Lung Cancer

SCOS 2021 Annual Conference Featuring ASCO Direct™ Highlights

The South Carolina Oncology Society and the Association of Community Cancer Centers

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Disclosure of Conflicts of Interest

Alberto Chiappori, MD reported the following relevant financial relationships or relationships they have with ineligible companies of any amount during the past 24 months:

- *Consultant:* AstraZeneca, Bristol Myers Squibb, and Jazz Pharmaceuticals.

- *Speaker's Bureau:* Amgen, Blueprint, Genentech, Merck & Co., Takeda.

Presentation Overview

- NSCLC - Early Stage Disease
  - 8504: Video-Assisted Thoracoscopic versus Open Lobectomy in Patients with Early Stage Lung Cancer. One year Results from a Randomized controlled Study (VIOLET)
  - 8500: Impower 010: Primary Results of a Phase 3 Global Study of Atezolizumab vs Best Supportive Care After Adjuvant Chemotherapy in Resected Stage IB-IIIA Non-Small Cell Lung Cancer (NSCLC)
- NSCLC - Advanced Disease
  - 9000: First-line nivolumab + ipilimumab + 2 cycles of chemotherapy versus chemotherapy alone (4 cycles) in patients with advanced non-small cell lung cancer: 2 year update from CheckMate 9LA
  - 9006: Amivantamab in combination with Lazertinib for the Treatment of Osimertinib-relapsed, Chemotherapy-naïve EGFR Mutant (EGFRm) Non-small Cell Lung Cancer (NSCLC) and Potential Biomarkers for Response
- NSCLC- Biomarkers (Racial Disparities)
  - 9005: Racial Disparities in Biomarker Testing and Clinical Enrollment in Non-Small Cell Lung Cancer (NSCLC)
- NSCLC – Safety (irAE)
  - 9002: Pooled Analyses of Immune-Related Adverse Events and Efficacy from the Phase 3 Trials Impower130, IMpower132 and IMpower150
- SCLC – Thoracic Radiotherapy
  - 8505: Phase III Comparison of High Dose Once Daily (QD) Thoracic Radiotherapy (TRT) with Standard Twice-Daily (BID) TRT in Limited Stage Small Cell Lung Cancer (LSCLC): CALGB 30610 (Alliance)/RTOG 0538
- Mesothelioma – Relapsed Disease
  - 8507: A Randomized Phase II trial of Oral Vinorelbine as Second-Line Therapy for Patients with Malignant Pleural Mesothelioma

2021 ASCO ANNUAL MEETING

VIDEO-ASSISTED THORACOSCOPIC VERSUS OPEN LOBECTOMY IN PATIENTS WITH EARLY-STAGE LUNG CANCER: ONE-YEAR RESULTS FROM A RANDOMIZED CONTROLLED TRIAL (VIOLET)

Eric Lim, Tim JP Batchelor, Joel Dunning, Michael Shackcloth, Vladimir Anikin, Babu Naidu, Elizabeth Belcher, Mahmoud Loubani, Vipin Zamvar, Rosie A Harris, Lucy Dabner, Holly E McKeon, Sangeetha Paramasivan, Alba Realpe, Daisy Elliott, Paulo De Sousa, Jane Blazeby, Chris A Rogers on behalf of The VIOLET Trialists

Violet STUDY

BRISTOL TRIALS CENTRE

Royal Brompton & Harefield NHS NHS Foundation Trust

Imperial College London

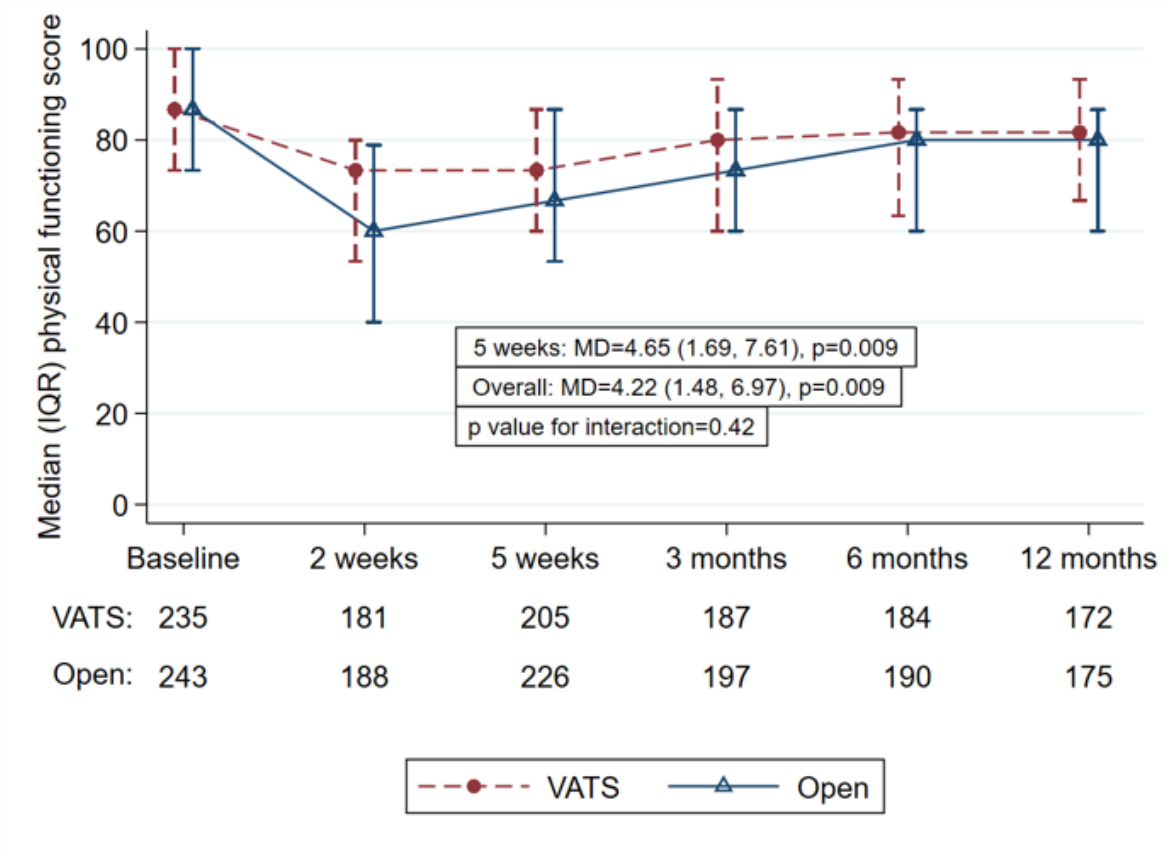
Background and Methods

- VIOLET is a UK National Institute of Health Research (NIHR 03/04/03) funded RCT conducted by the UK Thoracic Surgery Research Collaborative, to compare clinical and cost effectiveness of VATS versus open (thoracotomy) and lobectomy for lung cancer
- VIOLET is a UK multicentre RCT where participants with known or suspected primary lung cancer within cT1-3, cN0-1, M0 stage (TNM 8) were randomized (1:1 ratio) to VATS or open lobectomy
- Primary outcome (single measure to encompass “recovery”) was physical function at 5 weeks. Measured by a) EORTC QLQ C-30 physical function score and b) one category change in performance status
- Secondary outcomes included measures of clinical efficacy (pain, duration of hospital stay), procedural safety (complications, re-admissions), oncologic quality (lymph node upstaging, time to adjuvant chemotherapy, disease recurrence, survival) and cost-effectiveness up to one-year
- In hospital outcomes presented at 2019 World Conference of Lung Cancer: BMJ Open 2019;9:e029507. doi: 10.1136 / bmjopen-2019-029507
- At ASCO today we present our trial’s primary endpoint and results to one-year

Clinical efficacy (physical function to one year)

Outcome	Primary analysis		Analysis excluding benign patients	
	MD (95% CI)	p value[1]	MD (95% CI)	p value[1]
QLQ-C30 physical function at 5 weeks	4.65 (1.69, 7.61)	0.0089	4.66 (1.71, 7.62)	0.0089

Multiple imputation (50 imputed datasets) was used to account for missing data. Models could not be adjusted for operating surgeon or centre. [1] P values have been adjusted for multiple testing using the Benjamini-Hochberg method
MD=mean difference, CI=confidence interval



Higher scores indicate better physical function. MD=mean difference (95% confidence interval)

Procedural safety (complications & readmissions)

Outcome	Randomised to VATS (n=247)	Randomised to open surgery (n=255)	RR (95% CI)	p value
In-hospital before discharge				
Any in-hospital AE	81/247 (32.8%)	113/255 (44.3%)	RR=0.74 (0.66, 0.84)	<0.001
Any in-hospital SAE	20/247 (8.1%)	21/255 (8.2%)	RR=0.98 (0.59, 1.63)	0.948
After discharge following surgery (events/patients)				
Readmissions	117/70 (29.0%)	141/88 (35.9%)		
SAE	142/75 (30.7%)	207/94 (37.8%)	RR=0.81 (0.66, 1.00)	0.053

Data are n/N (%) unless otherwise specified.

AE=adverse event. SAE=Serous adverse event

Oncologic quality (in-hospital)

Outcome	Randomised to VATS (n=247)	Randomised to open surgery (n=255)
Total number of lymph node stations harvested	5 (4.0, 6.0)	5 (4.0, 6.0)
Mediastinal nodes harvested (stations 2 to 9)	3 (3.0, 4.0)	3 (3.0, 4.0)
Complete (R0) resection	210/215 (97.7%)	219/224 (97.8%)
Site of residual (R1) disease		
Bronchial margin	2/5 (40.0%)	3/5 (60.0%)
Vascular margin	0/5 (0.0%)	1/5 (20.0%)
Lung parenchymal margin	2/5 (40.0%)	0/5 (0.0%)
Other	1/5 (20.0%)	0/5 (0.0%)
No data	0/5 (0.0%)	1/5 (20.0%)

Data are median (IQR) or n/N (%). R0 resection=no residual tumour. R1 resection=microscopic residual tumour.

Outcome	Randomised to VATS (n=247)	Randomised to open surgery (n=255)
cN0 to pN1		
Yes	15/244 (6.2%)	13/252 (5.2%)
No	211/244 (86.5%)	219/252 (86.9%)
Not cancer	18/244 (7.4%)	20/252 (7.9%)
cN0/1 to pN2		
Yes	15/244 (6.2%)	12/252 (4.8%)
No	211/244 (86.5%)	220/252 (87.3%)
Not cancer	18/244 (7.4%)	20/252 (7.9%)

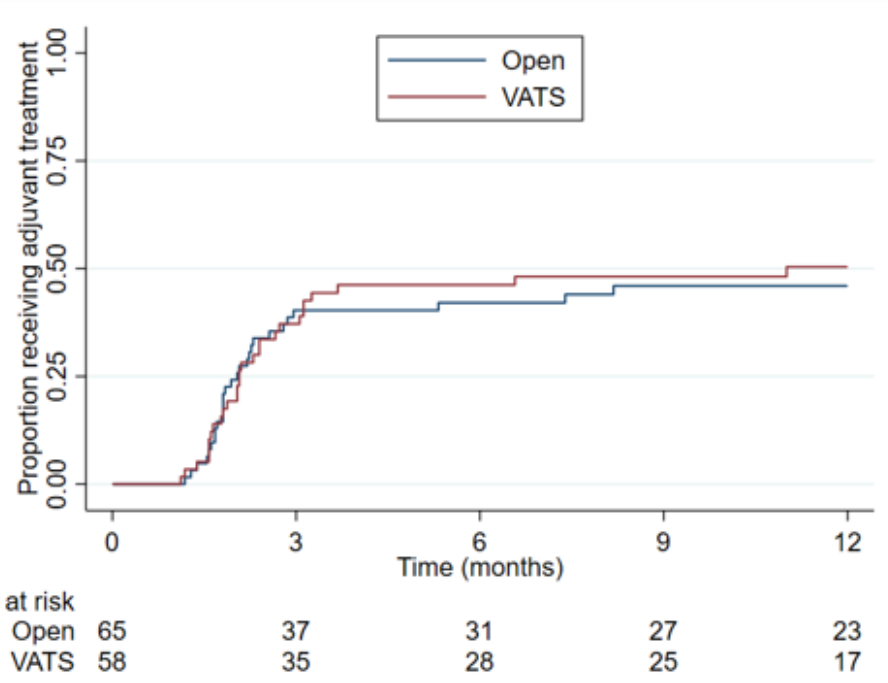
Data are presented as n/N (%).

Oncologic quality (adjuvant treatment)

Outcome	Randomised to VATS (n=247)	Randomised to open surgery (n=255)	HR (95% CI)	p value
Received adjuvant treatment	34/216 (15.7%)	39/216 (18.1%)		
Received adjuvant treatment (eligible subset [a])	28/55 (50.9%)	28/61 (45.9%)		
Time to uptake of adjuvant treatment (months)	-	-	HR=0.90 (0.50, 1.61)	0.716
Time to uptake of adjuvant treatment (eligible subset [a]) (months)	11.0 (2.1, -)	- (2.0, -)	HR=1.12 (0.62, 2.02)	0.716

Data are n/N (%). Analyses are adjusted for operating surgeon.

a Eligible if i) N1-2 disease and M0 disease after surgery, or ii) T2b to 4, N0 and M0 after surgery.



Median (IQR) time to adjuvant treatment (months) for eligible:

Open: n=28, Median= 1.89, IQR=(1.68, 2.43)
VATS: n=28, Median= 2.07, IQR=(1.63, 2.89)

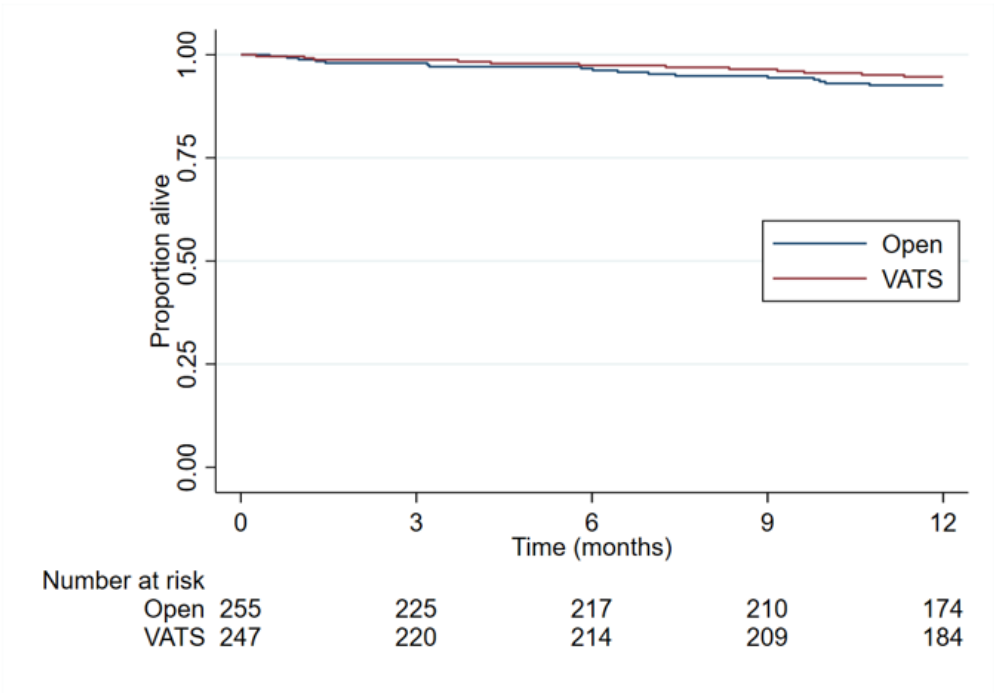
Oncologic quality (recurrence & new cancers)

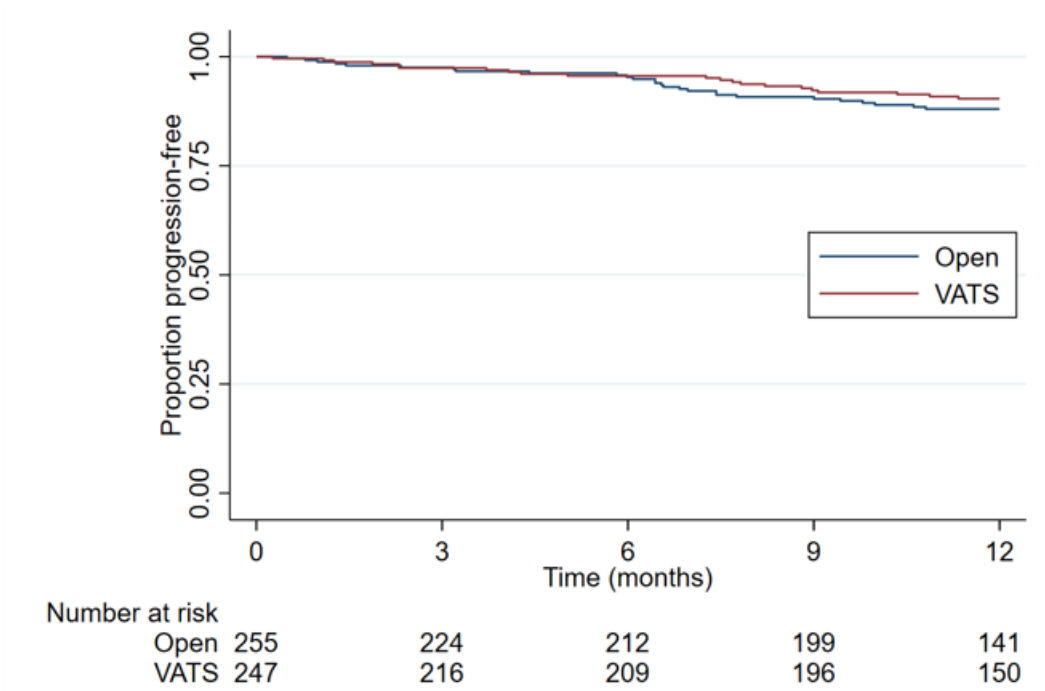
Type/location	Randomised to VATS (n=18)	Randomised to open surgery (n=21)
Loco-regional recurrence		
Lung	3/3 (16.7%)	7/6 (28.6%)
Mediastinal	4/4 (22.2%)	1/1 (4.8%)
Bronchus	0	1/1 (4.8%)
Pleura and lymph nodes	1/1 (5.6%)	0
Not collected[1]	3/2 (11.1%)	4/4 (19%)
Distant recurrence		
Adrenal gland	0	3/2 (9.5%)
Adrenal gland and liver	0	1/1 (4.8%)
Brain	1/1 (5.6%)	2/2 (9.5%)
Brain/spine	1/1 (5.6%)	0
Liver	2/2 (11.1%)	0
Liver, adrenal glands, intra-abdominal lymph nodes	1/1 (5.6%)	0
Thoracic and lumbar spine	1/1 (5.6%)	0
Not collected[1]	1/1 (5.6%)	4/4 (19%)
New cancer		
Prostate	1/1 (5.6%)	2/2 (9.5%)
Lung	1/1 (5.6%)	1/1 (4.8%)
Acute myeloid leukaemia	0	1/1 (4.8%)
Bowel	1/1 (5.6%)	0
Cholangiocarcinoma	1/1 (5.6%)	0
Sarcoma	0	1/1 (4.8%)
Not collected[1]	0	1/1 (4.8%)

Data are recurrences/patients (%).

a Data collection added part-way through the study so only available for a subset of patients

Oncologic quality (survival)





Outcome	Primary analysis		Analysis adjusting for pathological disease stage	
	HR (95% CI)	p value	HR (95% CI)	p value
Survival	HR=0.67 (0.32, 1.40)	0.283	HR=0.71 (0.34, 1.50)	0.366
Progression-free survival	HR=0.73 (0.42, 1.27)	0.262	HR=0.75 (0.42, 1.32)	0.312

Analyses are adjusted for operating surgeon and centre.

R=Hazard Ratio. CI=confidence interval

Conclusion

- VATS lobectomy was associated with less pain, significantly lower (total) complications, shorter length of stay achieved without any compromise to procedural oncologic outcomes (lymph node dissection, upstaging of mediastinal nodes, complete resection) or serious adverse events
- Superior recovery continued after discharge with improved physical function and vast majority of secondary measures of quality of life (up to one year)
- Fewer complications and re-admissions continued to be observed after discharge (up to one year)
- Without any difference in recurrence, disease-free and overall survival (up to one-year)
- A technique that is both more effective and less costly compared to thoracotomy

FUNDED BY
NIHR | National Institute for Health Research

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2021 ASCO ANNUAL MEETING

IMpower010: Primary Results of a Phase 3 Global Study of Atezolizumab vs Best Supportive Care After Adjuvant Chemotherapy in Resected Stage IB-IIIA Non-Small Cell Lung Cancer (NSCLC)

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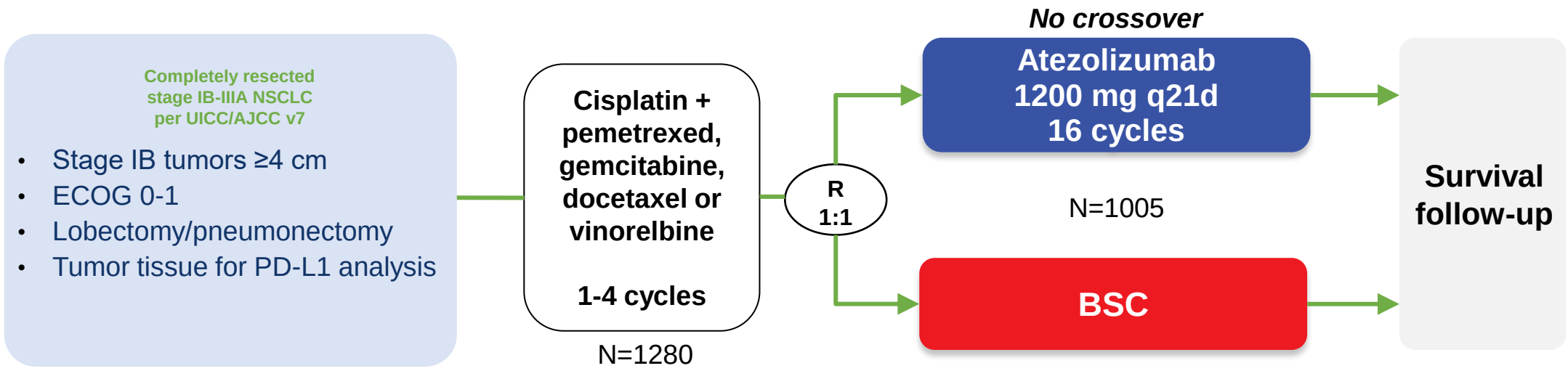
IMpower010: introduction

- Adjuvant platinum-based chemotherapy changed the standard of care for completely resected early-stage NSCLC (stage IB-IIIA) over 15 years ago[1-4]
    - DFS HR, 0.84 (95% CI: 0.78, 0.91)
    - OS HR, 0.89 (95% CI: 0.82, 0.96)
    - Leads to 4%-5% OS improvement at 5 years vs observation
- Osimertinib provides substantial DFS benefit in patients whose tumors harbor *EGFR* activating mutations,[5] but there remains a high unmet need for improved adjuvant treatment in other patients with NSCLC
- IMpower010 evaluated the efficacy and safety of adjuvant atezolizumab vs best supportive care (BSC) after adjuvant chemotherapy in patients with completely resected NSCLC

1. Pignon J-P, et al. J Clin Oncol 2008;26:3552-9; 2. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. V8.2020; 3. Postmus PE, et al. Ann Oncol 2017;28(suppl 4):iv1-21.
4. Vansteenkiste J, et al. Ann Oncol 2019;30(8):1244-53; 5. Wu Y-L, et al. N Engl J Med 2020;383:1711-23.

IMpower010: study design



Stratification factors
- Male/female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

Primary endpoints
- Investigator-assessed DFS tested hierarchically:
  - PD-L1 TC ≥1% (per SP263) stage II-IIIA population
  - All-randomized stage II-IIIA population
  - ITT population (stage IB-IIIA)

Key secondary endpoints
- OS in ITT population
- DFS in PD-L1 TC ≥50% (per SP263) stage II-IIIA population
- 3-y and 5-y DFS in all 3 populations

Both arms included observation and regular scans for disease recurrence on the same schedule.
ECOG, Eastern Cooperative Oncology Group; IC, tumor-infiltrating immune cells; ITT, intent to treat; TC, tumor cells. [a] Per SP142 assay.

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IMpower010 Interim Analysis
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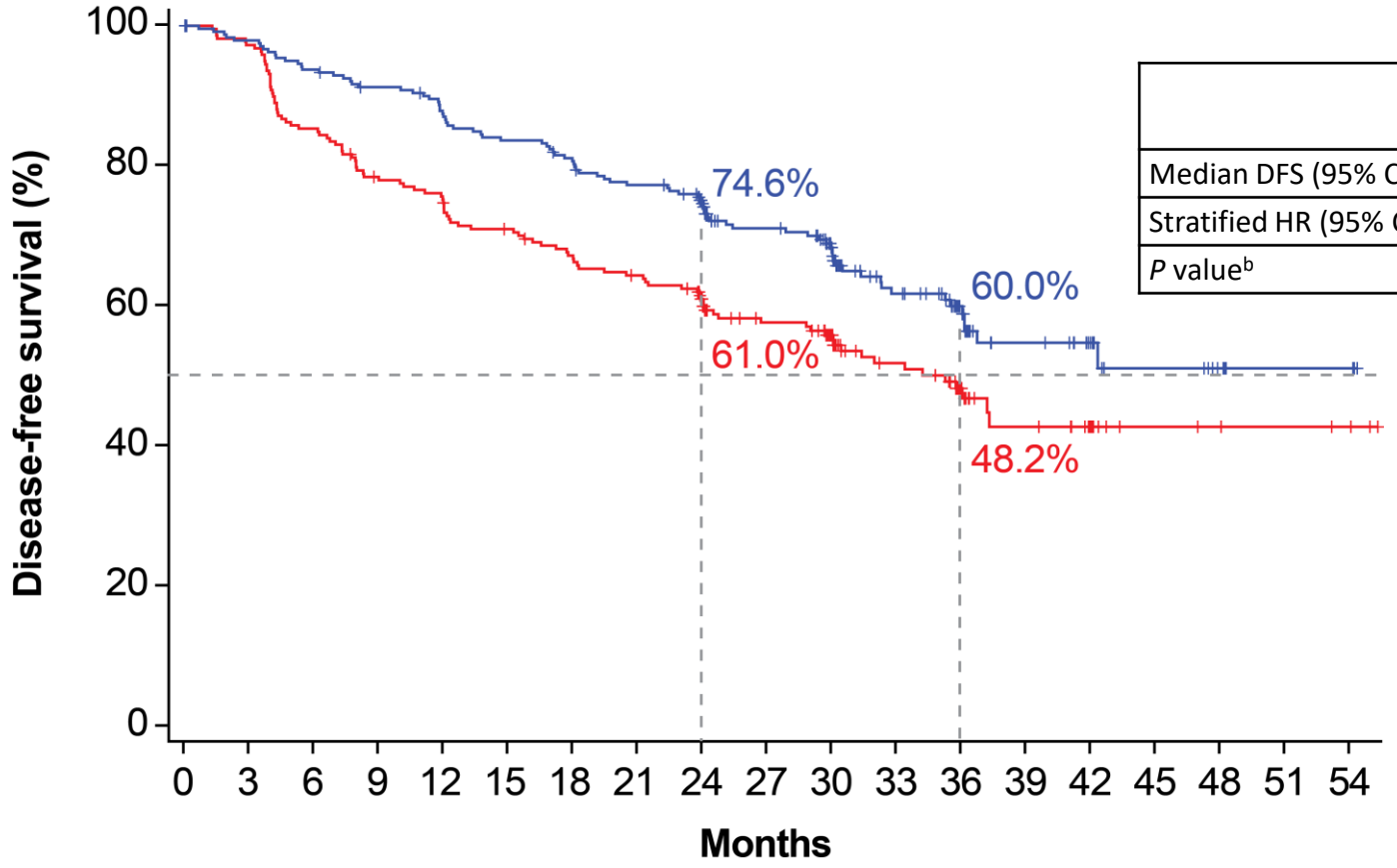
IMpower010: DFS in the PD-L1 TC ≥1%[a] stage II-IIIA population (primary endpoint)

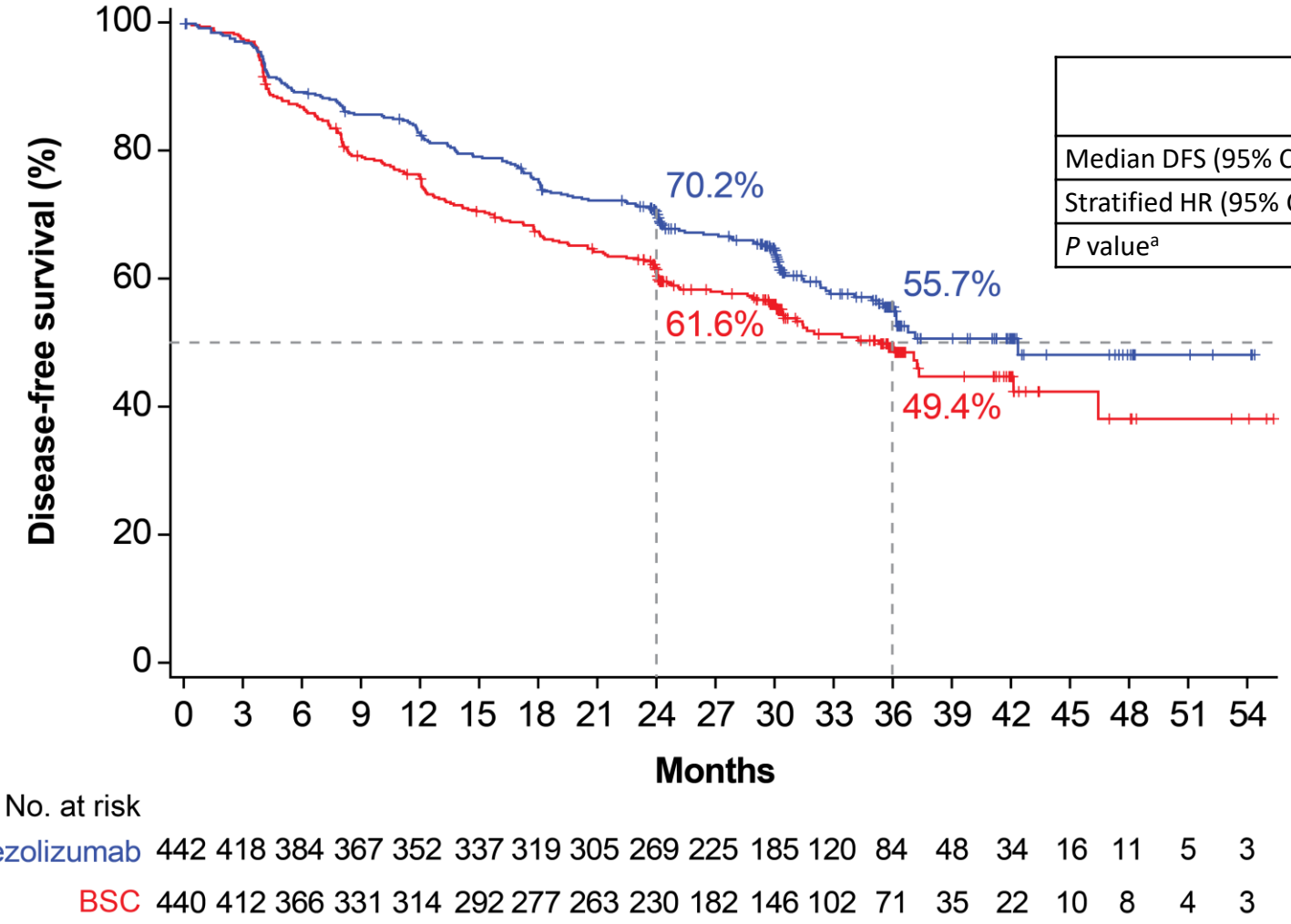


	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

Median follow-up: 32.8 mo (range, 0.1-57.5)

Clinical cutoff: January 21, 2021. CI, confidence interval; HR, hazard ratio; NE, not evaluable. [a] Per SP263 assay. [b] Stratified log-rank. [c] Crossed the significance boundary for DFS.

IMpower010: DFS in the all-randomized stage II-IIIA population (primary endpoint)



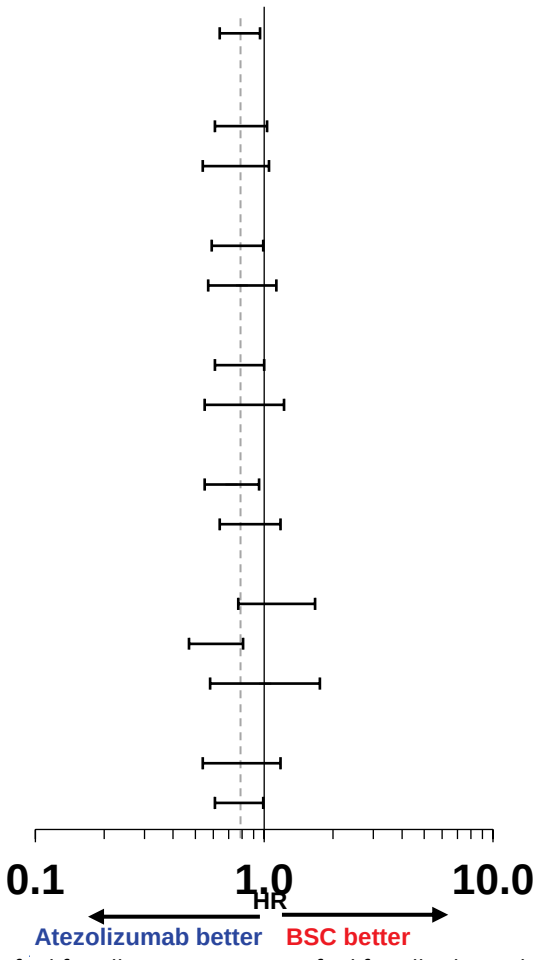
	Atezolizumab (n=442)	BSC (n=440)
Median DFS (95% CI), mo	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.79 (0.64, 0.96)	
P value[a]	0.02[b]	

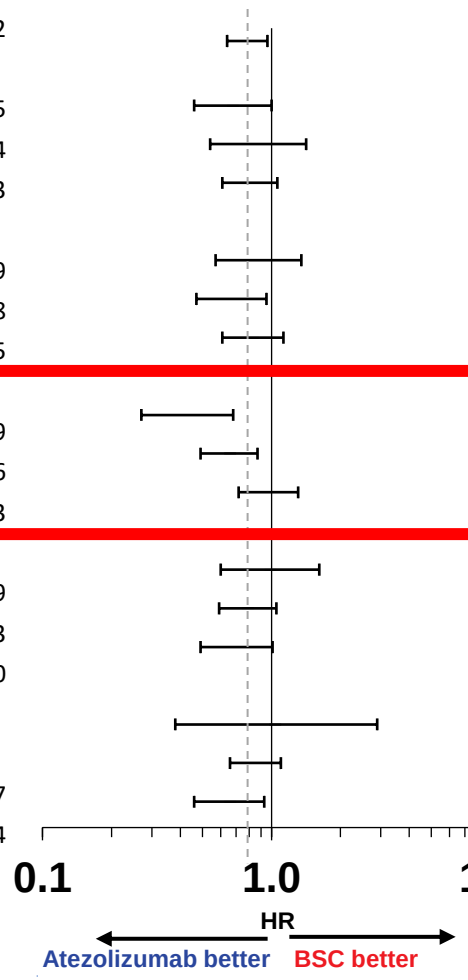
Median follow-up: 32.2 mo (range, 0-57.5)

Clinical cutoff: January 21, 2021. [a] Stratified log-rank. [b] Crossed the significance boundary for DFS.

IMpower010: DFS in key subgroups of the all-randomized stage II-IIIA population

Subgroup	N	HR (95% CI)[a]
All patients	882	0.79 (0.64, 0.96)
Age		
<65 y	544	0.79 (0.61, 1.03)
≥65 y	338	0.76 (0.54, 1.05)
Sex		
Male	589	0.76 (0.59, 0.99)
Female	293	0.80 (0.57, 1.13)
Race		
White	631	0.78 (0.61, 1.00)
Asian	227	0.82 (0.55, 1.22)
ECOG PS		
0	491	0.72 (0.55, 0.95)
1	388	0.87 (0.64, 1.18)
Tobacco use history		
Never	196	1.13 (0.77, 1.67)
Previous	547	0.62 (0.47, 0.81)
Current	139	1.01 (0.58, 1.75)
Histology		
Squamous	294	0.80 (0.54, 1.18)
Non-squamous	588	0.78 (0.61, 0.99)
Stage		
IIA	295	0.68 (0.46, 1.00)
IIB	174	0.88 (0.54, 1.42)
IIIA	413	0.81 (0.61, 1.06)
Regional lymph node stage (pN)		
N0	229	0.88 (0.57, 1.35)
N1	348	0.67 (0.47, 0.95)
N2	305	0.83 (0.61, 1.13)
SP263 PD-L1 status		
TC≥50%	229	0.43 (0.27, 0.68)
TC≥1%	476	0.66 (0.49, 0.87)
TC<1%	383	0.97 (0.72, 1.31)
***EGFR* mutation status**		
Yes	109	0.99 (0.60, 1.62)
No	463	0.79 (0.59, 1.05)
Unknown	310	0.70 (0.49, 1.01)
***ALK* rearrangement status**		
Yes	31	1.04 (0.38, 2.90)
No	507	0.85 (0.66, 1.10)
Unknown	344	0.66 (0.46, 0.93)





Clinical cutoff: January 21, 2021. [a] Stratified for all patients; unstratified for all other subgroups.

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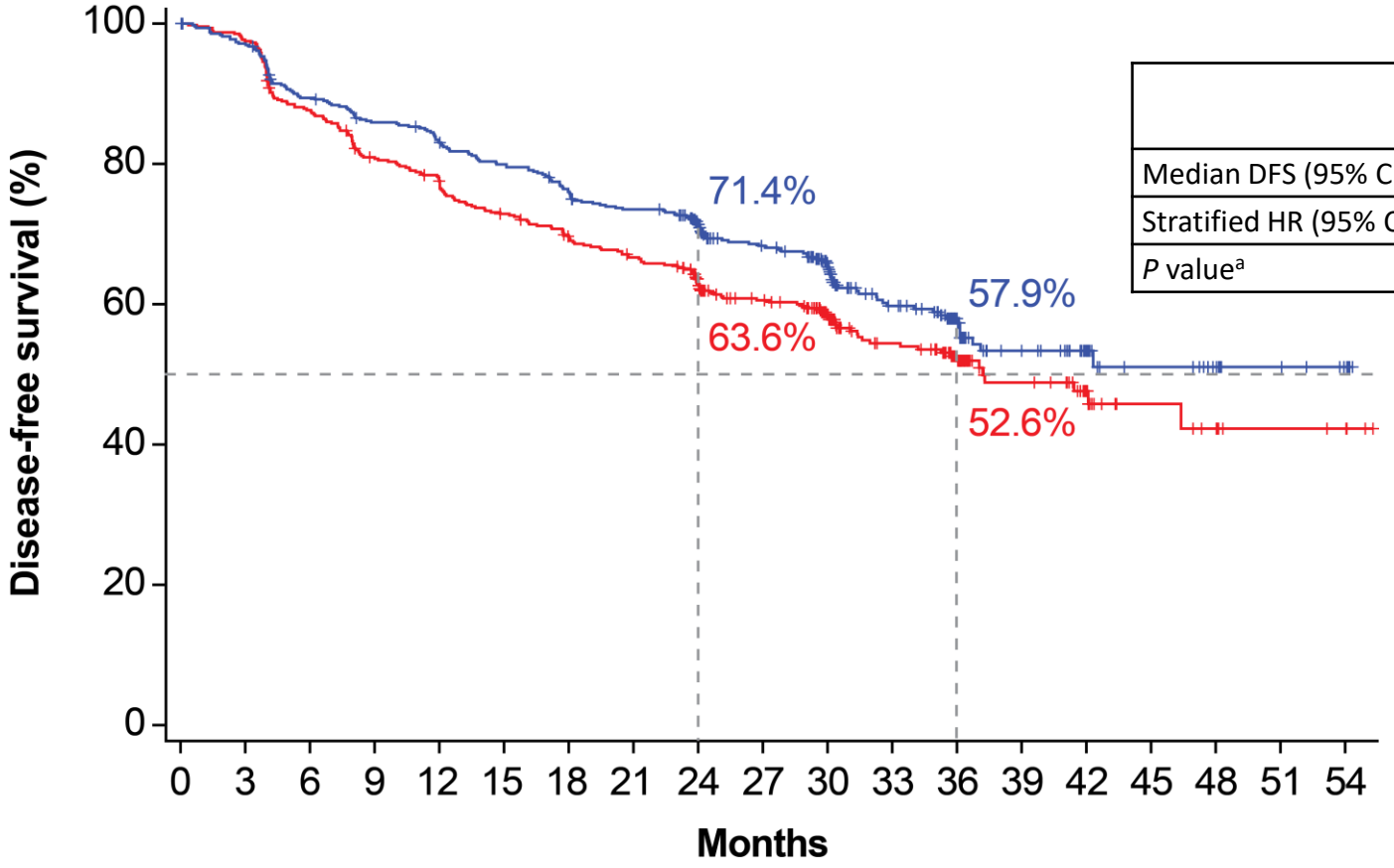
IMpower010: DFS in the ITT population (stage IB-IIIA; primary endpoint)



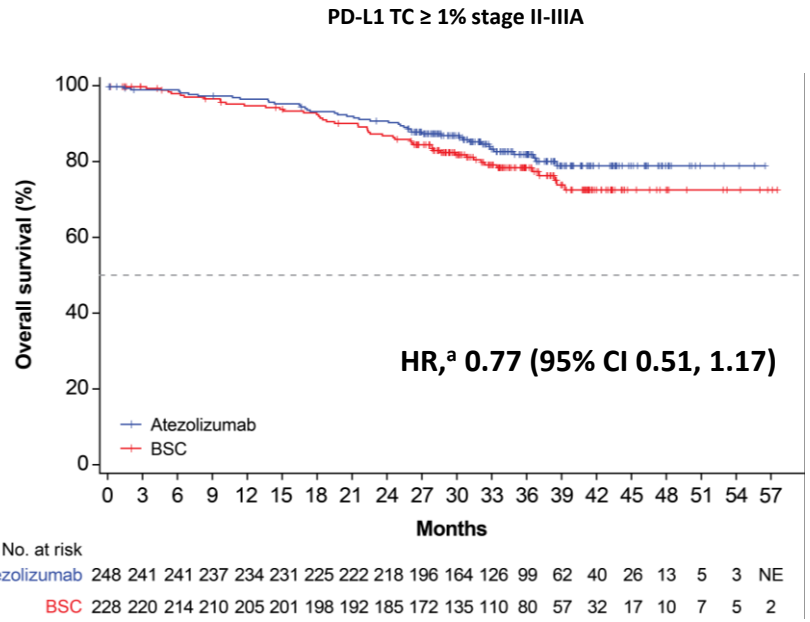
	Atezolizumab (n=507)	BSC (n=498)
Median DFS (95% CI), mo	NE (36.1, NE)	37.2 (31.6, NE)
Stratified HR (95% CI)	0.81 (0.67, 0.99)	
P value[a]	0.04[b]	

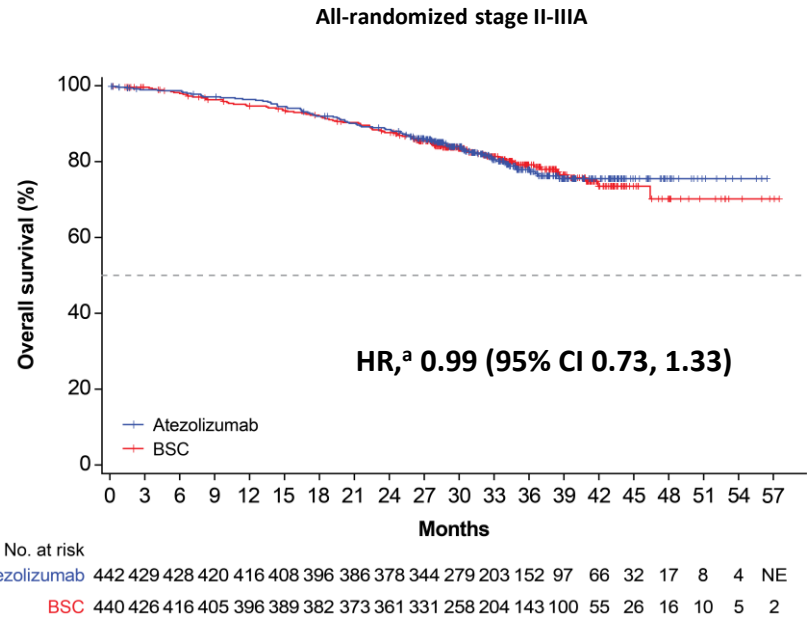
Median follow-up: 32.2 mo (range, 0-58.8)

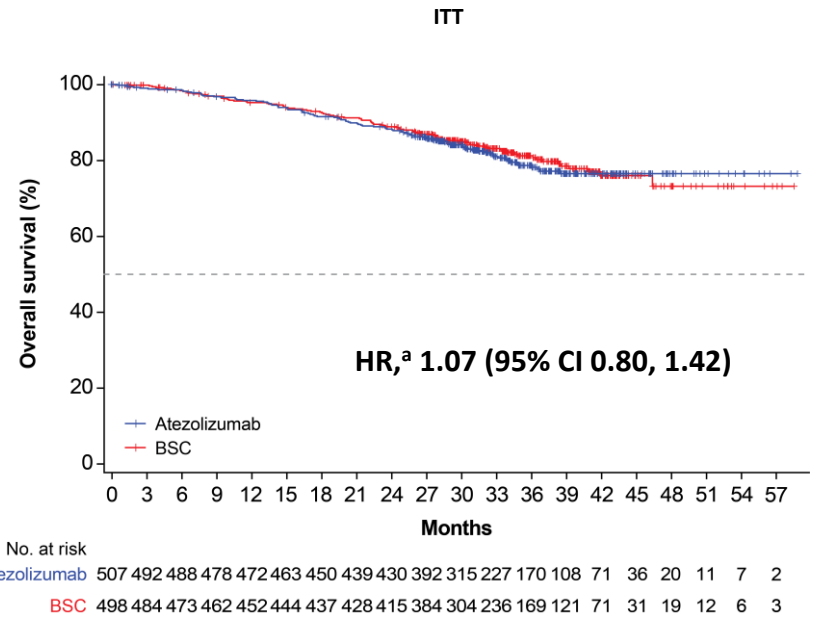
- DFS in the ITT population did not cross the significance boundary at this interim DFS analysis

Clinical cutoff: January 21, 2021. [a] Stratified log-rank. [b] The statistical significance boundary for DFS was not crossed.

IMpower010: early OS data at interim DFS analysis







- OS data were immature at this pre-planned DFS interim analysis
  - OS in the ITT population was not formally tested
  - A trend toward OS improvement with atezolizumab was seen in the PD-L1 TC ≥1% stage II-IIIA population

Clinical cutoff: January 21, 2021. [a] Stratified.

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IMpower010: conclusions

- IMpower010 is the first Phase III study of cancer immunotherapy to demonstrate DFS improvement in the adjuvant NSCLC setting after platinum-based chemotherapy
  - Adjuvant atezolizumab following complete resection and adjuvant chemotherapy showed statistically significant DFS benefit in the PD-L1 TC ≥1% stage II-IIIA (HR, 0.66; 95% CI: 0.50, 0.88) and all-randomized stage II-IIIA (HR, 0.79; 95% CI: 0.64, 0.96) populations, with enriched clinical benefit in patients whose tumors express PD-L1
- IMpower010 will continue for DFS and OS analyses in the ITT population
  - DFS in the ITT population, including patients with stage IB disease, did not cross the significance boundary at this interim DFS analysis
  - At this pre-planned interim DFS analysis, OS data were immature and not formally tested
- The safety profile of atezolizumab was consistent with prior experience of atezolizumab monotherapy across indications and lines of therapy
- Atezolizumab may be considered a practice-changing adjuvant treatment option for patients with PD-L1 TC ≥1% stage II-IIIA NSCLC

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2021 ASCO ANNUAL MEETING

First-line nivolumab + ipilimumab + 2 cycles of chemotherapy versus chemotherapy alone (4 cycles) in patients with advanced non-small cell lung cancer: 2-year update from CheckMate 9LA

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Abstract Number 9000

Introduction

- The combination of nivolumab (NIVO) and ipilimumab (IPI), which have distinct but complementary mechanisms of action,[1-3] has shown improved long-term OS benefit in advanced NSCLC, melanoma, RCC, and mesothelioma[4-7]
- In the randomized phase 3 CheckMate 9LA study (NCT03215706), 1L NIVO + IPI plus 2 cycles of chemotherapy (chemo) significantly improved OS, PFS, and ORR vs standard chemo (4 cycles), with no new safety signals[8]
  - This regimen is now approved in the US, EU, and several other countries as 1L treatment for adult patients with metastatic NSCLC and no *EGFR* or *ALK* genomic tumor aberrations[9,10]
- Here, we present updated efficacy and safety results from CheckMate 9LA with a minimum follow-up of 2 years, and a post hoc efficacy analysis in patients who discontinued NIVO + IPI + chemo due to treatment-related adverse events

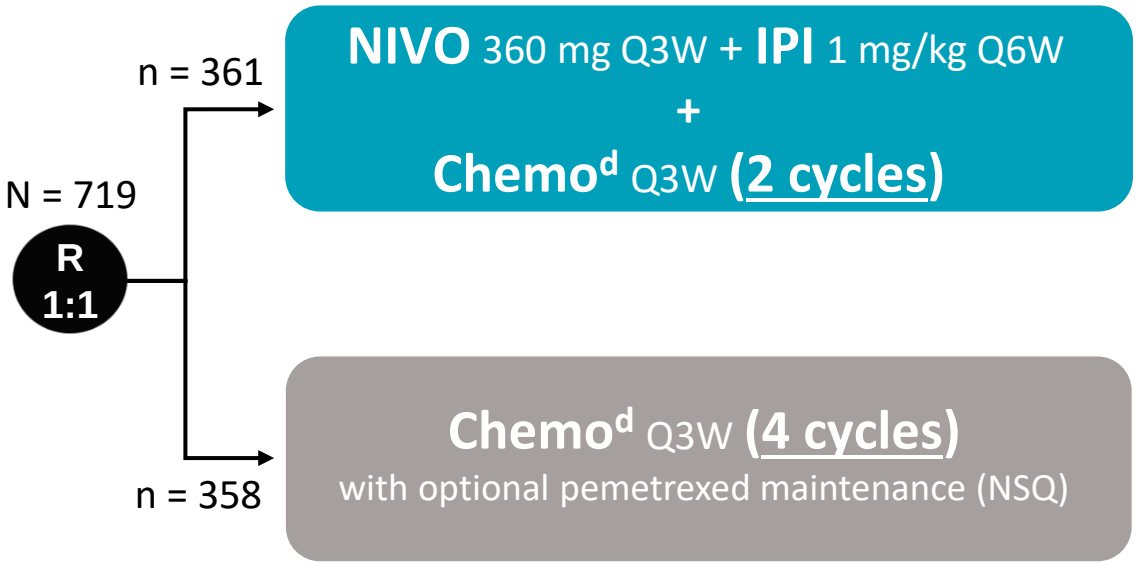
1. Sharma P, et al. *Nat Rev Immunol* 2020;20:75-76; 2. Wei SC, et al. *Cancer Discov* 2018;8:1069-1086; 3. Das R, et al. *J Immunol* 2015;194:950-959; 4. Ramalingam SS, et al. Oral presentation at the ASCO Annual Meeting; May 29-31, 2020; virtual. Abstract 9500; 5. Larkin J, et al. *N Engl J Med* 2019;381:1535-1546; 6. Motzer RJ, et al. *Lancet Oncol* 2019;20:1370-1385; 7. Baas P, et al. *Lancet* 2021;397:375-386; 8. Paz-Ares L, et al. *Lancet Oncol* 2021;22:198-211; 9. OPDIVO® (nivolumab) [package insert]. Princeton, NJ: Bristol Myers Squibb; April 2021; 10. eCancer. https://ecancer.org/en/news/19041-eu-approves-first-line-treatment-option-for-advanced-non-small-cell-lung-cancer. Published November 2, 2020. Accessed February 9, 2021.

CheckMate 9LA study design[a]

Key eligibility criteria

- Stage IV or recurrent NSCLC
- No prior systemic therapy
- No sensitizing *EGFR* mutations or known *ALK* alterations
- ECOG PS 0–1

Stratified by PD-L1[b] (< 1%[c] vs ≥ 1%), sex, and histology (SQ vs NSQ)



Until disease progression, unacceptable toxicity, *or* for 2 years for immunotherapy

Primary endpoint
- OS

Secondary endpoints
- PFS by BICR[e]
- ORR by BICR[e]
- Efficacy by tumor PD-L1 expression

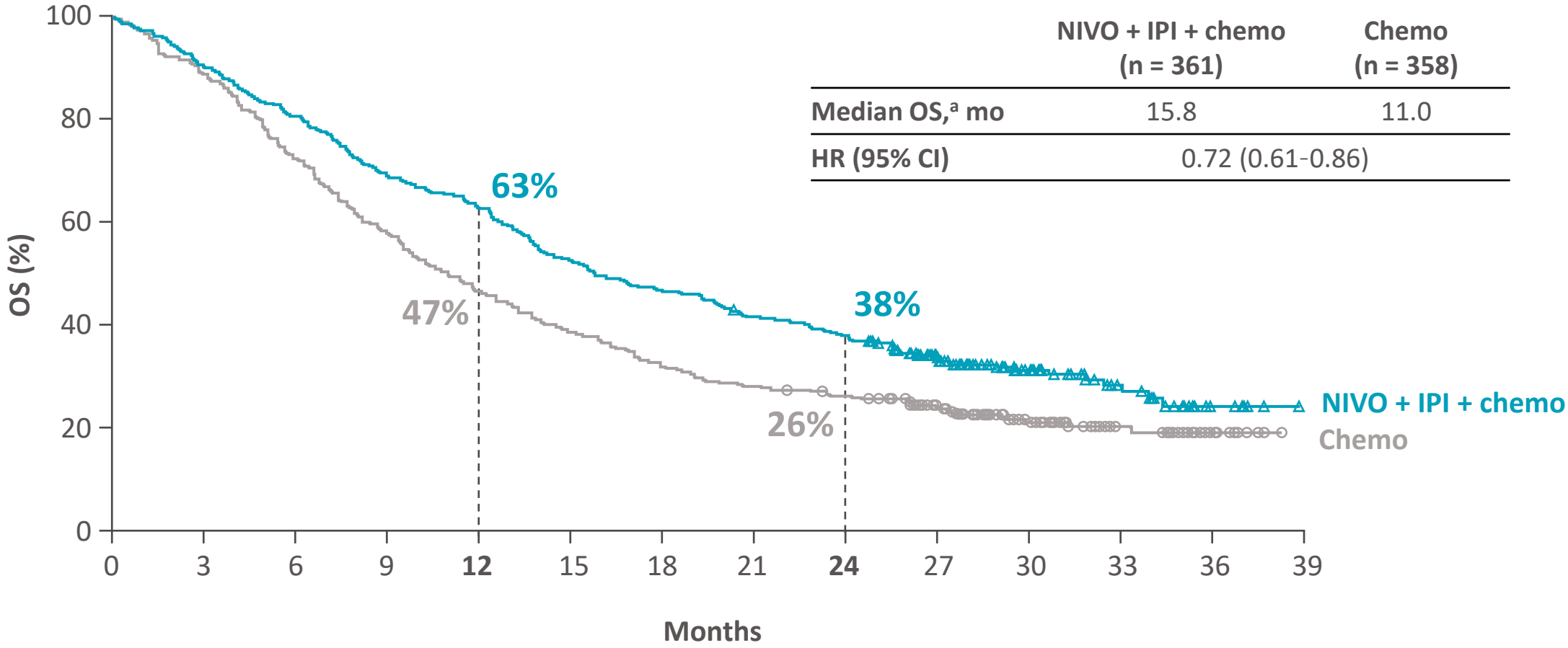
Exploratory endpoints
- Safety

DBL: February 18, 2021; minimum / median follow-up for OS: 24.4 months / 30.7 months.

[a]NCT03215706; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Patients unevaluable for PD-L1 were stratified to PD-L1 < 1% and capped to 10% of all randomized patients; [d]NSQ: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin; [e]Hierarchically statistically tested.

2-Year update: OS in all randomized patients

	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median OS,[a] mo	15.8	11.0
HR (95% CI)	0.72 (0.61-0.86)	



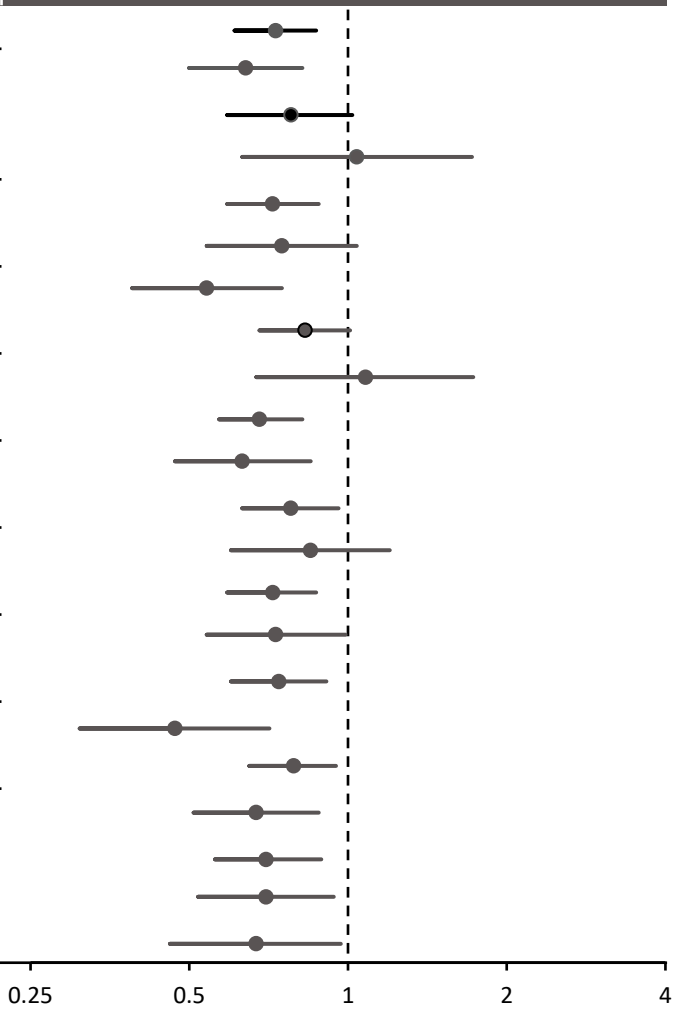
No. at risk														
NIVO + IPI + chemo	361	326	292	250	227	191	170	150	137	95	50	23	7	0
Chemo	358	319	260	208	168	139	115	102	93	69	40	18	8	0

Minimum follow-up: 24.4 months.

[a]95% CI = 13.9–19.7 (NIVO + IPI + chemo) and 9.5–12.7 (chemo).

2-Year update: OS subgroup analysis

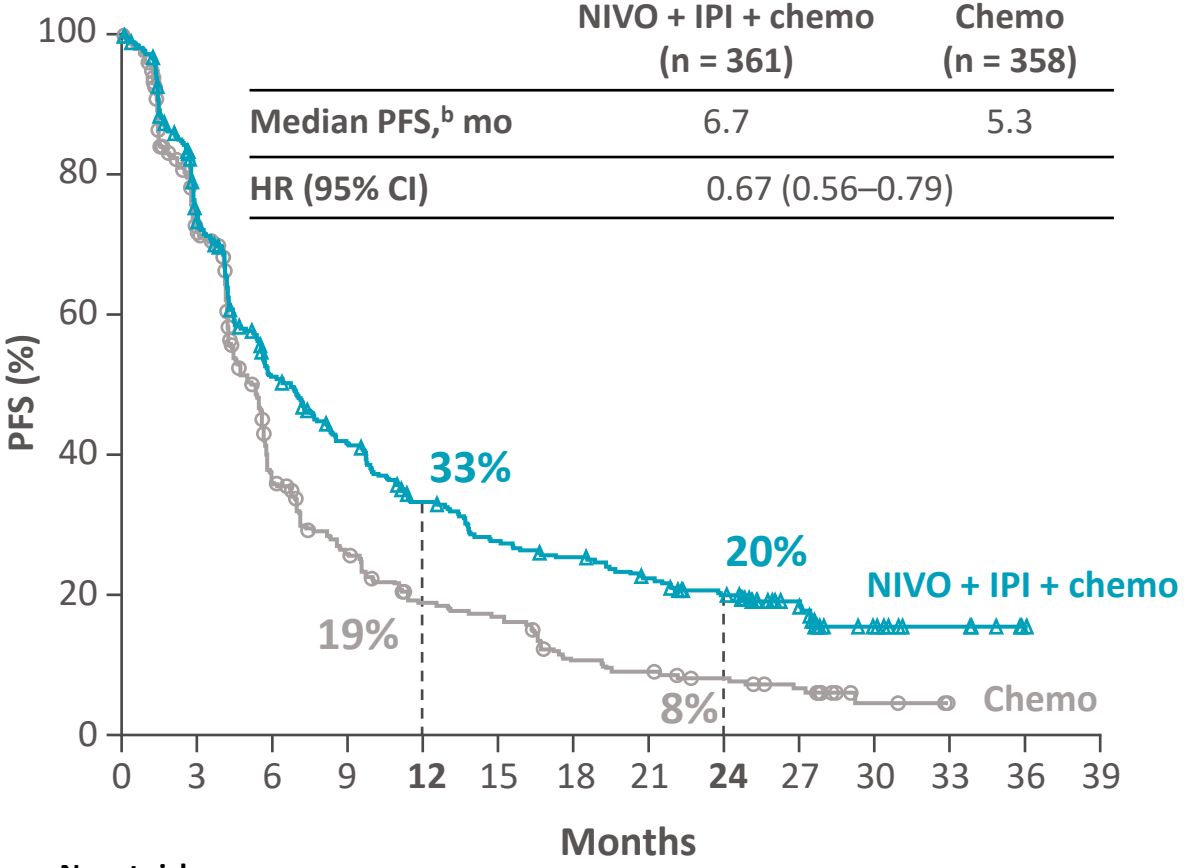
Subgroup	Median OS, mo		Unstratified HR	Unstratified HR (95% CI)
	NIVO + IPI + chemo n = 361	Chemo n = 358		
All randomized (N = 719)	15.8	11.0	0.73	
< 65 years (n = 354)	15.9	10.7	0.64	
≥ 65 to < 75 years (n = 295)	19.0	11.9	0.78	
≥ 75 years (n = 70)	8.5	11.5	1.04	
Male (n = 504)	14.2	9.8	0.72	
Female (n = 215)	22.2	15.9	0.75	
ECOG PS 0 (n = 225)	27.1	14.1	0.54	
ECOG PS 1 (n = 492)	13.6	9.7	0.83	
Never smoker (n = 98)	14.1	14.4	1.08	
Smoker (n = 621)	16.2	10.4	0.68	
SQ (n = 227)	14.5	9.1	0.63	
NSQ (n = 492)	17.8	12.0	0.78	
Liver metastases (n = 154)	10.2	8.1	0.85	
No liver metastases (n = 565)	19.3	12.4	0.72	
Bone metastases (n = 207)	11.9	8.3	0.73	
No bone metastases (n = 512)	19.7	12.4	0.74	
CNS metastases (n = 123)	19.9	7.9	0.47	
No CNS metastases (n = 596)	15.6	11.8	0.79	
PD-L1 < 1% (n = 264)	17.7	9.8	0.67	
PD-L1 ≥ 1% (n = 407)	15.8	10.9	0.70	
PD-L1 1–49% (n = 233)	15.2	10.4	0.70	
PD-L1 ≥ 50% (n = 174)	18.9	12.9	0.67	



2-Year update: PFS and DOR

PFS[a]

	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median PFS,[b] mo	6.7	5.3
HR (95% CI)	0.67 (0.56–0.79)	

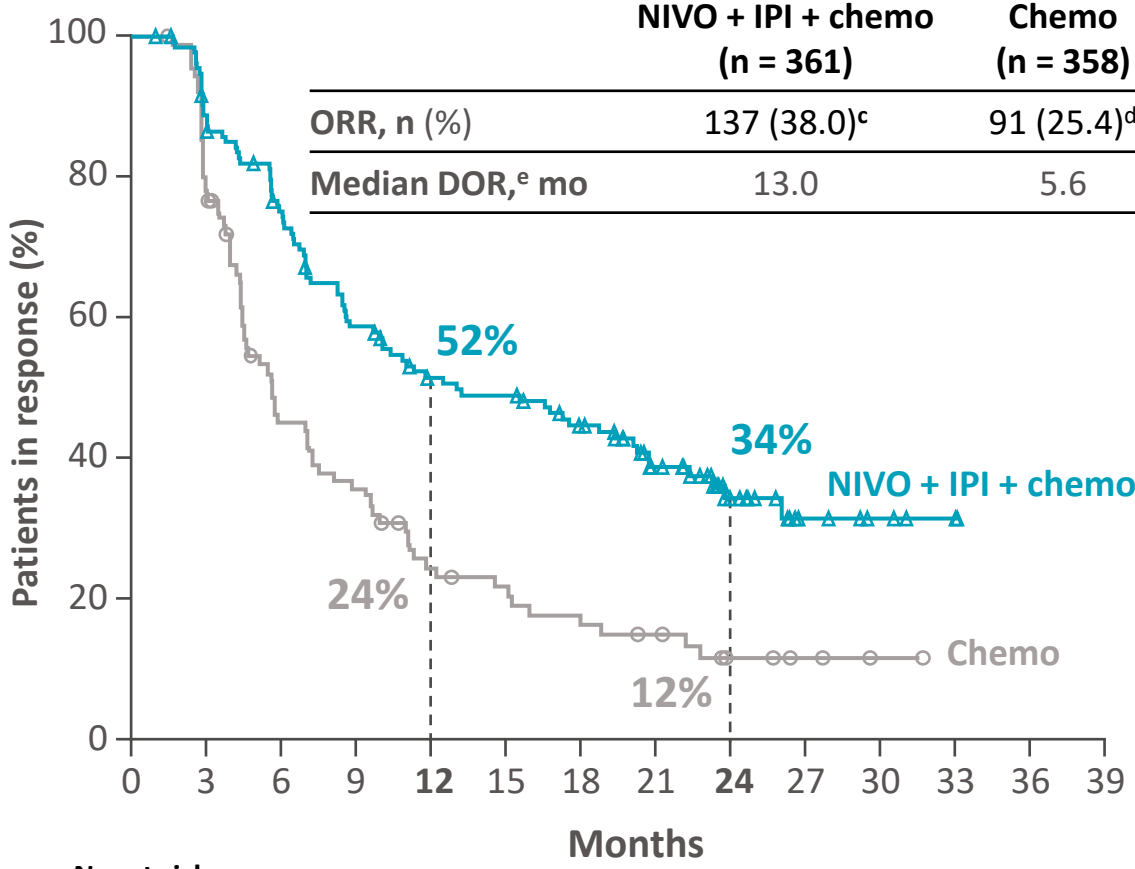


No. at risk

361	252	170	134	103	85	77	66	54	29	12	6	1	0
358	232	107	72	49	44	26	22	17	12	3	0	0	0

DOR[a]

	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
ORR, n (%)	137 (38.0)[c]	91 (25.4)[d]
Median DOR,[e] mo	13.0	5.6



No. at risk

137	116	97	75	62	59	50	35	17	7	4	2	0	0
91	70	38	30	19	16	12	10	5	3	1	0	0	0

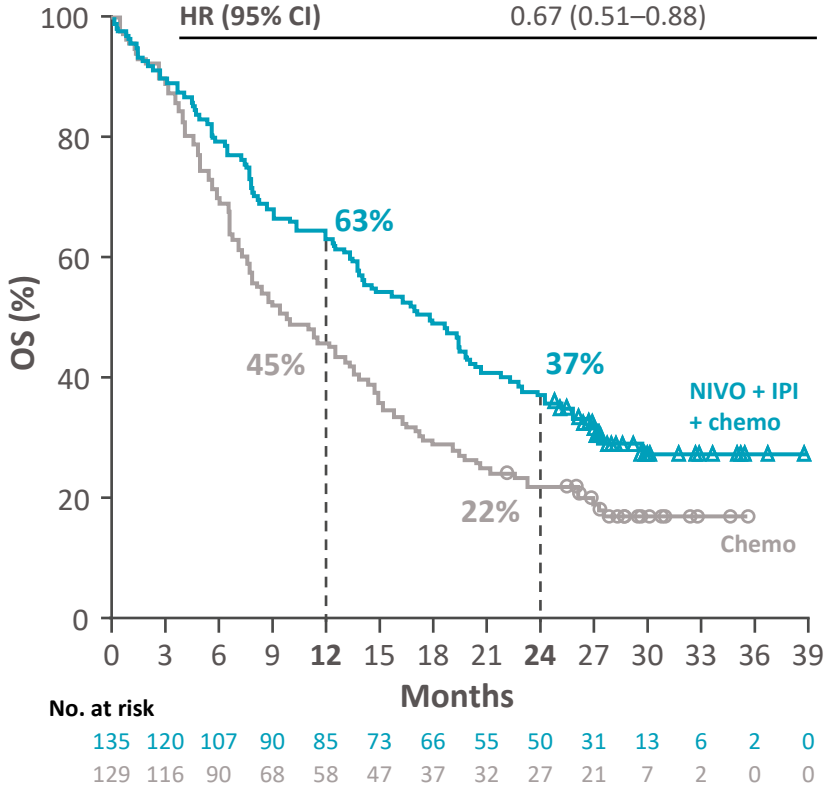
Minimum follow-up: 23.3 months.

[a]Per BICR; [b]95% CI = 5.6–7.8 (NIVO + IPI + chemo) and 4.4–5.6 (chemo); [c]Includes 3.3% CR and 34.6% PR; 4 patients who had a PR as best response at a previous DBL (12.2 months minimum follow-up for response) improved to CRs; [d]Includes 1.1% CR and 24.3% PR; [e]95% CI = 8.7–20.2 (NIVO + IPI + chemo) and 4.4–7.2 (chemo).

PD-L1 < 1%: efficacy outcomes

OS

	NIVO + IPI + chemo (n = 135)	Chemo (n = 129)
Median OS,[b] mo	17.7	9.8
HR (95% CI)	0.67 (0.51–0.88)	

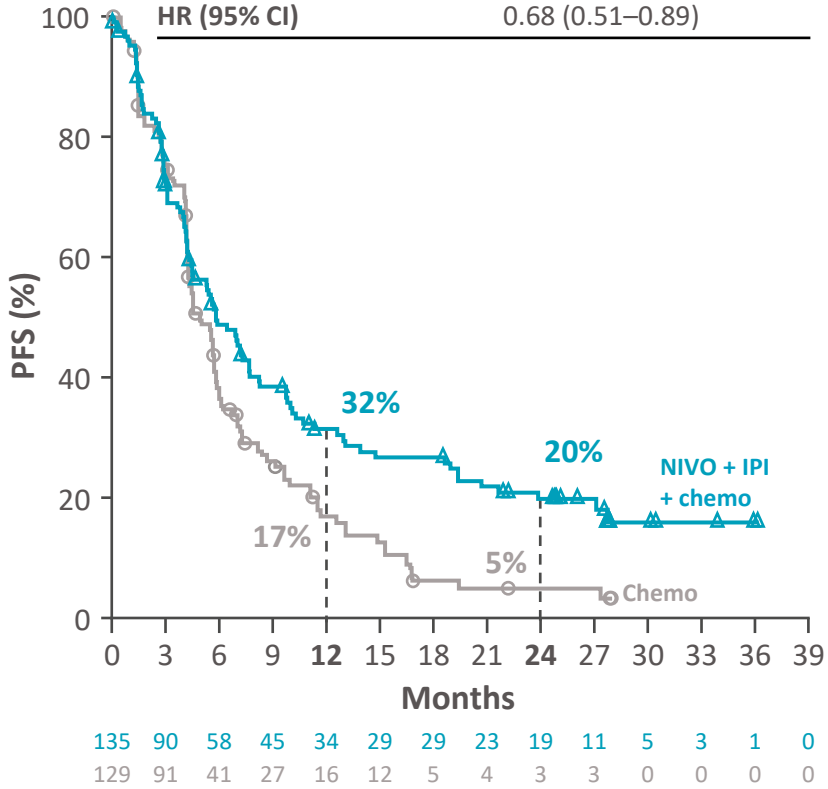


No. at risk

135	120	107	90	85	73	66	55	50	31	13	6	2	0
129	116	90	68	58	47	37	32	27	21	7	2	0	0

PFS[a]

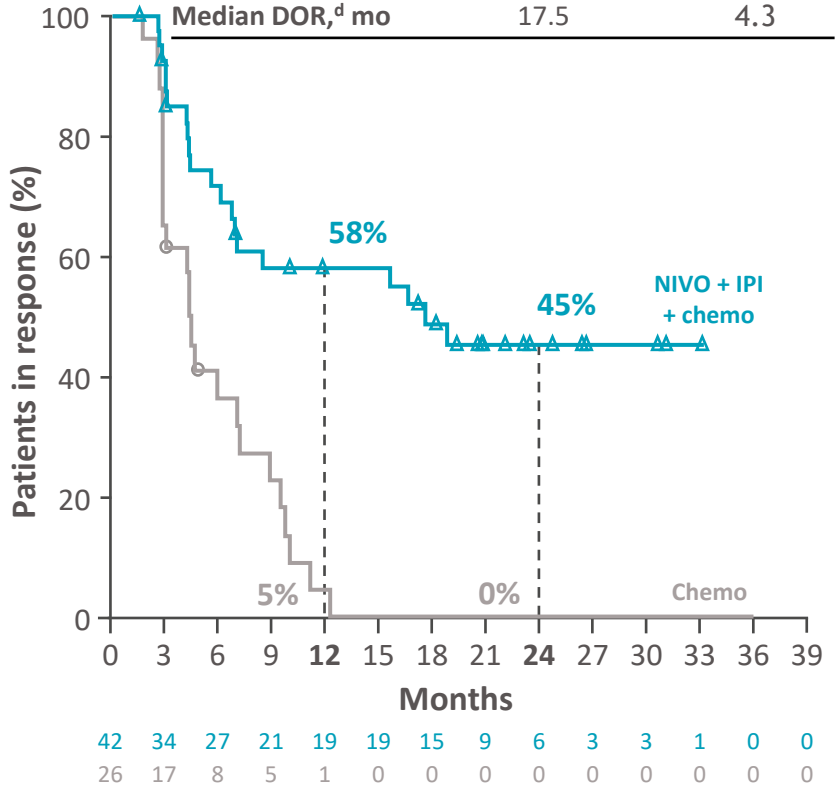
	NIVO + IPI + chemo (n = 135)	Chemo (n = 129)
Median PFS,[c] mo	5.8	4.9
HR (95% CI)	0.68 (0.51–0.89)	



135	90	58	45	34	29	29	23	19	11	5	3	1	0
129	91	41	27	16	12	5	4	3	3	0	0	0	0

DOR[a]

	NIVO + IPI + chemo (n = 135)	Chemo (n = 129)
ORR, n (%)	42 (31.1)	26 (20.2)
Median DOR,[d] mo	17.5	4.3



42	34	27	21	19	19	15	9	6	3	3	1	0	0
26	17	8	5	1	0	0	0	0	0	0	0	0	0

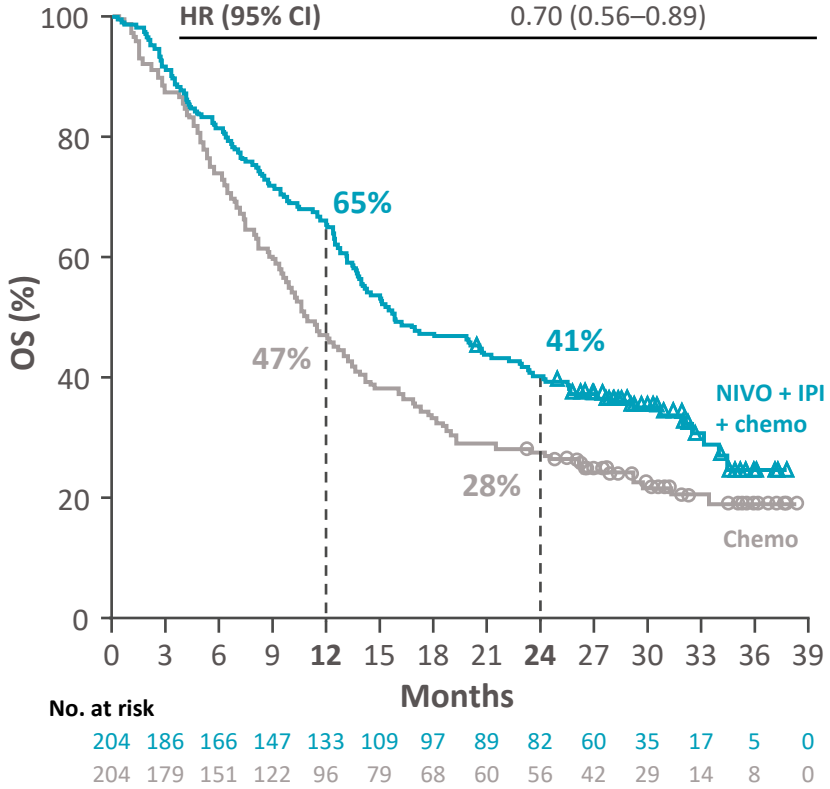
- Exploratory analysis of OS by histology in PD-L1 < 1% (HR; NIVO + IPI + chemo vs chemo): 0.75[e] (NSQ) and 0.48[f] (SQ)
  - 2-year OS rates were 38% vs 26% (NSQ) and 33% vs 11% (SQ)

[a]Per BICR; [b]95% CI = 13.7–20.3 (NIVO + IPI + chemo) and 7.7–13.5 (chemo); [c]95% CI = 4.4–7.6 (NIVO + IPI + chemo) and 4.2–5.7 (chemo); [d]95% CI = 6.7–NR (NIVO + IPI + chemo) and 2.8–7.1 (chemo); [e]95% CI = 0.54-1.04 (NSQ); [f]95% CI = 0.28-0.81 (SQ).

PD-L1 ≥ 1%: efficacy outcomes

OS

	NIVO + IPI + chemo (n = 204)	Chemo (n = 204)
Median OS,[b] mo	15.8	10.9
HR (95% CI)	0.70 (0.56–0.89)	

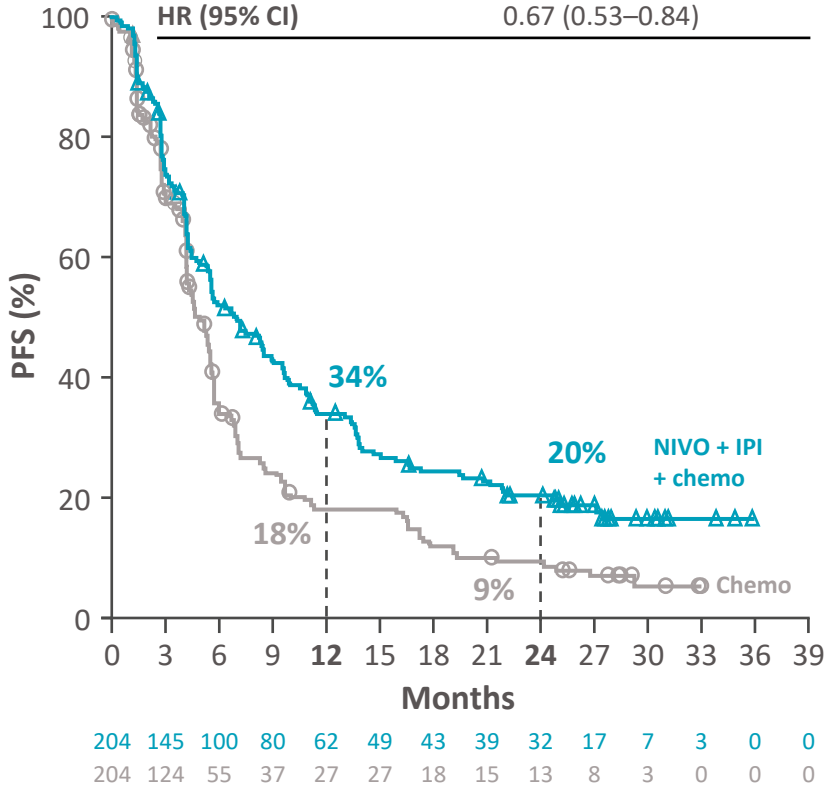


No. at risk

204	186	166	147	133	109	97	89	82	60	35	17	5	0
204	179	151	122	96	79	68	60	56	42	29	14	8	0

PFS[a]

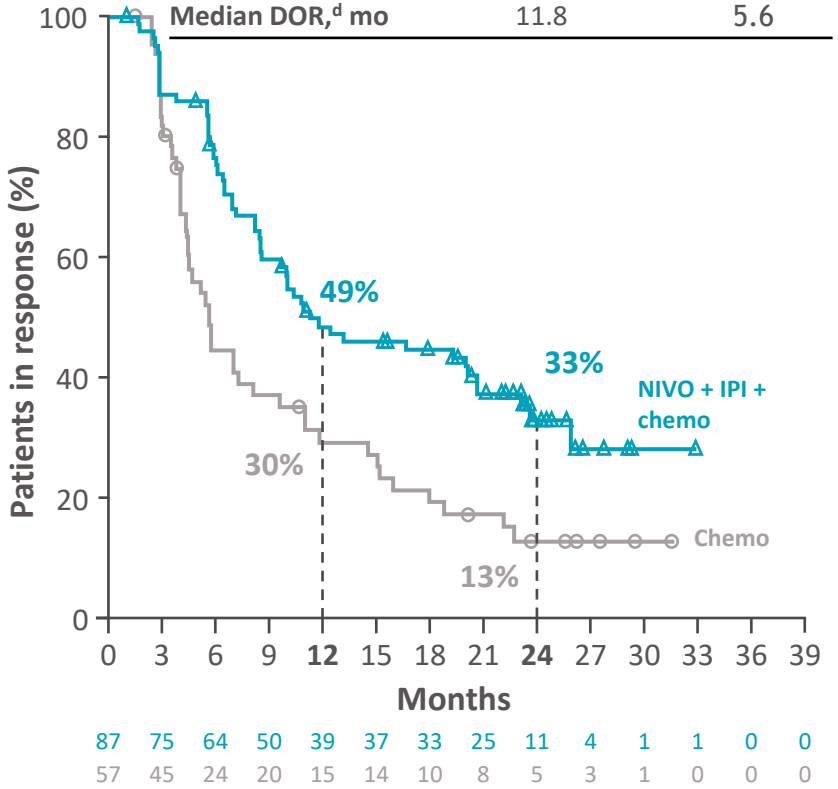
	NIVO + IPI + chemo (n = 204)	Chemo (n = 204)
Median PFS,[c] mo	7.0	5.0
HR (95% CI)	0.67 (0.53–0.84)	



204	145	100	80	62	49	43	39	32	17	7	3	0	0
204	124	55	37	27	27	18	15	13	8	3	0	0	0

DOR[a]

	NIVO + IPI + chemo (n = 204)	Chemo (n = 204)
ORR, n (%)	87 (42.6)	57 (27.9)
Median DOR,[d] mo	11.8	5.6



87	75	64	50	39	37	33	25	11	4	1	1	0	0
57	45	24	20	15	14	10	8	5	3	1	0	0	0

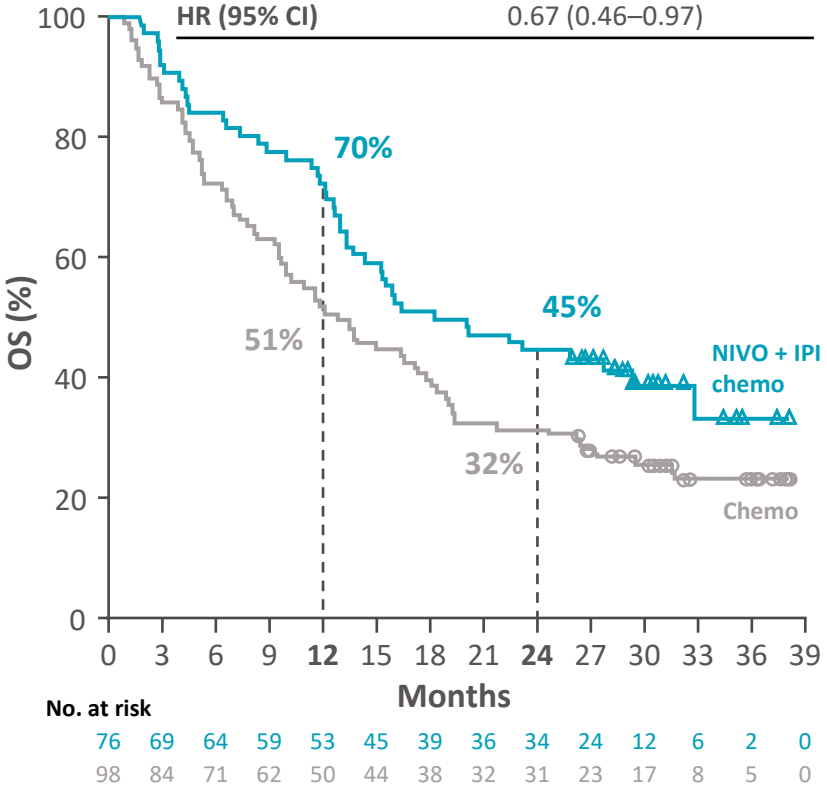
- Exploratory analysis of OS by histology in PD-L1 ≥ 1% (HR; NIVO + IPI + chemo vs chemo): 0.71[e] (NSQ) and 0.70[f] (SQ)
  - 2-year OS rates were 42% vs 29% (NSQ) and 38% vs 26% (SQ)

[a]Per BICR; [b]95% CI = 13.8–22.2 (NIVO + IPI + chemo) and 9.5–13.2 (chemo); [c]95% CI = 5.6–8.9 (NIVO + IPI + chemo) and 4.2–5.6 (chemo); [d]95% CI = 8.5–20.7 (NIVO + IPI + chemo) and 4.3–9.6 (chemo); [e]95% CI = 0.53-0.95 (NSQ); [f]95% CI = 0.48-1.01 (SQ).

PD-L1 ≥ 50%: efficacy outcomes

OS

	NIVO + IPI + chemo (n = 76)	Chemo (n = 98)
Median OS,[b] mo	18.9	12.9
HR (95% CI)	0.67 (0.46–0.97)	

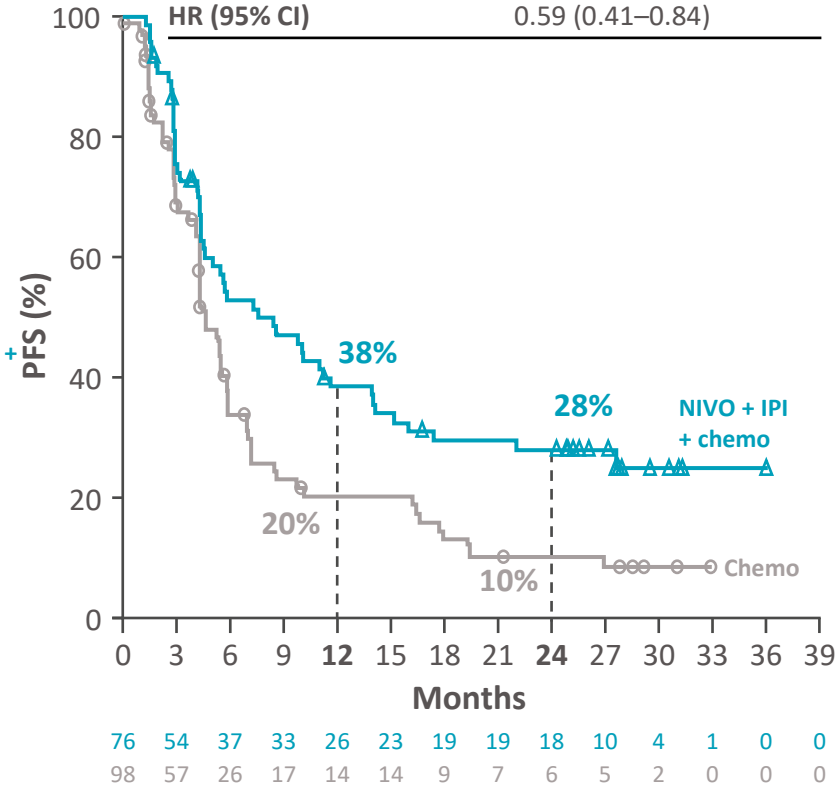


No. at risk

76	69	64	59	53	45	39	36	34	24	12	6	2	0
98	84	71	62	50	44	38	32	31	23	17	8	5	0

PFS[a]

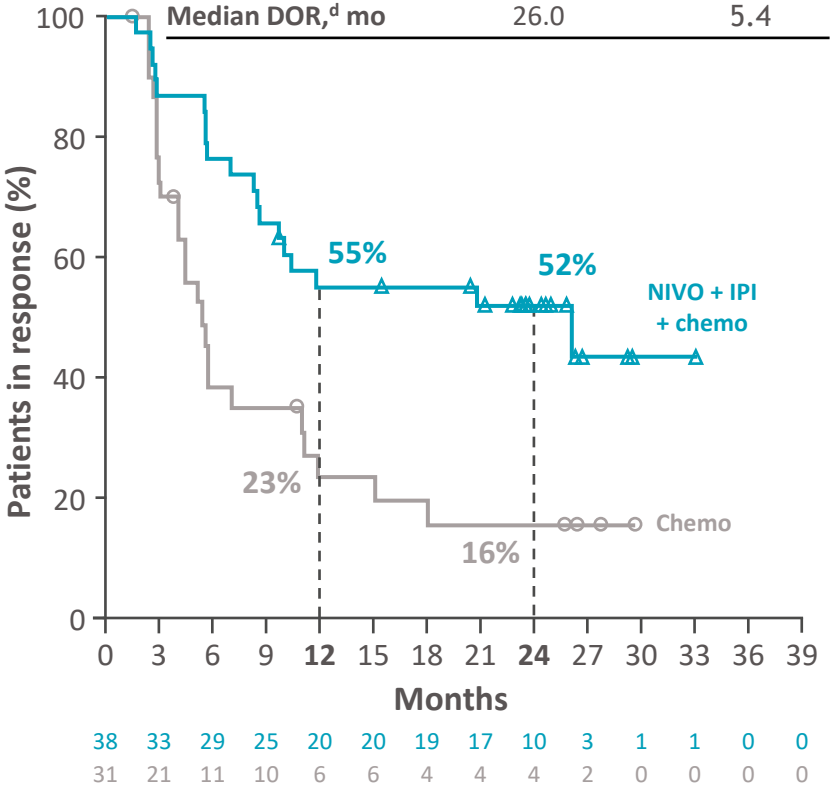
	NIVO + IPI + chemo (n = 76)	Chemo (n = 98)
Median PFS,[c] mo	7.5	4.5
HR (95% CI)	0.59 (0.41–0.84)	



76	54	37	33	26	23	19	19	18	10	4	1	0	0
98	57	26	17	14	14	9	7	6	5	2	0	0	0

DOR[a]

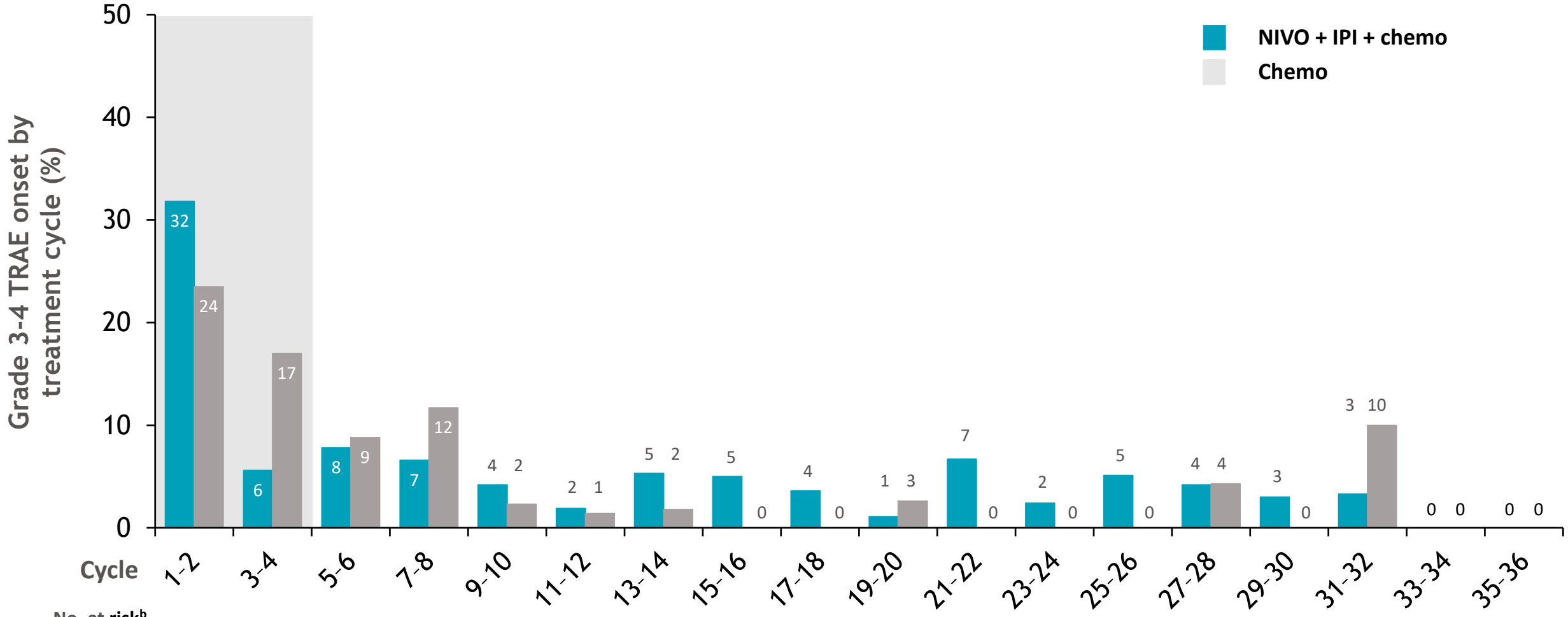
	NIVO + IPI + chemo (n = 76)	Chemo (n = 98)
ORR, n (%)	38 (50.0)	31 (31.6)
Median DOR,[d] mo	26.0	5.4



38	33	29	25	20	20	19	17	10	3	1	1	0	0
31	21	11	10	6	6	4	4	4	2	0	0	0	0

[a]Per BICR; [b]95% CI = 13.1–32.5 (NIVO + IPI + chemo) and 9.4–17.6 for (chemo); [c]95% CI = 4.4–11.5 (NIVO + IPI + chemo) and 4.1–5.6 (chemo); [d]95% CI = 8.6–NR (NIVO + IPI + chemo) and 3.9–10.9 (chemo).

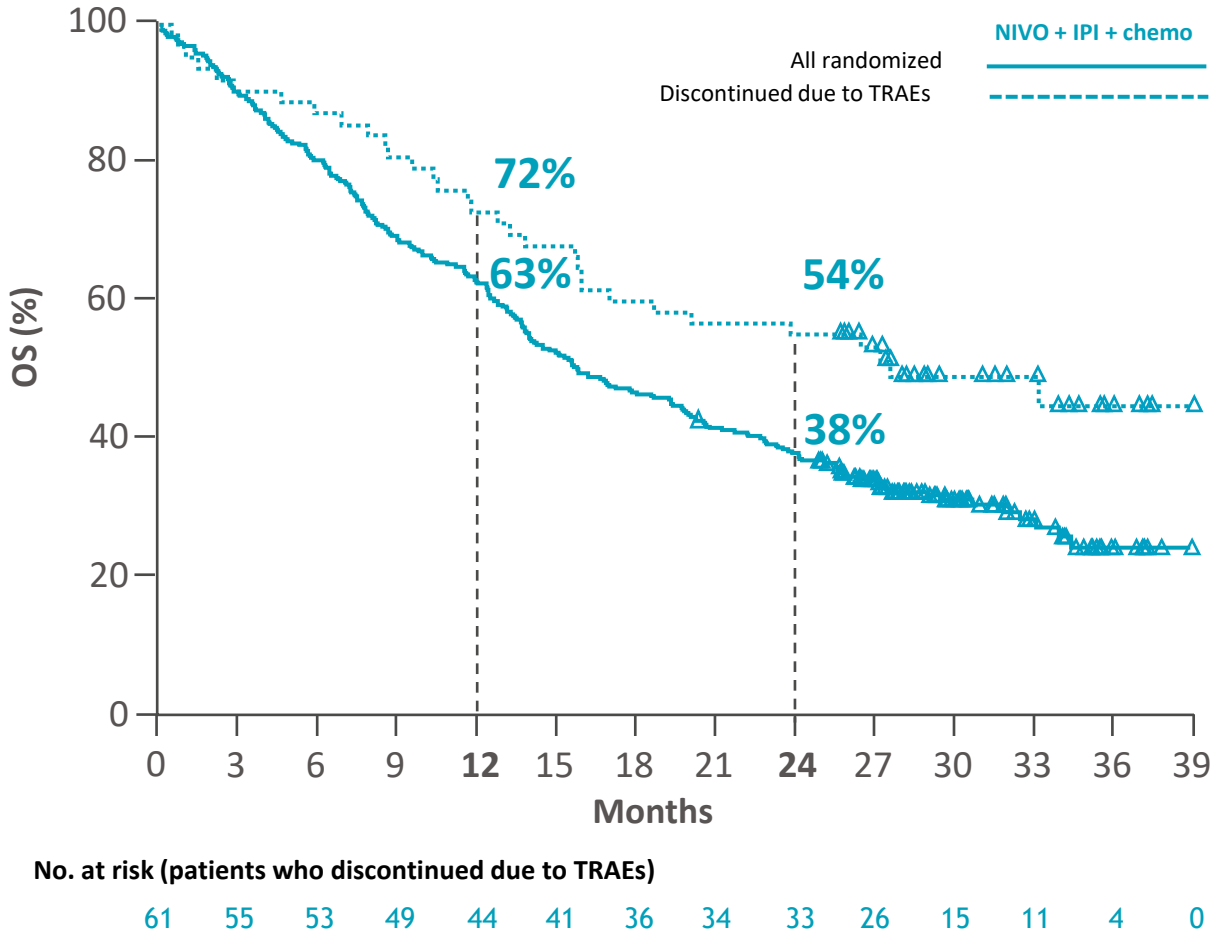
Grade 3-4 TRAE onset by treatment cycle[a]



No. at risk[b]																		
NIVO + IPI+ chemo	358	319	270	228	190	155	133	120	110	94	90	83	78	71	67	60	47	21
Chemo	349	282	159	120	88	70	56	44	41	38	36	31	28	23	20	20	17	15

X-axis shows 2-year maximum duration (~ cycle 35); there were no grade 3–4 TRAEs after cycle 32.
[a]Includes events reported between first dose and 30 days after last dose of study therapy; for both treatment arms, patients were counted once in each cycle interval if they experienced an onset of a grade 3–4 TRAEs in that cycle interval; [b]Patients were considered at risk in a cycle interval if exposed to any study drug during that interval.

Efficacy in patients who discontinued NIVO + IPI + chemo due to TRAEs[a]



Patients who discontinued all components of NIVO + IPI + chemo due to TRAEs

	NIVO + IPI + chemo (n = 61)
Median OS,[b] mo	27.5
2-year OS rate, %	54
ORR, n (%)	31 (51)
Median DOR after discontinuation,[c] mo	14.5
Ongoing response for ≥ 1 year after discontinuation,[c] %	56

Among patients who discontinued all components of NIVO + IPI + chemo due to TRAEs:

- Median (range) number of doses was 7 (1–33) for NIVO and 3 (1–17) for IPI
- Median (range) duration of treatment was 4.4 (0–23.3) months

[a]Post hoc analysis and includes patients with TRAEs (reported between first dose and 30 days after last dose of study treatment) that were considered leading to discontinuation of all components of study treatment; [b]95% CI = 15.8–NR; [c]2 responders (among patients who discontinued due to TRAEs) in the NIVO + IPI + chemo arm had their responses ended before treatment end date and therefore were excluded from the analysis of duration of response after discontinuation.

Summary

- At 2 years, OS with 1L NIVO + IPI + 2 cycles chemo was durable vs chemo (38% vs 26%) in patients with advanced NSCLC
  - PFS and DOR benefits were also maintained with longer follow-up
- Benefit with 1L NIVO + IPI + chemo vs chemo was observed across key subgroups, including by PD-L1 expression level, histology, and patients with CNS metastases
- No new safety signals were observed with longer follow-up; onset of most grade 3-4 TRAEs in the NIVO + IPI + chemo arm was during the 2 cycles of chemo treatment
- In a post hoc analysis, discontinuation of NIVO + IPI + chemo due to TRAEs did not have a negative impact on the long-term benefits seen in all randomized patients
  - 56% of the responders who had a TRAE leading to discontinuation maintained their responses for ≥ 1 year after treatment discontinuation[a]
- These updated results continue to support NIVO + IPI + 2 cycles of chemo as an efficacious 1L treatment option for patients with advanced NSCLC

[a]Rates reported are based on Kaplan–Meier estimates.

2021 ASCO ANNUAL MEETING

Amivantamab In Combination With Lazertinib For The Treatment Of Osimertinib-relapsed, Chemotherapy-naïve EGFR Mutant (EGFRm) Non-small Cell Lung Cancer (NSCLC) and Potential Biomarkers For Response

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Additional information can be viewed by scanning the QR code or accessing this link: https://www.oncologysciencehub.com/OncologyAM2021/amivantamab/Bauml

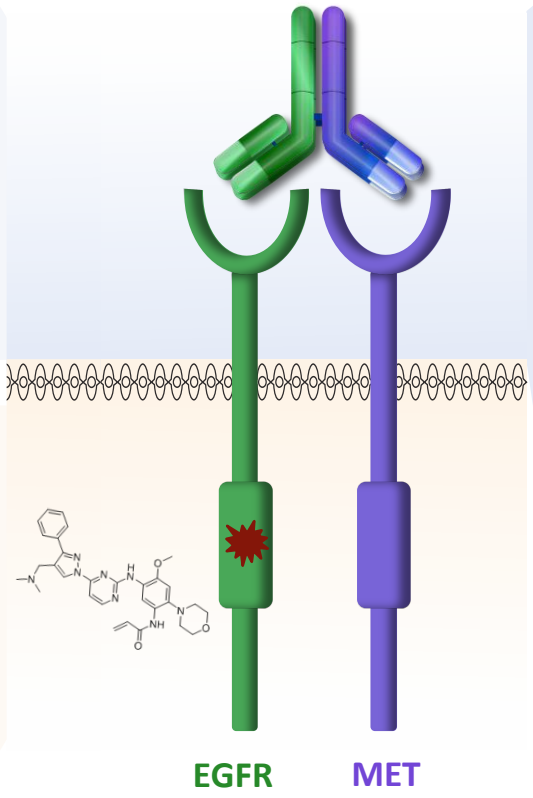
Amivantamab and Lazertinib

Amivantamab (am-e-van-tuh-mab)

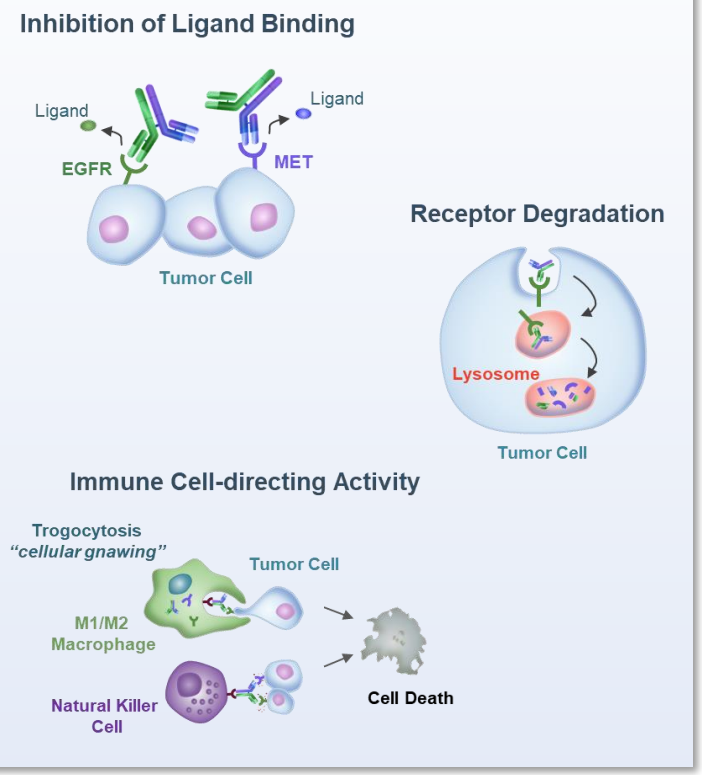
- Fully human bispecific antibody that targets EGFR and MET
- Fc portion has immune cell-directing activity[1]
- Demonstrated clinical activity across diverse EGFRm NSCLC[2-4]
- Granted Breakthrough Therapy Designation for EGFRm Exon20ins NSCLC post-chemotherapy in US (FDA APPROVED) and China

Lazertinib (la-zer-tin-ib)

- Potent 3rd-gen TKI with efficacy in activating EGFR mutations, T790M, and CNS disease[5-6]
- Low rates of EGFR-related toxicity such as rash and diarrhea[5]
- Low cardiovascular safety risk[7]
- Safety profile that supports combination with other anti-EGFR molecules



Amivantamab MOA



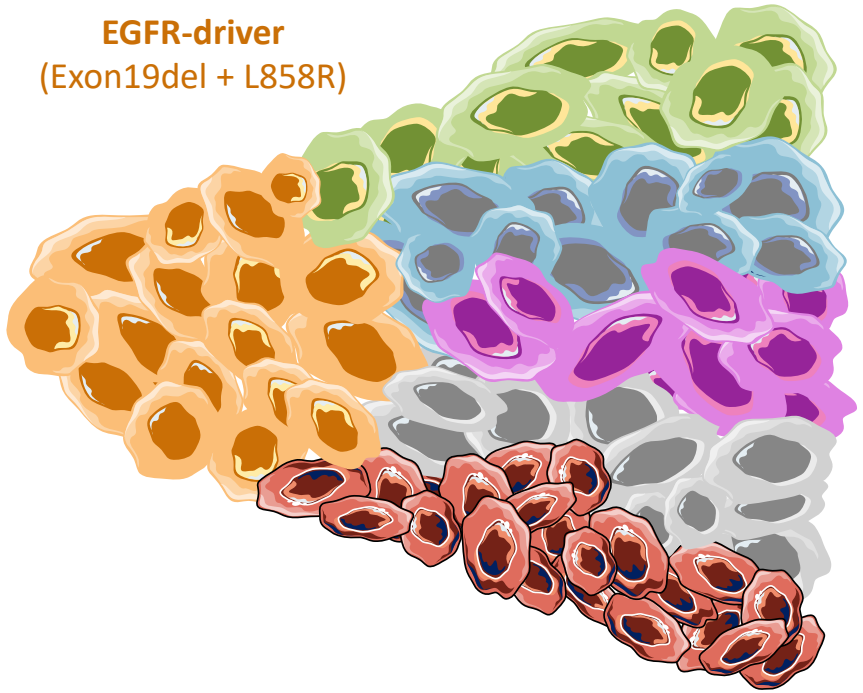
[1]Vijayaraghavan *Mol Cancer Ther* 19:2044; [2]Haura *JCO* 37:9009 (oral); [3]Park JCO 38:9512 (poster); [4]Sabari *JTO* 16:S108 (oral); [5]Ahn *Lancet Oncol* 20:P1681; [6]Kim *JCO* 38:9571 (poster); [7]Haddish-Berhane *JTO* 16:S677 (poster).
BTD, Breakthrough Therapy Designation; CNS, central nervous system; EGFRm, epidermal growth factor receptor mutant; gen, generation; MOA, mechanism of action; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor

Acquired Resistance to Osimertinib in EGFRm NSCLC

Osimertinib → **Platinum Chemotherapy**

Primary Mutations → **Resistance Mutations**

EGFR-driver
(Exon19del + L858R)



EGFR-dependent
(C797S)

MET-dependent
(MET amplification)

Other Pathways
(PIK3CA, RAS/RAF, Fusions, Cell Cycle)

Unknown
(~40-50%)

Transformations

Osimertinib resistance is complex

- Heterogenous patterns of resistance
- Co-occurrence of multiple resistance mechanisms
- NGS of ctDNA has been the most frequently used method to characterize osimertinib resistance mechanisms due to difficulties in obtaining tissue[1-2]

[1]Papadimitrakopoulou *Annals of Oncol* 29:VIII741; [2]Ramalingam *Annals of Oncol* 29:VIII740. ctDNA, circulating tumor DNA; Exon19del, exon 19 deletion; NGS, next generation sequencing

CHRYSALIS Phase 1 Study Design: Combination Cohort (NCT02609776)

Key Objectives

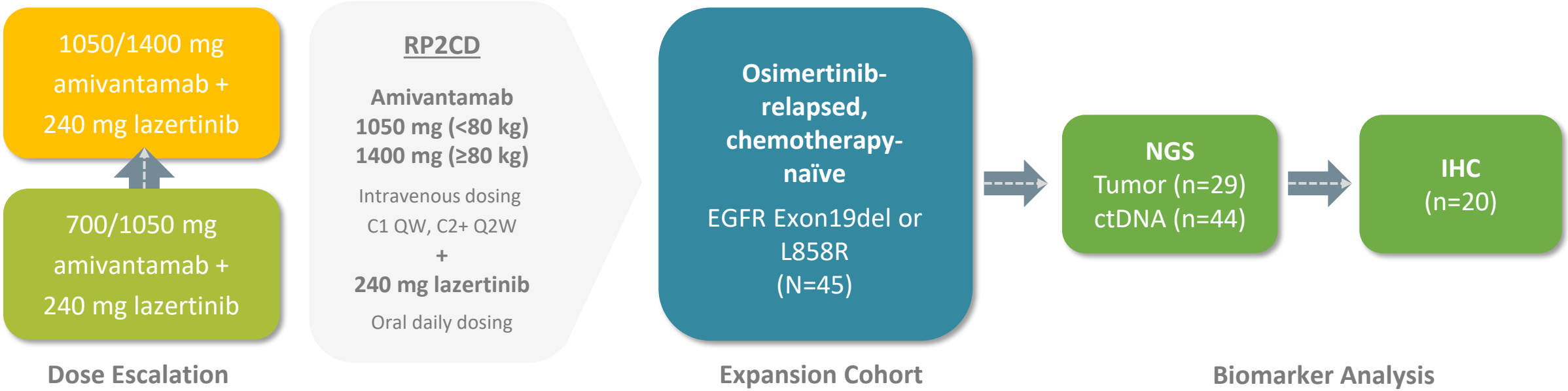
- Establish RP2CD
- Safety and efficacy at RP2CD

Key Eligibility Criteria

- Metastatic/unresectable NSCLC
- Measurable disease (expansion cohort)
- EGFR Exon19del or L858R mutation

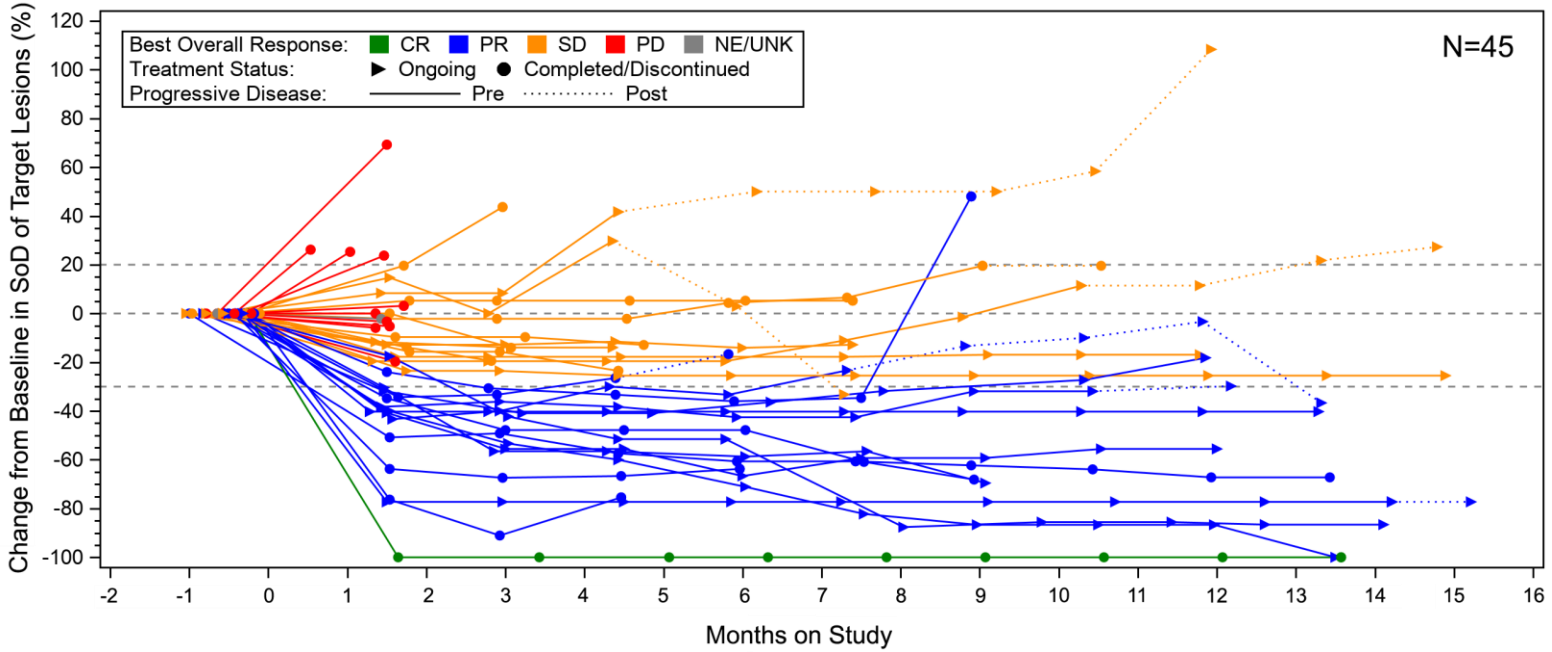
Biomarker Analysis[a]

- NGS of pretreatment tumor biopsy and ctDNA collected prospectively
- IHC for EGFR/MET expression



This presentation provides updated results with longer follow-up from the ESMO 2020 oral presentation (Cho *Ann Oncol* 31:S813 Oral #1258O). [a]≥1 alteration detected in 42/44 ctDNA and 29/45 tumor NGS analyses.
C, cycle; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; QW, weekly; Q2W, every 2 weeks; RP2CD, recommended phase 2 combination dose

Durable Responses Observed with Amivantamab + Lazertinib with Manageable Safety



Investigator-assessed Response (N=45) *mF/U: 11.0 months (range, 1.0–15.0)* *mDOT: 5.6 months (range, 0.5–14.8)*	
ORR	36% (95% CI, 22–51)
mDOR, months	9.6 (95% CI, 5.3–NR)
DOR ≥6 months	69%
CBR	64% (95% CI, 49–78)
mPFS, months	4.9 (95% CI, 3.7–9.5)

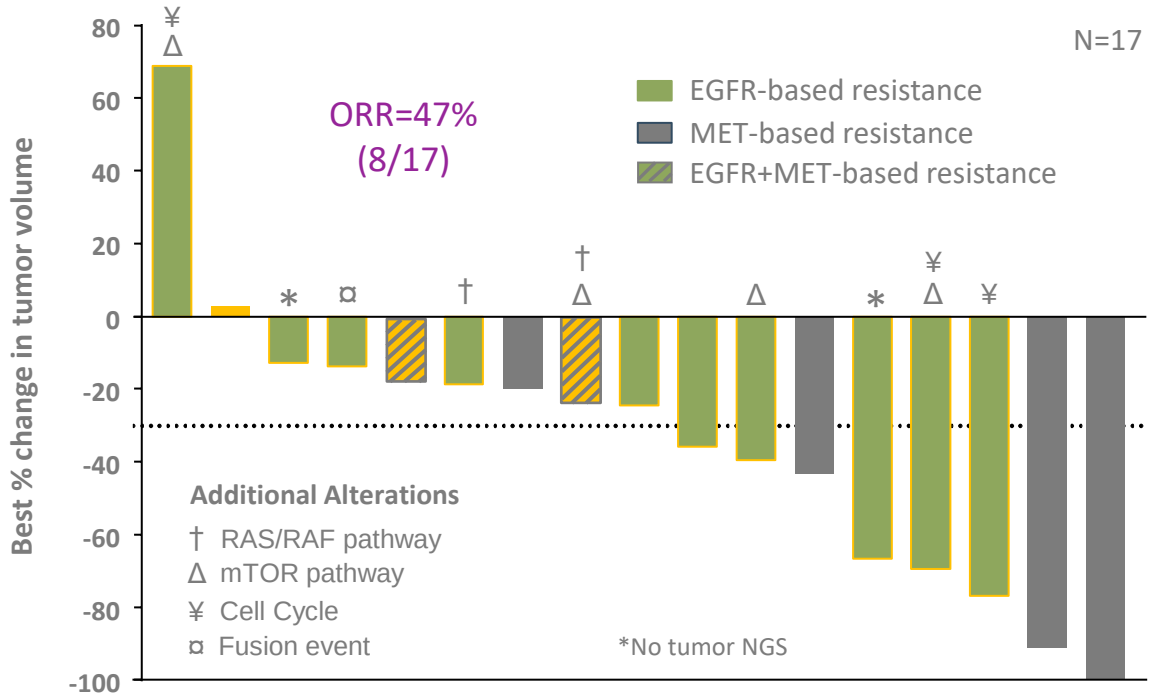
- Safety profile consistent with previous experience with amivantamab + lazertinib[1]
- Most common AEs were IRR (78%), rash (acneiform dermatitis, 51% + rash, 27%), and paronychia (49%)
  - Majority were grade 1–2
- Treatment-related: grade ≥3 AE (16%), discontinuations (4%), dose reductions (18%)

19 Apr 2021 clinical cutoff. Four patients did not have postbaseline disease assessments and are not included in the plot. [1]Cho *Ann Oncol* 31:S813 Oral #1258O.

AE, adverse event; CBR, clinical benefit rate (CR, PR, or SD ≥11 weeks); CR, complete response; IRR, infusion-related reaction; mDOR, median duration of response; mDOT, median duration of treatment; mF/U, median follow-up; mPFS, median progression-free survival; NE, not evaluable; NR, not reached; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of target lesion diameters; UNK, unknown

Response Among Patients with Identified EGFR/MET-based Resistance

- 17 of 45 patients were identified with either EGFR/MET-based resistance by NGS[a] (ctDNA/tissue)
- ORR in this subgroup was 47%, mDOR was 10.4 months, CBR was 82%, and mPFS was 6.7 months

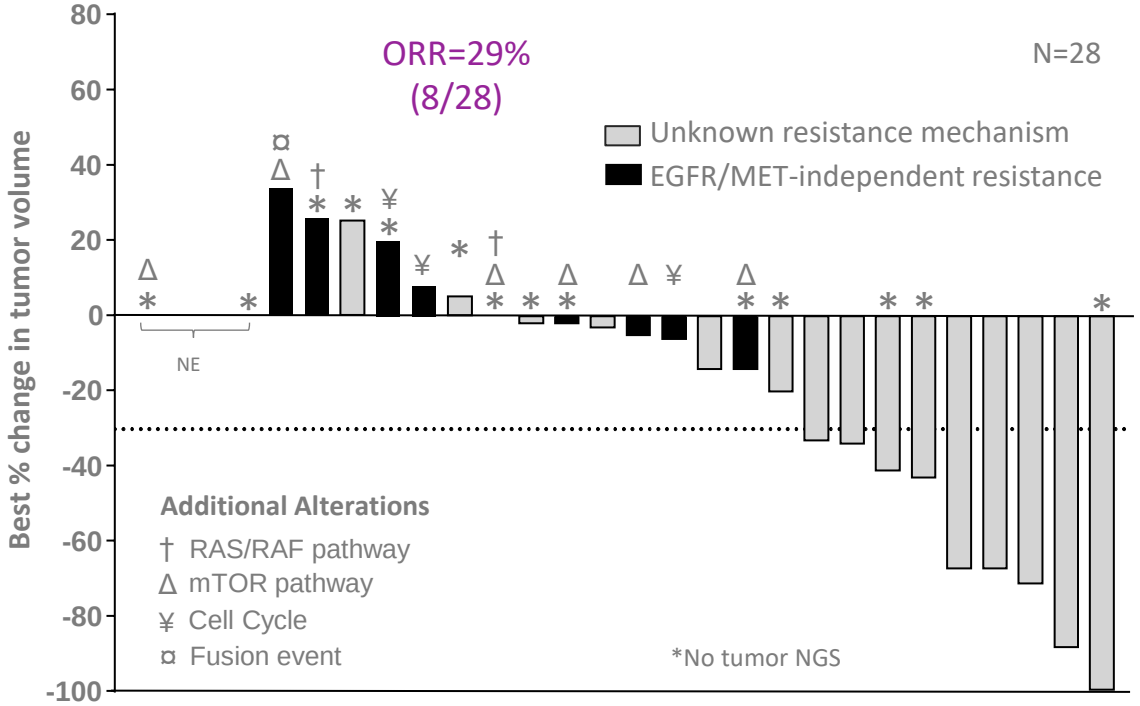


Resistance[b]	Alterations[c]	
EGFR-based	C797S (n=7) Amp (n=3) L718X (n=3) G724S (n=2)	L792H (n=1) G796S (n=1) E709K (n=1)
MET-based	Amp (n=5)	METex14 (n=1)
Additional	PIK3CA E542X (n=2) CCNE1 Amp (n=1) PIK3CA Amp (n=1) CCND1 Amp (n=1) CDK4 (n=1)	KRAS Amp (n=1) FGFR3-TACC3 fusion (n=1) KRAS G12D (n=1) CDKN2A G101W (n=1)

[a]Genomic analysis used Guardant360 for ctDNA NGS and ThermoFisher for tissue NGS; [b]EGFR amp (CNV ≥7) and MET amp (CNV ≥3) were based on tumor NGS; other amps were based on tumor NGS (CNV ≥7) or ctDNA NGS (CNV ≥3). Single nucleotide variants, insertion/deletions, and insertion call threshold was ≥1% allele frequency with >250 reads. [c]Eight patients had ≥1 alteration. Amp, amplification; CNV, copy number variation

Response Among Patients without Identified EGFR/MET-based Resistance

- Among the remaining 28 patients who did not have an identified EGFR/MET-based resistance by NGS[a], the ORR was 29%, mDOR was 8.3 months, CBR was 54%, and mPFS was 4.1 months
- All 8 responders in those without identified EGFR/MET-based resistance were unknown resistance by NGS

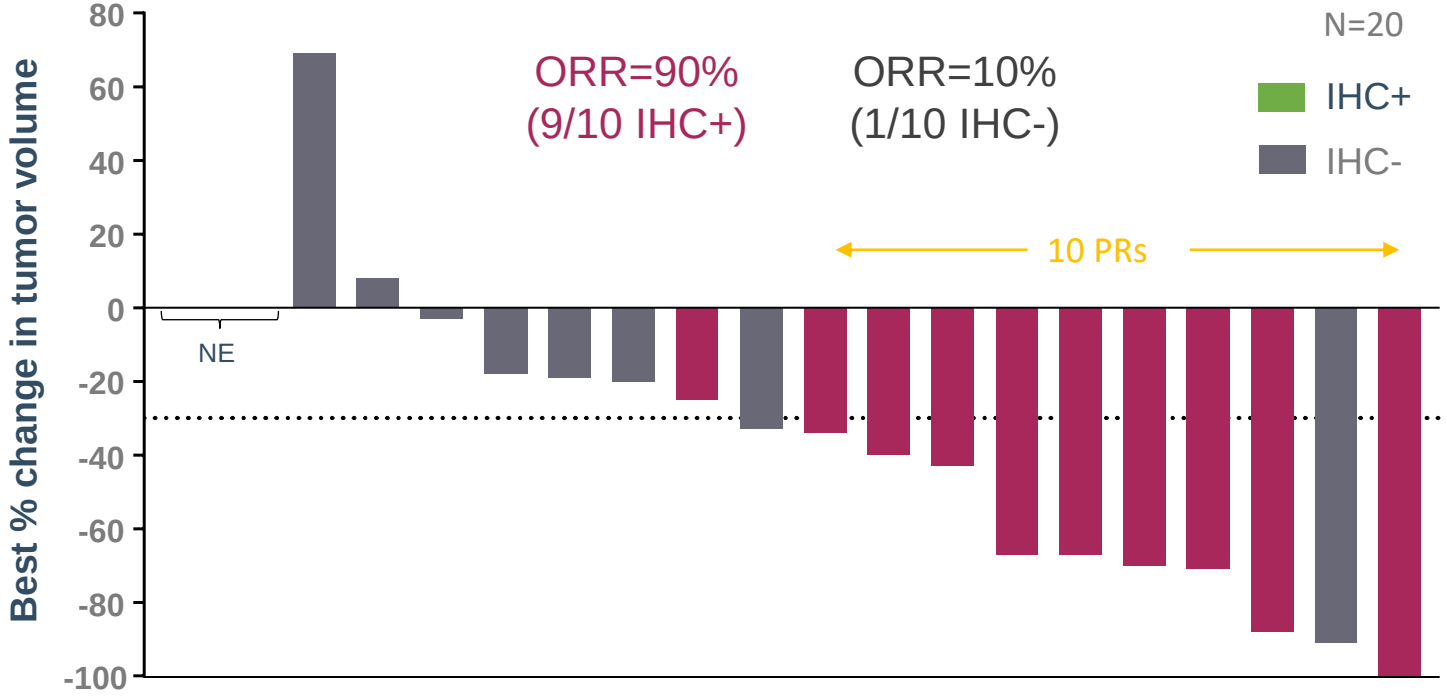


Resistance	Alterations[b]
EGFR/MET-independent	PIK3CA E545K (n=3) CCND1 Amp (n=2) CCND2 Amp (n=1) KRAS A18V (n=1) KRAS G12C (n=1) PIK3CA H1047R (n=1) PTEN I33del (n=1) PTEN N48K (n=1) SQSTM1-ALK fusion (n=1)
Not Identified (n=18)	

[a]Genomic analysis used Guardant360 for ctDNA NGS and ThermoFisher for tissue NGS. [b]Two patients had ≥1 alteration. NE, not evaluable (no postbaseline assessment for 4 patients)

Response Among Patients with EGFR/MET Expression Identified by IHC Staining

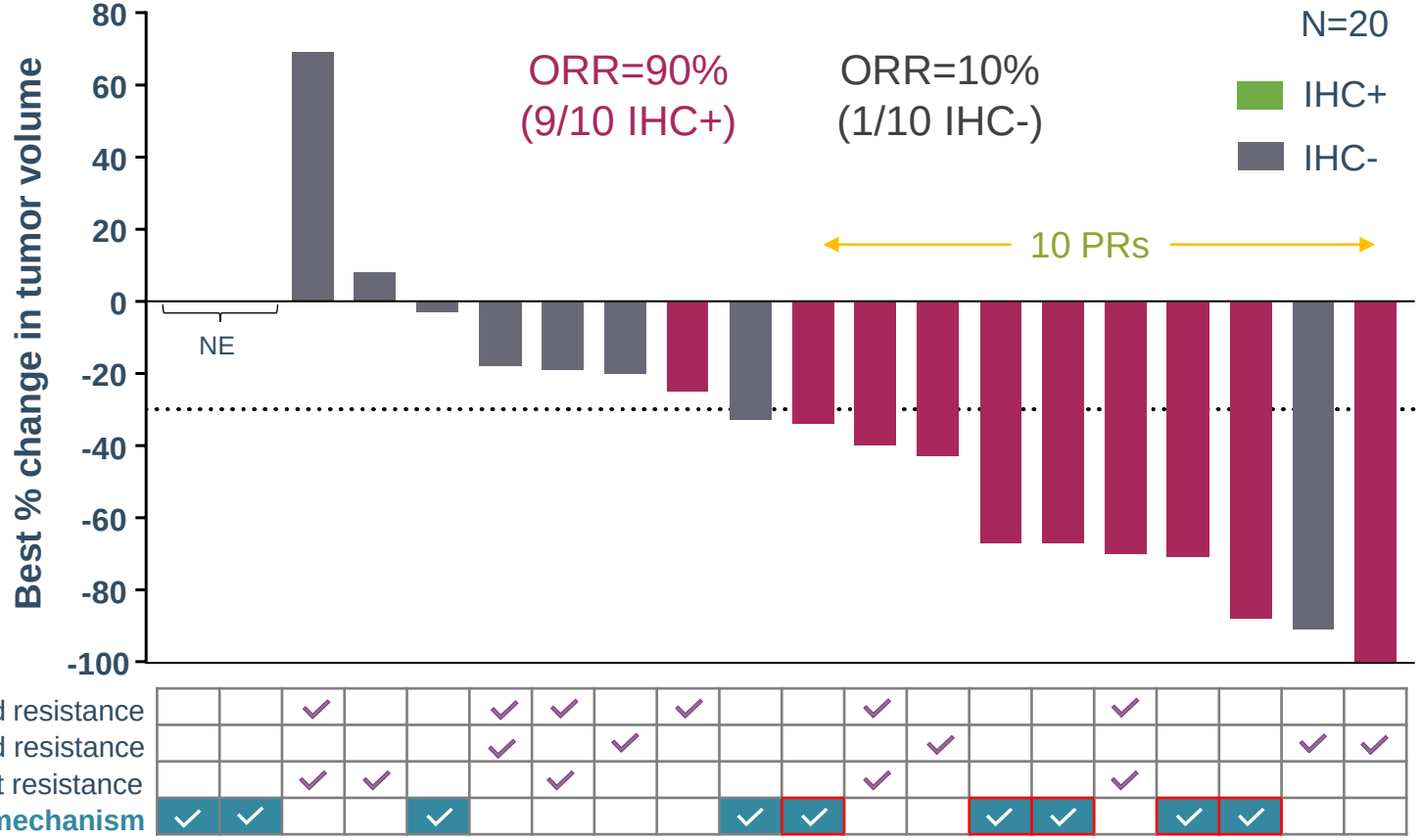
- 20/45 had tumor biopsy sufficient for IHC staining after tumor NGS
- 10 were IHC+ for EGFR/MET (combined EGFR+MET H score ≥400), with remainder defined as IHC-
- IHC+ patients had ORR of 90%, mDOR of 9.7 months, CBR of 100%, and mPFS of 12.5 months



IHC, immunohistochemistry; NE, not evaluable (no postbaseline assessment for 2 patients)

IHC Identified Patients Regardless of Underlying Genetic Resistance Mechanisms

- 5 responders in the IHC subgroup had unknown genetic mechanism of resistance



NE, not evaluable (no postbaseline assessment for 2 patients)

Conclusions

- Amivantamab in combination with lazertinib yielded durable responses in patients who progressed on osimertinib as prior line of therapy
  - 36% ORR, mDOR of 9.6 months, 64% CBR, and mPFS of 4.9 months
- NGS identified a subgroup of patients more likely to respond (EGFR/MET-based resistance)
  - However, half of the confirmed responders were not identified by NGS using these criteria
- IHC analysis suggests high EGFR and MET expression may be an alternative approach to identify potential responders
- CHRYSALIS-2[a], a phase 1/1b study, will seek to validate these biomarkers prospectively in a new cohort requiring tumor biopsy at entry (Cohort D) among post-osimertinib EGFRm NSCLC (NCT04077463)

[a]Poster TPS9132, "CHRYSALIS-2: A phase 1/1b study of lazertinib as monotherapy and in combination with amivantamab in patients with EGFR mutant NSCLC"

2021 ASCO ANNUAL MEETING

RACIAL DISPARITIES IN BIOMARKER TESTING AND CLINICAL TRIAL ENROLLMENT IN NON-SMALL CELL LUNG CANCER (NSCLC)

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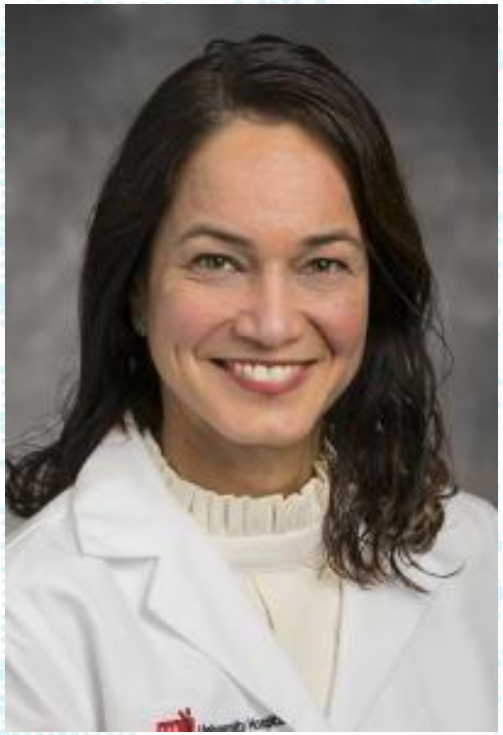
1. University Hospitals, Case Western Reserve University, Cleveland, OH

2. Eli Lilly and Company, Indianapolis, IN

June 4, 2021



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Biomarker Testing Impacts NSCLC Outcomes

- Lung cancer mortality
  - Leading cause of cancer-related deaths in the U.S. and worldwide[1,2]
  - Non-small cell lung cancer (NSCLC) accounts for 85% of all cases[3]
  - 57% of patients with stage IV upon presentation[5]
  - 5-yr OS of stage IV disease: 6%[2]

- Biomarker-driven therapies improve overall survival
  - Immunotherapy and kinase inhibitors lead to higher 5-yr OS in stage IV NSCLC subpopulations: 15-60%[5-7]
  - Biomarker testing is fundamental in advanced NSCLC

1. Siegel RL, Cancer J Clin 2021
2. WHO. https://www.who.int/news-room/fact-sheets/detail/cancer
3. Tan and Huq. NSCLC. Mescape. March 2021
4. Howlader N, SEER Cancer Statistics Review 1975-2017
5. Lin JJ, J Thorac Oncol 2016
6. Pacheco JM, J Thorac Oncol 2019
7. Garon EB, J Clin Oncol 2019

Comprehensive Biomarker Testing is Standard of Care for Stage IV NSCLC

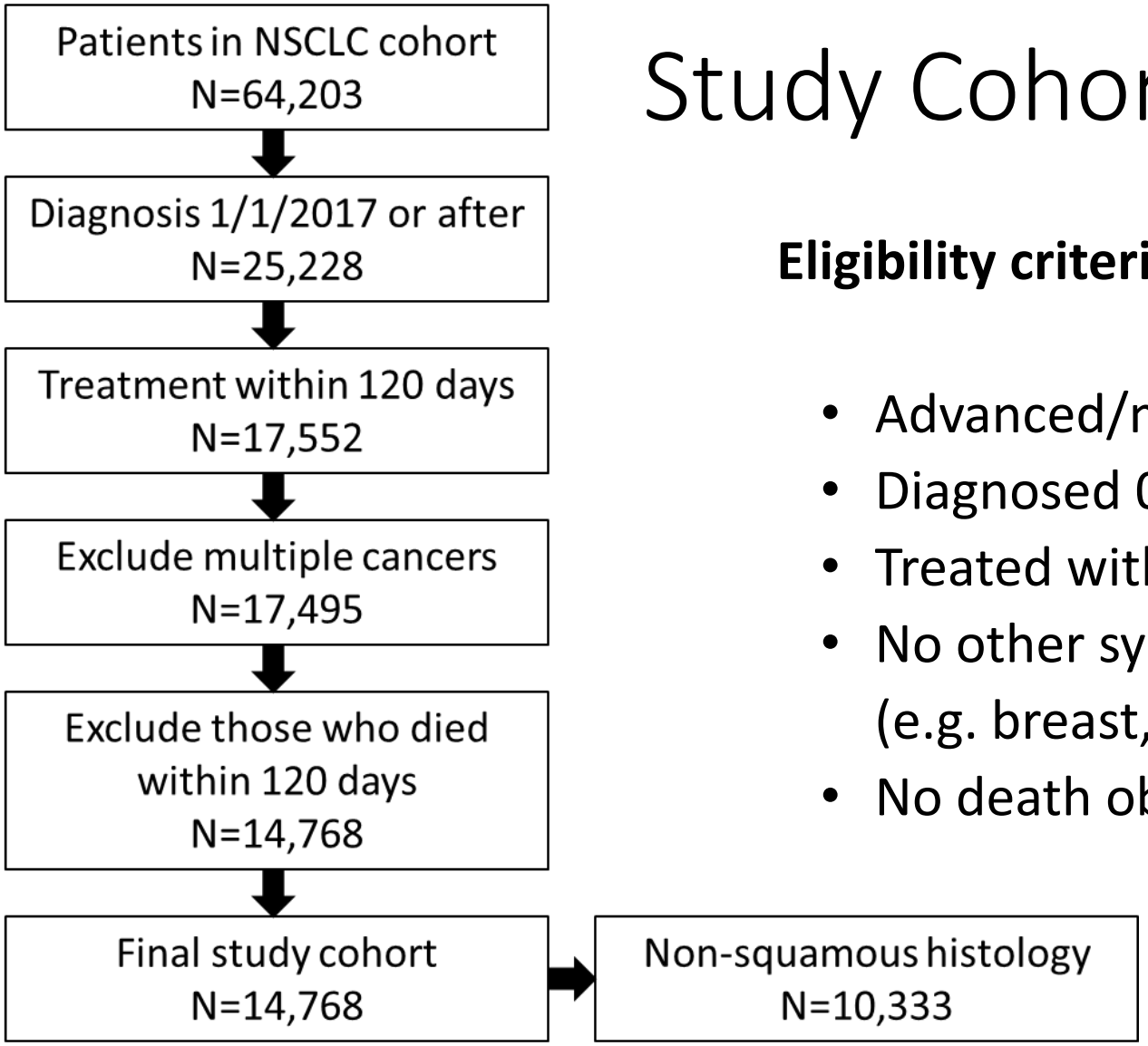
- NSCLC is a heterogeneous disease
  - Currently 7 genomic alterations and 3 PD-L1 subsets of stage IV NSCLC[1]
  - Since 2020: FDA approved 4 targeted therapies in 1L for MET exon 14 skipping, RET and ALK fusions
  - National guidelines recommend broad-based testing for PD-L1 and actionable mutations[1]
  - Genomic testing identifies best approved therapies and is an eligibility criteria for many clinical trials

- NSCLC survival disparities
  - Racial disparities in OS persist despite improvements in last ~20 years[2]
  - Access to high quality care and clinical trials may contribute to disparities[3]
  - Biomarker testing uptake in real practice – the impact of race is unknown

1. Ettinger DS, J Natl Compr Netw 2021
2. Howlader N, N Engl J Med 2020
3. Zaorsky NG, J Natl Compr Netw 2019

Methods

- Study Objective
  - To investigate racial differences in biomarker testing, use of targeted therapy and clinical trial enrollment among patients in the U.S. diagnosed with advanced/metastatic NSCLC
- Study Design
  - Retrospective cohort study of patients with advanced/metastatic NSCLC - Jan 2017 – October 2020
  - Flatiron Health Electronic Health Record (EHR)-derived de-identified database: ~800 sites of care
    - De-identified data are not considered human subjects research and is exempt from IRB review (Copernicus Group IRB)



Study Cohort

Eligibility criteria

- Advanced/metastatic NSCLC
- Diagnosed 01/01/17 – 10/31/20
- Treated within 120 days from diagnosis
- No other synchronous metastatic cancers (e.g. breast, colorectal, gastric)
- No death observed within 120 days

Biomarker Testing

All patients with NSCLC				
	NSCLC overall N=14,768	**White N=9,793**	**Black/AA N=1,288**	**P-value, White vs Black/AA**
Ever tested	11,297 (76.5%)	7477 (76.4%)	948 (73.6%)	0.03
Tested prior to first line therapy		6,064 (61.9%)	784 (60.9%)	0.47
Ever NGS tested	7,185 (48.7%)	**4,904 (50.1%)**	**513 (39.8%)**	**<0.0001**
NGS tested prior to first line therapy		**3,081 (31.5%)**	**332 (25.8%)**	**<0.0001**
Patients with non-squamous NSCLC				
	Non-squamous N=10,333	**White N=6,705**	**Black/AA N=922**	**P-value, White vs Black/AA**
Ever tested	8,786 (85.0%)	5,699 (85.0%)	764 (82.9%)	0.09
Tested prior to first line therapy		4,881 (72.8%)	662 (71.8%)	0.52
Ever NGS tested	5,494 (53.2%)	**3,668 (54.7%)**	**404 (43.8%)**	**<0.0001**
NGS tested prior to first line therapy		**2,452 (36.6%)**	**274 (29.7%)**	**<0.0001**

AA = African American; NGS = next-generation sequencing

Clinical Trial Participation*

All patients with NSCLC				
	NSCLC overall N=14,768	**White N=9,793**	**Black/AA N=1,288**	**P-value, white vs black**
Evidence of trial participation	484 (3.3%)	**385 (3.9%)**	**24 (1.9%)**	**0.0002**
No evidence of participation	14,284 (96.7%)	9,408 (96.1%)	1,264 (98.1%)	
Patients with non-squamous NSCLC				
	Non-squamous N=10,333	**White N=6,705**	**Black/AA N=922**	**P-value, white vs black**
Evidence of trial participation	343 (3.3%)	**261 (3.9%)**	**19 (2.1%)**	**0.006**
No evidence of participation	9,990 (96.7%)	6,444 (96.1%)	903 (97.9%)	

*Evidence of clinical trial participation = yes if one or more drugs received by the patient at any time after diagnosis indicated "clinical trial drug." There is no specific variable for clinical trial participation in the EHR database.

NGS Testing and Clinical Trial Participation*

All patients with NSCLC				
	NSCLC overall N=14,768	Ever NGS tested (n=7,185)	Never NGS tested (n=7,583)	P-value, tested vs not
Evidence of trial participation	484 (3.3%)	**318 (4.4%)**	**166 (2.2%)**	**<0.0001**
No evidence of participation	14,284 (96.7%)	6,867 (95.5%)	7,417 (97.8%)	
Patients with non-squamous NSCLC				
	Non-squamous N=10,333	Ever NGS tested (n=5,494)	Never NGS tested (n=4,839)	P-value, tested x not
Evidence of trial participation	343 (3.3%)	**236 (4.3%)**	**107 (2.2%)**	**<0.0001**
No evidence of participation	9,990 (96.7%)	5,258 (95.7%)	4,732 (97.8%)	

*Evidence of clinical trial participation = yes if one or more drugs received by the patient at any time after diagnosis indicated "clinical trial drug." There is no specific variable for clinical trial participation in the EHR database.

Conclusions

- Real world practice: Patients who are Black/AA are less likely to undergo NGS testing when compared to those who are White (39.8% versus 50.1%, p<0.0001)
- Black/AA patients in this cohort were significantly less likely to be treated in clinical trials
- Participation in clinical trials was higher in patients undergoing NGS testing
    - In adjusted analyses, factors associated with clinical trial participation among Black and White patients included: NGS testing, biomarker testing, age, histology, race, stage III vs IV, and practice volume
- While multiple factors are known to impact health care disparities, access to and receipt of appropriate biomarker testing may be an attenable goal in order to ensure equal access to quality care
- Ongoing robust set of adjusted analyses further investigating these relationships in other tumor types, including the use of additional data sets

Scan or click the QR code or use this URL (https://lillyscience.lilly.com/congress/AmOncMtgJun2021) for a list of all Lilly content presented at the congress

Debora Bruno, MD, MS

2021 ASCO ANNUAL MEETING

Pooled Analyses of Immune-Related Adverse Events and Efficacy From the Phase 3 Trials IMpower130, IMpower132 and IMpower150

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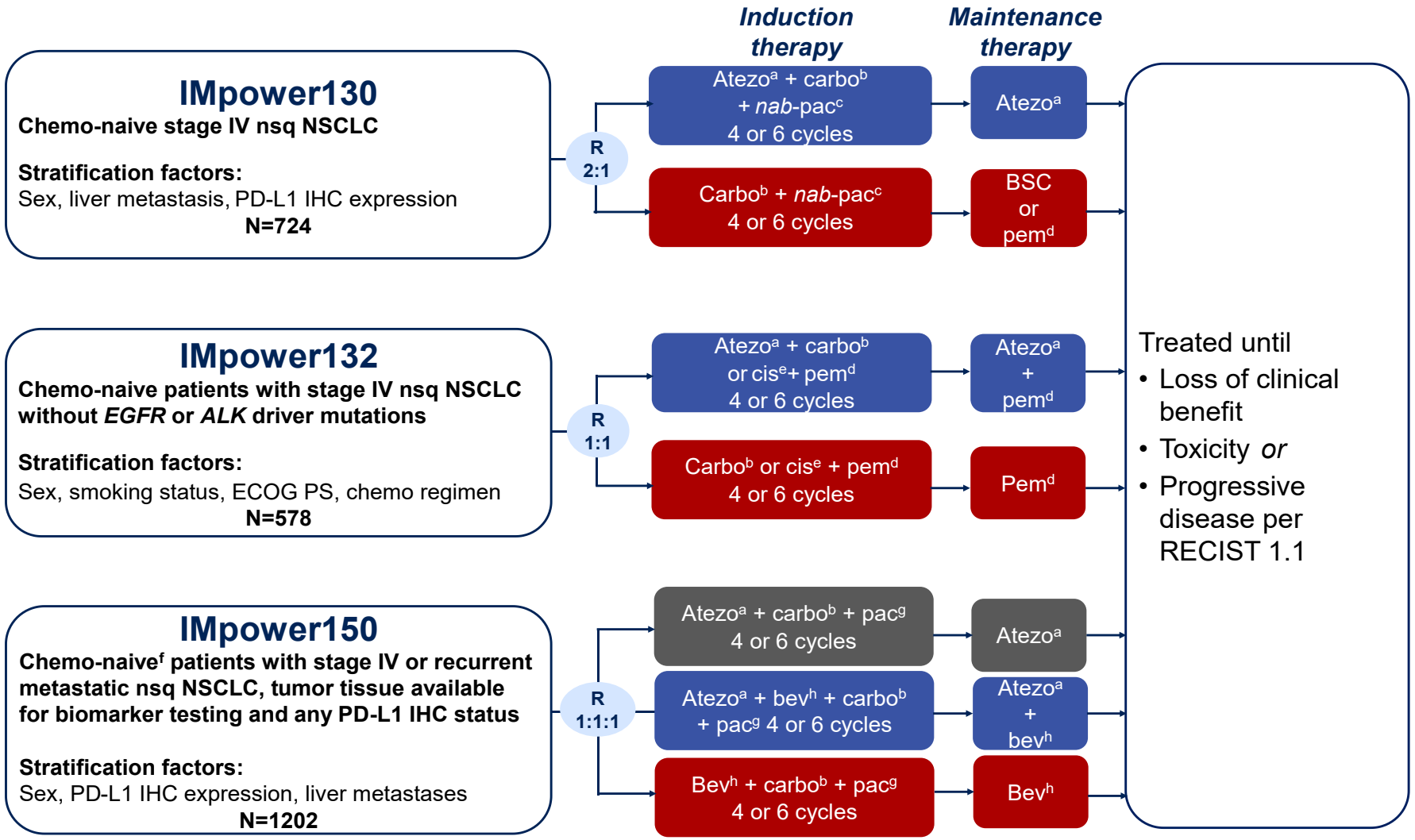
[1]AdventHealth Cancer Institute, Orlando, FL, USA; [2]Rocky Mountain Cancer Centers, Denver, CO, USA and US Oncology, Houston, TX, USA; [3]Istituto Nazionale Tumori "Regina Elena," Rome, Italy; [4]The Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; [5]State Key Laboratory of Translational Oncology, The Chinese University of Hong Kong, Hong Kong; [6]Lung Clinic Grosshansdorf, Airway Research Center North, German Center of Lung Research, Grosshansdorf, Germany; [7]Allegheny Health Network Cancer Institute, Pittsburgh, PA, USA; [8]Genentech, Inc., South San Francisco, CA, USA; [9]City of Hope Comprehensive Cancer Center, Duarte, CA, USA

Background

- Immune-related adverse events (irAEs), which are caused by off-target immune and inflammatory activity, have been reported in up to 80% of patients receiving immune checkpoint inhibitor (ICI) monotherapy and up to 95% of those receiving ICI combination therapy[1]
- Increasing evidence suggests that the occurrence of irAEs with PD-L1/PD-1 inhibitor therapy may be predictive of improved outcomes in cancers such as NSCLC[2-5]
- Atezolizumab (anti–PD-L1) has shown efficacy and tolerability in patients with NSCLC and is currently approved for use in the first- and second-line and beyond settings[6]
- The Phase III IMpower130 and IMpower132 trials evaluated the efficacy and safety of atezolizumab + chemotherapy for first-line treatment of advanced NSCLC; IMpower150 evaluated atezolizumab + chemotherapy ± bevacizumab[7-9]
  - IMpower130 and IMpower150 both met their co-primary OS and PFS endpoints, while IMpower132 met its co-primary PFS, but not OS, endpoint
- This post hoc exploratory analysis evaluated the association between irAEs and efficacy in IMpower130, IMpower132 and IMpower150 using pooled data

1. Jamal S, et al. J Rheumatol. 2020;47:166-75. 2. Remon J, et al. Thorac Oncol. 2019;14:963-7. 3. Zhou X, et al. BMC Med. 2020;18:87. 4. von Pawel J, et al. Ann Oncol. 2017;28:v469. 5. Haratani K, et al. JAMA Oncol. 2018;4:374-8. 6. TECENTRIQ (atezolizumab). Prescribing information. Genentech, 2020. 7. West H, et al. Lancet Oncol. 2019;20:924-37. 8. Nishio M, et al. J Thorac Oncol. 2021;16:653-64. 9. Socinski MA, et al. N Engl J Med. 2018;378:2288-301.

Study designs



Co-primary endpoints

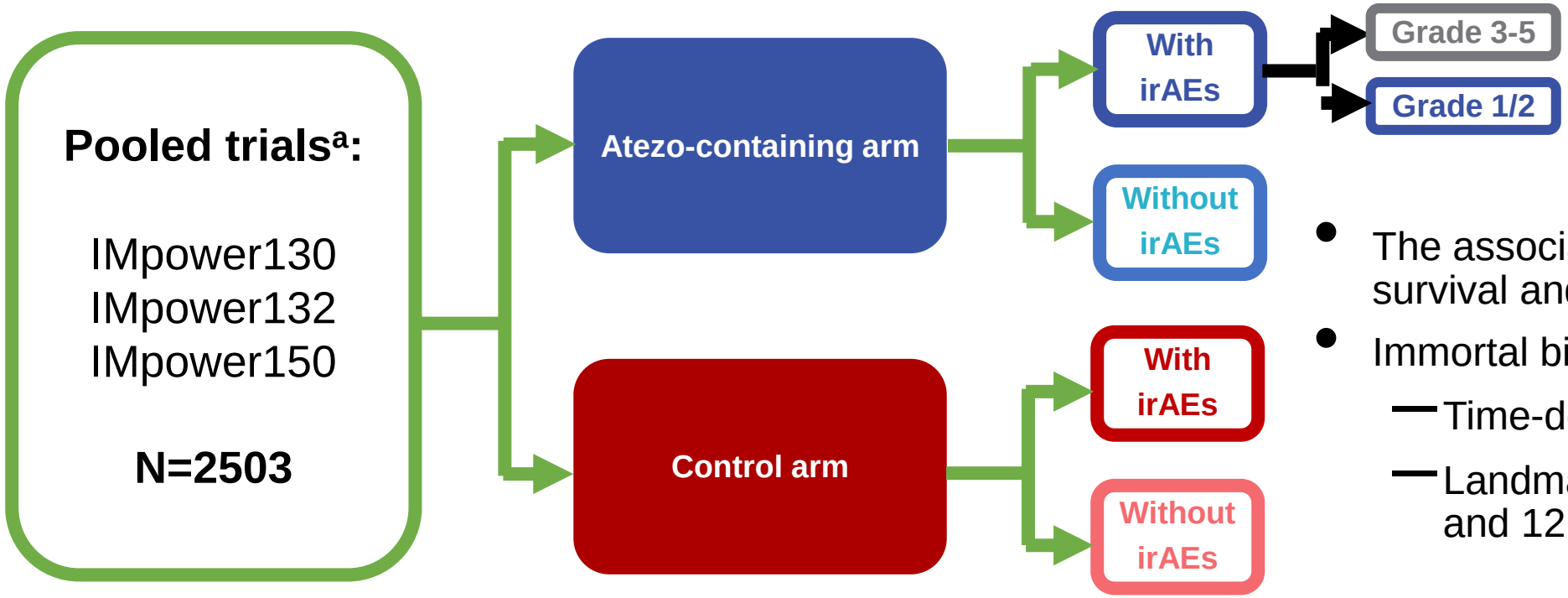
- INV-assessed PFS in WT population (ITT)
- OS in WT population (ITT)

- INV-assessed PFS
- OS

- INV-assessed PFS in WT population (ITT)
- INV-assessed PFS in Teff-high WT population
- OS in WT population

atezo; atezolizumab; BSC, best supportive care; bev, bevacizumab; carbo, carboplatin; chemo, chemotherapy; cis; cisplatin; IHC, immunohistochemistry; INV, investigator; nsq, non-squamous; pac, paclitaxel; pem; pemetrexed; WT, wild type.
[a] Atezo: 1200 mg IV q3w. [b] Carbo: AUC 6 mg/mL/min IV q3w. [c] *nab*-Pac: 100 mg/m^2 IV q3w. [d] Pem: 500 mg/m^2 IV q3w. [e] Cis: 75 mg/m^2 IV q3w. [f] Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have disease progression or had treatment intolerance with ≥1 approved targeted therapies. [g] Pac: 200 mg/m^2 IV q3w. [h] Bev: 15 mg/kg IV q3w.

Methods and analysis plan



- The association between overall survival and irAEs was explored
- Immortal bias was managed by using:
  - Time-dependent Cox model
  - Landmark analyses at 1, 3, 6 and 12 months

irAEs

Defined using the Medical Dictionary for Regulatory Activities preferred terms, which included diagnosed immune conditions as well as signs and symptoms potentially representative of immune-related events regardless of investigator-assessed causality

[a] Data cutoffs: March 15, 2018 (IMpower130); May 22, 2018 (IMpower132); September 13, 2019 (IMpower150).

Summary of irAEs[a]

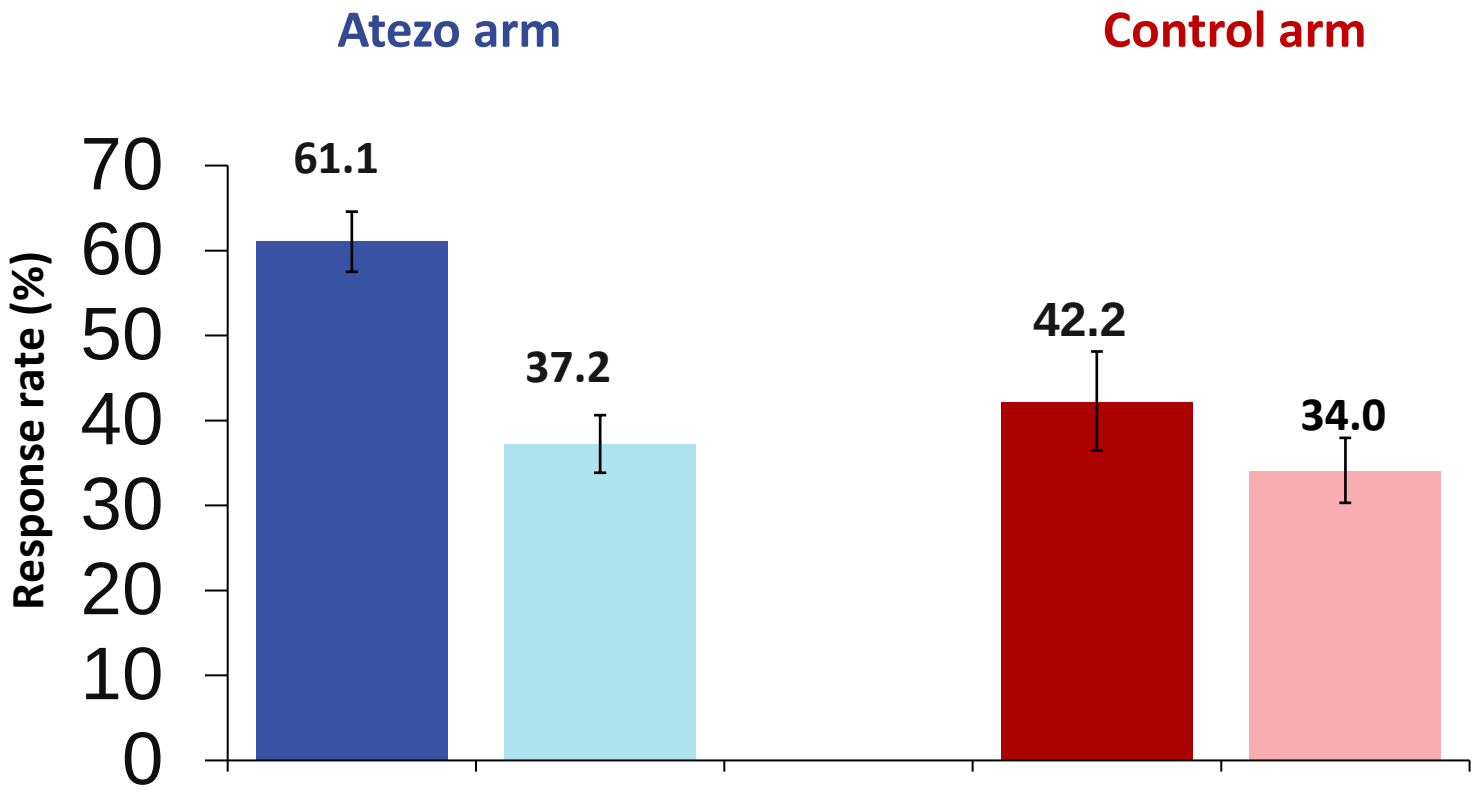
irAE, n (%)	Atezo arm (n=1557)		Control arm (n=900)	
	Any grade	Grade 3-5	Any grade	Grade 3-5
Any irAE	753 (48)	174 (11)	289 (32)	45 (5)
Rash	435 (28)	38 (2)	160 (18)	11 (1)
Hepatitis[b]	226 (15)	73 (5)	92 (10)	17 (2)
Hypothyroidism	192 (12)	6 (<1)	33 (4)	0
Pneumonitis	88 (6)	25 (2)	17 (2)	8 (1)
Hyperthyroidism	59 (4)	3 (<1)	14 (2)	0
Colitis	26 (2)	17 (1)	3 (<1)	2 (<1)
Infusion-related reactions	17 (1)	1 (<1)	6 (1)	1 (<1)
Adrenal Insufficiency	19 (1)	3 (<1)	3(<1)	1 (<1)
Pancreatitis	15 (1)	6 (<1)	4 (<1)	2 (<1)

The median time to onset of irAEs was 1.7 mo (range, 0.0-34.7) in the atezolizumab arm and 1.4 mo (range, 0.0-17.2) in the control arm

[a] Events represent medical concepts and are not single MedDRA preferred terms. Includes events occurring in >1% incidence in any arm. [b] Includes both hepatitis laboratory abnormalities and diagnosis.

Mark A. Socinski
IMpower130/132/150 pooled irAEs
https://bit.ly/3gZPrMq

ORR by irAE status



	With irAEs	Without irAEs	With irAEs	Without irAEs
Median time to response (range), mo	1.71 (1.1-29.7)	1.71 (1.0-27.1)	1.64 (1.1-11.3)	1.54 (1.1-13.4)

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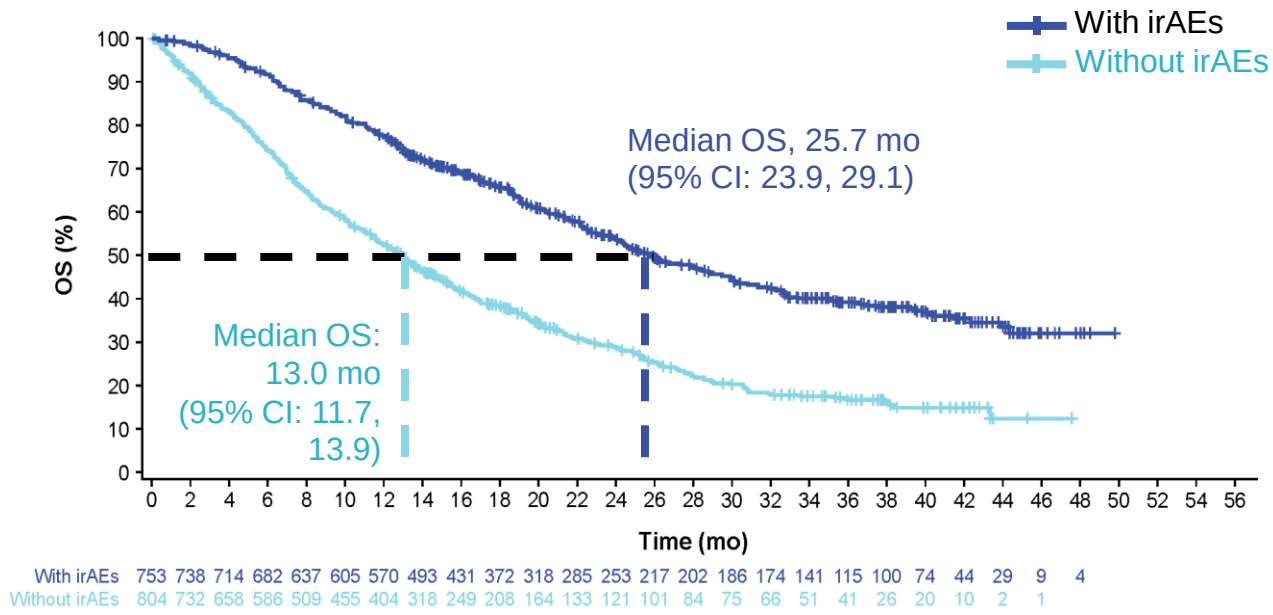
IMpower130/132/150 pooled irAEs
https://bit.ly/3gZPrMq

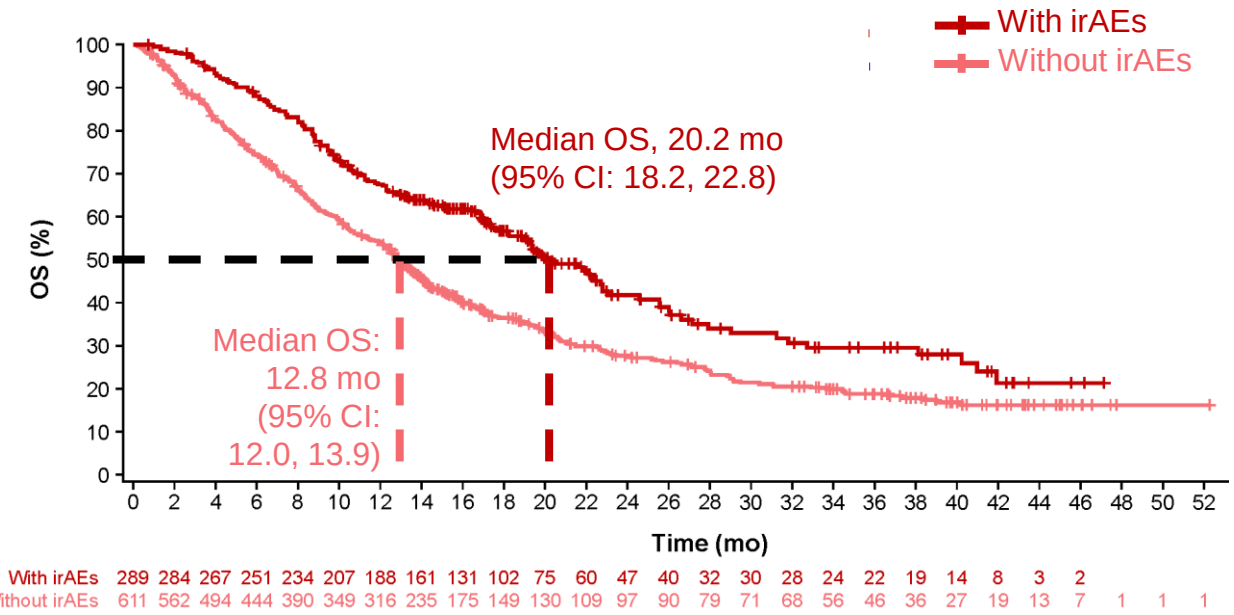
OS by irAE status[a,b]

Atezo arm



Time-dependent Cox model:
HR, 0.69 (95% CI: 0.60, 0.78)

Control arm



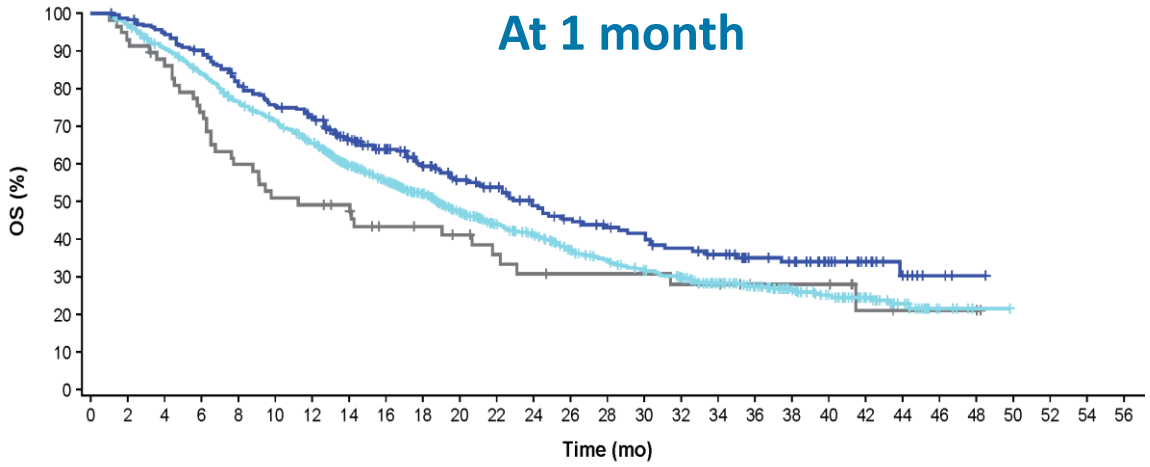
Time-dependent Cox model:
HR, 0.82 (95% CI: 0.68, 0.99)

Patients who experienced irAEs had longer OS than those without irAEs in both the atezo-containing and control arms

[a] Kaplan-Meier curves are not adjusted for the timing of irAE onset. [b] An interaction test of irAE status and treatment arms did not reveal statistical significance (*P*=0.13).

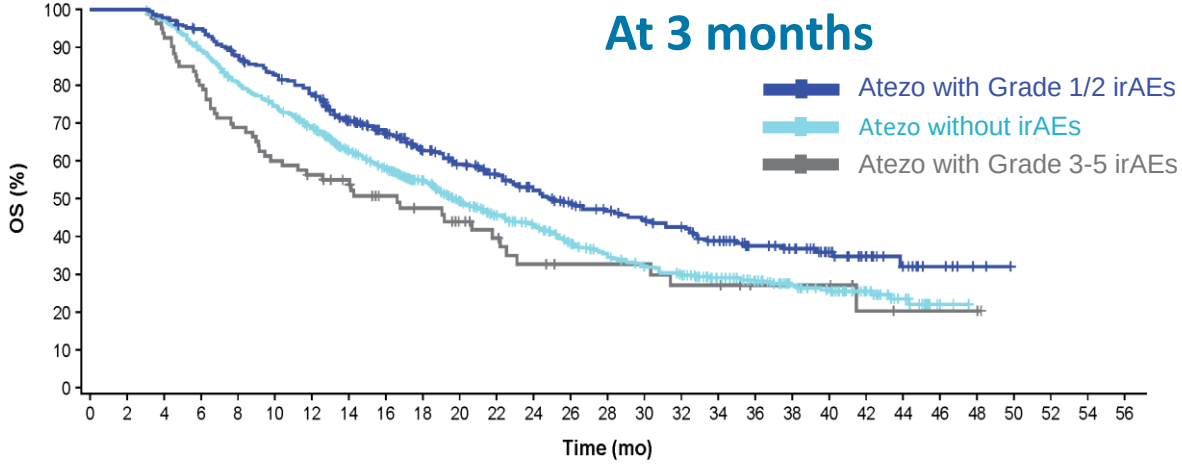
OS by irAE grade in the atezolizumab arm

At 1 month



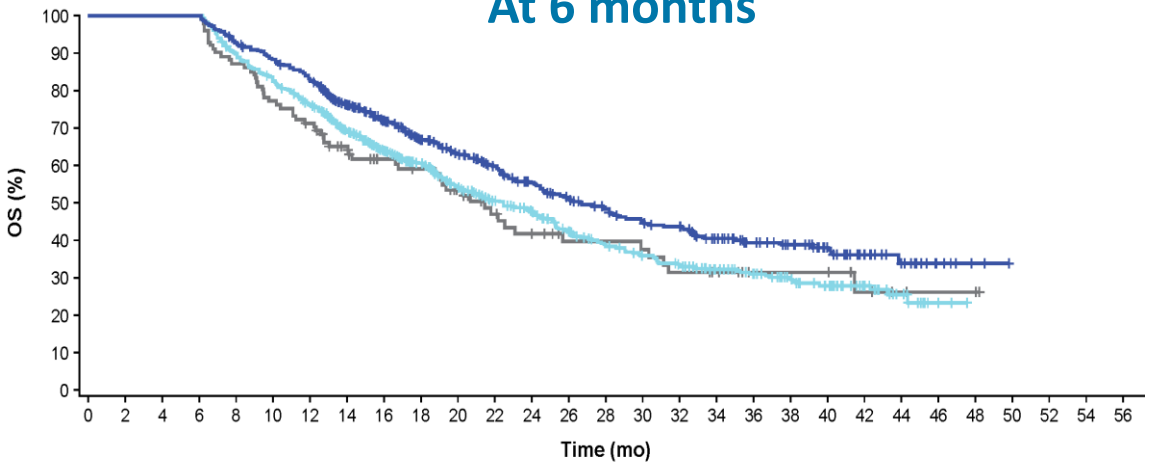
Atezo with Gr 1/2 irAEs	247	242	232	220	198	182	173	141	123	104	87	80	69	62	56	52	47	42	34	31	21	14	7	3	1
Atezo without irAEs	1210	1174	1090	1006	914	849	773	644	537	457	378	324	293	245	219	198	183	140	115	88	66	37	22	5	1
Atezo with Gr 3-5 irAEs	58	54	50	42	34	29	28	26	20	19	17	14	12	11	11	11	10	10	7	7	7	3	2	2	2

At 3 months



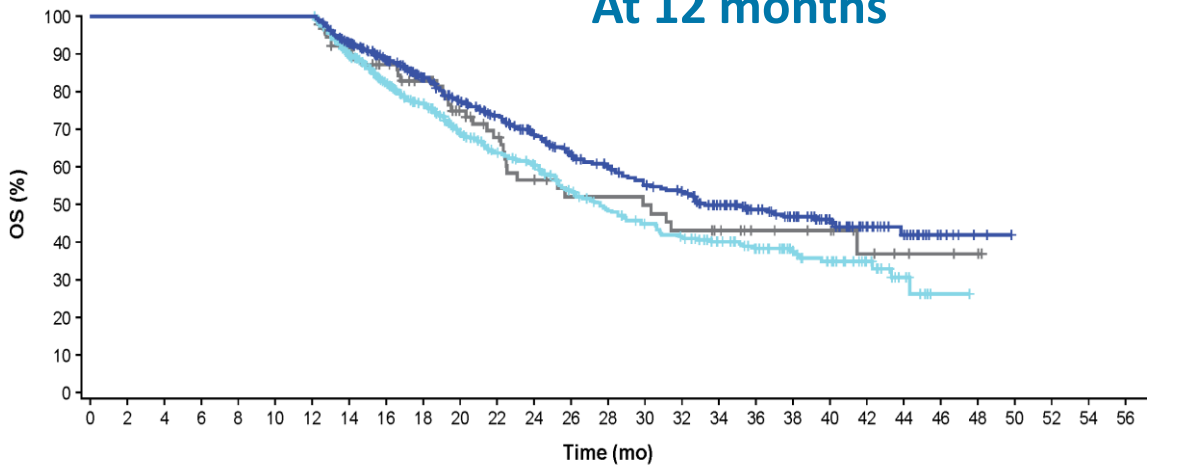
Atezo with Gr 1/2 irAEs	370	370	361	347	319	300	280	234	204	168	146	131	116	104	94	88	82	67	54	49	33	19	11	6	2
Atezo without irAEs	963	963	936	857	772	712	650	537	445	385	314	269	244	202	180	161	148	115	95	70	54	32	18	2	
Atezo with Gr 3-5 irAEs	81	81	75	64	55	48	44	40	31	27	22	18	14	12	12	12	10	10	7	7	7	3	2	2	2

At 6 months



Atezo with Gr 1/2 irAEs	431	431	431	431	399	378	353	297	258	214	185	164	144	128	116	107	101	82	68	60	41	23	14	6	2
Atezo without irAEs	736	736	736	736	659	604	550	455	375	323	262	226	206	171	151	136	124	97	79	57	44	26	14	2	
Atezo with Gr 3-5 irAEs	101	101	101	101	88	78	71	59	47	43	35	28	24	19	19	18	15	13	9	9	9	5	3	2	2

At 12 months



Atezo with Gr 1/2 irAEs	428	428	428	428	428	428	428	366	322	275	234	209	185	162	148	135	126	100	81	70	49	28	18	6	2
Atezo without irAEs	455	455	455	455	455	455	455	369	296	251	204	172	159	133	115	104	95	75	62	44	34	20	9	1	
Atezo with Gr 3-5 irAEs	91	91	91	91	91	91	91	76	62	54	44	37	30	23	23	22	19	17	13	12	11	6	4	3	2

Mark A. Socinski
IMpower130/132/150 pooled irAEs
https://bit.ly/3gZPrMq

Conclusions

- In these exploratory pooled analyses of the IMpower130, IMpower132 and IMpower150 trials, patients who experienced irAEs showed longer OS than those without irAEs in both the atezolizumab-containing and control arms
  - OS HRs from the time-dependent Cox model: atezolizumab arm, 0.69 (95% CI: 0.60, 0.78); control arm, 0.82 (95% CI: 0.68, 0.99)
  - Patients in the atezolizumab-containing arm with Grade 3-5 irAEs had the shortest OS vs those with Grade 1/2 irAEs or no irAEs, potentially due to treatment interruption/discontinuation
- In both arms, landmark analyses at 1, 3, 6 and 12 months showed longer OS in patients with irAEs vs those without irAEs; patients benefited from atezolizumab vs control regardless of whether they had experienced irAEs
- Data from these analyses suggest an association between irAEs and efficacy in patients with NSCLC and further support the use of atezolizumab combined with chemotherapy, with or without bevacizumab, in the first-line treatment setting

2021 ASCO ANNUAL MEETING

PHASE III COMPARISON OF HIGH DOSE ONCE DAILY (QD) THORACIC RADIOTHERAPY (TRT) WITH STANDARD TWICE-DAILY (BID) TRT IN LIMITED STAGE SMALL CELL LUNG CANCER (LSCLC): CALGB 30610 (ALLIANCE) / RTOG 0538

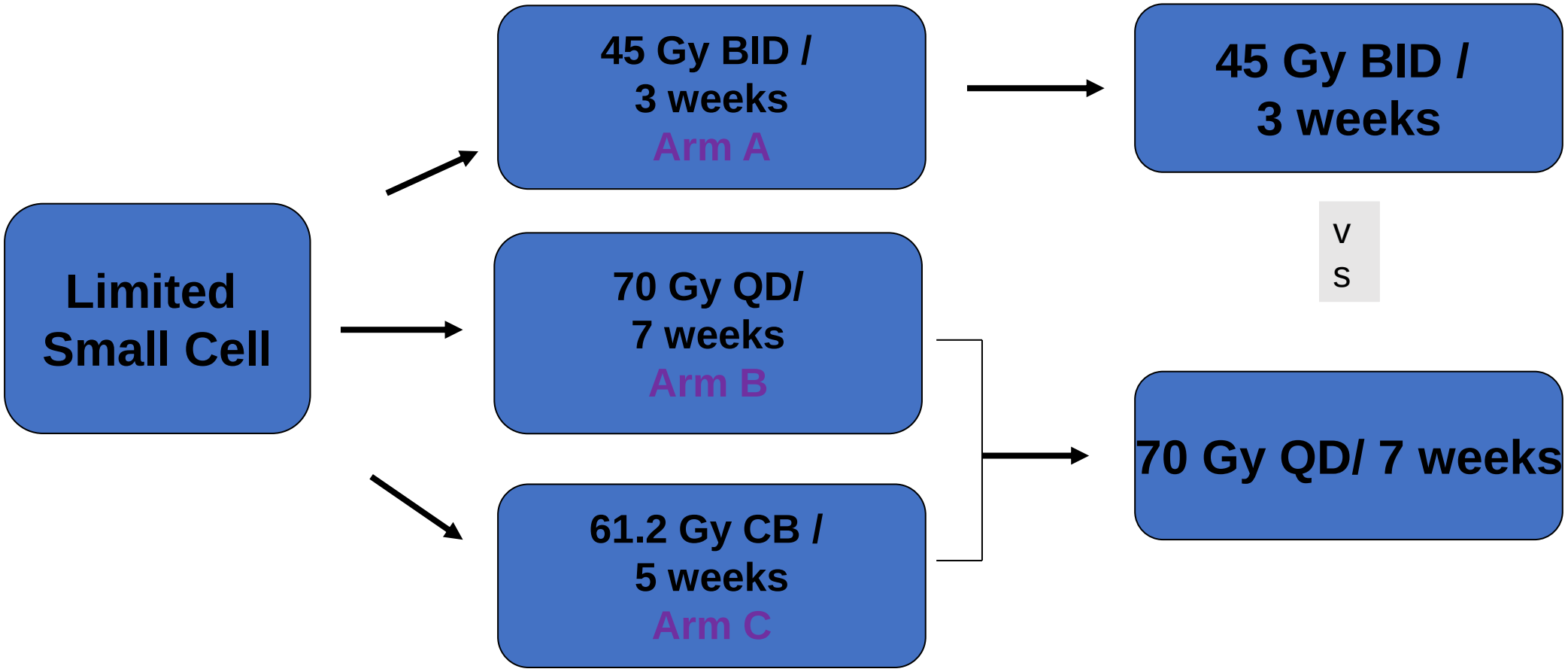
Jeffrey A. Bogart, Xiaofei Wang, Gregory Masters, Junheng Gao, Ritsuko Komaki, Laurie E. Gaspar, John Heymach, Michael Christian Dobelbower, Charles Kuzma, Saiama Waqar, William J Petty, Tom Stinchcombe, Jeffrey D. Bradley, Everett Vokes

Background

- The optimal TRT dose and schedule for LSCLC remains an area of active study
- Despite Level 1 evidence supporting 45 Gy BID TRT / 3 weeks (Intergroup 0096), most patients are treated with once-daily TRT in clinical practice
- Pilot trials from CALGB (C-39808) and RTOG (R-0239) studied high-dose TRT regimens with higher *predicted* biologic effective doses (BED) compared with 45 Gy BID

	Total Dose	Dose/fx	Frequency	Fractions	Duration
Standard	45 Gy	1.5 Gy	Twice-daily	30	3 weeks
CALGB	70 Gy	2.0 Gy	Once-daily	35	7 weeks
RTOG	61.2 Gy Concomitant Boost (CB)	1.8 Gy	QD x 16 days then BID x 9 days	34	5 weeks

Initial Schema

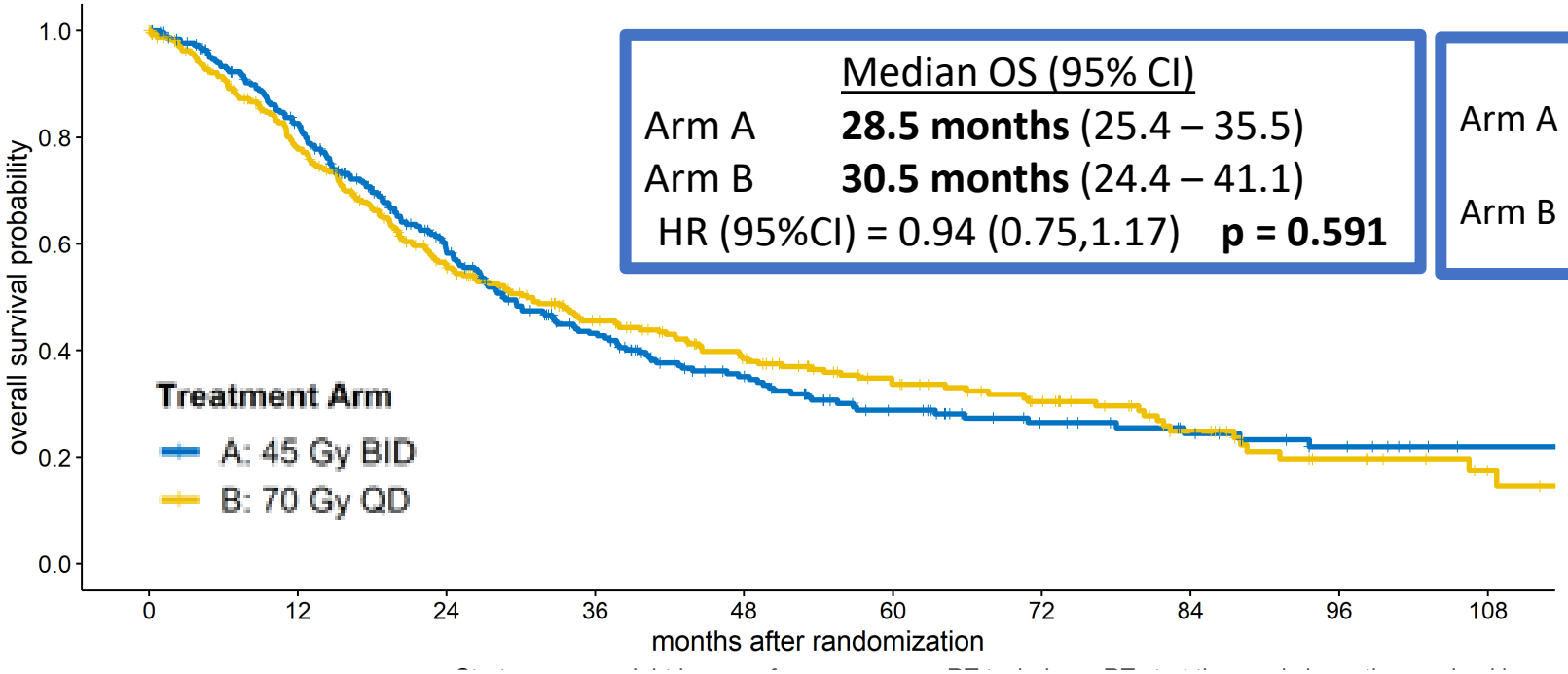


- **Chemotherapy** : Cisplatin 80 mg/m2 day 1 and etoposide 100mg/m2 day 1-3 q 21 days x 4 cycles
- **TRT to begin with the first cycle of chemotherapy**

Overall Survival

Median follow-up = 4 years

Figure 1. C30610 Kaplan-Meier Curve for Overall Survival



	Median OS (95% CI)
Arm A	**28.5 months** (25.4 – 35.5)
Arm B	**30.5 months** (24.4 – 41.1)

HR (95%CI) = 0.94 (0.75,1.17) **p = 0.591**

	2-yr OS	5-yr OS
Arm A	**58%** (53, 64)	**29%** (23, 35)
Arm B	**56%** (51, 62)	**34%** (23, 35)

number at risk

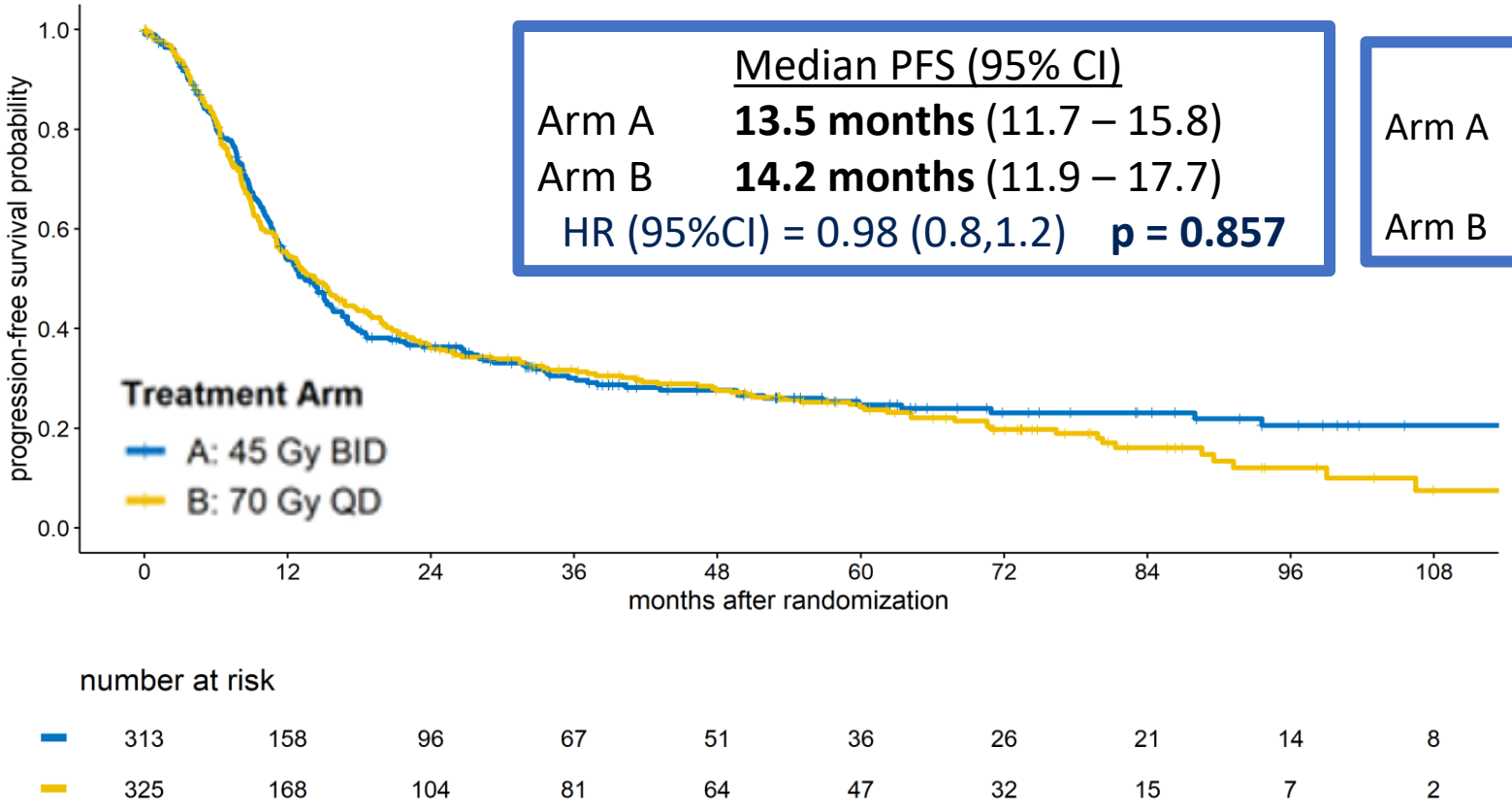
Arm A	313	239	150	99	66	44	30	23	16	9
Arm B	325	238	158	111	82	58	45	24	13	6

Arm A = 45 Gy BID

Arm B = 70 Gy QD

Progression-free Survival

Figure 2. C30610 Kaplan-Meier Curve for Progression-Free Survival



	Median PFS (95% CI)
Arm A	**13.5 months** (11.7 – 15.8)
Arm B	**14.2 months** (11.9 – 17.7)

HR (95%CI) = 0.98 (0.8,1.2) **p = 0.857**

	2-yr PFS	5-yr PFS
Arm A	**36%** (31, 42)	**25%** (20, 31)
Arm B	**36%** (31, 0.42)	**24%** (20, 30)

Arm A = 45 Gy BID

Arm B = 70 Gy QD

Adverse Events

Overall Maximum:	Arm	N(%)
Grade 3	A	93 (31.5%)
	B	78 (25.9%)
Grade 4	A	149 (50.5%)
	B	161 (53.5%)
Grade 5	A	**4 (1.4%)**
	B	**11 (3.7%)**
Hematologic Adverse Events (no Grade 5 AEs)		
Grade 3	A	66 (22.4%)
	B	70 (23.3%)
Grade 4	A	140 (47.5%)
	B	157 (52.2%)

Arm A = 45 Gy BID

Arm B = 70 Gy QD

Non-hematologic Adverse Events		
	Arm	N(%)
Grade 3	A	130 (44.1%)
	B	128 (42.5%)
Grade 4	A	36 (12.2%)
	B	49 (16.3%)
Grade 5	A	4 (1.4%)
	B	11 (3.7%)

	Arm A BID	Arm B QD
Dyspnea	13 (4.3%)	21 (7 %)
Pneumonitis	3 (1 %)	3 (1%)

Conclusions

- CALGB 30610 failed to prove that 70 Gy QD TRT significantly improves OS compared with standard 45 Gy BID TRT
- Outcomes in the 70 Gy cohort provide the best evidence available for high dose once - daily TRT in LSCLC
    - The study was not designed to assess whether 70 Gy QD was non-inferior to 45 Gy BID
- **Pending**:
    - In-depth analysis of adverse events according to treatment arm
    - Analysis of QoL, failure patterns, impact of variables including TRT timing, technique, and chemotherapy regimen
    - Dosimetry review to assess relationship between dose to normal tissues and outcomes

Additional points

Trial	Comparison	Med OS (months)	OS (5-year)
Intergroup 0096 (n=382)	45 Gy (1.5 Gy **BID**) 45 Gy (1.8 Gy **QD**)	**23** months **19** months HR: 1.2 p=0.04	**26%** **16%**
CONVERT (n=547)	45 Gy (1.5 Gy **BID**) 66 Gy (2 Gy **QD**)	**30** months **25** months HR: 1.18, p=0.14	**34%** **31%**
CALGB 30610 * (n=638)	45 Gy (1.5 Gy **BID**) 70 Gy (2 Gy **QD**)	**28.5** months **30.5** months HR: 0.94, p=0.59	**29%** **34%**

* Patients with N0 disease not eligible

TURRISI , NEJM 1999

FAIVRE-FINN, LANCET ONCOLGY 2017

A Randomized Phase II trial of Oral Vinorelbine as Second-Line Therapy for Patients with Malignant Pleural Mesothelioma

Dean Anthony Fennell[1], Angela Casbard, Catharine Porter, Robin Rudd, Jason Francis Lester, Marianne Nicolson, Bruno Morgan, Jeremy Peter Steele, Liz Darlison, Georgina Mary Gardner, Lisette Sheena Nixon, Terri Kitson, Ann White, Gareth Owen Griffiths, Charlotte Poile, Aarti Gaba, Sara Busacca, Catherine Jane Richards, VIM Trial Group

[1]University of Leicester and University Hospitals of Leicester, Leicester, United Kingdom

BACKGROUND

- All patients with malignant pleural mesothelioma (MPM) eventually relapse following standard chemotherapy.
- However, there is no standard treatment option in this setting.
- Vinorelbine exhibits useful clinical activity but has not been formally evaluated in a randomised clinical trial, despite its widespread off-label use worldwide.
- BRCA1 regulates spindle assembly checkpoint in MPM and predicts vinorelbine sensitivity in preclinical models [1,2], suggesting that BRCA1 negative patients may be chemoresistant.

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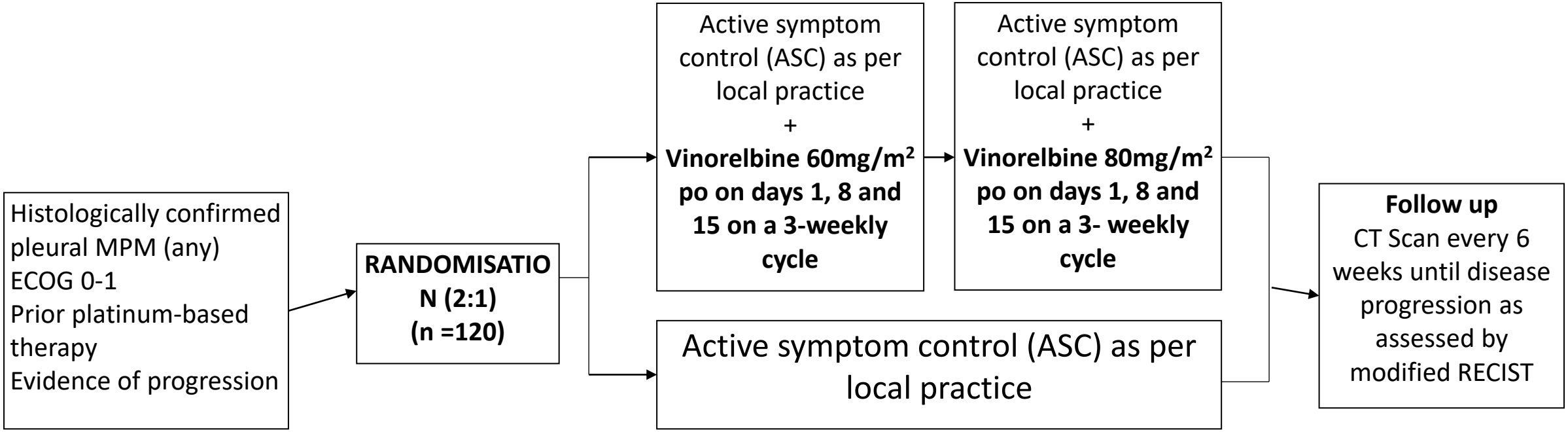
[1] Busacca et al, J Pathol 2012, 227(2), 200.
[2] Busacca et al, Mol Cancer Res, 2021, 20(2) 379.

VIM Trial Design



Primary outcome measure: To establish the anti-tumour activity of vinorelbine as measured by progression free survival (PFS)

Secondary Outcome measures:

•PFS by BRCA1 expression Overall survival (OS), & objective response rate (ORR) as assessed by modified RECIST

•Safety, tolerability (side effects) and feasibility of use (number of participants requiring dose delays or reductions and/or treatment withdrawal)

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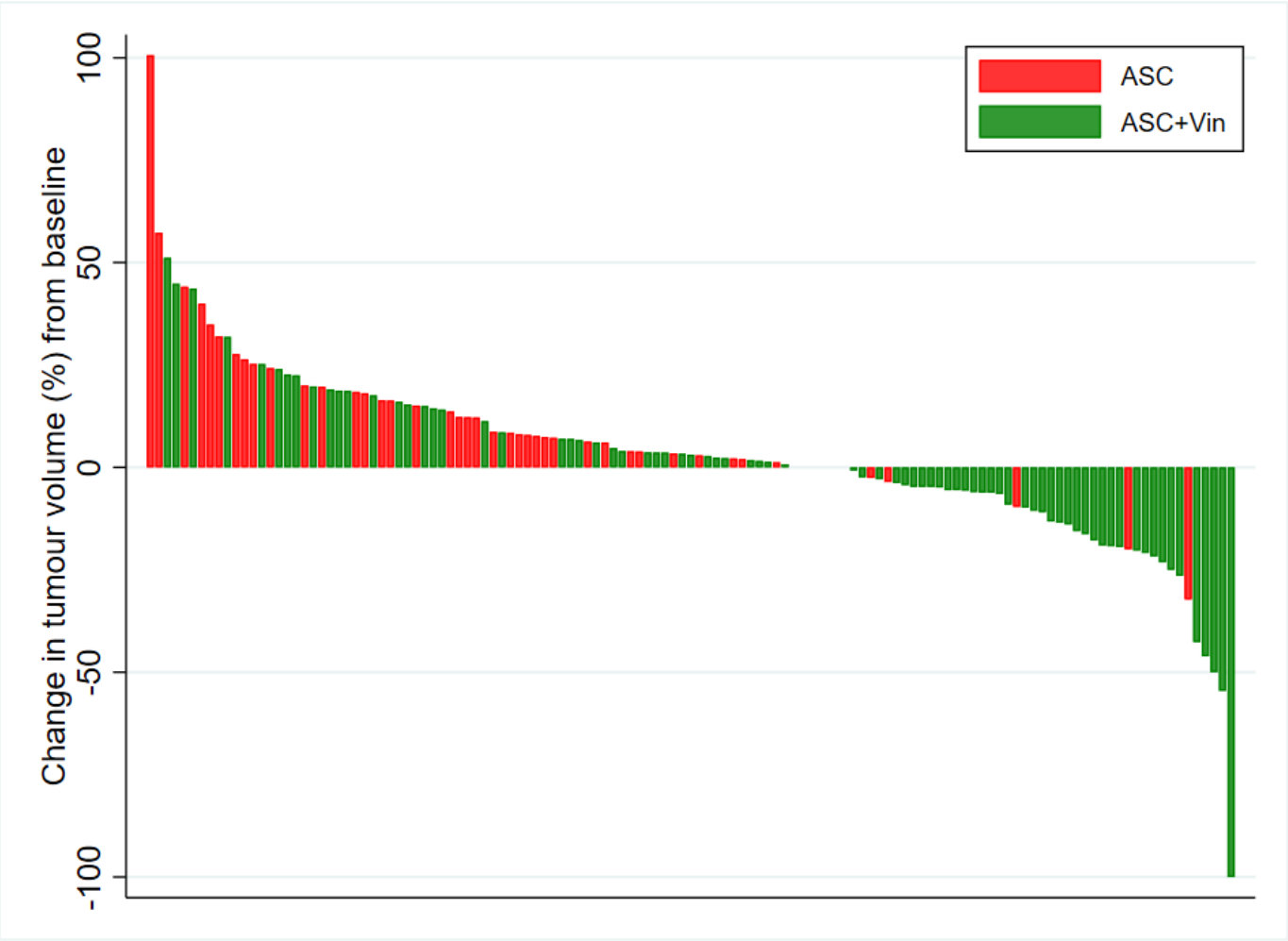
Response



Best response

	ASC+VIN (N=98)	ASC (N=56)
PR rate	3.1%	1.8%
SD rate	62.2%	46.4%
Median duration of response (95%CI) (months)	7.2 (3.1-8.5)	4.2 (4.2-4.2)
Median duration of PR/SD	4.2 (2.8-6.9)	3.7 (2.8-4.2)
PD rate	19.4%	28.6%

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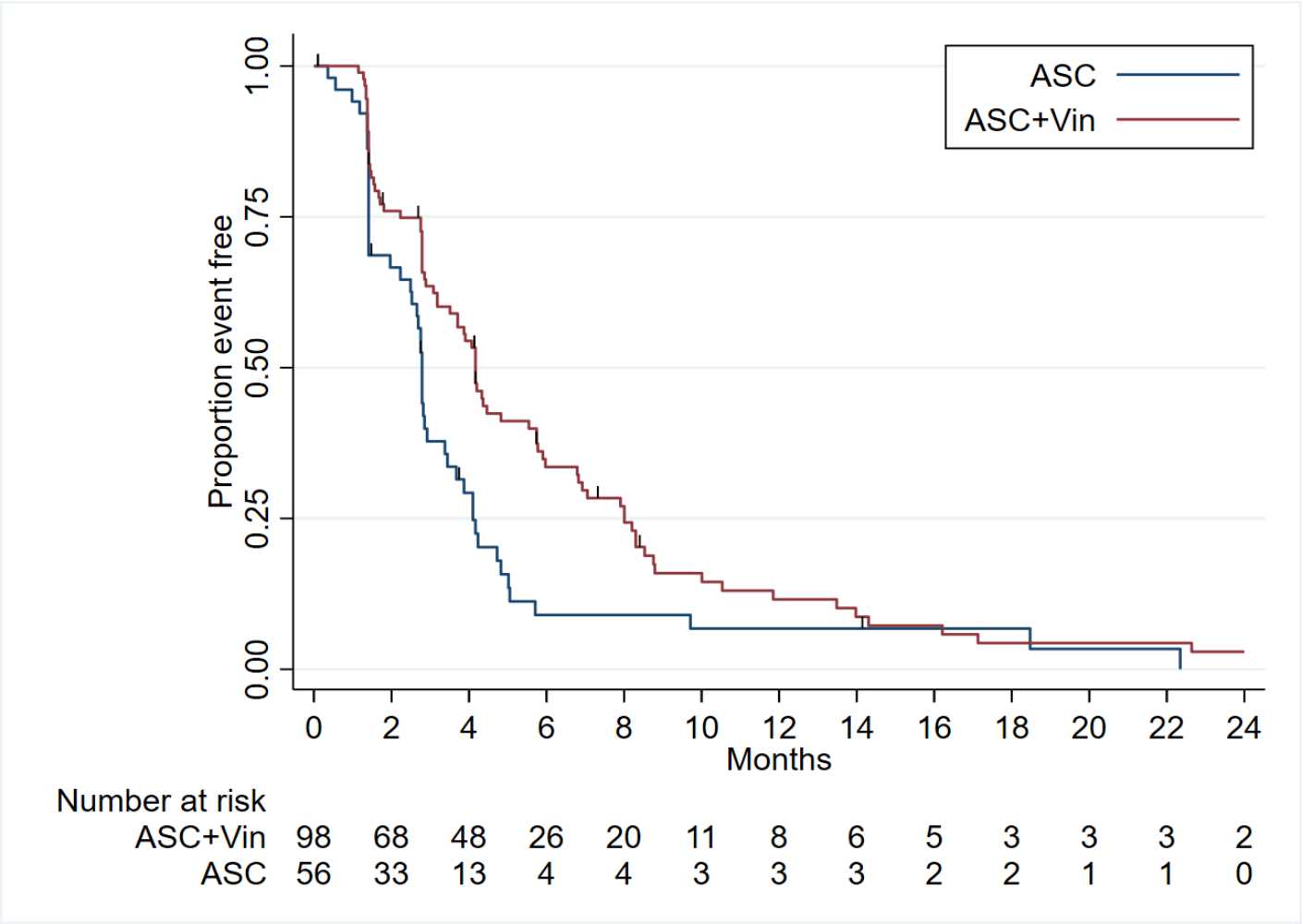
Progression Free Survival



	ASC+VIN (N=98)	ASC (N=56)
Median PFS (90%CI) (months)	4.2 (3.5-4.8)	2.8 (2.5-2.9)
HR (95% CI)	0.60 (0.41-0.86)	
Log rank test one-sided p-value	0.002	

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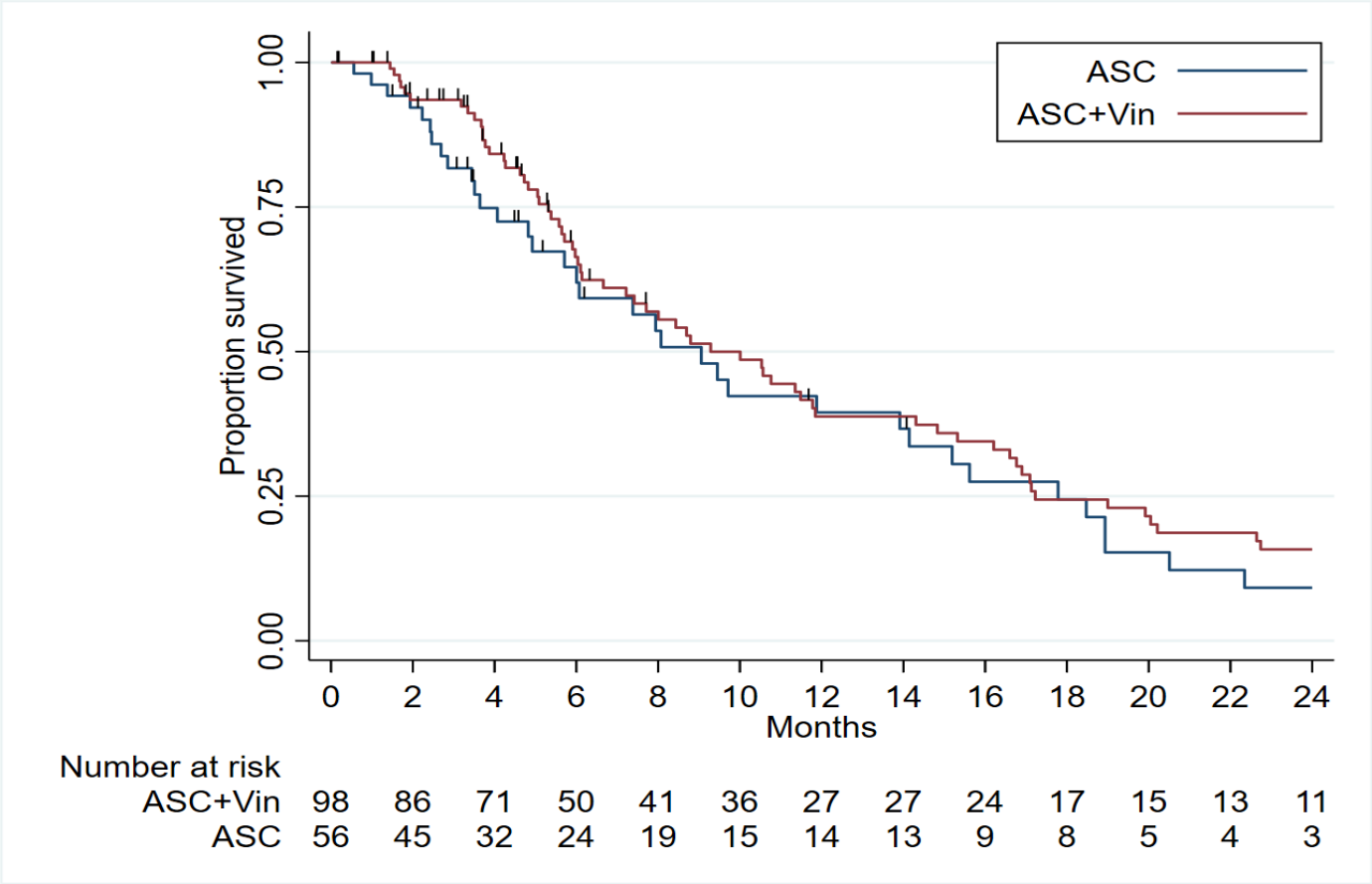
Overall Survival



	ASC+VIN (N=98)	ASC (N=56)
Median OS (95%CI) (months)	9.3 (6.7-11.8)	9.1 (5.7-14.1)
HR (95% CI)	0.79 (0.53-1.17)	
Two-sided log-rank test p-value	0.24	

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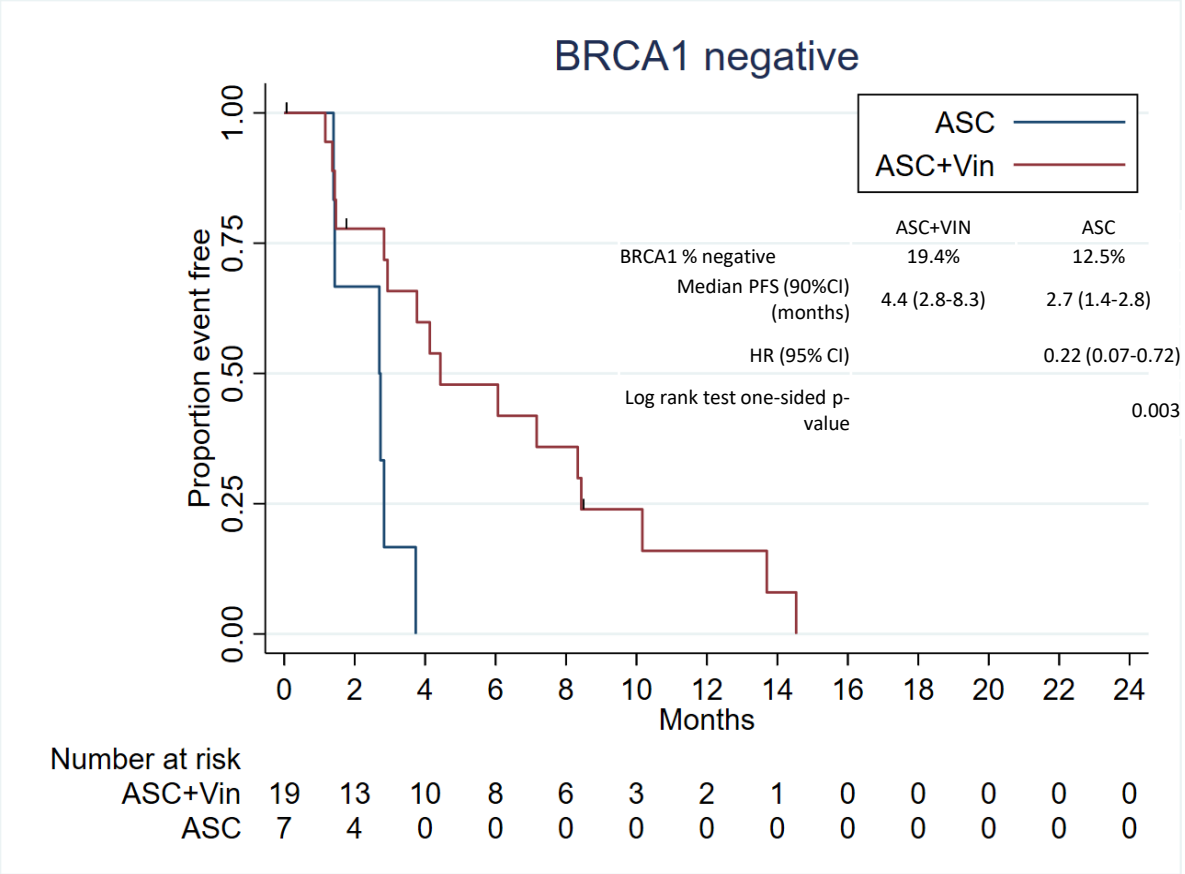
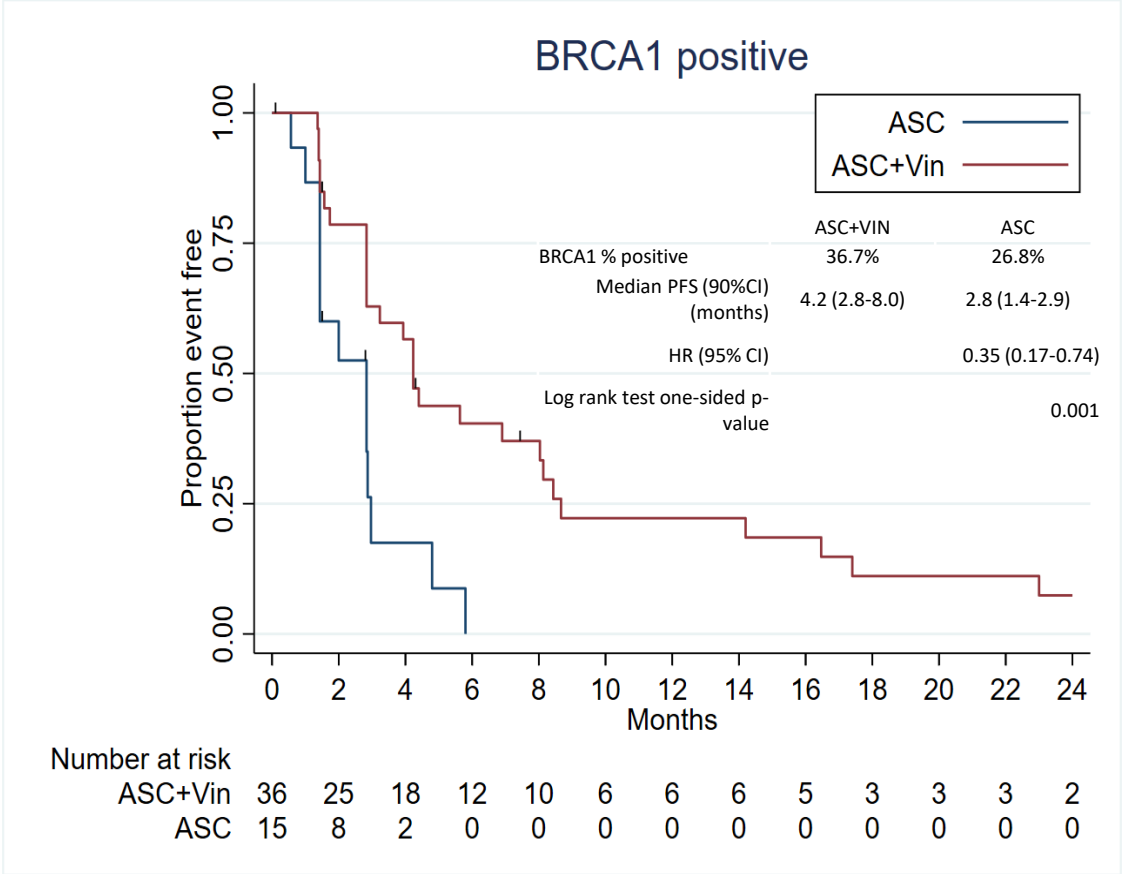
Progression Free Survival by BRCA1 expression





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CONCLUSIONS

- VIM met its endpoint of statistically improved PFS with vinorelbine versus ASC in relapsed malignant mesothelioma
- There was no evidence to support BRCA1 as being predictive
- Vinorelbine is a safe and effective treatment and should be considered a treatment option for patients with relapsed mesothelioma

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