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LBA1 – Durvalumab in Combination with Chemoradiotherapy for Patients with Unresectable, Stage III NSCLC: Final Results from PACIFIC-2

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Disclosures

- **Personal financial interests:** None
- **Institutional financial interests:** Varian Medical Systems
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- **Funding:** The PACIFIC-2 study (NCT03519971) was sponsored by AstraZeneca

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Background

- In the PACIFIC trial, concurrent CRT followed by 12 months of consolidation durvalumab resulted in sustained 5-year OS and PFS improvement, and is considered the global standard of care for patients with unresectable, stage III NSCLC[1–4]
- However, approximately 15–30% of patients may not be eligible to receive consolidation durvalumab due to disease progression during or immediately after cCRT, radiation pneumonitis, or other adverse events[5–9]
- There is preclinical evidence that supports starting IO concurrently with CRT, based on a hypothesized synergistic effect for concurrent administration of IO and radiotherapy,[1,10–14] which may:
  - provide an opportunity to benefit patients who may progress on CRT alone[10,15]
  - increase the rate and depth of response, potentially leading to prolonged clinical benefit[10,15]
- PACIFIC-2 is the first phase 3 study designed to assess the efficacy of concurrent IO (i.e., durvalumab) plus CRT (IO+CRT) followed by consolidation IO in patients with unresectable, Stage III NSCLC[10]

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cCRT, concurrent chemoradiotherapy; CRT, chemoradiotherapy; IO, immunotherapy; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival

1. Antonia SJ, et al. N Engl J Med. 2017;377:1919–1929. 2. Spigel DR, et al. J Clin Oncol. 2022;40:1301–1311. 3. Remon J, et al. Ann Oncol. 2021;32:1637–1642. 4. Daly ME, et al. J Clin Oncol. 2021;40:1356–1364. 5. Sakaguchi T, et al. Respir Investig. 2019;57:466–471. 6. Mountzios G, et al. Presented at ELCC 2024. Poster #593. 7. Eichkorn T, et al. Front Oncol. 2020;10:586449. 8. Brunt A, et al. Front Oncol. 2021;11:744956. 9. Feng J, et al. Presented at ESMO 2022. Poster 964P. 10. Bradley J, et al. J Clin Oncol. 2019;37(suppl 15):TPS8573. 11. Daly ME, et al. J Thorac Oncol. 2015;10:1685–1693. 12. Vidor CT-S, et al. Nature. 2015;520:373–377. 13. Pardoll DM. Nat Rev Cancer. 2012;12:252–264. 14. Szmol M, Chen L. Clin Cancer Res. 2013;19:5542. 15. Hosoya K, et al. Cancer Chemother Pharmacol. 2019;84:275–280.

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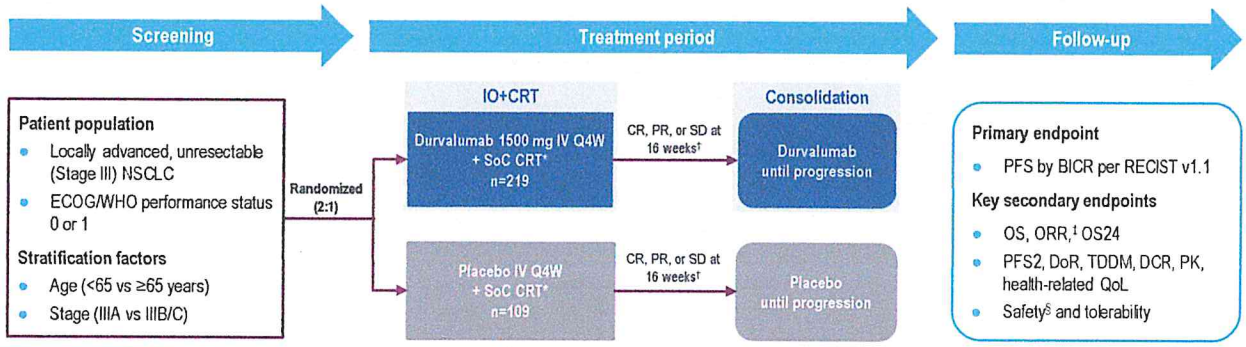
Study design

PACIFIC-2 (NCT03519971) is a phase 3, randomized, double-blind, placebo-controlled, multicenter, global study of durvalumab + CRT followed by durvalumab versus placebo + CRT followed by placebo



Patients were recruited from 29 March 2018 through 24 June 2019 across 106 sites in Asia, Eastern Europe, and the Americas, including: Brazil, Czech Republic, Hungary, India, Japan, Mexico, Peru, Philippines, Poland, Republic of Korea, Russia, Turkey, Thailand, and Vietnam

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BICR, blinded independent central review; CR, complete response; CRT, chemoradiotherapy; DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; Gy, gray; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; OS24, overall survival at 24 months; PFS, progression-free survival; PFS2, time from randomization to second progression; PK, pharmacokinetics; PR, partial response; Q4W, once every 4 weeks; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SoC, standard of care; TDDM, time to death or distant metastasis; WHO, World Health Organization.

*Platinum-based chemotherapy regimens include: cisplatin/etoposide, carboplatin/paclitaxel, pemetrexed/cisplatin (non-squamous only), or pemetrexed/carboplatin (non-squamous only), alongside radiation therapy (5 fractions/week for ~6 weeks [±3 days; total 60 Gy]). †Investigator assessed per RECIST v1.1. ‡Following a protocol amendment, ORR was moved from a primary endpoint to a key secondary endpoint. §Will be reviewed by an independent data monitoring committee in an unblinded manner.

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Key baseline patient characteristics (ITT population)

	Durvalumab + CRT (n=219)	Placebo + CRT (n=109)
Age group (years), n (%)		
<50	18 (8.2)	12 (11.0)
≥50 to <65	107 (48.9)	50 (45.9)
≥65 to <75	75 (34.2)	40 (36.7)
≥75	19 (8.7)	7 (6.4)
Median age (range), years	63.0 (36–84)	63.0 (39–84)
Sex, n (%)		
Male	166 (75.8)	80 (73.4)
Female	53 (24.2)	29 (26.6)
Race, n (%)		
White	141 (64.4)	62 (56.9)
Black or African American	2 (0.9)	0
Asian	65 (29.7)	39 (35.8)
American Indian or Alaska Native	7 (3.2)	7 (6.4)
Other	4 (1.8)	1 (0.9)
ECOG/WHO PS, n (%)		
0 – Normal activity	98 (44.7)	53 (48.6)
1 – Restricted activity	121 (55.3)	56 (51.4)
Histology type, n (%)		
Squamous	121 (55.3)	52 (47.7)
Non-squamous	98 (44.7)	57 (52.3)
PD-L1 status, n (%)*		
<1% (negative)	86 (39.3)	36 (33.0)
≥1% (positive)	113 (51.6)	60 (55.0)
Unknown	20 (9.1)	13 (11.9)

	Durvalumab + CRT (n=219)	Placebo + CRT (n=109)
***EGFR* mutation, n (%)**		
Positive	7 (3.2)	6 (5.5)
Negative	112 (51.1)	60 (55.0)
Unknown	100 (45.7)	43 (39.4)
AJCC stage, n (%)†		
IIIA	76 (34.7)	37 (33.9)
IIIB	109 (49.8)	51 (46.8)
IIIC	33 (15.1)	20 (18.3)
IV	1 (0.5)	1 (0.9)
TNM class at screening, n (%)		
Primary tumour		
TX	2 (0.9)	1 (0.9)
T1	15 (6.8)	10 (9.2)
T2	37 (16.9)	13 (11.9)
T3	39 (17.8)	32 (29.4)
T4	126 (57.5)	53 (48.6)
Regional lymph nodes		
N0	25 (11.4)	7 (6.4)
N1	16 (7.3)	14 (12.8)
N2	124 (56.6)	60 (55.0)
N3	54 (24.7)	28 (25.7)
Distant metastases		
M0	218 (99.5)	108 (99.1)
M1b	1 (0.5)	1 (0.9)

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AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ITT, intention-to-treat; PD-L1, programmed cell death ligand-1; PS, performance status; TNM, tumor, node, metastasis; WHO, World Health Organization

*PD-L1 testing was retrospective and performed centrally
†Per the 8th edition of the AJCC Cancer Staging Manual

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Key patient disposition (ITT population)

CRT disposition	Durvalumab + CRT (n=219)	Placebo + CRT (n=109)
Patients who received CRT, n (%)	218 (99.5)	109 (100)
Cisplatin/etoposide	11 (5.0)	11 (10.1)
Carboplatin/paclitaxel	166 (75.8)	81 (74.3)
Pemetrexed/cisplatin	18 (8.2)	8 (7.3)
Pemetrexed/carboplatin	23 (10.5)	9 (8.3)
Radiation therapy	215 (98.2)	107 (98.2)
Patients who completed CRT, n (%)	192 (88.1)	99 (90.8)
Patients who discontinued CRT, n (%)	26 (11.9)	10 (9.2)
Adverse event	20 (9.2)	5 (4.6)
Disease progression	4 (1.8)	2 (1.8)
Patient decision	2 (0.9)	1 (0.9)
Other	0	2 (1.8)

Durvalumab/placebo disposition	Durvalumab + CRT (n=219)	Placebo + CRT (n=109)
Patients who received durvalumab/placebo, n (%)	218 (99.5)	109 (100)
Patients who discontinued durvalumab/placebo at any time, n (%)	183 (83.9)	92 (84.4)
Adverse event	58 (26.6)	15 (13.8)
Disease progression	117 (53.7)	67 (61.5)
Patient decision	5 (2.3)	7 (6.4)
Development of study specific discontinuation criteria	0	1 (0.9)
Other	3 (1.4)	2 (1.8)

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CRT, chemoradiotherapy

Data cutoff: 7 September 2022

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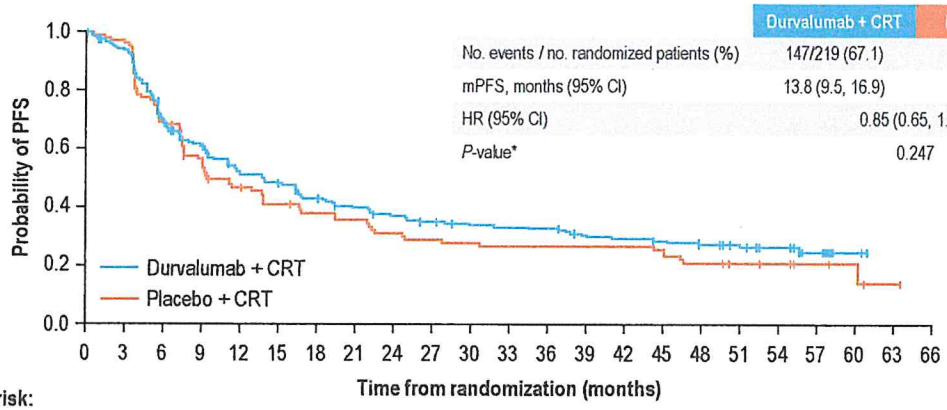
PFS by BICR (ITT population)



	Durvalumab + CRT	Placebo + CRT
No. events / no. randomized patients (%)	147/219 (67.1)	80/109 (73.4)
mPFS, months (95% CI)	13.8 (9.5, 16.9)	9.4 (7.5, 16.6)
HR (95% CI)	0.85 (0.65, 1.12)	
P-value*	0.247	

No. at risk:

Durvalumab + CRT	219	199	145	124	102	94	83	75	69	64	60	59	58	50	49	47	43	28	24	10	2	0	0
Placebo + CRT	109	104	72	58	44	38	34	32	28	26	25	24	24	24	24	23	19	15	12	7	3	1	0

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BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; mPFS, median PFS; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Per RECIST v1.1. Tick marks on the curves indicate censored observations.
*Based on the Lan and DeMets approach that approximates the O'Brien Fleming spending functions, the 2-sided p-value boundary for declaring statistical significance is 0.0416 for an overall 5% alpha.

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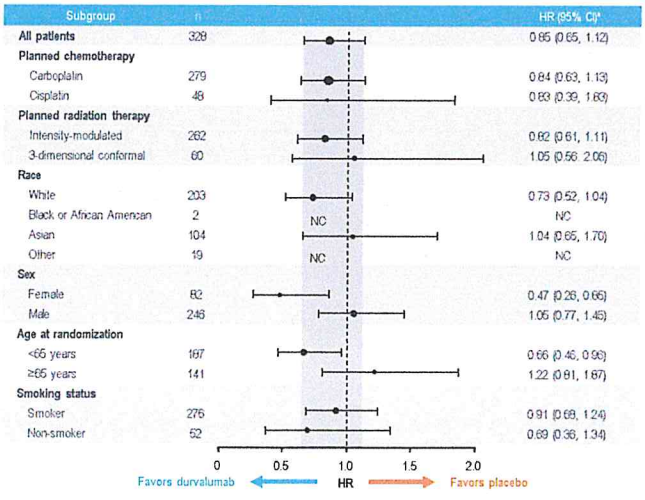
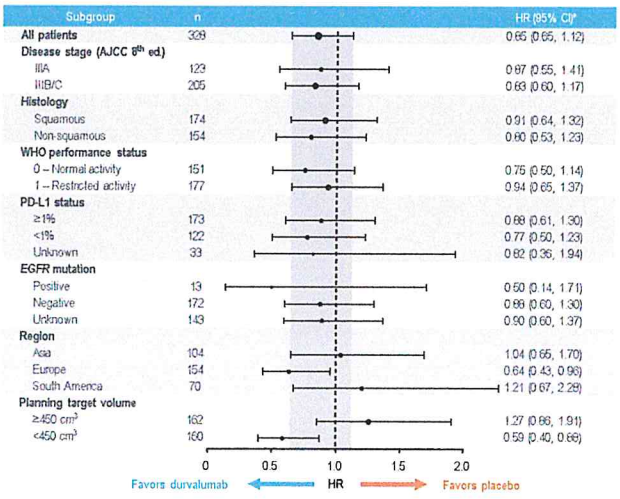
PFS by BICR (ITT population), subgroup analysis





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BICR, blinded independent central review; CI, confidence interval; ITT, intention to treat; NC, not calculable; HR, hazard ratio; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Per RECIST v1.1. A HR of <1 favors durvalumab and is associated with a longer event-free survival than placebo. The size of circle is proportional to the number of events. The gray band represents the 95% CI for the main PFS HR. For all patients, the analysis is based on the main stratified analysis while, for the subgroups, the HR and CI were calculated using an unstratified Cox proportional hazards model, with treatment as the only covariate and ties handled by Efron approach. *HRs and 95% CIs were not calculated if a subgroup had fewer than 5 events in each treatment arm.

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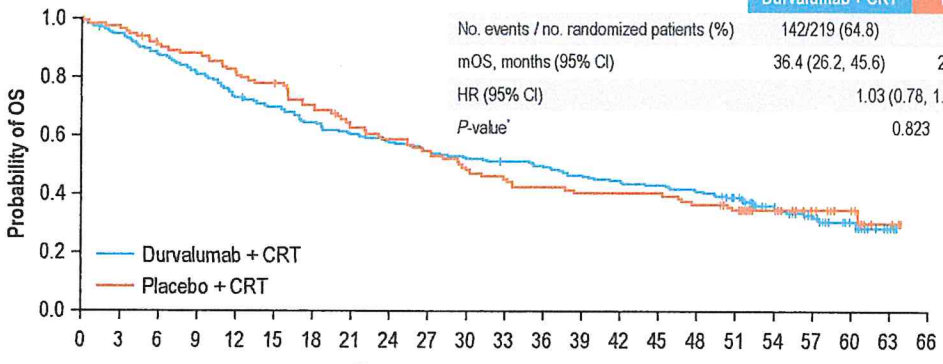
OS and ORR (ITT population)



	Durvalumab + CRT	Placebo + CRT
No. events / no. randomized patients (%)	142/219 (64.8)	69/109 (63.3)
mOS, months (95% CI)	36.4 (26.2, 45.6)	29.5 (23.2, 45.1)
HR (95% CI)	1.03 (0.78, 1.39)	
P-value*	0.823	

No. at risk:																							
Durvalumab + CRT	219	207	191	177	160	152	141	132	126	120	114	111	107	100	95	94	89	75	49	31	15	1	0
Placebo + CRT	109	106	98	95	87	83	75	66	62	57	51	47	45	43	43	43	39	35	27	17	9	2	0

There was no difference in ORR between the durvalumab (60.7%; 95% CI: 53.9, 67.2) and placebo (60.6%; 95% CI: 50.7, 69.8) arms (p=0.976).

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CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; mOS, median OS; OS, overall survival; ORR, objective response rate

Tick marks on the curves indicate censored observations.
*The 2-sided p value boundary for declaring statistical significance is 4.5% or 5% depending on the previous levels of the multiple testing procedure.

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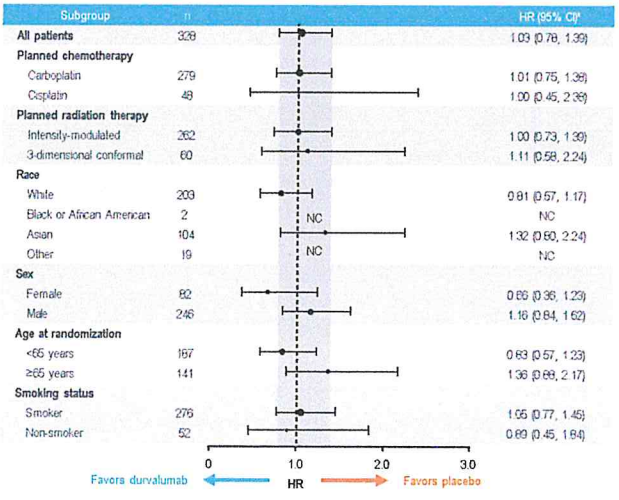
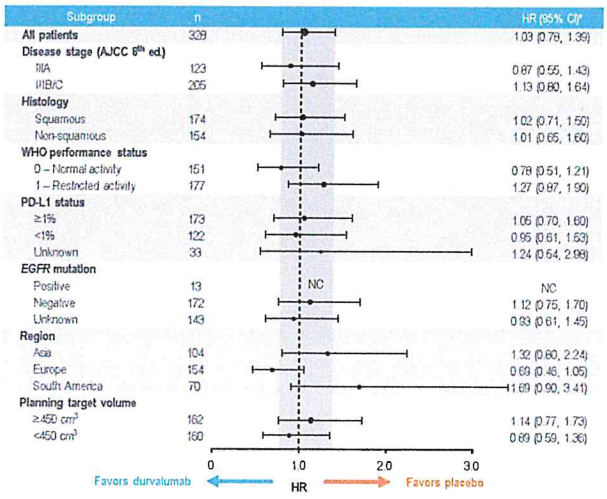
OS (ITT population), subgroup analysis





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CI, confidence interval; ITT, intention to treat; NC, not calculable; HR, hazard ratio; OS, overall survival

A HR of <1 favors durvalumab and is associated with a longer event-free survival than placebo.
The size of circle is proportional to the number of events. The gray band represents the 95% CI for the main OS HR.
For all patients, the analysis is based on the main stratified analysis while, for the subgroups, the HR and CI were calculated using an unstratified Cox proportional hazards model, with treatment as the only covariate and ties handled by Efron approach.
*HRs and 95% CIs were not calculated if a subgroup had fewer than 5 events in each treatment arm.

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Summary of AEs (safety population)

AE category, n (%)	Durvalumab + CRT (n=219)	Placebo + CRT (n=108)
Any AE	216 (98.6)	108 (100)
Maximum grade 3 or 4*	117 (53.4)	64 (59.3)
Outcome of death	30 (13.7)	11 (10.2)
SAE	103 (47.0)	56 (51.9)
Any AE leading to discontinuation of durvalumab/placebo†	56 (25.6)	13 (12.0)
0 to ≤4 months from start of treatment (approximates the duration of IO+CRT and ends at the first post-baseline scan)	31 (14.2)	6 (5.6)
>4 to ≤16 months from start of treatment (approximates the duration of consolidation IO in the SoC PACIFIC regimen)	12 (5.5)	6 (5.6)
>16 months from start of treatment (approximates treatment beyond the duration of consolidation IO in the SoC PACIFIC regimen)	13 (5.9)	1 (0.9)

- The most common treatment-emergent AEs with **durvalumab** + SoC CRT were:
  - Anemia (42.0%), pneumonitis or radiation pneumonitis (28.8%), neutropenia (27.4%), and nausea (25.6%)
- The most common treatment-emergent AEs with **placebo** + SoC CRT were:
  - Anemia (38.0%), constipation (28.7%), pneumonitis or radiation pneumonitis (28.7%), and neutropenia (25.9%)
- Combined rates of pneumonitis or radiation pneumonitis were similar in the **durvalumab** arm (28.8%) and **placebo** arm (28.7%)
  - Grade ≥3 pneumonitis or radiation pneumonitis occurred in 10 patients (4.6%) in the **durvalumab** arm and 6 (5.6%) in the **placebo** arm

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AE, adverse event; CRT, chemoradiotherapy; CTCAE, Common Terminology Criteria for Adverse Events; IO, immunotherapy; SAE, serious adverse event; SoC, standard of care

*Per CTCAE v5.0.
†Excludes any patients who experienced any AE of maximum CTCAE grade 5
‡At any time, regardless of discontinuation of CRT

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AEs based on timepoints (safety population)

Time to onset	Any AE*		AEs of maximum grade 3/4*†		AEs leading to death	
	Durvalumab + CRT (n=219)	Placebo + CRT (n=108)	Durvalumab + CRT (n=219)	Placebo + CRT (n=108)	Durvalumab + CRT (n=219)	Placebo + CRT (n=108)
Any time	216 (98.6)	108 (100)	117 (53.4)	64 (59.3)	30 (13.7)	11 (10.2)
0 to ≤4 months‡	216 (98.6)	107 (99.1)	125 (57.1)	57 (52.8)	15 (6.8)	5 (4.6)
>4 to ≤16 months§	142 (64.8)	74 (68.5)	34 (15.5)	16 (14.8)	5 (2.3)	5 (4.6)
>16 months¶	67 (30.6)	32 (29.6)	16 (7.3)	13 (12.0)	10 (4.6)	1 (0.9)

Type of fatal AEs based on time of onset 0 to ≤4 months		
Preferred term, n (%)	Durvalumab + CRT (n=219)	Placebo + CRT (n=108)
Infections/infestations	6 (2.7)	0
Cardiac disorders	1 (0.5)	1 (0.9)
Respiratory, thoracic, and mediastinal disorders‖	7 (3.2)	3 (2.8)
Injury, poisoning, and procedural complications	1 (0.5)	1 (0.9)

- From 0 to ≤4 months, infection was the primary driver of difference in fatal AEs

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AE, adverse event; CRT, chemoradiotherapy; CTCAE, Common Terminology Criteria for Adverse Events; IO, immunotherapy; SAE, serious adverse event; SoC, standard of care

Per CTCAE v5.0.
*Patients with multiple events in the same category are counted only once in that category. Patients with events in ≥1 category are counted once in each of those categories. Includes all AEs with an onset date or pre-treatment AEs that increase in severity on or after the date of first dose of randomized treatment and up to and including 90 days following the date of last dose of randomized treatment or up to the date of initiation of the first subsequent therapy (whichever occurs first). †Maximum grade 3/4 excludes any patients who experienced any AE of maximum CTCAE grade 5 in the corresponding time period. ‡Approximates the duration of IO+CRT and ends at the first post-baseline scan. §Approximates the duration of consolidation IO in the SoC PACIFIC regimen. ¶Approximates treatment beyond the duration of consolidation IO in the SoC PACIFIC regimen. ‖Fatal hemoptysis or pulmonary hemorrhage occurred in 5 (2.3%) patients in the durvalumab arm vs 0 in the placebo arm.

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Conclusions

- In PACIFIC-2, IO+CRT followed by consolidation IO did not significantly improve PFS for patients with unresectable, Stage III NSCLC
  - There was no OS benefit of treatment with IO+CRT followed by consolidation IO
- In the first 4 months of treatment (IO+CRT), a higher number of AEs leading to death or discontinuation occurred in the durvalumab arm
- Rates and severity of pneumonitis or radiation pneumonitis were similar between groups, and safety and tolerability were consistent with the known profiles for each treatment
- Concurrent CRT followed by consolidation durvalumab (i.e., the PACIFIC regimen) remains the standard of care for patients with unresectable, Stage III NSCLC[1-3]

AE, adverse event; CRT, chemoradiotherapy; IO, immunotherapy; NSCLC, non-small cell lung cancer

1. Antonia SJ, et al. N Engl J Med. 2017;377:1919–1929. 2. Remon J, et al. Ann Oncol. 2021;32:1637–1642. 3. Daly ME, et al. J Clin Oncol. 2021;40:1356–1364.

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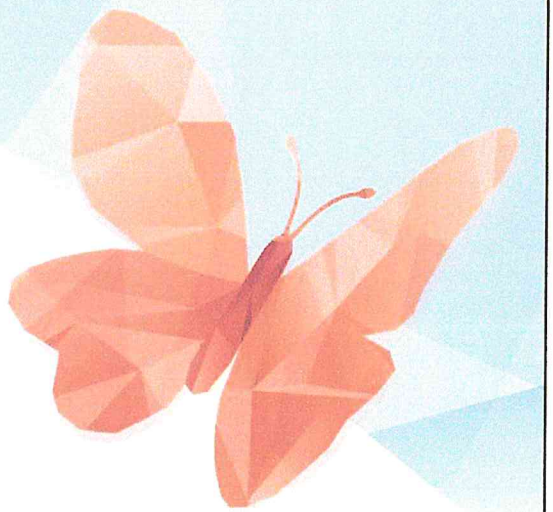

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Tumor Treating Fields therapy with standard systemic therapy versus standard systemic therapy alone in metastatic non-small-cell lung cancer following progression on or after platinum-based therapy (LUNAR): a randomised, open-label, pivotal phase 3 study

*Ticiana Leal, Rupesh Kotecha, Rodryg Ramlau, Li Zhang, Janusz Milanowski, Manuel Cobo, Jaromir Roubec, Lubos Petruzelka, Libor Havel, Sujith Kalmadi, Jeffrey Ward, Zoran Andric, Thierry Berghmans, David E Gerber, Goetz Kloecker, Rajiv Panikkar, Joachim Aerts, Angelo Delmonte, Miklos Pless, Richard Greil, Christian Rolfo, Wallace Akerley, Michael Eaton, Mussawar Iqbal, Corey Langer, on behalf of the LUNAR Study Investigators**

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See Comment page 946

*A complete list of trial investigators is provided in the appendix (pp 3–9)

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Summary

Background Tumor Treating Fields (TTFields) are electric fields that disrupt processes critical for cancer cell survival, leading to immunogenic cell death and enhanced antitumour immune response. In preclinical models of non-small-cell lung cancer, TTFields amplified the effects of chemotherapy and immune checkpoint inhibitors. We report primary results from a pivotal study of TTFields therapy in metastatic non-small-cell lung cancer.

Methods This randomised, open-label, pivotal phase 3 study recruited patients at 130 sites in 19 countries. Participants were aged 22 years or older with metastatic non-small-cell lung cancer progressing on or after platinum-based therapy, with squamous or non-squamous histology and ECOG performance status of 2 or less. Previous platinum-based therapy was required, but no restriction was placed on the number or type of previous lines of systemic therapy. Participants were randomly assigned (1:1) to TTFields therapy and standard systemic therapy (investigator's choice of immune checkpoint inhibitor [nivolumab, pembrolizumab, or atezolizumab] or docetaxel) or standard therapy alone. Randomisation was performed centrally using variable blocked randomisation and an interactive voice–web response system, and was stratified by tumour histology, treatment, and region. Systemic therapies were dosed according to local practice guidelines. TTFields therapy (150 kHz) was delivered continuously to the thoracic region with the recommendation to achieve an average of at least 18 h/day device usage. The primary endpoint was overall survival in the intention-to-treat population. The safety population included all patients who received any study therapy and were analysed according to the actual treatment received. The study is registered with ClinicalTrials.gov, NCT02973789.

Findings Between Feb 13, 2017, and Nov 19, 2021, 276 patients were enrolled and randomly assigned to receive TTFields therapy with standard therapy (n=137) or standard therapy alone (n=139). The median age was 64 years (IQR 59–70), 178 (64%) were male and 98 (36%) were female, 156 (57%) had non-squamous non-small-cell lung cancer, and 87 (32%) had received a previous immune checkpoint inhibitor. Median follow-up was 10·6 months (IQR 6·1–33·7) for patients receiving TTFields therapy with standard therapy, and 9·5 months (0·1–32·1) for patients receiving standard therapy. Overall survival was significantly longer with TTFields therapy and standard therapy than with standard therapy alone (median 13·2 months [95% CI 10·3–15·5] *vs* 9·9 months [8·1–11·5]; hazard ratio [HR] 0·74 [95% CI 0·56–0·98]; p=0·035). In the safety population (n=267), serious adverse events of any cause were reported in 70 (53%) of 133 patients receiving TTFields therapy plus standard therapy and 51 (38%) of 134 patients receiving standard therapy alone. The most frequent grade 3–4 adverse events were leukopenia (37 [14%] of 267), pneumonia (28 [10%]), and anaemia (21 [8%]). TTFields therapy-related adverse events were reported in 95 (71%) of 133 patients; these were mostly (81 [85%]) grade 1–2 skin and subcutaneous tissue disorders. There were three deaths related to standard therapy (two due to infections and one due to pulmonary haemorrhage) and no deaths related to TTFields therapy.

Interpretation TTFields therapy added to standard therapy significantly improved overall survival compared with standard therapy alone in metastatic non-small-cell lung cancer after progression on platinum-based therapy without exacerbating systemic toxicities. These data suggest that TTFields therapy is efficacious in metastatic non-small-cell lung cancer and should be considered as a treatment option to manage the disease in this setting.

Funding Novocure.

Research in context

Evidence before this study

A search of PubMed for ("tumor treating fields" OR TTFields OR (alternating electric fields AND therapy)) AND (non-small cell lung cancer) from Jan 1, 2003, to April 30, 2023, with no language restrictions, identified one pilot phase 1/2 study (EF-15; NCT00749346) of alternating electric fields delivered by a portable medical device (NovoTTF-100L, Novocure, Haifa, Israel) concomitant with pemetrexed. Patients recruited at institutes in Switzerland in 2008 and 2009 had advanced non-small-cell lung cancer progressing on previous therapy; 90% had received a platinum-based treatment. The study found that adding Tumor Treating Fields (TTFields) therapy to pemetrexed (a recommended second-line therapy when patients were enrolled) had preliminary signs of efficacy, including median progression-free survival of 22 weeks, median overall survival of 13·8 months, and a 1-year survival rate of 57%. Skin inflammation was the only common device-related adverse event, with mild (24% of patients) to moderate (2%) dermatitis beneath the arrays, which generally improved with the application of topical steroids, and no TTFields therapy-related serious adverse events were reported. Preclinical studies also suggested efficacy for TTFields in non-small-cell lung cancer; treatment reduced non-small-cell lung cancer cell line viability with maximum effect at a frequency of 150 kHz, and this effect was additive with several different systemic therapy agents. In addition, cell death induced by TTFields enhanced antitumour immune responses and the effect of immune checkpoint inhibitors in mouse lung cancer models. Clinical studies of TTFields therapy have also been conducted in six other oncology indications, including two randomised, pivotal phase 3 studies in glioblastoma. One of these (EF-14; NCT00916409) demonstrated significantly longer overall survival in patients receiving TTFields therapy with standard-of-care therapy, compared with standard-of-care therapy alone.

Added value of this study

To our knowledge, LUNAR is the first randomised, pivotal phase 3 study to examine TTFields therapy for non-small-cell lung cancer. Despite the advent of immune checkpoint inhibitors, an unmet need remains for new options that can extend survival without adding to disease or treatment burden in second-line therapy and beyond for patients with metastatic non-small-cell lung cancer. Before LUNAR, and since the OAK study of atezolizumab in 2017 (NCT02008227), no phase 3 study enrolling patients irrespective of tumour driver mutation status had shown a survival improvement after progression on platinum-based therapy.

Implications of all the available evidence

These data warrant consideration of TTFields therapy as an option for patients with metastatic non-small-cell lung cancer, as an innovative first-in-class treatment method that can be incorporated into daily life and added to existing therapies.

Introduction

Metastatic non-small-cell lung cancer remains incurable despite the introduction of many new and effective therapies, including immune checkpoint inhibitors as first-line therapy. Platinum agents are part of standard-of-care systemic therapy, either in combination with or after first line immune checkpoint inhibitor, or for patients who cannot tolerate immune checkpoint inhibitors.[1,2] However, once a patient's cancer has progressed on platinum-based therapy, treatment options to extend survival are limited. Current approaches include other chemotherapy regimens, mainly docetaxel with or without ramucirumab, or an immune checkpoint inhibitor.[1]

New treatments are needed to improve survival in non-small-cell lung cancer. Tumor Treating Fields (TTFields) are electric fields that disrupt multiple intracellular processes critical for cancer cell survival and proliferation. TTFields therapy is delivered locoregionally and non-invasively to the tumour site by a portable medical device that uses two pairs of arrays placed on the skin of the patient's thorax (appendix p 30). TTFields therapy has approval from the US Food and Drug Administration (FDA) and has the Conformité Européenne mark for glioblastoma on the basis of two randomised, pivotal, phase 3 studies,[3,4] as well as for unresectable pleural mesothelioma.[5] TTFields therapy is not associated with systemic toxicity; the most common device-related adverse event is manageable skin irritation that occurs due to skin contact with device components, not the electric fields themselves.[6,7] Additionally, patient-reported outcomes from a randomised clinical study of TTFields therapy in glioblastoma found no difference in health-related quality of life, with the exception of itchy skin, for patients using the device on the scalp with chemotherapy versus those receiving chemotherapy alone.[8]

Data from preclinical models of non-small-cell lung cancer have shown that the maximal anticancer effects of TTFields occur at 150 kHz (lower or higher frequencies are less effective)[9] and include disruption of mitosis with downstream induction of immunogenic cell death, leading to an enhanced antitumour immune response.[10,11] Additionally, TTFields treatment has been shown to amplify the effectiveness of immune checkpoint inhibitors or taxanes in preclinical models,[9–11] supporting the integration of these treatments. These data, as well as a pilot phase 1/2 study showing safety and feasibility in pretreated patients with advanced non-small-cell lung cancer receiving second-line treatment with pemetrexed,[12] provided the rationale for the pivotal phase 3 LUNAR study. Here we report the primary data from LUNAR, which compared the addition of TTFields therapy to standard systemic therapy (docetaxel or investigator's choice of immune checkpoint inhibitor) with standard

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See Online for appendix

systemic therapy alone in patients with metastatic non-small-cell lung cancer progressing on or after platinum-based therapy.

Methods

Study design and participants

LUNAR was a pivotal (the equivalent of phase 3 for medical device studies), randomised, open-label clinical study with 130 sites opened across 19 countries in North America, Europe, and Asia (appendix pp 3–9). The study design is shown in the appendix (p 31), and the full protocol and statistical analysis plan are available as supplementary material (appendix pp 37, 111).

An independent Data Monitoring Committee (comprising an oncologist, pulmonologist, and statistician) monitored data, assessed overall survival and safety results at an interim analysis, and provided recommendations to the sponsor. The protocol and all amendments were approved by the relevant ethics committee and competent authority at each participating site. This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was conducted in compliance with good clinical practice guidelines (EN ISO 14155:2011) and all relevant national and regional regulations.

Eligible participants were adults (aged ≥22 years, to meet the FDA definition of an adult patient according to device regulations) with a histological or cytological diagnosis of metastatic non-small-cell lung cancer (squamous or non-squamous) whose tumours had shown radiological progression at any site during or after platinum-based systemic therapy. No eligibility restriction or requirement was placed on the biomarker status of a patient or tumour, or on previous treatments, with the exception that all patients had received previous platinum-based therapy. Patients who had progression to metastatic disease within 6 months of completing platinum-based therapy in the adjuvant setting were also eligible. Eligibility stipulated an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and a life expectancy of at least 3 months. Patients were also ineligible if they had clinically significant (as determined by the investigator) haematological, hepatic, or renal dysfunction (defined as neutrophil count $<1{\cdot}5\times10^9$ cells per L and platelet count $<100\times10^9$ per L, bilirubin >1·5 times the upper limit of normal [ULN], aspartate aminotransferase or alanine aminotransferase [or both] >2·5 times ULN [or >5 times ULN if the patient had documented liver metastases], and serum creatinine >1·5 times ULN).

A protocol amendment on April 7, 2020, allowed inclusion of neurologically stable patients with treated central nervous system metastases. Key exclusion criteria were severe comorbidities (eg, clinically significant haematological, hepatic, renal, or cardiac dysfunction), cerebrovascular accident within 6 months of randomisation, or an unrelated malignancy within 3 years of entering the study (excluding stage 1 prostate cancer, non-melanoma skin cancer, and in-situ cervical cancer or breast cancer). All patients provided written informed consent. Full eligibility criteria are listed in the appendix (pp 10–11).

Randomisation

Patients were enrolled by the investigator. Within 28 days of providing informed consent, the investigator assigned eligible patients to a standard systemic therapy (an immune checkpoint inhibitor [nivolumab, pembrolizumab, or atezolizumab] or docetaxel) on the basis of the investigator's best clinical judgement, existing guidelines, availability, and according to standard practice. Patients were randomly assigned (1:1) to receive TTFields therapy to the thorax concomitant with standard therapy or to receive standard therapy alone. The choice of standard therapy was made before randomisation. Randomisation was determined centrally using variable blocked randomisation and an interactive voice–web response system and stratified by tumour histology (squamous or non-squamous), treatment (docetaxel or an immune checkpoint inhibitor), and region (North America, western Europe and Israel, and eastern Europe). The allocation sequence was generated by the sponsor. LUNAR was an open-label study and treatment allocation was not masked.

Procedures

Standard therapies were dosed according to local practice guidelines and instructions provided with each drug over the period patients received treatment in LUNAR (2017–22). The standard for docetaxel was intravenous (75 mg/m^2) administration over 1 h every 3 weeks. Nivolumab was administered intravenously at 240 mg every 2 weeks, 480 mg every 4 weeks, or as a bodyweight-based dose. Pembrolizumab was administered as an intravenous dose infusion at 200 mg every 3 weeks, 400 mg every 6 weeks (over 30 min), or as a bodyweight-based dose. Atezolizumab was administered as an intravenous infusion (840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks) over 1 h. All standard systemic therapies were administered until disease progression or unacceptable toxicity. Assessment of tumour PD-L1 status was not mandated; however, investigators reported PD-L1 expression test results in case report forms if available.

TTFields therapy (150 kHz) was delivered continuously to the thoracic region with the recommendation to achieve an average usage of at least 75% of each day (18 h/day) with the NovoTTF device system (device manufactured by Novocure, Root, Switzerland; appendix p 30); this usage threshold was associated with positive clinical benefit in glioblastoma.[13] Array layouts were determined by the investigator based on sex, disease burden, and patient body size (appendix p 32) and were modified as needed throughout the treatment period.

Patients who initiated the study using the NovoTTF-100L system were offered the option (by a protocol amendment on Oct 5, 2020) to have therapy delivered with the identical treatment parameters from the smaller and lighter (1·2 kg *vs* 2·7 kg) next-generation NovoTTF-200T system (appendix p 30). Patients and caregivers were trained to use the device by the investigator, other health-care provider, or a device support specialist (sponsor-provided). Arrays were replaced (and shifted back and forth approximately 2 cm from the original position to minimise the potential for skin irritation) every 3–4 days. TTFields therapy usage time (device-captured data) was reported monthly to investigators, presented as an average of monthly use during the period.

Follow-up visits were conducted every 6 weeks (±1 week) for radiological assessment of disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 for patients receiving docetaxel, or immune-related RECIST for patients receiving an immune checkpoint inhibitor.[14,15] A review of performance status, a physical examination (including of vital signs), complete blood count, and serum chemistry panel (including blood urea nitrogen or urea, creatinine, sodium, potassium, glucose, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin) were performed, and quality-of-life questionnaires were administered. The full schedule of visits and follow-up is described in the appendix (p 2).

Study therapy was continued until radiological progression per RECIST or immune-related RECIST as assessed by the investigator, intolerable toxicity, or patient request (for any reason). Treatment breaks of up to 3 weeks were allowed for TTFields therapy-related adverse events. After progression, patients were offered the investigator's choice of salvage therapy. Patients could continue to receive TTFields therapy with the next line of salvage therapy if they discontinued study systemic therapy due to progression outside of the field (and had in-field disease control), or if the patient had intolerable toxicity to systemic therapy.

Safety was assessed at each follow-up visit (from the time of randomisation until 100 days after terminating study treatment), with adverse events reported according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.[16] A modified grading system used to characterise TTFields therapy-related skin adverse events is shown in the appendix (p 12). Because TTFields therapy is used almost continuously (the device is portable to allow use inside and outside the home), the potential impact on quality of life is particularly relevant. As such, patient-reported outcomes were included in the LUNAR clinical study. Global health status was measured at baseline and every 6 weeks using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire, an established and validated instrument for collecting patient reported outcomes in oncology studies.[17] A paper copy of the questionnaire was completed according to EORTC guidelines by the patient at follow-up visits. Patient sex, race, and ethnicity were defined by the investigator and source-verified by the sponsor against medical records.

Outcomes

The primary endpoint was overall survival in patients receiving TTFields therapy with standard therapy compared with standard therapy alone. Key secondary endpoints were overall survival in subgroups receiving either docetaxel or an immune checkpoint inhibitor. Other secondary endpoints (reported here) were progression-free survival and overall response rate (both per radiological assessment); overall survival by squamous and non-squamous histology; measurement of patient-reported, health-related quality-of-life scores; and adverse events. Secondary endpoints of overall survival and progression-free survival in TTFields therapy-treated subgroups with average monthly device usage of more than 75% and 75% or less; progression-free survival by squamous and non-squamous histology; overall survival and progression-free survival in subgroups who received nivolumab, pembrolizumab, or atezolizumab; and overall survival of patients who received TTFields therapy with docetaxel compared with patients treated with an immune checkpoint inhibitor alone will be reported elsewhere as part of more extensive analyses.

Overall survival was defined as the time from randomisation to the date of death from any cause or censoring at the last follow-up date. Progression-free survival was defined as the time from date of randomisation until date of disease progression, or death by any cause. Deaths occurring after a patient missed two or more consecutive follow-up visits were censored at the last date of tumour assessment. Patients whose cancer had not progressed or who had not died at the time of analysis were censored at the date of the most recent evaluable tumour assessment. Patients with no post-baseline follow-up radiological tumour assessment were censored at the date of randomisation. Overall radiological response rate was defined as a complete or partial response, and best response (complete response, partial response, stable disease, progressive disease, or not evaluable) was calculated for each treatment group. The change in EORTC QLQ-C30 global health score from baseline is reported here; additional patient-reported outcomes collected in the study will be reported as a separate publication.

Statistical analysis

The study was designed to detect a hazard ratio (HR) of death of less than 0·75 in patients receiving TTFields therapy with standard therapy versus standard therapy alone using two-sided proportional hazards testing, a two-sided α of 0·05, and 80% power. This required a

sample size of 534 patients, after allowing for 10% patient loss during follow-up, with an 18-month study follow-up period. The key secondary endpoints of overall survival in the docetaxel and immune checkpoint inhibitor subgroups were to be tested hierarchically if the primary endpoint was met (to preserve type I error) at the 0·05 (two-sided) level.

Overall survival and progression-free survival were evaluated with two-sided log rank tests, at an α level of 0·05, stratified by treatment (immune checkpoint inhibitor or docetaxel) and tumour histology. A protocol amendment (on May 21, 2021) removed site as a stratification factor before analyses were performed. Medians, CIs, and rates were estimated using the Kaplan-Meier method. HRs with 95% CIs and p values were estimated using a stratified Cox proportional hazards model, with stratification variables introduced as covariates. The significance threshold for analyses was set at p values of less than 0·05. The time-to-event analysis included censoring of subjects who had not experienced an event. The majority of censoring related to patients who had not experienced an event by the data cutoff date. Other censoring was mostly informative and due to patient withdrawal or physician decision. The proportional hazards assumption was not violated, as assessed by visual inspection of log of the negative log of estimated survivor functions. Landmark survival rates at 1 year, 2 years, and 3 years were analysed post hoc. A multivariable analysis using a Cox proportional hazards regression model was performed post hoc to statistically test the effect of parameters (treatment group, type of standard treatment, histology, geographical region, age, sex, performance status, tumour PD-L1 biomarker status, and smoking history) on overall survival in the intention-to-treat population. For overall response rates, the 95% CI was calculated based on the exact binomial distribution (Clopper-Pearson).

Efficacy endpoints were analysed in all randomly assigned patients (intention-to-treat population). Progression-free survival in patients receiving an immune checkpoint inhibitor or docetaxel was a post-hoc analysis. For overall response rate and best response, patients lacking evaluable data were analysed as non-responders. Safety and treatment data were compiled from all patients who received any study therapy and were analysed according to the actual treatment received. For patient-reported outcomes, it was hypothesised that administration of TTFields therapy with standard therapy would not cause a greater decline in mean quality-of-life scores than standard therapy alone. The mean change from baseline in EORTC QLQ-C30 global health scores was calculated for each timepoint and, as previously validated, a change from baseline of ten points or more was considered to represent a clinically significant change.[18] Analyses were performed using SAS software, version 9.4. There was no imputation of missing data. Full details are provided in the statistical analysis plan (appendix p 111).

At the request of the Data Monitoring Committee due to ethical concerns of prolonged accrual, an interim analysis took place on March 31, 2021, after 48 months of active accrual (the expected entire study period, and with 28% of the expected overall survival events having occurred). This replaced the prespecified interim analysis planned for when 432 patients (of the original 534 sample) had been enrolled, and for which the Lan-DeMets method using the O'Brien and Fleming spending function had calculated an α level of approximately 0·00306, with α=0·04694 remaining for the final analysis. The alternative interim analysis was performed by the Data Monitoring Committee statistician and shared with the committee members. Based on these results, the Data Monitoring Committee concluded that continuing accrual to the planned 534 patients was likely to be unnecessary and possibly unethical. The Data Monitoring Committee recommended that accrual of approximately 276 patients, with a 12-month study follow-up period, would be sufficient to provide toxicity and efficacy data to evaluate the planned endpoints, while maintaining statistical power. The Data Monitoring Committee statistician indicated that the interim analysis had an efficacy boundary of 0·0038 and calculated a

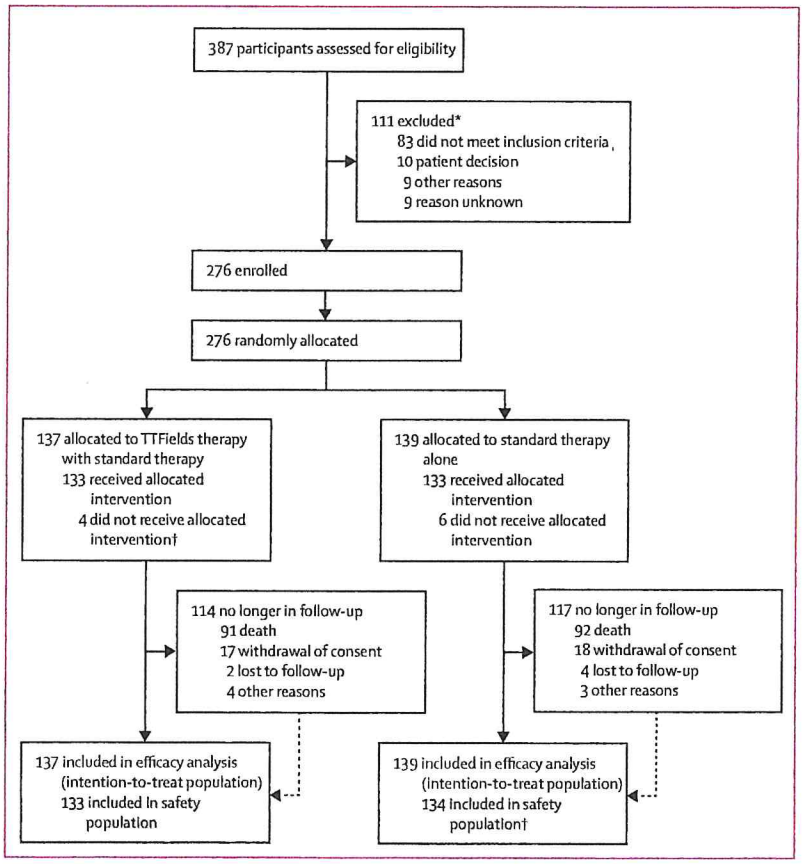

Figure 1: **Trial profile**
TTFields=Tumor Treating Fields. *One patient who failed screening was randomised. †One patient randomly assigned to TTFields therapy with standard therapy instead received standard therapy alone.

revised two-sided α of 0·0462 for the full analysis with the new target accrual. The sponsor and all investigators remained masked to all study data. The Data Monitoring Committee recommended no further changes to the study protocol. This study is registered with ClinicalTrials.gov, NCT02973789.

Role of the funding source

Novocure designed the study, collated data, conducted data analysis, contributed to data interpretation, funded editorial support, and reviewed the manuscript. The study was designed by the sponsor (Novocure) and the investigators. Data were collected by the investigators and analysed by sponsor-employed or sponsor-funded statisticians.

Results

Between Feb 13, 2017, and Nov 19, 2021, 276 patients were enrolled and randomly assigned to receive TTFields therapy with standard therapy (n=137) or standard therapy alone (n=139; figure 1). All eligible participants were

	TTFields therapy with standard therapy group (n=137)	Standard therapy group (n=139)	TTFields therapy with immune checkpoint inhibitor subgroup (n=66)	Immune checkpoint inhibitor subgroup (n=68)	TTFields therapy with docetaxel subgroup (n=71)	Docetaxel subgroup (n=71)
Age, years	63 (36–85)	65 (22–86)	64 (36–85)	65 (23–86)	63 (43–81)	65 (22–81)
Sex						
Female	46 (34%)	52 (37%)	22 (33%)	23 (34%)	24 (34%)	29 (41%)
Male	91 (66%)	87 (63%)	44 (67%)	45 (66%)	47 (66%)	42 (59%)
Race						
American Indian or Alaska Native	0	2 (1%)	0	1 (1%)	0	1 (1%)
Asian	16 (12%)	12 (9%)	7 (11%)	5 (7%)	9 (13%)	7 (10%)
Black or African American	3 (2%)	3 (2%)	1 (2%)	2 (3%)	2 (3%)	1 (1%)
Pacific Islander	1 (1%)	0	1 (2%)	0	0	0
White	111 (81%)	111 (80%)	54 (82%)	53 (78%)	57 (80%)	58 (82%)
Other or missing	6 (4%)	11 (8%)	3 (5%)	7 (10%)	3 (4%)	4 (6%)
Region						
North America	41 (30%)	43 (31%)	14 (21%)	17 (25%)	27 (38%)	26 (37%)
Western Europe and Israel	42 (31%)	41 (29%)	25 (38%)	24 (35%)	17 (24%)	17 (24%)
Eastern Europe	41 (30%)	43 (31%)	21 (32%)	22 (32%)	20 (28%)	21 (30%)
East Asia	13 (9%)	12 (9%)	6 (9%)	5 (7%)	7 (10%)	7 (10%)
ECOG performance status						
0	38 (28%)*	40 (29%)	20 (30%)*	22 (32%)	18 (25%)	18 (25%)
1	93 (68%)*	95 (68%)	44 (67%)*	46 (68%)	49 (69%)	49 (69%)
2	6 (4%)	4 (3%)	2 (3%)	0	4 (6%)	4 (6%)
Smoking history						
Never smoked	20 (15%)	23 (17%)	10 (15%)	12 (18%)	10 (14%)	11 (15%)
Current smoker	35 (26%)	29 (21%)	19 (29%)	17 (25%)	16 (23%)	12 (17%)
Former smoker	81 (59%)	87 (63%)	37 (56%)	39 (57%)	44 (62%)	48 (68%)
Unknown	1 (1%)	0	0	0	1 (1%)	0
Months since initial diagnosis	10·3 (2·7–127·2)	9·9 (2·5–164·6)	10·1 (2·8–98·4)	8·5 (2·7–164·6)	10·4 (2·7–127·2)	11·1 (2·5–68·9)
Previous therapy	137 (100%)	139 (100%)	66 (100%)	68 (100%)	71 (100%)	71 (100%)
Best response to previous therapy						
Complete response	8 (6%)	5 (4%)	4 (6%)	3 (4%)	4 (6%)	2 (3%)
Partial response	32 (23%)	36 (26%)	19 (29%)	13 (19%)	13 (18%)	23 (32%)
Stable disease	47 (34%)	44 (32%)	25 (38%)	21 (31%)	22 (31%)	23 (32%)
Progressive disease	29 (21%)	36 (26%)	10 (15%)	20 (29%)	19 (27%)	16 (23%)
Unknown	21 (15%)	17 (12%)	8 (12%)	10 (15%)	13 (18%)	7 (10%)
Missing	0	1 (1%)	0	1 (1%)	0	0
Previous lines of systemic therapy						
One	119 (87%)	121 (87%)	64 (97%)	63 (93%)	55 (77%)	58 (82%)
Two	9 (7%)	10 (7%)	2 (3%)	3 (4%)	7 (10%)	7 (10%)
Three or more	6 (4%)	2 (1%)	0	0	6 (8%)	2 (3%)
Missing	3 (2%)	6 (4%)	0	2 (3%)	3 (4%)	4 (6%)

(Table 1 continues on next page)

	TTFields therapy with standard therapy group (n=137)	Standard therapy group (n=139)	TTFields therapy with immune checkpoint inhibitor subgroup (n=66)	Immune checkpoint inhibitor subgroup (n=68)	TTFields therapy with docetaxel subgroup (n=71)	Docetaxel subgroup (n=71)
(Continued from previous page)						
Previous immune checkpoint inhibitor						
Yes	43 (31%)	44 (32%)	1 (2%)	2 (3%)	42 (59%)	42 (59%)
No	94 (69%)	95 (68%)	65 (98%)	66 (97%)	29 (41%)	29 (41%)
Histological type						
Non-squamous	79 (58%)	77 (55%)	37 (56%)	37 (54%)	42 (59%)	40 (56%)
Squamous	58 (42%)	62 (45%)	29 (44%)	31 (46%)	29 (41%)	31 (44%)
PD-L1 tumour proportion score						
<1%	23 (17%)	23 (17%)	12 (18%)	16 (24%)	11 (15%)	7 (10%)
1–49%	37 (27%)	40 (29%)	17 (26%)	18 (26%)	20 (28%)	22 (31%)
≥50%	10 (7%)	18 (13%)	5 (8%)	8 (12%)	5 (7%)	10 (14%)
Unknown	67 (49%)	58 (42%)	32 (48%)	26 (38%)	35 (49%)	32 (45%)
Liver metastasis	21 (15%)	22 (16%)	9 (14%)	8 (12%)	12 (17%)	14 (20%)‡
Brain metastasis†	0	2 (1%)	0	0	0	2 (3%)‡

Data are median (range) or n (%). Standard therapy refers to an immune checkpoint inhibitor or docetaxel. TTFields=Tumor Treating Fields. ECOG=Eastern Cooperative Oncology Group. NSCLC=non-small-cell lung cancer. *Baseline performance status was unavailable for two patients, who were instead assessed at the first follow-up visit. †Patients with brain metastases were excluded under the original study design, which was later amended to allow enrolment of patients with stable brain metastases. ‡One patient had both liver and brain metastasis.

Table 1: **Baseline characteristics of the intention-to-treat population**

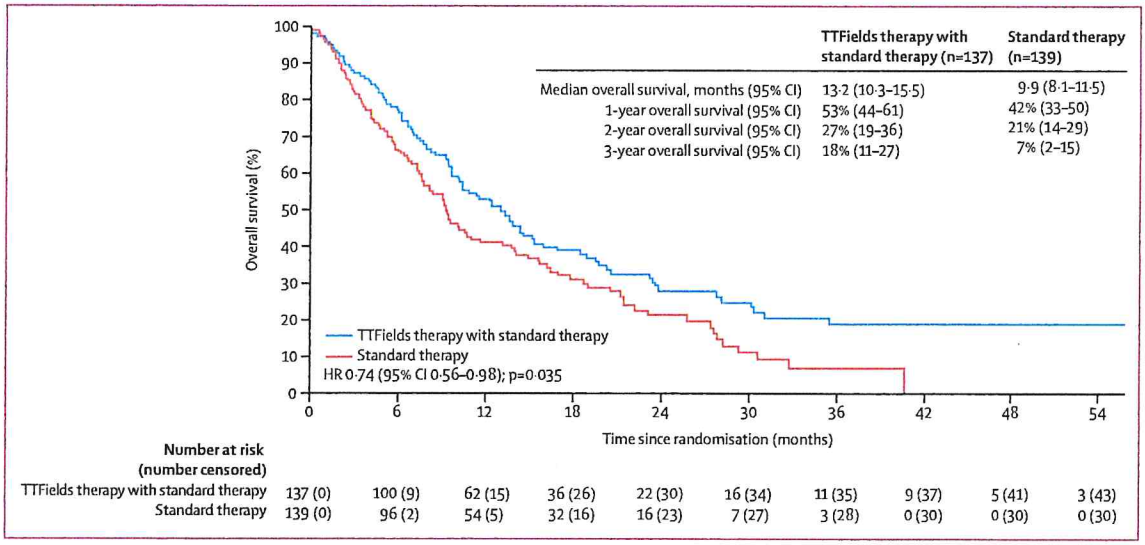

Figure 2: **Overall survival in the intention-to-treat population**
Kaplan-Meier estimate of overall survival. Standard therapy refers to an immune checkpoint inhibitor or docetaxel. HR=hazard ratio. TTFields=Tumor Treating Fields.

assigned to therapy (n=276). Their median age was 64 years (IQR 59–70), 178 (64%) were male and 98 (36%) were female, and 232 (84%) were current or former smokers. At baseline, the majority (156 [57%]) had non-squamous histology, 43 (16%) had liver metastasis, and ten (4%) had an ECOG performance score of 2. Other baseline demographics and characteristics were also similar across groups (table 1). Most participants (240 [87%]) had received only one previous line of systemic therapy; more patients in the docetaxel subgroup had received previous treatment with an immune checkpoint inhibitor than had those in the immune checkpoint inhibitor subgroup (84 [59%] of 142 patients *vs* three [2%] of 134 patients; table 1).

At data cutoff, median follow-up was 10·6 months (IQR 6·1–33·7) for patients assigned to TTFields therapy with standard therapy and 9·5 months (0·1–32·1) for patients assigned to standard therapy alone. Patients who received standard therapy (266 [97%]) were administered systemic therapy for a median of 12·5 weeks (IQR 5·1–25·1). The median duration of TTFields therapy

was 14·6 weeks (IQR 5·3–41·1) with an immune checkpoint inhibitor and 12·7 weeks (3·9–22·0) with docetaxel. 270 (98%) of 276 patients discontinued the study, mostly due to progression or death (167 [61%] of 276; appendix p 13). For patients with device usage data, TTFields therapy was delivered over the first 3 months with an immune checkpoint inhibitor for a median of 56% of each day (IQR 37–70), and with docetaxel for a median of 57% of each day (36–76). Over the entire course of the study, a monthly average device usage of at least 18 h/day (75% of each day) was reached by 13 (19%) of 67 patients in the immune checkpoint inhibitor subgroup and 17 (26%) of 66 patients in the docetaxel subgroup.

Of the 276 patients assigned to study therapy, 77 (28%) received salvage systemic therapy after discontinuing study therapy due to disease progression; the most frequent agents used were docetaxel (24 [31%] of 77 patients) and gemcitabine (21 [27%]; appendix p 14). 42 (32%) of the 133 patients who received TTFields therapy continued device use beyond disease progression after suspension of standard therapy; 22 in the immune checkpoint inhibitor subgroup (n=67) continued for a median of 34 days (IQR 17–57) after discontinuation, and 20 in the docetaxel subgroup (n=66) continued for a median of 18 days (5–43). Disease progression and occurrence of adverse events were the most common reasons for discontinuation of post-study TTFields therapy.

At data cutoff, 92 deaths had occurred in the group of 137 patients assigned to TTFields therapy and standard

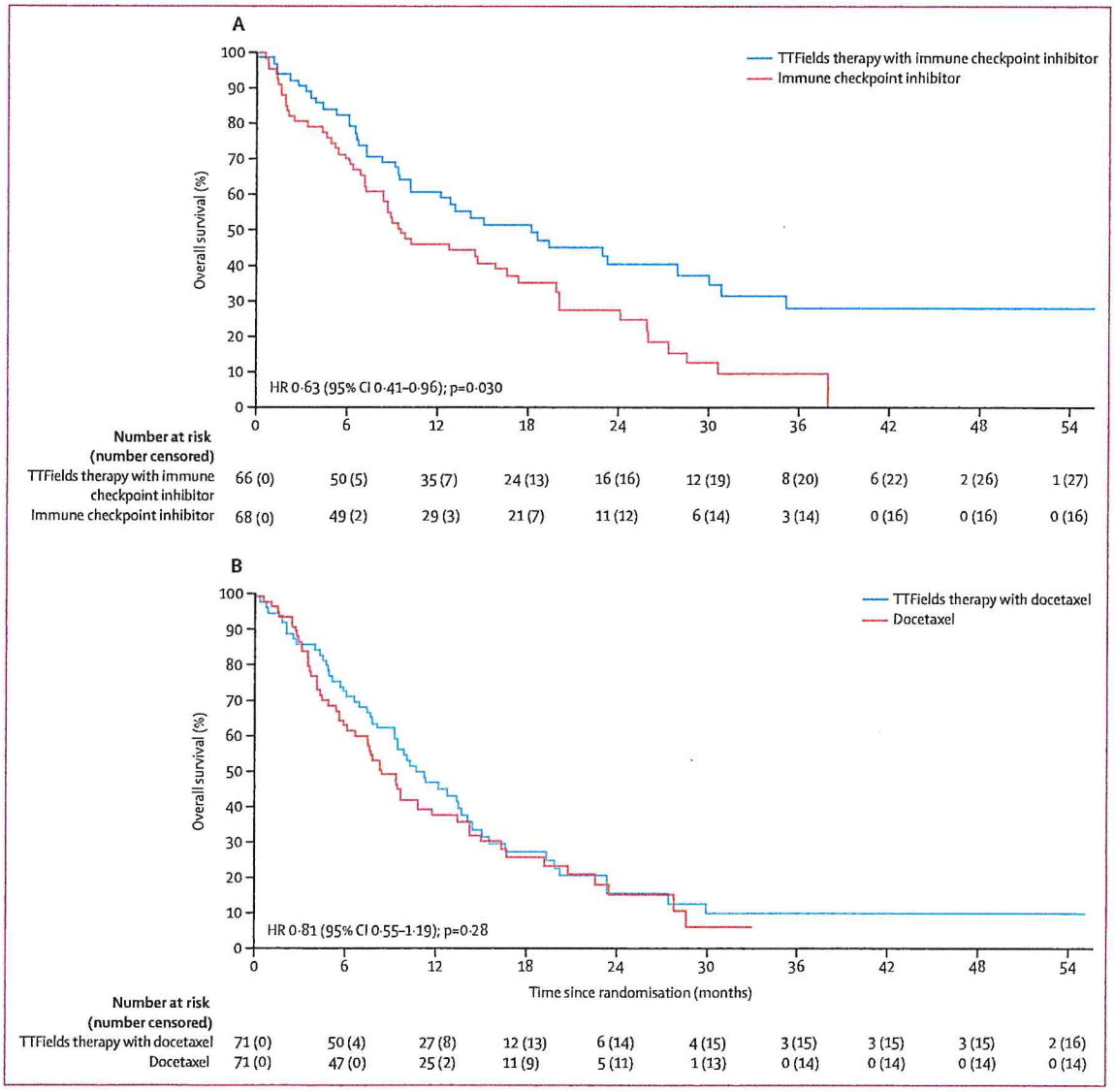

Figure 3: Overall survival in the immune checkpoint inhibitor subgroup (A) and docetaxel subgroup (B) of the intention-to-treat population
Kaplan-Meier estimates of overall survival. TTFields=Tumor Treating Fields.

therapy, and 109 deaths had occurred in the 139 patients assigned to standard therapy alone. Overall survival was significantly longer with TTFields therapy and standard therapy versus standard therapy alone (figure 2). Median overall survival was 13·2 months (95% CI 10·3–15·5) with TTFields therapy and standard therapy compared with 9·9 months (8·1–11·5) with standard therapy alone, yielding an HR of 0·74 (95% CI 0·56–0·98; p=0·035) in favour of TTFields therapy. The 1-year overall survival rate was 53% (95% CI 44–61) with TTFields therapy and standard therapy, and 42% (33–50) with standard therapy alone.

In the immune checkpoint inhibitor subgroup, 38 deaths occurred in the 66 patients assigned to receive TTFields therapy, and 52 deaths occurred in the 68 patients assigned to immune checkpoint inhibitor alone. The addition of TTFields therapy significantly improved overall survival compared with an immune checkpoint inhibitor alone, with respective median overall survival of 18·5 months (95% CI 10·6–30·3) and 10·8 months (8·2–18·4) and an HR of 0·63 (95% CI 0·41–0·96; p=0·030; figure 3A). The 1-year overall survival rate was 60% (95% CI 47–71) with TTFields therapy and an immune checkpoint inhibitor and 46% (33–57) with an immune checkpoint inhibitor alone.

In the subgroup receiving docetaxel, 54 deaths occurred in the 71 patients assigned to receive TTFields therapy, and 57 deaths occurred in the 71 patients assigned to docetaxel alone. Median overall survival was 11·1 months (95% CI 8·2–14·1) with TTFields therapy and docetaxel and 8·7 months (6·3–11·3) with docetaxel alone, with an HR of 0·81 (95% CI 0·55–1·19; p=0·28; figure 3B). The 1-year overall survival rate was 46% (95% CI 33–57) with TTFields therapy and docetaxel and 38% (27–49) with docetaxel alone.

Multivariable analysis using a Cox proportional hazards regression model identified a significant effect for TTFields therapy with standard therapy versus standard therapy, and for immune checkpoint inhibitor versus docetaxel as standard therapy, whereas other factors, including age, sex, ECOG performance status, PD-L1 status, smoking history, and histology did not significantly affect overall survival (appendix p 15). For overall survival results by histology, patients with non-squamous non-small-cell lung cancer assigned to TTFields therapy with standard therapy (n=79) had 50 deaths and median overall survival of 12·6 months (95% CI 8·8–19·8), and those assigned to standard therapy alone (n=77) had 58 deaths and median overall survival of 9·9 months (6·9–16·4; HR 0·80, 95% CI 0·54–1·16; p=0·28). Patients with squamous non-small-cell lung cancer assigned to TTFields therapy with standard therapy (n=58) had 42 deaths and median overall survival of 13·9 months (95% CI 9·7–17·1), and those assigned to standard therapy alone (n=62) had 51 deaths and median overall survival of 10·1 months (8·3–14·3; HR 0·67, 95% CI 0·44–1·01; p=0·050; appendix p 33).

104 progression events occurred in the group assigned to TTFields therapy and standard therapy and 118 progression events occurred in the group assigned to standard therapy alone; median progression-free survival was 4·8 months (95% CI 4·1–5·7) and 4·1 months (3·1–4·6), respectively (HR 0·85, 95% CI 0·67–1·11; p=0·23; figure 4). Progression-free survival in subgroups receiving an immune checkpoint inhibitor or docetaxel is shown in the appendix (p 34).

The overall response rate with TTFields therapy and standard therapy was 20·4% (95% CI 14·0–28·2) versus 17·3% (11·4–24·6) with standard therapy alone (two-sided p=0·50; table 2). All complete responses (n=5) occurred in patients receiving an immune checkpoint inhibitor (four with TTFields therapy, one with immune checkpoint inhibitor alone).

In the safety population of patients who received standard therapy, 16 (12%) of 133 in the group receiving TTFields with standard therapy and 19 (14%) of 134 in the group receiving standard therapy alone required dose reductions to the standard therapy regimen.

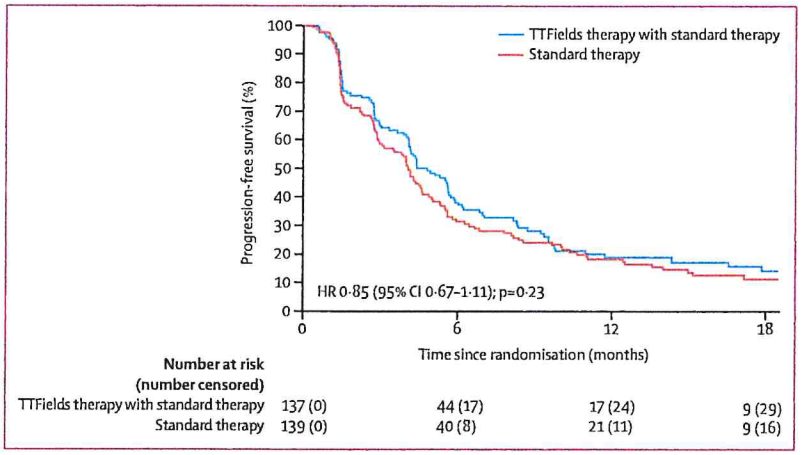

Figure 4: **Progression-free survival in the intention-to-treat population**
Kaplan-Meier estimates of progression-free survival. Standard therapy refers to an immune checkpoint inhibitor or docetaxel. TTFields=Tumor Treating Fields.

	TTFields therapy with standard therapy group (n=137)	Standard therapy group (n=139)
Patients with at least one post-baseline scan, n	122	127
Overall response, n (%; 95% CI)	28 (20·4%; 14·0–28·2)	24 (17·3%; 11·4–24·6)
Best overall response, n (%)		
Complete response	4 (3%)	1 (1%)
Partial response	24 (18%)	23 (17%)
Stable disease	67 (49%)	65 (47%)
Progressive disease	24 (18%)	36 (26%)
Not evaluable	3 (2%)	2 (1%)

Response rates were calculated from the intention-to-treat population. Standard therapy refers to an immune checkpoint inhibitor or docetaxel. TTFields=Tumor Treating Fields.

Table 2: **Response rates**

	TTFields therapy with an immune checkpoint inhibitor subgroup (n=67)				Immune checkpoint inhibitor subgroup (n=66)				TTFields therapy with docetaxel subgroup (n=66)				Docetaxel subgroup (n=68)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any adverse event	29 (43%)	29 (43%)	3 (4%)	5 (7%)	28 (42%)	20 (30%)	6 (9%)	6 (9%)	22 (33%)	22 (33%)	11 (17%)	8 (12%)	18 (26%)	23 (34%)	16 (24%)	4 (6%)
Blood and lymphatic system disorders																
Anaemia	12 (18%)	4 (6%)	1 (1%)	0	7 (11%)	2 (3%)	0	0	9 (14%)	5 (8%)	0	0	11 (16%)	9 (13%)	0	0
Leukopenia	1 (1%)	1 (1%)	1 (1%)	0	2 (3%)	0	2 (3%)	0	3 (5%)	6 (9%)	10 (15%)	0	3 (4%)	3 (4%)	14 (21%)	0
Thrombocytopenia	1 (1%)	1 (1%)	0	0	0	0	0	0	4 (6%)	2 (3%)	0	0	2 (3%)	0	1 (1%)	0
Febrile neutropenia	0	0	0	0	0	0	0	0	0	6 (9%)	0	0	0	3 (4%)	0	0
Lymphopenia	0	2 (3%)	0	0	0	0	0	0	2 (3%)	1 (2%)	0	0	1 (1%)	0	0	0
Cardiac disorders																
Myocardial infarction	0	0	0	0	0	0	0	0	0	1 (2%)	0	0	1 (1%)	1 (1%)	0	0
Pericardial effusion	0	1 (1%)	0	0	0	0	0	0	1 (2%)	0	1 (2%)	0	0	0	0	0
Cardiac failure	0	0	0	0	0	0	0	0	0	1 (2%)	1 (2%)	0	0	0	0	0
Coronary artery disease	0	0	0	0	0	0	0	0	0	0	0	1 (2%)	0	0	0	0
Gastrointestinal disorders																
Diarrhoea	11 (16%)	1 (1%)	0	0	13 (20%)	0	0	0	12 (18%)	1 (2%)	0	0	12 (18%)	0	0	0
Nausea	8 (12%)	0	0	0	10 (15%)	1 (2%)	0	0	17 (26%)	0	0	0	10 (15%)	0	0	0
Constipation	4 (6%)	0	0	0	5 (8%)	0	0	0	11 (17%)	0	0	0	10 (15%)	0	0	0
Vomiting	6 (9%)	0	0	0	6 (9%)	1 (2%)	0	0	7 (11%)	1 (2%)	0	0	7 (10%)	0	0	0
Abdominal pain	2 (3%)	0	0	0	5 (8%)	0	0	0	7 (11%)	0	0	0	3 (4%)	0	0	0
Dysphagia	4 (6%)	0	0	0	1 (2%)	0	0	0	9 (14%)	0	0	0	1 (1%)	0	0	0
Mouth ulceration	1 (1%)	0	0	0	4 (6%)	0	0	0	3 (5%)	2 (3%)	0	0	6 (9%)	0	0	0
Ileus	0	1 (1%)	0	0	0	0	0	0	0	0	0	0	0	1 (1%)	0	0
Intestinal perforation	0	0	0	1 (1%)	0	0	0	0	0	0	1 (2%)	0	0	0	0	0
General disorders and administration site conditions																
Fatigue	14 (21%)	2 (3%)	0	0	20 (30%)	2 (3%)	0	0	18 (27%)	3 (5%)	0	0	20 (29%)	8 (12%)	0	0
Localised oedema	6 (9%)	0	0	0	8 (12%)	0	0	0	13 (20%)	1 (2%)	0	0	11 (16%)	2 (3%)	0	0
Pain	8 (12%)	1 (1%)	0	0	3 (5%)	0	0	0	8 (12%)	1 (2%)	0	0	13 (19%)	1 (1%)	0	0
Pyrexia	5 (7%)	0	0	0	9 (14%)	0	0	0	3 (5%)	1 (2%)	0	0	9 (13%)	0	0	0
General physical health deterioration	1 (1%)	1 (1%)	0	0	2 (3%)	1 (2%)	1 (2%)	0	0	4 (6%)	0	0	0	0	0	0
Euthanasia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (1%)
Immune system disorders																
Drug hypersensitivity	0	0	0	0	0	1 (2%)	0	0	0	0	0	0	1 (1%)	1 (1%)	0	0
Infections and infestations																
Pneumonia	4 (6%)	4 (6%)	0	0	4 (6%)	3 (5%)	2 (3%)	2 (3%)	1 (2%)	9 (14%)	2 (3%)	0	4 (6%)	7 (10%)	1 (1%)	0
Respiratory tract infection	11 (16%)	2 (3%)	0	0	15 (23%)	0	0	0	5 (8%)	1 (2%)	0	1 (2%)	5 (7%)	0	0	0
Infection	5 (7%)	0	0	0	1 (2%)	0	0	0	3 (5%)	2 (3%)	0	1 (2%)	5 (7%)	0	0	0
Urinary tract infection	2 (3%)	1 (1%)	0	0	5 (8%)	1 (2%)	0	0	2 (3%)	2 (3%)	0	0	4 (6%)	0	0	0
Sepsis	0	0	1 (1%)	0	0	1 (2%)	1 (2%)	1 (2%)	0	0	3 (5%)	0	0	1 (1%)	1 (1%)	0
Gastroenteritis	0	0	0	0	1 (2%)	0	0	0	1 (2%)	1 (2%)	0	0	1 (1%)	1 (1%)	0	0

(Table 3 continues on next page)

	TTFields therapy with an immune checkpoint inhibitor subgroup (n=67)				Immune checkpoint inhibitor subgroup (n=66)				TTFields therapy with docetaxel subgroup (n=66)				Docetaxel subgroup (n=68)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)																
Injury, poisoning, and procedural complications																
Fracture	1 (1%)	1 (1%)	0	0	1 (2%)	0	0	0	2 (3%)	0	1 (2%)	0	2 (3%)	0	0	0
Investigations																
Hepatic enzyme increased	9 (13%)	0	0	0	7 (11%)	3 (5%)	0	0	4 (6%)	0	0	0	5 (7%)	1 (1%)	0	0
Weight decreased	2 (3%)	1 (1%)	0	0	5 (8%)	0	0	0	5 (8%)	1 (2%)	0	0	4 (6%)	0	0	0
Metabolism and nutrition disorders																
Anorexia	11 (16%)	0	0	0	8 (12%)	0	0	0	10 (15%)	1 (2%)	0	0	11 (16%)	0	0	0
Hypokalaemia	3 (4%)	1 (1%)	0	0	4 (6%)	0	0	0	7 (11%)	2 (3%)	0	0	8 (12%)	0	0	0
Hypoalbuminaemia	3 (4%)	0	0	0	9 (14%)	0	0	0	6 (9%)	1 (2%)	0	0	7 (10%)	1 (1%)	0	0
Hyponatraemia	4 (6%)	0	1 (1%)	0	6 (9%)	3 (5%)	0	0	5 (8%)	2 (3%)	0	0	3 (4%)	2 (3%)	0	0
Hypercalcaemia	1 (1%)	1 (1%)	0	0	2 (3%)	1 (2%)	0	0	5 (8%)	1 (2%)	0	0	6 (9%)	0	0	0
Hyperglycaemia	2 (3%)	2 (3%)	0	0	1 (2%)	1 (2%)	0	0	4 (6%)	0	0	0	2 (3%)	1 (1%)	0	0
Dehydration	3 (4%)	0	0	0	1 (2%)	0	0	0	4 (6%)	1 (2%)	0	0	1 (1%)	1 (1%)	0	0
Musculoskeletal and connective tissue disorders																
Musculoskeletal pain	22 (33%)	1 (1%)	0	0	12 (18%)	3 (5%)	0	0	22 (33%)	3 (5%)	0	0	19 (28%)	2 (3%)	0	0
Muscular weakness	3 (4%)	0	0	0	1 (2%)	0	0	0	3 (5%)	1 (2%)	0	0	2 (3%)	1 (1%)	0	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)																
Tumour pain	1 (1%)	0	0	0	0	1 (2%)	0	0	0	2 (3%)	0	0	0	1 (1%)	0	0
Metastases to central nervous system	0	0	0	0	0	0	0	0	0	3 (5%)	0	0	0	2 (3%)	0	0
Metastases to bone	0	1 (1%)	0	0	0	0	0	0	0	1 (2%)	0	0	0	0	0	0
Nervous system disorders																
Neuropathy peripheral	1 (1%)	1 (1%)	0	0	4 (6%)	1 (2%)	0	0	8 (12%)	1 (2%)	0	0	7 (10%)	3 (4%)	0	0
Headache	8 (12%)	0	0	0	5 (8%)	0	0	0	4 (6%)	0	0	0	6 (9%)	0	0	0
Syncope	0	0	0	0	0	0	0	0	0	1 (2%)	0	0	1 (1%)	2 (3%)	0	0
Dysarthria	0	1 (1%)	0	0	0	0	0	0	0	1 (2%)	0	0	0	0	0	0
Paresis	0	0	1 (1%)	0	0	0	0	0	0	0	0	0	0	1 (1%)	0	0
Psychiatric disorders																
Sleep disorder	3 (4%)	0	0	0	1 (2%)	0	0	0	5 (8%)	0	0	0	8 (12%)	0	0	0
Confusional state	2 (3%)	0	0	0	0	0	0	0	2 (3%)	1 (2%)	0	0	1 (1%)	0	1 (1%)	0
Respiratory, thoracic, and mediastinal disorders																
Dyspnoea	9 (13%)	2 (3%)	0	0	13 (20%)	1 (2%)	0	0	8 (12%)	7 (11%)	0	0	17 (25%)	2 (3%)	1 (1%)	0
Cough	11 (16%)	0	0	0	13 (20%)	1 (2%)	0	0	13 (20%)	0	0	0	12 (18%)	0	0	0
Pulmonary haemorrhage	0	2 (3%)	0	2 (3%)	6 (9%)	0	0	0	3 (5%)	0	0	3 (5%)	5 (7%)	1 (1%)	0	0
Pleural effusion	3 (4%)	1 (1%)	0	0	0	2 (3%)	0	0	1 (2%)	2 (3%)	0	0	3 (4%)	5 (7%)	0	0
Respiratory failure	1 (1%)	0	0	1 (1%)	0	0	1 (2%)	2 (3%)	0	2 (3%)	0	2 (3%)	0	0	0	3 (4%)
Pneumonitis	2 (3%)	1 (1%)	0	0	2 (3%)	2 (3%)	0	0	0	0	1 (2%)	0	1 (1%)	1 (1%)	0	0
Pulmonary embolism	0	1 (1%)	0	1 (1%)	0	2 (3%)	1 (2%)	0	1 (2%)	3 (5%)	0	0	0	1 (1%)	0	0
Chronic obstructive pulmonary disease	1 (1%)	1 (1%)	0	0	1 (2%)	1 (2%)	0	1 (2%)	0	1 (2%)	0	0	0	1 (1%)	0	0
Hypoxia	0	0	0	0	0	0	0	0	1 (2%)	1 (2%)	0	0	1 (1%)	2 (3%)	0	0

(Table 3 continues on next page)

Overall, 30 (11%) of 267 patients discontinued standard therapy due to toxicity related to the standard therapy. Of the 133 patients who received TTFields therapy, 18 (14%) discontinued due to toxicity related to device usage.

Almost all (251 [94%] of 267 patients) reported at least one adverse event of any cause. Adverse events of any cause were observed in 129 (97%) of the 133 patients receiving TTFields therapy with standard therapy and 122 (91%) of 134 patients receiving standard therapy alone (table 3); grade 3–5 adverse events were observed in 78 (59%) patients receiving TTFields therapy with standard therapy and 75 (56%) patients receiving standard therapy alone (appendix pp 16–22). With the exception of dermatitis (60 [22%] of 267 patients), the most frequently reported adverse events were associated with the systemic therapies or the underlying cancer: fatigue (87 patients; 33%), musculoskeletal pain (84; 32%), anaemia (60; 23%), dyspnoea (60; 23%), diarrhoea (50; 19%), leukopenia (46; 17%), cough (50; 19%), and nausea (46; 17%). Serious adverse events of any cause were reported in 70 (53%) of 133 patients receiving TTFields therapy plus standard therapy and 51 (38%) of 134 patients receiving standard therapy alone; there was no specific event or class of events that appeared to occur more frequently in either group (appendix pp 23–26). Adverse events of any cause leading to treatment discontinuation were reported in 48 (36%) of 133 patients receiving TTFields therapy plus standard therapy and 27 (20%) of 134 patients receiving standard therapy alone. Adverse events leading to death occurred in 13 (10%) and ten (8%), respectively.

Serious adverse events related to standard therapy were reported in 25 (19%) of 133 patients also receiving TTFields therapy, and 20 (15%) of 134 receiving only standard therapy. Serious adverse events related to TTFields therapy were reported in four (3%) of the patients receiving TTFields therapy (appendix pp 27–29). 95 (71%) patients receiving TTFields therapy had at least one device-related adverse event; eight (6%) were grade 3. There were no grade 4 toxicities attributable to TTFields therapy (appendix p 29). The most frequent TTFields therapy-related adverse events were grade 1 to 2 skin adverse events: dermatitis (52 patients [39%]), pruritus (16 [12%]), rash (12 [9%]), and skin ulcer (11 [8%]). The incidence of TTFields therapy-related adverse events was generally similar between treatment subgroups: 49 (73%) patients receiving an immune checkpoint inhibitor and 46 (70%) patients receiving docetaxel. The frequency of cardiac events was similar between patients receiving TTFields therapy with standard therapy or standard therapy alone (19 [14%] patients and 18 [13%] patients, respectively), and TTFields therapy did not appear to change the rate or severity of pneumonitis (three [5%] patients with TTFields therapy and immune checkpoint inhibitor; four [6%] patients with immune checkpoint inhibitor alone). There were three deaths related to

	TTFields therapy with an immune checkpoint inhibitor subgroup (n=67)				Immune checkpoint inhibitor subgroup (n=66)				TTFields therapy with docetaxel subgroup (n=66)				Docetaxel subgroup (n=68)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)																
Atelectasis	0	1 (1%)	0	0	0	0	0	0	0	0	0	0	1 (1%)	2 (3%)	0	
Bronchial obstruction	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2 (3%)	0
Skin and subcutaneous tissue disorders																
Dermatitis	31 (46%)	1 (1%)	0	0	1 (2%)	0	0	0	23 (35%)	2 (3%)	0	0	2 (3%)	0	0	0
Alopecia	0	0	0	0	1 (2%)	0	0	0	13 (20%)	0	0	0	21 (31%)	1 (1%)	0	0
Pruritus	11 (16%)	0	0	0	7 (11%)	0	0	0	10 (15%)	1 (2%)	0	0	0	0	0	0
Rash	9 (13%)	1 (1%)	0	0	1 (2%)	0	0	0	7 (11%)	0	0	0	2 (3%)	0	0	0
Skin ulcer	8 (12%)	0	0	0	1 (2%)	0	0	0	7 (11%)	1 (2%)	0	0	3 (4%)	0	0	0
Rash maculo-papular	3 (4%)	0	0	0	4 (6%)	0	0	0	7 (11%)	1 (2%)	0	0	3 (4%)	0	0	0
Vascular disorders																
Hypertension	2 (3%)	0	0	0	1 (2%)	0	0	0	3 (5%)	3 (5%)	0	0	1 (1%)	0	0	0
Embolism	0	0	0	0	0	1 (2%)	0	0	1 (2%)	1 (2%)	0	0	0	0	0	0
Deep vein thrombosis	0	1 (1%)	0	0	0	1 (2%)	0	0	0	0	0	0	0	0	0	0

Data are n (%). Adverse events were compiled from the safety population. Adverse events are shown that occurred in ≥10% patients in any group or subgroup, or for which at least two grade ≥3 events were reported (all grade 3–5 events are provided in the appendix p 16), or for which a grade 5 event was reported. In the population assigned to receive TTFields with docetaxel, one patient received TTFields with an immune checkpoint inhibitor, and one received an immune checkpoint inhibitor alone. In the population assigned to receive an immune checkpoint inhibitor, one patient received docetaxel. TTFields=Tumor Treating Fields.

Table 3: **Summary of adverse events**

standard therapy (two due to infections, and one due to pulmonary haemorrhage), and no deaths related to TTFields therapy.

Baseline patient-reported global health status, measured by EORTC QLQ-C30 questionnaire, was similar between patients assigned to TTFields therapy and standard therapy versus standard therapy alone. Global health status did not decline in either study group over 54 weeks of follow-up, and there was no difference between treatment groups that was considered clinically significant (appendix p 35).

Discussion

The randomised, pivotal phase 3 LUNAR study provides level 1 evidence that TTFields therapy, an innovative, locoregional treatment method, applied concomitantly with standard systemic therapy significantly improves overall survival in patients with metastatic non-small-cell lung cancer following progression on or after platinum-based therapy compared with standard systemic therapy alone. The overall survival benefit with TTFields therapy occurred without exacerbating the toxicities associated with systemic therapies; its safety profile was mostly limited to low-grade dermatological toxicity.

Docetaxel was established as second-line standard of care for metastatic non-small-cell lung cancer in 2000,[19,20] and remained standard until immune checkpoint inhibitor monotherapy showed a survival benefit after progression on platinum-based therapy 15 years later.[21–24] With immune checkpoint inhibitor therapy swiftly moving to the first-line setting, docetaxel regimens are again considered standard second-line therapy, providing a limited survival benefit with expected, but marked, toxicity.[25] Since the adoption of immune checkpoint inhibitors as first-line therapy, no additional phase 3 studies have shown a survival benefit after progression on platinum-based therapy. As such, a pressing need remains for additional, effective, and tolerable treatment options in the salvage setting.

Platinum-based therapy remains a standard of care in non-small-cell lung cancer, either in combination with immune checkpoint inhibitors (first-line therapy), or after disease progression on immune checkpoint inhibitor monotherapy (second-line therapy).[1] Optimising treatment after progression on platinum-based therapy remains an unmet need, particularly in the era of immune checkpoint inhibitors. In the LUNAR clinical study, overall survival was over 3 months longer with the addition of TTFields therapy, a clinically meaningful improvement that substantiates its use in this burdened patient population that has few other treatment options. A survival benefit of this magnitude is similar to the survival improvements observed in the landmark studies that established the role of immune checkpoint inhibitors as standard of care in second-line advanced non-small-cell lung cancer.[21–24] The survival benefit observed with the addition of TTFields therapy was also similar to that reported in a randomised phase 2 study[26] that evaluated combination pembrolizumab and ramucirumab versus standard-of-care therapy (median overall survival 14·5 months [80% CI 13·9–16·1] *vs* 11·6 months [9·9–13·0]) in patients whose disease had previously progressed on combination immune checkpoint inhibitor and platinum-based therapy, although these specific phase 2 findings require confirmation in an appropriately powered phase 3 study before being considered a standard of care. Our finding that TTFields therapy improves survival without increasing the toxicity burden of systemic therapy suggests potential for TTFields therapy use with other second-line treatment options, including ramucirumab regimens.

TTFields therapy yielded an 8-month survival benefit in the subgroup receiving an immune checkpoint inhibitor. These results are underscored by findings in preclinical lung cancer models, in which immunogenic cell death induced by TTFields primed an anticancer immune response that could then be sustained via immune checkpoint inhibitor treatment, in turn leading to enhanced effectiveness when both treatments were used together.[10,11] Of note, patients in the docetaxel subgroup were more heavily pretreated than those in the immune checkpoint inhibitor subgroup. More than 50% of patients receiving docetaxel were previously treated with an immune checkpoint inhibitor in addition to platinum-based therapy. LUNAR was designed to detect the primary endpoint at 80% power in the intention-to-treat population only. Furthermore, the ability to detect changes in subgroups was affected by the reduced sample size recommended by the Data Monitoring Committee. As a result, the treatment subgroup analyses should be interpreted with caution and do not definitively show a differential treatment effect for TTFields therapy based on selected concomitant standard therapy. Additional studies are therefore warranted to validate the benefit of TTFields therapy with standard systemic therapies in non-small-cell lung cancer. LUNAR data also highlight that the benefit of TTFields therapy for non-small-cell lung cancer should be examined in other settings. The pilot phase 2 Keynote B36 clinical study (EF-36; NCT04892472) is evaluating TTFields therapy with an immune checkpoint inhibitor in patients with previously untreated advanced non-small-cell lung cancer. It would also be interesting to examine whether TTFields therapy can combat the major clinical problem of resistance to immune checkpoint inhibitor therapy that occurs in some patients.

The similar progression-free survival for patients receiving TTFields therapy with standard therapy versus standard therapy alone is consistent with results from several immunotherapy studies in advanced non-small-cell lung cancer,[21,23,24,26] in which it has been proposed that a delayed tumour response to therapy or longer post-progression survival (or both) relative to cytotoxic chemotherapy might be characteristic of

immunotherapies.[21,24] Additionally, because TTFields therapy is delivered locoregionally, future analyses are needed to understand patterns of progression, and how responses vary by the field dose experienced by the tumour, the nature of the systemic treatment, and daily device usage. Although confirmatory studies are needed, the overall survival advantage of TTFields therapy in LUNAR was observed despite few patients achieving the recommended daily device usage of 18 h or more that had been chosen based on studies in glioblastoma.[13] With increased clinical experience in non-small-cell lung cancer, usage rates might improve in the future; we also note that the patient-reported data from LUNAR suggest there was no quality of life burden associated with adding TTFields therapy to standard therapy.

The TTFields therapy safety profile in LUNAR was limited to mild-to-moderate local skin irritation underneath the arrays, with no evidence of internal or systemic safety concerns, including cardiac events. Although the frequencies of some adverse events of any cause were higher in the group receiving TTFields therapy, this group also showed longer follow-up and thus was expected to have concomitantly higher adverse event reporting given the inherent disease burden and age. These safety data are also consistent with previous clinical and real-world studies of TTFields therapy in other tumour types[4,5,27–31] in which, although multifactorial in nature, the skin adverse events related to TTFields therapy primarily arose from skin contact with the adhesive or hydrogel on the arrays, and not because of the electric fields treatment. In most cases, skin irritation was effectively controlled using prophylaxis and topical therapies. These include careful replacement of the arrays every 3–4 days, with new arrays shifted by approximately 2 cm from the previous layout, prophylactic use of topical steroids or cream calcineurin inhibitors, and simple skin care techniques; increased patient and caregiver education might reduce the risk of their development.[6,7] Although the full analysis of quality-of-life data from LUNAR is ongoing, patient-reported outcomes in newly diagnosed glioblastoma studies have shown that the device did not impair quality of life, consistent with global health status scores reported here, as measured by the validated EORTC QLQ-C30 questionnaire. In fact, TTFields therapy postponed the decline in quality of life compared with patients receiving standard systemic therapy alone.[8]

Study limitations include the open-label design. This design is considered standard and appropriate for a medical device clinical study based on the ethical concerns of exposing patients to a sham device that is expected to cause skin toxicities without the possibility of therapeutic efficacy. Although an open-label design might affect investigator-assessed secondary endpoints including progression, we considered it unlikely to alter the objective assessment of overall survival for the primary and key secondary endpoints. Concerns for open-label response bias regarding safety reporting are in part mitigated through the randomised design of this study. The study was run with protocol-required safety assessments and processes for evaluating, documenting, and reporting adverse events. An independent data safety monitoring board also provided a review of safety data during the study. Other limitations are that the study enrolled a low number of patients with brain metastases, potentially affecting the generalisability of these findings to that population, and patient accrual proceeded more slowly than planned in the original study design. LUNAR was also initiated before the advent of standard genetic profiling by next-generation sequencing in non-small-cell lung cancer, and thus little information about the relationship between TTFields therapy efficacy and tumour genetic subtype is available. Nevertheless, the study was open to a broad population with no restrictions on tumour biomarker or histological status, or type of previous therapy beyond disease progression on platinum-based therapy. Additionally, this was an international study, and the demographics of participants were largely reflective of the real-world patient population receiving second-line therapy.

Overall, the randomised, pivotal, phase 3 LUNAR study showed that TTFields therapy significantly improved overall survival when added to standard systemic therapies for patients with metastatic non-small-cell lung cancer with progression on or after platinum-based therapy, in both squamous and non-squamous disease. There were no new safety signals, and TTFields therapy did not appear to exacerbate the systemic toxicities of either immune checkpoint inhibitors or docetaxel. These pivotal efficacy and safety data suggest that TTFields therapy should be considered as a treatment option to manage the disease in this setting.

Contributors

All authors made substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data, reviewed the manuscript critically for intellectual content, approved the final version to be published, and are accountable for all aspects of the work. TL and CL accessed and verified the data reported in the manuscript. All authors approved the final version and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Analysed, non-confidential data will be made available 3 years after the date of publication upon reasonable request from qualified researchers to Uri Weinberg, Chief Innovation Officer, Novocure (weinberg@novocure.com).

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ORIGINAL ARTICLE

Tarlatamab for Patients with Previously Treated Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

Tarlatamab, a bispecific T-cell engager immunotherapy targeting delta-like ligand 3 and CD3, showed promising antitumor activity in a phase 1 trial in patients with previously treated small-cell lung cancer.

METHODS

In this phase 2 trial, we evaluated the antitumor activity and safety of tarlatamab, administered intravenously every 2 weeks at a dose of 10 mg or 100 mg, in patients with previously treated small-cell lung cancer. The primary end point was objective response (complete or partial response), as assessed by blinded independent central review according to the Response Evaluation Criteria in Solid Tumors, version 1.1.

RESULTS

Overall, 220 patients received tarlatamab; patients had previously received a median of two lines of treatment. Among patients evaluated for antitumor activity and survival, the median follow-up was 10.6 months in the 10-mg group and 10.3 months in the 100-mg group. An objective response occurred in 40% (97.5% confidence interval [CI], 29 to 52) of the patients in the 10-mg group and in 32% (97.5% CI, 21 to 44) of those in the 100-mg group. Among patients with an objective response, the duration of response was at least 6 months in 59% (40 of 68 patients). Objective responses at the time of data cutoff were ongoing in 22 of 40 patients (55%) in the 10-mg group and in 16 of 28 patients (57%) in the 100-mg group. The median progression-free survival was 4.9 months (95% CI, 2.9 to 6.7) in the 10-mg group and 3.9 months (95% CI, 2.6 to 4.4) in the 100-mg group; the estimates of overall survival at 9 months were 68% and 66% of patients, respectively. The most common adverse events were cytokine-release syndrome (in 51% of the patients in the 10-mg group and in 61% of those in the 100-mg group), decreased appetite (in 29% and 44%, respectively), and pyrexia (in 35% and 33%). Cytokine-release syndrome occurred primarily during treatment cycle 1, and events in most of the patients were grade 1 or 2 in severity. Grade 3 cytokine-release syndrome occurred less frequently in the 10-mg group (in 1% of the patients) than in the 100-mg group (in 6%). A low percentage of patients (3%) discontinued tarlatamab because of treatment-related adverse events.

CONCLUSIONS

Tarlatamab, administered as a 10-mg dose every 2 weeks, showed antitumor activity with durable objective responses and promising survival outcomes in patients with previously treated small-cell lung cancer. No new safety signals were identified. (Funded by Amgen; DeLLphi-301 ClinicalTrials.gov number, NCT05060016.)

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*A list of the DeLLphi-301 investigators is provided in the Supplementary Appendix, available at NEJM.org.

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SMALL-CELL LUNG CANCER IS AN AGGRESsive disease associated with poor survival outcomes. Although a response to initial therapy occurs in most patients with extensive-stage small-cell lung cancer, progression usually occurs within months.[1,2] Second-line treatment options are limited, with a short duration of response (range, 3.6 to 5.3 months) and overall survival that rarely exceeds 8 months.[3-5]

Tarlatamab is a bispecific T-cell engager immunotherapy that directs the patient's T cells to cancer cells expressing delta-like ligand 3 (DLL3), independent of major histocompatibility complex (MHC) class I. Tarlatamab binds to both DLL3 on cancer cells and CD3 on T cells, leading to T-cell–mediated lysis of cancer cells. DLL3, a protein that inhibits Notch signaling, is typically localized intracellularly in normal cells but is abnormally expressed on the surface of small-cell lung-cancer cells.[6] DLL3 is expressed in 85 to 94% of patients with small-cell lung cancer, making it a potential target in the treatment of small-cell lung cancer.[6-8]

A phase 1 dose-exploration trial of tarlatamab in patients with previously treated small-cell lung cancer showed encouraging antitumor activity, with a median duration of response of 12.3 months.[8] Here, we report the results from the phase 2 DeLLphi-301 trial, in which the antitumor activity and safety of two different doses of tarlatamab were assessed in patients with previously treated extensive-stage small-cell lung cancer.

METHODS

TRIAL DESIGN

DeLLphi-301 is a phase 2, open-label, international trial designed to evaluate the antitumor activity, safety, side-effect profile, and pharmacokinetics of tarlatamab in patients with advanced small-cell lung cancer previously treated with two or more lines of therapy. The trial design consisted of three parts (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Part 1 was a dose-comparison assessment in approximately 180 patients who had been randomly assigned, in a 1:1 ratio, to receive 10 mg of tarlatamab or 100 mg of tarlatamab intravenously during a 60-minute infusion. A prespecified interim analysis was performed after 30 patients per group were able to be evaluated for objective response after the first post-treatment scan or had been followed for 13 weeks, whichever came first. A dose-selection committee independent of the trial team analyzed the totality of the data and recommended the target dose for parts 2 and 3 of the trial. Enrollment was not paused during the interim analysis, and randomization continued in part 1 until the dose-selection committee recommended the target dose for parts 2 and 3.

In part 2, patients were enrolled only at the selected dose until 100 patients (from parts 1 and 2 combined) had been enrolled at that selected dose. Part 3 was a substudy performed after the enrollment of patients in part 2 was completed in which we evaluated the safety of tarlatamab when inpatient monitoring during cycle 1 was reduced from 48 to 24 hours after the infusion.

In all three parts, patients received a step dose[8] of 1 mg of tarlatamab on day 1 of cycle 1, after which they received the target dose of either 10 mg or 100 mg on day 8 and day 15 of cycle 1 and every 2 weeks thereafter in 28-day cycles (two doses per cycle) until disease progression occurred. An 8-mg dose of dexamethasone was administered intravenously before tarlatamab was given on day 1 and day 8 of cycle 1, and prophylactic hydration (1 liter of normal saline) was administered intravenously after each dose in cycle 1. Imaging assessments were scheduled to occur every 6 weeks for the first year and then every 12 weeks thereafter. Treatment was allowed to continue after radiographic progression if the investigator judged that tarlatamab was clinically beneficial to the patient, provided that the criteria specified in the protocol (available at NEJM.org) were met. Safety follow-up occurred 6 weeks after the last dose of tarlatamab, and long-term follow-up occurred every 3 months for 1 year after the last dose of tarlatamab or every 3 months for 5 years after the first patient was enrolled, whichever occurred first.

OVERSIGHT

The trial was funded by the sponsor (Amgen) and designed by representatives of the sponsor in collaboration with investigators on the steering committee. The data were collected by the investigators and were analyzed by statisticians who were employed by the sponsor. Medical

writers who were employed or paid by the sponsor assisted the authors with the first draft of the manuscript and provided editorial assistance with subsequent drafts. The authors contributed to the interpretation of the data and critically reviewed the manuscript. The authors had full access to the trial data and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The protocol and amendments were approved by the institutional review board at each participating site and by regulatory authorities in the participating countries. All the patients provided written informed consent. A data-review team external to the trial team provided oversight of safety throughout the trial.

PATIENTS

Eligibility criteria included an age of at least 18 years; histologically or cytologically confirmed small-cell lung cancer that had relapsed after, or was refractory to, one platinum-based treatment regimen and at least one other line of therapy; measurable lesions as defined by the Response Evaluation Criteria in Solid Tumors, version 1.1; and an Eastern Cooperative Oncology Group performance-status grade of 0 or 1 (grades range from 0 to 5, with higher grades indicating greater disability). Positivity for DLL3 expression on tumor cells was not required for trial entry. Patients with asymptomatic, treated stable brain metastases were eligible. Detailed inclusion criteria are provided in the Supplementary Appendix; complete eligibility criteria are provided in the protocol.

END POINTS

The primary end point was confirmed objective response (complete or partial response), as assessed by blinded independent central review according to the Response Evaluation Criteria in Solid Tumors, version 1.1. Secondary end points included duration of objective response, disease control, duration of disease control, progression-free survival, overall survival, adverse events during the treatment period, serum concentration of tarlatamab, and formation of antitarlatamab antibody. Exploratory end points included cytokine levels, DLL3 expression in tumor tissue, immune-related biomarkers, and patient-reported outcomes as assessed with the use of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 and the Quality of Life Questionnaire Core 13. Expression of DLL3 was assessed retrospectively by means of immunohistochemical analysis of formalin-fixed, paraffin-embedded tissue specimens at Roche Tissue Diagnostics, with the use of the SP347 antibody.

STATISTICAL ANALYSIS

On the basis of an analysis of the published literature, an objective response of 15% was prespecified in the protocol as the historical control benchmark among patients with previously treated small-cell lung cancer.[9,10] Assuming that an objective response would occur with tarlatamab in 30% of the patients, we estimated that 100 patients receiving tarlatamab at the target dose determined during parts 1 and 2 of the trial would be needed to provide a probability of approximately 0.92 that the lower limit of the 97.5% confidence interval in the analysis of an objective response would exceed 15%. A 97.5% confidence interval was chosen for the primary end point to adjust for dose selection at the prespecified interim analysis. The analysis population for the assessment of antitumor activity included the intention-to-treat population, which included all patients in parts 1 and 2. Patients from part 3 were not included in this population because data from these patients were immature. The safety analysis population consisted of all the patients from parts 1, 2, and 3 who had received at least one dose of tarlatamab.

We calculated confidence intervals for percentages using the Clopper–Pearson method. Time-to-event end points were estimated with the use of the Kaplan–Meier method. Mixed models for repeated measurements were used to assess the change from baseline over time in health-related quality of life. We also analyzed the time to deterioration, which was defined as the time from baseline to the date of the first observation of clinically meaningful deterioration or the date of death from any cause, whichever occurred first. No adjustment for multiplicity was prespecified, so the width of confidence intervals should not be used in place of hypothesis testing.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Tarlatamab, 10 mg		Tarlatamab, 100 mg
	Parts 1 and 2 (N=100)	Part 3 (N=34)	Part 1 (N=88)
Median age (range) — yr	64.0 (35–82)	65.5 (49–80)	62.0 (34–80)
Sex — no. (%)			
Male	72 (72)	24 (71)	62 (70)
Female	28 (28)	10 (29)	26 (30)
Race or ethnic group — no. (%)†			
Asian	41 (41)	2 (6)	36 (41)
Black	0	1 (3)	0
White			
Overall	58 (58)	31 (91)	51 (58)
Hispanic or Latino	1 (1)	0	2 (2)
Not Hispanic or Latino	57 (57)	31 (91)	49 (56)
Other	1 (1)	0	1 (1)
Geographic region — no. (%)			
Asia	41 (41)	2 (6)	36 (41)
Europe	56 (56)	21 (62)	50 (57)
North America	3 (3)	11 (32)	2 (2)
Smoking history — no. (%)			
Never	8 (8)	1 (3)	5 (6)
Current	19 (19)	5 (15)	10 (11)
Former	73 (73)	28 (82)	73 (83)
ECOG performance-status grade — no. (%)‡			
0	26 (26)	10 (29)	24 (27)
1	74 (74)	24 (71)	64 (73)
Metastatic disease stage — no. (%)			
Yes	98 (98)	32 (94)	82 (93)
No	2 (2)	2 (6)	6 (7)
Brain metastases — no. (%)			
Yes	23 (23)	4 (12)	32 (36)
No	77 (77)	30 (88)	56 (64)
Liver metastases — no. (%)			
Yes	39 (39)	12 (35)	30 (34)
No	61 (61)	22 (65)	58 (66)
No. of previous lines of therapy — no. (%)			
1	2 (2)	0	2 (2)
2	65 (65)	22 (65)	48 (55)
3	19 (19)	6 (18)	22 (25)
>3	14 (14)	6 (18)	16 (18)
Median no. of previous lines of therapy (range)	2.0 (1–6)	2.0 (2–6)	2.0 (1–8)
Median sum of target-lesion diameters (range) — mm	93.0 (11.0–286.0)	106.0 (38.0–249.6)	85.5 (10.0–306.0)

Table 1. (Continued.)

Characteristic	Tarlatamab, 10 mg		Tarlatamab, 100 mg
	Parts 1 and 2 (N=100)	Part 3 (N=34)	Part 1 (N=88)
Previous use of PD-L1 or PD-1 inhibitor — no. (%)			
Yes	73 (73)	28 (82)	62 (70)
No	27 (27)	6 (18)	26 (30)
Duration of sensitivity to platinum-based treatment — no. (%)§			
<90 days	28 (28)	7 (21)	18 (20)
90 to <180 days	22 (22)	7 (21)	18 (20)
≥180 days	20 (20)	9 (26)	18 (20)
Unknown	30 (30)	11 (32)	34 (39)
DLL3 expression — no./total no. (%)¶	80/83 (96)	NA	71/74 (96)

* Part 1 of the trial was a dose-comparison assessment, part 2 was a dose-expansion assessment, and part 3 involved the reduction of inpatient monitoring during cycle 1 from 48 to 24 hours after the infusion. Percentages may not total 100 because of rounding. NA denotes not applicable, PD-1 programmed death 1, and PD-L1 programmed death ligand 1.

† Race and ethnic group were reported by the patient and recorded by the investigator. No patients of American Indian or Alaska Native or Native Hawaiian or other Pacific Islander race were enrolled.

‡ Eastern Cooperative Oncology Group (ECOG) performance-status grades range from 0 to 5, with higher grades indicating greater disability.

§ The duration of sensitivity is calculated as the interval between the end of first-line platinum therapy to the date on which disease progression was first detected.

¶ Delta-like ligand 3 (DLL3) expression was defined as detection of expression on more than 0% of tumor cells. Data are from patients with an evaluable sample.

RESULTS

PATIENTS

Between December 2021 and May 2023, a total of 222 patients were enrolled at 56 sites in 17 countries. In part 1 of the trial, 176 patients were randomly assigned to receive tarlatamab at a dose of 10 mg (88 patients) or 100 mg (88 patients) (Fig. S2 and Table S1). On the basis of results of the prespecified interim analysis, the 10-mg dose was selected for part 2 (dose expansion; 12 patients were enrolled) and for part 3 (reduced duration of inpatient monitoring; 34 patients were enrolled). As of the data cutoff date (June 27, 2023), the median duration of treatment was 5.1 months (range, 0.0 to 15.2) in the 10-mg group and 3.7 months (range, 0.0 to 15.2) in the 100-mg group. The demographic and clinical characteristics of the patients at baseline were similar in the two dose groups, except that brain metastases were present in a higher percentage of patients in the 100-mg group than in the 10-mg group (Table 1 and Table S2). At the time of the analysis, 23 patients had continued treatment after radiographic progression.

ANTITUMOR ACTIVITY

The analysis population for the assessment of antitumor activity included all 176 patients who underwent randomization in part 1 and the 12 patients who were enrolled in part 2. The median follow-up was 10.6 months (95% confidence interval [CI], 9.2 to 11.3) in the 10-mg group and 10.3 months (95% CI, 9.2 to 11.5) in the 100-mg group. The percentage of patients with an objective response as assessed by blinded independent central review was 40% (97.5% CI, 29 to 52) in the 10-mg group and 32% (97.5% CI, 21 to 44) in the 100-mg group (Table 2 and Fig. S3). The percentages of patients with an objective response, stratified according to prespecified subgroups, are shown in Figure S4. In most patients with an objective response (90% [61 of 68 patients]), the response was observed at the first planned evaluation, which occurred 6 weeks (within a ±1-week window) after the initiation

Table 2. Treatment Response According to Blinded Independent Central Review (Analysis Population for Antitumor Activity).*

Variable	Tarlatamab, 10 mg (N=100)	Tarlatamab, 100 mg (N=88)
Best overall response — no. (%)		
Objective response		
Confirmed complete response	1 (1)	7 (8)
Confirmed partial response	39 (39)	21 (24)
Stable disease	30 (30)	27 (31)
Progressive disease	20 (20)	13 (15)
Not evaluable†	2 (2)	4 (5)
Death before postbaseline scan†	6 (6)	13 (15)
No postbaseline scan†	2 (2)	3 (3)
Percentage of patients with objective response (97.5% CI)	40 (29–52)	32 (21–44)
Median duration of objective response (95% CI) — mo		
Overall	NE (5.9–NE)	NE (6.6–NE)
25th percentile	4.4 (2.8–7.1)	5.6 (2.8–7.6)
75th percentile	NE (NE–NE)	NE (NE–NE)
Observed duration of objective response — no./total no. (%)		
≥3 mo	35/40 (88)	25/28 (89)
≥6 mo	23/40 (58)	17/28 (61)
≥9 mo	10/40 (25)	10/28 (36)
Median time to objective response (range) — mo	1.4 (1.1–2.8)	1.4 (1.2–9.6)
Ongoing objective response at data cutoff — no./total no. (%)	22/40 (55)	16/28 (57)
Percentage of patients with disease control (95% CI)	70 (60–79)	63 (52–73)
Median duration of disease control (95% CI) — mo	6.9 (5.4–9.7)	6.7 (4.2–NE)

* The primary end point was objective response (complete or partial response), as assessed by blinded independent central review according to the Response Evaluation Criteria in Solid Tumors, version 1.1. Data from parts 1 and 2 of the trial are reported for the 10-mg group, and data from part 1 are reported for the 100-mg group. Percentages may not total 100 because of rounding. No adjustment for multiplicity was prespecified, so the width of the confidence intervals should not be used in place of hypothesis testing. NE denotes not evaluable.

† In the response analysis, patients who could not be evaluated, who died before the postbaseline scan, or who did not have a postbaseline scan were considered not to have had an objective response.

of tarlatamab treatment (Fig. 1A). Of the 68 patients with an objective response, the duration of the response was at least 6 months in 40 patients (59%) and at least 9 months in 20 patients (29%) (Fig. S5). Response assessments by the investigator were consistent with those by central review (Table S3). Objective responses at the time of data cutoff were ongoing in 22 of 40 patients (55%) in the 10-mg group and in 16 of 28 patients (57%) in the 100-mg group.

The median progression-free survival was 4.9 months (95% CI, 2.9 to 6.7) in the 10-mg group and 3.9 months (95% CI, 2.6 to 4.4) in the 100-mg group (Fig. 1B and Table S4). Kaplan–Meier estimates of progression-free survival at 6 months and 9 months were 40% (95% CI, 30 to 50) and 28% (95% CI, 19 to 38), respectively, in the 10-mg group and 34% (95% CI, 24 to 45) and 27% (95% CI, 17 to 37), respectively, in the 100-mg group. Kaplan–Meier estimates of overall survival at 6 months and 9 months were 73% (95% CI, 63 to 81) and 68% (95% CI, 57 to 77), respectively, in the 10-mg group and 71% (95% CI, 60 to 80) and 66% (95% CI, 54 to 75), respectively, in the 100-mg group (Fig. 1C and Table S5). The percentage of patients who were alive at the last follow-up visit was 57% (57 of 100 patients) in the 10-mg group and 51% (45 of 88 patients) in

the 100-mg group, with overall survival data yet to mature.

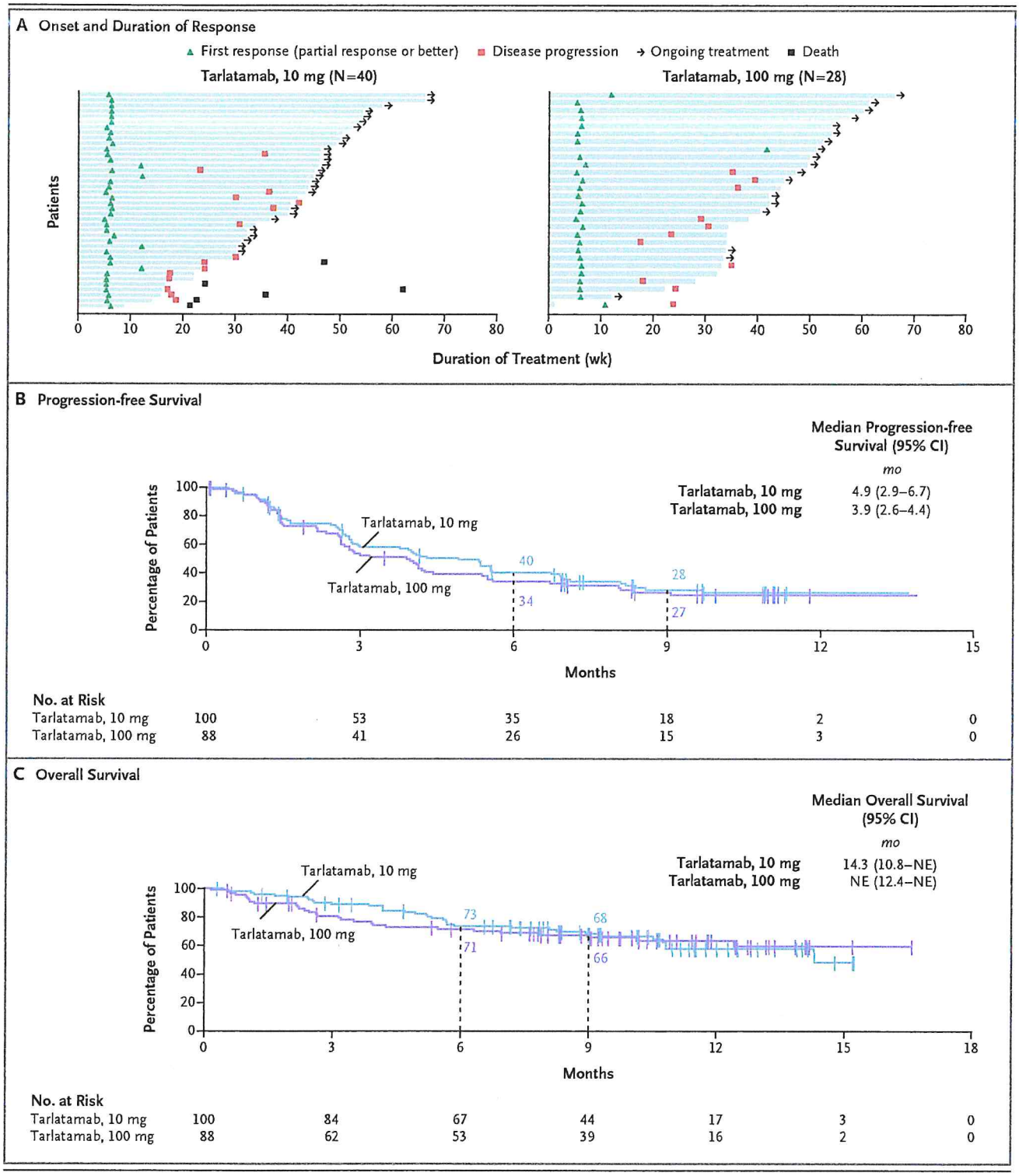
Of the 157 patients (84%) with an evaluable tumor-tissue sample (83 patients [83%] in the 10-mg group and 74 patients [84%] in the 100-mg group), 151 (96%) had a sample that tested positive for DLL3. Objective responses were seen in patients with tumor samples that tested positive for DLL3 expression, in patients with samples that tested negative for DLL3 expression, and in patients without an evaluable sample (Table S6).

SAFETY

Data on adverse events in all three parts of the trial are provided in Table 3 and Tables S7 through S10. Overall, the most common adverse events during the treatment period were cytokine-release syndrome (in 51% of the patients in the 10-mg group and in 61% of those in the 100-mg group), decreased appetite (in 29% and 44%, respectively), pyrexia (in 35% and 33%), constipation (in 27% and 25%), and anemia (in 26% and 25%). Grade 3 or higher adverse events occurred in 59% of the patients in the 10-mg group and in 64% of those in the 100-mg group. Grade 3 or higher adverse events related to the treatment occurred in 26% of the patients in the 10-mg group and in 33% of those in the 100-mg group. Adverse events related to the treatment led to dose interruption, dose reduction, or both in 13% of the patients in the 10-mg group and in 29% of those in the 100-mg group and led to treatment discontinuation in 3% and 3% of the patients, respectively. One patient (1%) in the 10-mg group died from an adverse event (respiratory failure) that was assessed by the investigator to be related to the trial treatment.

Cytokine-release syndrome occurred in 51% of the patients (68 of 133) in the 10-mg group and in 61% of those (53 of 87) in the 100-mg group. Cytokine-release syndrome was assessed predominantly as grade 1 (in 40 of 133 patients [30%] in the 10-mg group and in 28 of 87 patients [32%] in the 100-mg group) or grade 2 (in 27 [20%] and 20 [23%], respectively), and most events occurred after receipt of one of the first two doses (given on days 1 and 8 of cycle 1) (Fig. 2). Grade 3 cytokine-release syndrome occurred in 1% of the patients (1 of 133) in the 10-mg group and in 6% of those (5 of 87) in the 100-mg group. The most common symptoms among patients with cytokine-release syndrome were fever (temperature, ≥38°C; in 97% of the patients), hypotension (in 20%), and hypoxia (in 17%) (Table S11). The median time between the most recent tarlatamab dose and the onset of cytokine-release syndrome was 13.1 hours (interquartile range, 7.8 to 27.4). The median duration of cytokine-release syndrome was 4 days (interquartile range, 2 to 6). Most cases of cytokine-release syndrome were managed with supportive care that included acetaminophen, intravenous hydration, and glucocorticoids, alone or in combination. Additional interventions, such as tocilizumab (in 7 of 133 patients [5%] in the 10-mg group and in 9 of 87 patients [10%] in the 100-mg group), supplemental oxygen (in 11 [8%] and 8 [9%], respectively), and vasopressor support (in 1 [1%] and 1 [1%], respectively), alone or in combination, were seldom used (Table S12). Cytokine-release syndrome led to dose interruption, dose reduction, or both more frequently in the 100-mg group (in 8 of 87 patients [9%]) than in the 10-mg group (in 4 of 133 patients [3%]); nearly all cases (98%) resolved.

The severity of immune effector cell–associated neurotoxicity syndrome (ICANS) was graded according to the American Society for Transplantation and Cellular Therapy 2019 consensus guidelines.[11] Analyses of ICANS events included potentially associated neurologic adverse events identified on the basis of a broad search of preferred terms in the *Medical Dictionary for Regulatory Activities*, version 26.0. The full list of 61 preferred terms is provided in Table S13. ICANS and associated neurologic events occurred in 11 patients (8%) in the 10-mg group and in 24 patients (28%) in the 100-mg group. Grade 3 or higher events were not observed in the 10-mg group and occurred in 4 patients (5%) in the 100-mg group. Most of the ICANS and associated neurologic events occurred after receipt of a tarlatamab dose during cycle 1, with a median time to onset of 5 days (Fig. 2). ICANS and associated neurologic events were more common in the 100-mg group than in the 10-mg group and mainly included ICANS (in 10% vs. 5% of patients) and muscle weakness (in 7% vs. 3%) (Table S14). The most common signs and symptoms related to ICANS included confusion, impaired attention, tremor, and motor findings, weakness, or both. ICANS and associated neurologic events led to dose interruption, dose reduction, or both in 1 patient (1%) in the 10-mg group and in 5 patients



(6%) in the 100-mg group and led to treatment discontinuation in 1 patient in each dose group. The median time to resolution of ICANS and associated neurologic events was 6.5 days (95% CI, 4.0 to 17.0).

Neutropenia was observed in 17% of the patients in the 10-mg group and in 16% of those in the 100-mg group. Grade 3 febrile neutropenia was observed in 1 patient in each dose group. Neutropenia or febrile neutropenia did not lead

Figure 1 (facing page). **Antitumor Activity of Tarlatamab.** Panel A shows the time to response, the duration of response, and patient status as of the data cutoff date for all the patients who were assessed as having an objective response (complete or partial response; primary end point) to 10 mg or 100 mg of tarlatamab, as assessed by blinded independent central review according to the Response Evaluation Criteria in Solid Tumors, version 1.1. Panel B shows the Kaplan–Meier curve of progression-free survival in the analysis population for antitumor activity, which included 100 patients who had been assigned to receive 10 mg of tarlatamab in part 1 or part 2 of the trial and 88 patients who had been assigned to receive 100 mg of tarlatamab in part 1 of the trial. Panel C shows the Kaplan–Meier curve of overall survival in the analysis population for antitumor activity. The tick marks in Panels B and C indicate censored data. NE denotes not evaluable.

to treatment discontinuation in any patient. In the 10-mg group, the safety profile in patients with inpatient monitoring for 24 hours was similar to that in patients with inpatient monitoring for 48 hours.

PATIENT-REPORTED OUTCOMES

Exploratory analyses of patient-reported outcomes showed a trend toward an improvement from baseline to cycle 12 in global health status in the 10-mg group and the 100-mg group (Fig. S6). Similar findings in the two dose groups with respect to symptoms of lung cancer were observed, with a trend toward an improvement in chest pain and dyspnea, along with stabilization of cough. Time-to-deterioration analyses showed that patients who were treated for longer than 2 months did not have further clinical deterioration in global health status, chest pain, dyspnea, and cough (Fig. S7).

PHARMACOKINETICS

Tarlatamab showed an approximate dose-proportionate increase in serum levels across the range of evaluated doses. Steady-state levels of tarlatamab were present in serum by day 15 of cycle 2. After the initiation of the 2-week administration interval, the mean (±SD) trough concentrations at steady state (assessed before the dose on day 15 of cycle 2) were 0.5±0.2 μg per milliliter in the 10-mg group and 6.8±3.4 μg per milliliter in the 100-mg group. The results were consistent with those observed in the phase 1 trial[8] and support the 2-week administration interval.

IMMUNOGENICITY

Among the patients with at least one reportable assessment of immunogenicity after baseline, antitarlatamab binding antibody developed during the treatment period in 4 of 119 patients (3%) in the 10-mg group and in 3 of 80 patients (4%) in the 100-mg group. Antitarlatamab neutralizing antibodies did not develop in these patients. The presence of antitarlatamab antibodies did not appear to affect drug exposure, antitumor activity, or safety.

DISCUSSION

In this phase 2 DeLLphi-301 trial, tarlatamab had durable antitumor activity in patients with heavily pretreated small-cell lung cancer. The trial was designed to compare two active doses, which is consistent with the Food and Drug Administration Project Optimus initiative to reform the dose-optimization and dose-selection paradigm in the development of oncologic drugs.[12] The 10-mg dose was selected for subsequent tarlatamab trials because it had a more favorable benefit-to-risk profile than the 100-mg dose, with an objective response in 40% of the patients and a median overall survival of 14.3 months (the median duration of response was not evaluable). The objective response of 40% far exceeded the historical control benchmark of 15% for the primary end point.[9,10] Currently, patients with small-cell lung cancer face a dire prognosis, with no approved therapies for third-line use and beyond. Results from this trial can be viewed favorably in the context of real-world studies of drugs for third-line use and beyond, in which objective responses occurred in 14 to 21% of the patients, median response durations were less than 3 months, and median overall survival durations were less than 6 months.[7,13-16] Moreover, the findings from this trial, which include data on patient-reported outcomes, are promising relative to the outcomes of clinical trials of current standard-of-care second-line treatment options, such as topotecan (objective responses in 17% and 24% of the patients; median duration of response, 3.6 months and 4.2 months; and median overall survival, 6.3 months and 7.8 months[3,4]) and lurbinectedin (objective response in 35% of the patients; median duration of response, 5.3 months; and median overall survival, 9.3 months[5]).

Tarlatamab represents a new immunothera-

Table 3. Adverse Events (Safety Analysis Population).*

Adverse Events	Tarlatamab, 10 mg		Tarlatamab, 100 mg
	Parts 1 and 2 (N=99)	Part 3, Reduced Monitoring (N=34)	Part 1 (N=87)
	number of patients (percent)		
Events during treatment period			
According to severity			
Any grade	96 (97)	34 (100)	87 (100)
Grade ≥2	86 (87)	33 (97)	83 (95)
Grade ≥3	57 (58)	22 (65)	56 (64)
Grade ≥4	16 (16)	7 (21)	13 (15)
Fatal	3 (3)	4 (12)	5 (6)
Serious adverse event	58 (59)	14 (41)	62 (71)
Event leading to dose interruption, dose reduction, or both	31 (31)	5 (15)	39 (45)
Event leading to tarlatamab discontinuation	7 (7)	3 (9)	6 (7)
Events of interest during treatment period			
Cytokine-release syndrome†			
Overall	49 (49)	19 (56)	53 (61)
Grade ≥3 severity	0	1 (3)	5 (6)
Serious	26 (26)	5 (15)	32 (37)
Leading to tarlatamab discontinuation	0	0	1 (1)
Fatal	0	0	0
ICANS and associated neurologic events‡			
Overall	7 (7)	4 (12)	24 (28)
Grade ≥3 severity	0	0	4 (5)
Serious	2 (2)	2 (6)	11 (13)
Leading to tarlatamab discontinuation	1 (1)	0	1 (1)
Fatal	0	0	0
Neutropenia			
Overall	18 (18)	5 (15)	14 (16)
Grade ≥3 severity	6 (6)	2 (6)	9 (10)
Serious	2 (2)	0	3 (3)
Leading to tarlatamab discontinuation	0	0	0
Fatal	0	0	0
Events related to treatment			
According to severity			
Any grade	89 (90)	29 (85)	81 (93)
Grade ≥2	69 (70)	23 (68)	66 (76)
Grade ≥3	29 (29)	5 (15)	29 (33)
Grade ≥4	5 (5)	2 (6)	3 (3)
Fatal	0	1 (3)	0
Serious	37 (37)	7 (21)	46 (53)

Table 3. (Continued.)

Adverse Events	Tarlatamab, 10 mg		Tarlatamab, 100 mg
	Parts 1 and 2 (N=99)	Part 3, Reduced Monitoring (N=34)	Part 1 (N=87)
	number of patients (percent)		
Event leading to dose interruption, dose reduction, or both	14 (14)	3 (9)	25 (29)
Event leading to tarlatamab discontinuation	4 (4)	0	3 (3)

* The safety analysis population included all the patients in parts 1, 2, and 3 of the trial who had received at least one dose of tarlatamab. Adverse events were graded with the use of the Common Terminology Criteria for Adverse Events, version 5.0, which incorporates certain elements of *Medical Dictionary for Regulatory Activities* (MedDRA), version 26.0, terminology.

† Cytokine-release syndrome events were identified on the basis of a narrow search for preferred terms in the MedDRA, version 26.0, and were graded according to the American Society for Transplantation and Cellular Therapy 2019 consensus guidelines.[11]

‡ Immune effector cell–associated neurotoxicity syndrome (ICANS) events included associated neurologic events identified on the basis of a broad search for 61 preferred terms in the MedDRA, version 26.0. The severity of these events was graded according to the American Society for Transplantation and Cellular Therapy 2019 consensus guidelines.[11]

peutic approach for small-cell lung cancer, a tumor type that is characterized by an immunosuppressive microenvironment.[17,18] Although programmed death ligand 1 inhibitors are part of the standard-of-care chemoimmunotherapy regimen for extensive-stage small-cell lung cancer, down-regulation of MHC class I is a common mechanism of immune escape.[19] Tarlatamab does not rely on the presentation of MHC class I antigen but instead brings T cells into close proximity to small-cell lung-cancer cells by binding both DLL3 and CD3, which results in the formation of a cytolytic synapse and the lysis of the cancer cell.[6,20] This mechanism of action may make tarlatamab particularly relevant in the treatment of small-cell lung cancer.

Given the mechanism of action of tarlatamab, the safety profile included a risk of cytokine-release syndrome and ICANS and associated neurologic events, which are adverse events commonly associated with T-cell immunotherapies. Strategies to mitigate cytokine-release syndrome included the use of a step-dosing approach, prophylactic glucocorticoids, and intravenous hydration. Cytokine-release syndrome most often occurred after the first or second dose, was predominantly grade 1 or 2 in severity (fever with or without hypoxia or hypotension), and was generally managed with supportive care, such as acetaminophen, intravenous hydration, and glucocorticoids, alone or in combination. Grade 3 or higher cytokine-release syndrome was rare with the 10-mg dose of tarlatamab, occurring in only 1 patient (1%). ICANS and associated neurologic events occurred in 8% of the patients treated with 10 mg of tarlatamab, with no grade 3 or higher events. Most ICANS and cytokine-release syndrome events did not necessitate treatment discontinuation. Furthermore, a reduction from 48 to 24 hours in the duration of inpatient monitoring during cycle 1 did not worsen the safety profile of tarlatamab. Although the lack of a control group limits the interpretation of patient-reported outcomes, we observed a trend toward abatement or stabilization with respect to the severity of key lung-cancer symptoms of cough, dyspnea, and chest pain in the two dose groups. Death is a competing risk that can affect the assessment of the repeated measurement of patient-reported outcomes. The analyses of the patient-reported outcomes may have been confounded by death because no adjustments were made to account for the high mortality in this patient population.

Longer follow-up of patients in this phase 2 DeLLphi-301 trial will give more information about the long-term durability of the response and the long-term survival benefits. The continuation of progression-free survival beyond 9 months in approximately one quarter of the patients and a median overall survival duration of more than 14 months are encouraging observations. One

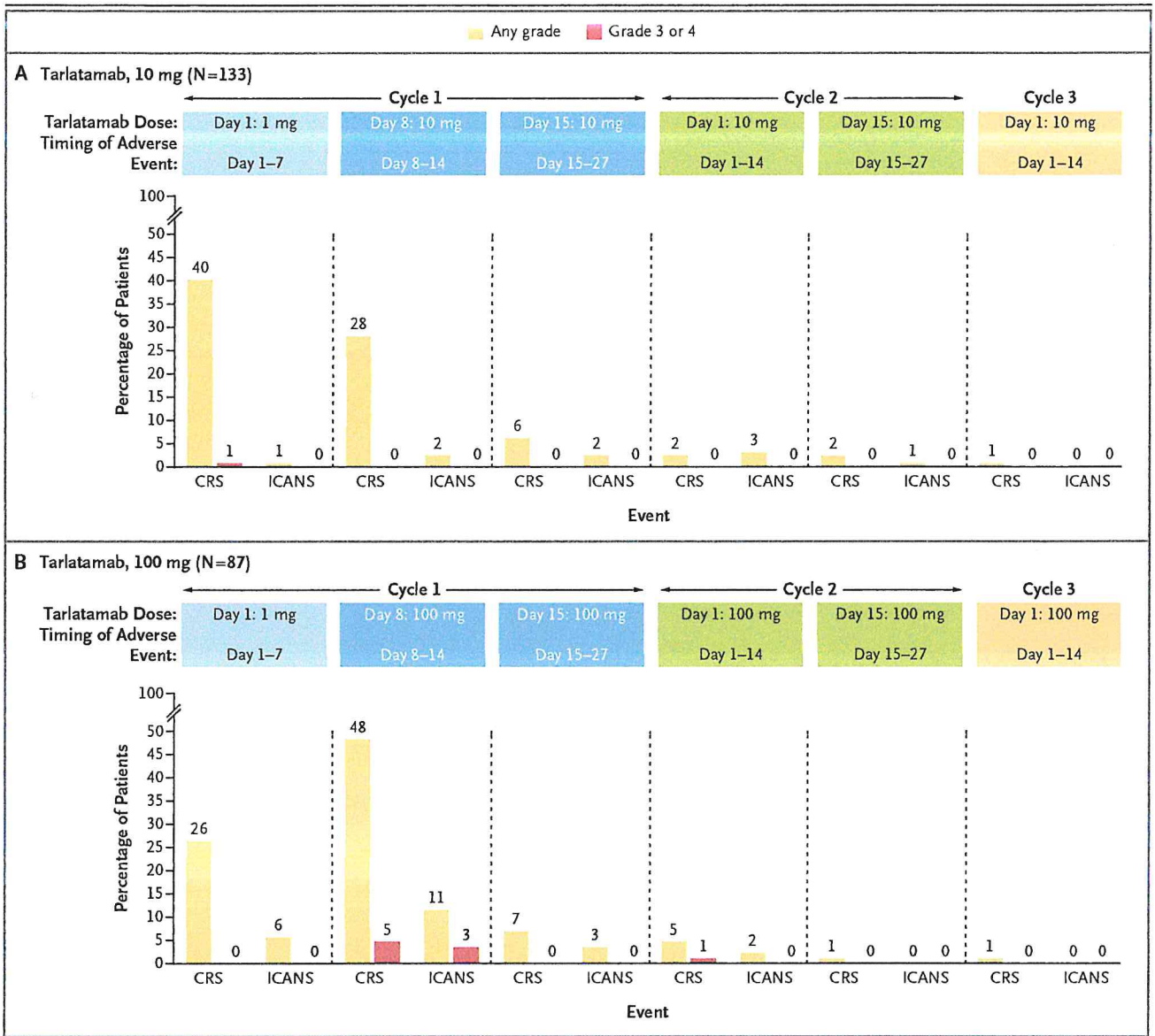


Figure 2. Cytokine-Release Syndrome and ICANS during the Treatment Period.

The incidence of cytokine-release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) according to severity and treatment cycle are shown for the safety analysis population, which included all the patients in parts 1, 2, and 3 of the trial who had received 10 mg of tarlatamab (Panel A) and all the patients in part 1 who had received 100 mg of tarlatamab (Panel B). Cytokine-release syndrome events were identified on the basis of a narrow search for preferred terms in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 26.0, and were graded according to the American Society for Transplantation and Cellular Therapy 2019 consensus guidelines.[11] ICANS data include associated neurologic events identified on the basis of a broad search for 61 preferred terms in the MedDRA.

limitation of the trial is the lack of a standard-care comparator therapy. In the ongoing phase 3 DeLLphi-304 trial (ClinicalTrials.gov number, NCT05740566), investigators are comparing tarlatamab (10 mg every 2 weeks) with standard care in patients with previously treated extensive-stage small-cell lung cancer.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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TTFields and Immune-Checkpoint Inhibitor in Metastatic Non-Small Cell Lung Cancer: PD-L1 Subgroups in the Phase 3 LUNAR Study

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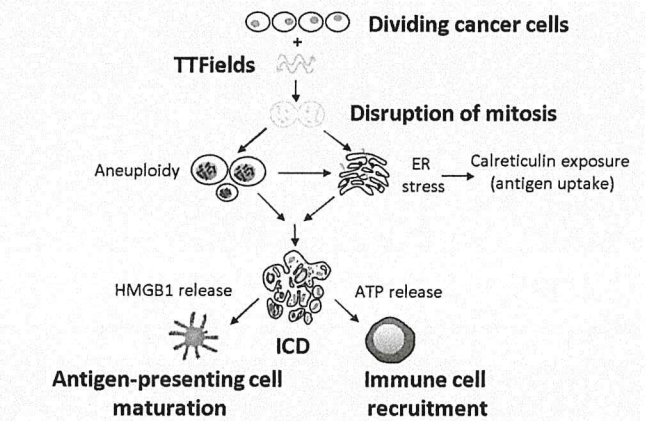
Tumor Treating Fields (TTFields)



Electric fields that exert physical forces on electrically charged components in dividing cancer cells, leading to antimitotic effects[1,2]

Downstream impacts include cell stress-induced immunogenic cell death (ICD) that triggers a systemic anti-tumor immune response[3,4]

ATP, adenosine triphosphate; ER, endoplasmic reticulum; HMGB1, high mobility group box 1 protein; ICD, immunogenic cell death; TTFields, Tumor Treating Fields.

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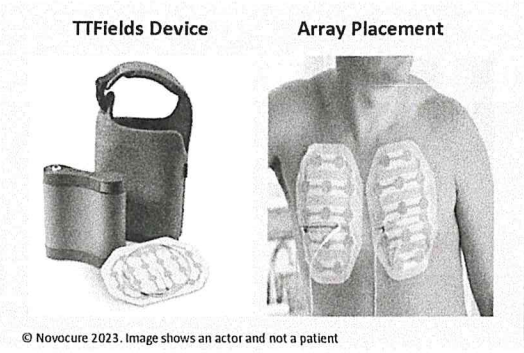
TTFields therapy for NSCLC

- Noninvasive anticancer treatment modality FDA-approved* for glioblastoma and malignant pleural mesothelioma[1–3]
- Delivered locoregionally by a wearable medical device and 2 pairs of arrays (adhesive bandages with biocompatible insulated ceramic discs covered by hydrogel)[4]
- Delivered to the patient's home with 24/7 phone support by a device technician; continuous use (~18 h/day)
- The global, randomized, pivotal phase 3 LUNAR study (NCT02973789) of TTFields therapy for metastatic NSCLC progressing on/after platinum-based therapy met its primary OS endpoint[5,6]
- **OS was significantly longer with TTFields therapy concomitant with an ICI or DTX, compared to an ICI or DTX alone, with a marked benefit in patients receiving an ICI[5,6]**



© Novocure 2023. Image shows an actor and not a patient

*TTFields therapy for glioblastoma was approved via the Premarket Approval (PMA) pathway. TTFields therapy for malignant pleural mesothelioma was approved via the Humanitarian Device Exemption (HDE) pathway.
DTX, docetaxel; FDA, US Food and Drug Administration; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; OS, overall survival; TTFields, Tumor Treating Fields.
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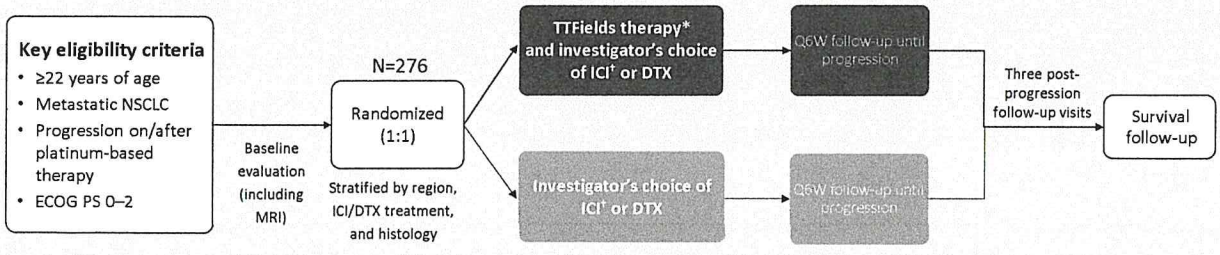
3

LUNAR Pivotal (Phase 3) Study Design

- LUNAR was designed to evaluate the efficacy and safety of TTFields therapy with standard of care at the time of design (an ICI or DTX), compared to an ICI or DTX alone, in metastatic NSCLC progressing on or after platinum-based therapy
- Here we present post-hoc exploratory analyses examining efficacy by PD-L1 status in the subgroup of patients who received an ICI



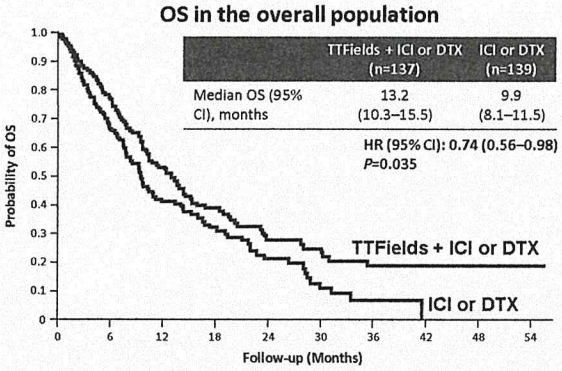
Data cut-off: November 26, 2022
Study sites: 130 in 19 countries (North America, Europe, Asia)
Primary endpoint: OS with TTFields + ICI/DTX vs ICI/DTX alone
Key secondary endpoints: OS in ICI-treated and DTX-treated subgroups

*150 kHz; average use ≥18 h/day. †Pembrolizumab, nivolumab, or atezolizumab.
DTX, docetaxel; ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed cell death ligand 1; Q6W, every 6 weeks; TTFields, Tumor Treating Fields.

4

Recap of Key Findings From LUNAR[1]

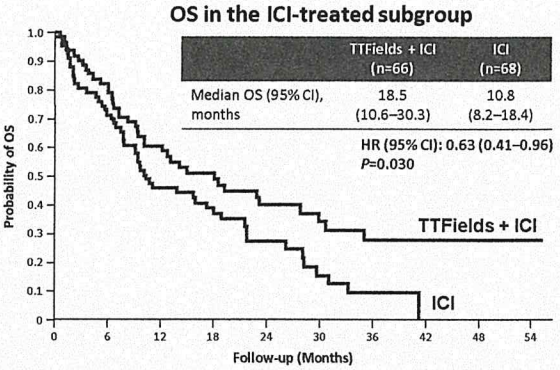
OS in the overall population



	TTFields + ICI or DTX (n=137)	ICI or DTX (n=139)
Median OS (95% CI), months	13.2 (10.3–15.5)	9.9 (8.1–11.5)

HR (95% CI): 0.74 (0.56–0.98)
P=0.035

OS in the ICI-treated subgroup



	TTFields + ICI (n=66)	ICI (n=68)
Median OS (95% CI), months	18.5 (10.6–30.3)	10.8 (8.2–18.4)

HR (95% CI): 0.63 (0.41–0.96)
P=0.030

- OS was significantly longer in the overall population and in patients receiving an ICI
- Median OS was 11.1 vs 8.7 months in patients receiving TTFields + DTX vs DTX

CI, confidence interval; DTX, docetaxel; ICI, immune checkpoint inhibitor; HR, hazard ratio; OS, overall survival; PD-L1, programmed cell death ligand 1; TTFields, Tumor Treating Fields.
1. Leal T et al. *J Clin Oncol*. 2023;41(17_Suppl):LBA9005

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Baseline Demographics and Characteristics of the ICI-Subgroup

	TTFields + ICI (n=66)	ICI (n=68)
Age, years, median (range)	64 (36–85)	65 (23–86)
Sex, male	67%	66%
ECOG PS, 0–1 vs 2	97% vs 3%	100% vs 0%
Smoking history, current or former vs never	85% vs 15%	82% vs 18%
Histology, non-squamous vs squamous	56% vs 44%	54% vs 46%
Liver metastasis	14%	12%
Prior lines of systemic therapy,* 1 vs 2	97% vs 3%	93% vs 4%
Prior ICI, yes	2%	3%
PD-L1 tumor proportion score (TPS)		
<1%	18%	24%
1–49%	26%	27%
≥50%	8%	12%
Unknown	49%	38%

- PD-L1 TPS reporting was optional
- TPS was provided for 83% of patients who received an ICI in the US

Percentages rounded to nearest integer; totals may not equal 100%. *Missing data from 2 patients. †PD-L1 status reporting was optional.
ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; PD-L1, programmed cell death ligand 1; TPS, tumor proportion score; TTFields, Tumor Treating Fields.

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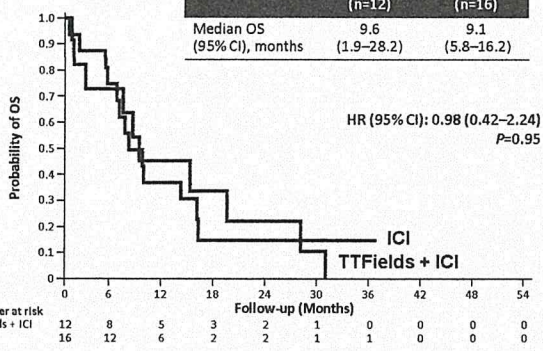
OS in the ICI Subgroup with TPS <1% vs TPS ≥1%

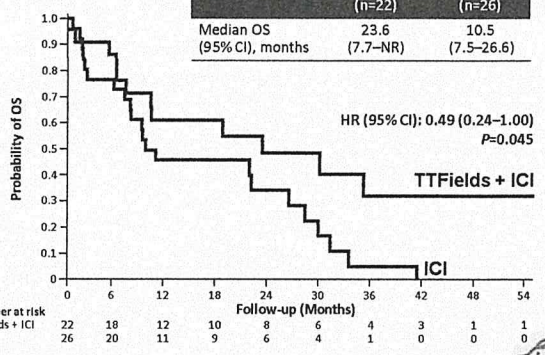
TPS <1%

	TTFields + ICI (n=12)	ICI (n=16)
Median OS (95% CI), months	9.6 (1.9–28.2)	9.1 (5.8–16.2)



TPS ≥1%

	TTFields + ICI (n=22)	ICI (n=26)
Median OS (95% CI), months	23.6 (7.7–NR)	10.5 (7.5–26.6)



CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; NR, not reached; OS, overall survival; PD-L1, programmed cell death ligand 1; TPS, tumor proportion score; TTFields, Tumor Treating Fields.

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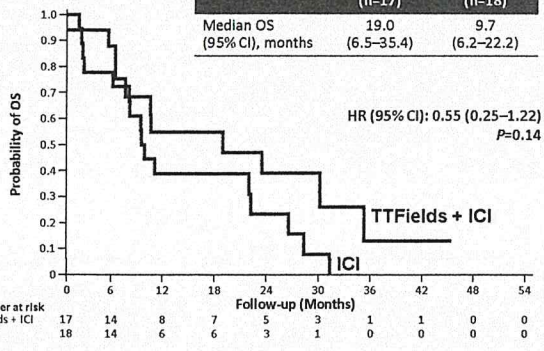
OS in the ICI Subgroup with Low vs High PD-L1 Tumor Expression

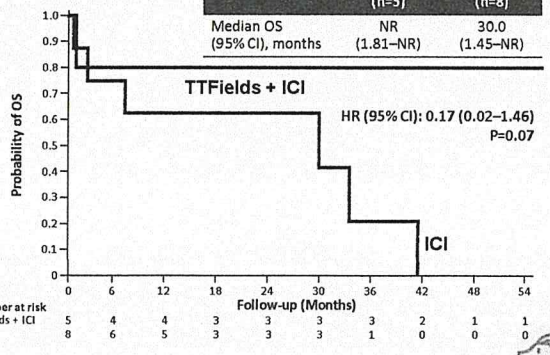
TPS 1–49%

	TTFields + ICI (n=17)	ICI (n=18)
Median OS (95% CI), months	19.0 (6.5–35.4)	9.7 (6.2–22.2)



TPS ≥50%

	TTFields + ICI (n=5)	ICI (n=8)
Median OS (95% CI), months	NR (1.81–NR)	30.0 (1.45–NR)



CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; NR, not reached; OS, overall survival; PD-L1, programmed cell death ligand 1; TPS, tumor proportion score; TTFields, Tumor Treating Fields.

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Safety and Tolerability in the ICI Subgroup: All-Cause AEs

%	TTFields + ICI (n=67)		ICI (n=66)	
	All grades	Grade ≥3	All grades	Grade ≥3
Any AE*	99	55	92	48
Most frequent AEs				
Dermatitis	**48**	**2**	**2**	**0**
Fatigue	24	3	33	3
Musculoskeletal pain	34	2	23	5
Respiratory tract infection	19	3	26	0
Anemia	25	7	14	3
Dyspnea	16	3	21	2
Diarrhea	18	2	20	0
Cough	16	0	21	2
Pneumonia	12	6	17	11
Anorexia	16	0	12	0
Any serious AE	51		35	
Any AE leading to discontinuation	34		18	
Any AE leading to death	8		9	

*Any AE; not necessarily related to treatment.
AE, adverse event; ICI, immune checkpoint inhibitor; TTFields, Tumor Treating Fields.

- AE frequencies were comparable between the TTFields + ICI (99%) and ICI alone (92%) groups, including pneumonitis (5% vs 6%)
  - Consistent with overall study results
- Device-related AEs occurred in 73% of patients receiving TTFields + ICI
  - Mostly grade 1/2 local skin irritation
  - Incidence of grade 3 AEs: 4.5%
  - No grade 4 AEs or deaths were attributed to TTFields therapy

Conclusions

1. **The survival benefit of TTFields therapy + ICI (vs ICI alone) appears more pronounced in patients with PD-L1-positive (TPS ≥1%) tumors**
   - **PD-L1-positive: median OS was 23.6 months vs 10.5 months; HR 0.49; *P*=0.045**
   - **PD-L1-negative: median OS was 9.6 months vs 9.1 months; HR 0.98; *P*=0.95**
2. **Evidence for a relationship between increasing PD-L1 expression and improved survival requires additional confirmation due to the small sample size and the exploratory nature of this analysis**
3. **TTFields therapy is a potentially paradigm shifting new treatment modality that should be considered part of management in metastatic NSCLC after progression on or after platinum-based therapy**
4. **Additional studies are examining TTFields therapy with first-line ICI (EF-36/Keynote B36/NCT04892472), as well as with consolidative ICI therapy for locally advanced disease**

HR, hazard ratio; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed cell death ligand 1; TPS, tumor proportion score; TTFields, Tumor Treating Fields.

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