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En partenariat avec les Cours St-Paul

RET et anti-TROP2 ADC

Pr. David Planchard, MD, PhD

Head of thoracic group
Department of Cancer Medicine
Institut Gustave Roussy

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

@dplanchard

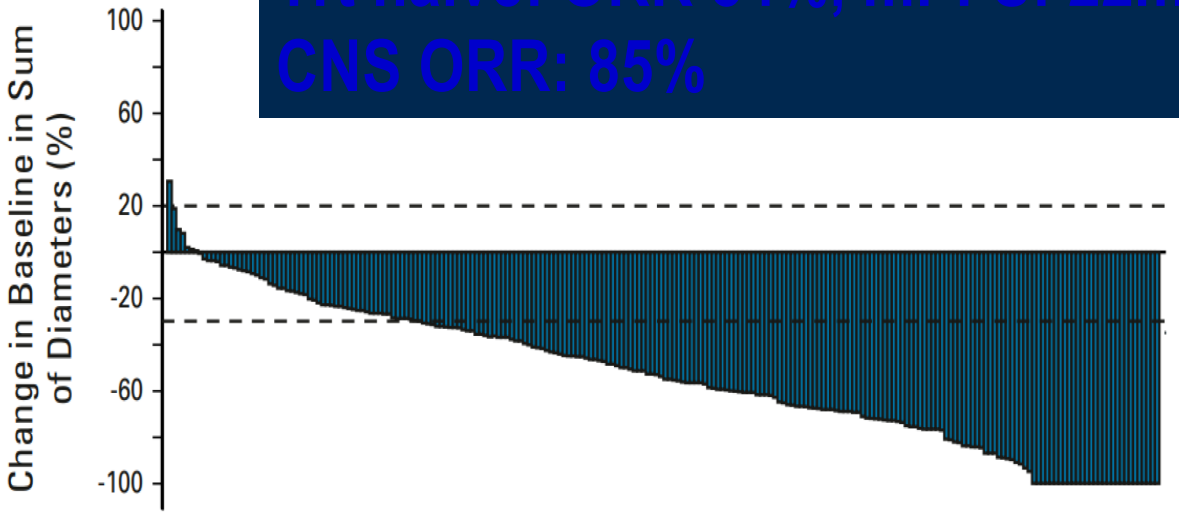
Selpercatinib - first data

FDA vs EMA approvals

LIBRETTO 001 (Phl/II)

Selpercatinib 160 mg BID

Trt naive: ORR 84%, mPFS: 22mo
CNS ORR: 85%



FDA

Accelerated approval in May 2020

Post-marketing requirement of additional patients and follow-up

Traditional approval in September 2022

EMA

Conditional approval in February 2021

Post-marketing requirement of randomized data vs. standard of care

LIBRETTO-431 phase 3 open-label study design

Key Eligibility Criteria

- Stage IIIB-IIIC[1], IV non-squamous NSCLC
- No prior systemic therapy for metastatic disease
- *RET* fusion identified via NGS or PCR
- ECOG PS 0-2
- Symptomatic CNS metastases excluded

BM:20%

Stratification factors:

- Geography (East Asian vs. non-East Asian)
- Brain metastases (present vs. absent/unknown)[2]
- Investigator's choice of treatment with pembrolizumab

R 2:1[3]

Selpercatinib (160 mg BID)
N= 159

Carboplatin (AUC 5) or **Cisplatin** (75 mg/m^2)
+ **Pemetrexed** (500 mg/m^2)
+/- **Pembrolizumab** (200 mg)
N= 102

Pembro:81%

Optional Crossover

Selpercatinib
(Upon BICR confirmed PD)

Cross over 62%

Gated Primary Endpoints: PFS by blinded independent central review (BICR) in ITT-Pembrolizumab[4] and ITT population

Secondary Endpoints:

- **Efficacy** ([OS, ORR, DOR], CNS [ORR, DOR, time to progression][5])
- **Safety**
- **Patient Reported Outcomes** (NSCLC-SAQ [tertiary endpoint EORTC QLQ-C30])

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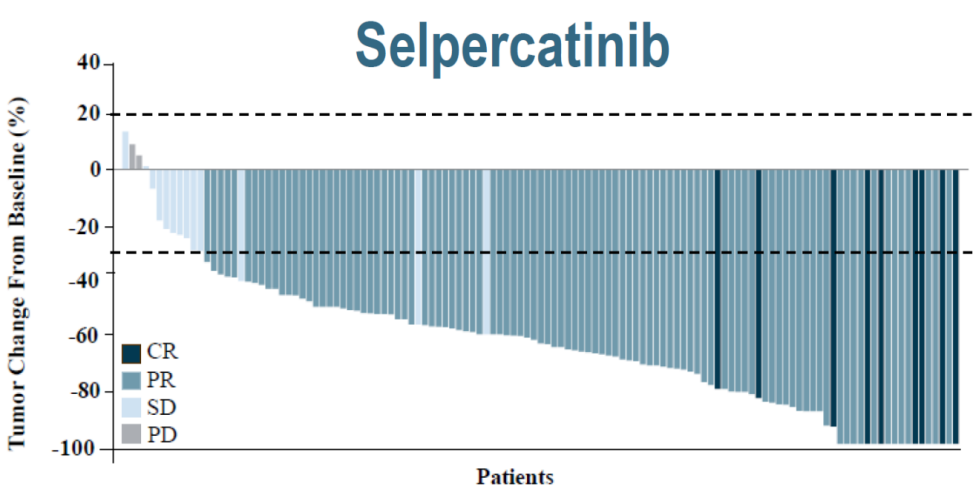
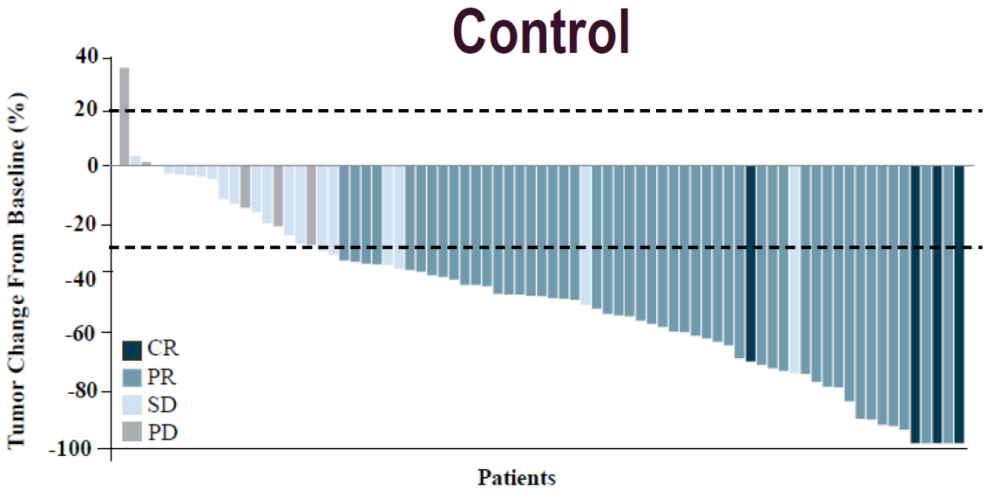
LIBRETTO-431 – Systemic ORR





ORR: 83.7%

	Selpercatinib N= 129	Control N= 83
ORR, % (95% CI)	83.7 (76.2, 89.6)	65.1 (53.8, 75.2)
CR	7.0 (3.2, 12.8)	6.0 (2.0, 13.5)
PR	76.7 (68.5, 83.7)	59.0 (47.7, 69.7)
SD	10.9 (6.1, 17.5)	24.1 (15.4, 34.7)
PD	1.6 (0.2, 5.5)	6.0 (2.0, 13.5)
NE	3.9 (1.3, 8.8)	4.8 (1.3, 11.9)

ORR: 65.1%

IC-ORR (n=17 and 12pts): 82.4 vs 58.3%

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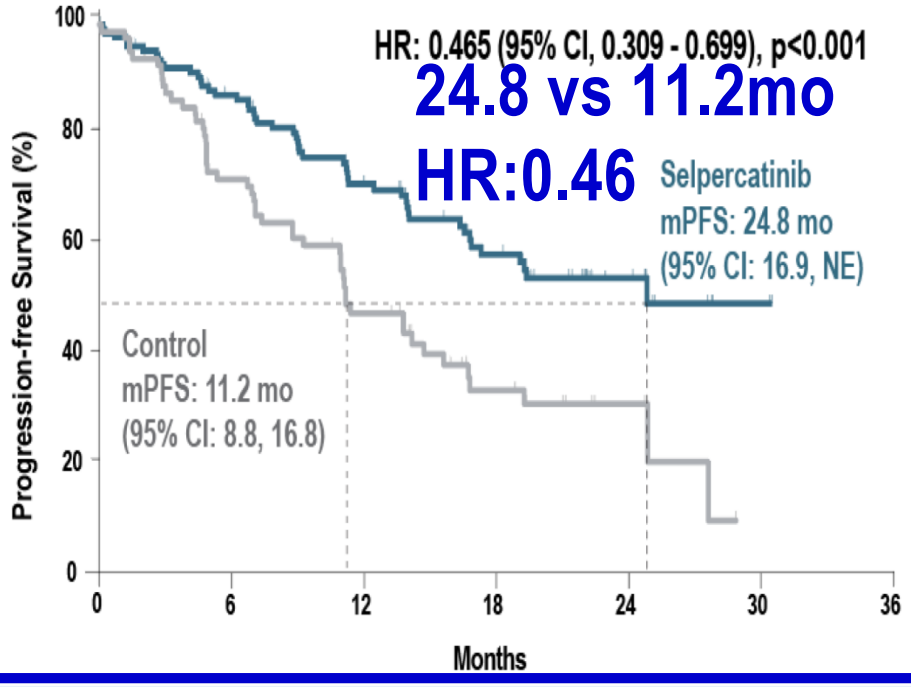
Progression-free survival (PFS) assessed by BICR

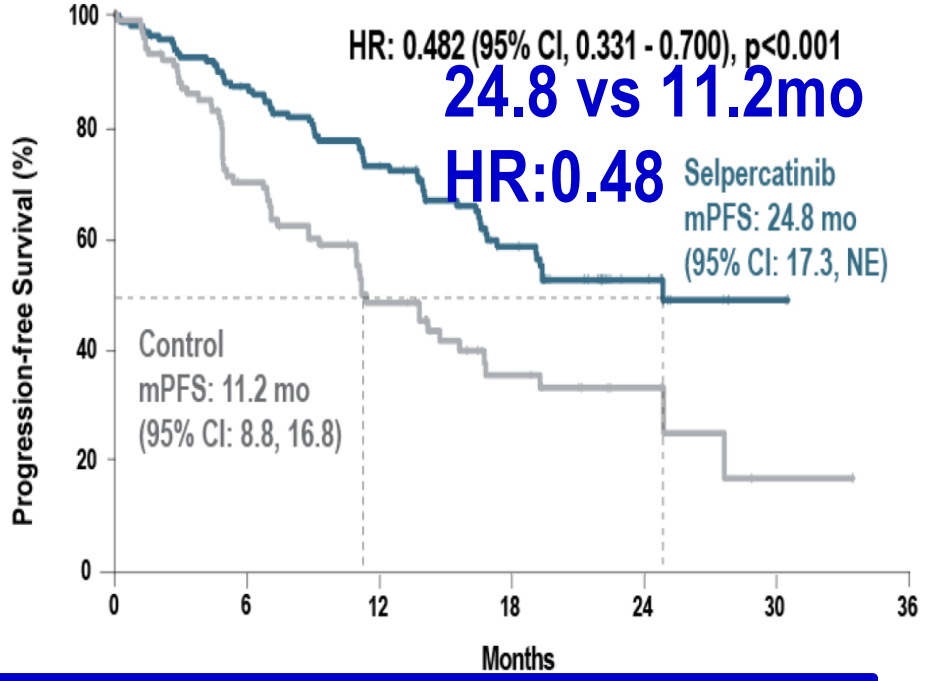
ITT-Pembrolizumab Population

(Median follow-up of ~19 mo)



ITT Population

(Median follow-up of ~18 mo)



The primary endpoints were met, as selpercatinib resulted in a statistically significant improvement in PFS in both pre-specified populations

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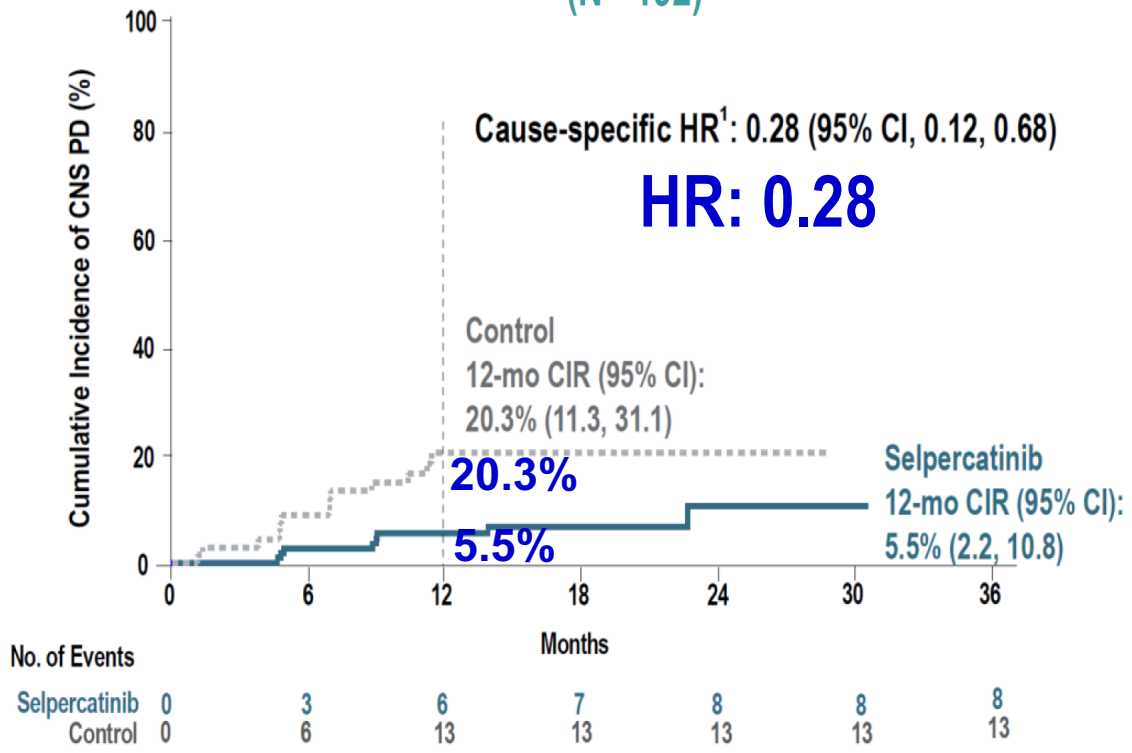
Cumulative incidence rate of CNS progression

Patients with and without Baseline CNS Metastases
(N= 192)



Time to CNS progression was delayed with selpercatinib

Risk of CNS Progression

Without CNS Metastases at Baseline	Selpercatinib (N= 99)	Control (N= 51)
12-month CIR, % (95% CI)	1.1% (0.1, 5.2)	14.7% (5.7, 27.6)
Cause-specific HR[1] (95% CI)	0.17 (0.04, 0.69)	

With CNS Metastases at Baseline	Selpercatinib (N= 21)	Control (N= 21)
12-month CIR, % (95% CI)	25.7% (8.8, 46.7)	33.3% (14.3, 53.8)
Cause-specific HR[1] (95% CI)	0.61 (0.19, 1.92)	

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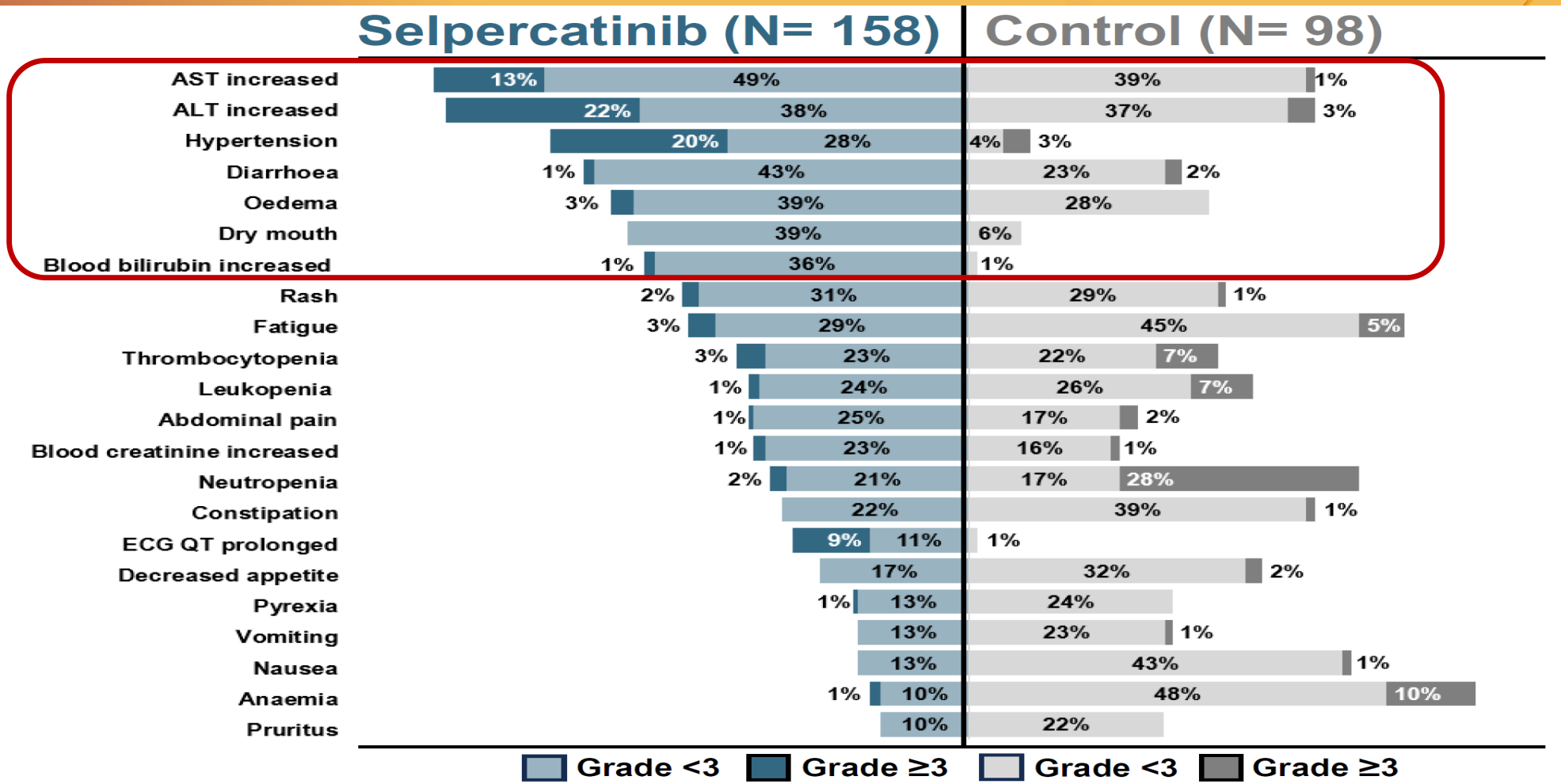
Safety



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Selpercatinib should be considered a first-line standard of care in *RET* fusion-positive advanced NSCLC. These results reinforce the importance of genomic testing to identify *RET* fusions at the time of diagnosis to inform initial therapy

Next gen RET inhibitors

Several ongoing trials + pre-clinical data on new molecules

Drug	Company	Status	Activity
LOXO-260	LOXO-Lilly	Phase I	Active against solvent front and gatekeeper mutations
SY-5007	Shouyao Holdings	Phase I completed (ASCO 2023): ORR 62%, DCR 94% Phase II ongoing	Selective RET inhibitor
TPX-0046	Turning Point Therapeutics	Phase I/II	RET/SRC inhibitor, active against solvent front mutations
TY-1091	TYK Medicines	Phase I/II	Active against solvent front and gatekeeper mutations
TAS0953/HM06	Helsinn Healthcare	Phase I/I	Active against solvent front and gatekeeper mutations

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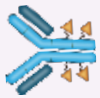
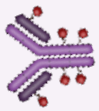
Select ADCs under investigation in NSCLC

		Target	Drug	Payload	Linker	DAR
Biomarker selection not required		HER3	Patritumab-DXd	Topoisomerase Inhibitor	Cleavable	8
		TROP2	Sacituzumab govitecan	Topoisomerase Inhibitor	Cleavable	7.6
		TROP2	Datopotamab-DXd	Topoisomerase Inhibitor	Cleavable	4
Biomarker selection required		HER2*	Trastuzumab-DXd	Topoisomerase Inhibitor	Cleavable	8
		CEACAM5	Tusamitamab ravtansine	Microtubule Inhibitor	Cleavable	3.8
		c-Met	Telisotuzumab vedotin	Microtubule Inhibitor	Cleavable	3.1
		c-Met	ABBV-400[2]	Topoisomerase Inhibitor	Cleavable	–

*Approved by the FDA.

1. Passaro A, et al. J Clin Oncol. 2023;24:JCO2300013. 2. Sharma RM, et al. P3015. ASCO. June 2-6, 2023.

Datopotamab deruxtecan (Dato-DXd) vs docetaxel in previously treated advanced/metastatic NSCLC:

Results of the randomized phase 3 study TROPION-Lung01

Key Eligibility Criteria

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0 or 1
- No prior docetaxel

Without actionable genomic alterations[a]

- 1 or 2 prior lines, including platinum CT and anti–PD-(L)1 mAb therapy

With actionable genomic alterations

- Positive for *EGFR*, *ALK*, *NTRK*, *BRAF*, *ROS1*, *MET* exon 14 skipping, or *RET*
- 1 or 2 prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb

R 1:1

Dato-DXd
6 mg/kg Q3W
(N=299)

Docetaxel
75 mg/m^2 Q3W
(N=305)

Dual Primary Endpoints

- PFS by BICR
- OS

Secondary Endpoints

- ORR by BICR
- DOR by BICR
- Safety

Stratified by: histology,[b] actionable genomic alteration,[c] anti–PD-(L)1 mAb included in most recent prior therapy, geography[d]

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Demographics and Baseline Characteristics

Characteristic		Dato-DXd N=299	Docetaxel N=305
Age, median (range), years		63 (26-84)	64 (24-88)
Male, n (%)		183 (61)	210 (69)
Race, n (%)	Asian	119 (40)	120 (39)
	White	123 (41)	126 (41)
	Black or African American	6 (2)	4 (1)
	Other[a]	51 (17)	55 (18)
ECOG PS, n (%)	0	89 (30)	94 (31)
	1	210 (70)	211 (69)
Histology, n (%)	Non-squamous	234 (78)	234 (77)
	Squamous	65 (22)	71 (23)

Characteristic		Dato-DXd N=299	Docetaxel N=305
Current or former smoker, n (%)		238 (80)	251 (82)
Actionable genomic alterations, n (%)	Present	50 (17)	51 (17)
	EGFR mutation	39 (13)	45 (15)
Brain metastasis at baseline, n (%)[b]		50 (17)	47 (15)
Prior lines of therapy, n (%)	1	167 (56)	174 (57)
	2	108 (36)	102 (33)
	≥3	22 (7)	28 (9)
Previous systemic therapy, n (%)[c]	Platinum containing	297 (99)	305 (100)
	Anti–PD-(L)1	263 (88)	268 (88)
	Targeted	46 (15)	50 (16)

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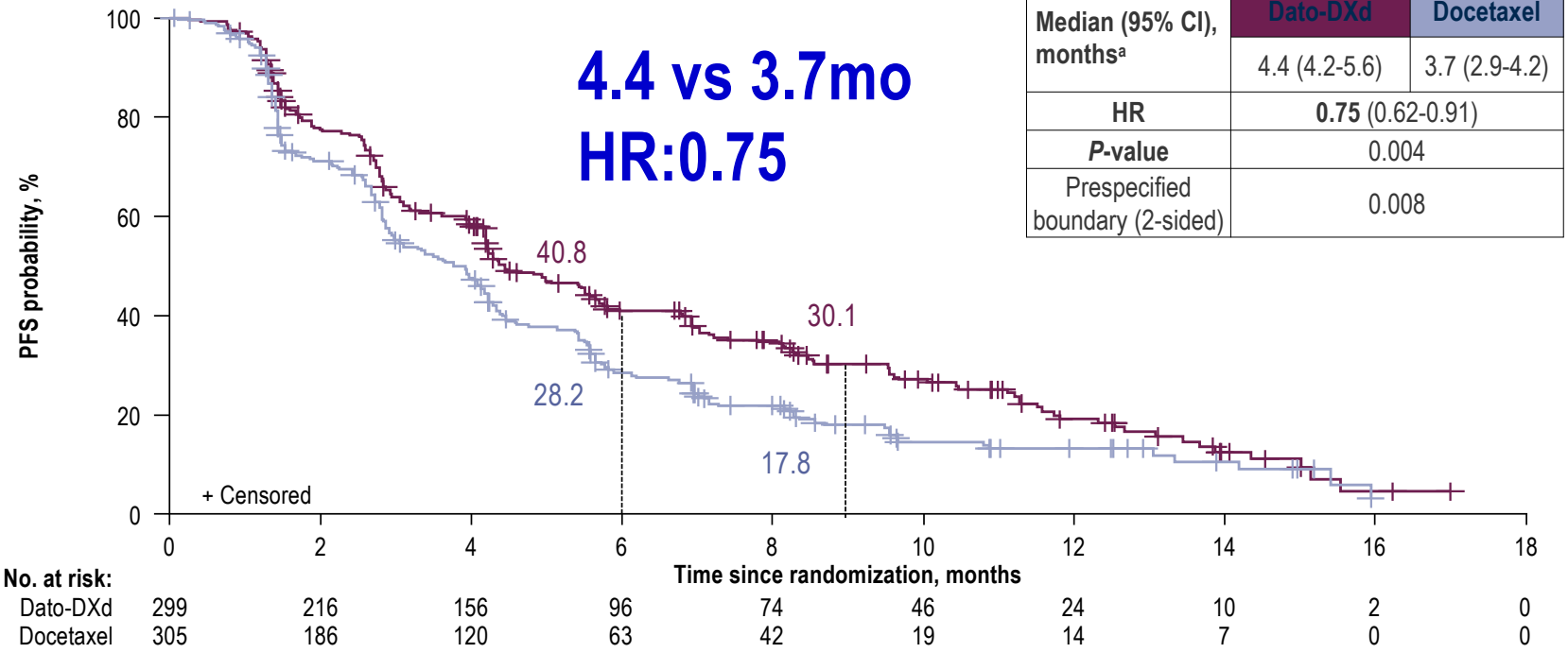
Progression-Free Survival: ITT



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	

	Dato-DXd	Docetaxel
ORR (95% CI), %[b]	**26.4** (21.5-31.8)	**12.8** (9.3-17.1)
DOR (95% CI), mo	**7.1** (5.6-10.9)	**5.6** (5.4-8.1)

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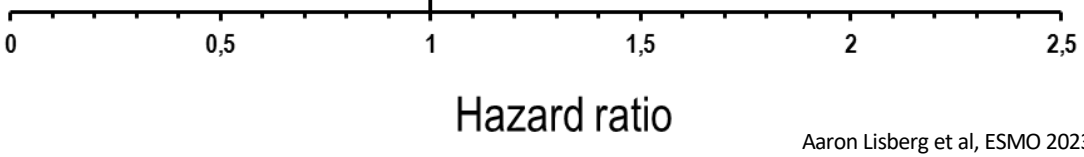
PFS in Key Subgroups

		Events/n		HR
		Dato-DXd	Docetaxel	
Age at randomization	<65 years	118/162	115/155	0.67
	≥65 years	95/137	103/150	0.83
Sex	Male	136/183	158/210	0.79
	Female	77/116	60/95	0.71
Race	Asian	76/119	82/120	0.77
	Non-Asian	131/172	129/177	0.76
Smoking status	Never	36/61	33/52	0.67
	Former/current	177/238	184/251	0.77
Brain metastasis at baseline	With	33/50	31/47	0.64
	Without	180/249	187/258	0.76
Histology	Non-squamous	156/229	168/232	0.63
	Squamous	57/70	50/73	1.38
Actionable genomic alterations[a]	Absent	189/252	184/255	0.84
	Present	24/47	34/50	0.38



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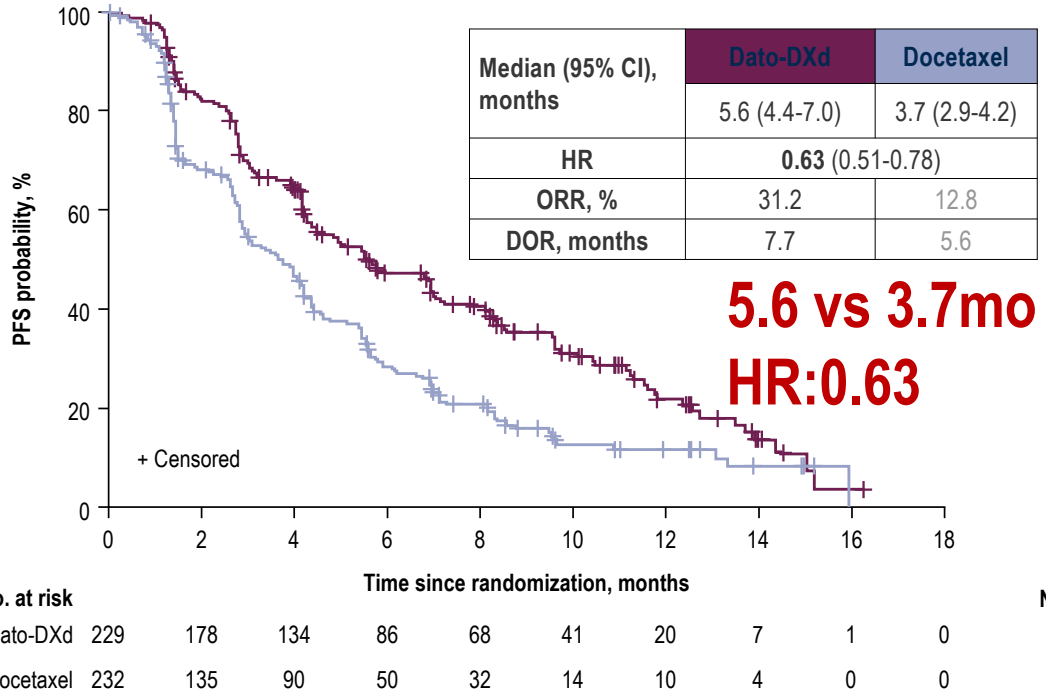
PFS by Histology

Non-squamous

(with and without AGAs)



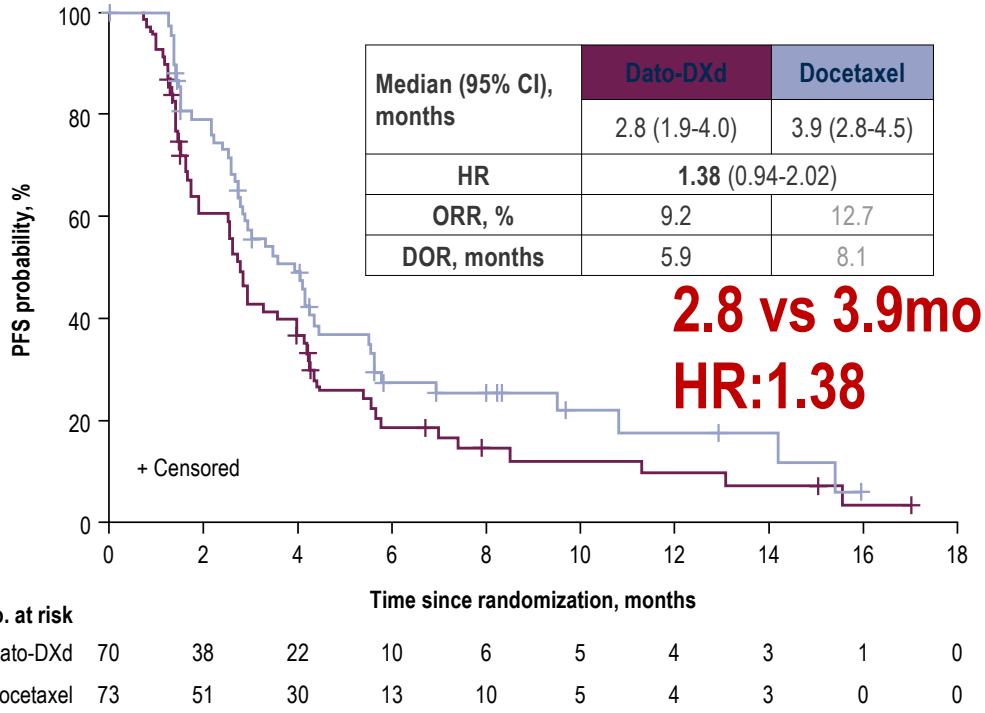
Median (95% CI), months	Dato-DXd	Docetaxel
	5.6 (4.4-7.0)	3.7 (2.9-4.2)
HR	**0.63** (0.51-0.78)	
ORR, %	31.2	12.8
DOR, months	7.7	5.6

5.6 vs 3.7mo
HR:0.63

No. at risk										
Dato-DXd	229	178	134	86	68	41	20	7	1	0
Docetaxel	232	135	90	50	32	14	10	4	0	0

Squamous

(with and without AGAs)



Median (95% CI), months	Dato-DXd	Docetaxel
	2.8 (1.9-4.0)	3.9 (2.8-4.5)
HR	**1.38** (0.94-2.02)	
ORR, %	9.2	12.7
DOR, months	5.9	8.1

2.8 vs 3.9mo
HR:1.38

No. at risk										
Dato-DXd	70	38	22	10	6	5	4	3	1	0
Docetaxel	73	51	30	13	10	5	4	3	0	0

PFS HR for non-squamous without AGAs: 0.71 (0.56, 0.91)

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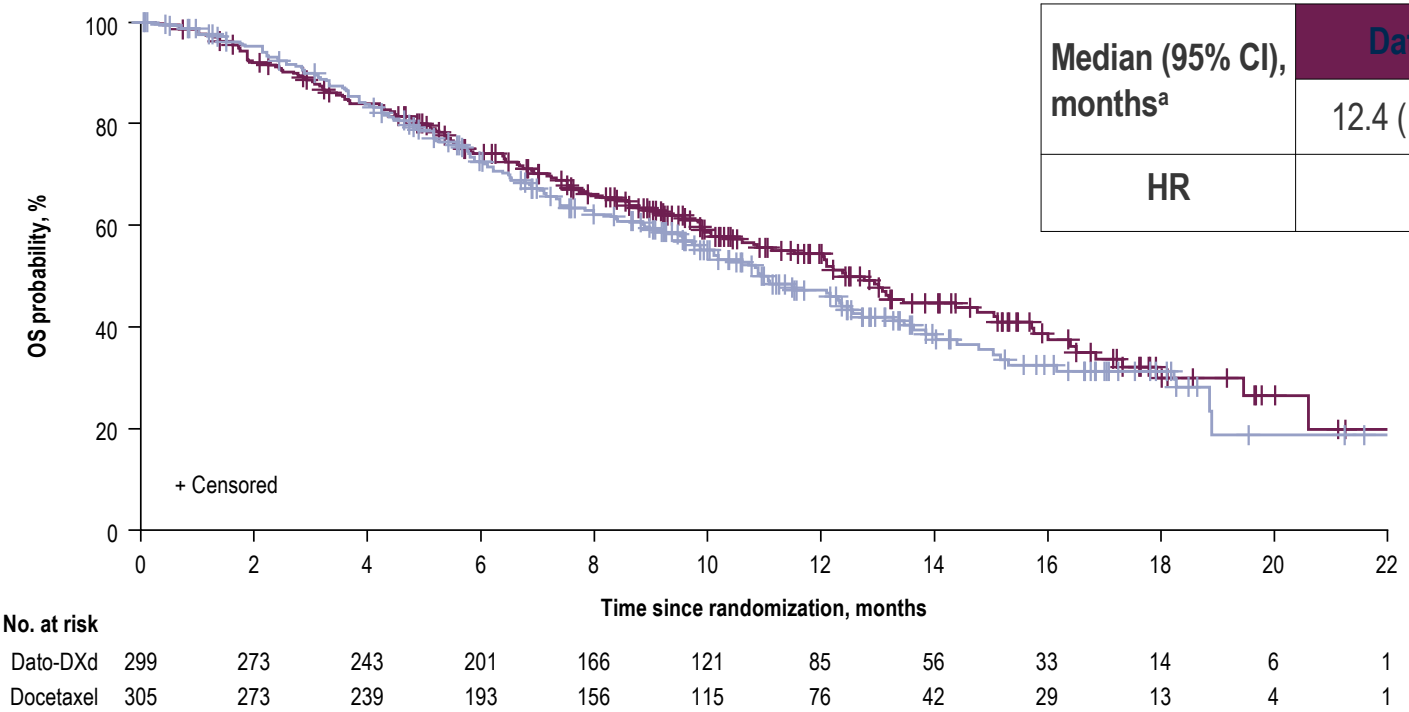
Interim Overall Survival: ITT



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)

Trial is continuing to final OS analysis

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TRAEs Occurring in ≥10% of Patients

System organ class Preferred term, n (%)	Dato-DXd N=297 Any grade	Dato-DXd N=297 Grade ≥3	Docetaxel N=290 Any grade	Docetaxel N=290 Grade ≥3
Blood and lymphatic system				
Anemia	43 (15)	11 (4)	59 (20)	11 (4)
Neutropenia[a]	12 (4)	2 (1)	76 (26)	68 (23)
Gastrointestinal				
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)
General				
Asthenia	55 (19)	8 (3)	55 (19)	5 (2)
Fatigue	34 (11)	2 (1)	40 (14)	6 (2)
Metabolism and nutrition				
Decreased appetite	68 (23)	1 (0.3)	45 (16)	1 (0.3)
Skin and subcutaneous				
Alopecia	95 (32)	0	101 (35)	1 (0.3)[b]
Rash	36 (12)	0	18 (6)	0
Pruritus	30 (10)	0	12 (4)	0

Adverse Events of Special Interest

AESI, n (%)	Dato-DXd N=297	Docetaxel N=290
Stomatitis/oral mucositis[a]		
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[d]		
All grades	25 (8)	12 (4)
Grade ≥3	10 (3)	4 (1)
Grade 5	7 (2)	1 (0.3)

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TROPION – Lung 05

- **Dato-DXd** is a TROP2-directed ADC consisting of a humanized anti-TROP2 IgG1 monoclonal antibody covalently linked to a highly potent topoisomerase I inhibitor payload via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker[1]
- In the **Phase 1 TROPION-PanTumor01** study, Dato-DXd showed promising efficacy in patients with actionable genomic alterations[2]
- **TROPION-Lung05** (NCT04484142) is a **Phase 2**, single-arm study evaluating Dato-DXd in patients with **advanced or metastatic NSCLC with actionable genomic alterations** who progressed on or after targeted therapy and platinum-based chemotherapy

Screening

Key Inclusion Criteria

- Stage IIIB, IIIC or IV NSCLC
- Presence of ≥1 actionable genomic alteration (*EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET* exon 14 skipping, or *RET*)
- ECOG PS = 0 or 1
- ≥1 line of targeted therapy
- 1 to 2 prior cytotoxic agent-containing therapies in the metastatic setting
- Radiographic disease progression after targeted therapy

Treatment

Dato-DXd
6 mg/kg
Q3W

Endpoints[a]

Primary: ORR by BICR

Secondary:

- By BICR and investigator: DOR, DCR, CBR, PFS, TTR
- By investigator: ORR
- OS, safety, PK, immunogenicity

ADC, antibody drug conjugate; BICR, blind independent central review; CBR, clinical benefit rate; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IgG1, immunoglobulin G1; NSCLC, non small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; TROP2, trophoblast cell-surface antigen 2; TTR, time to response.

[a]The primary completion date will occur when all patients have had either a minimum of 9 months of follow-up after the start of study treatment or have discontinued from the study.

1. Okajima D, et al. *Mol Cancer Ther.* 2021;20:2329-2340. **2.** Shimizu T, et al. *J Clin Oncol.* Published online June 16, 2023.

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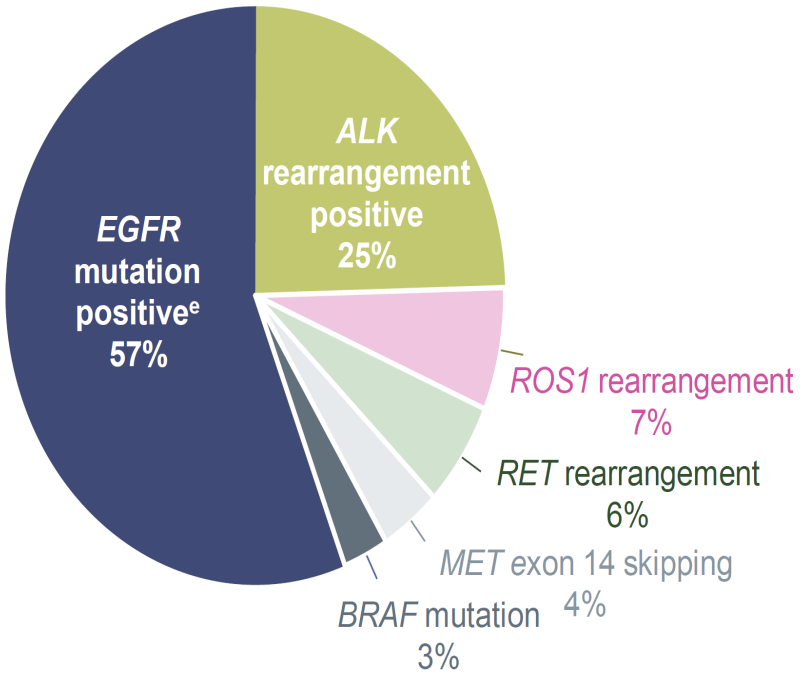
Patient Characteristics and Disposition

Demographic characteristics	Dato-DXd (N=137)
Median age, years (range)	60 (29-79)
Female, n (%)	83 (61)
Histology, n (%)	
Adenocarcinoma	130 (95)
History of brain metastasis, n (%)[a]	70 (51)
Prior lines of therapy, n (%)	137 (100)
≥3 prior lines of therapy for adv/met disease	98 (72)
Prior platinum chemotherapy	137 (100)
Prior anti-PD-1/anti-PD-L1 immunotherapy	49 (36)
1 prior line of targeted therapy for indicated genomic alteration	55 (40)
≥2 prior lines of targeted therapies for indicated genomic alteration	82 (60)

Relative Frequency of Genomic Alterations[b,c,d]



Disposition

At the time of data cutoff (December 14, 2022):

- Median (range) treatment duration was 4 (1-21) months
- 60 participants (44%) were ongoing in study
- 20 participants (15%) were ongoing on study treatment

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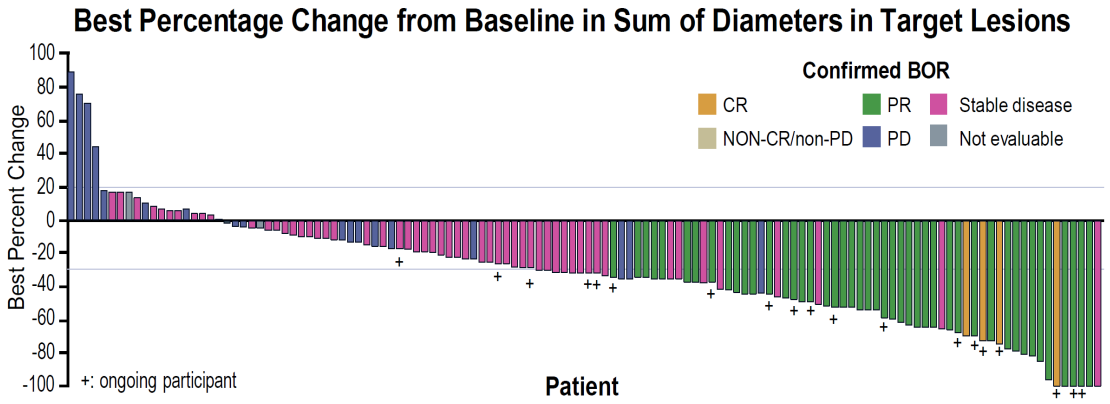
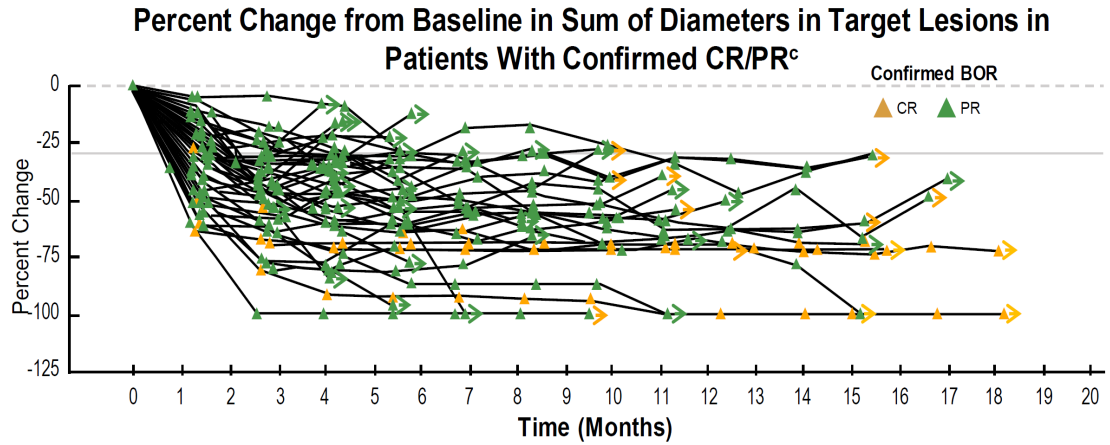
Efficacy Summary

Response per BICR	All treated (N=137)	Patients with *EGFR* mutations (N=78)	Patients with *ALK* rearrangement (N=34)
ORR confirmed, n (%) [95% CI][a]	49 (35.8) [27.8,44.4]	34 (43.6) [32.4,55.3]	8 (23.5) [10.7,41.2]
Median DOR, months[b] [95% CI]	7.0 [4.2,9.8]	7.0 [4.2,10.2]	7.0 [2.8,8.4]
DCR confirmed, n (%) [95% CI][a]	108 (78.8) [71.0,85.3]	64 (82.1) [71.7,89.8]	25 (73.5) [55.6,87.1]
Median PFS, months[b] [95% CI]	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 (3%) patients achieved a CR and 45 (33%) patients achieved a PR





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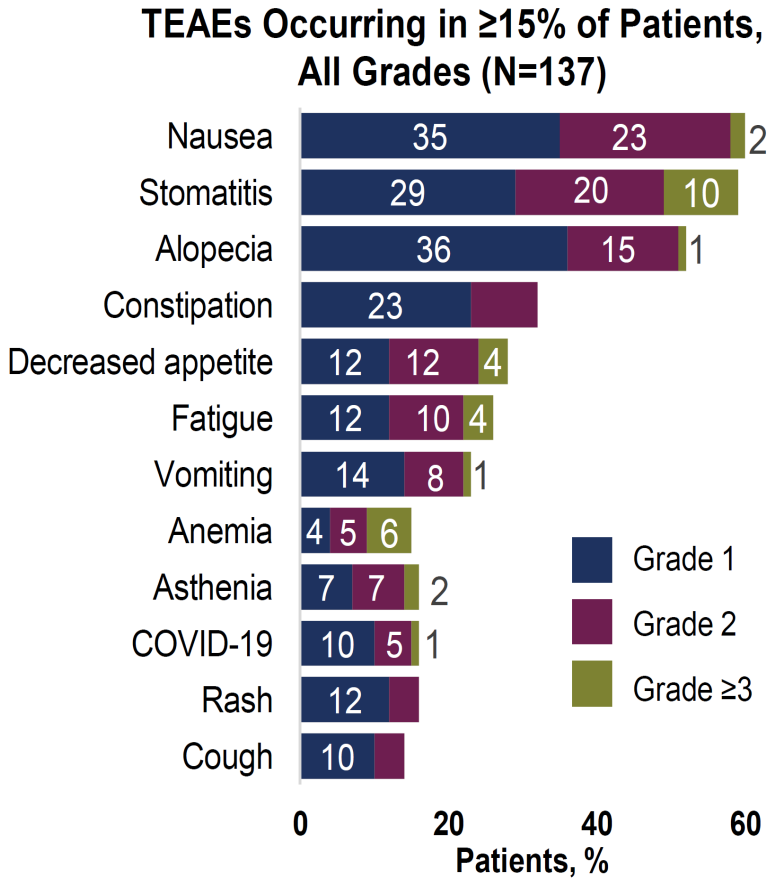
Safety Summary



- 137 (100%) patients experienced **TEAEs** (47% grade ≥3)
  - 129 (94%) experienced **treatment-related TEAEs** (29% grade ≥3)
  - 34 (25%) experienced **serious AEs** (5% grade ≥3)
- 30 (22%), 13 (10%), and 2 (2%) patients experienced TEAEs associated with **dose reduction, dose withdrawal, and death**,[a] respectively

AESI Incidence by Grade[b]

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

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- **DATO-DXd has benefit over SOC docetaxel in 2nd line Non-Squamous NSCLC**
- DATO-DXd has a reasonably safe toxicity profile
- Translational research is urgently needed to elucidate the mechanisms of drug action and generate effective biomarkers of response