Current Paradigm and Future Directions for Immunotherapy in the Treatment of Metastatic Non-Small Cell Lung Cancer

A CME/MOC-Accredited Virtual Event

Tuesday, November 1, 2022
5:00 PM – 6:00 PM ET

Faculty

John V Heymach, MD, PhD
Stephen V Liu, MD

Moderator

Neil Love, MD

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Faculty

John V Heymach, MD, PhD
Professor and Chair
Thoracic/Head and Neck Medical Oncology
The University of Texas
MD Anderson Cancer Center
Houston, Texas

MODERATOR
Neil Love, MD
Research To Practice

Stephen V Liu, MD
Associate Professor of Medicine
Georgetown University Hospital
Washington, DC

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Commercial Support

This activity is supported by an educational grant from AstraZeneca Pharmaceuticals LP.

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI BioPharma Corp, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Corporation, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Kronos Bio Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc and Zymeworks Inc.

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Data and Safety Monitoring Board/Committee	Candel

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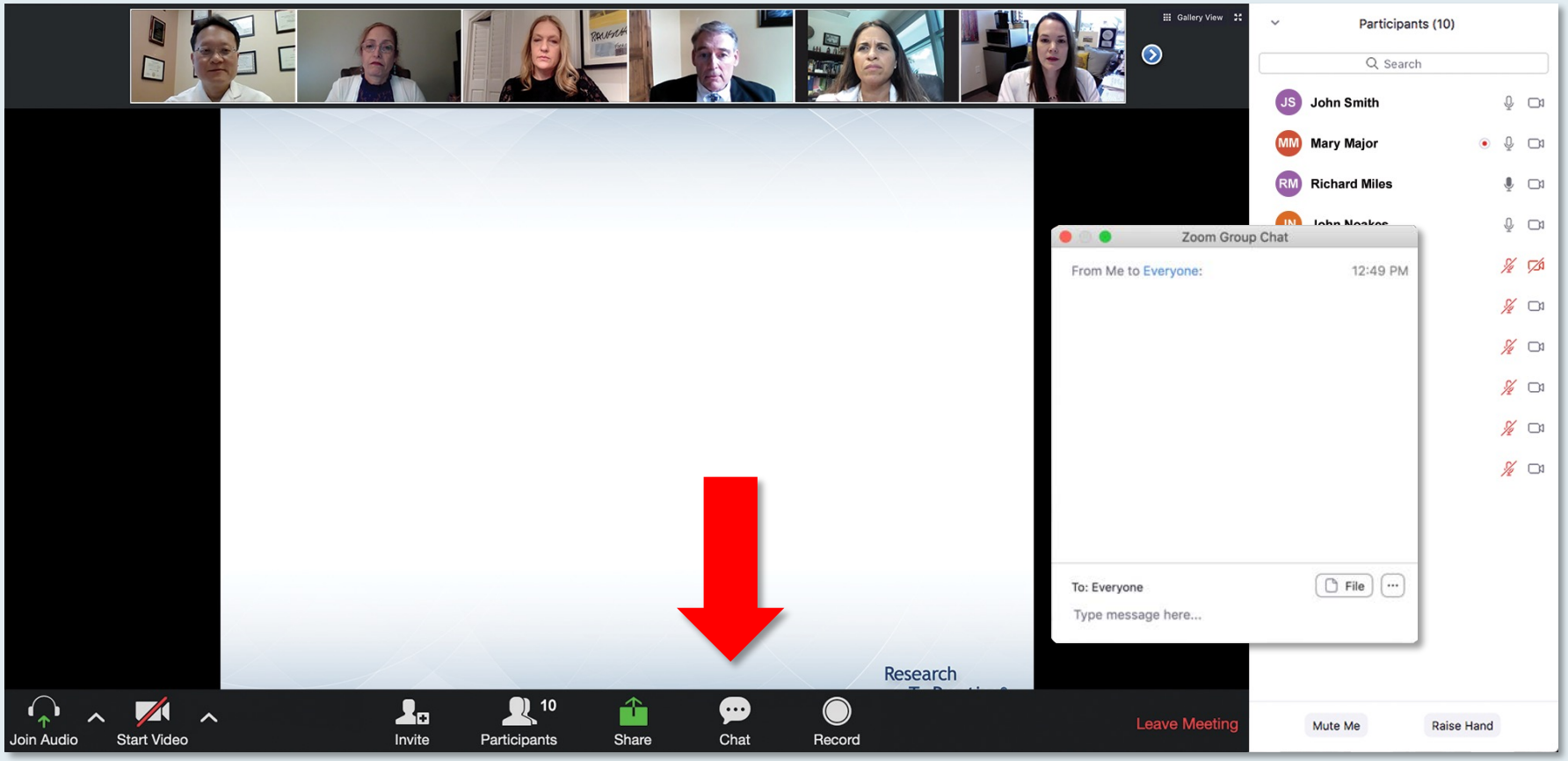

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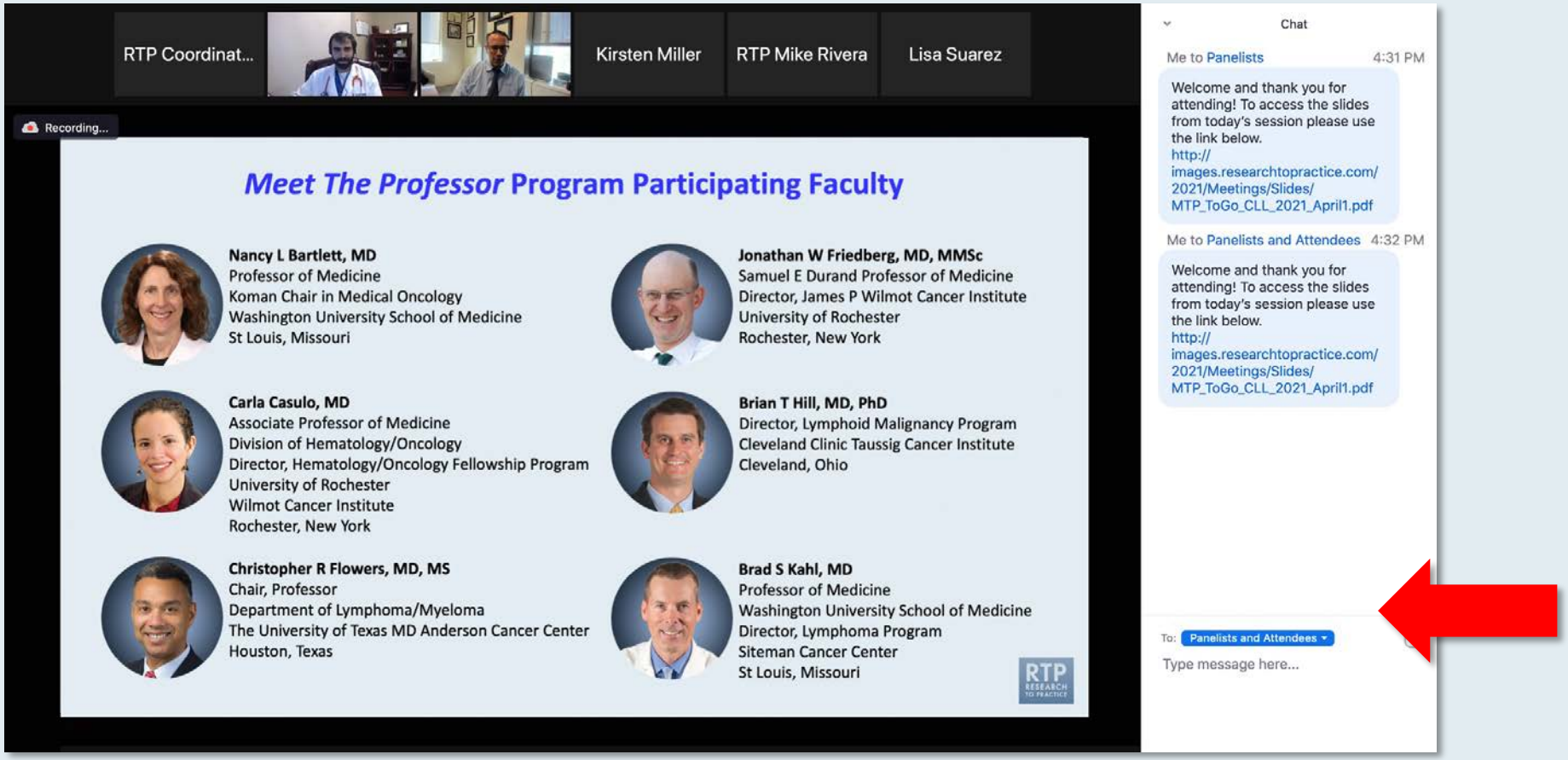
Expand chat submission box



Drag the white line above the submission box up to create more space for your message.

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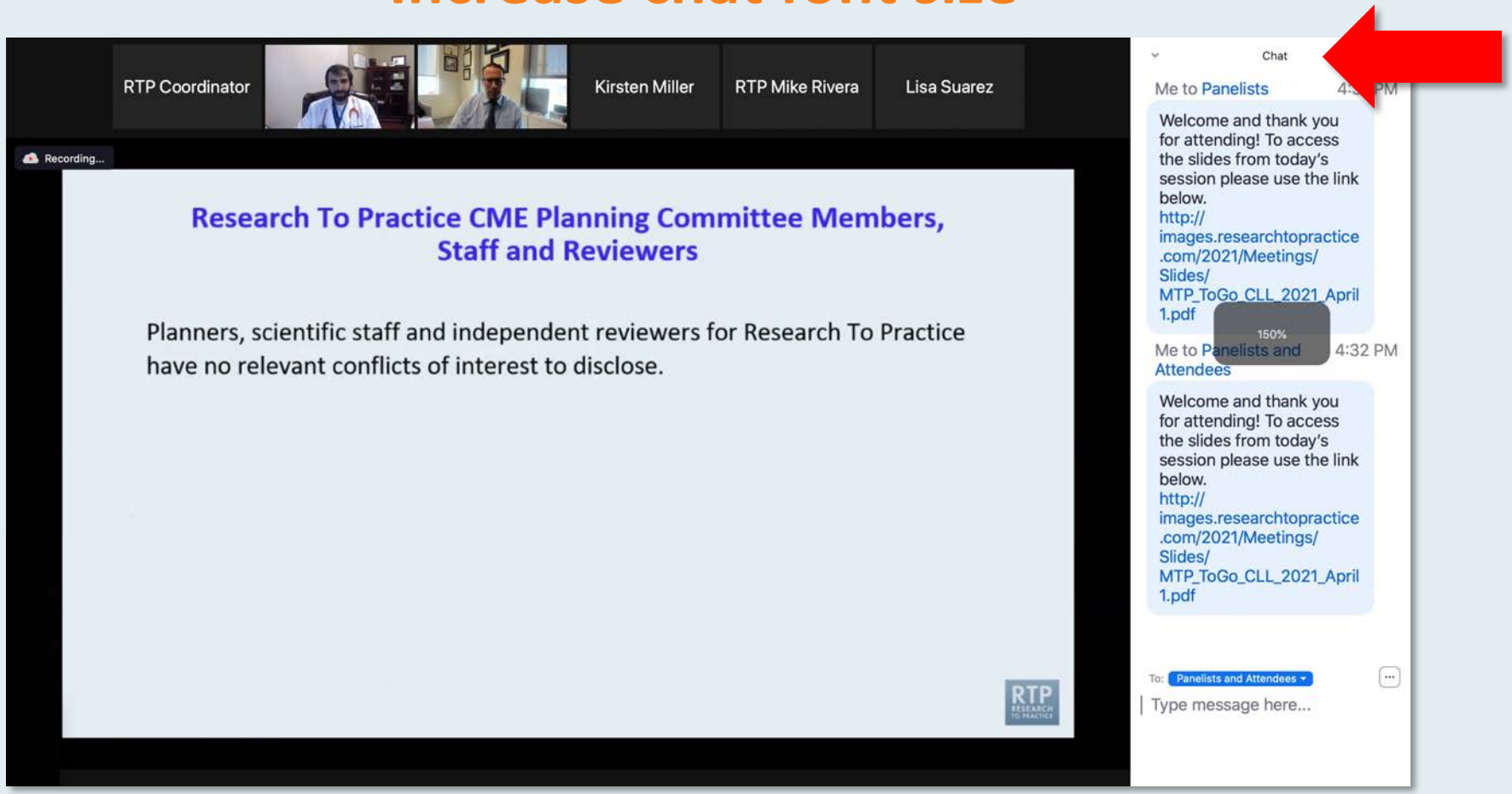
Familiarizing Yourself with the Zoom Interface

Increase chat font size



Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

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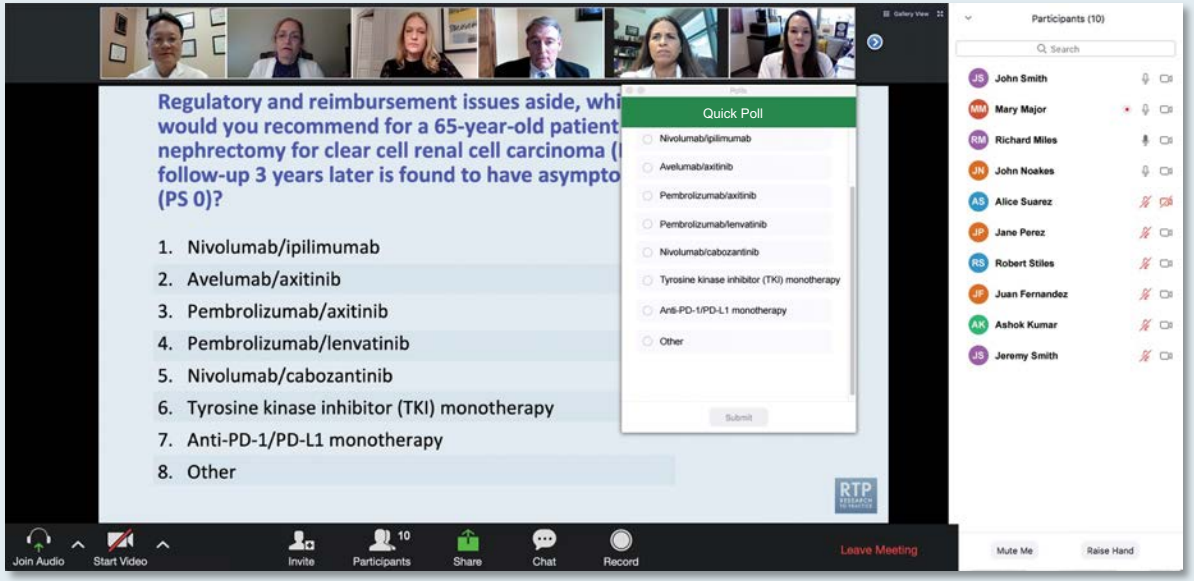

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ONCOLOGY TODAY

WITH DR NEIL LOVE

Management of RET Fusion-Positive Non-Small Cell Lung Cancer

DR JUSTIN GAINOR

MASSACHUSETTS GENERAL HOSPITAL

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Consensus or Controversy? Documenting and Discussing Clinical Investigators' Practice Patterns in Ovarian Cancer

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Thursday, November 3, 2022
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Debra L Richardson, MD

Moderator

Neil Love, MD

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RESEARCH TO PRACTICE

Meet The Professor

Optimizing the Management of HER2-Positive Breast Cancer

Tuesday, November 8, 2022
5:00 PM – 6:00 PM ET

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Meet The Professor

Optimizing the Use of Hormonal Therapy in the Management of Prostate Cancer

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Meet The Professor
Optimizing the Management of Multiple Myeloma

Tuesday, November 15, 2022
5:00 PM – 6:00 PM ET

Faculty

Paul G Richardson, MD

Moderator

Neil Love, MD

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What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of HER2-Positive Breast Cancer

Part 1 of a 2-Part CME Satellite Symposium Series Held in Conjunction with the 2022 San Antonio Breast Cancer Symposium®

Wednesday, December 7, 2022

7:15 PM – 9:15 PM CT (8:15 PM – 10:15 PM ET)

Faculty

Erika Hamilton, MD

Sara A Hurvitz, MD

Ian E Krop, MD, PhD

Shanu Modi, MD

Sara M Tolaney, MD, MPH

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Matthew P Goetz, MD

Virginia Kaklamani, MD, DSc

Kevin Kalinsky, MD, MS

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Moderator

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Sagar Lonial, MD
Robert Z Orlowski, MD, PhD
Noopur Raje, MD

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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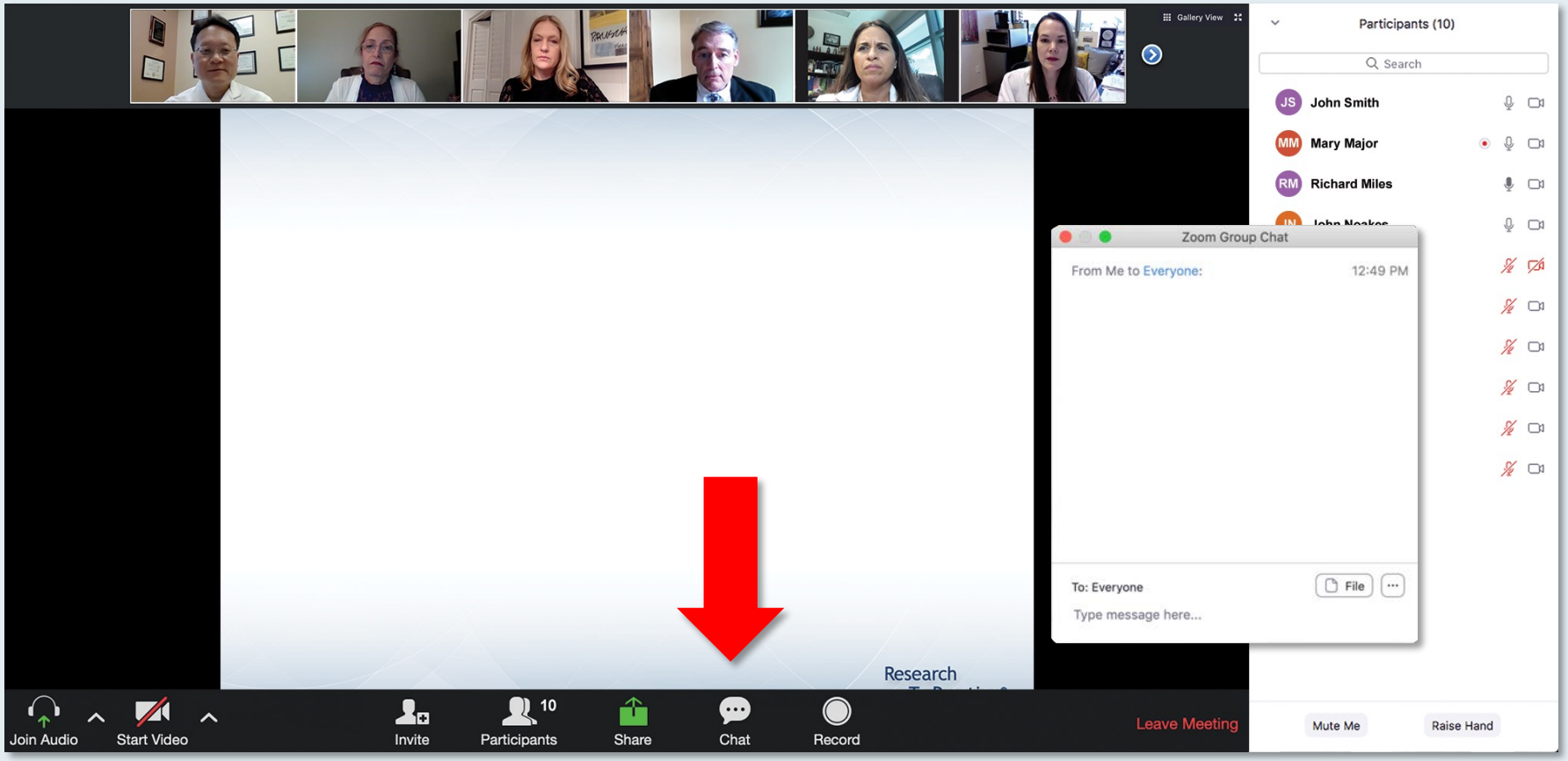

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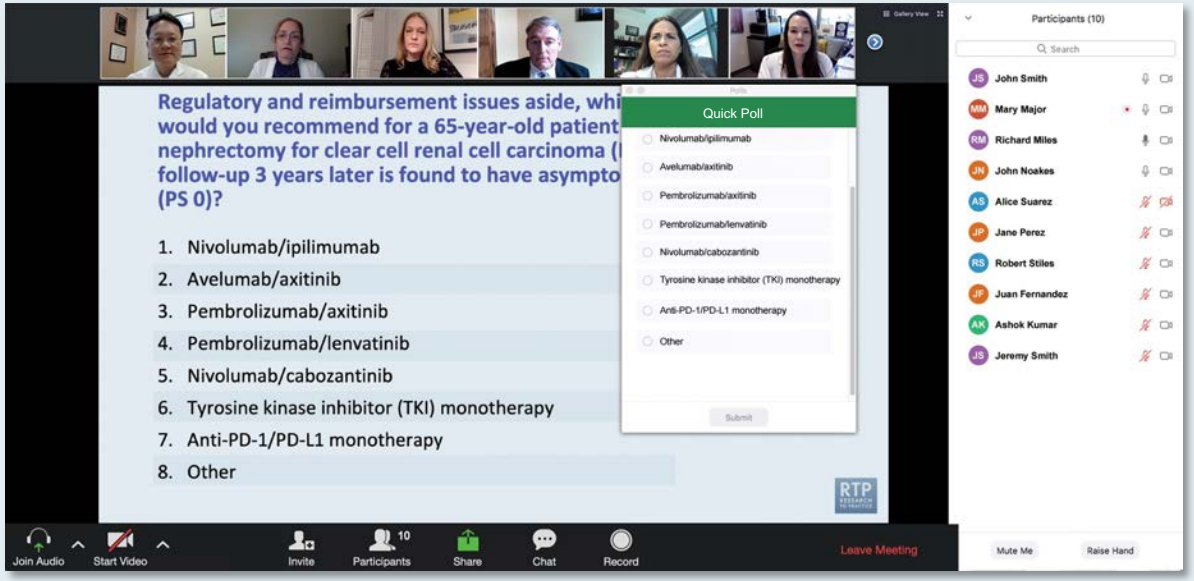

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What were you doing in 2015?

1. Had not started working in oncology yet
2. Working in oncology for less than 10 years
3. Working in oncology for more than 10 years

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GU Cancers Symposium
February 27, 2015

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Timeline of Select Immunotherapy Approvals in Non-Small Cell Lung Cancer (NSCLC)

March 4, 2015	Nivolumab approved for second-line treatment of metastatic NSCLC
October 2, 2015	Pembrolizumab approved for second-line treatment of metastatic NSCLC (PD-L1-positive)
October 1, 2016	Pembrolizumab approved for first-line treatment of metastatic NSCLC (PD-L1 ≥50%)
May 1, 2017	Pembrolizumab in combination with chemotherapy receives accelerated approval for first-line treatment of metastatic NSCLC
August 20, 2018	Pembrolizumab in combination with chemotherapy approved for first-line treatment of metastatic NSCLC

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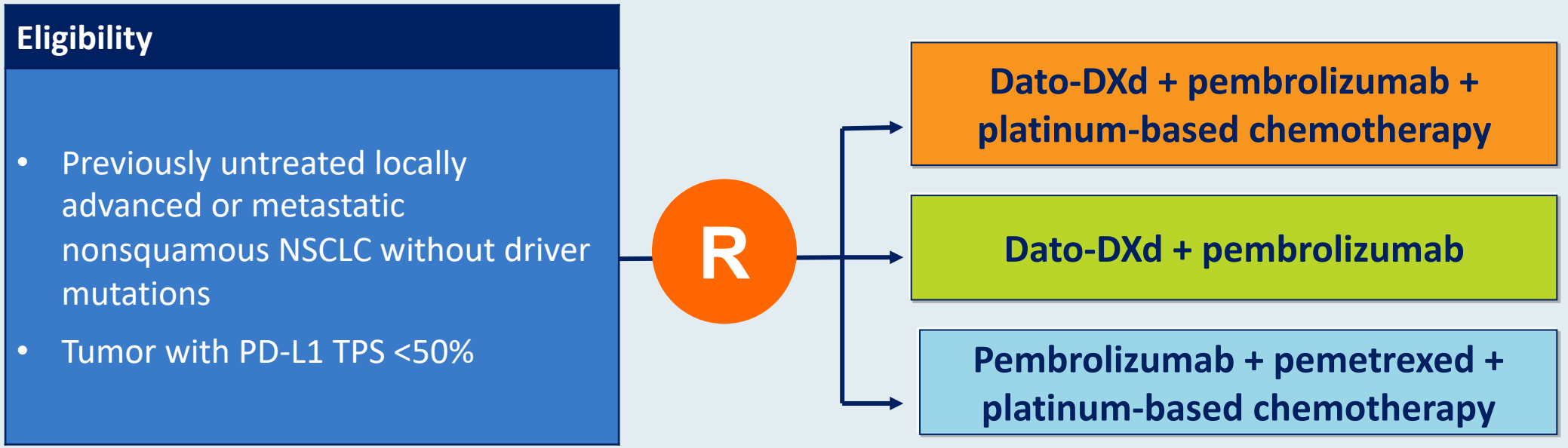
TROPION-Lung07: Phase III Trial of First-Line Dato-DXd and Pembrolizumab with or without Platinum Chemotherapy for Advanced/Metastatic NSCLC without Actionable Genomic Alterations

Trial identifier: NCT05555732 (not yet recruiting)
Estimated enrollment: 975
Phase III



TPS = tumor proportion score

Coprimary endpoints: Progression-free survival by blinded independent central review and overall survival

www.clinicaltrials.gov. Accessed November 2022.

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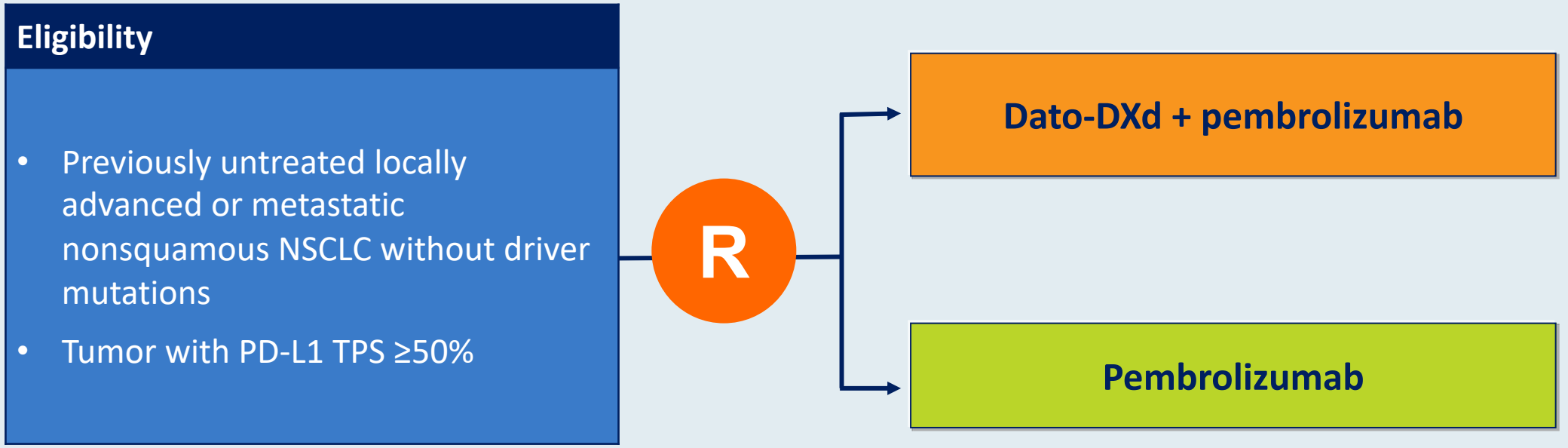
TROPION-Lung08: Phase III Trial of First-Line Dato-DXd with Pembrolizumab Compared to Pembrolizumab Alone for Advanced/Metastatic NSCLC without Actionable Genomic Alterations

Trial identifier: NCT05215340 (open)
Estimated enrollment: 740
Phase III



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Current Utility of Immunotherapy-Based Strategies in NSCLC

Stephen V. Liu, MD
Associate Professor of Medicine
Director of Thoracic Oncology
Head of Developmental Therapeutics
Georgetown University

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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Future Directions in the Management of NSCLC

John V. Heymach MD, PhD
Professor and Chair
Thoracic/Head and Neck Medical Oncology
The University of Texas MD Anderson Cancer Center

Research To Practice

October 20, 2022

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Agenda

MODULE 1: Current Immunotherapy-Based Strategies in NSCLC

MODULE 2: Future Directions in the Management of NSCLC

Agenda

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MODULE 2: Future Directions in the Management of NSCLC

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NCI CCC *A Comprehensive Cancer Center Designated by the National Cancer Institute*

http://lombardi.georgetown.edu
Lombardi CancerLine: 202.444.4000

PD(L)1 Monotherapy

- Three approved monotherapy options in NSCLC
  - Pembrolizumab (PD-L1 positive, favored for high)
    - FDA approved October 24, 2016 for PD-L1 ≥ 50%
    - FDA approved April 11, 2019 for PD-L1 ≥ 1%
  - Atezolizumab (PD-L1 high)
    - FDA approved May 18, 2020 for PD-L1 ≥ 50%
  - Cemiplimab (PD-L1 high)
    - FDA approved February 22, 2021 for PD-L1 ≥ 50%

FDA-Approved Single-Agent Immunotherapy Options for First-Line Therapy

Monotherapy	FDA approval	Pivotal study	Histologic type	HR (OS)
Pembrolizumab[1,2] (q3wk or q6wk)	4/11/19 10/24/16	KEYNOTE-042 KEYNOTE-024	PD-L1 TPS ≥1%	0.63
Atezolizumab[3] (q2wk, q3wk or q4wk)	5/18/20	IMpower110	PD-L1 TPS ≥50, EGFR and/or ALK wt	0.59
Cemiplimab[4] (q3wk)	2/22/21	EMPOWER-Lung 1 (Study 1624)	PD-L1 TPS ≥50, EGFR and/or ALK and/or ROS1 wt	0.57

OS = overall survival

[1] Mok. *Lancet* 2019. [2] Reck. *J Clin Oncol* 2019. [3] Herbst. *N Engl J Med* 2020. [4] Sezer. *Lancet* 2021.

FDA-Approved Immunotherapy Combination Options for First-Line Therapy

Combination regimen	FDA approval	Pivotal study	Histologic type	HR (OS)
Pembrolizumab (q3wk or q6wk) + platinum and pemetrexed[1]	8/20/18	KEYNOTE-189	Nonsquamous	0.56
Pembrolizumab (q3wk or q6wk) + carboplatin, paclitaxel or *nab* paclitaxel[2]	10/30/18	KEYNOTE-407	Squamous	0.71
Atezolizumab (q3wk) + carboplatin and paclitaxel and bevacizumab[3]	12/6/18	IMpower150	Nonsquamous	0.80
Atezolizumab (q3wk) + carboplatin and *nab* paclitaxel[4]	12/3/19	IMpower130	Nonsquamous	0.79
Nivolumab (q2wk) + ipilimumab[5]	5/15/20	CheckMate 227	PD-L1 TPS ≥1, EGFR and/or ALK wt	0.76
Nivolumab (q3wk) + ipilimumab and chemotherapy[6]	5/26/20	CheckMate 9LA	EGFR and/or ALK wt	0.72

[1] Rodriguez-Abreu. *Ann Oncol* 2021. [2] Paz-Ares. *J Thorac Oncol* 2020. [3] Socinski *J Thorac Oncol* 2021. [4] West. *Lancet Oncol* 2019.
[5] Paz-Ares. ASCO 2021;Abstract 9016. [6] Reck. ASCO 2021;Abstract 9000.

First-Line Immunotherapy Options on the Horizon?

Agent/regimen	Study	Setting	HR (OS)
Atezolizumab	IPSOS	• Platinum ineligible • EGFR/ALK wild type, any PD-L1	0.78
Durvalumab +/- tremelimumab + chemotherapy	POSEIDON	EGFR/ALK wild type	0.75 0.84

Lee MS et al. ESMO 2022;Abstract LBA11; Johnson ML et al. ESMO 2022;Abstract LBA59.

Front-Line Immunotherapy

- Immunotherapy is our SOC
  - Many options for delivery
    - PD(L)1 alone
    - Dual checkpoint
    - Chemo-IO
  - Tailor to specific clinical situation, experience, non-clinical factors

Discussion Question

Do you believe that a correlation exists between autoimmune toxicity and treatment benefit for patients receiving immune checkpoint inhibitors?

- Yes
- No
- I’m not sure

Discussion Question

A patient who has never smoked presents with highly symptomatic metastatic nonsquamous NSCLC requiring immediate treatment and begins chemotherapy while awaiting next-generation sequencing (NGS). PD-L1 tumor proportion score (TPS) is 90%. Would you recommend adding an anti-PD-1/PD-L1 antibody?

- Yes
- No

RTP RESEARCH TO PRACTICE

Discussion Question

A patient with an extensive smoking history presents with highly symptomatic metastatic nonsquamous NSCLC requiring immediate treatment and begins chemotherapy while awaiting NGS. PD-L1 TPS is 90%. Would you recommend adding an anti-PD-1/PD-L1 antibody?

- Yes
- No

Discussion Question

Regulatory and reimbursement issues aside, in which line of therapy would you generally offer an immune checkpoint inhibitor, alone or in combination with chemotherapy, to a patient with metastatic nonsquamous NSCLC and an EGFR exon 19 deletion?

- First line
- Second line
- Third line
- Beyond third line
- I would not offer an immune checkpoint inhibitor for this patient

RTP RESEARCH TO PRACTICE

Discussion Question

Regulatory and reimbursement issues aside, in which line of therapy would you generally offer an immune checkpoint inhibitor, alone or in combination with chemotherapy, to a patient with metastatic nonsquamous NSCLC and an ALK rearrangement?

- First line
- Second line
- Third line
- Beyond third line
- I would not offer an immune checkpoint inhibitor for this patient

RTP RESEARCH TO PRACTICE

Discussion Question

Regulatory and reimbursement issues aside, which first-line treatment would you most likely recommend to a 65-year-old asymptomatic patient presenting with low-volume, nonvisceral disease, a PD-L1 TPS of 5% and no actionable driver mutations?

- Immunotherapy (IO) monotherapy
- IO with chemotherapy
- IO with anti-CTLA-4 therapy
- IO with anti-CTLA-4 therapy and chemotherapy
- Other
- I’m not sure

Discussion Question

Regulatory and reimbursement issues aside, which first-line treatment would you most likely recommend for a 65-year-old asymptomatic patient presenting with low-volume, nonvisceral disease, a PD-L1 TPS of 0% and no actionable driver mutations?

- IO monotherapy
- IO with chemotherapy
- IO with anti-CTLA-4 therapy
- IO with anti-CTLA-4 therapy and chemotherapy
- Other
- I’m not sure

Discussion Question

Which of the following 3 agents has the best risk-benefit profile when administered as monotherapy to a patient with metastatic NSCLC with no targetable mutations and high PD-L1 (TPS ≥50%)?

- Pembrolizumab
- Atezolizumab
- Cemiplimab
- There is no significant difference
- I’m not sure

RTP RESEARCH TO PRACTICE

Discussion Question

For a patient with metastatic NSCLC and high PD-L1 (TPS ≥50%) to whom you've decided to administer anti-PD-1/PD-L1 antibody monotherapy, if one of the 3 approved agents were priced 50% below the others, would you use it preferentially?

- Yes
- Yes, depending on the agent
- No
- I'm not sure

RTP RESEARCH TO PRACTICE

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PATIENT CARE
RESEARCH
EDUCATION
COMMUNITY

Cases From My Practice

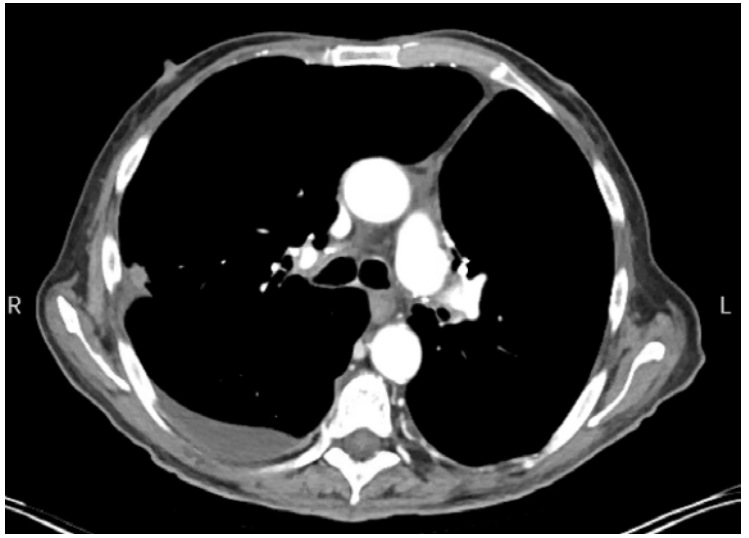
Stephen V. Liu, MD
Associate Professor of Medicine
Director, Thoracic Oncology
Georgetown University

NCI CCC *A Comprehensive Cancer Center Designated by the National Cancer Institute*

http://lombardi.georgetown.edu
Lombardi CancerLine: 202.444.4000

Case Presentation: Dr Stephen Liu

- 77-year-old male non-smoker
  - Presents with progressive cough and dyspnea
  - Imaging revealed bilateral lung nodules, enlarged nodes, large pericardial effusion
  - Pericardial window pathology showed adenocarcinoma
  - NGS showed 0% PD-L1 expression, KRAS G12D mutation

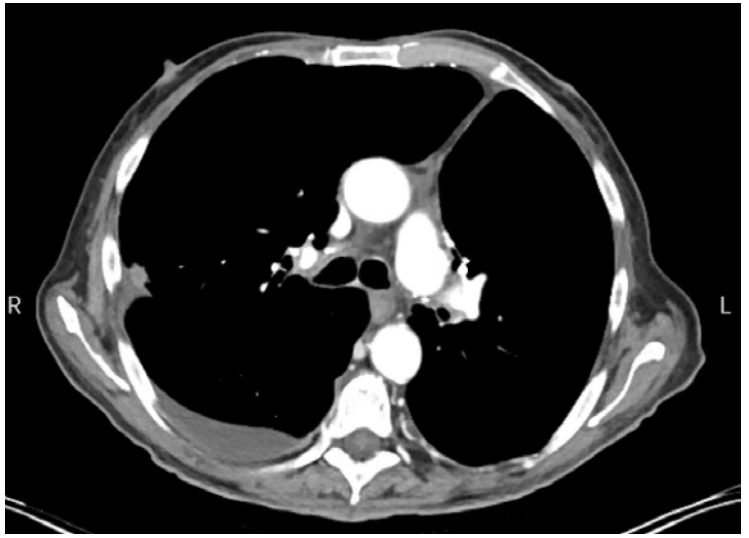


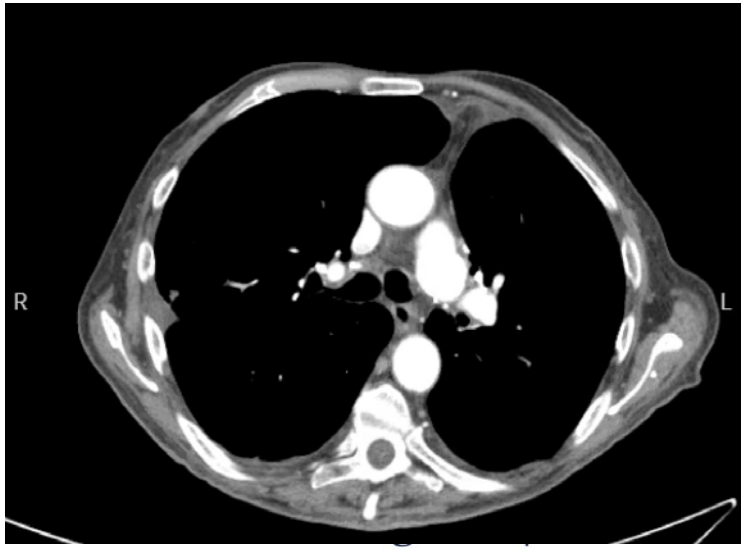
Case Presentation: Dr Stephen Liu (cont)

- With no PD-L1 expression, SOC is IO
  - PD(L)1 monotherapy, is not approved for PD-L1 0%
  - Dual checkpoint blockade is active but not approved here
  - Chemo-immunotherapy is the standard of care
    - Carboplatin, pemetrexed, pembrolizumab
    - Carboplatin, bevacizumab, paclitaxel, atezolizumab
    - Carboplatin, nab-paclitaxel, atezolizumab
    - Nivolumab + ipilimumab + chemotherapy
    - Durvalumab ± tremelimumab + chemotherapy

Case Presentation: Dr Stephen Liu (cont)

- 77-year-old male non-smoker
  - Opted to receive carboplatin, paclitaxel plus durvalumab
    - Ongoing clinical trial
  - Toxicity: hypothyroidism
  - CT after second cycle with response
  - Ongoing after 13 months

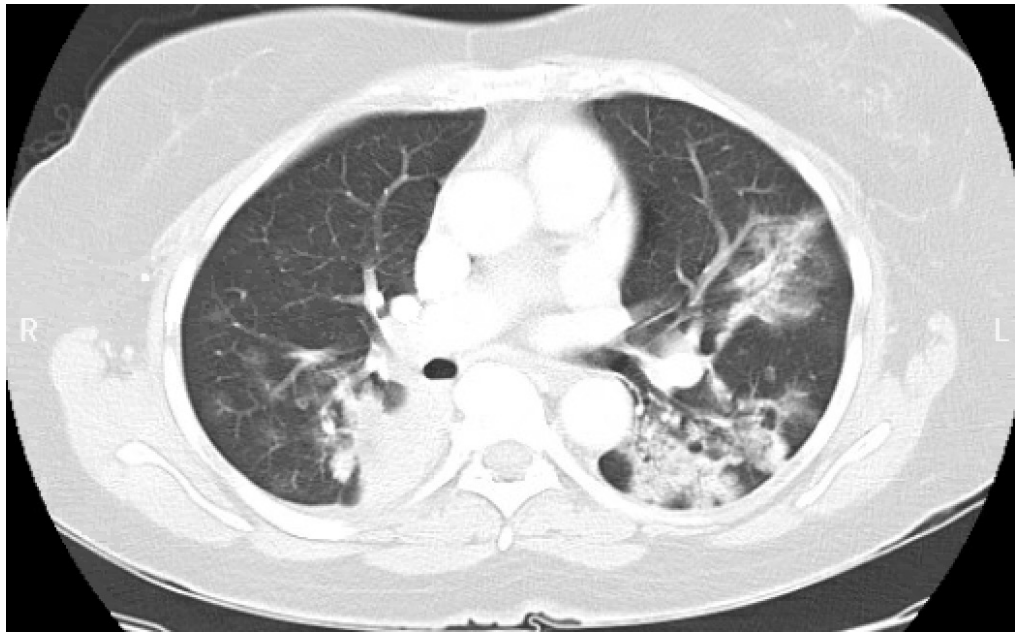




Case Presentation: Dr Stephen Liu

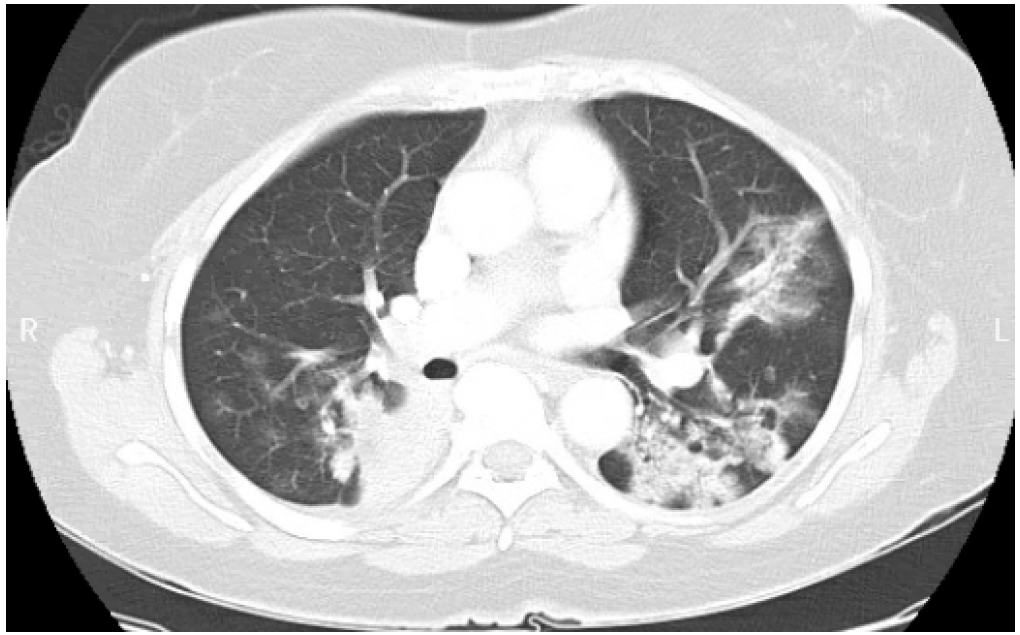
- 70-year-old female non-smoker
  - Baseline impaired creatinine clearance
  - Developed pleuritic chest pain
  - CT scan showed multifocal nodular infiltrates
  - Given courses of antibiotics
  - Bronchoscopy with biopsy revealed adenocarcinoma
  - NGS showed no actionable alterations, PD-L1 25%

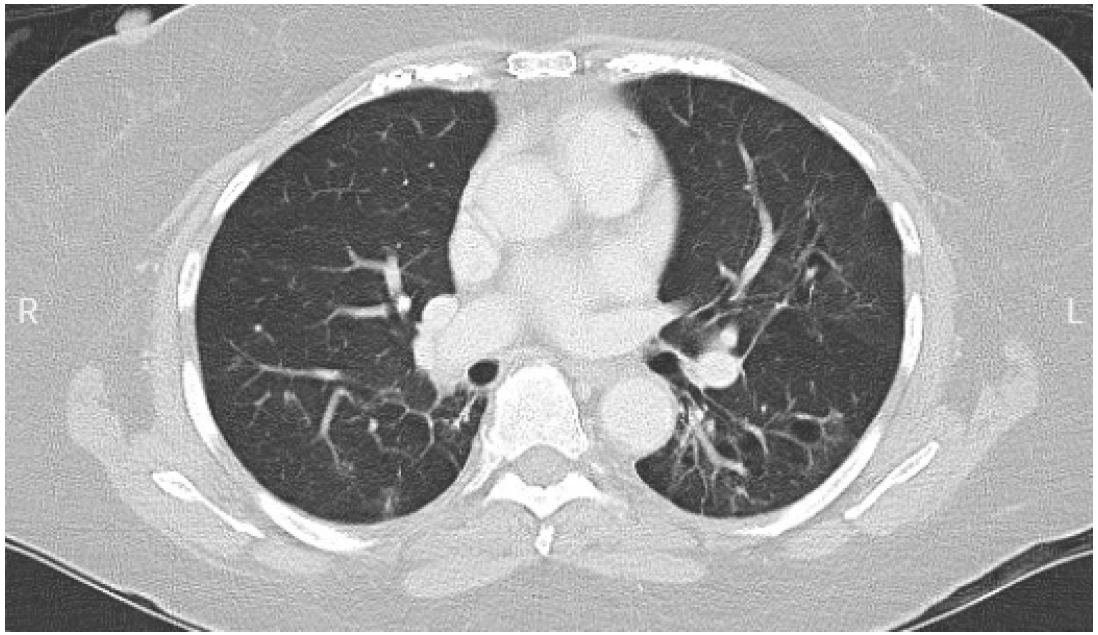
Case Presentation: Dr Stephen Liu (cont)



- 70-year-old female
  - Treated with carboplatin, nab-paclitaxel, atezolizumab
    - Immediate response with no significant toxicity
  - Transitioned to maintenance atezolizumab

Case Presentation: Dr Stephen Liu (cont)



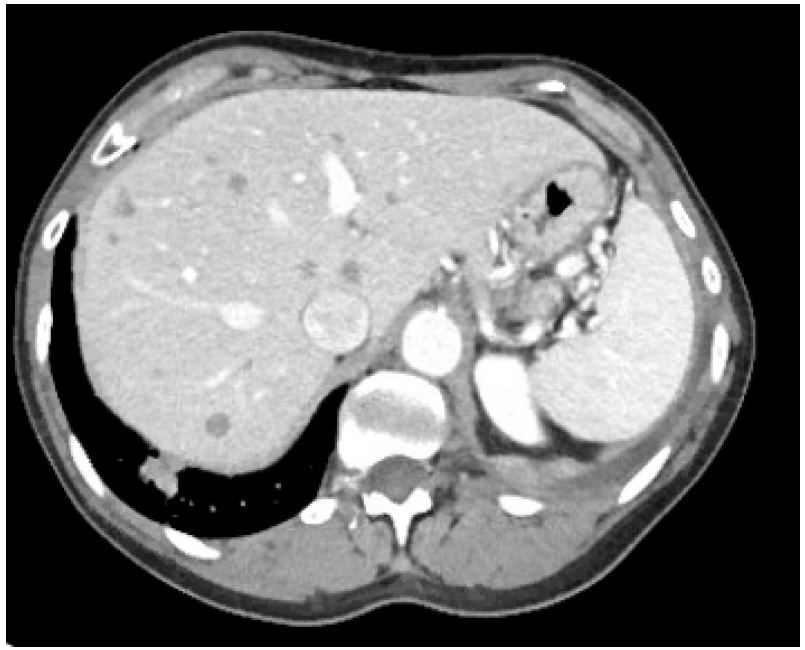


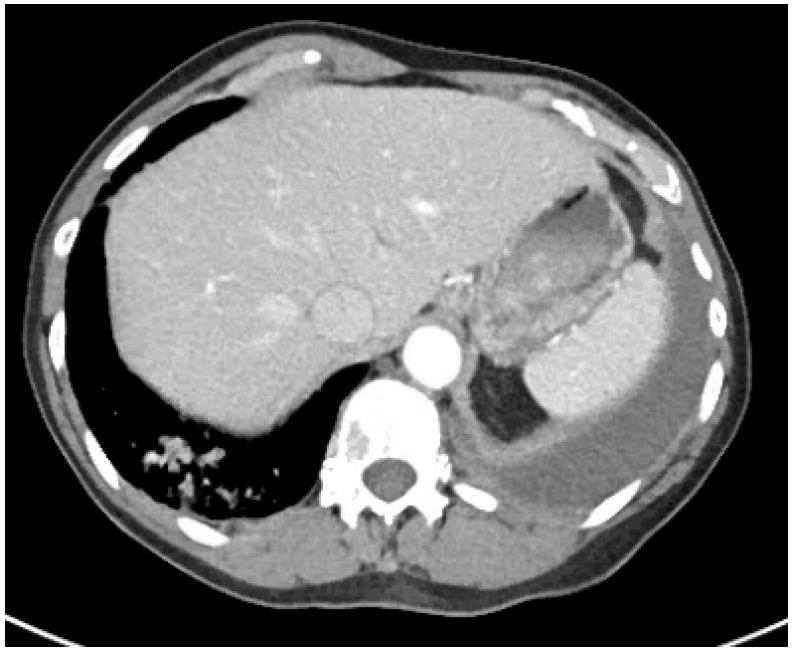
- Ongoing response and no toxicity at two years
  - Patient asks why should we stop?

Case Presentation: Dr Stephen Liu

- 62-year-old female smoker
  - Persistent cough since COVID infection early 2021
  - CT showed 2cm RML nodule
  - Biopsy revealed non-squamous NSCLC
    - NGS showed TP53 mutation, high TMB
    - PD-L1 = 10%
  - PET showed multiple liver metastases
  - MRI showed multiple subcm brain metastases

Case Presentation: Dr Stephen Liu (cont)





- Started nivolumab + ipilimumab
  - First scan after 6 weeks showed minor response
  - Second scan after 12 weeks showed near complete response

Case Presentation: Dr Stephen Liu (cont)

- 62-year-old female smoker with NSCLC
  - Near complete response with nivolumab + ipilimumab
  - After 3 months, noted mild diarrhea for 2 days
  - Progressed to severe diarrhea, hospitalized
  - Given steroids and diarrhea improved, tapered over 6w
  - Restarted nivolumab alone
  - Diarrhea has not recurred
  - Tentative plan to complete 2 years on nivolumab

Agenda

MODULE 1: Current Immunotherapy-Based Strategies in NSCLC

MODULE 2: Future Directions in the Management of NSCLC

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Future Directions in the Management of NSCLC

John V. Heymach MD, PhD
Professor and Chair
Thoracic/Head and Neck Medical Oncology
The University of Texas MD Anderson Cancer Center

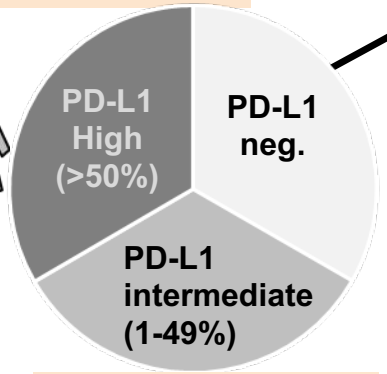
Research To Practice

October 20, 2022

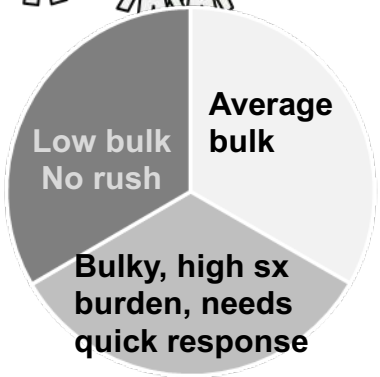
NSCLC 2022: Precision therapy for driver oncogenes, but immunotherapy based on PD-L1, and subjective “clinical factors”

NSCLC

Driver negative: the immune pie (60%)



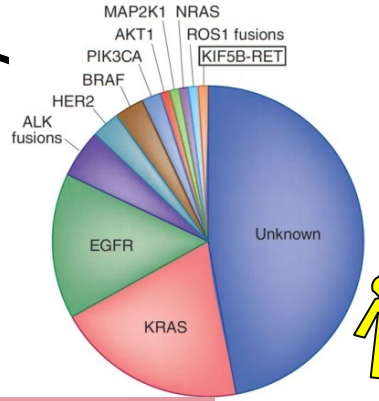
PD-L1 status



Clinical urgency

Other tumor features

Driver positive: the genomic pie (40%)



- EGFR mutant (12-15%)
  - Classical
  - Atypicals
  - Exon 20
  - Resistance (T790M, C797S)
- KRAS G12C 12%
- ALK fusion (4%)
- BRAF mutant (3%)
- MET ex14 (3%)
- HER2 mutant (2%)
- NTRK mutant (1%)
- ROS-1 mutant (1%)
- RET fusion (1%)
- Other thin slices (1-3%) NRG fusions, etc

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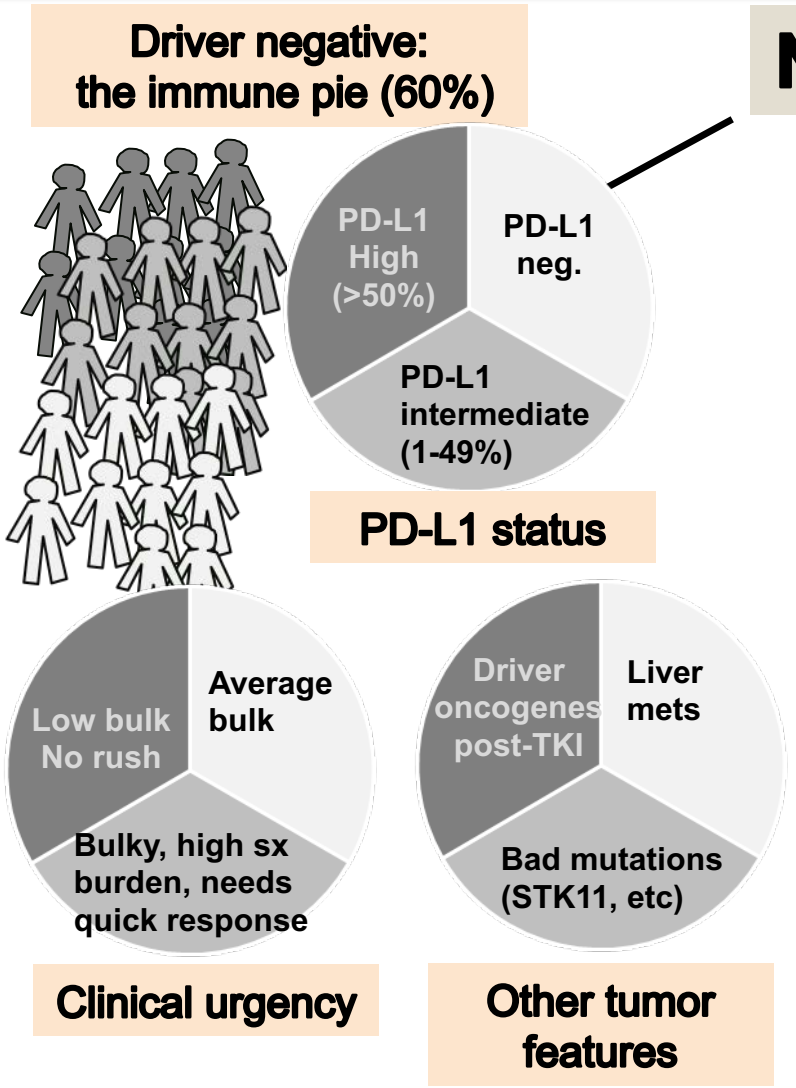
Future of immunotherapy: how do we design more personalized, and more effective, treatments?



NSCLC

- PD-L1 levels are a moderately predictive downstream epiphenomenon
- There are multiple different ways for a tumor to become immunologically “hot” or “cold”
- **Can we identify markers to tailor immune therapies for 1L and CPI-refractory patients?**
- **How do we incorporate ADCs?**

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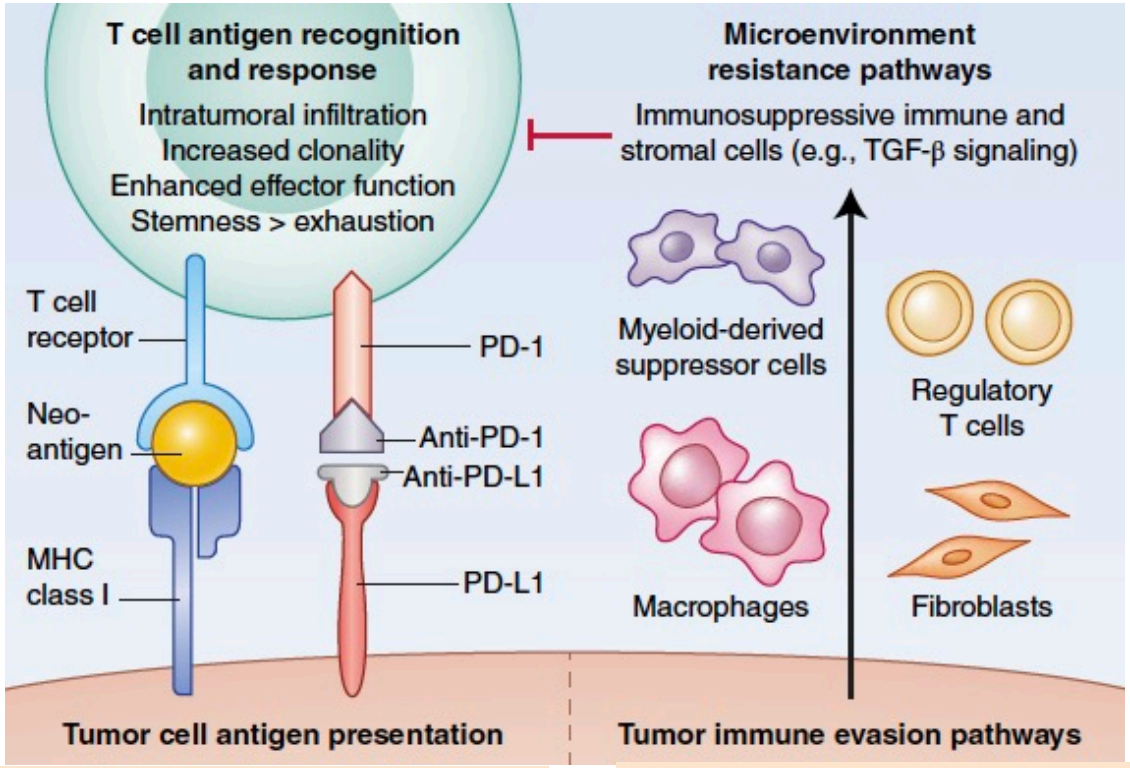
Mechanisms of primary and acquired resistance to CPI

Potential mechanisms of resistance to checkpoint inhibitors



Tumor cell/antigen

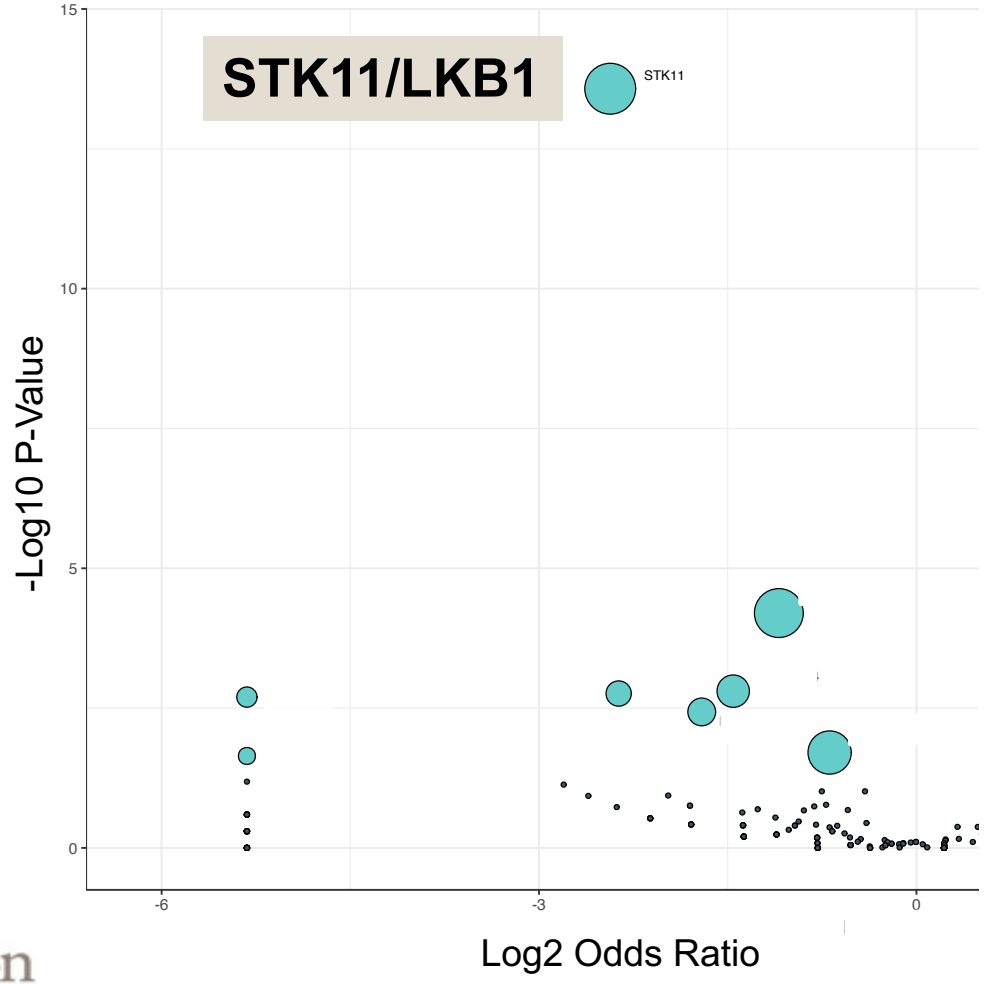
- Low number of neoantigens
- Loss of MHC
- T cells suppressed
- T cells excluded/exhausted

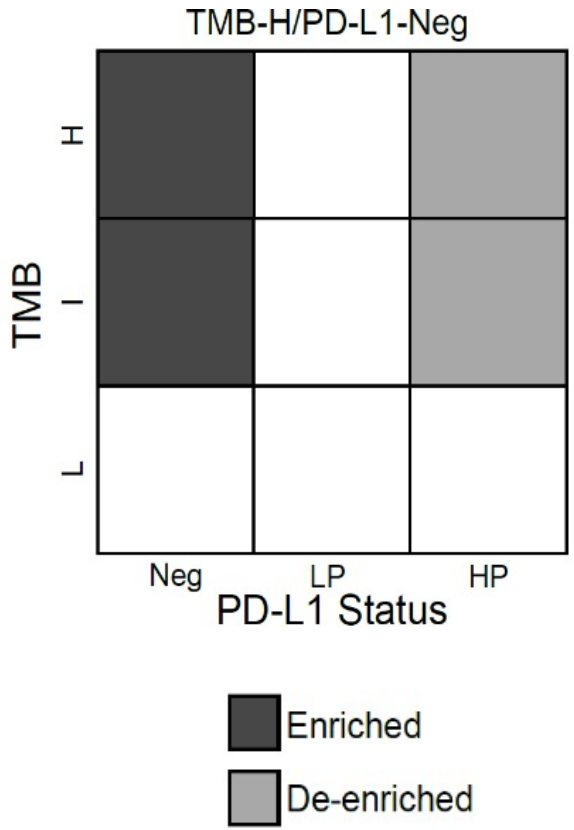
Tumor microenvironment

- Suppressive myeloid cells
- Tregs
- Suppressive cytokines (e.g. IL-6)

Keenan et al, Nature Med 2019

Genomic markers associated with an immunologically “cold,” PD-L1 negative phenotype: STK11/LKB1 is coldest





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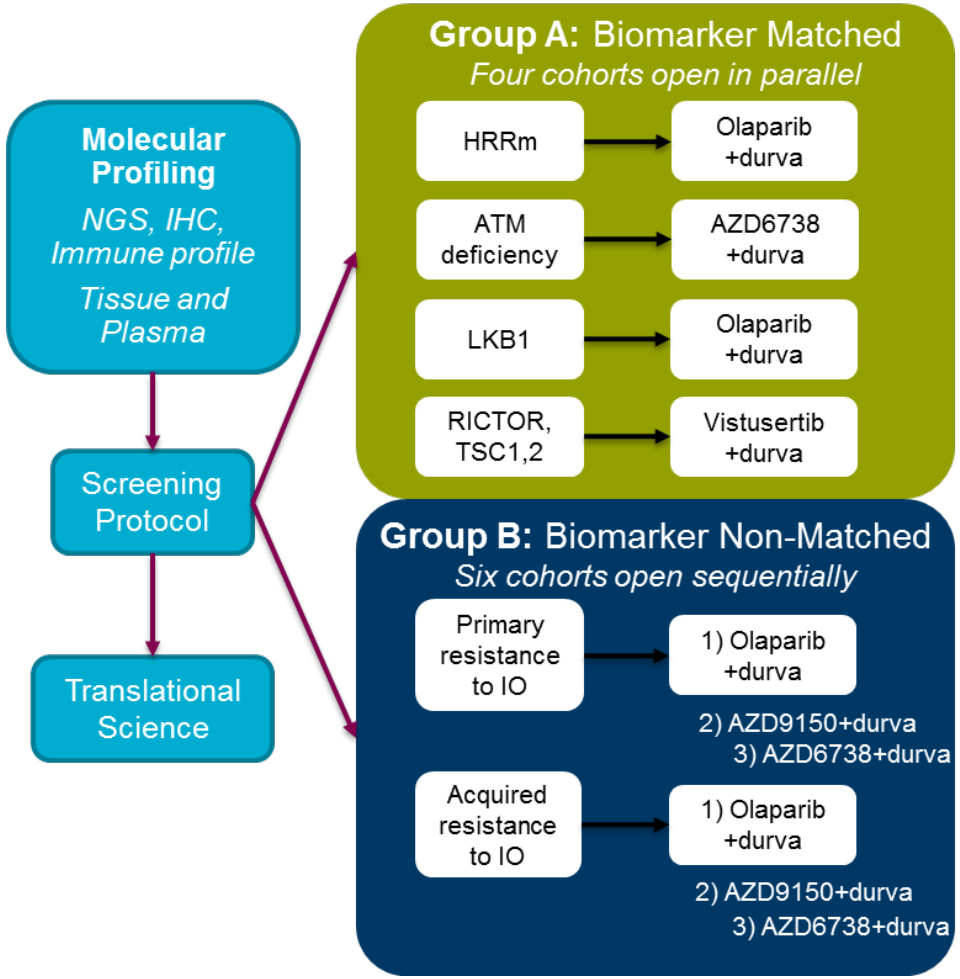
Collaboration with Albacker et al, FM; Skoulidis, Cancer Discovery; 2018

The HUDSON study: biomarker-driven combinations for CPI-refractory NSCLC

HUDSON: A Biomarker-Directed, multicenter phase II study in NSCLC patients who have progressed on anti-PD-1/PD-L1

- Biomarker "Matched" and "Non-matched" cohorts.
- Modular design to explore specific emerging hypotheses for overcoming primary or acquired resistance to antiPD-1/PD-L1



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- Besse B, Awad MM, Forde PM, …Dressman M, Barry ST, Heymach JV, OA15.05. J. Thor. Oncol, 17:9 (2022) S41-S42, DOI:https://doi.org/10.1016/j.jtho.2022.07.074

HUDSON: rationale for treatment arms

Combination agent	Mechanism of action	Mechanism of anti-PD-(L)1 resistance targeted	HUDSON biomarkers
Ceralasertib (AZD6738)	ATR inhibitor	Improving tumor immunogenicity and tumor immune microenvironment via DDR pathway inhibition, to sensitize cancer cells to anti-PD-L1/PD-1 therapy[1]	ATM alteration
Olaparib	PARP inhibitor	Alterations to DDR pathways affect anti-PD-(L)1 sensitivity;[2] PARP inhibition promotes DDR pathway defects[3]	HRRm *STK11/LKB1m*
Danvatirsen	STAT3 inhibitor	Interferon-γ signalling defects arising from JAK-STAT pathway mutations associated with acquired resistance[4]	Not applicable
Oleclumab	Anti-CD73 monoclonal antibody	Immunosuppressive tumor immune microenvironment due to production of adenosine, mediated by CD73[5]	High CD73 expression

1. Kwon et al. J ImmunoTher Cancer 2022;10:e005041; 2. Mouw et al. Cancer Discov 2017;7:675–693; 3. Rouleau et al. Nat Rev Cancer 2010;10:293–301; 4. Schoenfeld & Hellmann. Cancer Cell 2020;37:443–455; 5. Roh et al. Curr Opin Pharmacol 2020;53:66–76.
ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3-relatedprotein kinase; CD73, cluster of differentiation 73; DDR, DNA damage response and repair; HRRm, homologous recombination repair mutated; STK11/LKB1m, STK11/LKB1 aberration; PARP, Poly-(ADP-ribose) polymerase; PD-(L)1, programmed death (ligand)-1

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- Besse B, Awad MM, Forde PM, …Dressman M, Barry ST, Heymach JV, OA15.05. J. Thor. Oncol, 17:9 (2022) S41-S42, DOI:https://doi.org/10.1016/j.jtho.2022.07.074

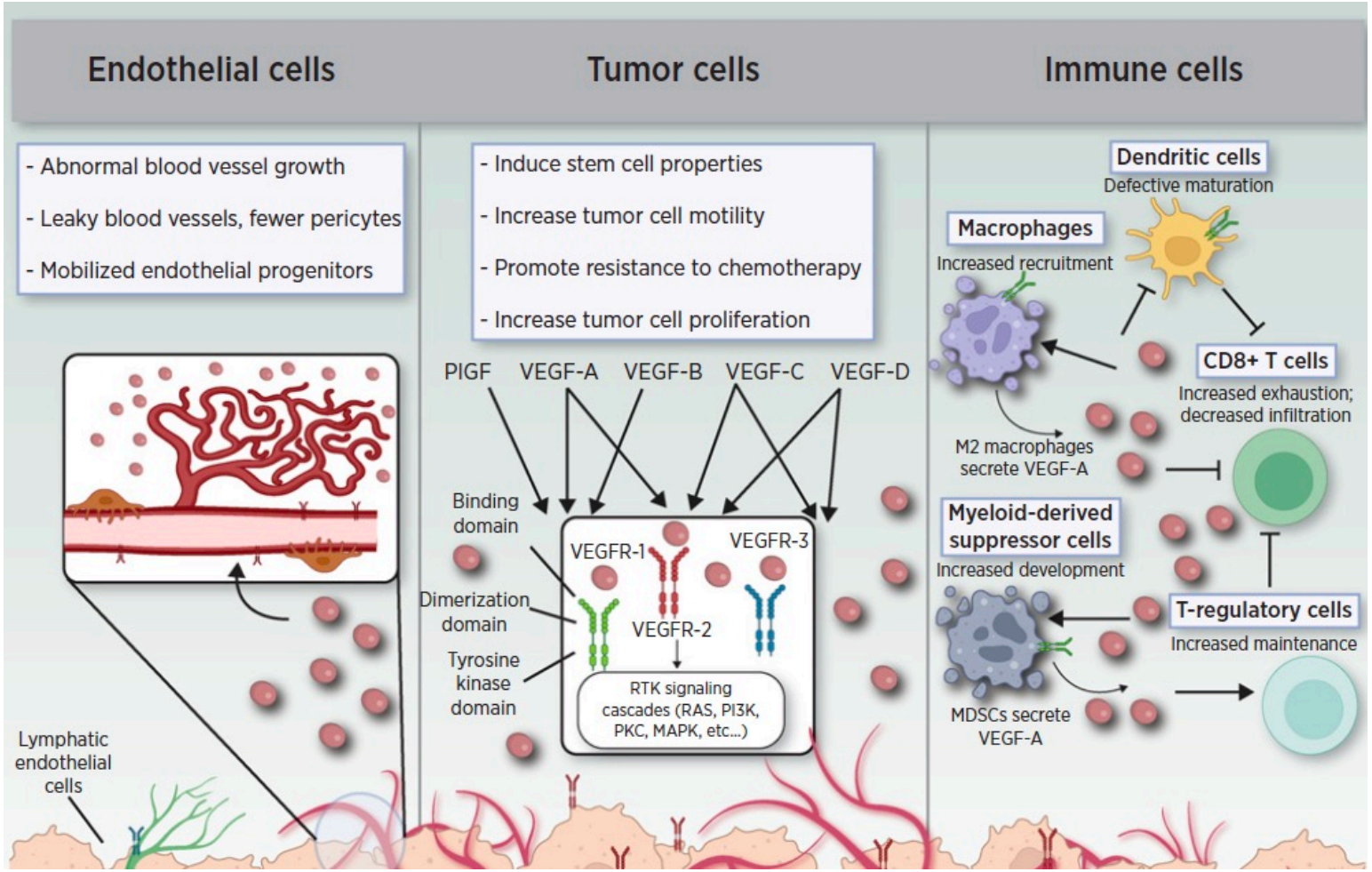
HUDSON: Treatment efficacy by regimen in PD-(L)1i-refractory NSCLC

	Durvalumab + ceralasertib n=66	Durvalumab + olaparib n=87	Durvalumab + danvatirsen n=45	Durvalumab + oleclumab n=57
Median treatment duration, months				
Durvalumab*	**7.3**	3.7	2.8	2.9
Other agent†	**6.3**	3.2	2.8	2.9
12-week disease control rate, %	**60.6**	36.8	26.7	29.8
24-week disease control rate, %	**42.4**	17.2	13.3	15.8
ORR, %	**16.7%**	4.6%	0%	1.8%

ORR, objective response rate.
*Treatment duration for durvalumab calculated as (the earliest of (last infusion date + 27, date of death, date of cut-off) – first infusion date + 1) / (365.25/12).
†Treatment duration for:
- Olaparib calculated as (Last dose date – first dose date + 1) / (365.25/12)
- Danvatirsen calculated as (Last infusion date – first infusion date + 1) / (365.25/12), if the last cycle is Cycle 0 and there were less than 3 doses, or (the earliest of (last infusion date + 6, death date, date of cut-off) – first infusion date + 1) / (365.25/12) for all other cases
- Ceralasertib calculated as (Last dose date – first dose date + 1) / (365.25/12)
- Oleclumab calculated as (the earliest of (last infusion date + 13, death date, date of cut-off) – first infusion date + 1) / (365.25/12) if the last cycle is Cycle 1 or 2, or as (the earliest of (last infusion date + 27, death date, date of cut-off) – first infusion date + 1) / (365.25/12), for all other cases.

- Besse B, Awad MM, Forde PM, …Dressman M, Barry ST, Heymach JV, OA15.05. J. Thor. Oncol, 17:9 (2022) S41-S42, DOI:https://doi.org/10.1016/j.jtho.2022.07.074

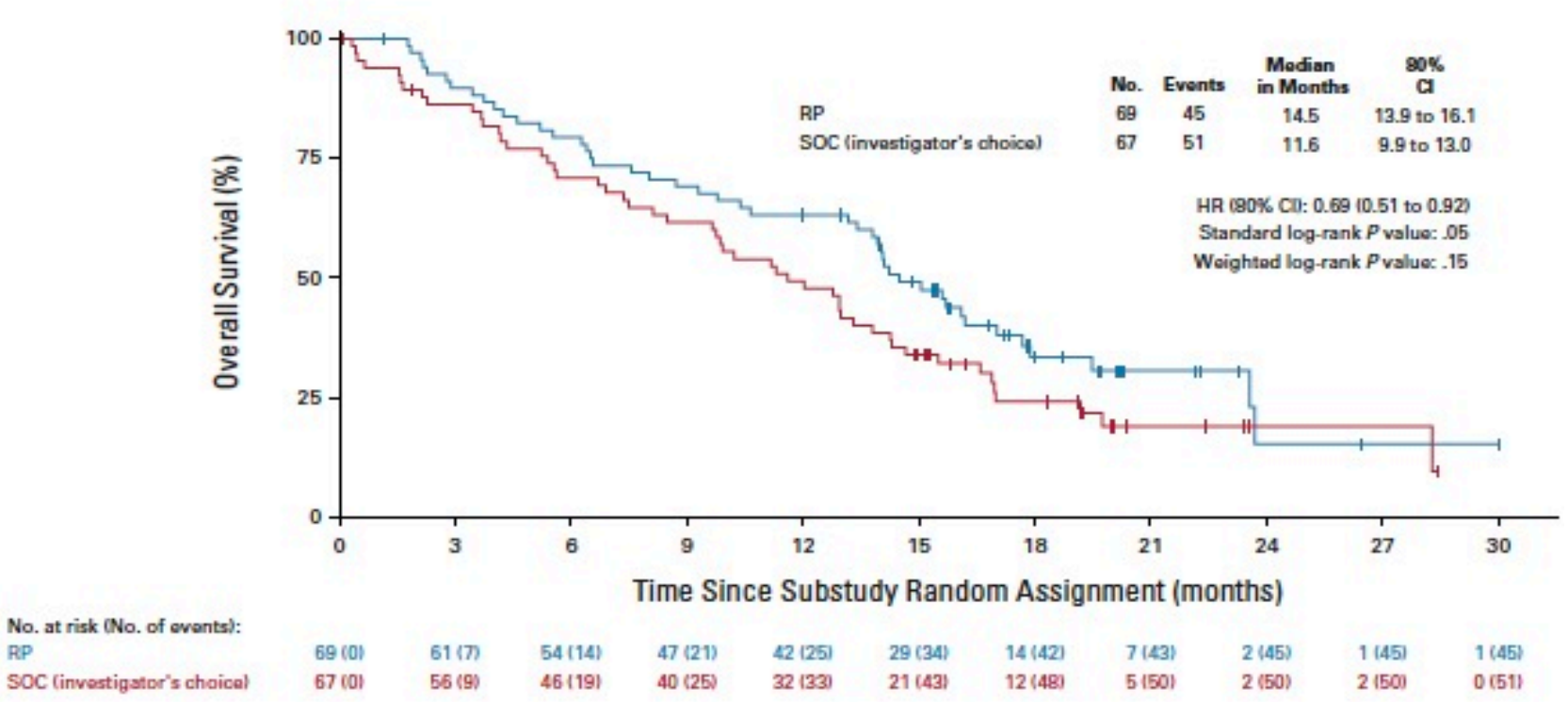
VEGF/VEGFR pathway promotes an immunosuppressive tumor microenvironment in addition to other effects on TCs and ECs



Patel et al, CCR 2022

Randomized phase II of pembro+ramucirumab vs SOC in PD-(L)1i-refractory NSCLC (SWOG 1800A)

mOS: 14.5 vs 11.5 months (HR 0.69)



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Reckamp et al, JCO 2022

Mechanism of Action and Rationale for Targeting TROP2 via ADCs:

Datopotamab Deruxtecan (Dato-DXd) and Sacituzumab Govitecan (SG)

Trop-2 Association with Tumor Progression

- Trop-2 overexpression is linked to increased tumor growth and cell migration, contributing to tumor progression[1]
- In *in vitro* studies, overexpression of Trop-2 was found to be “necessary and sufficient” to stimulate transformed cell growth[2]
- In breast tumors, Trop-2 overexpression may be associated with a less favorable phenotype (ie, ER-negative/HER2-positive)[3]

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; Trop-2, trophoblast cell surface antigen 2.

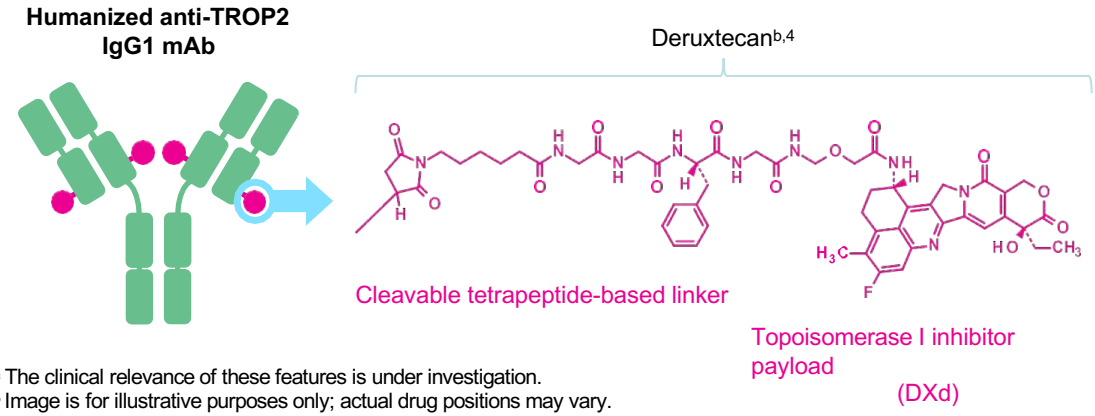
1. Goldenberg DM, et al. *Oncotarget*. 2018;9:28989-29006; 2. Treretola M, et al. *Oncogene*. 2013;32:222-233; 3. Huang H, et al. *Clin Cancer Res*. 2005;11:4357-4364; 4. Shvartsur A and Bonavida B. *Genes Cancer*. 2015;6:84-105; 5. Lin H, et al. *Exp Mol Pathol*. 2013;94:73-78; 6. Ambrogi F, et al. *PLoS One*. 2014;9:e96993.

From Levy et al, Proc IASLC 2022

Datopotamab deruxtecan (Dato-DXd; DS-1062) with potent topoisomerase inhibitor payload

Dato-DXd is an ADC composed of 3 components[1,2]:

- A humanized anti-TROP2 IgG1[3] monoclonal antibody attached to:
- A topoisomerase I inhibitor payload, an exatecan derivative, via
- A tetrapeptide-based cleavable linker



[a] The clinical relevance of these features is under investigation.
[b] Image is for illustrative purposes only; actual drug positions may vary.
[c] Based on animal data.

Payload mechanism of action: topoisomerase I inhibitor [a,1]

High potency of payload [a,2]

Optimized drug to antibody ratio ≈4 [a,c,1]

Payload with short systemic half-life [a,c,2]

Stable linker-payload [a,2]

Tumor-selective cleavable linker [a,2]

Bystander antitumor effect [a,2,5]

1. Okajima D, et al. Poster presented at: AACR-NCI-EORTC International Conference; October 26-30, 2019; Boston, MA [abstract C026].
2. Nakada T, et al. *Chem Pharm Bull*. 2019;67(3):173-185. (DS-8201 drug discovery MS)
3. Daiichi Sankyo Co. Ltd. DS-1062. Daiichi Sankyo.com. Accessed October 6, 2020. https://www.daiichisankyo.com/media_investors/investor_relations/ir_calendar/files/005438/DS-1062%20Seminar%20Slides_EN.pdf
4. Krop I, et al. Oral presentation at: SABCS Symposium; December 10-14, 2019; San Antonio, TX [abstract GS1-03].
5. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4946713/pdf/CAS-107-1039.pdf - DS-8201 preclin MS

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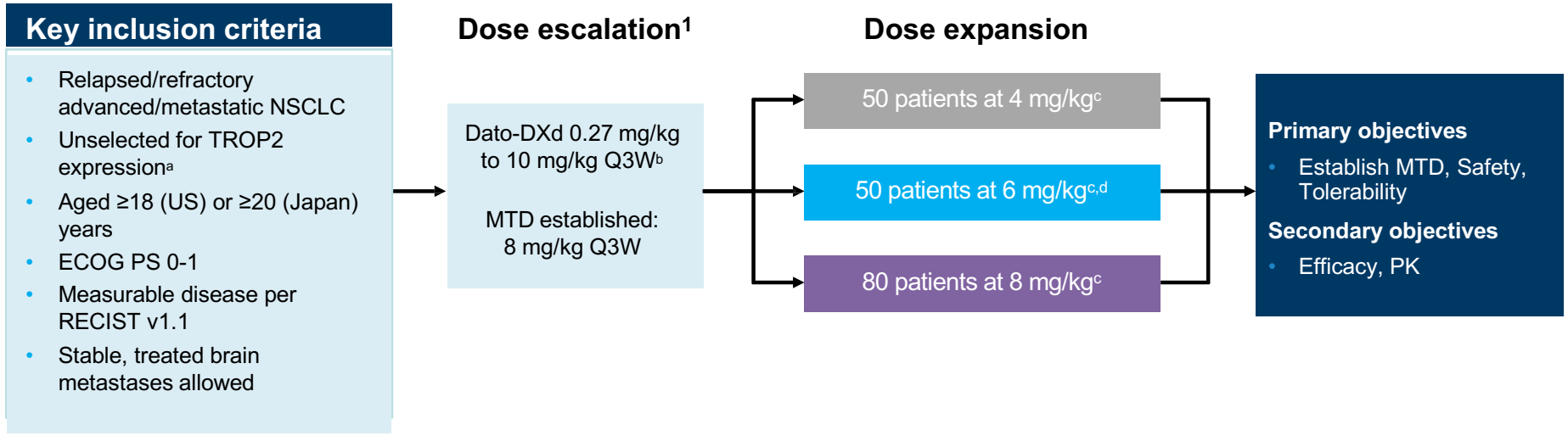
From Levy et al, Proc IASLC 2022

TROPION-PanTumor01 (NCT03401385) Study Design

Phase 1 FIH Dose Escalation and Expansion Study



- NSCLC enrollment complete[d]
- TNBC cohort 6 mg/kg Q3W is enrolling; cohorts in other tumor types may be added
- Here we report updated results for the NSCLC dose expansion cohort (175 patients treated at 4, 6, or 8 mg/kg of Dato-DXd)

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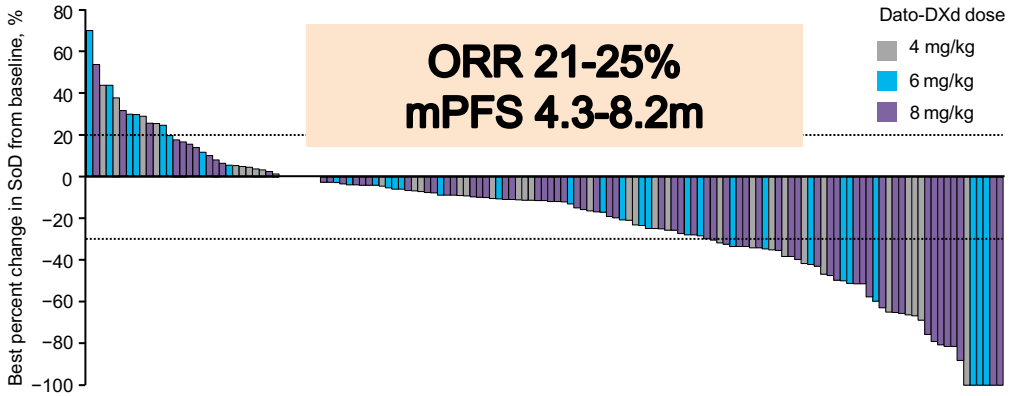
[a]Pretreatment tumor tissue was required for retrospective analysis of TROP2 expression. [b]The 4, 6, and 8 mg/kg dose levels are being further evaluated for safety and efficacy. A TNBC cohort is currently open for enrollment at 6 mg/kg, although no TNBC patients are included in this analysis. [c]Inclusive of patients treated in dose escalation and dose expansion. [d]The current analysis includes 45 patients treated at the 6 mg/kg dose (data cutoff: 4 September 2020).
ECOG PS, Eastern Cooperative Oncology Group performance status; FIH, first-in-human; MTD, maximum tolerated dose; NSCLC, non–small cell lung cancer; PK, pharmacokinetics; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TNBC, triple-negative breast cancer; TROP2, trophoblast cell surface antigen 2; Q3W, once every 3 weeks; US, United States.

1. Lisberg AE, et al. Presented at: ASCO Annual Meeting; May 29-June 2, 2020; virtual meeting. Abstract 9619.

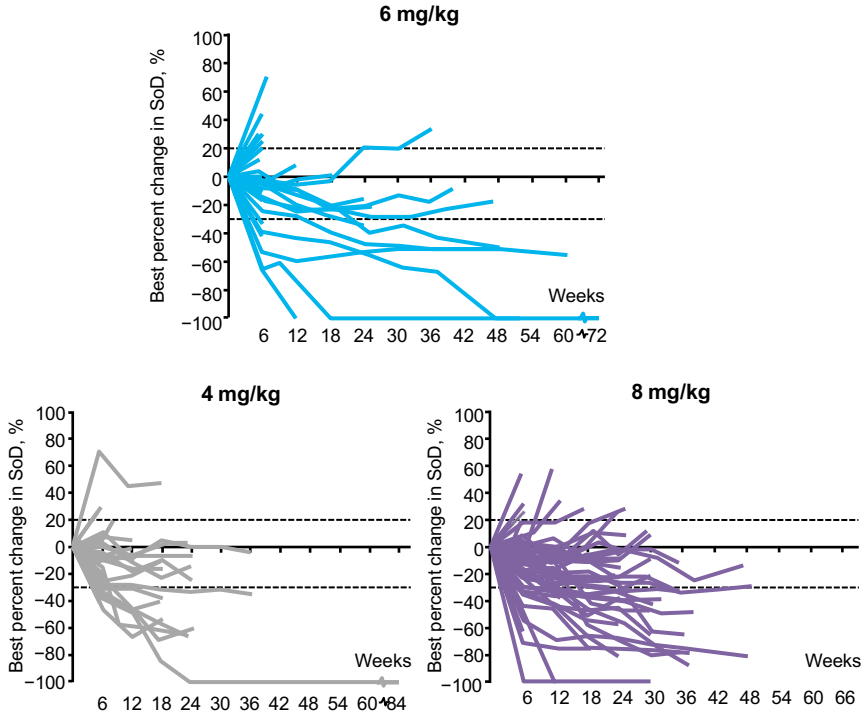
Antitumor Activity of Dato-DXd in Relapsed/Refractory NSCLC

Best Change in Sum of Diameters and Overall Response (BICR)



Dato-DXd dose	Response-evaluable patients,[a] n	Confirmed CR/PR,[b] n	CR/PR (too early to be confirmed),[b] n	ORR,[b] % (n)	DCR, % (n)	PD, % (n)
4 mg/kg	40	7	2	23 (9)	73 (29)	15 (6)
6 mg/kg	39	6	2	21 (8)	67 (26)	21 (8)
8 mg/kg	80	19	1	25 (20)	80 (64)	9 (7)

Change in Sum of Diameters for Target Lesions (BICR)



Preliminary Progression-free Survival (BICR)[c]

- Median PFS (95% CI)
  - 4 mg/kg: 4.3 months (2.0-NE), 6 mg/kg: 8.2 months (1.5-11.8), 8 mg/kg: 5.4 months (4.1-7.1)

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Data cutoff: 4 September 2020.

[a]Includes patients with ≥1 postbaseline scan or who discontinued treatment.
[b]Responses are confirmed (CRs/PRs; n = 32) plus those CRs/PRs too early to be confirmed (n = 5).
[c]Preliminary PFS limited by earlier censoring by data cutoff due to immature duration of follow-up for 4 and 6 mg/kg dose cohorts.
AE, adverse event; BICR, blinded independent central review; CI, confidence interval; CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, overall response rate; PFS, progression-free survival; PD, progressive disease; PR, partial response; SoD, sum of diameter.

Phase I TROPION-PanTumor01 (NSCLC Cohort): Antitumor Activity of Dato-DXd for NSCLC with Actionable Genomic Alterations (AGAs)

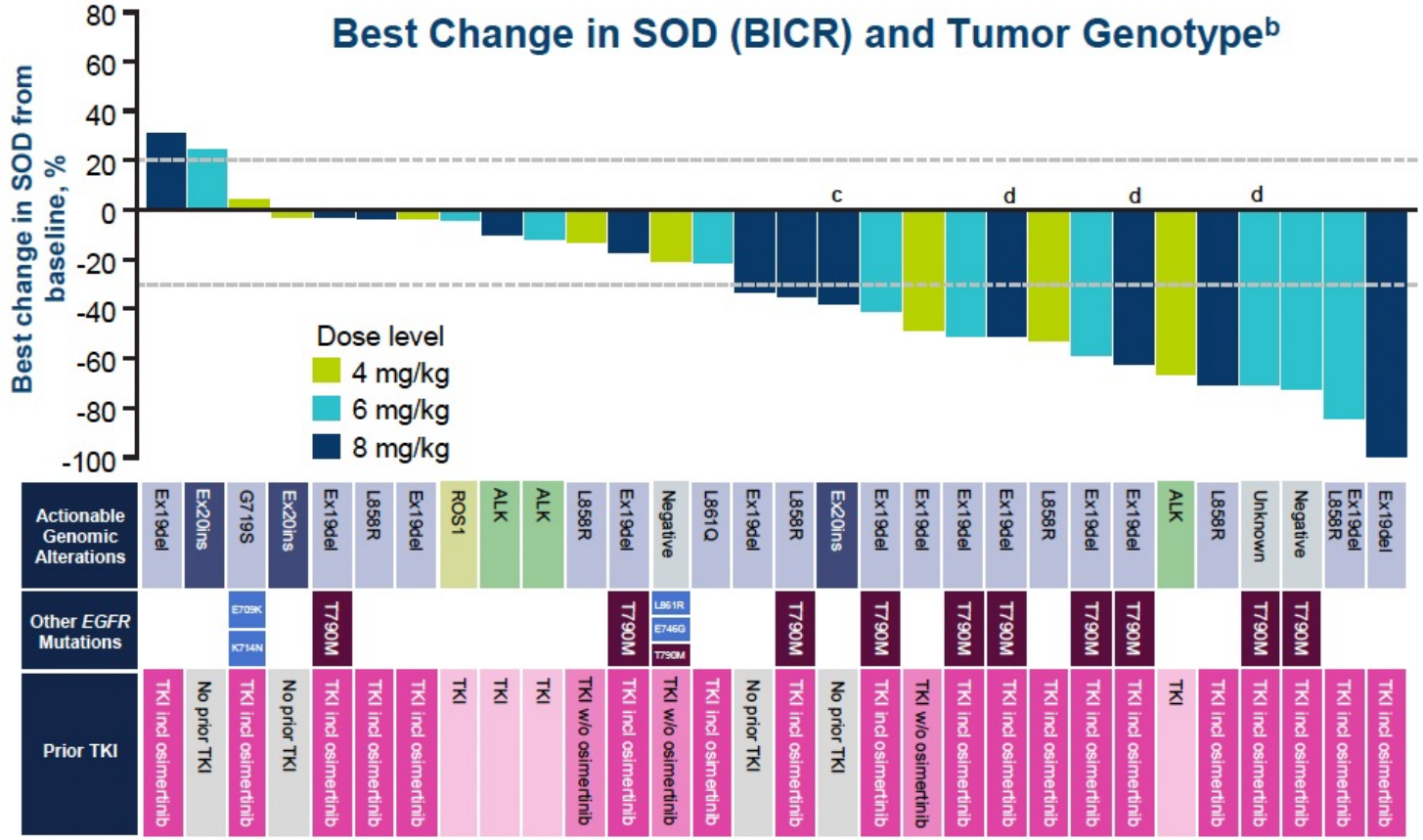
Best Overall Response (BICR)

Patients[a]	Dato-DXd n=34
ORR, n (%)	12 (35)
CR	0
PR	12 (35)
SD, n (%)	14 (41)
Non-CR/PD, n (%)	2 (6)
PD, n (%)	2 (6)
NE, n (%)	4 (12)
DOR, median (95% CI), mo	9.5 (3.3-NE)

- Clinical activity was observed in *EGFR* (Ex19del, L858R) including after osimertinib and across other AGAs

Data cutoff: April 6, 2021.

Best Change in SOD (BICR) and Tumor Genotype[b]



SOD, sum of diameter

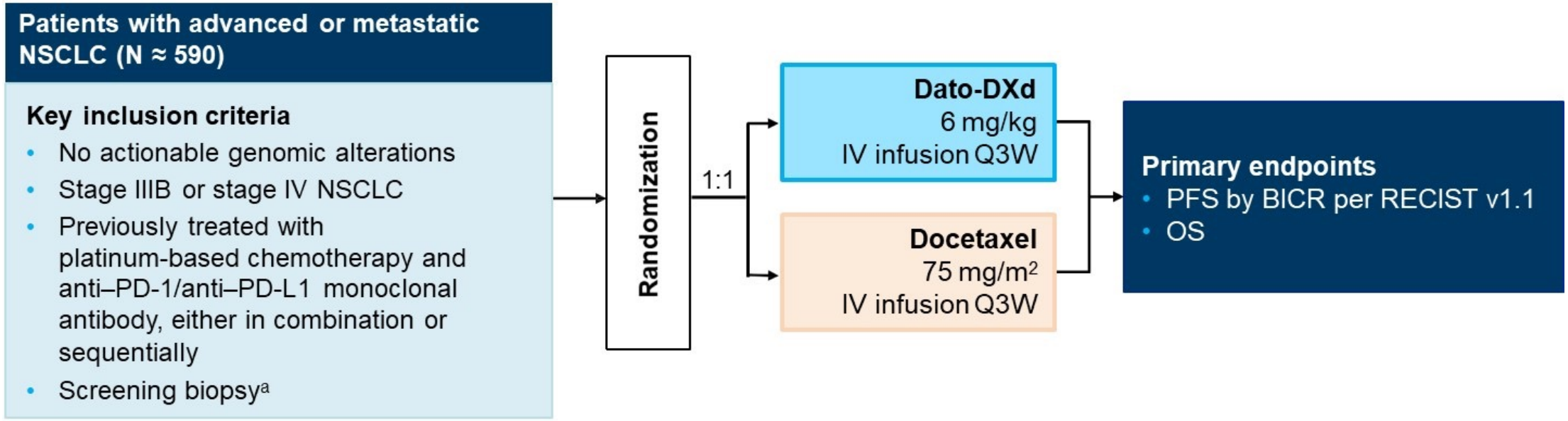
Garon EB et al. ESMO 2021;Abstract LBA49.

RTP RESEARCH TO PRACTICE

Randomized Phase III TROPION-Lung01 Study

(NCTNCT04526691)

- This phase 3 study is open for enrollment



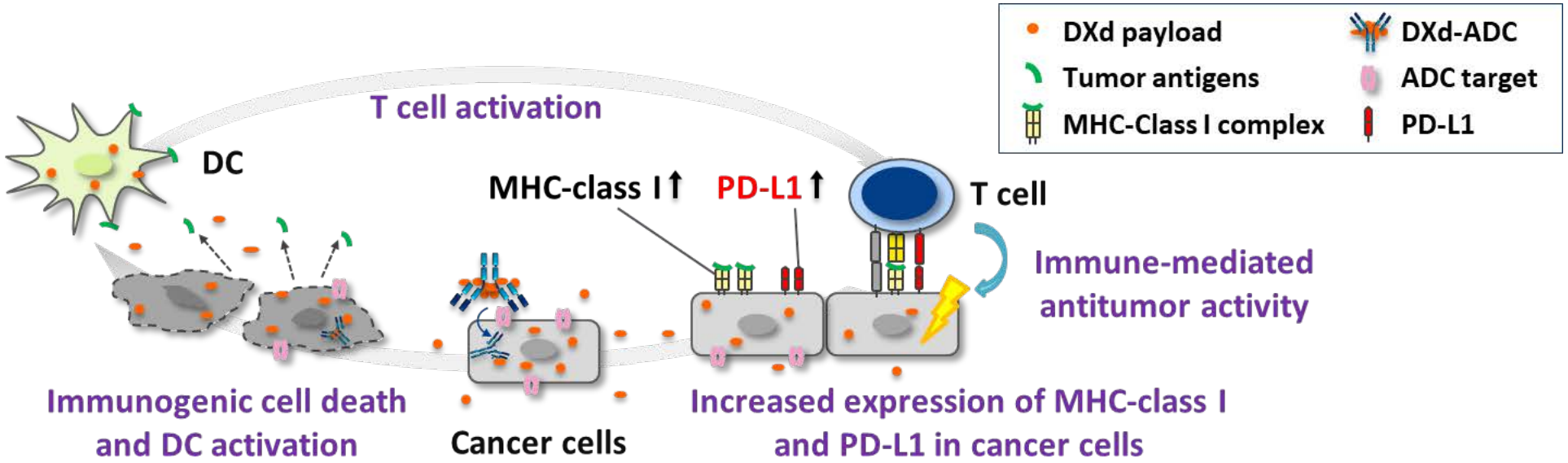
Data cutoff: 4 September 2020.

[a]To date, no correlation between TROP2 expression and Dato-DXd clinical activity in NSCLC has been observed.

BICR, blinded independent central review; NSCLC, non–small cell lung cancer; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PFS, progression-free survival; Q3W, once every 3 weeks; RECIST: Response Evaluation Criteria in Solid Tumors; TROP2, trophoblast cell surface antigen 2.

From Levy et al, Proc IASLC 2022

Combination with anti-PD-1/PD-L1 may enhance antitumor activity of DXd-ADC



1) DXd-ADC induces immunogenic cancer cell death and activates DCs
2) DXd-ADC increases MHC-class I and PD-L1 expression in cancer cells
3) Activated DCs induce immune-mediated antitumor activity

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Iwata T. *et al*., Mol Cancer Ther 2018, Haratani K. *et al*. J Clin Invest 2020

Datopotamab Deruxtecan (Dato-DXd; DS-1062) Clinical Program in Lung Cancer

Advanced Solid Tumors	**Phase 1** **Relapsed / Refractory Disease**	**TROPION-PanTumor01** *Advanced/ metastatic NSCLC or TNBC Relapsed or Refractory to SOC* (DS1062-A-J101, NCT03401385, JapicCTI-173812) *Recruiting* *North America, Asia*
Advanced or Metastatic NSCLC	**Phase 1b** **Comb. w/ Pembrolizumab**	**TROPION-Lung02** *Combination With Pembrolizumab – Without Actionable Genomic Alterations and Previously Treated With Platinum-Based Chemotherapy With or Without Prior Immunotherapy* (DS1062-A-U102, NCT04526691) *Recruiting* *North America, Asia*
	Phase 1b **Comb. w/ Durvalumab**	**TROPION-Lung04** *Combination With Durvalumab – Without Actionable Genomic Alterations and Previously Treated With Platinum-Based Chemotherapy With or Without Prior Immunotherapy* (DS1062-A-U104, NCT04612751) *Recruiting* *North America, Asia*
	Phase 2 **NSCLC w/ Actionable Genomic Alterations**	**TROPION-Lung05** *Actionable Genomic Alterations and Progressed On or After Kinase Inhibitor Therapy and Platinum-Based Chemotherapy* (DS1062-A-U202, NCT04484142, 2020-002774-27) *Recruiting* *North America, Europe, Asia*
	Phase 3 **Relapsed / Refractory NSCLC vs Docetaxel**	**TROPION-Lung01** *Compared to Docetaxel – Without Actionable Genomic Alterations and Previously Treated With Platinum-Based Chemotherapy and Immunotherapy* (DS1062-A-U301, NCT04656652) *Recruiting* *North America, South America, Europe, Asia*

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Ongoing datopotamab deruxtecan (Dato-DXd; DS-1062) clinical trials posted on ClinicalTrials.gov, JapicCTI, and EudraCT, excluding safety, drug-drug interactions, and pharmacokinetic studies.

1. Press Release: https://dsi.com/press-releases/-/article/364091/11614366. Accessed December 15, 2020.

From Levy et al, Proc IASLC 2022

TROPION-Lung02: Datopotamab Deruxtecan with Pembrolizumab and Platinum Chemotherapy for Advanced NSCLC

Antitumor Activity

In the overall population:

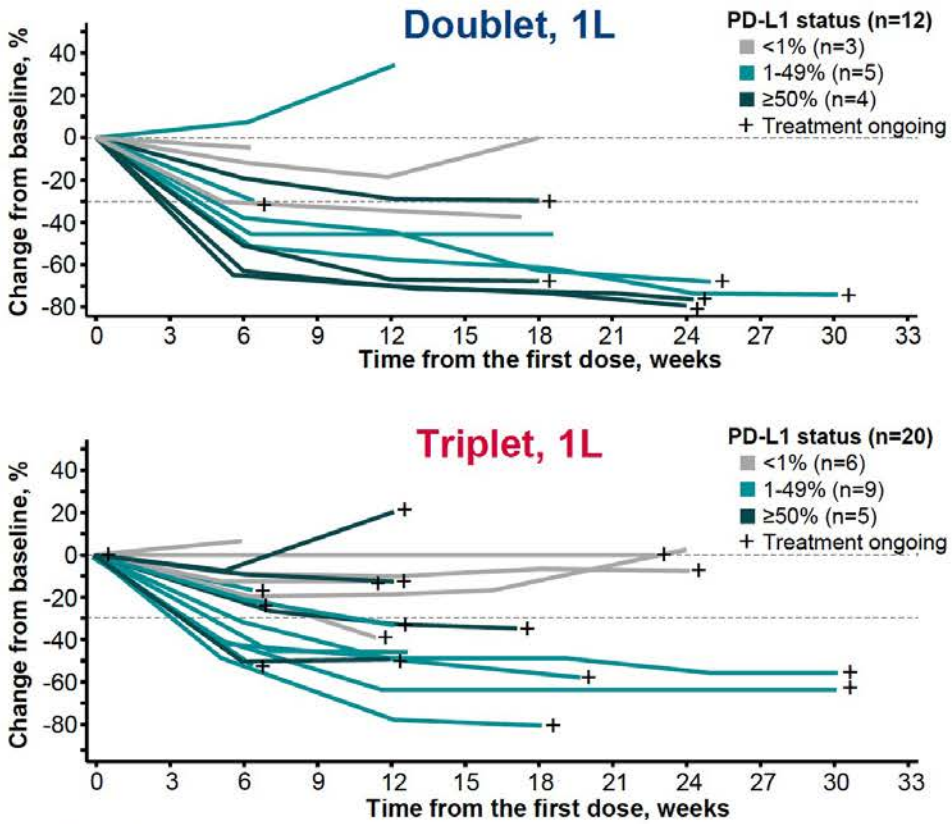
ORRs (confirmed + pending) of 37% and 41% were seen with doublet (n=38) and triplet (n=37) therapy, respectively; both groups had 84% DCR

BOR With 1L Therapy For Advanced NSCLC[a,b]

Response, n (%)	Doublet (n=13)	Triplet (n=20)
ORR confirmed + pending	**8 (62%)**	**10 (50%)**
CR	0	0
PR confirmed	8 (62%)	7 (35%)
PR pending	0	3 (15%)
SD	5 (39%)	8 (40%)
DCR	13 (100%)	18 (90%)

- As 1L therapy, the doublet and triplet yielded ORRs (confirmed + pending) of 62% and 50%, respectively
- As 2L+ therapy, respective ORRs (confirmed + pending) were 24% and 29%

Percent Change in Sum of Diameters[a]



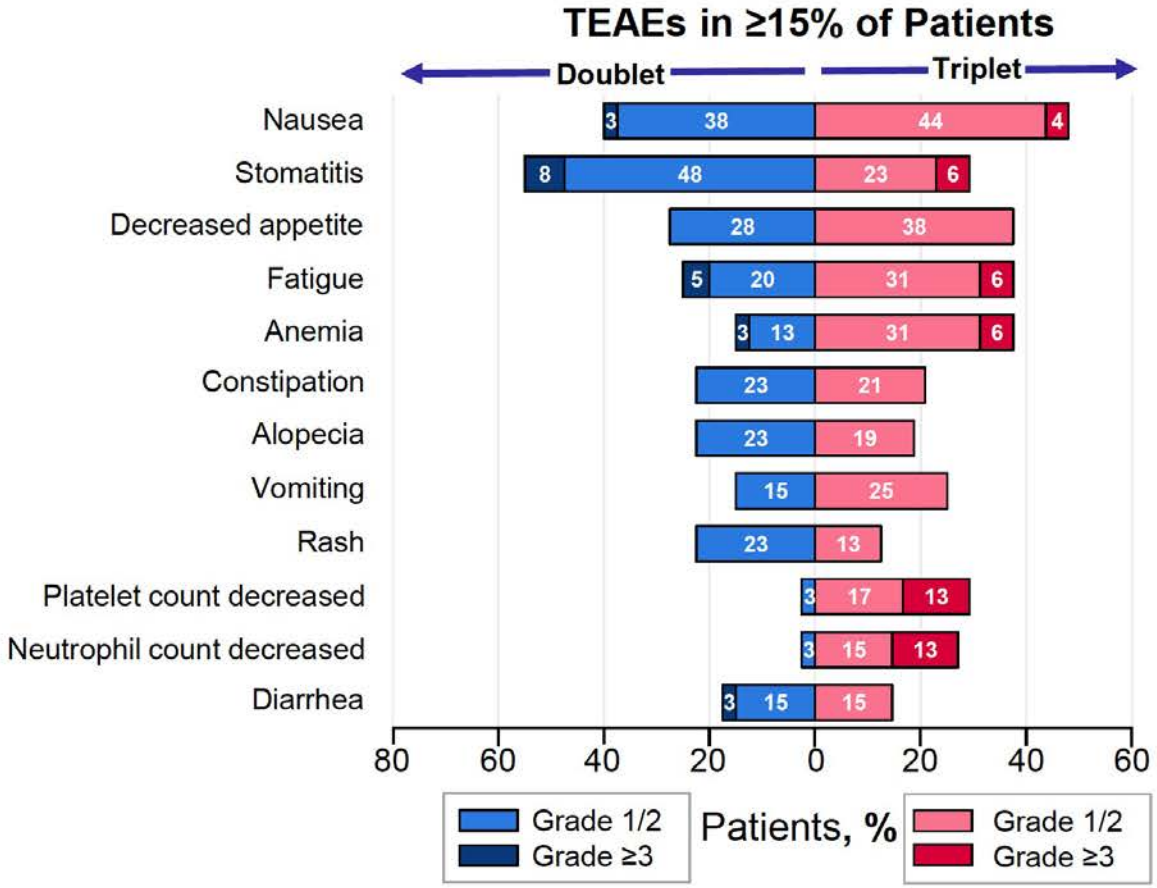
Data cutoff: May 2, 2022.
BOR, best overall response; CR, complete response; DCR, disease control rate; ORR, overall response rate; PR, partial response; SD, stable disease.
[a] By investigator. [b] BOR is based on response evaluable patients who have ≥1 postbaseline tumor assessment or discontinued.

Levy B et al. IASLC 2022;Abstract MA13.07.

TROPION-Lung02: Datopotamab Deruxtecan with Pembrolizumab and Platinum Chemotherapy for Advanced NSCLC

Safety

Events, n (%)	Doublet (n=40)	Triplet (n=48)
TEAEs	37 (93%)	47 (98%)
Study treatment-related[a]	33 (83%)	46 (96%)
Grade ≥3 TEAEs	16 (40%)	29 (60%)
Study treatment-related[a]	14 (35%)	26 (54%)
Serious TEAEs	9 (23%)	13 (27%)
Study treatment-related	4 (10%)	7 (15%)
TEAEs associated with		
Death[b]	2 (5%)	1 (2%)
Discontinuation due to any drug	9 (22%)	9 (19%)
Discontinuation due to Dato-DXd	6 (15%)	5 (10%)
ILD adjudicated as drug related[c]		
Grade 1/2	2 (5%)	0
Grade 3	1 (3%)	1 (2%)



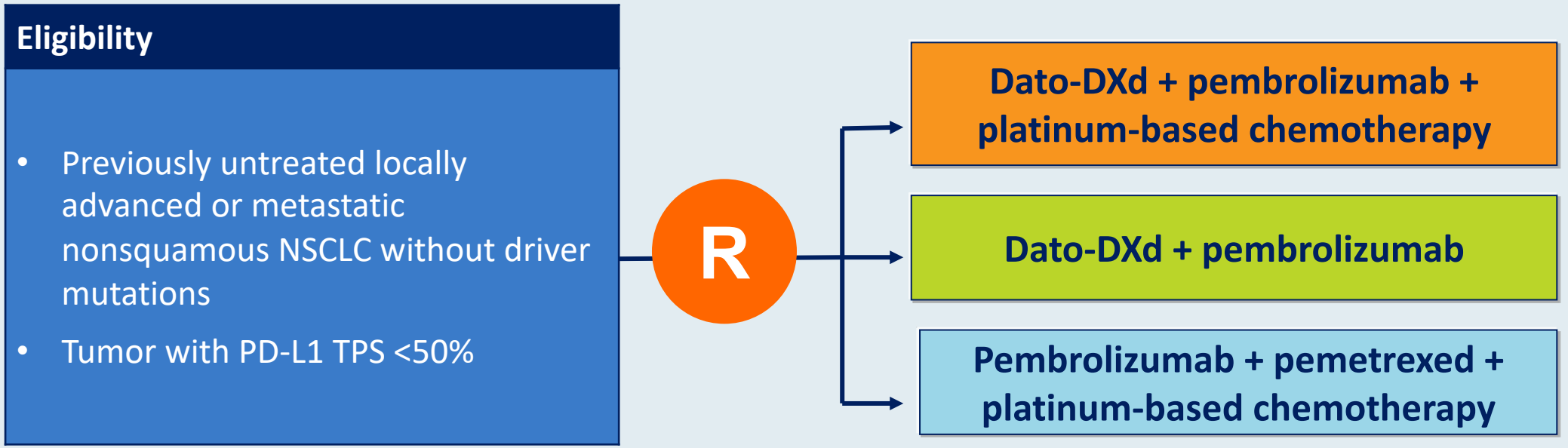
Data cutoff: May 2, 2022.
ILD, interstitial lung disease. TEAE, treatment emergent adverse event.
[a] Drug related TEAEs may be associated with any component of the study treatment: Dato-DXd, pembro, cisplatin, or carboplatin. [b] TEAEs associated with death (encephalopathy, respiratory failure, and death) were considered unrelated to study treatment. [c] Three ILD cases (1 grade 1, 1 grade 3, and 1 grade 5), are pending adjudication.

Levy B et al. IASLC 2022;Abstract MA13.07.

RTP RESEARCH TO PRACTICE

TROPION-Lung07: Phase III Trial of First-Line Dato-DXd and Pembrolizumab with or without Platinum Chemotherapy for Advanced/Metastatic NSCLC without Actionable Genomic Alterations

Trial identifier: NCT05555732 (not yet recruiting)
Estimated enrollment: 975
Phase III



TPS = tumor proportion score

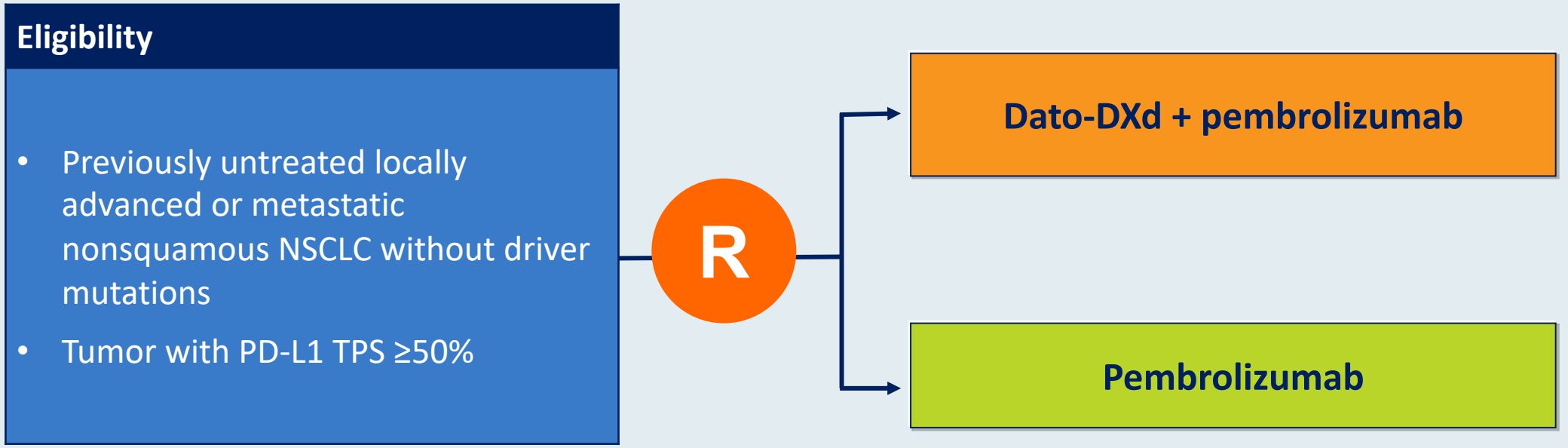
Coprimary endpoints: Progression-free survival by blinded independent central review and overall survival

www.clinicaltrials.gov. Accessed November 2022.

RTP RESEARCH TO PRACTICE

TROPION-Lung08: Phase III Trial of First-Line Dato-DXd with Pembrolizumab Compared to Pembrolizumab Alone for Advanced/Metastatic NSCLC without Actionable Genomic Alterations

Trial identifier: NCT05215340 (open)
Estimated enrollment: 740
Phase III

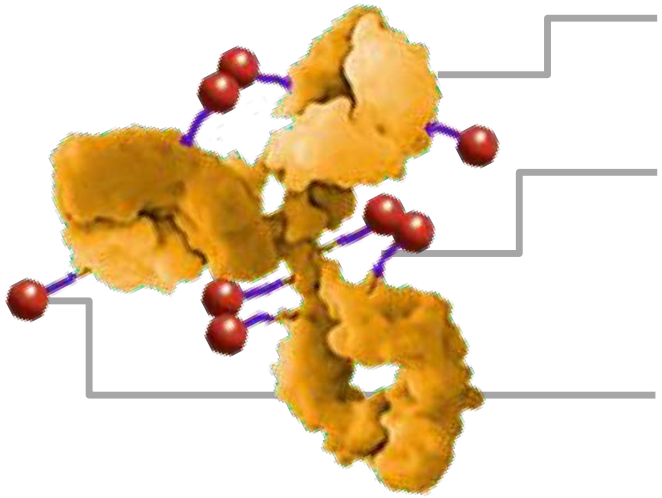


Coprimary endpoints: Progression-free survival by blinded independent central review and overall survival

www.clinicaltrials.gov. Accessed November 2022.

RTP RESEARCH TO PRACTICE

Sacituzumab Govitecan (SG) is a Trop-2–directed ADC with SN-38 topoisomerase I inhibitor and high DAR



Monoclonal antibody (hRS7)

Binds to Trop-2, a cell surface antigen highly expressed by several cancers, including TNBC

Hydrolyzable linker (CL2A)

- Helps to ensure that an active concentration of SN-38 is maintained in the tumor
- Hydrolysis of the linker releases the cytotoxic intracellularly and in the tumor microenvironment to kill cells

Cytotoxic (SN-38)

The payload is SN-38, a topoisomerase I inhibitor that blocks DNA replication by stabilizing Top1-DNA complex during replication, leading to dsDNA breaks through multiple mechanisms.

SG binds to the antigen Trop-2 and concentrates the cytotoxic SN-38 in tumor tissue

SG linker lends itself to a Bystander Effect

Favorable Therapeutic Index

- SG has a high DAR (7–8 molecules of SN-38 per antibody) enhancing drug delivery to tumor
- Moderate drug potency mitigates toxicity, while increased intratumoral drug release enhances efficacy

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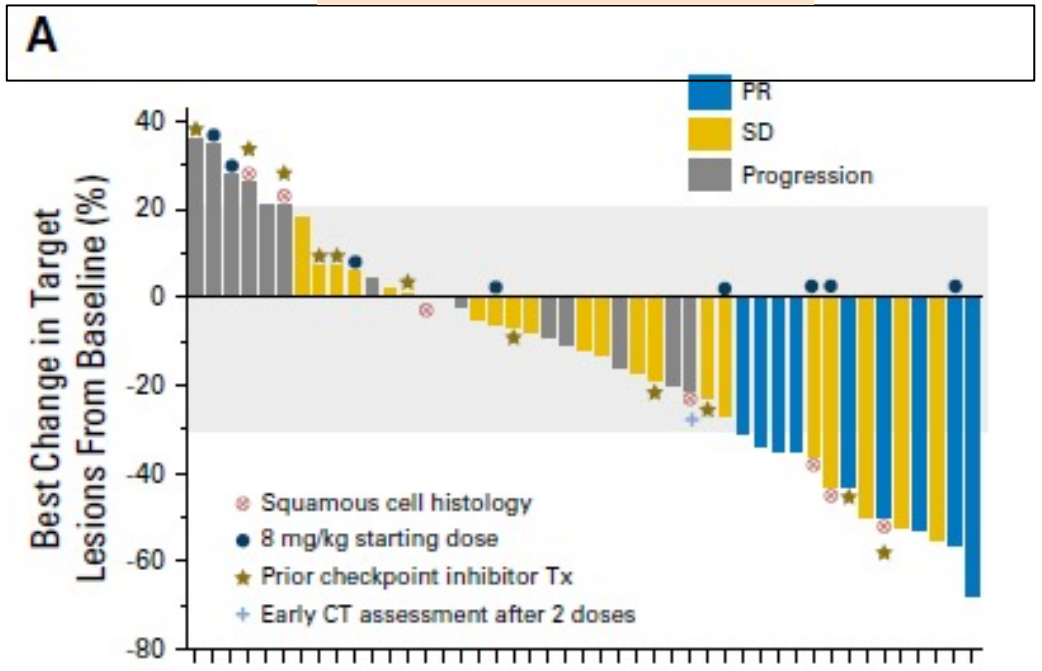
Trop-2, trophoblast cell surface antigen 2; DAR, Drug Antibody Ratio;

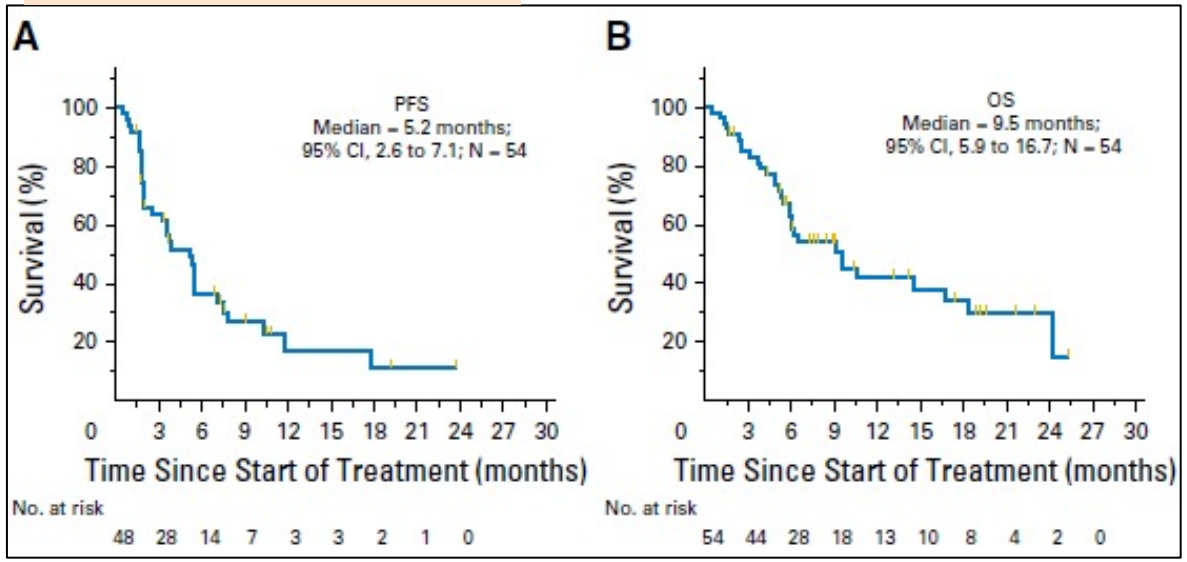
Goldenberg DM, et al. *Oncotarget*. 2015;6(26):22496-512. Gray JE, et al. *Clin Cancer Res*. 2017;23:5711-5719. Takimoto CH, Arbuck SG. Camptothecins. In: Chabner BA, Long DL, editors. Cancer chemotherapy and biotherapy. 2nd ed. Philadelphia, PA: Lippincott-Raven; 1966. p. 463–84.

Phase 1/2 open-label study of Sacituzumab Govitecan in NSCLC patients

ORR 19%



mPFS 5.2m



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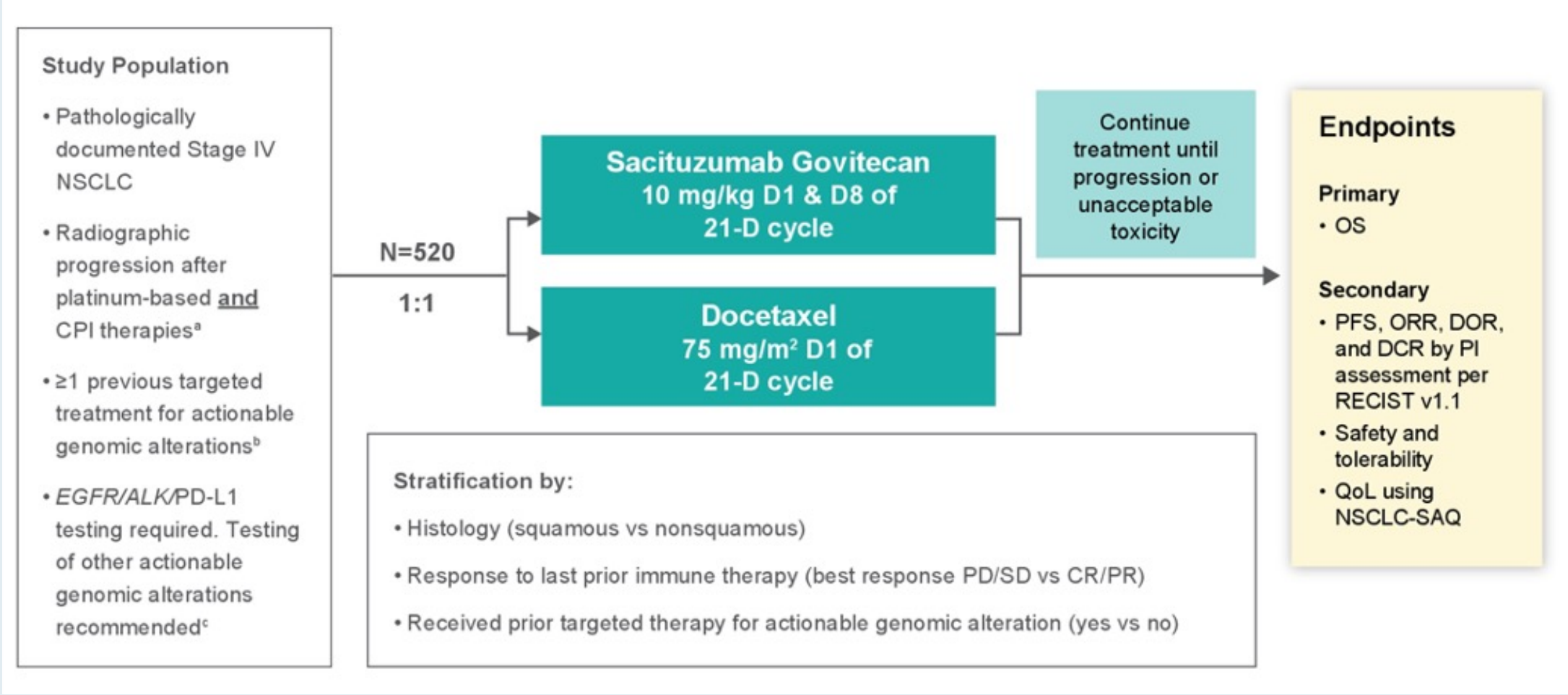
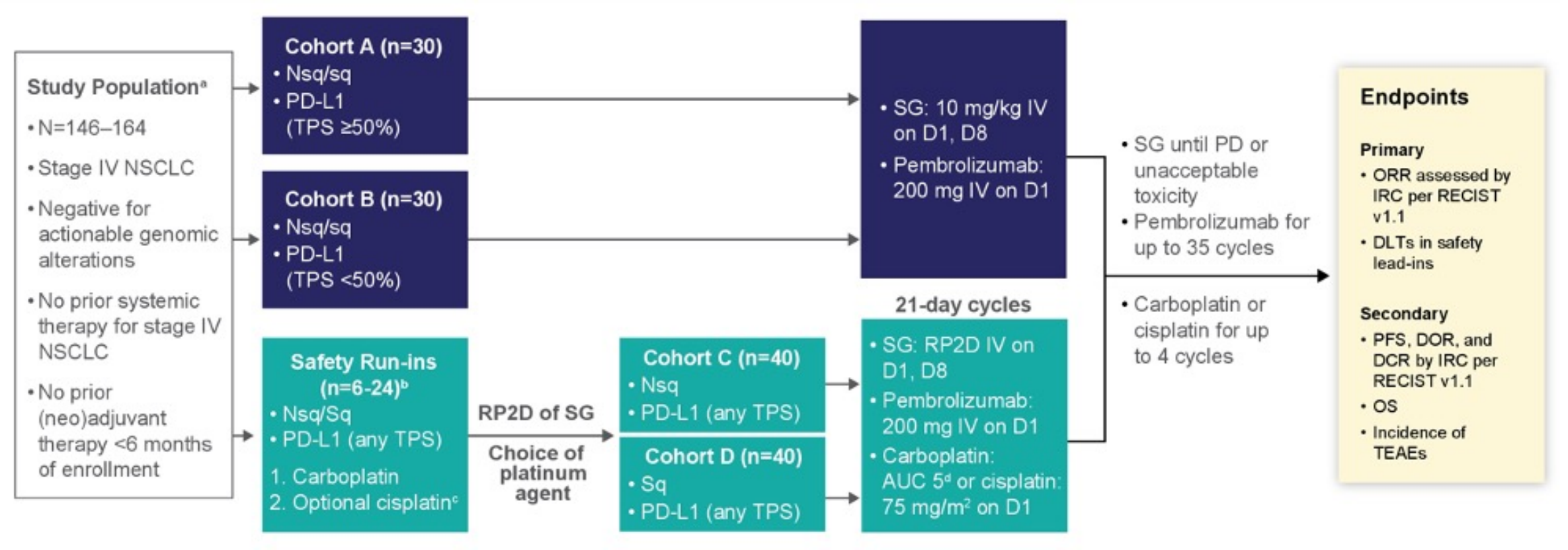
Heist et al. JCO 2017.

EVOKE-01: An Ongoing Phase III Trial Comparing Sacituzumab Govitecan to Docetaxel for NSCLC Progressing on or After Platinum-Based Chemotherapy and Checkpoint Inhibitors



Garassino MC et al. ASCO 2022;Abstract EP08.01-073.

EVOKE-02: Phase II Trial of First-Line Sacituzumab Govitecan and Pembrolizumab with or without Platinum Chemotherapy for Metastatic NSCLC without Actionable Genomic Alterations



Garon EB et al. ASCO 2022;Abstract TPS9146.

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Lung Cancer Case Studies

John V. Heymach MD, PhD

Chairman and Professor
Thoracic/Head and Neck Medical Oncology
MD Anderson Cancer Center

Oct. 20, 2022

Case Presentation: Dr John Heymach

- 55 year old Asian woman with 10 pack year history of smoking (quit 20y ago), presented with malignant pleural effusion and persistent pulmonary infections.
- Evaluation revealed lung adenocarcinoma, with multiple bone metastases and two small brain metastases
- Profiling revealed KRAS G12D as well as STK11 and KEAP1 mutations

Case Presentation: Dr John Heymach (cont)

- She was initially treated at an outside institution with chemo+pembrolizumab and had disease progression at cycle 3.
- She was enrolled in the Hudson study and received the ATR inhibitor ceralasertib plus durvalumab.
- Minor response lasting more than 6 months.
- Eventually developed PD and was treated with subsequent lines of chemo+bev+atezo (Impower150) and docetaxel
- Died approximately 14 months after diagnosis.

Case Presentation: Dr John Heymach

- 58 year old small maritime business owner and light former smoker presenting with metastatic lung adenocarcinoma
- Molecular profiling shows KRAS G12V and KEAP1 mutation
- Options discussed with patient include chemo/pembro and a clinical study with Ipi/nivo +/- local consolidation therapy with RT (Lonestar)

Case Presentation: Dr John Heymach (cont)

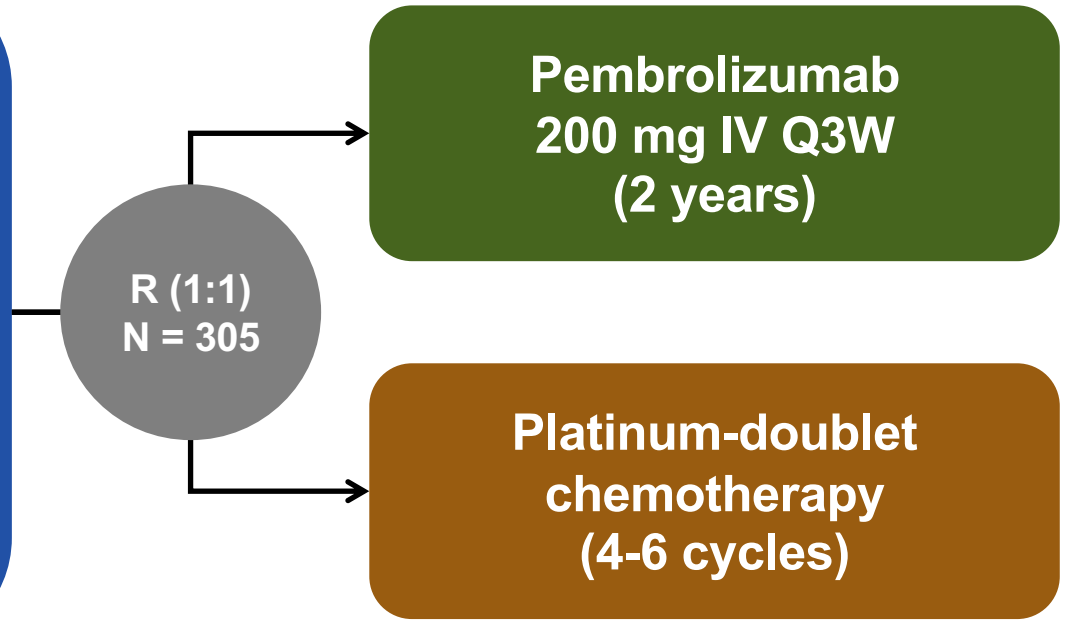
- Enrolled in Lonestar
- After 3 cycles experienced tumor shrinkage as well as mild shortness of breath, rise in CK
- Cardiac biopsy confirmed Gr2 myocarditis and gr1 skin toxicity
- Patient was treated with steroids, recovered, and was restarted on treatment
- Patient remains on treatment now 2.5 years with no signs of active disease.

Appendix

KEYNOTE-024: Pembrolizumab

Key Eligibility Criteria

- Untreated stage IV NSCLC
- PD-L1 TPS ≥50%
- ECOG PS 0-1
- No activating *EGFR* mutation or *ALK* translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy



Key Endpoints

- **Primary:** PFS (RECIST v1.1 per blinded, independent central review)
- **Secondary:** OS, ORR, safety
- **Exploratory:** DOR

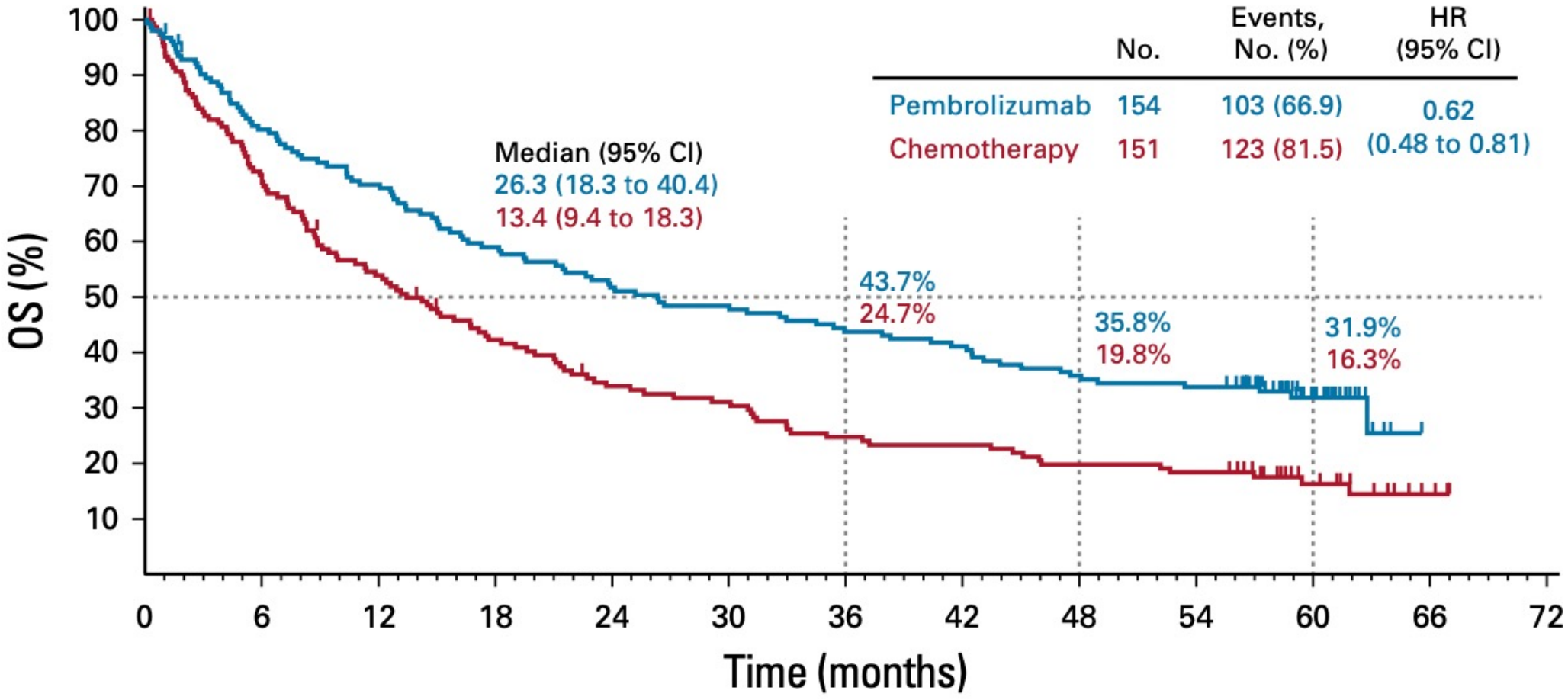
Reck, NEJM 2016

KEYNOTE-024: Pembrolizumab

- Initial outcomes strongly favored pembrolizumab
  - After median follow up of 11.2 months
  - RR favors pembrolizumab (45% vs 28%)
    - Median time to response 2.2m in both arms
  - PFS favors pembrolizumab (10.3m vs 6.0m, HR 0.50)
  - OS favors pembrolizumab (HR 0.60)
- Longer follow up (5 years)
  - PFS favors pembrolizumab (7.7m vs 5.5m, HR 0.50)
  - OS favors pembrolizumab (26.3m vs 13.4m, HR 0.62)

Reck, NEJM 2016; Reck, JCO 2021

KEYNOTE-024: Pembrolizumab



Reck, JCO 2021

KEYNOTE-042: Pembrolizumab

Key Eligibility Criteria

- Untreated stage IV NSCLC
- PD-L1 TPS ≥1%
- ECOG PS 0-1
- No activating *EGFR* mutation or *ALK* translocation
- No untreated brain metastases
- No history of pneumonitis requiring systemic corticosteroids

R (1:1)
N = 1274

Pembrolizumab 200 mg IV Q3W (2 years)

Platinum-doublet chemotherapy (4-6 cycles)

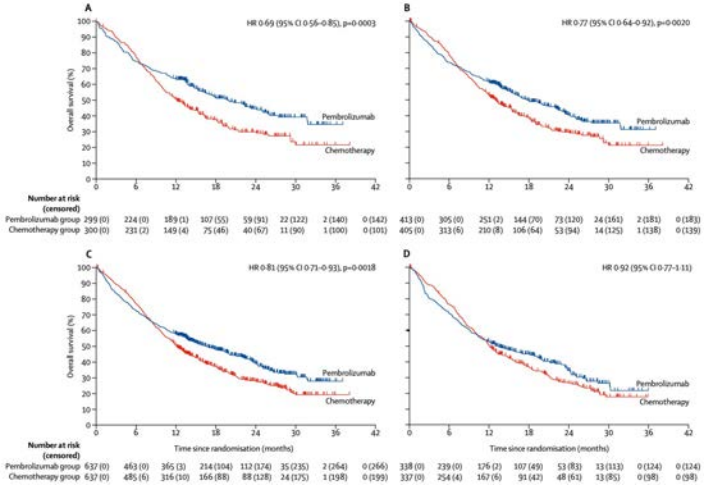
Key Endpoints

- **Primary:** OS (in PD-L1 TPS ≥50%, ≥20%, and ≥1%
- **Secondary:** PFS and ORR in TPS ≥50%, ≥20%, and ≥1%; safety
- **Exploratory:** TPS 1-49%

Lopes, ASCO 2018

KEYNOTE-042: Pembrolizumab

- Pembrolizumab superior to chemotherapy overall
  - PD-L1 ≥ 50%
    - OS 20.0m vs 12.2m, HR 0.69
  - PD-L1 ≥ 20%
    - OS 17.7m vs 13.0m, HR 0.77
  - PD-L1 ≥ 1%
    - OS 16.7m vs 12.1m, HR 0.81
  - Primary endpoint met leading to FDA approval for ≥ 1%
  - Exploratory subset of PD-L1 low (1-49%)
    - OS 13.4m vs 12.1m, HR 0.92



Mok, Lancet Oncol 2019

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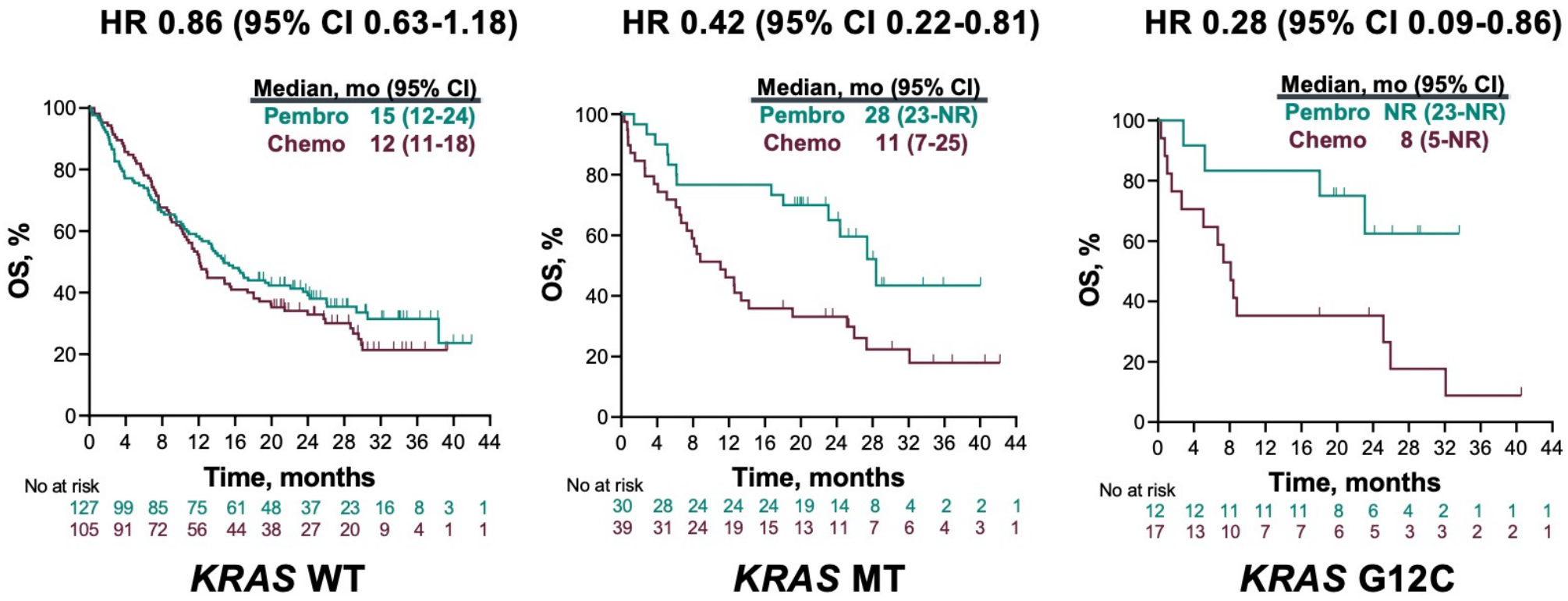
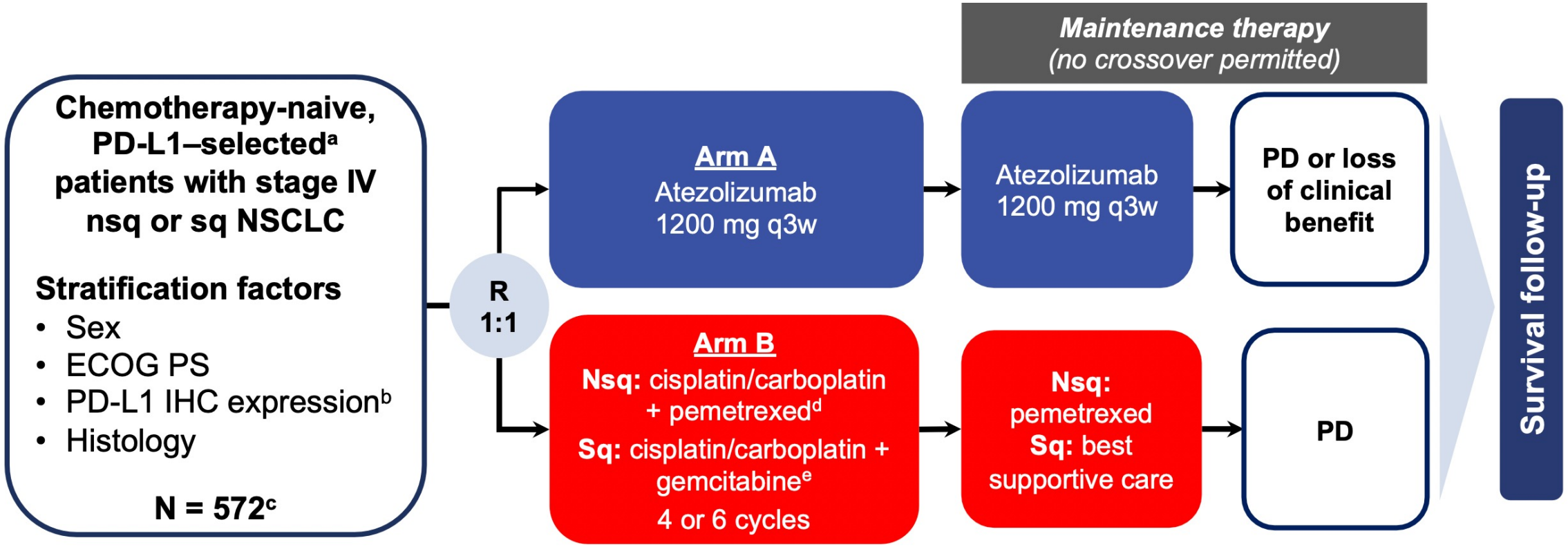
KEYNOTE-042: Pembrolizumab

- Outcomes in KRAS mutant NSCLC



Herbst, ESMO IO 2019

IMpower110: Atezolizumab



Spigel, ESMO 2019

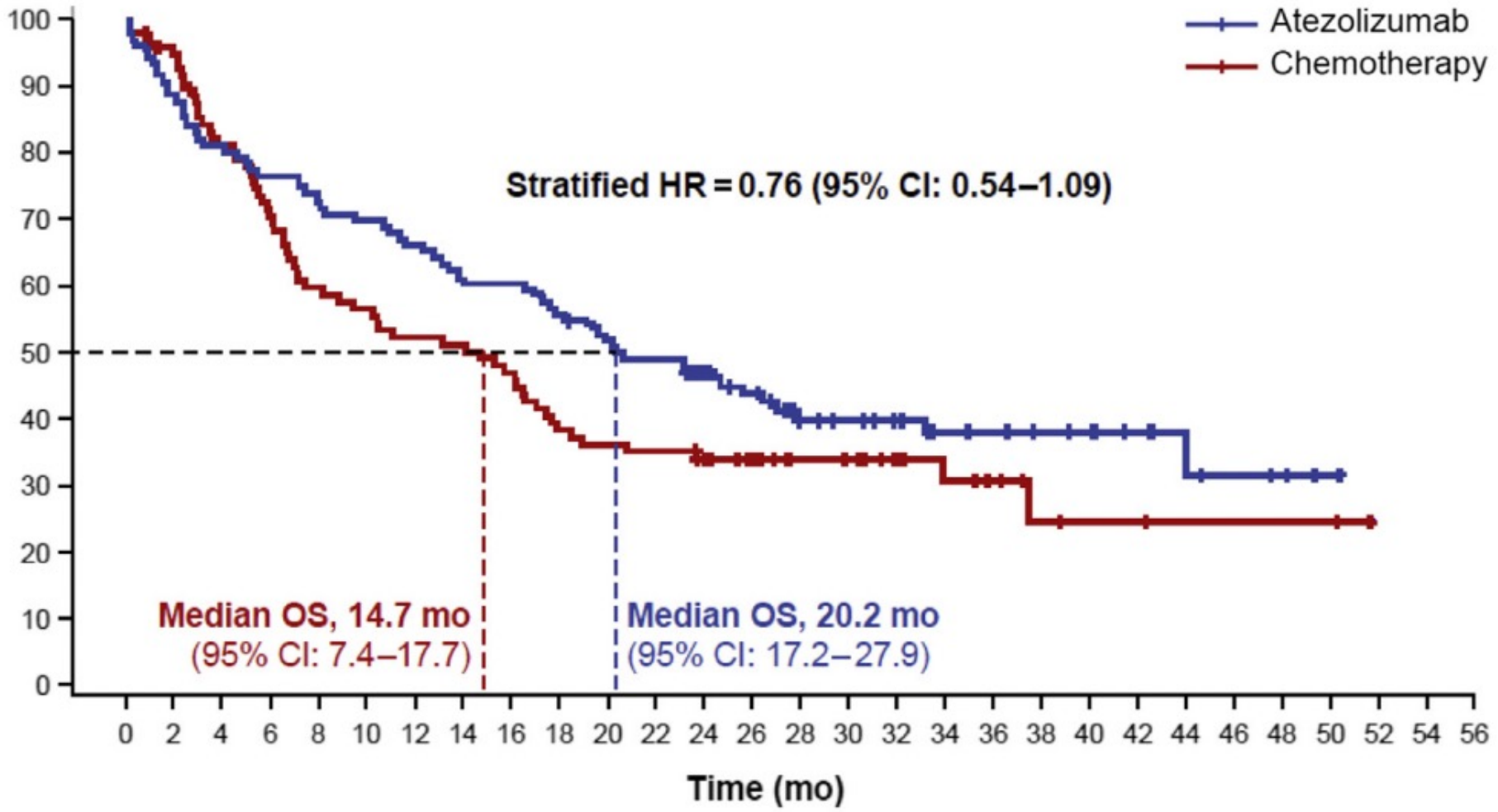
Georgetown | Lombardi

IMpower110: Atezolizumab

- Outcomes in PD-L1 high NSCLC
  - OS favors atezolizumab (20.2m vs 13.1m, HR 0.59)
  - PFS favors atezolizumab (8.1m vs 5.0m, HR 0.63)
- Outcomes in PD-L1 positive NSCLC
  - No OS difference (17.5m vs 14.1m, HR 0.83, ns)
- With longer follow up (median 31m)
  - OS favors atezolizumab (20.2m vs 14.7m, HR 0.76)

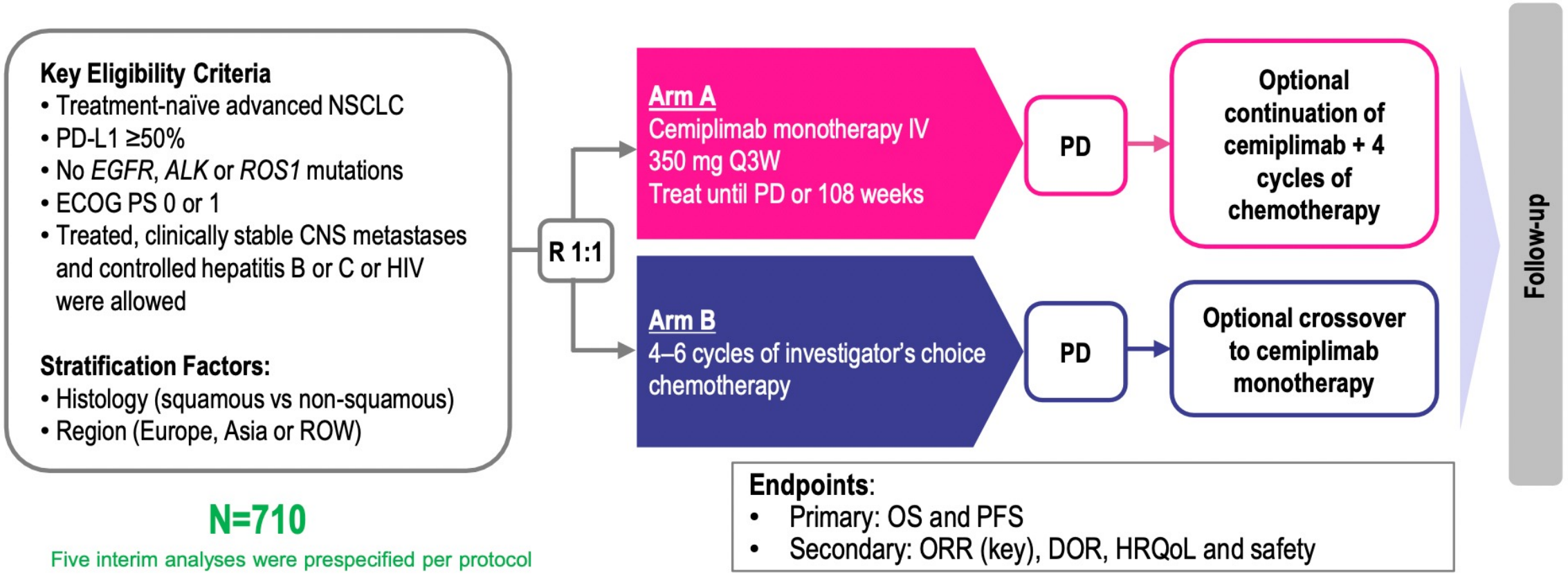
Herbst, NEJM 2020; Jassem, JTO 2021

IMpower110: Atezolizumab



Herbst, NEJM 2020

EMPOWER-Lung 1: Cemiplimab



N=710

Five interim analyses were prespecified per protocol

Endpoints:
- Primary: OS and PFS
- Secondary: ORR (key), DOR, HRQoL and safety

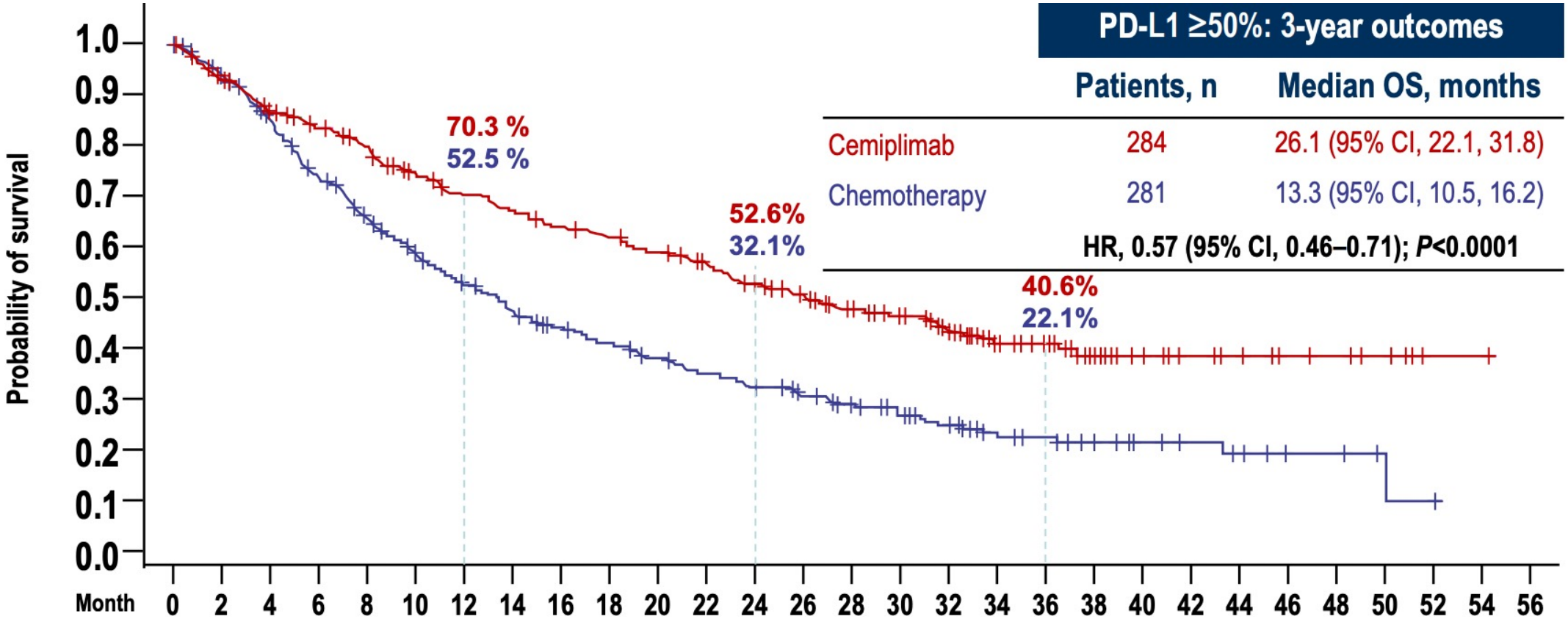
Sezer, ESMO 2020

EMPOWER-Lung 1: Cemiplimab

- Initial outcomes in PD-L1 ≥50% NSCLC
  - OS favors cemiplimab (NR vs 14.2m, HR 0.57)
  - PFS favors cemiplimab (8.2m vs 5.7m, HR 0.54)
- With longer follow up (median 3y) in PD-L1 ≥50%
  - OS favors cemiplimab (26.1m vs 13.3m, HR 0.57)
  - PFS favors cemiplimab (8.1m vs 5.3m, HR 0.51)
  - RR favors cemiplimab (46.5% vs 21.0%)
  - DOR favors cemiplimab (23.6m vs 5.9m)

Ozguroglu, NACLC 2022

EMPOWER-Lung 1: Cemiplimab



PD-L1 ≥50%: 3-year outcomes

	Patients, n	Median OS, months
Cemiplimab	284	26.1 (95% CI, 22.1, 31.8)
Chemotherapy	281	13.3 (95% CI, 10.5, 16.2)

HR, 0.57 (95% CI, 0.46–0.71); *P*<0.0001

Ozguroglu, NACLC 2022

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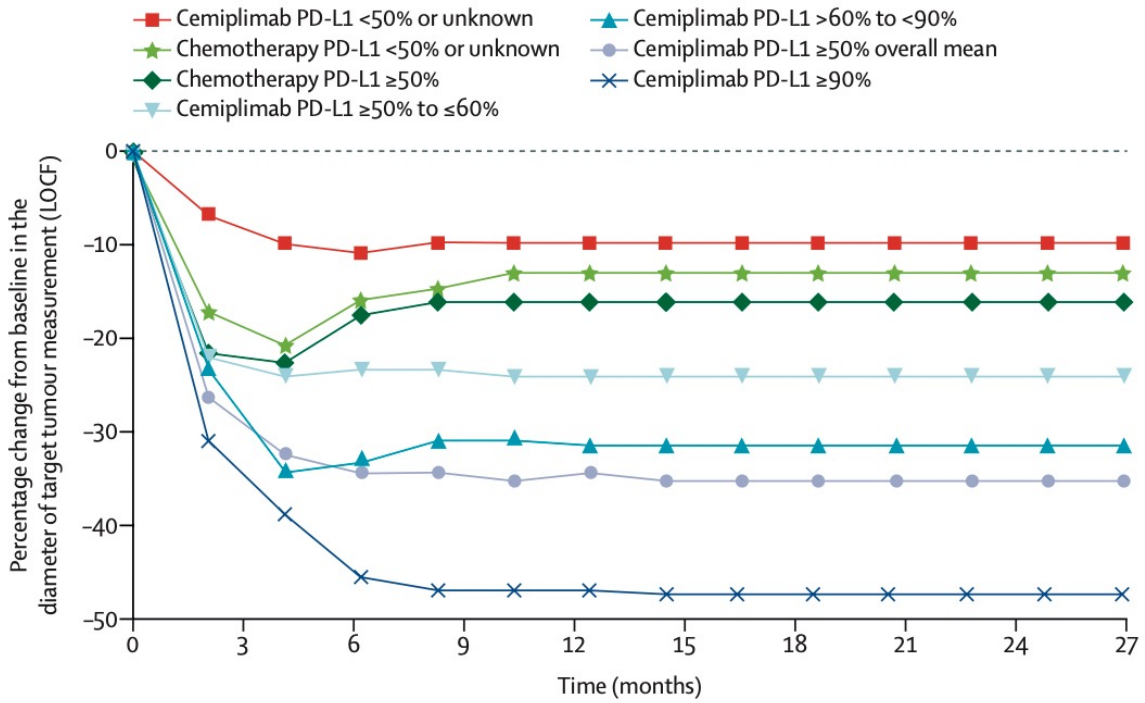
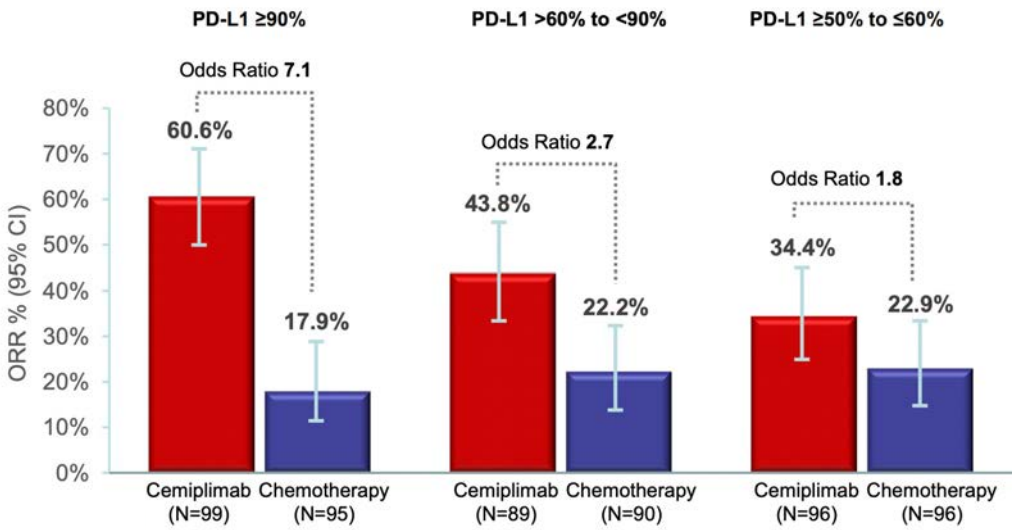
EMPOWER-Lung 1: Cemiplimab

- PD-L1 is a continuous variable





Sezer, Lancet 2021; Ozguroglu, NACLC 2022

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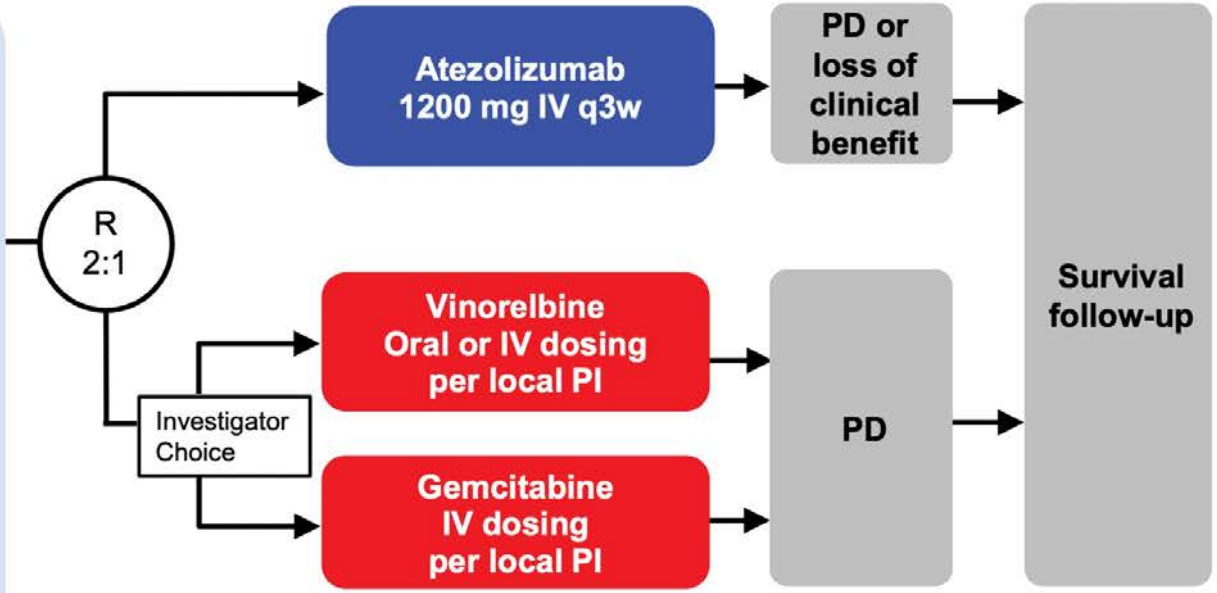
IPSOS: Atezolizumab

- Front-line atezolizumab vs chemotherapy in platinum ineligible patients (EGFR/ALK wild type, any PD-L1)

Treatment-naive stage IIIB[a]/IV (AJCC 7th edition) NSCLC

- Squamous or non-squamous histology
- Platinum ineligible because of:
  - ECOG PS 2 or 3
  - ECOG PS 0 or 1 permitted if ≥70 years of age with substantial comorbidities or other contraindictions to platinum chemotherapy
- *EGFR*+ (L858R or exon 19 deletion) or *ALK*+ excluded
- Patients with treated asymptomatic brain metastases permitted

n=453

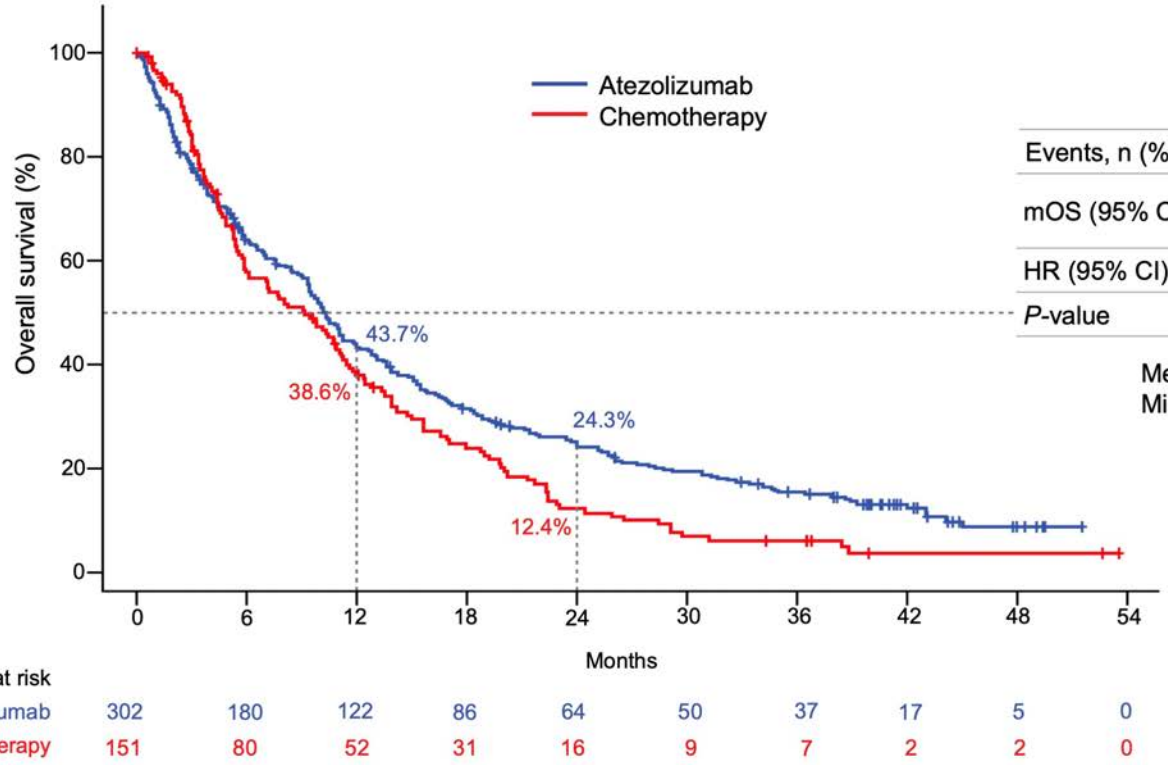


Lee, ESMO 2022

Georgetown | Lombardi

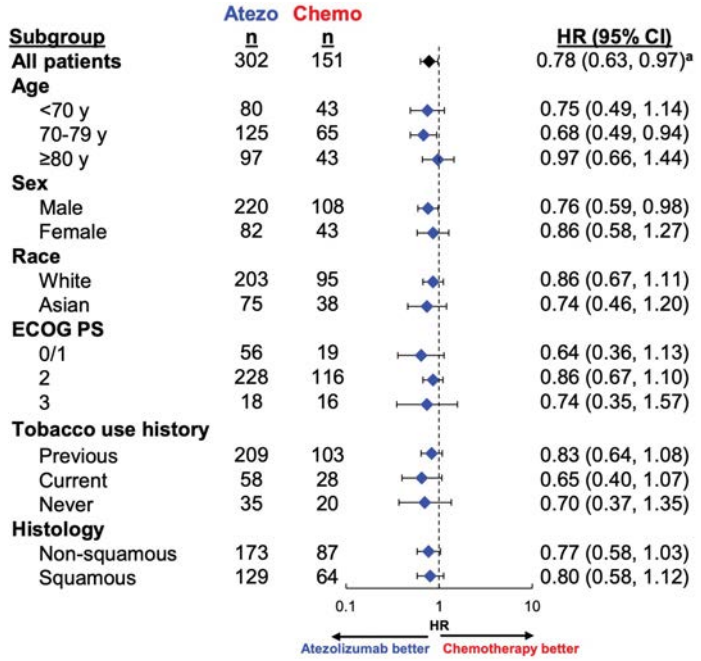
IPSOS: Atezolizumab

- Atezolizumab superior OS (HR 0.78)



	Atezo (n=302)	Chemo (n=151)
Events, n (%)	249 (82.5)	130 (86.1)
mOS (95% CI), mo	10.3 (9.4, 11.9)	9.2 (5.9, 11.2)
HR (95% CI)[a]	**0.78 (0.63, 0.97)**	
P-value	0.028[b]	

Median follow-up: 41.0 months
Minimum follow-up: 32.0 months



Lee, ESMO 2022

Georgetown | Lombardi

KEYNOTE-189

Key Eligibility Criteria

- Untreated stage IV nonsquamous NSCLC
- No sensitizing *EGFR* or *ALK* alteration
- ECOG PS 0-1
- Provision of a sample of PD-L1 assessment
- No symptomatic brain metastases
- No pneumonitis requiring systemic steroids

R (2:1)

n = 410

Pembrolizumab 200 mg + pemetrexed 500 mg/m² + carboplatin AUC 5, or cisplatin 75 mg/m² Q3W for 4 cycles

Pembrolizumab 200 mg Q3W for up to 31 cycles + pemetrexed 500 mg/m² Q3W

n = 206

Placebo (normal saline) + pemetrexed 500 mg/m² + carboplatin AUC 5, or cisplatin 75 mg/m² Q3W for 4 cycles

Placebo (normal saline) for up to 31 cycles + pemetrexed 500 mg/m² Q3W

Stratification Factors

- PD-L1 expression (TPS <1% vs ≥1%)
- Platinum (cisplatin vs carboplatin)
- Smoking history (never vs former/current)

- **Primary endpoints:** OS and PFS

Gandhi, NEJM 2018

Georgetown | Lombardi

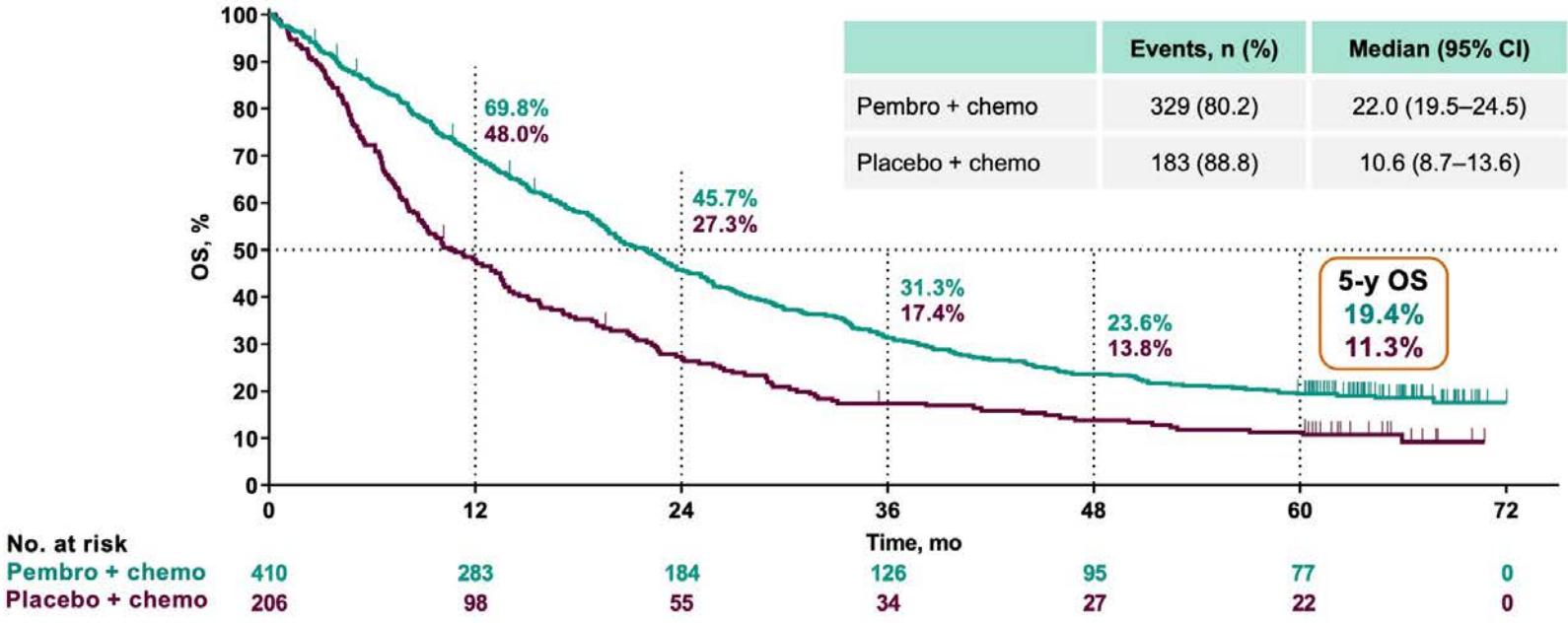
KEYNOTE-189

- Addition of pembrolizumab significantly improved response, PFS, overall survival
  - Response rate 48% vs. 19%
    - In PD-L1 ≥ 50%, response rate 61% vs. 23%
    - In PD-L1 1-49%, response rate 48% vs. 21%
    - In PD-L1 < 1%, response rate 32% vs. 14%
  - Survival HR 0.49
    - In PD-L1 ≥ 50%, OS HR 0.42
    - In PD-L1 1-49%, OS HR 0.55
    - In PD-L1 < 1%, OS HR 0.59

Gandhi, NEJM 2018

KEYNOTE-189

- With longer follow up (5 years), benefit persists



	Events, n (%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	329 (80.2)	22.0 (19.5–24.5)	0.60 (0.50–0.72)
Placebo + chemo	183 (88.8)	10.6 (8.7–13.6)	

	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 132)	Placebo + chemo (n = 70)	Pembro + chemo (n = 128)	Placebo + chemo (n = 58)	Pembro + chemo (n = 127)	Placebo + chemo (n = 63)
OS HR (95% CI)	0.68 (0.49–0.96)		0.65 (0.46–0.90)		0.55 (0.39–0.76)	
5-y OS rate,[a] %	29.6	21.4	19.8	7.7	9.6	5.3

Garassino, ESMO 2022

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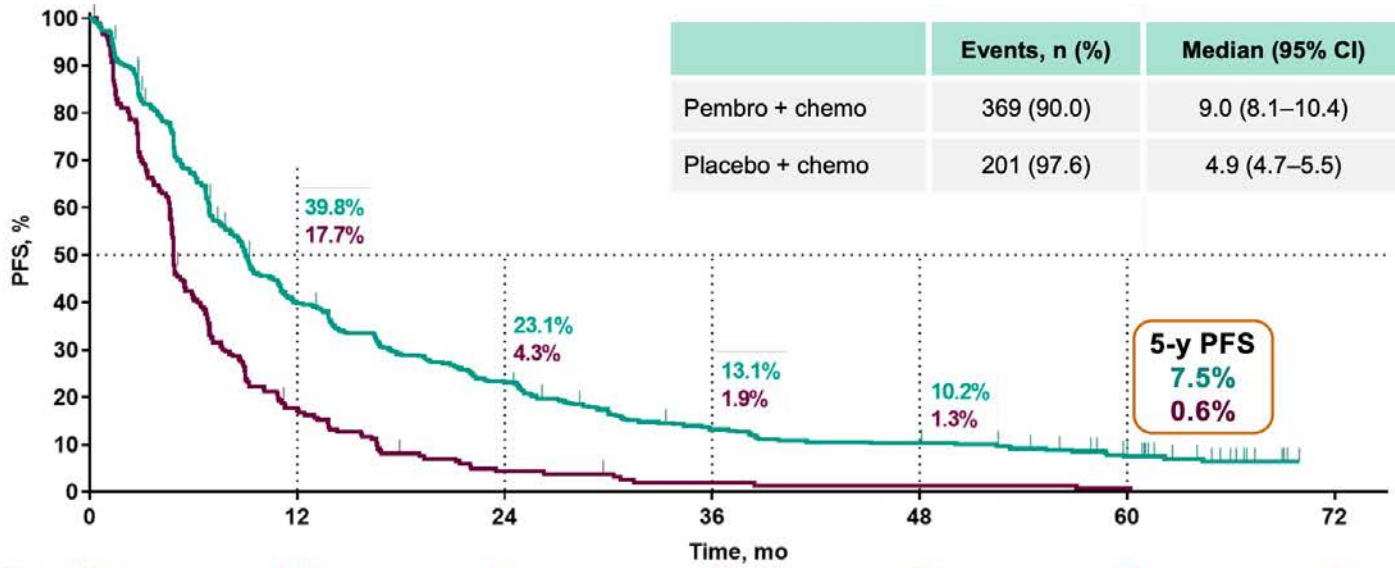
KEYNOTE-189

- With longer follow up (5 years), benefit persists



	Events, n (%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	369 (90.0)	9.0 (8.1–10.4)	0.50 (0.42–0.60)
Placebo + chemo	201 (97.6)	4.9 (4.7–5.5)	

No. at risk							
Pembro + chemo	410	158	91	49	37	21	0
Placebo + chemo	206	35	8	3	2	1	0

	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 132)	Placebo + chemo (n = 70)	Pembro + chemo (n = 128)	Placebo + chemo (n = 58)	Pembro + chemo (n = 127)	Placebo + chemo (n = 63)
PFS HR (95% CI)	0.35 (0.25–0.49)		0.57 (0.41–0.80)		0.67 (0.49–0.92)	
5-y PFS rate,[b] %	12.8	0	6.5	1.9	2.4	0

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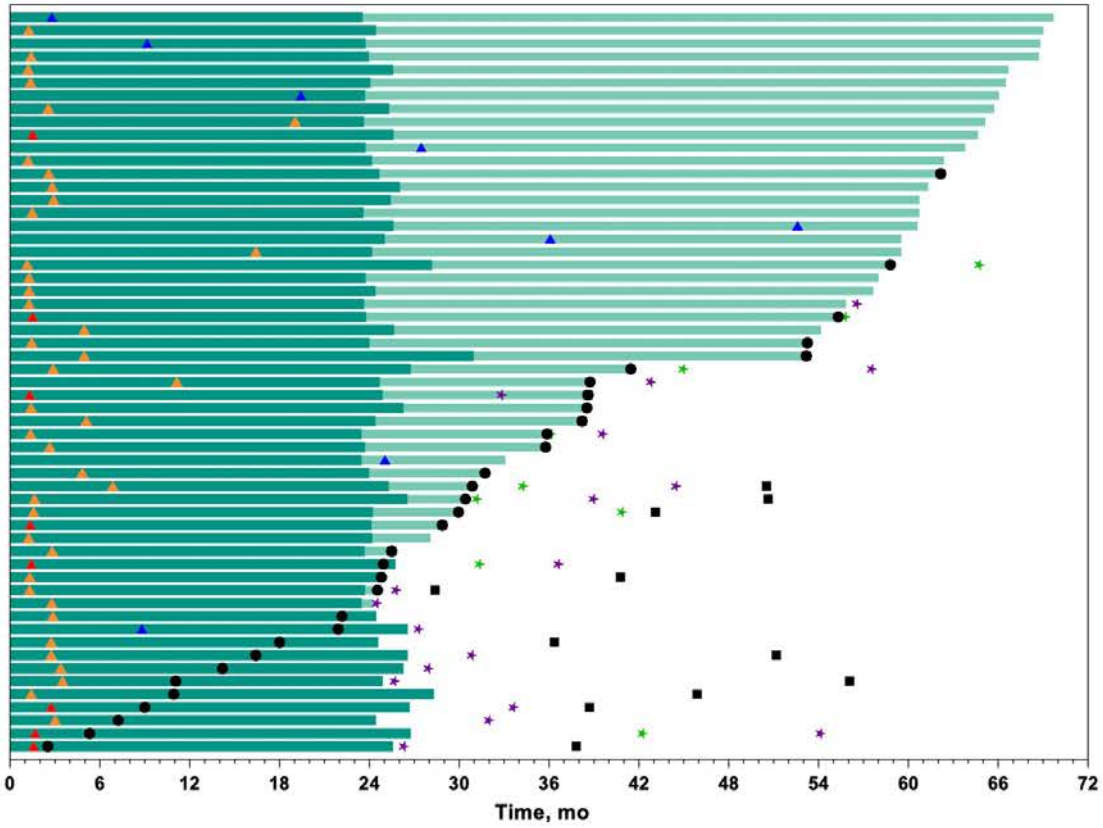
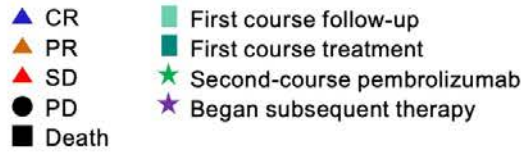
KEYNOTE-189

- Outcomes in patients who completed 2y of therapy



	n = 57
ORR (95% CI),[a] %	86.0 (74.2–93.7)
Best overall response, n (%)	
CR	8 (14.0)
PR	41 (71.9)
Median DOR (range),[b] mo	57.7 (4.2 to 68.3+)
3-y OS rate after completing 35 cycles[c]	71.9%
Alive without PD or subsequent therapy, n (%)	23 (40.4)



Garassino, ESMO 2022

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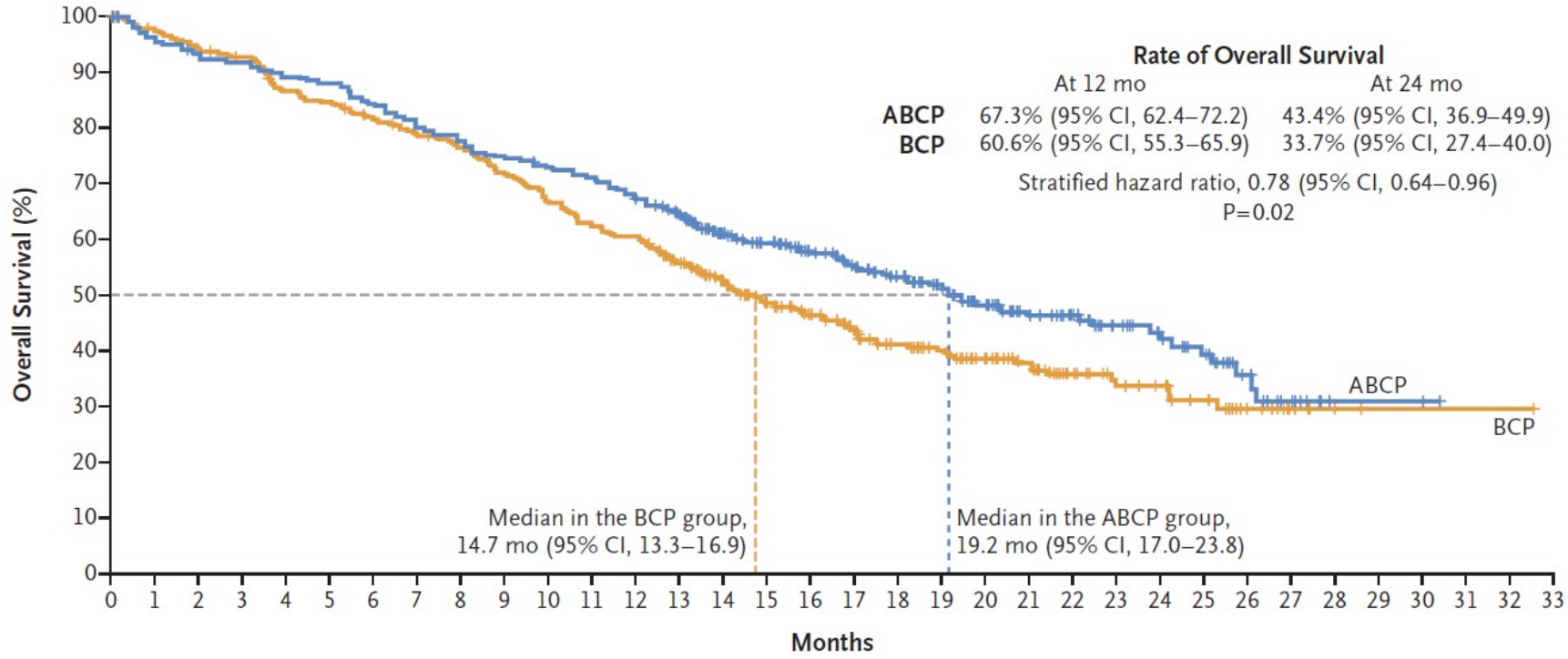
IMpower-150

- Carbo/pac/bev vs Carbo/pac/bev/atezo
  - Addition of atezolizumab improved outcomes
    - PFS 8.3 vs. 6.8 months (HR 0.62; 0.52-.074)
    - OS 19.2 vs. 14.7 months (HR 0.78; 0.64-0.96)

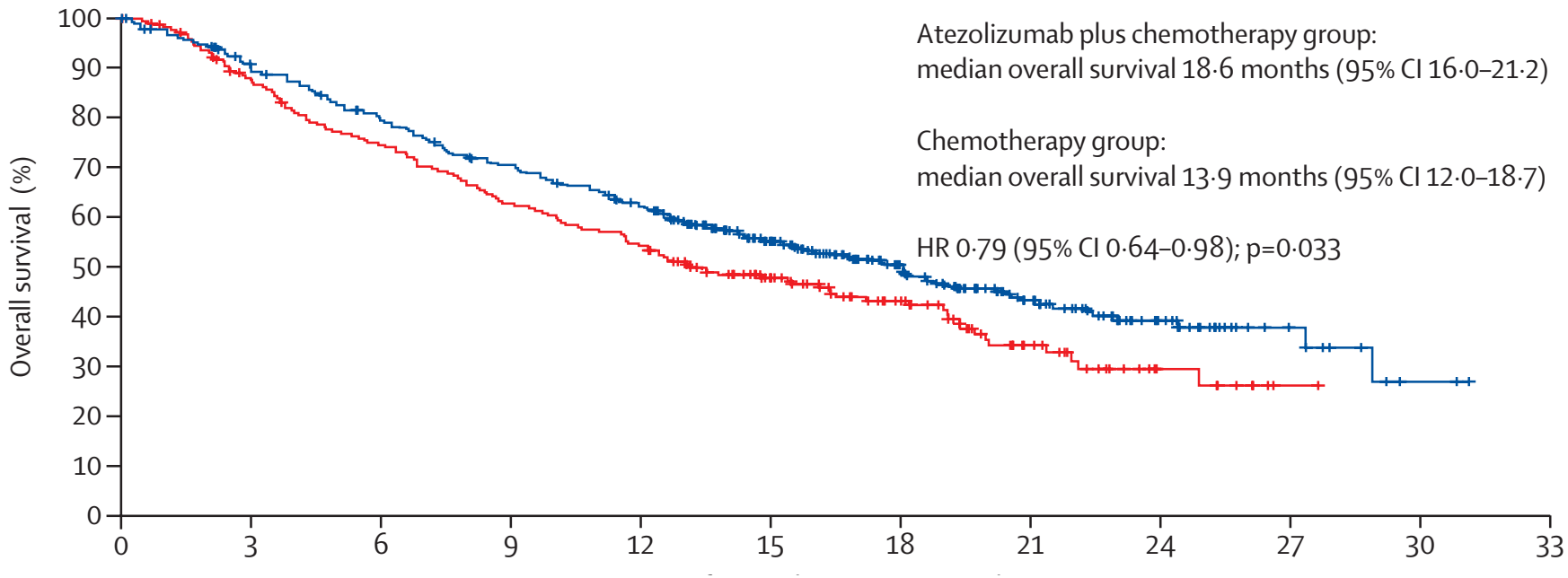


Socinski, NEJM 2018

Georgetown | Lombardi

IMpower-130

- Carbo/nab-pac +/- atezolizumab in non-squamous
  - Addition of atezolizumab improved outcomes
    - PFS 7.0 vs 5.5 months (HR 0.64)
    - OS 18.6 vs 13.9 months (HR 0.79)



West, Lancet Oncol 2019

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KEYNOTE-407

Key Eligibility Criteria

- Untreated stage IV squamous NSCLC
- ECOG PS 0-1
- Provision of a sample of PD-L1 assessment
- No symptomatic brain metastases
- No pneumonitis requiring systemic steroids

R (1:1)

n = 278

Pembrolizumab 200 mg + carboplatin AUC 5 + paclitaxel 200 mg/m² d1 or nab-paclitaxel 100 mg/m² d1, 8, 15 Q3W for 4 cycles

Pembrolizumab 200 mg Q3W for up to 31 cycles

n = 281

Placebo (normal saline) + carboplatin AUC 5 + paclitaxel 200 mg/m² d1 or nab-paclitaxel 100 mg/m² d1, 8, 15 Q3W for 4 cycles

Placebo (normal saline) for up to 31 cycles

- **Primary endpoints:** OS and PFS

Stratification Factors

- PD-L1 expression (TPS <1% vs ≥1%)
- Taxane (paclitaxel vs nab-paclitaxel)
- Geographic region (East Asia vs rest of world)

Paz-Ares, NEJM 2018

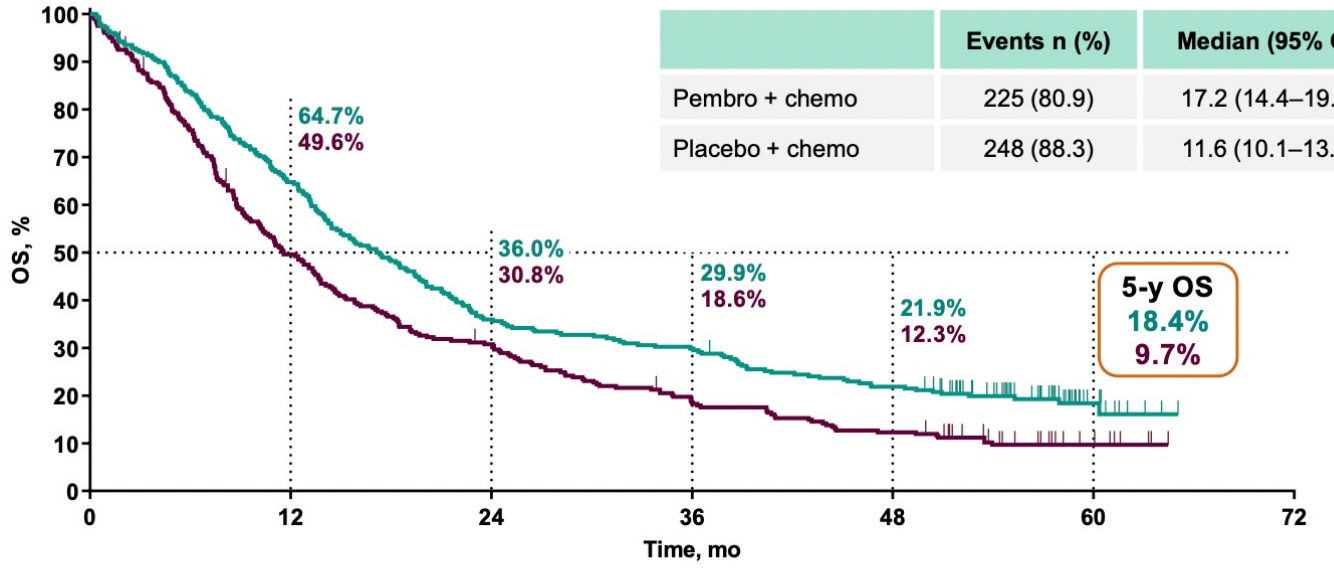
KEYNOTE-407

- Addition of pembrolizumab to chemotherapy significantly improved response, PFS, overall survival
  - Response rate 58% vs. 38%
    - In PD-L1 ≥ 50%, response rate 60% vs. 33%
    - In PD-L1 1-49%, response rate 50% vs. 41%
    - In PD-L1 < 1%, response rate 63% vs. 40%
  - Survival HR 0.64
    - In PD-L1 ≥ 50%, OS HR 0.64
    - In PD-L1 1-49%, OS HR 0.57
    - In PD-L1 < 1%, OS HR 0.61

Paz-Ares, NEJM 2018

KEYNOTE-407

- With longer follow up (5 years), benefit persists



	Events n (%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	225 (80.9)	17.2 (14.4–19.7)	0.71 (0.59–0.85)
Placebo + chemo	248 (88.3)	11.6 (10.1–13.7)	

No. at risk							
Pembro + chemo	278	180	100	83	60	10	0
Placebo + chemo	281	137	84	50	33	7	0

	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 73)	Placebo + chemo (n = 73)	Pembro + chemo (n = 103)	Placebo + chemo (n = 104)	Pembro + chemo (n = 95)	Placebo + chemo (n = 99)
OS HR (95% CI)	0.68 (0.47–0.97)		0.61 (0.45–0.83)		0.83 (0.61–1.13)	
5-y OS rate,[a] %	23.3	8.3	20.6	7.6	10.7	13.1

Novello, ESMO 2022

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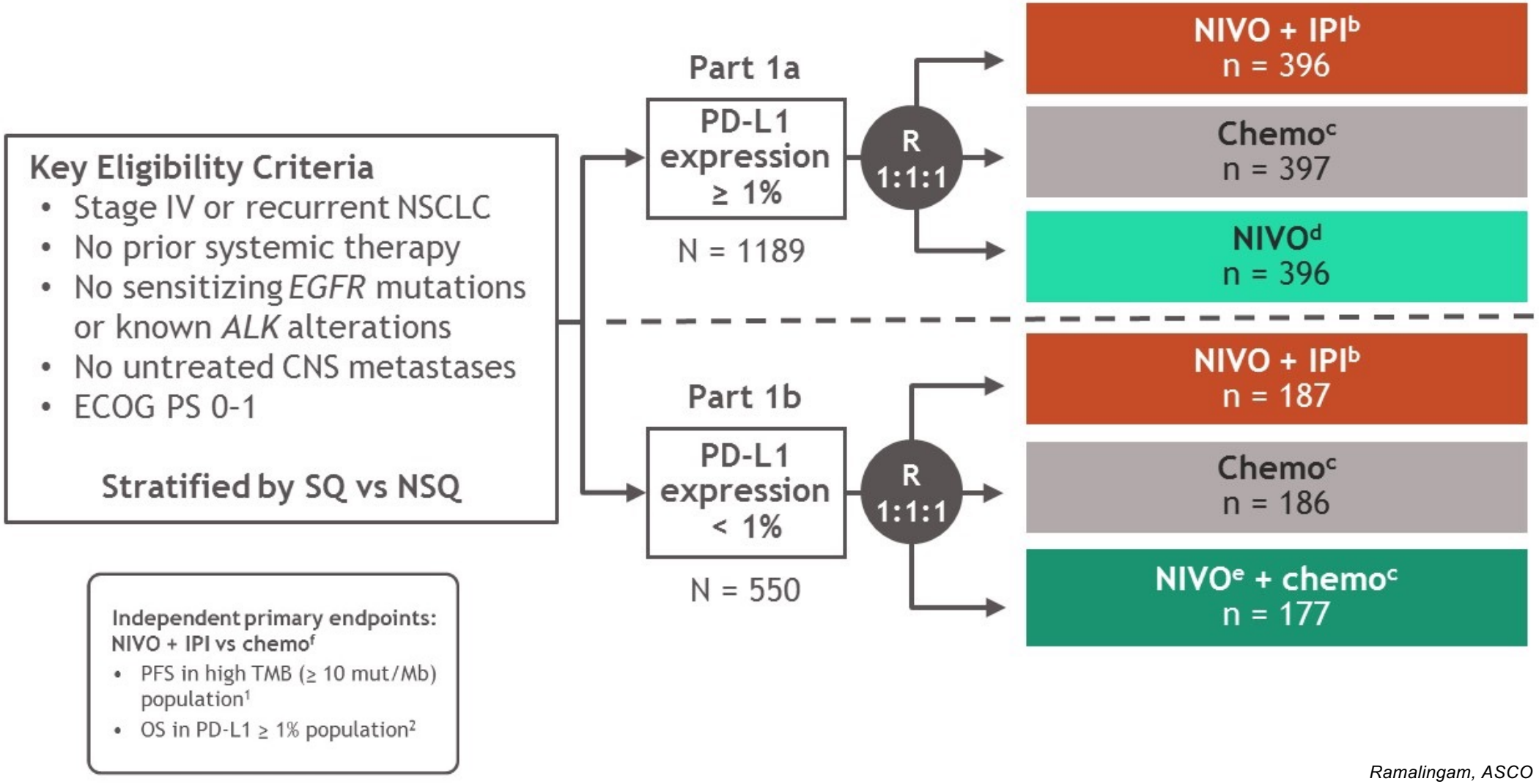
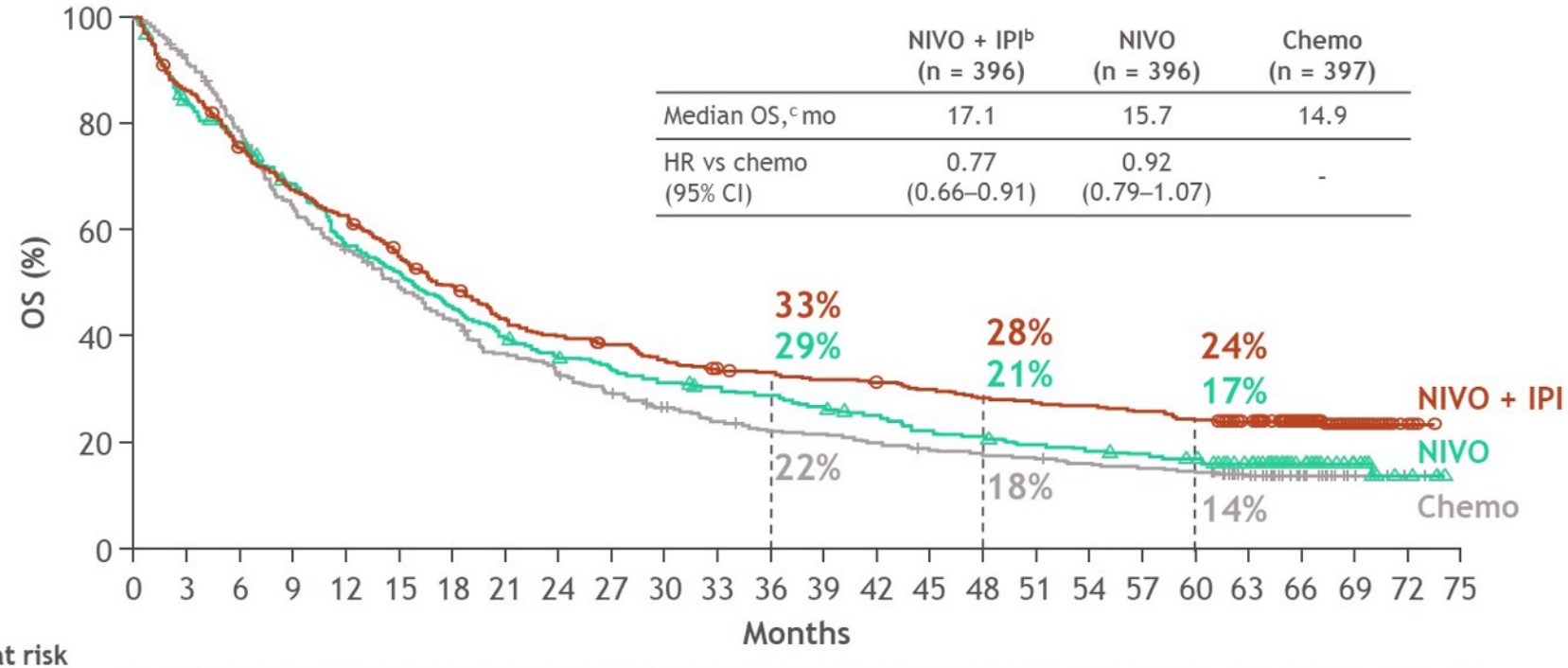
CheckMate 227: Nivo/Ipi



Ramalingam, ASCO 2020

CheckMate 227: Nivo/Ipi

- Nivolumab + ipilimumab superior to chemo in PD-L1+



	NIVO + IPI[b] (n = 396)	NIVO (n = 396)	Chemo (n = 397)
Median OS,[c] mo	17.1	15.7	14.9
HR vs chemo (95% CI)	0.77 (0.66–0.91)	0.92 (0.79–1.07)	-

No. at risk																										
NIVO + IPI	396	341	296	265	246	214	192	166	154	146	134	126	123	118	115	110	104	101	99	95	89	74	47	20	3	0
NIVO	396	330	299	265	220	201	176	153	139	129	119	112	108	98	91	80	75	70	66	63	59	46	27	12	3	0
Chemo	397	358	306	250	218	190	166	141	126	112	98	87	80	78	72	66	63	60	56	53	50	37	18	5	2	0

Brahmer, ASCO 2022

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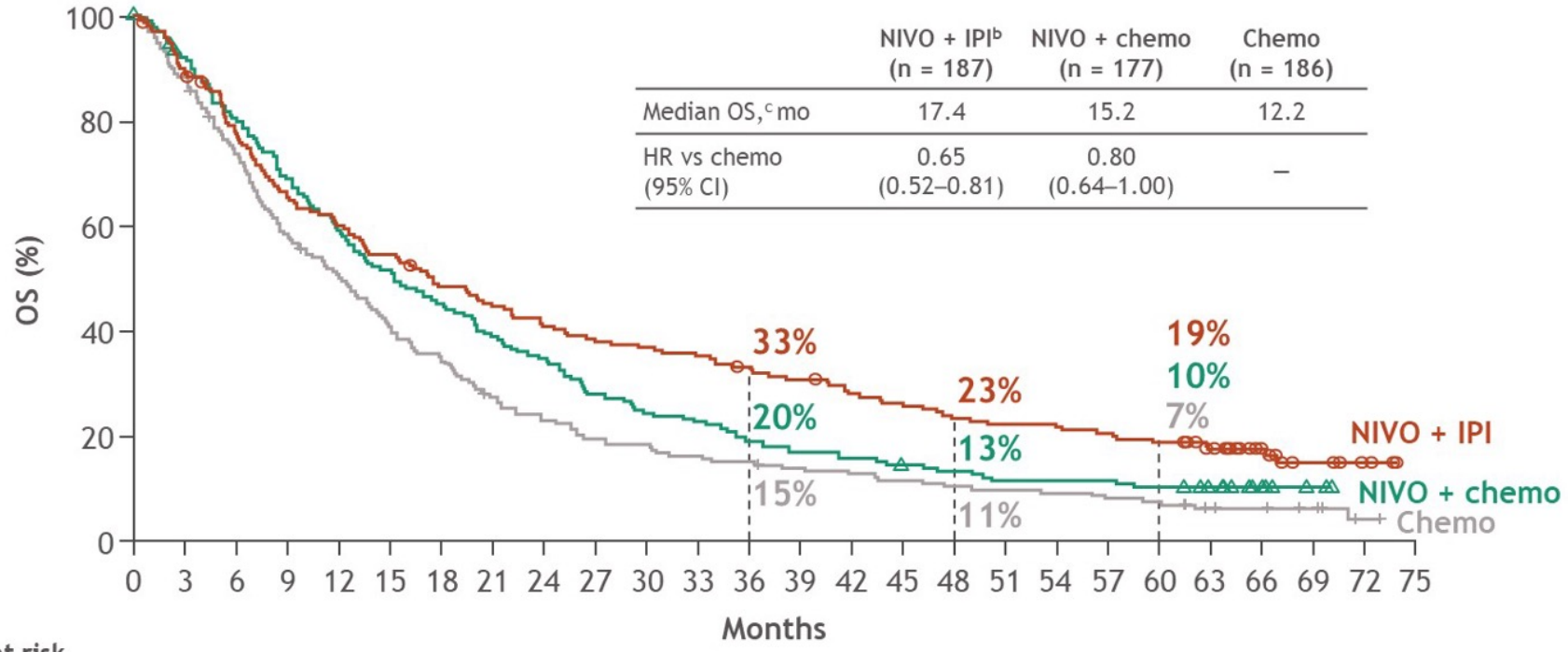
CheckMate 227: Nivo/Ipi

- Nivolumab + ipilimumab superior to chemo in PD-L1-



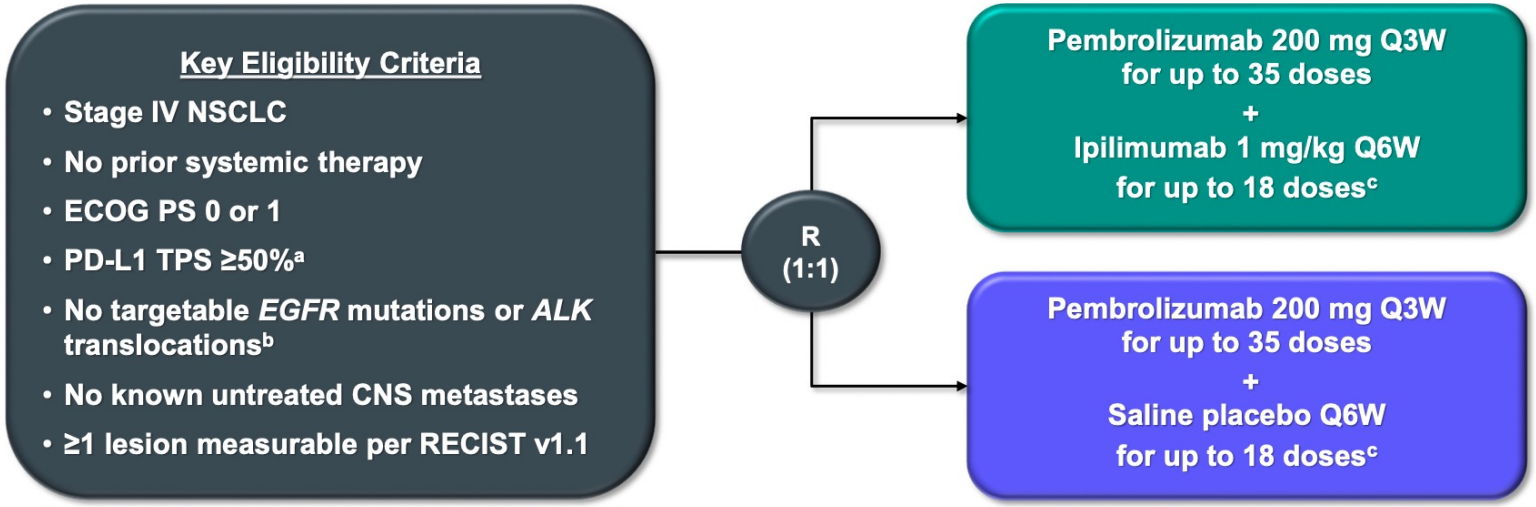
	NIVO + IPI[b] (n = 187)	NIVO + chemo (n = 177)	Chemo (n = 186)
Median OS,[c] mo	17.4	15.2	12.2
HR vs chemo (95% CI)	0.65 (0.52–0.81)	0.80 (0.64–1.00)	–

No. at risk																										
NIVO + IPI	187	165	142	120	110	100	88	81	74	69	67	64	59	55	49	45	41	39	38	36	33	27	15	8	3	0
NIVO + chemo	177	159	139	119	102	88	78	67	60	48	42	39	34	29	27	24	22	19	19	19	17	14	7	2	0	0
Chemo	186	164	135	107	92	74	62	49	41	35	33	29	27	24	22	20	18	17	16	14	12	8	7	5	1	0

Brahmer, ASCO 2022

KEYNOTE-598

- Randomized phase III study of 1L pembrolizumab with ipilimumab/placebo for NSCLC with PD-L1 ≥ 50%



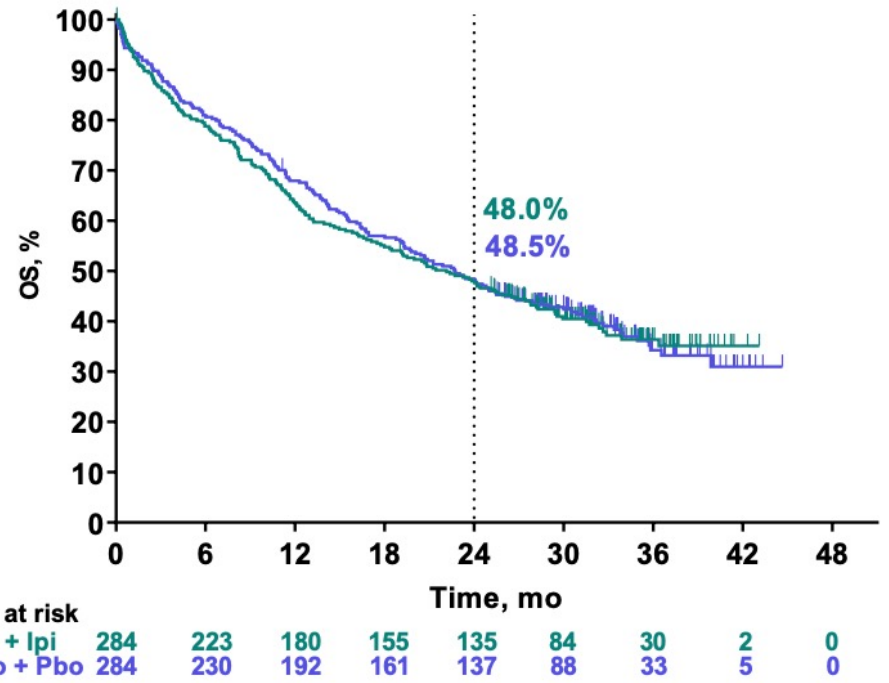
Endpoints

- **Dual primary:** OS and PFS per RECIST version 1.1 by BICR
- **Key secondary:** ORR and DOR per RECIST version 1.1 by BICR and safety

Boyer, JCO 2020

KEYNOTE-598

- No difference in OS
- No difference in PFS
- No difference in RR
- More G3-5 AEs with ipilimumab
  - 35.1% vs 20.3%
  - Discontinuation of all drugs 19.1% vs 7.8%
- Stopped for futility



	Events, n (%)	Median (95% CI)	OS HR (95% CI)
Pembro + Ipi	173 (60.9)	22.1 (17.1–27.4)	1.05 (0.85–1.29)
Pembro + Pbo	176 (62.0)	22.7 (19.0–26.8)	

Rodriguez-Abreu, ELCC 2022

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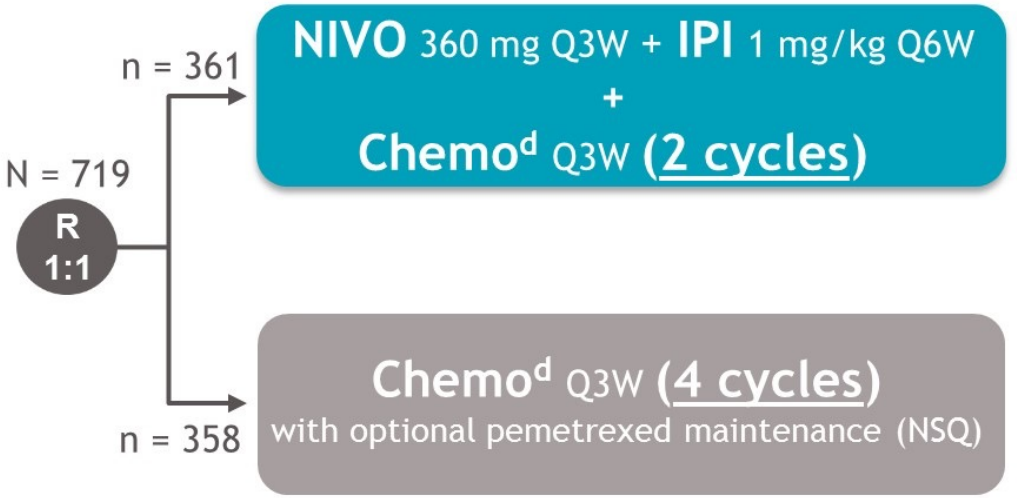
CheckMate 9LA

Key Eligibility Criteria

- Stage IV or recurrent NSCLC
- No prior systemic therapy
- No sensitizing *EGFR* mutations or known *ALK* alterations
- ECOG PS 0-1

Stratified by PD-L1[b] (< 1%[c] vs ≥ 1%), sex, and histology (SQ vs NSQ)



Until disease progression, unacceptable toxicity, *or* for 2 years for immunotherapy

Primary endpoint
- OS

Secondary endpoints
- PFS by BICR[e]
- ORR by BICR[e]
- Efficacy by tumor PD-L1 expression

Reck, ASCO 2020

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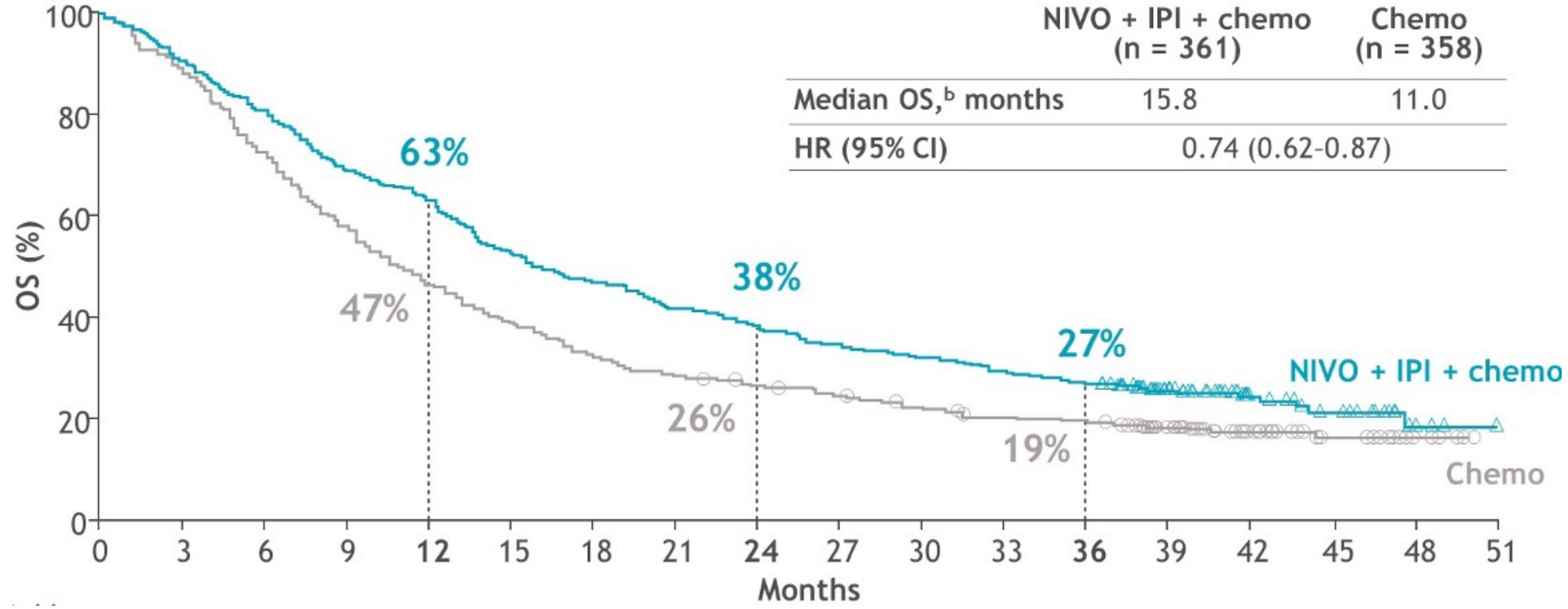
CheckMate 9LA

- Primary endpoint: OS



	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median OS,[b] months	15.8	11.0
HR (95% CI)	0.74 (0.62-0.87)	

Paz Ares, ASCO 2022

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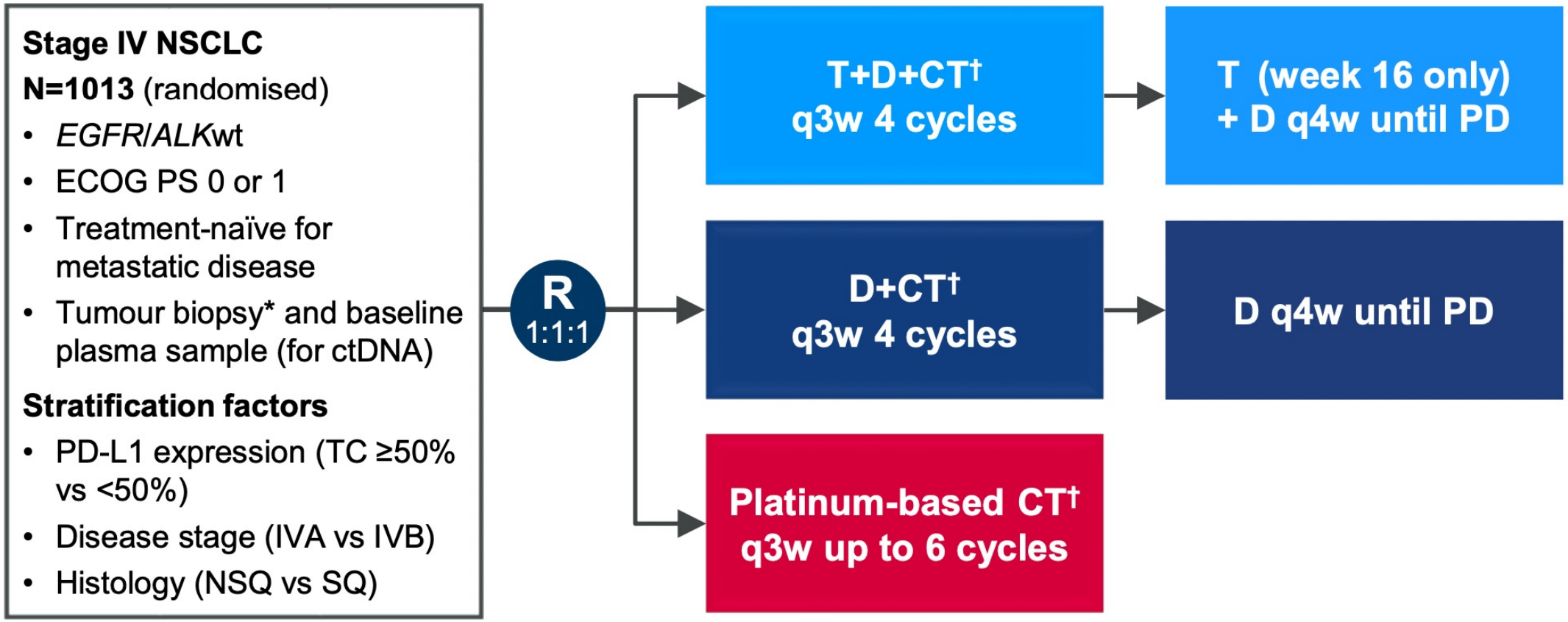
POSEIDON: Durva/Treme/Chemo



Johnson, ESMO 2022

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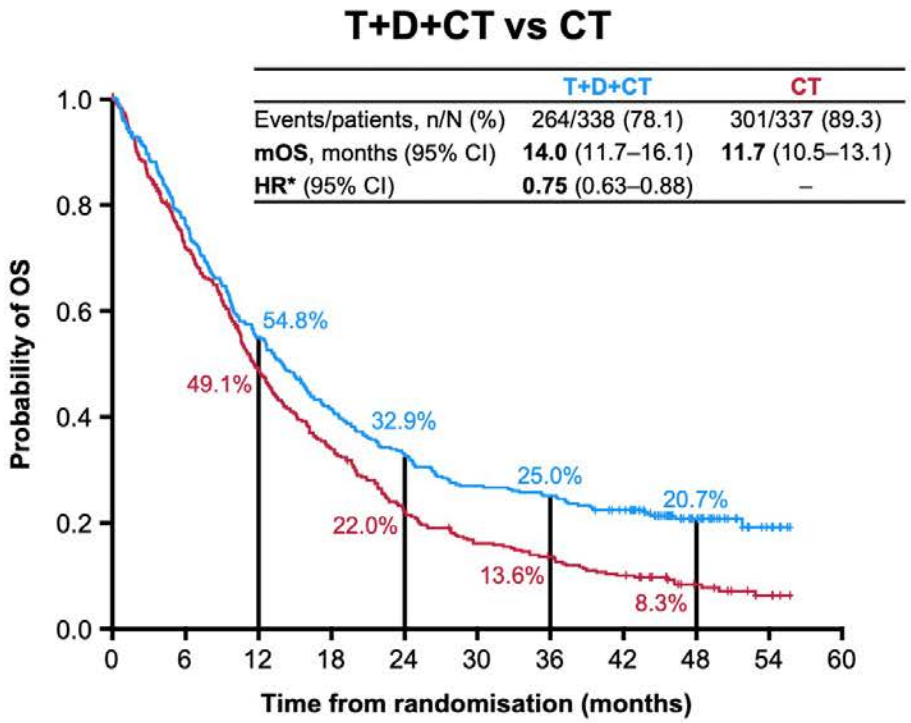
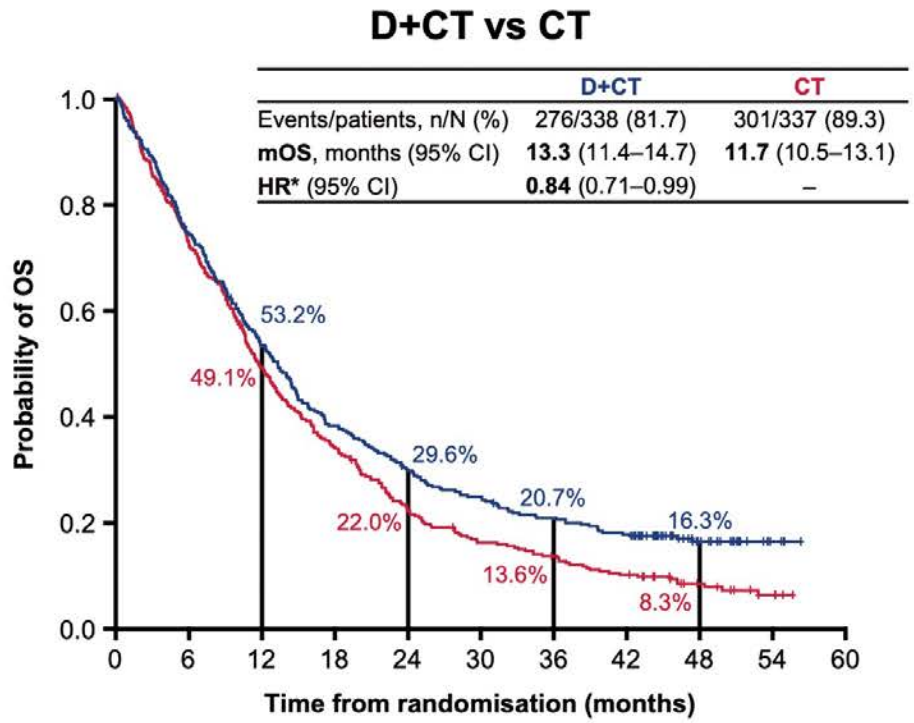
POSEIDON: Durva/Treme/Chemo

- Durvalumab + tremelimumab + chemo offered sustained survival advantage over chemotherapy





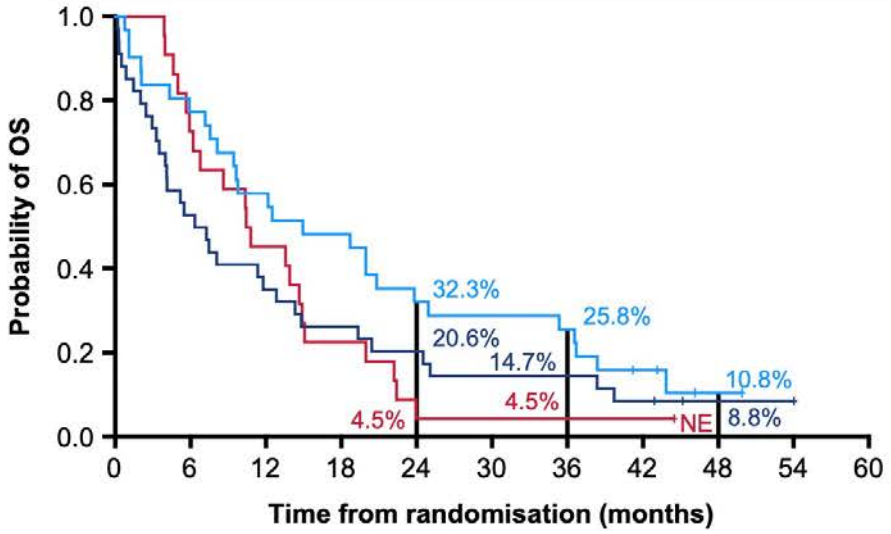
Johnson, ESMO 2022

POSEIDON: Durva/Treme/Chemo

- Durvalumab + tremelimumab + chemo offered sustained survival advantage over chemotherapy

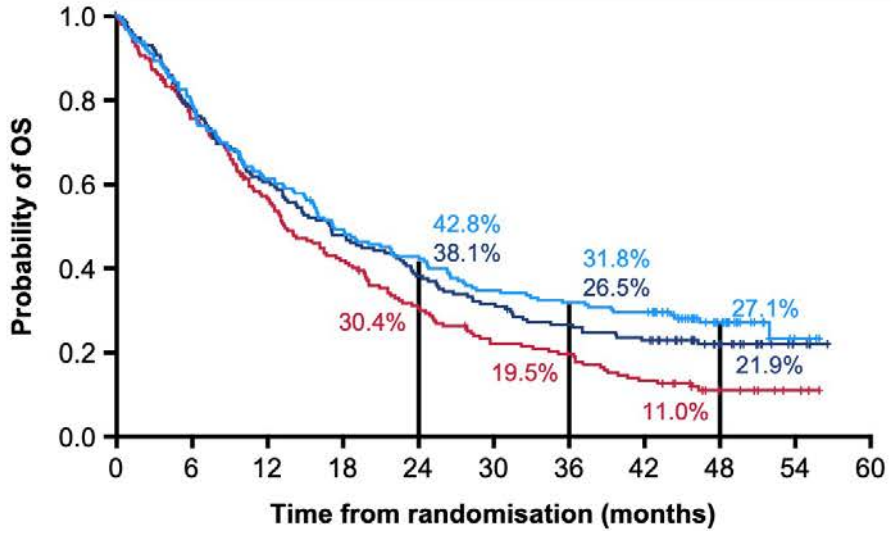
***STK11*m**

	T+D+CT	D+CT	CT
Events/patients, n/N	27/31	31/34	21/22
mOS, months (95% CI)	**15.0** (8.2–23.8)	**6.9** (3.6–12.9)	**10.7** (6.0–14.9)
HR* (95% CI)	**0.62** (0.34–1.12)	**1.06** (0.61–1.89)	–



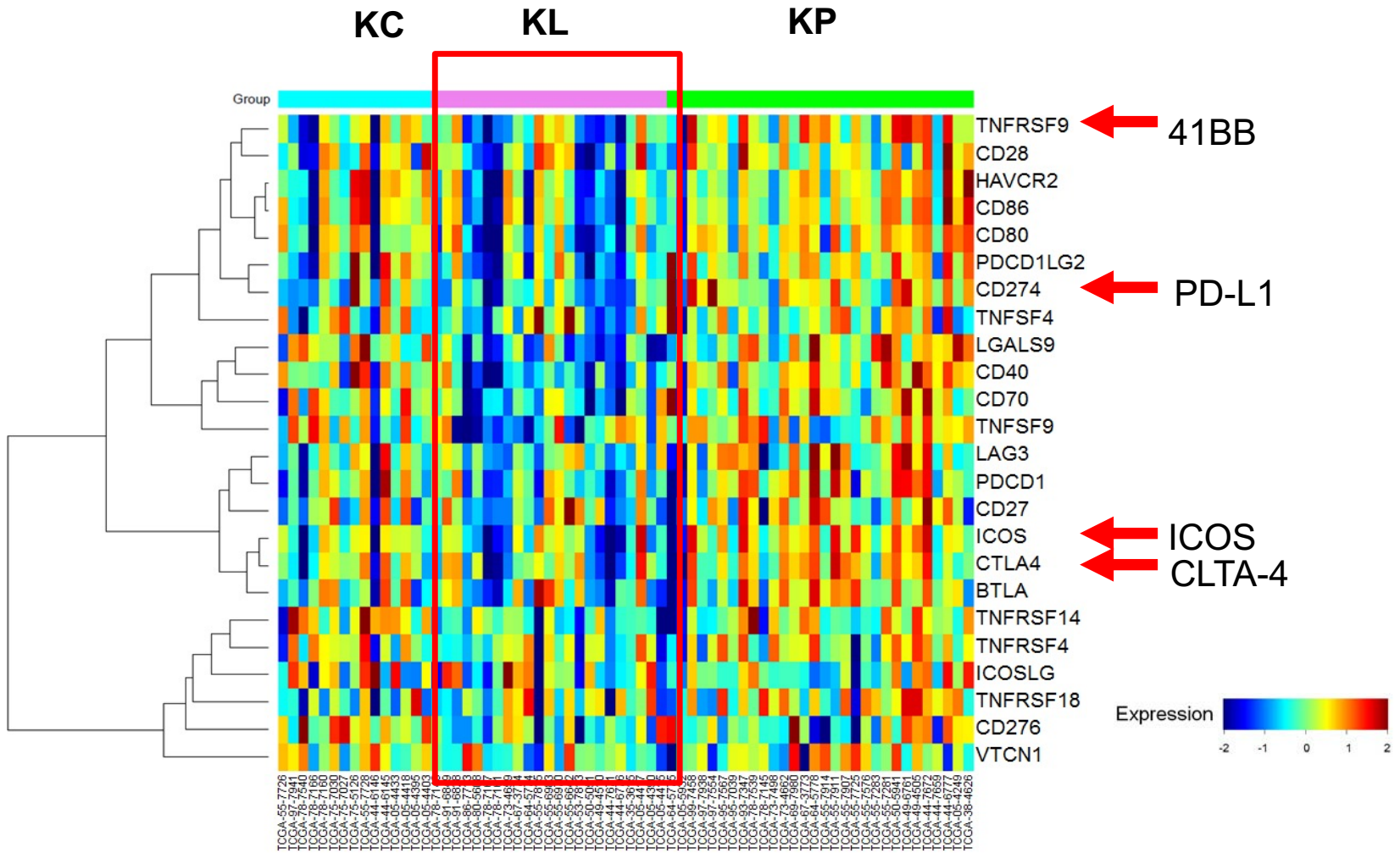
***STK11*wt**

	T+D+CT	D+CT	CT
Events/patients, n/N	127/177	129/169	151/179
mOS, months (95% CI)	**17.2** (14.9–22.1)	**17.1** (13.3–22.3)	**13.4** (11.5–17.5)
HR* (95% CI)	**0.70** (0.55–0.89)	**0.77** (0.61–0.98)	–



Johnson, ESMO 2022

KL tumors enriched in STK11/LKB1 and KEAP1 mutations appear to be immunologically “cold”



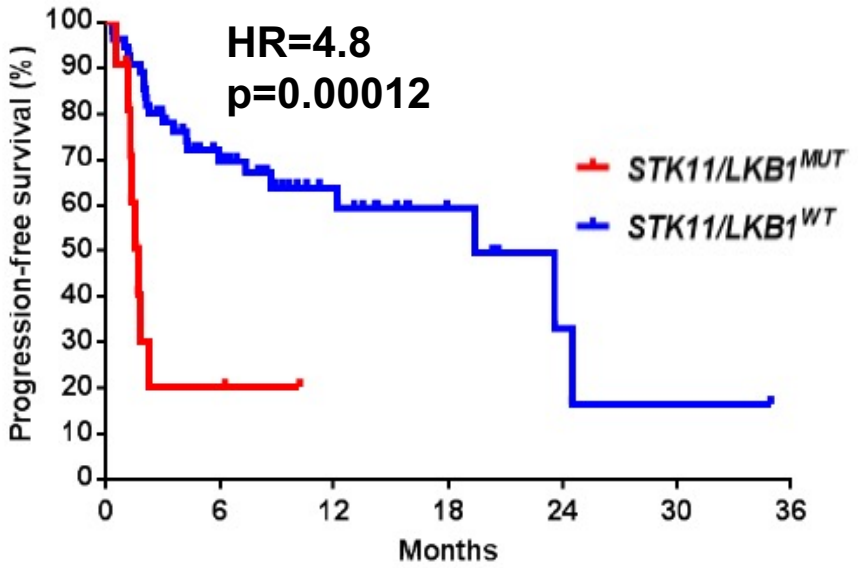
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Skoulidis, Cancer Discovery; 2018

STK11/LKB1 status predicts response to immunotherapy in PD-L1+ LUAC patients

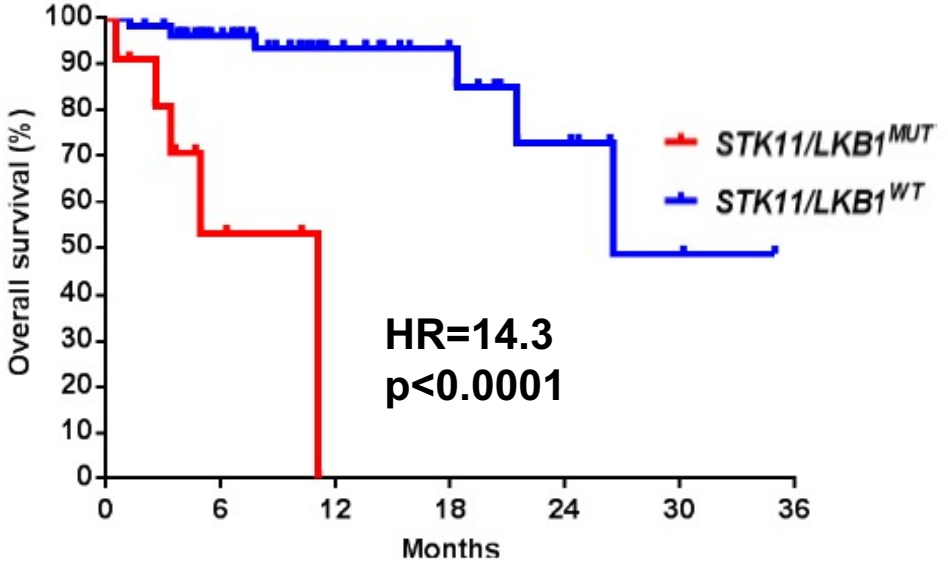
A.

GROUP	mPFS
STK11/LKB1 mutant	1.7m
STK11/LKB1 wt	19.3m



B.

GROUP	mOS
STK11/LKB1 mutant	11.1m
STK11/LKB1 wt	26.5m



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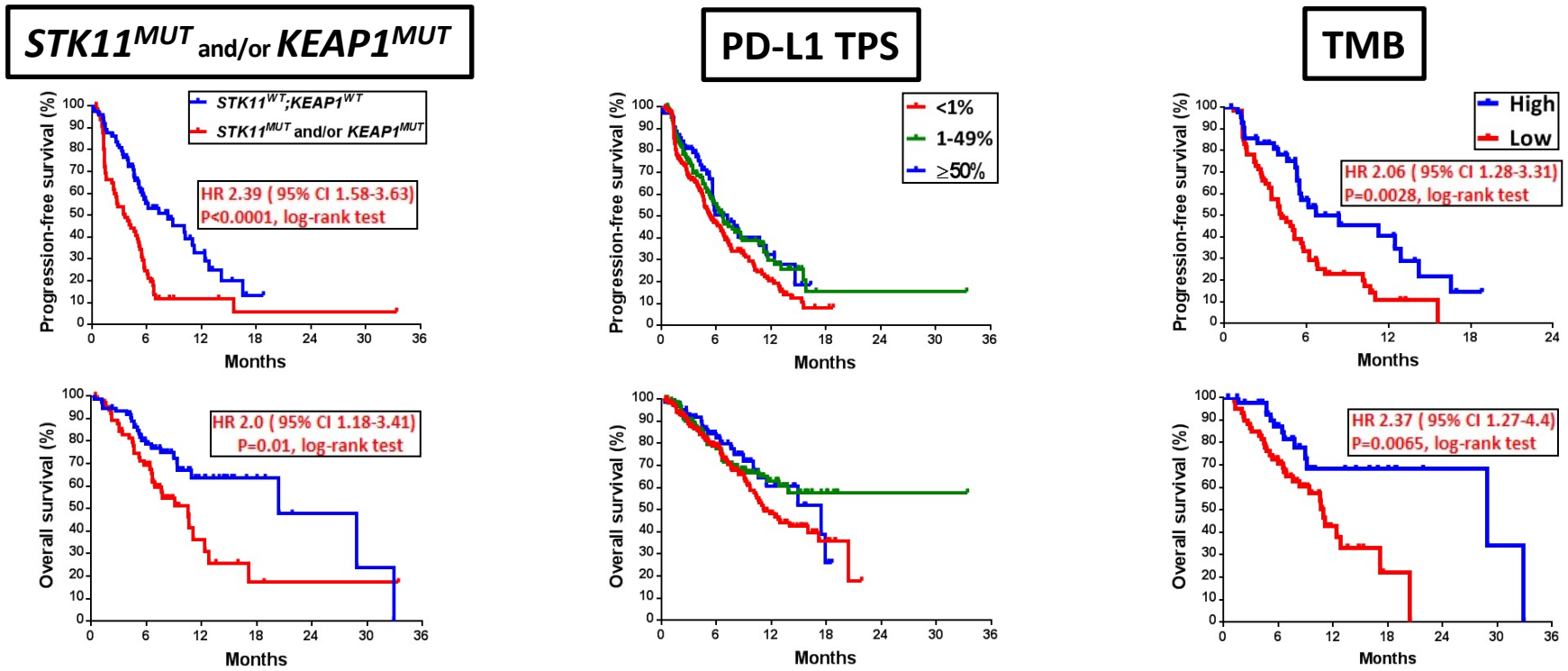
Making Cancer History®

Skoulidis, et al. Cancer Discovery 2018

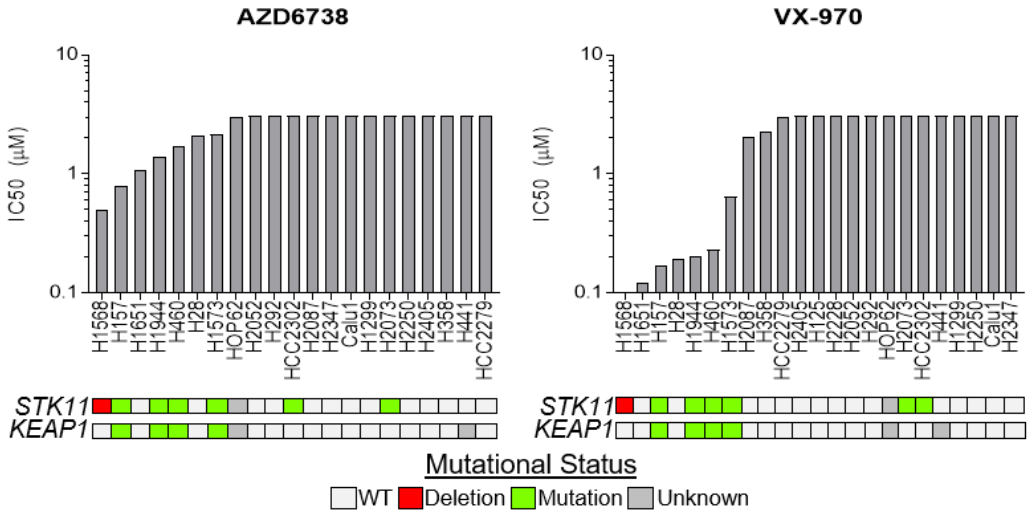
LKB1/*STK11* and KEAP1 are associated with shorter PFS and OS in patients treated with chemo+CPI

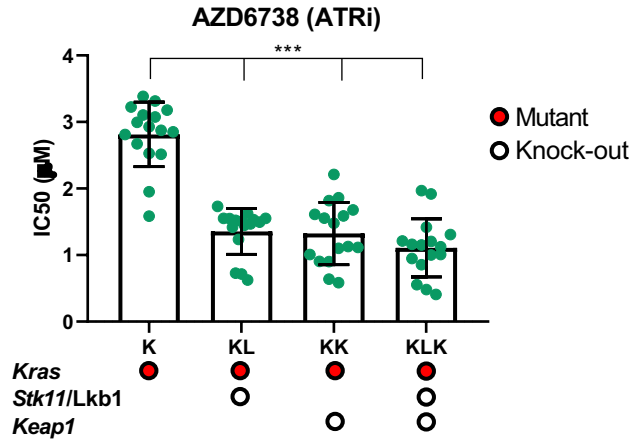


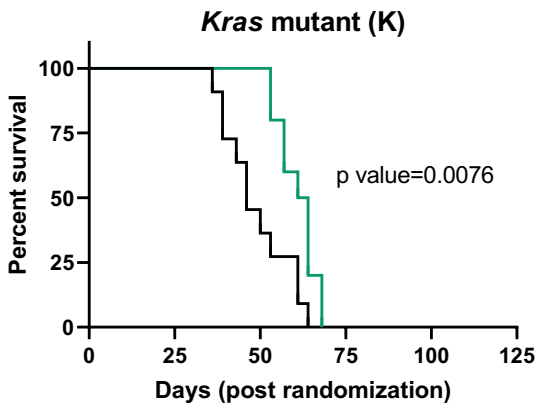
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

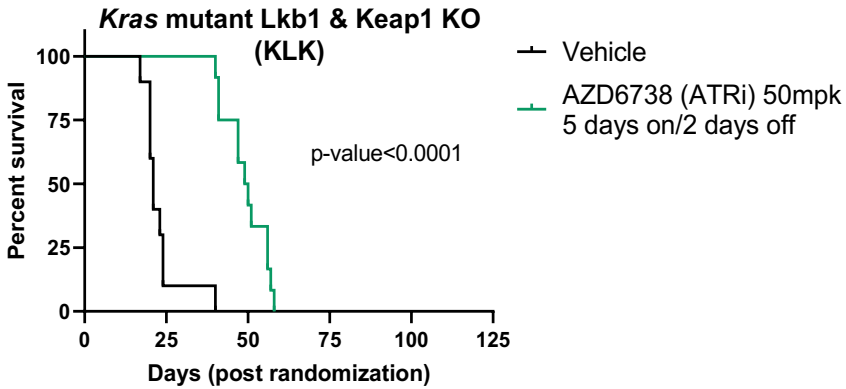
Skoulidis. ASCO 2019

In preclinical models, STK11/LKB1 or KEAP1 mutations lead to enhanced sensitivity to the ATR inhibitor ceralasertib









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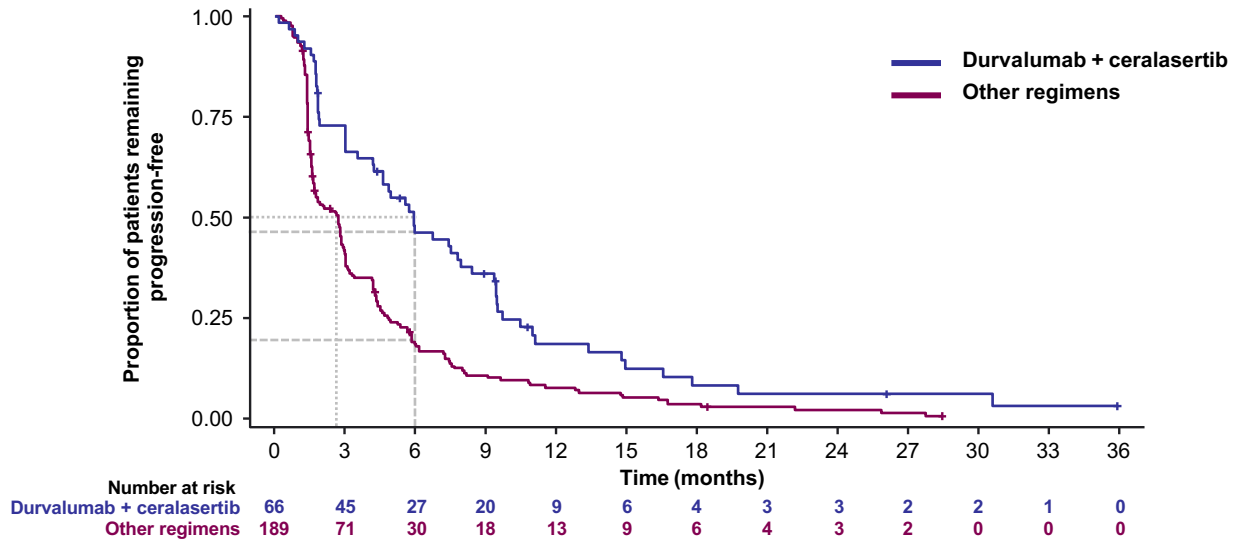
Galan-Cobo *et al*, unpublished.

HUDSON: improved PFS for ceralasertib/durvalumab combination vs other combinations in PD-(L)1i-refractory NSCLC



	Durvalumab + ceralasertib. n=66	Other regimens n=189
Median PFS, months (80% CI)	6.0 (4.6–7.5)	2.7 (1.8–2.8)
6-month PFS, % (80% CI)	46.3 (37.9–54.2)	18.0 (14.5–21.9)

PFS, progression-free survival.

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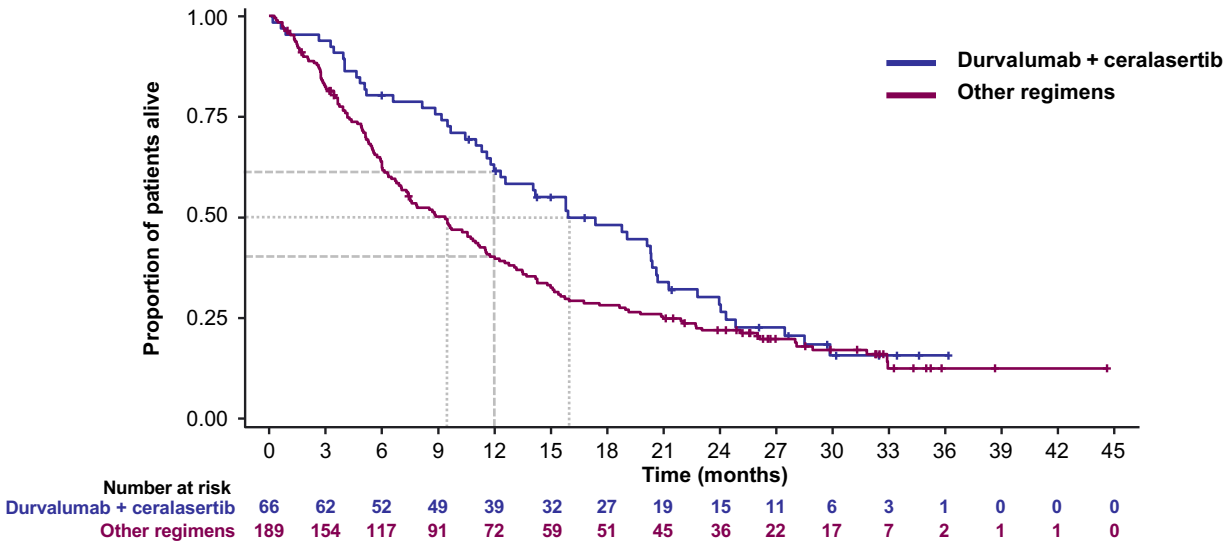
- Besse B, Awad MM, Forde PM, …Dressman M, Barry ST, Heymach JV, OA15.05. J. Thor. Oncol, 17:9 (2022) S41-S42, DOI:https://doi.org/10.1016/j.jtho.2022.07.074

HUDSON: improved OS for ceralasertib/durvalumab combination vs other combinations in PD-(L)1i-refractory NSCLC



	Durvalumab + ceralasertib. n=66	Other regimens n=189
Median OS, months (80% CI)	15.9 (14.1–20.3)*	9.4 (7.5–10.6)
12-month OS, % (80% CI)	61.6 (53.4–68.8)	39.7 (35.1–44.3)

*Data are still accruing; this median value for OS may change. OS, overall survival.

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- Besse B, Awad MM, Forde PM, …Dressman M, Barry ST, Heymach JV, OA15.05 HUDSON: An Open-Label, Multi-Drug, Biomarker-Directed Phase 2 Study in NSCLC Patients Who Progressed on Anti-PD-(L)1 Therapy, JOURNAL OF THORACIC ONCOLOGY, VOLUME 17, ISSUE 9, SUPPLEMENT, SEPTEMBER 2022, PAGES S41-S42, DOI:https://doi.org/10.1016/j.jtho.2022.07.074

Adverse events in phase 1/2 open-label study of Sacituzumab Govitecan in NSCLC patients

Most common AEs include nausea, diarrhea, fatigue, alopecia (GR≥3 in less than 10%), neutropenia.

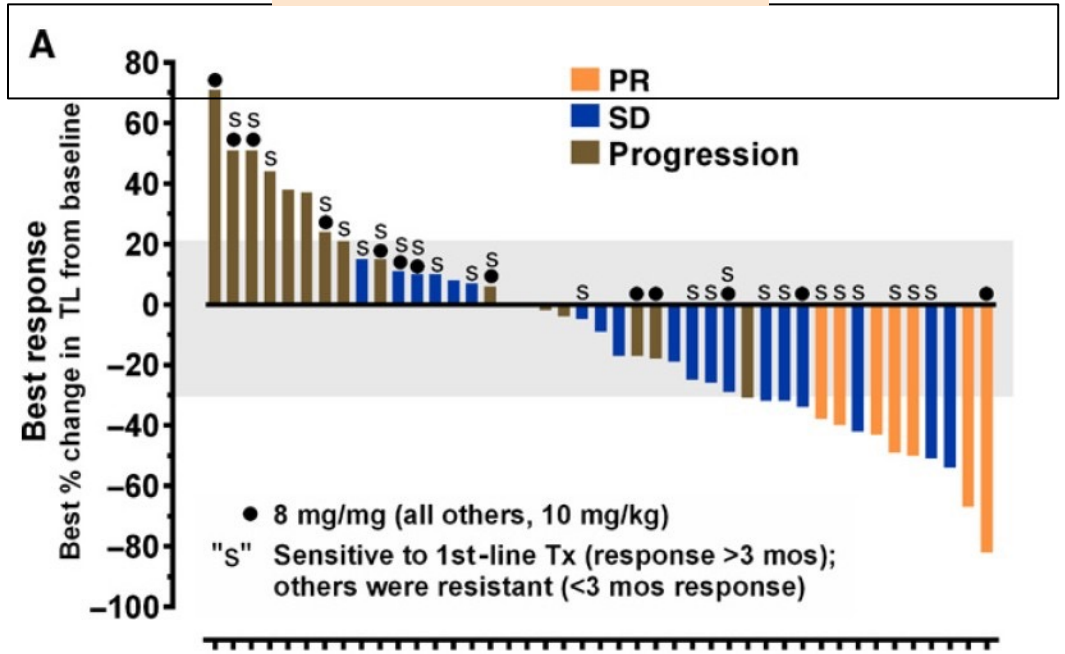
Table 2 Frequency of Adverse Events Regardless of Causality

Adverse Event	All Grades, No. (%)			Grade ≥ 3, No. (%)		
	All Patients	8 mg/kg Dose	10 mg/kg Dose	All Patients	8 mg/kg Dose	10 mg/kg Dose
No. of patients	54	8	46	54	8	46
Nausea	43 (80)	7 (88)	36 (78)	4 (7)	0 (0)	4 (9)
Diarrhea	33 (61)	5 (63)	28 (61)	4 (7)	1 (13)	3 (7)
Fatigue	25 (46)	3 (38)	22 (48)	3 (6)	0 (0)	3 (7)
Alopecia	21 (39)	3 (38)	18 (39)	NA	NA	NA
Neutropenia	20 (37)	2 (25)	18 (39)	15 (28)	1 (13)	14 (30)

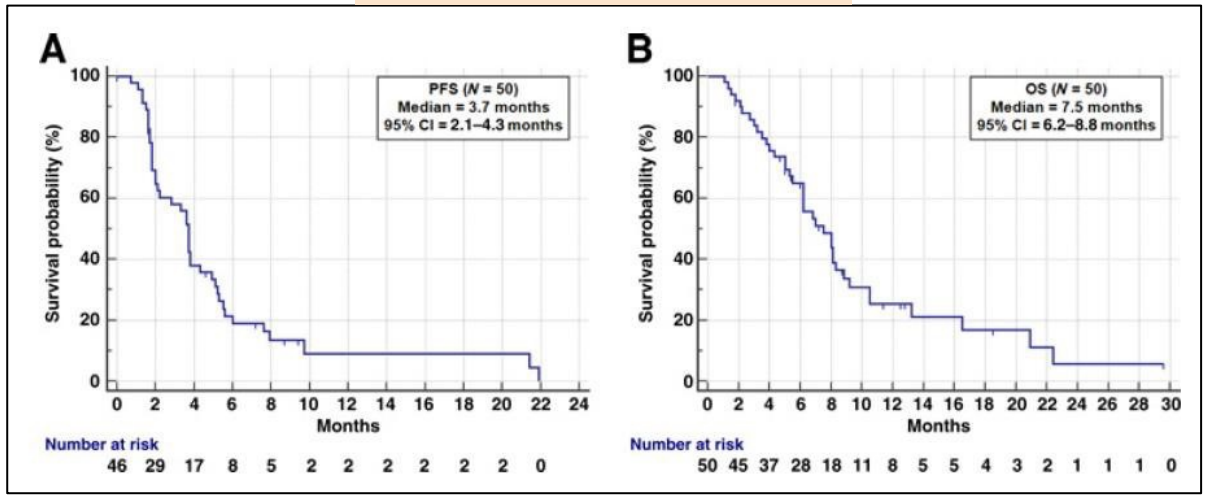
Gray et al. CCR 2017; Heist et al. JCO 2017.

Phase 1/2 open-label study of Sacituzumab Govitecan in SCLC patients

ORR 14%



mPFS 3.7m



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Gray et al. CCR 2017.

Summary

1. Resistance to PD-(L)1i can arise through tumor cell instrinsic factors (e.g. antigen presentation), T-cell factors (e.g. exhaustion) or TIME (e.g. high VEGF)
2. STK11 and KEAP1 mutations promote primary CPI resistance
3. Regimens with substantial activity in CPI-resistant NSCLC include:
   - ATRi ceralasertib plus durva: promising activity in HUDSON
   - VEGFR2 inhibitor ramucirumab plus pembro
4. TROP2-targeting ADCs dato-DXd and SG have topoisomerase payload. Activity seen in refractory NSCLC (ORR 19-25%) and SCLC (ORR 14%)

- RP2 vs docetaxel and CPI combos pending

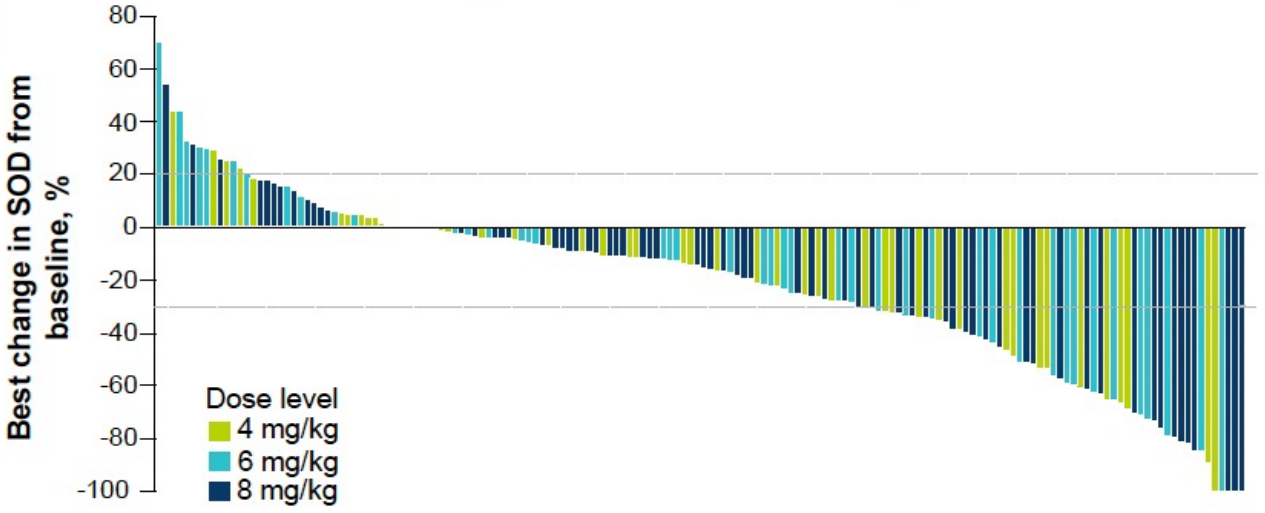
TROPION-PanTumor01: Antitumor Activity of Dato-DXd

Best Overall Response (BICR)

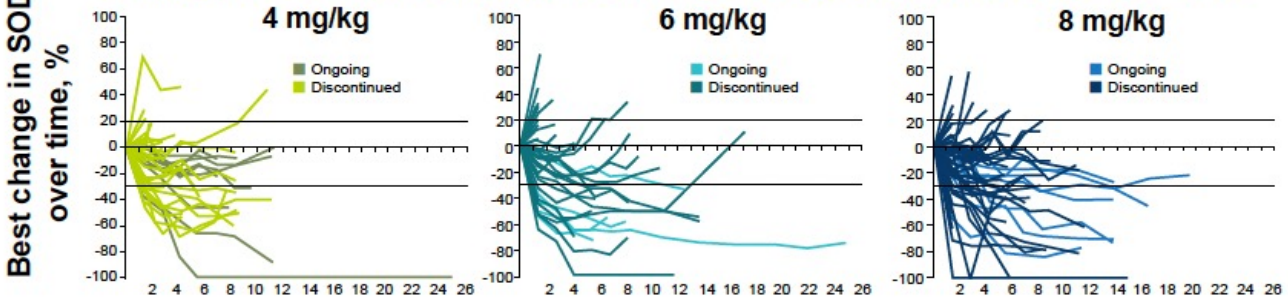
Patients[a]	Dato-DXd dose		
	4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
ORR, n (%)[b]	12 (24)	14 (28)	19 (24)
CR, n (%)	0	0	1 (1)
PR, n (%)[b]	12 (24)	14 (28)	18 (23)
SD, n (%)	25 (50)	20 (40)	42 (53)
Non-CR/PD, n (%)	1 (2)	2 (4)	2 (3)
PD, n (%)	7 (14)	10 (20)	8 (10)
NE, n (%)	5 (10)	5 (10)	9 (11)
DOR, median (95% CI), mo	NE (2.8-NE)	10.5 (5.6-NE)	9.4 (5.8-NE)

- Antitumor activity was observed at 4-, 6-, and 8-mg/kg doses of Dato-DXd
- Most responses were durable over time, including a median duration of response of 10.5 months in the 6-mg/kg cohort

Best Change in Sum of Diameters (per BICR)



Change in Sum of Diameters of Target Lesion (per BICR) Over Time

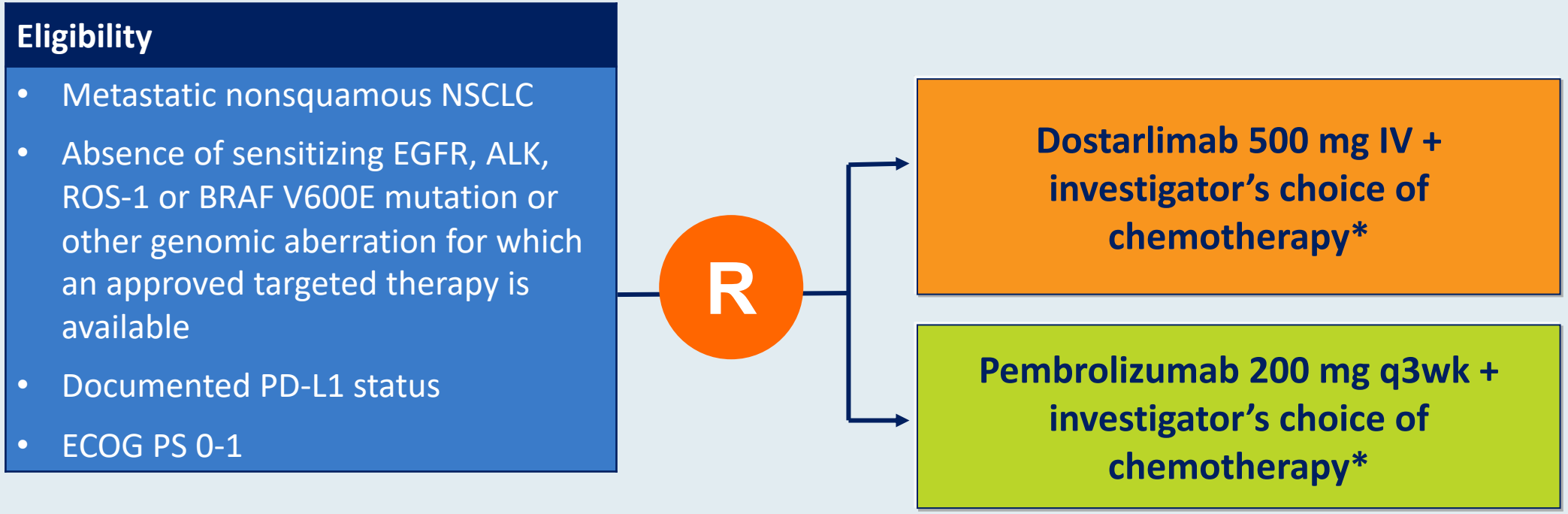


Garon EB et al. WCLC 2021;Abstract MA03.02.

RTP RESEARCH TO PRACTICE

PERLA: An Ongoing Phase II Trial Comparing Dostarlimab with Chemotherapy to Pembrolizumab with Chemotherapy for Metastatic Nonsquamous NSCLC

Trial identifier: NCT04581824 (open)
Estimated enrollment: 244



* Investigator's choice of chemotherapy: Pemetrexed 500 mg/m^2 IV q3wk followed by either cisplatin 75 mg/m^2 or carboplatin 5 mg/mL per minute

Primary endpoint: Overall response rate by RECIST v1.1

www.clinicaltrials.gov. Accessed October 31, 2022.

RTP RESEARCH TO PRACTICE

Positive Headline Results Announced from PERLA, the Phase II Trial of Dostarlimab with Chemotherapy for Patients with Metastatic Nonsquamous Non-Small Cell Lung Cancer

Press Release: October 5, 2022

Positive headline results were announced from the PERLA Phase II trial, which met its primary endpoint of ORR by RECIST criteria as determined by blinded independent central review. The trial evaluated first-line dostarlimab in combination with chemotherapy versus pembrolizumab in combination with chemotherapy in patients with metastatic nonsquamous non-small cell lung cancer. The PERLA Phase II trial is a randomized, double-blind trial of 243 patients and is the largest global head-to-head trial of programmed death receptor-1 (PD-1) inhibitors in this population. The trial was not designed to demonstrate superiority. The safety and tolerability profile of dostarlimab in the PERLA Phase II trial was consistent with previous clinical trials of similar regimens.

Full results from the PERLA Phase II trial will be presented at an upcoming scientific meeting. It was also announced that both arms of the COSTAR Lung trial will be advancing into Phase III.

https://www.gsk.com/en-gb/media/press-releases/gsk-announces-positive-headline-results-from-perla-the-phase-ii-trial-of-jemperli-dostarlimab-plus-chemotherapy-in-patients-with-metastatic-non-squamous-non-small-cell-lung-cancer/

Consensus or Controversy? Documenting and Discussing Clinical Investigators' Practice Patterns in Ovarian Cancer

A CME/MOC-Accredited Virtual Event

Thursday, November 3, 2022
5:00 PM – 6:00 PM ET

Faculty

Ursula Matulonis, MD
Debra L Richardson, MD

Moderator

Neil Love, MD

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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