Updates in Immunotherapy for Metastatic NSCLC

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Disclosures

- Received honoraria for ABBvie, Merck, Bergen Bio, Armo, Mirati, Caris, Sanofi/Regeron, Daiichi

Approved Immunotherapy Agents in NSCLC

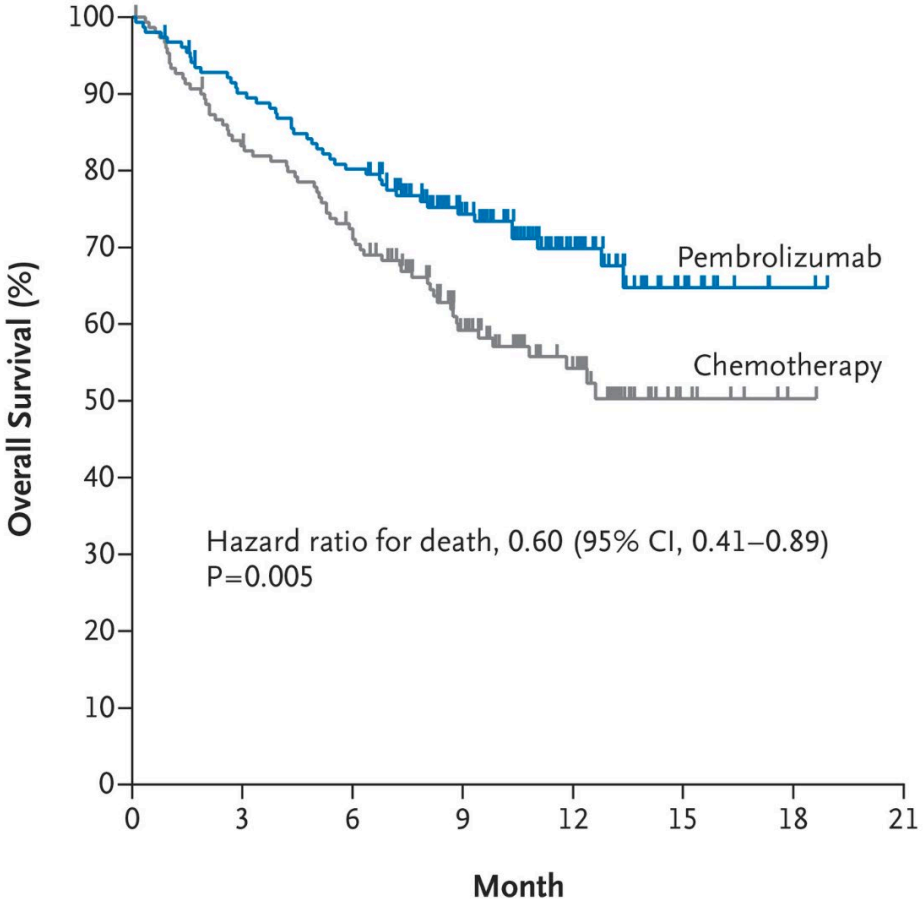
- Metastatic disease
  - 1st Line
    - Pembrolizumab with or without chemotherapy
    - Atezolizumab with chemotherapy and bevacizumab
    - Nivolumab and Ipilimumab with or without chemotherapy
    - Cemiplimab
  - 2nd line
    - Pembrolizumab
    - Nivolumab
    - Atezolizumab
- Adjuvant Therapy
  - Atezolizumab
  - Pembrolizumab
- Stage III after Chemo-RT
  - Durvalumab
- Neoadjuvant Therapy
  - Chemotherapy plus Nivolumab
- Perioperative Therapy
  - Pembrolizumab (soon?)

PD-L1 High - Keynote 24

- Phase 3 randomized trial
- Compared pembrolizumab 200mg q3week vs investigator choice chemotherapy in first line NSCLC
- Patients needed to have 50% or greater PD-L1 staining in tumor cells using PD-L1 IHC 22C3 pharmDx assay to be enrolled
- This biomarker cutoff was predefined
- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, Safety

Reck et al. NEJM 2016

Keynote 24

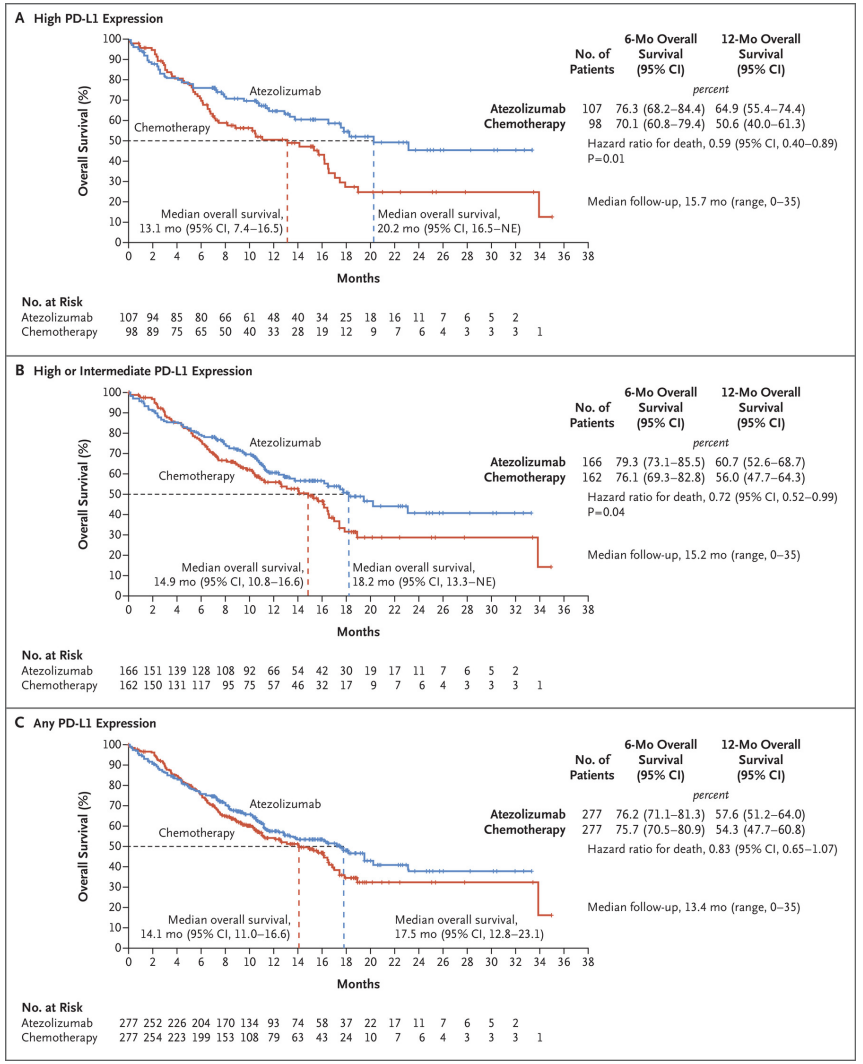


No. at Risk								
Pembrolizumab	154	136	121	82	39	11	2	0
Chemotherapy	151	123	106	64	34	7	1	0

Reck et al. NEJM 2016

IMpower110

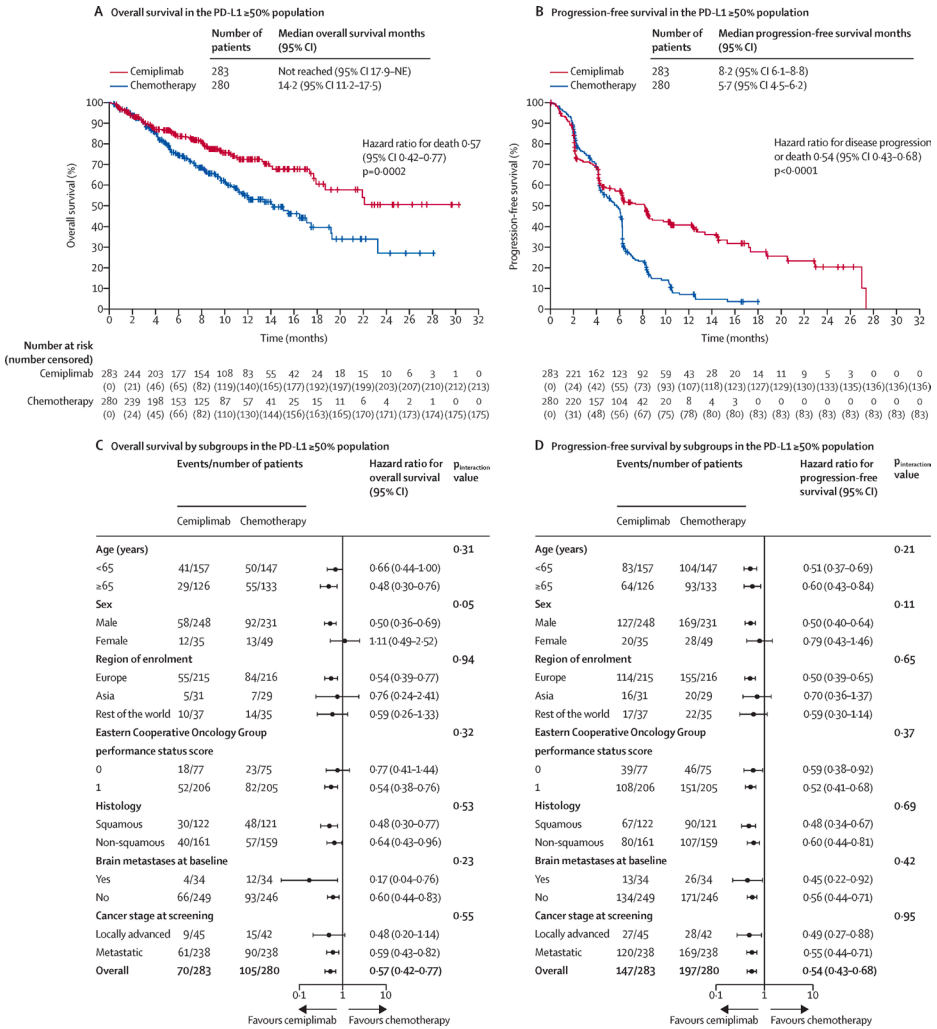
- Similar to Keynote-024, but utilized atezolizumab
- 572 patients PD-L1 expression on at least 1% of tumor cells or tumor-infiltrating immune cells covering at least 1% of the tumor area as determined by the SP142 assay was required
- For pts who had the highest expression of PD-L1 (≥50% of tumor cells or ≥10% of tumor-infiltrating immune cells) (205 patients), the median overall survival was 20.2 months for atezolizumab vs.13.1 months for chemotherapy; HR 0.59



Herbst et al. NEJM 2020

EMPOWER-Lung 1

- Similar to Keynote-024, but utilized cemiplimab
- 710 patients
- Median OS was not reached with cemiplimab vs 14.2 months with chemotherapy, HR 0.57
- Median progression-free survival was 8.2 months with cemiplimab versus 5.7 months with chemotherapy, HR 0.54



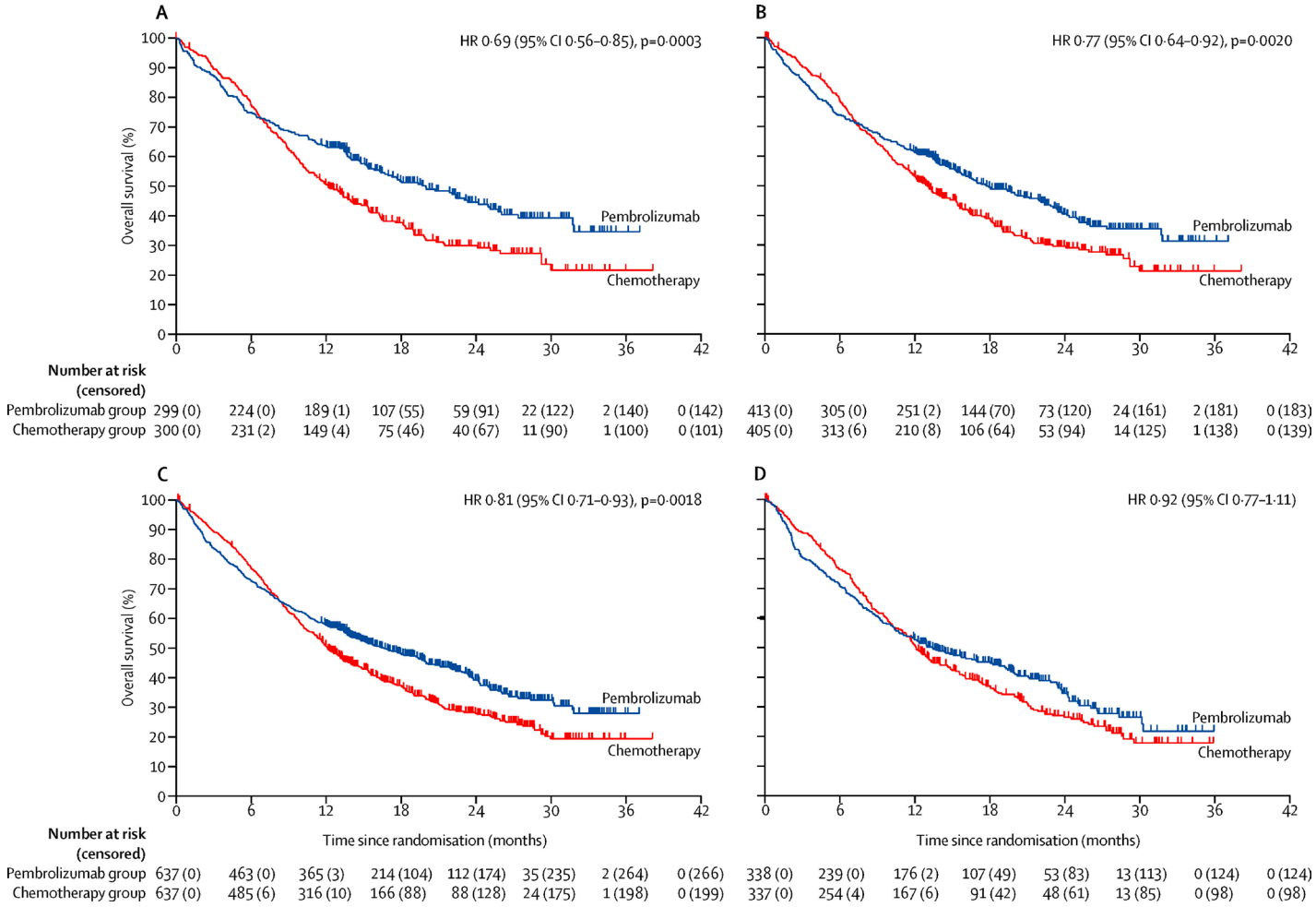
Sezer et al. Lancet 2021

Keynote-042

- Phase 3 study comparing pembrolizumab vs platinum-based chemotherapy for metastatic NSCLC
- Tumors must express PD-L1 at 1% or higher
- Primary endpoints were overall survival in patients with a TPS of 50% or greater, 20% or greater, and 1% or greater, assessed sequentially
- 1274 patients enrolled

Mok et al. Lancet 2019

Keynote-042



(A) PD-L1 TPS 50% or greater population. (B) PD-L1 TPS 20% or greater population. (C) PD-L1 TPS 1% or greater population. (D) PD-L1 TPS 1–49% population (exploratory analysis). Tick marks indicate censoring of the data at the last time the patient was known to be alive.

Mok et al. Lancet 2019

Keynote-042 was a positive trial and led to FDA approval for pembrolizumab for PD-L1 positive patients. However, the data is weak for PD-L1 1-49% (HR 0.92), and unless a frail patient, do not favor immuno-monotherapy for this patient population

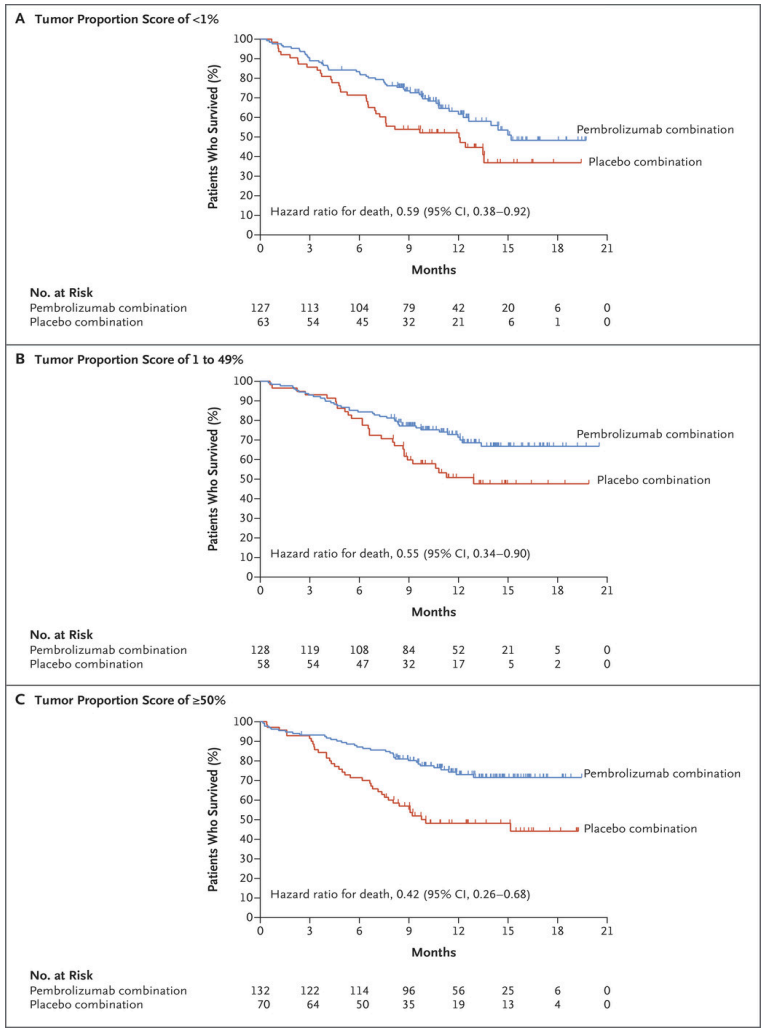
Chemo + IO- Keynote 189

- Phase 3 randomized trial
- Compared pembrolizumab 200mg q3week + platinum and pemetrexed vs chemotherapy in first line nonsquamous NSCLC
- All PD-L1 staining allowed on study, stratified by PD-L1 by 1% or higher
- Primary endpoint: OS and PFS
- 616 enrolled

L Gandhi et al. N Engl J Med 2018

Keynote 189

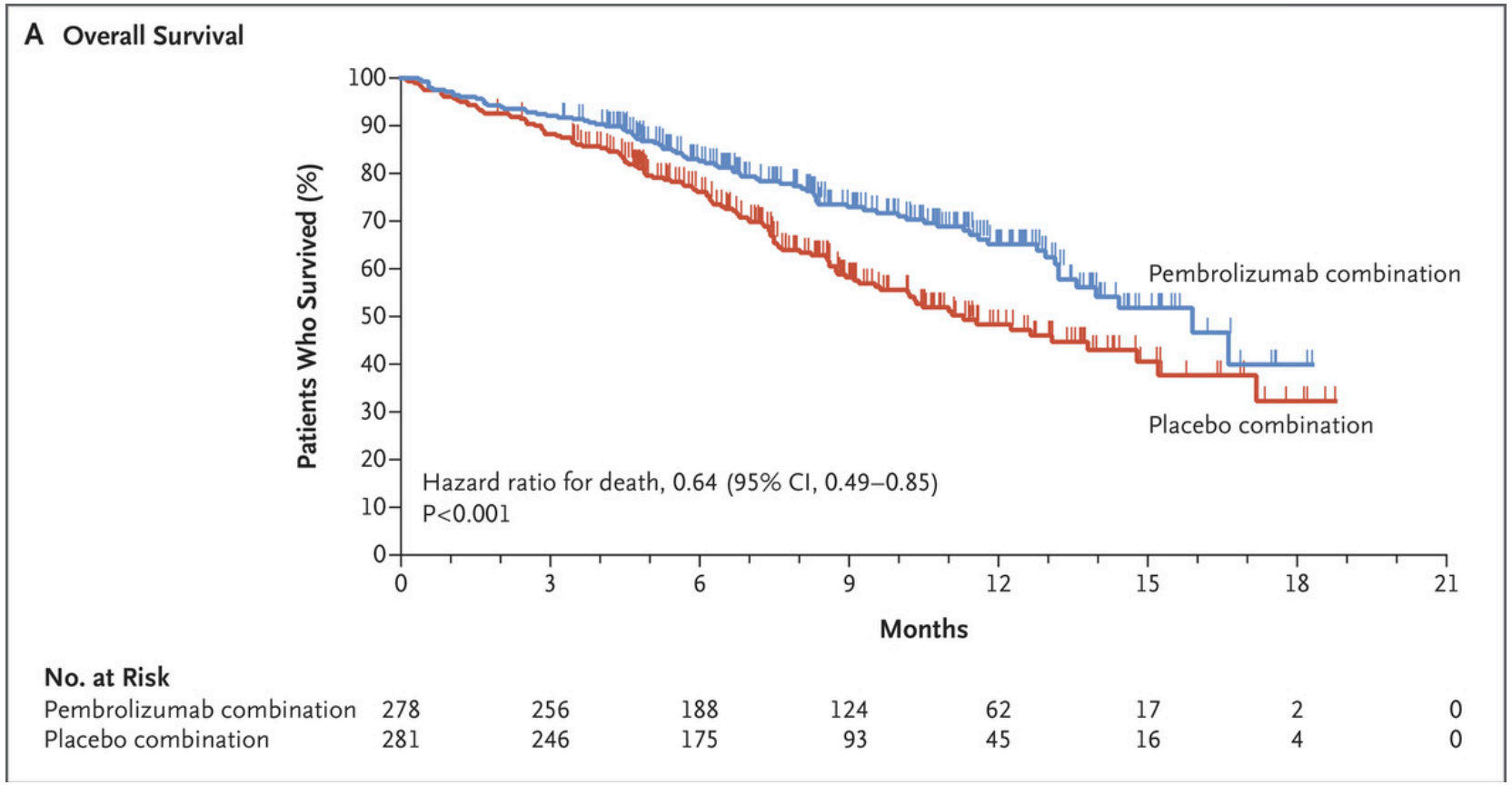
OS



L Gandhi et al. N Engl J Med 2018

Keynote 407

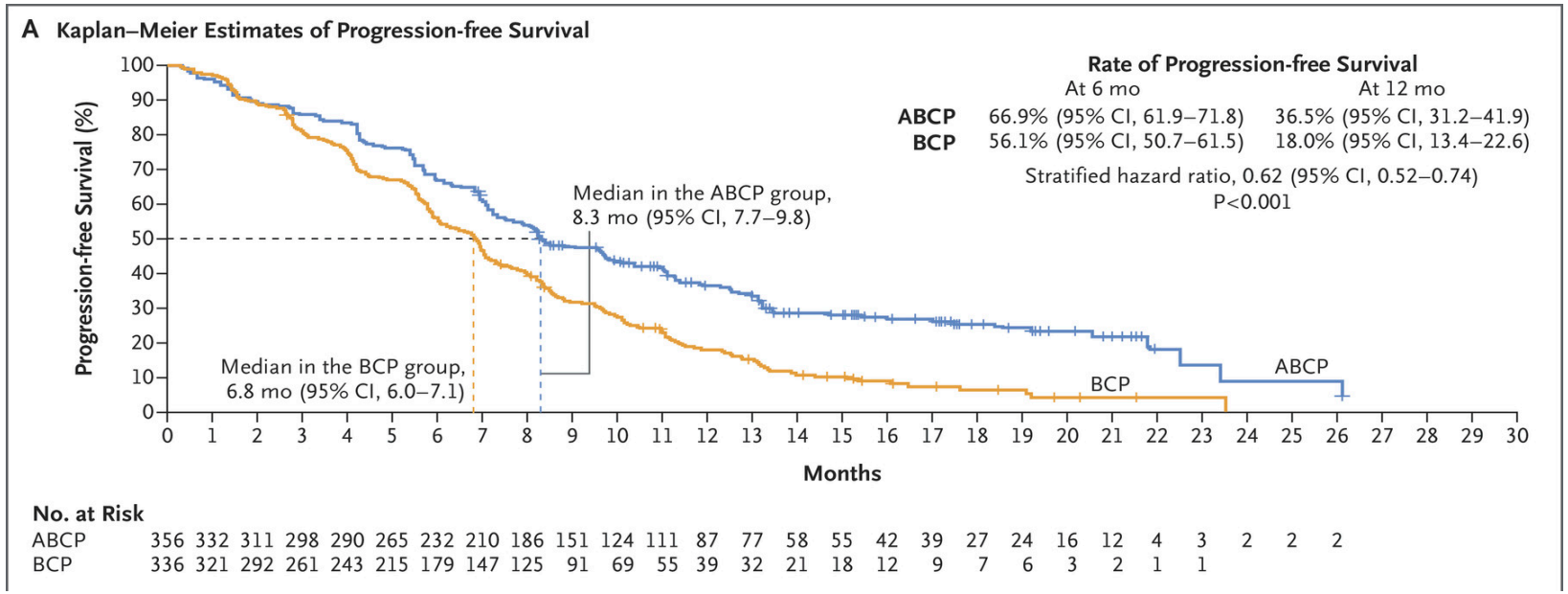
Platinum + Taxane + Pembrolizumab vs. Chemotherapy alone in SCC NSCLC



L Paz-Ares et al. N Engl J Med 2018

IMpower 150

- Phase 3 study comparing atezolizumab with chemotherapy and the VEGF inhibitor bevacizumab (ABCP) vs. atezolizumab with chemotherapy alone (ACP) vs. the control arm of chemotherapy with bevacizumab (BCP) for non-SCC NSCLC
- ABCP was shown to improve overall survival vs. BCP (HR 0.78)

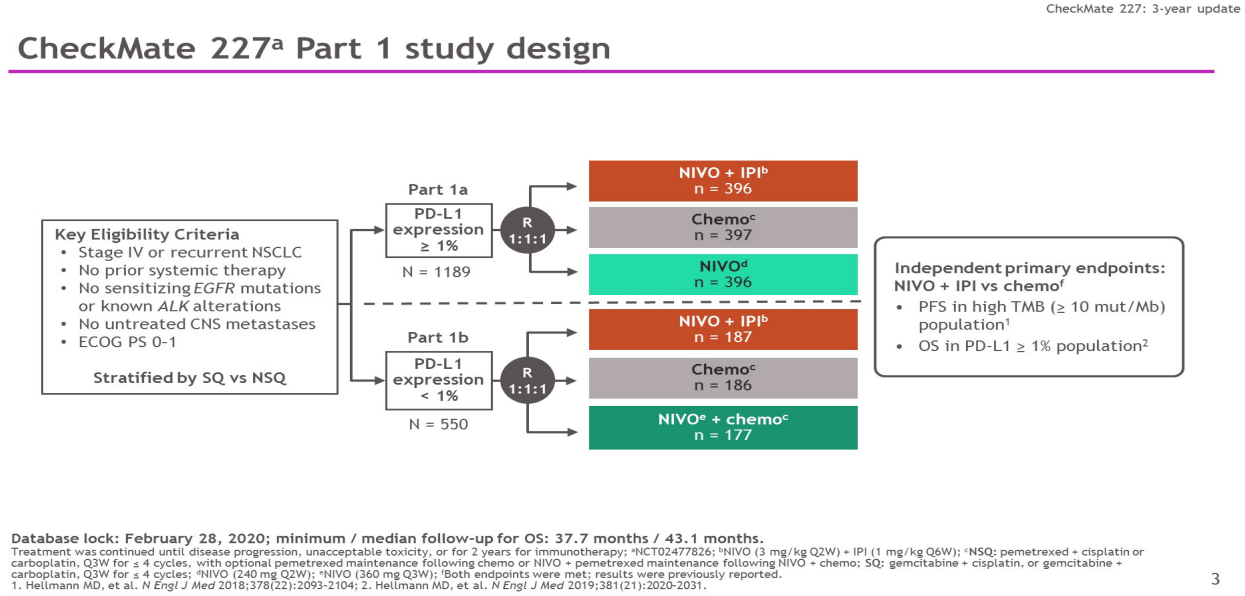


Socinski et al. NEJM 2018

Checkmate-227

- Multicenter phase 3 randomized study of Nivolumab and Ipilimumab vs SOC chemotherapy
- Independent primary endpoint PFS in high TMB patients, OS in PD-L1 ≥ 1%
- First line therapy for squamous or non-squamous histology, no activating mutations

CheckMate 227: 3-year update

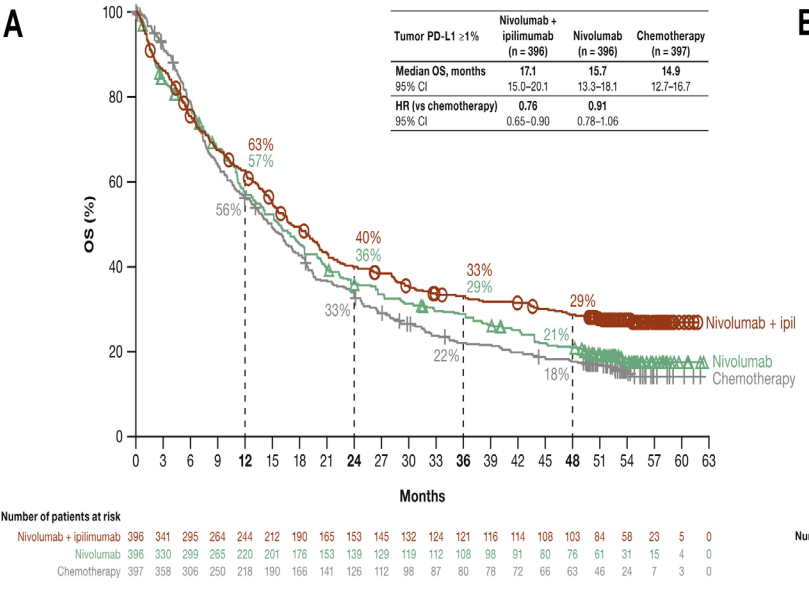


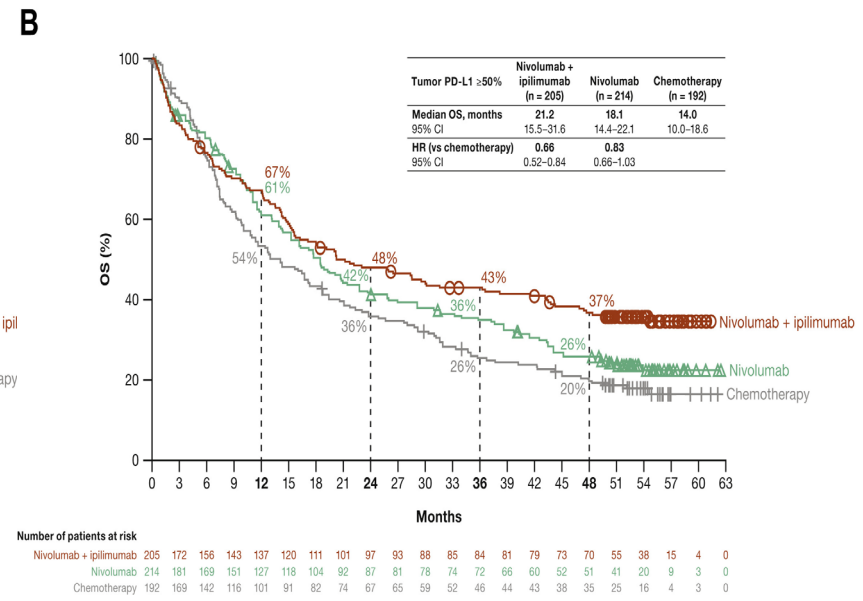
Database lock: February 28, 2020; minimum / median follow-up for OS: 37.7 months / 43.1 months.
Treatment was continued until disease progression, unacceptable toxicity, or for 2 years for immunotherapy; [a]NCT02477826; [b]NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W); [c]NSQ: pemetrexed + cisplatin or carboplatin, Q3W for ≤ 4 cycles, with optional pemetrexed maintenance following chemo or NIVO + pemetrexed maintenance following NIVO + chemo; SQ: gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤ 4 cycles; [d]NIVO (240 mg Q2W); [e]NIVO (360 mg Q3W); [f]Both endpoints were met; results were previously reported.
1. Hellmann MD, et al. *N Engl J Med* 2018;378(22):2093-2104; 2. Hellmann MD, et al. *N Engl J Med* 2019;381(21):2020-2031.

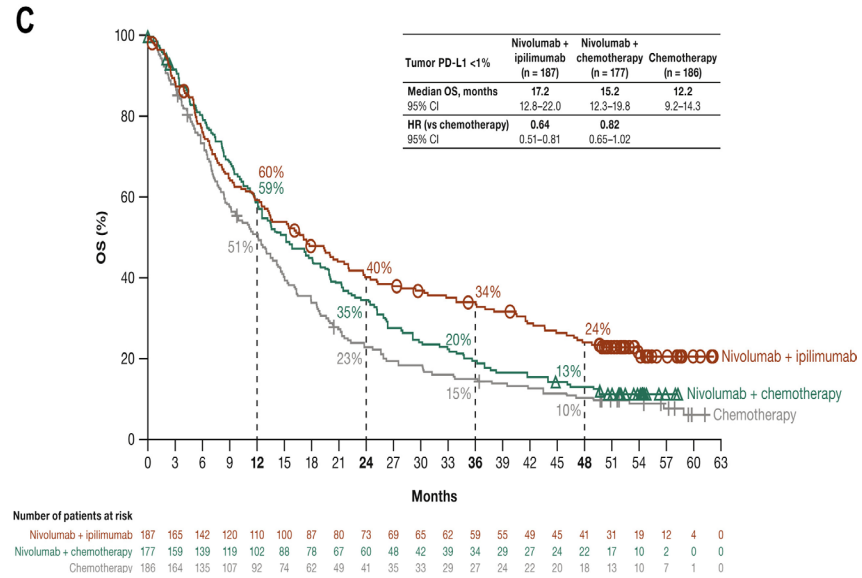
Ramalingam et al. ASCO 2020

Checkmate-227, 4-Year Update

- 1739 patients enrolled overall
- 4-year OS rate with nivolumab plus ipilimumab versus chemotherapy was 29% versus 18% (PD-L1 ≥1%); and 24% versus 10% (PD-L1 <1%)
- All patients off immunotherapy for 2 years







Led To FDA approval for Nivo-IPI ≥ 1%

Paz-Ares et al. JTO 2021

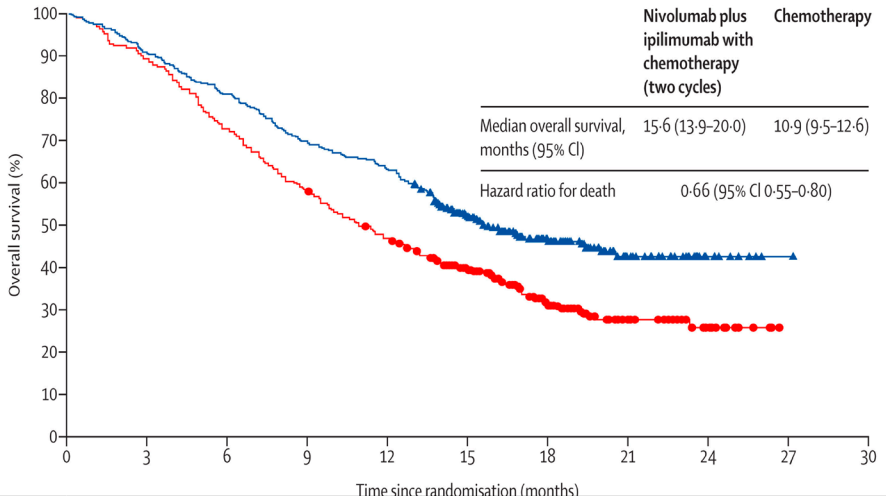
Checkmate 9LA

- Phase 3 study examining Nivo-IPI combined with chemotherapy (for only 2 cycles) vs SOC chemotherapy for untreated metastatic NSCLC
- 719 patients randomized
- Primary endpoint was overall survival
- OS favored IO-IO combination(15.6 months vs 10.9 months in the control group (HR 0.66)
- 40% of patients had PD-L1 < 1%

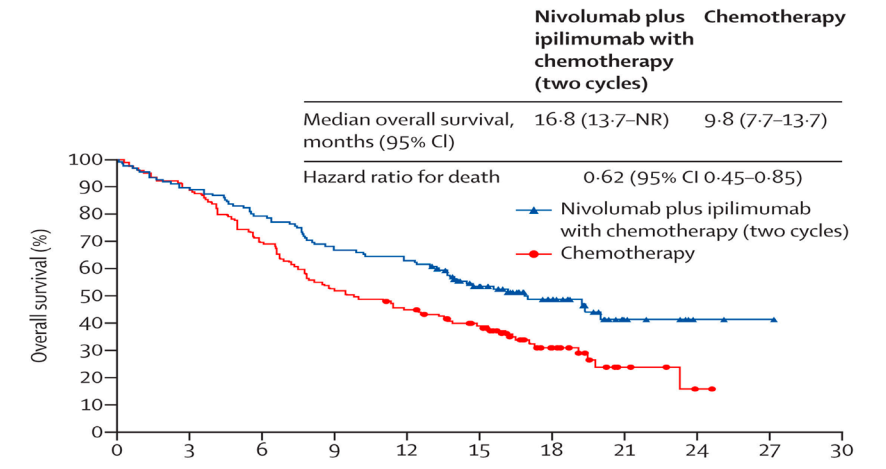
Paz-Ares Lancet Onc. 2021

Checkmate 9LA

Overall Population



PD-L1 < 1% Population



Paz-Ares Lancet Onc. 2021

9LA update

	PD-L1 < 1%		PD-L1 ≥ 1%		SQ		NSQ		All randomized	
	N + I + C n = 135	C n = 129	N + I + C n = 204	C n = 204	N + I + C n = 115	Cn = 112	N + I + C n = 246	C n = 246	N + I + C n = 361	C n = 358
Median OS, mo	17.7	9.8	15.8	10.9	14.5	9.1	17.8	12.0	15.8	11.0
OS HR vs C (95% CI)	0.66 (0.50–0.86)	-	0.74 (0.60–0.92)	-	0.64 (0.48–0.84)	-	0.80 (0.66–0.97)	-	0.74 (0.63–0.87)	-
4-y OS rate, %	23	13	21	16	20	10	22	19	21	16
4-y PFS rate, %	12	3	12	6	8	4	13	5	12	5
ORR, n (%)	42 (31)	26 (20)	87 (43)	56 (27)	56 (49)	35 (31)	81 (33)	55 (22)	137 (38)	90 (25)
Median duration of response, mo	17.5	4.3	11.8	5.6	10.8	3.9	20.0	7.1	12.4	5.6
Responders with ongoing response ≥ 4 y, %	29	0	24	15	17	6	30	16	25	12

Chemo–IO and IO-IO are reasonable options regardless of PD-L1 status for metastatic NSCLC

How to choose between the options, especially for PD-L1 high patients?

Exploratory OS, PFS, and ORR: NSCLC PD-L1 ≥50%

FDA

	Chemo-IO (*N*=455)	IO-alone (*N*=1,298)
OS		
Median, months (95% CI)	25.0 (19.0, NE)	20.9 (18.5, 23.1)
HR (95% CI)	0.82 (0.62, 1.08)	
PFS		
Median, months (95% CI)	9.6 (8.4, 11.1)	7.1 (6.3, 8.3)
HR (95% CI)	0.69 (0.55, 0.87)	
ORR		
% (95% CI)	61 (56, 66)	43 (41, 46)
Odds ratio	1.2 (1.1, 1.3)	

Abbreviations: Chemo-IO=platinum-based doublet chemotherapy plus immunotherapy; CI=confidence interval; HR-hazards ratio; IO=immunotherapy; *N*=number; NSCLC=non-small-cell lung cancer; NE=not estimable; ORR=objective response rate; OS=overall survival; PD-L1=programmed death ligand-1; PFS=progression-free survival.

Toxicity- IO alone is the clear winner

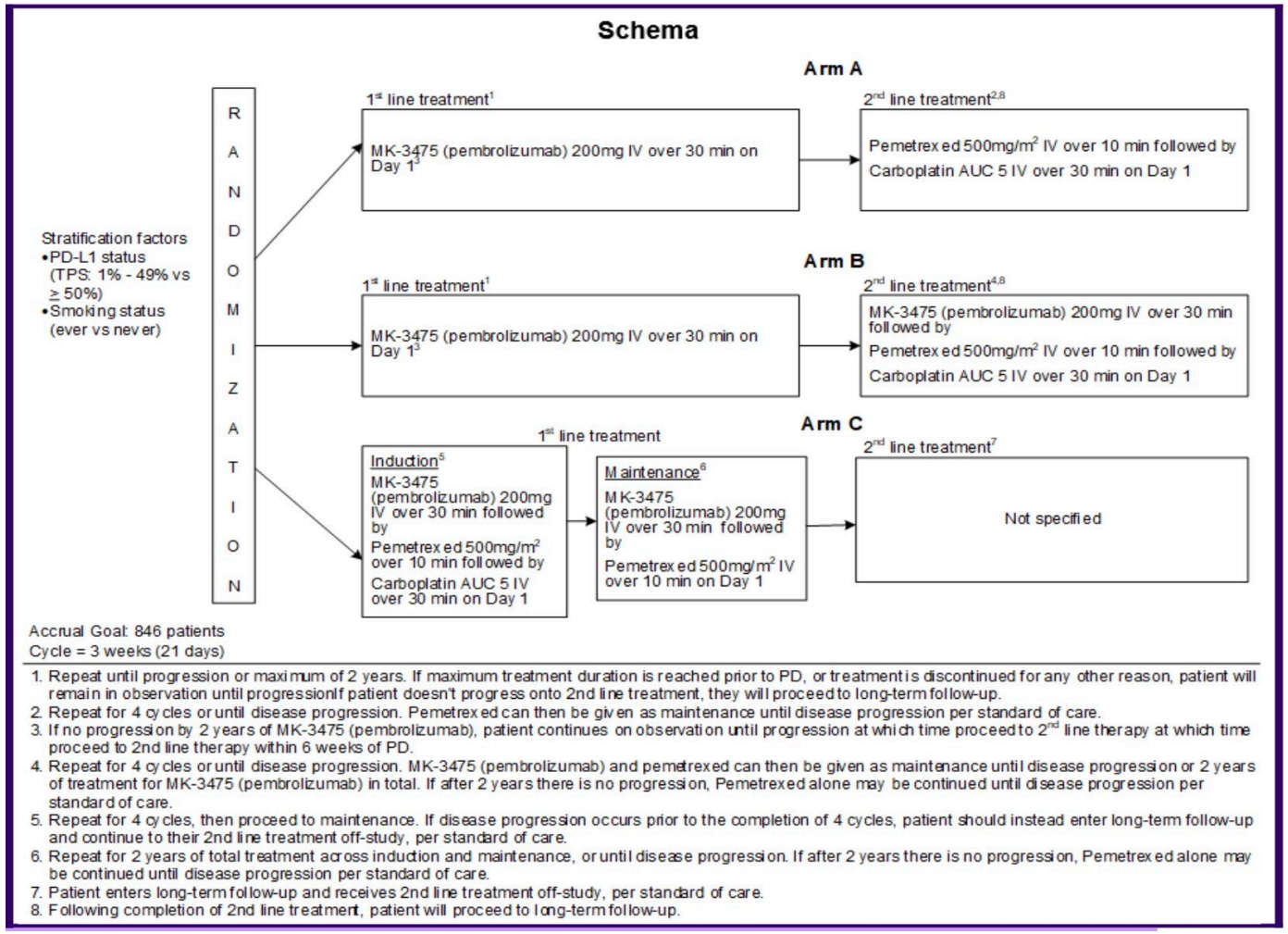
	Keynote 24	Keynote 42	Keynote 189	Keynote 407
Toxicity	IO alone	IO alone	Chemo-IO	Chemo-IO
% of pts with any TRAE	73.4%	63%	99.8%	98.2%
% of pts with grade 3-5 TRAEs	26.6%	18%	67.2%	69.8%
Discontinuation due to TRAE	7.1%	9%	13.8%	13.3%
TRAE leading to death	1/154 (<1%)	13/636 (2%)	27/405 (6.7%)	8.3%
Most common AEs	Diarrhea (14.3%) Fatigue (10.4%) Pyrexia (10.4%)	Hypothyroidism (11%) Fatigue (8%) Pruritis (7%)	Nausea (55.6%) Anemia (46.2%) Fatigue (40.7%)	Anemia (53.2%) Alopecia (46%) Neutropenia (37.8%)
Most common grade 3 and above AEs	Skin reaction (3.9%) Diarrhea (3.9%) Pneumonitis (2.6%)	Pneumonitis (3%) ALT/AST increase (1%) Diarrhea (1%)	Anemia (16.3%) Neutropenia (15.8%) Thrombocytopenia (7.9%)	Neutropenia (22.7) Anemia (15.5%) Thrombocytopenia (6.8%)
IRAEs	29.2%	28%	22.7%	28.8%
Grade 3 or above IRAEs	9.7%	8%	8.9%	10.8%

Reck et al. NEJM 2016, Mok et al. Lancet 2019, Paz-Ares et al. NEJM 2018, Gandhi et al. NEJM 2018

Some important questions:

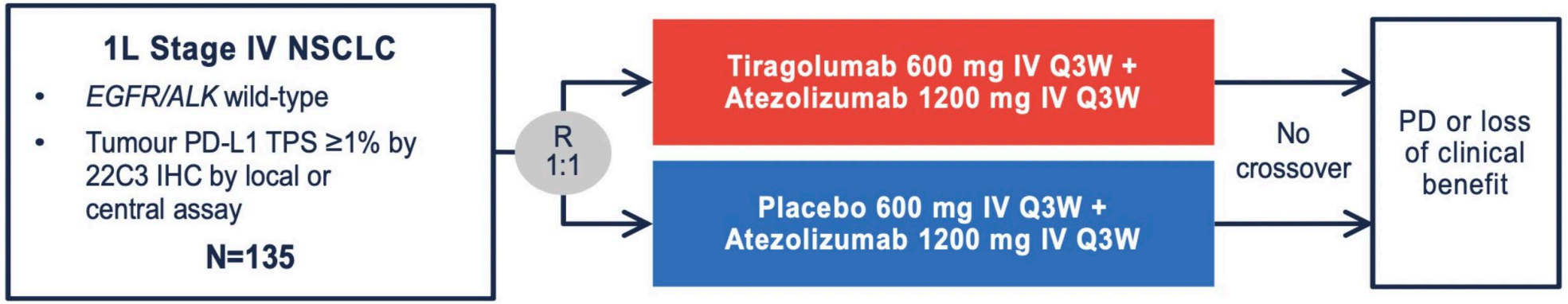
- What is the PD-L1?
- How fit is the patient? Age, PS, comorbities etc.
- How much is a more immediate response needed?
- What is the patient preference?

Insignia Clinical Trial



https://ecog-acrin.org/wp-content/uploads/2021/03/EA5163-physician-fact-sheet.pdf

CITYSCAPE: randomised Phase II study of tiragolumab + atezolizumab in PD-L1+ patients with NSCLC



Stratification factors
- PD-L1 TPS (1–49% vs ≥50%)
- Histology (non-squamous vs squamous)
- Tobacco use (yes vs no)

Co-primary endpoints
- ORR and PFS

Key secondary endpoints
- Safety, DOR, OS

Exploratory endpoints
- Efficacy analysis by PD-L1 status, PROs

Primary analysis[1]
- Cut-off date of 30 June 2019
- Median follow-up of 5.9 months

Updated analysis
- Follow-up performed to assess safety and efficacy
- Cut-off date of 16 August 2021
- Median follow-up of 30.4 months

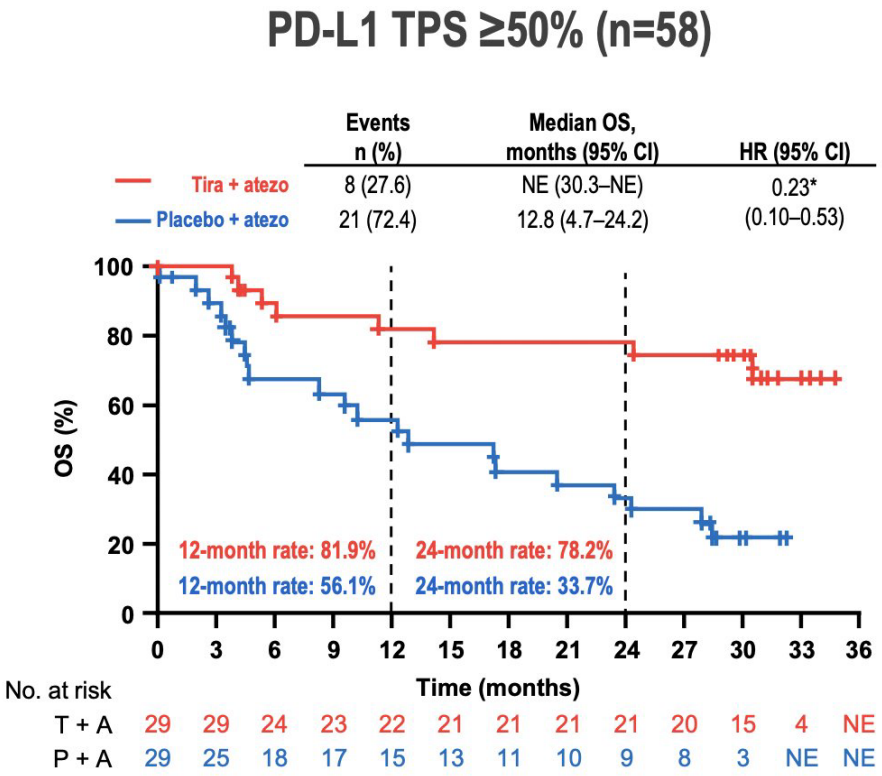
ESMO IMMUNO-ONCOLOGY

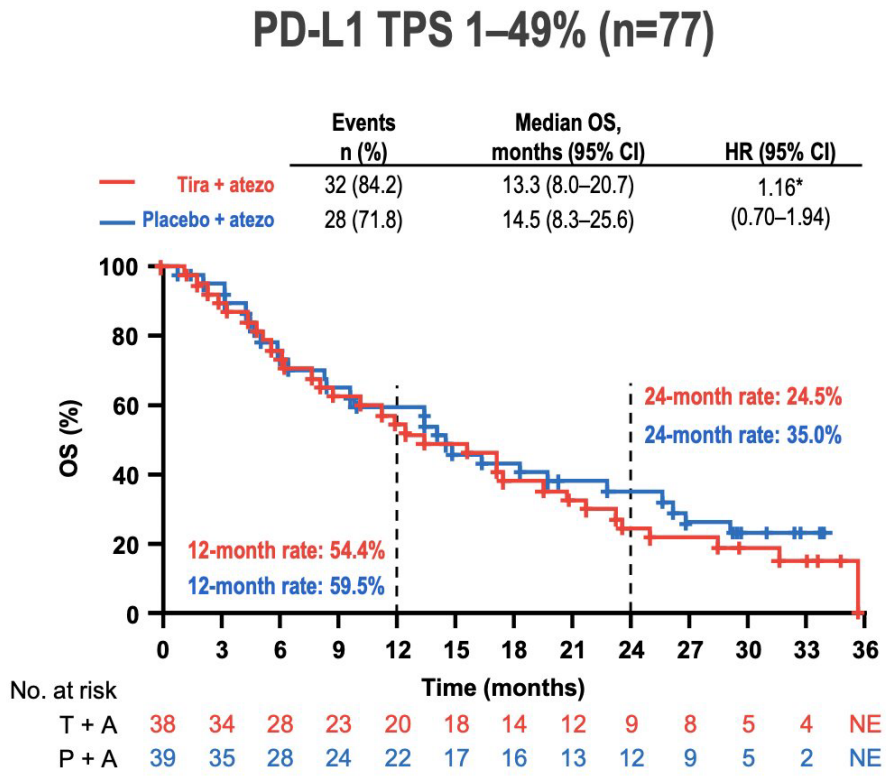
1. Rodriguez-Abreu et al. ASCO 2020

DOR, duration of response; IHC, immunohistochemistry; ORR, confirmed overall response rate; OS, overall survival; PD, progressive disease PFS, progression-free survival; PROs, patient-reported outcomes; Q3W, every 3 weeks; TPS, tumour proportion score

Cho et al. ESMO 2021

Overall survival: PD-L1 subgroups





ESMO IMMUNO-ONCOLOGY

*Unstratified
Updated analysis data cut-off: 16 August 2021 (median follow-up: 30.4 months)

- But press release reports that phase 3 SKYSCRAPER-01 failed to meet its co-endpoint of PFS

Cho et al. ESMO 2021

2022 ASCO® ANNUAL MEETING

SWOG CANCER RESEARCH NETWORK | NCI National Clinical Trials Network | NCI Community Oncology Research Program

Overall survival from a phase II randomized study of ramucirumab plus pembrolizumab versus standard of care for advanced non-small cell lung cancer previously treated with immunotherapy—Lung-MAP non-matched sub-study S1800A

Karen L. Reckamp, M.D.[1], Mary W. Redman, PhD[2], Konstantin H. Dragnev, M.D.[3], Liza Villaruz, M.D.[4], Bryan Faller, MD[5]; Tareq Al Baghdadi, MD[6], Susan Hines, MD[7], Lu Qian, M.S.[2], Katherine Minichiello, M.S.[2], David R. Gandara, M.D.[8], Karen Kelly, MD[8], Roy S. Herbst, M.D., Ph.D.[9]

[1]Cedars-Sinai Medical Center, Los Angeles, CA; [2]SWOG Statistics and Data Management Center & Fred Hutchinson Cancer Research Center, Seattle, WA; [3]Dartmouth-Hitchcock Norris Cotton Cancer Center, Lebanon, NH/Alliance for Clinical Trials in Cancer; [4]University of Pittsburgh Medical Center (UPMC) Hillman Cancer Center; [5]Missouri Baptist Medical Center, St. Louis, MO/Heartland NCORP; [6]IHA Hematology Oncology Consultants-Ann Arbor/Michigan CRC NCORP; [7]Novant Health Cancer Institute - Mount Airy/Southeast Clinical Oncology Research Consortium NCORP); [8]UC Davis Comprehensive Cancer Center, Sacramento, CA; [9]Yale University, New Haven, CT

2022 ASCO ANNUAL MEETING #ASCO22

PRESENTED BY:
Karen L. Reckamp, MD, MS

LUNG-MAP

ASCO® AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

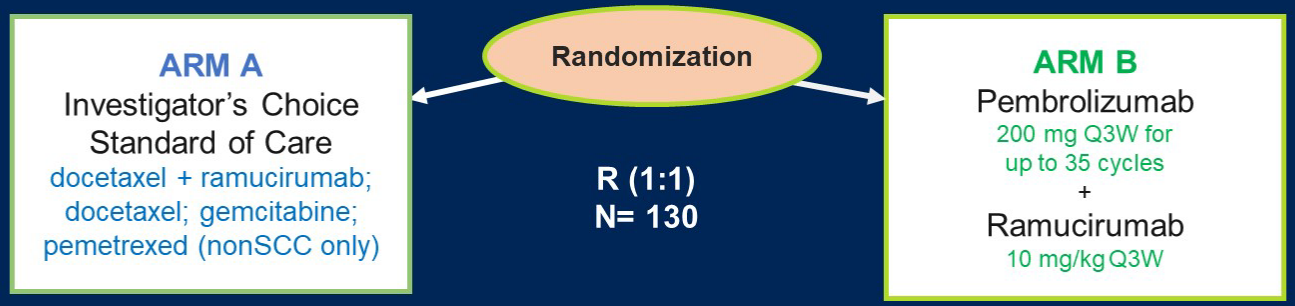
S1800A Schema—Randomized Phase II trial

NCT03971474

Stratified by 1) PD-L1 expression, 2) histology, 3) intent to receive ramucirumab in standard of care arm

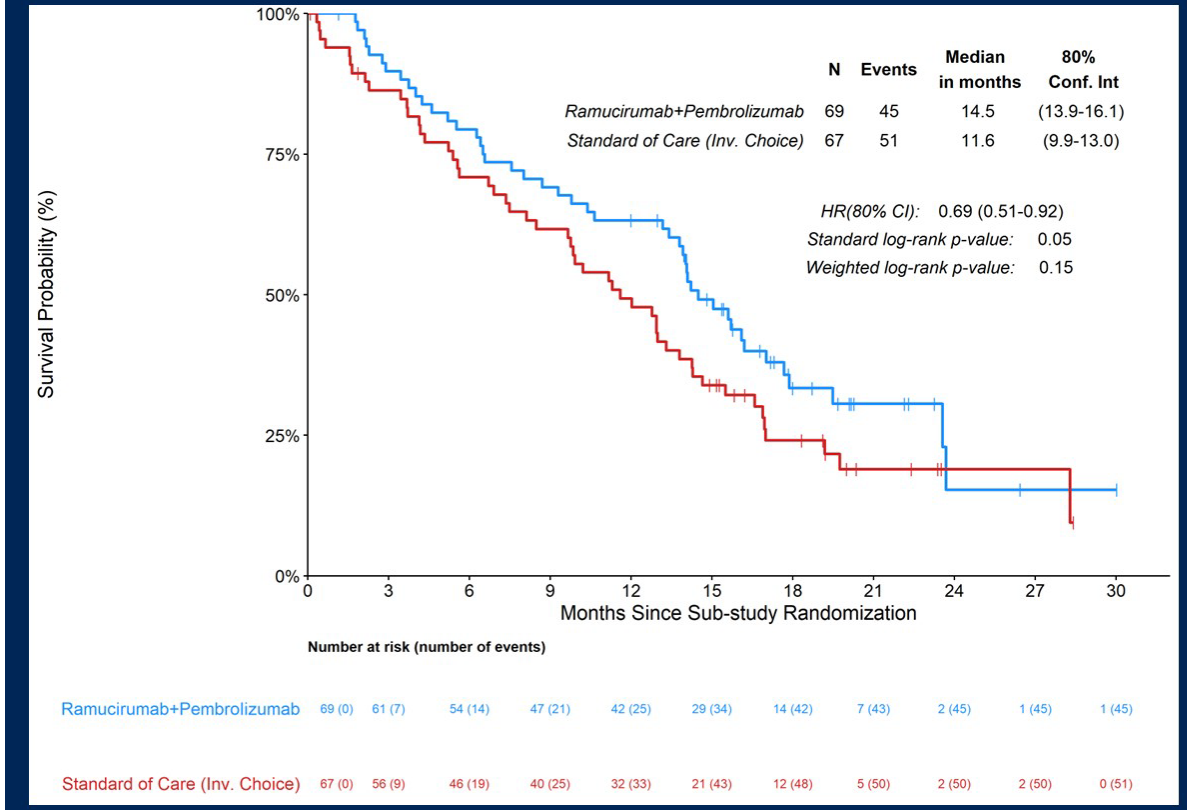
Primary endpoint: OS

Secondary endpoints: RR, DCR, DoR, PFS, Toxicities



Key eligibility: 1) Previously received both PD-1 or PD-L1 inhibitor therapy and platinum-based doublet chemotherapy either sequentially or combined, with PD on at least 84 days after initiation of ICI and platinum-based doublet therapy; 2) ECOG 0-1; 3) all patients met eligibility to receive ramucirumab

Overall survival



- Median OS for RP 14.5 months v. SOC 11.6 months
- HR= 0.69; SLR p-value 0.05

Standard of care therapy received:
- Docetaxel + Ramucirumab (n = 45)
- Docetaxel (n = 3)
- Gemcitabine (n = 12)
- Pemetrexed (n = 1)
- No treatment (n = 6)

LBA9005. Session Date: Tuesday, June 6, 2023. Time: 9:45 AM–12:45 PM

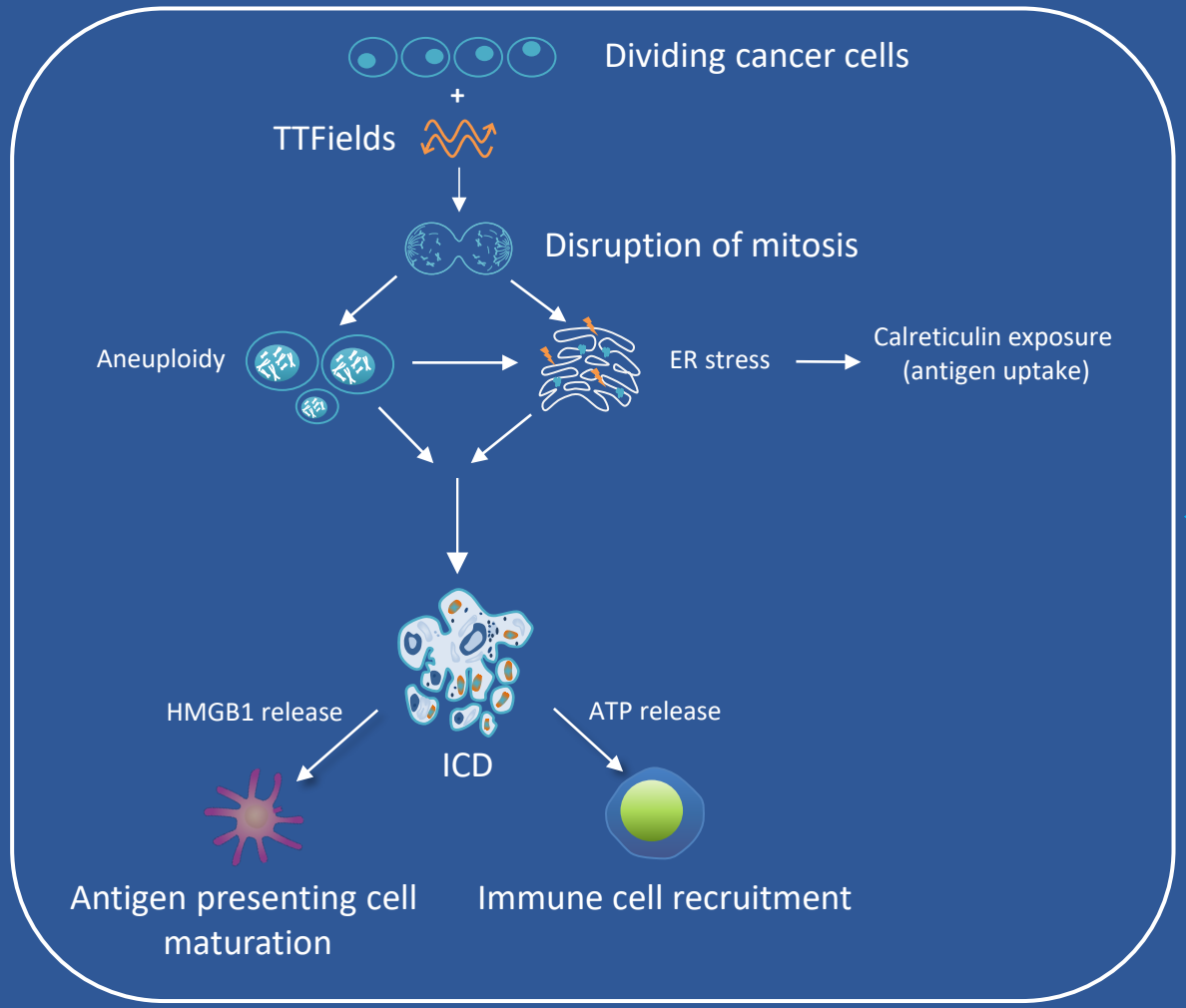
2023 ASCO® ANNUAL MEETING

Tumor Treating Fields (TTFields) Therapy with Standard of Care (SOC) in Metastatic Non-Small Cell Lung Cancer (mNSCLC) After Platinum-based Therapies: Randomized, Phase 3 LUNAR Study

Ticiana Leal[1], Rupesh Kotecha[2], Rodryg Ramlau[3], Li Zhang[4], Janusz Milanowski[5], Manuel Cobo[6], Jaromir Roubec[7], Lubos Petruzelka[8], Libor Havel[9], Sujith Kalmadi[10], Jeffrey Ward[11], Zoran Andric[12], Thierry Berghmans[13], David E. Gerber[14], Goetz Kloecker[15], Rajiv Panikkar[16], Joachim Aerts[17], Angelo Delmonte[18], Miklos Pless[19], Richard Greil[20], Christian Rolfo[21], Wallace Akerley[22], Michael Eaton[23], Mussawar Iqbal[24], and Corey Langer[25]; *on behalf of the LUNAR study investigators*

[1]Winship Cancer Institute at Emory University, Atlanta, GA, USA; [2]Miami Cancer Institute, Baptist Health South Florida, Miami, FL, USA; [3]Rodryg Ramlau, Poznan University of Medical Sciences, Poznan, Poland; [4]Sun Yat-sen University Cancer Center (SYSUCC), Guangzhou, China; [5]Medical University of Lublin, Lublin, Poland; [6]Medical Oncology Intercenter Unit, Regional and Virgen de la Victoria University Hospitals, IBIMA, Málaga, Spain; [7]Nemocnice AGEL Ostrava-Vítkovice, Ostrava, Czech Republic; [8]General University Hospital in Prague, Prague, Czech Republic; [9]Thomayer Hospital, Prague, Czech Republic; [10]Ironwood Cancer & Research Centers, Chandler, AZ, USA; [11]Washington University School of Medicine, St. Louis, MO, USA; [12]Clinical Hospital Centre Bezanijska Kosa, Belgrade, Serbia; [13]Jules Bordet Institute, Hôpitaux Universitaires de Bruxelles, Université Libre de Bruxelles, Brussels, Belgium; [14]Harold C. Simmons Comprehensive Cancer Center, UT Texas Southwestern Medical Center, Dallas, TX, USA; [15]University of Louisville, Louisville, KY, USA; [16]Geisinger Cancer Institute, Danville, PA, USA; [17]Erasmus University Medical Center, Erasmus MC Cancer Institute, Rotterdam, The Netherlands; [18]IRCCS Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" (IRST), Meldola, Italy, Meldola, Italy; [19]Kantonsspital Winterthur, Winterthur, Switzerland; [20]Salzburg Cancer Research Institute-Center for Clinical Cancer and Immunology Trials (SCRI-CCCIT); Paracelsus Medical University Salzburg; Cancer Cluster, Salzburg, Austria; [21]Center for Thoracic Oncology, Tisch Cancer Institute at Icahn School of Medicine, Mount Sinai, New York, NY, USA; [22]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [23]St Francis Hospital, Indianapolis, IN, USA; [24]College of Medicine, University of Saskatchewan, Saskatoon, Canada; [25]Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, PA, USA

Tumor Treating Fields (TTFields) Mechanism of Action



- TTFields are electric fields that exert physical forces on electrically charged components in dividing cancer cells, leading to an antimitotic effect[1,2]

- Downstream effects include cell stress-induced immunogenic cell death (ICD), triggering 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.

1. Mun EJ et al. *Clin Cancer Res.* 2018;24(2):266–275; **2.** Giladi M et al. *Sci Rep.* 2015;5:18046; **3.** Voloshin T et al. *Cancer Immunol Immunother.* 2020;69(7):1191–1204; **4.** Barsheshet Y et al. *Int J Mol Sci*. 2022;23(22):14073. Figure adapted from: Shteingauz A et al. *Cell Death Dis.* 2018;9(11):1074.

TTFields Therapy

- Noninvasive anticancer treatment modality
- Delivered locoregionally to the chest by a wearable medical device and 2 pairs of arrays (adhesive bandages with biocompatible insulated ceramic discs covered by hydrogel)[1]
- Delivered to the patient's home with 24/7 phone support by a device technician; continuous use (~18 h/day)
- FDA-approved* for glioblastoma and malignant pleural mesothelioma[2–4]
- Pilot study demonstrated safety and feasibility of TTFields therapy with pemetrexed in advanced NSCLC[5]

TTFields Device

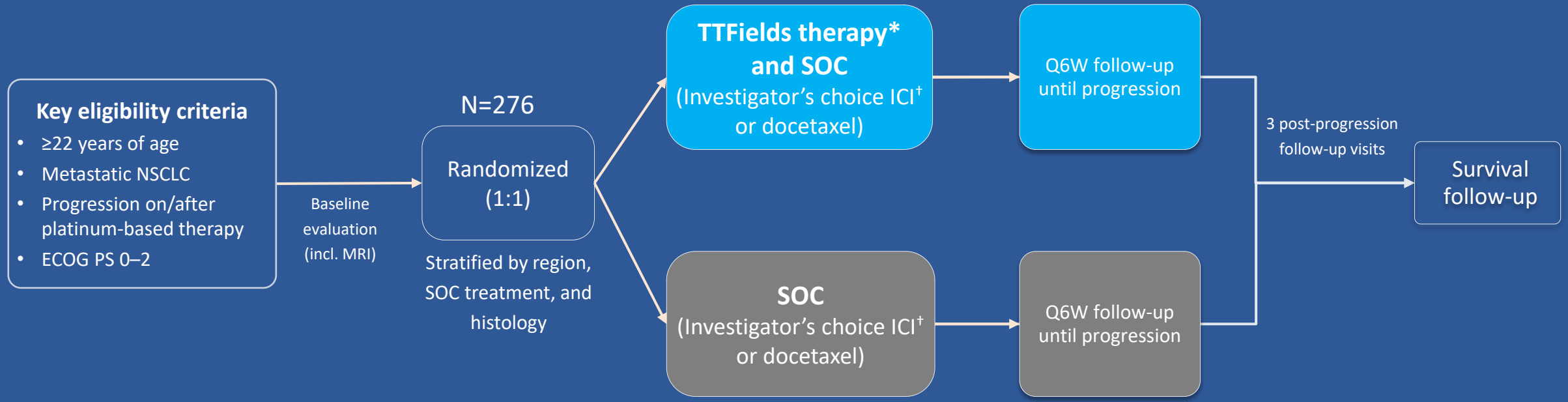
Array Placement

*TTFields for glioblastoma was approved via the Premarket Approval (PMA) pathway. TTFields for malignant pleural mesothelioma was approved via the Humanitarian Device Exemption (HDE) pathway.
NSCLC, non-small cell lung cancer; TTFields, Tumor Treating Fields. Image shows an actor. Used with permission from Novocure GmbH.

1. Novocure. NovoTTF™-100L system: instructions for use for unresectable pleural malignant mesothelioma; **2.** Stupp R et al. *Eur J Cancer.* 2012;48(14):2192–2202;
3. Stupp R et al. *JAMA.* 2017;318(23):2306–2316; **4.** Ceresoli GL et al. *Lancet Oncol.* 2019;20(12):1702–1709; **5.** Pless M et al. *Lung Cancer.* 2013;81(3):445–450.

LUNAR Phase 3 Study Design

Objective: To evaluate safety and efficacy of TTFields therapy with standard of care (SOC) compared to SOC alone in metastatic NSCLC progressing on or after platinum-based therapy



Data cut-off: November 26, 2022
Study sites: 124 in 17 countries (North America, Europe, Asia)

*150 kHz; ≥18 h/day; †pembrolizumab, nivolumab, or atezolizumab.
ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; Q6W, every 6 weeks; SOC, standard of care; TTFields, Tumor Treating Fields.

Baseline Disease Characteristics

	TTFields + SOC (n=137)	SOC (n=139)	Overall (N=276)
Histology			
Non-squamous/squamous	58%/42%	55%/45%	56%/44%
PD-L1			
<1%	17%	17%	17%
1–49%	27%	29%	28%
≥50%	7%	13%	10%
Unknown*	49%	42%	45%
Prior lines of systemic therapy**			
1	89%	89%	89%
2+	11%	10%	11%
Prior ICI	31%	31%	31%
Best response to any prior therapy			
Complete response	6%	4%	5%
Partial response	23%	26%	25%
Stable disease	34%	32%	33%
Progressive disease	21%	26%	24%
Unknown	15%	13%	14%
Liver metastasis†	15%	16%	16%
CNS metastasis‡	0	1%	1%

Percentages rounded to nearest integer; totals may not equal 100%

- Available PD-L1 data showed no differences between arms
- 58% of patients in the TTFields + docetaxel subgroup received a prior ICI vs 2% in the TTFields + ICI subgroup

*PD-L1 status reporting was optional and was available for 83% of patients in the United States; **Missing data for 1 patient in the ICI group. †1 patient had liver and CNS metastasis. ‡Patients with CNS metastases were excluded under the original study design; later amended to allow stable CNS metastases.

CNS, central nervous system; ICI, immune checkpoint inhibitor; PD-L1, programmed cell death ligand 1; SOC, standard of care; TTFields, Tumor Treating Fields.

Response Rates in the ITT Population

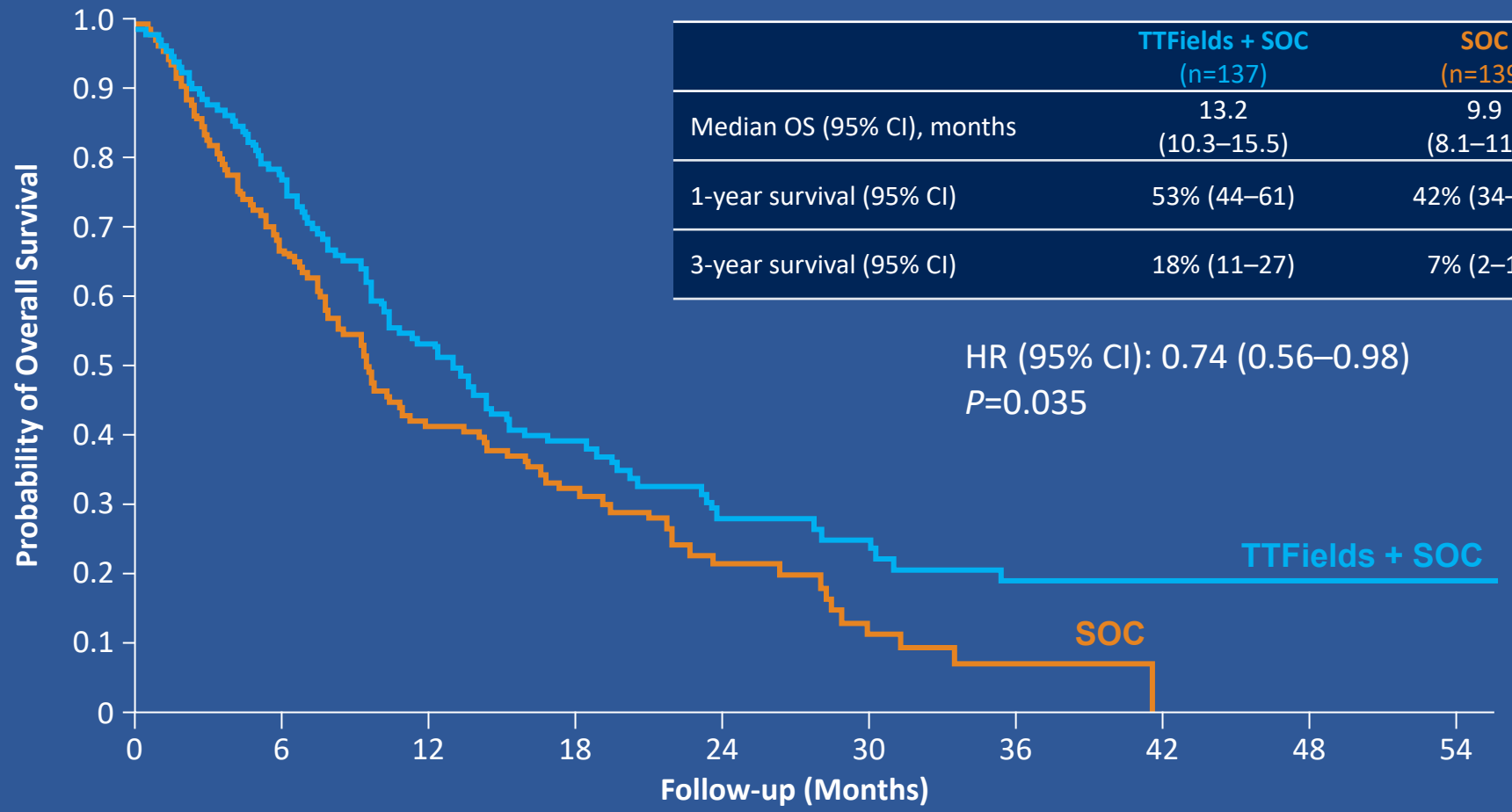
	TTFields + SOC (n=137)	SOC (n=139)
Patients with a follow-up scan	n=122	n=127
ORR, % (95% CI)	20% (14–28)	17% (11–25)
Difference in ORR, % (95% CI)	3% (-8.5–15.0) *P*=0.5	
Best overall response, %		
Complete response	3%	1%
Partial response	18%	17%
Stable disease	49%	47%
Progressive disease	18%	26%
Not evaluable	2%	1%

- All 5 complete responses occurred in patients receiving an ICI
  - 4 with TTFields therapy
  - 1 with ICI alone
- Analysis of patterns of progression (infield* vs outfield) is ongoing

*Infield=thorax and upper abdomen

CI, confidence interval; ICI, immune checkpoint inhibitor; ITT, intent-to-treat; ORR, overall response rate; SOC, standard of care; TTFields, Tumor Treating Fields.

Overall Survival in the ITT Population



	TTFields + SOC (n=137)	SOC (n=139)
Median OS (95% CI), months	13.2 (10.3–15.5)	9.9 (8.1–11.5)
1-year survival (95% CI)	53% (44–61)	42% (34–50)
3-year survival (95% CI)	18% (11–27)	7% (2–15)

HR (95% CI): 0.74 (0.56–0.98)
P=0.035

No. at Risk:

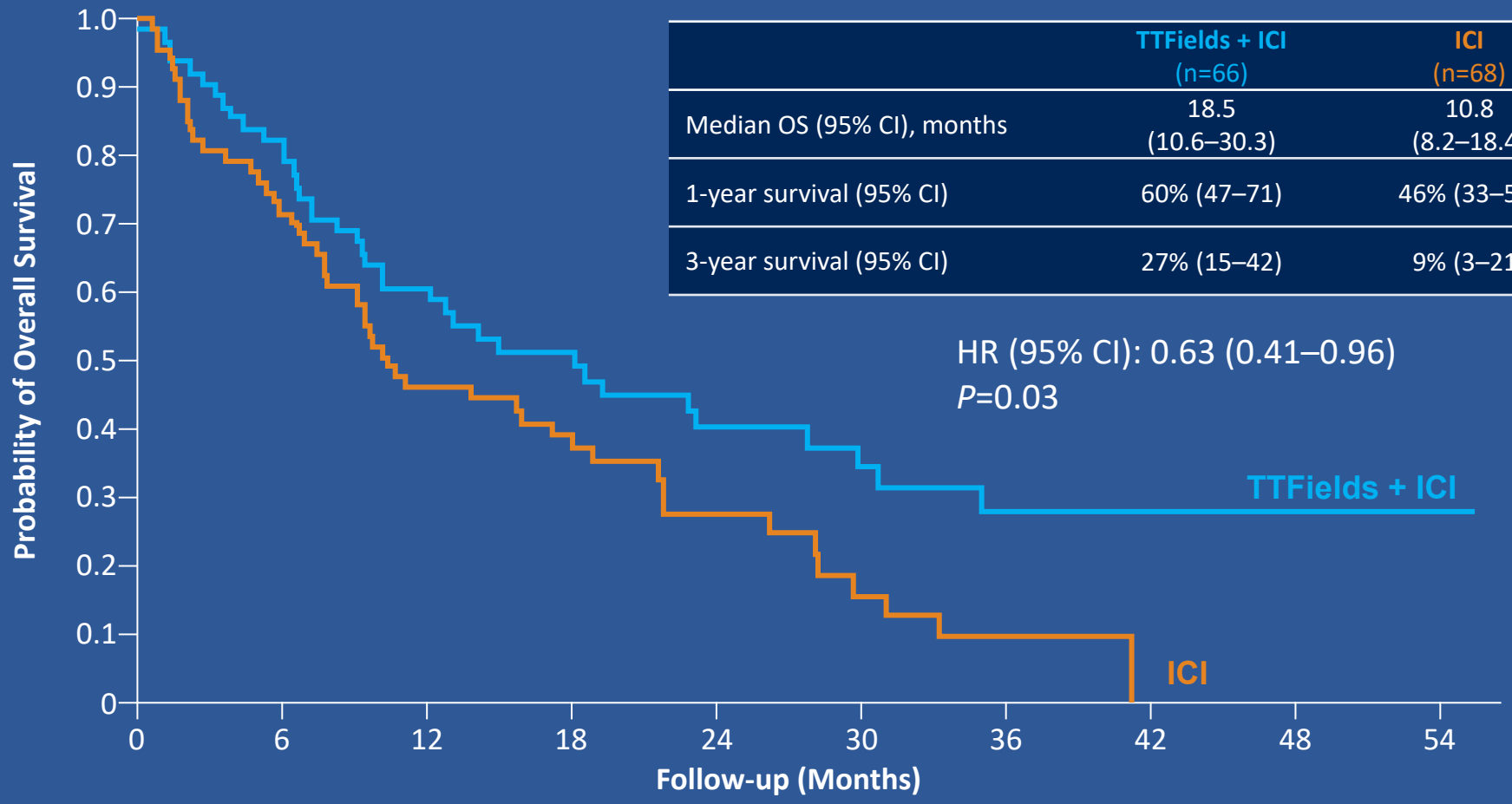
TTFields + SOC	137	100	62	36	22	16	11	9	5	3
SOC	139	96	54	32	16	7	3	0	0	0

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; SOC, standard of care; TTFields, Tumor Treating Fields.

Median (range) follow-up: 10.0 (0.03–58.7) months

Overall Survival in ICI-Treated Patients

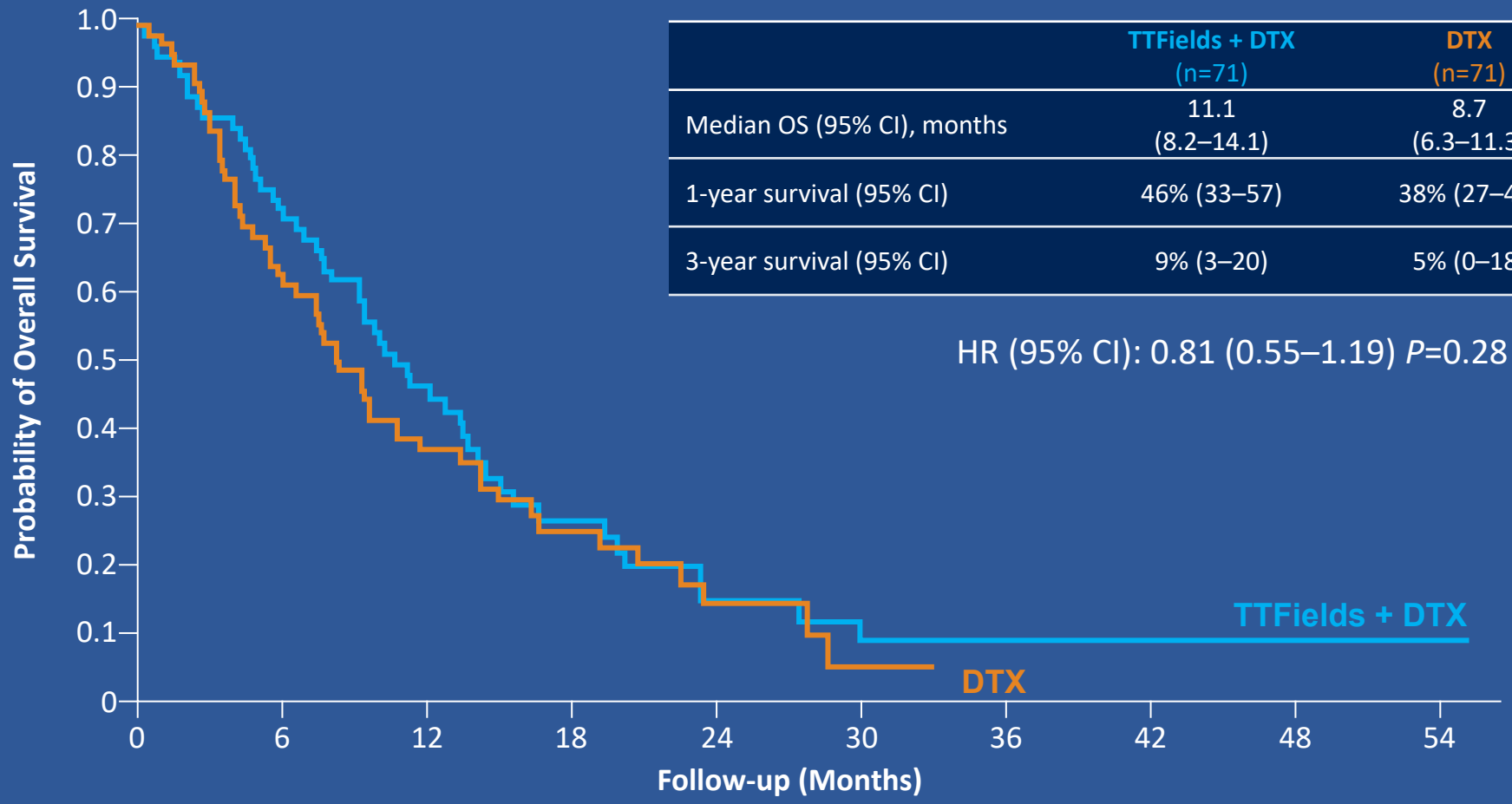
	TTFields + ICI (n=66)	ICI (n=68)
Median OS (95% CI), months	18.5 (10.6–30.3)	10.8 (8.2–18.4)
1-year survival (95% CI)	60% (47–71)	46% (33–57)
3-year survival (95% CI)	27% (15–42)	9% (3–21)



No. at Risk:										
TTFields + ICI	66	50	35	24	16	12	8	6	2	1
ICI	68	49	29	21	11	6	3	0	0	0

CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; OS, overall survival; TTFields, Tumor Treating Fields.

Overall Survival in DTX-Treated Patients



	TTFields + DTX (n=71)	DTX (n=71)
Median OS (95% CI), months	11.1 (8.2–14.1)	8.7 (6.3–11.3)
1-year survival (95% CI)	46% (33–57)	38% (27–49)
3-year survival (95% CI)	9% (3–20)	5% (0–18)

HR (95% CI): 0.81 (0.55–1.19) *P*=0.28

No. at Risk:										
TTFields + DTX	71	50	27	12	6	4	3	3	3	2
DTX	71	47	25	11	5	1	0	0	0	0

CI, confidence interval; DTX, docetaxel; HR, hazard ratio; OS, overall survival; TTFields, Tumor Treating Fields.

Safety and Tolerability

	TTFields + SOC (n=133)		SOC (n=134)	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**
Any AE*	97%	59%	91%	56%
Most frequent AEs				
Dermatitis	**43%**	**2%**	**2%**	**0%**
Fatigue	28%	4%	37%	8%
Musculoskeletal pain	36%	3%	27%	4%
Dyspnea	20%	7%	25%	3%
Anemia	23%	8%	22%	8%
Diarrhea	19%	2%	19%	0%
Cough	18%	0%	19%	1%
Nausea	19%	0%	16%	1%
Leukopenia	17%	14%	18%	14%
Pneumonia	15%	11%	17%	11%
Alopecia	10%	0%	17%	1%
Respiratory tract infection	15%	3%	16%	0%
Localized edema	15%	1%	16%	2%
Any serious AE	53%		38%	
Any AE leading to discontinuation	36%		20%	
Any AE leading to death	10%		8%	

*Any AE; not necessarily related to treatment.
AE, adverse event; SOC, standard of care; HRQoL. Health-related quality of life; TTFields, Tumor Treating Fields.

- Majority of patients (94%) had ≥1 AE
- Comparable incidence of grade ≥3 AEs between arms
- No difference in rate of pneumonitis or other immune-related AEs
- No notable differences in HRQoL when TTFields therapy was added to SOC (detailed analysis ongoing)

2023 ASCO ANNUAL MEETING

TROPION-Lung02: Datopotamab Deruxtecan (Dato-DXd) Plus Pembrolizumab With or Without Platinum Chemotherapy in Advanced Non-Small Cell Lung Cancer

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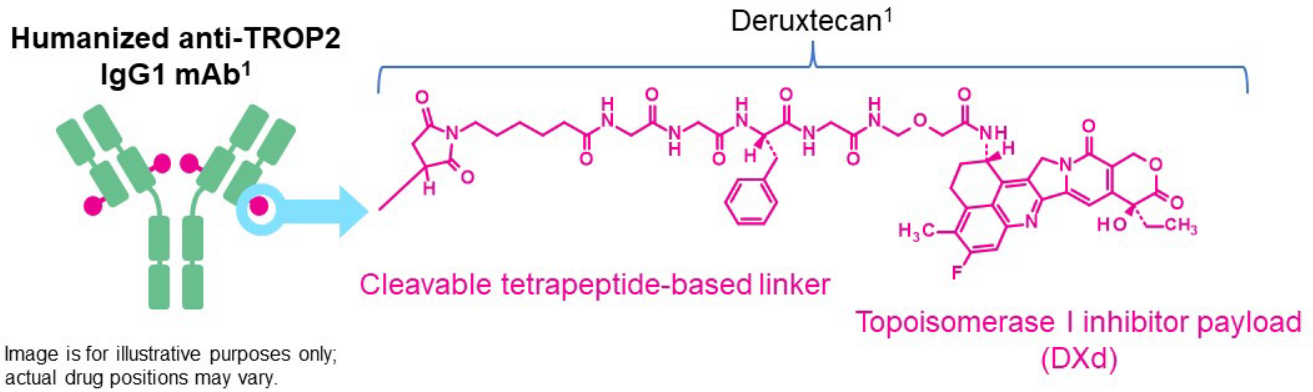
Introduction

- Dato-DXd is an antibody-drug conjugate composed of a TROP2-directed monoclonal antibody covalently linked to a highly potent cytotoxic payload via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker[1-5]
- Dato-DXd 6-mg/kg monotherapy demonstrated encouraging antitumor activity, with an ORR of 28% and a median DOR of 10.5 months, in patients with heavily pretreated advanced/metastatic NSCLC[6]



Dato-DXd, datopotamab deruxtecan; DOR, duration of response; IgG1, immunoglobulin G1; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; ORR, objective response rate; TROP2, trophoblast cell-surface antigen 2.

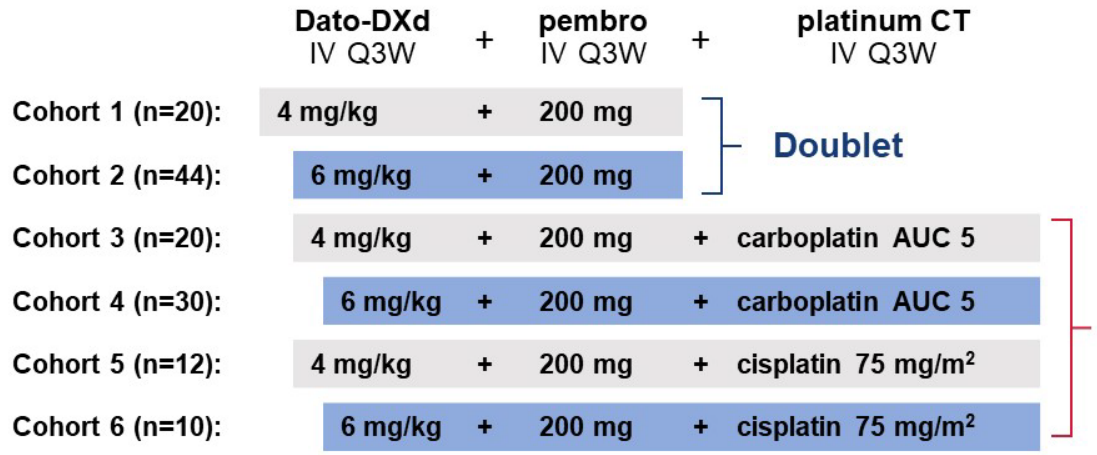
1. Okajima D, et al. *Mol Cancer Ther*. 2021;20(12):2329-2340. **2.** Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173-185. **3.** Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. **4.** Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046. **5.** Shiose Y, et al. *Biol Pharm Bull*. 2007;30(12):2365-2370. **6.** Garon EB, et al. IASLC WCLC 2021. Abstract MA03.02.

TROPION-Lung02: Phase 1b Study

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

Key eligibility criteria

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



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

Data cutoff: April 7, 2023.

AUC, area under the curve; CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; DLT, dose-limiting toxicity; IV, intravenous; NSCLC, non-small cell lung cancer; pembro, pembrolizumab; Q3W, every 3 weeks.

[a] Administered sequentially at the same visit. [b] Patients with known actionable *EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *RET*, or *MET* mutations or alterations in other actionable oncogenic driver kinases were not eligible for this study. Testing for *EGFR* and *ALK* alterations was not required for patients with squamous histology who were smokers or ≥40 years of age. [c] The first 3 to 6 patients in each cohort were enrolled to confirm acceptable safety/DLT rate; the remaining patients are considered part of dose expansion (for which enrollment was ongoing at the time of data cutoff). [d] Prior therapy requirements are for treatment in the advanced/metastatic setting.

Patient Baseline Characteristics

Characteristic	Doublet (n=64)	Triplet (n=72)
Age, median (range), years	65 (44-83)	64 (33-84)
Male, n (%)	48 (75)	48 (67)
Histology, n (%)		
Adenocarcinoma	45 (70)	49 (68)
Squamous	16 (25)	15 (21)
History of brain metastases, n (%)	11 (17)	14 (19)
PD-L1 expression, n (%)[a]		
<1%	23 (36)	29 (40)
1%-49%	28 (44)	24 (33)
≥50%	13 (20)	18 (25)
Prior lines of therapy, median (range)[b]	0 (0-4)[c]	0 (0-3)[c]
Previous systemic treatment, n (%)		
Immunotherapy	12 (19)	18 (25)
Platinum chemotherapy	24 (38)	17 (24)
Dato-DXd combination line of therapy, n (%)[d]		
1L	37 (58)	54 (75)
2L+	27 (42)	18 (25)

- Of patients receiving doublet or triplet therapy, 58% and 75%, respectively, were treated in the 1L setting
- Immunotherapy was previously given in 19% of patients receiving doublet therapy and 25% of patients receiving triplet therapy

Data cutoff: April 7, 2023.
1L, first line; 2L+, second line and later; Dato-DXd, datopotamab deruxtecan; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1.
[a] PD-L1 expression testing was not performed in 1 patient (1%) receiving triplet therapy. [b] Prior therapy for advanced/metastatic NSCLC. [c] Additional prior lines of therapy were permitted under earlier versions of the protocol.
[d] In the advanced/metastatic setting.

Antitumor Activity

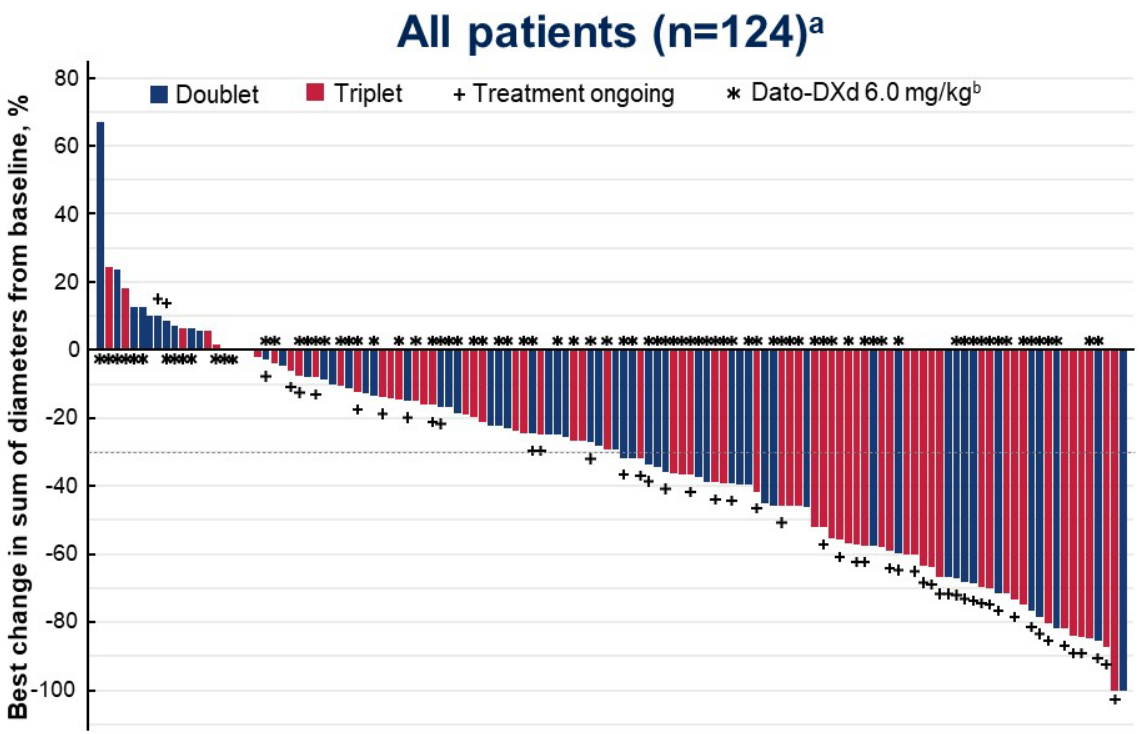
Response[a]	All patients: Doublet (n=61)[b]	All patients: Triplet (n=71)[b]	Patients in 1L: Doublet (n=34)[b]	Patients in 1L: Triplet (n=53)[b]
Confirmed + pending ORR, n (%)[c,d] [95% CI]	23 (38) [26-51]	35 (49) [37-61]	17 (50) [32-68]	30 (57) [42-70]
Confirmed + pending BOR, n (%)[d,e]				
Confirmed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

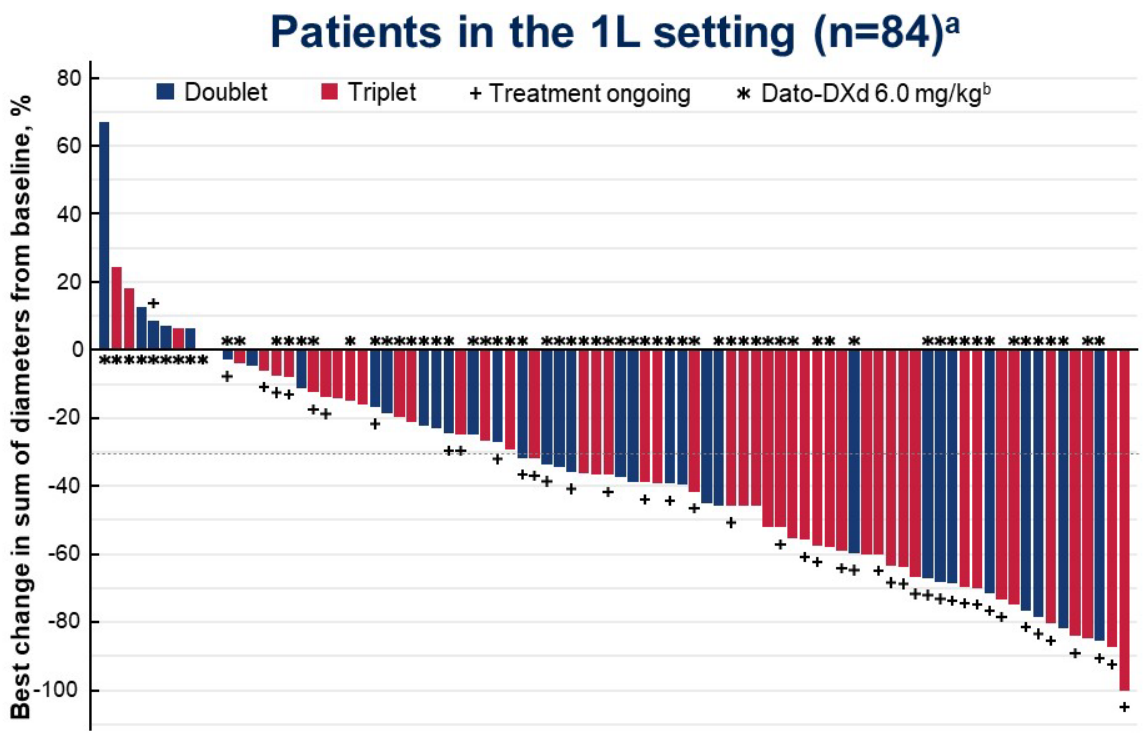
- In the 1L setting, the ORR (confirmed and pending)[d] was 50% in patients receiving doublet therapy and 57% in those receiving triplet therapy
- Among all patients, the DCR was 84% (doublet) and 87% (triplet); in the 1L setting, the DCR was 91% in both therapy subgroups

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

Data cutoff: April 7, 2023.
1L, first line; 2L+, second line and later; BOR, best overall response; CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; PR, partial response; SD, stable disease.
[a] By investigator. [b] Response-evaluable patients, which includes patients with ≥1 postbaseline overall response and those who discontinued without a postbaseline overall response. [c] ORR defined as BOR of CR + PR. [d] Responses pending confirmation. [e] BOR was determined using tumor assessments at different evaluation time points from the date of the first dose of study treatment until documented disease progression or the start of the next line of nonpalliative anticancer therapy (inclusive), whichever was earlier. [f] SD defined as ≥1 SD assessment (or better) ≥5 weeks after starting treatment and before progression without qualification for CR or PR (includes pending responses). [g] DCR defined as BOR of confirmed CR + confirmed PR + SD. [h] Preliminary PFS is limited by immature duration of follow-up.

Best Overall Tumor Change From Baseline





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

Adverse Events of Special Interest

AESI, n (%)[a,b]	Doublet (n=64)		Triplet (n=72)	
	All grades	Grade ≥3	All grades	Grade ≥3
Oral mucositis/stomatitis	37 (58)	5 (8)	31 (43)	4 (6)
ILD/pneumonitis adjudicated as drug related[c]	11 (17)	2 (3)	16 (22)	2 (3)
Ocular surface toxicity[d]	10 (16)	1 (2)	17 (24)	2 (3)
IRR[e]	15 (23)	0	10 (14)	0

- Oral mucositis/stomatitis was the most common AESI and was predominantly grade 1/2
- No grade 5 AESIs have occurred
- There were no grade 4 or 5 adjudicated ILD/pneumonitis events[f]

Data cutoff: April 7, 2023.
AESI, adverse event of special interest; ILD, interstitial lung disease; IRR, infusion-related reaction.
[a] AESIs listed in this slide include all preferred terms that define the medical concept. [b] No cases of mucosal inflammation occurred in patients receiving doublet or triplet therapy. [c] Five ILD cases are pending adjudication. [d] The majority of these events were cases of dry eye (n=12 patients) and lacrimation increased (n=8 patients); grade ≥3 events were keratitis (n=2 patients) and dry eye (n=1 patient). [e] IRR refers to all IRR events that occurred in a patient who experienced any of the preselected preferred terms within the same day of Dato-DXd infusion. [f] There was 1 grade 5 event initially adjudicated as drug-related ILD in a patient receiving triplet therapy; this event was ultimately readjudicated to be grade 2.

Thank you!