Promising Investigational Agents and Strategies for Patients with Metastatic Non-Small Cell Lung Cancer Who Experience Disease Progression on Immune Checkpoint Inhibitor Therapy

Wednesday, January 26, 2022
5:00 PM – 6:00 PM ET

Faculty

Edward B Garon, MD, MS

Moderator

Neil Love, MD

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Edward B Garon, MD, MS
Professor
Director, Thoracic Oncology Program
Director, Signal Transduction and Therapeutics Research Program
David Geffen School of Medicine at UCLA
Jonsson Comprehensive Cancer Center
Los Angeles, California

Moderator
Neil Love, MD
Research To Practice
Miami, Florida

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Commercial Support

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Dr Love — Disclosures

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Dr Garon — Disclosures

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ONCOLOGY TODAY

WITH DR NEIL LOVE

NSCLC with EGFR Exon 20 Insertion Mutations

DR GREGORY RIELY
MEMORIAL SLOAN KETTERING CANCER CENTER

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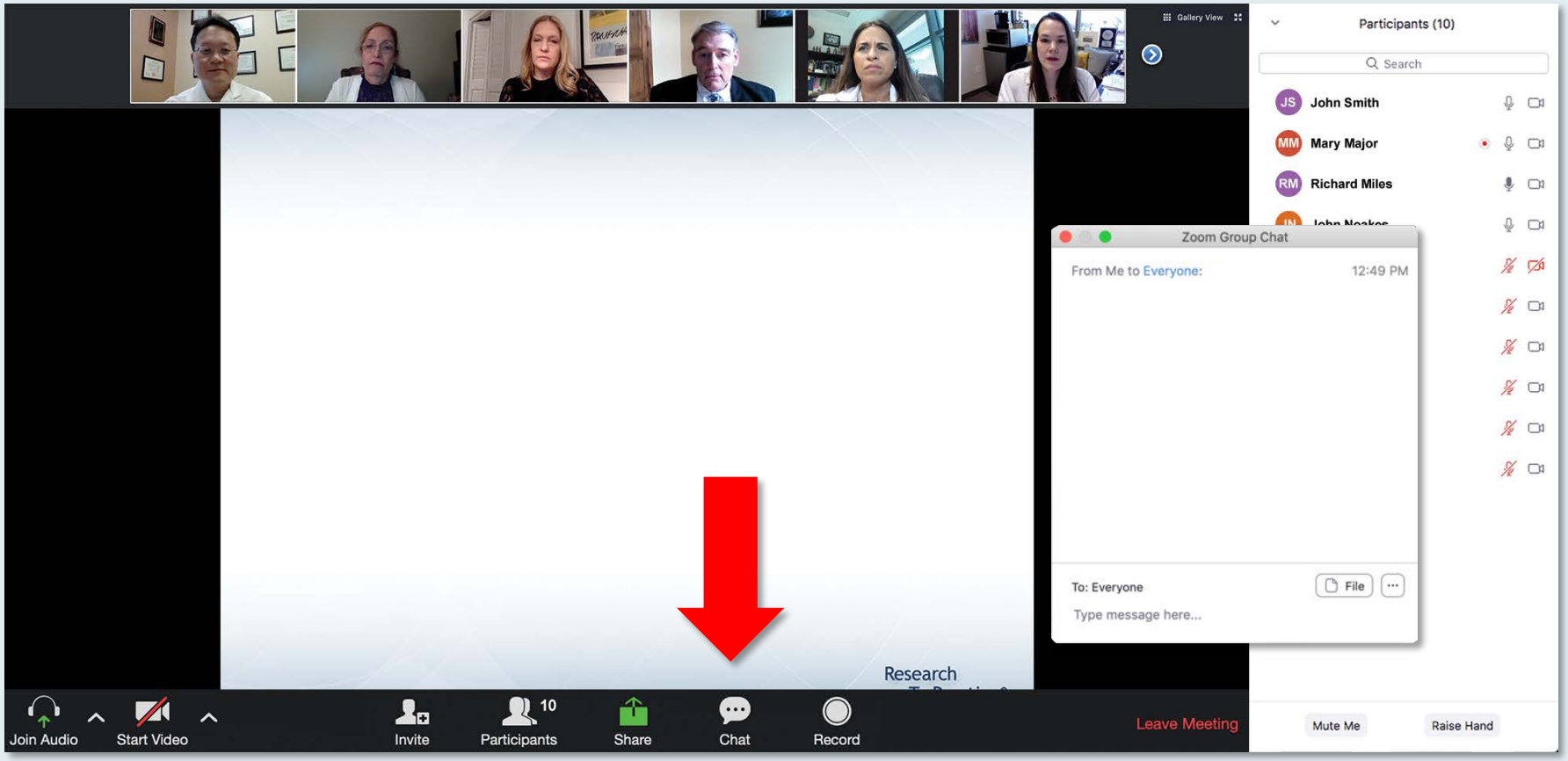
We Encourage Clinicians in Practice to Submit Questions



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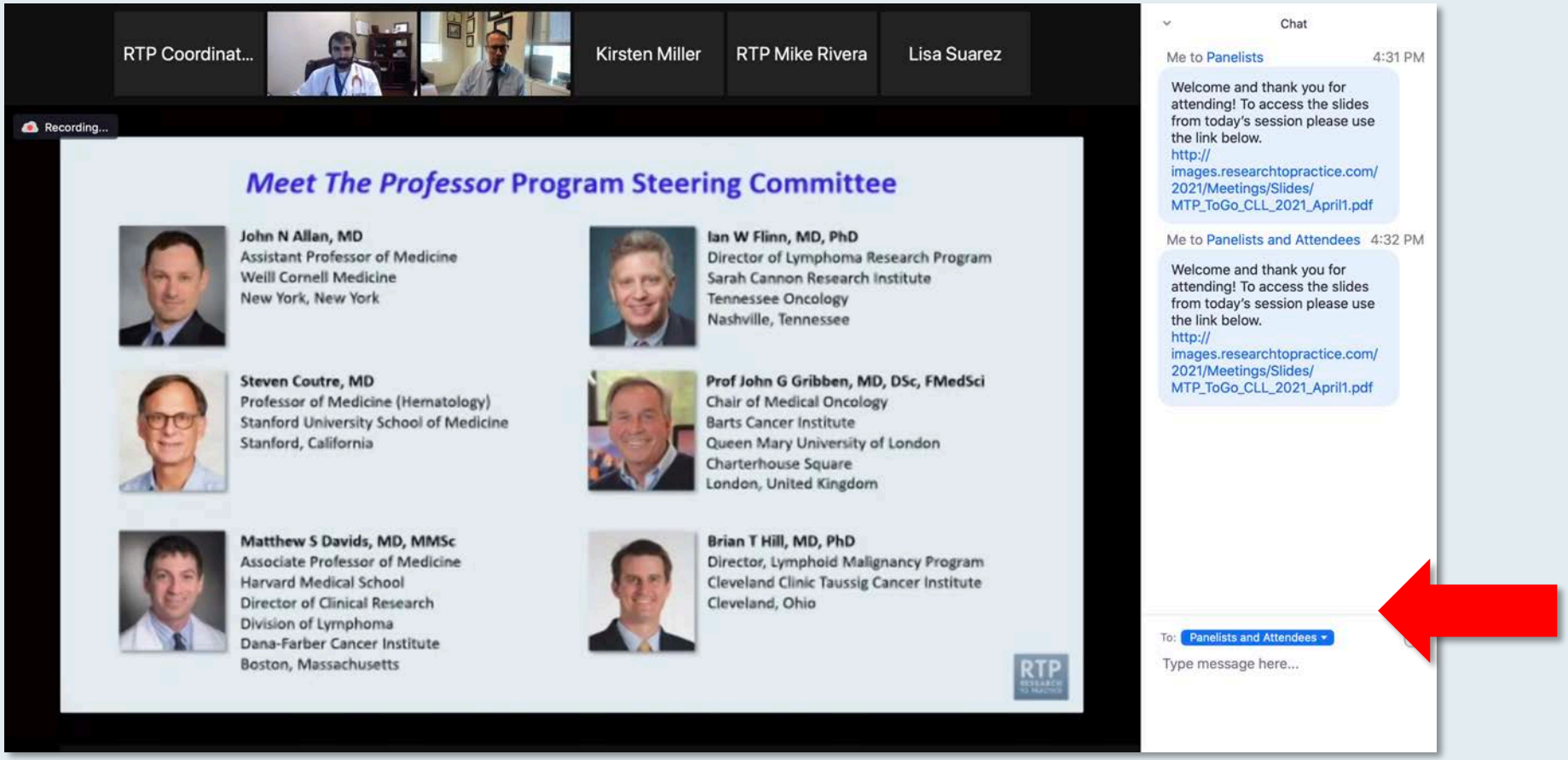

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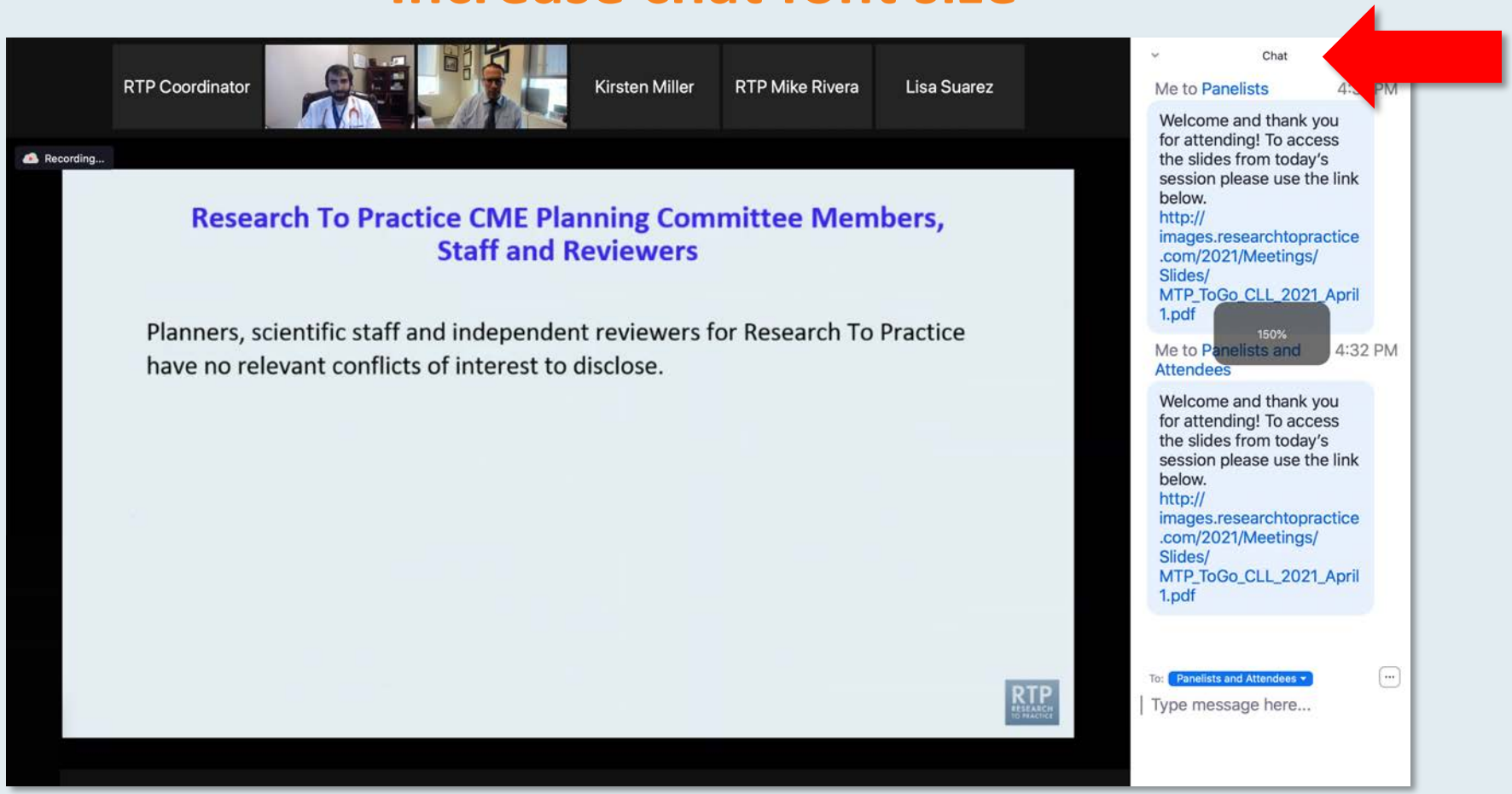
Increase chat font size



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You may do this as many times as you need for readability.

Year in Review – Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology:

Acute Myeloid Leukemia and Myelodysplastic Syndromes

Thursday, January 27, 2022
5:00 PM – 6:00 PM ET

Faculty

Daniel A Pollyea, MD, MS
Gail J Roboz, MD

Moderator

Neil Love, MD

RTP Year in Review 2022

Year in Review – Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology: Gastric, Gastroesophageal Junction and Esophageal Cancer

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

Faculty

David H Ilson, MD, PhD

Zev Wainberg, MD, MSc

Moderator

Neil Love, MD

RTP Year in Review 2022

Exploring the Current and Changing Paradigm for the Management of Newly Diagnosed Diffuse Large B-Cell Lymphoma

Wednesday, February 2, 2022
5:00 PM – 6:00 PM ET

Faculty

Christopher R Flowers, MD, MS
Neha Mehta-Shah, MD, MSCI
Grzegorz Nowakowski, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Exploring the Current and Future Role of B-Cell Maturation Antigen-Directed Therapy in the Management of Multiple Myeloma

Monday, February 7, 2022
5:00 PM – 6:00 PM ET

Faculty

Jesús G Berdeja, MD
Noopur Raje, MD

Moderator

Neil Love, MD

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Key Considerations in the Optimal Clinical Care of Patients with Small Cell Lung Cancer

Wednesday, February 9, 2022
5:00 PM – 6:00 PM ET

Faculty

Luis Paz-Ares, MD, PhD
Jared Weiss, MD

Moderator

Neil Love, MD

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Recent Advances and Real-World Implications in Medical Oncology: A Daylong Multitumor Educational Symposium in Partnership with the North Carolina Oncology Association and the South Carolina Oncology Society

Saturday, February 12, 2022
8:30 AM – 4:00 PM ET

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Recent Advances and Real-World Implications in Medical Oncology: Agenda

Module 1 — Chronic Lymphocytic Leukemia and Lymphomas
8:35 AM – 9:40 AM

Module 2 — Multiple Myeloma 9:40 AM – 10:45 AM

Module 3 — Genitourinary Cancers 10:45 AM – 11:50 AM

Module 4 — Breast Cancer 12:30 PM – 1:35 PM

Module 5 — Gastrointestinal Cancers 1:35 PM – 2:40 PM

Module 6 — Lung Cancer 2:40 PM – 3:45 PM

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Thank you for attending!

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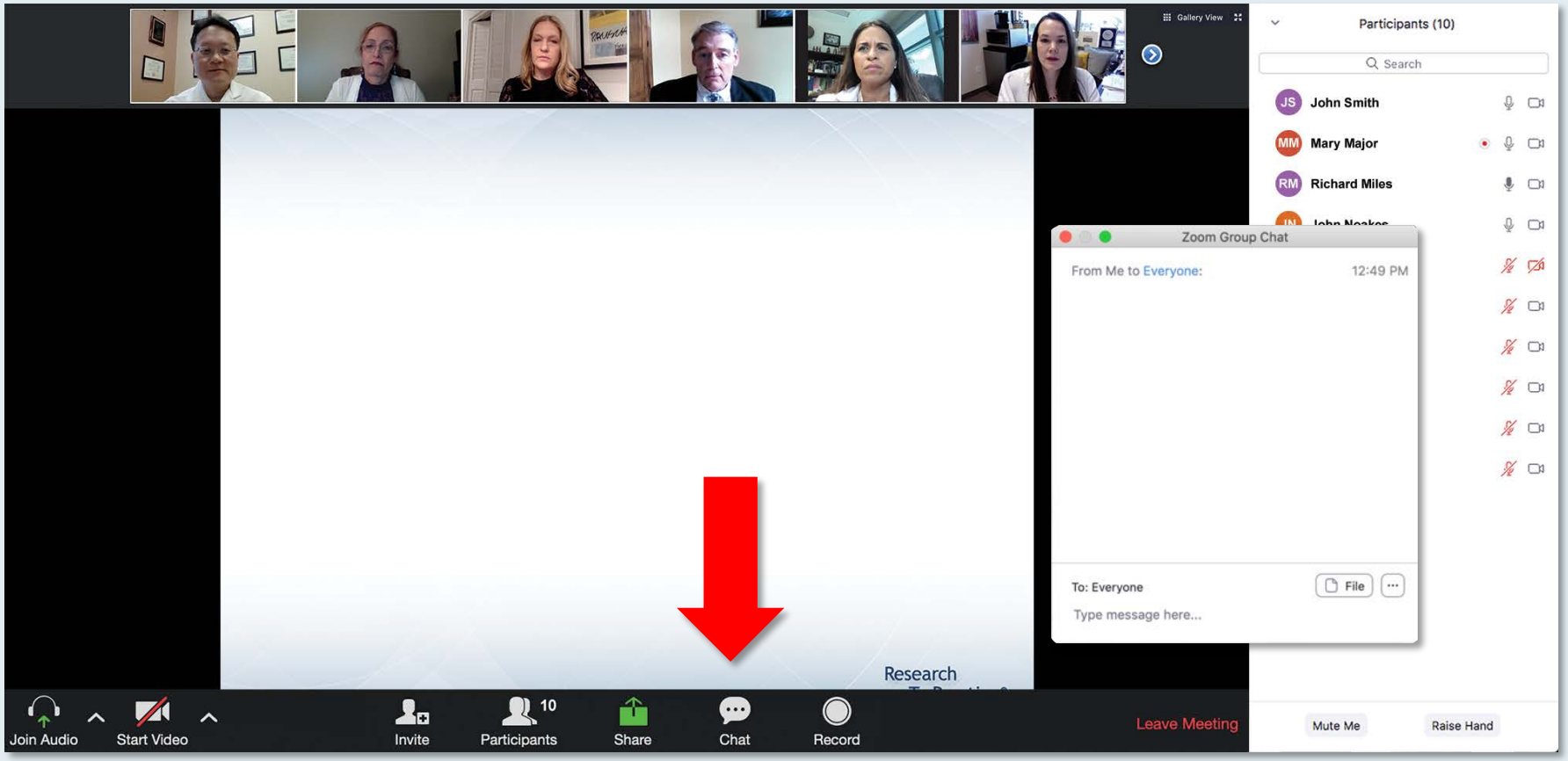

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Agenda

Introduction: Metastatic Non-Small Cell Lung Cancer (NSCLC) in Clinical Practice

MODULE 1: Sequencing of Therapies in Metastatic NSCLC

MODULE 2: New Agents Part 1 – Antibody-Drug Conjugates

MODULE 3: New Agents Part 2 – Other Novel Strategies

MODULE 4: Clinical Situations for Special Consideration

Agenda

Introduction: Metastatic Non-Small Cell Lung Cancer (NSCLC) in Clinical Practice

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MODULE 3: New Agents Part 2 – Other Novel Strategies

MODULE 4: Clinical Situations for Special Consideration

Approximately how many patients with metastatic NSCLC without a targetable mutation (s/p immunotherapy) currently in your care have survived more than 3 years?

1. None
2. 1
3. 2-5
4. 6-10
5. More than 10

Approximately how many patients with metastatic NSCLC without a targetable mutation (s/p IO) currently in your care are receiving second- or later-line systemic treatment?

1. 1
2. 2-5
3. 6-10
4. More than 10

Agenda

Introduction: Metastatic Non-Small Cell Lung Cancer (NSCLC) in Clinical Practice

MODULE 1: Sequencing of Therapies in Metastatic NSCLC

- Pembrolizumab
- Ipilimumab/nivolumab with or without chemotherapy
- Pembrolizumab/pemetrexed/carboplatin
- Pembrolizumab/paclitaxel/carboplatin

MODULE 2: New Agents Part 1 – Antibody-Drug Conjugates

MODULE 3: New Agents Part 2 – Other Novel Strategies

MODULE 4: Clinical Situations for Special Consideration

ASCO Gastrointestinal Cancers Symposium 2022

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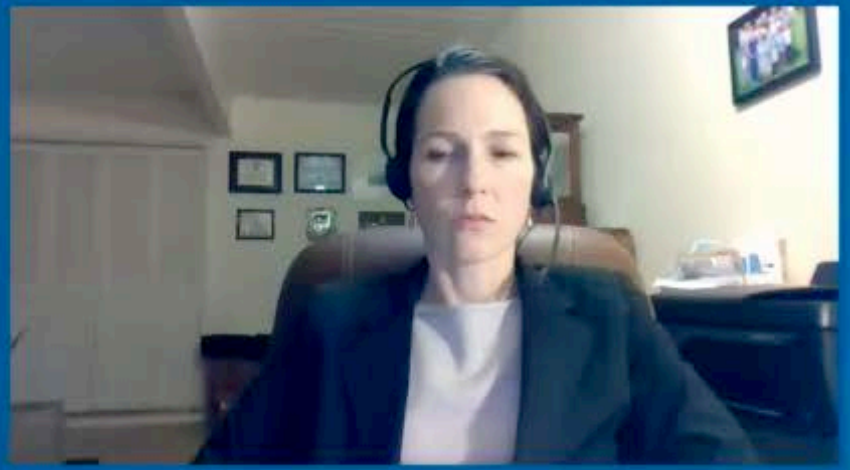


HIMALAYA study design

HIMALAYA was an open-label, multicenter, global, Phase 3 trial

Study population
- Patients with confirmed uHCC
- BCLC B (not eligible for locoregional therapy) and C
- No prior systemic therapy
- ECOG PS 0–1
- Child-Pugh A
- No main portal vein thrombosis
- EGD was not required

Stratification factors
- Macrovascular invasion: Y / N
- Etiology of liver disease: HBV / HCV / others
- Performance status: ECOG 0 / 1

R
N=1324

T300+D (n=393):
Tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W*

Durvalumab (n=389):
Durvalumab monotherapy 1500 mg Q4W*

Sorafenib (n=389):
Sorafenib 400 mg BID*

T75+D (n=153): *arm closed*†
Tremelimumab 75 mg Q4W × 4 doses + durvalumab Q4W*

Primary objective
- OS for T300+D vs sorafenib

Key secondary objective
- OS for durvalumab vs sorafenib

Additional secondary objectives
- PFS, ORR, and DoR as assessed by investigator per RECIST v1.1
- Safety

Multiple testing procedure

OS *superiority* for T300+D vs sorafenib

↓

OS *noninferiority* for durvalumab vs sorafenib
Noninferiority margin: 1.08

↓

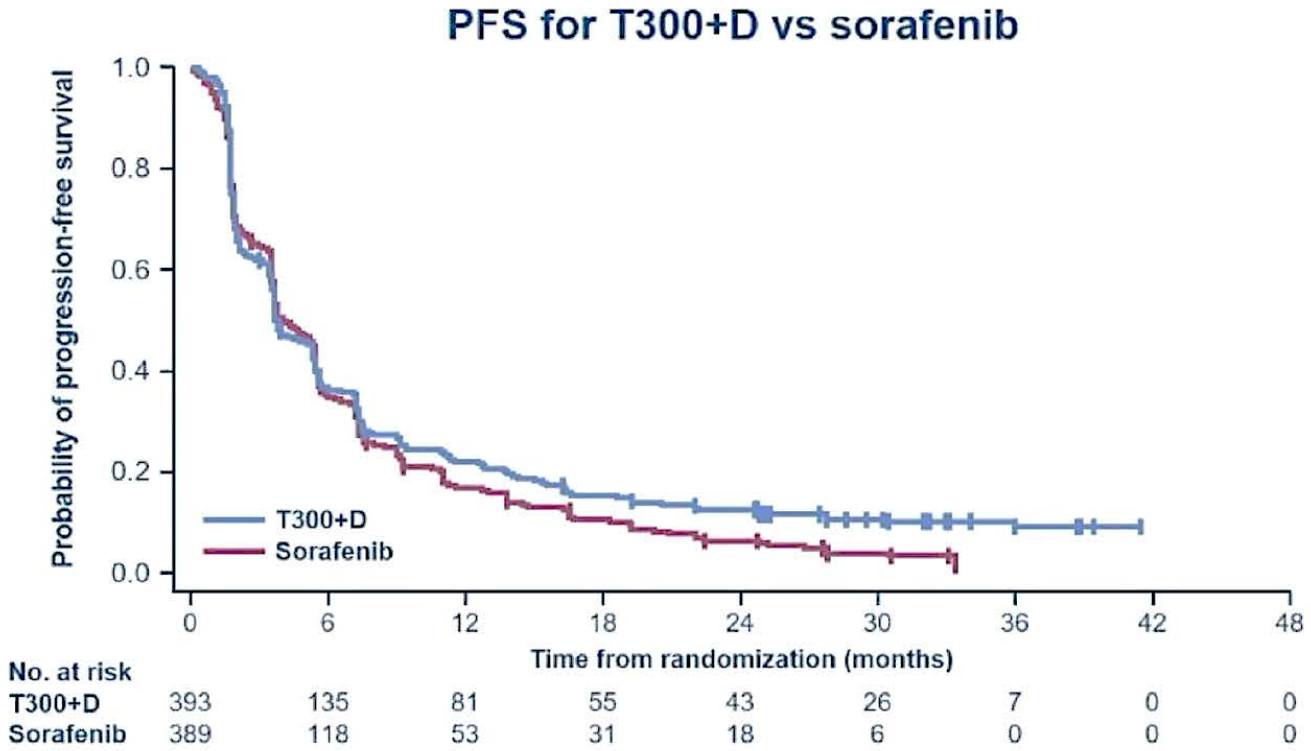
OS *superiority* for durvalumab vs sorafenib

*Treatment continued until disease progression. Patients with progressive disease who, in the investigator's opinion, continued to benefit from treatment and met the criteria for treatment in the setting of progressive disease could continue treatment. †The T75+D arm was closed following a preplanned analysis of a Phase 2 study. Patients randomized to this arm (n=153) could continue treatment following arm closure. Results from this arm are not reported in this presentation.

BID, twice a day; EGD, esophagogastroduodenoscopy; Q4W, every 4 weeks.

PRESENTED BY: Ghassan K Abou-Alfa, MD, MBA

Progression-free survival



	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
PFS events, n (%)	335 (85.2)	345 (88.7)	327 (84.1)
Median PFS (95% CI), months	3.78 (3.68–5.32)	3.65 (3.19–3.75)	4.07 (3.75–5.49)
PFS HR* (95% CI)	0.90 (0.77–1.05)	1.02 (0.88–1.19)	–
Progression-free at DCO, n (%)	49 (12.5)	32 (8.2)	19 (4.9)
Median TTP (95% CI), months	5.42 (3.81–5.62)	3.75 (3.68–5.42)	5.55 (5.13–5.75)
Treated ≥1 cycle beyond progression, n (%)†	182 (46.9)	188 (48.5)	134 (34.4)

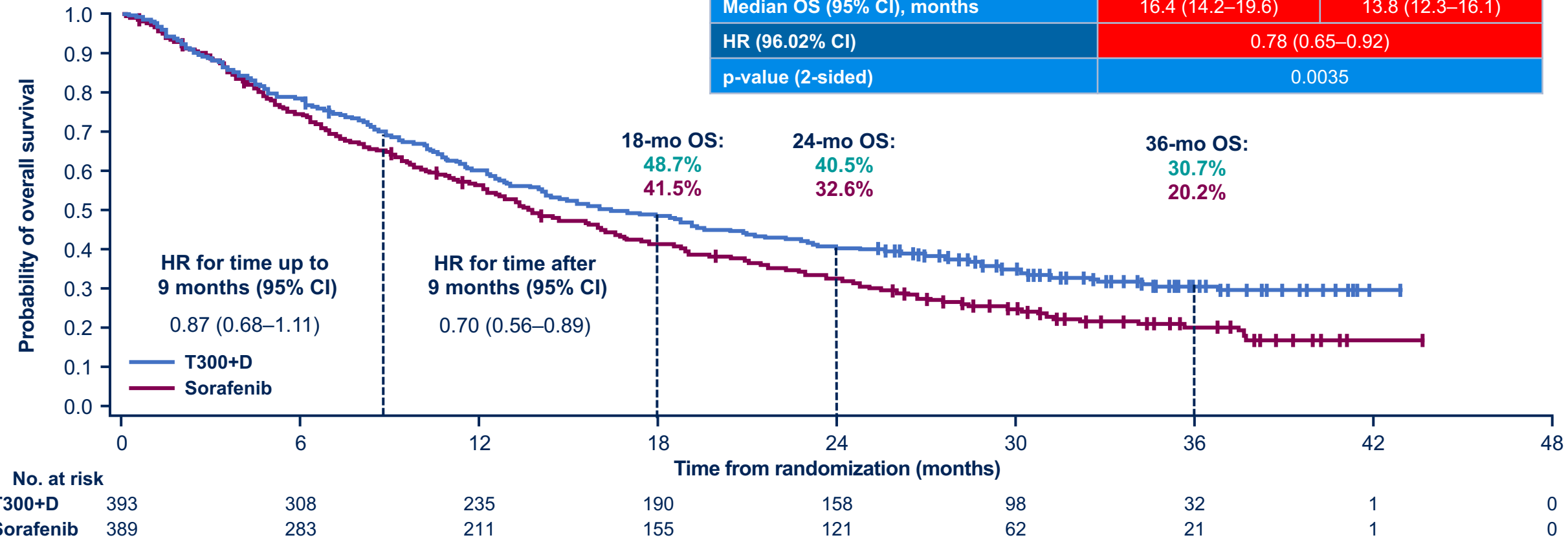
*Versus sorafenib. †Percent calculated from total patients in the safety analysis set: T300+D, N=388; durvalumab, N=388, sorafenib, n=374.

CI, confidence interval; DCO, data cutoff; HR, hazard ratio; PFS, progression-free survival; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TTP, time to progression.

PRESENTED BY: Ghassan K Abou-Alfa, MD, MBA

HIMALAYA T300+D vs Sorafenib OS

	T300+D (n=393)	Sorafenib (n=389)
OS events, n (%)	262 (66.7)	293 (75.3)
Median OS (95% CI), months	16.4 (14.2–19.6)	13.8 (12.3–16.1)
HR (96.02% CI)	0.78 (0.65–0.92)	
p-value (2-sided)	0.0035	



No. at risk								
T300+D	393	308	235	190	158	98	32	1	0
Sorafenib	389	283	211	155	121	62	21	1	0

Data cut-off: August 27, 2021. Median duration of follow-up was 33.18 (95% CI, 31.74–34.53) months for T300+D and 32.23 (95% CI, 30.42–33.71) months for sorafenib.

CI, confidence interval; HR, hazard ratio; OS, overall survival; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Which first-line treatment regimen would you recommend for a 65-year-old patient with metastatic nonsquamous lung cancer, no identified targetable mutations and a PD-L1 TPS of 0%?

 Dr Aggarwal	Carboplatin/pemetrexed/ pembrolizumab	 Dr Hanna	Carboplatin/pemetrexed/ pembrolizumab
 Dr Goldberg	Carboplatin/pemetrexed/ pembrolizumab	 Dr Liu	Carboplatin/pemetrexed/ pembrolizumab
 Dr Govindan	Carboplatin/pemetrexed/ pembrolizumab	 Dr Ramalingam	Ipilimumab/nivolumab

RTP RESEARCH TO PRACTICE

Which first-line treatment regimen would you recommend for a 65-year-old patient with metastatic nonsquamous lung cancer, no identified targetable mutations and a PD-L1 TPS of 10%?

 Dr Aggarwal	Carboplatin/pemetrexed/ pembrolizumab	 Dr Hanna	Carboplatin/pemetrexed/ pembrolizumab
 Dr Goldberg	Carboplatin/pemetrexed/ pembrolizumab	 Dr Liu	Carboplatin/pemetrexed/ pembrolizumab
 Dr Govindan	Carboplatin/pemetrexed/ pembrolizumab	 Dr Ramalingam	Carboplatin/pemetrexed/ pembrolizumab

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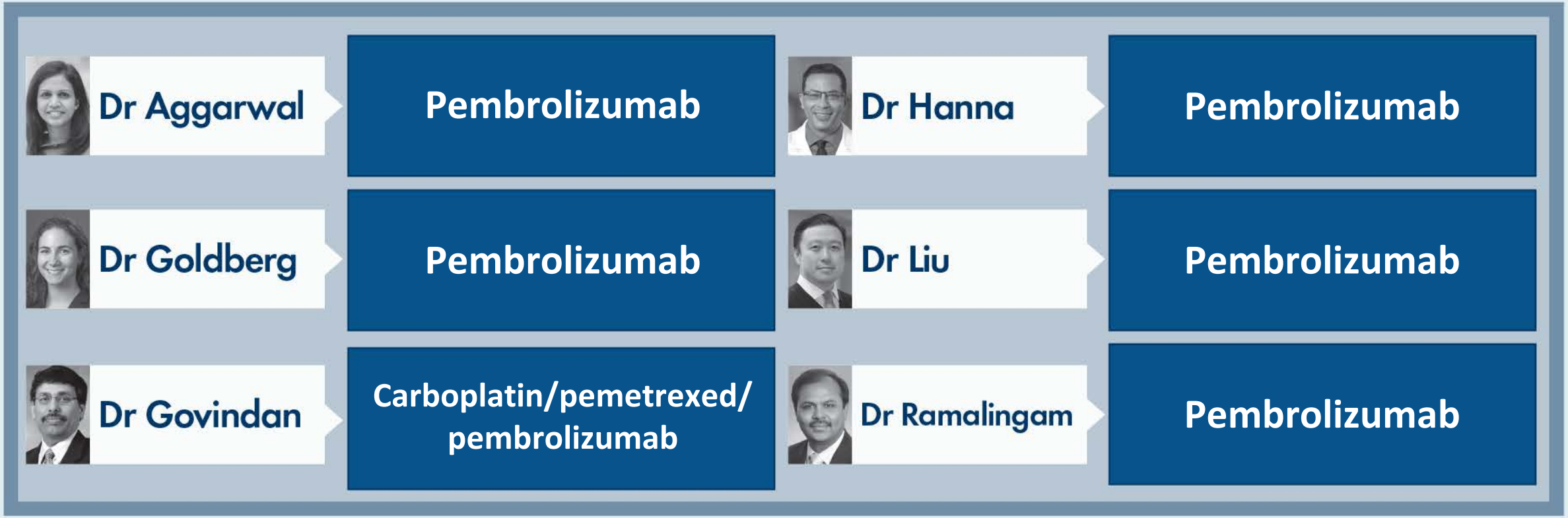
Which first-line treatment regimen would you recommend for a 65-year-old patient with metastatic nonsquamous lung cancer, no identified targetable mutations and a PD-L1 TPS of 50%?



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Which first-line treatment regimen would you recommend for a 65-year-old patient with metastatic squamous lung cancer, no identified targetable mutations and a PD-L1 TPS of 0%?

 Dr Aggarwal	Carboplatin/*nab* paclitaxel/pembrolizumab	 Dr Hanna	Carboplatin/paclitaxel/ pembrolizumab
 Dr Goldberg	Carboplatin/paclitaxel/ pembrolizumab	 Dr Liu	Ipilimumab/nivolumab + chemotherapy
 Dr Govindan	Carboplatin/*nab* paclitaxel/pembrolizumab	 Dr Ramalingam	Ipilimumab/nivolumab

RTP RESEARCH TO PRACTICE

Which first-line treatment regimen would you recommend for a 65-year-old patient with metastatic squamous lung cancer, no identified targetable mutations and a PD-L1 TPS of 10%?

 Dr Aggarwal	Carboplatin/*nab* paclitaxel/pembrolizumab	 Dr Hanna	Carboplatin/paclitaxel/ pembrolizumab
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RTP RESEARCH TO PRACTICE

Which first-line treatment regimen would you recommend for a 65-year-old patient with metastatic squamous lung cancer, no identified targetable mutations and a PD-L1 TPS of 50%?

 Dr Aggarwal	Pembrolizumab	 Dr Hanna	Pembrolizumab
 Dr Goldberg	Pembrolizumab	 Dr Liu	Pembrolizumab
 Dr Govindan	Carboplatin/*nab* paclitaxel/pembrolizumab	 Dr Ramalingam	Pembrolizumab

Case Presentation – Dr Lorber: A 66-year-old man with metastatic adenocarcinoma of the lung – PD-L1 60%, TMB 14 mut/Mb

Dr Jeremy Lorber

- Presented with highly symptomatic malignant pleural effusion
- Lung mass biopsy: consistent with non-small cell adenocarcinoma
  - PD-L1 60%, TMB 14 mut/Mb
  - No driver mutations
- Pembrolizumab with a near complete response lasting 28 months
- Developed progression of lung mass and a single vertebral metastasis

Question

- Given his prolonged response to checkpoint inhibitor therapy, should it continue to be included as part of his second-line therapy?

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Lorber: A 66-year-old man with metastatic adenocarcinoma of the lung – PD-L1 60%, TMB 14 mut/Mb (continued)

Dr Jeremy Lorber

- Presented with highly symptomatic malignant pleural effusion
- Lung mass biopsy: consistent with non-small cell adenocarcinoma
  - PD-L1 60%, TMB 14 mut/Mb
  - No driver mutations
- Pembrolizumab with a near complete response lasting 28 months
- Developed progression of lung mass and a single vertebral metastasis
- ***RT to vertebra metastasis, added carboplatin/pemetrexed to pembrolizumab***

Case Presentation – Dr Apuri: A 69-year-old man with metastatic adenocarcinoma of the lung and brain metastases

Dr Susmitha Apuri

- 80 pack year tobacco use
- Presents with dizziness and progressive SOB x 2 months
- Imaging and biopsy: Lung mass c/w adenocarcinoma and liver and brain metastases
- Whole brain radiation therapy and carboplatin/pemetrexed/pembrolizumab
- Liquid NGS: EGFR A67T, FGFR and PDGFRA amplification, ROS1 VUS
- PD-L1 <1%

Questions

- Would you recommend ipilimumab/nivolumab in a patient on active steroid therapy, who just completed radiation therapy? How might it impact their treatment?
- Would penetration of the BBB be more than with a chemotherapy and immunotherapy combination approach?

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Professor
Director of Thoracic Oncology Program
David Geffen School of Medicine at UCLA
January 3, 2022

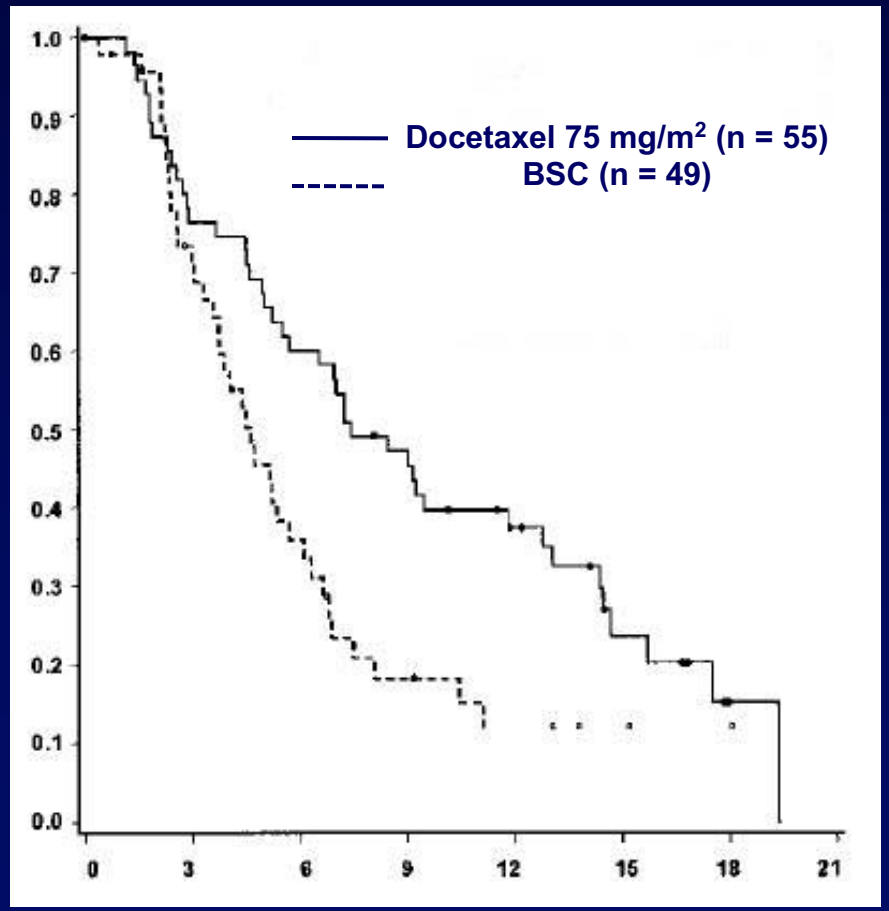
What is the Current Standard?

- **In patients who receive frontline immunotherapy only, platinum based chemotherapy is standard, albeit with essentially no comparative data supporting the approach**
- **Often in the United States, the immunotherapy is also continued despite even less supportive data**

How about in patients who received chemoimmunotherapy?

Docetaxel in Previously Treated NSCLC

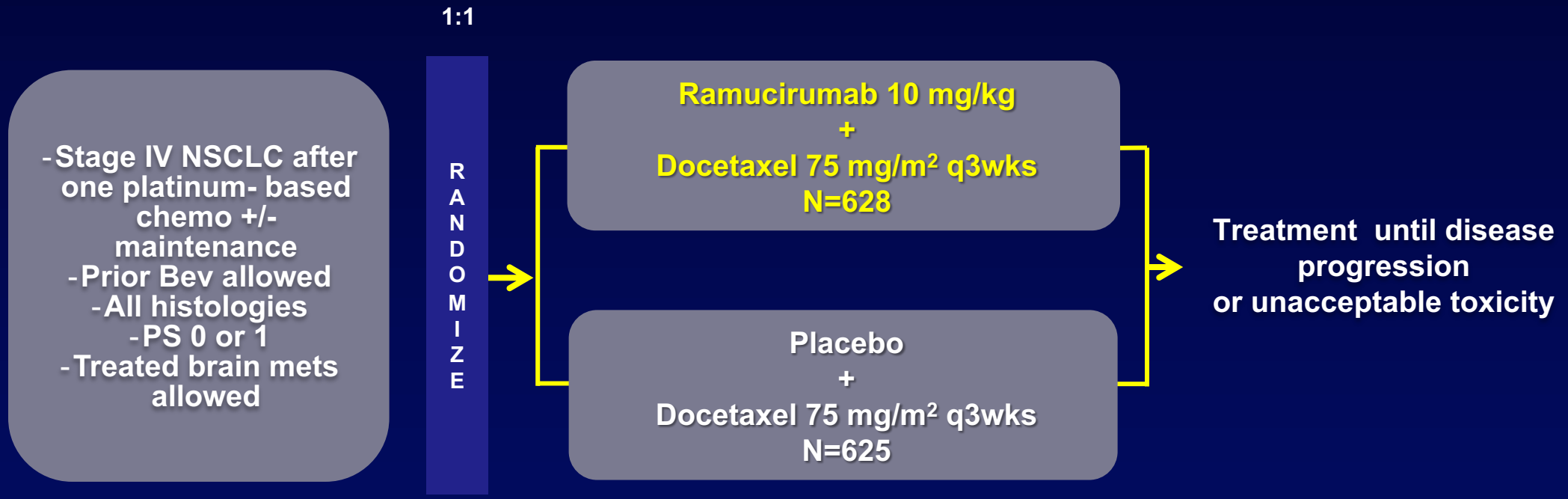
TAX 317 Trial



- Median OS
  - Docetaxel 7.0 mo
  - BSC 4.6 mo
  - Log-rank $P = 0.047$
- Median TTP
  - Docetaxel 10.6 wk
  - BSC 6.7 wk
  - $P < 0.001$
- Docetaxel ORR 7.1%

Shepherd FA, et al. *J Clin Oncol.* 2000;18:2095-2193.

Phase III REVEL: Study Design



Stratification factors:

- ECOG PS 0 *vs* 1
- Gender
- Prior maintenance
- East-Asia vs. ROW

Primary endpoint: **Overall Survival**

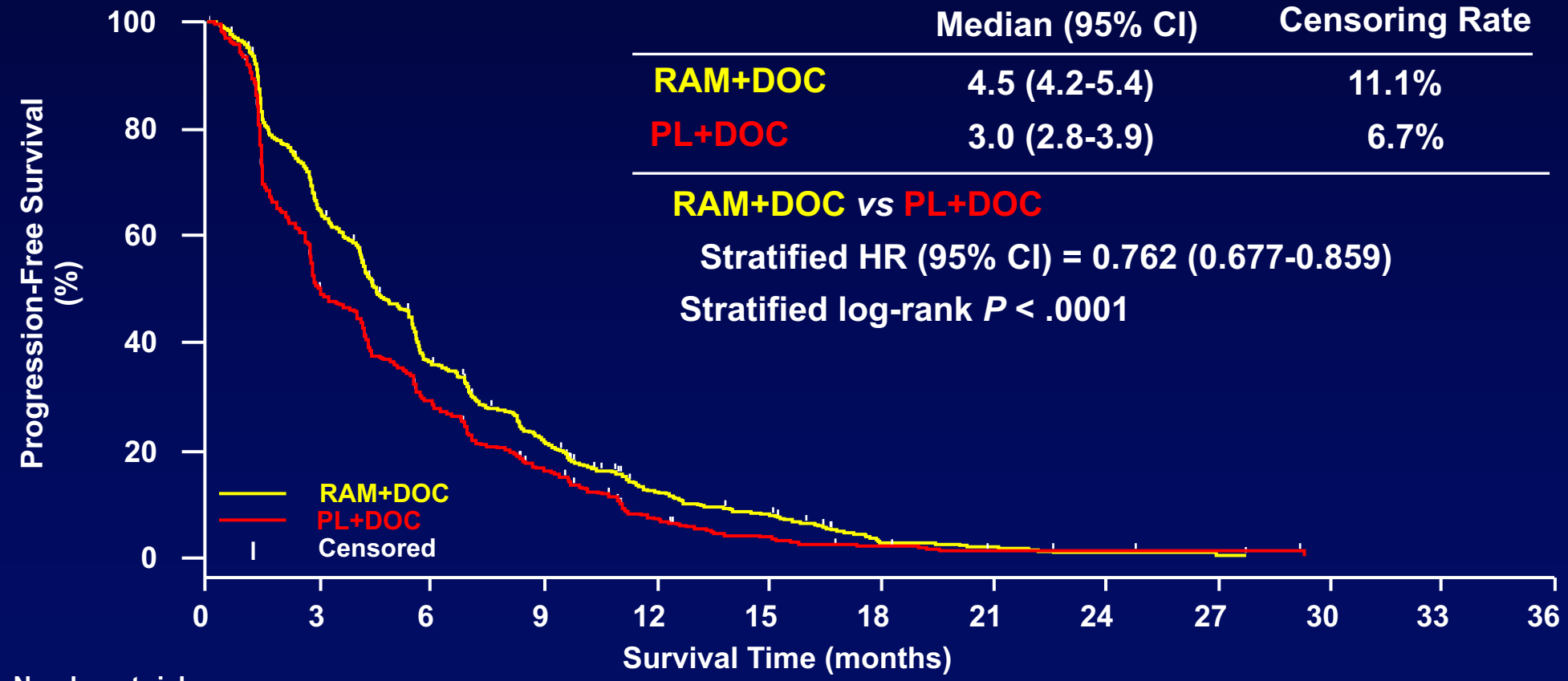
Secondary endpoints:
PFS, ORR, safety, patient-reported outcomes

Abbreviations: Bev=bevacizumab; ECOG PS=Eastern Cooperative Oncology Group performance status; ORR=objective response rate; PFS=progression-free survival; ROW=rest of the world; q3wks=every 3 weeks.

Garon E et al. The Lancet. 384 (9944): 665–673, 23 August 2014

Progression-Free Survival

ITT Population, Investigator Assessment



	Median (95% CI)	Censoring Rate
RAM+DOC	4.5 (4.2-5.4)	11.1%
PL+DOC	3.0 (2.8-3.9)	6.7%

RAM+DOC *vs* PL+DOC

Stratified HR (95% CI) = 0.762 (0.677-0.859)

Stratified log-rank $P < .0001$

Number at risk

RAM+DOC	628	383	204	120	59	38	11	7	3	3	0	0	0
PL+DOC	625	301	172	95	37	17	9	4	3	2	0	0	0

Perol M, ASCO 2014; Garon EB et al. The Lancet. 384 (9944): 665–673, 23 August 2014

Agenda

Introduction: Metastatic Non-Small Cell Lung Cancer (NSCLC) in Clinical Practice

MODULE 1: Sequencing of Therapies in Metastatic NSCLC

MODULE 2: New Agents Part 1 – Antibody-Drug Conjugates

- Polatuzumab vedotin
- Trastuzumab deruxtecan
- Tisotumab vedotin
- Enfortumab vedotin
- Belantamab mafodotin
- Disitamab vedotin
- Datopotamab deruxtecan
- Sacituzumab govitecan
- Patritumab deruxtecan

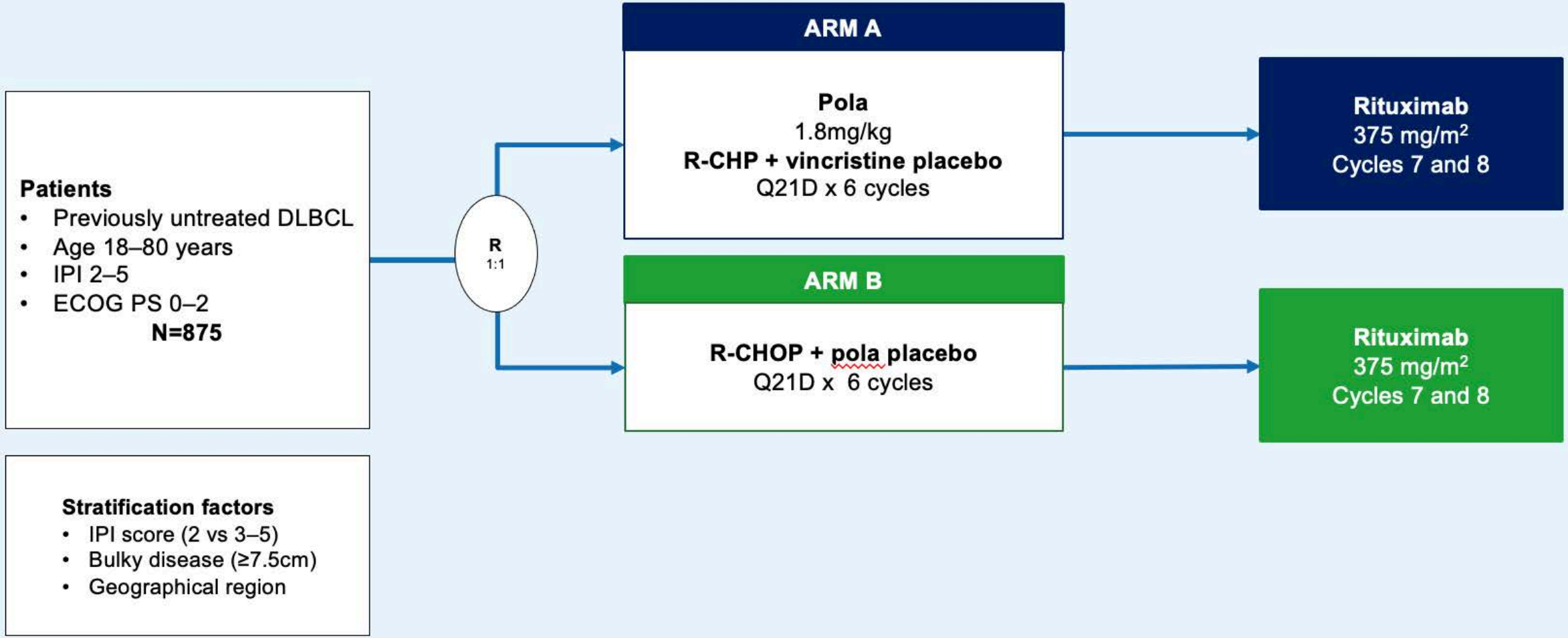
MODULE 3: New Agents Part 2 – Other Novel Strategies

MODULE 4: Clinical Situations for Special Consideration

RTP RESEARCH TO PRACTICE

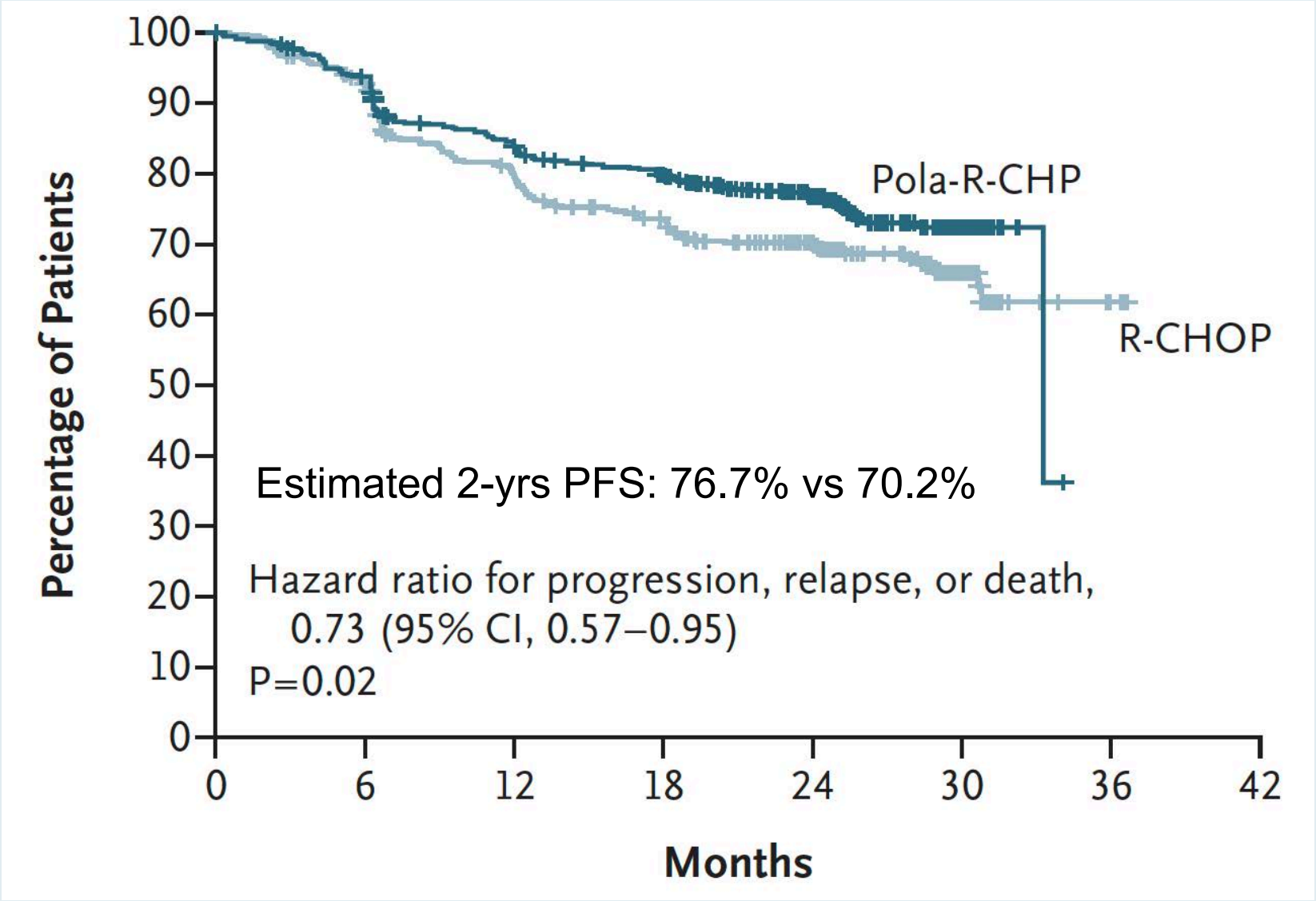
ADCs in the News

POLARIX Phase III Trial Design



Courtesy of Gilles Salles MD, PhD

POLARIX: Investigator-Assessed Progression-Free Survival (Primary Endpoint)



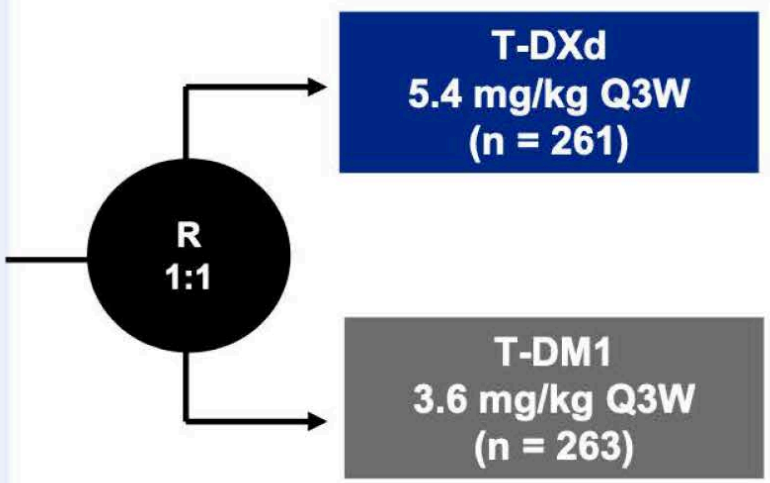
Tilly H et al. *N Engl J Med* 2021;[Online ahead of print].

DESTINY-Breast03 Phase III Trial Schema

An open-label, multicenter study (NCT03529110)

Patients
- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

Stratification factors
- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease



Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

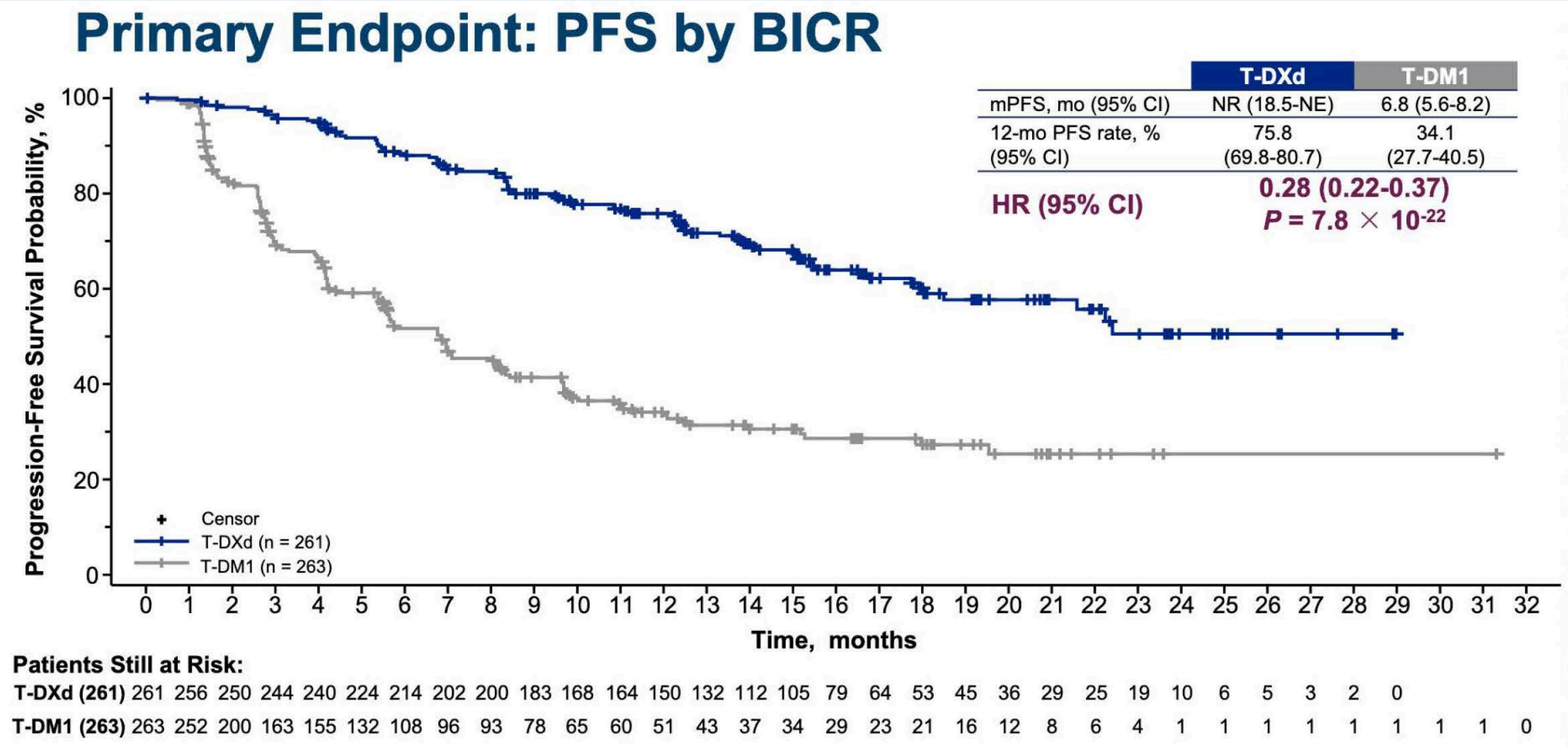
Secondary endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

Interim analysis for PFS (data cutoff: May 21, 2021)
- Efficacy boundary for superiority: $P < 0.000204$ (based on 245 events)
- IDMC recommendation to unblind study (July 30, 2021)

Key secondary endpoint, OS: boundary for efficacy: $P < 0.000265$ (based on 86 events)

Cortés J et al. ESMO 2021;Abstract LBA1.

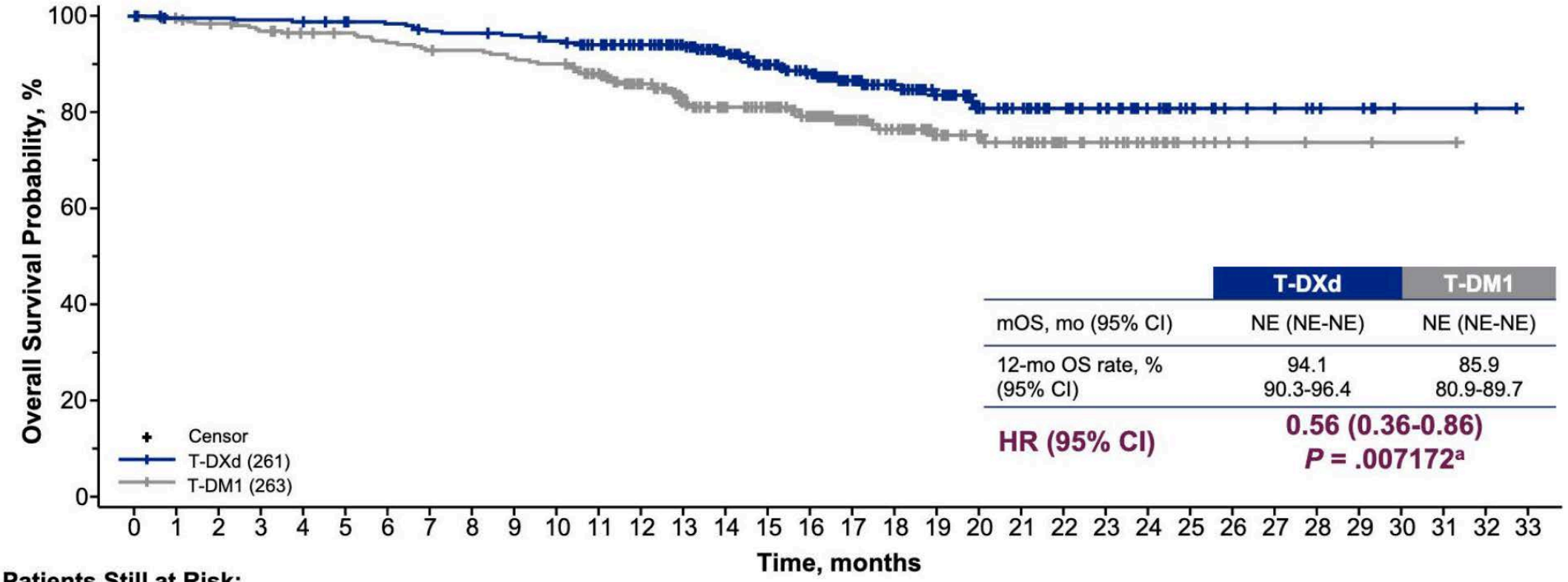
DESTINY-Breast03: Progression-Free Survival by BICR



Cortés J et al. ESMO 2021;Abstract LBA1.

DESTINY-Breast03: Overall Survival by BICR

Key Secondary Endpoint: OS



	T-DXd	T-DM1
mOS, mo (95% CI)	NE (NE-NE)	NE (NE-NE)
12-mo OS rate, % (95% CI)	94.1 90.3-96.4	85.9 80.9-89.7
HR (95% CI)	**0.56 (0.36-0.86)**	
	***P* = .007172[a]**	

Patients Still at Risk:

T-DXd (261)	261	256	256	255	254	251	249	244	243	241	237	230	218	202	180	158	133	108	86	71	56	50	42	33	24	18	11	10	7	6	2	2	1	0
T-DM1 (263)	263	258	253	248	243	241	236	232	231	227	224	210	188	165	151	140	120	91	75	58	52	44	32	27	18	11	5	4	3	3	1	1	0	

2021 ESMO congress

Early OS data with relatively few events (33 in the T-DXd arm, 53 in the T-DM1 arm)

[a]*P* = .007172, but does not cross pre-specified boundary of *P* < .000265

Cortés J et al. ESMO 2021;Abstract LBA1.

RTP RESEARCH TO PRACTICE

DESTINY-Breast03: Adverse Events of Special Interest

Adjudicated as drug-related ILD/pneumonitis[a], n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
T-DM1 (n = 261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)

- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd

LVEF decrease, n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	1 (0.4)[b]	6 (2.3)[c]	0	0	0	7 (2.7)
T-DM1 (n = 261)	0	1 (0.4)[c]	0	0	0	1 (0.4)

- In the T-DXd arm, all reported adverse events of LVEF decrease were asymptomatic and no cases of cardiac failure occurred

Cortés J et al. ESMO 2021;Abstract LBA1.

FDA Accelerated Approval Granted to Tisotumab Vedotin-tftv for Previously Treated Recurrent or Metastatic Cervical Cancer

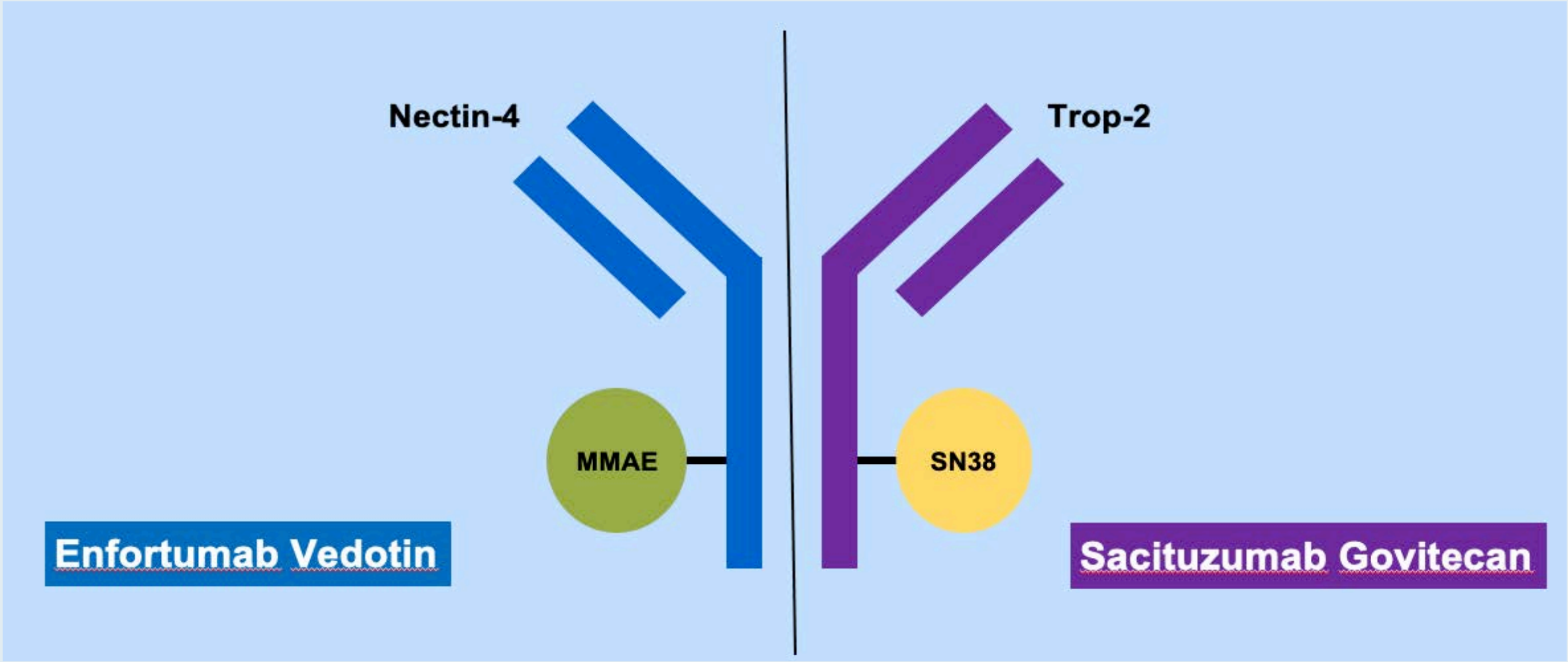
Press Release – September 20, 2021

"[It was announced today that the FDA] has granted accelerated approval to tisotumab vedotin-tftv, the first and only approved antibody-drug conjugate (ADC) for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. Tisotumab vedotin-tftv is approved under the FDA's Accelerated Approval Program based on tumor response and the durability of the response. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials."

The accelerated approval is based on results from the innovaTV 204 trial. InnovaTV 301, a global, randomized Phase III clinical trial intended to support global registrations, is under way. The prescribing information for tisotumab vedotin-tftv includes a BOXED WARNING for ocular toxicity and warnings for peripheral neuropathy, hemorrhage, pneumonitis and embryo-fetal toxicity.

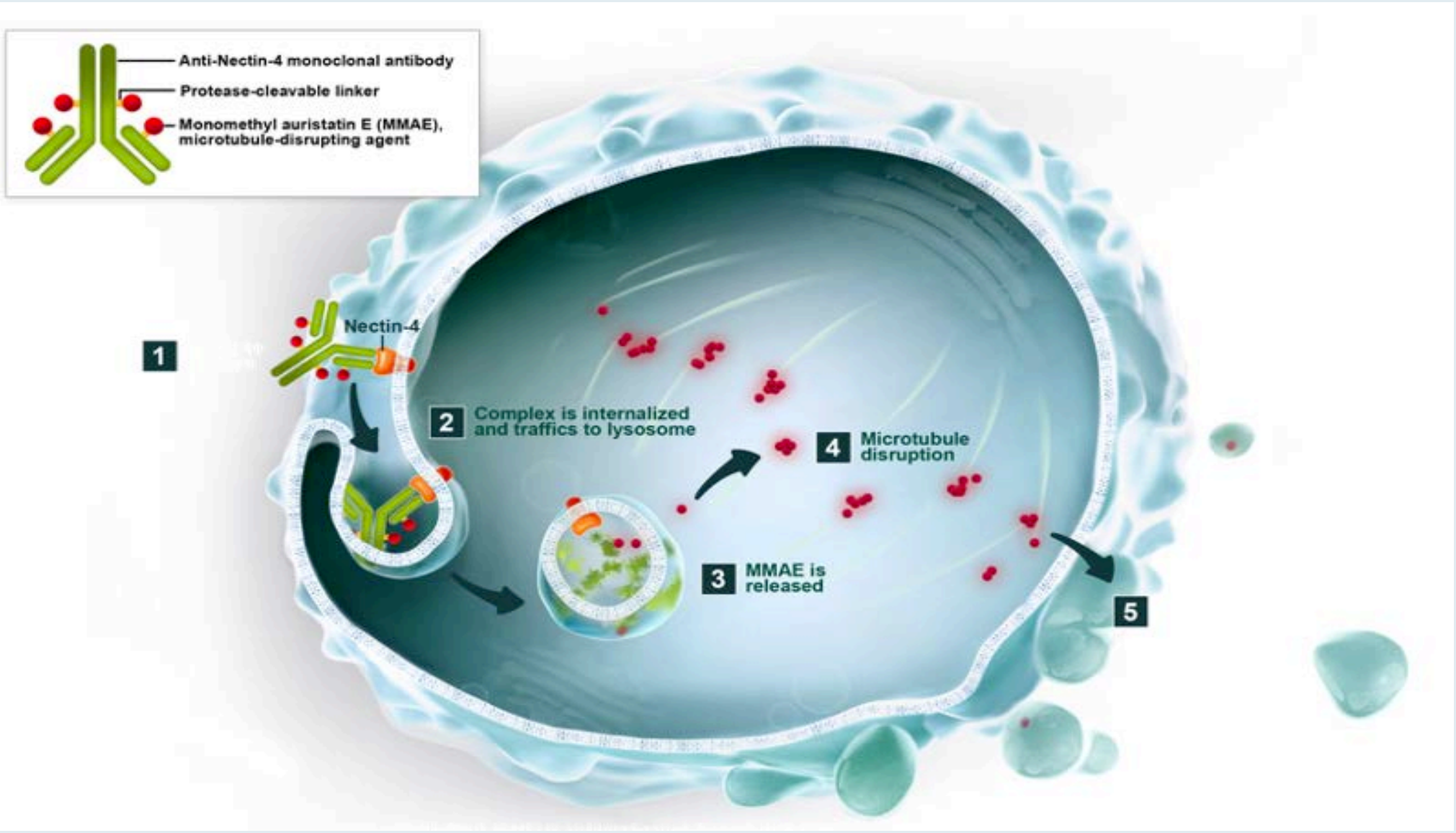
https://investor.seagen.com/press-releases/news-details/2021/Seagen-and-Genmab-Announce-FDA-Accelerated-Approval-for-TIVDAK-tisotumab-vedotin-tftv-in-Previously-Treated-Recurrent-or-Metastatic-Cervical-Cancer/default.aspx

Antibody-Drug Conjugates in UBC



Courtesy of Matthew Galsky, MD.

Enfortumab Vedotin: Nectin-4-Targeted Therapy



Courtesy of Jonathan Rosenberg, MD

RTP RESEARCH TO PRACTICE

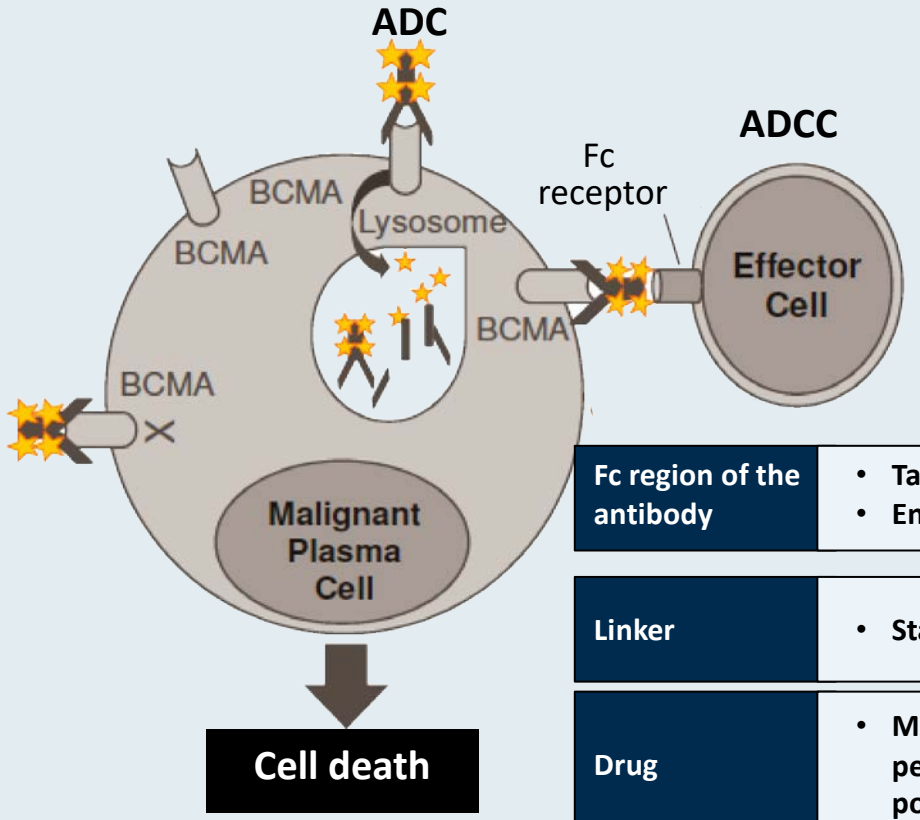
TROPHY-U-01: A Phase II Open-Label Study of Sacituzumab Govitecan in Patients With Metastatic Urothelial Carcinoma Progressing After Platinum-Based Chemotherapy and Checkpoint Inhibitors

Scott T. Tagawa, MD, MS[1]; Arjun V. Balar, MD[2]; Daniel P. Petrylak, MD[3]; Arash Rezazadeh Kalebasty, MD[4]; Yohann Loriot, MD, PhD[5]; Aude Fléchon, MD, PhD[6]; Rohit K. Jain, MD[7]; Neeraj Agarwal, MD[8]; Manojkumar Bupathi, MD, MS[9]; Philippe Barthelemy, MD, PhD[10]; Philippe Beuzeboc, MD, PhD[11]; Phillip Palmbos, MD, PhD[12]; Christos E. Kyriakopoulos, MD[13]; Damien Pouessel, MD, PhD[14]; Cora N. Sternberg, MD[1]; Quan Hong, MD[15]; Trishna Goswami, MD[15]; Loretta M. Itri, MD[15]; and Petros Grivas, MD, PhD[16]

J Clin Oncol 2021;39(22):2474-85.

Belantamab Mafodotin: Anti-BCMA Antibody-Drug Conjugate

- B-cell maturation factor (BCMA) expression is restricted to B cells at later stages of differentiation and is required for survival of plasma cells
- BCMA is broadly expressed at variable levels on malignant plasma cells
- Belantamab mafodotin is a humanized, afucosylated IgG1 anti-BCMA antibody conjugated to microtubule disrupting agent MMAF via a stable, protease-resistant maleimidocaproyl linker



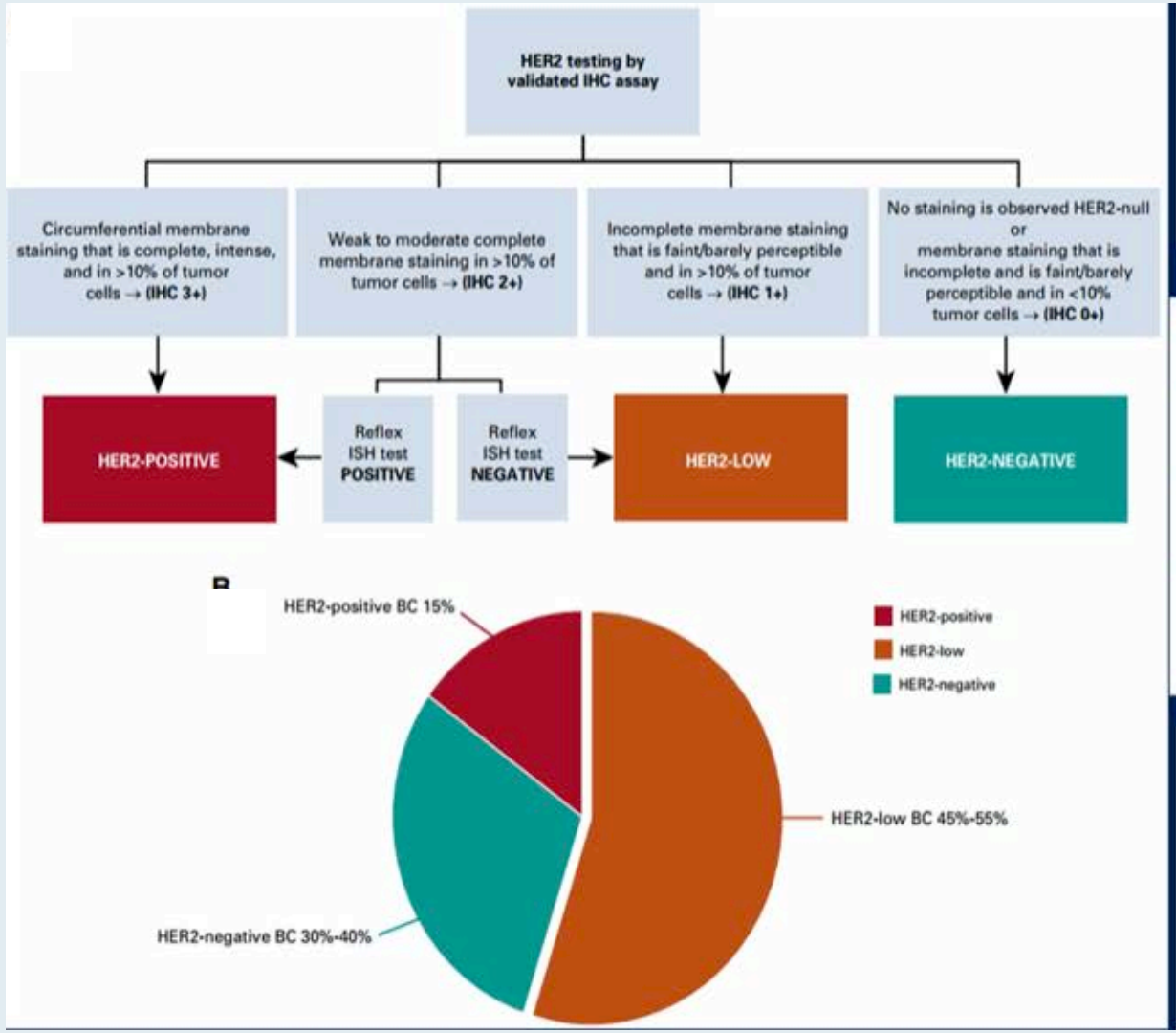
Fc region of the antibody	• **Target specific** • **Enhanced ADCC**
Linker	• **Stable in circulation**
Drug	• **MMAF (non cell permeable, highly potent auristatin)**

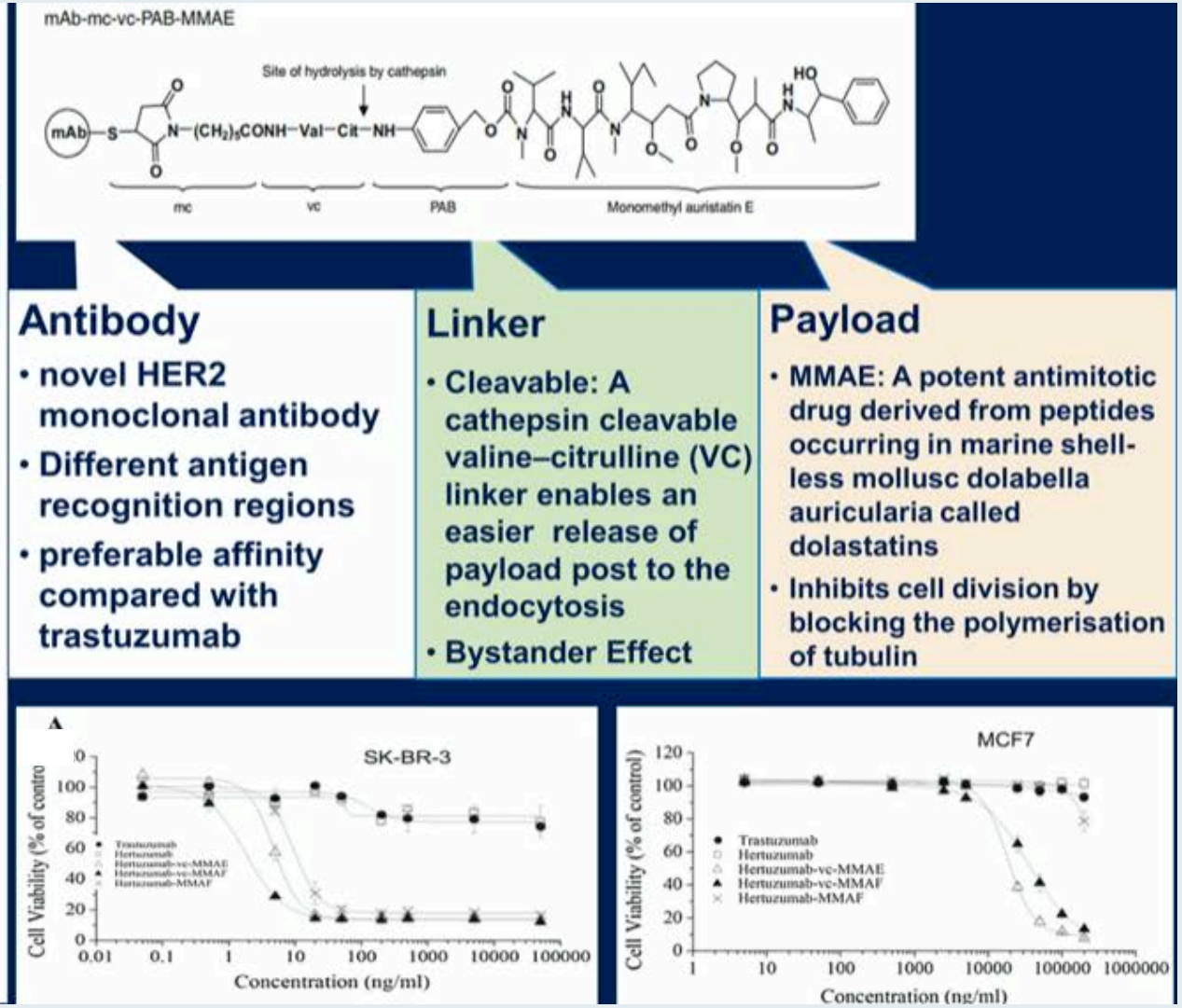
Mechanisms of action:
- ADC mechanism
- ADCC mechanism
- Immunogenic cell death
- BCMA receptor signaling inhibition

Tai YT et al. *Blood* 2014;123(20):3128-38.

RTP RESEARCH TO PRACTICE

Disitamab Vedotin: A Novel HER2-Targeted ADC





Wang J et al. ASCO 2021;Abstract 1022.

RTP RESEARCH TO PRACTICE

TROPION-PanTumor01: Updated Results From the NSCLC Cohort of the Phase 1 Study of Datopotamab Deruxtecan in Solid Tumors

Edward B. Garon, MD, MS

David Geffen School of Medicine at UCLA
Los Angeles, CA, USA

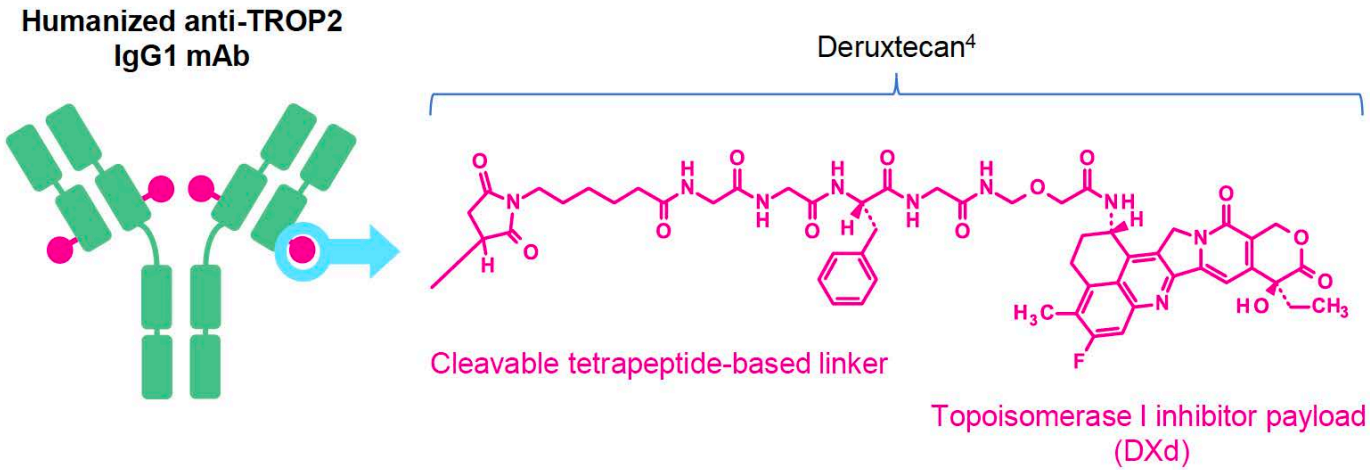
Edward B. Garon,[1] Melissa Johnson,[2] Aaron E. Lisberg,[1] Alexander Spira,[3] Noboru Yamamoto,[4] Rebecca S. Heist,[5] Jacob M. Sands,[6] Kiyotaka Yoh,[7] Funda Meric-Bernstam,[8] Satoru Kitazono,[9] Jonathan Greenberg,[10] Fumiaki Kobayashi,[11] Ferdinand Guevara,[10] Yui Kawasaki,[11] Toshio Shimizu[4]

[1]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [2]Sarah Cannon Research Institute, Tennessee Oncology, PLLC, OneOncology, Nashville, TN, USA; [3]Virginia Cancer Specialists and US Oncology Research, Fairfax, VA, USA; [4]National Cancer Center Hospital, Tokyo, Japan; [5]Massachusetts General Hospital, Boston, MA, USA; [6]Dana-Farber Cancer Institute, Boston, MA, USA; [7]National Cancer Center Hospital East, Chiba, Japan; [8]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [9]The Cancer Institute Hospital of JFCR, Tokyo, Japan; [10]Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; [11]Daiichi Sankyo Co, Ltd, Tokyo, Japan

IASLC 2021 World Conference on Lung Cancer
SEPTEMBER 8 - 14, 2021 I WORLDWIDE VIRTUAL EVENT

Dato-DXd Structure and 7 Key Attributes

- Datopotamab deruxtecan is an antibody drug conjugate composed of a humanized anti-trophoblast cell-surface antigen 2 (TROP2) IgG1 monoclonal antibody[1] attached to a topoisomerase I inhibitor payload, an exatecan derivative,[2,3] via a tetrapeptide-based cleavable linker[2,3]



Payload mechanism of action: topoisomerase I inhibitor[2,a]
High potency of payload[3,a]
Optimized drug-to-antibody ratio ≈4[2,a,b]
Payload with short systemic half-life[3,a,b]
Stable linker-payload[3,a]
Tumor-selective cleavable linker[3,a]
Bystander antitumor effect[3,5,a]

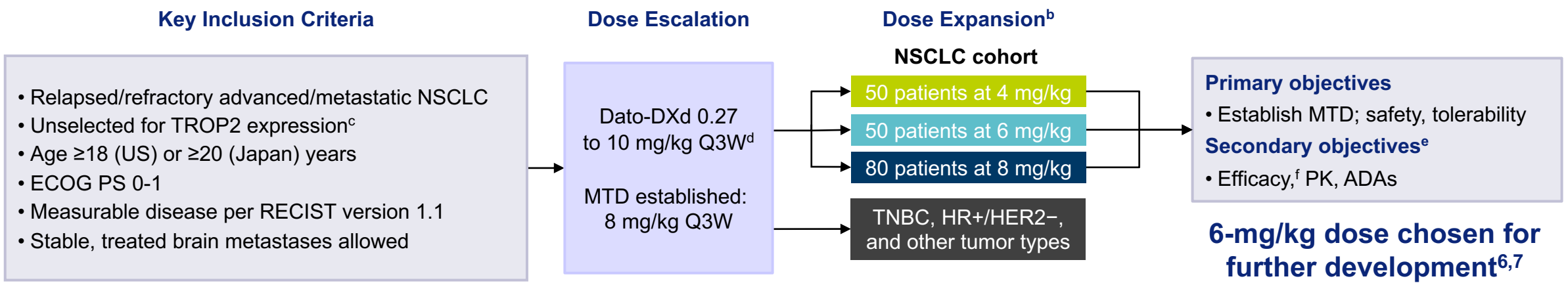
[a] The clinical relevance of these features is under investigation. [b] Based on animal data.

1. Daiichi Sankyo Co, Ltd. Accessed October 6, 2020. https://www.daiichisankyo.com/media_investors/investor_relations/ir_calendar/files/005438/DS-1062%20Seminar%20Slides_EN.pdf. 2. Okajima D, et al. AACR-NCI-EORTC 2019. Abstract C026. 3. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173-185. 4. Krop I, et al. SABCS 2019. Abstract GS1-03. 5. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

Introduction and Methods

- Patients with advanced or metastatic NSCLC represent a high unmet need[1]
- TROP2 is highly expressed in NSCLC and has been associated with poor prognosis[2-4]
- Datopotamab deruxtecan (Dato-DXd) is an antibody drug conjugate composed of a humanized anti-TROP2 monoclonal antibody conjugated to a potent topoisomerase I inhibitor payload via a stable tetrapeptide-based cleavable linker; this enables a bystander tumor effect resulting in elimination of both target tumor cells and surrounding cells[5,6]
- Previous results from the TROPION-PanTumor01 first-in-human study of Dato-DXd (NCT03401385) demonstrated highly encouraging antitumor activity with a manageable safety profile in patients with NSCLC.[6,7] Here we present updated results from the NSCLC cohort, with a data cutoff of April 6, 2021[a]

TROPION-PanTumor01 Study Design



6-mg/kg dose chosen for further development[6,7]

ADA, antidrug antibody; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; PK, pharmacokinetics; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TNBC, triple-negative breast cancer; TROP2, trophoblast cell-surface antigen 2.

[a] This analysis in the NSCLC cohort was performed 6 months after the last patient received their first dose of study drug on October 6, 2020. [b] Includes patients treated in the dose-escalation and dose-expansion portions. [c] Pretreatment tumor tissue was required for retrospective analysis of TROP2 expression. [d] The 4-, 6-, and 8-mg/kg dose levels are being further evaluated for safety and efficacy. [e] Additional exploratory objectives include analyses of biomarkers associated with response. [f] Response assessments are based on RECIST v1.1.

1. Simeone JC, et al. *Future Oncol.* 2019;15(30):3491-3502. 2. Mito R, et al. *Pathol Int.* 2020;70(5):287-294. 3. Inamura K, et al. *Oncotarget.* 2017;8(17):28725-28735. 4. Jiang A, et al. *Oncol Lett.* 2013;6(2):375-380. 5. Okajima D, et al. AACR-NCI-EORTC 2019. Abstract C026. 6. Meric-Bernstam F, et al. ASCO 2021. Abstract 9058. 7. Spira A, et al. WCLC 2020. Abstract 3407.

Baseline Characteristics and Patient Disposition

Characteristic	Dato-DXd dose		
	4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
Age, median (range), years	61 (35-82)	63 (38-76)	64 (31-84)
Age ≥65 years, %	36	40	46
Weight, median (range), kg	72 (38-156)	66 (39-104)	70 (38-115)
Male, %	54	56	51
Country, %			
United States	58	76	79
Japan	42	24	21
Histology, %			
Nonsquamous	82	90	88
Squamous	18	10	13
≥3 Prior lines of therapy, %	54	62	64
Previous systemic treatment, %			
Immunotherapy	88	74	88
Platinum-based chemotherapy	96	96	98
Tyrosine kinase inhibitor	20	18	19
***EGFR* mutations, %**	14	16	19
History of brain metastases, %	36	34	41

Treatment status	Dato-DXd dose		
	4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
Ongoing study treatment, n (%)[a]	9 (18)	5 (10)	7 (9)
Discontinued from study treatment, n (%)	41 (82)	45 (90)	73 (91)
Progression[b]	31 (62)	34 (68)	43 (54)
Adverse events	8 (16)	6 (12)	20 (25)
Death	0	1 (2)	1 (1)
Other[c]	2 (4)	4 (8)	9 (11)
Duration on study, median (range), mo	12.1 (7-29)	9.5 (6-27)	16.8 (10-25)
Exposure, median (range), mo	4.1 (0.7-27.6)	3.5 (0.7-26.2)	3.3 (0.7-20.4)

- Patients were heavily pretreated, with 74%-88% having received prior immunotherapy and 96%-98% having received prior platinum-based chemotherapy across dose cohorts

Data cutoff: April 6, 2021.
EGFR, epidermal growth factor receptor.
[a] Due to a later time of enrollment, follow-up was shorter for patients treated with the 4- and 6-mg/kg doses than for those treated with the 8-mg/kg dose. [b] Includes progressive disease per RECIST v1.1 and clinical progression. [c] Includes physician decision, withdrawal by subject, and other.

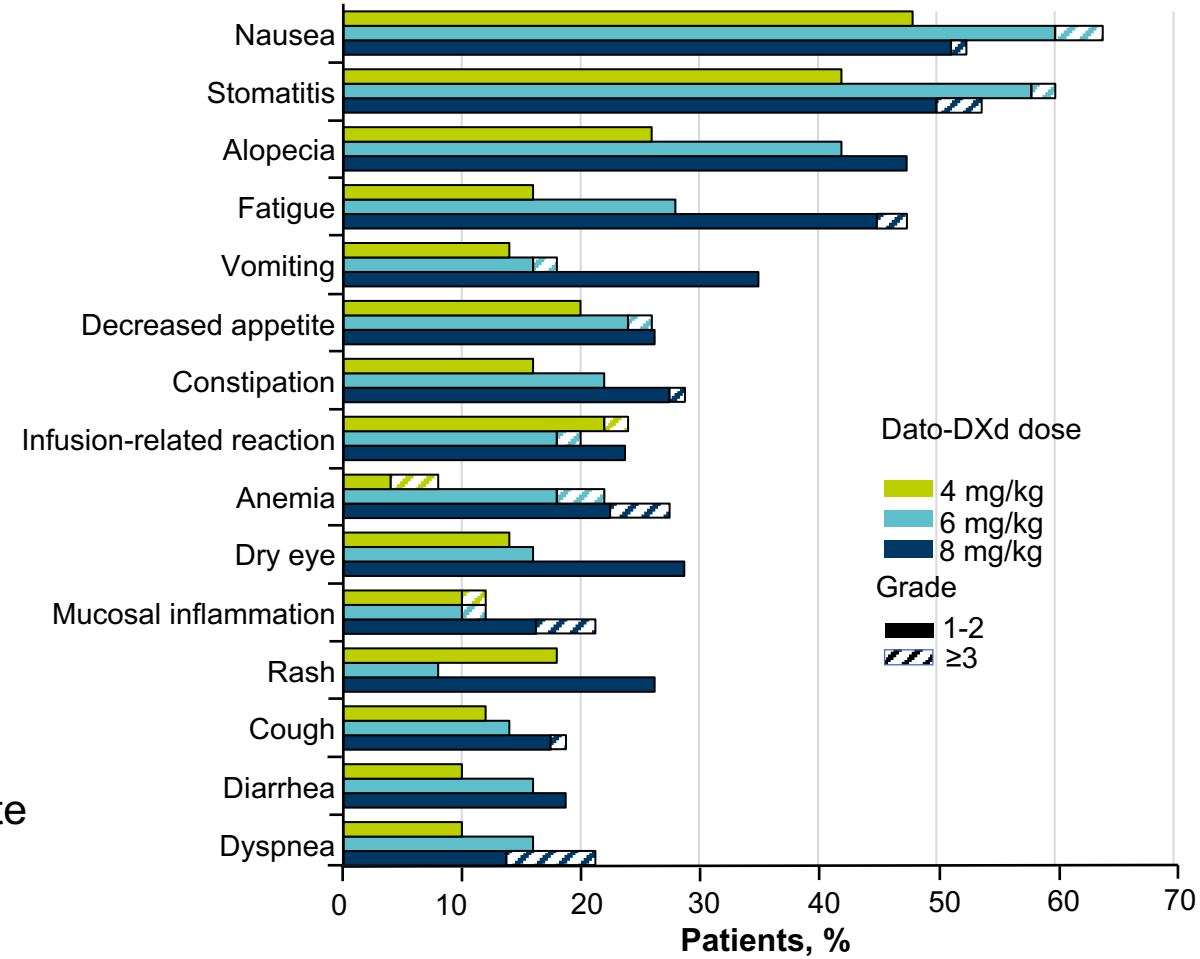
Safety

Overall Safety Summary

Patients, n (%)	Dato-DXd dose		
	4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
TEAE	49 (98)	49 (98)	80 (100)
Grade ≥3	15 (30)	27 (54)	46 (58)
Drug-related TEAE	47 (94)	41 (82)	78 (98)
Grade ≥3	7 (14)	13 (26)	28 (35)
Serious TEAE	10 (20)	24 (48)	40 (50)
Grade ≥3	10 (20)	18 (36)	37 (46)
Dose adjustments			
TEAEs associated with discontinuation	8 (16)	7 (14)	19 (24)
TEAEs associated with dose interruption	4 (8)	15 (30)	29 (36)
TEAEs associated with dose reduction	1 (2)	5 (10)	23 (29)
ILD adjudicated as drug related[a]	5 (10)	3 (6)	11 (14)
Grade ≤2	4 (8)	2 (4)	7 (9)
Grades 3-4	1 (2)	1 (2)	1 (1)
Grade 5	0	0	3 (4)

- The safety profile was manageable with mainly mild/moderate toxicity; TEAEs were primarily nonhematologic

TEAEs in ≥15% of Patients[b]



Data cutoff: April 6, 2021.
ILD, interstitial lung disease; TEAE, treatment-emergent adverse event.
[a] Cases of ILD adjudicated as drug related comprised 5 patients in the 4-mg/kg cohort (1 grade 1, 3 grade 2, 1 grade 3), 3 patients in the 6-mg/kg cohort (2 grade 2, 1 grade 4), and 11 patients in the 8-mg/kg cohort (2 grade 1, 5 grade 2, 1 grade 3, 3 grade 5). [b] Of 180 patients (4 mg/kg [n=50]; 6 mg/kg [n=50]; 8 mg/kg [n=80]).

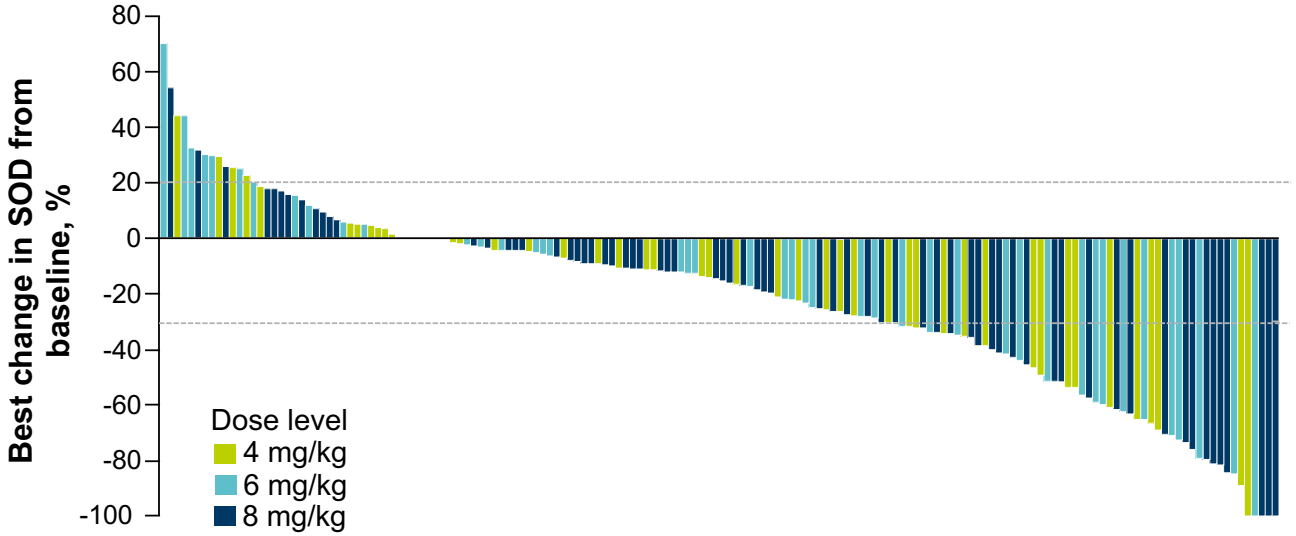
Antitumor Activity of Dato-DXd

Best Overall Response (BICR)

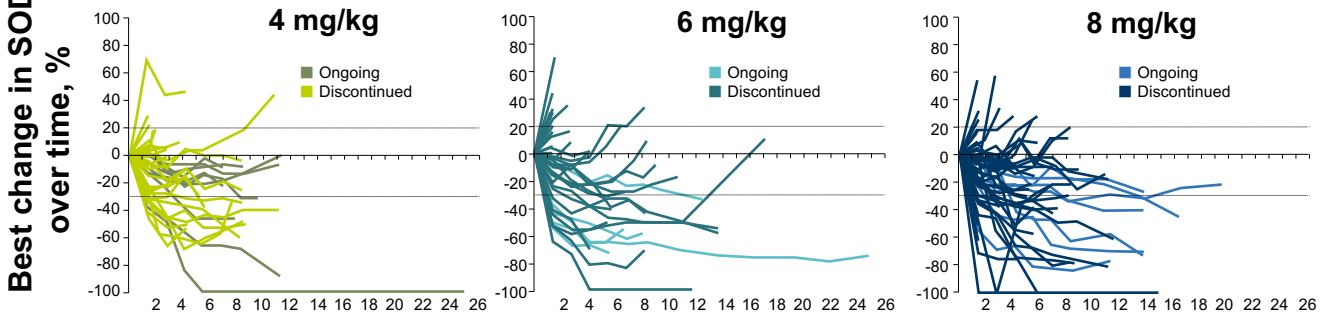
Patients[a]	Dato-DXd dose		
	4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
ORR, n (%)[b]	12 (24)	14 (28)	19 (24)
CR, n (%)	0	0	1 (1)
PR, n (%)[b]	12 (24)	14 (28)	18 (23)
SD, n (%)	25 (50)	20 (40)	42 (53)
Non-CR/PD, n (%)	1 (2)	2 (4)	2 (3)
PD, n (%)	7 (14)	10 (20)	8 (10)
NE, n (%)	5 (10)	5 (10)	9 (11)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



Data cutoff: April 6, 2021.
BICR, blinded independent central review; CR, complete response; DOR, duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SOD, sum of diameters; SD, stable disease.
[a] Includes response-evaluable patients who had ≥1 postbaseline tumor assessment or discontinued treatment. [b] ORR and CR/PR include 1 response in the 6-mg/kg cohort that is pending confirmation.

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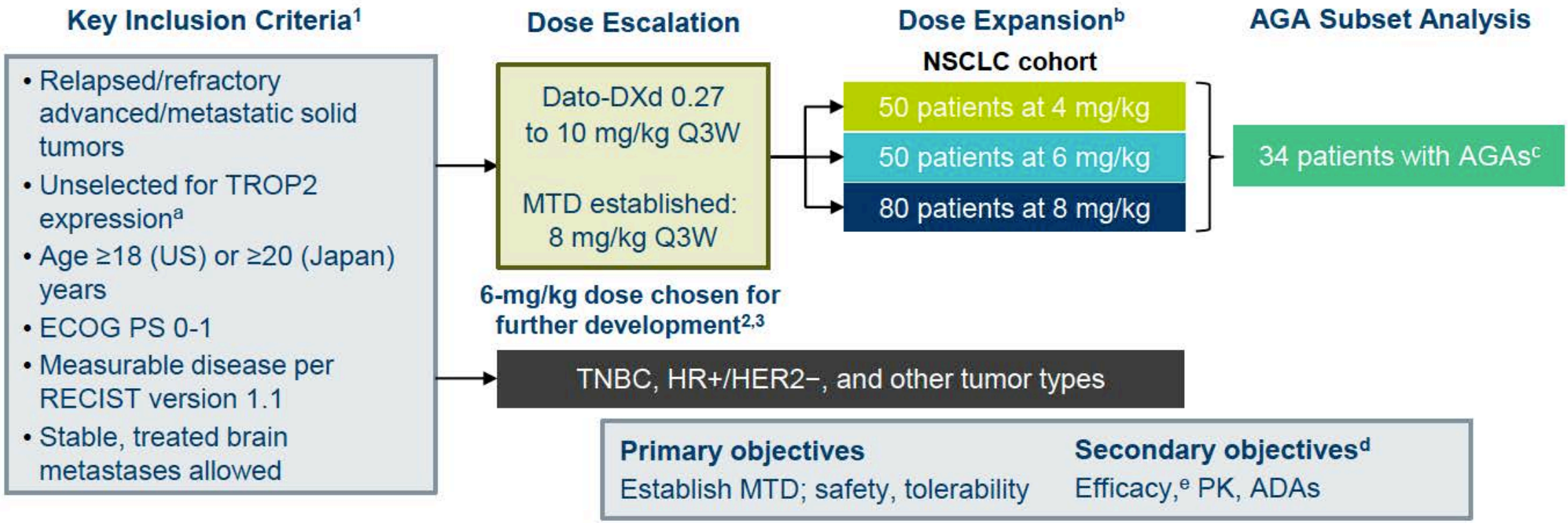
Efficacy of Datopotamab Deruxtecan (Dato-DXd) in Patients With Advanced/Metastatic Non-Small Cell Lung Cancer (NSCLC) and Actionable Genomic Alterations (AGAs): Preliminary Results From the Phase 1 TROPION-PanTumor01 Study

Edward B. Garon,[1] Melissa L. Johnson,[2] Aaron E. Lisberg,[1] Alexander Spira,[3] Noboru Yamamoto,[4] Rebecca S. Heist,[5] Jacob M. Sands,[6] Kiyotaka Yoh,[7] Funda Meric-Bernstam,[8] Satoru Kitazono,[9] Jonathan Greenberg,[10] Fumiaki Kobayashi,[11] Yui Kawasaki,[11] Lori Jukofsky,[10] Kota Nakamura,[10] Toshio Shimizu[4]

[1]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [2]Sarah Cannon Research Institute, Tennessee Oncology, PLLC/OneOncology, Nashville, TN, USA; [3]Virginia Cancer Specialists, Fairfax, VA, USA; [4]Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan; [5]Massachusetts General Hospital, Boston, MA, USA; [6]Dana-Farber Cancer Institute, Boston, MA, USA; [7]National Cancer Center Hospital East, Chiba, Japan; [8]The University of Texas, MD Anderson Cancer Center, Houston, TX, USA; [9]The Cancer Institute Hospital of JFCR, Tokyo, Japan; [10]Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; [11]Daiichi Sankyo Co, Ltd, Tokyo, Japan

TROPION-PanTumor01 Study Design



ADA, antidrug antibody; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MTD, maximum tolerated dose; PK, pharmacokinetics; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TNBC, triple-negative breast cancer.

[a] Pretreatment tumor tissue was required for retrospective analysis of TROP2 expression. [b] Includes patients treated in the dose-escalation and dose-expansion portions. [c] AGAs were investigator reported. [d] Additional exploratory objectives include analyses of biomarkers associated with response. [e] Response assessments are based on RECIST 1.1.

1. ClinicalTrials.gov. Accessed August 26, 2021. https://clinicaltrials.gov/ct2/show/NCT03401385. 2. Meric-Bernstam F, et al. ASCO 2021. Abstract 9058. 3. Spira A, et al. WCLC 2020. Abstract 3407.

Garon EB et al. ESMO 2021: Abstract LBA49

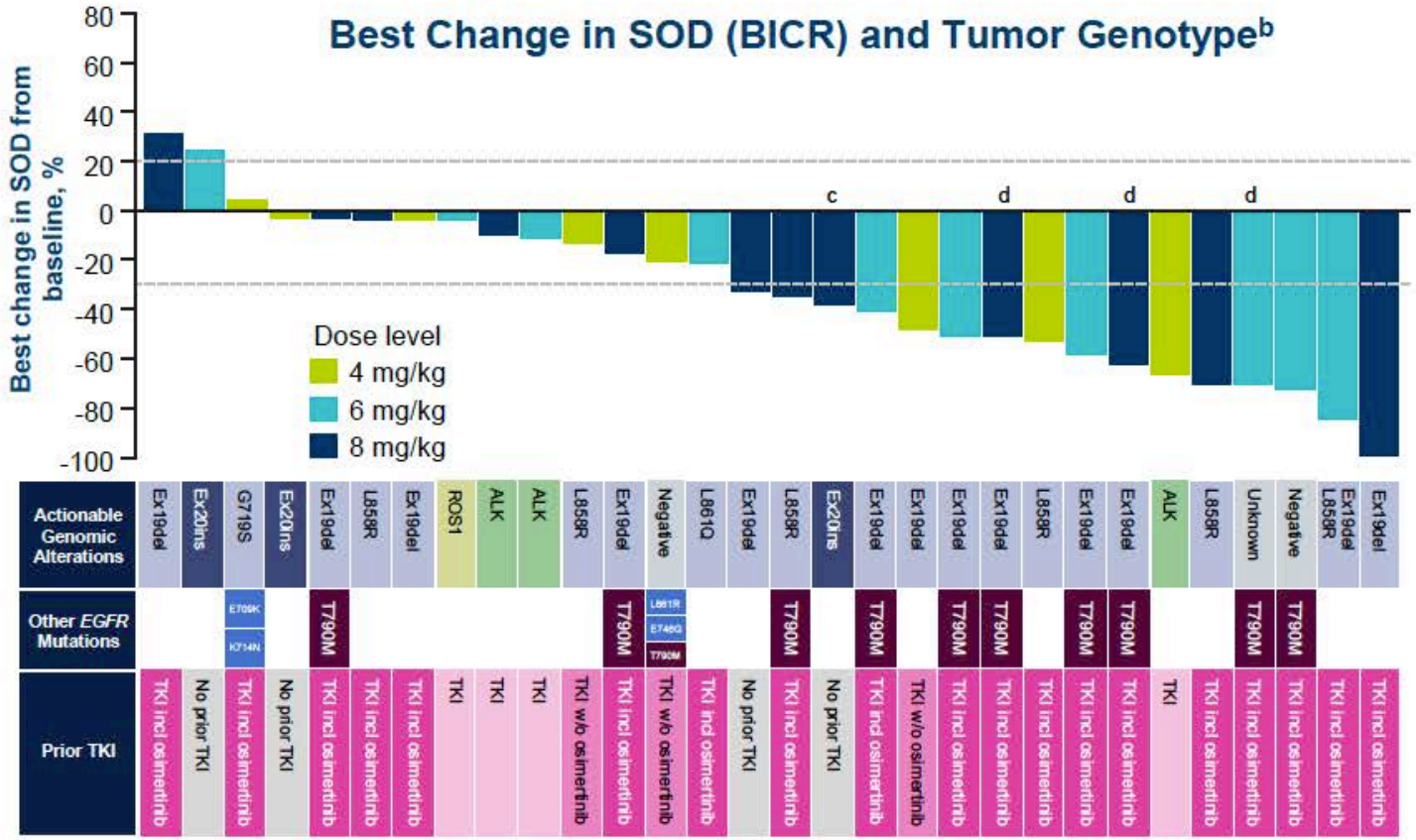
NSCLC With AGAs: Antitumor Activity

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

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



Data cutoff: April 6, 2021.

BICR, blinded independent central review; CR, complete response; DOR, duration of response; incl, including; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SOD, sum of diameters; SD, stable disease; w/o, without.

[a] Includes response-evaluable patients who had ≥1 postbaseline tumor assessment or discontinued treatment. [b] 4 patients were not included in the waterfall plot: 2 who did not have a target lesion per BICR and 2 who did not have on-study treatment images. [c] Patient NE. [d] Patients with unconfirmed PR.

2021 ESMO congress

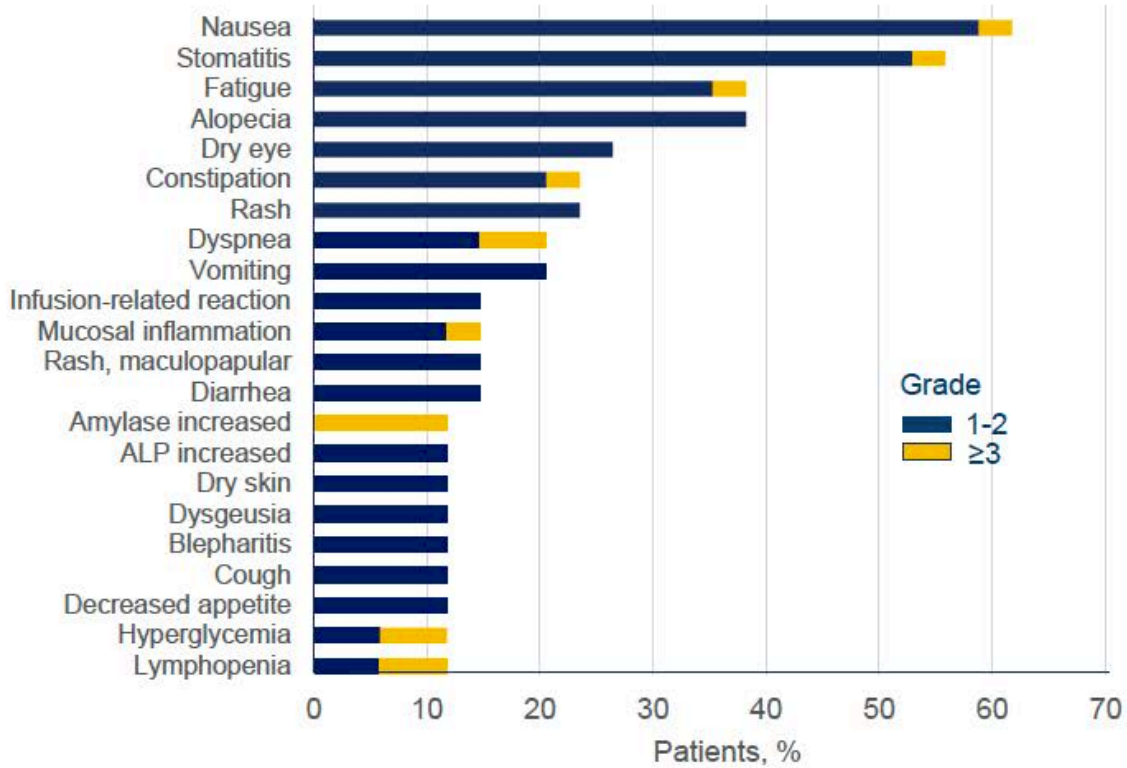
Edward B. Garon, MD, MS

Garon EB et al. ESMO 2021: Abstract LBA49

NSCLC With AGAs: Safety

Adverse events, n (%)	Dato-DXd n=34
TEAE, %	100
Grade ≥3	53
Drug-related TEAE, %	88
Grade ≥3	38
Serious TEAE, %	35
Grade ≥3	29
Dose adjustments, %	
TEAEs associated with discontinuation	15
TEAEs associated with dose interruption	27
TEAEs associated with dose reduction	15
ILD adjudicated as drug related, n[a]	1
Grade ≤2	0
Grade 3/4	0
Grade 5	1

TEAEs in ≥10% of Patients[b] (n=34)



- The safety profile of Dato-DXd was manageable and consistent with that observed in the overall NSCLC population in TROPION-PanTumor01; TEAEs were primarily nonhematologic

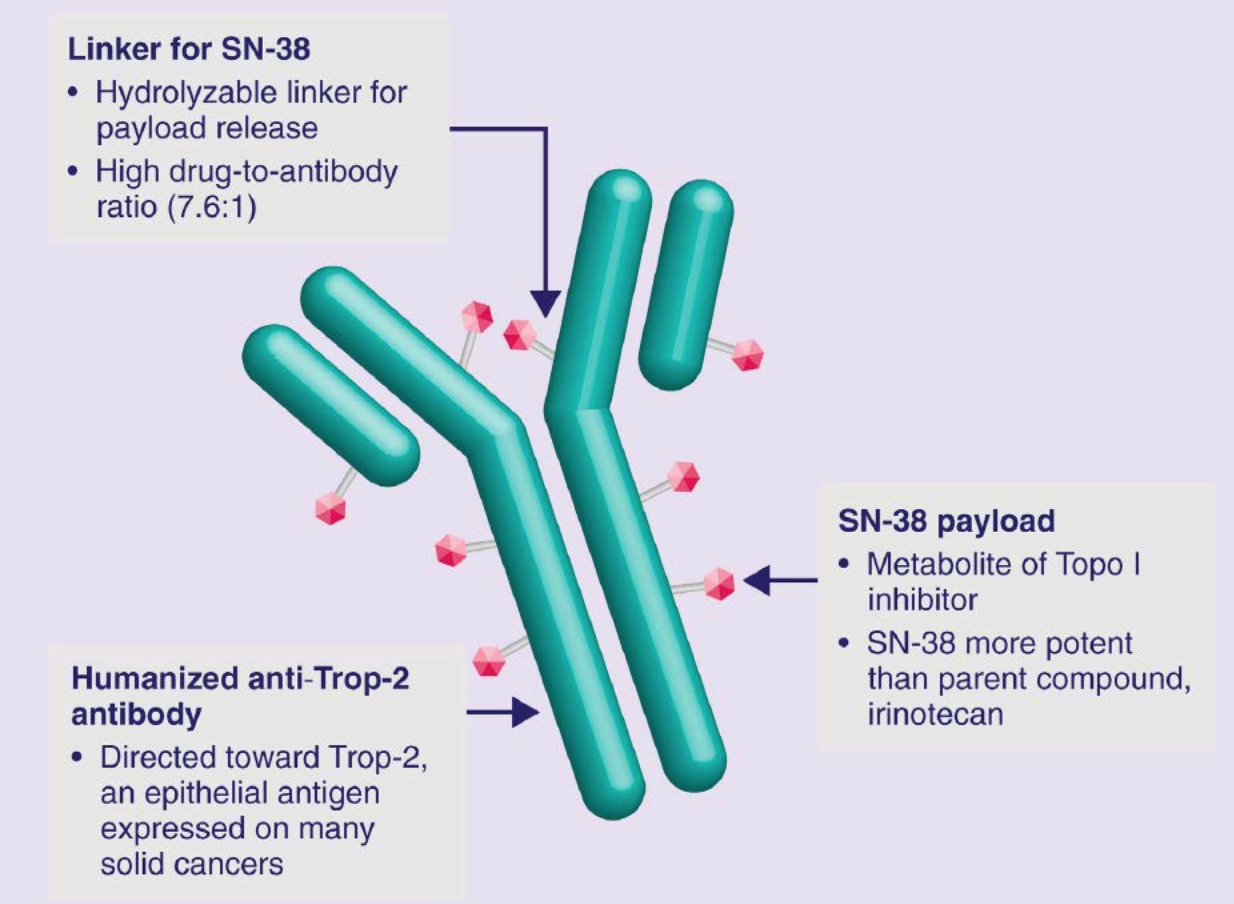
Data cutoff: April 6, 2021.
ALP, alkaline phosphatase; ILD, interstitial lung disease; TEAE, treatment-emergent adverse event.
[a] The case of adjudicated ILD occurred in a patient who received Dato-DXd 8 mg/kg. [b] Any grade TEAEs occurring in <10% of patients but with grade ≥3 occurring in ≥5% of patients included ulcerative keratitis.
Garon EB, et al. WCLC 2021. Abstract MA03.02.

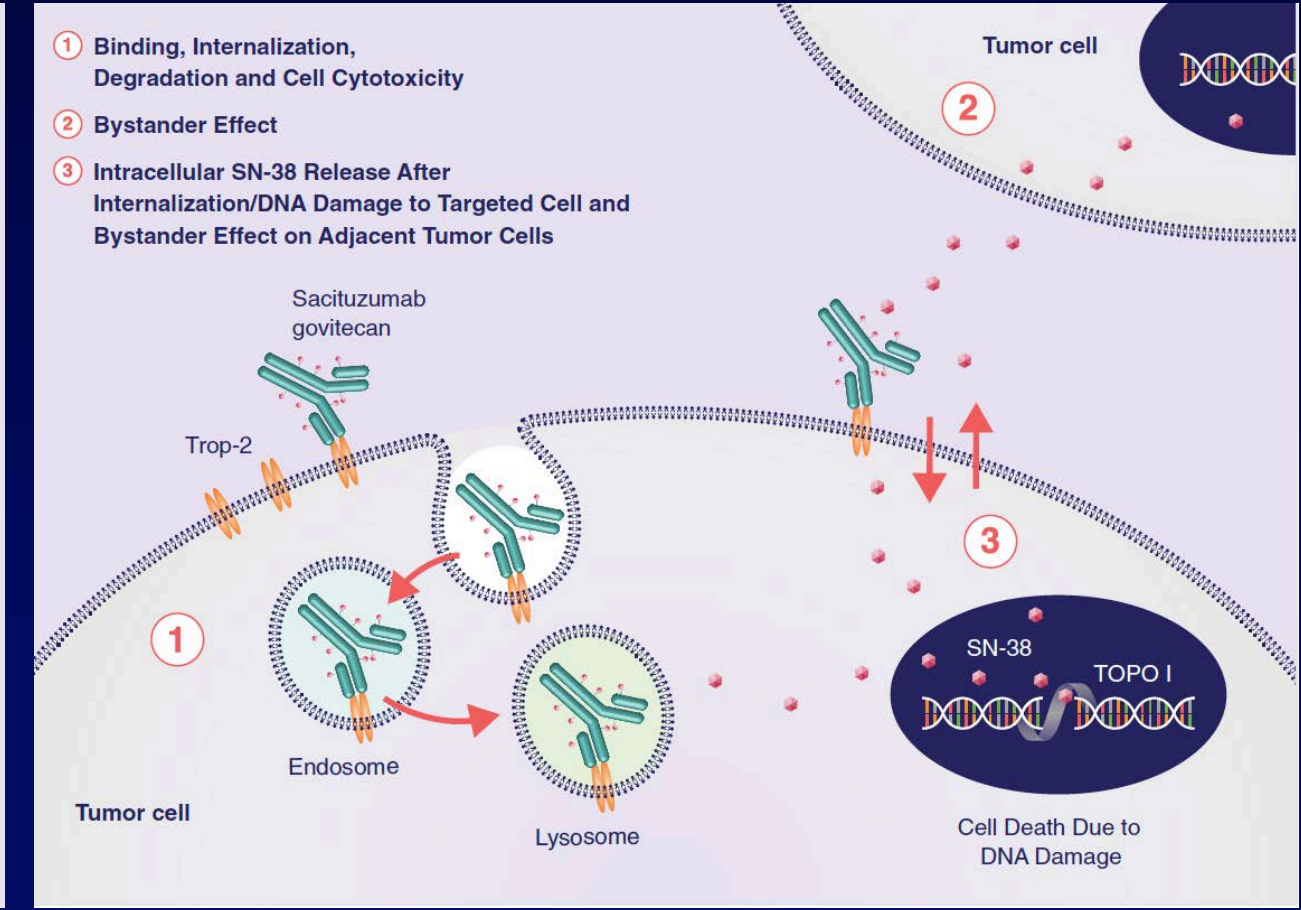
2021 ESMO congress

Edward B. Garon, MD, MS

Garon EB et al. ESMO 2021: Abstract LBA49

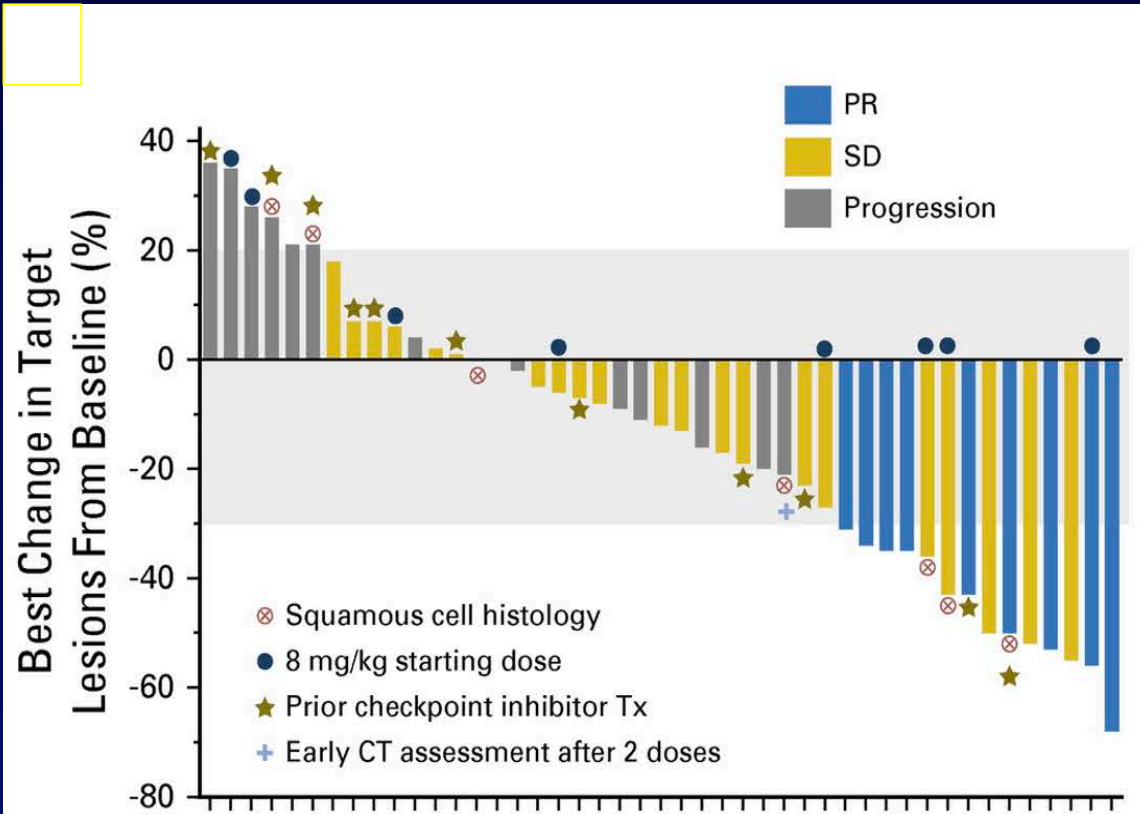
Sacituzumab Govitecan Is a First-in-Class TROP-2-Directed Antibody-Drug Conjugate

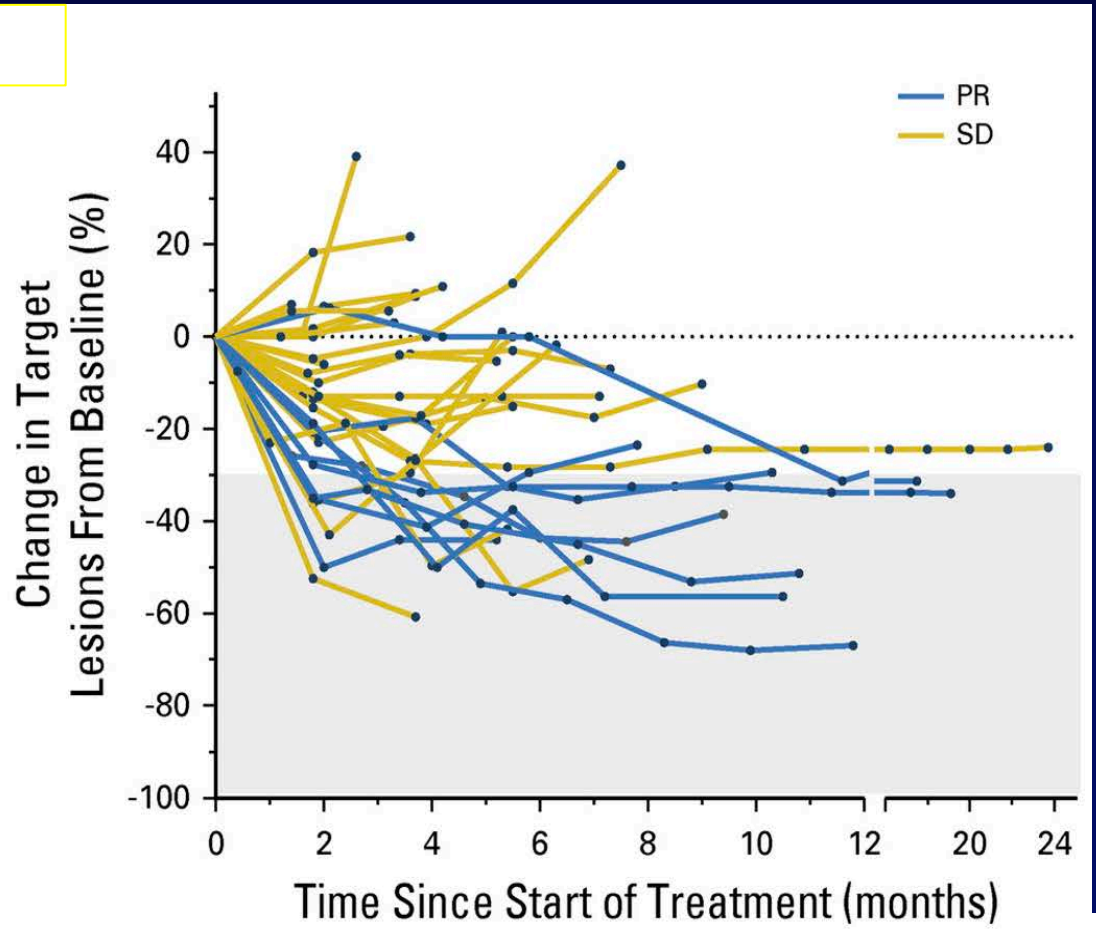




Rugo H et al. *Future Oncol* 2020;16(12):705-15.

Phase I/II study of Sacituzumab Govitecan in patients with heavily pre-treated metastatic NSCLC





Heist R, et al. J Clin Oncol. 2017

Ongoing studies of Sacituzumab Govitecan for patients with progressive NSCLC

- **A Phase I/II Study of Sacituzumab Govitecan Plus Berzosertib in Small Cell Lung Cancer and Homologous Recombination-Deficient Cancers Resistant to PARP Inhibitors**

- **Study of Sacituzumab Govitecan-hziy (SG) Versus Docetaxel in Participants With Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) With Progression on or After Platinum-Based Chemotherapy and Anti-programmed Death Protein 1 (PD-1)/Programmed Death Ligand 1 (PD-L1) Immunotherapy (EVOKE-01)**

Comment > Cancer Discov. 2022 Jan;12(1):74-89. doi: 10.1158/2159-8290.CD-21-0715.
Epub 2021 Sep 21.

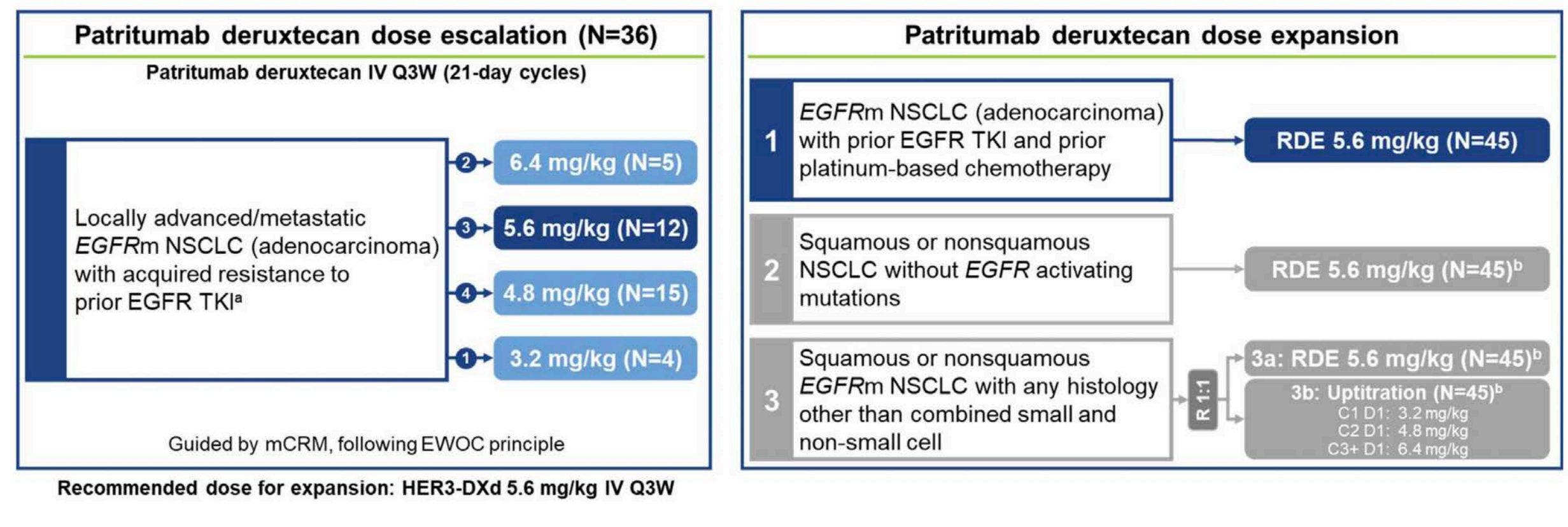
Efficacy and Safety of Patritumab Deruxtecan (HER3-DXd) in EGFR Inhibitor–Resistant, *EGFR*–Mutated Non–Small Cell Lung Cancer

Pasi A Jänne [1], Christina Baik [2], Wu-Chou Su [3], Melissa L Johnson [4], Hidetoshi Hayashi [5], Makoto Nishio [6], Dong-Wan Kim [7], Marianna Koczywas [8], Kathryn A Gold [9], Conor E Steuer [10], Haruyasu Murakami [11], James Chih-Hsin Yang [12], Sang-We Kim [13], Michele Vigliotti [14], Rong Shi [14], Zhenhao Qi [14], Yang Qiu [14], Lihui Zhao [14], David Sternberg [14], Channing Yu [14], Helena A Yu [15]

Affiliations + expand

PMID: 34548309 DOI: 10.1158/2159-8290.CD-21-0715

Efficacy and Safety of Patritumab Deruxtecan (HER3-DXd) for EGFR Inhibitor-Resistant, EGFR-Mutated NSCLC



Jänne PA et al. *Cancer Discovery* 2022;12(1):74-89.

RTP RESEARCH TO PRACTICE

Agenda

Introduction: Metastatic Non-Small Cell Lung Cancer (NSCLC) in Clinical Practice

MODULE 1: Sequencing of Therapies in Metastatic NSCLC

MODULE 2: New Agents Part 1 – Antibody-Drug Conjugates

MODULE 3: New Agents Part 2 – Other Novel Strategies

- Plinabulin
- Tumor treating fields
- Anti-PD-1/PD-L1 with anti-CTLA-4
- Anti-PD-1/PD-L1 with tyrosine kinase inhibitors

MODULE 4: Clinical Situations for Special Consideration

Approaches to Replace the Current Standard of Care

- **Add on to the current standard of care**
- **Replace the current standard of care**

2021 ESMO congress

DUBLIN-3 (BPI-2358-103): A Global Phase 3 Trial with the Plinabulin/Docetaxel combination vs. Doc in 2nd/3rd Line NSCLC Patients with EGFR-wild type Progressing on a Prior Platinum-Based Regimen (NCT02504489)

Presented by:

Trevor Feinstein, MD
Piedmont Cancer Institute, Atlanta, Georgia

on behalf of

Baohui Han, MD
Department of Pulmonary Medicine
Shanghai Chest Hospital, Shanghai, China

Abstract # 3797

DUBLIN -3 STUDY OVERVIEW

Plinabulin/Docetaxel combination vs. Docetaxel (NCT02504489)

DUBLIN - 3

- Non-squamous or squamous NSCLC
- Stage IIIb/IV
- ECOG performance status ≤ 2
- Progression during or after treatment with one or two treatment regimen containing platinum
- Must have at least one measurable lung lesion
- Prior checkpoint inhibitor therapy allowed
- Written consent

Randomized 1:1
21-day cycle
(n=559)

Docetaxel + Plinabulin (N=278)
All Cycles:
Day 1:Docetaxel 75 mg/m2 + Plinabulin 30mg/m2
Day 8: Plinabulin 30mg/m2

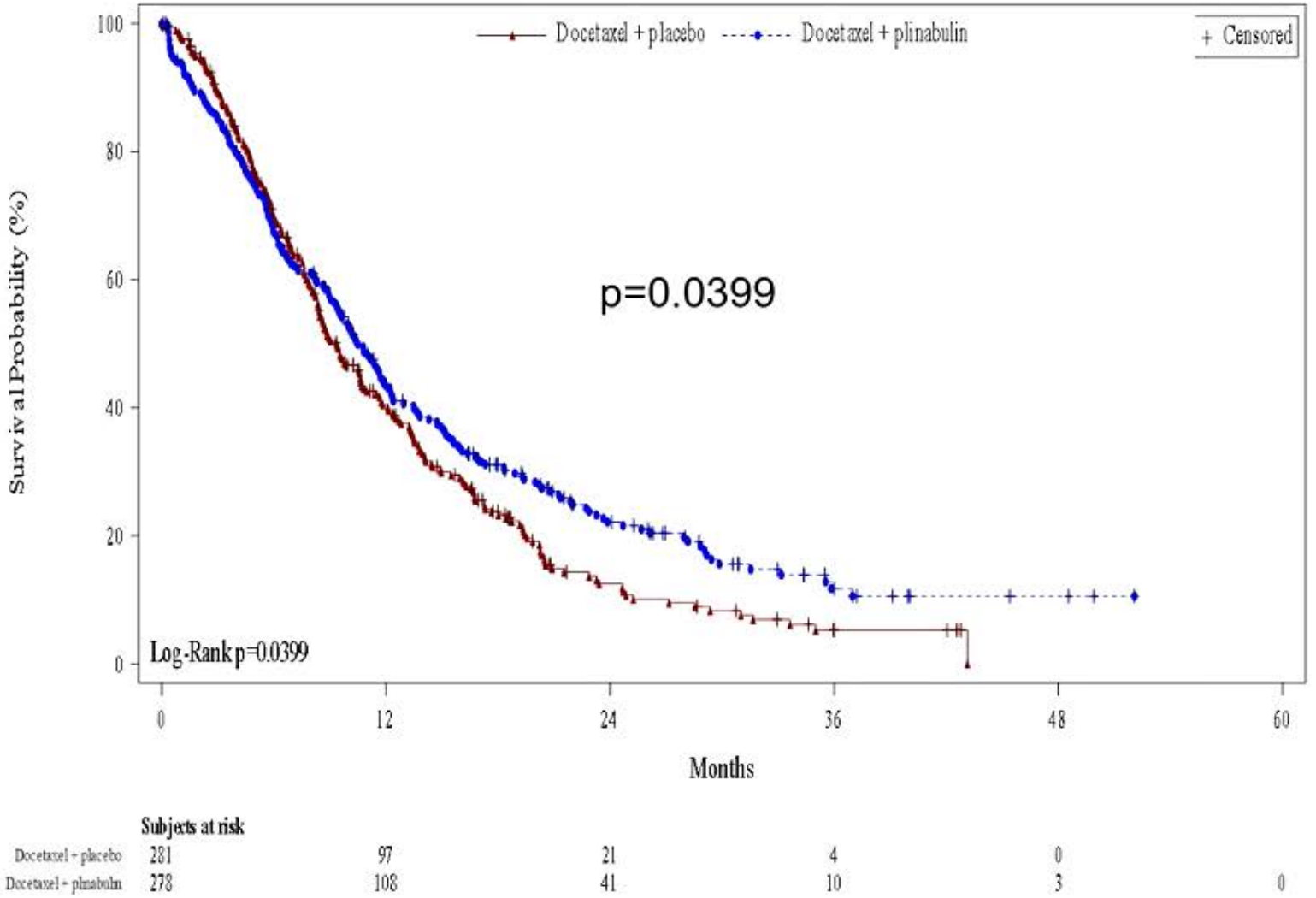
→ PD

Docetaxel + Placebo (N=281)
All Cycles:
Day1: Docetaxel 75 mg/m2 + Placebo
Day 8:Placebo

→ PD

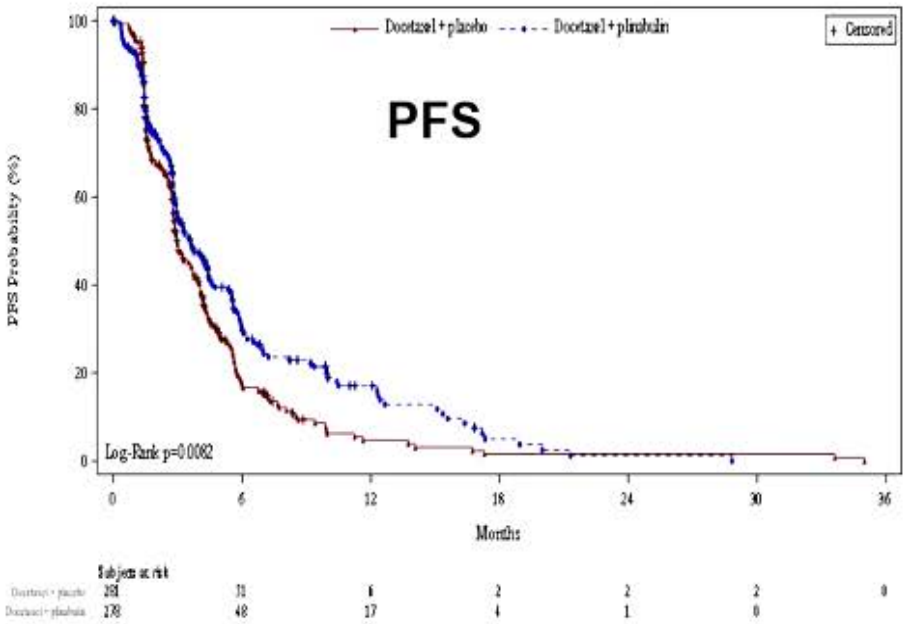
- ✓ **Primary endpoint**: Overall Survival (OS)
- ✓ **Secondary endpoints:** ORR, PFS , Percent of patients with grade 4 neutropenia on C1D8, Month 24 OS rate, Month 36 OS rate , DoR , Q-TWiST, QoL, % patients who received docetaxel >8 cycles, >10 cycles, and >12 cycles

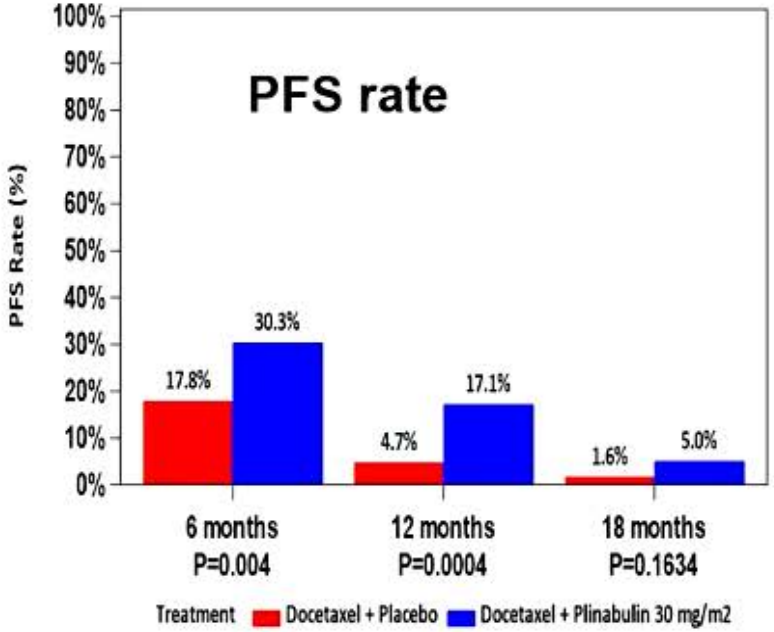
Met Primary Study Objective in Overall Survival (OS)

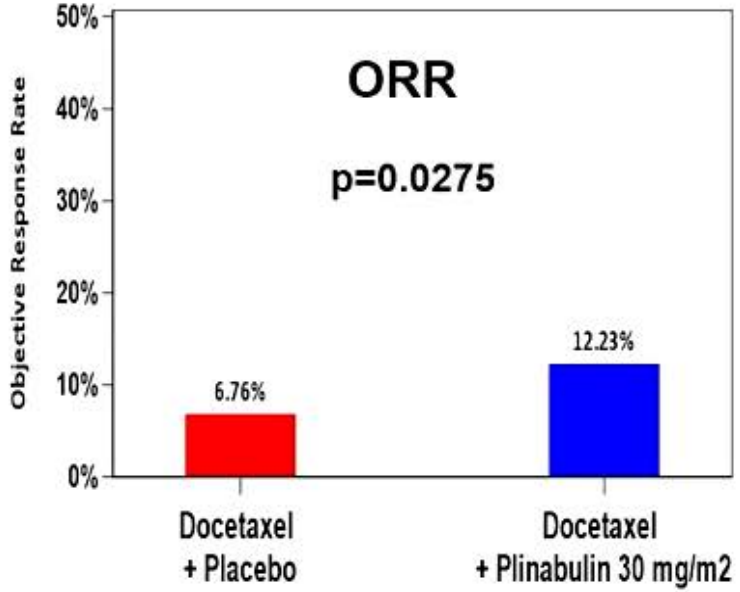


ITT population	Docetaxel (75 mg/m2) N=281	Plinabulin (30 mg/m2) + Docetaxel (75 mg/m2) N=278
OS (Months)	Mean OS (SE): 12.77 (0.676) Median OS (95% CI): 9.4 (8.4, 10.7)	Mean OS (SE): 15.08 (0.848), p=0.0332 Median OS (95% CI): 10.5 (9.3, 11.9) Log-rank p=0.0399; HR = 0.82 (0.68,0.99)

Significant Improvement in PFS, Double ORR with Plinabulin





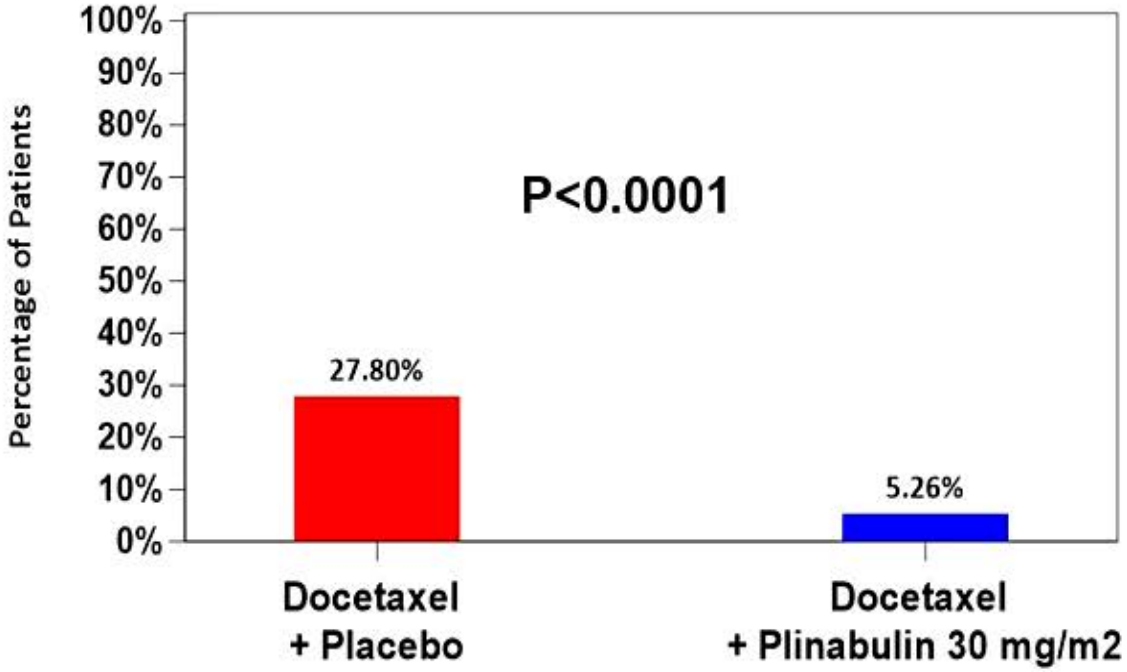


Secondary Endpoint (ITT population)	Docetaxel(75 mg/m2) N=281	Plinabulin (30 mg/m2) + Docetaxel (75 mg/m2) N=278
PFS* (months or M)	Mean PFS (SE): 4.4 Median PFS (95% CI): 3.0 (2.8, 3.7)	Mean PFS (SE): 6.0; p=0.0062 Median PFS (95% CI): 3.6 (3.0, 4.4), Log-rank p=0.0082; HR=0.76 (0.63, 0.93)

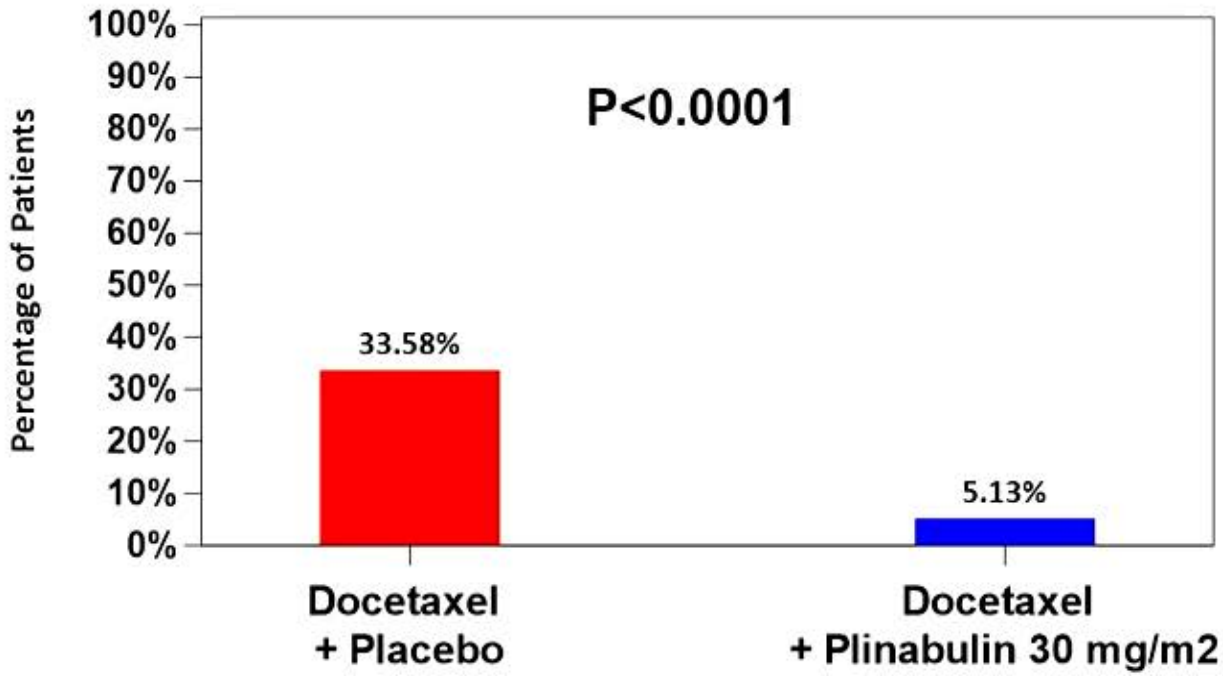
*Investigator-Assessed

Significant Reduction in Grade 4 Neutropenia
Cycle 1 Day 8 and All Cycles Day 8

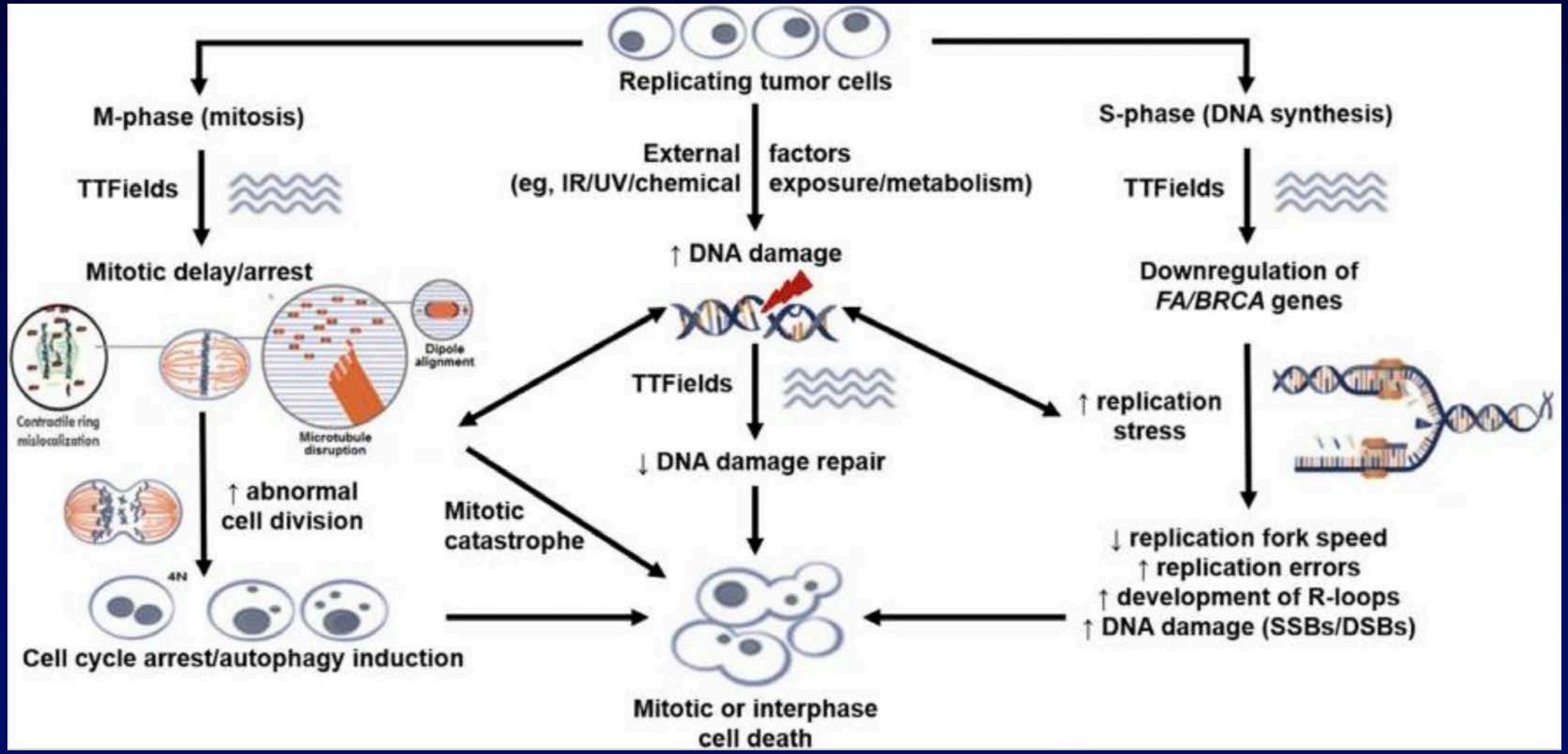
Grade 4 neutropenia, Cycle 1 Day 8



Grade 4 neutropenia, All Cycles Day 8



Mechanism of Tumor Treating Fields (TTFs)



Ghiaseddin AP, et al. Curr Treat Options Oncol. 2020

Phase III LUNAR trial of TTFs for patients with progressive, metastatic NSCLC

"Results from a prespecified interim update to the phase 3 LUNAR trial (NCT02973789) of tumor-treating fields (TTFields) in patients with stage IV non–small cell lung cancer (NSCLC) after progression on or after platinum-base chemotherapy concluded with a favorable recommendation to continue.

The interim analysis included data taken from 210 patients with a data monitoring committee (DMC) recommendation to reduce the sample size to approximately 276 patients. Continued accrual and randomization of 534 patients, which was formerly set at the target enrollment for the study, was deemed to be unnecessary or possibly unethical given the available data. Of note, there was no evidence of increased systemic toxicity when patients were treated with TTFields."

https://www.cancernetwork.com/view/phase-3-trial-of-tumor-treating-fields-for-nsclc-impresses-at-interim-analysis

KEYNOTE B36: A single arm, open label study to evaluate TTFs with pembrolizumab

“The KEYNOTE B36 study is a pilot, single arm, open-label study designed to evaluate the safety and effectiveness of Tumor Treating Fields (TTFields). Study patients use the device concomitant with pembrolizumab for first line treatment of advanced or metastatic intrathoracic non-small cell lung cancer (NSCLC). The study is expected to enroll 66 patients.

The KEYNOTE B36 Study Design

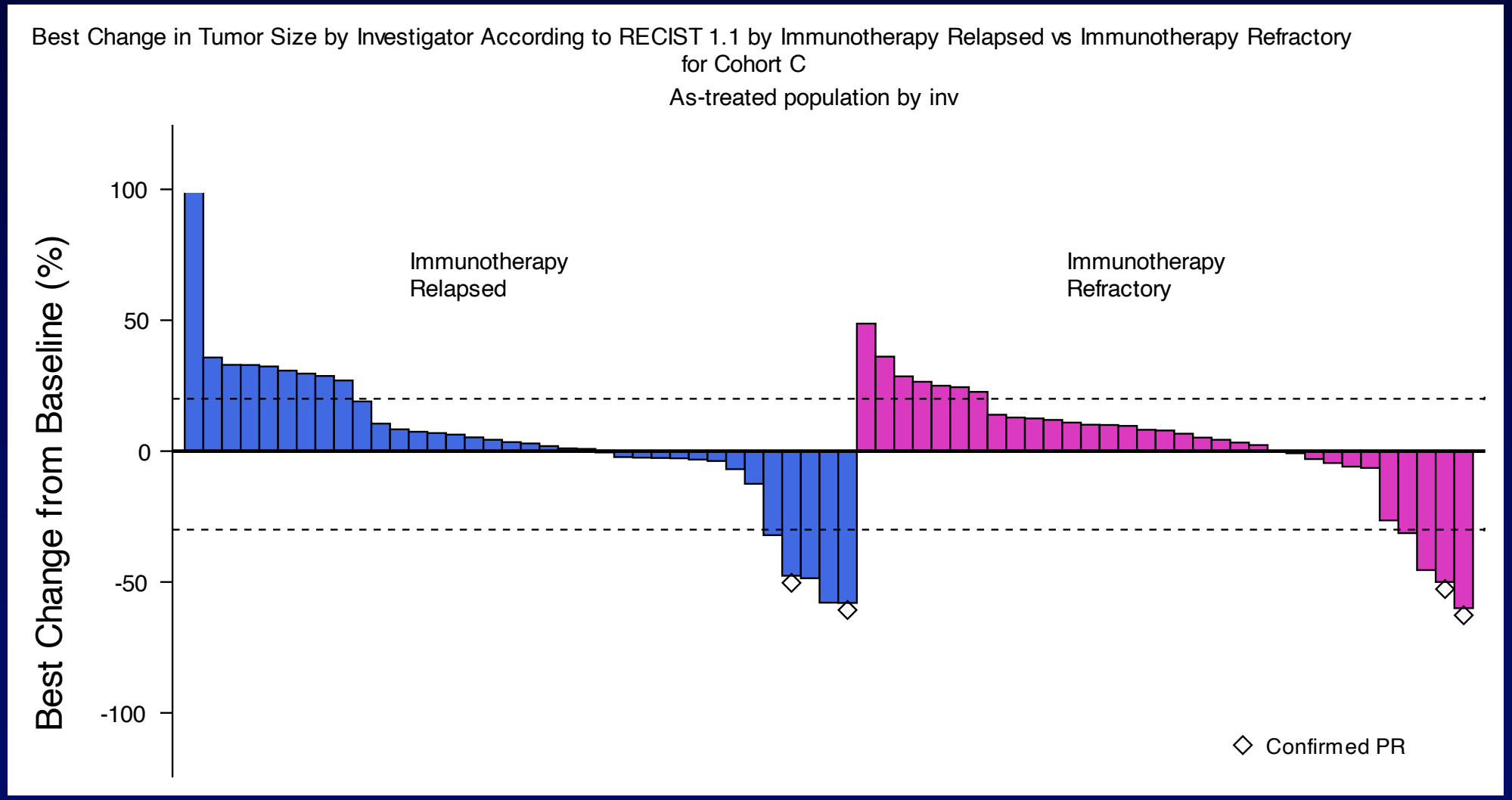
The study is for newly-diagnosed advanced or metastatic intrathoracic NSCLC. Final eligibility can only be determined by the clinical study physician in one of the clinical study centers.

All patients enrolled in the study will receive TTFields treatment, delivered for at least 18 hours a day on average... together with pembrolizumab, a standard immunotherapy agent, which is delivered intravenously.”

https://www.novocuretrial.com/trial/keynote-b36/

RTP RESEARCH TO PRACTICE

PD-L1 + CTLA4 Blockade



Garon EB et al. ASCO 2018

MRTX-500: Phase 2 Trial of Sitravatinib + Nivolumab in Patients With Nonsquamous Non–Small-Cell Lung Cancer Progressing on or After Prior Checkpoint Inhibitor Therapy

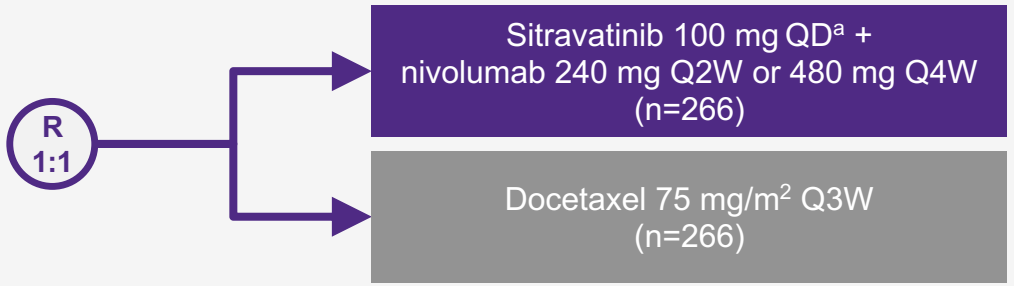
Ticiana A. Leal[1], David Berz[2], Igor I. Rybkin[3], Wade T. Iams[4], Debora S. Bruno[5], Collin M. Blakely[6], Alexander I. Spira[7], Manish R. Patel[8], David M. Waterhouse[9], Donald A. Richards[10], Anthony Pham[11], Robert Jotte[12], Edward B. Garon[13], David S. Hong[14], Ronald Shazer[15], Xiaohong Yan[15], Lisa Latven[15], Kai He[16]

[1]University of Wisconsin Carbone Cancer Center, Madison, WI, USA; Emory University, Atlanta, GA,USA; [2]Department of Cellular Therapeutics, Beverly Hills Cancer Center, Beverly Hills, CA, USA; [3]Henry Ford Cancer Institute, Detroit, MI, USA; [4]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [5]University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH, USA; [6]Department of Medicine, University of California, San Francisco, and Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; [7]Virginia Cancer Specialists, Fairfax, VA, USA; US Oncology Research, The Woodlands, TX, USA; [8]Division of Hematology, Oncology and Transplantation, University of Minnesota Masonic Cancer Center, Minneapolis, MN, USA; [9]OHC, Cincinnati, OH, USA; Texas Oncology; [10]Texas Oncology Tyler, Tyler, TX, USA; US Oncology Research Network, The Woodlands, TX, USA; [11]Northwest Cancer Specialists, Tigard, OR, USA; [12]Rocky Mountain Cancer Centers, Denver, CO, USA; US Oncology Research, The Woodlands, TX, USA; [13]Department of Medicine, Division of Hematology/Oncology, David Geffen School of Medicine at the University of California, Los Angeles, CA, USA; [14]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [15]Mirati Therapeutics, Inc., San Diego, CA, USA; [16]The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA.

SAPPHIRE: Phase 3, Randomized, Open-Label Trial of 2L/3L Sitravatinib + Nivolumab vs Docetaxel After Progression on or Following CPI in Advanced NSCLC

Key Eligibility Criteria (n=532)

- Advanced, nonsquamous NSCLC
- Prior PD-1/L1 therapy for ≥4 months (prior anti–CTLA-4 therapy allowed)
- Progression on or following PD-1/L1 inhibitor in combination with or following chemotherapy
- Excludes patients with known driver mutations



Primary Endpoint:
- OS

Secondary Endpoints:
- PFS
- ORR
- Safety

[a]Newly randomized patients will receive sitravatinib malate capsule formulation administered orally at starting dose of 100 mg once daily (QD). Patients enrolled in the United States who began treatment with the sitravatinib free-base capsule formulation will remain on the free-base capsule formulation throughout the duration of the study; the starting dose of sitravatinib free-base capsule formulation is 120 mg QD.

Presented at the European Society for Medical Oncology (ESMO) Congress, 18 September 2021

KEYNOTE-146: Phase IB/II Trial of Lenvatinib/Pembrolizumab in Advanced Solid Cancers

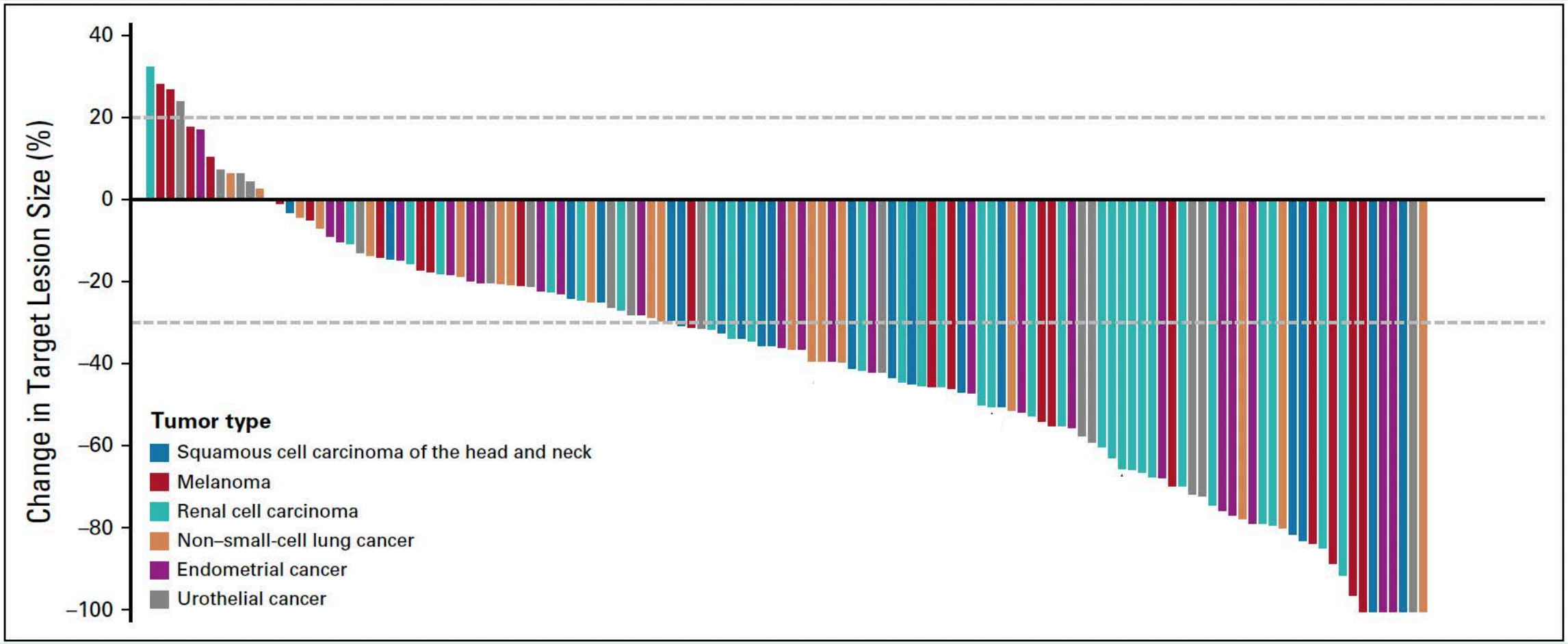
Efficacy in the Metastatic NSCLC Population				
N	**Line of therapy**	**ORR**	**Median DOR**	**Median PFS**
21	Any	33%	10.9 mo	5.9 mo

DOR = duration of response

Summary of Treatment-Related Adverse Events (TREAs): All Patients	
Parameter	**(N = 137)**
Serious AEs	26%
TREAs leading to pembrolizumab dose interruption	45%
TREAs leading to pembrolizumab discontinuation	15%
TREAs leading to lenvatinib dose reduction and/or interruption	85%
TREAs leading to lenvatinib discontinuation	13%

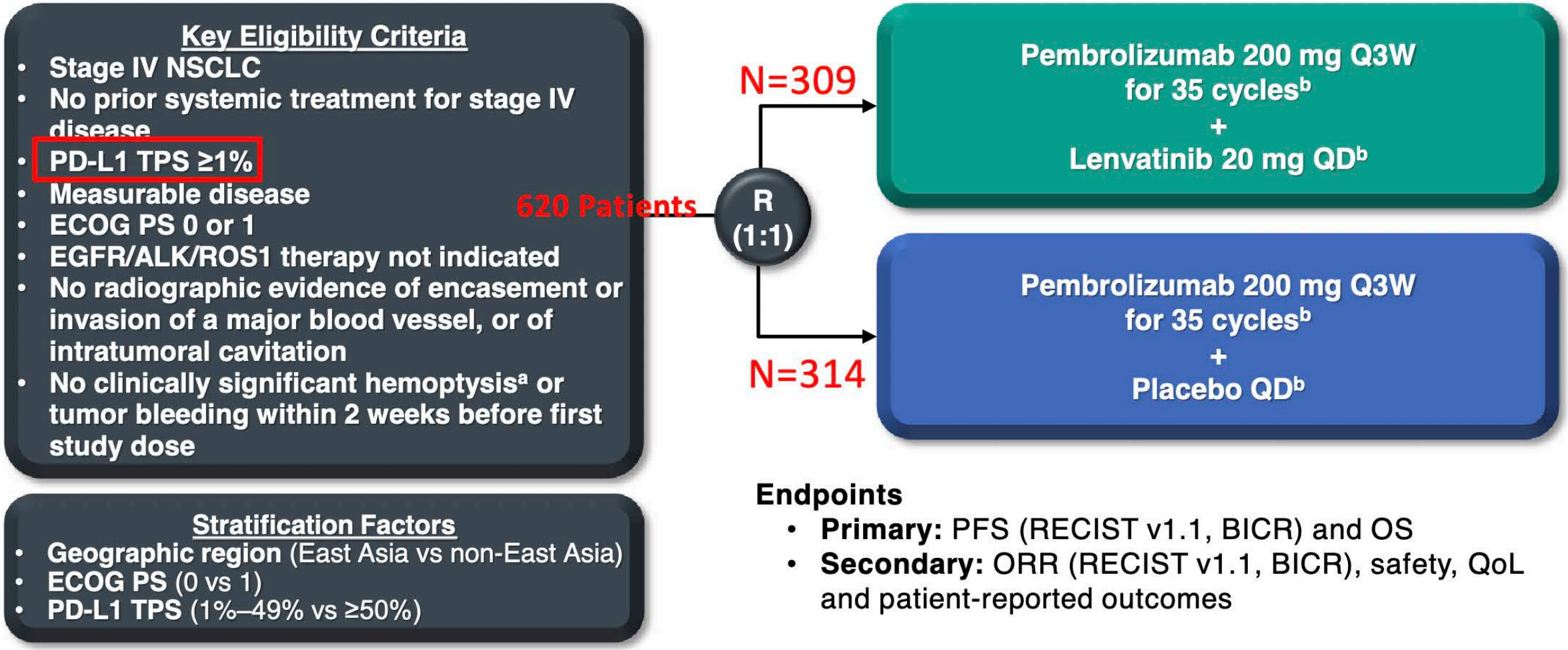
Taylor MH et al. *J Clin Oncol* 2020;38:154-63.

KEYNOTE-146: Maximum Change in Target Lesion Size (All Patients)



Taylor MH et al. *J Clin Oncol* 2020;38:154-63.

LEAP-007 Study Design (NCT03829332)

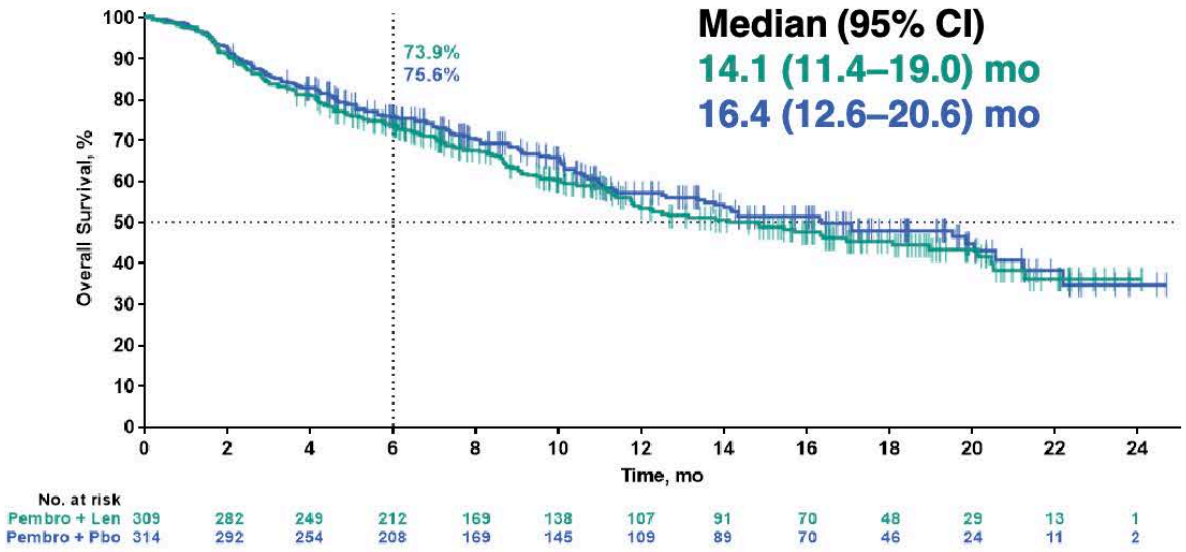


Endpoints

- **Primary:** PFS (RECIST v1.1, BICR) and OS
- **Secondary:** ORR (RECIST v1.1, BICR), safety, QoL and patient-reported outcomes

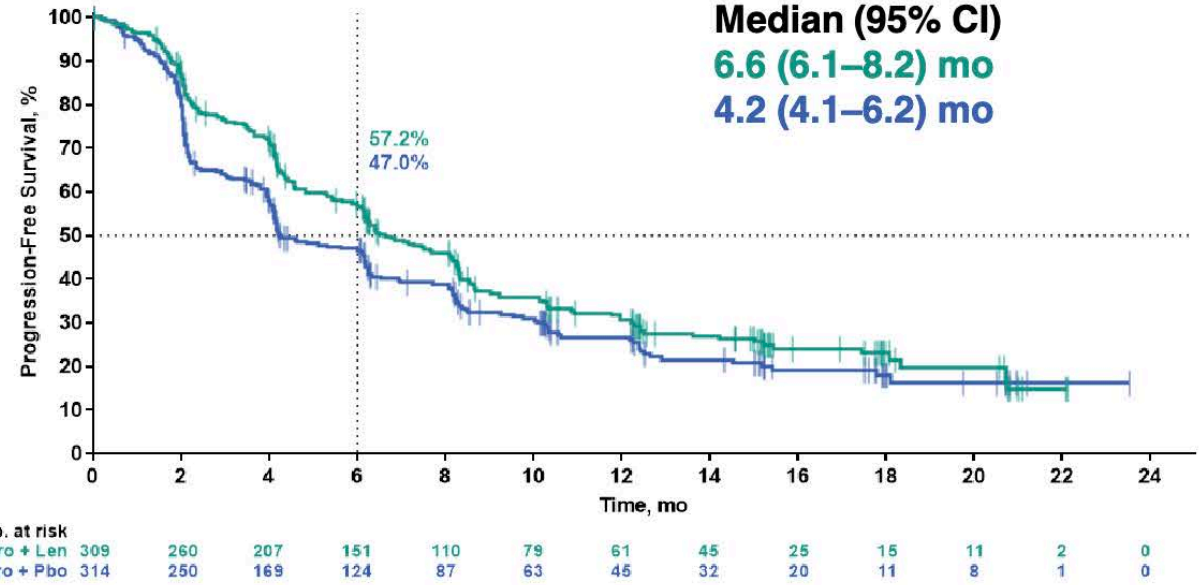
[a]At least 0.5 teaspoon of bright red blood. [b]Treatment continued until progression or recurrence or occurrence of any malignancy that required active treatment, intercurrent illness, medical condition, or personal circumstance preventing further treatment administration; withdrawal of consent; pregnancy; or interruption of study treatment administration for >28 days (lenvatinib/placebo) or >12 weeks (pembrolizumab); or completion of the prescribed number of treatment cycles (for pembrolizumab).

OS Analysis, LEAP-007

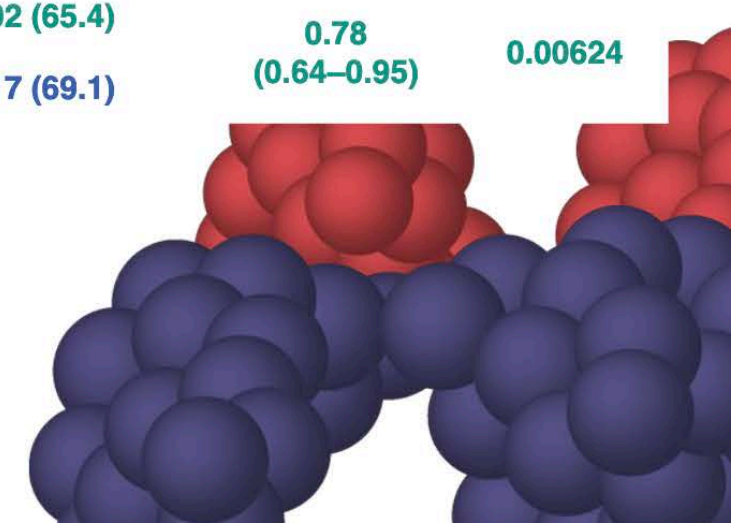


	Pts with Event, n (%)	HR (95% CI)	*P* value
Pembro + len	149 (48.2)	1.10 (0.87–1.39)	0.79744[a]
Pembro + pbo	137 (43.6)		

PFS Analysis, LEAP-007

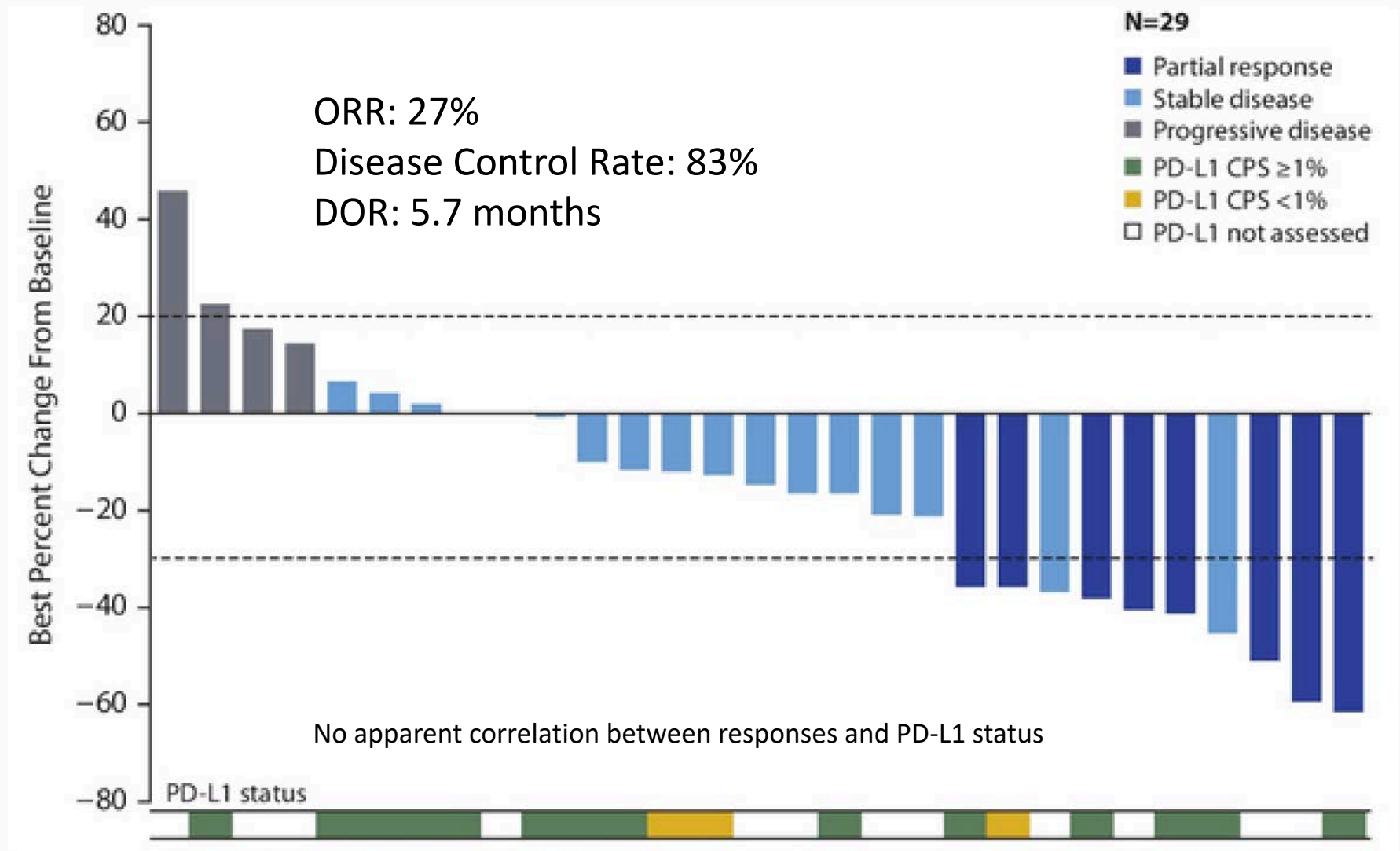


	Pts with Event, n (%)	HR (95% CI)	*P* value
Pembro + len	202 (65.4)	0.78 (0.64–0.95)	0.00624
Pembro + pbo	217 (69.1)		



H. Borghaei, Discussant for LEAP-007

COSMIC-021 (Cohort 7): Best Change from Baseline with Cabozantinib/Atezolizumab for Metastatic NSCLC



Patient population

- Radiographic progression on or after 1 prior ICI treatment
- ≤2 lines of prior systemic anticancer therapy for metastatic NSCLC
- No EGFR mutations, ALK or ROS1 rearrangements or BRAF V600E mutation

Neal JW et al. ASCO 2020;Abstract 9610.

RTP RESEARCH TO PRACTICE

COSMIC-021 (Cohort 7): Immune-Related Adverse Events with Cabozantinib/Atezolizumab for Metastatic NSCLC

	NSCLC Cohort 7 (N=30)	
	Any Grade	Grade 3
Any AE, n (%)	6 (20)	0
Hyperthyroidism	1 (3.3)	0
Hypothyroidism	1 (3.3)	0
Lipase increased	1 (3.3)	0
Myocarditis*	1 (3.3)	0
Pain	1 (3.3)	0
Pneumonitis*	1 (3.3)	0
Rash	1 (3.3)	0

*One patient experienced grade 5 pneumonitis and myocarditis; pneumonitis was assessed as the cause of death

Neal JW et al. ASCO 2020;Abstract 9610.

Agenda

Introduction: Metastatic Non-Small Cell Lung Cancer (NSCLC) in Clinical Practice

MODULE 1: Sequencing of Therapies in Metastatic NSCLC

MODULE 2: New Agents Part 1 – Antibody-Drug Conjugates

MODULE 3: New Agents Part 2 – Other Novel Strategies

MODULE 4: Clinical Situations for Special Consideration

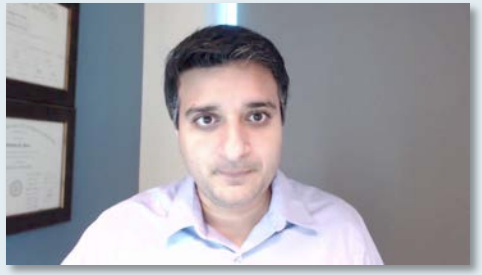
- Consolidation durvalumab
- Adjuvant chemotherapy/atezolizumab
- KRAS p.G12C mutations
- HER2 mutations

RTP
RESEARCH
TO PRACTICE

In general, what adjvuant treatment, if any, would you recommend for an otherwise healthy 65-year-old patient with Stage IIB nonsquamous NSCLC and PD-L1 TPS = 50%?

 Dr Aggarwal	Cisplatin/pemetrexed → atezolizumab	 Dr Hanna	Cisplatin/pemetrexed → atezolizumab
 Dr Goldberg	Cisplatin/pemetrexed → atezolizumab	 Dr Liu	Cisplatin/pemetrexed → atezolizumab
 Dr Govindan	Cisplatin/pemetrexed → atezolizumab	 Dr Ramalingam	Cisplatin/pemetrexed → atezolizumab

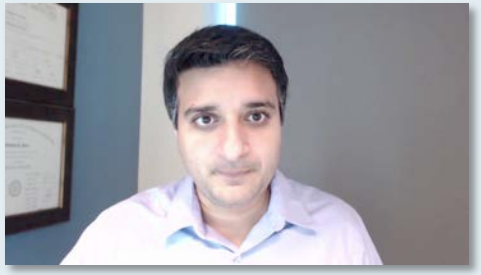
Case Presentation – Dr Patel: A 57-year-old man with metastatic NSCLC and no actionable mutations



Dr Sandip Patel

- Diagnosed with metastatic NSCLC
- On baseline O^2 due to COPD
- Chemoimmunotherapy initiated with decrease in oxygen requirement and improvement in lean muscle mass within 6 weeks
- CT: Nearly 50% increase in size of multiple mediastinal lymph nodes in the chest

Case Presentation – Dr Patel: A 57-year-old man with metastatic NSCLC and no actionable mutations (continued)



Dr Sandip Patel

- Diagnosed with metastatic NSCLC
- On baseline O^2 due to COPD
- Chemoimmunotherapy initiated with decrease in oxygen requirement and improvement in lean muscle mass within 6 weeks
- CT: Nearly 50% increase in size of multiple mediastinal lymph nodes in the chest
- ***Therapy continued with patient monitoring for 6 to 8 weeks***
- ***Follow-up CT: 50% decrease of multiple mediastinal lymph nodes***

Case Presentation – Dr Malik: A 56-year-old man with metastatic adenocarcinoma of the lung – HER2 amplification

Dr Henna Malik

- Presents with cough and treated for bronchitis with antibiotics and steroids, with minimal improvement
- CXR: Suspicious nodule in his RUL → CT scan: Multiple b/l pulmonary nodules
- Weight loss of 10 lbs over the past 3 months, worsening cough and back pain
- PET scan: Bone metastases mostly in the lumbar spine.
- Pathology: Adenocarcinoma of lung primary. PD-L1: 1%, no actionable mutations
- HER2 amplification detected
- Pembrolizumab/cisplatin/pemetrexed, with PD in 6 months
- Switched to docetaxel/trastuzumab, with response x 6 months

Question

- Would trastuzumab deruxtecan be helpful as upfront therapy for these patients with HER2-positive lung cancer, with or without chemotherapy?

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Case Presentation – Dr Meerasahib: An 82-year-old man with mNSCLC – PD-L1 75%, KRAS G12C mutation

Dr Anish Meerasahib

- 2015-2017: Retired family practitioner with 5-7 mm lung nodule followed and stable, but patient missed a few years of surveillance scans
- 3/2020 CT: Lung nodule grew to 1.9 cm, hypermetabolic by PET
  - Biopsy-confirmed adenocarcinoma, MSS, TMB-intermediate, PD-L1: 75%
  - NGS: ARID1A, KRAS G12C and RBM10 mutations
- Patient does not desire surgery → 5/2020: SBRT to primary lung lesion
- 8/2020: 1-cm satellite lesion LUL → patient declines systemic therapy → SBRT
- 12/2020: Right scapula lesion
- 2/2021: Pembrolizumab, with RT to right scapula, which resolved pain

Questions

- Are we seeing positive results with the KRAS 12GC-targeted agent sotorasib in lung cancer?
- Is immunotherapy the right treatment for him, and would you consider adding chemotherapy?

Appendix: Faculty Cases

Case 1

- **Mid-70s African American woman transfers care to be closer to family**
- **Generally healthy with exception of CLL which has been previously treated and stable**
- **Non-G12C KRAS mutation; PD-L1 15%**
- **Started on single agent pembrolizumab**

Case 1 Continued

- **After 18 months, disease is stable except for a lung and right adrenal lesion**
- **Both lesions are radiated and pembrolizumab is continued**
- **After another year a left adrenal gland increases in size**
- **After discussion we decide to monitor**
- **Lesion has waxed and waned over a year**

Case 2

- **Mid 70's Asian Man with stage IV adenocarcinoma of lung**
- **Non-G12C KRAS mutation. PD-L1 75%**
- **History of CAD and other chronic medical issues, but reasonable performance status**
- **Starts single agent pembrolizumab, with carboplatin and pemetrexed added after first set of scans show progression.**
- **Enrolls on sitravatinib/nivolumab trial**

Case 3

- **Mid-40s Hispanic Woman with stage IV non-small cell lung cancer**
- **EGFR exon 19 deletion**
- **Received multiple EGFR inhibitors, platinum based chemotherapy, immunotherapy clinical trial**
- **Initiated on Dato-DXd trial**

Year in Review – Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology:

Acute Myeloid Leukemia and Myelodysplastic Syndromes

Thursday, January 27, 2022
5:00 PM – 6:00 PM ET

Faculty

Daniel A Pollyea, MD, MS
Gail J Roboz, MD

Moderator

Neil Love, MD

RTP Year in Review 2022

Thank you for attending!

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