Datopotamab Deruxtecan vs Docetaxel in Patients with Non-Small Cell Lung Cancer: Final Overall Survival from TROPION-Lung01

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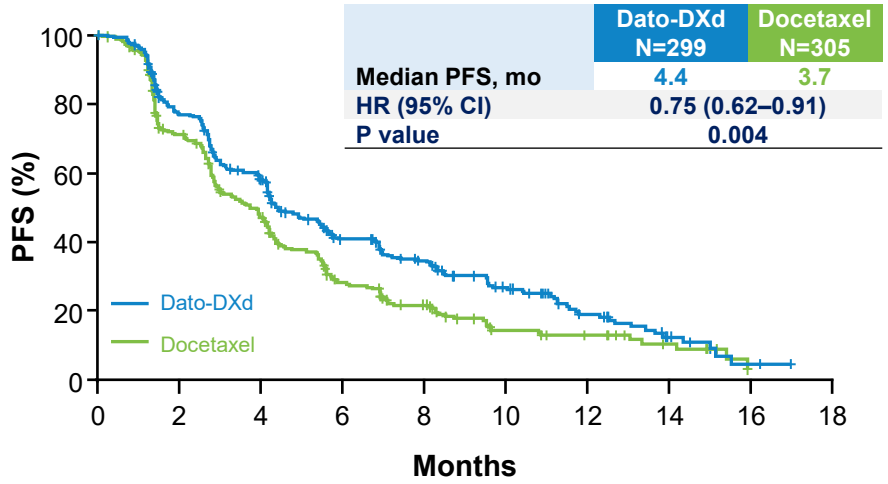
Background

TROPION-Lung01

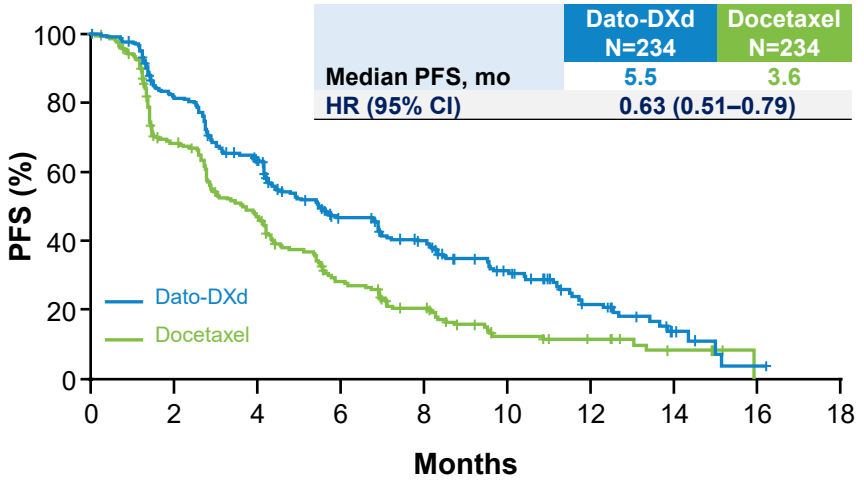
- Survival outcomes for patients with advanced NSCLC on docetaxel-based regimens in the second-line setting and beyond remain poor, and multiple trials of novel treatment regimens have failed in this setting, underscoring a high unmet need[1,2]
- **TROPION-Lung01** met its dual primary endpoint of **PFS with a statistically significant improvement** in favor of **datopotamab deruxtecan** (**Dato-DXd**) vs docetaxel[3]; a 37% reduction in relative risk of progression and more than doubling of response rate were seen in the NSQ subgroup[4]

ITT



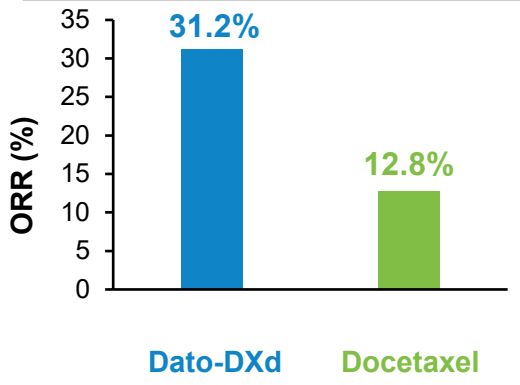
	Dato-DXd N=299	Docetaxel N=305
Median PFS, mo	4.4	3.7
HR (95% CI)	0.75 (0.62–0.91)	
P value	0.004	

NSQ



	Dato-DXd N=234	Docetaxel N=234
Median PFS, mo	5.5	3.6
HR (95% CI)	0.63 (0.51–0.79)	

	Dato-DXd N=234	Docetaxel N=234
Median DOR, mo	7.7	5.6



- Differential PFS outcomes by histology for Dato-DXd have been independently reported in two other NSCLC trials[5,6]

Here, we report the final analysis of the dual primary endpoint of overall survival for TROPION-Lung01

1. Fossella FV, et al. *J Clin Oncol* 18:2354-2362, 2000; 2. Reck M, et al. *Lancet Oncol* 15:143-155, 2014; 3. Ahn M-J, et al. Presented at ESMO 2023, Madrid, Spain, October 20–24, 2023 (Abstract 509MO);
4. Girard N, et al. Presented at ELCC 2024, Prague, Czech Republic, March 20–23, 2024 (Poster 59P); 5. Planchard D, et al. *J Clin Oncol* 42:8501, 2024; 6. Sun Y, et al. *J Clin Oncol* 42:8548, 2024.
CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DOR, duration of response; HR, hazard ratio; ITT, intention to treat; mo, months; NSCLC, non-small cell lung cancer; NSQ, nonsquamous; ORR, objective response rate; PFS, progression-free survival.

Study Design

Randomized, Phase 3, Open-Label, Global Study (NCT04656652)

TROPION-Lung01

Key eligibility criteria

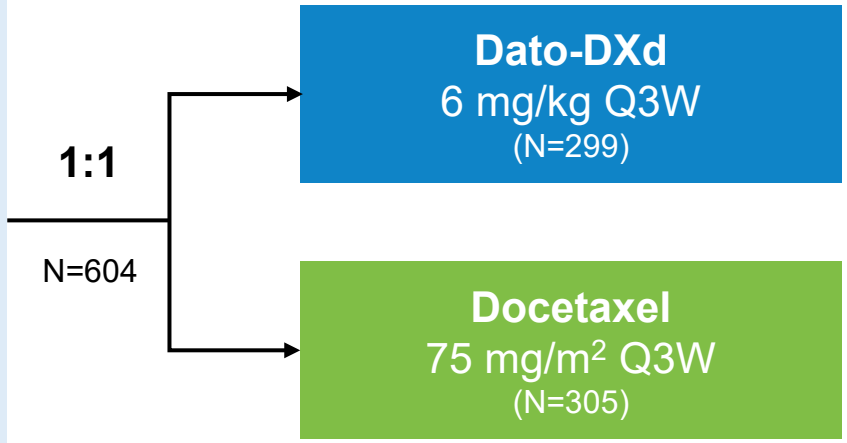
- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0–1
- No prior docetaxel

Without actionable genomic alterations

- One to two prior lines, including platinum-based 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*
- One to two prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb



Dual primary endpoints

- PFS by BICR[a]
- OS

Secondary endpoints

- ORR[a]
- DOR[a]
- Safety and tolerability

Stratified by histology (nonsquamous vs squamous), actionable genomic alteration status,[b] anti–PD-(L)1 mAb included in most recent prior therapy, and geography[c]

Statistical considerations: Study is deemed positive if either of the dual primary endpoints (PFS by BICR or OS) were statistically significant; the pre-specified P-value boundary for the OS analysis was α=0.045

[a]Evaluated per RECIST v1.1. [b]Presence vs absence. [c]United States/Japan/Western Europe vs rest of world.
BICR, blinded independent central review; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; mAb, monoclonal antibody; OS, overall survival; PD-(L)1, programmed cell death 1 (ligand 1); Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours.

Demographics and Baseline Characteristics

TROPION-Lung01

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

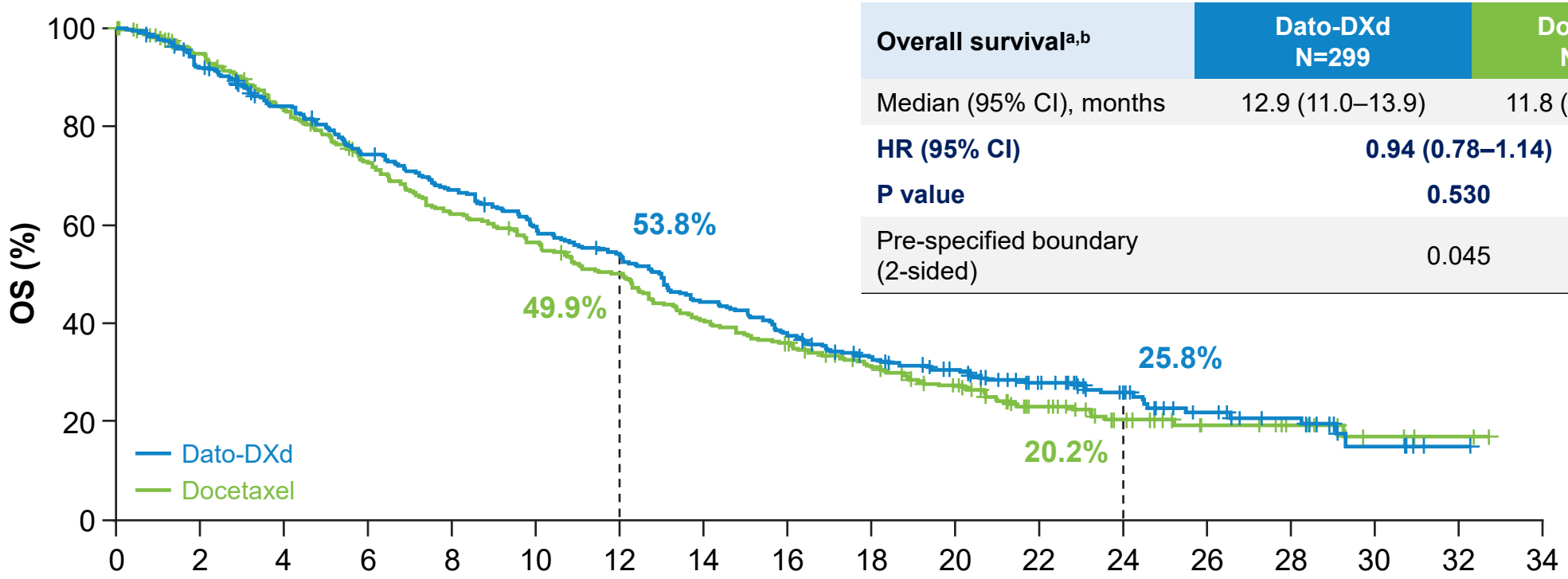
Characteristic, n (%)		Dato-DXd N=299	Docetaxel N=305
Current or former smoker		238 (80)	251 (82)
Actionable genomic alterations	Present	50 (17)	51 (17)
Brain metastasis at baseline[b]		79 (26)	91 (30)
Prior lines of therapy[c]	1	167 (56)	174 (57)
	2	108 (36)	102 (33)
	3	17 (6)	23 (8)
	≥4	5 (2)	5 (2)
Previous systemic therapy	Platinum containing	297 (99)	305 (100)
	Anti–PD-(L)1	263 (88)	268 (88)
	Targeted	46 (15)	50 (16)

[a]Screening score. [b]Patients with clinically stable brain metastases could be included. Clinically stable defined as asymptomatic, previously treated, or untreated. [c]Two patients in the Dato-DXd treatment group and one patient in the docetaxel treatment group had no prior lines of systemic therapy in the advanced/metastatic setting.
Per investigator reporting, these patients received prior systemic anti-cancer therapy in settings other than the advanced/metastatic setting.

Overall Survival: ITT

TROPION-Lung01

Overall survival[a,b]	Dato-DXd N=299	Docetaxel N=305
Median (95% CI), months	12.9 (11.0–13.9)	11.8 (10.0–12.8)
HR (95% CI)	**0.94 (0.78–1.14)**	
P value	**0.530**	
Pre-specified boundary (2-sided)	0.045	



No. at risk:

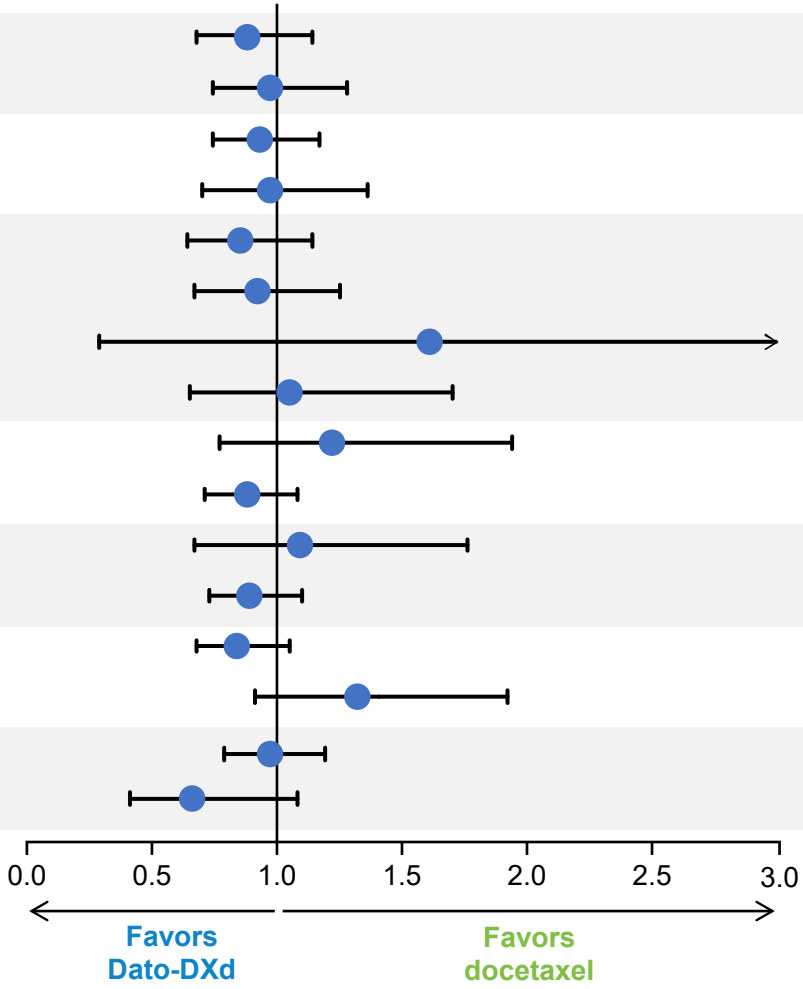
Dato-DXd	299	272	242	213	190	168	151	124	106	84	71	51	35	22	16	5	1	0
Docetaxel	305	273	239	205	175	157	138	112	98	81	63	41	26	15	11	4	2	0

[a]Median (95% CI) OS follow-up was 23.1 (22.0, 24.8) months for Dato-DXd and 23.1 (21.7, 24.2) months for docetaxel. [b]At primary OS analysis (data cutoff: March 1, 2024), 433 OS events (IF) were observed.
IF, information fraction.

Overall Survival: Subgroup Analyses

TROPION-Lung01

		No. of events/No. of patients		HR
		Dato-DXd	Docetaxel	
Age at randomization	<65 years	117/162	112/155	0.88
	≥65 years	98/137	106/150	0.97
Sex	Male	136/183	156/210	0.93
	Female	79/116	62/95	0.97
Race	White	90/123	95/126	0.85
	Asian	83/121	79/120	0.92
	Black/African American	4/6	2/4	1.61
	Other	33/43	35/47	1.05
Smoking status	Never	43/60	31/52	1.22
	Former/current	172/239	186/251	0.88
Brain metastases at baseline	With	37/50	31/47	1.09
	Without	178/249	187/258	0.89
Histology	Nonsquamous	160/234	163/234	0.84
	Squamous	55/65	55/71	1.32
Actionable genomic alterations[a]	Absent	182/249	185/254	0.97
	Present	33/50	33/51	0.66



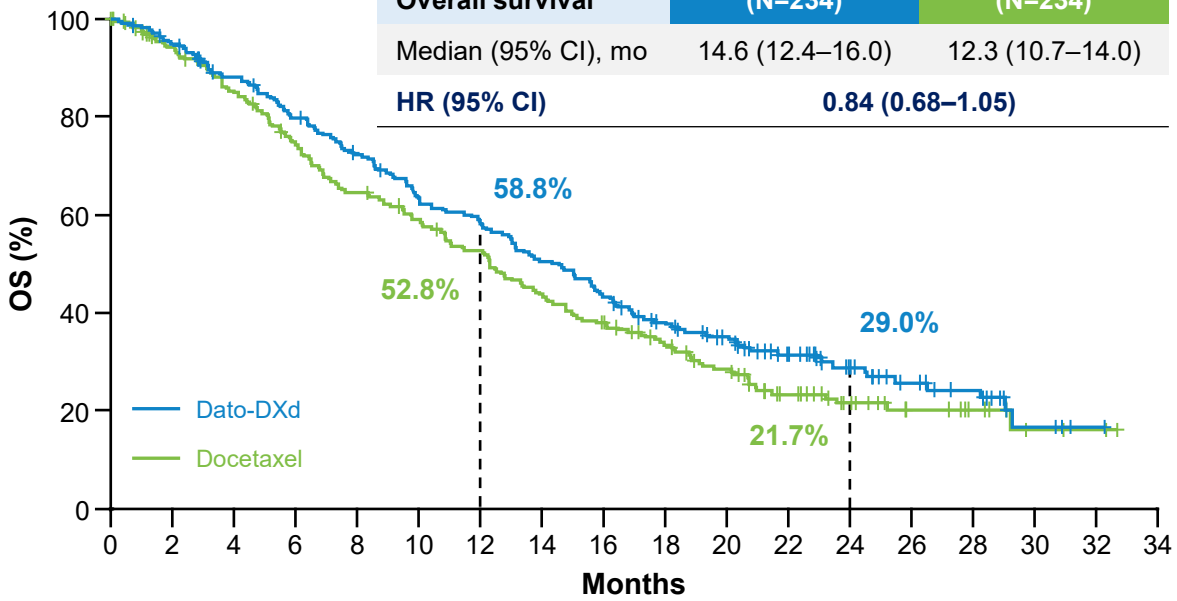
Data cutoff: March 1, 2024.
[a]Regardless of histology.

Overall Survival by Histology

TROPION-Lung01

Nonsquamous

Overall survival	Dato-DXd (N=234)	Docetaxel (N=234)
Median (95% CI), mo	14.6 (12.4–16.0)	12.3 (10.7–14.0)
HR (95% CI)	0.84 (0.68–1.05)	

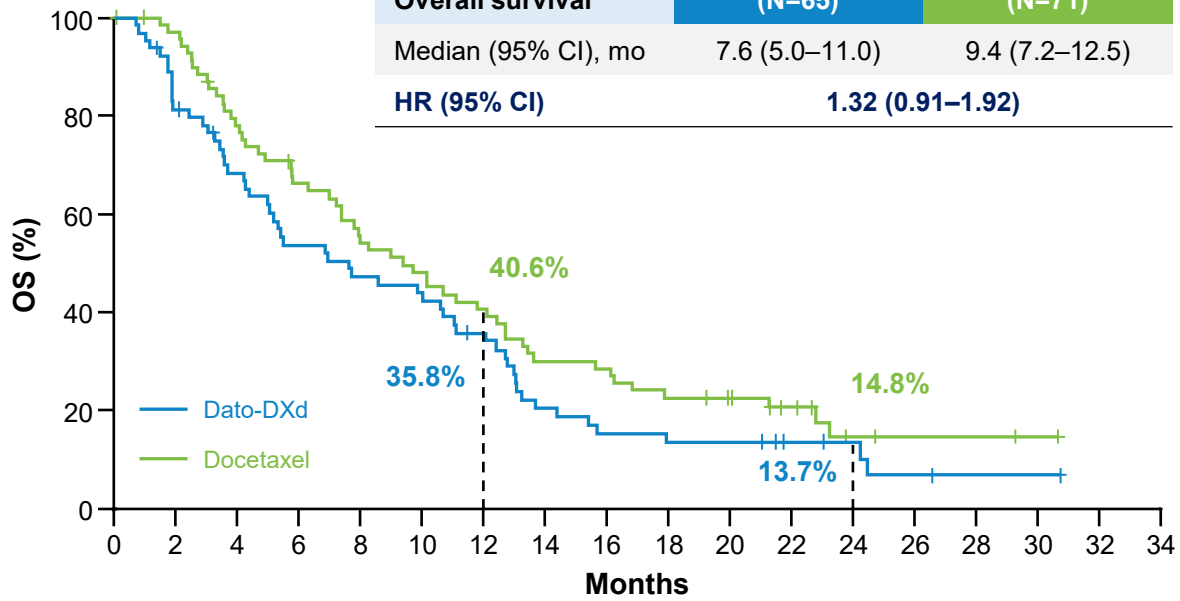


No. at risk:

Dato-DXd	234	220	200	180	161	141	130	112	97	76	63	46	31	20	15	4	1	0
Docetaxel	234	206	186	161	139	125	111	92	79	66	50	32	22	12	8	3	2	0

Squamous

Overall survival	Dato-DXd (N=65)	Docetaxel (N=71)
Median (95% CI), mo	7.6 (5.0–11.0)	9.4 (7.2–12.5)
HR (95% CI)	1.32 (0.91–1.92)	



	65	52	42	33	29	27	21	12	9	9	9	5	4	2	1	1	0	0
	71	67	53	44	36	32	27	20	19	15	13	9	4	3	3	1	0	0

- In patients with NSQ histology, 16% risk reduction for death and 2.3-month improvement in median OS with Dato-DXd
- OS improvements in the NSQ subset were seen regardless of actionable genomic alteration status[a]:
  - **Present**: 15.6 vs 9.8 months (HR [95% CI], 0.65 [0.40–1.08]); **Absent:** 13.6 vs 12.3 months (HR [95% CI], 0.89 [0.70–1.13])

Data cutoff: March 1, 2024.
[a]Based on the number of patients in the respective actionable genomic alteration subsets. Values were calculated based on patient data in the electronic case report forms.

Impact of Subsequent Anti-cancer Therapy

TROPION-Lung01

- **Sensitivity analyses** in the NSQ patient population found **no meaningful impact** on OS by:
  - Removing the effect of subsequent use of docetaxel in the Dato-DXd arm after failure of therapy
  - Removing the effect of all post-treatment anti-cancer therapies in both arms

NSQ population	Dato-DXd (N=234)	Docetaxel (N=234)
Patients receiving any post-treatment anti-cancer therapy, n (%)	125 (53.4)	132 (56.4)
Median OS (95% CI), months	14.6 (12.4–16.0)	12.3 (10.7–14.0)
HR	0.84 (0.68–1.05)	
Sensitivity analysis[a]: Docetaxel in Dato-DXd arm		
Median OS (95% CI), months	14.8 (12.1–16.9)	12.3 (10.7–14.0)
HR	0.84 (0.66–1.07)	
Sensitivity analysis[a]: All post-treatment anti-cancer therapies in both arms		
Median OS (95% CI), months	12.1 (7.5–17.3)	9.6 (7.5–13.0)
HR	0.79 (0.54–1.15)	

Data cutoff: March 1, 2024.
[a]Analysis was performed using inverse-probability-of-censoring weighting.

Safety Summary: All Treated Patients

TROPION-Lung01

TRAEs, n (%)	Dato-DXd N=297	Docetaxel N=290
Any	260 (88)	252 (87)
Grade ≥3	76 (26)	122 (42)
Associated with:		
Dose reduction	60 (20)	86 (30)
Treatment discontinuation	24 (8)	35 (12)
Death[a]	3 (1)	2 (<1)
Serious	33 (11)	37 (13)
Grade ≥3	28 (9)	34 (12)

- Compared with the prior PFS data cutoff, with an additional ~11 months follow-up:
  - Overall safety profile was consistent
  - No late-onset toxicities were observed
- Fewer grade ≥3 TRAEs were observed with Dato-DXd compared with docetaxel
- Fewer TRAEs leading to dose reductions or discontinuations were seen with Dato-DXd compared with docetaxel

The median treatment durations for Dato-DXd and docetaxel were 4.2 and 2.8 months, respectively

Data cutoff: March 1, 2024.
[a]Two cases of ILD/pneumonitis and one of sepsis (Dato-DXd), and one case of ILD/pneumonitis and one of septic shock (docetaxel).
ILD, interstitial lung disease; TRAE, treatment-related adverse event.

TRAEs ≥15% and Adjudicated Drug-Related ILD

TROPION-Lung01

TRAEs,[a] n (%)	Dato-DXd (N=297)		Docetaxel (N=290)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Stomatitis	141 (47)[b]	20 (7)	45 (16)	3 (1)
Nausea	101 (34)	7 (2)	48 (17)	3 (1)
Alopecia	95 (32)	0	101 (35)	1 (<1)[c]
Decreased appetite	68 (23)	1 (<1)	46 (16)	1 (<1)
Asthenia	56 (19)	8 (3)	56 (19)	5 (2)
Anemia[d]	44 (15)	12 (4)	60 (21)	12 (4)
Diarrhea	30 (10)	1 (<1)	55 (19)	4 (1)
Neutropenia[e]	14 (5)	2 (1)	76 (26)	68 (23)
Leukopenia[f]	9 (3)	0	45 (16)	38 (13)
Adjudicated drug-related ILD or pneumonitis	26 (9)[g]	11 (4)	12 (4)	4 (1)

- Stomatitis events, the most common TRAE with Dato-DXd, were primarily grade 1 (23%) or grade 2 (18%)
- Hematologic toxicities, including neutropenia and febrile neutropenia[h], were more common with docetaxel
- No new adjudicated drug-related ILD events or deaths occurred since the PFS database lock
- Similar safety profiles were seen for the full safety analysis set and the NSQ subgroup

Data cutoff: March 1, 2024.
[a]Occurring in ≥15% of patients in either treatment group, plus all events of adjudicated drug-related ILD or pneumonitis. [b]Due to rounding, summed rates may not reflect total percentage of TRAEs. [c]Includes an event incorrectly reported as grade 3. [d]Grouped preferred terms of anemia, hemoglobin decreased, and red blood cell count decreased. [e]Grouped preferred terms of neutropenia and neutrophil count decreased. [f]Grouped preferred terms of leukopenia and white blood cell count decreased. [g]Includes one patient in the Dato-DXd group who experienced a grade 2 event that was adjudicated to be drug-related ILD by the adjudication committee. The investigator attributed the event to disease progression and removed the patient from the clinical database. [h]0.7% vs 7.2% for Dato-DXd and docetaxel, respectively.

Conclusions

TROPION-Lung01

- TROPION-Lung01 **met its dual primary endpoint of PFS** with a statistically significant improvement for Dato-DXd over docetaxel in the overall population
- The dual primary endpoint of **OS showed a numerical improvement** but **was not statistically significant**
- Consistent benefit seen with Dato-DXd across all efficacy endpoints in patients with **NSQ histology**
- The tolerability profile remains manageable and **no new safety signals** were identified
- TROP2 normalized membrane ratio as measured by quantitative continuous scoring has been shown to predict clinical response to Dato-DXd in an exploratory TROPION-Lung01 analysis[1]

The results of TROPION-Lung01 support the use of Dato-DXd as a potential new therapeutic option for patients with previously treated NSQ NSCLC who are eligible for subsequent therapy

1. Garassino M, et al. Presented at WCLC 2024, San Diego, CA, USA, September 7–10, 2024 (Abstract PL02.11).

Acknowledgments

TROPION-Lung01

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2024 ASCO ANNUAL MEETING

Can We Enhance the Benefit of Immunotherapy in Non–Small Cell Lung Cancer?

William N. William Jr., MD

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Key Takeaway Points

- Local consolidative therapy did not improve progression-free survival or overall survival of patients with NSCLCs in the largest trial conducted to date
  - we need to better understand the potential benefits (if any) of this approach in specific patients before it can be routinely recommended in clinic

- Ivonescimab (bi-specific anti-PD-1/VEGF) improved progression-free survival in patients with NSCLCs with an EGFR mutation after progression on TKIs
  - there is renewed enthusiasm (especially if the secondary endpoint of OS is met) for the strategy of dual PD-(L)1/VEGF inhibition in this setting

Abstracts

- #8506 - NRG-LU002: Randomized phase II/III trial of maintenance systemic therapy versus local consolidative therapy (LCT) plus maintenance systemic therapy for limited metastatic non-small cell lung cancer (NSCLC)

  Iyengar et al.

- #8508 - Ivonescimab combined with chemotherapy in patients with EGFR-mutant non-squamous non-small cell lung cancer who progressed on EGFR tyrosine-kinase inhibitor treatment (HARMONi-A): A randomized, double-blind, multi-center, phase 3 trial

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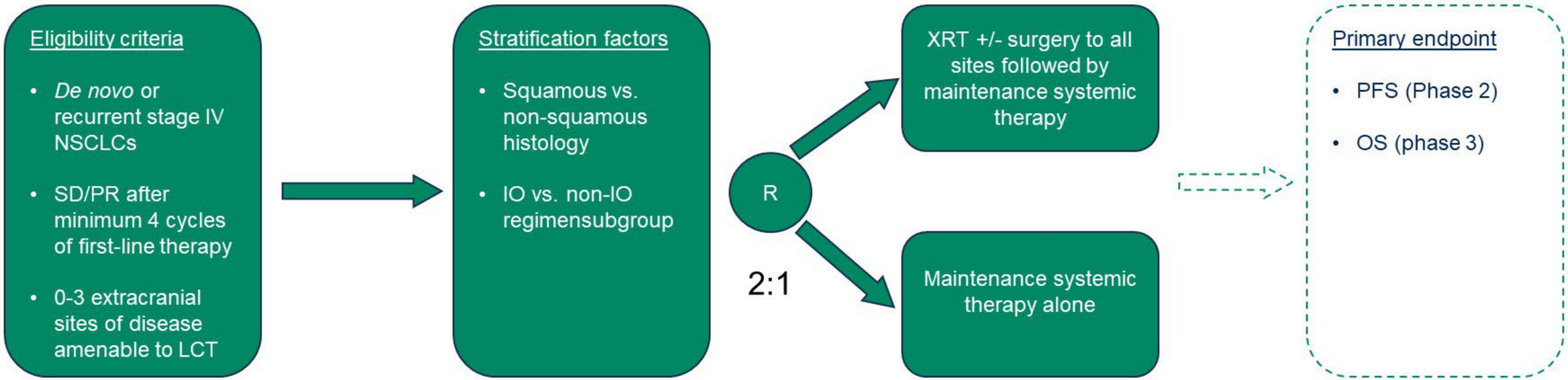
NRG-LU002: Clinical Trial Design and Features

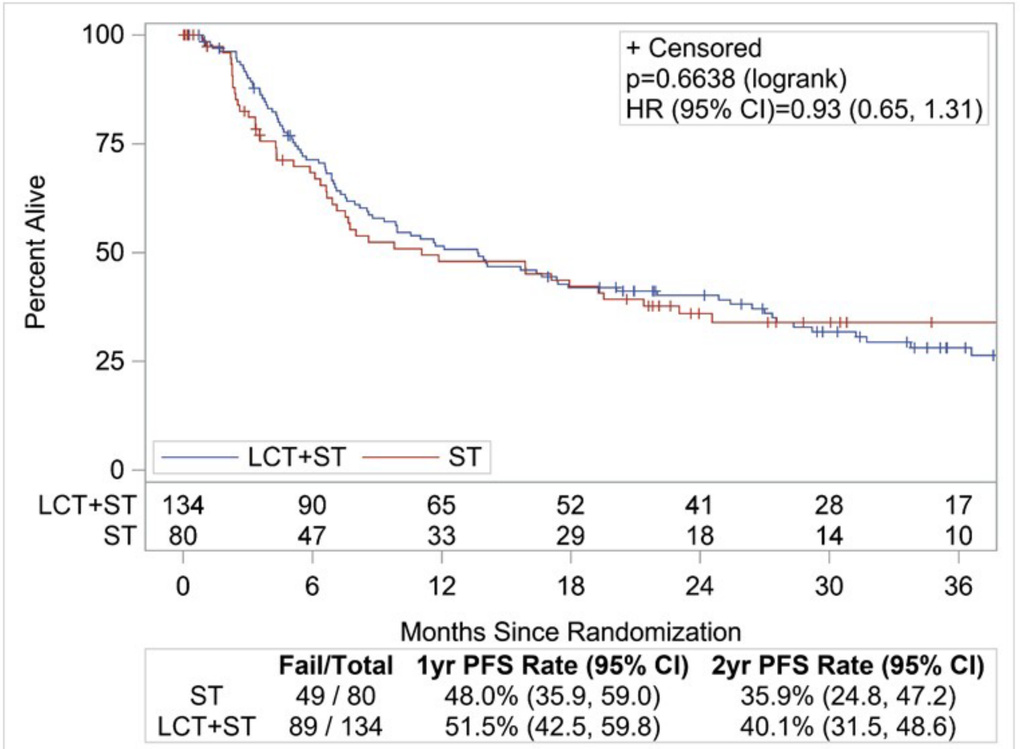


Key features

- 91% patients received immunotherapy-based systemic treatment
- 85% patients had 1-2 lesions after 1st line Tx
- **Patients had up to 25 lesions at baseline**
- XRT to primary tumor in 31% patients only
- **No subgroup analysis yet (clinical factors or biomarkers)**

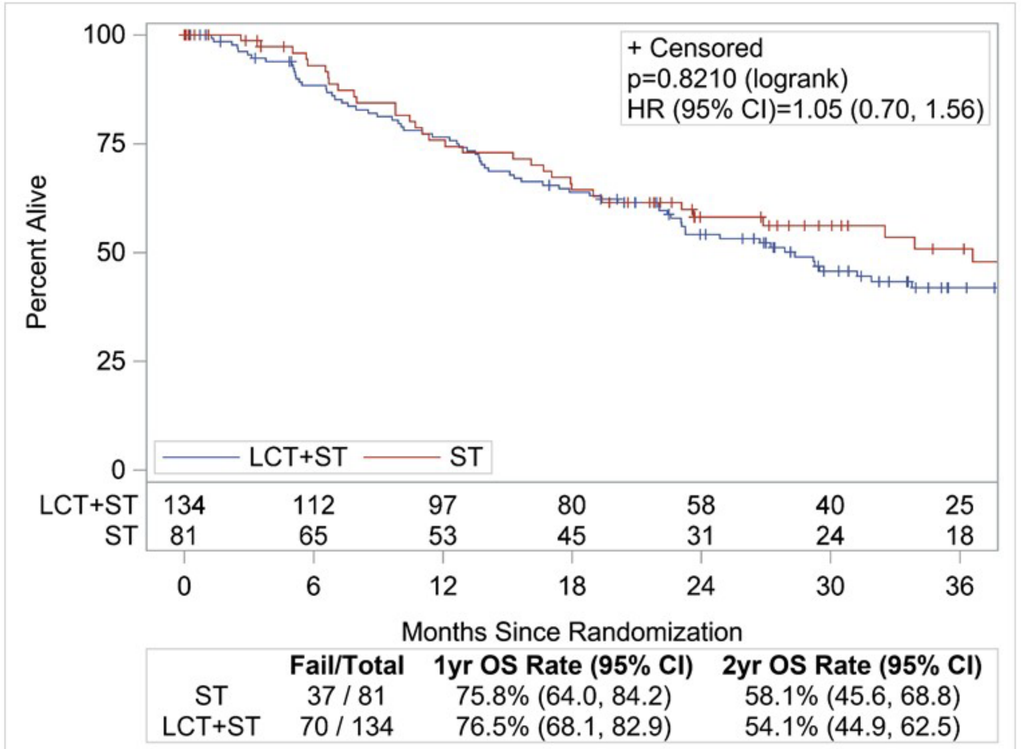
NRG-LU002: Key Results

Progression-free survival



	Fail/Total	1yr PFS Rate (95% CI)	2yr PFS Rate (95% CI)
ST	49 / 80	48.0% (35.9, 59.0)	35.9% (24.8, 47.2)
LCT+ST	89 / 134	51.5% (42.5, 59.8)	40.1% (31.5, 48.6)

Overall survival



	Fail/Total	1yr OS Rate (95% CI)	2yr OS Rate (95% CI)
ST	37 / 81	75.8% (64.0, 84.2)	58.1% (45.6, 68.8)
LCT+ST	70 / 134	76.5% (68.1, 82.9)	54.1% (44.9, 62.5)

- None of the HRs were statistically significant, although there was a trend towards a delay in in-filed recurrences and new lesion development in the LCT arm
- More grade 2+ toxicities (84% vs 73%) and grade 3+ pneumonitis (10% vs 1%) in LCT arm

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NRG-LU002: In Perspective

	Gomez et al.	Iyengar et al.	Palma et al.	NRG-LU002
Max. number of lesions after induction therapy	3 + primary tumor	6 (including primary tumor)	5 + controlled primary tumor	3
Sample size	49	29	99 (18 lung)	215
ORR to first-line therapy	37%	NA	NA	33%
PFS – no LCT median (months)	4.4[1]	3.5	5.4[1]	~12
PFS – LCT median (months)	14.2[1]	9.7	11.6[1]	~12
PFS HR (CI)	0.35 (0.18-0.66)[2]	0.30 (0.11-0.82)	0.48 (0.31-0.76)[1]	0.93 (0.65-1.31)
OS – no LCT median (months)	17	17	28	NA
OS – LCT median (months)	41.2	not reached	50	NA
OS HR (95% CI)	NA	NA	0.47 (0.27-081)	1.05 (0.7-1.56)

[1]Based on the long-term follow-up report. [2]Based on the primary report

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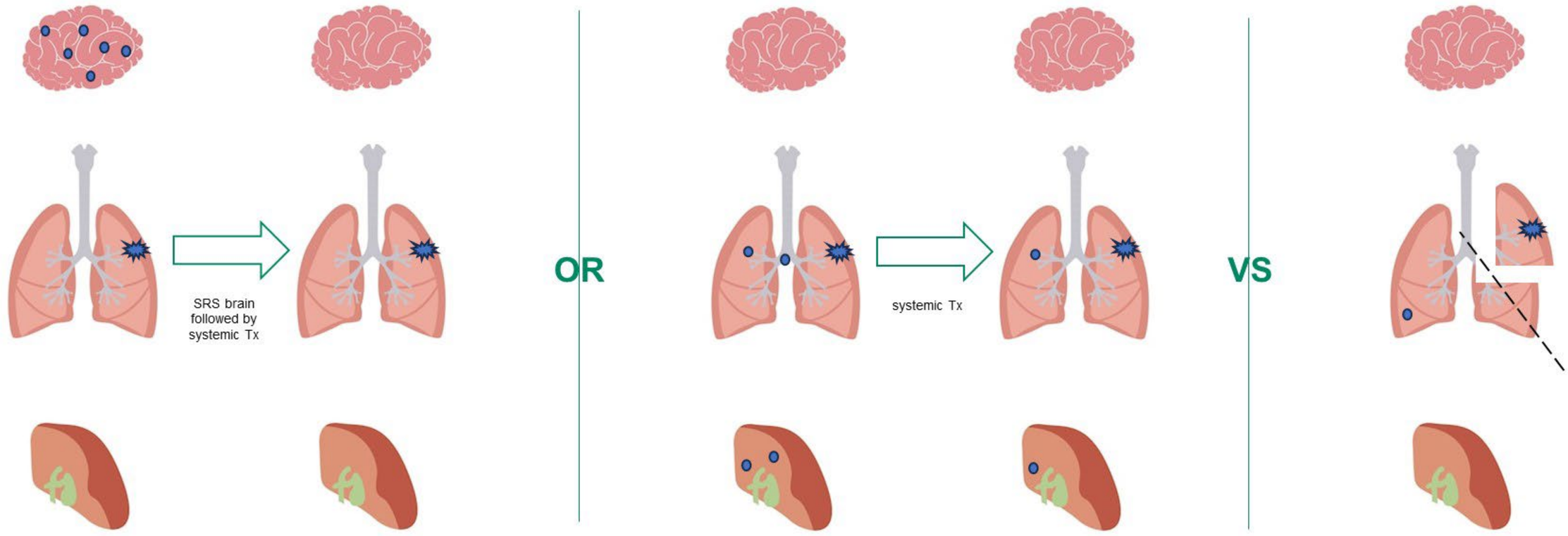
Lancet Oncol. 2016 Dec;17(12):1672-1682; J Clin Oncol. 2019 Jun 20;37(18):1558-1565; JAMA Oncol. 2018 Jan 11;4(1):e173501; J Clin Oncol. 2020 Sep 1;38(25):2830-2838.

NRG-LU002: Why Was PFS Not Improved?

- Many patients with less favorable disease for LCT?



NRG-LU002: Why Was PFS Not Improved?

- Many patients with less favorable disease for LCT?
- Did the long-term immunotherapy benefits wash away the XRT benefits?
- Were there imbalances in treatment arms?
  - Less patients in the LCT arm received maintenance therapy (93% vs 87%)
  - More patients with favorable immunotherapy biomarkers (e.g., high PD-L1) assigned to the control arm?
- Bad luck?

NRG-LU002: Conclusions

- LCT cannot be considered a standard of care for patients with oligometastatic NSCLCs with no disease progression after first-line immunotherapy-based systemic treatment
- Even in selected patients, the 10% incidence of grade 3+ treatment-related pneumonitis warrants careful considerations, in the setting of non-statistically significant differences in PFS, OS, time to in-filed failure, and time to new lesion development
- Given the robust background data and rationale that led to this trial, this strategy should continue to be evaluated in clinical studies with improved, clinical and/or (possibly) biomarker-based eligibility criteria

Abstracts

- #8506 - NRG-LU002: Randomized phase II/III trial of maintenance systemic therapy versus local consolidative therapy (LCT) plus maintenance systemic therapy for limited metastatic non-small cell lung cancer (NSCLC)

  Iyengar et al.

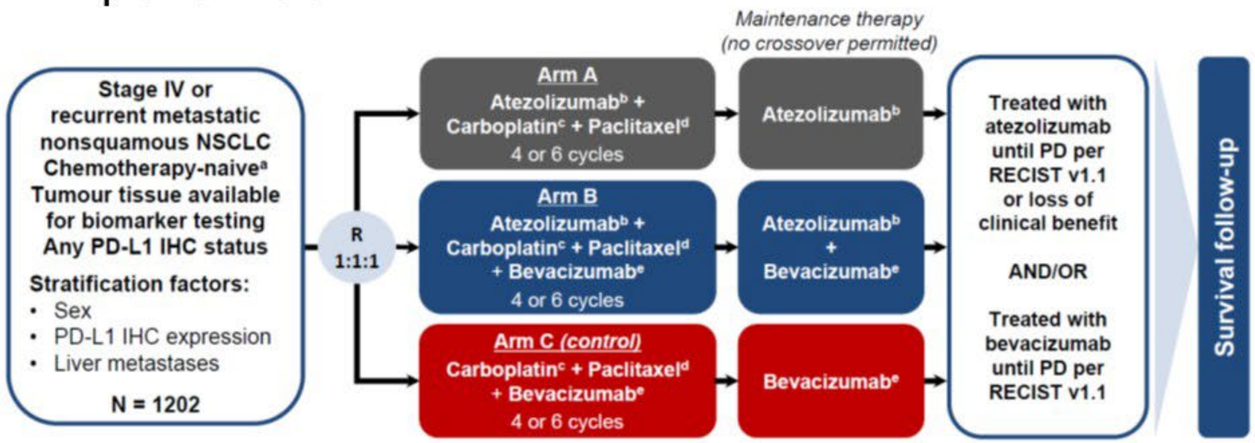
- #8508 - Ivonescimab combined with chemotherapy in patients with EGFR-mutant non-squamous non-small cell lung cancer who progressed on EGFR tyrosine-kinase inhibitor treatment (HARMONi-A): A randomized, double-blind, multi-center, phase 3 trial

  Zhang et al.

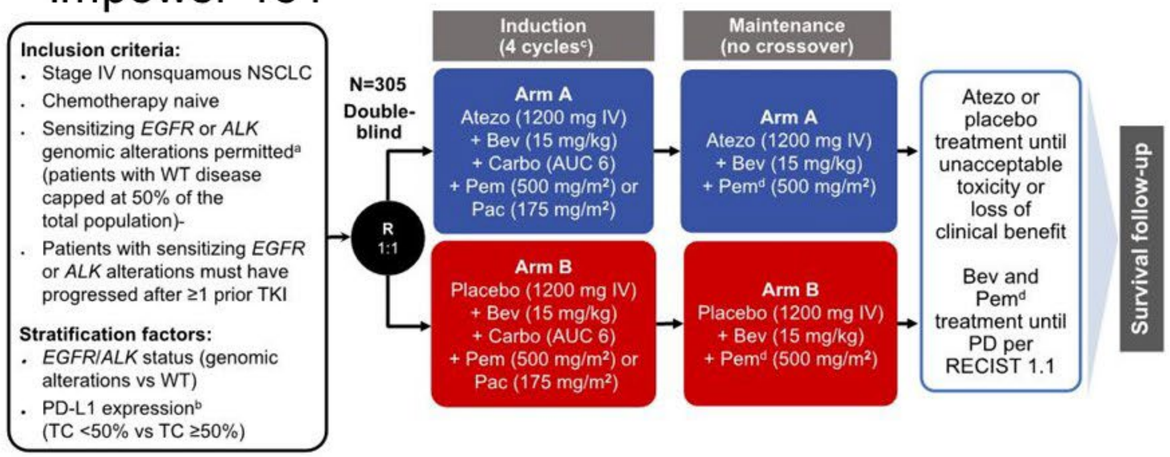
Chemo plus VEGF and PD-(L)1 Inhibition in EGFR+ NSCLC

Control arm with anti-VEGF

Impower 150

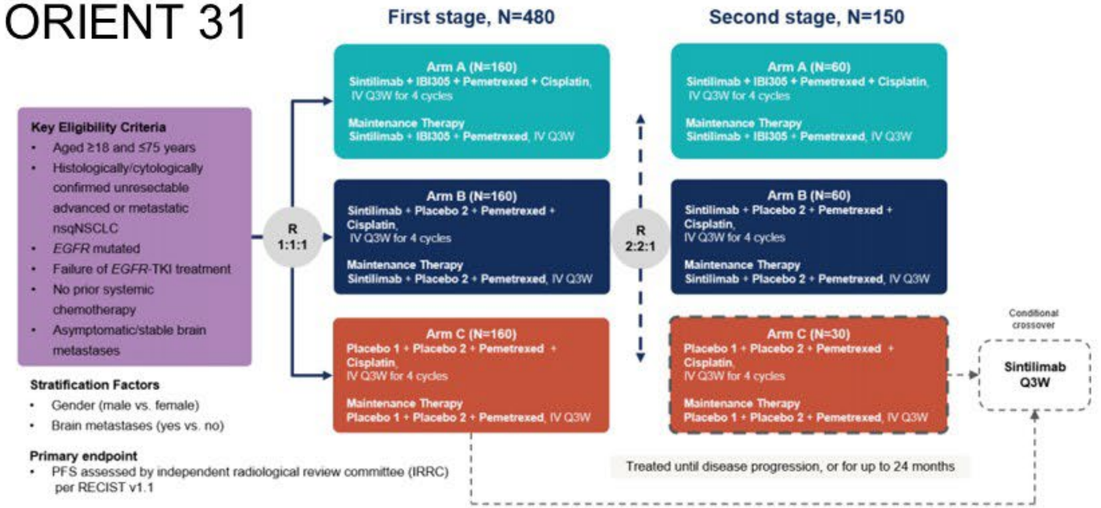


Impower 151

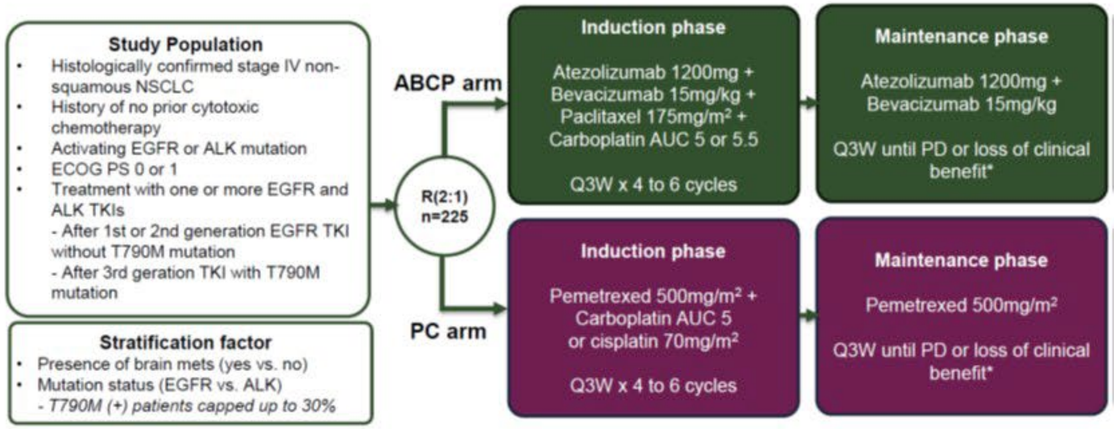


Control arm without anti-VEGF

ORIENT 31



ATTLAS



PRESENTED BY: William N. William Jr., MD

Lancet Respir Med. 2019 May;7(5):387-401; ; J Thorac Oncol. 2023 Nov 18(11 suppl):S64-65; J Thorac Oncol. 2022 Feb;17(2):309-323; J Clin Oncol. 2024 Apr 10;42(11):1241-1251.

HARMONi-A: Clinical Trial Design and Features

Key Eligibility Criteria

- nsq-NSCLC (Stage IIIB/C ineligible for surgery or local therapy and IV)
- EGFR sensitive mutation positive
- ECOG PS 0 or1
- Regardless PD-L1 expression

Stratification Factors:

- Exposure to 3rd EGFR-TKI before (yes vs. no)
- Brain metastases (yes vs. no)

R (1:1)

Ivonescimab 20mg/kg + Pemetrexed 500 mg/m^2 Carboplatin AUC5 Q3W for 4 cycles → Ivonescimab 20mg/kg Q3W + Pemetrexed 500 mg/m^2 Q3W

Placebo + Pemetrexed 500 mg/m^2 Carboplatin AUC5 Q3W for 4 cycles → Placebo Q3W + Pemetrexed 500 mg/m^2 Q3W

Treatment until:

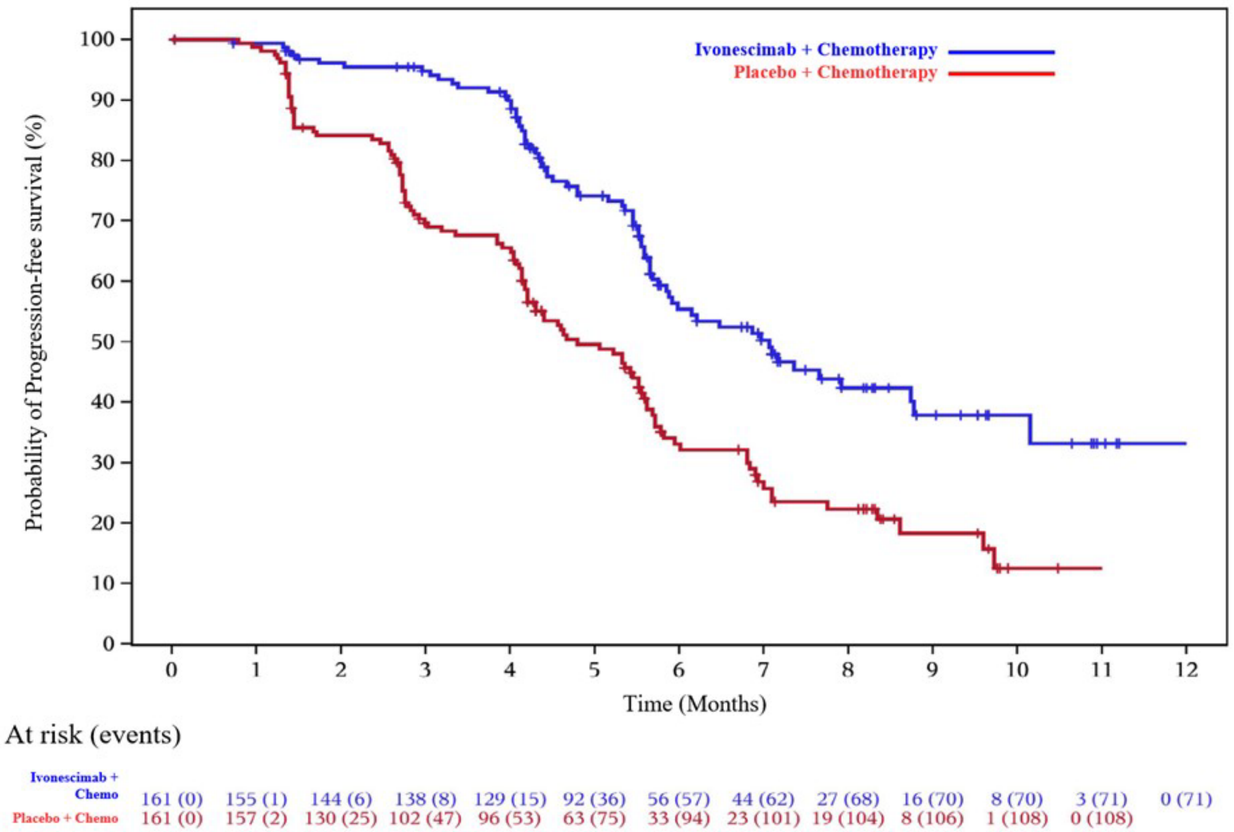
- Intolerable toxicity
- No clinical benefit
- Initiation of new anti-tumor therapy

Key features

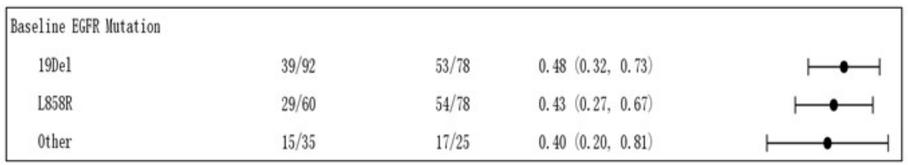
- Multi-center, placebo-controlled study
- Brain mets allowed (present in 22% of pts)
- 19% non-exon-19 del / L858R EGFR mutations (slightly higher in experimental arm)
- 86% exposed to 3rd Gen TKI (only 33% 3rd Gen TKI upfront - pts switched to 3rd Gen TKI irrespective of T790M)
- **No anti-VEGF in the control arm**
- No biomarker data yet (e.g., PD-L1)

PRESENTED BY: William N. William Jr., MD

HARMONi-A : Key Results



	Ivonescimab + Chemotherapy	Placebo + Chemotherapy
Events, n(%)	71 (44.1)	108 (67.1)
Median PFS, month (95% CI)	**7.1** (5.9, 8.7)	**4.8** (4.2, 5.6)
HR (95% CI) P-value	**0.46 (0.34, 0.62) p < 0.001**	
6-month rate (95% CI)	55.4 (46.1, 63.7)	33.1 (25.0, 41.3)
9-month rate (95% CI)	37.9 (27.6, 48.2)	18.3 (11.0, 27.1)



- Study met the primary endpoint: 54% reduction in the risk of disease progression or death – statistically significant and clinically relevant
- Low rate of grade 3+ VEGF- or PD-1-inhibitor-related AEs of special interest

PRESENTED BY: William N. William Jr., MD

HARMONi-A : In Perspective – Select EGFR+ Studies

	IMpower 150 N=124[1]	IMpower 151 N=162[1,2]	Orient-31 N=474[1]	ATTLAS N=215[1,2]	HARMONi-A N=322[1]
PFS – chemo[3] median (months)	6.9	8.3	4.3	5.6	4.8
PFS – chemo plus anti-PD-(L)1 median (months)	6.9	-	5.5	-	-
PFS – chemo plus anti-PD-(L)1 plus anti-VEGF median (months) HR (95% CI) [vs. chemo[3]]	10.2 0.61 (0.36-1.03)	8.5 0.86 (0.61-1.21)	7.2 0.51 (0.39-0.67)	8.5 0.62 (0.45-0.86)	7.1 0.46 (0.34-0.62)
ORR – chemo[3]	41.9%	-	29.4%	41.9%	35.4%
ORR – chemo plus anti-PD-(L)1	35.6%	-	34.8%	-	-
ORR – chemo plus anti-PD-(L)1 plus anti-VEGF	70.6%	-	48.1%	69.5%	50.6%
OS HR (95% CI) [chemo plus anti-PD-(L)1 plus anti-VEGF vs. chemo[3]]	0.91 (0.53–1.59)	-	0.98 (0.72-1.34)	1.01 (0.69-1.46)	0.72 (0.48-1.09)

[1]Includes patients with EGFR mutations other than exon 19 deletions and L858R mutations. [2]Includes patients with ALK translocations. [3]In IMpower 150 and IMpower 151, chemo denotes chemotherapy plus bevacizumab

Lancet Respir Med. 2019 May;7(5):387-401; ; J Thorac Oncol. 2023 Nov 18(11 suppl):S64-65; J Thorac Oncol. 2022 Feb;17(2):309-323; J Clin Oncol. 2024 Apr 10;42(11):1241-1251.

HARMONi-A : In Perspective – Alternative Options

- Chemotherapy plus amivantamab (MARIPOSA-2 study)
  - PFS HR 0.48 (95% CI 0.36-0.64)
  - Response rates 64%
  - OS HR 0.77 (95% CI 0.49-1.21)
  - Intracranial activity
  - Attention to toxicities

- MET-targeted strategies
  - TKIs and ADCs with promising response rates and PFS
  - Address specific mechanism of resistance
  - Could be used before chemo-based approaches?

HARMONi-A : In Perspective – Impact of First-Line Tx

Osimertinib monotherapy (FLAURA)	Amivantamab + Lazertinib (MARIPOSA)	Osimertinib + chemo (FLAURA-2)
HARMONi-A reasonable option	HARMONi-A possibly a reasonable option	Less enthusiastic about HARMONi-A (unless long platinum-free interval?)

HARMONi-A: Conclusions

- HARMONi-A met its primary endpoint of improving PFS and the regimen could become another standard-of-care treatment option for EGFR+ NSCLCs progressing on a TKI (it already is in China)
- Unclear if the benefits seen are related to VEGF inhibition or the combination of VEGF and PD-1 inhibition
- Unclear if this strategy is superior to chemo + bevacizumab + atezolizumab
- Overall survival results eagerly awaited
- Biomarker results are even more eagerly awaited – we should strive to continue to develop precision medicine

Key Takeaway Points

- Local consolidative therapy did not improve progression-free survival or overall survival of patients with NSCLCs in the largest trial conducted to date
  - we need to better understand the potential benefits (if any) of this approach in specific patients before it can be routinely recommended in clinic

- Ivonescimab (bi-specific anti-PD-1/VEGF) improved progression-free survival in patients with NSCLCs with an EGFR mutation after progression on TKIs
  - there is renewed enthusiasm (especially if the secondary endpoint of OS is met) for the strategy of dual PD-(L)1/VEGF inhibition in this setting

Normalized Membrane Ratio of TROP2 by Quantitative Continuous Scoring is Predictive of Clinical Outcomes in TROPION-Lung01

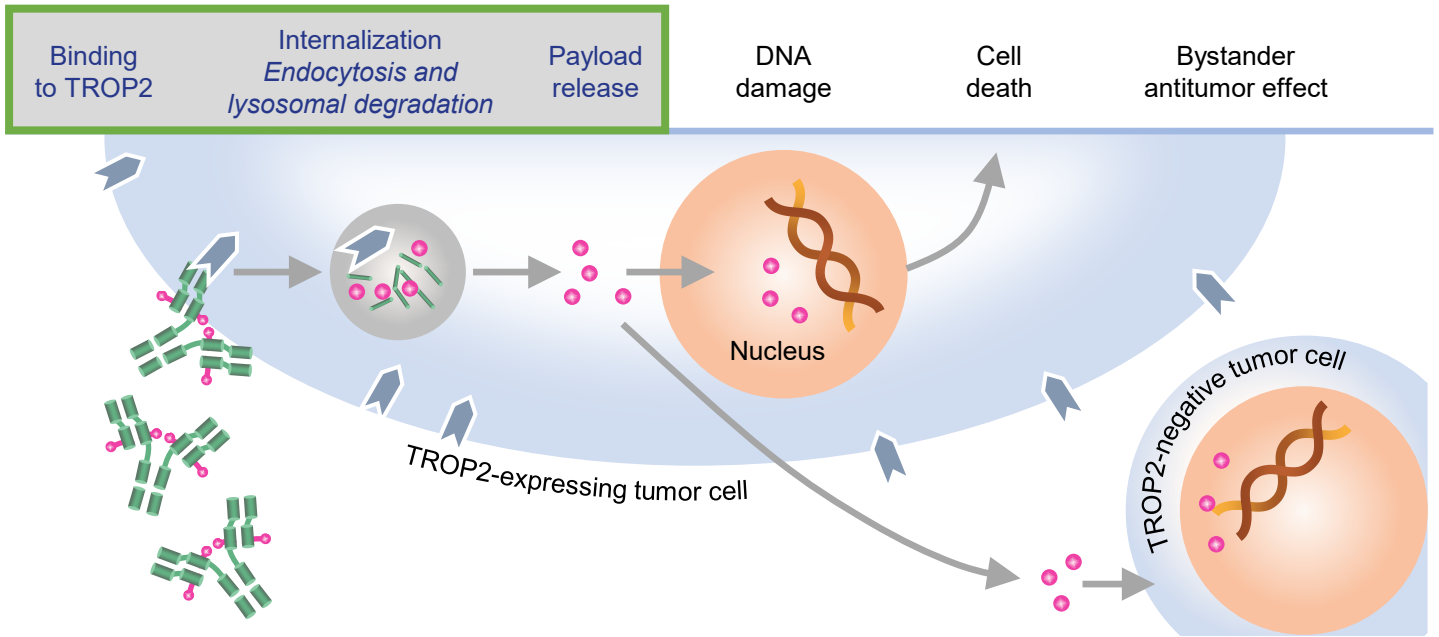
Marina Chiara Garassino,[1] Jacob Sands,[2] Luis Paz-Ares,[3] Aaron Lisberg,[4] Melissa Johnson,[5] Maurice Pérol,[6] Danielle Carroll,[7] Ansh Kapil,[8] Vincent Haddad,[7] Deise Uema,[9] Hadassah Sade,[8] Myung-Ju Ahn,[10]

[1]The University of Chicago, Chicago, IL, USA; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]Universidad Complutense & CiberOnc, Hospital Universitario 12 de Octubre, Madrid, Spain; [4]Jonsson Comprehensive Cancer Center at UCLA, Los Angeles, CA, USA; [5]Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN, USA; [6]Léon-Bérard Cancer Center, Lyon, France; [7]AstraZeneca, Cambridge, UK; [8]AstraZeneca, Munich, Germany; [9]Daiichi Sankyo, Basking Ridge, NJ, USA; [10]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Background

- Datopotamab deruxtecan (Dato-DXd) is a TROP2-directed ADC with a plasma-stable linker[1,2]
- Dato-DXd must bind to membrane TROP2 and be internalized to release the cytotoxic payload[2]
- Dato-DXd has demonstrated statistically significant PFS improvement vs docetaxel in patients with advanced/metastatic NSCLC[3]
- Conventional IHC scoring has not predicted response to TROP2-directed ADCs in patients with NSCLC[4,5]
- Initial biomarker discovery was conducted on samples from patients with NSCLC in the TROPION-PanTumor01 study[6]

Dato-DXd mechanism of action[2]



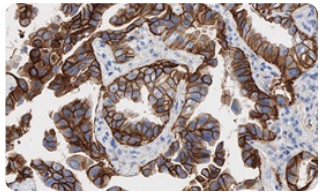
We hypothesized that a more precise and quantitative assessment of TROP2 expression **on the cell membrane and in the cytoplasm** may predict efficacy of Dato-DXd in patients with NSCLC

1. Okajima D, et al. Mol Cancer Ther 2021;20:2329–40; 2. Dent R, et al. Future Oncol 2023;19:2349–59;
3. Ahn MJ, et al. Oral presentation at ESMO 2023 (Abstract LBA12); 4. Shimizu T, et al. J Clin Oncol 2023;41:4678–87;
5. Heist RS, et al. J Clin Oncol 2017;35:2790–7; 6. Spitzmueller A, et al, 2023; International Patent Application No. PCT/IB2023/052428.
ADC, antibody-drug conjugate; Dato-DXd, datopotamab deruxtecan; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; PFS, progression-free survival; TROP2, trophoblast cell-surface antigen 2.

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

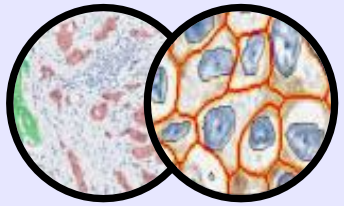
QCS is a novel, fully-supervised computational pathology approach that precisely quantifies and locates targets like TROP2

1 IHC with TROP2 Assay

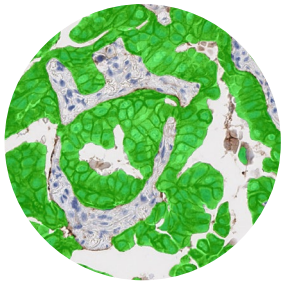


2 Whole Slide Imaging

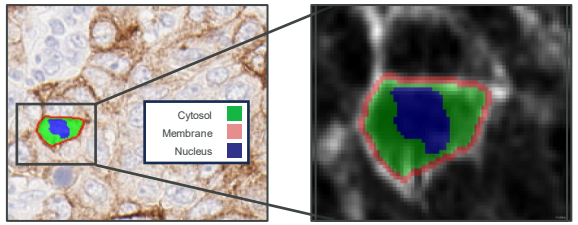
3 Automated Image Analysis (QCS)



Differentiates tumor from non-tumor



Measures OD in each tumor cell



Membrane and cytoplasm optical density (OD)

Calculates TROP2 NMR for every tumor cell

$$\frac{\text{Membrane OD}}{\text{Membrane OD + Cytoplasm OD}}$$

Lower NMR → higher cytoplasm proportion

4 Patient Biomarker Status Determination

\+ ≥75% of tumor cells with TROP2 NMR ≤0.56

\- <75% of tumor cells with TROP2 NMR ≤0.56*

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OD, optical density (a measure of staining intensity).
*Or >25% of cells with an NMR >0.56

TROPION-Lung01

Study Design (NCT04656652)[1]

Key Eligibility Criteria

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

Without AGA*
- 1 or 2 prior lines, including platinum CT and anti–PD-(L)1 mAb therapy

With AGA
- 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

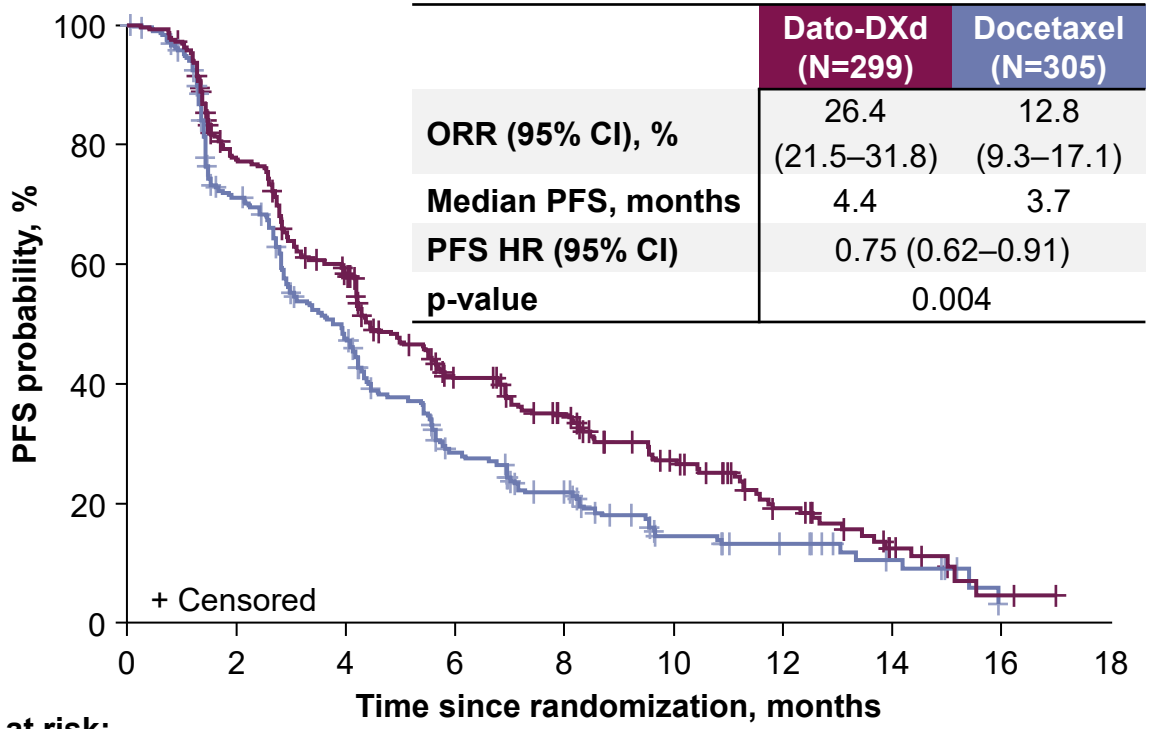
Dato-DXd
6 mg/kg q3w
N=299

Docetaxel
75 mg/m² q3w
N=305

Stratified by:
Histology†, AGA‡, anti–PD-(L)1 mAb included in most recent prior therapy, geography§

Dual Primary Endpoints: PFS by BICR; OS
Secondary Endpoints: ORR by BICR; DOR by BICR; Safety

PFS by BICR and ORR[1]



	Dato-DXd (N=299)	Docetaxel (N=305)
ORR (95% CI), %	26.4 (21.5–31.8)	12.8 (9.3–17.1)
Median PFS, months	4.4	3.7
PFS HR (95% CI)	0.75 (0.62–0.91)	
p-value	0.004	

No. at risk:

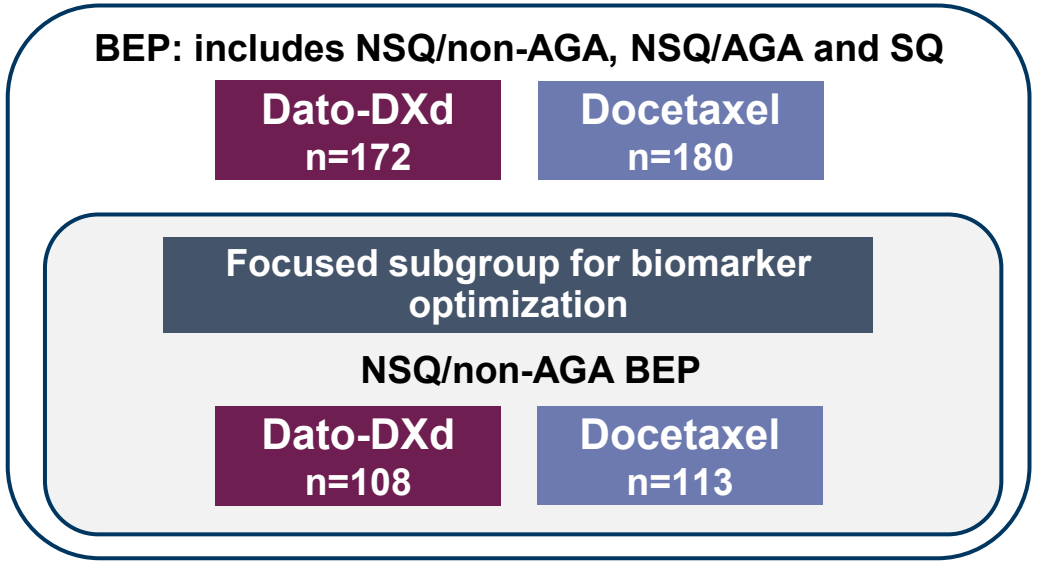
Dato-DXd	299	216	156	96	74	46	24	10	2	0
Docetaxel	305	186	120	63	42	19	14	7	0	0

1. Ahn MJ, et al. Oral presentation at ESMO 2023 (Abstract LBA12).
Enrollment period: February 19, 2021, to November 7, 2022. Data cutoff: March 29, 2023.
AGA, actionable genomic alterations; BICR, blinded independent central review; CI, confidence interval; CT, chemotherapy; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; mAb, monoclonal antibody; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed cell death (ligand) 1; q3w, every 3 weeks; R, randomized.
*Patients with *KRAS* mutations in the absence of known actionable genomic alterations are eligible; must meet prior therapy requirements for patients without actionable genomic alterations. †Squamous vs non-squamous. ‡Presence vs absence. §United States/Japan/Western Europe vs other geographic regions.

TROP2 QCS-NMR in TROPION-Lung01

Population and Methods

- Biomarker evaluable population (BEP) are those patients with available tissue samples for QCS determination
- Biomarker cut-points were optimized for PFS in NSQ/non-AGA patients from TROPION-Lung01
- Cut-points were confirmed through a robust statistical analysis plan (including bootstrapping, cross validation, and sensitivity analyses) and replication



Prevalence

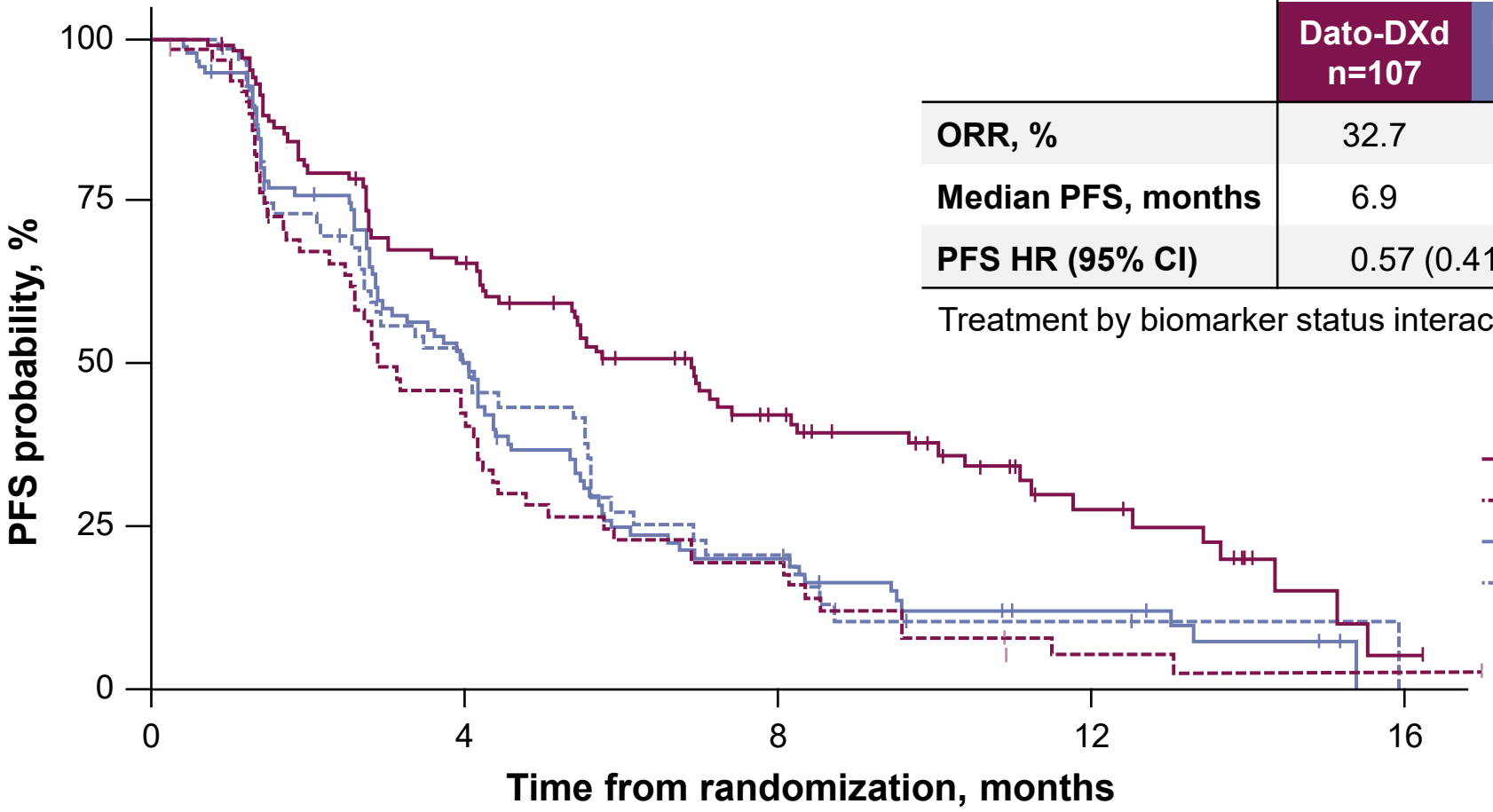
Histology subgroup	Prevalence of TROP2 QCS-NMR+, % (n)
Biomarker-evaluable population, n=352	
NSQ	66% (179/272)
NSQ/non-AGA	63% (140/221)
NSQ/AGA	76% (39/51)
SQ	44% (35/80)

NSQ, non-squamous; SQ, squamous.

Overall BEP: Efficacy by TROP2 QCS-NMR Status

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

Biomarker-evaluable population, n=352



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

Treatment by biomarker status interaction: p=0.0063

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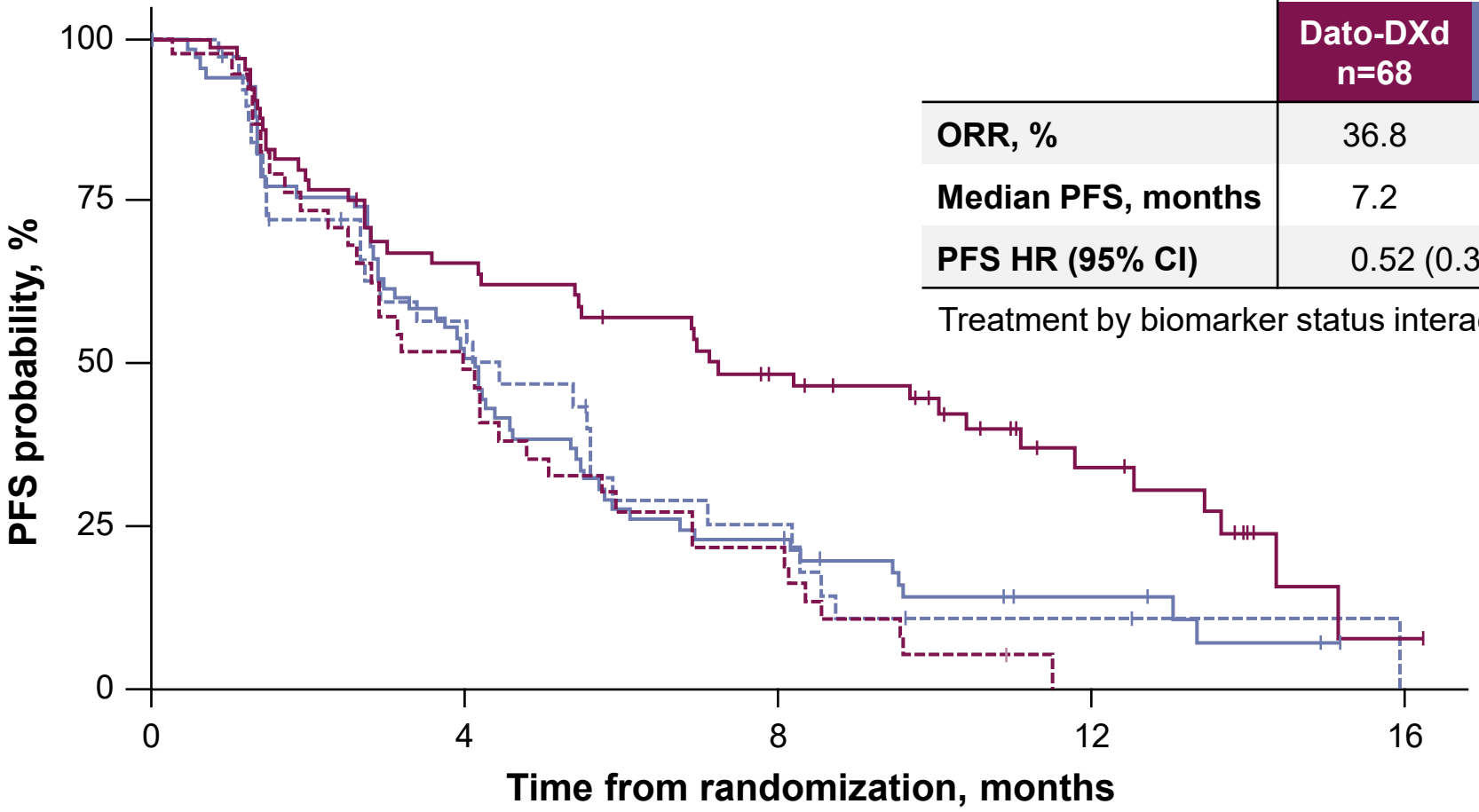
Data cutoff: March 29 2023

PFS HR (95% CI) by TROP2 QCS-NMR status (+ vs -) within treatment: Dato-DXd: 0.48 [0.33-0.69]; Docetaxel:0.97 [0.68-1.39]

NSQ/non-AGA BEP: Efficacy by TROP2 QCS-NMR Status

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

NSQ/non-AGA BEP, n=221



	TROP2 QCS-NMR+		TROP2 QCS-NMR–	
	Dato-DXd n=68	Docetaxel n=72	Dato-DXd n=40	Docetaxel n=41
ORR, %	36.8	15.3	22.5	12.2
Median PFS, months	7.2	4.1	4.0	4.4
PFS HR (95% CI)	0.52 (0.35–0.78)		1.22 (0.74–2.00)	

Treatment by biomarker status interaction: p=0.0098

Data cutoff: March 29 2023

PFS HR (95% CI) by TROP2 QCS-NMR status (+ vs -) within treatment: Dato-DXd: 0.40 [0.25-0.64]; Docetaxel:0.94 [0.60-1.49]

Safety by TROP2 QCS-NMR Status

Treatment-related adverse events (TRAEs), n (%)		Biomarker-evaluable population (n=344*)			
		TROP2 QCS-NMR+		TROP2 QCS-NMR–	
		Dato-DXd n=106	Docetaxel n=102	Dato-DXd n=65	Docetaxel n=71
Any TRAE	All grades	92 (87)	94 (92)	56 (86)	58 (82)
	Grade ≥3	31 (29)	47 (46)	14 (22)	19 (27)
Treatment-related AESIs					
Stomatitis	All grades	57 (54)	23 (23)	29 (45)	10 (14)
	Grade ≥3	7 (7)	3 (3)	2 (3)	–
Ocular surface events	All grades	27 (25)	6 (6)	7 (11)	6 (8)
	Grade ≥3	3 (3)	–	1 (2)	–
Adjudicated ILD†	All grades	8 (8)	3 (3)	4 (6)	1 (1)
	Grade ≥3	3 (3)	1 (1)	1 (2)	–

Data cutoff: March 29 2023.
*Biomarker-evaluable population in safety analysis excludes patients who were randomized but did not receive treatment.
†ILD includes events that were adjudicated as ILD and related to use of Dato-DXd or docetaxel (includes cases of potential ILD/pneumonitis based on MedDRA v26.0 for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and preferred terms of respiratory failure and acute respiratory failure).
AESIs, adverse event of special interest; ILD interstitial lung disease; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, standardized MedDRA query.

Conclusions

- TROP2 normalized membrane ratio (NMR) as measured by QCS reflects the expression of TROP2 in the membrane relative to total TROP2 (membrane and cytoplasm) and predicts outcomes in an exploratory TROPION-Lung01 analysis:
  - TROP2 QCS-NMR+ was more prevalent in patients with NSQ vs SQ histology (66% vs 44%)
  - Patients receiving Dato-DXd who were TROP2 QCS-NMR+ had a higher ORR and longer PFS compared with those who were TROP2 QCS-NMR–
  - Overall/grade 3+ adverse event rates with Dato-DXd were similar regardless of TROP2 QCS-NMR status
- Further investigation of this promising biomarker is ongoing in the first-line advanced/metastatic NSCLC trials AVANZAR (NCT05687266) and TROPION-Lung 10 (NCT06357533)

TROP2 QCS-NMR has the potential to be the first TROP2 biomarker and the first computational pathology biomarker for predicting clinical response to Dato-DXd in NSCLC

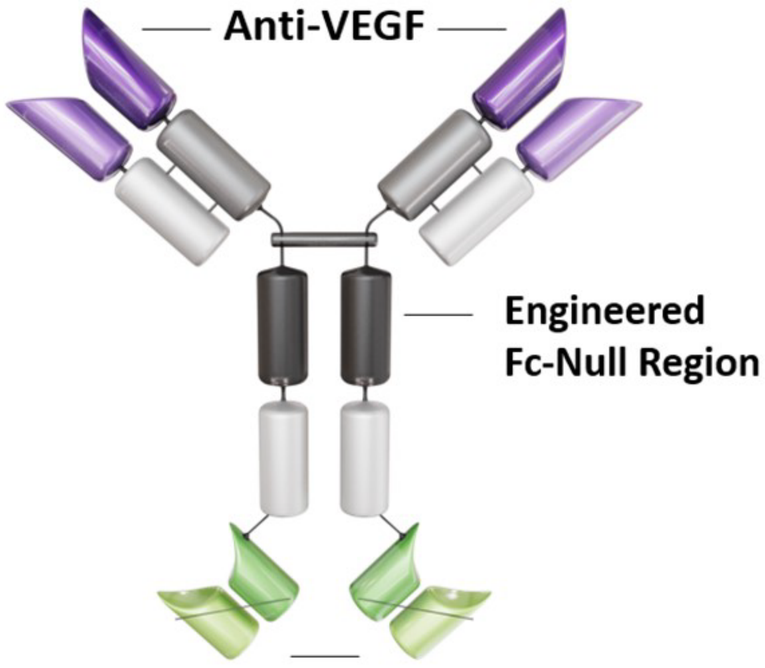
2024 ASCO ANNUAL MEETING

Ivonescimab combined with chemotherapy in patients with EGFR-mutant non-squamous non-small cell lung cancer who progressed on EGFR-TKIs treatment: a randomized, double-blind, multi-center, phase 3 trial (HARMONi-A study)

Li Zhang[1], Wenfeng Fang[1], Yuanyuan Zhao[1], Yongzhong Luo[2], Runxiang Yang[3], Yan Huang[1], Zhiyong He[4], Hui Zhao[5], Mingjun Li[6], Kai Li[7], Qibing Song[8], Xiaobo Du[9], Yulan Sun[10], Wei Li[11], Fei Xu[12], Zhiyu Wang[13], Kunning Yang[14], Yun Fan[15], Wenting Li[16], Michelle Xia[16]

[1]Sun Yat-sen University Cancer Center, Guangzhou, China; [2]Hunan Cancer Hospital, Changsha, China; [3]Yunnan Cancer Hospital, Kunming, China; [4]Fujian Provincial Tumor Hospital, Fuzhou, China; [5]The Second Hospital of Anhui Medical University, Hefei, China; [6]The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; [7]Tianjin Medical University Cancer Institute&Hospital. Tianjin, China; [8]Renmin Hospital of Wuhan University, Wuhan, China; [9]Mianyang Central Hospital, Mianyang, China; [10]Shandong Cancer Prevention and Treatment Institute, Jinan, China; [11]The First Affiliated Hospital of Bengbu Medical University, Bengbu, China; [12]The First Affiliated Hospital of Nanchang University, Nanchang, China; [13]The Fourth Hospital of Hebei Medical University, Shijiazhuang, China; [14]Weifang No.2 People's Hospital, Weifang, China; [15]Zhejiang Cancer Hospital, Hangzhou, China; [16]Akeso Biopharma, Inc., Zhongshan, China

Background



- For patients with EGFR-mutant NSCLC, upfront treatment with tyrosine kinase inhibitors is standard. However, drug resistance remains a challenge, and an effective therapy after progression is needed.
- Ivonescimab (AK112/SMT112) is an anti-PD-1/VEGF bispecific antibody displaying cooperative binding characteristics.
- Phase II clinical studies have shown potential efficacy of Ivonescimab plus chemotherapy in NSCLC patients with EGFR mutations who progressed on prior EGFR-TKIs therapies[1-2].
- This phase 3 study aimed to evaluate and confirm the efficacy and safety of ivonescimab combined with chemotherapy compared to chemotherapy alone in this population (NCT05184712).

1. L Zhang et al: ASCO 2023; 2. YY Zhao et al: eClinicalMedicine 2023;62: 102106.

HARMONi-A Study Design

Key Eligibility Criteria

- nsq-NSCLC (Stage IIIB/C ineligible for surgery or local therapy and IV)
- EGFR sensitive mutation positive
- ECOG PS 0 or1
- Regardless PD-L1 expression

Stratification Factors:

- Exposure to 3rd EGFR-TKI before (yes vs. no)
- Brain metastases (yes vs. no)

R (1:1)

Ivonescimab
20mg/kg
+
Pemetrexed 500 mg/m^2
Carboplatin AUC5
Q3W for 4 cycles

Ivonescimab
20mg/kg Q3W
+
Pemetrexed 500 mg/m^2 Q3W

Placebo
+
Pemetrexed 500 mg/m^2
Carboplatin AUC5
Q3W for 4 cycles

Placebo
Q3W
+
Pemetrexed 500 mg/m^2 Q3W

Treatment until:

- Intolerable toxicity
- No clinical benefit
- Initiation of new anti-tumor therapy

Up to 24 months

Endpoints

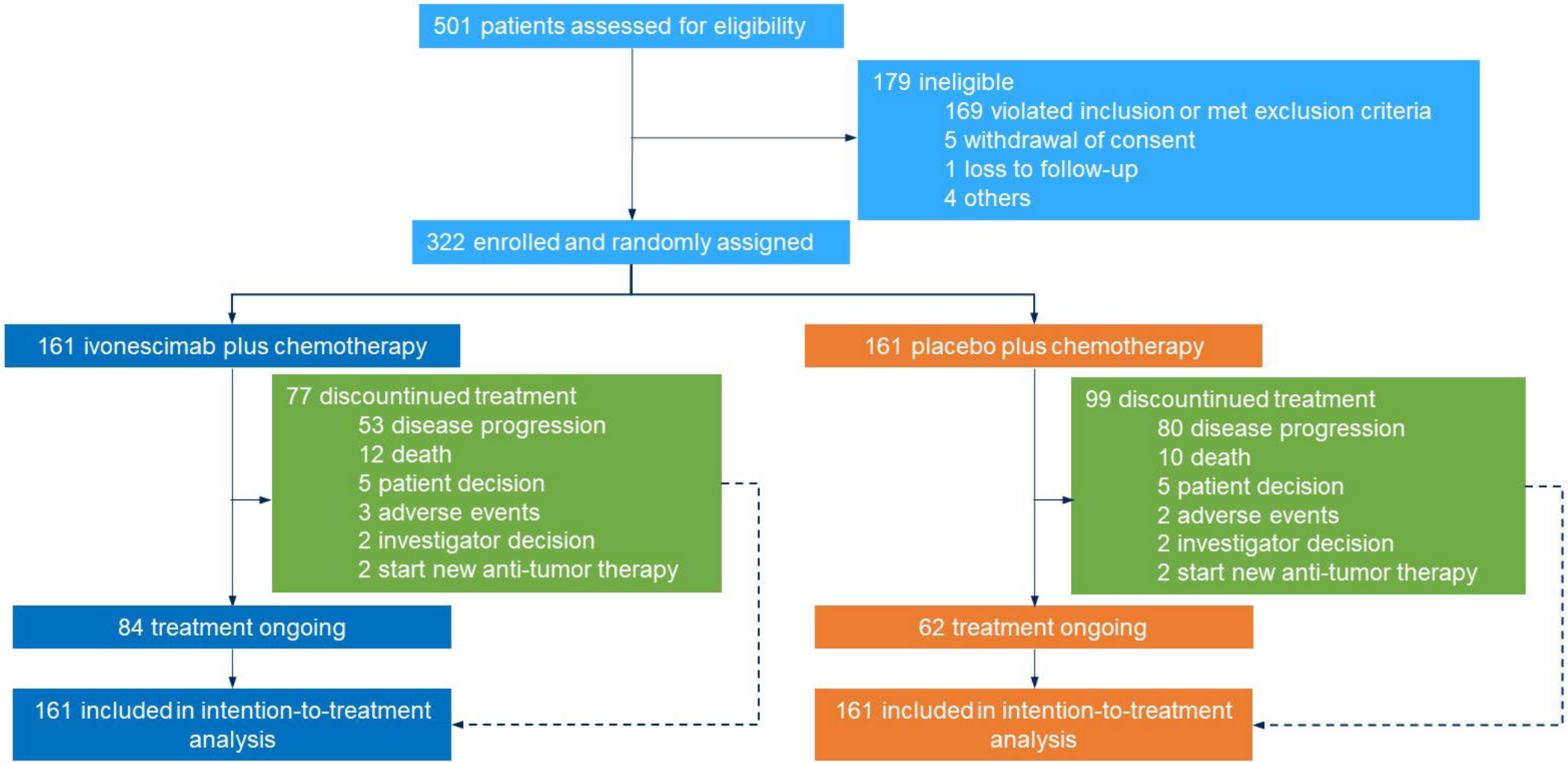
- Primary: Progression-free survival by independent radiologic review committee (IRRC)
- Secondary: Overall survival, Response rate, Duration of response, Time to response and Safety

ClinicalTrials.gov, NCT05184712; NSCLC, non-small cell lung carcinoma; EGFR, epidermal growth factor receptor; ECOG, eastern copperative oncology group; TKI, tyrosine-kinase inhibitor; Q3W, every 3 weeks.

Statistical Analyses

- **Estimated sample size:**
  - 320 patients (assuming HR=0.65, overall α=0.025 [one-side], power=89% for PFS)
- **Analysis methods:**
  - A stratified log-rank test was used to compare PFS between treatment groups
  - PFS was estimated using the Kaplan-Meier method and HR was through a stratified Cox regression model
- **All data (except OS) are based on the clinical data cutoff of March 2023, at which point the median follow-up duration was 7.89 months.**

Disposition of Study Treatment

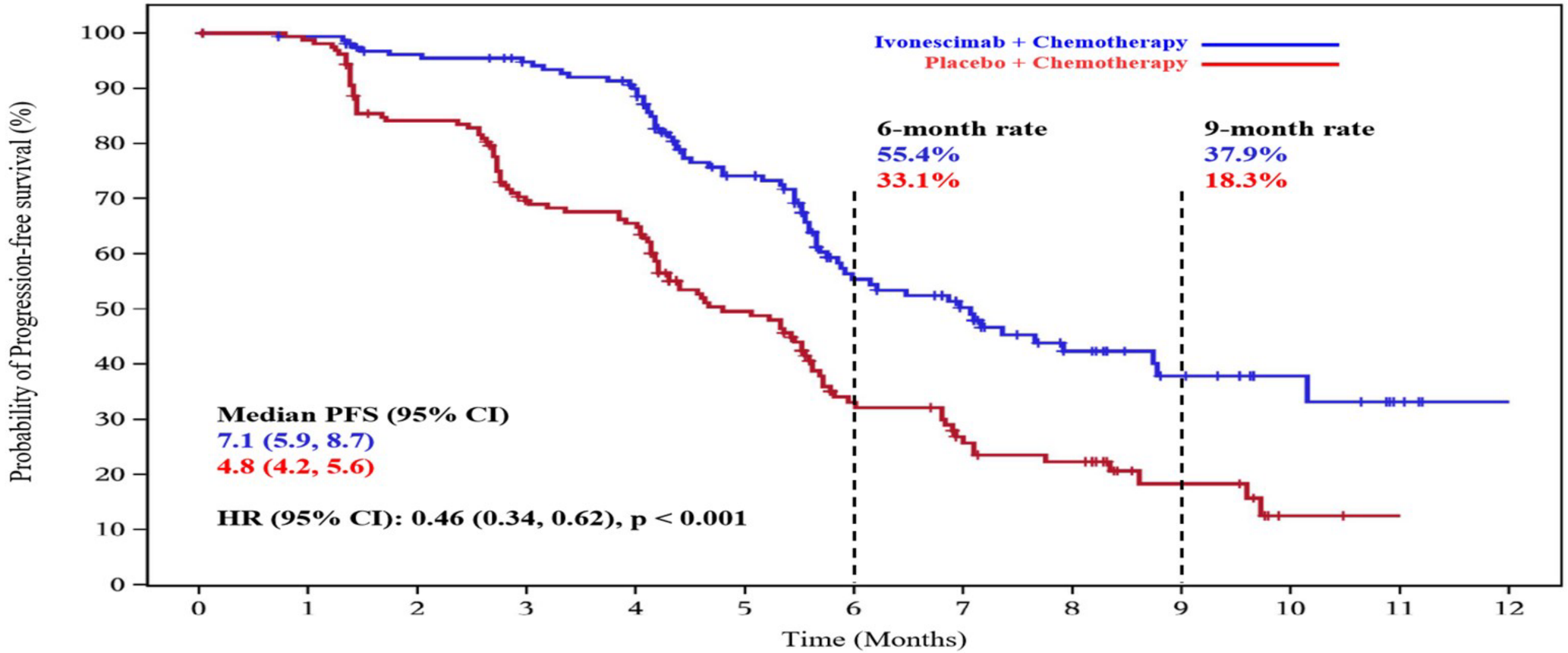


Baseline Characteristics

	Ivonescimab + Chemotherapy (N=161)	Placebo + Chemotherapy (N=161)
Age, n(%)		
Median (rang), years	59.6 (32.3, 74.9)	59.4 (36.2, 74.2)
<65	111 (68.9)	110 (68.3)
≥65	50 (31.1)	51 (31.7)
Sex, n(%)		
Male	77 (47.8)	79 (49.1)
Female	84 (52.2)	82 (50.9)
ECOG, n(%)		
0	24 (14.9)	34 (21.1)
1	137 (85.1)	127 (78.9)
Smoking status, n(%)		
Never	112 (69.6)	115 (71.4)
Current or former	49 (30.4)	46 (28.6)
Stage, n(%)		
IIIB or IIIC	3 (1.9)	5 (3.1)
IV	158 (98.1)	156 (96.9)
Brain metastasis, n (%)	35 (21.7)	37 (23.0)
Liver metastasis, n (%)	21 (13.0)	17 (10.6)
Distant metastases≥3, n(%)	74 (46.0)	68 (42.2)
EGFR mutation, n (%)		
Exon 19 Del	92 (57.1)	78 (48.4)
Exon L858R	60 (37.3)	78 (48.4)
Other	35 (21.7)	25 (15.5)
T790M status, n (%)		
Negative	26 (16.1)	27 (16.8)
Positive	26 (16.1)	18 (11.2)
Unknown	109 (67.7)	116 (72.0)
Previous EGFR-TKI treatment, n (%)		
1st/2nd Gen TKI only	22 (13.7)	24 (14.9)
3rd Gen TKI only	49 (30.4)	58 (36.0)
1st/2nd Gen TKI, then 3rd Gen TKI	90 (55.9)	79 (49.1)

ECOG, eastern copperative oncology group; EGFR, epidermal growth factor receptor; TKI, tyrosine-kinase inhibitor; Gen, generation.

Study Met Primary Endpoint of PFS per IRRC



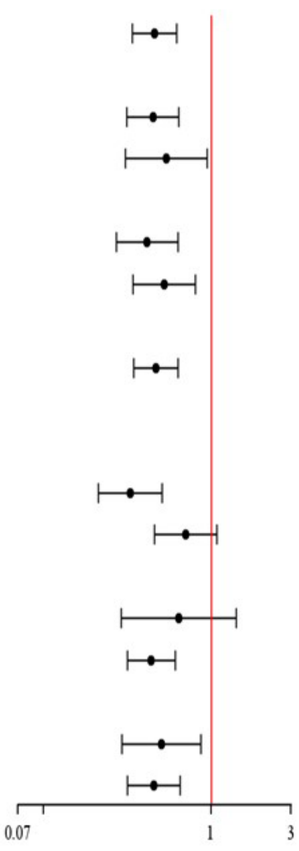
At risk (events)

Ivonescimab + Chemo	161 (0)	155 (1)	144 (6)	138 (8)	129 (15)	92 (36)	56 (57)	44 (62)	27 (68)	16 (70)	8 (70)	3 (71)	0 (71)
Placebo + Chemo	161 (0)	157 (2)	130 (25)	102 (47)	96 (53)	63 (75)	33 (94)	23 (101)	19 (104)	8 (106)	1 (108)	0 (108)	

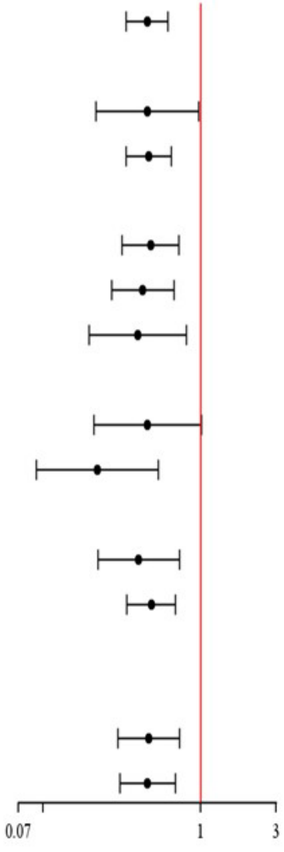
HR and P-value were stratified by previous 3rd Gen EGFR-TKI ues (yes vs. no) and presence of brain metastases (yes vs. no), and were calculated with stratified Cox model and log rank test. The two-sided P-value boundary is 0.024 as calculated using Lan-Demets spending function with O'Brien-Fleming approximation.
HR, hazard ratio; CI, confidence interval; IRRC, independent radiology review committee.

Subgroup Analysis of PFS per IRRC

	No. of events/No. of patients		HR (95% CI)
	Ivonescimab + Chemo	Placebo + Chemo	
All Subjects	71/161	108/161	0.46 (0.34, 0.62)
Age			
<65 years	51/111	75/110	0.45 (0.31, 0.64)
>=65 years	20/50	33/51	0.54 (0.31, 0.95)
Sex			
Male	34/77	57/79	0.41 (0.27, 0.64)
Female	37/84	51/82	0.52 (0.34, 0.80)
Clinical Stage at Study Entry			
IV	69/158	105/156	0.47 (0.34, 0.63)
Number of Distant Metastasis Sites at Baseline			
<3	30/87	64/93	0.33 (0.21, 0.51)
>=3	41/74	44/68	0.70 (0.46, 1.08)
Liver Metastasis			
Presence	13/21	12/17	0.64 (0.29, 1.41)
Absence	58/140	96/144	0.44 (0.32, 0.61)
Smoking History			
Yes	23/49	31/46	0.50 (0.29, 0.87)
No	48/112	77/115	0.45 (0.32, 0.65)

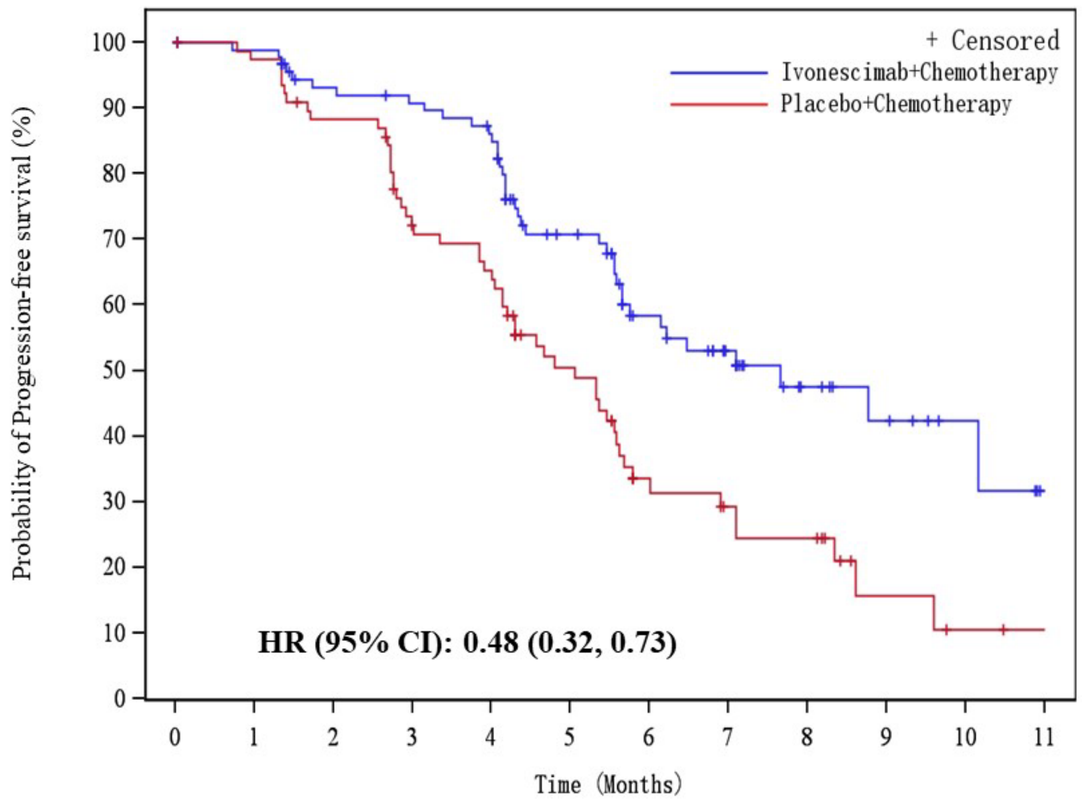


	No. of events/No. of patients		HR (95% CI)
	Ivonescimab + Chemo	Placebo + Chemo	
All Subjects	71/161	108/161	0.46 (0.34, 0.62)
Baseline ECOG Score			
0	10/24	22/34	0.46 (0.22, 0.97)
1	61/137	86/127	0.47 (0.33, 0.65)
Baseline EGFR Mutation			
19Del	39/92	53/78	0.48 (0.32, 0.73)
L858R	29/60	54/78	0.43 (0.27, 0.67)
Other	15/35	17/25	0.40 (0.20, 0.81)
T790M Mutation Status			
Negative	10/26	17/27	0.46 (0.21, 1.01)
Positive	12/26	13/18	0.22 (0.09, 0.54)
Baseline Brain Metastasis			
Presence	19/35	28/37	0.40 (0.22, 0.73)
Absence	52/126	80/124	0.48 (0.34, 0.69)
Previously Received EGFR-TKI Treatment			
One Line	30/71	52/82	0.47 (0.30, 0.73)
Two or More Lines	41/90	56/79	0.46 (0.31, 0.69)



PFS of 19del and L858R

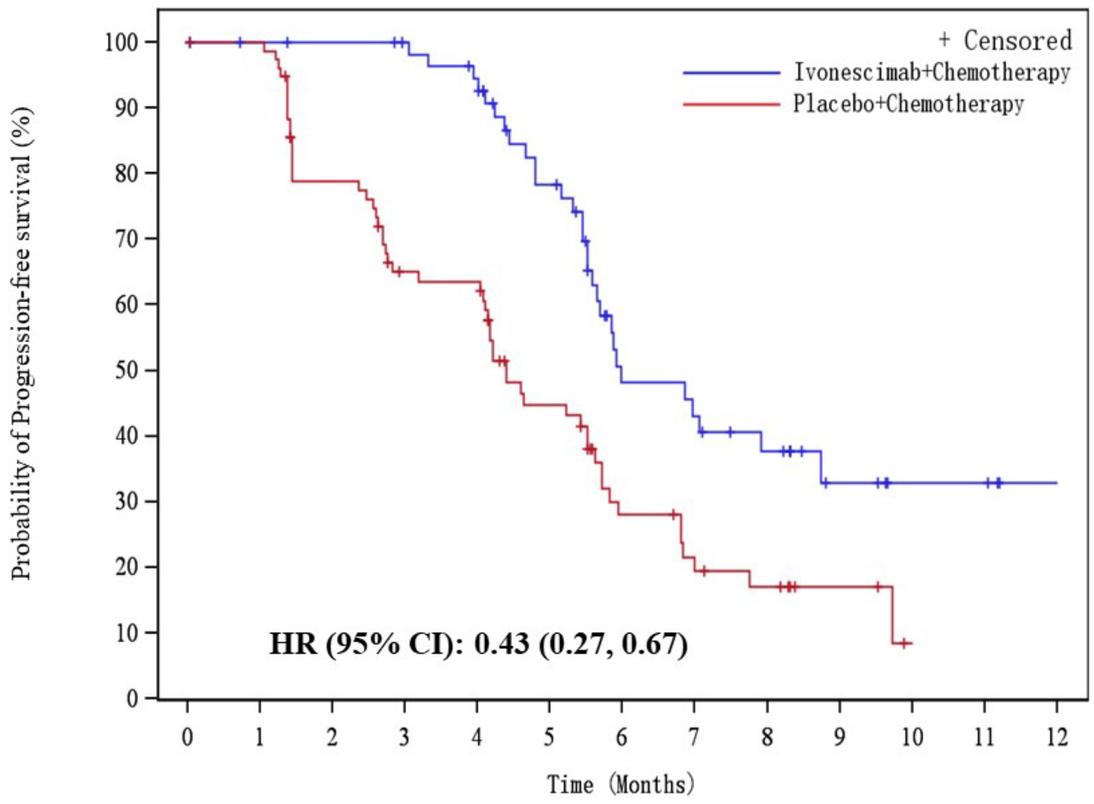
PFS Kaplan Meier Curve Evaluated by IRRC
with 19del



Number of Subjects at Risk (Number of Events)

Ivonescimab+Chemotherapy	92 (0)	89 (1)	79 (6)	76 (8)	71 (12)	50 (24)	33 (32)	23 (35)	12 (37)	8 (38)	4 (38)	0 (39)
Placebo+Chemotherapy	78 (0)	75 (2)	67 (9)	52 (21)	47 (26)	31 (36)	16 (46)	12 (48)	10 (50)	3 (52)	1 (53)	0 (53)

PFS Kaplan Meier Curve Evaluated by IRRC
with L858R

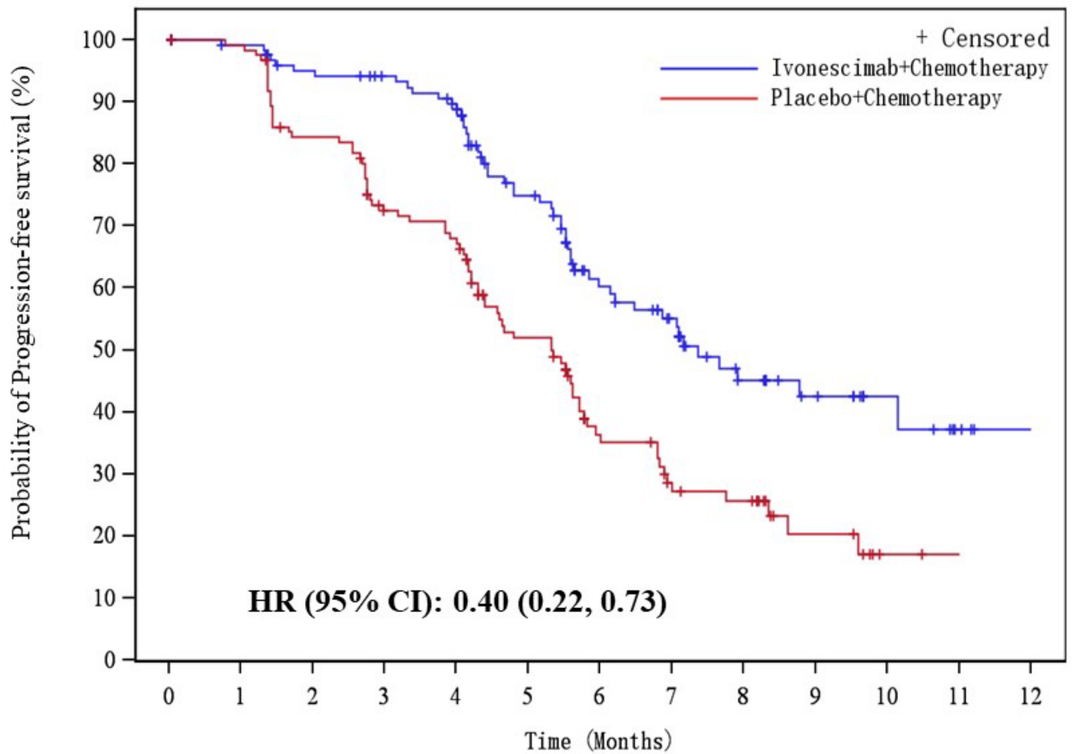


Number of Subjects at Risk (Number of Events)

Ivonescimab+Chemotherapy	60 (0)	58 (0)	57 (0)	55 (0)	51 (3)	38 (11)	19 (24)	17 (26)	13 (28)	6 (29)	3 (29)	3 (29)	0 (29)
Placebo+Chemotherapy	78 (0)	77 (0)	58 (16)	45 (26)	44 (27)	27 (39)	14 (48)	9 (52)	7 (53)	3 (53)	0 (54)		

PFS by Presence of Brain Metastases

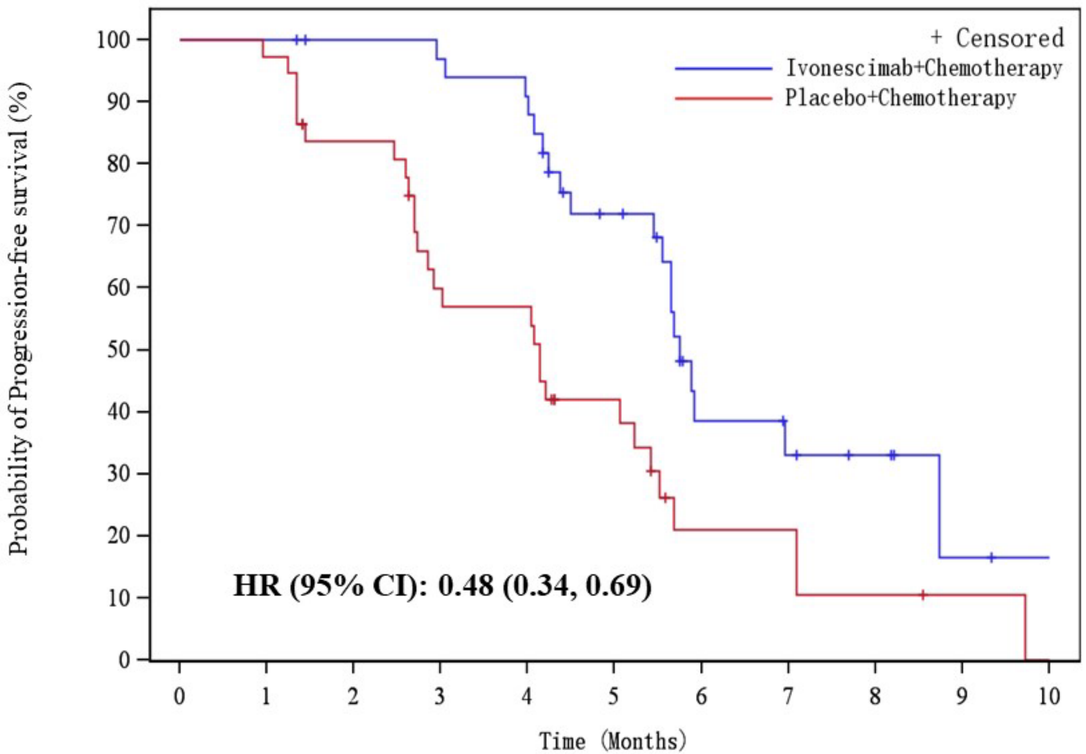
PFS Kaplan Meier Curve Evaluated by IRRC
without Brain Metastasis



Number of Subjects at Risk (Number of Events)

Ivonescimab+Chemotherapy	126 (0)	120 (1)	111 (6)	106 (7)	99 (12)	72 (27)	48 (40)	38 (44)	23 (50)	15 (51)	8 (51)	3 (52)	0 (52)
Placebo+Chemotherapy	124 (0)	121 (1)	101 (19)	82 (33)	77 (38)	52 (55)	29 (69)	19 (76)	17 (77)	7 (79)	1 (80)	0 (80)	

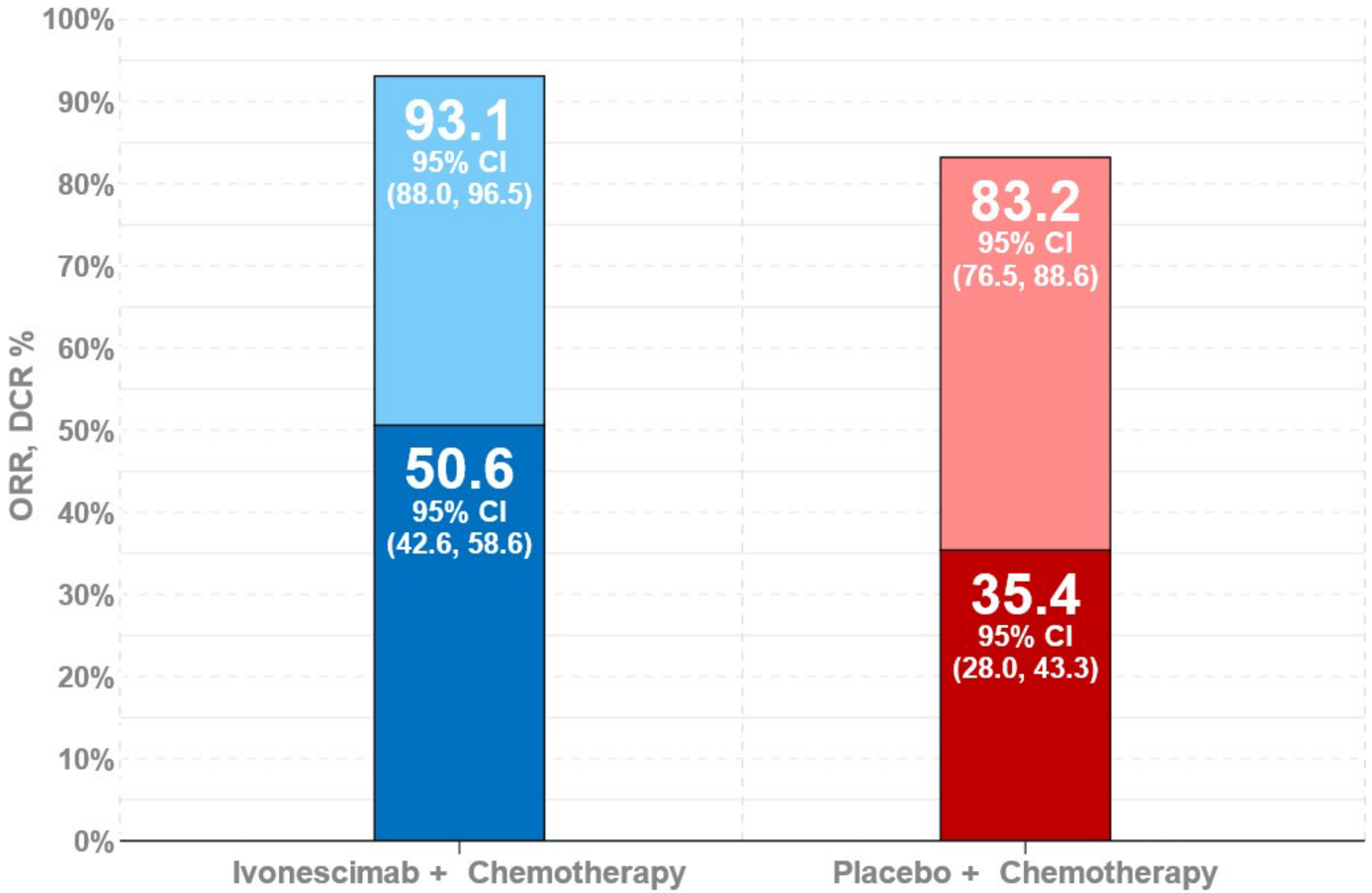
PFS Kaplan Meier Curve Evaluated by IRRC
with Brain Metastasis



Number of Subjects at Risk (Number of Events)

Ivonescimab+Chemotherapy	35 (0)	35 (0)	33 (0)	32 (1)	30 (3)	20 (9)	8 (17)	6 (18)	4 (18)	1 (19)	0 (19)
Placebo+Chemotherapy	37 (0)	36 (1)	29 (6)	20 (14)	19 (15)	11 (20)	4 (25)	4 (25)	2 (27)	1 (27)	0 (28)

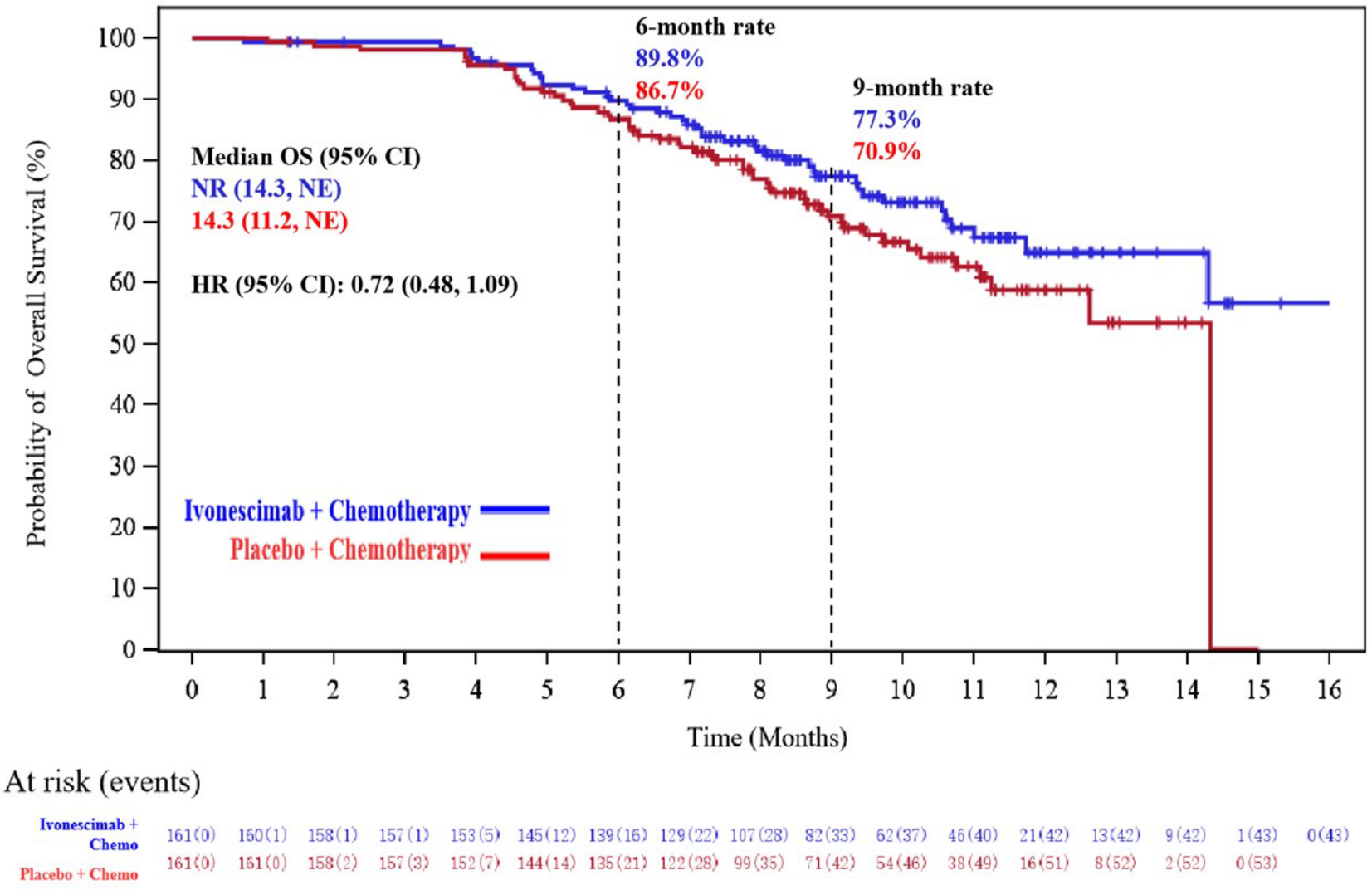
ORR, DCR and DoR per IRRC



	Ivonescimab + Chemo	Placebo + Chemo
ORR, % (95% CI)	**50.6** (42.6, 58.6)	**35.4** (28.0, 43.3)
DCR, % (95% CI)	**93.1** (88.0, 96.5)	**83.2** (76.5, 88.6)
Median DoR, month (95% CI)	**6.6** (4.3, 7.6)	**4.2** (3.0, 4.7)

RD, rate difference; CI, confidence interval.
RD and CI were calculated using Miettinen-Nurminen method stratified by exposure to 3rd generation EGFR-TKI before (yes vs.no) and brain metastases (yes vs. no)

Overall Survival (at 30% of data maturity)



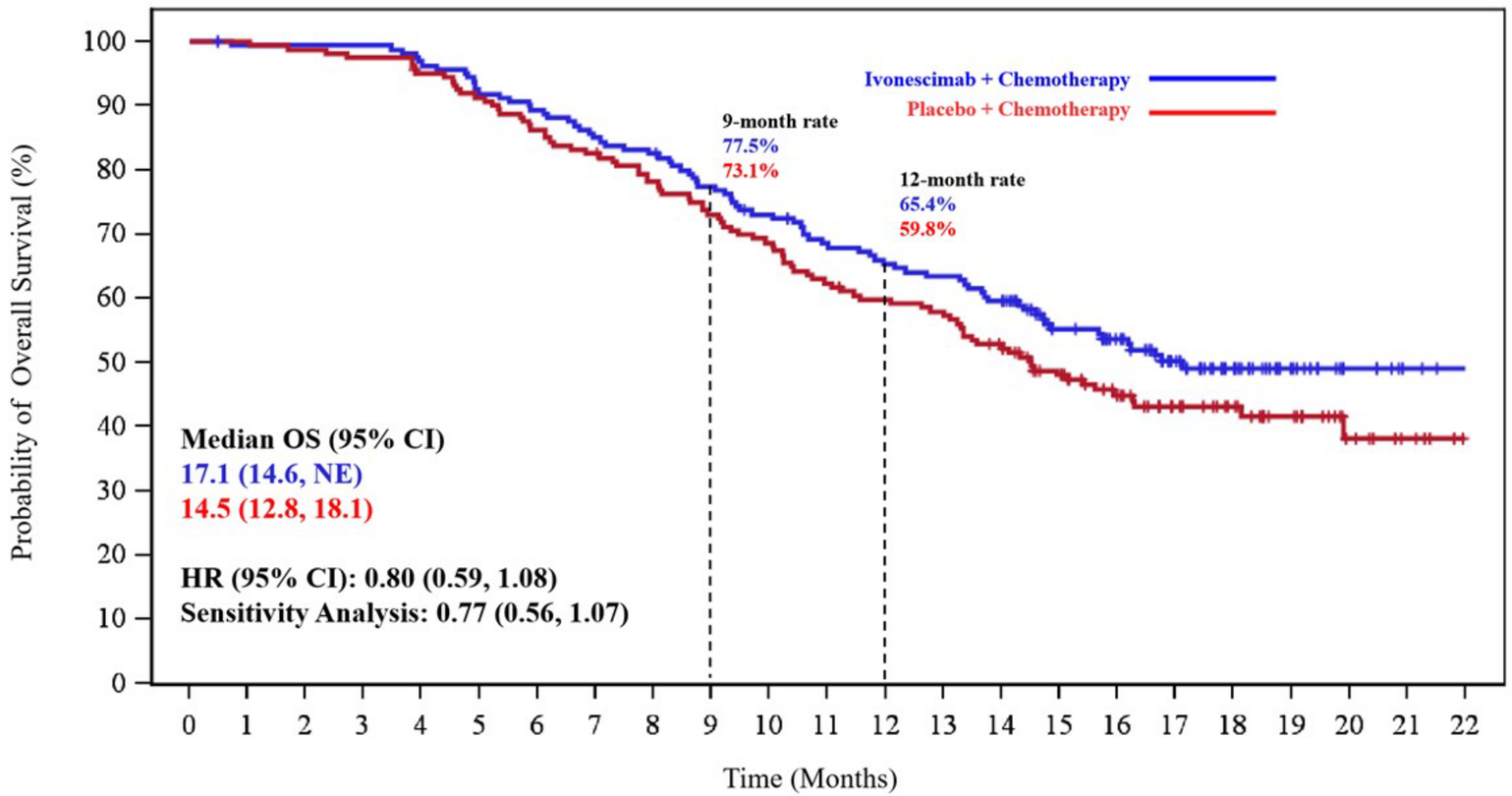
HR: 0.72 (0.48, 1.09) after 96 events, 30% data maturity

Two OS analyses were performed per request by Chinese Regulatory Authority (1st analysis at 30% and 2nd at 52% of data maturity)

Data cutoff date: June 25, 2023 (median follow-up of 10.2 months)

HR, hazard ratio; CI, confidence interval.

Overall Survival (at 52% of Data Maturity)



HR: 0.80 (0.59, 1.08) after 52% of data maturity

OS is consistent for both analysis

Data cutoff date: December 2023 (median follow-up of 17.6 months)

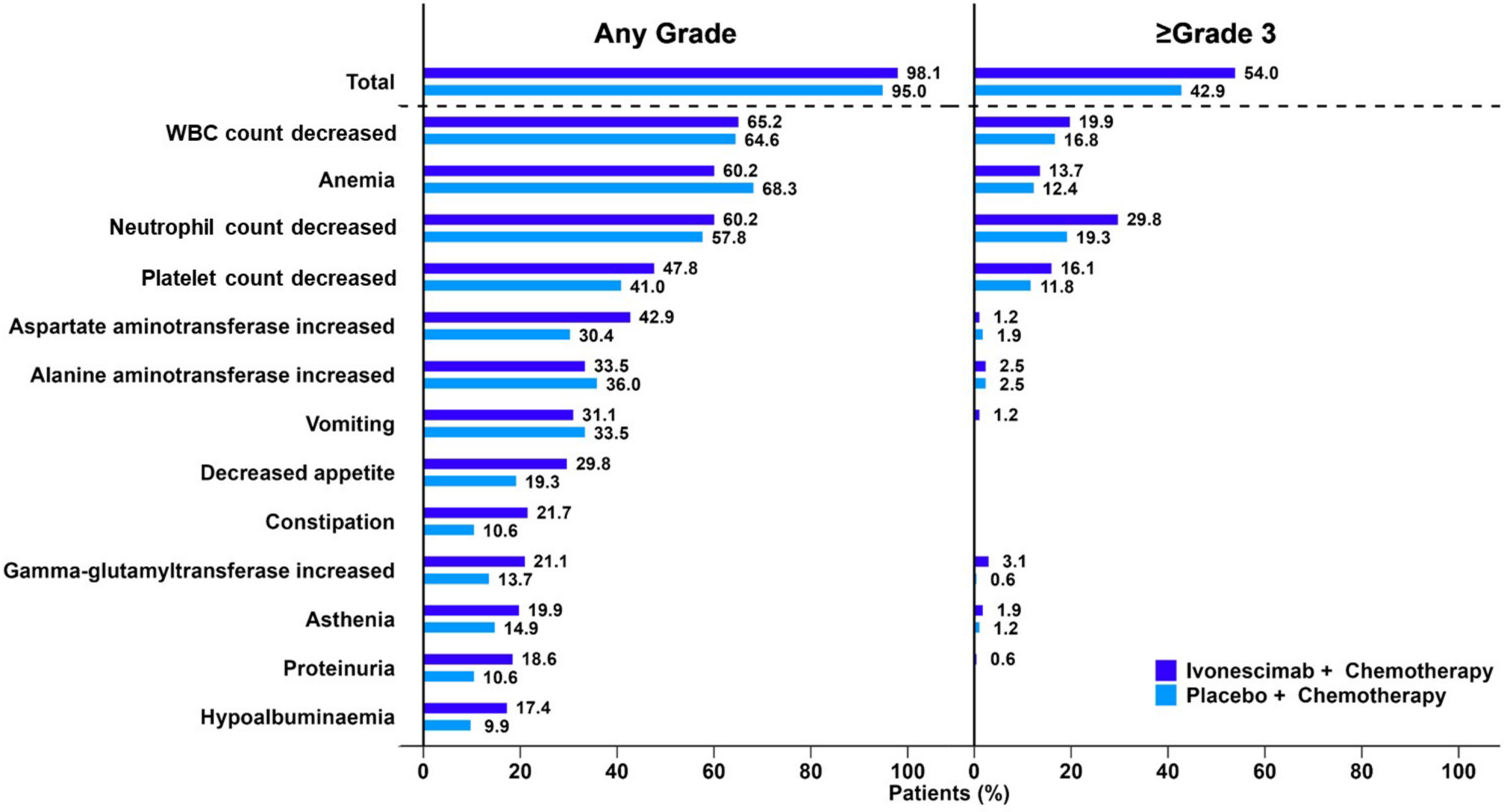
HR, hazard ratio; CI, confidence interval.

Safety Summary

TRAE, n(%)	Ivonescimab + Chemotherapy (N=161)	Placebo + Chemotherapy (N=161)
Any grade	158 (98.1)	153 (95.0)
Grade≥3	87 (54.0)	69 (42.9)
Serious*	46 (28.6)	26 (16.1)
Led to discontinuation of ivonescimab/placebo	9 (5.6)	4 (2.5)
Led to death	0 (0.0)	0 (0.0)
Grade≥3 immune-related	10 (6.2)	4 (2.5)
Grade≥3 VEGF-related	5 (3.1)	4 (2.5)

* For any PT (excluding PD) in SAE, the PT with more than 2 cases in the experimental group compared to the control group were platelet count decreased (7.5% vs. 4.3%) and hepatic function abnormal (2.5% vs. 0%).
TRAE, treatment-related adverse event (related to any drug); PT, preferred term; PD, disease progression; SAE, serious adverse event.

The Most Common Adverse Events (incidence ≥ 15%)



Immune-related Adverse Events (irAE)

Categories Preferred Term, n(%)	Ivonescimab + Chemotherapy (N=161)		Placebo + Chemotherapy (N=161)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
irAE	39 (24.2)	10 (6.2)	10 (6.2)	4 (2.5)
Hypothyroidism	17 (10.6)	1 (0.6)	0	0
Hyperthyroidism	9 (5.6)	0	0	0
Rash	6 (3.7)	4 (2.5)	2 (1.2)	1 (0.6)
Hyperglycaemia	4 (2.5)	0	3 (1.9)	0
Blood TSH increased	3 (1.9)	0	1 (0.6)	0
Interstitial lung disease	3 (1.9)	2 (1.2)	1 (0.6)	1 (0.6)
Pneumonitis	2 (1.2)	1 (0.6)	1 (0.6)	0
Dermatitis	2 (1.2)	2 (1.2)	1 (0.6)	0
Thyroid hormones increased	1 (0.6)	0	0	0
Cortisol abnormal	1 (0.6)	0	0	0
Pruritus	1 (0.6)	0	0	0
Hepatic function abnormal	1 (0.6)	1 (0.6)	0	0
Blood creatinine increased	1 (0.6)	0	0	0
Diarrhoea	0	0	1 (0.6)	1 (0.6)
Lipase increased	0	0	1 (0.6)	1 (0.6)

Adverse Events of Special Interest (AESI)

Categories Preferred Term, n(%)	Ivonescimab + Chemotherapy (N=161)		Placebo + Chemotherapy (N=161)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
AESI	48 (29.8)	5 (3.1)	25 (15.5)	4 (2.5)
Proteinuria	28 (17.4)	1 (0.6)	13 (8.1)	0
Haemorrhage	11 (6.8)	0	8 (5.0)	0
Urinary occult blood positive	4 (2.5)	0	3 (1.9)	0
Haemoptysis	2 (1.2)	0	0	0
Epistaxis	3 (1.9)	0	1 (0.6)	0
Mouth haemorrhage	1 (0.6)	0	0	0
Gastrointestinal haemorrhage	0	0	1 (0.6)	0
Gingival bleeding	1 (0.6)	0	0	0
Eye haemorrhage	1 (0.6)	0	2 (1.2)	0
Vaginal haemorrhage	0	0	1 (0.6)	0
Occult blood positive	0	0	1 (0.6)	0
Hypertension	13 (8.1)	3 (1.9)	5 (3.1)	3 (1.9)
Arterial thromboembolism	1 (0.6)	0	1 (0.6)	1 (0.6)
Cardiac failure congestive	1 (0.6)	1 (0.6)	0	0

Conclusions

- Ivonescimab plus chemotherapy significantly improved PFS in patients who progressed on prior EGFR-TKIs treatments: **PFS HR 0.46 (95% CI: 0.34, 0.62), P<0.001**
- The prespecified subgroup analysis showed PFS benefit favoring patients receiving ivonescimab over those receiving the placebo across all subgroups.
- OS analyses show a favorable trend for prolonged OS for ivonescimab-chemotherapy
- The safety profile was generally manageable, without any unexpected adverse events and a low rate of treatment discontinuation.
- This study is being expanded globally, HARMONi (NCT06396065), to include patients from North America and Europe.

With the recent approval in China, ivonescimab plus chemotherapy is a new standard treatment option for NSCLC patients who progress after EGFR-TKI treatment

Acknowledgement

We thank all the patients and their families, investigators and all team members for supporting this trial.

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Ivonescimab Plus Chemotherapy in Non–Small Cell Lung Cancer With *EGFR* Variant

A Randomized Clinical Trial

HARMONi-A Study Investigators

IMPORTANCE For patients with non–small cell lung cancer whose disease progressed while receiving EGFR tyrosine kinase inhibitor (EGFR-TKI) therapy, particularly third-generation TKIs, optimal treatment options remain limited.

OBJECTIVE To compare the efficacy of ivonescimab plus chemotherapy with chemotherapy alone for patients with relapsed advanced or metastatic non–small cell lung cancer with the epidermal growth factor receptor (*EGFR*) variant.

DESIGN, SETTING, AND PARTICIPANTS Double-blind, placebo-controlled, randomized, phase 3 trial at 55 sites in China enrolled participants from January 2022 to November 2022; a total of 322 eligible patients were enrolled.

INTERVENTIONS Participants received ivonescimab (n = 161) or placebo (n = 161) plus pemetrexed and carboplatin once every 3 weeks for 4 cycles, followed by maintenance therapy of ivonescimab plus pemetrexed or placebo plus pemetrexed.

Visual Abstract

Supplemental con

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JAMA Network

Low-dose CT screening among never-smokers with or without a family history of lung cancer in Taiwan: a prospective cohort study

Gee-Chen Chang, Chao-Hua Chiu*, Chong-Jen Yu*, Yeun-Chung Chang, Ya-Hsuan Chang, Kuo-Hsuan Hsu, Yu-Chung Wu, Chih-Yi Chen, Hsian-He Hsu, Ming-Ting Wu, Cheng-Ta Yang, Inn-Wen Chong, Yu-Ching Lin, Te-Chun Hsia, Meng-Chih Lin, Wu-Chou Su, Chih-Bin Lin, Kang-Yun Lee, Yu-Feng Wei, Gong-Yau Lan, Wing P Chan, Kao-Lun Wang, Mei-Han Wu, Hao-Hung Tsai, Chih-Feng Chian, Ruay-Sheng Lai, Jin-Yuan Shih, Chi-Liang Wang, Jui-Sheng Hsu, Kun-Chieh Chen, Chun-Ku Chen, Jiun-Yi Hsia, Chung-Kan Peng, En-Kuei Tang, Chia-Lin Hsu, Teh-Ying Chou, Wei-Chih Shen, Ying-Huang Tsai, Chun-Ming Tsai, Yuh-Min Chen, Yu-Chin Lee, Hsuan-Yu Chen, Sung-Liang Yu†, Chien-Jen Chen†, Yung-Liang Wan†, Chao Agnes Hsiung†, Pan-Chyr Yang, on behalf of the TALENT Investigators‡*

Summary

Background In Taiwan, lung cancers occur predominantly in never-smokers, of whom nearly 60% have stage IV disease at diagnosis. We aimed to assess the efficacy of low-dose CT (LDCT) screening among never-smokers, who had other risk factors for lung cancer.

Methods The Taiwan Lung Cancer Screening in Never-Smoker Trial (TALENT) was a nationwide, multicentre, prospective cohort study done at 17 tertiary medical centres in Taiwan. Eligible individuals had negative chest radiography, were aged 55–75 years, had never smoked or had smoked fewer than 10 pack-years and stopped smoking for more than 15 years (self-report), and had one of the following risk factors: a family history of lung cancer; passive smoke exposure; a history of pulmonary tuberculosis or chronic obstructive pulmonary disorders; a cooking index of 110 or higher; or cooking without using ventilation. Eligible participants underwent LDCT at baseline, then annually for 2 years, and then every 2 years up to 6 years thereafter, with follow-up assessments at each LDCT scan (ie, total follow-up of 8 years). A positive scan was defined as a solid or part-solid nodule larger than 6 mm in mean diameter or a pure ground-glass nodule larger than 5 mm in mean diameter. Lung cancer was diagnosed through invasive procedures, such as image-guided aspiration or biopsy or surgery. Here, we report the results of 1-year follow-up after LDCT screening at baseline. The primary outcome was lung cancer detection rate. The p value for detection rates was estimated by the χ^2 test. Univariate and multivariable logistic regression analyses were used to assess the association between lung cancer incidence and each risk factor. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of LDCT screening were also assessed. This study is registered with ClinicalTrials.gov, NCT02611570, and is ongoing.

Findings Between Dec 1, 2015, and July 31, 2019, 12 011 participants (8868 females) were enrolled, of whom 6009 had a family history of lung cancer. Among 12 011 LDCT scans done at baseline, 2094 (17·4%) were positive. Lung cancer was diagnosed in 318 (2·6%) of 12 011 participants (257 [2·1%] participants had invasive lung cancer and 61 [0·5%] had adenocarcinomas in situ). 317 of 318 participants had adenocarcinoma and 246 (77·4%) of 318 had stage I disease. The prevalence of invasive lung cancer was higher among participants with a family history of lung cancer (161 [2·7%] of 6009 participants) than in those without (96 [1·6%] of 6002 participants). In participants with a family history of lung cancer, the detection rate of invasive lung cancer increased significantly with age, whereas the detection rate of adenocarcinoma in situ remained stable. In multivariable analysis, female sex, a family history of lung cancer, and age older than 60 years were associated with an increased risk of lung cancer and invasive lung cancer; passive smoke exposure, cumulative exposure to cooking, cooking without ventilation, and a previous history of chronic lung diseases were not associated with lung cancer, even after stratification by family history of lung cancer. In participants with a family history of lung cancer, the higher the number of first-degree relatives affected, the higher the risk of lung cancer; participants whose mother or sibling had lung cancer were also at an increased risk. A positive LDCT scan had 92·1% sensitivity, 84·6% specificity, a PPV of 14·0%, and a NPV of 99·7% for lung cancer diagnosis.

Interpretation TALENT had a high invasive lung cancer detection rate at 1 year after baseline LDCT scan. Overdiagnosis could have occurred, especially in participants diagnosed with adenocarcinoma in situ. In individuals who do not smoke, our findings suggest that a family history of lung cancer among first-degree relatives significantly increases the risk of lung cancer as well as the rate of invasive lung cancer with increasing age. Further research on risk factors for lung cancer in this population is needed, particularly for those without a family history of lung cancer.

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See Comment page 93

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Research in context

Evidence before this study

We searched PubMed for studies of low-dose CT (LDCT) screening among never-smokers, published in English between Jan 1, 2000, and March 31, 2023, using the search terms "low-dose CT", "lung cancer screening", "never smokers", " family history of lung cancer", "risk factors", and "clinical trial". Our search identified 15 studies. According to the US National Lung Screening Trial, lung cancer screening is considered most effective for individuals aged 55–74 years who are at high risk of lung cancer, with a smoking history of at least 30 pack-years, including current smokers and former smokers who have quit smoking within the previous 15 years. Similar studies have been performed among heavy smokers. Globally, at least 25% of people with lung cancer are never-smokers; however, the prevalence of lung cancer among women who have never smoked is high in southern and eastern Asia (>60%). Lung cancer screening based on previously developed risk models could miss many individuals who would benefit from early detection and curative treatment. In a prospective lung cancer screening study of 12 114 Japanese participants between 2004 and 2012, LDCT detected lung cancer in 1·1% of never-smokers and smokers. A systematic review and meta-analysis that included 13 LDCT lung cancer screening studies from Asia (141 396 ever-smokers, 109 251 never-smokers; 1961 lung cancer cases) found that the relative risk of lung cancer diagnosis in Asian women who had never smoked was 1·78 (95% CI 1·41–2·24) compared with Asian men who had never smoked, 1·22 (0·89–1·68) compared with male ever-smokers, and 0·99 (0·65–1·50) compared with male and female ever-smokers at high risk of lung cancer (≥30 pack-years).

Added value of this study

Previous lung cancer screening studies with LDCT in Asia were retrospective or did not include other risk factors, such as a family history of lung cancer and environmental factors. The Taiwan Lung Cancer Screening in Never-Smoker Trial (TALENT) is the first national study of LDCT among never-smokers who had other risk factors for lung cancer. TALENT had a high invasive lung cancer detection rate, especially among female participants, participants aged over 60 years, and those with a family history of lung cancer. Of note, a family history of lung cancer among first-degree relatives significantly increased the risk of lung cancer as well as the rate of invasive lung cancer with increasing age, and participants whose mother or sibling had lung cancer were at an increased risk.

Implications of all the available evidence

Our data show that even if the benefits of lung cancer screening for never-smokers in western countries are small, the high risk of lung cancer among never-smokers in Asia suggests that Asian-specific risk models are necessary to optimise eligibility and weighting even for well-known risk factors for lung cancer. Risk factors for lung cancer can differ between the sexes, and strategies to identify high-risk individuals for lung cancer screening might need to be tailored for each sex. In the absence of a non-screened control group, we cannot exclude the possibility of overdiagnosis in this cohort, especially in those screening participants diagnosed with adenocarcinoma in situ. Furthermore, half of participants included in our study had a family history of lung cancer, potentially increasing the overall lung cancer detection rate. Additional lung cancer risk factors need to be investigated among never-smokers without a family history of lung cancer.

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, including in Taiwan.[1] Tobacco smoking is the major cause of lung cancer globally.[2] However, the global tobacco-attributable fraction of lung cancer is high among men (81%) but relatively low among women (58%).[3] Our comprehensive proteogenomics study[4] identified distinct signatures of oncogenesis and progression in individuals with lung cancer who were never-smokers, suggesting that both endogenous genetic susceptibility and exogenous environmental carcinogens might contribute.

Low-dose CT (LDCT) scans have been found to effectively screen for lung cancer and reduce mortality in heavy smokers.[5] However, data from the National Taiwan Cancer Registry collected between 2011 and 2015 indicated that 53% of patients with newly diagnosed lung cancer and 93% of female patients had never smoked.[1] In Taiwan, among patients with lung cancer who were never-smokers, nearly 60% had stage IV disease at diagnosis.[1] This scenario is more common in eastern Asia than in other areas.[6] Alternative screening strategies for lung cancer need to be developed for individuals with high risk due to factors other than smoking. Several risk factors for lung cancer in never-smokers have been identified, including a family history of lung cancer among first-degree relatives,[7] environmental exposure to tobacco smoke,[8] cumulative exposure to cooking, cooking without using ventilation,[9] and a history of chronic lung diseases.[10]

The effectiveness of LDCT screening among never-smokers remains to be elucidated with regard to acceptability, affordability, and safety, in routine practice. On the basis of this unmet need, we aimed to assess the efficacy of a LDCT screening programme over an 8-year follow-up period among individuals with risk factors for lung cancer who are never-smokers. We hypothesised that family history of lung cancer and environmental factors would be important risk factors for lung cancer in never-smokers. Here, we report the results of the 1-year follow-up after LDCT screening at baseline.

Methods

Study design and participants

The Taiwan Lung Cancer Screening in Never-Smoker Trial (TALENT) was a nationwide, multicentre,

prospective cohort study done at 17 tertiary medical centres in Taiwan. The study protocol was approved by the individual institutional review boards. Written informed consent was obtained from all participants.

Participants were eligible to participate in the study if they had a negative chest radiograph, were aged 55–75 years (individuals with a family history of cancer aged 50–54 years, and those aged <50 years who were older than the age of onset of the youngest lung cancer proband in the family were also considered eligible), had never smoked or were light ex-smokers (smoked <10 pack-years and stopped smoking more than 15 years previously [self-report]), and had one of the following risk factors: a family history of lung cancer up to third-degree relatives; passive smoke exposure (appendix p 10);[7] a history of pulmonary tuberculosis or chronic obstructive pulmonary disorders; a cooking index[9,11] of 110 or higher (ie, cooking by pan frying, stir frying, or deep frying twice a day in 1 week [up to a maximum of 21] × years cooking; appendix p 11); or cooking without using ventilation. Full exclusion criteria are provided in the appendix (p 4).

Procedures

Eligible participants were invited to undergo LDCT screening, with the first round of screening within 2 weeks of negative chest radiography prescreening (ie, defined as no obvious opacity suggesting lung cancer; appendix p 4). LDCT scans were done at enrolment (baseline screen), then annually for 2 years (annual screen 1 and 2), then every 2 years for 6 years (total of six scans). Follow-up is planned for 8 years and is ongoing. LDCT scans and reports were performed according to a standard protocol, and lung imaging reporting and data system (Lung-RADS) version 1.0 categories were assessed for each participant (appendix pp 13–15). A solid or part-solid nodule larger than 6 mm in mean diameter or a pure ground-glass nodule larger than 5 mm in mean diameter was designated as positive by LDCT. A standard management protocol for diagnostic work-up and follow-up strategy was recommended for nodules seen on baseline LDCT (appendix pp 16–17). To resolve the operator effects of radiologists for study quality assurance and reduction of overdiagnosis and underdiagnosis, the training and consensus on image report was reached before study commencement (appendix p 12).

The criteria used for selection of participants for invasive procedures were as follows: (1) solid or part-solid nodules larger than 4 mm with size increase in follow-up images or baseline nodules larger than 8 mm; (2) ground-glass nodules larger than 5 mm with size increase or appearance of a solid component; or (3) baseline nodules larger than 10 mm (appendix p 4). Negative LDCT scans were divided into three categories: (1) solid or part-solid nodules of 4–6 mm in diameter; (2) minor abnormality with non-calcified solid or part-solid nodules of 4 mm in diameter or less, ground-glass nodules of less than 5 mm in diameter, or the presence of ground-glass opacities of an irregular shape; or (3) negative finding (ie, no nodules identified). Participants without lung nodules and with benign lung nodules, non-calcified solid or part-solid nodules 4 mm in diameter or less, or ground-glass nodules of 5 mm or less in diameter at baseline underwent CT annually for 2 years and then biennially for 6 years. Subsequent screening was not offered to participants with newly diagnosed lung cancer (appendix p 5).

Lung cancer staging was determined based on the 8th edition of the American Joint Committee on Cancer staging system (appendix p 5).

Outcomes

The primary outcome was lung cancer detection rate. The primary objective was validity of LDCT for lung cancer screening among never-smokers assessed by true positive, false positive, true negative, and false negative rates of LDCT screening. Consequently, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of LDCT screening were also assessed.

Statistical analysis

The estimated sample size was 12 047 based on a lung cancer detection rate of 2% and a desired total 95% CI

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	All participants (n=12 011)	Family history of lung cancer (n=6009)	No family history of lung cancer (n=6002)	p value
Sex				
Female	8868 (73·8%)	4322 (71·9%)	4546 (75·7%)	<0·0001
Male	3143 (26·2%)	1687 (28·1%)	1456 (24·3%)	..
Age, years				
Mean (SD)	61·2 (6·2)	59·6 (6·8)	62·9 (5·0)	<0·0001
Range	24–75	24–75	55–75	..
BMI, kg/m^2				
Underweight (<18·5)	343 (2·9%)	183 (3·0%)	160 (2·7%)	0·193
Normal (≥18·5 to <24)	6208 (51·7%)	3137 (52·2%)	3071 (51·2%)	..
Overweight (≥24 to <27)	3476 (28·9%)	1699 (28·3%)	1777 (29·6%)	..
Obese (≥27)	1984 (16·5%)	990 (16·5%)	994 (16·6%)	..
Smoking history				
Never-smoker	11 201 (93·3%)	5596 (93·1%)	5605 (93·4%)	0·572
Light ex-smoker*	810 (6·7%)	413 (6·9%)	397 (6·6%)	..
Family history of lung cancer				
First-degree relative	5579 (46·4%)	5579 (92·8%)	NA	..
Second-degree relative	366 (3·0%)	366 (6·1%)	NA	..
Third-degree relative	64 (0·5%)	64 (1·1%)	NA	..
Passive smoke exposure	9923 (82·6%)	4492 (74·8%)	5431 (90·5%)	<0·0001
History of chronic lung disease	1142 (9·5%)	422 (7·0%)	720 (12·0%)	<0·0001
Cooking index ≥110	4395 (36·6%)	1514 (25·1%)	2881 (48·0%)	<0·0001
Cooking without ventilation	211 (1·8%)	82 (1·4%)	129 (2·1%)	0·001

Data are n (%), unless otherwise stated. *Defined as previously smoking <10 pack-years and having stopped smoking for more than 15 years.

Table 1: **Baseline characteristics**

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	Invasive lung cancer (n=257)	Non-invasive lung cancer* (n=61)	No cancer (n=11 693)	All participants (n=12 011)
All participants				
Positive LDCT scan	236 (91·8%)	57 (93·4%)	1801 (15·4%)	2094 (17·4%)
Negative LDCT scan	21 (8·2%)	4 (6·6%)	9892 (84·6%)	9917 (82·6%)
Solid or part-solid nodule 4–6 mm in diameter	11 (4·3%)	2 (3·3%)	1014 (8·7%)	1027 (8·6%)
Minor abnormality	9 (3·5%)	2 (3·3%)	4818 (41·2%)	4829 (40·2%)
Negative finding†	1 (0·4%)	0	4060 (34·7%)	4061 (33·8%)
Participants with a family history of lung cancer				
Positive LDCT scan	147/161 (91·3%)	34/36 (94·4%)	884/5812 (15·2%)	1065/6009 (17·7%)
Negative LDCT scan	14/161 (8·7%)	2/36 (5·6%)	4928/5812 (84·8%)	4944/6009 (82·3%)
Solid or part-solid nodule 4–6 mm in diameter	10/161 (6·2%)	2/36 (5·6%)	473/5812 (8·1%)	485/6009 (8·1%)
Minor abnormality	3/161 (1·9%)	0	2370/5812 (40·8%)	2373/6009 (39·5%)
Negative finding*	1/161 (0·6%)	0	2085/5812 (35·9%)	2086/6009 (34·7%)
Participants without a family history of lung cancer				
Positive LDCT scan	89/96 (92·7%)	23/25 (92·0%)	917/5881 (15·6%)	1029/6002 (17·1%)
Negative LDCT scan	7/96 (7·3%)	2/25 (8·0%)	4964/5881 (84·4%)	4973/6002 (82·9%)
Solid or part-solid nodule 4–6 mm in diameter	1/96 (1·0%)	0	541/5881 (9·2%)	542/6002 (9·0%)
Minor abnormality	6/96 (6·2%)	2/25 (8·0%)	2448/5881 (41·6%)	2456/6002 (40·9%)
Negative finding	0	0	1975/5881 (33·6%)	1975/6002 (32·9%)
Lung-RADS categories				
All participants				
Category 0	0	0	14 (0·1%)	14 (0·1%)
Category 1	1 (0·4%)	0	4655 (39·8%)	4656 (38·8%)
Category 2	38 (14·8%)	18 (29·5%)	5146 (44·0%)	5202 (43·3%)
Category 3	71 (27·6%)	29 (47·5%)	1530 (13·1%)	1630 (13·6%)
Category 4A	71 (27·6%)	9 (14·8%)	259 (2·2%)	339 (2·8%)
Category 4B	44 (17·1%)	3 (4·9%)	62 (0·5%)	109 (0·9%)
Category 4X	32 (12·5%)	2 (3·3%)	27 (0·2%)	61 (0·5%)
Participants with a family history of lung cancer				
Category 0	0	0	5/5812 (0·1%)	5/6009 (0·1%)
Category 1	1/161 (0·6%)	0	2391/5812 (41·1%)	2392/6009 (39·8%)
Category 2	30/161 (18·6%)	9/36 (25·0%)	2581/5812 (44·4%)	2620/6009 (43·6%)
Category 3	41/161 (25·5%)	20/36 (55·6%)	670/5812 (11·5%)	731/6009 (12·2%)
Category 4A	45/161 (28·0%)	4/36 (11·1%)	113/5812 (1·9%)	162/6009 (2·7%)
Category 4B	25/161 (15·5%)	2/36 (5·6%)	34/5812 (0·6%)	61/6009 (1·0 %)
Category 4X	19/161 (11·8%)	1/36 (2·8%)	18/5812 (0·3%)	38/6009 (0·6%)
Participants without a family history of lung cancer				
Category 0	0	0	9/5881 (0·2%)	9/6002 (0·1%)
Category 1	0	0	2264/5881 (38·5%)	2264/6002 (37·7%)
Category 2	8/96 (8·3%)	9/25 (36·0%)	2565/5881 (43·6%)	2582/6002 (43·0%)
Category 3	30/96 (31·2%)	9/25 (36·0%)	860/5881 (14·6%)	899/6002 (15·0%)
Category 4A	26/96 (27·1%)	5/25 (20·0%)	146/5881 (2·5%)	177/6002 (2·9%)
Category 4B	19/96 (19·8%)	1/25 (4·0%)	28/5881 (0·5%)	48/6002 (0·8%)
Category 4X	13/96 (13·5%)	1/25 (4·0%)	9/5881 (0·2%)	23/6002 (0·4%)

LDCT=low-dose CT. *Adenocarcinoma in situ. †One lung cancer was diagnosed in a negative LDCT; this was a false negative LDCT reading, as an 8 mm ground-glass nodule at the left lower lobe was missed by the radiologist but captured by the thoracic surgeon, and surgery was performed after 9 months of follow-up (pathology: minimally invasive adenocarcinoma).

Table 2: **Baseline LDCT scan findings and Lung-RADS version 1·0 categories by lung cancer family history and lung cancer diagnosis**

width of 0·5%. We ensured that half of the enrolled participants had a family history of lung cancer to further analyse hereditary effects. The final follow-up assessment for this analysis was done on Sept 30, 2020. For continuous variables, means, SDs, and ranges are presented. Differences in the distributions of baseline characteristics of participants between groups with or without a family history of lung cancer were analysed using Pearson's χ^2 tests for categorical variables and 2-sample *t* tests for continuous variables. The 95% CI estimation of detection rates was based on the standard normal distribution. The rate ratio (RR) was determined by unconditional maximum likelihood estimation, and the 95% CI of RRs was calculated using normal approximation (Wald interval). The p value of the trend

test of detection rates was estimated using the χ^2 test. Univariate and multivariable logistic regression analyses were used to assess the associations between number of relatives affected with lung cancer and lung cancer risk and the effect of each risk factor. All statistical tests were done using SPSS statistical software (version 15·0). A two-tailed p value less than 0·05 was considered significant. Although some of the follow-up data are not complete, in the future we plan to compare whether there were different lung cancer detection rates in subsequent years with the last follow-up date of Dec 31, 2021. This study is registered with ClinicalTrials.gov, NCT02611570.

Role of the funding source

The study funder was involved in soliciting project specifications and regularly reviewing the progress of projects. The funder had no involvement in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Dec 1, 2015, and July 31, 2019, 12 011 participants were enrolled and underwent LDCT. 6009 (50%) of 12 011 participants had a family history of lung cancer (appendix p 18). 8868 (73·8%) of 12 011 participants were female, the mean age was 61·2 years (SD 6·2), and 11 201 (93·3%) were never-smokers. Of 6009 with a family history of lung cancer, 5579 (92·8%) had a first-degree relative with lung cancer. 9923 (83·2%) had passive smoke exposure, 1142 (9·8%) had a history of chronic lung disease (pulmonary tuberculosis or chronic obstructive pulmonary disorder), 4395 (36·7%) had a cooking index of 110 or higher, and 211 (1·8%) cooked without using ventilation (table 1). The adherence rate to the second scheduled screening was 92·4% (11 098 of 12 011 participants).

Among the 12 011 baseline LDCT scans, 2094 (17·4%) were considered positive; 3018 positive nodules were identified, including 989 (32·8%) solid, 450 (14·9%) part-solid, and 1579 (52·3%) ground-glass nodules (appendix p 19). 1065 (17·7%) of 6009 participants with a family history of lung cancer and 1029 (17·1%) of 6002 participants without a family history of lung cancer had positive LDCT scans. On scanning, 1027 (8·6%) showed solid or part-solid

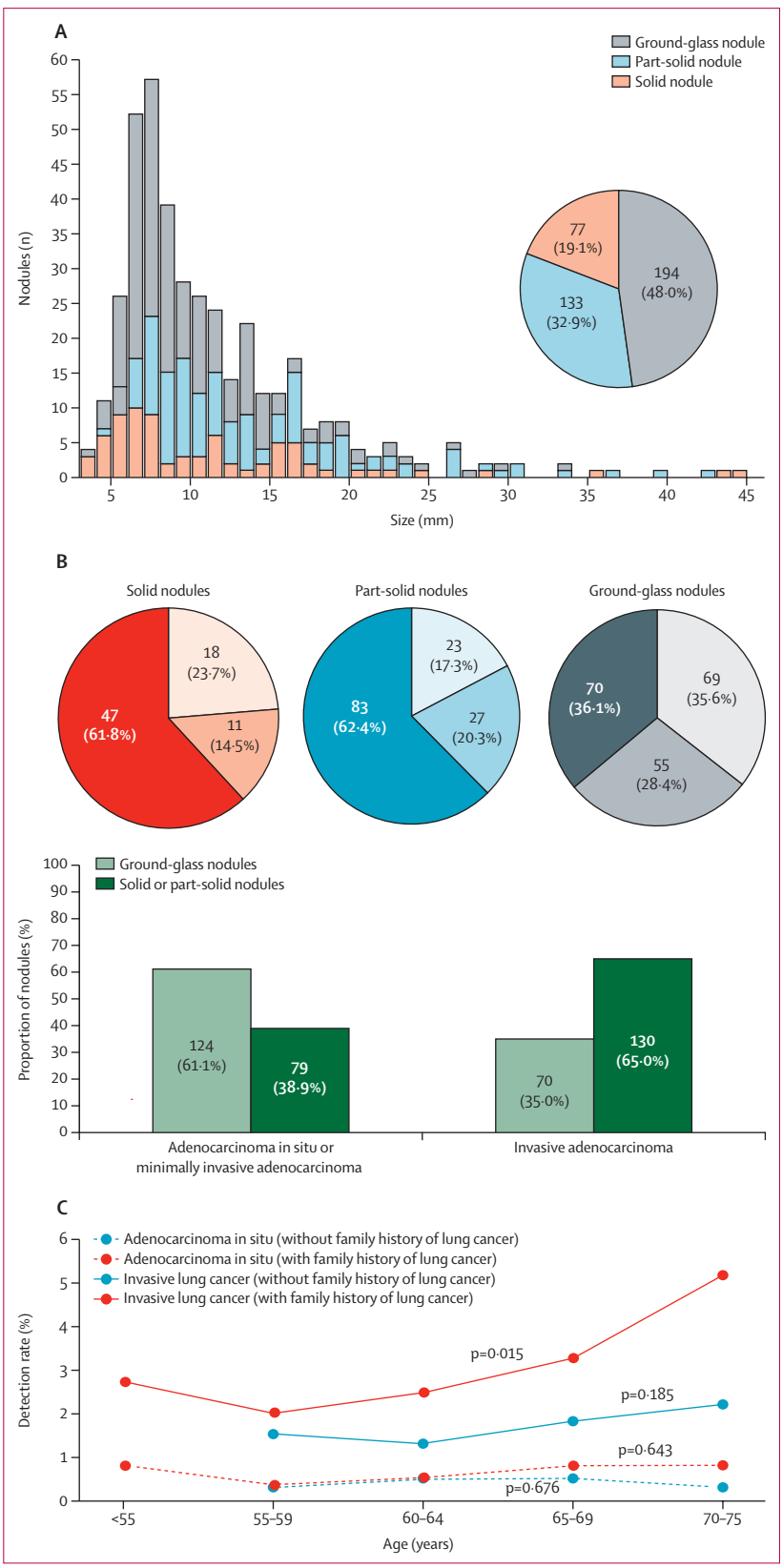

Figure 1: **Lung cancer size, CT features, and age distribution**
(A) Size and CT feature distribution of all lung cancer nodules identified on LDCT scans (n=404). (B) Proportion of lung cancers diagnosed as adenocarcinoma in situ, minimally invasive adenocarcinoma, and invasive adenocarcinoma with solid, part-solid, and ground-glass nodules; dark shading indicates invasive adenocarcinomas, medium shading indicates minimally invasive adenocarcinomas, and light shading indicates adenocarcinomas in situ. (C) Detection rates of invasive lung cancer and adenocarcinoma in situ by age group, in participants with or without a family history of lung cancer. One solid nodule was diagnosed as adenosquamous cell carcinoma, thus the total number for solid and part-solid nodules in part B (n=209) differs from that in part A (n=210).

	All participants (n=12 011)	Family history of lung cancer (n=6009)	No family history of lung cancer (n=6002)	p value
Lung cancer	318 (2·6%)	197 (3·3%)	121 (2·0%)	<0·0001
Invasive lung cancer	257 (2·1%)	161 (2·7%)	96 (1·6%)	<0·0001
Stage	..	..	..	0·7301
0 (adenocarcinoma in situ)	61 (19·2%)	36 (18·3%)	25 (20·7%)	..
IA	220 (69·2%)	140 (71·1%)	80 (66·1%)	..
IB	26 (8·2%)	14 (7·1%)	12 (9·9%)	..
IIA	0	0	0	..
IIB	3 (0·9%)	2 (1·0%)	1 (0·8%)	..
IIIA	2 (0·6%)	2 (1·0%)	0	..
IIIB	1 (0·3%)	1 (0·5%)	0	..
IIIC	0	0	0	..
IV	5 (1·6%)	2 (1·0%)	3 (2·5%)	..
Histology	..	..	..	0·1102
Adenocaricnoma in situ	61 (19·2%)	36 (18·3%)	25 (20·7%)	..
Minimally invasive adenocarcinoma	79 (24·8%)	57 (28·9%)	22 (18·2%)	..
Invasive adenocarcinoma	177 (55·7%)	103 (52·3%)	74 (61·2%)	..
Adenosquamous cell carcinoma	1 (0·3%)	1 (0·5%)	0	..

LDCT=low-dose CT.

Table 3: **Stage and histology of lung cancers by family history**

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See Online for appendix

nodules 4–6 mm in diameter, 4829 (40·2%) showed minor abnormalities, and 4061 (33·8%) scans were negative for intrapulmonary lesions (categorised as negative LDCT scans; table 2). 339 (2·8%) of 12 011 LDCT scans were categorised as Lung-RADS (version 1.0) category 4A, 109 (0·9%) as 4B, and 61 (0·5%) as 4X, while others (95·8%) were in categories 0 (14 [0·1%]), 1 (4656 [38·8%]), 2 (5202 [43·3%]), and 3 (1630 [13·6%]).

404 participants had lung biopsies or surgeries in the first year after the baseline LDCT scan (appendix p 25). Of 2094 participants with positive LDCT scans, 330 (15·8%) underwent surgery and 24 (1·1%) had a biopsy, and 1740 (83·1%) proceeded to LDCT follow-up, according to our protocol. Overall, 409 lung cancers were diagnosed in 318 participants, with an overall lung cancer detection rate of 2·6% (318/12 011). 25 (7·9%) of 318 participants had a negative baseline LDCT. Lung cancer detection rates were 31·6% (161/509) in Lung-RADS category 4 and 1·4% (157/11502) in categories 0, 1, 2, and 3 (table 2). The median duration from LDCT examination to lung cancer diagnosis was 83·5 days (range 9–362).

Five lung cancer lesions in four participants with multiple primary lung cancers were not identified by LDCT scans, even with second reviews by a panel of chest radiologists, but were identified microscopically after surgery. Among 404 visible lung cancer nodules identified from baseline images, 77 (19·1%) were solid, 133 (32·9%) part-solid, and 194 (48·0%) were ground-glass nodules. The mean diameter was 11·5 mm (SD 8·2) for solid nodules, 13·7 mm (7·3) for part-solid nodules, and 10·1 mm (4·9) for ground-glass nodules (figure 1A).

Among all lung adenocarcinomas diagnosed, 47 (61·8%) of 76 solid nodules, 83 (62·4%) of 133 part-solid nodules, and 70 (36·1%) of 194 ground-glass nodules were diagnosed as invasive adenocarcinoma. Among 194 ground-glass nodules, 124 (63·9%) were adenocarcinoma in situ and minimally invasive adenocarcinoma. In all invasive adenocarcinomas, 130 (65·0%) of 200 were solid or part-solid nodules, and 70 (35·0%) were ground-glass nodules (figure 1B).

57 (17·9%) of 318 participants had multiple primary lung cancers according to the American Joint Committee on Cancer staging system, which was corroborated by pathological identification: 37 participants had two tumours, 11 participants had three tumours, six participants had four tumours, one participant had five tumours, and two participants had six tumours. 43 nodules deemed suspicious of lung cancer by imaging were not pathologically confirmed. There was a higher risk of multiple primary lung cancers in participants who had a low BMI (<24 kg/m²) than in those with a higher BMI (≥24 kg/m²), and in participants with a first-degree relative with lung cancer (especially a mother or multiple relatives) compared with those with no first-degree relative with lung cancer (appendix p 24).

A positive LDCT scan had 92·1% sensitivity, 84·6% specificity, a PPV of 14·0%, and a NPV of 99·7%. The PPV was higher in individuals with a family history of lung cancer than those without a family history of lung cancer (17·0% *vs* 10·9%; p<0·0001).

Benign diseases were diagnosed in 28 (90·3%) of 31 participants who had a lung biopsy and 52 (13·9%) of 373 participants who had surgery. The overall benign invasive procedure rate was 19·8% (80/404) and the benign resection rate was 13·9% (52/373). Five (1·2%) of 404 participants had malignancies other than primary lung cancer, and one (0·2%) had undetermined pathology (appendix p 25). No deaths related to procedures were reported.

Among 12 011 participants, 318 (2·6%) were diagnosed with lung cancer, of whom 257 (2·1%) had invasive lung cancer (178 [1·5%] after excluding 79 [0·7%] participants with minimally invasive adenocarcinomas). 61 (0·5%) participants were diagnosed with adenocarcinoma in situ. Overall, all but one lesion was adenocarcinoma, and 246 (77·4%) of 318 were at stage I (167 [52·5%] of 318 after the exclusion of minimally invasive adenocarcinomas; table 3).

The overall lung cancer and invasive lung cancer detection rates were significantly higher in individuals with a family history of lung cancer (197 [3·3%] of 6009 for lung cancer; 161 [2·7%] of 6009 for invasive lung cancer) than in participants without a family history (121 [2·0%] of 6002 for lung cancer; 96 [1·6%] of 6002 for invasive lung cancer; both p<0·0001; table 3; 1·2% [74/6002] after excluding adenocarcinoma in situ and minimally invasive adenocarcinoma). In participants with a family history of lung cancer, as the participant age increased, the

incidence of invasive lung cancer increased significantly (p=0·015), and the rate of adenocarcinoma in situ remained stable. In participants without a family history of lung cancer, only the invasive lung cancer rate showed an upward trend with increased participant age, but this was not statistically significant (figure 1C). In participants younger than 55 years, the detection rate for invasive lung cancer in those with a family history of lung cancer formed a J-shaped curve (ie, the detection rate of lung cancer was high in participants younger than 55 years, and lower in participants aged 55–59 years, but increased after age 59 years), which might be due to early-onset lung cancer within the family. The difference in detection rate between invasive lung cancer and adenocarcinoma in situ increased with age. If the progression of adenocarcinoma in situ to invasive lung cancer was absent or occurred in only a small proportion of people, the incidence of adenocarcinoma in situ would usually increase with age (appendix p 21). In a post-hoc analysis, lung cancer incidence decreased at subsequent follow-ups from baseline to the 6-year follow-up: 2·7% (318/12 011) at baseline, 0·6% (64/11 693) at 1 year after baseline scan, 0·4% (45/11 629) at 2 years, 0·2% (21/10 830) at 3 years, 0·1% (16/8793) at 4 years, 0·1% (8/5488) at 5 years, and 0·07% (3/4280) at 6 years (appendix pp 22–23).

Of all 12 011 participants, in the univariate analysis, female sex (odds ratio [OR] 1·80 [95% CI 1·32–2·42]), BMI lower than 24 kg/m² (0·96 [0·93–0·99]), and a family history of lung cancer (1·5 [1·31–2·07]) were significantly associated with an increased risk of lung cancer; in the multivariable analysis, the risk factors for overall lung cancer and invasive lung cancer were female sex (2·06 [1·50–2·83]), age older than 60 years (1·03 [1·01–1·05]), and a family history of lung cancer (1·67 [1·31–2·13]; table 4; appendix p 26). Passive smoke exposure, cumulative exposure to cooking, cooking without ventilation, and history of chronic lung disease were not associated with a significant increase in risk for lung cancer. In multiple logistic regression, no correlation was identified between age and cooking index (appendix p 29). In univariate analysis, in participants with a family history of lung cancer, female sex and a BMI lower than 24 kg/m² were significantly associated with an increased risk of lung cancer; in the multivariable analysis, the risk factors for overall lung cancer and invasive lung cancer were female sex and age older than 60 years (table 4; appendix p 27).

In participants with a family history of lung cancer, lung cancer and invasive lung cancer were detected in 190 (3·4%) of 5579 and 155 (2·8%) of 5579 participants with a first-degree relative with lung cancer, six (1·6%) of 366 and five (1·4%) of 366 participants with a second-degree relative with lung cancer, and one (1·6%) of 64 and one (1·6%) of 64 participants with a third-degree relative with lung cancer, respectively. Participants whose mother or sibling had lung cancer had a significantly

	Detection rate, n/N (%)	Univariate logistic regression model		Multivariable logistic regression model	
		OR (95% CI)	p value	OR (95% CI)	p value
All participants					
Sex					
Female	212/8868 (2·4%)	1·69 (1·22–2·34)	0·002	2·01 (1·42–2·84)	<0·001
Male	45/3143 (1·4%)	..	..	..	..
Age, years					
>60	142/6401 (2·2%)	1·01 (0·99–1·03)	0·463	1·03 (1·01–1·05)	0·005
≤60	115/5610 (2·0%)	..	..	..	..
BMI, kg/m²					
≥24	99/5460 (1·8%)	0·97 (0·93–1·00)	0·070	0·98 (0·94–1·02)	0·234
<24	158/6551 (2·4%)	..	..	..	..
Family history of lung cancer					
Yes	161/6009 (2·7%)	1·70 (1·32–2·19)	<0·0001	1·70 (1·29–2·23)	<0·0001
No	96/6002 (1·6%)	..	..	..	..
Passive smoke exposure					
Yes	205/9923 (2·1%)	0·83 (0·61–1·13)	0·227	0·96 (0·70–1·32)	0·801
No	46/1999 (2·3%)	..	..	..	..
History of chronic lung disease					
Yes	18/1142 (1·6%)	0·71 (0·44–1·15)	0·164	0·75 (0·46–1·22)	0·249
No	230/10 568 (2·2%)	..	..	..	..
Cooking index					
≥110	80/4395 (1·8%)	0·78 (0·60–1·02)	0·068	0·65 (0·49–0·88)	0·005
<110	177/7591 (2·2%)	..	..	..	..
Cooking without ventilation					
Yes	7/211 (3·3%)	1·58 (0·74–3·39)	0·243	1·57 (0·73–3·38)	0·251
No	250/11 800 (2·1%)	..	..	..	..
Participants with a family history of lung cancer					
Sex					
Female	135/4322 (3·1%)	2·07 (1·35–3·16)	0·001	2·35 (1·51–3·66)	<0·0001
Male	26/1687 (1·5%)	..	..	..	..
Age, years					
>60	79/2628 (3·0%)	1·02 (1·00–1·05)	0·078	1·04 (1·01–1·06)	0·005
≤60	82/3381 (2·4%)	..	..	..	..
BMI, kg/m²					
≥24	57/2689 (2·1%)	0·95 (0·90–1·00)	0·039	0·96 (0·92–1·01)	0·131
<24	104/3320 (3·1%)	..	..	..	..
Passive smoke exposure					
Yes	116/4492 (2·6%)	0·87 (0·61–1·23)	0·430	0·89 (0·63–1·27)	0·532
No	41/1460 (2·8%)	..	..	..	..
History of chronic lung disease					
Yes	7/422 (1·7%)	0·59 (0·28–1·27)	0·180	0·59 (0·27–1·27)	0·177
No	148/5459 (2·7%)	..	..	..	..
Cooking index					
≥110	36/1514 (2·4%)	0·85 (0·59–1·24)	0·404	0·60 (0·40–0·91)	0·015
<110	125/4479 (2·8%)	..	..	..	..
Cooking without ventilation					
Yes	2/82 (2·4%)	0·90 (0·22–3·70)	0·885	0·82 (0·20–3·37)	0·780
No	159/5927 (2·7%)	..	..	..	..

(Table 4 continues on next page)

	Detection rate, n/N (%)	Univariate logistic regression model		Multivariable logistic regression model	
		OR (95% CI)	p value	OR (95% CI)	p value
(Continued from previous page)					
Participants without a family history of lung cancer					
Sex					
Female	77/4546 (1·7%)	1·31 (0·79–2·17)	0·298	1·53 (0·86–2·70)	0·145
Male	19/1456 (1·3%)	..	..	..	..
Age, years					
>60	63/3773 (1·7%)	1·01 (0·97–1·05)	0·559	1·02 (0·98–1·06)	0·345
≤60	33/2229 (1·5%)	..	..	..	..
BMI, kg/m²					
≥24	42/2771 (1·5%)	0·99 (0·94–1·06)	0·859	1·00 (0·94–1·07)	0·975
<24	54/3231 (1·7%)	..	..	..	..
Passive smoke exposure					
Yes	89/5431 (1·6%)	1·35 (0·62–2·92)	0·452	1·36 (0·62–3·00)	0·440
No	5/539 (0·9%)	..	..	..	..
History of chronic lung disease					
Yes	11/720 (1·5%)	0·95 (0·50–1·78)	0·862	0·96 (0·51–1·84)	0·890
No	82/5109 (1·6%)	..	..	..	..
Cooking index					
≥110	44/2881 (1·5%)	0·92 (0·61–1·37)	0·673	0·78 (0·50–1·24)	0·292
<110	52/3112 (1·7%)	..	..	..	..
Cooking without ventilation					
Yes	5/129 (3·9%)	2·55 (1·02–6·39)	0·046	2·49 (0·99–6·25)	0·052
No	91/5873 (1·5%)	..	..	..	..

OR=odds ratio.

Table 4: **Univariate and multivariable analysis of invasive lung cancer risk among all participants, and by family history of lung cancer and risk factors**

	Detection rate, n/N (%; 95% CI)	RR (95% CI)	p value
First-degree relative			
No	102/6432 (1·6%; 1·3–1·9)	1 (ref)	<0·0001
Yes	155/5579 (2·8%; 2·3–3·2)	1·75 (1·37–2·24)	..
Father			
No	230/10 377 (2·2%; 1·9–2·5)	1 (ref)	0·143
Yes	27/1634 (1·7%; 1·0–2·3)	0·75 (0·50–1·10)	..
Mother			
No	206/10 241 (2·0%; 1·7–2·3)	1 (ref)	0·020
Yes	51/1770 (2·9%; 2·1–3·7)	1·43 (1·06–1·94)	..
Sibling			
No	157/9373 (1·7%; 1·4–1·9)	1 (ref)	<0·0001
Yes	100/2638 (3·8%; 3·1–4·5)	2·26 (1·77–2·90)	..
Offspring			
No	254/11 768 (2·2%; 1·9–2·4)	1 (ref)	0·325
Yes	3/243 (1·2%; 0·0–2·6)	0·57 (0·19–1·77)	..
Second-degree relative			
No	252/11 645 (2·2%; 1·9–2·4)	1 (ref)	0·299
Yes	5/366 (1·4%; 0·2–2·6)	0·63 (0·26–1·52)	..
Third-degree relative			
No	256/11 947 (2·1%; 1·9–2·4)	1 (ref)	1·000
Yes	1/64 (1·6%; 0·0–4·7)	0·73 (0·10–5·12)	..

RR=rate ratio.

Table 5: **Invasive lung cancer detection rates by family history of lung cancer**

increased lung cancer risk; no increased risk for overall lung cancer was observed in people whose father or offspring had lung cancer (table 5; appendix p 30). The greater the number of first-degree relatives affected by lung cancer, the higher an individual's lung cancer risk (figure 2A). Females who had one relative affected by lung cancer were at a significantly higher risk than females with no family history of lung cancer (figure 2B), whereas this association was only significant for males with at least three affected first-degree relatives (figure 2C). For participants with one first-degree relative with lung cancer, the adjusted OR for invasive lung cancer was 1·8 (95% CI 1·3–2·5) in female participants, and 1·2 (0·6–2·5) in male participants (appendix p 31). Among participants without a family history of lung cancer, female sex was significantly associated with an increased risk for overall lung cancer (appendix p 28); however, no associations were identified between any subgroups and risk for invasive lung cancer (table 4).

Discussion

In the first round of screening of TALENT, the detection rate was 2·6% for lung cancer and 2·1% for invasive lung cancer (1·5% after the exclusion of minimally invasive adenocarcinomas) in never-smokers with other risk factors for lung cancer, which were higher than those in the US National Lung Screening Trial (NLST; 1·1%) and the European NELSON study (0·9%) done in people with frequent tobacco use.[5,11] Female sex, family history of lung cancer, and age (>60 years) significantly increased the risk of lung cancer. No associations were identified between risk of lung cancer and passive smoke exposure, cooking index, and cooking without ventilation, or previous history of chronic lung diseases and risk of lung cancer. A high proportion of lung cancers are adenocarcinomas in situ, thus overdiagnosis is possible. Half of participants included in our study had a family history of lung cancer, which was higher than our previous case-control study in never-smokers (12·2%–14·7%), thus this might have increased the overall lung cancer detection rate.

In this study, 96·5% of lung cancers were stage 0 or I (19·2% adenocarcinomas in situ, 24·8% minimally invasive adenocarcinomas, and 77·4% stage I), which was considerably higher than the figures reported the NLST (50·0%) and NELSON (58·6%) studies,[5,12] but similar (52·5%) after the exclusion of adenocarcinomas in situ and minimally invasive adenocarcinomas, since the risk of recurrence of both is low after resection.[13] All participants had negative chest radiography before entry into the study. Participants in whom chest radiography suggested lung cancer did not proceed with LDCT screening. Such exclusions would have meant that larger

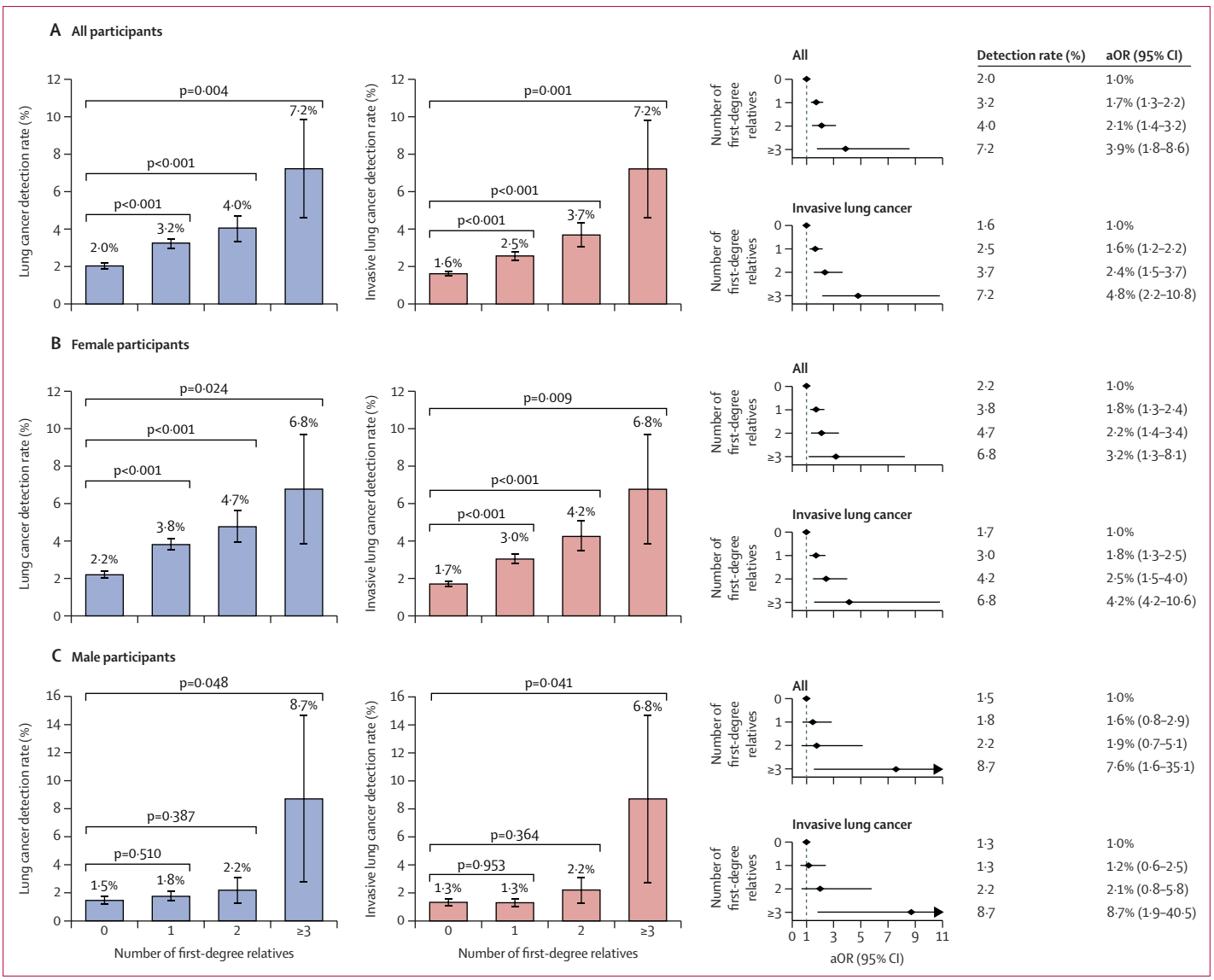

Figure 2: **Lung cancer detection rates in participants by number of first-degree relatives with lung cancer**
Detection rates of lung cancer and invasive lung cancer, and forest plots of lung cancer risk by number of first-degree relatives with lung cancer in all participants (A), female participants (B), and male participants (C). Error bars show 95% CIs. aOR=adjusted odds ratio.

tumours, visible on x-ray, were selectively removed from this study population, which would have resulted in a higher proportion of early-stage disease compared with studies such as NLST or NELSON, which did not include negative chest radiography as an inclusion criterion.

The high percentage (44·0%) of adenocarcinomas in situ and minimally invasive adenocarcinomas identified in TALENT implies that lung cancer in never-smokers has slow disease progression. However, in participants with a family history of lung cancer, the incidence of adenocarcinoma in situ remained stable with increasing age, and the incidence of invasive lung cancer increased with age. The incidence of adenocarcinoma in situ would increase with age if there was an absence of or only a small degree of progression to invasive lung cancer. This finding implies that lung cancer in never-smokers could become lethal if not detected and managed early, despite its slow progression. The preliminary findings in this study showed a low incidence of interval cancers with a low detection rate at subsequent follow-up assessments, and most of the lung cancers were prevalent cancers diagnosed from a nodule at the baseline LDCT scan in subsequent follow-ups; therefore, the initial annual follow-up interval could be increased to every 2 years in individuals with negative findings.

In a post-hoc analysis, lung cancer incidence decreased at subsequent follow-ups, which could be due to the fact that most slow-growing lung lesions were treated after

identification on initial LDCT scans. Overdiagnosis is possible, but approximately a third of pure ground-glass nodules were invasive adenocarcinomas. This finding suggests that LDCT screening might result in stage shifting (ie, diagnosis of cancers at an earlier stage) and could possibly reduce lung cancer mortality among never-smokers in Asia. However, from the results of our previous prospective LDCT screening study, most advanced lung cancers developed from initially negative or semi-positive nodules.[11]

In this study, participants with a family history of lung cancer, especially those with an affected first-degree relative, had a significantly increased risk of lung cancer. In individuals with lung cancer who have never smoked, both genetic factors and exposure to environmental carcinogens shared by family members might contribute to population differences,[14] especially in lung adenocarcinoma.[4] In a pooled analysis, individuals with a family history of lung cancer among first-degree relatives had a 1·51 times higher risk of lung cancer than individuals without a family history of lung cancer, after adjustment for other known lung cancer risk factors, and risk was higher in cases of early onset.[15] Female participants were more likely to be affected than male participants, regardless of family history of lung cancer status. Participants with a family history of lung cancer whose mother or sibling were affected had an increased risk of lung cancer, while those whose father and offspring were affected did not. This finding might imply that never-smokers with a mother who has lung cancer have higher risk than those with fathers who have lung cancer. Similar results were found in one retrospective case-control study of never-smokers.[16] Such a high risk of maternal transmission, rather than paternal transmission, might be associated with alterations in sex chromosomes, sex-specific hormonal factors, mitochondrial DNA, and genomic imprinting.[17]

Female sex was another important risk factor for lung cancer in TALENT. A meta-analysis of LDCT lung cancer screening studies of ever-smokers and never-smokers, predominantly from Asia, found that relative risk (RR) of a lung cancer diagnosis was significantly higher for Asian female never-smokers than male never-smokers and male ever-smokers, and similar to ever-smokers (≥30 pack-years) at high risk of lung cancer.[18] Globally, the prevalence of lung cancer among female never-smokers is highest in south and east Asia, at more than 60%, whereas, for comparison, in the USA it is 15%.[6] Risk factors for lung cancer can differ between the sexes, and strategies to identify individuals at high risk for lung cancer screening might need to be tailored for each sex. Lung cancer screening based on previously developed risk models could miss many individuals who could benefit from early detection and curative treatment.[19] The high risk of lung cancer among Asian never-smokers suggests that risk models specific to Asia are necessary to optimise eligibility.

This study is the first prospective LDCT screening study in never-smokers; however, it has some limitations. The unprecedentedly high lung cancer detection rate in this study could be due to several major causes. First, in this population, the proportion of adenocarcinomas in situ (19·2%) was relatively high. There was no unscreened control group; thus, the overdiagnosis rate could not be estimated. 47 (77%) of 61 participants had Lung-RADS category 2 or 3 adenocarcinoma in situ, which could be due to slow-growing lung cancer in never-smokers and could possibly have introduced overdiagnosis bias. Overdiagnosis of lung cancer by LDCT screening has raised concerns globally, especially among female never-smokers in Asian populations.[20–22] The major concern is that the incidence of indolent early-stage lung cancer increased markedly,[20–22] but no change was observed in the incidence of late-stage disease or mortality. In our previous study,[23] 32·0% of pure ground-glass nodules with a diameter of less than 2 cm were diagnosed as invasive adenocarcinoma (cutoff value 7 mm), not including minimally invasive adenocarcinoma. In TALENT, in all pure ground-glass nodules with lung cancer, 36·1% were diagnosed as invasive adenocarcinoma. In Taiwan, in our most recent analysis, despite an increasing incidence of lung cancer in the past three decades, the annual percentage change in mortality rate gradually decreased from 0·41% between 1995 and 2002 to –2·41% between 2015 and 2020.[24]

63·9% of identified cancers were adenocarcinomas in situ and minimally invasive adenocarcinomas in ground-glass nodules, thus biomarkers, radiomics, and artificial intelligence are needed for precision diagnosis. Overtreatment is another important issue. TALENT was established in 2014, at which time the NCCN 2014 guideline suggested that if ground-glass nodules increased in size or became solid or part-solid, even with a diameter of less than 5 mm, surgical excision should be considered. At that time of launching TALENT, there was still discrepancy between NCCN and Lung-RADS with regard to the management of lung nodules. Thoracic surgery for resection of small ground-glass nodules might be relevant to these recommendations. The management of pure ground-glass nodules in TALENT is detailed in the appendix (pp 6–8). Furthermore, characteristics on CT for invasive and preinvasive lung adenocarcinoma overlap, although the majority of pure ground-glass nodules are more likely to be lepidic-predominant lung adenocarcinoma. The majority of pure ground-glass nodules are removed via wedge resection, which is a minimally invasive procedure usually completed without impairing pulmonary function. Adherence to the screening programme might not be easy for participants with concerns about the malignant potential of invasive lung cancer, especially if they have family members with advanced lung cancer. Randomised controlled trials are needed for the evaluation of benefit using LDCT screening in never-smokers. Second, half of the participants had a

family history of lung cancer, with a high lung cancer detection rate (3·3%), which might have resulted in the overestimation of overall lung cancer detection rate. 50% of participants with a family history of lung cancer is higher than the the proportion in the available case control study in Taiwan (appendix p 8). Third, more than 70% of the participants were female and the incidence of lung cancer was high (2·4%), which was also observed in a retrospective LDCT screening study in China among hospital employees with a high detection rate in female never-smokers (2·5%); however, no data were collected about family history of lung cancer or environmental exposures.[25] Fourth, the incidence of invasive lung cancer among never-smokers who did not have a family history of lung cancer was 1·6% (1·2% after excluding minimally invasive adenocarcinomas), which is higher than that reported in the NLST and NELSON studies, but no differences were found in subgroup analysis of all risk factors (sex, age, BMI, passive smoke exposure, history of chronic lung disease, cooking index, and cooking without ventilation). This restricts the applicability of our findings to other populations outside of Taiwan. One of the possible causes could be differences in ethnic variation and occupational and environmental risk factors. Air pollution is one of the important factors leading to lung cancer formation that was not included in this study, since its importance has been demonstrated in a prospective trial, especially in lung adenocarcinoma.[26] The association between air pollution exposure and lung cancer, especially *EGFR* mutation, is described in the appendix (pp 8–9). Fifth, 6·7% of participants were self-reported former smokers and misclassification of smoking status might have caused overestimation of the lung cancer detection rate. In former smokers, the relative risk of lung cancer decreased to 1 when quit-years reached 7 years in a Chinese population meta-analysis.[27] Therefore, we can consider that participants with less than 10 pack-years of smoking who quit more than 15 years previously are similar to never-smokers. Sixth, there was a lower risk between high cooking index and lung cancer, probably due to the small number of participants cooking without ventilation. Further studies are needed in the future.

Lung cancer in never-smokers is an increasing public health threat worldwide. At 1-year follow-up after the baseline LDCT in TALENT, the detection rate of invasive lung cancers was high, especially for early-stage disease. The prevalence of invasive lung cancer was higher in participants with a family history of lung cancer than in those without a family history of lung cancer. Female sex, a family history of lung cancer, and older age were significant risk factors for lung cancer in never-smokers. Family history of lung cancer among first-degree relatives, especially mothers or siblings, was found to significantly increase the risk of lung cancer as well as the rate of invasive lung cancer with increasing age. The environmental factors included and previous history of chronic lung diseases had no significant effect on the risk for lung cancer, even after stratification by family history of lung cancer. No subgroup of patients without family history of lung cancer had an increased risk of invasive lung cancer. The identification of more risk factors for lung cancer in never-smokers is needed to inform future screening strategies.

Contributors

All authors were involved in the conception and design of the study and the analysis and interpretation of the data. Participant data were collected by G-CC, C-HC, C-JY, K-HH, Y-CW, C-YC, C-TY, I-WC, Y-CL, T-CH, M-CL, W-CS, C-BL, K-YL, Y-FW, C-FC, R-SL, J-YS, C-LW, K-CC, J-YH, C-KP, E-KT, C-LH, Y-HT, C-MT, Y-MC, Y-CL, and P-CY, and the TALENT investigators. Y-CC, H-HH, M-TW, G-YL, W-PC, K-LW, M-HW, H-HT, J-SH, C-KC, T-YC, W-CS, Y-HC, H-YC, S-LY, C-JC, Y-LW, and C-AH verified the data and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors had full access to the data and contributed to the preparation of the manuscript. All authors approved the manuscript for submission and verified the accuracy and completeness of the data and the fidelity of the study to the protocol.

Declaration of interests

We declare no competing interests.

Data sharing

The protocol, definition, and derivation of clinical characteristics and outcomes, and training materials are available online. Qualified researchers can request data from the corresponding author.

For more on the **protocol, definition and derivation of clinical characteristics and outcomes, and training materials** see https://clinicaltrials.gov/study/NCT02611570

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Taletrectinib: TRUST in the Continued Evolution of Treatments for *ROS1* Fusion–Positive Lung Cancer

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The genomically defined diagnostic and therapeutic approach to non–small-cell lung cancer (NSCLC) exemplifies the precision oncology paradigm. Across multiple molecular subsets of NSCLC, effective targeted therapies now represent standard first-line treatment for patients with advanced-stage disease.[1] Early experiences with tyrosine kinase inhibitors (TKIs) for epidermal growth factor receptor (*EGFR*)-mutated and anaplastic lymphoma kinase (*ALK*) fusion–positive (ALK+) NSCLC have highlighted the pivotal challenge of disease relapse due to acquired TKI resistance.[2] This lesson has motivated the development of next-generation TKIs with increasing potency and selectivity, CNS penetrance, and coverage of on-target resistance mutations, offering potential not only as later-line, postprogression options after early-generation TKIs but also as upfront therapies that enable more prolonged disease control and, ideally, better tolerability.

Gene fusions involving ROS proto-oncogene 1, receptor tyrosine kinase (*ROS1*) are oncogenic drivers identified in 1%-2% of patients with NSCLC and—at variable frequencies—other adult and pediatric cancers.[3,4] The development of targeted therapies for *ROS1* fusion–positive (ROS1+) NSCLC has followed a trajectory akin to that for *EGFR*-mutated and ALK+ NSCLC. Crizotinib, a multikinase inhibitor of ALK, ROS1, and MET, was the first TKI approved by the US Food and Drug Administration (FDA) and globally for patients with metastatic ROS1+ NSCLC. This approval was based on the phase I trial PROFILE 1001, which demonstrated an objective response rate (ORR) of 72% and a median progression-free survival (mPFS) of 19.2 months.[5] Subsequently, entrectinib, a ROS1 and tropomyosin receptor kinase (TRK) inhibitor, showed efficacy in this patient population with an ORR of 68% and an mPFS of 15.7 months.[6] Most recently, the next-generation ROS1 and TRK TKI repotrectinib entered the treatment landscape. In the phase I/II registrational trial TRIDENT-1, repotrectinib demonstrated an ORR of 79% and an mPFS of 35.7 months in patients with TKI-naïve disease and an ORR of 38% and an mPFS of 9 months in patients who previously received one ROS1 TKI and no chemotherapy, resulting in FDA approval in November 2023 for advanced ROS1+ NSCLC.[7] Although several additional ROS1 inhibitors have been evaluated to date, repotrectinib currently represents the only next-generation ROS1 TKI FDA-approved for first-line use and the only TKI approved for use after a previous ROS1 inhibitor. Furthermore, access to these TKIs globally remains variable (eg, repotrectinib approved solely in the United States).

In the article accompanying this editorial, Li et al[8] report results from the phase II trial TRUST-I that evaluated the efficacy and safety of the next-generation ROS1 TKI taletrectinib in Chinese patients with advanced or metastatic ROS1+ NSCLC. Taletrectinib demonstrated promise as an effective therapeutic option for both TKI-naïve patients and those previously treated with first-generation TKI crizotinib (Fig 1), with robust systemic and intracranial efficacy, ability to overcome on-target resistance mutations, and relatively low rates of neurologic adverse events (AEs).

A central question in the treatment of metastatic ROS1+ NSCLC is defining optimal first-line therapy, and a major consideration herein is systemic efficacy. In TRUST-I, taletrectinib showed excellent and durable systemic efficacy among TKI-naïve patients (n = 106, of whom 21.7% had received previous anticancer therapy), with confirmed ORR per independent review committee (IRC) of 90.6%, IRC-assessed mPFS not reached after median follow-up of 23.5 months (investigator-assessed mPFS of 31.8 months), and 24-month PFS of 70.5% (Fig 2).[8] These findings suggest a longer PFS achieved with taletrectinib than that historically reported with first-generation ROS1 TKIs crizotinib and entrectinib (medians

THE TAKEAWAY

In the article that accompanies this editorial, Li et al[8] report results from the phase II trial TRUST-I, in which taletrectinib, a next-generation ROS proto-oncogene 1, receptor tyrosine kinase (ROS1) tyrosine kinase inhibitor (TKI), demonstrated robust systemic and intracranial efficacy, ability to overcome on-target *ROS1* resistance mutations, and relatively low rates of neurologic adverse events among TKI-naïve and crizotinib-pretreated patients in China with advanced *ROS1* fusion–positive (ROS1+) non–small-cell lung cancer (NSCLC). These findings represent another step forward in the efforts to improve outcomes for patients with ROS1+ NSCLC, and the global phase II trial TRUST-II is ongoing to further explore the efficacy and safety of taletrectinib in a broader population.

ranging from 15.9 to 22.8 months across selected studies for crizotinib and 15.7 months in integrated phase I/II analysis for entrectinib) and are reminiscent of PFS with repotrectinib in TRIDENT-1 (TKI-naïve setting: mPFS of 35.7 months, 18-month PFS rate of 70%).[4-7] As TRUST-I was limited to patients from China, the ongoing global phase II study TRUST-II (ClinicalTrials.gov identifier: NCT04919811) is vital to evaluate the efficacy of taletrectinib in a broader population.[11] Regardless, together with TRIDENT-1, these data indicate next-generation ROS1 TKIs may achieve higher efficacy than a first-generation TKI as initial therapy for metastatic ROS1+ NSCLC, recapitulating the precedent of next-generation TKIs supplanting first-generation TKIs in *EGFR*-mutated and ALK+ lung cancers.[2] TRIDENT-3 (ClinicalTrials.gov identifier: NCT06140836) is a phase III trial comparing repotrectinib with crizotinib in TKI-naïve ROS1+ NSCLC. Emerging data from such studies, TRUST-II, and trials evaluating other next-generation TKIs like zidesamtinib (NVL-520)—a ROS1-selective TKI under investigation in a global phase II trial ARROS-1 (ClinicalTrials.gov identifier: NCT05118789) including in TKI-naïve patients[12]—will collectively refine the first-line treatment paradigm for metastatic ROS1+ NSCLC.

Another key consideration in assessing ROS1 TKIs is CNS efficacy, as rates of brain metastases in ROS1+ NSCLC reach 20%-30% at initial diagnosis and 30%-50% cumulatively.[13,14] Crizotinib has poor CNS penetration and activity, and the brain is a common site of disease progression on crizotinib.[13] In contrast, entrectinib and repotrectinib have shown CNS efficacy (intracranial ORR of 80% with entrectinib and 89% with repotrectinib in TKI-naïve patients).[6,7] In TRUST-I, taletrectinib achieved an intracranial ORR of 87.5% in eight TKI-naïve and 73.3% in 15 crizotinib-pretreated patients, identifying taletrectinib as another CNS-active ROS1 TKI.[8] Further studies are needed to confirm these findings in larger numbers of patients, assess durability of CNS responses, and determine intracranial activity after CNS progression on previous brain-active TKIs (eg, entrectinib or repotrectinib). In addition, intracranial PFS and cumulative incidence of CNS progression (with or without baseline brain metastases) were not measured end points in TRUST-I and warrant evaluation.

As efficacious ROS1 TKI options expand, TKI-associated AE profiles influence treatment selection. In TRUST-I, taletrectinib showed overall favorable safety with 19.1% requiring dose reductions and 5.2% requiring treatment discontinuations due to treatment-emergent AEs (TEAEs). The most common TEAEs were increased AST (76.3%), diarrhea (69.9%), and increased ALT (67.6%); although most were grade 1-2 AST and ALT increase, grade 3-4 increase occurred in 8.1% and 5.2% of patients, respectively.[8] Of note, all currently approved ROS1 TKIs inhibit additional non-ROS1 kinases, resulting in undesirable toxicities.[4-7,15] A common theme across ROS1/TRK inhibitors (eg, entrectinib, repotrectinib) is risk of TRK inhibition–mediated neurologic AEs due to physiologic expression of TRK proteins in the nervous system and their involvement in neuron signaling.[16] For example, repotrectinib potently inhibits TRKA/B/C (in vitro IC_{50} 0.53, <0.05, and 0.07 nM, respectively) in addition to ROS1 (IC_{50} < 0.05 nM),[11] and in TRIDENT-1, it had high incidence of neurologic AEs, including dizziness (58%), dysgeusia (50%), paresthesia (30%), and ataxia (20%).[7] In biochemical kinase assays, taletrectinib shows approximately 20-fold selectivity for ROS1 (IC_{50} 0.07) over TRKA (IC_{50} 1.26) and TRKB (IC_{50} 1.47) and approximately 2.5-fold selectivity over TRKC (IC_{50} 0.18).[11] The relative selectivity for ROS1 over TRKA/B may explain the overall lower rates of neurologic AEs reported in TRUST-I. However, any-grade dizziness still occurred in 23.1% of patients.[8] Since TRKC is involved in proprioception (with *Ntrk3*-null mice exhibiting abnormal posture and movements),[17] potential contribution of TRKC inhibition to taletrectinib-associated neurologic AEs cannot be excluded. Zidesamtinib, of note, was designed to be ROS1-selective and TRK-sparing, with preliminary phase I analyses yielding no reports of treatment-related neurologic AEs,[9,12] further supporting that highly selective ROS1 inhibition may improve tolerability.

Effective therapeutic options after progression on first-generation ROS1 TKIs (crizotinib or entrectinib) represent another important area of unmet need given their prevalent usage globally, with repotrectinib remaining the only FDA-approved option for TKI-pretreated patients. In TRUST-I, taletrectinib was active in crizotinib-pretreated patients (n = 66) with IRC-assessed ORR of 51.5% and mPFS of

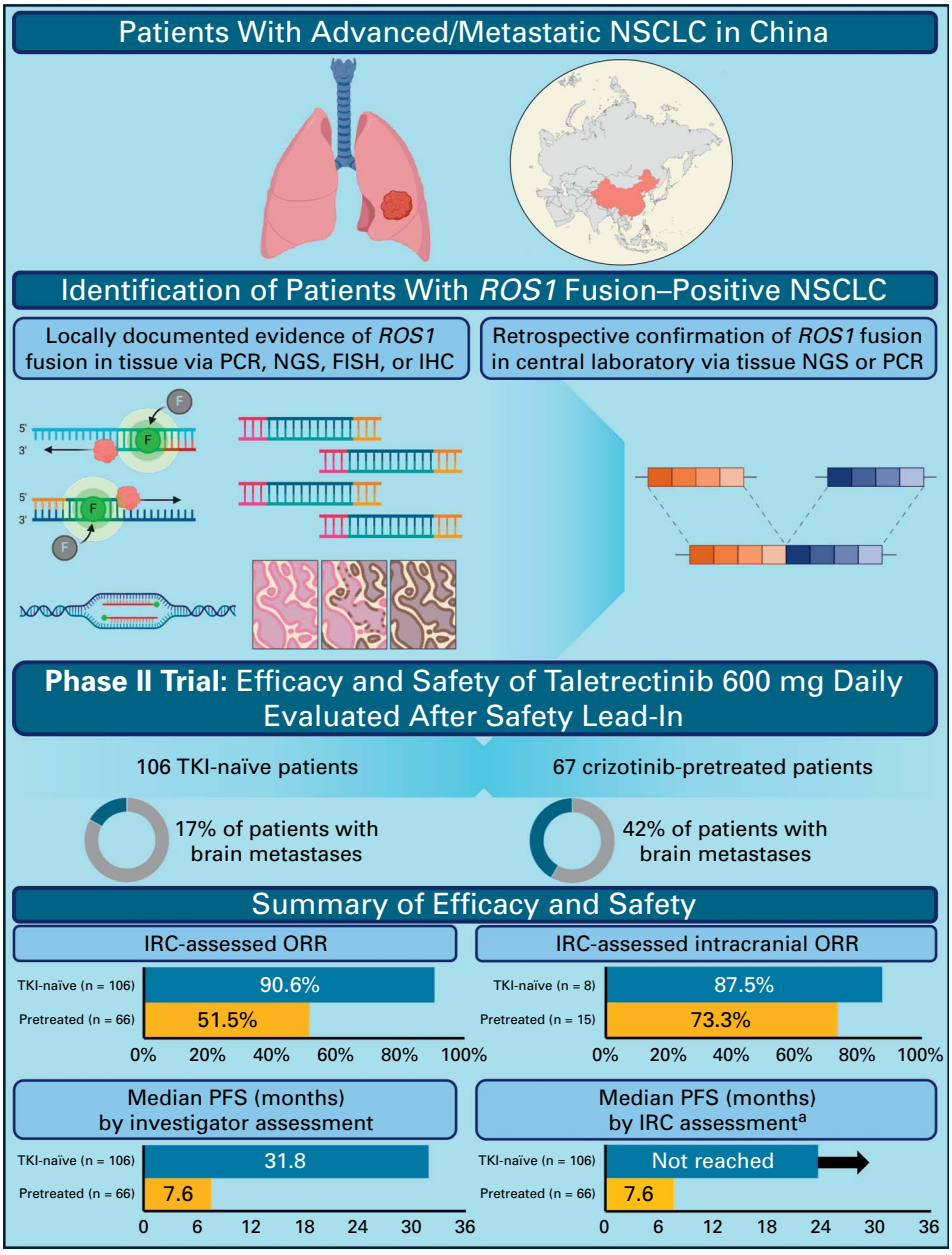

FIG 1. Summary of TRUST-I clinical trial design and select efficacy and safety results. [a]The median PFS per IRC assessment was not reached among TKI-naïve patients after a median follow-up of 23.5 months. FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; IRC, independent review committee; NGS, next-generation sequencing; NSCLC, non–small-cell lung cancer; ORR, objective response rate; PCR, polymerase chain reaction; PFS, progression-free survival; *ROS1*, ROS proto-oncogene 1, receptor tyrosine kinase; TKI, tyrosine kinase inhibitor.

7.6 months, indicating utility after crizotinib.[8] Efficacy after progression on previous entrectinib or repotrectinib was not evaluated in TRUST-I and remains unknown. TRUST-II is evaluating the efficacy of taletrectinib in various treatment settings, including after one previous ROS1 TKI (crizotinib or entrectinib) and after ≥2 previous TKIs,[11] and will illuminate its role in the current treatment landscape.

A fundamental consideration in the later-line treatment setting is activity against on-target *ROS1* resistance mutations. Acquired *ROS1* mutations are a recurrent mechanism of resistance to early-generation TKIs, identified in 8.3%-38% of patients after previous crizotinib,[18,19] 26% after first-line entrectinib,[10] and 46% after lorlatinib.[18] In particular, G2032R is the most frequently detected *ROS1* resistance

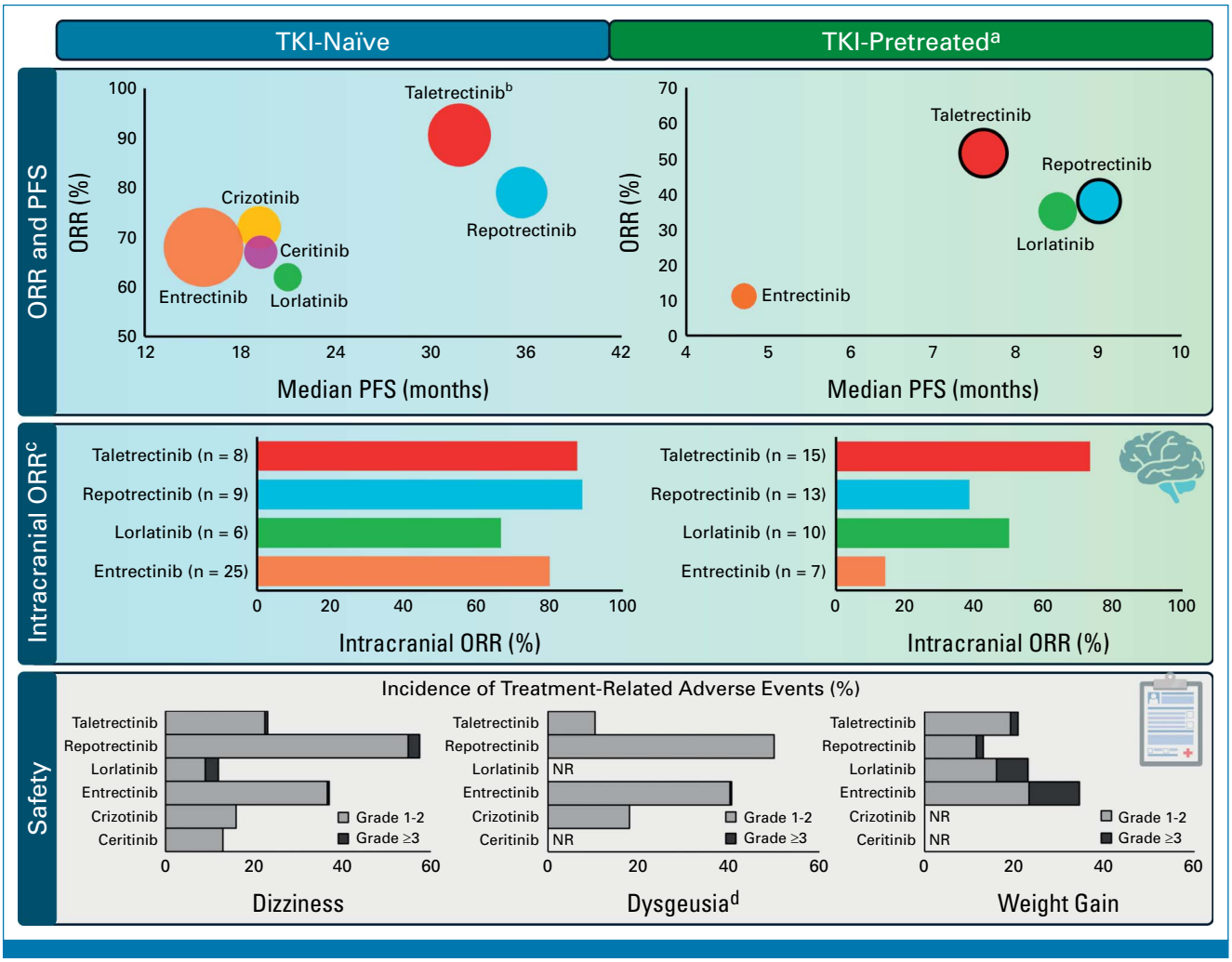

FIG 2. Comparison of efficacy and select treatment-emergent neurologic adverse events of ROS1 inhibitors in *ROS1* fusion–positive lung cancer.[4-9] ROS1 inhibitors currently FDA-approved or included in NCCN guidelines,[10] in addition to taletrectinib,[8] are shown. Bubble plots demonstrating comparative efficacy show mPFS on the *x*-axis and ORR on the *y*-axis, with circle sizes representing sample sizes from respective trials.[4-9] Activity against *ROS1* G2032R in TKI-pretreated patients is indicated using black circle borders. [a]The mPFS shown for taletrectinib (31.8 months) in TKI-naïve patients is per investigator assessment in TRUST-I; mPFS per independent review committee was not reached after a median follow-up of 23.5 months.[8] [b]Pretreated patients received previous crizotinib only for lorlatinib, entrectinib, and taletrectinib and one previous TKI (82% crizotinib, 16% entrectinib, 2% ceritinib) for repotrectinib.[4-8] [c]Intracranial ORRs are shown for those with baseline measurable CNS disease only. Crizotinib is not CNS-active. Zidesamtinib (NVL-520), a next-generation ROS1-selective TKI, is not shown as PFS data are not yet available from the ongoing ARROS-1 trial; ORR was 48% (10/21) in TKI-pretreated patients (80% received ≥2 previous ROS1 TKIs with or without chemotherapy) and 78% (7/9) in those with *ROS1* G2032R, with intracranial objective responses in three of three patients with baseline measurable brain metastases.[9] [d]Breakdown of grade of dysgeusia with taletrectinib in TRUST-1 was not reported. FDA, US Food and Drug Administration; mPFS, median progression-free survival; NCCN, National Comprehensive Cancer Network; NR, not reported; ORR, objective response rate; PFS, progression-free survival; *ROS1*, ROS proto-oncogene 1, receptor tyrosine kinase; TKI, tyrosine kinase inhibitor.

mutation.[18] In TRUST-I, taletrectinib was effective against on-target resistance mutations, with systemic ORR of 66.7% among 12 patients with known *ROS1* G2032R and 60% among 15 patients with any known acquired *ROS1* mutations.[8] Other next-generation ROS1 TKIs repotrectinib and zidesamtinib are also active in patients with known *ROS1* G2032R after previous ROS1 TKI.[7,12] Of note, although lorlatinib (ALK/ROS1 TKI) is included in National Comprehensive Cancer Network guidelines as a subsequent next-line option and offers robust CNS activity,[10] it is not active against G2032R (ORR 0%).[15] Across phase I/II trials including TRUST-I,[7-9] next-generation inhibitors induced numerically higher ORRs in patients whose tumors harbored *ROS1* resistance mutations compared with those without such mutations (eg, ORR 60.0% *v* 38.5% in TRUST-I), supporting a role for rebiopsy to identify patients more likely to respond to next-generation TKIs. On the other hand, in the same trials, next-generation ROS1 TKIs still induced some—albeit lower rates of—responses in tumors without on-target resistance mutations, suggesting that a subset of these

tumors remain ROS1-dependent and can be controlled with more potent ROS1 inhibition.

In summary, TRUST-I demonstrated compelling systemic and intracranial activity of taletrectinib in both upfront and post-crizotinib settings, with relatively low rates of neurologic AEs and ability to overcome crizotinib-resistant *ROS1* mutations. These findings represent another step forward in the efforts to improve outcomes for patients with ROS1+ NSCLC. The ongoing TRUST-II trial will be essential in confirming and expanding upon these findings in a global population. Several important questions remain. First, appraising in totality the systemic and CNS efficacy and long-term tolerability from multiple ongoing trials will be imperative in crystallizing optimal treatment sequencing for metastatic ROS1+ NSCLC. In addition, to date, most data on mechanisms of ROS1 TKI resistance are from the post-crizotinib context.[4,18,19] As next-generation ROS1 TKIs begin moving into first-line use, the resulting ROS1 resistance landscape merits investigation to inform subsequent therapeutic strategies. In *EGFR*-mutated and ALK+ lung cancers, prevalence of on-target resistance has diminished with first-line use of next-generation rather than first-generation TKIs.[2] A similar shift in the ROS1 resistance landscape is likely,[7] warranting dedicated endeavors to delineate and address off-target mechanisms of resistance. Nevertheless, *ROS1* mutations refractory to next-generation TKIs will still emerge. Indeed, *ROS1* L2086F, resistant to all type I ROS1 TKIs,[18,20] has already been reported in the taletrectinib-refractory setting.[21] Finally, all currently approved ROS1 inhibitors are for NSCLC indication only, with limited data on non-NSCLC ROS1+ tumors. TRUST-I enrollment also was restricted to patients with NSCLC. Clinical trials of TRK and RET inhibitors in *NTRK* and *RET* fusion–positive solid tumors, respectively, have demonstrated tumor-type agnostic efficacy,[22-25] setting precedent for genomic biomarker-driven, histology-agnostic therapy development and approvals. Going forward, academy-industry collaborations should strive toward tumor-agnostic indications for therapies targeting biomarkers shared across tumor types to maximize and broaden delivery of pharmacologic innovations to patients in need.

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