VII CONVEGNO NAZIONALE DELLA
RETE ONCOLOGICA SIFaCT

Oltre il modello mutazionale e l'oncologia di precisione: la medicina personalizzata

ONCOFARMA

Sifact
SOCIETÀ ITALIANA DI FARMACIA CLINICA E TERAPIA

Milano 23-24 Giugno 2023

News from ASCO: la medicina personalizzata

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FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI

Disclosures

Commercial Interest	Relationship(s)
AstraZeneca, Roche, MSD, Bristol Myers Squibb, Sanofi/Regeneron	Honorarium
AstraZeneca, Roche, MSD	Travel accommodation, Roche
AstraZeneca, Roche, MSD, Janssen	Advisory Board
Janssen, Pfizer, Lilly, Spectrum Pharmaceuticals, Roche, MSD, BMS, AstraZeneca	Principal Investigator in clinical trials

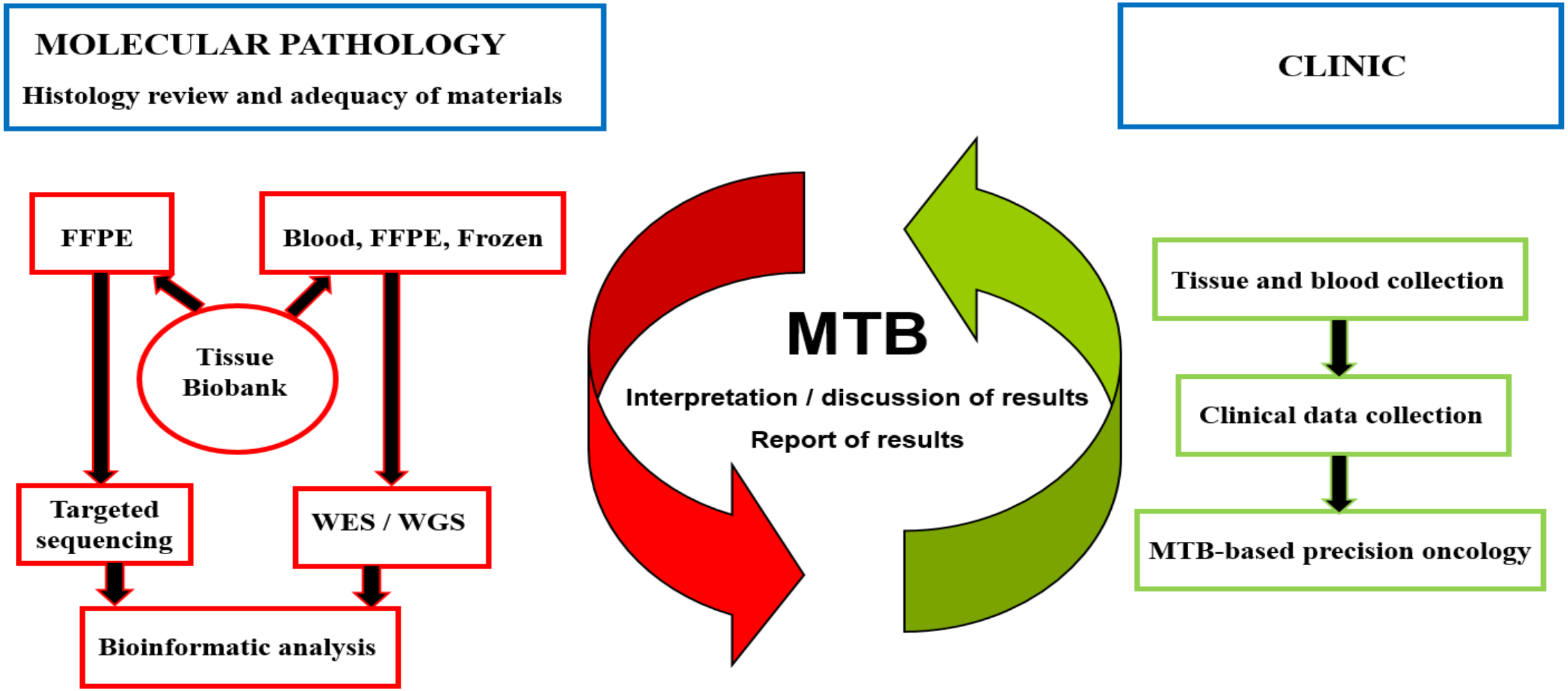
AGENDA

NEWS from ASCO 2023

- **TARGET THERAPY**
  - **Non Small Cell Lung cancer** → EGFR, KRAS, ROS1, BRAF
  - **Urothelial carcinoma** → FGFR
  - **Biliary tract cancer** → HER2

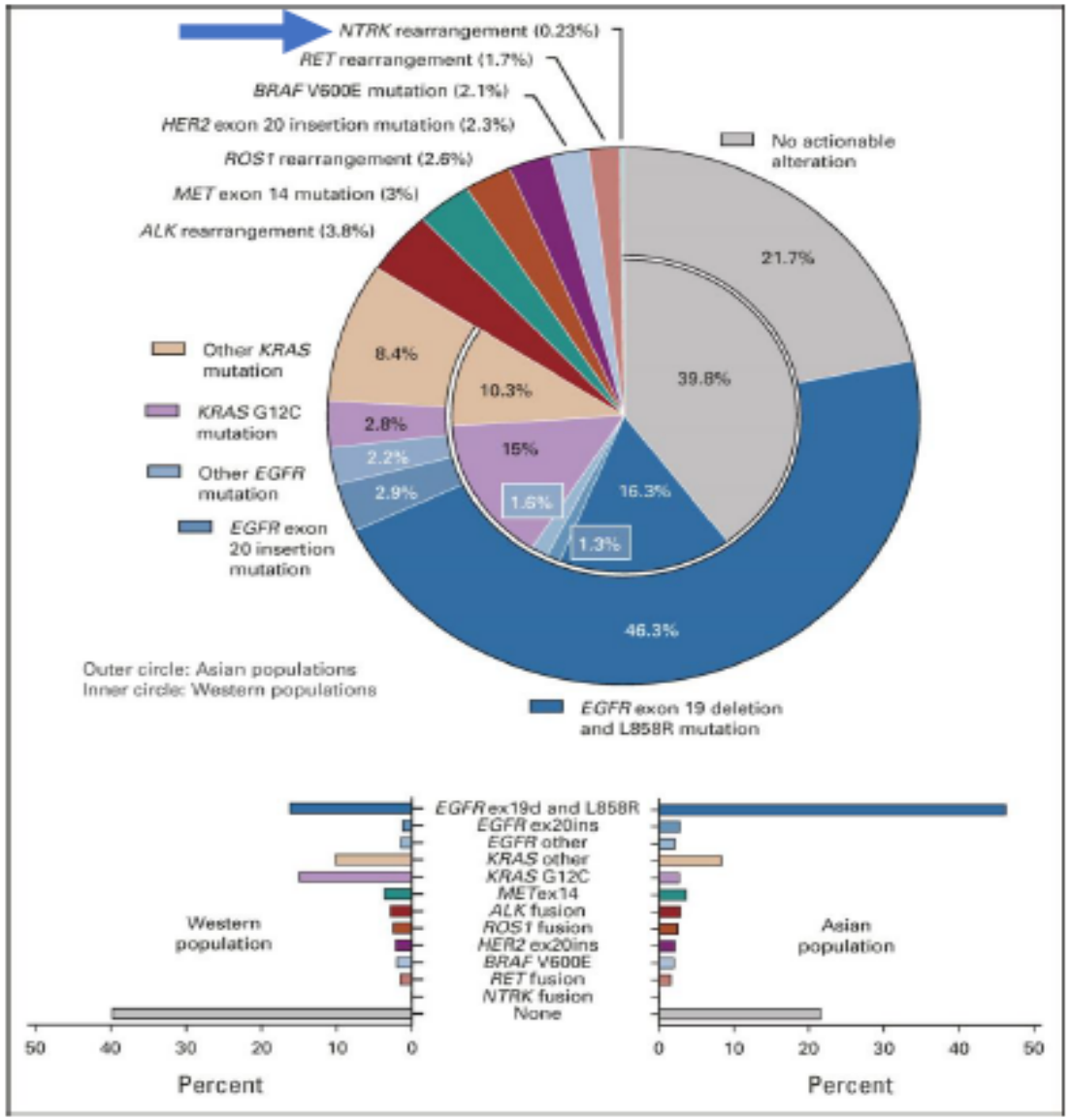
- **ANTIBODY DRUG CONITUGATES**
  - **Non small cell lung cancer, Breast Cancer** → anti TROP2
  - **Breast cancer** → anti HER2 and HER3
  - **Solid tumors** → anti HER2

Molecular Tumor Board: precision oncology decision support



Luchini C et al. Trends in oncology; 2020

MOLECULAR TARGETS IN NSCLC



- **EGFR mutations**
- **ALK rearrangements**
- **ROS1 rearrangements**
- **BRAF mutations**
- **NTRK gene fusions**
- **RET rearrangements**
- **MET alterations**
- KRAS mutations
- HER2 alterations

EGFR mutant NSCLC

ADAURA trial: **Adjuvant osimertinib** in patients with resected EGFR mutated stage IB-IIIA NSCLC

ADAURA Phase III study design

Patients with completely resected stage* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:
≥18 years (Japan / Taiwan: ≥20)
WHO performance status 0 / 1
Confirmed primary non-squamous NSCLC Ex19del / L858R‡
Brain imaging, if not completed pre-operatively
Complete resection with negative margins§
Maximum interval between surgery and randomization:
- 10 weeks without adjuvant chemotherapy
- 26 weeks with adjuvant chemotherapy

Stratification by:
Stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
Race (Asian vs non-Asian)

Randomization 1:1 (N=682)

Osimertinib 80 mg, once daily

Placebo, once daily

Planned treatment duration: 3 years

Treatment continued until:
- Disease recurrence
- Treatment completion
- Discontinuation criterion met

Follow-up:
- Until recurrence: Week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly

Endpoints
- **Primary endpoint:** DFS by investigator assessment in stage II–IIIA patients
- **Key secondary endpoints:** DFS in the overall population (stage IB–IIIA), landmark DFS rates, OS, safety, health-related quality of life

*At the time of recruitment, staging was determined by the AJCC / UICC Staging Manual 7th edition. Patients with stage IB disease were not eligible in Japan. †Pre-operative, post-operative, or planned radiotherapy was not allowed. ‡Centrally confirmed in tissue. §Patients received a CT scan after resection and within 28 days prior to treatment.

AJCC, American Joint Committee on Cancer; CT, computerized tomography; DFS, disease-free survival; EGFRm, epidermal growth factor receptor-mutated; Ex19del, exon 19 deletion; NSCLC, non-small cell lung cancer; OS, overall survival; UICC, Union for International Cancer Control; WHO, World Health Organization

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PRESENTED BY: Roy S. Herbst

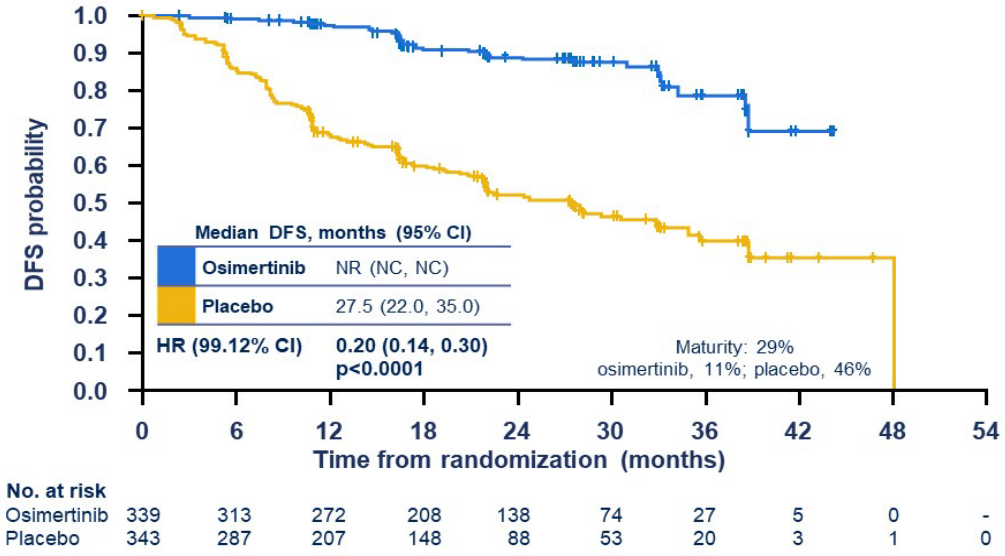
ADAURA trial: DFS results

Adjuvant osimertinib has significantly improved DFS

- Adjuvant osimertinib demonstrated highly statistically significant[1,2] and clinically meaningful improvement in DFS in completely resected EGFRm NSCLC vs placebo in both the primary (stage II–IIIA) and overall (IB–IIIA) populations, along with a tolerable safety profile[1–4]

ADAURA primary DFS analysis[1,2] (stage IB–IIIA)*

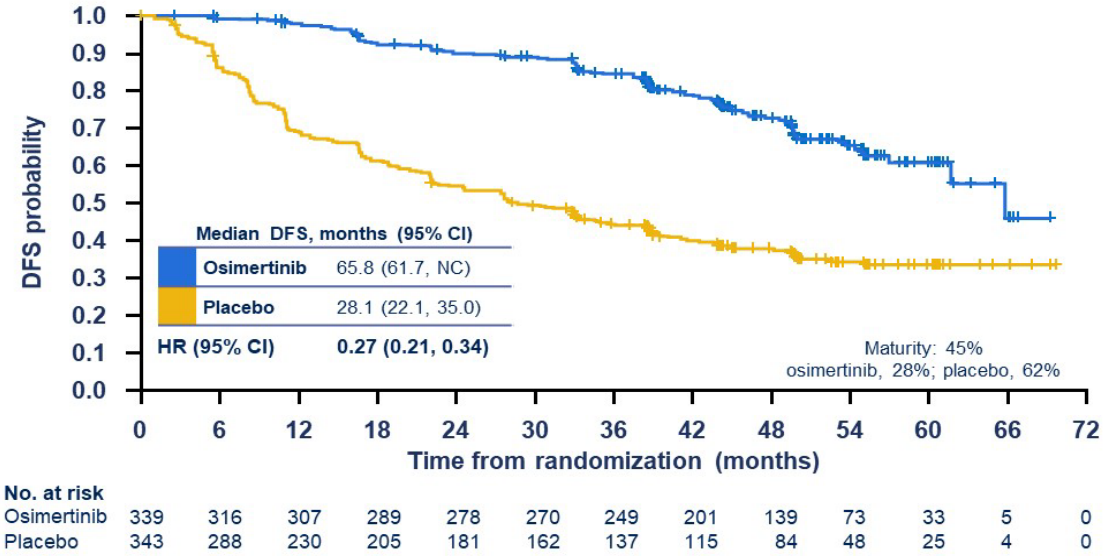
NEJM October 2020



No. at risk										
Osimertinib	339	313	272	208	138	74	27	5	0	-
Placebo	343	287	207	148	88	53	20	3	1	0

ADAURA updated DFS analysis[3,4] (stage IB–IIIA)†

JCO January 2023



No. at risk													
Osimertinib	339	316	307	289	278	270	249	201	139	73	33	5	0
Placebo	343	288	230	205	181	162	137	115	84	48	25	4	0

*Data cut-off: January 17, 2020. †Data cut-off: April 11, 2022.

1. Wu et al. N Engl J Med 2020;383:1711–1723; 2. Herbst et al. J Clin Oncol 2020;38(Suppl 18): abstract / oral LBA5; 3. Herbst et al. J Clin Oncol 2023;41:1830–1840; 4. Tsuboi et al. Ann Oncol 2022;33(Suppl 7): abstract / oral LBA47.

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CI, confidence interval; DFS, disease-free survival; EGFRm, epidermal growth factor receptor-mutated; HR, hazard ratio; NC, not calculable; NR, not reached; NSCLC, non-small cell lung cancer

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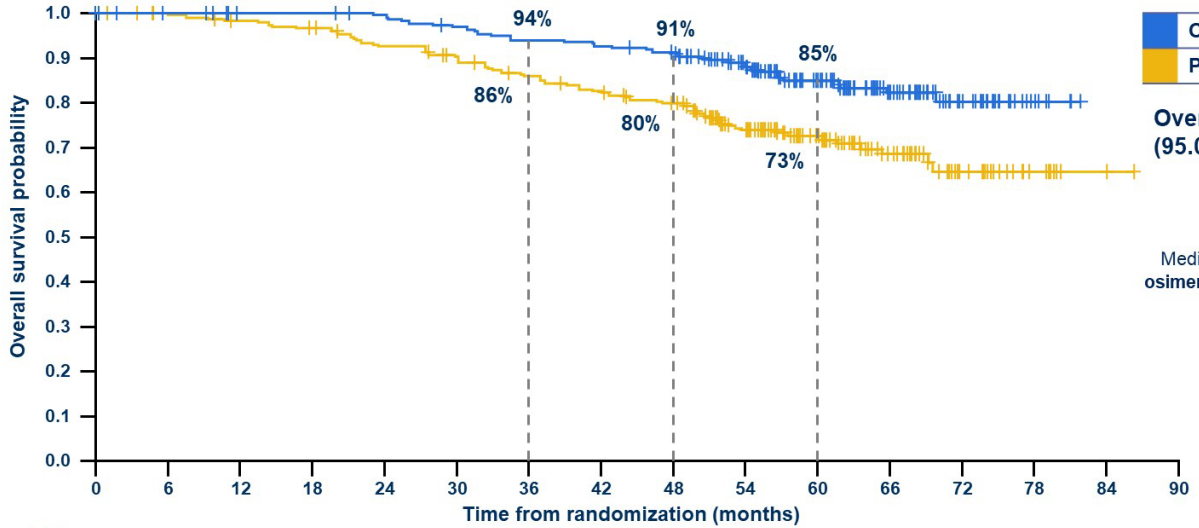
ADAURA trial: **Overall Survival analysis**

Overall survival: patients with stage II / IIIA disease

- Adjuvant osimertinib demonstrated a statistically and clinically significant improvement in OS vs placebo in the primary population of stage II–IIIA disease



5-year OS rate, % (95% CI)	
Osimertinib (n=233)	85 (79, 89)
Placebo (n=237)	73 (66, 78)

Overall OS HR (95.03% CI) **0.49 (0.33, 0.73); p=0.0004**

Maturity: 21%
osimertinib 15%, placebo 27%

Median follow-up for OS* (censored patients):
osimertinib 61.7 months, placebo 60.4 months

Tick marks indicate censored data. Alpha allocation of 0.0497. *Median follow-up for OS

CI, confidence interval; HR, hazard ratio; OS, overa

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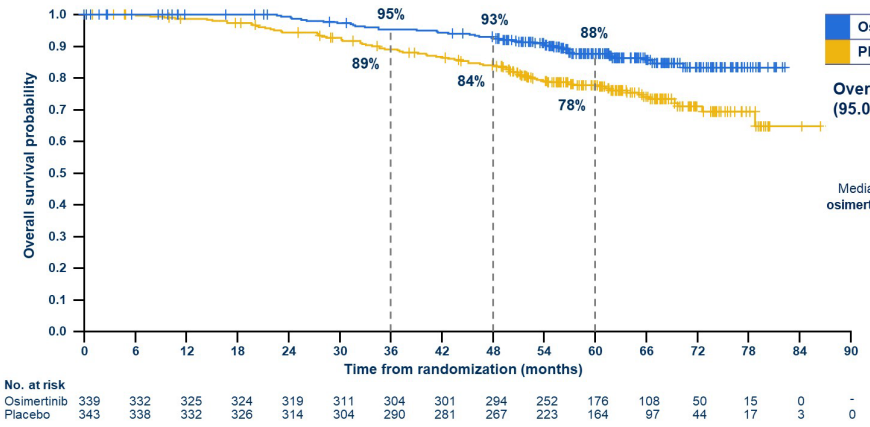
Herbst RS, ASCO 2023

Overall survival: patients with stage IB / II / IIIA disease

- Adjuvant osimertinib demonstrated a statistically and clinically significant improvement in OS vs placebo in the overall population of stage IB–IIIA disease



5-year OS rate, % (95% CI)	
Osimertinib (n=339)	88 (83, 91)
Placebo (n=343)	78 (73, 82)

Overall OS HR (95.03% CI) **0.49 (0.34, 0.70); p<0.0001**

Maturity: 18%
osimertinib 12%, placebo 24%

Median follow-up for OS* (censored patients):
osimertinib 61.5 months, placebo 61.5 months

Data cut-off: January 27, 2023.
Tick marks indicate censored data. Alpha allocation of 0.0497. *Median follow-up for OS (all patients): osimertinib 60.4 months; placebo 59.4 months.

CI, confidence interval; HR, hazard ratio; OS, overall survival

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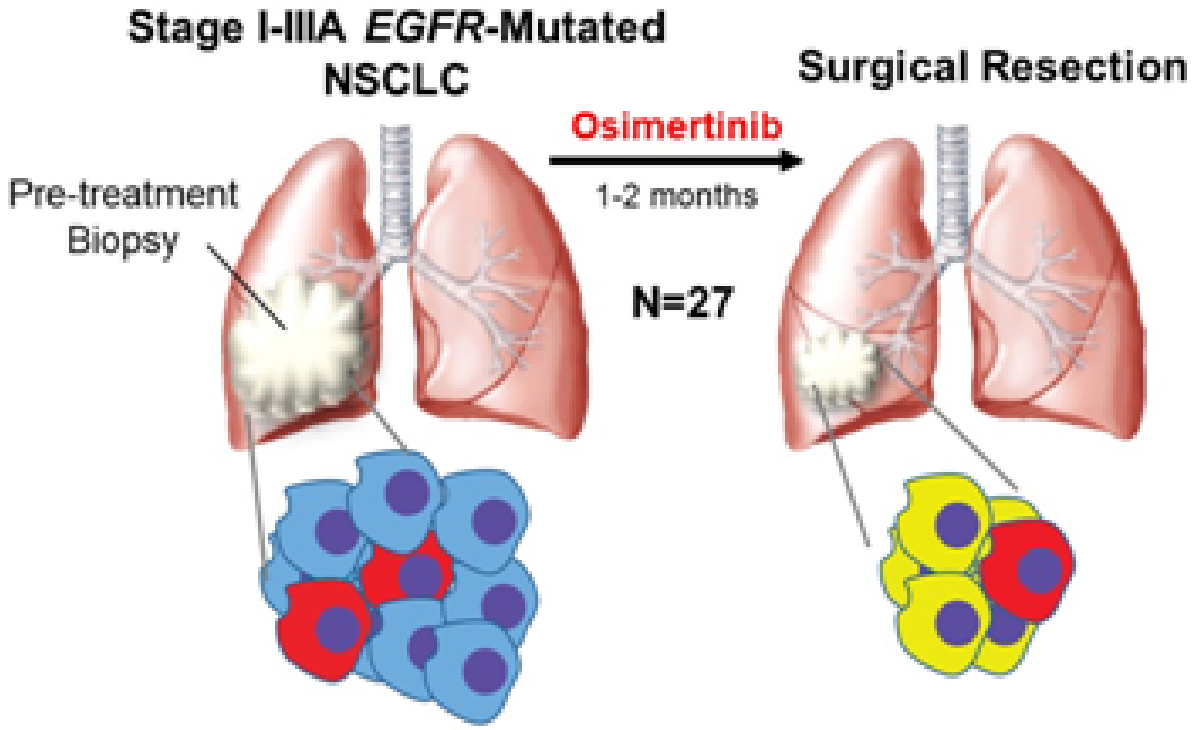
Phase II trial of **Neoadjuvant Osimertinib** for surgically resectable EGFR-Mutated Non-Small Cell Lung cancer



Primary Endpoint:
Major Pathological Response (MPR) Rate
(Powered to detect MPR ~ 50%)

Secondary Endpoints:

Safety:
Surgical Complications
Unresectability Rate

Efficacy:
Lymph Node Downstaging
Pathological Response Rate
pCR Rate
5-year DFS/OS

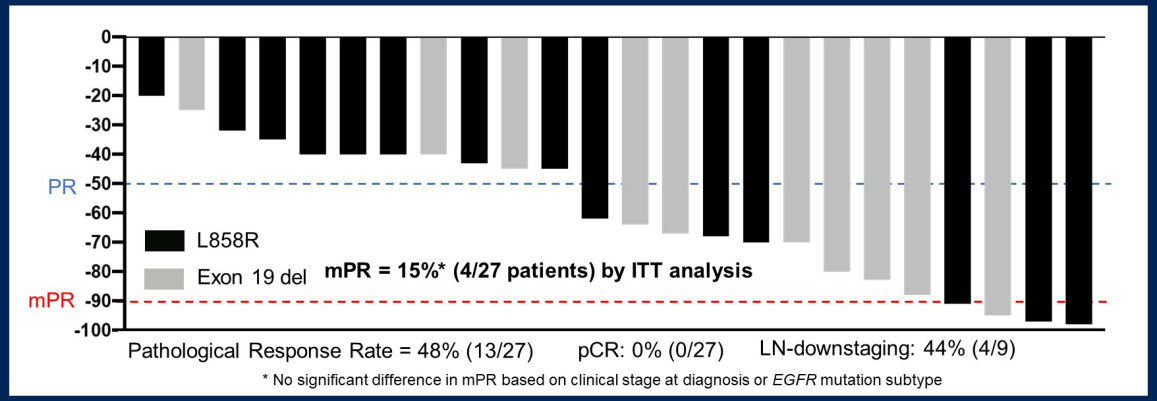
Exploratory Endpoint:
Identify mechanisms underlying disease persistence

Primary endpoint: Major Pathological Response Rate (**MPR**)

Modified by Aredo JV, ASCO 2023

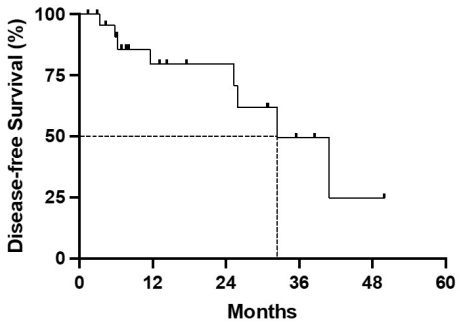
Neoadjuvant osimertinib: efficacy results

Primary Endpoint:
Major Pathologic Response Rate = 15%

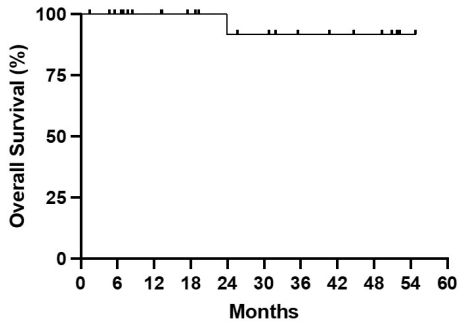


Median duration of neoadjuvant osimertinib: 56 days (IQR 41-62)

Preliminary DFS and OS



Median DFS = 32.4 months (95% CI 25.9-NR)



Median Follow-up = 21.6 months (IQR 8.2-41.7)

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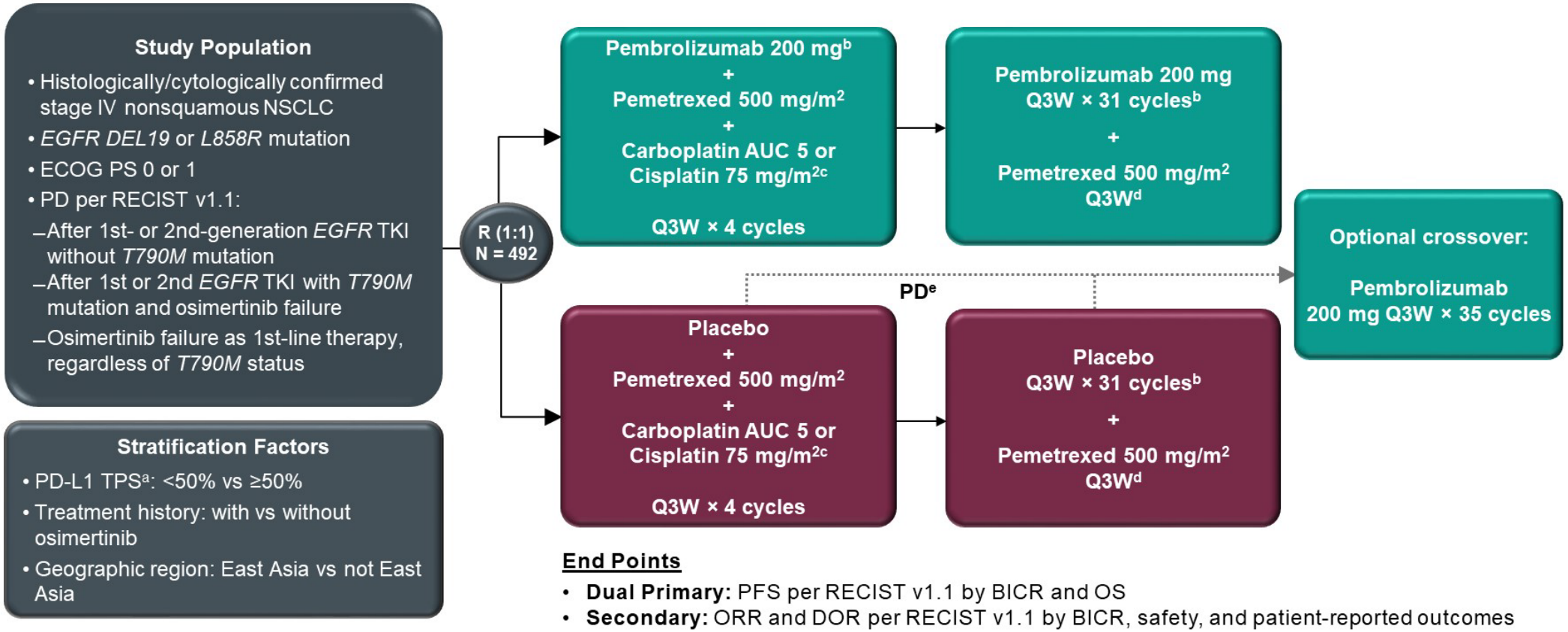
Neoadjuvant osimertinib did not meet the primary endpoint of a MPR of 50%

Aredo JV, ASCO 2023

KEYNOTE 789: **CT with or without IO** in EGFR+ NSCLC

KEYNOTE-789: Phase 3 Randomized Study (NCT03515837)



End Points

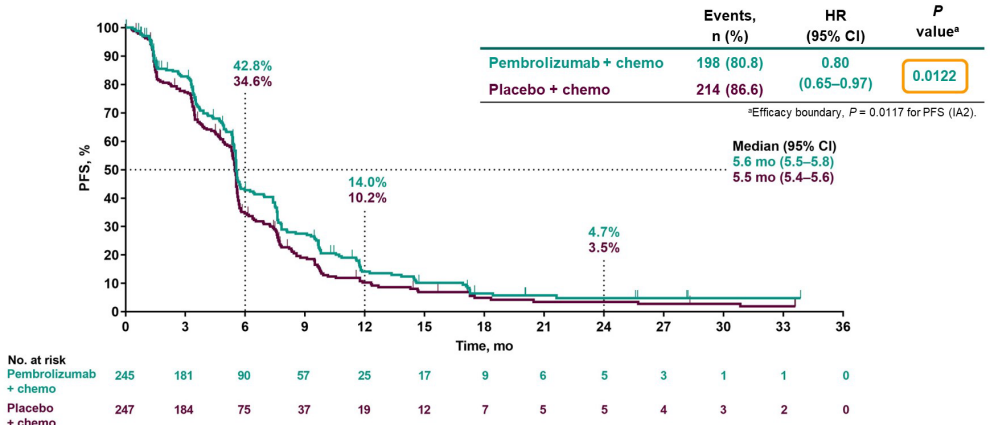
- **Dual Primary:** PFS per RECIST v1.1 by BICR and OS
- **Secondary:** ORR and DOR per RECIST v1.1 by BICR, safety, and patient-reported outcomes

[a]PD-L1 expression was centrally assessed using PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA). [b]If a patient has documented PD but is benefiting clinically, they may receive pembrolizumab monotherapy to complete a total of 35 pembrolizumab administrations. [c]Carboplatin or cisplatin therapy is at the investigator's choice. [d]Maintenance pemetrexed may continue past 35 cycles until reaching a discontinuation criterion if the patient is receiving benefit; however, pembrolizumab or saline placebo are limited to 35 cycles. [e]Patients could crossover at any time during the treatment. To be eligible for crossover, PD must have been verified by BICR.

Yang JCH, ASCO 2023

KEYNOTE 789: efficacy results

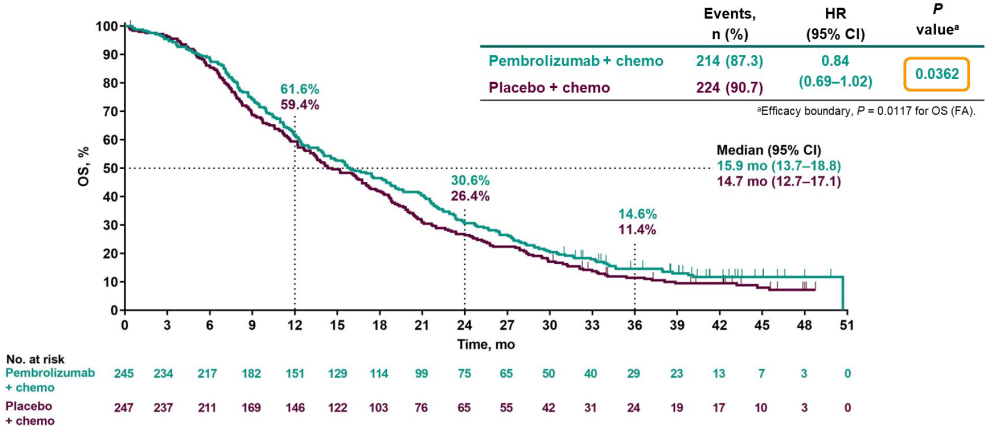
Progression-Free Survival at IA2
(RECIST v1.1, BICR)



	Events, n (%)	HR (95% CI)	P value[a]
Pembrolizumab + chemo	198 (80.8)	0.80 (0.65–0.97)	0.0122
Placebo + chemo	214 (86.6)		

[a]Efficacy boundary, $P = 0.0117$ for PFS (IA2).

Overall Survival at FA

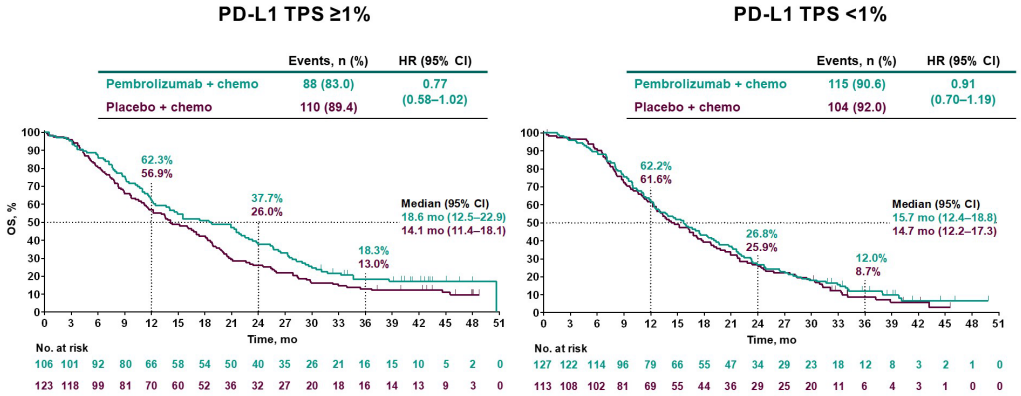


	Events, n (%)	HR (95% CI)	P value[a]
Pembrolizumab + chemo	214 (87.3)	0.84 (0.69–1.02)	0.0362
Placebo + chemo	224 (90.7)		

[a]Efficacy boundary, $P = 0.0117$ for OS (FA).

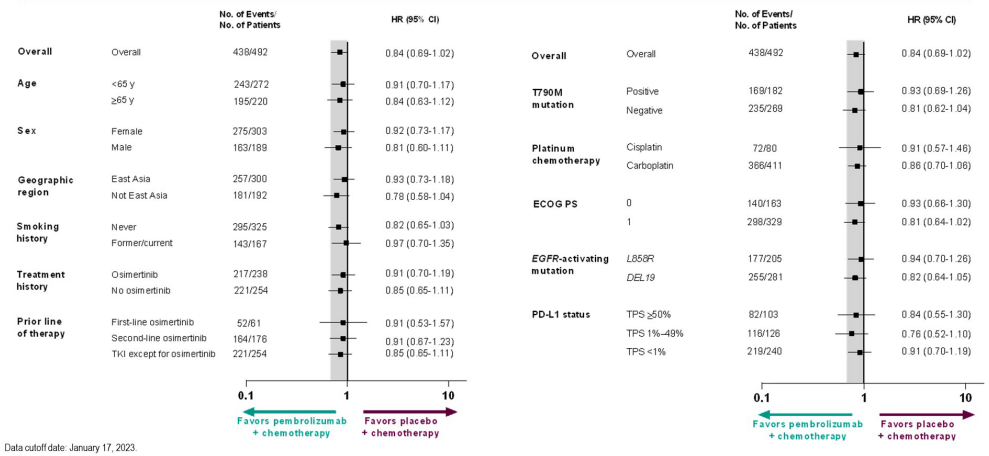
Median (range) time from randomization to data cutoff: 42.0 (29.5–53.9) months.
Data cutoff date: January 17, 2023.

Overall Survival in PD-L1 TPS ≥1% and <1% at FA



Data cutoff date: January 17, 2023.

Overall Survival Across Subgroups at FA



Data cutoff date: January 17, 2023.

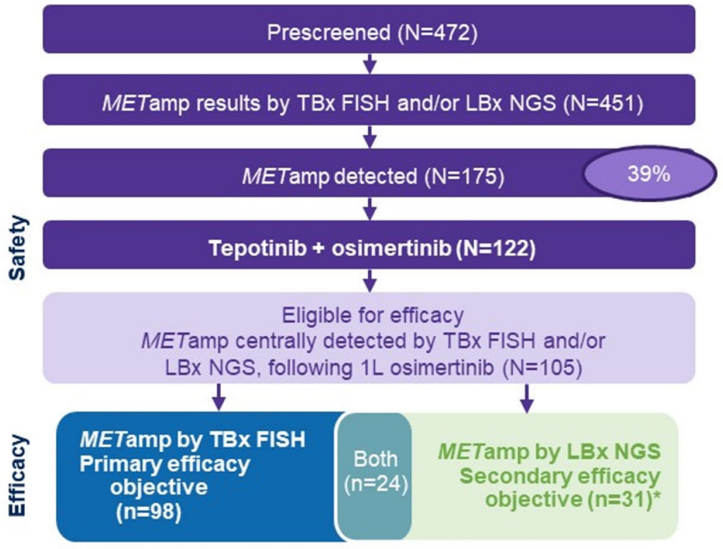
Yang JCH, ASCO 2023

INSIGHT 2: **tepotinib + osimertinib** in MET ampl NSCLC after 1L osimertinib

INSIGHT 2: Patients

- In the Phase II INSIGHT 2 study (NCT03940703), patients with advanced *EGFR*m NSCLC with *MET*amp after progression on 1L osimertinib received tepotinib 500 mg (450 mg active moiety) + osimertinib 80 mg once daily

- ***MET*amp detected** by: **TBx FISH** (*MET* GCN ≥5 and/or *MET*/*CEP7* ≥2) and/or by **LBx NGS** (*MET* GCN ≥2.3; Archer®)
- Comprehensive analysis of prescreening *MET*amp by **TBx FISH** & **LBx NGS** is reported by Yu et al. (**Poster 9074, ASCO 2023**)
- **Primary endpoint:** objective response by IRC for patients with centrally detected *MET*amp by **TBx FISH**



- At data cut-off (September 26, 2022), efficacy population had ≥3 months' follow-up
- Primary analysis will be conducted at ≥9 months' follow-up

Baseline characteristics, n (%)		Tepotinib + osimertinib (N=122)
Median age, years (range)		61 (20–84)
Sex	Female	73 (59.8)
	Male	49 (40.2)
Race†	Asian	73 (59.8)
	White	43 (35.2)
Smoking status	Never	83 (68.0)
	Former/Current	39 (32.0)
ECOG PS	0	34 (27.9)
	1	88 (72.1)
Brain metastases (IRC)	Yes	21 (17.2)
***EGFR* mutation‡**	Del19	72 (59.0)
	L858R	44 (36.1)
Time on 1L osimertinib§	<12 months	35 (28.7)
	≥12 months	79 (64.8)

*Seven patients had *MET*amp detected by central LBx NGS only (TBx FISH was not evaluable in five patients; TBx FISH was negative in two patients). †Race was Other/Not collected for six patients. ‡*EGFR* mutations were Other exon 21 mutation/Other for six patients. §Eight patients did not receive 1L osimertinib.

1L, first line; CEP7, centromere 7; ECOG PS, Eastern Cooperative Oncology Group performance status; Del19, exon 19 deletion; EGFR, epidermal growth factor receptor; FISH, fluorescent in situ hybridization; GCN, gene copy number; IRC, independent review committee; LBx, liquid biopsy; MET, mesenchymal–epithelial transition factor; *MET*amp, *MET* amplification; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; TBx, tissue biopsy.

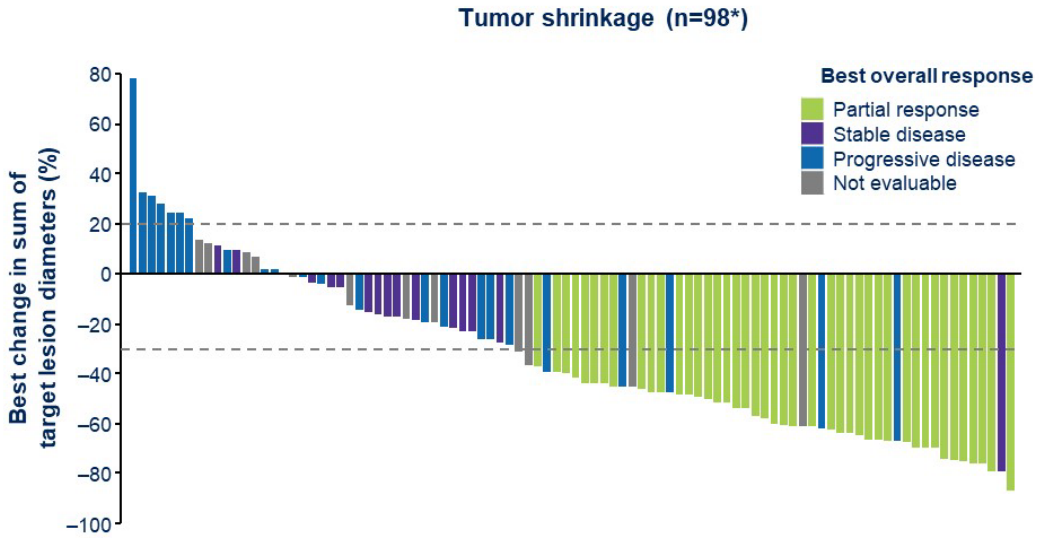
PRESENTED BY: Daniel Shao-Weng Tan, Senior Consultant Medical Oncologist

INSIGHT 2: **tepotinib + osimertinib** in MET ampl NSCLC after 1L osimertinib

INSIGHT 2: Efficacy TBx FISH+

- Of 98 patients with **TBx FISH+** *MET*amp (primary analysis set), BOR was PR in 43 patients, for an ORR of 43.9% (95% CI: 33.9, 54.3)
- As the data matures, six additional PRs have been confirmed

		TBx FISH+ (n=98)
BOR, n (%)	PR	43 (43.9)
	SD	15 (15.3)
	PD	23 (23.5)
	NE	17 (17.3)
ORR	% (95% CI)	**43.9** (33.9, 54.3)
DOR	Median, months (95% CI)	**9.7** (5.6, ne)
	Events, n (%)	11 (25.6)
PFS	Median, months (95% CI)	**5.4** (4.2, 7.1)
	Events, n (%)	51 (52.0)
OS	Median, months (95% CI)	**ne** (11.1, ne)
	Events, n (%)	23 (23.5)



*Four patients were excluded due to baseline/post-baseline measurement not being available.

BOR, best overall response; CI, confidence interval; DOR, duration of response; FISH, fluorescent in situ hybridization; MET, mesenchymal–epithelial transition factor; *MET*amp, *MET* amplification; ne, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TBx, tissue biopsy.

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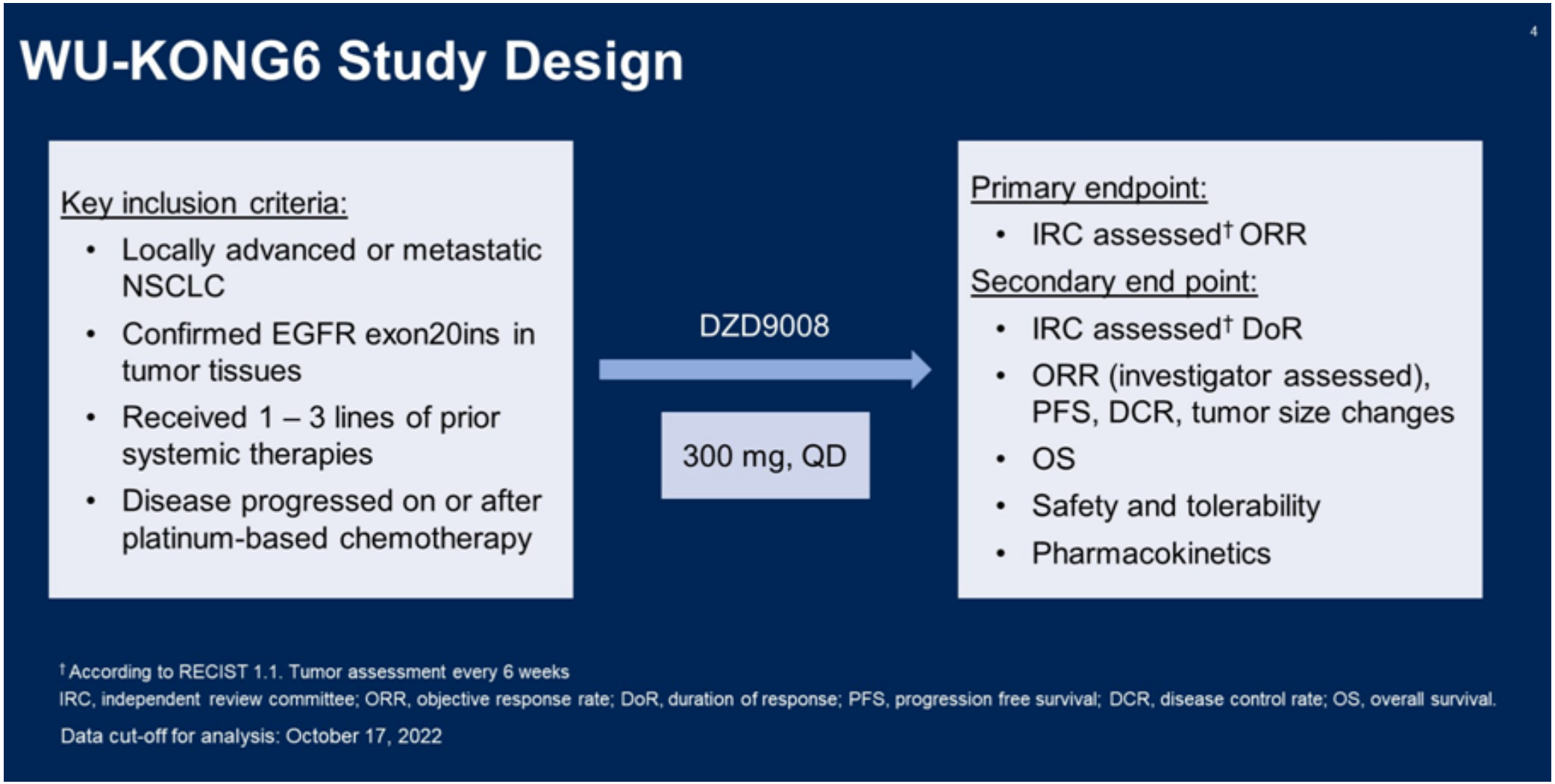
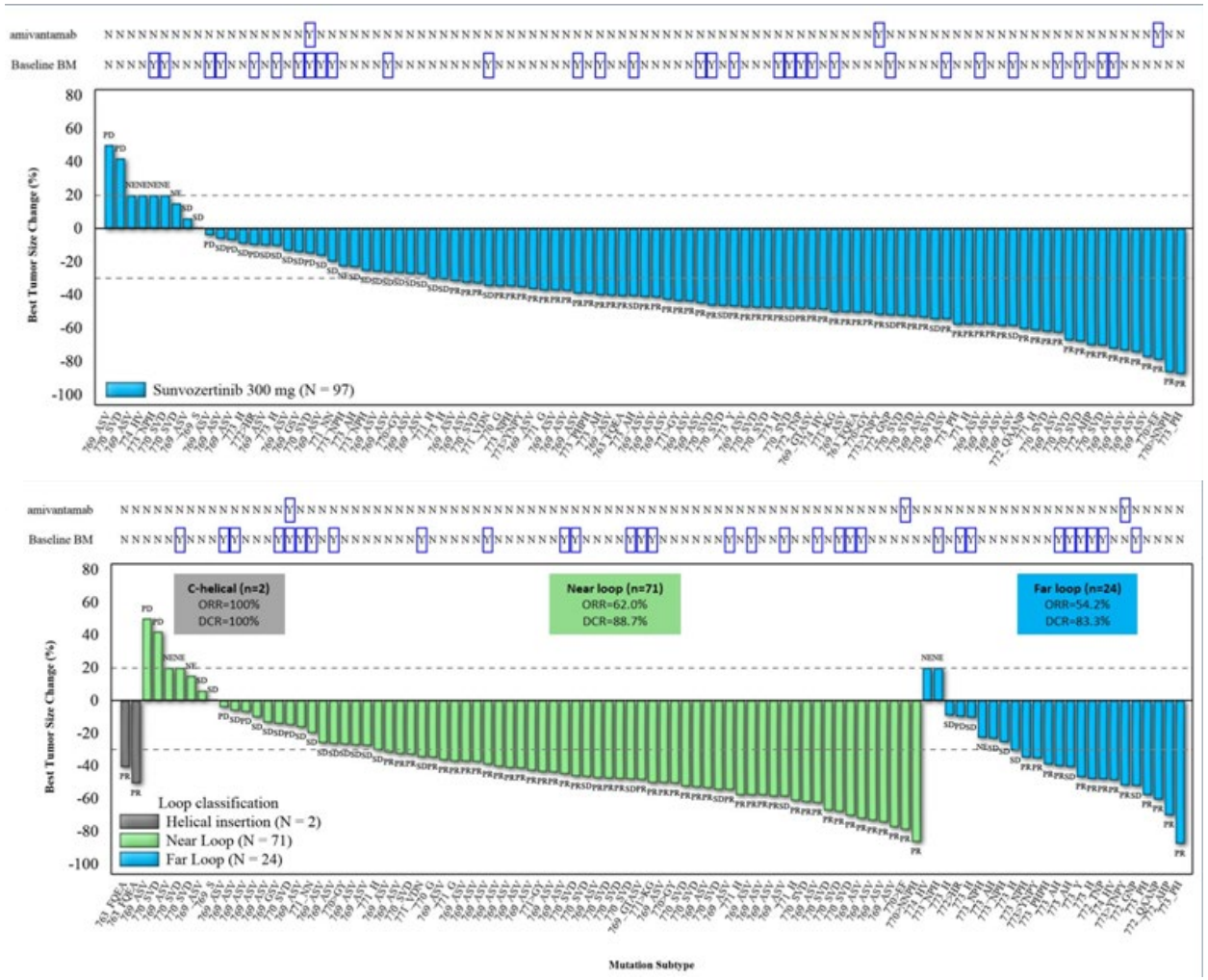
WU-KONG6 study: **Sunvozertinib** for the treatment of NSCLC with EGFR exon20 insertion mutations



Wang M, ASCO 2023

WU-KONG6 study: efficacy and safety results



Anti-tumor Efficacy	N = 97
Tumor Response, n (%)	
Partial response (confirmed)	59 (60.8)
Stable disease	26 (26.8)
Progression disease	6 (6.2)
Not evaluable	6 (6.2)
Objective Response Rate (ORR), n (%)	59 (60.8)
(95% CI)	(50.4, 70.6)
P value	< 0.0001
Disease Control Rate (DCR), n (%)	85 (87.6)
(95% CI)	(79.4%, 93.4%)

Common TEAE by PT	N = 104 All Grade	N = 104 ≥ Grade 3
Diarrhea	70 (67.3)	8 (7.7)
Blood CPK increase	60 (57.7)	18 (17.3)
Rash	56 (53.8)	1 (1.0)
Anemia	51 (49.0)	6 (5.8)
Blood creatinine increase	39 (37.5)	0 (0.0)
Paronychia	34 (32.7)	2 (1.9)
Body weight decrease	30 (28.8)	1 (1.0)
White blood cell decrease	27 (26.0)	0 (0.0)
Lipase increase	27 (26.0)	2 (1.9)
Vomiting	25 (24.0)	1 (1.0)
Decreased appetite	25 (24.0)	2 (1.9)
Mouth ulceration	24 (23.1)	0 (0.0)

The IRC assessed ORR was 60.8%.

Safety profile of suvozertinib was similar to other EGFR TKIs. Majorities of Aes were G1 or G2

Efficacy

	Mobocertinib[1] (N=114)	Amivantamab[2] (N=81)	Sunvozertinib (DZD9008) (N=97) WUKONG6[3]
Investigator assessed			
ORR, %	**35%**	**36%**	**46.4%**
Disease control rate, %	**78%**	**73%**	
Duration of response, mos	**11.2 mo**	**-**	
IRC assessed (95% CI)			
ORR, % (95% CI)	**28% (20-37%)**	**40% (29-51%)**	**60.8% (50.4-70.6%)**
Disease control rate, %	**78%**	**74%**	**87.6%**
Duration of response, months	**17.5 mo**	**11.1 mo**	**64.4% responding at median fup of 5.6 mo.**
PFS, months	**7.3 mo**	**8.3 mo**	-
Brain Mets, ORR (N=)	**-**	**-**	**44% (N=25)[4]**

1. Zhou C. et al. *JAMA Oncol.* 2021 Oct 14;e214761. 2. Park K, et al. *J Clin Oncol.* 2021;39:3391-3404. 3. M. Wang et al ASCO 2023. ABS7 9002. 4. L. Bazhenoza et al NACLC 2022.

Safety

EGFR Exon 20 Tx	Trial	Diarrhea	Rash	Other Major Notable
Amivantamab	CHRYSALIS[2]	12% (2% G3+)	86% (4% G3+)	Infusion-related reaction 66% (8% G3+), Paronychia
Mobocertinib	EXCLAIM[1]	93% (16% G3+)	45% (0% G3+)	lipase, amylase, other GI, lipase, amylase elevation
Sunvozertinib	WUKONG6[4]	67.3% (7.7% G3+)	53.8% (1% G3+)	CPK Elevation (57.7%, 17.3% G3+)

*WUKONG 1,2,6 pooled at 300 mg dose [5]

Other EGFR Exon 20 ins TKI with Putative CNS Penetration in Development

- TAS6417 (CLN-081)
- Blu-451
- Oric-114
- Furmonertinib

KRAS G12C mutation

A single arm, phase II study of **sotorasib plus CT** in advanced non-squamous, NSCLC patients with KRAS G12C mutation

SCARLET: study schema

Key inclusion criteria

- Advanced non-Sq, NSCLC
- With KRAS G12C
- Naïve for Cytotoxic chemotherapy and KRAS inhibitor
- With measurable lesion
- ECOG PS 0-1
- Asymptomatic CNS mets allowed

Induction phase

Sotorasib 960mg
+ CBDCA (AUC5)/ PEM 500 mg/m ^{2}
[q3W, 4 cycles]
(n = 30)

Maintenance phase

Sotorasib + PEM
[q3W, until PD]

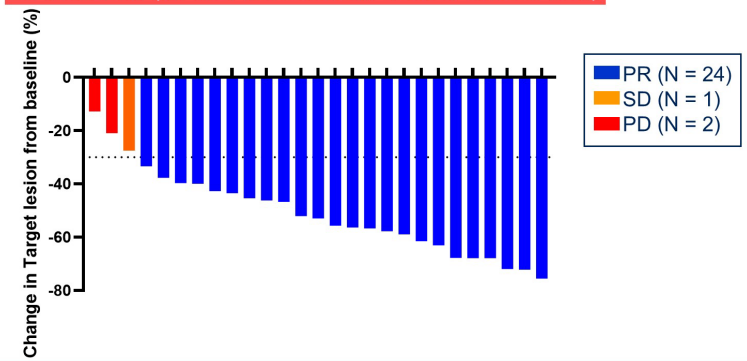
- Primary endpoint; ORR by blinded independent central review (BICR)
- Secondary endpoints; DCR, PFS, DOR, OS and AEs
- Translational research; NGS analysis (tissue and plasma [at baseline, 3 wks, and PD])

Trial identifier: jRCT2051210086

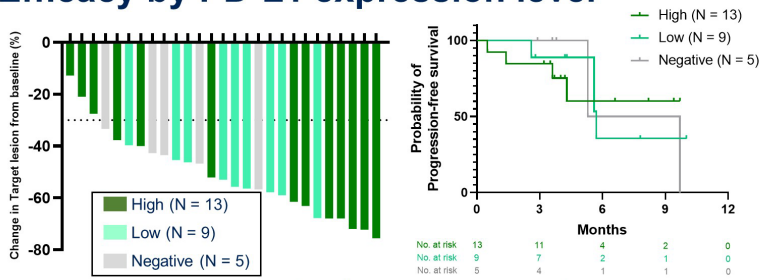
SCARLET study: efficacy and safety results

Primary endpoint: ORR by BICR

ORR 88.9% (80%CI 76.9-95.8%, 95%CI 70.8-97.6%)

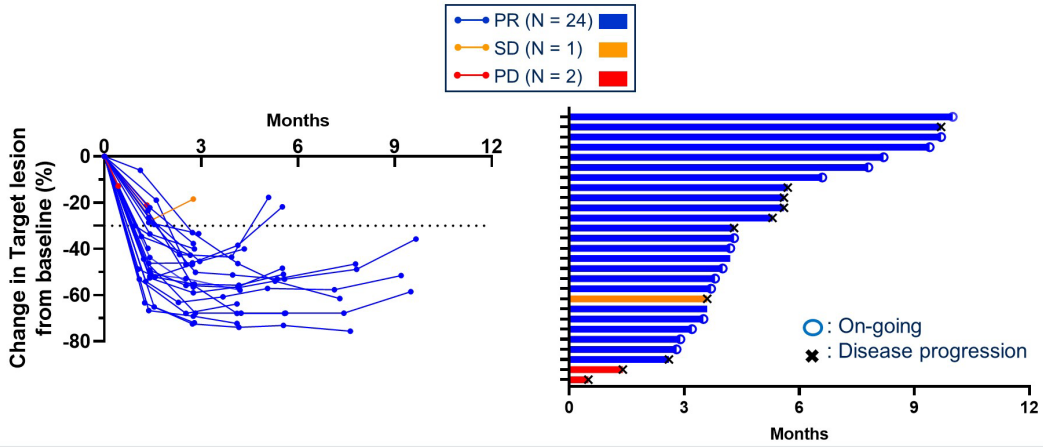


Efficacy by PD-L1 expression level



PD-L1 expression level	N	ORR	Median PFS (mo)
High (≥50%)	13	76.9% (95%CI 46.2-95.0%)	Not reached
Low (1-49%)	9	100% (95%CI 66.4-100%)	5.7
Negative (<1%)	5	100% (95%CI 47.8-100%)	7.5

Spider plot / Swimmer's plot



Treatment-related AEs (≥ 15% or any severe cases)

	Any Grade		>=Grade 3		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any adverse event	29	100.0	21	72.4	1	3.4	7	24.1	14	48.3	6	20.7	1	3.4
Anaemia	21	72.4	11	37.9	2	6.9	8	27.6	10	34.5	1	3.4	0	0.0
PLT decreased	13	44.8	7	24.1	4	13.8	2	6.9	5	17.2	2	6.9	0	0.0
Neutrophil decreased	12	41.4	7	24.1	0	0.0	5	17.2	4	13.8	3	10.3	0	0.0
Decreased appetite	10	34.5	0	0.0	4	13.8	6	20.7	0	0.0	0	0.0	0	0.0
Nausea	10	34.5	0	0.0	3	10.3	7	24.1	0	0.0	0	0.0	0	0.0
WBC decreased	10	34.5	6	20.7	1	3.4	3	10.3	4	13.8	2	6.9	0	0.0
Malaise	8	27.6	0	0.0	5	17.2	3	10.3	0	0.0	0	0.0	0	0.0
Constipation	7	24.1	0	0.0	4	13.8	3	10.3	0	0.0	0	0.0	0	0.0
Diarrhoea	7	24.1	2	6.9	3	10.3	2	6.9	2	6.9	0	0.0	0	0.0
γ-GTP increased	6	20.7	1	3.4	4	13.8	1	3.4	1	3.4	0	0.0	0	0.0
Neutropenia	5	17.2	3	10.3	0	0.0	2	6.9	3	10.3	0	0.0	0	0.0
Hiccups	5	17.2	0	0.0	4	13.8	1	3.4	0	0.0	0	0.0	0	0.0
ALT increased	5	17.2	1	3.4	2	6.9	2	6.9	0	0.0	1	3.4	0	0.0
Blood Cre increased	5	17.2	0	0.0	4	13.8	1	3.4	0	0.0	0	0.0	0	0.0
AST increased	4	13.8	2	6.9	2	6.9	0	0.0	2	6.9	0	0.0	0	0.0
Hyperkalaemia	3	10.3	1	3.4	0	0.0	2	6.9	1	3.4	0	0.0	0	0.0
Lymph decreased	3	10.3	1	3.4	1	3.4	1	3.4	1	3.4	0	0.0	0	0.0
Cellulitis	2	6.9	1	3.4	0	0.0	1	3.4	1	3.4	0	0.0	0	0.0
Pneumonia	2	6.9	1	3.4	0	0.0	1	3.4	0	0.0	0	0.0	1	3.4
Thrombocytopenia	2	6.9	1	3.4	0	0.0	1	3.4	0	0.0	1	3.4	0	0.0
Anaphylactic reaction	1	3.4	1	3.4	0	0.0	0	0.0	1	3.4	0	0.0	0	0.0
Gastritis	1	3.4	1	3.4	0	0.0	0	0.0	1	3.4	0	0.0	0	0.0
Cholecystitis	1	3.4	1	3.4	0	0.0	0	0.0	1	3.4	0	0.0	0	0.0

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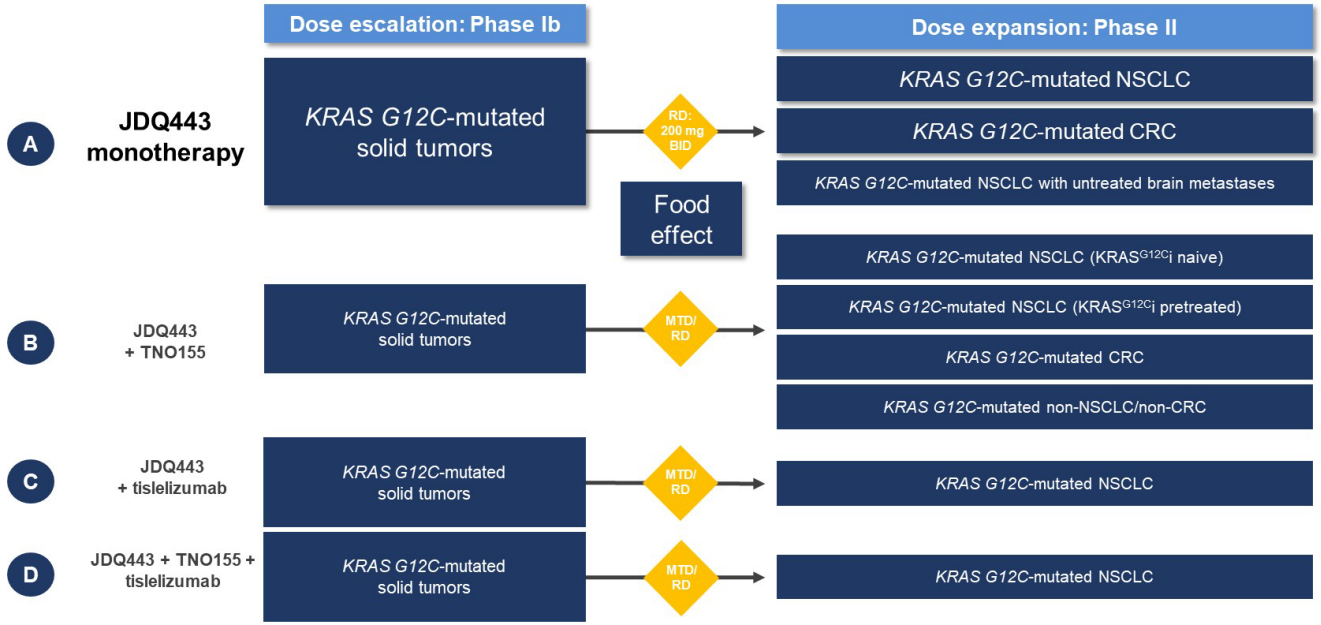
KontRast-01 update: safety and efficacy of **JDQ443** in KRAS-mutated G12C solid tumors including NSCLC

KontRASt-01: Overall study design



Data presented are from a cut-off date of February 1, 2023.
BID, twice daily; CRC, colorectal cancer; KRAS, Kirsten rat sarcoma viral oncogene homolog; KRASG12Ci, KRASG12C inhibitor;

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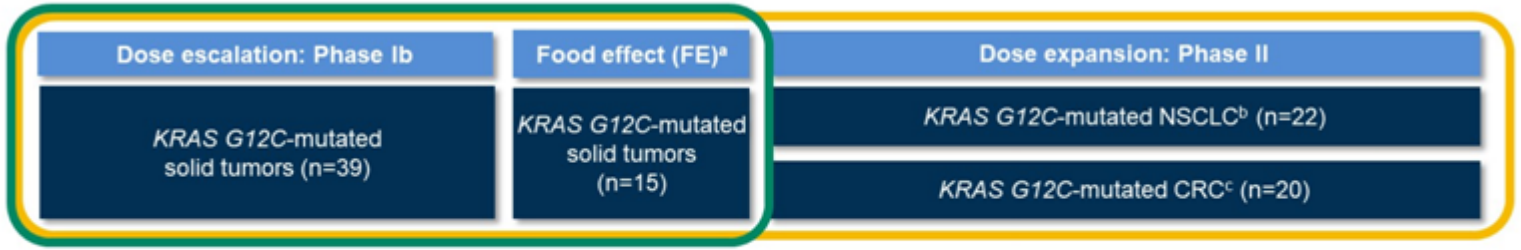


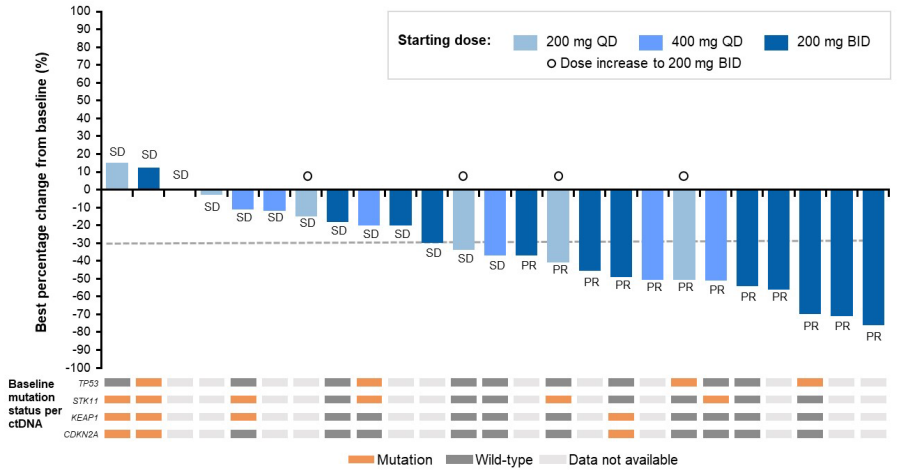
Safety data set: All patients (N=96) across dose escalation, FE and dose expansion cohorts

Efficacy data set: Patients with NSCLC (N=27) from dose escalation and FE cohorts

Pre-planned analyses in the Phase II NSCLC expansion group will be the subject of future presentations.

KontRast-01 update: safety results and efficacy results in KRAS G12C mutated NSCLC

NSCLC: Best overall response



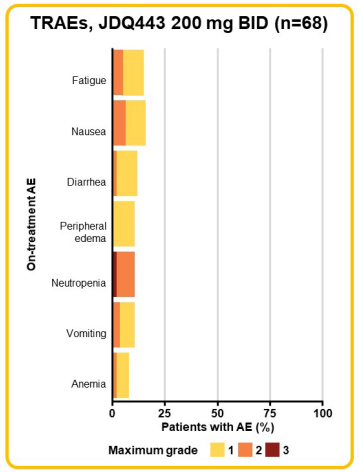
	JDQ443 200 mg BID (n=14)	JDQ443 All dose levels, pooled (n=27)
Confirmed ORR	**57.1%**	44.4%
DCR	**92.9%**	92.6%
BOR[a], n (%)		
PR	8 (57.1)	12 (44.4)
SD	5 (35.7)	13 (48.1)
PD	0	0
Unknown	1 (7.1)	2 (7.4)

Data presented with a cut-off date of February 1, 2023. Waterfall plot: 25 (92.6%) patients with NSCLC with available change from baseline tumor assessments; data are plotted out of n=27 patients with NSCLC who received JDQ443 single-agent. Patients were enrolled in dose escalation and food effect cohorts. [a]Best overall response per RECIST 1.1 based on investigator's assessment. Intra-patient dose escalation, per protocol, occurred in four patients from 200 mg QD to 200 mg BID. Mutation detection: plasma ctDNA at baseline; assay validated to 0.5% allele frequency. 95% CI for ORR: 28.9–82.3 for 200 mg BID; 25.5–64.7 for all dose levels.
BID, twice daily; CI, confidence interval; ctDNA, circulating tumor DNA; DCR, disease control rate; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD, progressive disease; PR, partial response; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Treatment-related adverse events (≥10% of all patients)

	JDQ443 200 mg QD escalation (n=10)		JDQ443 400 mg QD escalation (n=11)		JDQ443 300 mg BID escalation (n=11)		JDQ443 200mg BID escalation + FE + expansion (n=68)		All dose levels, pooled (N=96)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Number of patients with at least one event, n (%)	**8 (80.0)**	**2 (20.0)**	**8 (72.7)**	**1 (9.1)**	**6 (85.7)**	**5 (71.4)**	**51 (75.0)**	**4 (5.9)**	**73 (76.0)**	**12 (12.5)**
Fatigue	5 (50.0)	2 (20.0)	3 (27.3)	–	4 (57.1)	1 (14.3)	11 (16.2)	–	23 (24.0)	3 (3.1)
Nausea	3 (30.0)	–	1 (9.1)	–	–	–	12 (17.6)	–	16 (16.7)	–
Diarrhea	2 (20.0)	–	2 (18.2)	–	1 (14.3)	–	9 (13.2)	–	14 (14.6)	–
Peripheral edema	2 (20.0)	–	2 (18.2)	–	1 (14.3)	–	8 (11.8)	–	13 (13.5)	–
Neutropenia	–	–	1 (9.1)	–	2 (28.6)	1 (14.3)	8 (11.8)	2 (2.9)	11 (11.5)	3 (3.1)
Vomiting	2 (20.0)	–	–	–	–	–	8 (11.8)	–	10 (10.4)	–
Anemia	2 (20.0)	–	2 (18.2)	–	–	–	6 (8.8)	–	10 (10.4)	–

- **TRAEs were low-frequency, low-grade events**
- **There were no Grade 4 or 5 TRAEs**
- **No nausea/vomiting/diarrhea higher than Grade 2**

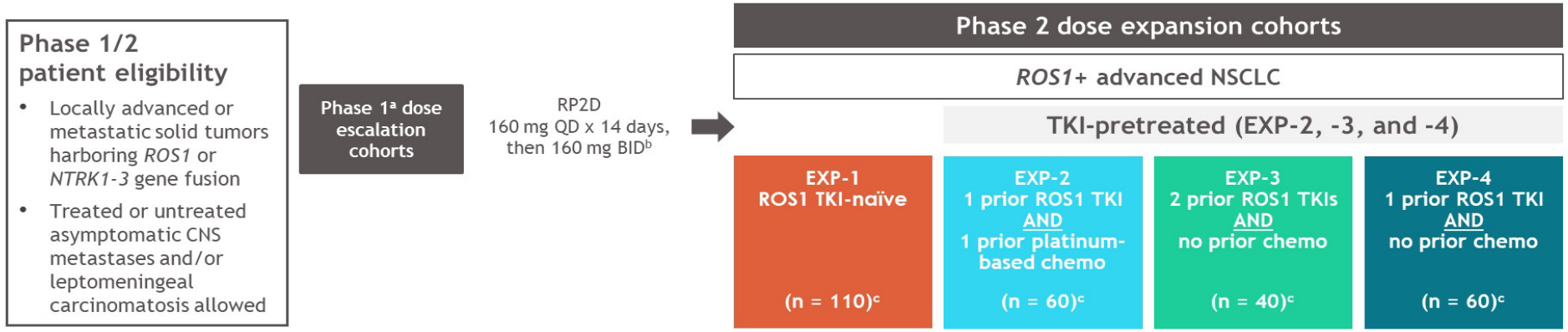


Data presented with a cut-off date of February 1, 2023. All AEs were graded per CTCAE version 5.0. Two patients experienced treatment-related SAEs: Grade 3 photosensitivity reaction and Grade 2 rash erythematous in one patient; Grade 3 bullous dermatitis in one patient; all occurred at 300 mg BID. Treatment was discontinued by three patients for treatment-related events: Two patients due to elevated ALT and one patient due to nausea, diarrhea, and vomiting. Seven patients had dose reductions across the following groups: 200 mg QD (n=2), 200 mg BID (n=2), and 300 mg BID (n=3). Two patients from the 200 mg BID group had dose reductions: One patient due to Grade 3 ALT elevation and Grade 3 AST elevation, and one patient due to Grade 2 peripheral neuropathy.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; FE, food effect; QD, once daily; SAE, serious AE; TRAE, treatment-related AE.

ROS1 rearrangement

TRIDENT -1 trial: phase 1/2 repotrectinib in ROS+ NSCLC

Overview of the phase 1/2 TRIDENT-1 trial



- MRI was mandated for all patients with and without baseline brain metastases in phase 2 at screening and at protocol-specified intervals until progression
- Primary efficacy population includes patients pooled from phases 1[e] and 2 that began repotrectinib treatment at least 8 months before data cutoff date of June 20, 2022

Phase 2 (*ROS1*+ advanced NSCLC cohorts)

Primary endpoint

cORR by BICR using RECIST v1.1

Key secondary endpoint

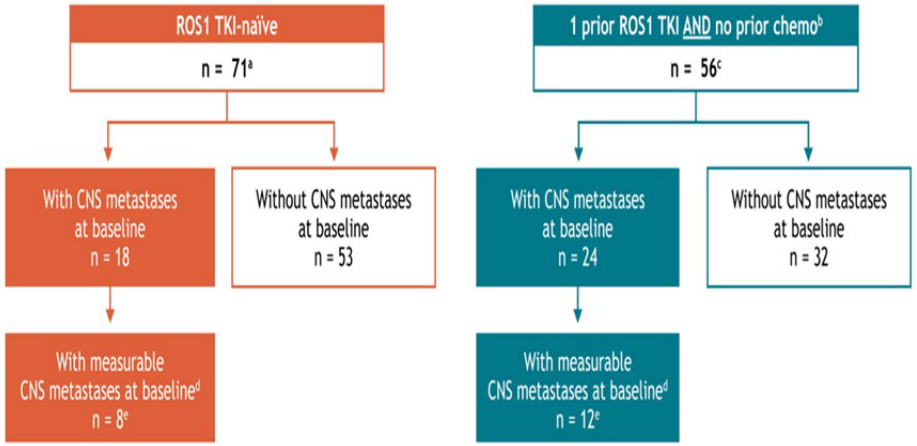
icORR by mRECIST v1.1 in patients with measurable brain metastases

Data cutoff date: June 20, 2022.

[a]Phase 1 primary endpoints: DLT, MTD, RP2D. [b]Based on tolerability. [c]N's for expansion cohorts indicate enrollment targets. [d]MRI brain scans performed at Cycle 3 day 1 (± 7 days), every 2 cycles (± 7 days) up to Cycle 19 and then every 3 cycles (± 7 days) up to Cycle 37 and then every 4 cycles (± 7 days); brain CT was acceptable if brain MRI was contraindicated. [e]Patients from phase 1 received 40 mg QD to 160 mg QD and 160 mg BID. [f]By RECIST v1.1.

TRIDENT trial: Systemic efficacy of repotrectinib

Systemic Efficacy of repotrectinib was comparable between patients with CNS metastasis and without in both TKI naïve and TKI pretreated by BICR



25.3% (18/71) BM
11.2% (8/71) meas BM

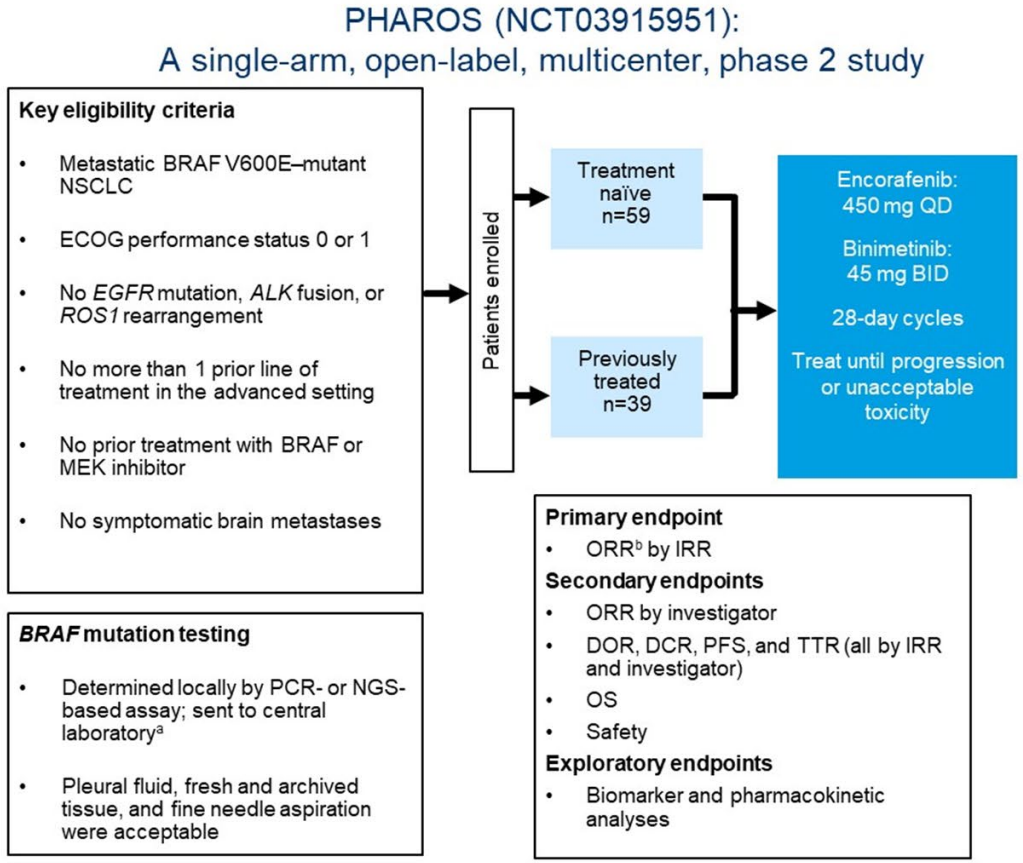
42.8% (24/56) BM
21.4% (12/56) meas BM

	ROS1 naïve (n=71)		ROS1 pretreated (n=56)	
	with CNS (n=18)	without CNS (n=53)	with CNS (n=24)	without CNS (n=32)
ORR	89%	75%	33%	41%
PFS	87% (PFS at 12m)	77% (PFS at12m)	57% (PFS at 6m)	75% (PFS at 6m)

BRAF V600E mutation

PHAROS study: encorafenib plus binimetinib in patients with BRAF V600E-mutant metastatic NSCLC

- The combination of encorafenib (BRAF inhibitor) plus binimetinib (MEK inhibitor) has demonstrated clinical efficacy with an acceptable safety profile in patients with metastatic BRAF V600E/K–mutant melanoma[1]
- For patients with metastatic BRAF V600E–mutant NSCLC the combination of dabrafenib and trametinib was approved by the US FDA and is a current standard of care [2]
  - This approval was based on the results of a single-arm, phase 2 study that showed meaningful antitumor activity and a manageable safety profile[3,4]
    - In treatment-naïve and previously treated patients, the ORR by IRR was 64% and 63%, respectively
    - The median DOR by IRR was 15.2 months and 9.0 months, respectively
- Given the observed efficacy and safety profile of encorafenib plus binimetinib in patients with BRAF V600E/K–mutant metastatic melanoma, this combination therapy was assessed in patients with metastatic BRAF V600E–mutant NSCLC

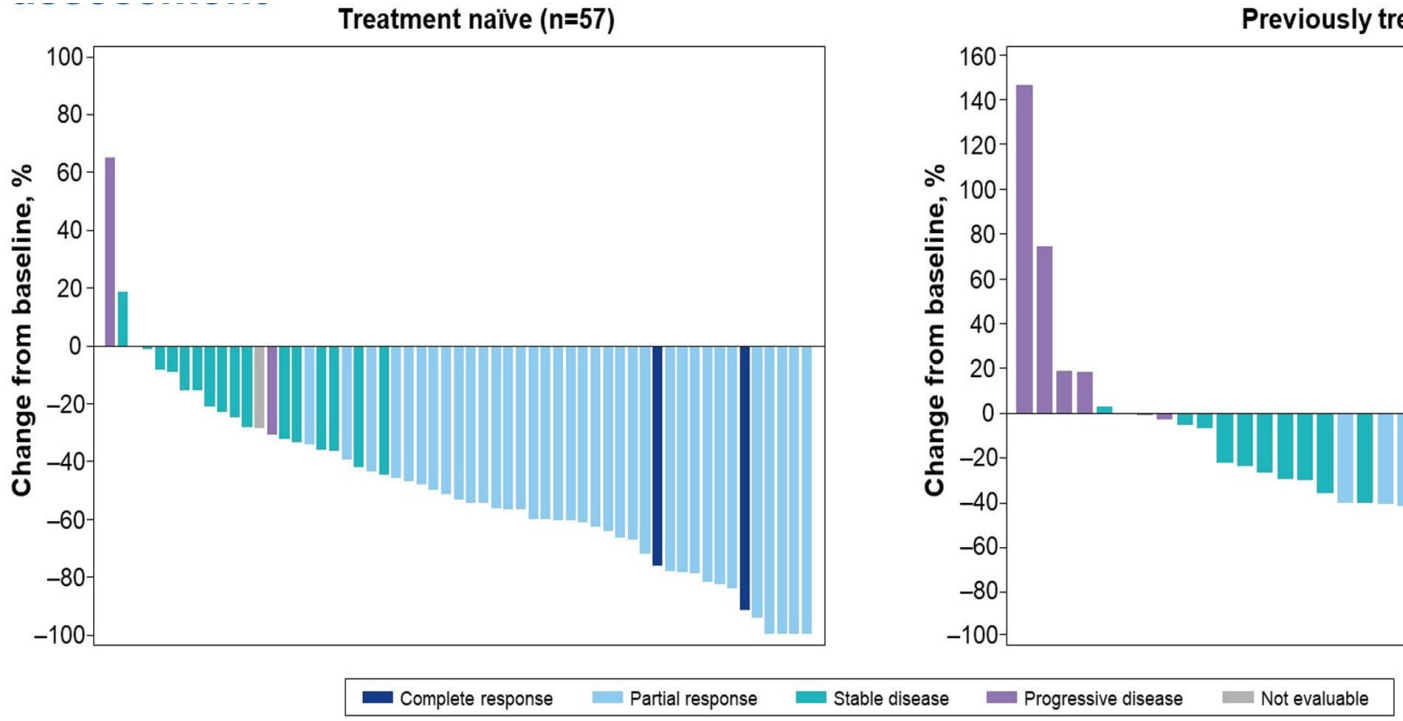


BID, twice daily; **DCR**, disease control rate; **DOR**, duration of response; **ECOG**, Eastern Cooperative Oncology Group; **IRR**, independent radiology review; **ORR**, objective response rate; **NGS**, next-generation sequencing; **OS**, overall survival; **PCR**, polymerase chain reaction; **PFS**, progression-free survival; **QD**, once daily; **TTR**, time to response.

[a]BRAF V600 mutations were retrospectively confirmed by FoundationOne CDx (Foundation Medicine, Cambridge, MA). [b]According to RECIST 1.1.

1. Dummer R, et al. *Lancet Oncol.* 2018;19(5):603-615. 2. Dabrafenib prescribing information. June 2022. 3. Planchard D, et al. *Lancet Oncol.* 2016;17(7):984-993. 4. Planchard D, et al. *Lancet*

PHAROS study: efficacy and safety results



Encorafenib plus binimetinib in metastatic BRAF-V600E mutant NSCLC
Incidence of TRAEs of any grade >10% in all patients

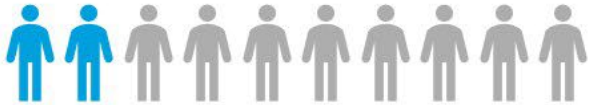
	Overall (N=98)		
	Any grade	Grade 3	Grade 4
Any TRAEs, n (%)[a]	92 (94)	37 (38)	3 (3)[b]
Nausea	49 (50)	3 (3)	0
Diarrhea	42 (43)	4 (4)	0
Fatigue	31 (32)	2 (2)	0
Vomiting	28 (29)	1 (1)	0
Anemia	18 (18)	3 (3)	0
Vision blurred	17 (17)	1 (1)	0
Constipation	13 (13)	0	0
ALT increased	12 (12)	5 (5)	0
AST increased	12 (12)	7 (7)	0
Pruritus	12 (12)	0	0
Blood creatine phosphokinase increased	11 (11)	0	0
Edema peripheral	11 (11)	0	0

Note: Any-grade abdominal pain, alopecia, asthenia, and dry skin occurred in 10% of patients; any-grade pyrexia occurred in 8% of patients.
ALT, alanine aminotransferase; **AST**, aspartate aminotransferase; **TRAE**, treatment-related adverse event.
[a]One patient died due to intracranial hemorrhage, which was assessed as treatment related by the investigator. [b]Grade 4 TRAEs were colitis, disseminated intravascular coagulation, increased γ-glutamyl transferase, and hyponatremia.

FGFR alterations

Erdafitinib is a Pan-FGFR Inhibitor With Activity in Metastatic Urothelial Carcinoma

- ***FGFRalt*** are observed in **~20% of advanced or mUC** and may function as oncogenic drivers[1,2]

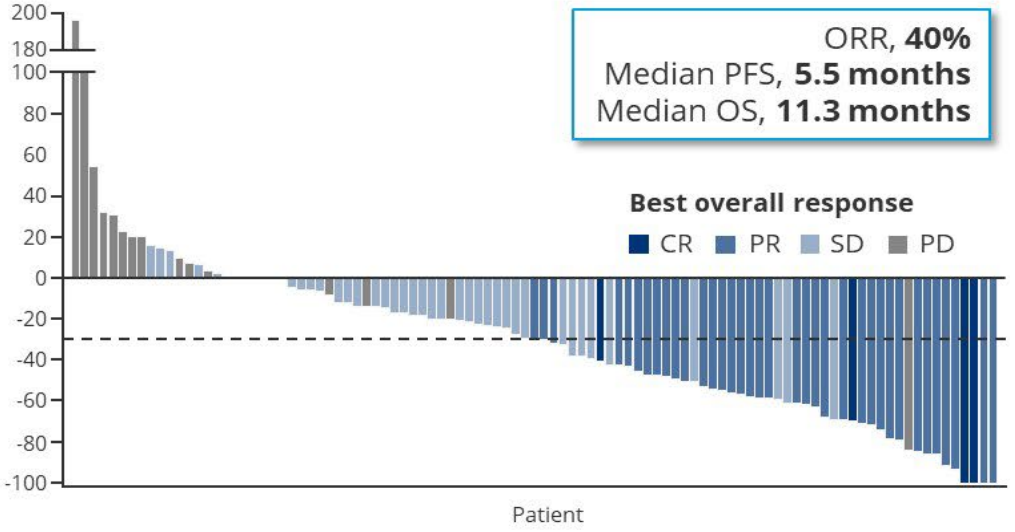


Erdafitinib is an oral selective pan-FGFR tyrosine kinase inhibitor[3]

- Erdafitinib was granted accelerated approval in the United States and is approved in 17 other countries to treat locally advanced or mUC in adults with susceptible *FGFR3/2alt* who have progressed after platinum-containing chemotherapy[4-6]

- **THOR** is a confirmatory, randomized phase 3 study:
  - Cohort 1 assessed whether erdafitinib improved survival over chemotherapy in patients with *FGFRalt* mUC who progressed on or after ≥1 prior treatment that included anti–PD-(L)1

In the single-arm phase 2 BLC2001 trial, erdafitinib showed a benefit in patients with *FGFR-altered* advanced urothelial cancer[4]

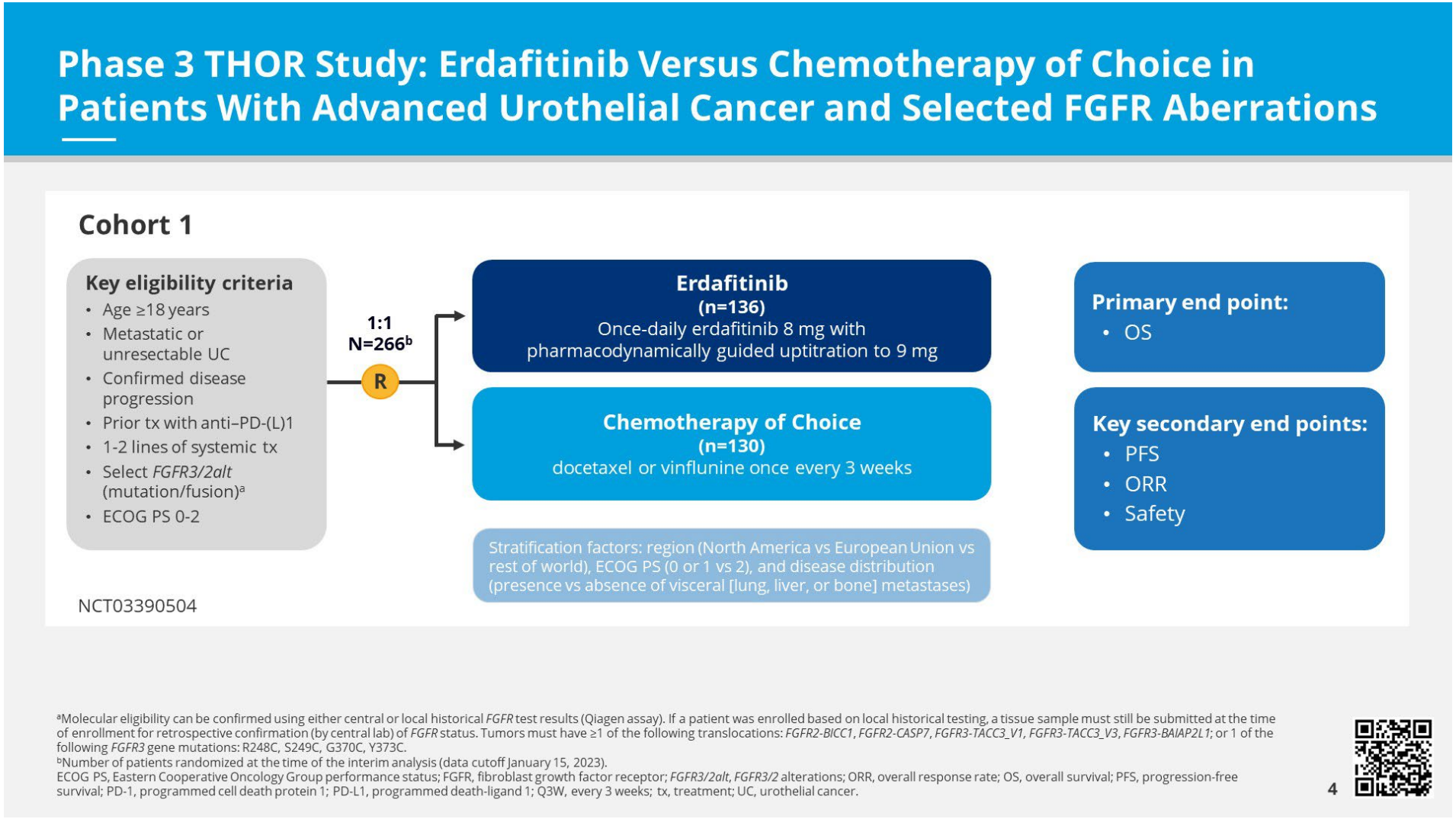


Patients received erdafitinib 8 mg/d with pharmacodynamically guided uptitration to 9 mg/d.

FGFR, fibroblast growth factor receptor; *FGFRalt*, *FGFR* alterations; mUC, metastatic urothelial carcinoma; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival.
[a]Patients received erdafitinib 8 mg/d with pharmacodynamically guided uptitration to 9 mg/d.

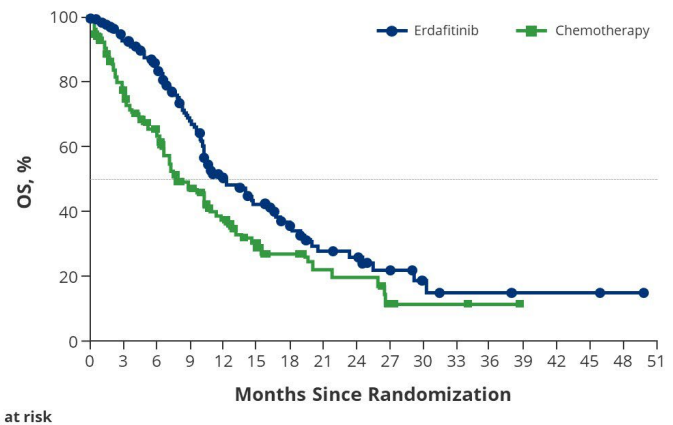
1. Necchi A, et al. *Eur Urol Focus*. 2019;5:853-586; 2. di Martino E, et al. *Future Oncol.* 2016;12:2243-2263; 3. Perera TPS, et al. *Mol Cancer Ther.* 2017;16:1010-1020; 4. Loriot Y, et al. *N Engl J Med.* 2019;381:338-348; 5. BALVERSA® (erdafitinib) [package insert]. Horsham, PA: Janssen Products, LP; 2023; 6. Siefker-Radtke AO, et al. *Lancet Oncol.* 2022;23:248-258.

Phase 3 THOR study: erdafitinib vs CT in patients with advanced UC with selected FGFR alterations



Phase 3 THOR study: efficacy results

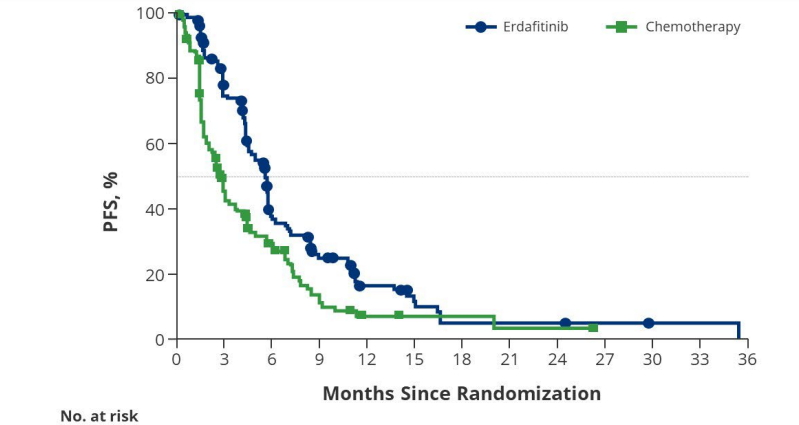
Overall Survival for Erdafitinib Was Superior to Investigator's Choice of Chemotherapy



- Median follow-up was 15.9 months
- Median OS was 12.1 months for erdafitinib versus 7.8 months for chemotherapy
- Erdafitinib reduced the risk of death by 36% versus chemotherapy
  - HR, 0.64 (95% CI, 0.47-0.88; *P* = 0.005)[a]
- Based on these interim analysis results, the IDMC recommended to stop the study, unblind data, and cross over patients from chemotherapy to erdafitinib

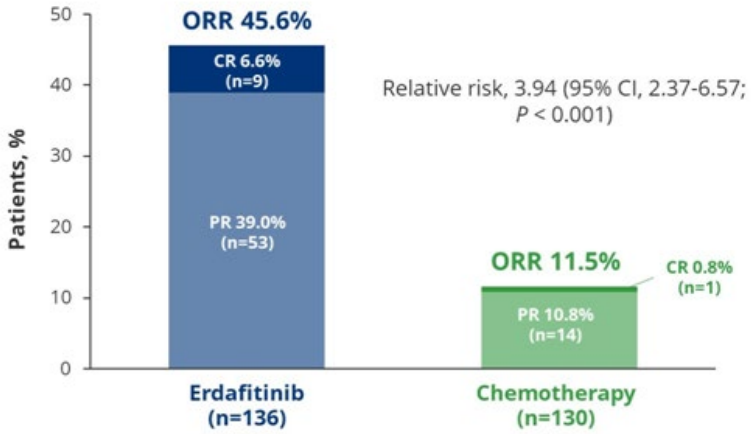
CI, confidence interval; HR, hazard ratio; IDMC, independent data monitoring committee; OS
[a]The significance level for stopping for efficacy was p=0.019, corresponding to a HR of 0.69.

Erdafitinib Significantly Improved Progression-Free Survival Versus Chemotherapy

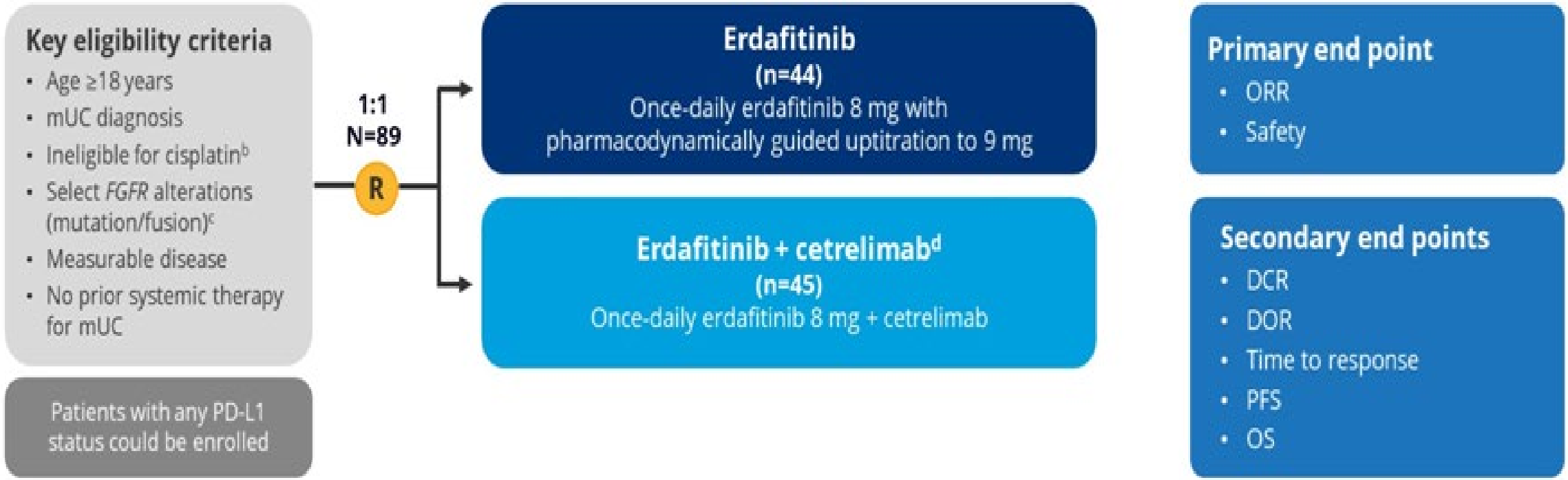


- Median PFS was 5.6 versus 2.7 months for erdafitinib versus chemotherapy
- Erdafitinib reduced the risk of progression or death by 42% versus chemotherapy
  - HR, 0.58 (95% CI, 0.44-0.78; *P* = 0.0002)

, confidence interval; HR, hazard ratio; PFS, progression-free survival.



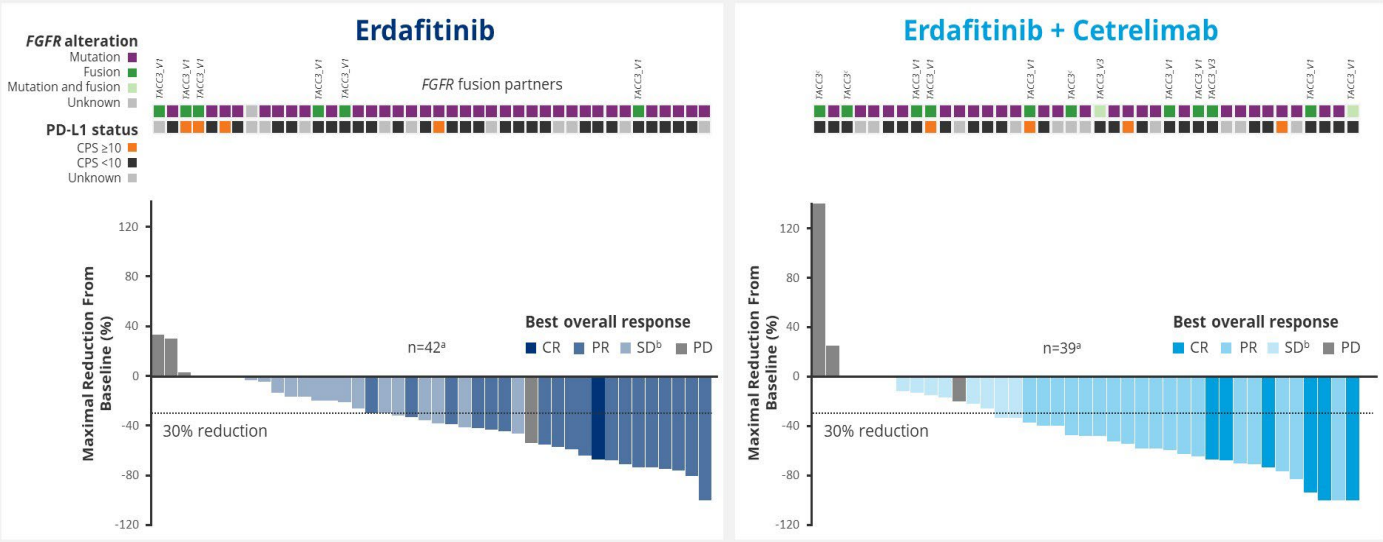
NORSE phase II study: erdafitinib vs erdafitinib + cetrelimab in mUC inelegible for cisplatin with FGFR alterations



Radtke , ASCO 2023

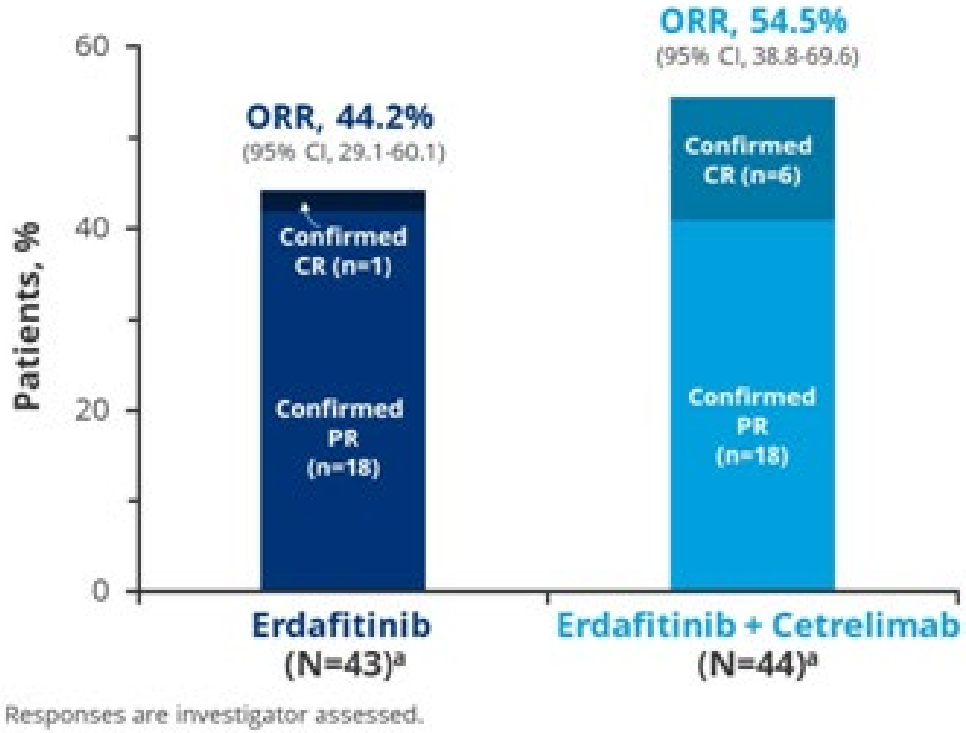
NORSE study: efficacy results

Erdafitinib Alone and in Combination With Cetrelimab Showed Responses in the Cisplatin-Ineligible Population



[a]1 patient in the erdafitinib group and 5 patients in the erdafitinib plus cetrelimab group were inevaluable.
[b]For a response to qualify as SD, follow-up measurements must have met the stable disease criteria at least once at a minimum interval ≤6 weeks after the first dose of study agent.
[c]*FGFR-TACC* fusion was detected by local testing or central blood sample, but not confirmed by central tissue testing.
CPS, combined positive score; CR, complete response; FGFR, fibroblast growth factor receptor; PD, disease progression; PR, partial response; SD, stable disease.

8



Responses are investigator assessed.

HER2 alterations

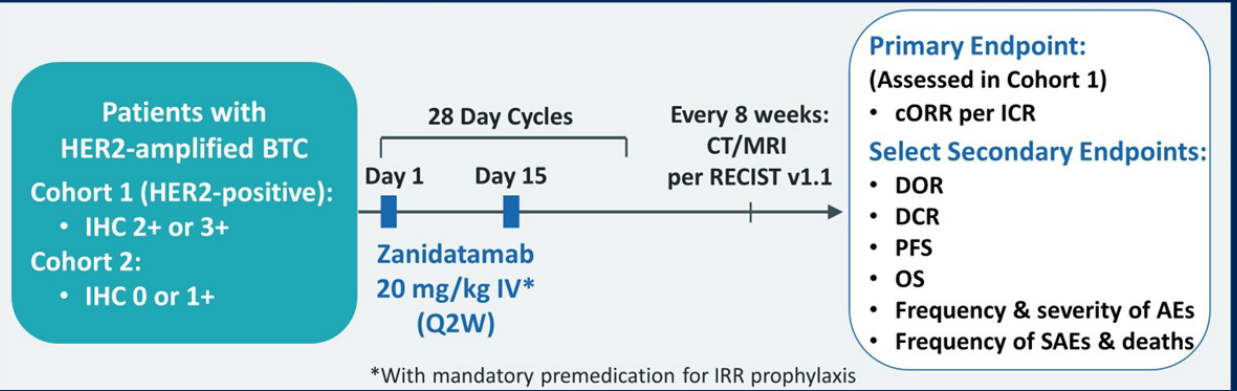
HERIZON_BTC-01: Zanidatamab in HER2 ampl BTC

HERIZON-BTC-01 Study Design

- Phase 2b study of zanidatamab monotherapy in patients with HER2-amplified BTC

Key Eligibility Criteria

- Locally advanced or metastatic BTC[1]
- Tissue required to confirm HER2 status by central lab
- Progressed after treatment with a gemcitabine-containing regimen
- No prior HER2-targeted therapies
- ECOG PS of 0 or 1



[1] Excludes ampullary

AE = adverse event; cORR = confirmed objective response rate; CT = computed tomography scan; DCR = disease control rate; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; ICR = independent central review; IHC = immunohistochemistry; IRR = infusion-related reaction; IV = intravenous; MRI = magnetic resonance imaging; OS = overall survival; Q2W = every two weeks; RECIST= Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

HERIZON_BTC-01: Zanidatamab in HER2 ampl BTC

Disease Response in Patients with HER2-positive BTC (Cohort 1)

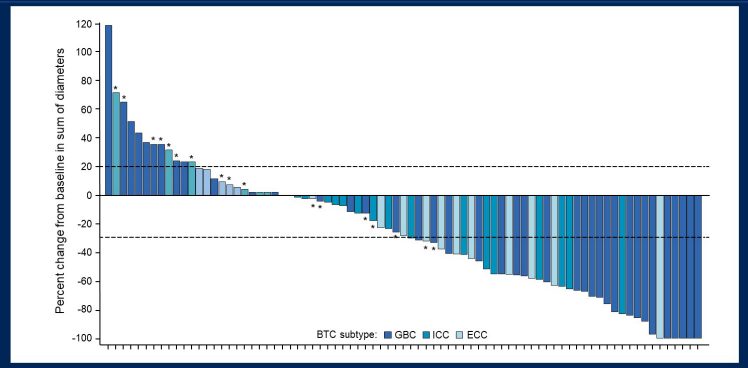
- 16 patients had ongoing responses at the time of data cutoff

		By ICR Assessment (N = 80)	By Investigator Assessment (N = 80)
cORR, % (95% CI)		41.3 (30.4, 52.8)	41.3 (30.4, 52.8)
Confirmed BOR, n (%)	CR	1 (1.3)	4 (5.0)
	PR	32 (40.0)	29 (36.3)
	SD	22 (27.5)	21 (26.3)
	PD	24 (30.0)	25 (31.3)
	NE[1]	1 (1.3)	1 (1.3)
DCR [CR + PR + SD], % (95% CI)		68.8 (57.4, 78.7)	67.5 (56.1, 77.6)
CBR [CR + PR + (SD ≥ 6 months)], % (95% CI)		47.5 (36.2, 59.0)	47.5 (36.2, 59.0)

CBR = clinical benefit rate; CI = confidence interval; CR = complete response; DCR = disease control rate; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

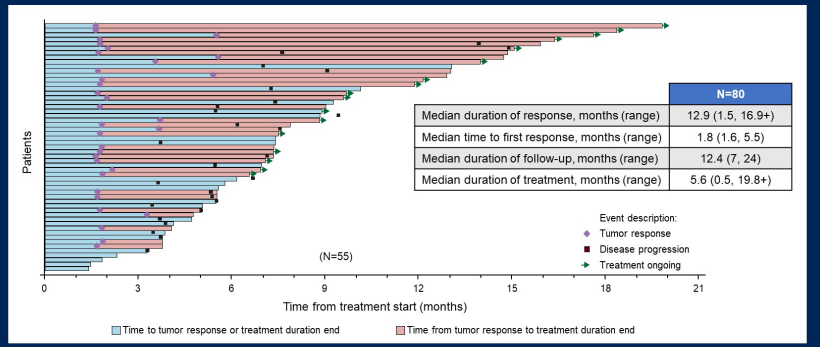
[1] NE = one patient died prior to first post-baseline tumor assessment.

Majority of evaluable patients (68.4%) had a decrease in target lesions (Cohort 1)



*Indicates patients with IHC 2+ status; all other patients had IHC status of 3+.
Dotted lines indicate 20% increase and 30% decrease in sum of diameters of target tumors.

Treatment Duration for Patients with Response (CR or PR) or Stable Disease per RECIST v1.1 by ICR (Cohort 1)



	N=80
Median duration of response, months (range)	12.9 (1.5, 16.9+)
Median time to first response, months (range)	1.8 (1.6, 5.5)
Median duration of follow-up, months (range)	12.4 (7, 24)
Median duration of treatment, months (range)	5.6 (0.5, 19.8+)

Note: Decisions to discontinue zanidatamab were based on investigator assessment. One patient with non-responding tumors was still on treatment.

Tucatinib and trastuzumab in HER2+ solid tumors

Study Design

- SGNTUC-019 (NCT04579380) is an open-label phase 2 basket study evaluating antitumor activity and safety of tucatinib and trastuzumab[a] in patients with HER2-altered solid tumors

Key eligibility criteria

- HER2 overexpression, amplification, or mutation per IHC/ISH or NGS testing determined locally
- Unresectable locally advanced or metastatic cancer
- Baseline measurable disease
- Previously treated with ≥1 prior systemic treatment for locally advanced or metastatic disease
- No prior HER2-directed therapy[b]

→

- Cohort 1: Cervical (overexpression or amplification)
- Cohort 2: Uterine (overexpression or amplification)
- **Cohort 3: Biliary Tract (overexpression or amplification)[c]**
- Cohort 4: Urothelial (overexpression or amplification)
- Cohort 5: Nonsquamous NSCLC (overexpression or amplification)
- Cohort 6: Other solid tumors (overexpression or amplification)
- Cohort 7: Nonsquamous NSCLC (mutation)
- Cohort 8: Breast (mutation)
- Cohort 9: Other solid tumors (mutation)

Outcomes

Primary endpoint:
Confirmed ORR per RECIST 1.1 by investigator

Secondary endpoints:
Safety, DCR, DOR, PFS, and OS

a Tucatinib dose: 300 mg PO BID; trastuzumab dose: 6 mg/kg IV Q3W (loading dose of 8 mg/kg C1D1); each treatment cycle is 21 days. b Except for patients with uterine serous carcinoma or HER2-mutated gastroesophageal cancer without HER2-overexpression or amplification. c The cohort aimed to enroll up to 30 patients, a number calculated per the 90% exact CI given a range of expected confirmed ORR of 10% to 30%.
BID, twice daily; C1D1, Day 1 of Cycle 1; DCR, disease control rate; DOR, duration of response; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenous; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

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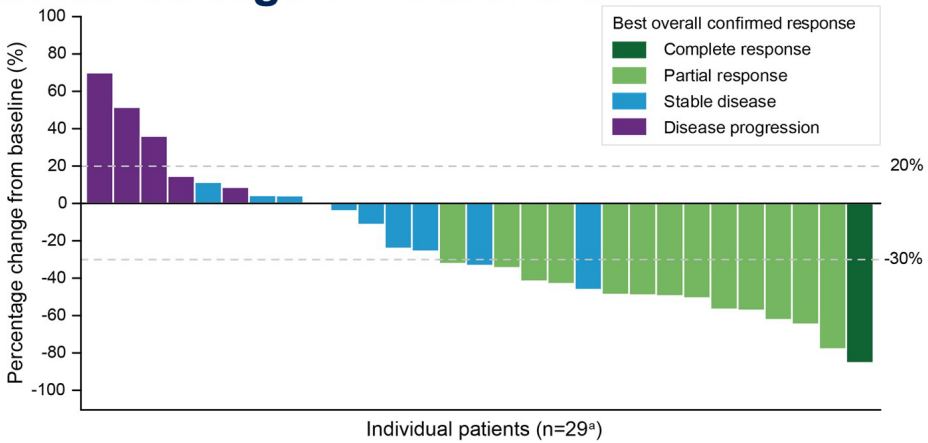
Cohort 3: Tucatinib and trastuzumab in HER2+ BTC

Response to Treatment

		Total (N=30)
Best overall response, n (%)	CR	1 (3.3)
	PR	13 (43.3)
	SD	9 (30.0)
	PD	6 (20.0)
	Not available	1 (3.3)[a]
cORR, % (90% CI)		**46.7 (30.8-63.0)**
Median DOR, months (90% CI)		6.0 (5.5-6.9)
DCR, n (%)		23 (76.7)

Data cutoff: Jan 30, 2023.
a The patient had no postbaseline response assessment.
cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; DOR, duration of response; PD, progressive disease; PR, partial response; SD, stable disease.

Maximum Change in Tumor Size



Twenty-one patients (70.0%[b]) had a reduction in tumor size
Median time to first response was 2.1 months (range, 1.2-4.3)

Data cutoff: Jan 30, 2023.
a Excludes 1 patient with no postbaseline response assessment. b Percentage was calculated with 30 as the denominator.

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Antibody drug coniugates (ADC)

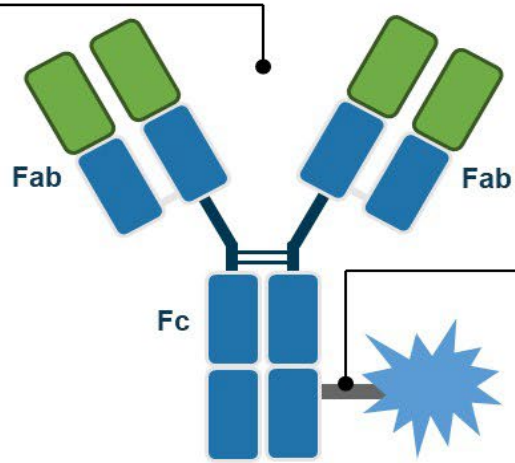
Antibody-Drug Conjugates: New kids on the block

Important Properties of the ADC Components and Target Antigen

Antigen
- High homogeneous expression on tumor
- Low or no expression on healthy tissues
- High affinity and avidity for antibody recognition

Antibody
- High affinity and avidity for tumor antigen
- Chimeric or humanized to decrease immunogenicity
- Long half-life and high molecular weight

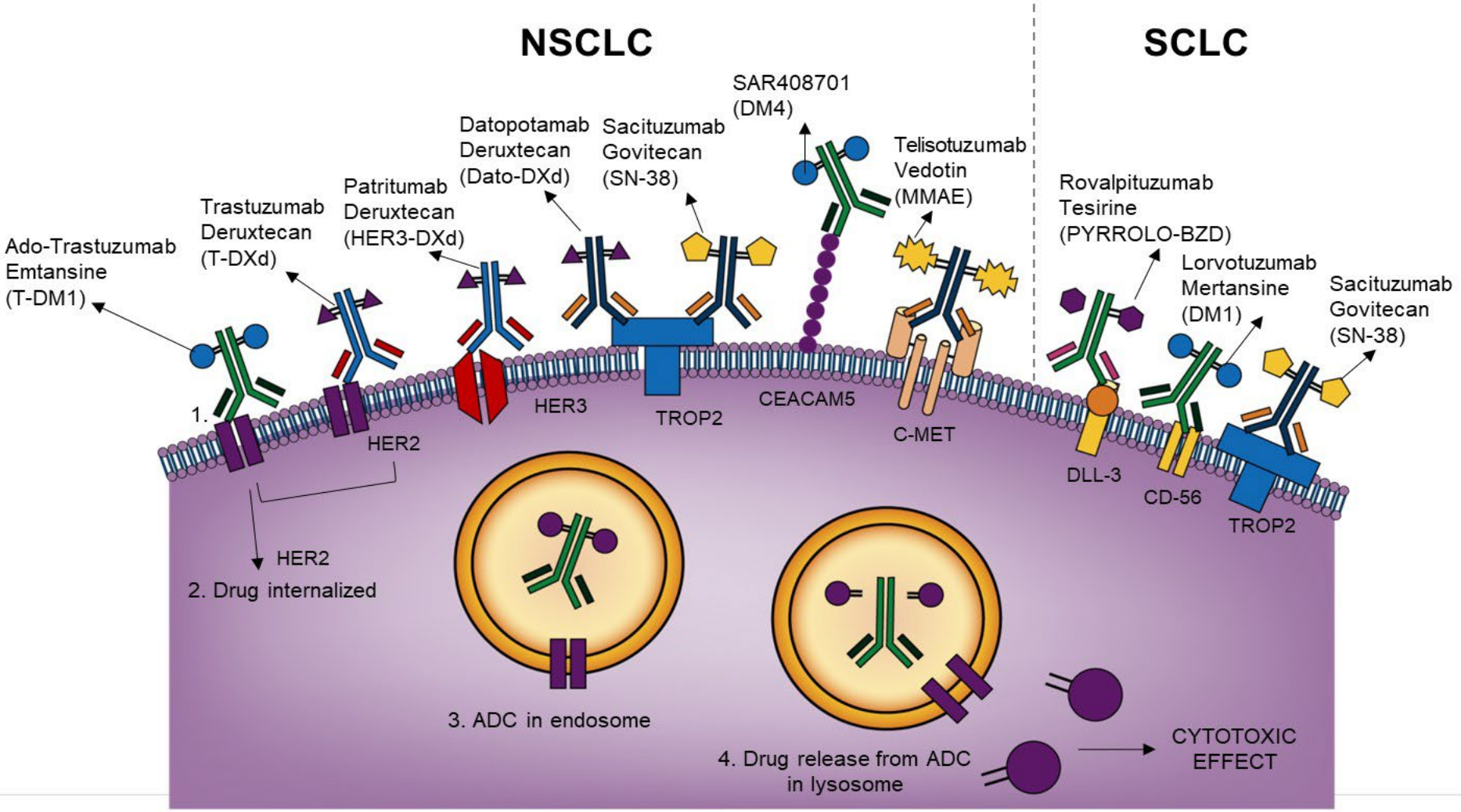
Cytotoxic Payload
- Highly potent agents:
  - Calicheamicin
  - Maytansine derivative (DM1 or DM4)
  - Auristatin (MMAE or MMAF)
  - SN-38
  - DXd topoisomerase I inhibitor
- Optimal DAR (range: 2 to 8)



Linker
- Stable in circulation
- Efficient release of payload at target site
- Prevents premature release of payload at nontarget tissue
- Efficient linker technology **(cleavable vs noncleavable)**
- Site of conjugation
- DAR affects drug distribution and pharmacokinetics

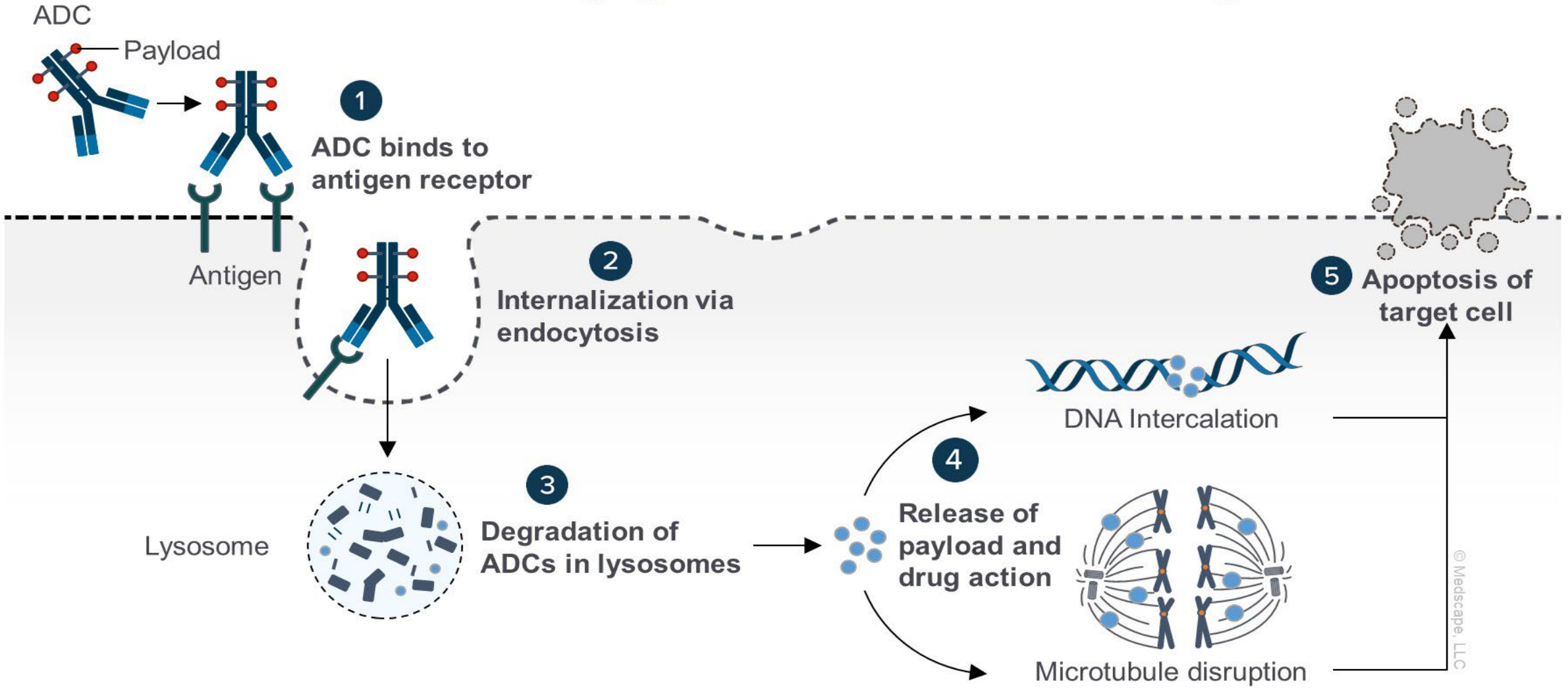
Cleavable Linkers
Depend on physiological conditions: pH, proteolysis, or high intracellular glutathione
Noncleavable Linkers
Depend on lysosomal degradation

The Antigen: Ideal Characteristics for ADCs



Desai A et al. Lung Cancer. 2022

Antibody-Drug Conjugates
Mechanism 1: mAB engagement of cell surface antigen



Chau CH, et al. Lancet. 2019

TROPION-lung02: **datopotamab deruxtecan** plus pembrolizumab with or without platinum chemotherapy in advanced NSCLC

TROPION-Lung02: Phase 1b Study

- TROPION-Lung02 is the first study evaluating Dato-DXd + pembrolizumab ± platinum CT[a] in advanced NSCLC without actionable genomic alterations[b] (NCT04526691)
  - The safety of the Dato-DXd + pembrolizumab doublet was established prior to evaluation of the platinum-containing triplet
  - The safety of Dato-DXd 4-mg/kg combinations was established prior to evaluation of 6-mg/kg combinations

Key eligibility criteria

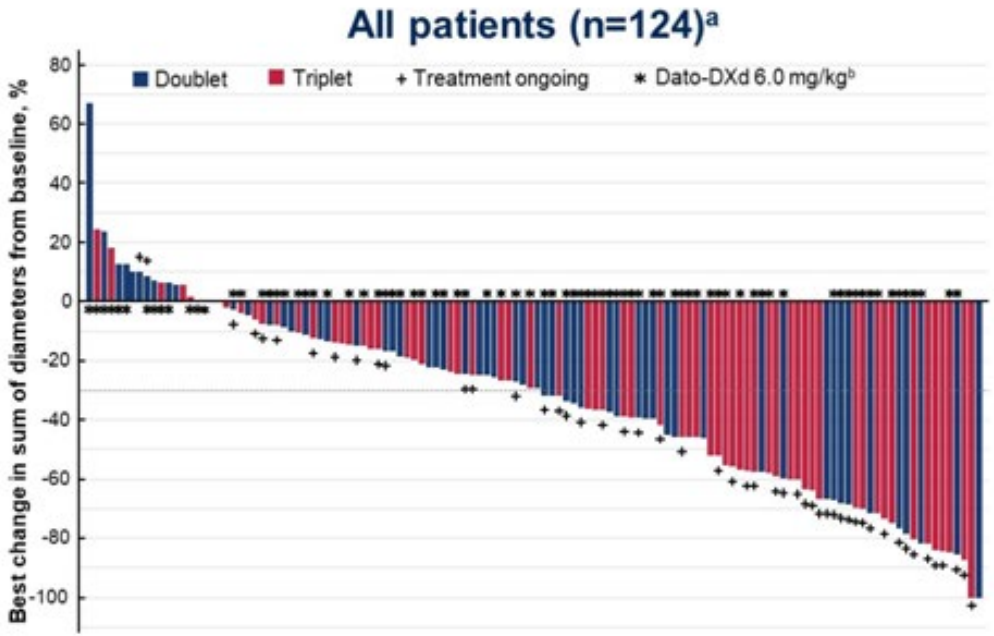
- **Advanced/metastatic NSCLC**
- **Dose escalation**[c]: ≤2 lines of prior therapy[d]
- **Dose expansion**
  - ≤1 line of platinum-based CT (cohorts 1 and 2)[d]
  - Treatment naive (cohort 2; enrollment after Jun 30, 2022)[d]
  - Treatment naive (cohorts 3-6)[d]

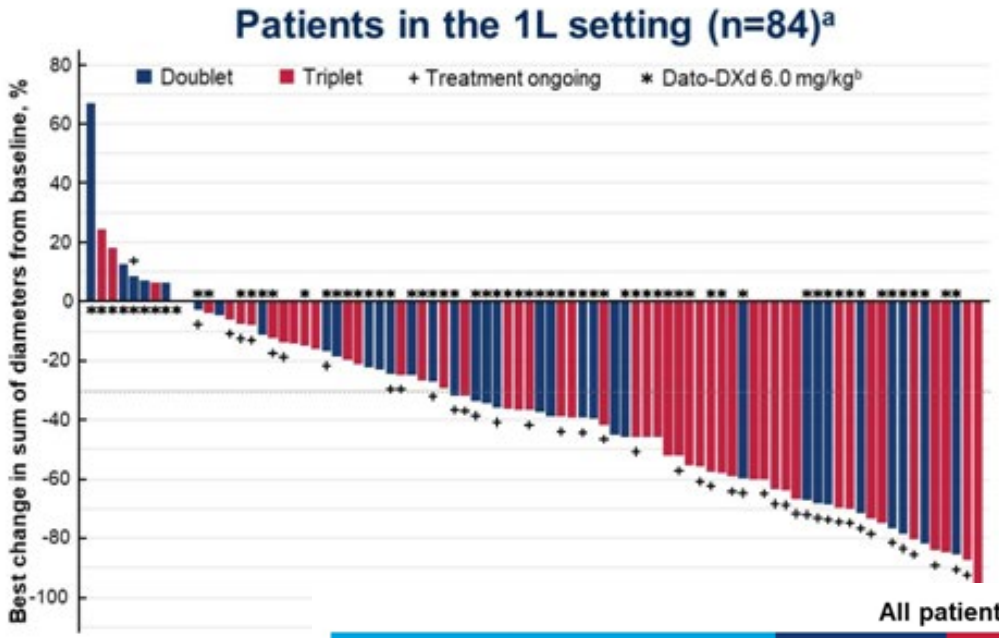
	Dato-DXd IV Q3W	+	pembro IV Q3W	+	platinum CT IV Q3W	
Cohort 1 (n=20):	4 mg/kg	+	200 mg			Doublet
Cohort 2 (n=44):	6 mg/kg	+	200 mg			
Cohort 3 (n=20):	4 mg/kg	+	200 mg	+	carboplatin AUC 5	Triplet
Cohort 4 (n=30):	6 mg/kg	+	200 mg	+	carboplatin AUC 5	
Cohort 5 (n=12):	4 mg/kg	+	200 mg	+	cisplatin 75 mg/m^2	
Cohort 6 (n=10):	6 mg/kg	+	200 mg	+	cisplatin 75 mg/m^2	

- **Primary objectives:** safety and tolerability
- **Secondary objectives:** efficacy, pharmacokinetics, and antidrug antibodies

Data cutoff: April 7, 2023.
AUC, area under the curve; CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; DLT, dose-limiting toxicity; IV, intravenous; NSCLC, non-small cell lung cancer; pembro, pembrolizumab; Q3W, every 3 weeks.
[a] Administered sequentially at the same visit. [b] Patients with known actionable *EGFR, ALK, ROS1, NTRK, BRAF, RET,* or *MET* mutations or alterations in other actionable oncogenic driver kinases were not eligible for this study. Testing for *EGFR* and *ALK* alterations was not required for patients with squamous histology who were smokers or ≥40 years of age. [c] The first 3 to 6 patients in each cohort were enrolled to confirm acceptable safety/DLT rate; the remaining patients are considered part of dose expansion (for which enrollment was ongoing at the time of data cutoff). [d] Prior therapy requirements are for treatment in the advanced/metastatic setting.

TROPION-lung02: efficacy results





Data cutoff: April 7, 2023.
1L, first line.
[a] Patients with no baseline target lesions or no postbaseline tumor assessments were excluded from the waterfall plots. [b] Planned dose level.

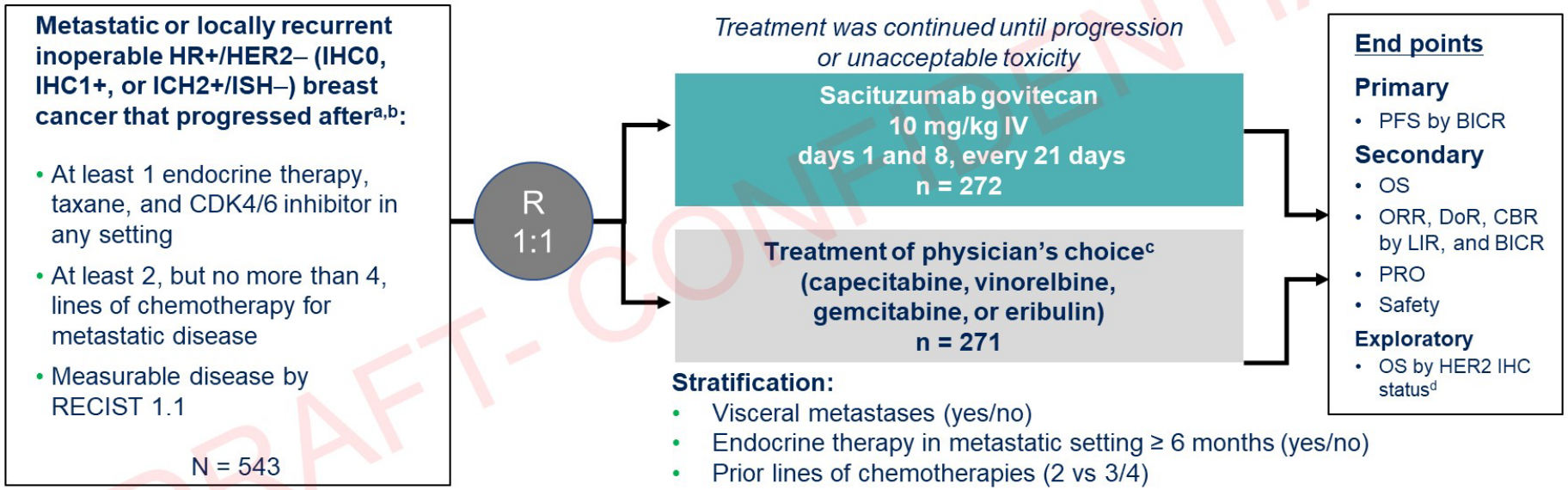
	All patients		Patients in 1L	
Response[a]	**Doublet (n=61)[b]**	**Triplet (n=71)[b]**	**Doublet (n=34)[b]**	**Triplet (n=53)[b]**
Confirmed + pending ORR, n (%)[c,d] [95% CI]	23 (38) [26-51]	35 (49) [37-61]	17 (50) [32-68]	30 (57) [42-70]
Confirmed + pending BOR, n (%)[d,e]				
Confirmed CR	0	1 (1)	0	1 (2)
Pending CR[d]	0	0	0	0
Confirmed PR	21 (34)	34 (48)	15 (44)	29 (55)
Pending PR[d]	2 (3)	0	2 (6)	0
SD, n (%)[f]	30 (49)	27 (38)	16 (47)	18 (34)
DCR, n (%)[g]	51 (84)	62 (87)	31 (91)	48 (91)
Median DOR, months [95% CI]	NE [8.8-NE]	NE [5.8-NE]	NE [5.5-NE]	NE [5.7-NE]

Preliminary PFS in all patients, median (95% CI), months: doublet, 8.3 (6.8-11.8); triplet 7.8 (5.6-11.1)[h]

Goto Y, ASCO 2023

TROPICS-02 study: sacituzumab govitecam

TROPiCS-02: A Phase 3 Study of SG in Patients with HR+/HER2– mBC[1]



ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; DoR, duration of response; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormonal receptor-positive; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenously; LIR, local investigator review; ORR, objective response rate; OS, overall survival; PFS, progression-free survival, PRO, patient-reported outcomes; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.
[a]ClinicalTrials.gov. NCT03901339. [b]Disease histology based on the ASCO/CAP criteria. [c]Single-agent standard-of-care treatment of physician's choice was specified prior to randomization by the investigator. [d]HER2-low was defined as IHC score of 1+, or score of 2+ with negative ISH result; HER2 IHC0 was defined as IHC score of 0. 1. Rugo HS, et al. *J Clin Oncol*. 2022;40:3365-3376.

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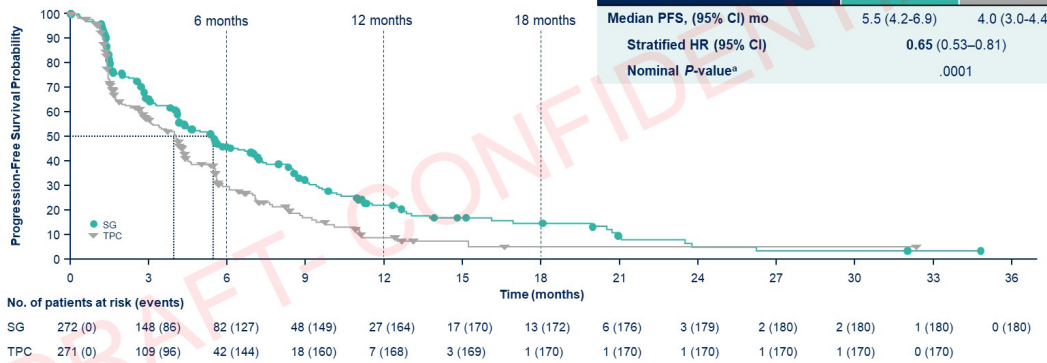
TROPICS-02 study: efficacy results

Progression-Free Survival



BICR analysis	SG (n = 272)	TPC (n = 271)
Median PFS, (95% CI) mo	5.5 (4.2-6.9)	4.0 (3.0-4.4)
Stratified HR (95% CI)	**0.65** (0.53–0.81)	
Nominal *P*-value[a]	.0001	

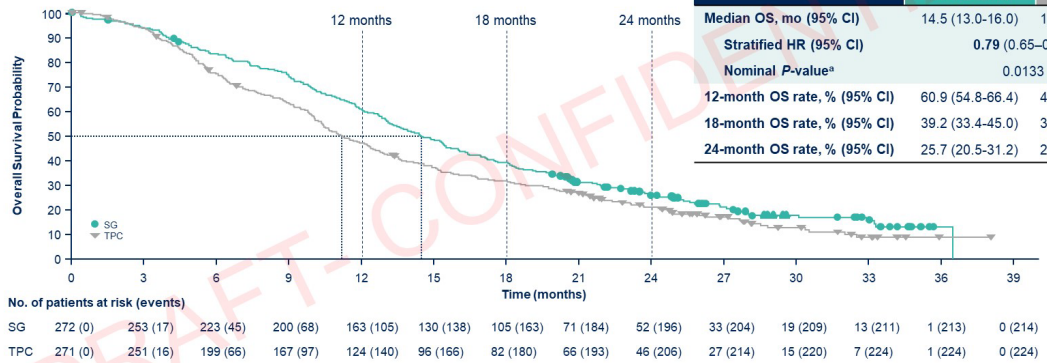
No. of patients at risk (events)

SG	272 (0)	148 (86)	82 (127)	48 (149)	27 (164)	17 (170)	13 (172)	6 (176)	3 (179)	2 (180)	2 (180)	1 (180)	0 (180)
TPC	271 (0)	109 (96)	42 (144)	18 (160)	7 (168)	3 (169)	1 (170)	1 (170)	1 (170)	1 (170)	1 (170)	0 (170)	

SG continued to demonstrate improvement in PFS vs TPC at longer follow-up, with 35% reduction in risk of disease progression or death, and a higher proportion of patients remained alive and progression-free at each landmark

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
[a]Stratified log rank *P*-value.

Overall Survival



	SG (n = 272)	TPC (n = 271)
Median OS, mo (95% CI)	14.5 (13.0-16.0)	11.2 (10.2-12.6)
Stratified HR (95% CI)	**0.79** (0.65–0.95)	
Nominal *P*-value[a]	0.0133	
12-month OS rate, % (95% CI)	60.9 (54.8-66.4)	47.1 (41.0-53.0)
18-month OS rate, % (95% CI)	39.2 (33.4-45.0)	31.7 (26.2-37.4)
24-month OS rate, % (95% CI)	25.7 (20.5-31.2)	21.1 (16.3-26.3)

No. of patients at risk (events)

SG	272 (0)	253 (17)	223 (45)	200 (68)	163 (105)	130 (138)	105 (163)	71 (184)	52 (196)	33 (204)	19 (209)	13 (211)	1 (213)	0 (214)
TPC	271 (0)	251 (16)	199 (66)	167 (97)	124 (140)	96 (166)	82 (180)	66 (193)	46 (206)	27 (214)	15 (220)	7 (224)	1 (224)	0 (224)

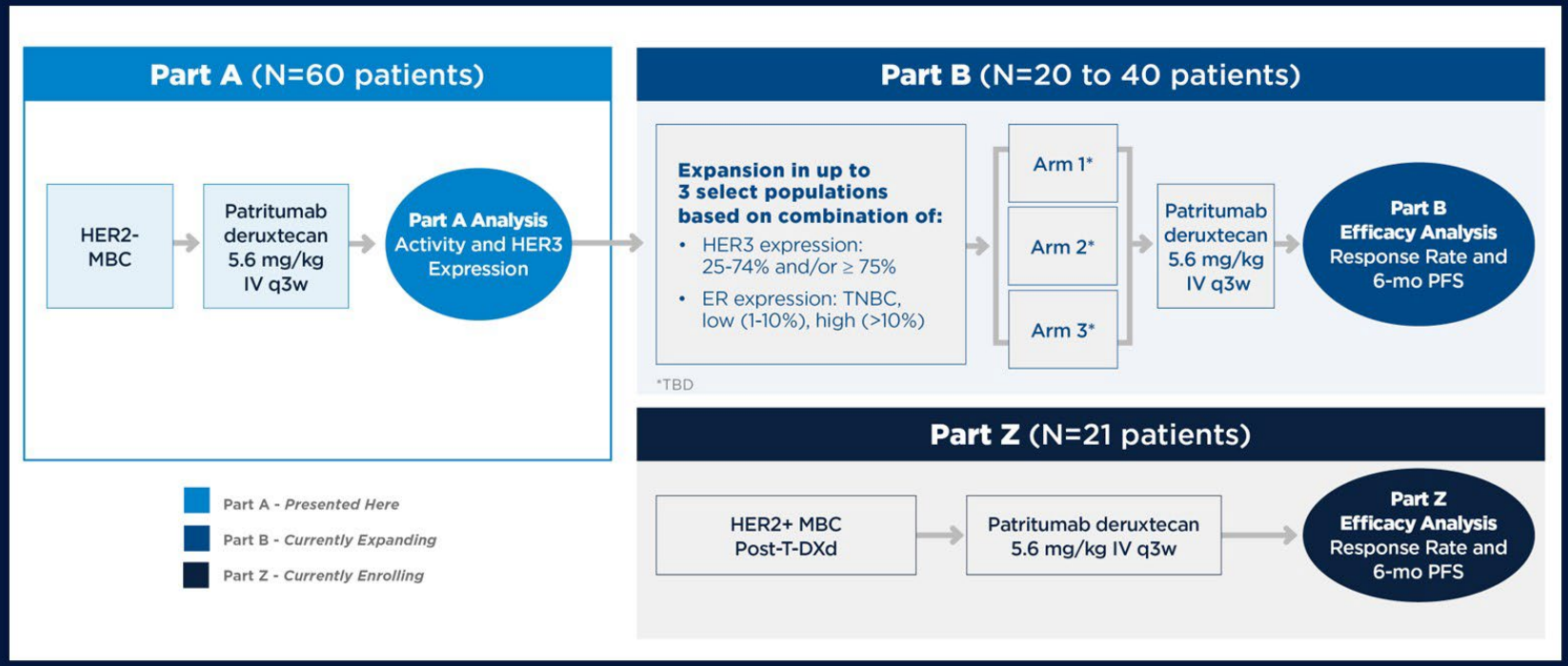
SG continued to demonstrate improvement in OS vs TPC at longer follow-up, with 21% reduction in risk of death and a higher proportion of patients remaining alive at each landmark

blinded independent central review; CI, confidence interval; HR, hazard ratio; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
fied log rank *P*-value.

A phase II study of **Patritumab-Dxd** in patients with metastatic breast cancer

Study Design

- This Phase II study (NCT04699630) examines the efficacy and safety of patritumab deruxtecan administered in patients with locally advanced or metastatic BC.
- Here, we present data for Part A.



HER3 expression was not an enrollment criterion for Part A; HER3 expression was retrospectively assessed using immunohistochemistry.

PRESENTED BY: Erika P. Hamilton, MD

A phase II study of HER3-Dxd in patients with metastatic breast cancer

Response – Investigator Assessment

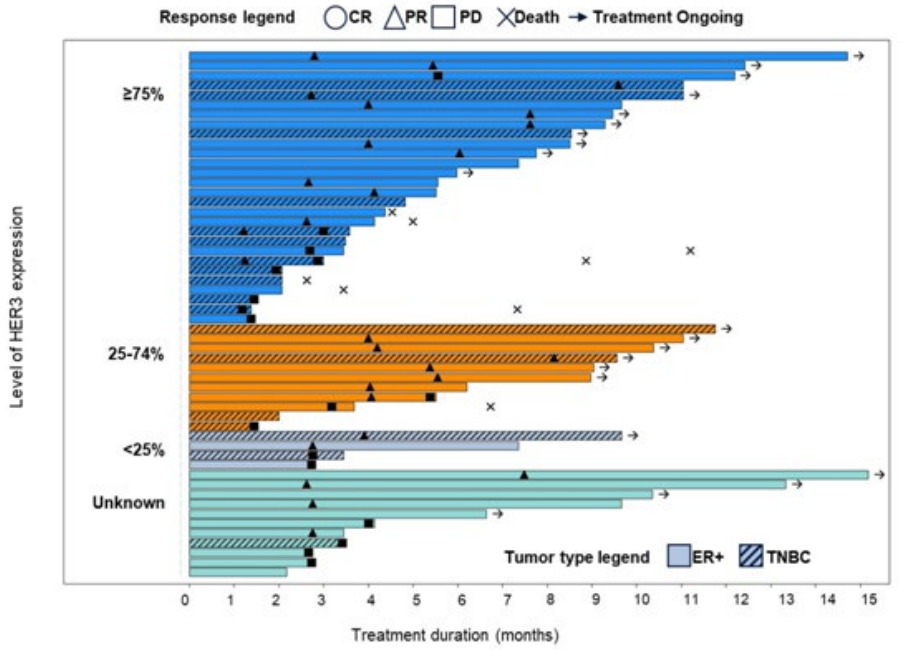
	Membrane HER3 ≥75% (N=30)	Membrane HER3 25%- 74% (N=13)	Membrane HER3 <25% (N=4)	Unknown Membrane HER3 Expression* (N=13)	Total (N=60) N (%)
Best Overall Response, n (%)					
Complete response (CR)	0	0	0	0	0
Partial response (PR)	**10 (33.3)**	**6 (46.2)**	**2 (50.0)**	**3 (23.1)**	**21 (35.0)**
Stable disease (SD)	13 (43.3)	4 (30.8)	1 (25.0)	8 (61.5)	26 (43.3)
Progressive disease (PD)	5 (16.7)	1 (7.7)	1 (25.0)	0	7 (11.7)
Missing/no post baseline	2 (6.7)	2 (15.4)	0	2 (15.4)	6 (10.0)
ORR, n (%)	**10 (33.3)**	**6 (46.2)**	**2 (50.0)**	**3 (23.1)**	**21 (35.0)**
95% CI	(17.3, 52.8)	(19.2, 74.9)	(6.8, 93.2)	(5.0, 53.8)	(23.1, 48.4)
CBR, n (%)**	**12 (40.0)**	**7 (53.8)**	**2 (50.0)**	**5 (38.5)**	**26 (43.3)**
95% CI	(22.7, 59.4)	(25.1, 80.8)	(6.8, 93.2)	(13.9, 68.4)	(30.6, 56.8)
DoR ≥6 months, n (%)†	4 (40.0)	2 (33.3)	2 (100)	2 (66.7)	10 (47.6)

*HER3 results available for 47 pts. Remaining 13 pts had tissue not available/testing result unevaluable.
**CBR=CR, PR, or SD ≥180 days
†Percentage calculation uses the number of pts who responded as the denominator.

Among patients with heavily pretreated BC, all-comer ORR was 35%, overall CBR was 43%, and DoR was at least 6 months in nearly half of all patients who responded.

Abbreviations: CBR, clinical benefit rate; CI, confidence interval; DoR, duration of response; ORR, objective response rate.

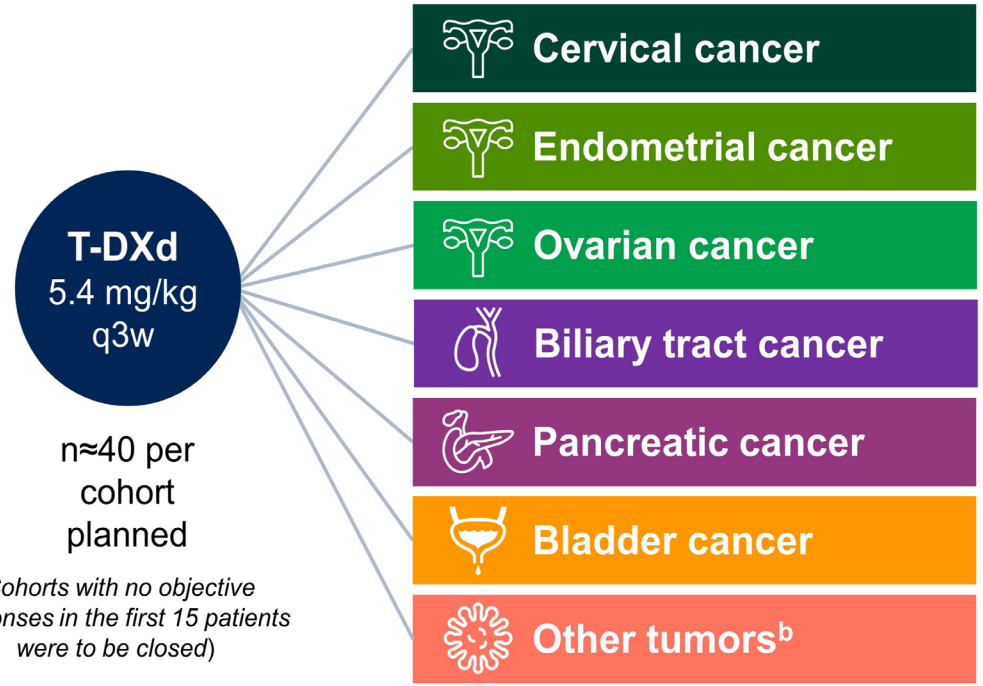
Data cutoff: September 6, 2022.



DESTINY-PanTumor02: A Phase 2 Study of T-DXd for HER2-Expressing Solid Tumors

An open-label, multicenter study (NCT04482309)

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer guidelines[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1



n≈40 per cohort planned

(*Cohorts with no objective responses in the first 15 patients were to be closed*)

Primary endpoint

- Confirmed ORR (investigator)[c]

Secondary endpoints

- DOR[c]
- DCR[c]
- PFS[c]
- OS
- Safety

Data cut-off for analysis:

- Nov 16, 2022

[a]Patients were eligible for either test. All patients were centrally confirmed. [b]Patients with tumors that express HER2, excluding tumors in the tumor-specific cohorts, and breast cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer.
[c]Investigator-assessed per Response Evaluation Criteria In Solid Tumors version 1.1.
2L, second-line; ASCO, American Society of Clinical Oncology; DCR, disease control rate; CAP, College of American Pathologists; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization.

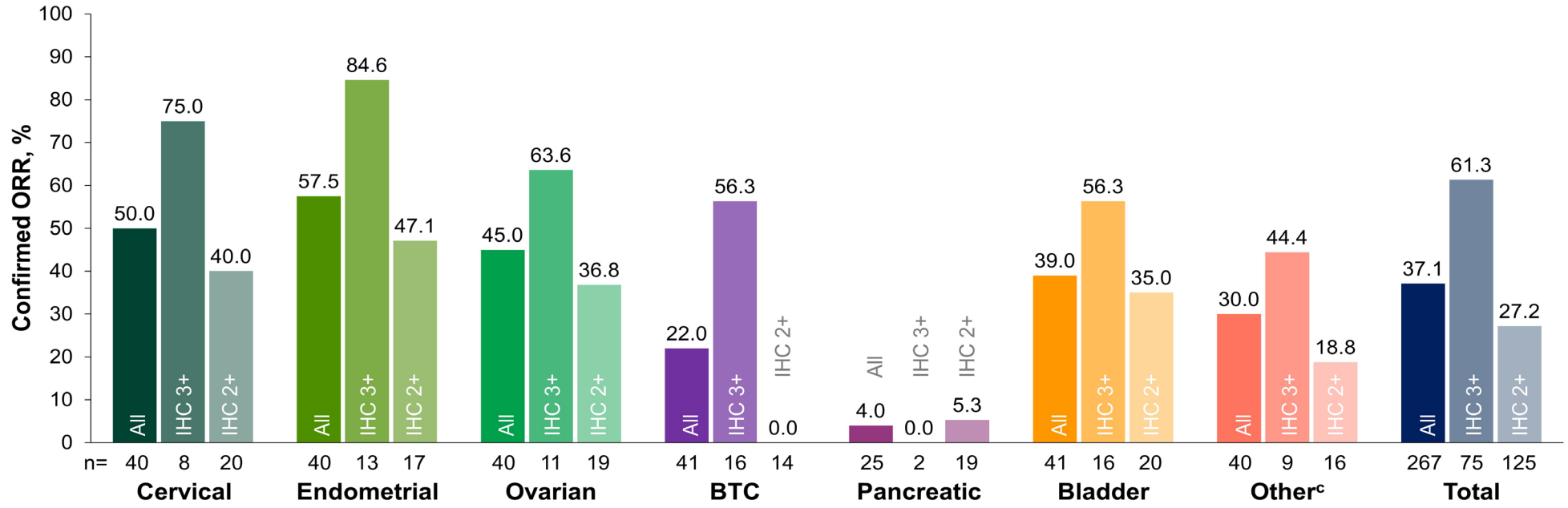
1. Hofmann M, et al. *Histopathology 2008*;52(7):797–805.

PRESENTED BY: Funda Meric-Bernstam, MD

Destiny-pantumor02: trastuzumab deruxtecan in solid tumors

DESTINY-PanTumor02

Objective Response Rate by HER2 status



	All patients (N=99)	IHC 3+ (n=46)	IHC 2+ (n=34)
Median DOR, months (95% CI)	11.8 (9.8–NE)	22.1 (9.3–NE)	9.8 (4.2–12.6)

Analysis of ORR was performed in patients who received ≥1 dose of T-DXd; all patients (n=267; including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=75) or IHC 2+ (n=125) status. Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd; all patients (n=99; including 19 patients with IHC 1+ [n=6], IHC 0 [n=9], or unknown IHC status [n=4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=46) or IHC 2+ (n=34) status. [a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.
BTC, biliary tract cancer; CI, confidence interval; DOR, duration of response; IHC, immunohistochemistry; NE, non-estimable; ORR, objective response rate.

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…Take home messages

- ✓A complete biomolecular carachterization is required to choose the best therapeutic strategies
- ✓ A new era with personalized therapy in early stage has just began
- ✓The identification of a target may represent a valid therapeutic alternative
- ✓ADC are emerging as a promising option in several cancers
- ✓The enrollment in clinical trial has to be evaluated in presence of molecular target

…Thank you!