. NE: not evaluable
Ramalingam, S. et al. Poster 1268P presented at ESMO 2020.

JASPER Results – safety and tolerability

Summary of treatment emergent adverse events (TEAEs)

TEAEs in >2 patients in either cohort, N (%)	Cohort 1 PD-L1 TPS ≥50% (N=17)	Cohort 2 PD-L1 TPS 1-49% (N=21)
Any TEAE	17 (100)	21 (100)
Any TEAE related to either study drug	15 (88.2)	18 (85.7
Any niraparib-related TEAE	15 (88.2)	16 (76.2)
Any pembrolizumab-related TEAE	14 (82.4)	15 (71.4)
Any grade ≥3 TEAE	15 (88.2)	18 (85.7)
Deaths due to AEs	1 (5.9)	3 (14.3)
Discontinued niraparib due to TEAE	10 (58.8)	8 (38.1)
Discontinued pembrolizumab due to TEAE	4 (23.5)	5 (23.8)

TEAEs in >2 patients in either cohort, N (%)	Cohort 1 PD-L1 TPS ≥50% (N=17)	Cohort 2 PD-L1 TPS 1–49% (N=21)
Most common TEAEs		
Fatigue	7 (41.2)	7 (33.3)
Nausea	6 (35.3)	9 (42.9)
Decreased appetite	5 (29.4)	8 (38.1)
Anemia	4 (23.5)	7 (33.3)
Most common grade ≥3 TEAEs		
Anemia	4 (23.5)	6 (28.6)
Pneumonia	4 (23.5)	4 (19.0)

TPS: Tumor proportion score. SD: Stable disease. PR: Partial response. CR: Complete response. TEAE: Treatment emergent adverse event. AE: Adverse event.
Ramalingam, S. et al. Poster 1268P presented at ESMO 2020.

JASPER Conclusions

- Niraparib in combination with pembrolizumab induced durable responses in patients with advanced or metastatic NSCLC in both study cohorts
- Greater efficacy was observed in Cohort 1 with patients with PD-L1–high tumors (PD-L1 TPS ≥50%)
- The safety profile of the combination was consistent with prior clinical experience with niraparib and pembrolizumab, as monotherapy or in combination, in other tumor types

- While the number of patients is relatively small, **these results suggest that niraparib plus a PD-1 inhibitor is an active and well-tolerated combination and support further evaluation of this novel combination approach in advanced NSCLC**

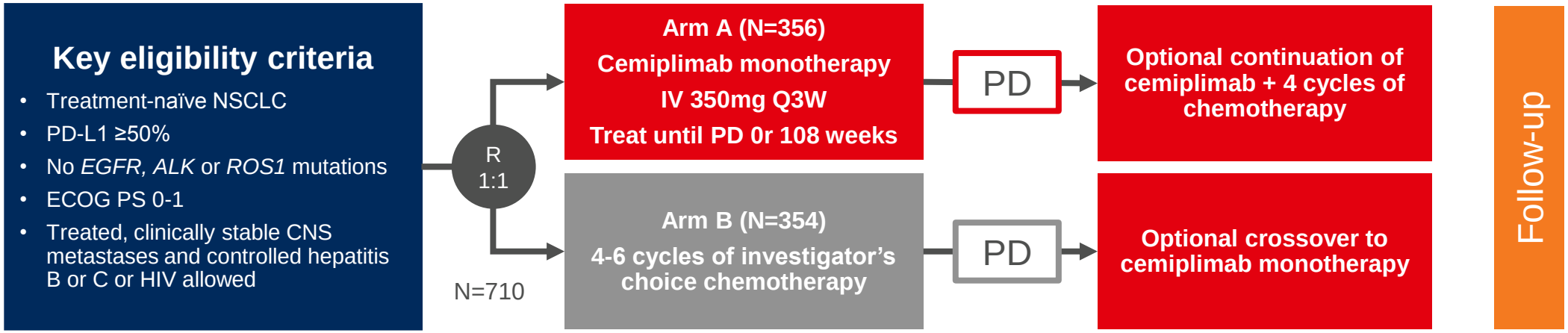
NSCLC. Non small cell lung cancer. TPS: Tumor proportion score.
Ramalingam, S. et al. Poster 1268P presented at ESMO 2020.

EMPOWER-Lung 1

PD-1 inhibitor cemiplimab vs chemotherapy in 1L treatment of advanced NSCLC with PD-L1 ≥50%

EMPOWER-Lung 1 Study design

Randomized, open-label, multi-national, phase 3 trial of cemiplimab, a human PD-1 monoclonal antibody, vs chemotherapy in 1L treatment of advanced NSCLC with PD-L1 ≥50%



Stratification factors:
- Histology (squamous vs non-squamous)
- Region (Europe, Asia or ROW

Primary endpoint: OS and PFS
Secondary enpoints: ORR (key), DOR, HRQoL and safety

- 5 interim analyses were prespecified per protocol
- 2nd interim analysis (1st March 2020) presented here

NSCLC: Non small cell lung cancer. ECOG: Eastern Cooperative Oncology Group. CNS: Central nervous system. IV: Intravenous. Q3W: Every 3 weeks. PD: Progressive disease. HRQoL: Health related quality of life. ORR: Objective response rate.
Sezer, A. et al, 2020. Abstract LBA52 presented at ESMO 2020

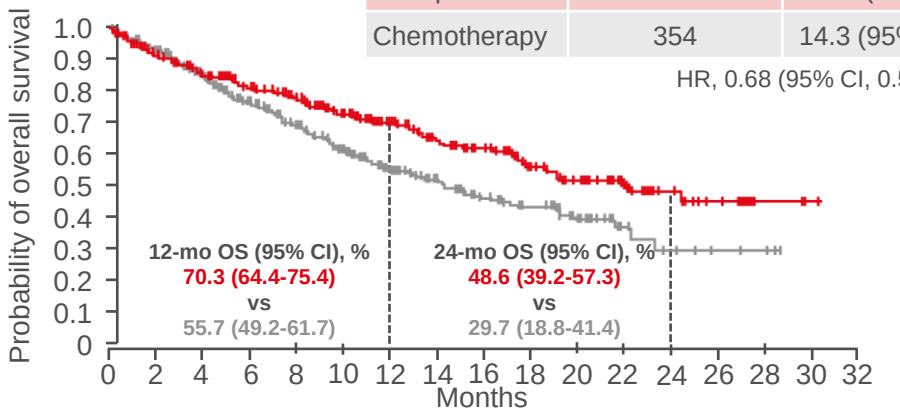
EMPOWER-Lung 1 Results - efficacy

Overall survival

ITT population

	No. of Patients	Median OS (95% CI) mo
Cemiplimab	356	22.1 (95% CI, 17.7-NE)
Chemotherapy	354	14.3 (95% CI, 11.7-19.2)

HR, 0.68 (95% CI, 0.53-0.87); P=0.0022



No. at risk															
356	304	254	223	198	147	120	87	71	48	37	27	18	8	3	1	0
354	303	254	205	172	126	93	73	52	41	27	12	7	4	3	0	0

Median duration of follow-up:
Cemiplimab -> 13.1 months (range: 0.1-31.9)
Chemotherapy -> 13.1 months (range: 0.2-32.4)

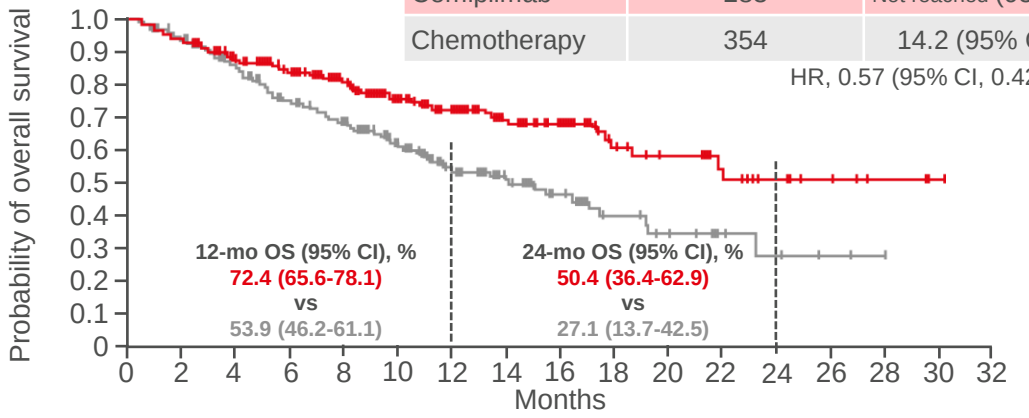
Cemiplimab vs chemotherapy

- 7.8-month improvement in median OS (HR 0.68)
- 12-month OS 70.3% vs 55.7%
- 24-month OS 48.6% vs 29.7%

PD-L1 ≥50% ITT

	No. of Patients	Median OS (95% CI) mo
Cemiplimab	283	Not reached (95% CI, 17.9-NE)
Chemotherapy	354	14.2 (95% CI, 11.2-17.5)

HR, 0.57 (95% CI, 0.42-0.77); P=0.0002



No. at risk															
283	244	203	177	154	108	83	55	42	24	18	15	10	6	3	1	0
280	239	198	153	125	87	57	41	25	15	11	6	4	2	1	0	0

Median duration of follow-up:
Cemiplimab -> 10.8 months (range: 0.1-31.9)
Chemotherapy -> 10.2 months (range: 0.2-29.5)

Cemiplimab vs chemotherapy

- Median OS NR vs 14.2 months (HR 0.57)
- 12-month OS 72.4% vs 53.9%
- 24-month OS 50.4% vs 27.1%

OS: Overall survival. ITT: Intention to treat. CI: Confidence interval. HR: Hazard ratio. NR: Not reached. NE: not evaluable
Sezer, A. et al, 2020. Abstract LBA52 presented at ESMO 2020

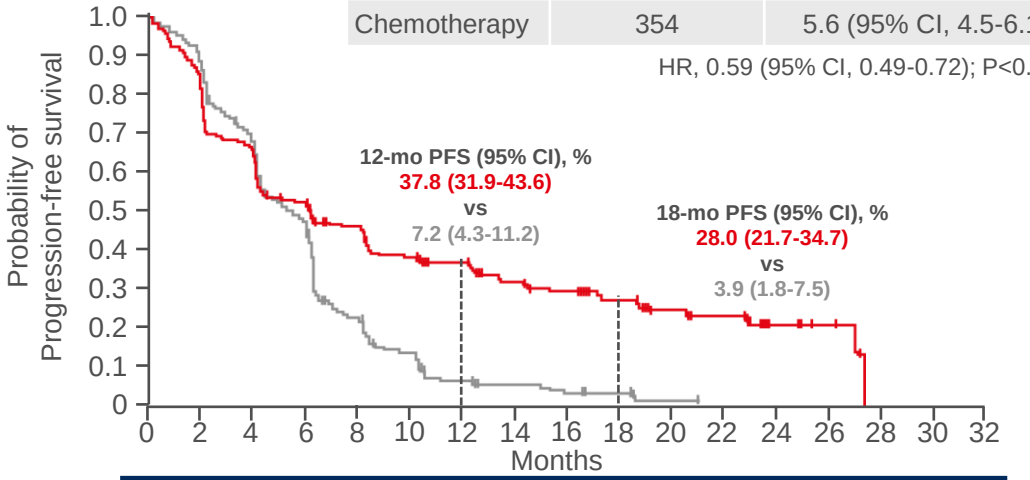
EMPOWER-Lung 1 Results - efficacy

Progression-free survival

ITT population

	No. of Patients	Median OS (95% CI) mo
Cemiplimab	356	6.2 (95% CI, 4.5-8.3)
Chemotherapy	354	5.6 (95% CI, 4.5-6.1)

HR, 0.59 (95% CI, 0.49-0.72); P<0.0001



No. at risk																
356	278	202	149	115	77	61	42	34	26	17	13	7	4	0	0	0
354	280	204	135	58	30	13	9	6	3	1	0	0	0	0	0	0

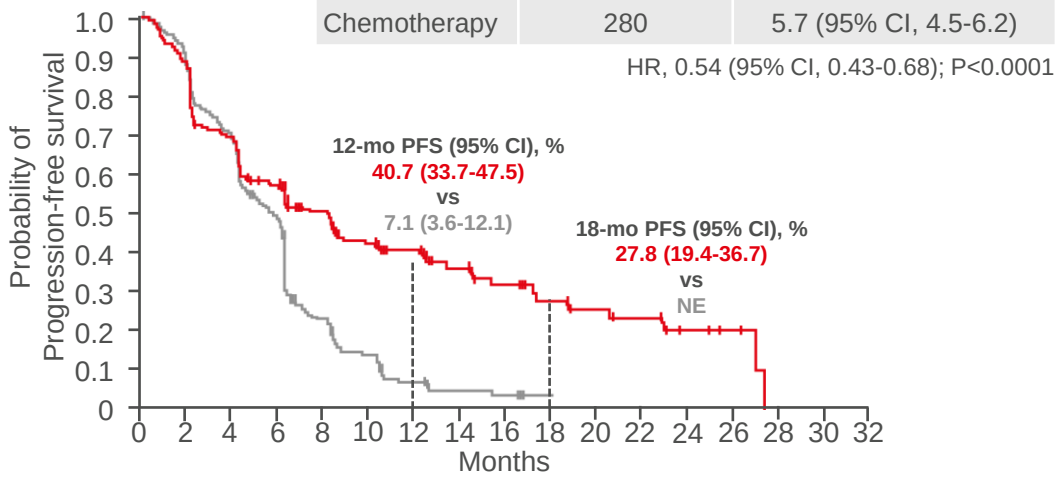
Cemiplimab vs chemotherapy

- 0.6-month improvement in median PFS (HR 0.59)
- 12-month PFS 37.8% vs 7.2%
- 24-month PFS 28.0% vs 3.9%

PD-L1 ≥50% ITT

	No. of Patients	Median OS (95% CI) mo
Cemiplimab	283	8.2 (95% CI, 6.1-8.8)
Chemotherapy	280	5.7 (95% CI, 4.5-6.2)

HR, 0.54 (95% CI, 0.43-0.68); P<0.0001



No. at risk																
283	221	162	123	92	59	43	28	20	14	11	9	5	3	0	0	0
280	220	157	104	42	20	8	4	3	0	0	0	0	0	0	0	0

Cemiplimab vs chemotherapy

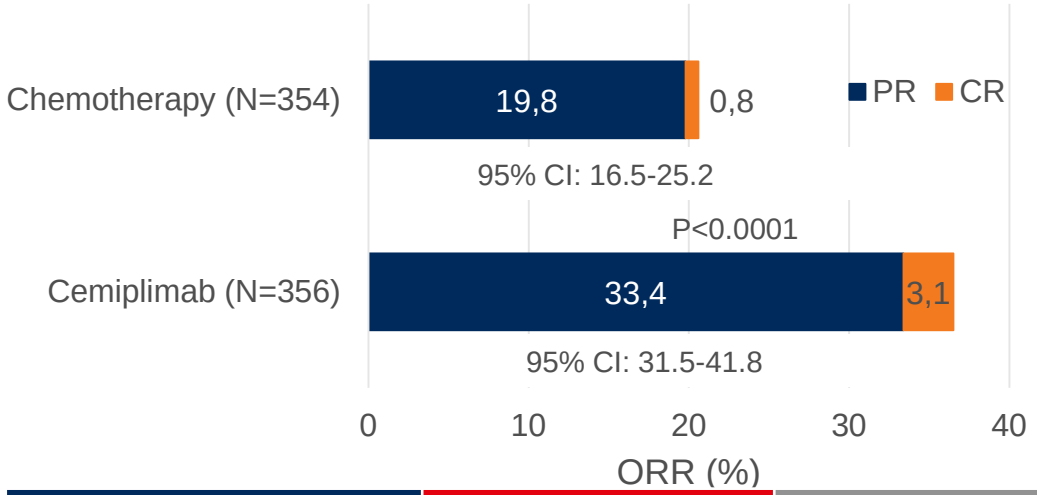
- 2.5-month improvement in median PFS (HR 0.54)
- 12-month PFS 40.7% vs 7.1%
- 24-month PFS 27.8% vs NE

PFS: Progression free survival. ITT: Intention to treat. CI: Confidence interval. HR: Hazard ratio. NE: Not evaluable.
Sezer, A. et al, 2020. Abstract LBA52 presented at ESMO 2020

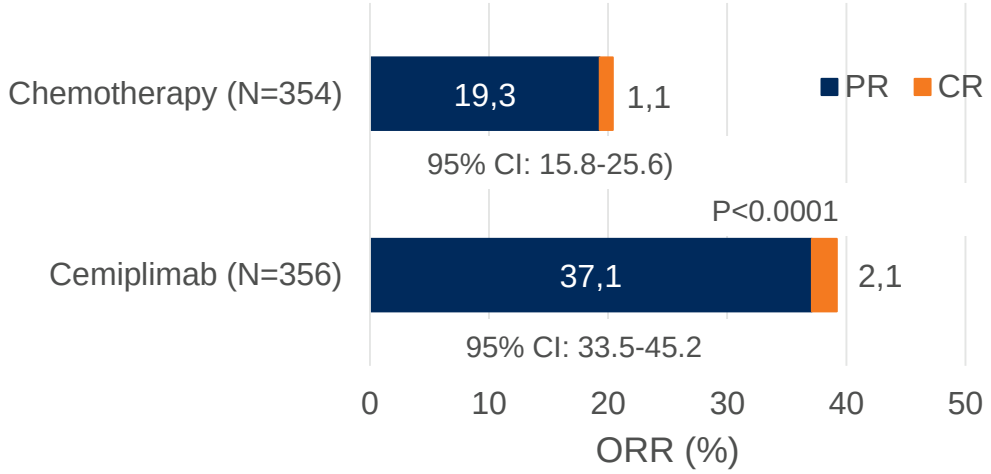
EMPOWER-Lung 1 Results - efficacy

Tumor response and duration of response (DOR)

ITT population



PD-L1 ≥50% ITT



N (%), unless stated	Cemiplimab ITT (N=356)	Chemotherapy ITT (N=354)	Cemiplimab PD-L1 ≥50% ITT (N=283)	Chemotherapy PD-L1 ≥50% ITT (N=280)
Median DOR, months (95% CI)	21.0 (14.9-NE)	6.0 (4.3-6.4)	16.7 (12.5-22.8)	6.0 (4.3-6.5)
Median observed time to response, months (range)	2.1 (1.4-10.4)	2.1 (1.4-6.7)	2.1 (1.4-10.4)	2.1 (1.4-6.3)

DOR: Duration of response. ORR: Objective response rate. ITT: Intention to treat. CI: Confidence interval.
Sezer, A. et al, 2020. Abstract LBA52 presented at ESMO 2020

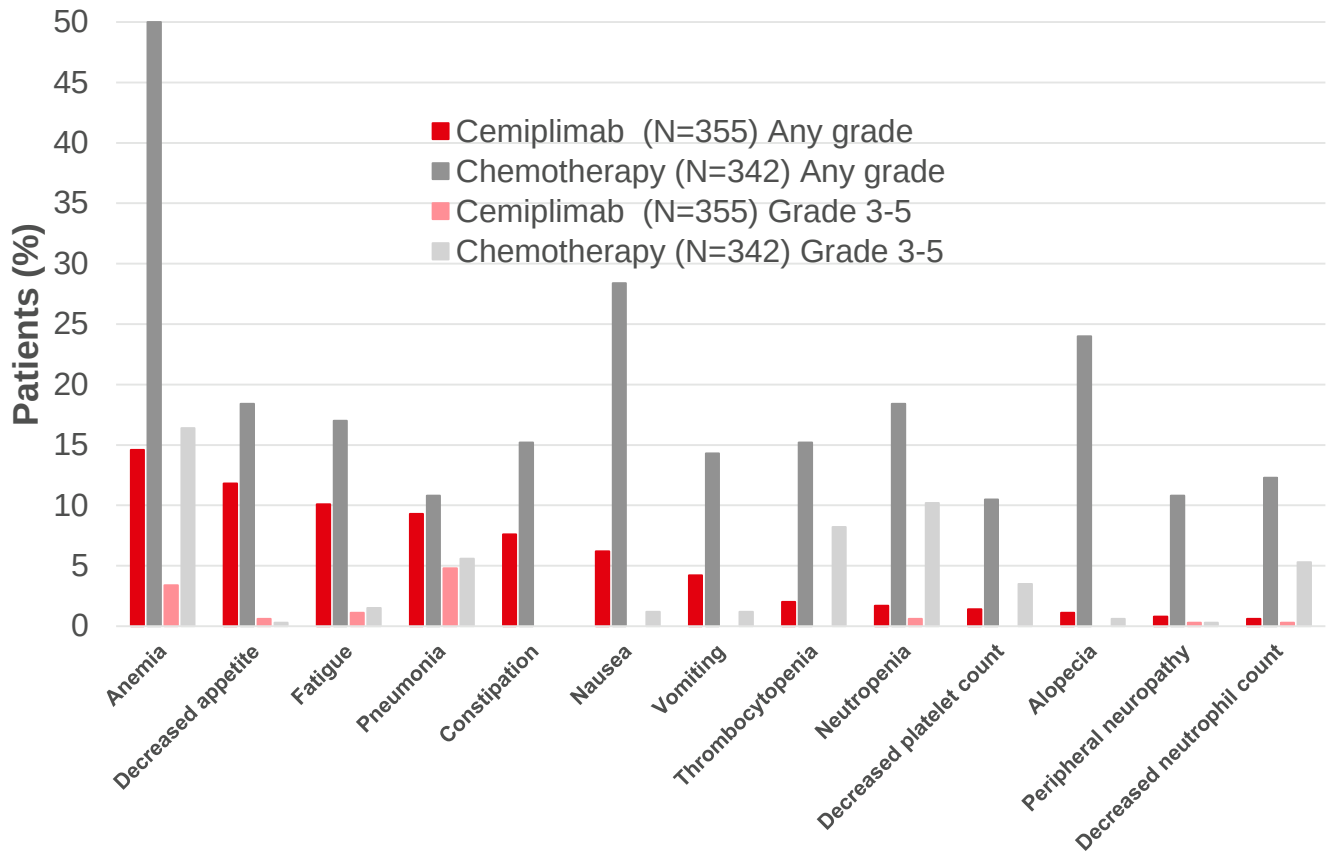
EMPOWER-Lung 1 Results – Safety and tolerability

Safety summary

N (%), unless stated	Cemiplimab (N=355)		Chemotherapy (N=342)	
Median duration of exposure (range), weeks	27.3 (0.3-115.0)		17.7 (0.6-86.7)	
TEAEs, regardless of attribution	**Any grade**	**Grade 3-5**	**Any grade**	**Grade 3-5**
Overall	313 (88.2)	132 (37.2)	322 (94.2)	166 (48.5)
Led to discontinuation	23 (6.5)	15 (4.2)	14 (4.1)	8 (2.3)
Led to death	34 (9.6)	34 (9.6)	31 (9.1)	31 (9.1)
TRAEs				
Overall	204 (57.5)	50 (14.1)	303 (88.6)	134 (39.2)
Led to discontinuation	18 (5.1)	9 (2.5)	12 (3.5)	8 (2.3)
Led to death	9 (2.5)	9 (2.5)	7 (2.0)	7 (2)
Sponsor-identified immine-related AEs				
Overall	62 (17.5)	13 (3.7)	8 (2.3)	1 (0.3)
Led to discontinuation	9 (2.5)	5 (1.4)	0	0
Led to death	1 (0.3)	1 (0.3)	0	0

TRAEs in ≥50% of patients in either arm

- Overall, 88.2% patients had an any-grade TRAE in the cemiplimab arm vs 94.2% in the chemotherapy arm



TEAE: Treatment emergent adverse event. TRAE: Treatment related adverse event. AE: Adverse event.
Sezer, A. et al, 2020. Abstract LBA52 presented at ESMO 2020

EMPOWER-Lung 1 Conclusions

- EMPOWER-Lung 1 met its primary and secondary endpoints
  - Cemiplimab monotherapy significantly improved OS and PFS (primary endpoints) vs chemotherapy in patients with advanced NSCLC with PD-L1 ≥50%
  - Cemiplimab produced higher ORR and longer DOR vs chemotherapy
  - Cemiplimab produced early and increasing improvements from baseline in global health status and HRQoL (data not shown)
- Significant improvement in OS achieved despite high crossover rate (74%)
- Increasing PD-L1 expression levels correlated with better outcomes with cemiplimab but not chemotherapy
- Despite substantially longer exposure to cemiplimab, the safety profile and patient-reported HRQoL support the positive benefit-risk profile of cemiplimab
- **Taken together, these data provide rationale for cemiplimab as a new 1L monotherapy option for patients with advanced NSCLC with PD-L1 ≥50%**

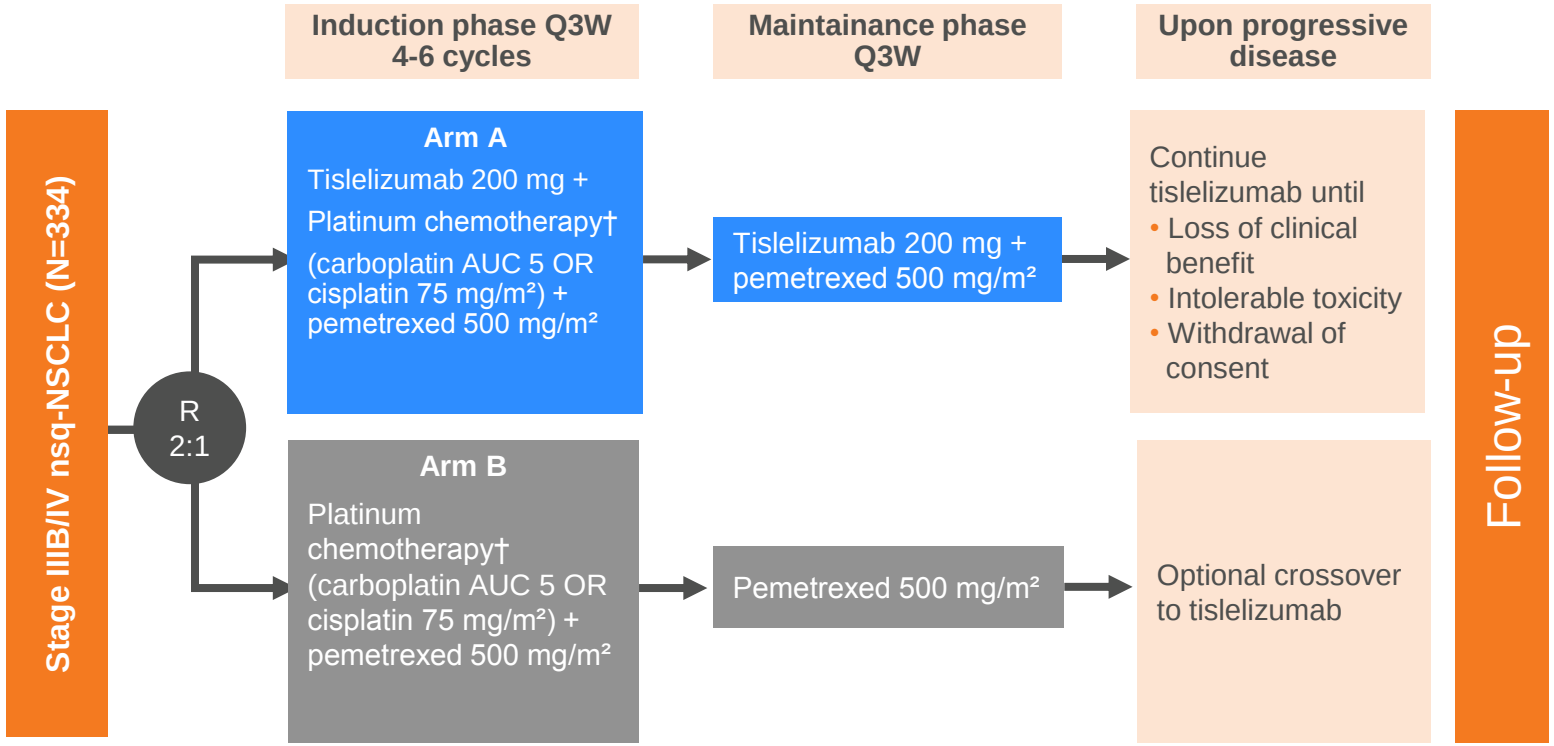
OS: Overall survival. PFS: Progression free survival. NSCLC: Non small cell lung cancer. ORR: Objective response rate. DOR: Duration of response HRQoL: health-related quality of life
Sezer, A. et al, 2020. Abstract LBA52 presented at ESMO 2020

RATIONALE 304

PD-1 inhibitor tislelizumab in Nonquamous NSCLC

RATIONALE 304 Study design

A phase 3, open-label, multicenter, randomized study to evaluate efficacy and safety of PD-1 inhibitor tislelizumab in combination with platinum (cisplatin or carboplatin) and pemetrexed vs platinum and pemetrexed alone as first-line treatment in patients with stage IIIB or IV nonsquamous (nsq)-NSCLC



Primary objective

- Compare progression free survival (PFS), assessed by the Independent Review Committee (PFSIRC), between tislelizumab plus platinum-pemetrexed (Arm A) and platinum-pemetrexed alone (Arm B)

Additional objectives

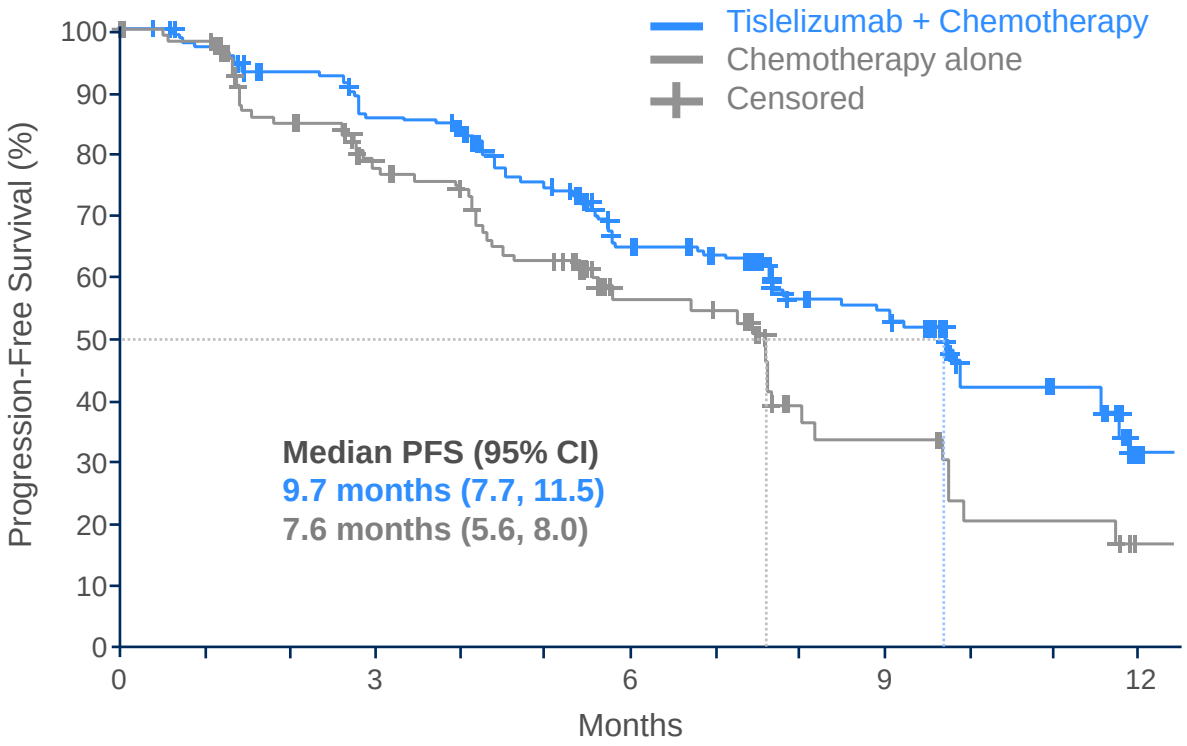
- Investigator assessed PFS (PFSINV)
- IRC assessed objective response rate (ORRIRC), disease control rate (DCRIRC), and duration of response (DORIRC)
- Overall survival (OS) and safety/tolerability of study treatment

PD-1: Programmed cell death protein-1. NSCLC: Non-small cell lung cancer. Q3W: Every 3 weeks. R: Randomized. PD-L1: Programmed death ligand 1. TEAE: Treatment emergent adverse event. ECG: Electrocardiogram. RECIST: Response Evaluation Criteria in Solid Tumors. †Investigators choice

Lu, S. et al, 2020. Poster 1263P presented at ESMO 2020.

RATIONALE 304 Results - efficacy

Progression-free survival by IRC (ITT Analysis Set)



No. at risk				
223	176	106	59	8
111	69	30	12	2

	Tislelizumab + Chemotherapy	Chemotherapy alone
Events	**46.6%**	**49.5%**
	HR (95% CI) = 0.645 (0.462, 0.902) *P* = 0.0044	
Median PFS (95% CI)	**9.7 months** (7.7, 11.5)	**7.6 months** (5.6, 8.0)

- **PFS_{IRC} significantly longer with tislelizumab in combination with chemotherapy vs chemotherapy alone**
- Similar median PFS results observed for Arm A vs Arm B (HR=0.561 [95% CI: 0.411,0.767]; P=0.0001) when assessed by investigator

PFS: Progression free survival:IRC: Independent review committee. ITT: Intention to treat.. CI: Confidence interval. HR, hazard ratio.
Lu, S. et al, 2020. Poster 1263P presented at ESMO 2020.

RATIONALE 304 Results - efficacy

PFS by IRC (ITT Analysis Set)

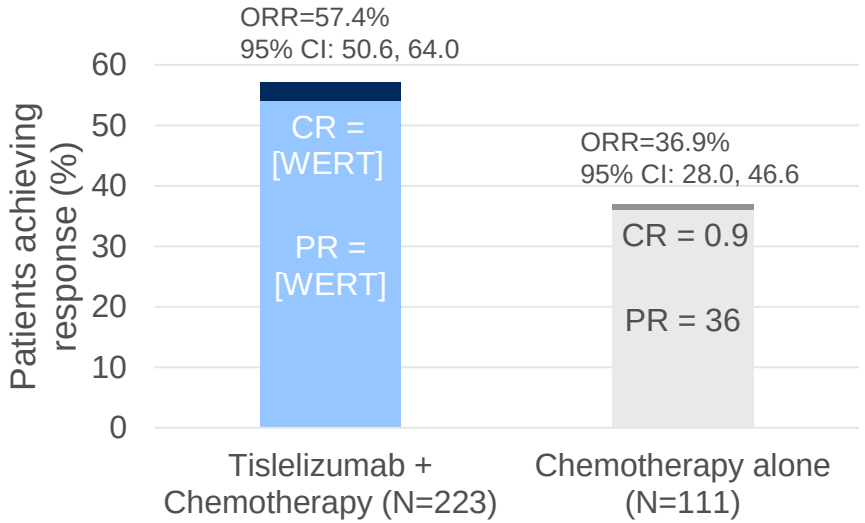
		Events/Patients (N)	Hazard Ratio (95% CI)
Overall		159/334	0.645 (0.462, 0.902)
Age	<65 years	112/237	0.606 (0.403, 0.911)
	≥65 years	47/97	0.727 (0.407, 1.297)
Sex	Female	43/87	0.946 (0.487, 1.840)
	Male	116/247	0.538 (0.367, 0.789)
ECOG performance status	0	34/78	0.834 (0.386, 1.800)
	1	125/256	0.601 (0.416, 0.868)
Smoking status	Never	56/121	1.075 (0.596, 1.940)
	Current or former	103/213	0.466 (0.311, 0.697)
Disease stage	IIIB	30/61	0.664 (0.319, 1.379)
	IV	129/273	0.632 (0.436, 0.917)
Liver metastasis	Yes	21/37	0.370 (0.153, 0.898)
	No	138/297	0.729 (0.505, 1.052)
PD-L1 expression in TC	<1%	78/144	0.758 (0.469, 1.224)
	≥1%	81/190	0.549 (0.347, 0.869)
	1-49%	36/80	1.058 (0.507, 2.209)
	≥50%	45/110	0.308 (0.167, 0.567)
ALK rearrangement	Negative	119/245	0.636 (0.434, 0.930)
	Unknown	40/89	0.669 (0.345, 1.297)

- **Subgroup analyses of prespecified demographic and baseline disease characteristics indicated consistent PFS benefit observed across most subgroups analyzed**
- With >75% of patients censored in both arms, median OS was not reached in either arm

IRC: Independent review committee. ITT: Intention to treat. ECOG, Eastern cooperative oncology group. PFS: Progression free survival. OS: Overall survival.
Lu, S. et al, 2020. Poster 1263P presented at ESMO 2020.

RATIONALE 304 Results - efficacy

Best overall response per IRC



Disease control rate (95%) CI	**89.2%** (84.4, 93.0)	81.1% (72.5, 87.9)
Duration of response, median (95% CI)	**8.5 months** (6.80, 10.58)	**6.0 months** (4.99, NE)

- **Higher ORR_{IRC} and DCR_{IRC} observed in the tislelizumab plus chemotherapy arm vs chemotherapy alone**
- Among 128 responders with tislelizumab combination therapy, median DOR_{IRC} was 8.5 months (95% CI: 6.80, 10.58)
- In the 41 patients who achieved a response with chemotherapy alone, median DOR_{IRC} was 6.0 months (95% CI: 4.99, NE)
- At data cut-off, >62% of patients were censored in each arm, suggesting DOR_{IRC} was not fully mature in either arm

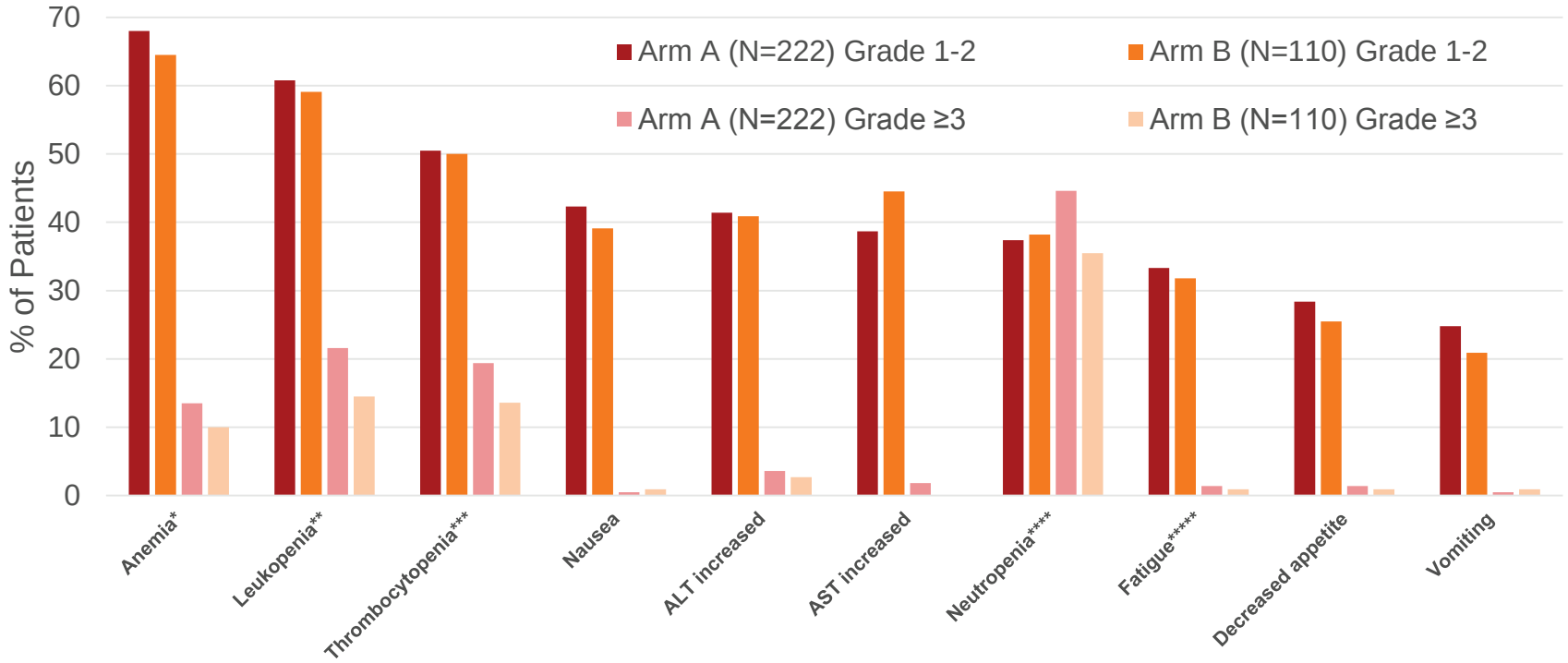
IRC: Independent review committee. ORR: Objective response rate. CI: Confidence interval. CR: Complete response. DCR: Disease control rate. DOR: Duration of response. IRC: Independent Review Committee. NE: Not estimable. ORR: Objective response rate. PR: Partial response. NE: Not estimable

Lu, S. et al, 2020. Poster 1263P presented at ESMO 2020.

RATIONALE 304 Results – safety and tolerability

- Most commonly reported TRAEs were hematologic in nature (e.g., anemia, leukopenia, thrombocytopenia) and primarily mild-to-moderate in severity

Incidence of TRAEs occurring in ≥20% of patients treated with tislelizumab plus chemotherapy or chemotherapy alone



Safety and tolerability Arm A vs Arm B	Arm A N=222	Arm B N=111
≥1 TEAE **%** (N)	**100** (222)	**99.1** (109)
Grade ≥3 TEAEs **%** (N)	**67.6** (150)	**53.6** (59)
TEAEs leading to permanent discontinuation of any component of study drug **%** (N)	**25.7** (57)	**9.1** (10)

TEAE: Treatment emergent adverse event. PFS: Progression free survival IRC: Independent review committee. OS: Overall survival. ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. *Anemia included reports of anemia, hemoglobin decreased, and red blood cell count decreased. ** Leukopenia included reports of white blood cell count decreased and leukopenia. ***Thrombocytopenia included reports of platelet count decreased and thrombocytopenia. ****Neutropenia included reports of neutrophil count decreased and neutropenia. *****Fatigue included asthenia, fatigue, and malaise.

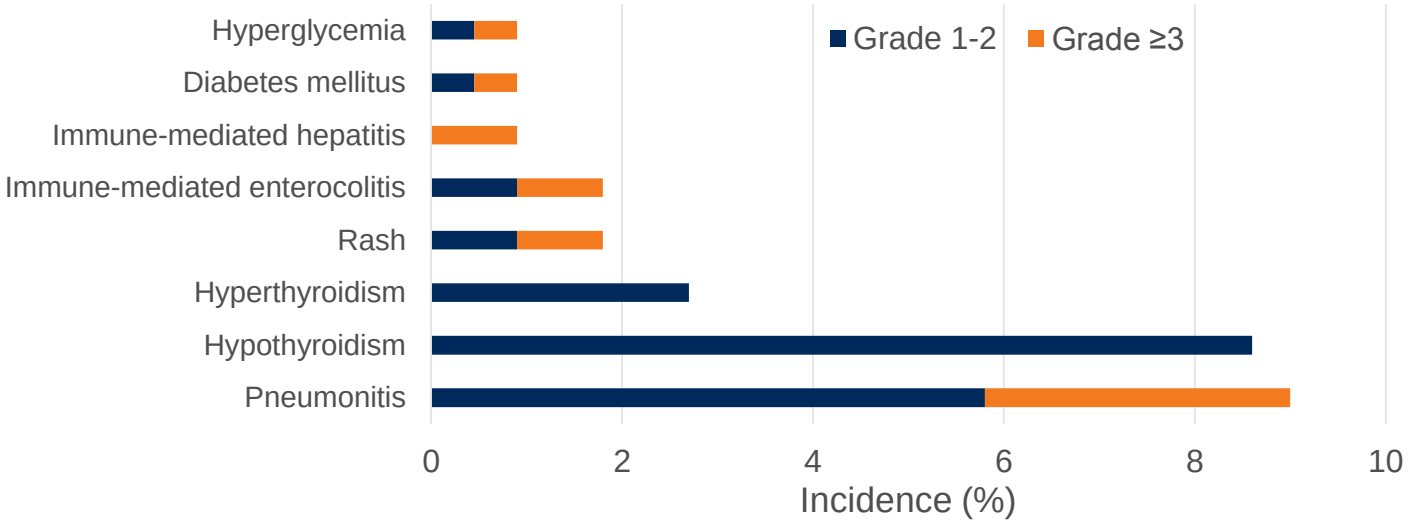
Lu, S. et al, 2020. Poster 1263P presented at ESMO 2020.

RATIONALE 304 Results – safety and tolerability

Across the entire study, 9 patients experienced a TEAE that led to death

- **Arm A**: Total 7 fatal TEAEs; pneumonitis (N=3), asphyxia, atrial fibrillation, cerebellar hemorrhage, and unspecified death (N=1 each)
- **Arm B:** Total 2 fatal TEAEs; pneumonitis and embolism (N=1 each)
- Four patients experienced AEs leading to death considered by investigator as related to any component of study treatment (1%; N=3 [A]; N=1 [B]; all were pneumonitis)

Immune-mediated AEs by preferred term occurring in ≥2 patients treated with combination therapy



- Immune-mediated AEs reported in 57 patients (25.7%) in Arm A; 30 of which treated with systemic corticosteroids/immunosuppressive drugs
- Most commonly reported immune-mediated AEs were:
  - Pneumonitis (N=20, 9.0%)
  - Hypothyroidism (n=19, 8.6%)
  - Hyperthyroidism (n=6, 2.7%)
- Most were mild to moderate in severity

TEAE: Treatment emergent adverse event. AE: Adverse event.
Lu, S. et al, 2020. Poster 1263P presented at ESMO 2020.

RATIONALE 304 Conclusions

- Addition of tislelizumab resulted in significantly improved PFS_{IRC} (9.7 months vs 7.6 months; P=0.0044, HR=0.645 [95% CI: 0.462, 0.902]) as well as higher ORR_{IRC} and longer DOR_{IRC} than observed with chemotherapy alone in patients with advanced nsq-NSCLC
- First-line treatment with tislelizumab in combination with platinum and pemetrexed was generally well tolerated
  - Most AEs mild or moderate in severity and manageable
  - No new safety signals identified with addition of tislelizumab to standard chemotherapy

- **Results from this pivotal phase 3 study support tislelizumab in combination with platinum and pemetrexed as a potential new standard for first-line treatment of advanced nsq-NSCLC**

PFS: Progression free survival. IRC: Independent review committee. ORR. Objective response rate. DOR: Duration of response. nsq-NSCLC: Non-small cell lung cancer. AE: Adverse event.
Lu, S. et al, 2020. Poster 1263P presented at ESMO 2020.

RATIONALE 307

Tislelizumab, a PD-1 inhibitor, in squamous NSCLC: Updated analysis

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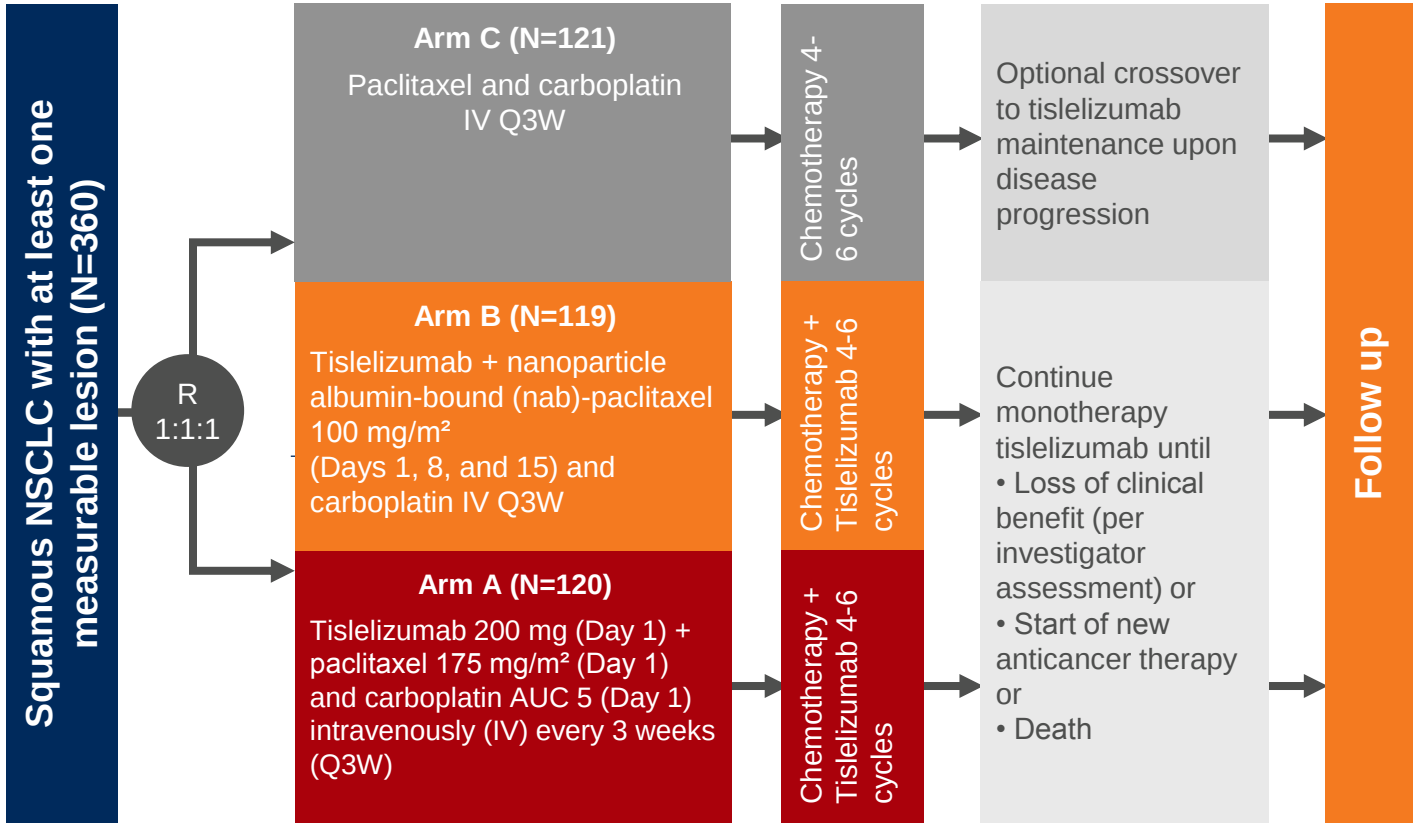
RATIONALE 307 Study design

A pivotal open-label phase 3 clinical trial conducted in China of tislelizumab in combination with platinum-doublet chemotherapy as first-line treatment for patients with advanced squamous NSCLC



Primary objective

- Compared progression-free survival assessed by Independent Review Committee (PFSIRC) per RECIST v1.1, between tislelizumab combined with either paclitaxel and carboplatin (Arm A) or nab-paclitaxel and carboplatin (Arm B), and paclitaxel and carboplatin alone (Arm C)

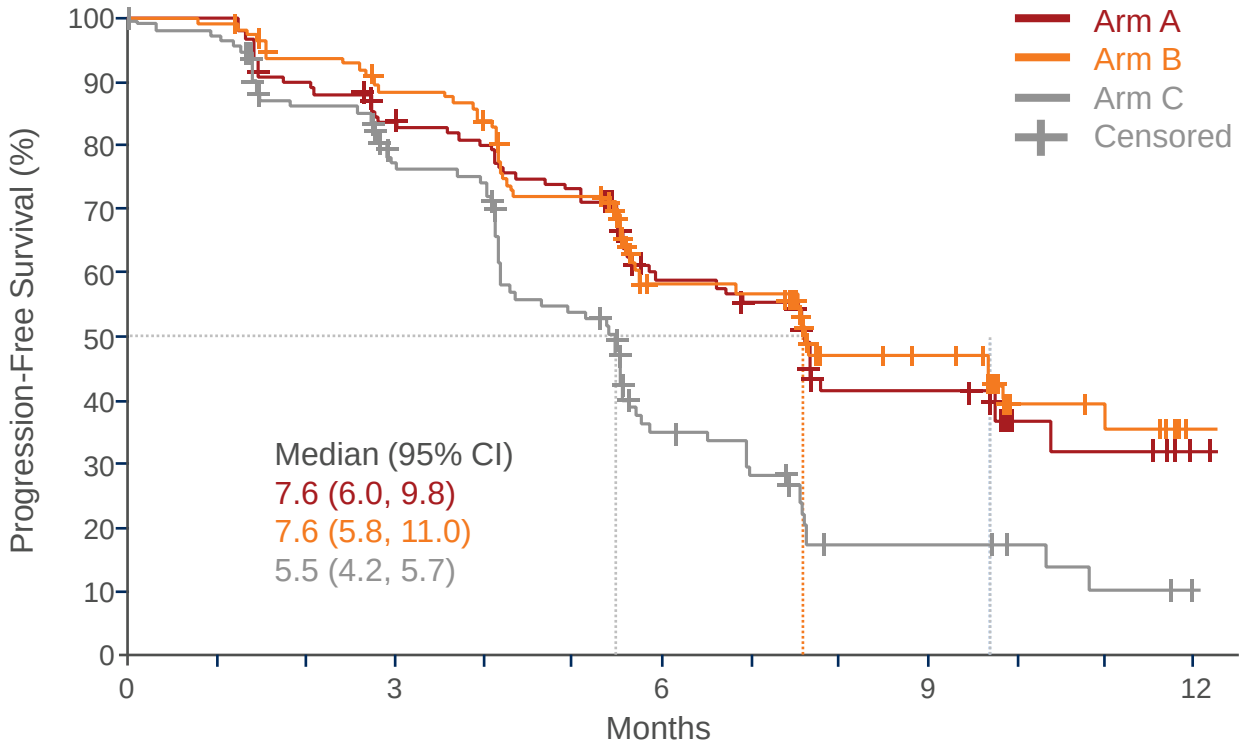
Additional objectives

- Compared overall survival (OS) as well as duration of response (DOR) and objective response rate (ORR) by IRC
- PFS assessed by investigators (PFSINV)
- Safety/tolerability profile and association of bloodTMB (bTMB) with efficacy between Arms A or B and Arm C

PD-1: Programmed cell death protein-1. PD-L1: Programmed death ligand 1. NSCLC: Non-small cell lung cancer. Q3W: Every 3 weeks. R: Randomized. ITT: Intention to treat. PFS: Progression free survival. bTMB: blood tumor mutational burden. TEAE: Treatment emergent adverse event. AE: Adverse event. IV: Intravenous. AUC: Area under the curve.
Wang, J. et al, 2020. Poster 1264P presented at ESMO 2020.

RATIONALE 307 Results - efficacy

Progression-Free Survival by IRC



No. at risk				
120	95	50	23	1
119	98	47	23	1
121	74	27	10	0

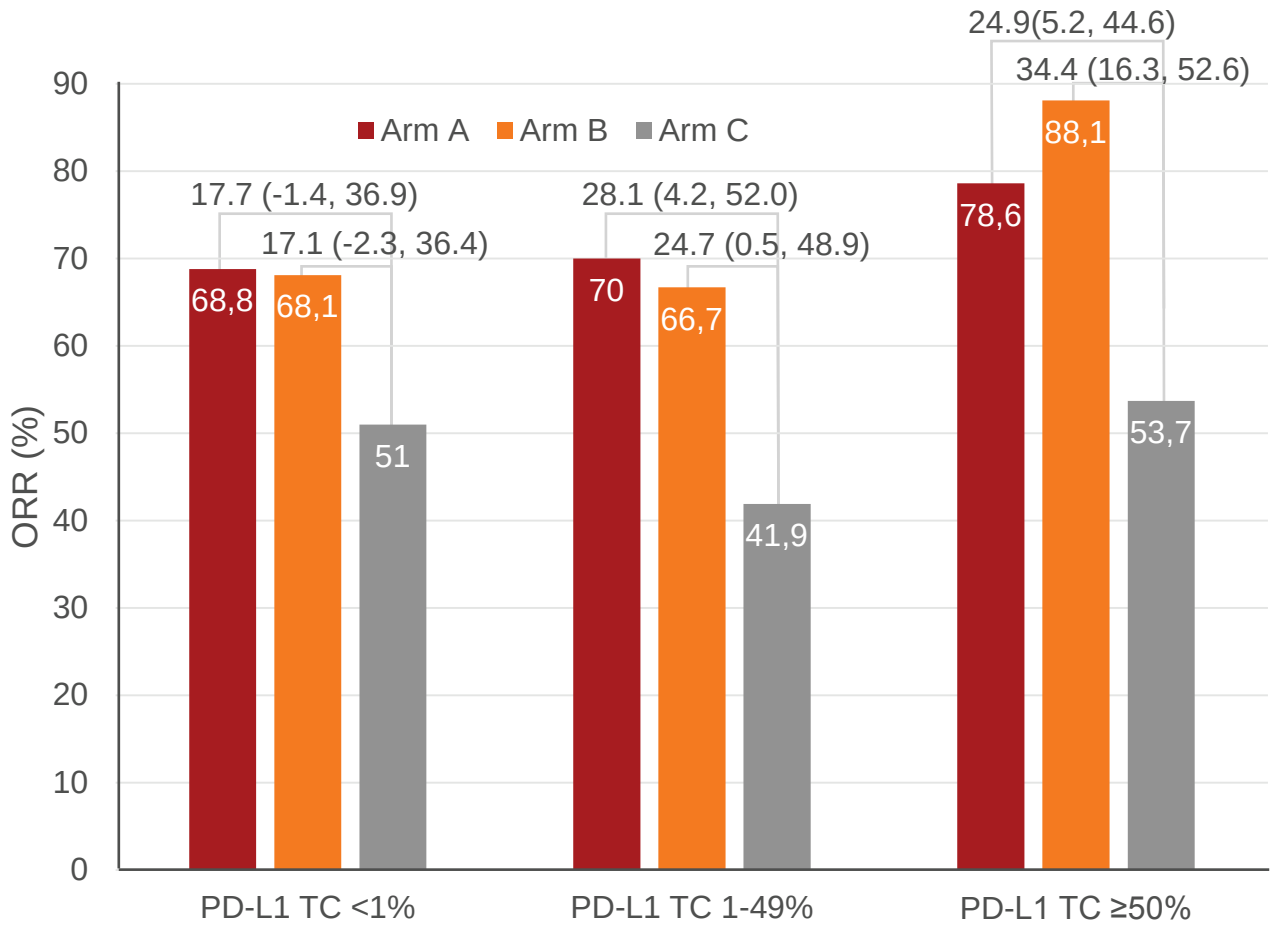
	Arm A (Tislel + Chemo)	Arm B (Tislel + Chemo)	Arm C (Chemo only)
Events Stratified HR (95% CI) Log-rank test *P*-value	**50.0%** 0.524 (0.370, 0.742) 0.0001	**47.1%** 0.478 (0.336, 0.679) <0.0001	**62.8%**
Median PFS 95% CI	**7.6 months** 6.0, 9.8	**7.6 months** 5.8, 11.0	**5.5 months** (4.2, 5.7)

- **Median PFS_{IRC} was 7.6 months (95% CI: 6.0, 9.8) in Arm A and 7.6 months (95% CI: 5.8, 11.0) in Arm B; both significantly longer than median PFS in Arm C** (5.5 months [95% CI: 4.2, 5.7])
- Similar results were reported for PFS assessed by investigators. Median PFS_{INV} for Arm A vs Arm C (P<0.0001; HR: 0.335 [0.231, 0.487]) and Arm B vs Arm C (P<0.0001; HR: 0.354 [0.243, 0.516])

IRC: Independent review committee. PFS: Progression free survival. CI: Confidence interval. HR, hazard ratio. INV: Investigator.
Wang, J. et al, 2020. Poster 1264P presented at ESMO 2020.

RATIONALE 307 Results - efficacy

Objective response rate by PD-L1 expression as assessed by IRC (ORR_{IRC})



- Arm A: Overall ORR 73% (95% CI: 63.6, 80.3)
- Arm B: Overall ORR 75% (95% CI: 66.0, 82.3)
- Both higher than ORR in Arm C (50% [95% CI: 40.4, 58.8])

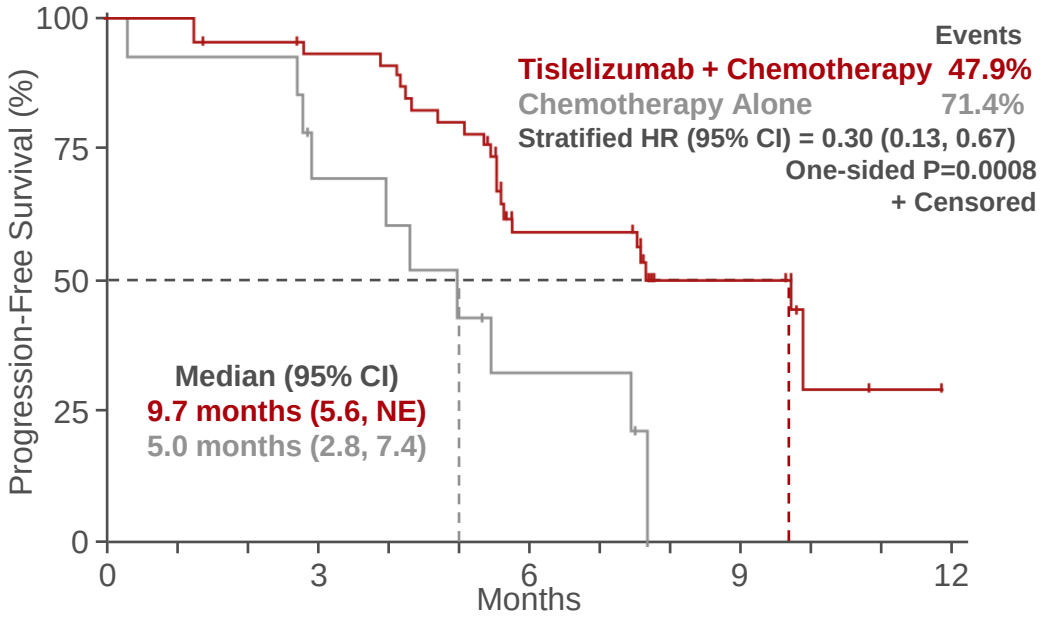
- **Tislelizumab plus chemotherapy demonstrated increased ORR in Arm A and B vs chemotherapy alone regardless of PD-L1 expression level**
- Duration of response was longer in both tislelizumab-containing arms vs chemotherapy alone
- OS not reached at median follow up 8.6 months

ORR: Objective response rate. PD-L1: Programmed death ligand. CI: Confidence interval. Data presented above the bars are the treatment differences (95% CI)
Wang, J. et al, 2020. Poster 1264P presented at ESMO 2020.

RATIONALE 307 Results - efficacy

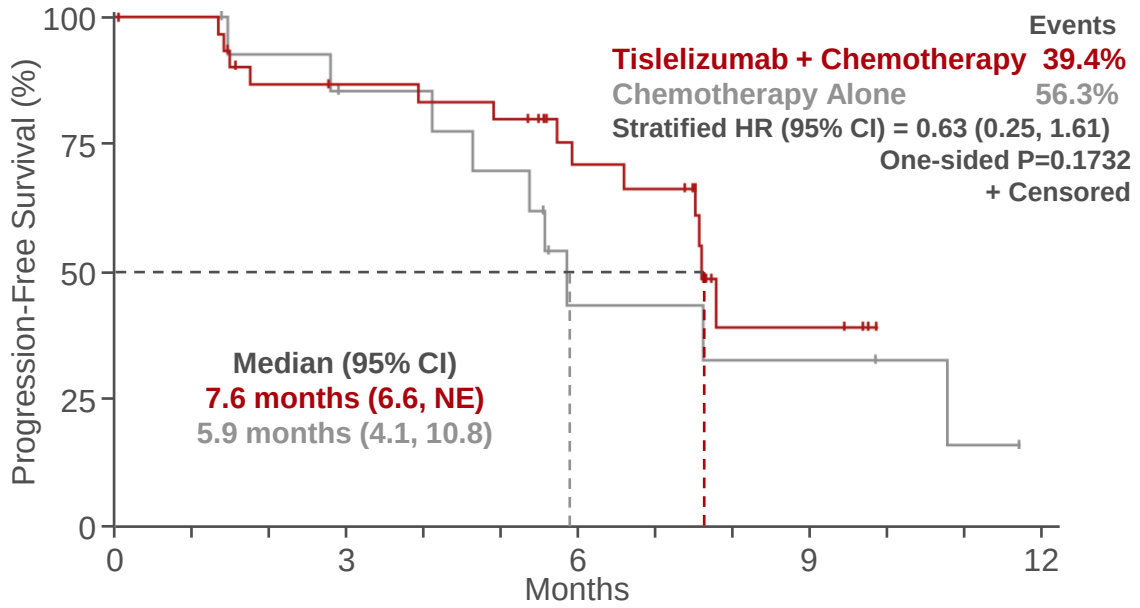
Progression-free survival (PFS_{IRC}) by blood tumor mutational burden (bTMB) status

Patients with bTMB-High (≥6 mutations/Mb) status



No. at risk				
48	43	22	10	0
14	8	3	0	0

Patients with bTMB-Low (<6 mutations/Mb) status



No. at risk				
33	25	16	4	0
16	11	4	3	0

ORR: Objective response rate. PD-L1: Programmed death ligand 1. CI: Confidence interval. HR: Hazard ratio. bTMB: Blood tumor mutational burden. IRC: independent review committee

Wang, J. et al, 2020. Poster 1264P presented at ESMO 2020.

RATIONALE 307 Results – efficacy

Exploratory analysis of blood tumor mutational burden (bTMB)

- Across all 3 cohorts, 111 patients had evaluable bTMB (Arm A and B, n=81; Arm C, n=30)
  - Due to limited sample size, Arm A and Arm B were combined and analyzed as tislelizumab plus chemotherapy vs chemotherapy alone to balance baseline characteristics and efficacy
- Using a cut-off of six mutations/Mb, tislelizumab plus chemotherapy demonstrated ORR and PFS benefit vs chemotherapy in both bTMB-high and bTMB-low subgroups
- With an optimized bTMB cutoff of six mutations/Mb, combination therapy improved PFS over chemotherapy in patients with both high- and low-bTMB

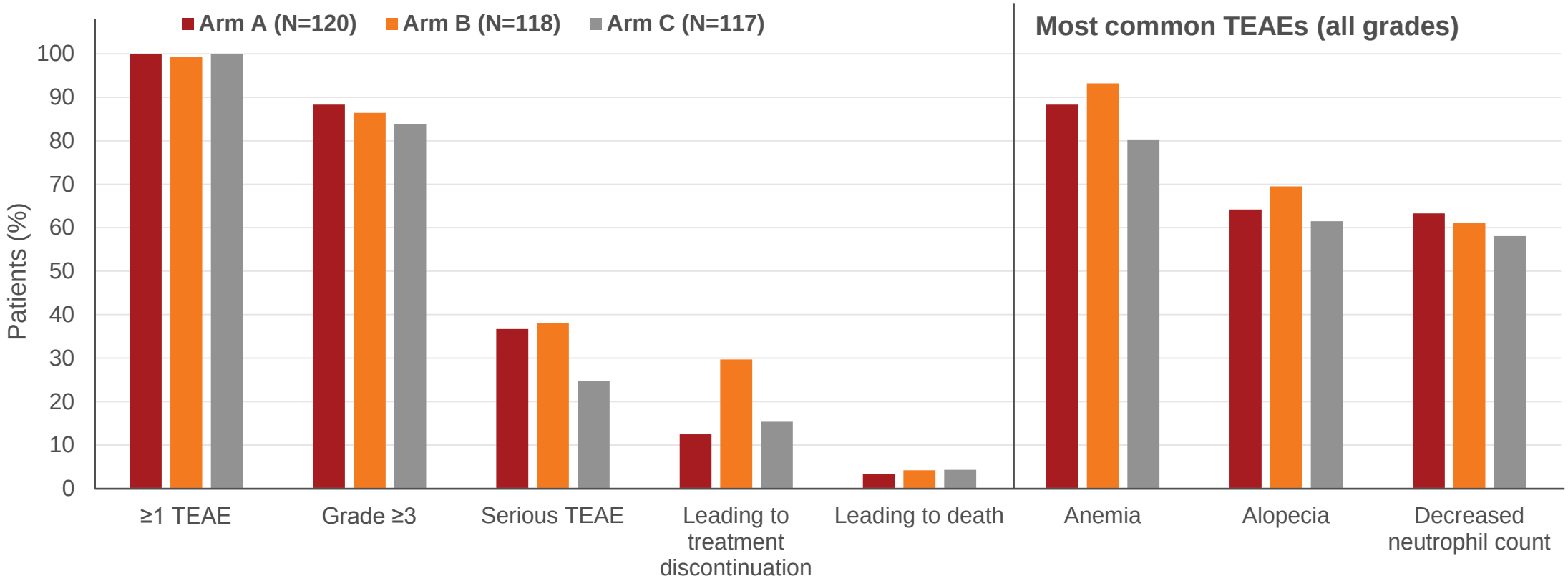
Interaction analysis for bTMB as a Predictive Biomarker

Tislelizumab + Chemotherapy vs Chemotherapy alone	bTMB-High (≥6 mutations/ Mb)	bTMB-Low (<6 mutations/ Mb)	Ratio of bTMB-High vs bTMB-Low	P-value of interaction: odds ratio
ORR Odds ratio	4.04 (1.13, 14.41)	0.63 (0.19, 2.18)	6.38 (1.07, 37.88)	0.042
PFS Hazard ratio	0.30 (0.13, 0.67)	0.63 (0.25, 1.61)	0.47 (0.14, 1.63)	0.234

bTMB: Blood tumor mutational burden. PFS: Progression free survival.ORR: Objective response rate. CI: Confidence interval. Mb: Megabase.
Wang, J. et al, 2020. Poster 1264P presented at ESMO 2020.

RATIONALE 307 Results – safety and tolerability

Summary of treatment emergent adverse events (TEAEs)



TEAE: Treatment emergent adverse event. TRAE: Treatment related adverse event. AE: Adverse event IRC: Independent review committee. PFS: Progression free survival. CI: Confidence interval. HR, hazard ratio. INV: Investigator.

Wang, J. et al, 2020. Poster 1264P presented at ESMO 2020.

RATIONALE 307 Results – safety and tolerability

Treatment-related adverse event (TRAEs)

- TRAEs occurred in 353 patients (99.4%); the most commonly reported TRAEs were hematological (e.g., anemia, alopecia, and decreased neutrophil count)
- Most immune-mediated AEs were mild or moderate in severity, did not require corticosteroid treatments, and did not lead to discontinuation of any treatment component

N (%)	Arm A (N=120)	Arm B (N=118)	Arm C (N=117)
Serious TRAEs	27 (22.5)	28 (23.7)	17 (14.5)
Most common serious TRAEs	Decreased neutrophil count: 4 (3.3) Febrile neutropenia: 2 (1.7) Pneumonitis: 3 (2.5)	Decreased neutrophil count: 4 (3.4) Febrile neutropenia: 3 (2.5)	Thrombocytopenia: 3 (2.6)
TRAEs leading to death (None solely attributed to tislelizumab)	1 (0.8)	2 (1.7)	3 (2.6)
Potential immune-mediated AEs	62 (51.7)	56 (47.5)	22 (18.8)
Most common potential immune-mediated AEs Hyperglycemia Hypothyroidism Pneumonia	 19 (15.8) 14 (11.7) 13 (10.8)	 11 (9.3) 15 (12.7) 8 (6.8)	 Not specified

TRAE: Treatment-related adverse event. AE: Adverse event.
Wang, J. et al, 2020. Poster 1264P presented at ESMO 2020.

RATIONALE 307 Conclusions

- Tislelizumab plus chemotherapy resulted in significantly improved PFS, higher ORR, and longer DOR vs chemotherapy alone in patients with advanced squamous NSCLC, addressing a high unmet need in this patient population
- Addition of tislelizumab to standard chemotherapy demonstrated clinical benefit across all subgroups, regardless of PD-L1 expression and bTMB status
- First-line treatment with tislelizumab in combination with paclitaxel and carboplatin or nab-paclitaxel and carboplatin was generally well tolerated
  - Incidence and frequency of TEAEs (including grade ≥3) were similar across the three arms
  - Most AEs were mild or moderate in severity and manageable
- **Results from this pivotal phase 3 study support tislelizumab in combination with paclitaxel and carboplatin or nab-paclitaxel and carboplatin as a potential new standard for first-line treatment of advanced squamous NSCLC**

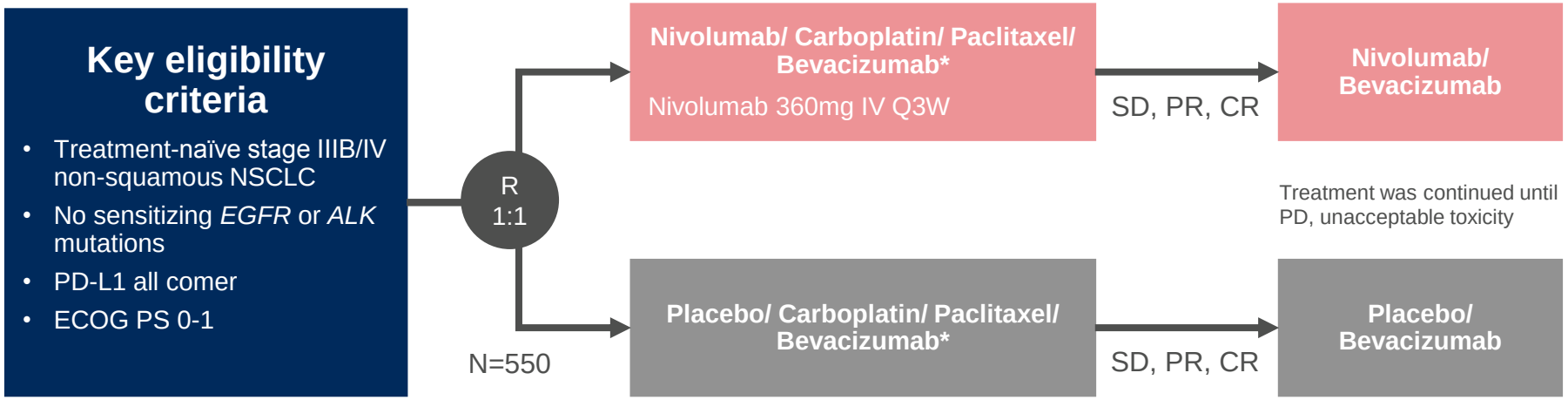
PFS: Progression free survival. ORR. Overall response rate. DOR: Duration of response. NSCLC: Non-small cell lung cancer. PD-L1: : Programmed death ligand 1. TEAE: Treatment emergent adverse event. AE: Adverse event. bTMB: blood tumor mutational burden.
Wang, J. et al, 2020. Poster 1264P presented at ESMO 2020..

TASUKI-52

PD-1 inhibitor nivolumab + chemotherapy + bevacizumab for 1L treatment of nonsquamous NSCLC

TASUKI-52 Study design

Randomized phase III trial of nivolumab in combination with carboplatin, paclitaxel, and bevacizumab as first line treatment for patients with advanced or recurrent non-squamous NSCLC



Primary endpoint:
- PFS assessed by IRRC

Secondary endpoint
- OS, ORR, safety

Stratification factors
- PD-L1 (IHC 28-8): ≥50%, 1%-49%, <1% or intermediate
- ECOG PS: 0, 1
- Sex: Male, female

*Carboplatin (AUC6), paclitaxel (200mg/m^2) Q3W for up to 6 cycles.

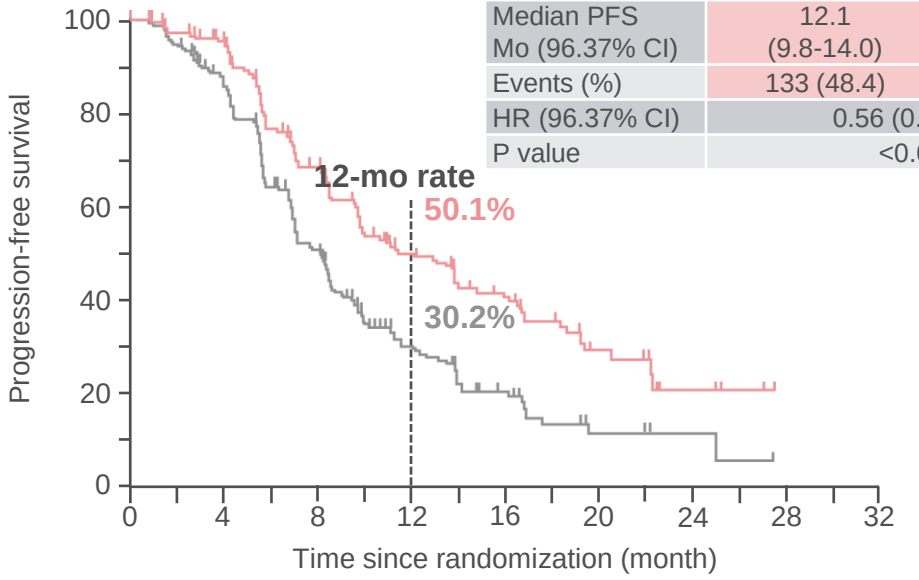
NSCLC: Non small cell lung cancer. PFS: Progression-free survival. IRRC: Independent Radiographic Review Committee. IV: Intravenous. SD: Stable disease. PR: Partial response. CR: Complete response. PD: progressive disease. Q3W: Every 3 weeks. ECOG: Eastern Cooperative Oncology Group.
Lee, J-S. et al, 2020. Abstract LBA54 presented at ESMO 2020

TASUKI-52 Results – efficacy

Primary endpoint – PFS at interim analysis (IRRC)

- **Nivolumab arm demonstrated significant and clinically meaningful PFS improvements vs placebo arm**
- 4 months median PFS improvement
- 19.9% improvement at 12-month PFS rate

	Nivolumab Arm N = 275	Placebo Arm N = 275
Median PFS Mo (96.37% CI)	12.1 (9.8-14.0)	8.1 (7.0-8.5)
Events (%)	133 (48.4)	173 (62.9)
HR (96.37% CI)	0.56 (0.43-0.71)	
P value	<0.0001	

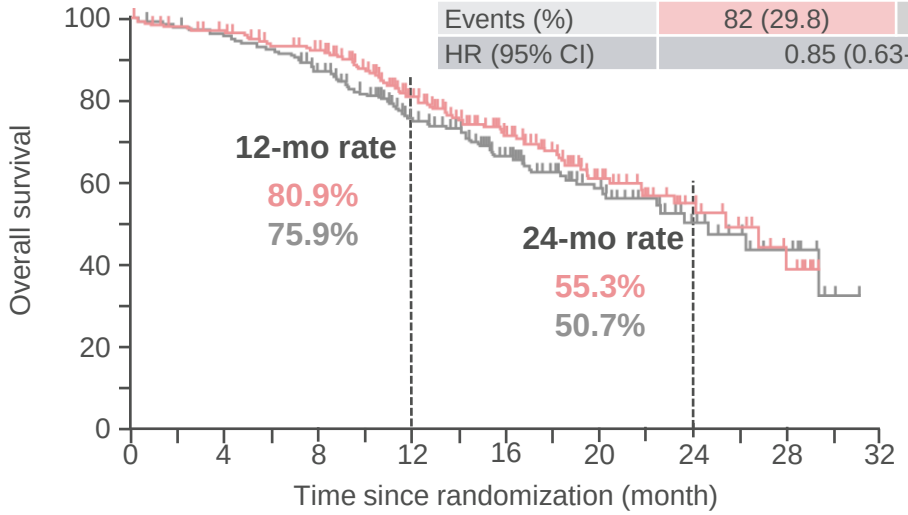


No. at risk									
275	226	145	79	45	15	4	0	0
275	215	104	41	21	4	2	0	0

OS at interim analysis

- OS tended to be longer in the nivolumab group, but data not yet mature
- Long-term follow up required

	Nivolumab Arm N = 275	Placebo Arm N = 275
Median OS Mo (95% CI)	25.4 (21.8-NR)	24.7 (20.2-NR)
Events (%)	82 (29.8)	93 (33.8)
HR (95% CI)	0.85 (0.63-1.14)	



No. at risk									
275	257	234	161	102	57	23	8	0
275	258	224	156	93	52	19	10	0

PFS: Progression-free survival. HR: Hazard ratio. IRRC: Independent Radiographic Review Committee. CI: Confidence interval. OS: Overall survival, NR: not reached

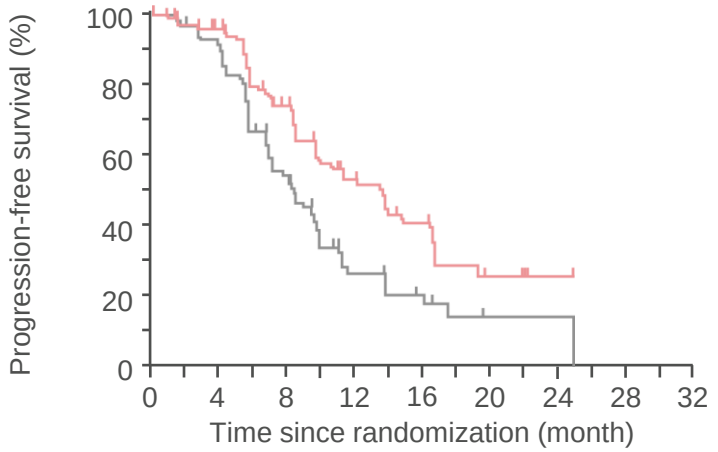
Lee, J-S. et al, 2020. Abstract LBA54 presented at ESMO 2020

TASUKI-52 Results – efficacy

PFS by PD-L1 expression level

- PFS prolonged in nivolumab arm vs placebo arm regardless of PD-L1 status

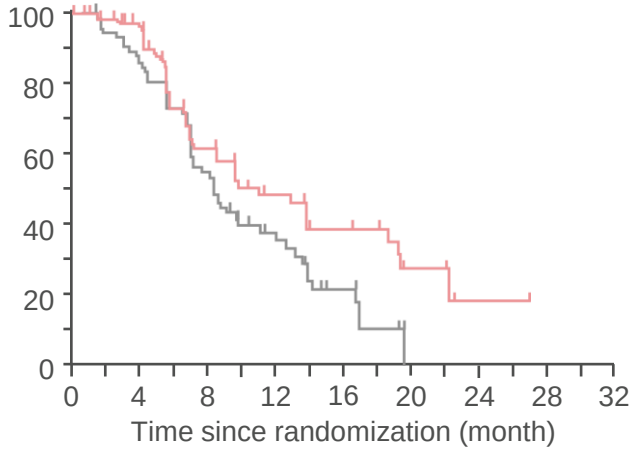
PD-L1 <1% or indeterminate



No. at risk								
120	98	65	34	18	5	1	0	0
120	100	46	14	8	1	1	0	0

	Nivolumab Arm N = 120	Placebo Arm N = 120
Median PFS, mo (95% CI)	13.6 (9.8-16.6)	8.4 (7.0-9.8)
HR (95% CI)	0.55 (0.38-0.78)	

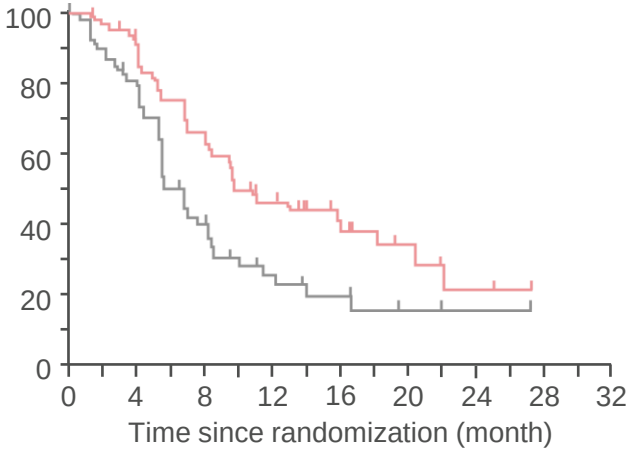
PD-L1 1%−49%



No. at risk								
82	67	39	21	13	4	1	0	0
81	62	35	17	7	0	0	0	0

	Nivolumab Arm N = 82	Placebo Arm N = 81
Median PFS, mo (95% CI)	11.0 (7.2-18.6)	8.4 (7.0-11.1)
HR (95% CI)	0.63 (0.42-0.96)	

PD-L1 ≥50%



No. at risk								
73	61	41	24	14	6	2	0	0
74	53	23	10	6	3	1	0	0

	Nivolumab Arm N = 73	Placebo Arm N = 74
Median PFS, mo (95% CI)	9.9 (8.3-18.3)	6.9 (5.6-8.3)
HR (95% CI)	0.55 (0.36-0.83)	

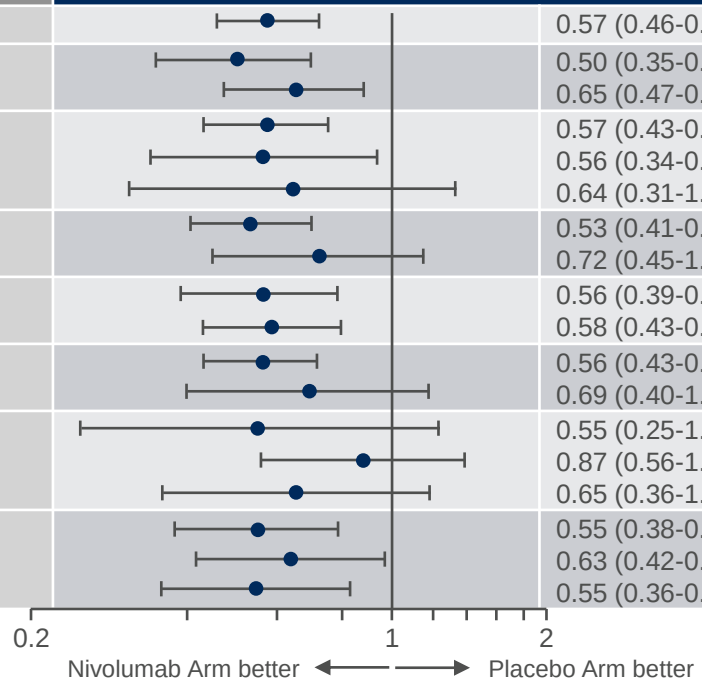
PFS: Progression-free survival. HR: IRRC: Independent Radiographic Review Committee. Hazard ratio. CI: Confidence interval. ECOG: Eastern Cooperative Oncology Group.
Lee, J-S. et al, 2020. Abstract LBA54 presented at ESMO 2020

TASUKI-52 Results – efficacy

PFS in key subgroups

- Consistent PFS benefit in nivolumab arm vs placebo arm across almost all subgroups

Subgroup	Median PFS, mo		Unstratified HR (95% CI)
	Nivolumab Arm N =275	Placebo Arm N = 275	
All randomized (n = 550)	12.1	8.1	0.57 (0.46-0.72)
< 65 years (n = 242)	11.4	7.0	0.50 (0.35-0.69)
≥ 65 years (n = 308)	12.9	8.3	0.65 (0.47-0.88)
Japan (n =371)	13.4	8.2	0.57 (0.43-0.75)
Korea (n = 125)	10.6	7.1	0.56 (0.34-0.93)
Taiwan (n =54)	9.7	8.5	0.64 (0.31-1.32)
Male (n =411)	12.9	7.7	0.53 (0.41-0.69)
Female (n =139)	10.0	8.7	0.72 (0.45-1.15)
ECOG PS 0 (n = 257)	13.8	8.4	0.56 (0.39-0.78)
ECOG PS 1 (n = 293)	9.9	7.6	0.58 (0.43-0.79)
Current / Former smoker (n =435)	13.0	7.7	0.56 (0.43-0.71)
Never smoker (n =115)	9.7	8.7	0.69 (0.40-1.18)
Liver metastases (n = 39)	5.8	5.5	0.55 (0.25-1.23)
Bone metastases (n = 139)	8.3	7.1	0.87 (0.56-1.37)
Brain metastases (n = 77)	10.6	7.1	0.65 (0.36-1.18)
PD-L1 < 1% or indeterminate (n = 240)	13.6	8.4	0.55 (0.38-0.78)
PD-L1 1%−49% (n = 163)	11.0	8.4	0.63 (0.42-0.96)
PD-L1 ≥ 50% (n = 147)	9.9	6.9	0.55 (0.36-0.83)



ORR and DOR (IRRC)

- ORR 11% higher in nivolumab arm vs placebo arm. DOR 4 months longer

	Nivolumab arm N=275	Placebo arm N=275
ORR, N (%)	169 (61.5)	139 (50.5)
Odds ratio	1.55 (1.11-2.17)	
BOR, N (%) CR PR SD PD NE	 14 (5.1) 155 (56.4) 71 (25.8) 5 (1.8) 30 (10.9)	 8 (2.9) 131 (47.6) 108 (39.9) 11 (4.0) 17 (6.2)
DOR, median (range), months	11.0 (1.1*-25.8*)	7.0 (1.2*-26.0*)
Patients with ongoing response at data cutoff, N (%)	61/69 (36.1)	21/39 (15.1)

*Censored

ORR: Objective response rate. DOR: Duration of response. IRRC: Independent Radiographic Review Committee. SD: Stable disease. PR: Partial response. CR: Complete response. PD: Progressive disease. NE: Not evaluable. BOR: Best overall response.

Lee, J-S. et al, 2020. Abstract LBA54 presented at ESMO 2020

TASUKI-52 Results – Safety and tolerability

Summary of treatment related adverse events (TRAEs)

Patients, N (%)	Nivolumab arm N=273	Placebo arm N=275
Any TRAEs	269 (98.5)	274 (99.6)
Any TRAEs Grade 3/4	201 (76.3)	198 (72.0)
Serious TRAEs	114 (41.8)	74 (26.9)
TRAEs leading to discontinuation	45 (16.5)	12 (4.4)
TRAEs leading to dose delay	132 (48.4)	123 (44.7)
TRAEs leading to death	5 (1.8)*	4 (1.5)**

*Treatment related deaths in nivolumab arm (N=5; 1for each event) were due to sepsis, cholangitis, febrile neutropenia, hemoptysis, and pneumonitis. **Treatment related deaths in the placebo arm (N=4); 1 for each event were due to sepsis, intestinal perforation, pneumonia klebsiella, and upper gastrointestinal hemorrhage.

Serious TRAEs and TRAEs leading to treatment discontinuation markedly higher in nivolumab arm vs placebo arm

TRAEs with incidence rate of ≥20%

Patients, n (%)	Nivolumab arm (N=273)		Placebo arm (N=275)	
	Any grade	Grade 3-5	Any grade	Grade 3-5
Alopecia	143 (52.4)	0 (0.0)	150 (54.5)	0 (0.0)
Peripheral sensory neuopathy	120 944.0)	3 (1.1)	118 (42.9)	7 (2.5)
Neutrophil count decreased	116 (42.5)	87 (31.9)	139 (50.5)	98 (25.6)
WBC decreased	93 (34.1)	40 (14.7)	98 (35.6)	41 (14.9)
Constipation	85 (31.1)	3 (1.1)	81 (29.5)	1 (0.4)
Decreased appetite	81 (29.7)	8 (2.9)	96 (34.9)	13 (4.7)
Rash	81 (29.7)	13 (4.8)	40 (14.5)	1 (0.4)
Anemia	78 (28.6)	15 (5.5)	92 (33.5)	17 (6.2)
Arthralgia	69 (25.3)	0 (0.0)	75 (27.3)	2 (0.7)
Nausea	68 (24.9)	3 (1.1)	83 (30.2)	5 (1.8)
Malaise	68 (24.9)	1 (0.4)	71 (25.8)	0 (0.0)
Myalgia	66 (24.2)	0 (0.0)	78 (28.4)	0 (0.0)
Hypertension	65 (23.8)	37 (13.6)	79 (28.7)	42 (15.3)
Proteinurea	65 (23.8)	13 (4.8)	69 (25.1)	10 (3.6)
Neuropathy peripheral	59 (21.6)	1 (0.4)	62 (22.5)	2 (0.7)
Platelet count decreased	59 (21.6)	16 (5.9)	61 (22.5)	6 (2.2)

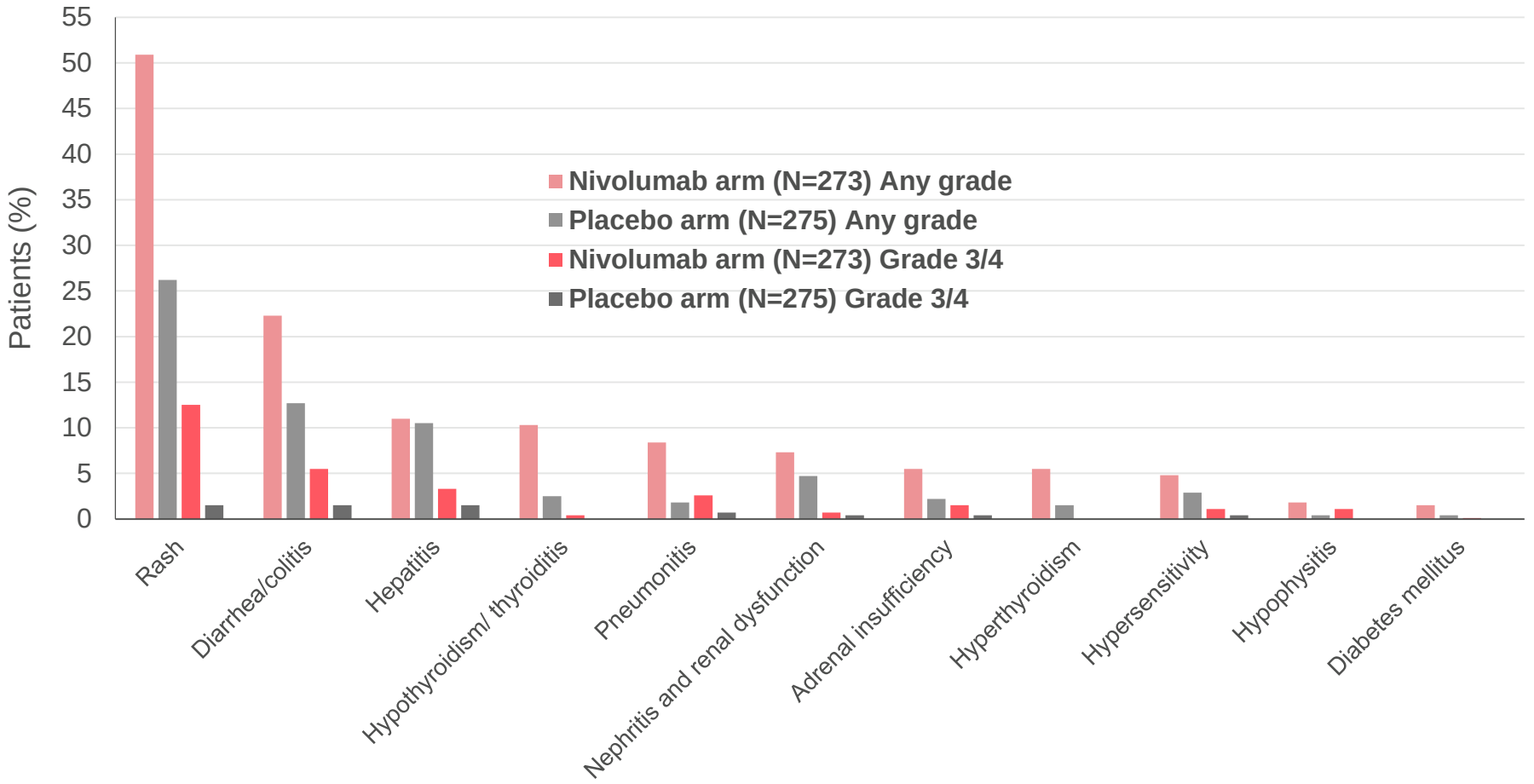
Most TRAEs were chemotherapy- or bevacizumab-related

TRAE: Treatment related adverse event.

Lee, J-S. et al, 2020. Abstract LBA54 presented at ESMO 2020

TASUKI-52 Results – Safety and tolerability

Adverse events (AEs) of special interest



- **Safety profiles consistent with previous reports**
- **No new safety signals observed**

These data include events defined as TRAEs that required immune-modulating medication (with the exception of those of endocrine origin) and were reported up to 100 days after the last dose

AE: Adverse event. TRAE:Treatment related adverse events.
Lee, J-S. et al, 2020. Abstract LBA54 presented at ESMO 2020

TASUKI-52 Conclusions

- PFS was significantly improved in nivolumab arm vs placebo arm, with median PFS 12.1 vs 8.1 months (HR 0.56; 96.37% CI, 0.43-0.71, *P*<0.0001)
  - Benefit observed regardless of PD-L1 expression
  - Subgroup analysis showed consistent PFS benefit with nivolumab in almost all subgroups
- OS, while not mature, tended to be longer in nivolumab arm vs placebo arm (HR, 0.85; 95% CI, 0.63-1.14)
- No new safety signals observed in nivolumab arm

- **Addition of nivolumab to chemotherapy plus bevacizumab demonstrates a significant and clinically meaningful improvement in PFS among patients with non-squamous NSCLC as a first line treatment, providing a potential treatment option for these patients**

PFS: Progression free survival. HR: Hazard ratio. CI: Confidence interval. OS: Overall survival. NSCLC: Non small cell lung cancer.
Lee, J-S. et al, 2020. Abstract LBA54 presented at ESMO 2020

Abbreviations

AE: Adverse event
BID: Twice daily
CI: Confidence interval
CR: Complete response
DoR: Duration of response
ECOG: Eastern Cooperative Oncology Group
HR: Hazard ratio
IRC: Independent Review Committee
IRRC: Independent Radiographic Review Committee
NSCLC: Non-small cell lung cancer
nsq-NSCLC: non-squamous non-small cell lung cancer
ORR: Objective response rate
OS: Overall survival
PARP: Poly (ADP-ribose) polymerase
PD: Progressive disease
PD-1: Programmed cell death protein-1
PD-L1: Programmed death-ligand 1
PFS: Progression free survival
PO: Orally
PR: Partial response
Q3W: Every 3 weeks
QoL: Quality of life
R: Randomized
RECIST: Response Evaluation Criteria in Solid Tumors
SAE: Severe adverse event
TEAE: Treatment emergent adverse event
TRAE: Treatment related adverse event

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