Antibody Drug Conjugates and Bispecific Therapy in Non-small Cell Lung Cancer

Hatim Husain MD

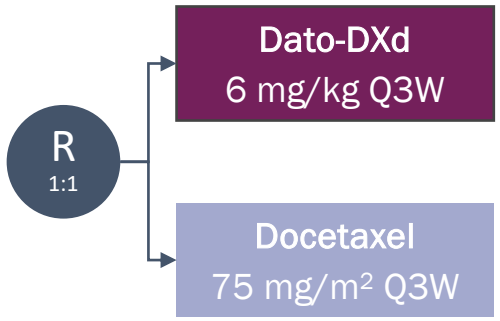
Associate Professor

University of California San Diego

Phase 3 TROPION-Lung01 Study of Dato-DXd vs Docetaxel in Pretreated mNSCLC ± Actionable Genomic Alterations (AGAs): Study Design and Patients

Key Eligibility Criteria

- NSCLC (stage IIIB/C or IV)
- ECOG PS 0 or 1
- No prior docetaxel
- **Without AGAs:**
  - 1-2 prior lines, including plt-chemo and anti-PD(L)1
- **With AGAs:**
  - *EGFR, ALK, NTRK, BRAF, ROS1, MET* or *RET* alterations
  - 1-2 prior approved targeted therapies + plt-chemo, and ≤1 anti-PD(L)1



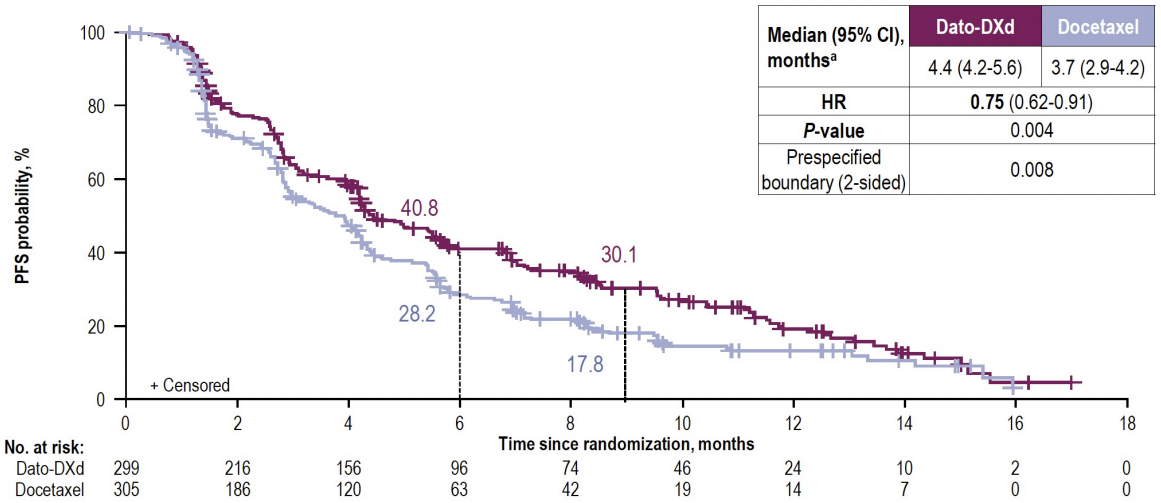
Primary endpoints: PFS (by BICR) and OS
Secondary endpoints: ORR (by BICR), DOR (by BICR), and safety

Patient Characteristics		Dato-DXd (n=299)	Docetaxel (n=305)
Median age (range), years		63 (26-84)	64 (24-88)
ECOG PS, n (%)	0	89 (30)	94 (31)
	1	210 (70)	211 (69)
Histology, n (%)	Nonsquamous	234 (78)	234 (77)
	Squamous	65 (22)	71 (23)
Current or former smoker, n (%)		238 (80)	251 (82)
AGAs, n (%)	Present	50 (17)	51 (17)
	EGFRmut	39 (13)	45 (15)
Brain mets at baseline, n (%)		50 (17)	47 (15)
Prior lines of therapy, n (%)	1	167 (56)	174 (57)
	2	108 (36)	102 (33)
	≥3	22 (7)	28 (9)
Prior systemic therapy, n (%)	Plt-containing	297 (99)	305 (100)
	Anti–PD-(L)1	263 (88)	268 (88)
	Targeted	46 (15)	50 (16)

Lisberg AE, et al. ESMO 2023. Abstract LBA12.

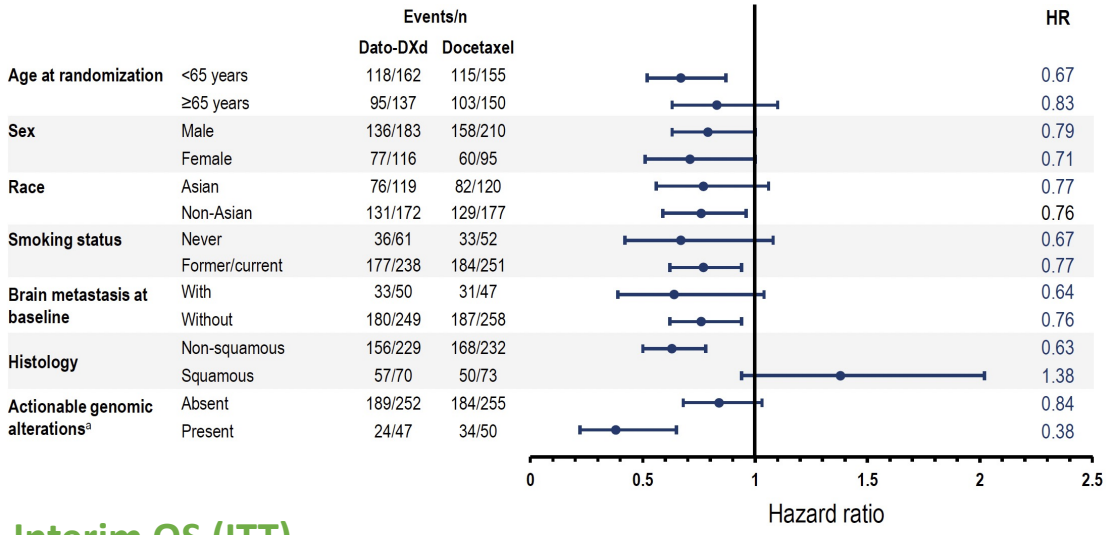
Phase 3 TROPION-Lung01 Study of Dato-DXd vs Docetaxel in Pretreated mNSCLC ± AGAs: Efficacy Outcomes

PFS (ITT)

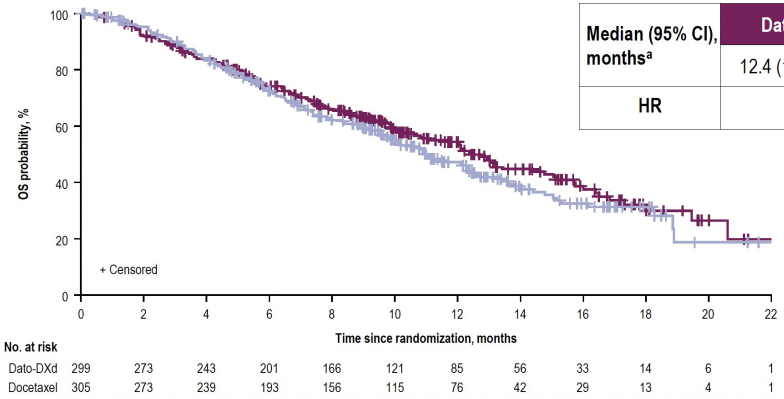


Median (95% CI), months[a]	Dato-DXd	Docetaxel
	4.4 (4.2-5.6)	3.7 (2.9-4.2)
HR	**0.75** (0.62-0.91)	
P-value	0.004	
Prespecified boundary (2-sided)	0.008	

PFS in Key Subgroups



Interim OS (ITT)



Median (95% CI), months[a]	Dato-DXd	Docetaxel
	12.4 (10.8-14.8)	11.0 (9.8-12.5)
HR	**0.90** (0.72-1.13)	

Information fraction at interim analysis (events/total events required): **74%**.

Non-squamous HR (95% CI): **0.77** (0.59-1.01); **Squamous HR** (95% CI): **1.32** (0.87-2.00)

Response	Dato-DXd (n=299)	Docetaxel (n=305)
ORR, % (95% CI)	26.4 (21.5-31.8)	12.8 (9.3-17.1)
Median DOR, months (95% CI)	7.1 (5.6-10.9)	5.6 (5.4-8.1)
Median follow-up, months	13.1	13.0

Lisberg AE, et al. ESMO 2023. Abstract LBA12.

Phase 3 TROPION-Lung01 Study of Dato-DXd vs Docetaxel in Pretreated mNSCLC ± AGAs: Safety Outcomes

TRAE Summary, n (%)		Dato-DXd (n=297)	Docetaxel (n=290)
All grades		257 (87)	252 (87)
Grade ≥3		73 (25)	120 (41)
Associated with	Dose reduction	58 (20)	85 (29)
	Dose delay	49 (17)	31 (11)
	Discontinuation	23 (8)	34 (12)
	Death[a]	3 (1)	2 (1)
Serious TRAEs		30 (10)	36 (12)
Grade ≥3		25 (8)	33 (11)

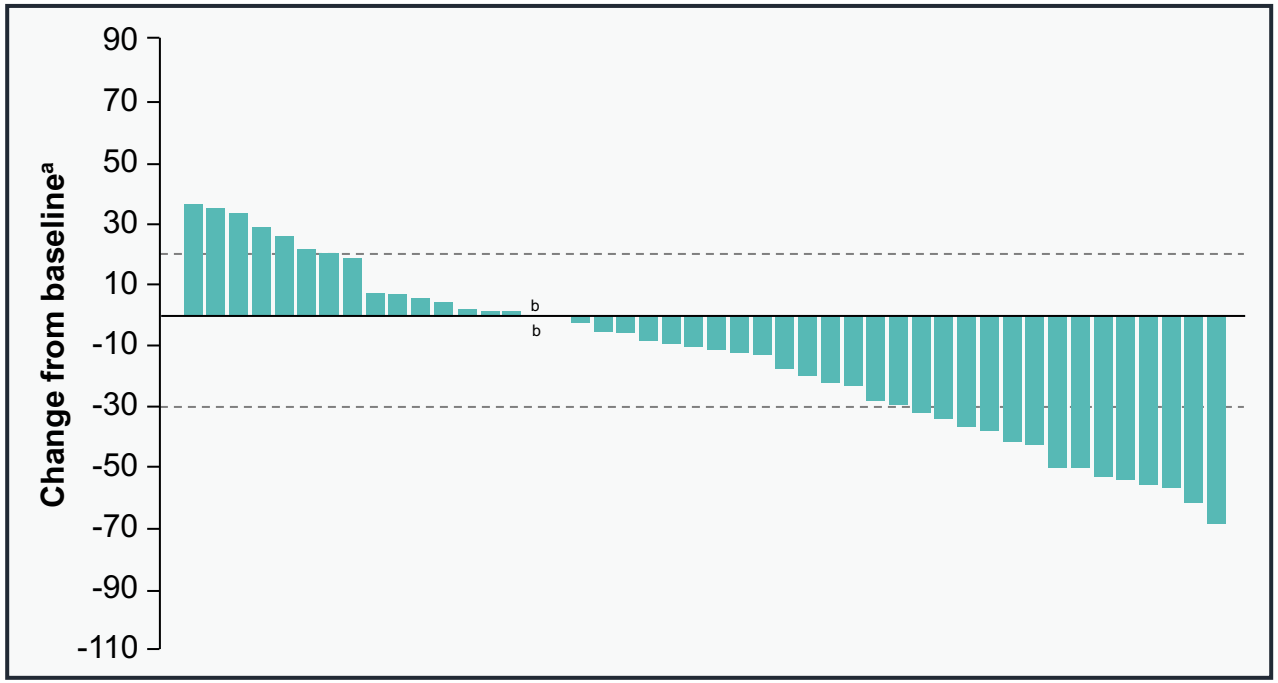
AESI, n (%)		Dato-DXd	Docetaxel
Stomatitis/oral mucositis	All grades	160 (54)	59 (20)
	Grade ≥3	19 (6)	4 (1)
Ocular events[b]	All grades	57 (19)	27 (9)
	Grade ≥3	5 (2)[c]	0
Adjudicated drug-related ILD	All grades	25 (8)	12 (4)
	Grade ≥3	10 (3)	4 (1)
	Grade 5	7 (2)[d]	1 (0.3)

TRAEs (in ≥10%), n (%)	Dato-DXd (n=297)		Docetaxel (n=290)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Anemia	43 (15)	11 (4)	59 (20)	11 (4)
Neutropenia	12 (4)	2 (1)	76 (26)	68 (23)
Stomatitis	140 (47)	19 (6)	45 (16)	3 (1)
Nausea	100 (34)	7 (2)	48 (17)	3 (1)
Vomiting	38 (13)	3 (1)	22 (8)	1 (0.3)
Constipation	29 (10)	0	30 (10)	0
Diarrhea	28 (9)	1 (0.3)	55 (19)	4 (1)
Asthenia	55 (19)	8 (3)	55 (19)	5 (2)
Fatigue	34 (11)	2 (1)	40 (14)	6 (2)
↓ appetite	68 (23)	1 (0.3)	45 (16)	1 (0.3)
Alopecia	95 (32)	0	101 (35)	1 (0.3)
Rash	36 (12)	0	18 (6)	0
Pruritus	30 (10)	0	12 (4)	0

- IRRs were observed in 8% of patients in each arm, all were grade ≤2 except for 1 grade 3 event with Dato-DXd

Lisberg AE, et al. ESMO 2023. Abstract LBA12.

Ph1/2 IMMU-132-01 Sacituzumab Govitecan (SG) in Epithelial Cancers, NSCLC Cohort: Efficacy Outcomes



	NSCLC[1,c] (N=54)
Response Outcomes	
ORR, % (n/N)	17% (9/54)
CR, n	0
PR, n	9%
SD, n	41%
DOR (mo), median (95% CI)	6.0 (2.5-21.0)
CBR (CR + PR + SD ≥6 mo), % (n/N)	24 (13/54)
Survival Outcomes	
PFS (mo), median (95% CI)	4.4 (2.5-5.4)
OS (mo), median (95% CI)	7.3 (5.6-14.6)

- Among 14 pts receiving prior CPI (median: 3 [range: 1-5] prior lines): **2 pts had a PR; 7 pts had SD**; 5 had PD
- 5 pts had durable disease control lasting >5 mos

Bardia A, et al. *Ann Oncol*. 2021;32:746-756.

Ph1/2 IMMU-132-01 Sacituzumab Govitecan (SG) in Epithelial Cancers, NSCLC Cohort: Safety Outcomes

- Serious events (≥Gr3) that occurred in ≥5% of pts were: neutropenia (28%), leukopenia (9%), pneumonia (9%), diarrhea (7%), nausea (7%), fatigue (6%)
- 2 pts had febrile neutropenia
- Discontinuation due to treatment-related AEs occurred in 2 pts (4%)
- No treatment-related deaths
- 49% of pts experienced a 25% dose reduction

Adverse Event[a]	All Grades, % of Patients		Grade ≥3, % of Patients	
	All patients (n=54)	10 mg/kg (n=46)	All patients (n=54)	10 mg/kg (n=46)
Nausea	80	78	7	9
Diarrhea	61	61	7	7
Fatigue	46	48	6	7
Alopecia	39	39	NA	NA
Neutropenia	37	39	28	30
Vomiting	35	33	4	2
Anemia	31	35	4	4
Constipation	28	28	2	2
Anorexia	28	28	2	2
Hypophosphatemia	22	24	2	2
Dehydration	19	22	0	0
Weight decrease	19	22	0	0
Leukopenia	19	17	9	9
Hypomagnesemia	17	20	0	0
Pneumonia	13	13	9	11

Heist RS, et al. *J Clin Oncol*. 2017;35:2790-2797.

HERTHENA-Lung01 Efficacy, Including in Patients With CNS Metastases

- HERTHENA-Lung01 is a phase 2 trial assessing patritumab deruxtecan (HER3-DXd) in patients with locally advanced or metastatic *EGFR*-mutated NSCLC who have previously received EGFR TKI and platinum-based chemotherapy

Confirmed Responses and Survival		Prior EGFR TKI (any) and PBC (N=225)	Subset With Prior 3rd- Gen EGFR TKI and PBC (n=209)
cORR (95% CI), %		**29.8 (23.9-36.2)**	**29.2 (23.1-35.9)**
BICR, n (%)	CR	1 (0.4)	1 (0.5)
	PR	66 (29.3)	60 (28.7)
	SD[a]	99 (44.0)	91 (43.5)
	PD	43 (19.1)	41 (19.6)
	NE[b]	16 (7.1)	16 (7.7)
DCR (95% CI), %		73.8 (67.5-79.4)	72.7 (66.2-78.6)
DOR, median (95% CI), mo		6.4 (4.9-7.8)	6.4 (5.2-7.8)
PFS, median (95% CI), mo		5.5 (5.1-5.9)	5.5 (5.1-6.4)
OS, median (95% CI), mo		11.9 (11.2-13.1)	11.9 (10.9-13.1)

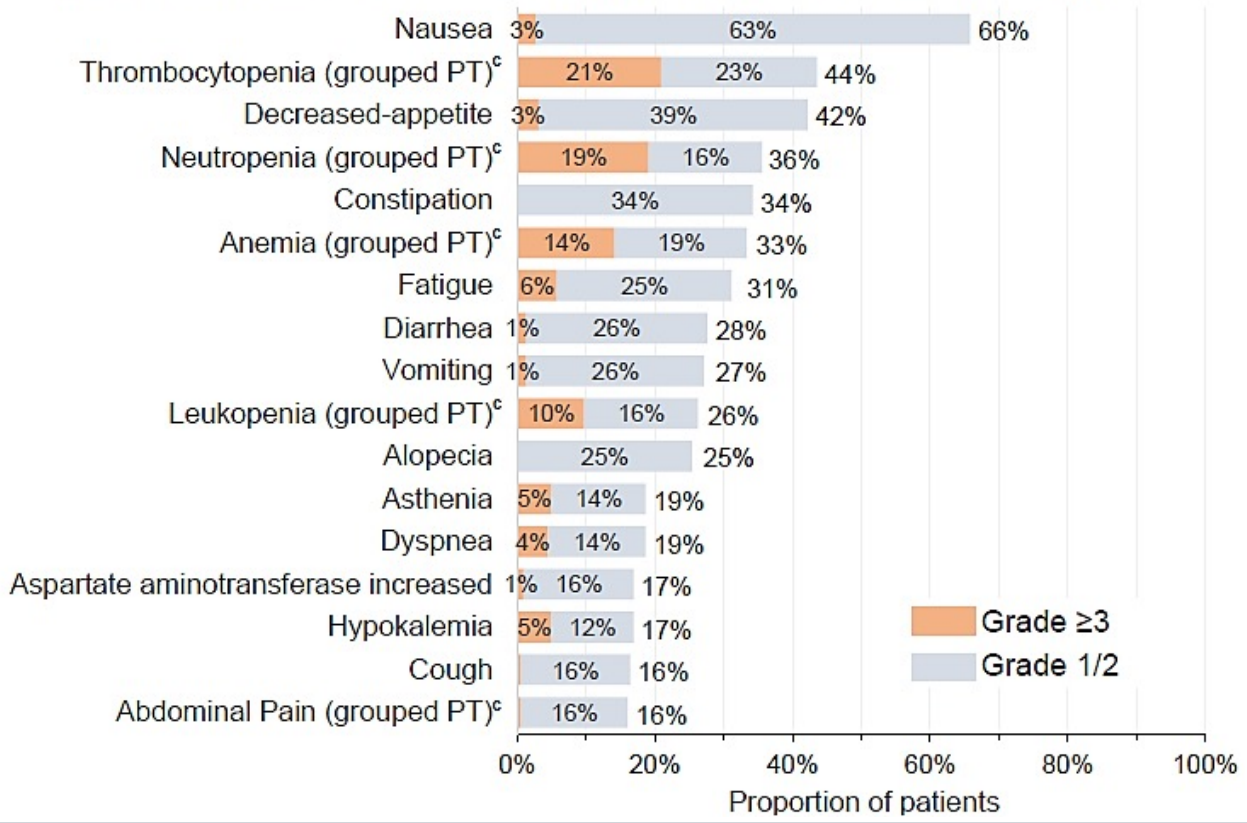
Responses by CNS BICR		All Patients With Baseline BM by CNS BICR (n=95)	Patients Whose Baseline BM Had Not Been Irradiated (n=30)[c]
CNS cORR (95% CI), %		**20.0 (12.5, 29.5)**	**33.3 (17.3-52.8)**
BICR, n (%)	CR	15 (15.8)	9 (30.0)[d]
	PR	4 (4.2)	1 (3.3)
	SD/non-CR /non-PD	57 (60.0)	13 (43.3)
	PD	13 (13.7)	4 (13.3)
	NE	6 (6.3)	3 (10.0)
CNS DCR (95% CI), %		80.0 (70.5-87.5)	76.7 (57.7-90.1)
CNS DOR, median (95% CI), mo		9.2 (8.1-11.1)	8.4 (5.8-9.2)

1. Yu HA, et al. WCLC 2023. Abstract OA05.03. **2**. Johnson ML, et al. ESMO 2023. Abstract 1319MO.

HERTHENA-Lung01 Safety

Safety Summary	HER3-DXd 5.6 mg/kg (N=225)
Any TEAE, n (%)	224 (99.6)
Associated with treatment discontinuation[a]	16 (7.1)
Associated with treatment dose reduction	48 (21.3)
Associated with treatment dose interruption	91 (40.4)
Grade ≥3 TEAE, n (%)	146 (64.9)
Treatment-related TEAE, n (%)	215 (95.6)
Associated with death[b]	4 (1.8)
Grade ≥3	102 (45.3)
Serious TEAE	34 (15.1)
Adjudicated interstitial lung disease, n (%) [All were adjudicated as treatment-related]	12 (5.3)
Grade 1	1 (0.4)
Grade 2	8 (3.6)
Grade 3	2 (0.9)
Grade 4	0
Grade 5	1 (0.4)

Most Common TEAEs Occurring in ≥15% of Patients (N=225)



Yu HA, et al. WCLC 2023. Abstract OA05.03.

TROPION-Lung05 Efficacy and Safety in Patients With Actionable Genomic Alterations

- TROPION-Lung05 is a phase 2 trial assessing datopotamab deruxtecan (Dato-DXd) in patients with advanced or metastatic NSCLC with actionable gene alterations that progressed on or after targeted therapy and platinum-based chemotherapy

Response per BICR	All Treated Patients (N=137)	Pts With *EGFR* Mutations (N=78)	Pts With ALK Rearrangement (N=34)
ORR confirmed, n (%) [95% CI]	49 (35.8) [27.8-44.4]	34 (43.6) [32.4-55.3]	8 (23.5) [10.7-41.2]
Median **DOR** (95% CI), mo	7.0 (4.2-9.8)	7.0 (4.2-10.2)	7.0 (2.8-8.4)
DCR confirmed, n (%) [95% CI]	108 (78.8) [71.0-85.3]	64 (82.1) [71.7-89.8]	25 (73.5) [55.6-87.1]
Median **PFS**, (95% CI), mo	5.4 (4.7-7.0)	5.8 (5.4-8.3)	4.3 (2.6-6.9)

- **BOR**: In the overall population (N=137), 4 patients (3%) achieved a CR and 45 (33%) achieved a PR
- ***EGFR* subset**: Among patients with sensitizing or T790M mutations (N=68), the ORR was 49.1% in those previously treated with osimertinib

AESI, n (%)[a]	Total	Grade 1	Grade 2	Grade ≥3
Oral mucositis/stomatitis	90 (66)	45 (33)	30 (22)	15 (11)
Ocular surface toxicity[b]	36 (26)	26 (19)	7 (5)	3 (2)[c]
IRR	22 (16)	15 (11)	7 (5)	0
Adjudicated drug-related ILD	5 (4)	1 (1)	3 (2)	1 (1)[d]

- 137 pts (100%) experienced **TEAEs** (grade ≥3, 47%)
  - 129 (94%) experienced **TRAEs** (grade ≥3, 29%)
  - 34 (25%) experienced **serious AEs** (grade ≥3, 5%)
- Most common TEAEs[e] that occurred in ≥15% of pts were **nausea** (grade 1-2, 58%; grade ≥3, 2%), **stomatitis** (grade 1-2, 49%; grade ≥3, 10%), **alopecia**[f] (grade 1-2, 52%; grade ≥3, 0%), constipation (grade 1-2, 32%, grade ≥3, 0%)

Paz-Ares L, et al. ESMO 2023. Abstract 1314MO.

MARIPOSA 2 – Amivantamab+chemotherapy post progression on osimertinib

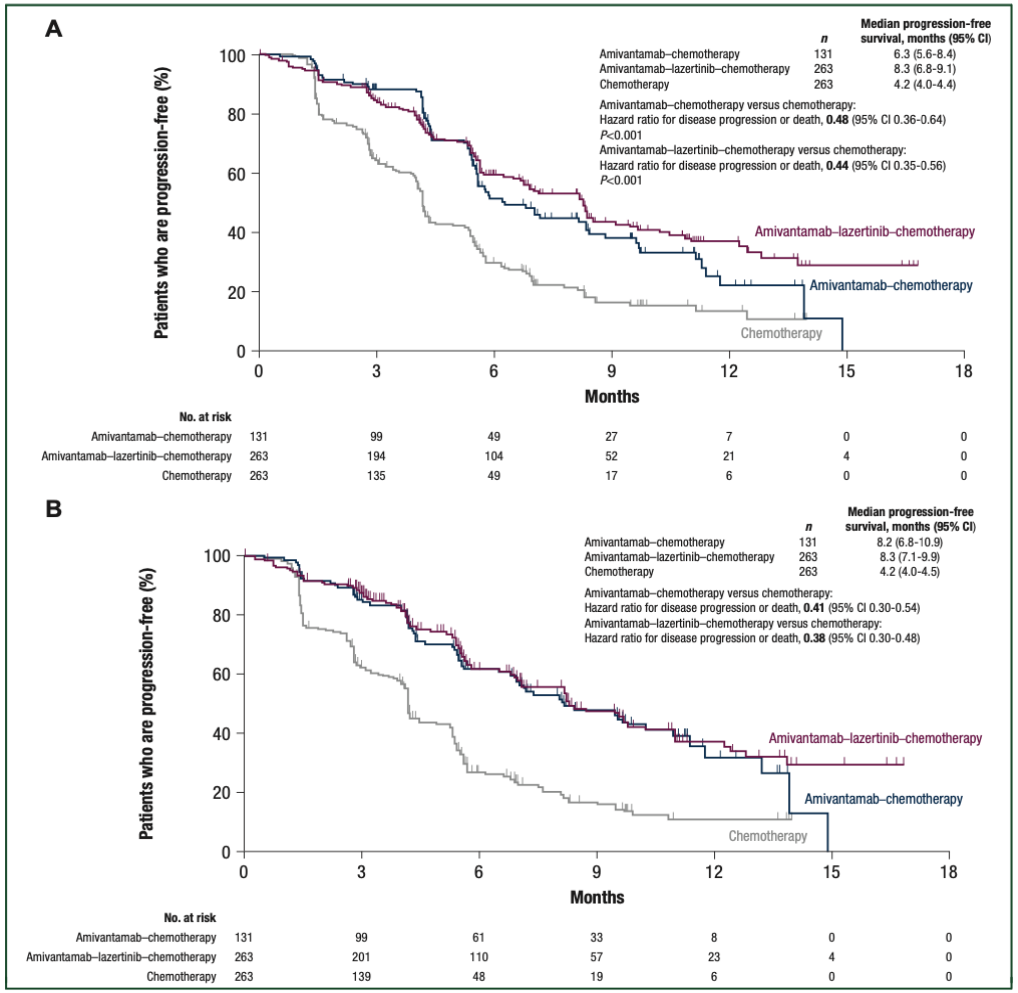


Figure 1. Progression-free survival by blinded independent central review and by investigator.
Shown are Kaplan—Meier estimates of progression-free survival assessed by blinded independent central review (A) and investigator assessment (B). The efficacy analysis set included all randomized patients. Tick marks indicate censoring of data. CI, confidence interval.

Passaro et al Ann Onc 2023

Table 2. Key efficacy endpoints by blinded independent central review

Endpoint	Chemotherapy (n = 263)	Amivantamab—chemotherapy (n = 131)	Amivantamab—lazertinib—chemotherapy (n = 263)
Progression-free survival			
No. of months, median (95% CI)	4.2 (4.0-4.4)	6.3 (5.6-8.4)	8.3 (6.8-9.1)
% of patients progression-free at 6 months (95% CI)	30 (23-36)	51 (41-60)	59 (52-65)
% of patients progression-free at 12 months (95% CI)	13 (8-20)	22 (12-34)	37 (29-45)
Objective response rate,[a] % (95% CI)	36 (30-42)	64 (55-72)	63 (57-69)
Duration of response[b]			
No. of months, median (95% CI)[b]	5.6 (4.2-9.6)	6.9 (5.5-NE)	9.4 (6.9-NE)
Intracranial progression-free survival			
No. of months, median (95% CI)	8.3 (7.3-11.3)	12.5 (10.8-NE)	12.8 (11.1-14.3)
% of patients progression-free at 6 months (95% CI)	66 (59-72)	78 (69-85)	79 (74-84)
% of patients progression-free at 12 months (95% CI)	34 (23-45)	50 (35-64)	54 (45-63)

Efficacy analysis included all randomly assigned patients.
CI, confidence interval; NE, not estimable.
[a]No. of patients with measurable disease at baseline by blinded independent central review was 260 for chemotherapy, 130 for amivantamab—chemotherapy, and 259 for amivantamab—lazertinib—chemotherapy.
[b]Duration of response among confirmed responders.

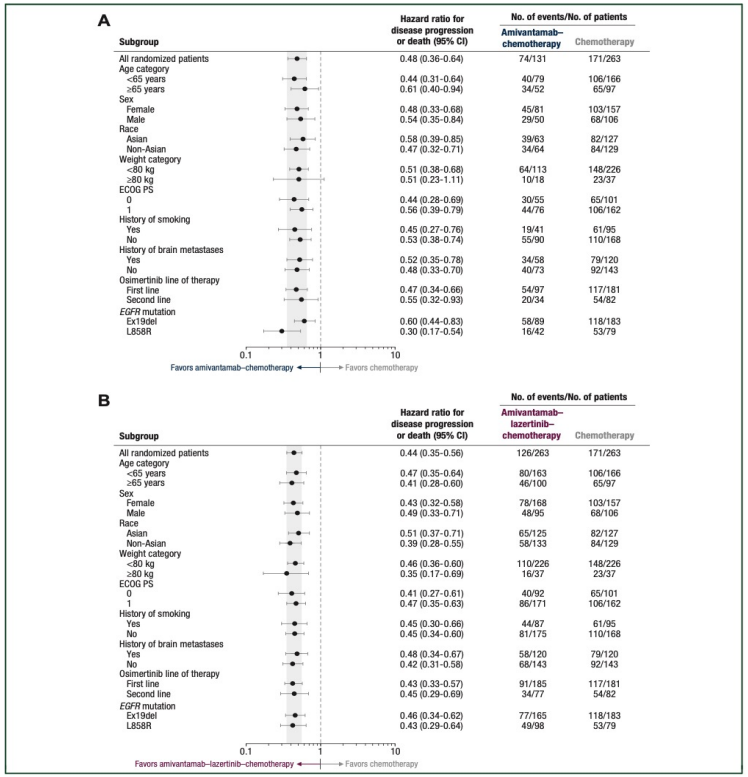
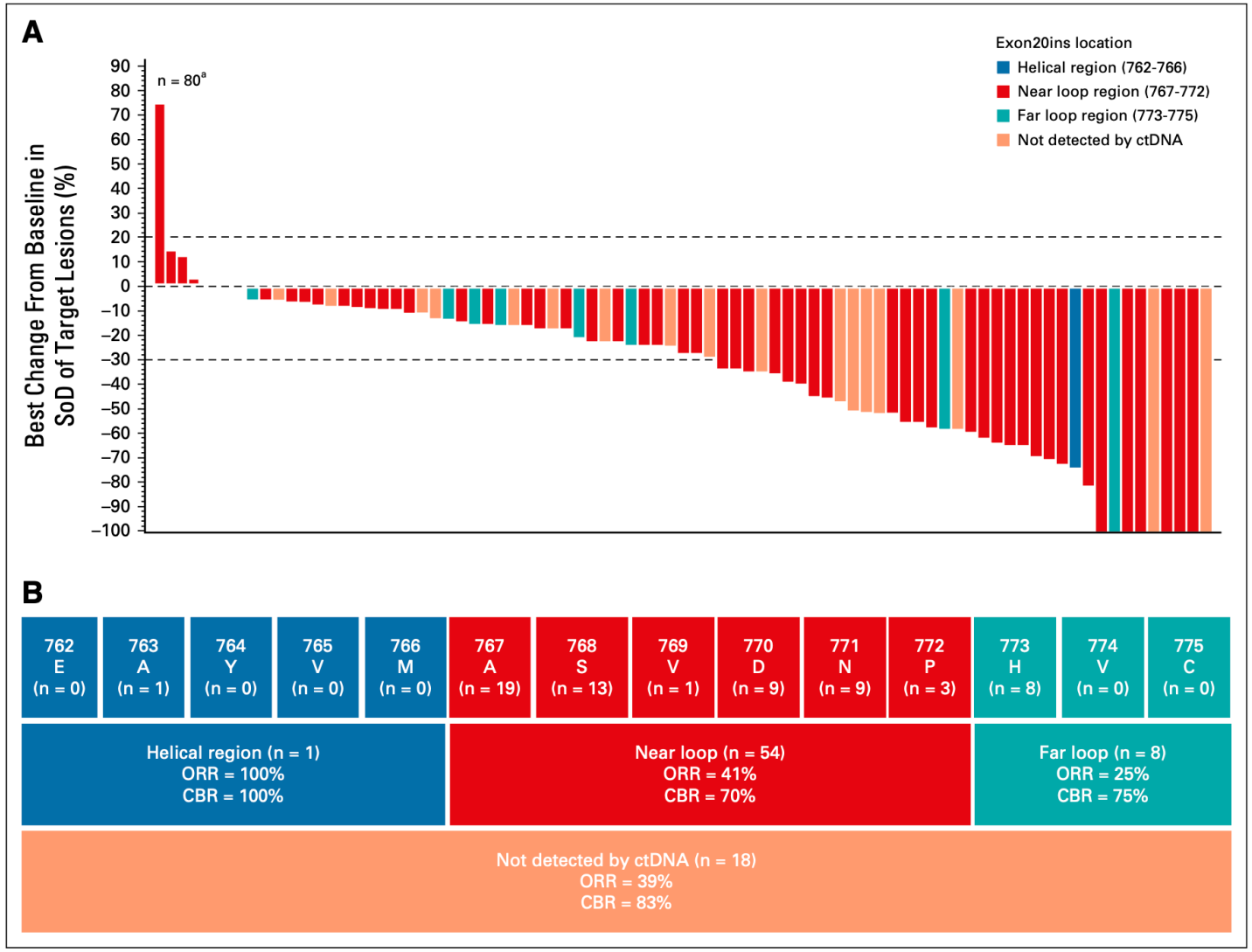


Figure 2. Progression-free survival by blinded independent central review of patient subgroups.
Shown are forest plots of progression-free survival in patient subgroups assessed by blinded independent central review for amivantamab—chemotherapy versus chemotherapy (A) and for amivantamab—lazertinib—chemotherapy versus chemotherapy (B). The efficacy analysis set included all randomized patients. The shaded areas indicate the 95% CI for the overall hazard ratio (all patients). CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status.

CHRYSALIS: Amivantamab in EGFR Exon20 Insertion–Mutated NSCLC



Park et al JCO 2021

PAPILLON – First Line Amivantamab+chemotherapy for EGFR Ex20 insertions

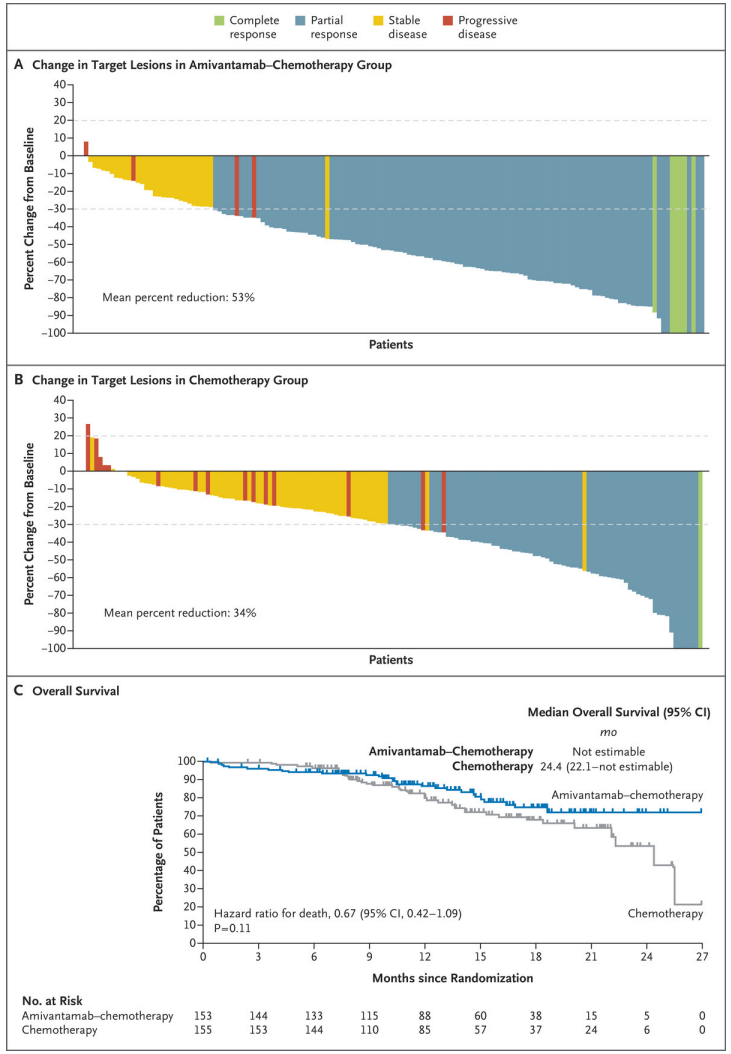


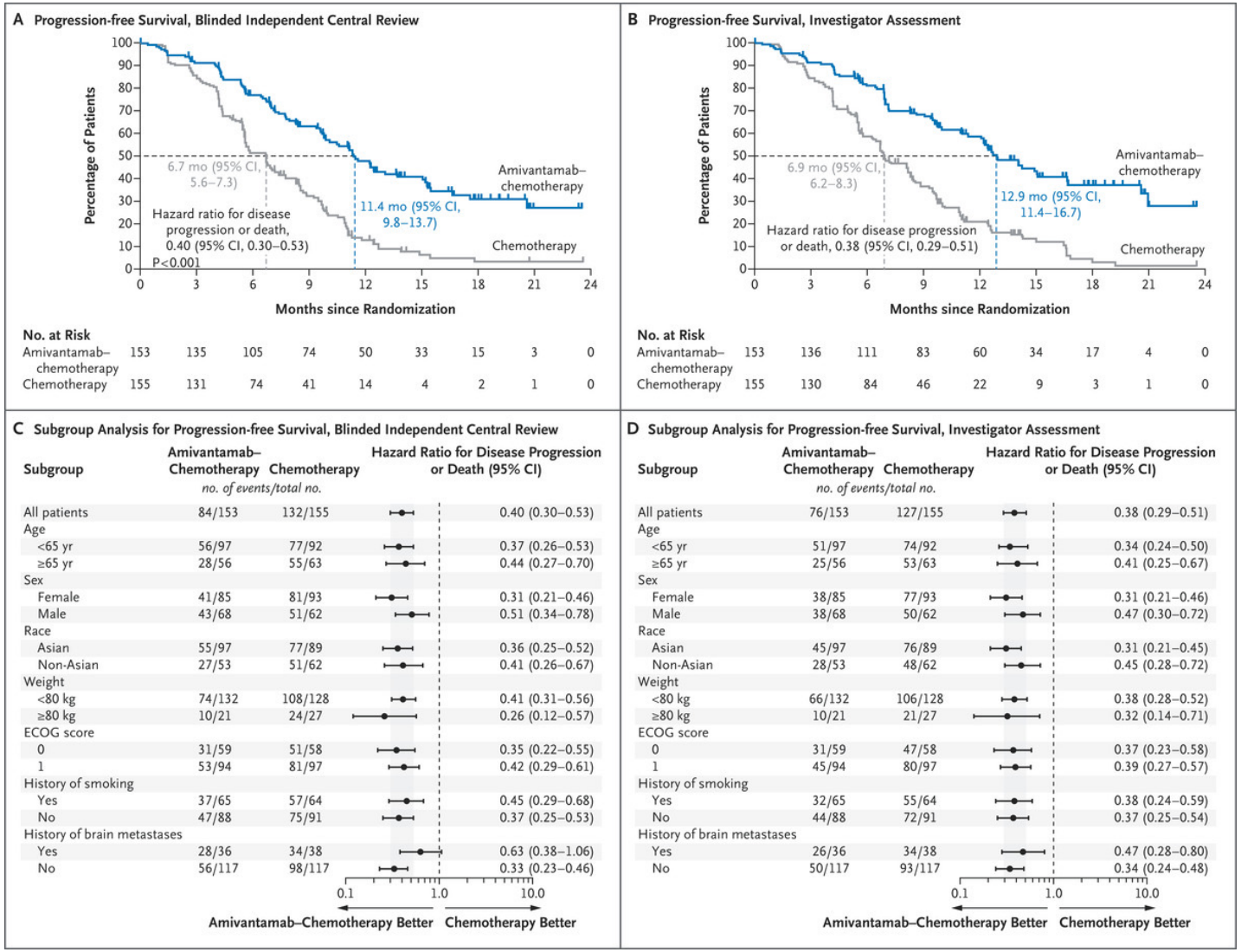
Table 2. Key Efficacy Outcomes.*

Outcome	Amivantamab–Chemotherapy (N=153)	Chemotherapy (N=155)	Treatment Effect (95% CI)	P Value
Progression-free survival†				
Median (95% CI) — mo	11.4 (9.8–13.7)	6.7 (5.6–7.3)	Hazard ratio, 0.40 (0.30–0.53)	<0.001
Patients (95% CI) — %				
At 6 mo	77 (69–83)	51 (43–59)		
At 12 mo	48 (39–56)	13 (8–19)		
At 18 mo	31 (22–40)	3 (1–9)		
Objective response‡				
Patients (95% CI) — %	73 (65–80)	47 (39–56)	Rate ratio, 1.50 (1.32–1.68)	<0.001
Overall survival				
Median (95% CI) — mo	NE	24.4 (22.1–NE)	Hazard ratio, 0.67 (0.42–1.09)	0.11
Patients (95% CI) — %				
At 12 mo	86 (79–91)	82 (74–87)		
At 18 mo	74 (64–82)	68 (58–76)		
At 24 mo	72 (61–81)	54 (37–68)		

* The efficacy population included all the patients who had undergone randomization. NE denotes not estimable.
† Progression-free survival (the primary outcome) was assessed by blinded independent central review.
‡ The objective response (complete or partial response) was assessed by blinded independent central review. Included in the analysis were 152 patients with measurable disease at baseline in each group.

Zhou et al NEJM 2023

PAPILLON – First Line Amivantamab+chemotherapy for EGFR Ex20 insertions



Zhou et al NEJM 2023

Conclusions

- Current approval for anti-Her2 antibody drug conjugates
- ADCs have advanced with additional approvals expected soon around anti-TROP2 and anti-Her3
- Currently being tested in the first and subsequent line space
- Combinations with anti-PD1/L1 antibodies ongoing and certain TKI therapies are being tested
- Amivantamab bispecifics approved in EGFR ex20 ins NSCLC patients
- Ongoing investigations of amivantamab in the EGFR Ex19del and L858R pts