Novel Treatments in NSCLC: Antibody Drug Conjugates (ADC), Bi-Specifics and Vaccines

Mary Jo Fidler, MD

Alice Pirie Wirtz Professor of Medical Oncology

Rush MD Anderson Cancer Center

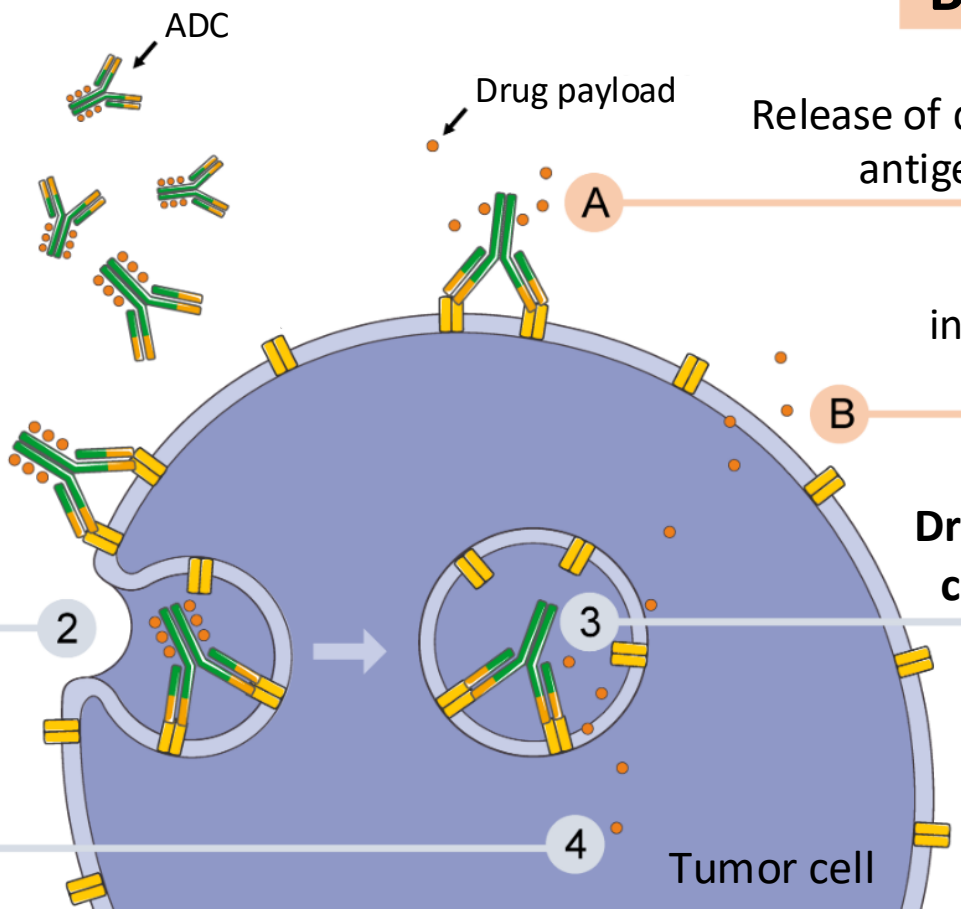
Antibody Drug Conjugate: Mechanism of Action

Classical ADC Mode of Action

ADC binding to receptor (1)

Internalization by endocytosis (2)

Cytotoxic effect induced by drug payload (4)



Bystander Killing Effect

Release of drug payload from antibody after antigen binding, before internalization (A)

Release of drug payload into intercellular space because of high drug membrane permeability (B)

Drug payload release after linker cleavage by lysosomal enzymes (3)

A high drug-to-antibody ratio increases antitumoral efficacy despite low antigen density on tumor cells

- Some ADCs require internalization for payload cleavage, but others can be hydrolyzed extracellularly

ADC, antibody-drug conjugate.

ADC generalities

Toxicities

- Nausea
- Cytopenias
- Decreased appetite
- Constipation
- Diarrhea
- Alopecia
- Transaminitis
- Ocular toxicities
- neuropathy

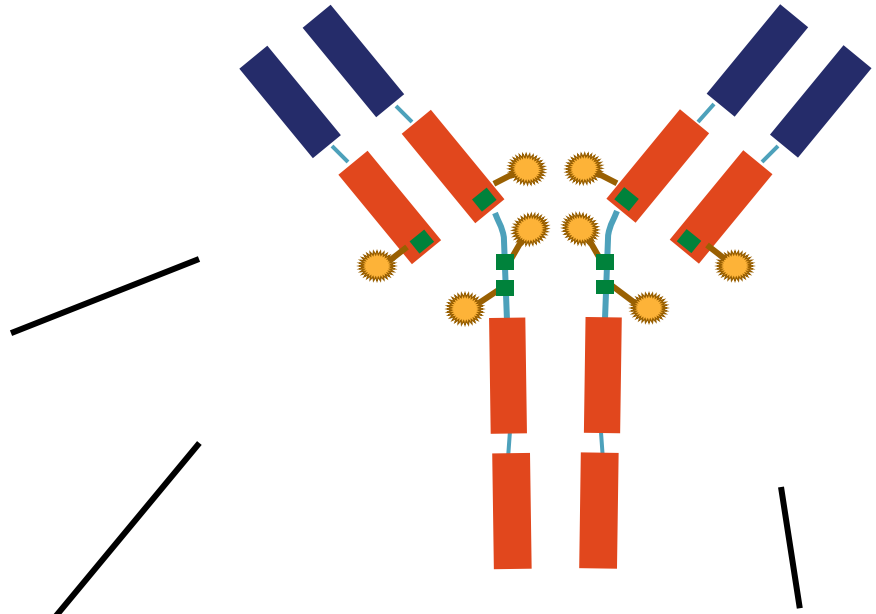
Variable correlation with level of target by IHC

- Trastuzumab deruxtecan has pan tumor approval in IHC high HER2 + disease
- General lack of correlation for many
  - Bystander effect
  - Broad expression of targets

Sacituzumab govitecan: Anti-TROP2 Monoclonal Antibody

SN-38 Payload

- Metabolite of Topo-1 inhibitor, irinotecan
- SN-38 more potent than parent compound



7.6:1 drug-to-antibody ratio

Linker for SN-38

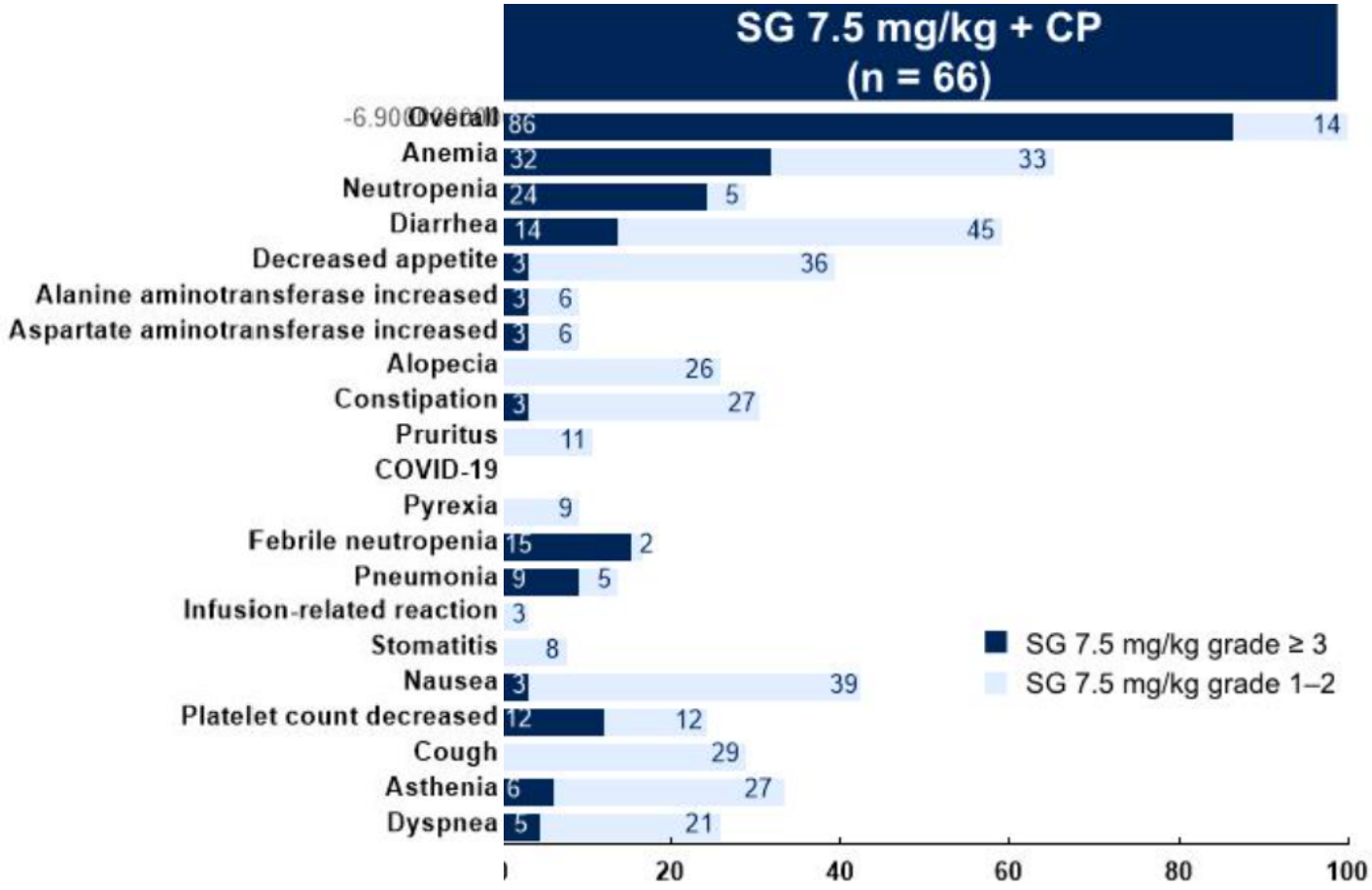
- Hydrolyzable linker for payload release

- Overall survival primary endpoint not met: 11.1 vs 9.8 months vs docetaxel p = .054
- Favorable toxicity profile and benefit trend in those not responsive to prior PD1 targeting therapy

Topo-I, topoisomerase I; TROP-2, trophoblast cell surface antigen-2. Rugo H, et al. *J Clin Oncol.* 2022;40:3365-3376. 3. Paz-Ares LG JCO 2024

Sacituzumab govitecan in combination with pembrolizumab and carboplatin

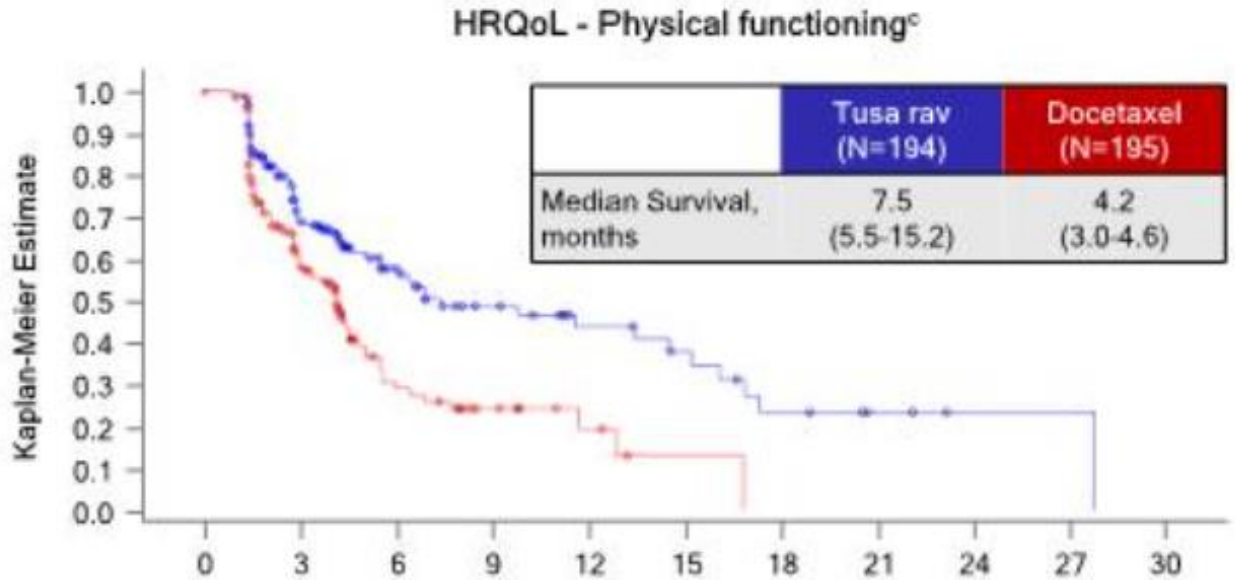
- **Recommended dose: 7.5mg/kg**
- **Front line phase III (EVOKE-3) in PD-L1 ≥50% based on phase 1 signal**
- **Phase II studies with pembrolizumab regardless of PD-L1**
- **With PD1 and tigit inhibition**



Gray, J WCLC 2024

CEACAM5 topoisomerase Tusamitamab ravtansine

- CARMEN-LC03 randomized phase III study of Tusa-Rav vs docetaxel
- The study did not meet the PFS and OS dual primary endpoint though the control docetaxel arm had a median PFS of 5.9 months
- Favorable QOL endpoints



Besse B WCLC24

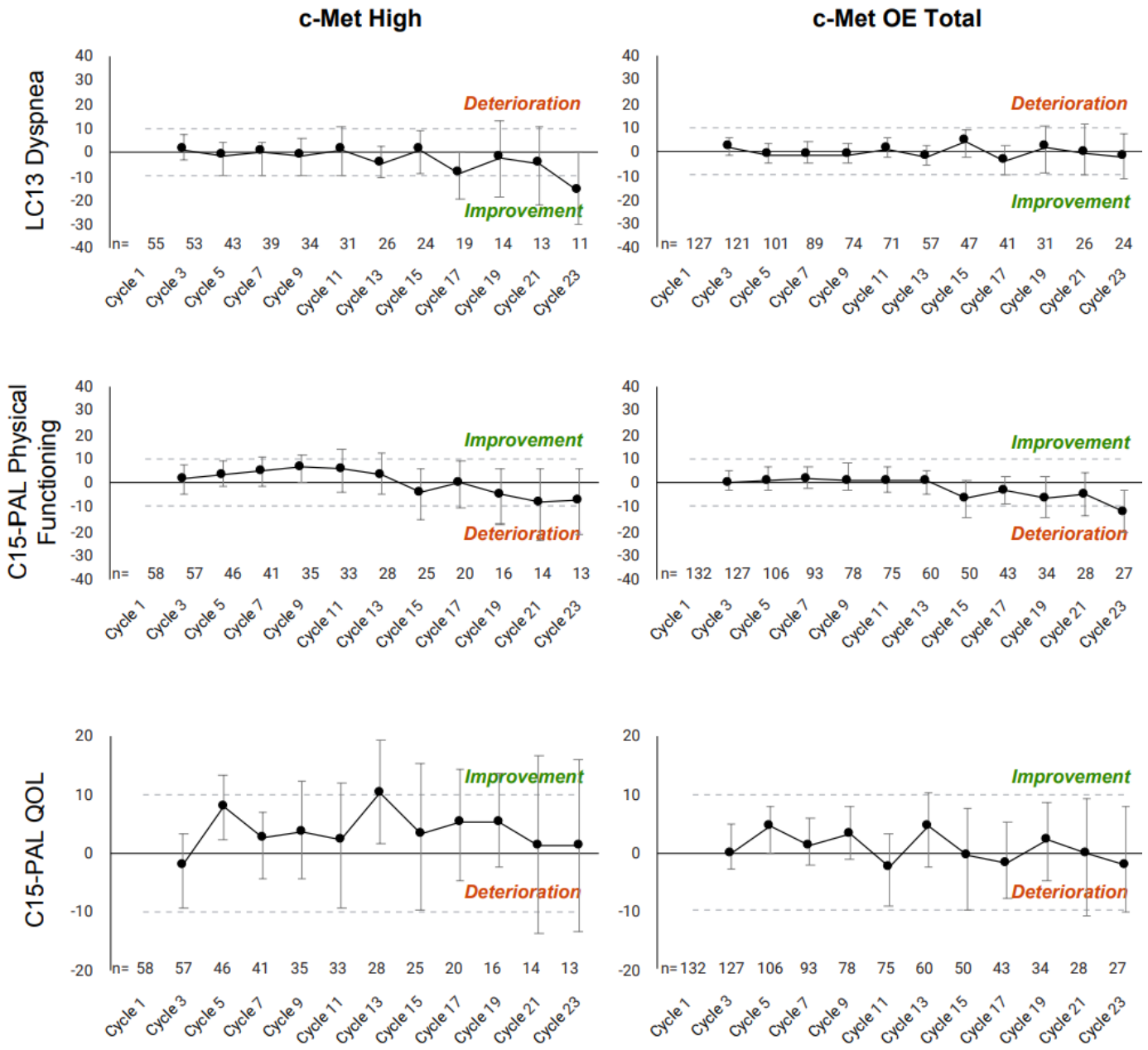
Telisotuzumab vedotin - LUMINOSITY trial

- Monomethy auristatin E cytotoxic payload
- C-MET overexpression ≥25% staining with 3+ (high if ≥50%)
- Previously trated c-MET positive NSCLC

- ORR 28.6%, 34.6% high with median duration of response 8.3 months
- Median PFS 5.7 months, 5.5 in high
- Median OS 14.5 months, 14.6 in high
- Peripheral neuropathy 30%, 7% grade 3
- edema 16%, fatigue 14%

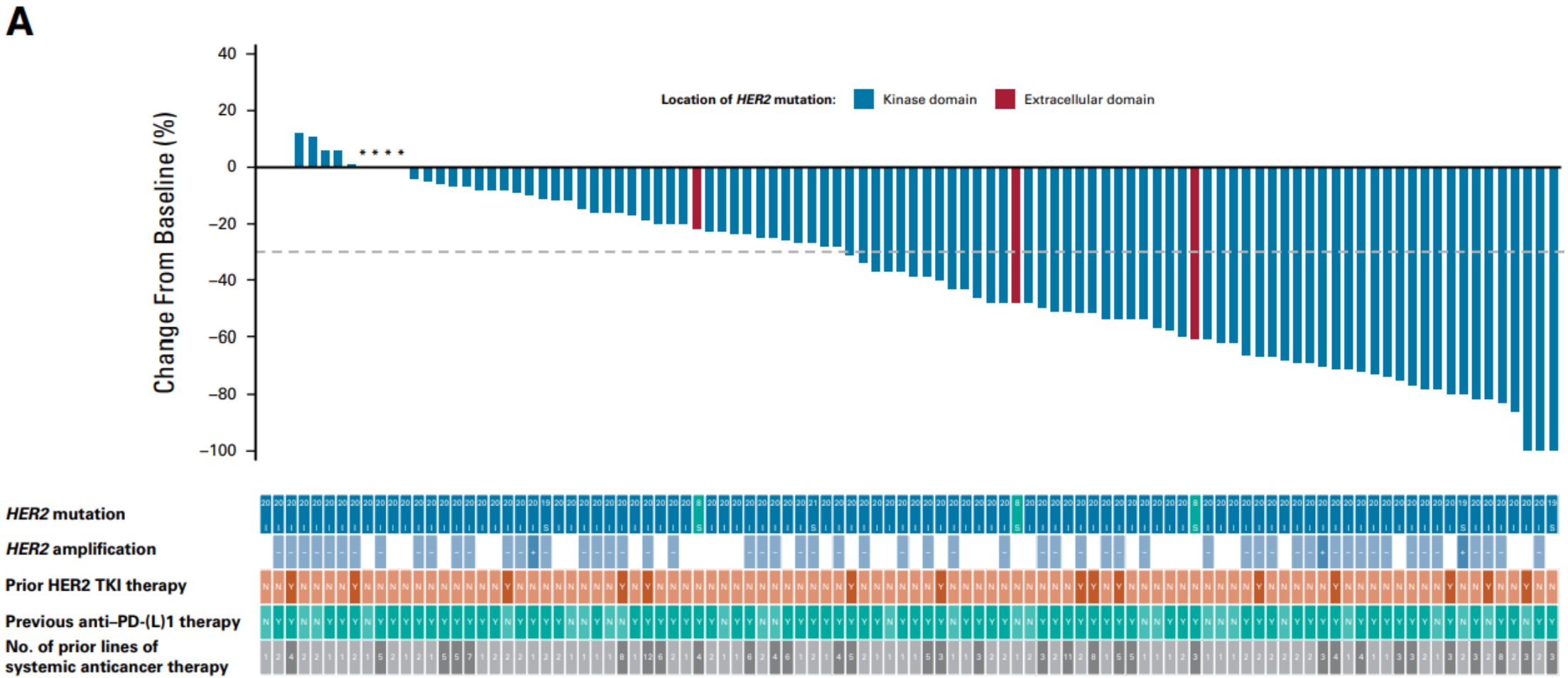
Camidge, R JCO Vol 42(25) ASCO 2024

- Responders maintained QOL for longer time
- Overall improvement in dyspnea, physical functioning, stable QOL



Girard, N ESMO 2024

Trastuzumab deruxtecan (T-DXd): DESTINYLung02 building on data for Her2 mutated tumors: 5.4mg/kg dosing



Li BT NEJM 2022, Goto K JCO 2023

HER-2 overexpression with T-dxd

- Cohorts 1 and 1A, 6.4mg/kg and 5.4mg/kg, respectively with majority having received platinum doublet and IO
- HER2 overexpressed according to the gastric algorithm
- Primary endpoint ORR

	Cohort 1 (n=49)	Cohort 1A (n=41
Female	39%	46%
IHC 3+	20%	41%
CNS metastasis present	35%	29%
HER2 or EGFR TKI	29%	17%
Never smoking history	33%	22%

Smit EF Lancet Oncology 2024

T-DXD in HER2 overexpressed

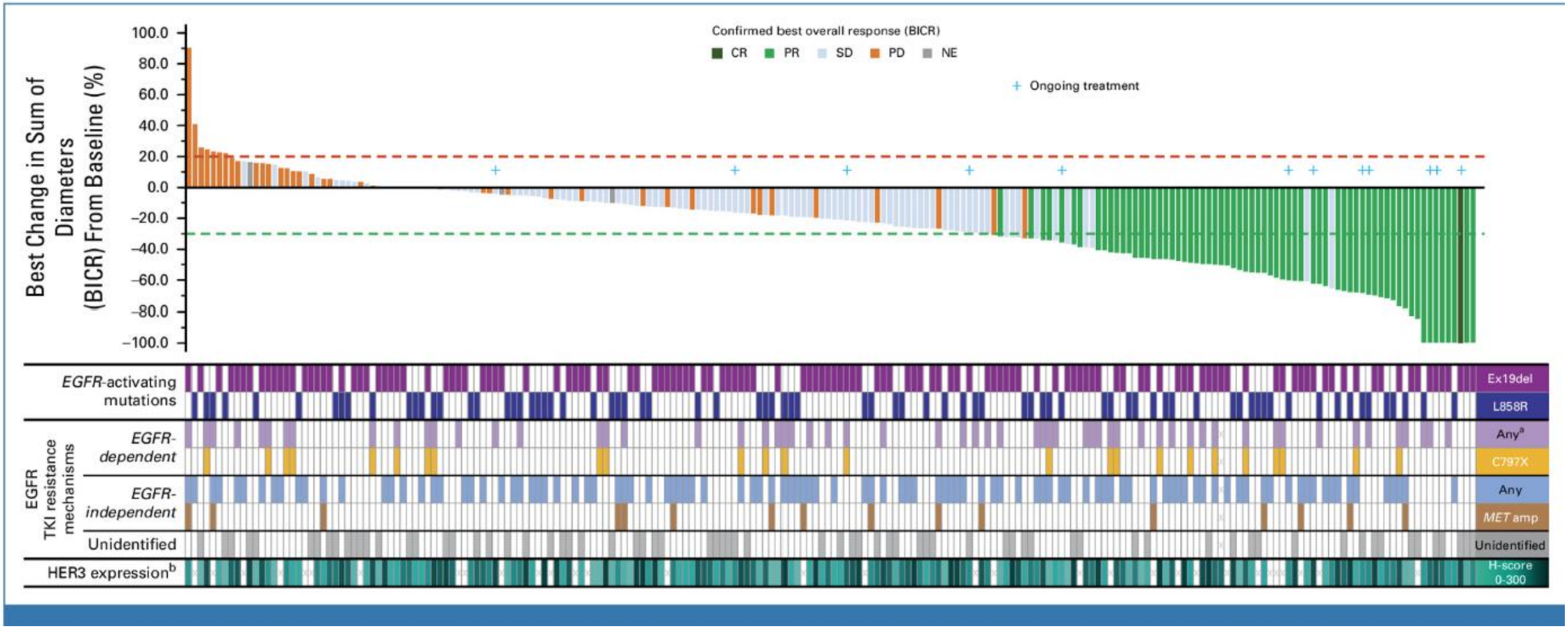
	Cohort 1 (6·4 mg/kg; N=49)	Cohort 1A (5·4 mg/kg; N=41)
Confirmed objective response rate, n (%; 95% CI)	13 (26·5%; 15·0–41·1)	14 (34·1%; 20·1–50·6)
Response outcomes, n (%)		
Complete response	0	2 (5%)
Partial response	13 (27%)	12 (29%)
Stable disease	21 (43%)	18 (44%)
Progressive disease	11 (22%)	4 (10%)
Not evaluable	4 (8%)	5 (12%)
Disease control rate, n (%; 95% CI)	34 (69·4%; 54·6–81·8)	32 (78·0%; 62·4–89·4)
Duration of response, months, median (95% CI)	5·8 (4·3–not evaluable)	6·2 (4·2–9·8)

Patritumab deruxtecan: HERTHENA-Lung01

- HER3 expression in 85-100% of EGFR mutated NSCLC
  - Phase 2 fixed dose vs up-titration, primary endpoint ORR in patients s/p Osimertinib and platinum doublet chemotherapy, 51% with brain metastases
  - More than 70% received at least 3 lines of therapy

Yu H JCO 2023

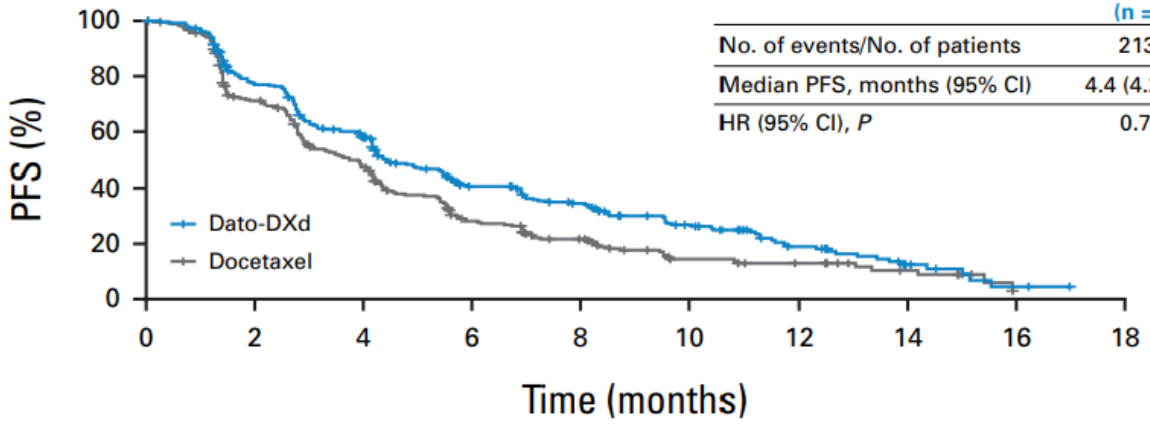
Response data



Yu H JCO 2023

Dato-DXd: Anti-TROP2 IgG1 Monoclonal Antibody

A



	Dato-DXd (n = 299)	Docetaxel (n = 305)
No. of events/No. of patients	213/299	218/305
Median PFS, months (95% CI)	4.4 (4.2 to 5.6)	3.7 (2.9 to 4.2)
HR (95% CI), *P*	0.75 (0.62 to 0.91), *P* = .004	

- PFS better in non-squamous cell group
- HR for those with actionable driver mutations 0.35

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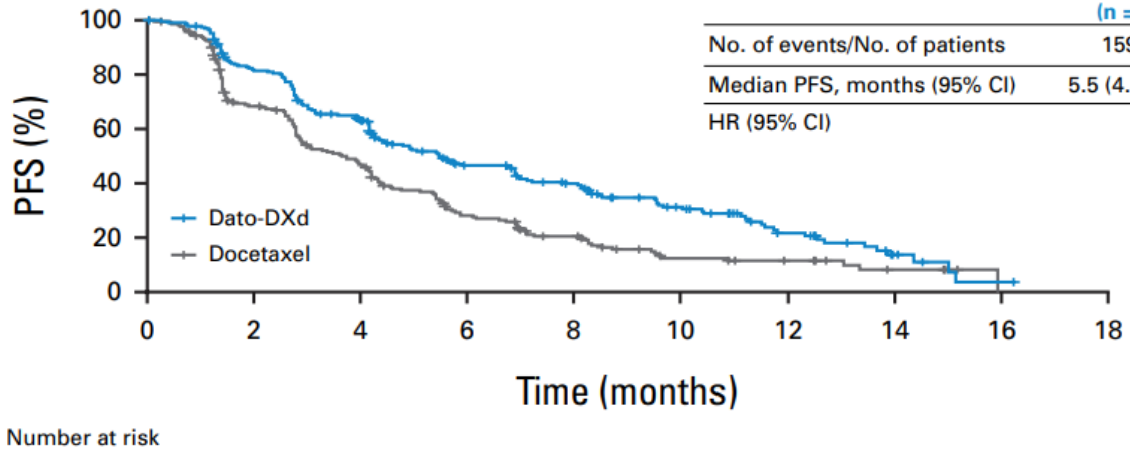


	Dato-DXd (n = 234)	Docetaxel (n = 234)
No. of events/No. of patients	159/234	170/234
Median PFS, months (95% CI)	5.5 (4.3 to 6.9)	3.6 (2.9 to 4.2)
HR (95% CI)	0.63 (0.51 to 0.79)	

Number at risk

Ahn M-J J Clin Oncol. 2025 Jan 20;43(3):260-272

•. 2025 Jan 6:
  •. 2025 Jan 6

TROPION-Lung05 phase II trial in patients with actionable gene alterations (AGA)

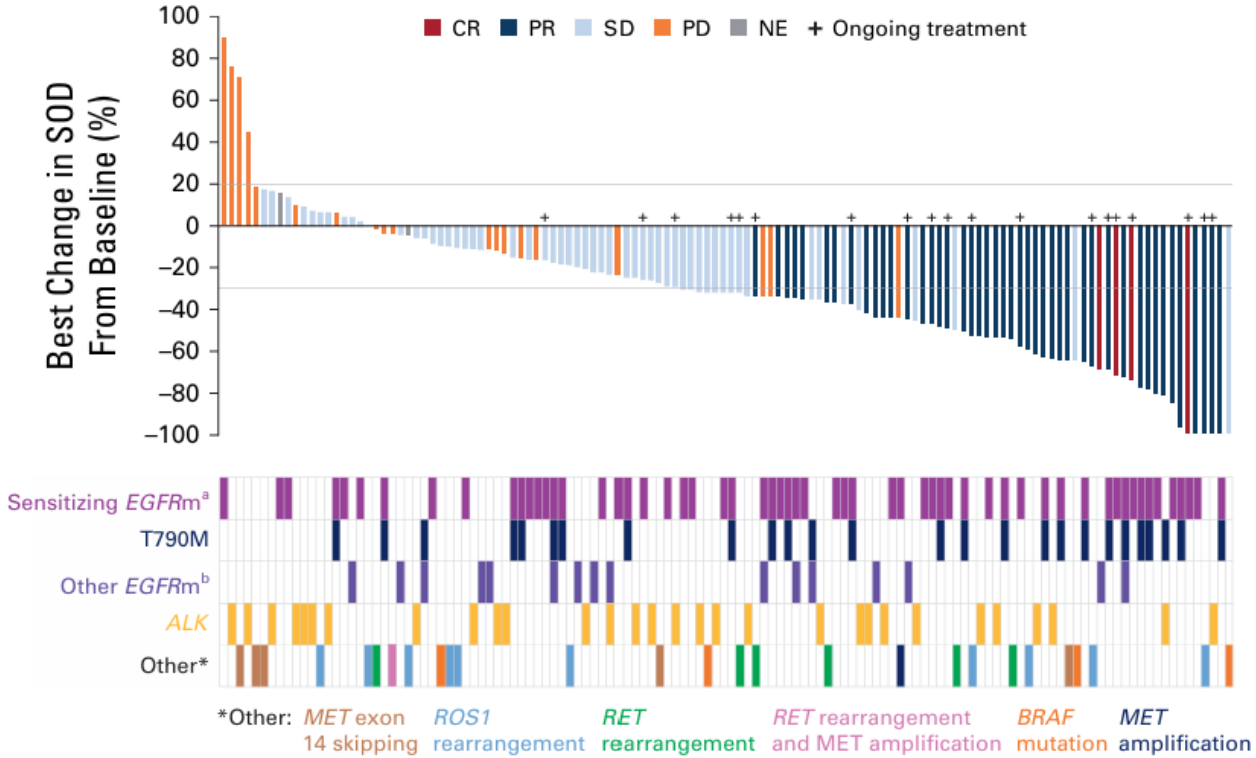
Summary of mutation types,[e] No. (%)	
EGFR	78 (56.9)
Exon 19 deletion	41 (29.9)
Exon 20 T790M	26 (19.0)
Exon 21 L858R	25 (18.2)
Exon 18 G719	5 (3.6)
Exon 21 L861Q	3 (2.2)
Exon 20 insertion	2 (1.5)
ALK rearrangement	34 (24.8)
ROS1 rearrangement	10 (7.3)
RET rearrangement	8 (5.8)
MET exon 14 skipping	5 (3.6)
BRAF mutation	4 (2.9)
MET amplification[f]	3 (2.2)

- 100% had platinum-based chemotherapy
- 35.8% had anti-PD-1/PD-L!
- 100% with target specific therapy
- Median prior therapies: 3

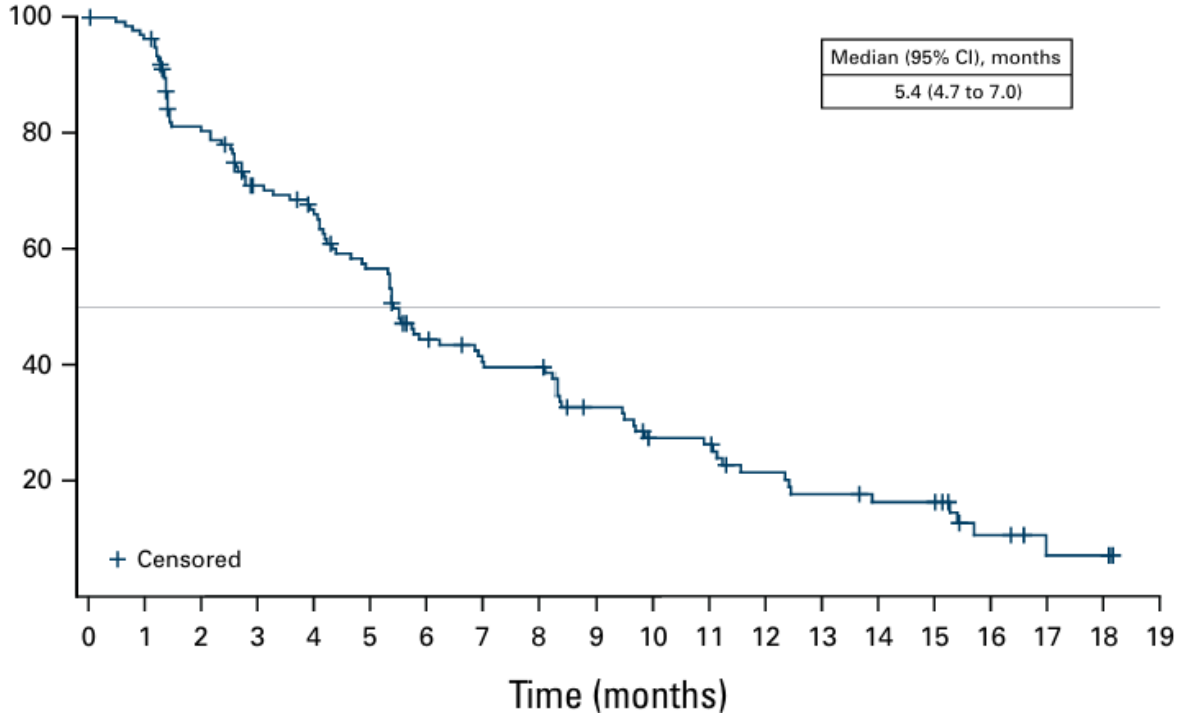
Sands, J JCO 2025

Dato-DXD in patients with actionable mutations

A



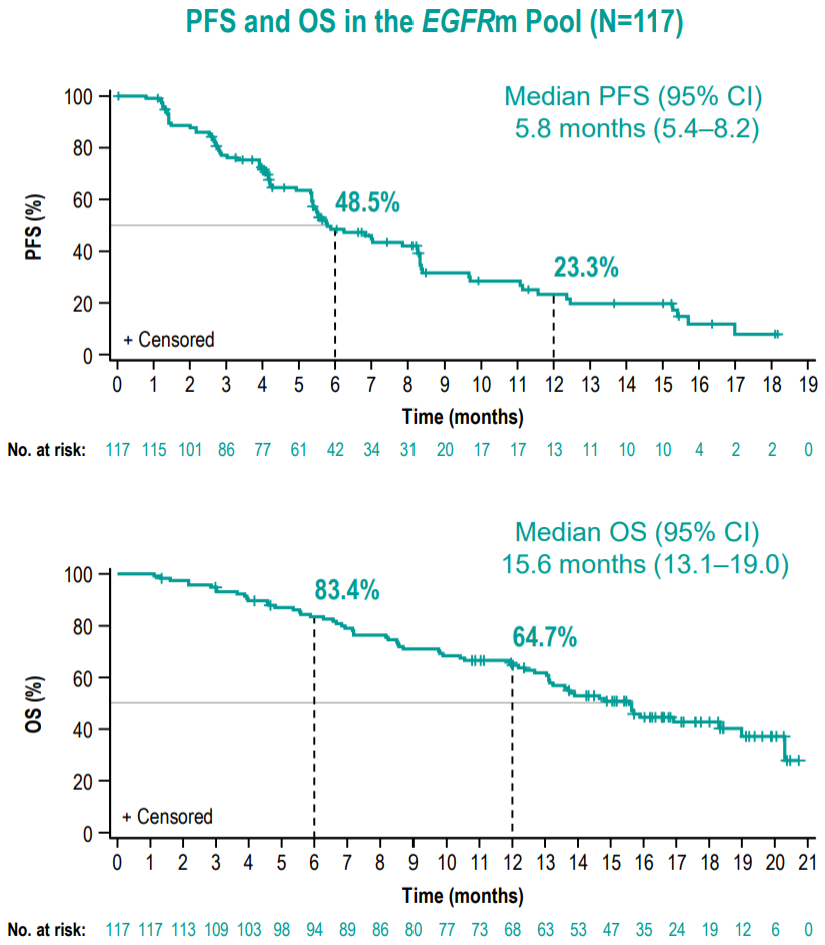
Progression free survival



Sands, J JCO 2025

Pooled analysis: EGFR mutated cancer in TROPION-Lung01 and TROPION-Lung05

- ORR: 42.7%, 44.8% with prior Osimertinib
- Median DOR: 7.0 months, 6.9 months with prior Osimertinib

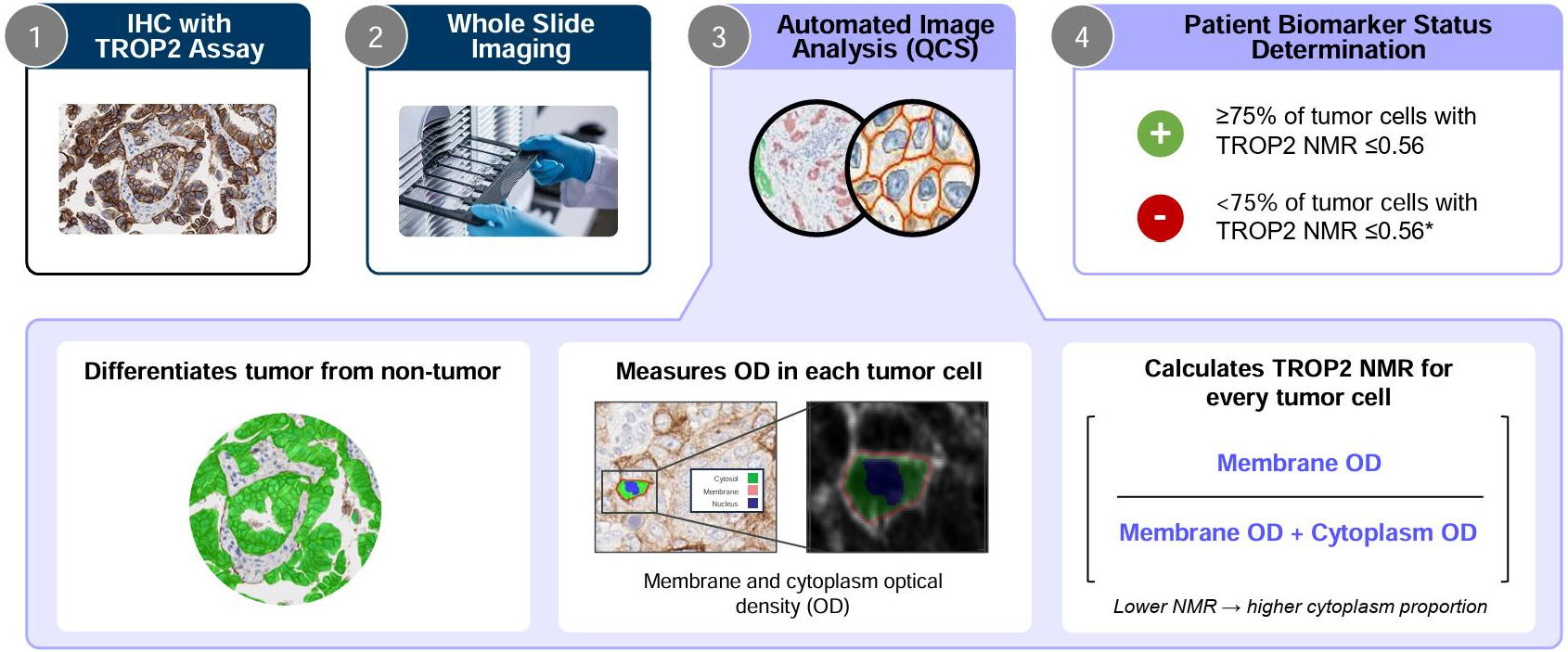


Ahn MJ ESMO 2024

Is there a better way to select patients?

TROP2 Normalized Membrane Ratio (NMR) measured by Quantitative Continuous Scoring (QCS)

QCS is a novel, fully-supervised computational pathology approach that precisely quantifies and locates targets like TROP2

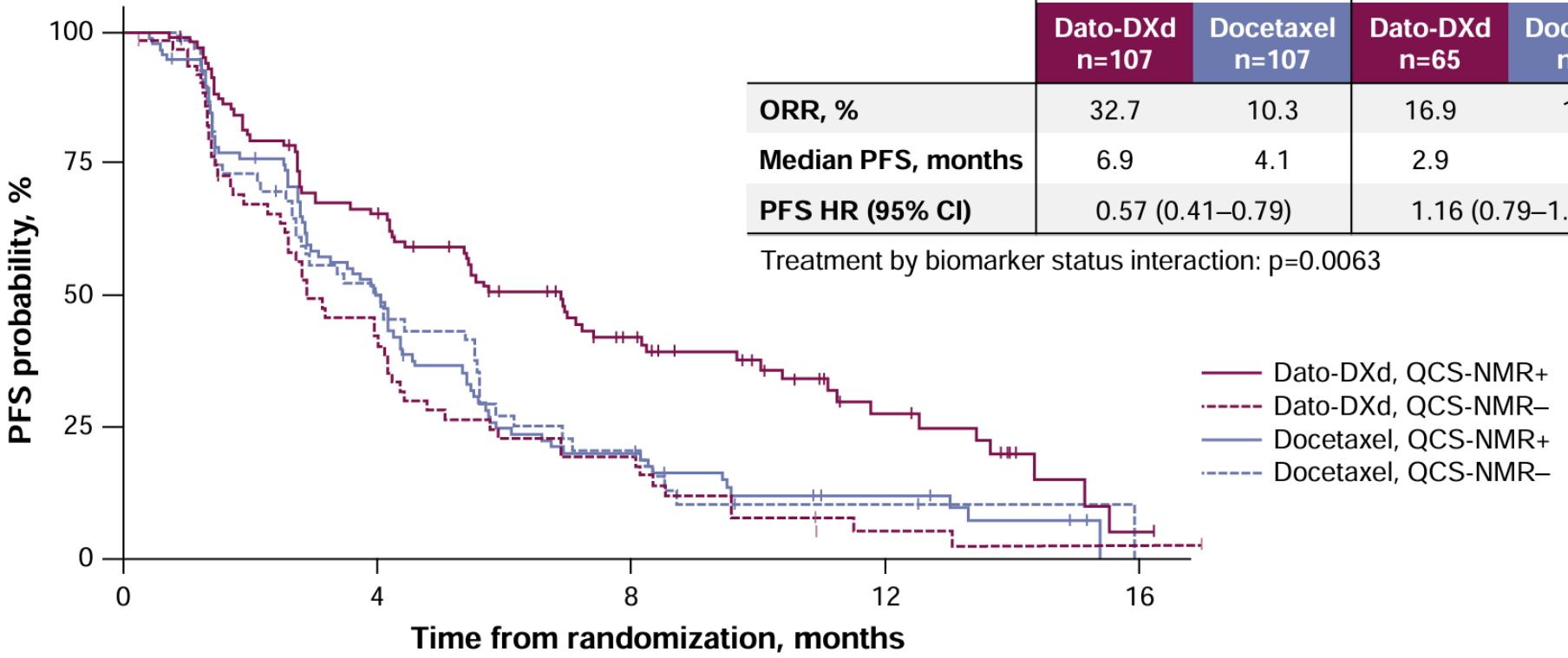


Garassino MC WCLC 2024

Overall BEP: Efficacy by TROP2 QCS-NMR Status

TROP2 QCS-NMR positivity is predictive for longer PFS with Dato-DXd in the biomarker-evaluable population

Biomarker-evaluable population, n=352



	TROP2 QCS-NMR+		TROP2 QCS-NMR–	
	Dato-DXd n=107	Docetaxel n=107	Dato-DXd n=65	Docetaxel n=73
ORR, %	32.7	10.3	16.9	15.1
Median PFS, months	6.9	4.1	2.9	4.0
PFS HR (95% CI)	0.57 (0.41–0.79)		1.16 (0.79–1.70)	

Treatment by biomarker status interaction: p=0.0063

Prevalence of positive score (n=352):

NonSq AGA 63%, AGA 76%, SQ 44%

Garassino MC WCLC 2024

Vaccines for advanced NSCLC

Vaccine strategies

- Over-expressed proteins
  - MUC-1, NY-ESO-1, MAGE, EGF
  - Cost effective but may trigger autoimmune responses
- Neoantigens
  - Abnormal proteins generated by coding region mutations in the tumor genome
  - Bioinformatic algorithms predict immunogenicity, HLA binding affinity and corresponding HLA allele
  - Shared EGFR mutations, Shared ALK mutations, KRAS
  - Personalized strategize limitations: cost, prep time, and potential fluctuation of targets, requires adjuvants

Chen, S Int J Cancer 2024, Fan T Signal Transduction and Targeted Therapy, 2023

Vaccine strategies (cont.)

- Autologus and allogenic whole tumor vaccines
  - Entire antigen epitope unrestricted by MHC molecules
  - Example: Belagenpumatucel-L that showed promise within 12 weeks of chemotherapy or after radiation therapy
  - High cost
- Dedritic cell-based vaccines
  - Ex-vivo expansion of isolated PBMCs loaded with antigens, high cost
- DNA vaccines
  - Antigen encoding genes via plasmids
  - Limitations: genomic integration and difficulty reaching cell nucleus

Chen, S Int J Cancer 2024

Vaccine strategies (cont.) – mRNA vaccines

BNT116 phase I 130 patients world wide is goal

- Previously treated patients with NSCLC (platinum and PD1/PDL1
- Cohort for patients who are not chemotherapy candidates as long as TPS $\geq$1% and perioperative resectable cohort
- Being tested with and without cemiplimab

INTerpath-002 phase III 868 patients

- Resected treated with pembrolizumab vs pembrolizumab + mRNA-4157
- Phase I AEs: pyrexia, flu like illness, injection site pain

Chen, S Int J Cancer 2024

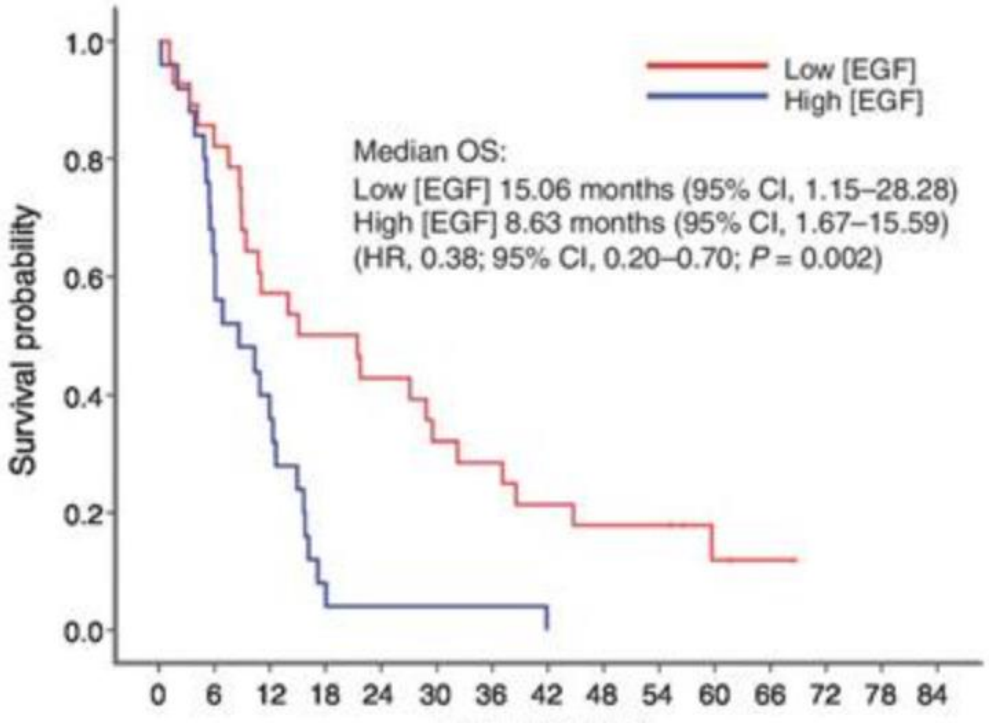
CIMAvax-EGF – patients with adv. NSCLC

- 4-6 weeks after chemo 2:1 randomization to 4 doses of CIMAvax-EGF vs supportive care
- 405 patients enrolled, 270 in vaccine, 135 control
- 5 year survival benefit 14.4% vs 7.9%, Harrington-Plemming weighted log rank p=0.04
- Per protocol population, OS 12.43 vs 9.43 months, HR 0.77, p – 0.036

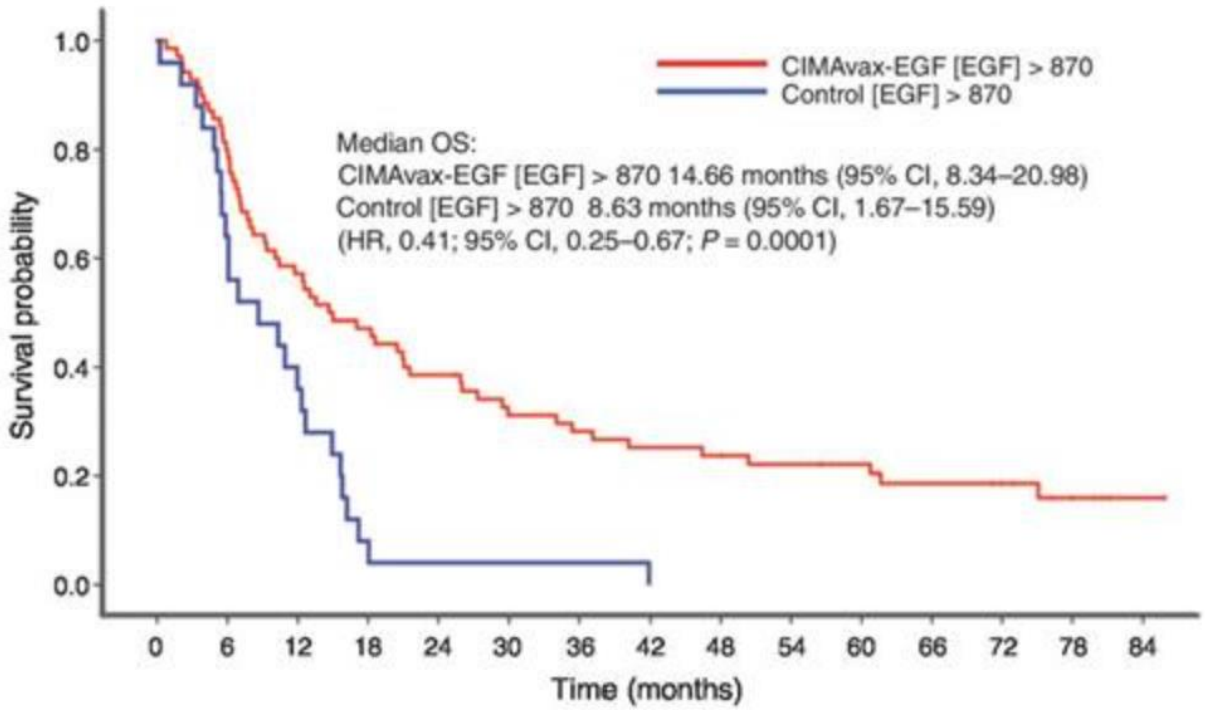
Rodriguez PC Clin Cancer Res. 2016

EGF level above and below median

High EGF poor prognosis in SOC arm



Median OS benefit for patients with high EGF



Rodriguez PC Clin Cancer Res. 2016

Adverse events of interest

Adverse events	Vaccine (*n* = 246)	%	Controls (*n* = 132)	%
Injection site reactions	116	46.6	0	0
Fever	91	36.5	10	7.6
Dyspnea	79	31.7	38	28.8
Vomiting	58	23.3	5	3.8
Headache	56	22.5	9	6.8
Nausea	45	18.1	11	8.3

Rodriguez PC Clin Cancer Res. 2016

Bispecific antibodies

Bispecific antibodies

- Zenocutuzumab
  - NRG1 fusion proteins bind to HER3 through an EGF-like binding domain, triggering HER2–HER3 heterodimerization
  - Known activity of afatinib, second generation EGFR TKI due to cross reactivity
  - 12/4/25 FDA accelerated approval or NRG1+ NSCLC
    - 66 adults ORR was 33%, median DOR was 7.4 months MEDI5752 – targets PD-1 and CTLA4
- INBRX-105: anti PD-L1 and anti CD137 (human 4-1BB)
  - Enhance T cell proliferation and costimulation to PD-L1 rich environment
  - 4-1BB activation at sites of high PDL1 expression via crosslinking of PDL1 to 4-1BB (NCT03809624)

Schram, AM NEJM 2025, Park JC JITC 2023

Rilvegostomig

- Rilvegostomig: PD-1x TIGIT bispecific antibody
- Checkpoint inhibitor naïve metastatic disease PDL1 TPS > 1%
- 16% received chemotherapy
- Median PFS in prespecified > 50% immature
- 2.1% grade ≥3 immune events, 4.2% discontinuation
- Registrational trials including Dato-DXD and in PD-L1 TC ≥ 50%

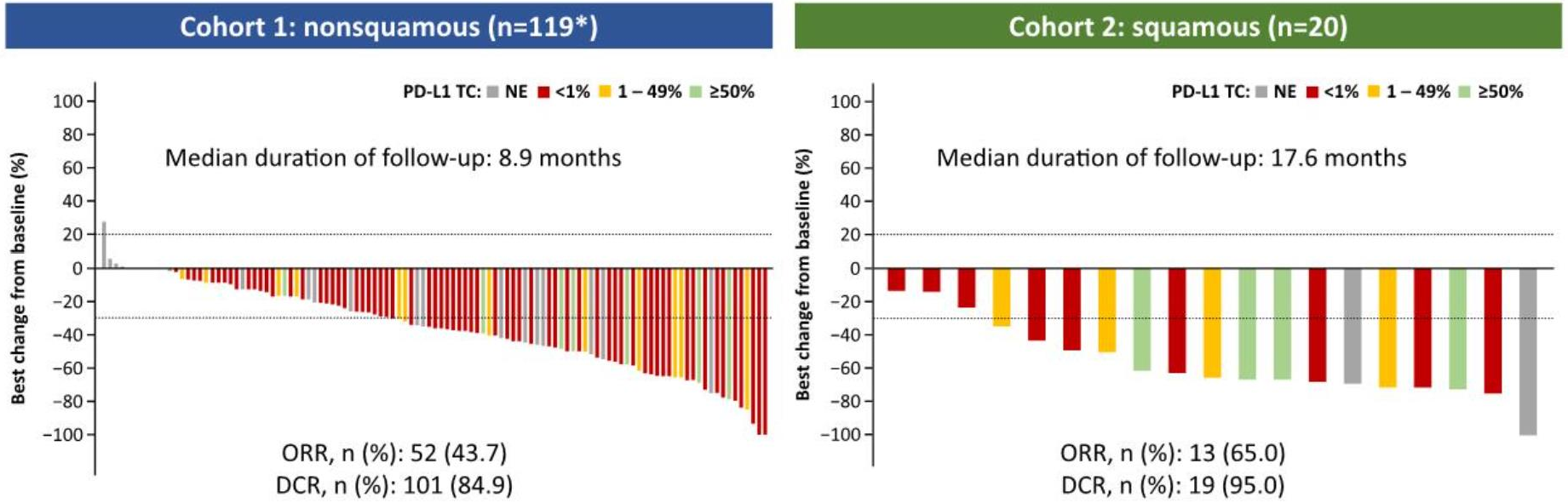
n (%)	PD-L1 1–49% TPS (n=31)	PD-L1 ≥50% TPS (n=34)
ORR, confirmed + pending [95%CI]	**9 (29%)** [14.2, 48.0]	**21 (61.8%)** [43.6, 77.8]
Continuing treatment	12 (38.7%)	24 (70.6%)

Hiltermann J WCLC 2023

Volrustomig - phase 1b PD1-CTLA4 with concurrent chemotherapy for first line

Volrustomig 750 mg + CTx	All (N=140)	Nonsquamous Cohort 1A (n=66)	Nonsquamous Cohort 1B (n=54)	Squamous Cohort 2 (n=20)
Median age (range), years	68.0 (36–86)	68.0 (36–83)	68.0 (40–86)	67.5 (49–82)
Male, n (%)	103 (73.6)	50 (75.8)	40 (74.1)	13 (65.0)
White / Asian, n (%)	93 (66.4) / 41 (29.3)	45 (68.2) / 19 (28.8)	34 (63.0) / 17 (31.5)	14 (70.0) / 5 (25.0)
ECOG PS 0 / 1, n (%)	45 (32.1) / 95 (67.9)	15 (22.7) / 51 (77.3)	20 (37.0) / 34 (63.0)	10 (50.0) / 10 (50.0)
Former or current smoker, n (%)	124 (88.6)	58 (87.9)	48 (88.9)	18 (90.0)
Brain metastases, n (%)	21 (15.0)	13 (19.7)	6 (11.1)	2 (10.0)
Liver metastases, n (%)	22 (15.7)	11 (16.7)	9 (16.7)	2 (10.0)
PD-L1 TC* <1%, n (%)	89 (63.6)	49 (74.2)	30 (55.6)	10 (50.0)

Spigel DR WCLC 2024



- 30% discontinuation rates of volrustomig
- Median PFS in pts with non-SQ, PD-L1 TC <1% of 6.1 months
- Phase trial with PD-L1 <50%

Select TRAEs (preferred term), n %	Any grade	Grade 3/4
Rash	38 (27.1)	4 (2.9)
ALT increase	33 (23.6)	9 (6.4)
AST increase	32 (22.9)	6 (4.3)
Hyperthyroidism	18 (12.9)	0
Pneumonitis	10 (7.1)	4 (2.9)
Diarrhea	15 (10.7)	2 (1.4)

Spigel DR WCLC 2024

Amivantamab

- EGFR-MET bispecific antibody
- Ligand blocking, receptor degrading and immune effector cell engagement
- CNS protective effect with no apparent benefit of TKI continuation
- IV formulation approved for three indications:
  - Classical EGFR mutated NSCLC front line in combination with Lazertinib
  - Classical EGFR mutant NSCLC in combination with carboplatin pemetrexed in patients previously treated with an EGFR TKI
  - EGFR Exon 20 insertion mutations as single agent for previously treated and in combination with carboplatin pemetrexed first line

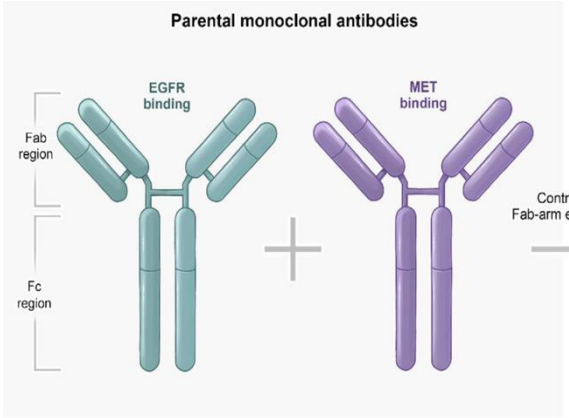
https://www.drugs.com/history/rybrevant.html; Cho BC NEJM 2024, Passaro A Ann of Oncol 2024

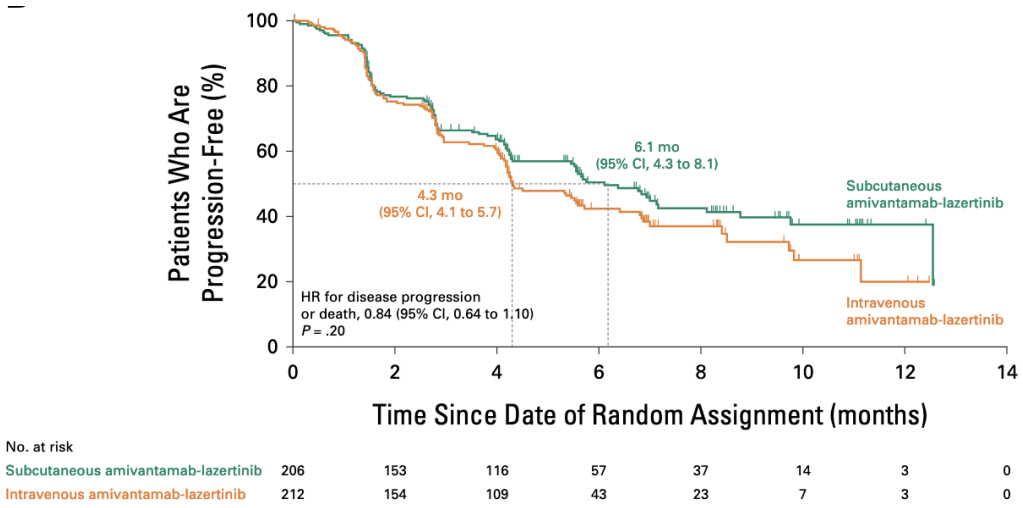
Unique amivantamab toxicity

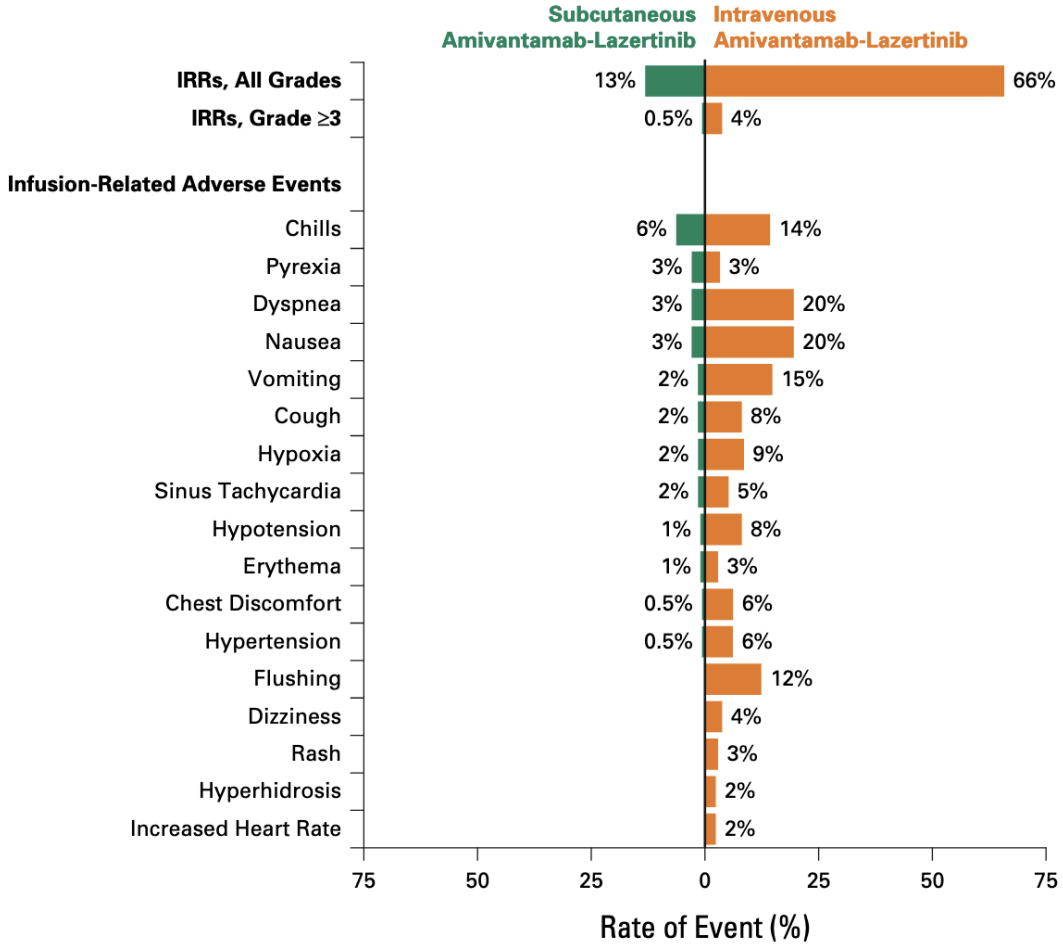
- Infusion related reactions are seen in 2/3 of patients with cycle 1, day 1
  - May be mitigated with dexamethasone premedication
- 71% of patients had rash, 10% grade 3 with chemotherapy
  - Prophylactive oral minocycline/doxycycline for first 2 weeks along with skin care regimen
- Venous thromboembolism
  - Highest with ami-laz, 37% vs single agent osimertinib
  - 62% within first 4 months prompting recommendation for prophylactic anticoagulation during this time period
  - Amivantamab plus chemotherapy: 10% all grades (vs 5% chemo alone) with no increased risk of grade $\geq$3

Passaro A NEJM 2024,

Amivantamab IV vs SC: PALOMA-3 trial







Cho BC et al. Clinic Lung Cancer. 2023.

Leighl et al. JCO. 2024.

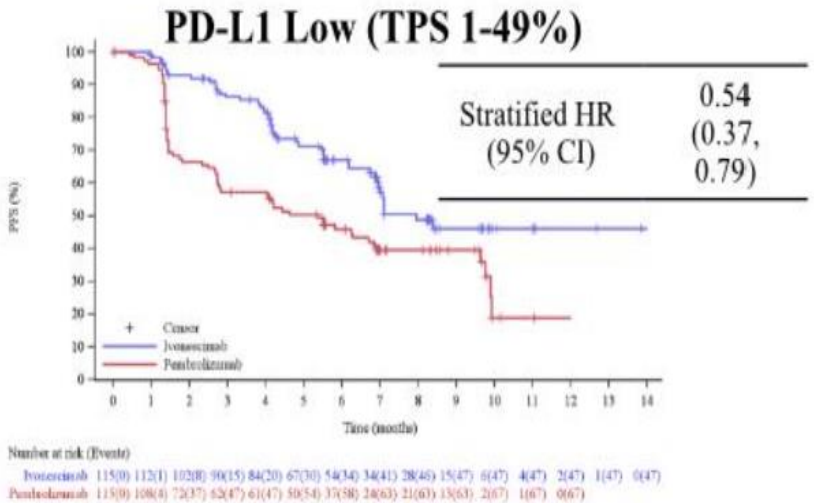
Ivonescimab- HARMONi-2

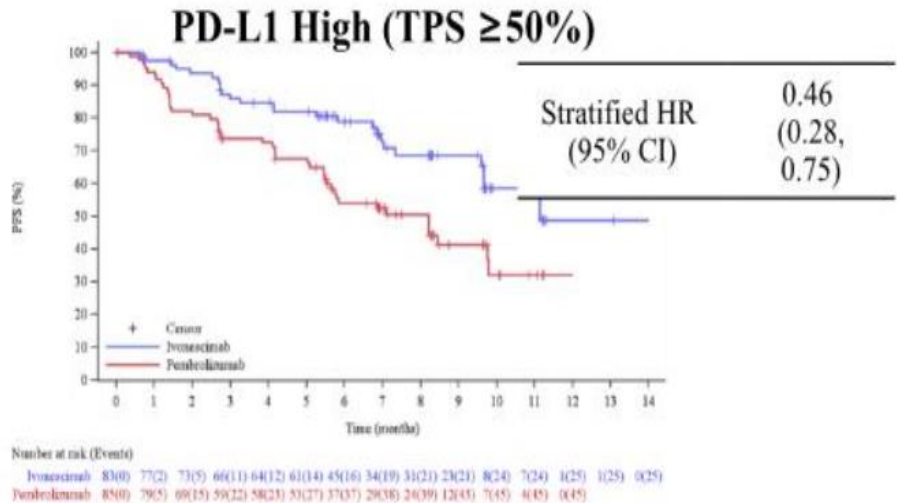
- Bispecific against PD-1 and VEGF tested against pembrolizumab in PDL1 positive NSCLC in front line setting

Characteristics, n (%)		Ivonescimab (n = 198[a])	Pembrolizumab (n = 200[a])
Age (years)	<65	97 (49.0)	85 (42.5)
	≥65	101 (51.0)	115 (57.5)
Sex	Male	164 (82.8)	169 (84.5)
	Female	34 (17.2)	31 (15.5)
ECOG PS	0	25 (12.6)	26 (13.0)
	1	173 (87.4)	174 (87.0)
Smoker	Never	39 (19.7)	38 (19.0)
	Current	39 (19.7)	42 (21.0)
	Former	120 (60.6)	120 (60.0)
Clinical stage	IIIB/C	15 (7.6)	16 (8.0)
	IV	183 (92.4)	184 (92.0)
Pathology	SQ	90 (45.5)	91 (45.5)
	Tumor centrally located[b]	65 (72.2)	57 (62.6)
	Tumor with cavitation/necrosis[b]	9 (10.0)	7 (7.7)
	Tumor encasing large blood vessel[b]	6 (6.7)	1 (1.1)
	Non-SQ	108 (54.5)	109 (54.5)
PD-L1 TPS	≥50%	83 (41.9)	85 (42.5)
	1-49%	115 (58.1)	115 (57.5)

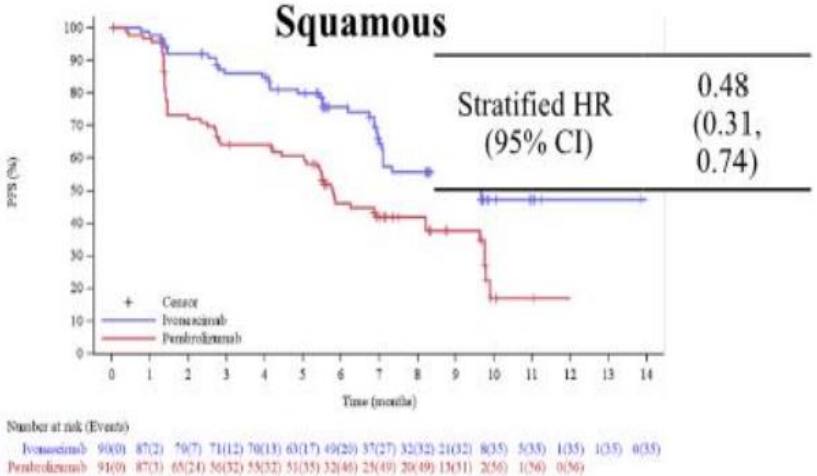
Key PFS Subgroup Analyses

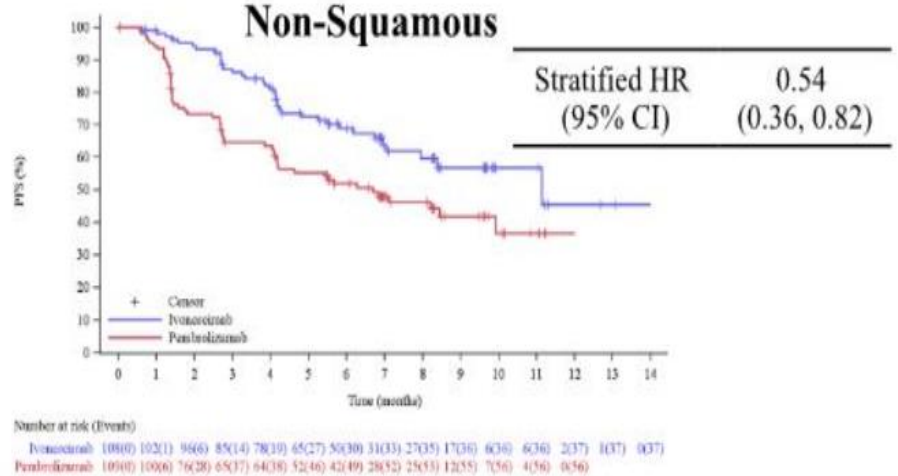
PD-L1 expression





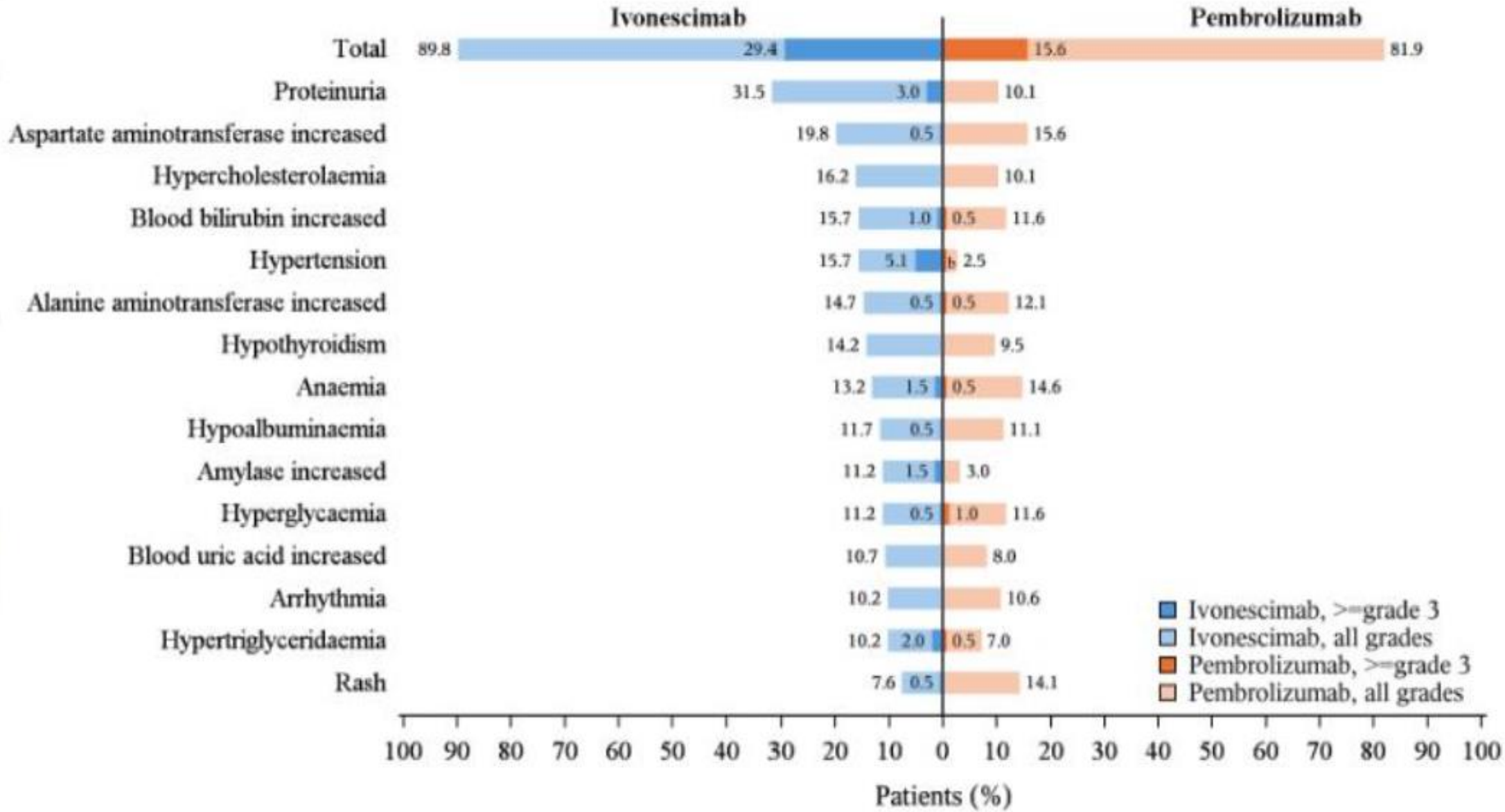
NSCLC Histology



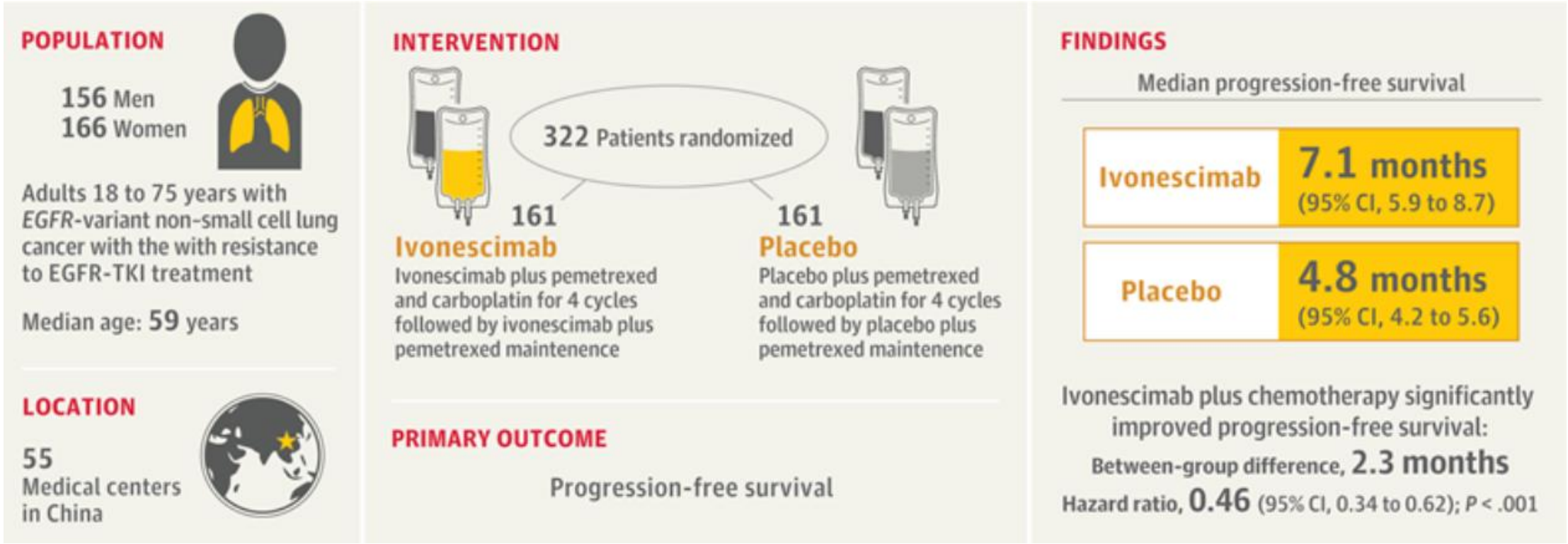


Ivonescimab showed meaningful improvement in PFS vs. pembrolizumab in patients with both low and high PD-L1, with squamous or non-squamous advanced NSCLC.

The Most Common TRAEs (incidence ≥10%)



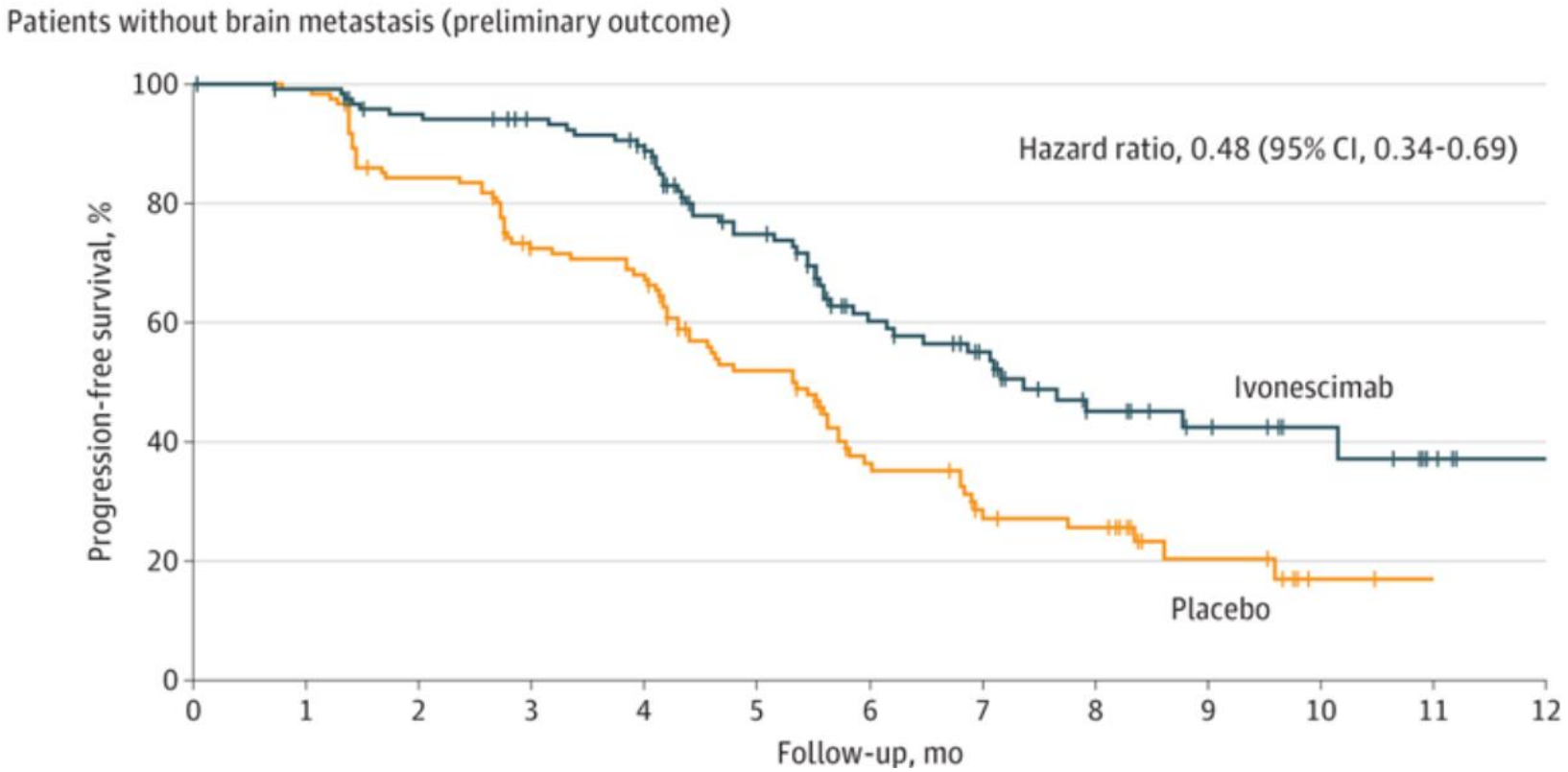
Ivonescimab in patients with EGFR



86% of patients had exposure to 3rd generation TKI

Zhang L JAMA 2024;332(7):561-570

PFS primary outcome, OS not mature



AESIs were proteinuria (17.4% vs 8.1%), bleeding (6.8% vs 5.0%), and hypertension (8.1% vs 3.1%)

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Conclusions

- Antibody drug conjugates is a rapidly expanding class of drugs with, at times, more questions than answers
- Though vaccines have been tested in advanced NSCLC for many years, there is renewed excitement with mRNA vaccines in combination of immune checkpoint inhibition
- Bispecific antibodies have a wide spectrum of targets in NSCLC and we wait further data to hopefully garner additional FDA approvals with this class of drugs