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

Melanoma and Nonmelanoma Skin Cancers

Thursday, July 13, 2023
5:00 PM – 6:00 PM ET

Faculty

Omid Hamid, MD

Evan J Lipson, MD

Moderator

Neil Love, MD

RTP Year in Review 2023

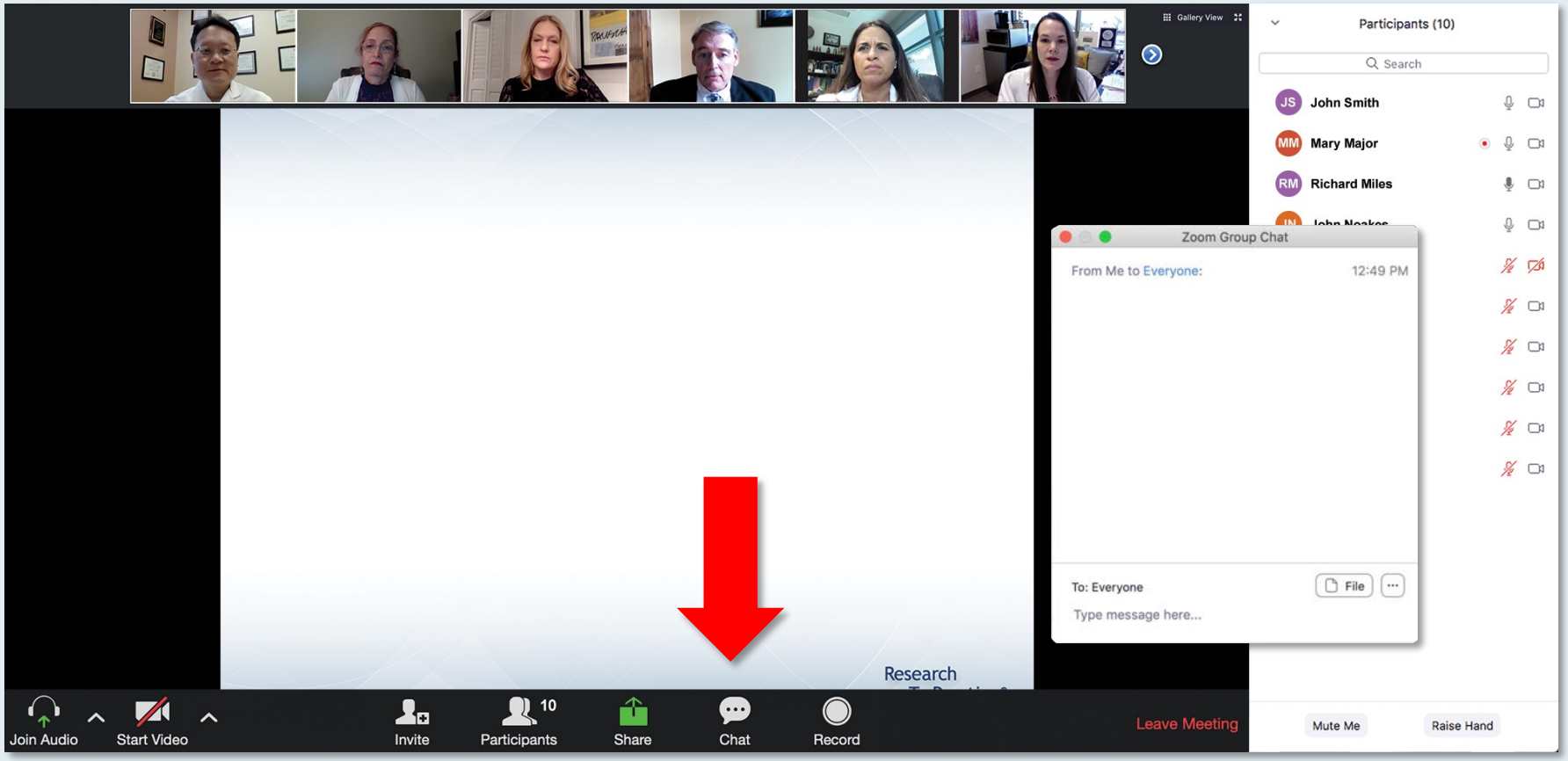
Faculty

Omid Hamid, MD
Chief of Research/Immuno-Oncology
Co-Director, Cutaneous Malignancy Program
The Angeles Clinic and Research Institute, a Cedars-Sinai Affiliate
Los Angeles, California

Evan J Lipson, MD
Associate Professor, Medical Oncology
Bloomberg-Kimmel Institute for Cancer Immunotherapy
Johns Hopkins School of Medicine
The Sidney Kimmel Comprehensive Cancer Center
Baltimore, Maryland

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

We Encourage Clinicians in Practice to Submit Questions



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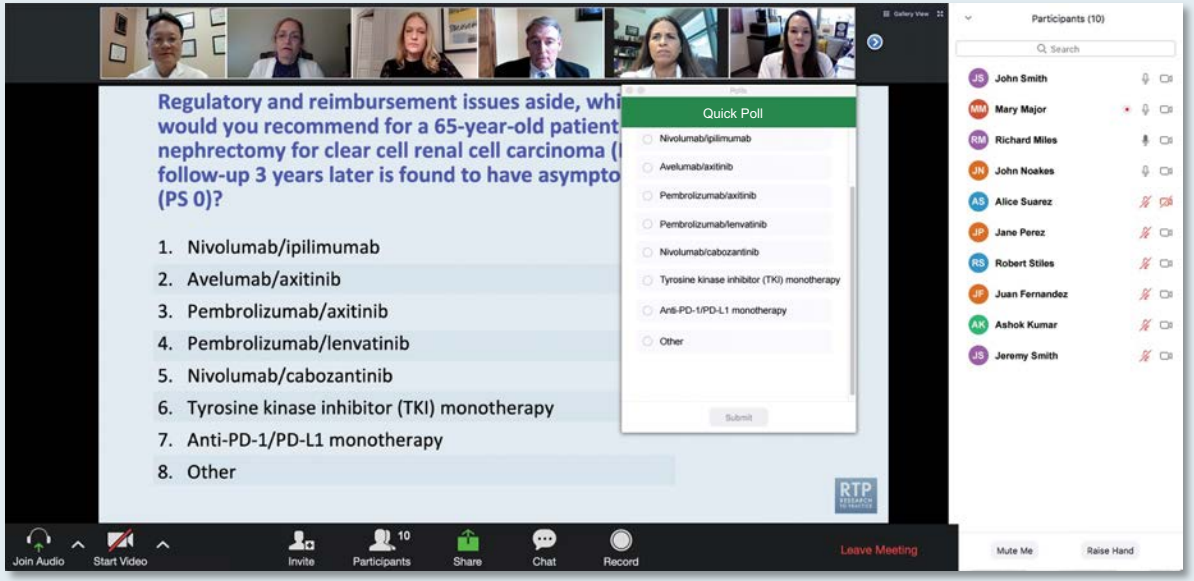

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ONCOLOGY TODAY

WITH DR NEIL LOVE

Novel Immunotherapeutic Strategies in Melanoma

DR OMID HAMID

THE ANGELES CLINIC AND RESEARCH INSTITUTE

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RESEARCH TO PRACTICE

Meet The Professor

Optimizing the Management of Soft Tissue Sarcoma and Related Connective Tissue Disorders

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Inside the Issue: The Current and Future Role of CD20 x CD3 Bispecific Antibodies in the Management of Non-Hodgkin Lymphoma

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This activity is supported by an educational grant from Regeneron Pharmaceuticals Inc.

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, 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 US Inc, Gilead Sciences Inc, Grail Inc, GSK, 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, SpringWorks Therapeutics Inc, Stemline Therapeutics Inc, 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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Thank you for joining us!

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

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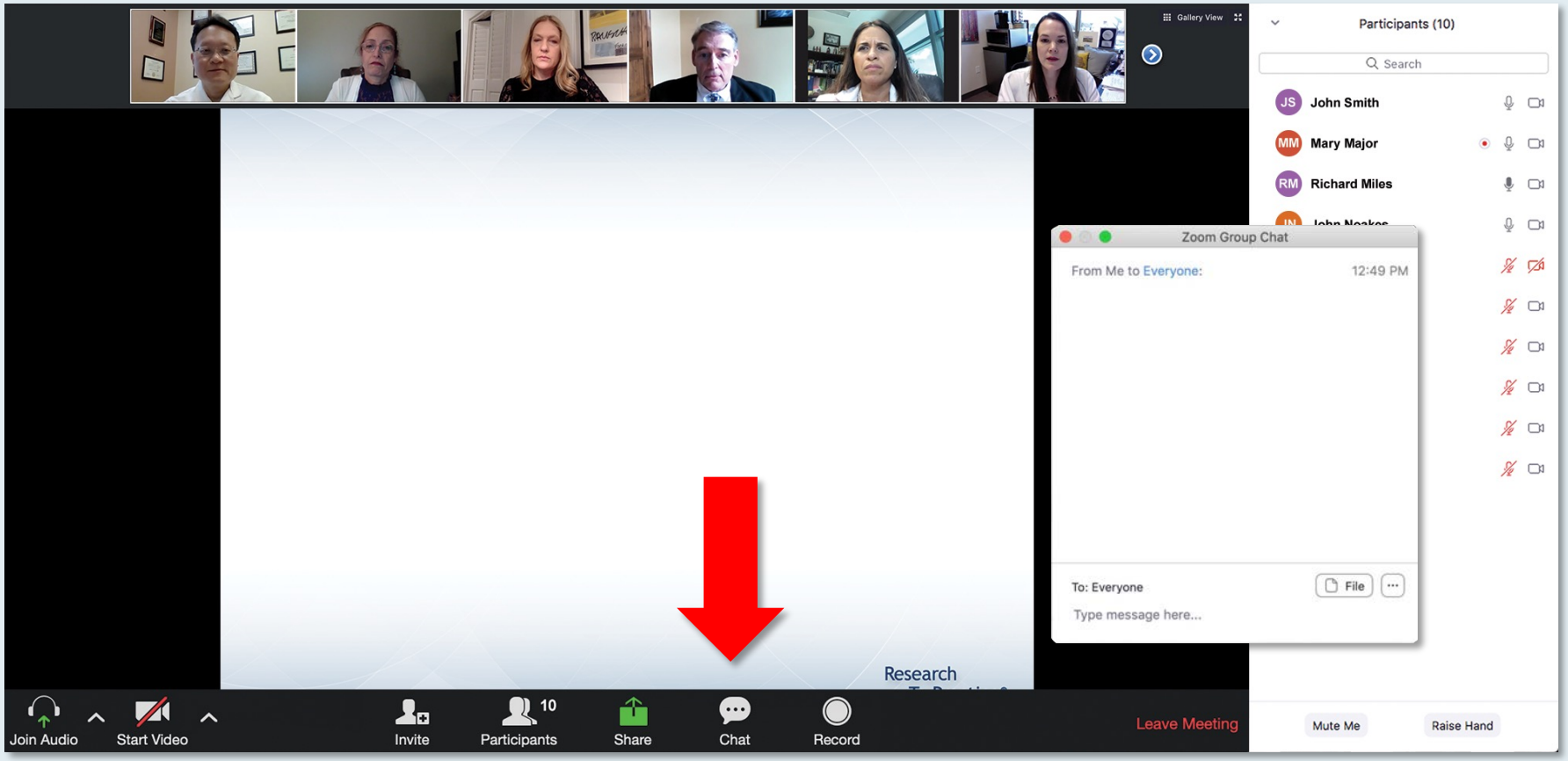

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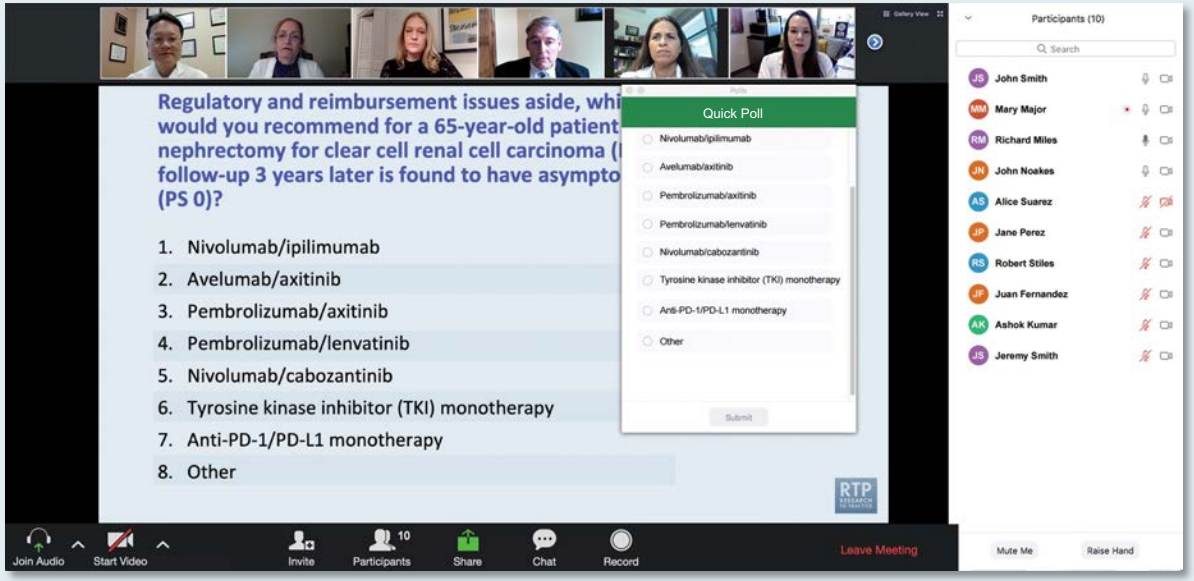

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Research To Practice

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Chief, Translational Research/Immuno-Oncology, Co-Director, Cutaneous Malignancies,
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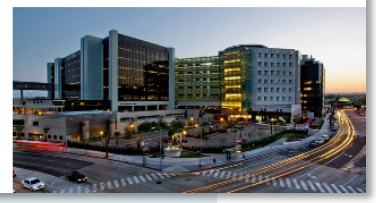

Localized Melanoma and Other Types of Skin Cancer

Evan J Lipson, MD
Associate Professor, Medical Oncology
Bloomberg-Kimmel Institute for Cancer Immunotherapy
Johns Hopkins School of Medicine
The Sidney Kimmel Comprehensive Cancer Center
Baltimore, Maryland

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Key Data Sets

Omid Hamid, MD

- Seth R et al. Systemic therapy for melanoma: ASCO guideline rapid recommendation update. *J Clin Oncol* 2022;40(21):2375-7.
- Atkins MB et al. Combination dabrafenib and trametinib versus combination nivolumab and ipilimumab for patients with advanced BRAF-mutant melanoma: The DREAMseq trial-ECOG-ACRIN EA6134. *J Clin Oncol* 2023;41(2):186-97.
- Ascierto PA et al. Sequencing of ipilimumab plus nivolumab and encorafenib plus binimetinib for untreated BRAF-mutated metastatic melanoma (SECOMBIT): A randomized, three-arm, open-label Phase II trial. *J Clin Oncol* 2023;41(2):212-21.
- Dummer R et al. COLUMBUS 5-year update: A randomized, open-label, Phase III trial of encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF V600-mutant melanoma. *J Clin Oncol* 2022;40(36):4178-88.
- Wolchok JD et al. Durable clinical outcomes in patients (pts) with advanced melanoma and progression-free survival (PFS) ≥3y on nivolumab (NIVO) ± ipilimumab (IPI) or IPI in CheckMate 067. ASCO 2023;Abstract 9542.

Key Data Sets

Omid Hamid, MD (continued)

- Tawbi HA et al. Nivolumab (NIVO) plus relatlimab (RELA) vs NIVO in previously untreated metastatic or unresectable melanoma: 2-year results from RELATIVITY-047. ASCO 2023;Abstract 9502.
- Hamid O et al. Phase I study of fianlimab, a human lymphocyte activation gene-3 (LAG-3) monoclonal antibody, in combination with cemiplimab in advanced melanoma (mel). ESMO 2022;Abstract 790MO.
- Hamid O et al. Significant durable response with fianlimab (anti-LAG-3) and cemiplimab (anti-PD-1) in advanced melanoma: Post adjuvant PD-1 analysis. ASCO 2023;Abstract 9501.
- Baramidze A et al. A phase 3 trial of fianlimab (anti–LAG-3) plus cemiplimab (anti–PD-1) versus pembrolizumab in patients with previously untreated unresectable locally advanced or metastatic melanoma. ASCO 2023;Abstract TPS9602.
- Kjeldsen JW et al. A phase 1/2 trial of an immune-modulatory vaccine against IDO/PD-L1 in combination with nivolumab in metastatic melanoma. *Nat Med* 2021;27(12):2212-23.
- Switzer B et al. Evolving management of stage IV melanoma. *Am Soc Clin Oncol Educ Book* 2023;43:e397478.

Key Data Sets

Omid Hamid, MD (continued)

- Sarnaik A et al. Lifileucel TIL cell monotherapy in patients with advanced melanoma after progression on immune checkpoint inhibitors (ICI) and targeted therapy: Pooled analysis of consecutive cohorts (C-144-01 study). SITC 2022;Abstract 2409.
- Haanen J et al. Treatment with tumor-infiltrating lymphocytes (TIL) versus ipilimumab (IPI) for advanced melanoma: Results from a multicenter, randomized phase III trial. ESMO 2022;Abstract LBA3.
- O'Malley D et al. Phase 2 efficacy and safety of autologous tumor-infiltrating lymphocyte (TIL) cell therapy in combination with pembrolizumab in immune checkpoint inhibitor-naïve patients with advanced cancers. SITC 2021;Abstract 492.
- Rohaan MW et al. Tumor-infiltrating lymphocyte therapy or ipilimumab in advanced melanoma. *N Engl J Med* 2022;387(23):2113-25.
- Olson D et al. A phase 3 study (TILVANCE-301) to assess the efficacy and safety of lifileucel, an autologous tumor-infiltrating lymphocyte cell therapy, in combination with pembrolizumab compared with pembrolizumab alone in patients with untreated unresectable or metastatic melanoma. ASCO 2023;Abstract TPS9607.

Key Data Sets

Omid Hamid, MD (continued)

- Middleton MR et al. Updated overall survival (OS) data from the phase 1b study of tebentafusp (tebe) as monotherapy or combination therapy with durvalumab (durva) and/or tremelimumab (treme) in metastatic cutaneous melanoma (mCM). ASCO 2022;Abstract 104.
- Hamid O et al. Results from phase I dose escalation of IMC-F106C, the first PRAME × CD3 ImmTAC bispecific protein in solid tumors. ESMO 2022;Abstract 728O.
- Schadendorf D et al. Adjuvant nivolumab (NIVO) alone or in combination with ipilimumab (IPI) versus placebo in stage IV melanoma with no evidence of disease (NED): Overall survival (OS) results of IMMUNED, a randomized, double-blind multi-center phase II DeCOG trial. ESMO 2022;Abstract 784O.

Key Data Sets

Evan J Lipson, MD

- Weber JS et al. Adjuvant therapy of nivolumab combined with ipilimumab versus nivolumab alone in patients with resected Stage IIIB-D or Stage IV melanoma (CheckMate 915). *J Clin Oncol* 2023;41(3):517-27.
- Luke JJ et al. Pembrolizumab versus placebo as adjuvant therapy in stage IIB or IIC melanoma: Final analysis of distant metastasis-free survival in the phase 3 KEYNOTE-716 study. ASCO 2023;Abstract LBA9505.
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- Patel SP et al. Neoadjuvant-adjuvant or adjuvant-only pembrolizumab in advanced melanoma. *N Engl J Med* 2023;388(9):813-23.
- Khattak MA et al. Distant metastasis-free survival results from the randomized, phase 2 mRNA-4157-P201/KEYNOTE-942 trial. ASCO 2023;Abstract LBA9503.
- Panella TJ et al. A phase 3 trial comparing fianlimab (anti–LAG-3) plus cemiplimab (anti–PD-1) to pembrolizumab in patients with completely resected high-risk melanoma. ASCO 2023;Abstract TPS9598.

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- Van Akkooi ACJ et al. Phase III study of adjuvant encorafenib plus binimetinib versus placebo in fully resected stage IIB/C BRAFV600-mutated melanoma: COLUMBUS-AD study design. ASCO 2023;Abstract TPS9601.
- Carvajal RD et al. Clinical and molecular response to tebentafusp in previously treated patients with metastatic uveal melanoma: A phase 2 trial. *Nat Med* 2022;28(11):2364-73.
- Silk AW et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of nonmelanoma skin cancer. *J Immunother Cancer* 2022;10(7):e004434.
- Zuur CL et al. Towards organ preservation and cure via 2 infusions of immunotherapy only, in patients normally undergoing extensive and mutilating curative surgery for cutaneous squamous cell carcinoma: An investigator-initiated randomized phase II trial—The MATISSE trial. ASCO 2023;Abstract 9507.
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Key Data Sets

Evan J Lipson, MD (continued)

- Gross ND et al. Neoadjuvant cemiplimab for Stage II to IV cutaneous squamous-cell carcinoma. *N Engl J Med* 2022;387(17):1557-68.
- Hanna et al. Cemiplimab for kidney organ transplant recipients with advanced cutaneous squamous cell carcinoma: CONTRAC-1. ASCO 2023;Abstract 9519.
- Lewis KD et al. Health-related quality of life in patients with metastatic basal cell carcinoma treated with cemiplimab: Analysis of a Phase 2 open-label clinical trial. EADO 2023;Abstract HSR23-097.
- Bhatia S et al. Non-comparative, open-label, international, multicenter phase I/II study of nivolumab (NIVO) ± ipilimumab (IPI) in patients (pts) with recurrent/metastatic merkel cell carcinoma (MCC) (CheckMate 358). ASCO 2023;Abstract 9506.

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Introduction: Immunology of Melanoma

MODULE 1: Melanoma

- Sequencing of BRAF-targeted agents and immunotherapy for BRAF-mutant metastatic melanoma
- Choice of first-line immunotherapy for metastatic melanoma
- Adjuvant treatment of localized melanoma

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MODULE 3: Basal Cell Carcinoma and Merkel Cell Carcinoma

MODULE 4: Novel Agents and Strategies

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- Atkins MB et al. Combination **dabrafenib and trametinib** versus combination **nivolumab and ipilimumab** for patients with advanced **BRAF-mutant** melanoma: The **DREAMseq trial-ECOG-ACRIN EA6134**. *J Clin Oncol* 2023;41(2):186-97.
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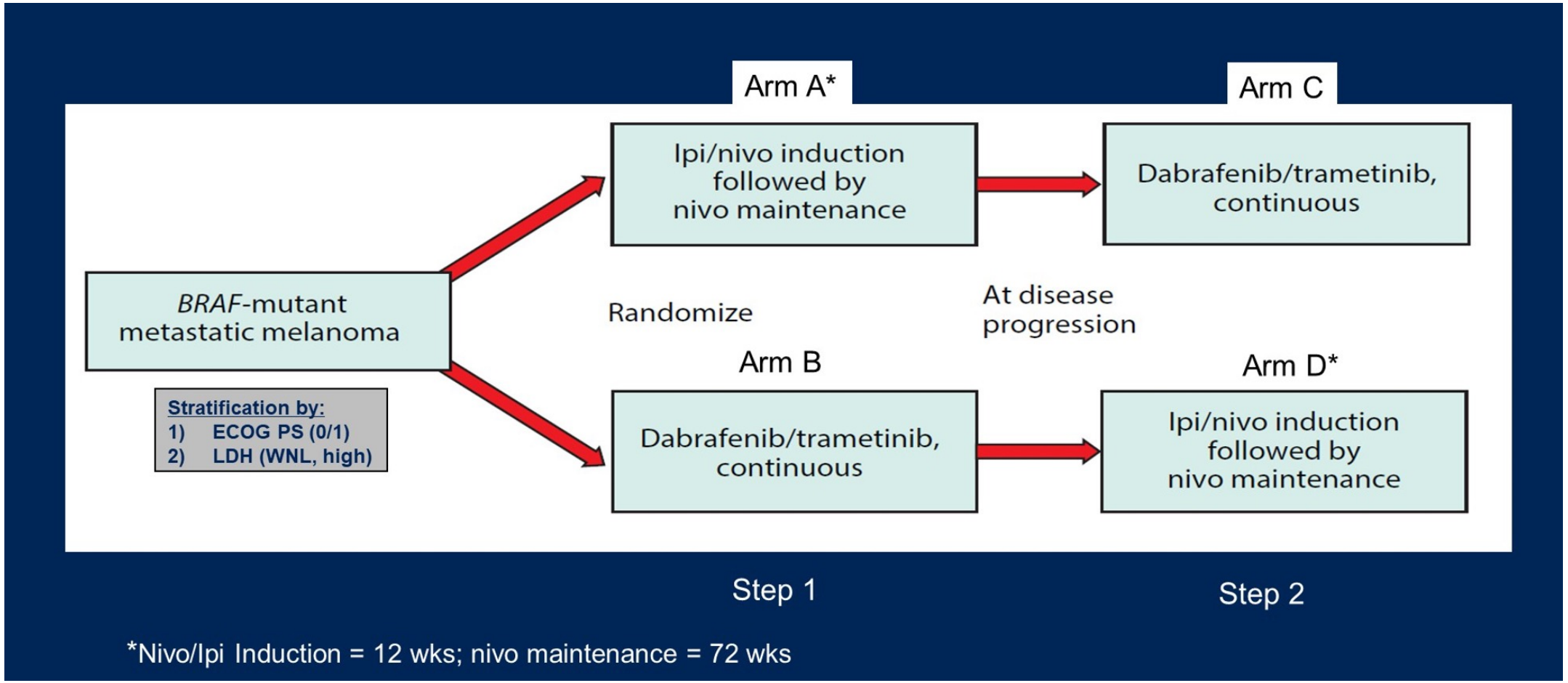
DREAMseq: Sequencing Immune Checkpoint Inhibitors and BRAF-Targeted Therapies in BRAF-Mutant Advanced Melanoma



Atkins MB. ASCO 2022

Courtesy of Omid Hamid, MD

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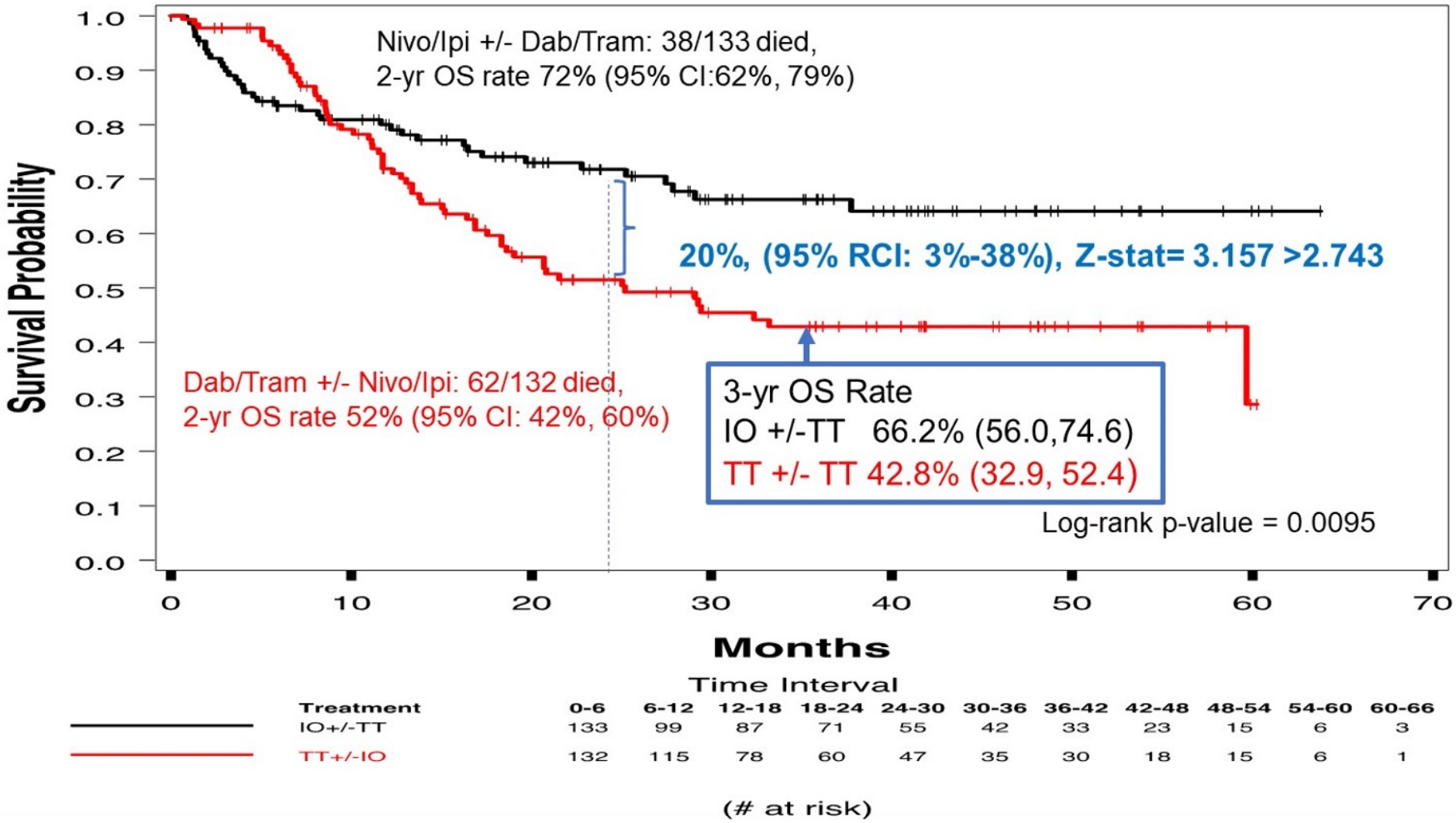
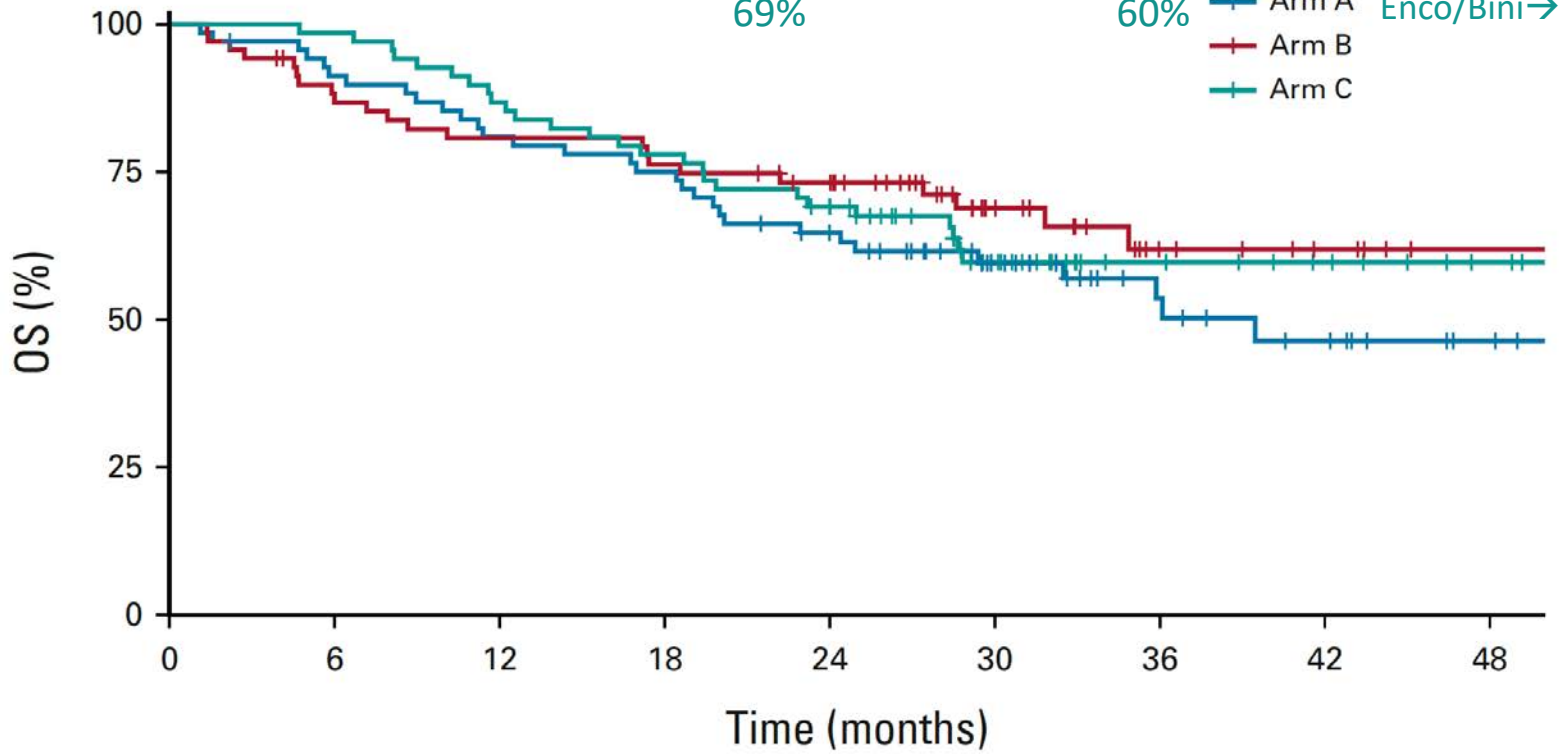


Atkins MB. ASCO 2022; Atkins J Clin Oncol 2022

Courtesy of Omid Hamid, MD

SECOMBIT Phase II Study: Sequencing Immunotherapy in BRAF-Mutant Advanced Melanoma – Survival by Treatment Arm

	2-yr OS	3-yr OS
Enco/Bini→Ipi/Nivo	65%	54%
Ipi/Nivo→Enco/Bini	73%	62%
Enco/Bini→Ipi/Nivo→Enco/Bini	69%	60%



No. at risk:

Arm A	69	62	55	51	42	27	16	11	5
Arm B	69	59	54	51	46	25	12	8	4
Arm C	68	67	59	53	46	26	13	9	4

Ascierto PA et al. *J Clin Oncol* 2023 Jan;41(2):212-221.

Courtesy of Omid Hamid, MD

Key Data Sets – Metastatic Melanoma
Choice of First-Line Immunotherapy

Omid Hamid, MD (continued)

- Wolchok JD et al. Durable clinical outcomes in patients (pts) with advanced melanoma and progression-free survival (PFS) ≥3y on **nivolumab (NIVO) ± ipilimumab (IPI)** or **IPI** in **CheckMate 067**. ASCO 2023;Abstract 9542.
- Tawbi HA et al. **Nivolumab (NIVO)** plus **relatlimab (RELA)** vs **NIVO** in **previously untreated** metastatic or unresectable melanoma: 2-year results from **RELATIVITY-047**. ASCO 2023;Abstract 9502.
- Hamid O et al. Phase I study of **fianlimab**, a human lymphocyte activation gene-3 **(LAG-3)** monoclonal antibody, in combination **with cemiplimab** in advanced melanoma (mel). ESMO 2022;Abstract 790MO.
- Hamid O et al. Significant durable response with **fianlimab (anti-LAG-3)** and **cemiplimab (anti-PD-1)** in advanced melanoma: Post adjuvant PD-1 analysis. ASCO 2023;Abstract 9501.
- Baramidze A et al. A phase 3 trial of **fianlimab (anti–LAG-3)** plus **cemiplimab (anti–PD-1)** versus **pembrolizumab** in patients with **previously untreated** unresectable locally advanced or metastatic melanoma. ASCO 2023;Abstract TPS9602.

Durable clinical outcomes in patients with advanced melanoma who were progression-free at 3 years on nivolumab ± ipilimumab or ipilimumab in CheckMate 067

F. Stephen Hodi,[1] Vanna Chiarion-Sileni,[2] Rene Gonzalez,[3] Jean-Jacques Grob,[4] Piotr Rutkowski,[5] Christopher D. Lao,[6] C. Lance Cowey,[7] Dirk Schadendorf,[8] John Wagstaff,[9] Reinhard Dummer,[10] Paola Queirolo,[11] Michael Smylie,[12] Marcus O. Butler,[13] Andrew G. Hill,[14] Iván Márquez-Rodas,[15] Corey Ritchings,[16] Leon A. Sakkal,[16] Peter Wang,[16] Jedd D. Wolchok,[17*] James Larkin[18*]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; [3]University of Colorado Cancer Center, Aurora, CO; [4]Aix Marseille University, Hôpital de la Timone, Marseille, France; [5]Maria Sklodowska-Curie National Institute of Oncology Center, Warsaw, Poland; [6]University of Michigan, Rogel Cancer Center, Ann Arbor, MI; [7]Texas Oncology-Baylor Charles A. Sammons Cancer Center

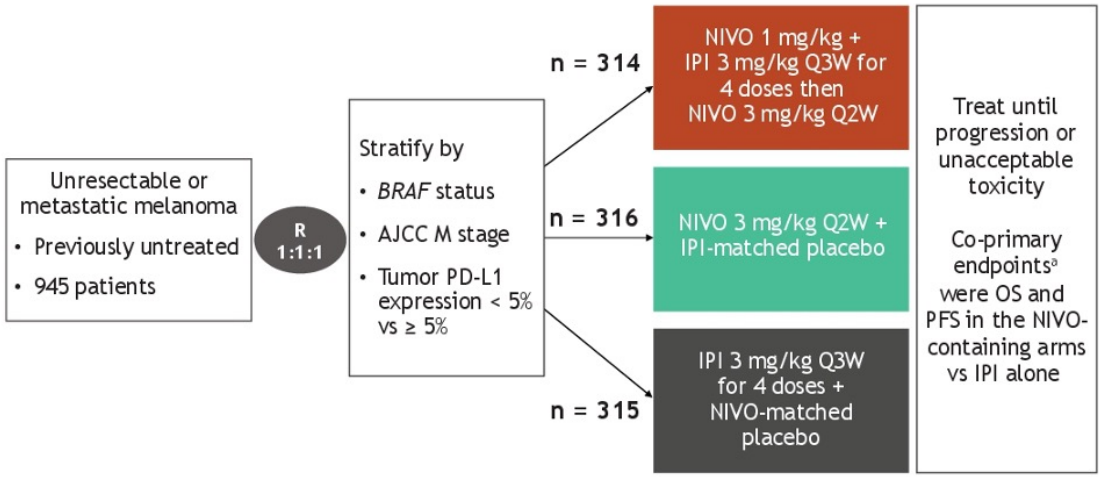
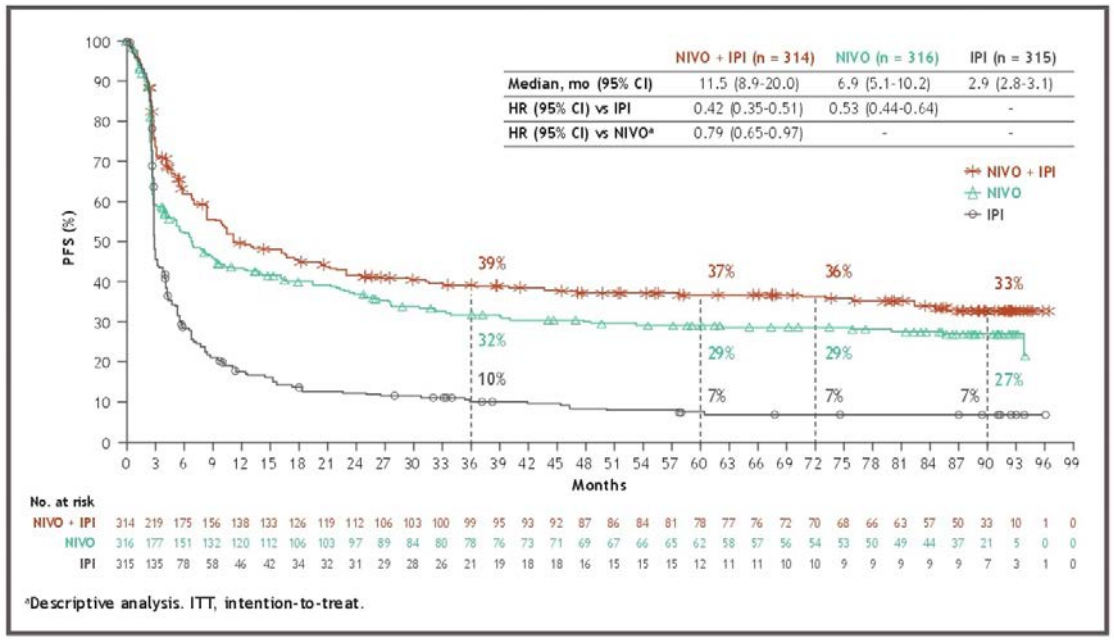
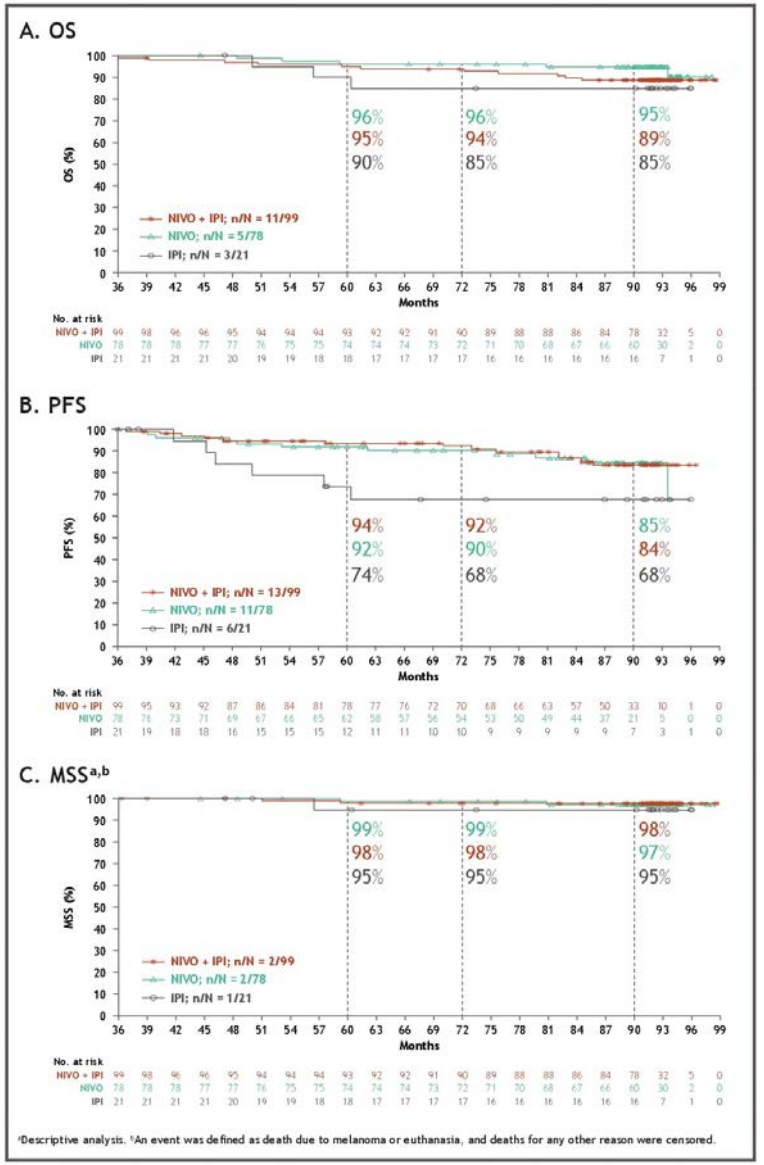


Figure 1. PFS in the ITT population of CheckMate 067[2]





Wolchok ASCO 2023; Abstract 9542

Courtesy of Omid Hamid, MD

2023 ASCO® ANNUAL MEETING

Nivolumab (NIVO) plus relatlimab (RELA) vs NIVO in previously untreated metastatic or unresectable melanoma: 2-year results from RELATIVITY-047

Hussein A. Tawbi,[1] F. Stephen Hodi,[2] Evan J. Lipson,[3] Dirk Schadendorf,[4] Paolo Antonio Ascierto,[5] Luis Matamala,[6] Erika Castillo Gutiérrez,[7] Piotr Rutkowski,[8] Helen Gogas,[9] Christopher D. Lao,[10] Juliana Janoski De Menezes,[11] Stéphane Dalle,[12] Ana Maria Arance,[13] Jean-Jacques Grob,[14] Barbara Ratto,[15] Saima Rodriguez,[15] Yuanfang Xu,[15] Peter Wang,[15] Sonia Dolfi,[15] Georgina V. Long[16]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Dana-Farber Cancer Institute, Boston, MA; [3]Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; [4]University of Essen and the German Cancer Consortium, Essen, Germany; [5]Istituto Nazionale dei Tumori IRCCS "Fondazione G. Pascale", Naples, Italy; [6]Instituto Oncológico Fundación Arturo López Pérez and Department of Oncology, Instituto Nacional del Cáncer, Santiago, Chile; [7]FAICIC Clinical Research, Veracruz, Mexico; [8]Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [9]National and Kapodistrian University of Athens, Athens, Greece; [10]Michigan Medicine, Rogel Cancer Center, University of Michigan, Ann Arbor, MI; [11]Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil; [12]Hospices Civils de Lyon, Cancer Research Center of Lyon, Pierre-Bénite, France; [13]Hospital Clinic Barcelona and IDIBAPS, Barcelona, Spain; [14]Aix-Marseille University, CHU Timone, Marseille, France; [15]Bristol Myers Squibb, Princeton, NJ; [16]Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, NSW, Australia

Abstract number 9502

Courtesy of Omid Hamid, MD

Study design

- RELATIVITY-047 is a global, randomized, double-blind, phase 2/3 study

Key eligibility criteria
- Previously untreated, unresectable, or metastatic melanoma
- ECOG PS 0–1

R 1:1

NIVO 480 mg + RELA 160 mg FDC IV Q4W

NIVO 480 mg IV Q4W

Primary endpoint
- PFS by BICR[a]

Secondary endpoints
- OS[b]
- ORR by BICR[c]

Stratified by: LAG-3,[d] PD-L1,[e] *BRAF,* and AJCC v8 M stage

Endpoints were tested in hierarchy: PFS → OS → ORR

Database lock	**March 9, 2021**	**October 28, 2021**	**October 27, 2022**
Min. follow-up[f]	1.3 months	8.7 months	21.0 months
Median follow-up	13.2 months	19.3 months	25.3 months
Endpoint(s)	PFS per BICR	OS, ORR per BICR, and updated PFS per BICR	Updated PFS per BICR, OS, and ORR per BICR

RELATIVITY-047 (NCT03470922).
[a]First tumor assessment (RECIST v1.1) was performed 12 weeks after randomization, every 8 weeks up to 52 weeks, and then every 12 weeks. [b]OS boundary for statistical significance was $P < 0.04302$ (2-sided) analyzed at 69% power; target HR, 0.75. [c]ORR could not be formally tested and was descriptively analyzed. [d]LAG-3 expression on immune cells (1%) was determined by an analytically validated IHC assay (Labcorp, Burlington, NC, USA). [e]PD-L1 expression on tumor cells (1%) was determined by a validated Agilent Dako PD-L1 IHC 28-8 pharmDx test (Agilent, Santa Clara, CA, USA). [f]Minimum potential follow-up was defined as the time from last patient randomized to last patient, last visit.

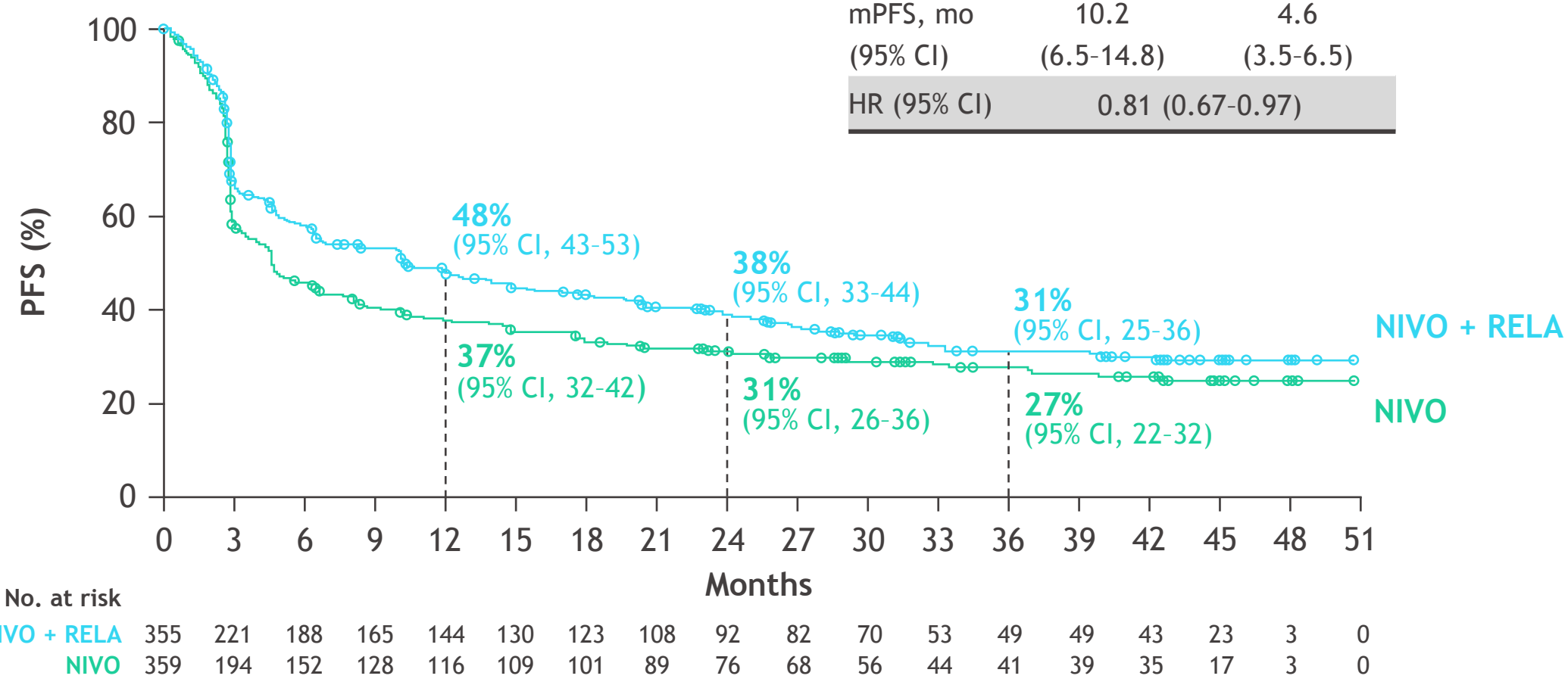
Tawbi ASCO 2023;Abstract 9502

Courtesy of Omid Hamid, MD

RELATIVITY-047: PFS by BICR with Nivolumab plus Relatinib

Updated primary endpoint

	NIVO + RELA (n = 355)	NIVO (n = 359)
mPFS, mo	10.2	4.6
(95% CI)	(6.5-14.8)	(3.5-6.5)
HR (95% CI)	0.81 (0.67-0.97)	



RELATIVITY-047 (NCT03470922). Median follow-up: 25.3 months.
Descriptive analysis. Statistical model for HR: stratified Cox proportional hazard model. Stratified by LAG-3, *BRAF* mutation status, and AJCC M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

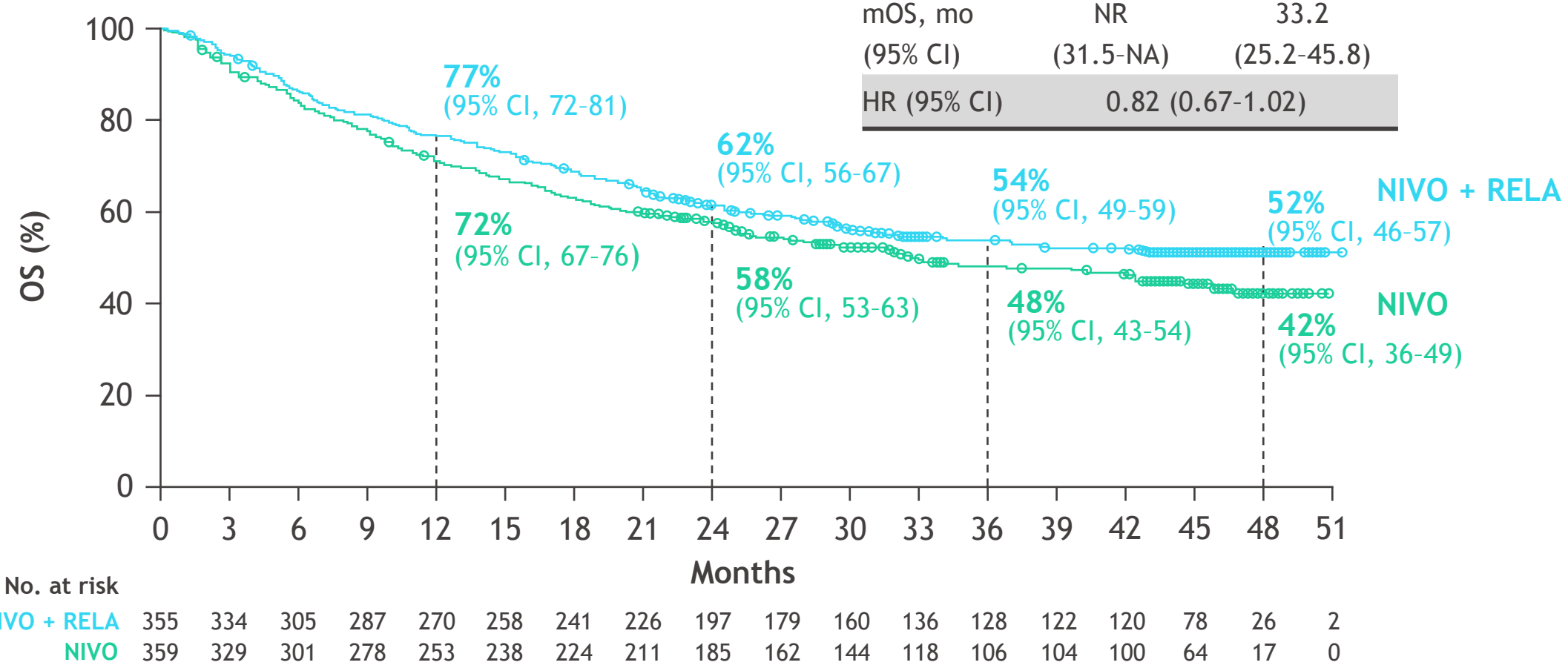
Tawbi ASCO 2023;Abstract 9502

Courtesy of Omid Hamid, MD

RELATIVITY-047: OS

Updated secondary endpoint

	NIVO + RELA (n = 355)	NIVO (n = 359)
mOS, mo	NR	33.2
(95% CI)	(31.5-NA)	(25.2-45.8)
HR (95% CI)	0.82 (0.67-1.02)	



RELATIVITY-047 (NCT03470922). Median follow-up: 25.3 months.
Descriptive analysis. Statistical model for HR: stratified Cox proportional hazard model. Stratified by LAG-3, *BRAF* mutation status, and AJCC M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

Tawbi ASCO 2023;Abstract 9502

Courtesy of Omid Hamid, MD

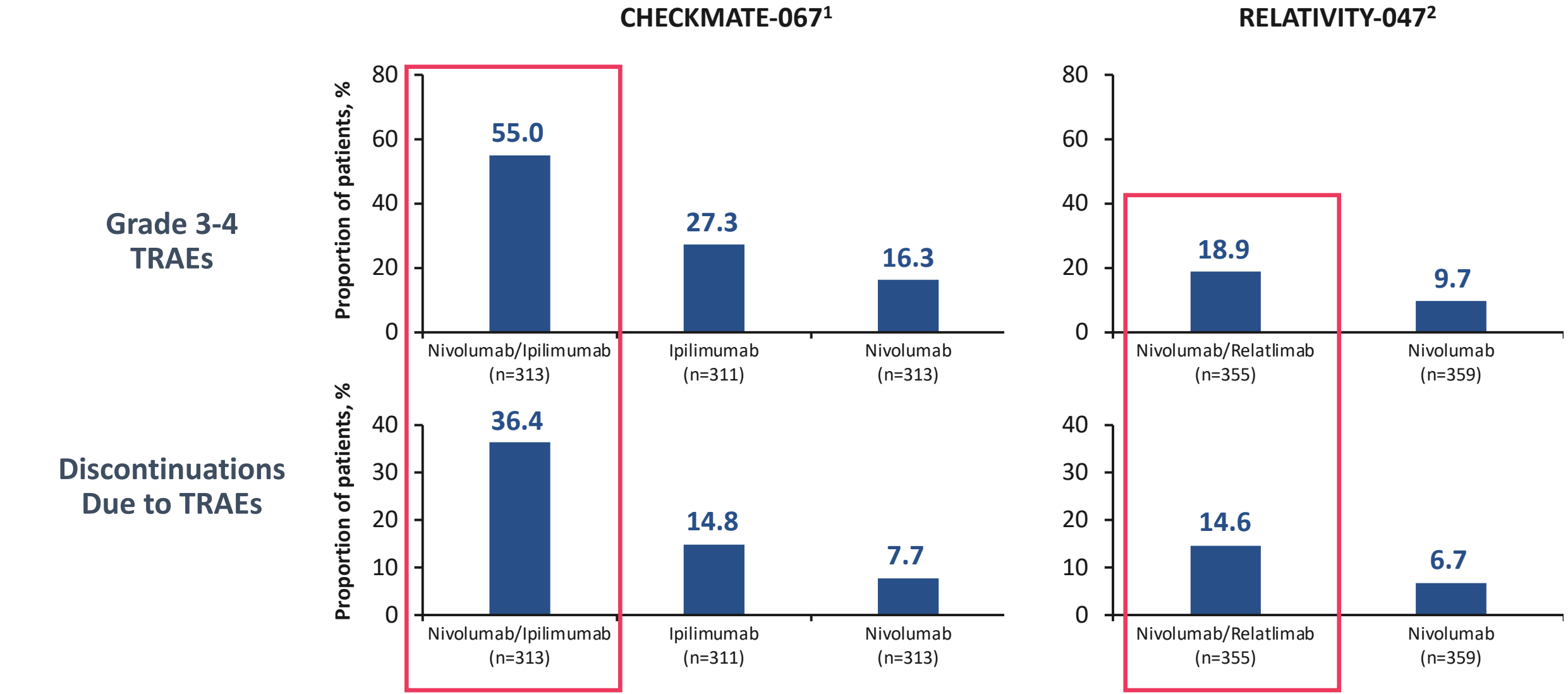
RELATIVITY-047: Subgroup Comparisons HR vs Nivolumab monotherapy

CM 067		Rela 047[a,b]	
PFS Nivo Ipi vs Nivo	HR	PFS Nivo Rela vs Nivo	HR
BRAF Mutant	0.59	BRAF Mutant	0.77
Wild Type	0.89	Wild Type	0.78
PDL-1. ≥ 1%	0.90	PDL-1. ≥ 1%	0.96
≤ 1%	0.67	≤ 1%	0.68

a. Tawbi HA, et al. N Engl J Med 2022;386:24–34. b: Long GV et al. NEJM Evid 2023;2(4)

Courtesy of Omid Hamid, MD

PD-1/LAG-3 Blockade May Be Associated With Fewer Severe Adverse Events and Discontinuations Due to TRAEs



1. Larkin J et al. *N Engl J Med*. 2015;373:23-34. 2. Tawbi HA et al. *N Engl J Med*. 2022;386:24-34.

Courtesy of Omid Hamid, MD

PARIS 2022 ESMO congress

Phase 1 study of fianlimab, a human lymphocyte activation gene-3 (LAG-3) monoclonal antibody, in combination with cemiplimab in advanced melanoma

Omid Hamid,[1] Karl Lewis,[2] Amy Weise,[3] Meredith McKean,[4] Kyriakos P Papadopoulos,[5] John Crown,[6] Tae Min Kim,[7] Nehal J Lakhani,[8] John Kaczmar,[9] Ragini Kudchadkar,[10] Alexander Spira,[11] Guilherme Rabinowits,[12] Kevin Kim,[13] Richard Carvajal,[14] Stephen Williamson,[15] Ella Ioffe,[16] Shuquan Chen,[16] Jayakumar Mani,[16] Vladimir Jankovic,[16] Laura Brennan,[16] Glenn Kroog,[16] Tasha Sims,[16*] Israel Lowy,[16] Giuseppe Gullo[16]

[1]The Angeles Clinical and Research Institute, a Cedars-Sinai Affiliate, Los Angeles, CA, USA; [2]University of Colorado Hospital, CO, USA; [3]Henry Ford Hospital, Detroit, MI, USA; [4]Sarah Cannon Research Institute/Tennessee Oncology PLLC, Nashville, TN, USA; [5]START San Antonio, San Antonio, TX, USA; [6]St Vincent's University Hospital, Dublin, Ireland; [7]Seoul National University Hospital, Seoul, South Korea; [8]START Midwest, Grand Rapids, MI, USA; [9]MUSC Hollings Cancer Center, North Charleston, SC, USA; [10]Emory University School of Medicine, Atlanta GA, USA; [11]Virginia Cancer Specialists, Fairfax, VA, USA; [12]Miami Cancer Institute, Miami, FL, USA; [13]Sutter Health Research Enterprise, San Francisco, CA, USA; [14]Columbia University Medical Center, New York, NY, USA; [15]University of Kansas Medical Center, Fairway, KS, USA; [16]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

*Formerly with Regeneron Pharmaceuticals, Inc.

Tumour response among anti–PD-(L)1–naive patients (cohorts 6 + 15)†

% (n), unless otherwise stated	Anti–PD-(L)1 naive† Cohort 6 (N=40)	Anti–PD-(L)1 naive† Cohort 15 (N=40)	Cohorts 6 + 15 (N=80)
ORR, % (95% CI)	**62.5 (45.8, 77.3)**	**65 (48.3, 79.4)**	**63.8 (52.2, 74.2)**
Complete response	15.0 (6)	2.5 (1)	8.8 (7)
Partial response	47.5 (19)	62.5 (25)	55.0 (44)
Stable disease	17.5 (7)	15.0 (6)	16.3 (13)
Progressive disease	15.0 (6)	15.0 (6)	15.0 (12)
NE	5.0 (2)	5.0 (2)	5.0 (4)
DCR	80.0 (32)	80.0 (32)	80.0 (64)
KM-estimated PFS, median (95% CI), months	**24 (4.2, NE)**	**NR (7.5, NE)**	**24 (9.9, NE)**
DOR, median (95% CI), months	NR (11.9, NE)	NR (6.3, NE)	NR (22.6, NE)
ORR: baseline LDH, n/N1 (%)			
LDH > ULN	10/17 (58.8)	6/11 (54.5)	16/28 (57.1)
LDH normal	15/23 (65.2)	18/24 (75.0)	33/47 (70.2)
ORR: liver metastasis, n/N2 (%)			
Yes	6/14 (42.9)	3/5 (60.0)	9/19 (47.4)
No	19/26 (73.1)	23/35 (65.7)	42/61 (68.9)

% (n), unless otherwise stated	Anti–PD-(L)1 naive† Cohort 6 (N=40)	Anti–PD-(L)1 naive† Cohort 15 (N=40)	Cohorts 6 + 15 (N=80)
Patients completed planned treatment‡	15.0 (6)	5.0 (2)	10.0 (8)
Ongoing treatment	15.0 (6)	52.5 (21)	33.8 (27)
Discontinued treatment	70.0 (28)	42.5 (17)	56.3 (45)
Disease progression	45.0 (18)	17.5 (7)	31.3 (25)
AE	15.0 (6)	15.0 (6)	15.0 (12)
Patient decision	5.0 (2)	0	2.5 (2)
Death	2.5 (1)	5.0 (2)	3.8 (3)
Physician decision	2.5 (1)	5.0 (2)	3.8 (3)
Duration of exposure, median (range), weeks	**37.1 (2–110)**	**24.2 (3–56)**	**30.9 (2–110)**

†Prior systemic therapies, including prior adjuvant therapies, excluded for cohort 15.
‡Planned treatment; 1 year + additional 1 year given based on investigator discretion.

CI, confidence interval; DCR, disease control rate; DOR, duration of response; KM, Kaplan-Meier; LDH, lactase dehydrogenase; n, number; N1, proportion of patients with the listed LDH status; N2, proportion of patients with the listed liver metastasis status; NE, not evaluable; NR, not reached; ORR, objective response rate; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; ULN, upper limit of normal.

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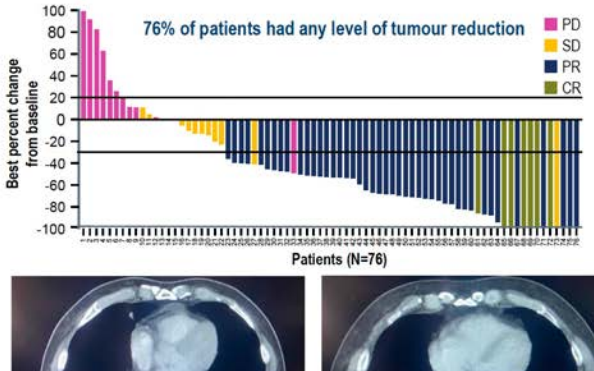
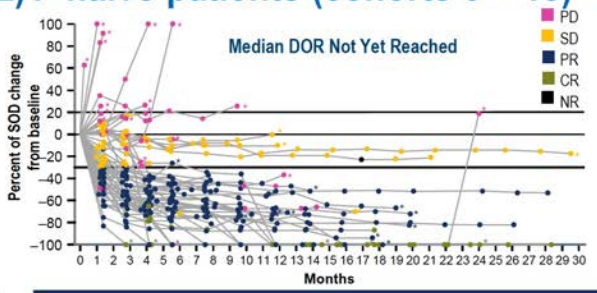
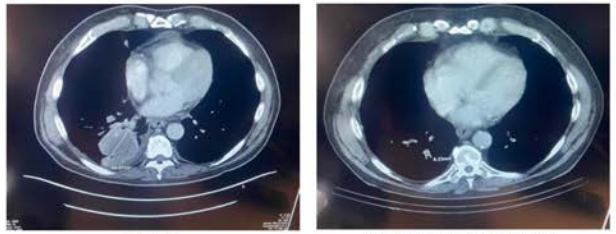
Data cut-off date: 1 Jul 2022

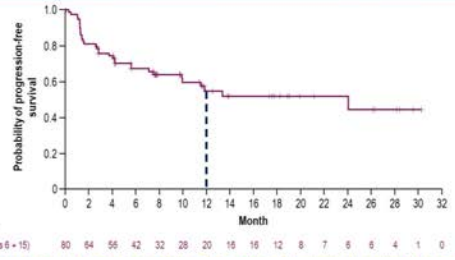
Efficacy overview among anti–PD-(L)1–naive patients (cohorts 6 + 15)†







Kaplan-Meier estimation of PFS by investigator assessment	Anti–PD-(L)1 naive† (N=80)
PFS, median (95% CI), months	24.0 (9.9, NE)
Estimated event-free probability at 12 months, % (95% CI)	55.0 (41.6, 66.5)



†Prior systemic therapies, including prior adjuvant therapies, excluded for cohort 15. †Patients with ongoing status (missing study complete status).
CI, confidence interval; CR, complete response; DOR, duration of response; NE, not estimable; NR, not reached; PD, progressive disease; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PR, partial response; SD, stable disease; SOD, sum of diameters.

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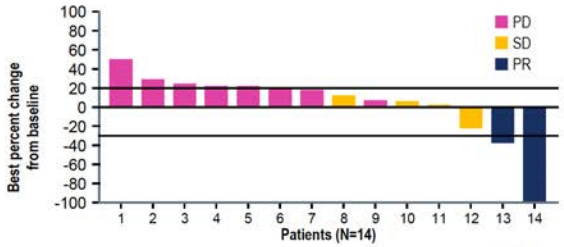
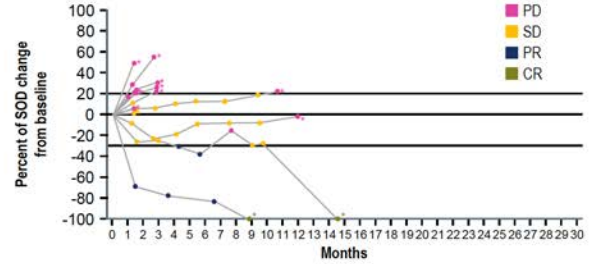
Data cut-off date: 1 Jul 2022

Clinical activity among anti–PD-(L)1–experienced patients (cohort 7)

% (n), unless otherwise stated	Total (N=15)
ORR, % (95% CI)	**13.3 (1.7–40.5)**
Complete response	0
Partial response	13.3 (2)
Stable disease	26.7 (4)
Progressive disease	53.3 (8)
NE	6.7 (1)
DCR	40.0 (6)
KM-estimated PFS, median (95% CI), months	1.5 (1.3–7.7)
DOR, median (95% CI), months	NR (3.4–NE)
ORR by LAG-3 expression, %	
<1%	NA
≥1%	18.2
ORR by PD-L1 expression, %	
<1%	18.2
≥1%	0





- Both patients that experienced CR had PD-L1 expression <1% and LAG-3 expression >1%.

CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; KM, Kaplan-Meier; LAG-3, lymphocyte activation gene-3; NA, not available; NE, not evaluable; NR, not reached; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PR, partial response; SD, stable disease; SOD, sum of diameters.

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Courtesy of Omid Hamid, MD

2023 ASCO® ANNUAL MEETING

Significant durable response with fianlimab (anti-LAG-3) and cemiplimab (anti-PD-1) in advanced melanoma: post adjuvant PD-1 analysis

Omid Hamid,[1] Karl D Lewis,[2] Amy Weise,[3] Meredith McKean,[4] Kyriakos P Papadopoulos,[5] John Crown,[6] Sajeve S Thomas,[7] Eugenia Girda,[8] John Kaczmar,[9] Kevin B Kim,[10] Nehal J Lakhani,[11] Melinda Yushak,[12] Tae Min Kim,[13] Guilherme Rabinowits,[14] Alexander Spira,[15] Jayakumar Mani,[16] Fang Fang,[16] Shuquan Chen,[16] JuAn Wang,[16] Laura Brennan,[16] Vladimir Jankovic,[16] Anne Paccaly,[16] Sheila Masinde,[16] Mark Salvati,[16] Matthew G Fury,[16] Israel Lowy,[16] Giuseppe Gullo[16]

[1]The Angeles Clinical and Research Institute, a Cedars-Sinai Affiliate, Los Angeles, CA, USA; [2]University of Colorado Cancer Center, Aurora, CO, USA; [3]Henry Ford Hospital, Detroit, MI, USA; [4]Sarah Cannon Research Institute/Tennessee Oncology PLLC, Nashville, TN, USA; [5]START, San Antonio, TX, USA; [6]St Vincent's University Hospital, Dublin, Ireland; [7]University of Florida Health Cancer Center at Orlando Health, Orlando, FL; [8]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [9]MUSC Hollings Cancer Center, North Charleston, SC, USA; [10]Center for Melanoma Research and Treatment, California Pacific Medical Center Research Institute, San Francisco, CA, USA; [11]START Midwest, Grand Rapids, MI, USA; [12]Department of Hematology and Medical Oncology at Emory University School of Medicine, Atlanta, GA, USA; [13]Seoul National University Hospital, Seoul, South Korea; [14]Department of Hematology and Oncology, Miami Cancer Institute/Baptist Health South Florida, Miami, FL, USA; [15]Virginia Cancer Specialists and US Oncology Research, Fairfax, VA, USA; [16]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

Study design: three serial expansion cohorts in advanced melanoma setting

Treatment:
Fianlimab 1600 mg + cemiplimab 350 mg IV every 3 weeks, for up to 51 weeks*

Initial cohort MM1# (n=40)

1L or 2L advanced melanoma patients who have never received anti-PD-(L)1

Confirmatory cohort MM2# (n=40)

1L advanced melanoma patients who have never received anti-PD-(L)1

PD-1 experienced cohort MM3# (n=18)

1L advanced melanoma patients with prior (neo)adjuvant systemic therapy‡, including 13/18 patients who received anti-PD-1

Primary endpoint

- ORR per RECIST 1.1 criteria

Secondary endpoints

- PFS
- DoR
- DCR
- Safety
- PK

Key inclusion criteria

- Metastatic or inoperable locally advanced non-uveal melanoma
- ≥18 years of age
- ECOG PS of 0 or 1
- At least one lesion measurable by RECIST 1.1

Key exclusion criteria

- Uveal melanoma
- Prior treatment with a LAG-3 targeting agent
- Radiation therapy within 2 weeks prior to enrollment

‡: Prior exposure to (neo)adjuvant systemic treatment (including anti-PD-1) with recurrence >6 months after adjuvant therapy
MM1#, Cohort 6; MM2#, Cohort 15; MM3#, Cohort 16. *With an option for an additional 51 weeks.
1L, first-line; 2L, second-line; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance score; IV, intravenous; LAG-3, lymphocyte activation gene-3; MM, metastatic melanoma; NHL, non-Hodgkin lymphoma; ORR, objective response rate; PD-(L)1, programmed cell death-(ligand)1; PFS, progression-free survival; PK, pharmacokinetics; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Fianlimab (anti-LAG-3) and Cemiplimab (anti-PD-1) in Advanced Melanoma: Post Adjuvant PD-1 Analysis: Tumor Response by Cohort

Response endpoints	Initial cohort MM1# (n=40)	Confirmatory cohort MM2# (n=40)	PD-1 experienced cohort MM3# (n=18)*
Median follow-up (IQR), months	**20.8 (11.2–30.8)**	**11.5 (8.9–13.9)**	**9.7 (4.8–14.1)**
Treatment exposure, median (IQR), weeks	**37 (20–81)**	**35 (15–51)**	**23 (12–37)**
ORR, (n)	**63% (25)**	**63% (25)**	**56% (10)**
95% CI for ORR	(46–77)	(46–77)	(31–79)
DoR, median (95% CI), months	**NR (12–NE)**	**NR (NE–NE)**	**NR (6–NE)**
DCR, (n)	**80% (32)**	**80% (32)**	**67% (12)**
95% CI for DCR	(64–91)	(64–91)	(41–87)
Best overall response, (n)			
CR	15% (6)	13% (5)	6% (1)
PR	48% (19)	50% (20)	50% (9)
SD	18% (7)	18% (7)	11% (2)
PD	15% (6)	15% (6)	28% (5)
NE	5% (2)	5% (2)	6% (1)
KM-estimated PFS, median (95% CI), months	**24 (4–NE)**	**15 (7–NE)**	**12 (1–NE)**

Courtesy of Omid Hamid, MD

Tumor responses compared with historical controls

Response endpoints	Cohorts MM1[#] + MM2[#] + MM3[#] Advanced Melanoma (N=98)	Nivo Relativity-047[1] (N=359)	Nivo + Rela Relativity-047[1] (N=355)	Ipi + Nivo CheckMate-067[2,3] (N=314)
Median follow-up, months	12.6	19.3	19.3	57.5
ORR, (95% CI)	61% (51–71)	33% (28–38)	43% (38–48)	58% (53–64)
DCR	78%	51%	63%	71%
DoR, median (95% CI), months	NR (23–NE)	NR (30–NR)	NR (30–NR)	NR (62–NR)
KM-estimated PFS, median (95% CI), months	15 (9–NE)	5 (3–6)	10 (7–15)	12 (9–19)

MM1[#], Cohort 6; MM2[#], Cohort 15; MM3[#], Cohort 16. CI, confidence interval; DCR, disease control rate; DoR, duration of response; Ipi, ipilimumab; KM, Kaplan-Meier; MM, metastatic melanoma; n, number; Nivo, nivolumab; ORR, objective response rate; PFS, progression-free survival; Rela, relatlimab.

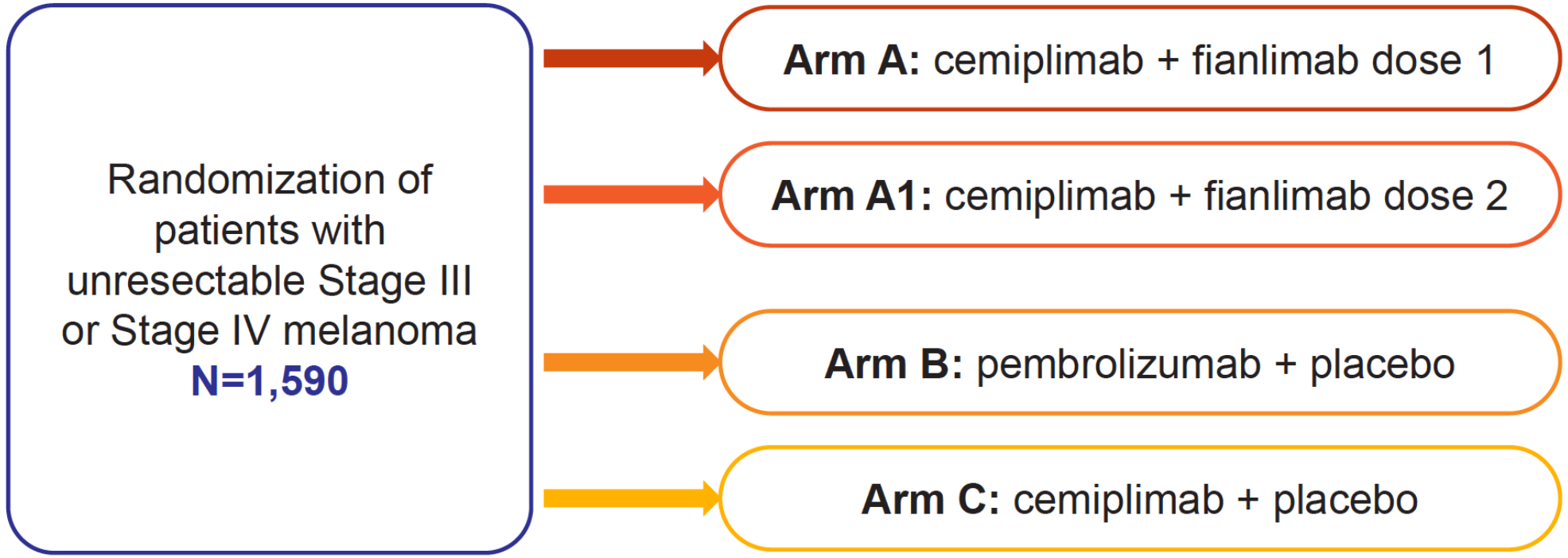
1. Long G et al. *NEJM Evid* 2023; 2 (4). 2. Larkin J et al. *N Engl J Med* 2019;381(16):1535–1546. *3.* Wolchok JD et al. *J Clin Oncol 2022 ;40(2):127-137*

Abstract TPS9602: A Phase 3 trial of fianlimab (anti-LAG-3) plus cemiplimab (anti-PD-1) versus pembrolizumab in patients with previously untreated unresectable locally advanced or metastatic melanoma

Ana Baramidze,[1] Miranda Gogishvili,[2] Tamta Makharadze,[3] Mariam Zhvania,[4] Khatuna Vacharadze,[5] John Crown,[6] Tamar Melkadze,[1] Omid Hamid,[7] Georgina V Long,[8] Caroline Robert,[9] Mario Sznol,[10] Hector Martinez-Said,[11] Jayakumar Mani,[12] Usman Chaudhry,[12] Mark Salvati,[12] Israel Lowy,[12] Matthew G Fury,[12] Giuseppe Gullo[12]

[1]Todua Clinic, Tbilisi, Georgia; [2]High Technology Medical Centre, University Clinic Ltd., Tbilisi, Georgia; [3]LTD High Technology Hospital Med Center, Batumi, Georgia; [4]Consilium Medullla, Tbilisi, Georgia; [5]LTD TIM Tbilisi Institute of Medicine, Tbilisi, Georgia; [6]St Vincent's University Hospital, Dublin, Ireland; [7]The Angeles Clinical and Research Institute, a Cedars-Sinai Affiliate, Los Angeles, CA, USA; [8]Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, Australia; [9]Gustave Roussy and Paris Saclay University, Villejuif, France; [10]Yale Cancer Center, CT, USA; [11]Melanoma Clinic, Instituto Nacional de Cancerologia, Mexico; [12]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

Figure 1. Study design



Stratification:

1. *M stage (Stage III vs. M1a–b vs. M1c vs. M1d)*
2. *LDH level (normal vs. elevated)*
3. *Prior exposure to anti-PD-1/PD-L1 therapy in the adjuvant setting.*

LDH, lactate dehydrogenase; PD-1, programmed death-1; PD-L1, programmed death-ligand 1.

Courtesy of Omid Hamid, MD

Key Data Sets – Localized Melanoma

Omid Hamid, MD

- Schadendorf D et al. **Adjuvant nivolumab** (NIVO) **alone** or in **combination** with **ipilimumab** (IPI) versus placebo in **stage IV** melanoma with no evidence of disease **(NED)**: Overall survival (OS) results of **IMMUNED**, a randomized, double-blind multi-center phase II DeCOG trial. ESMO 2022;Abstract 784O.

Evan J Lipson, MD

- Weber JS et al. **Adjuvant** therapy of **nivolumab** combined **with ipilimumab** versus **nivolumab alone** in patients with **resected Stage IIIB-D or Stage IV** melanoma **(CheckMate 915)**. *J Clin Oncol* 2023;41(3):517-27.
- Luke JJ et al. **Pembrolizumab** versus **placebo** as **adjuvant** therapy in **stage IIB or IIC** melanoma: Final analysis of distant metastasis-free survival in **the phase 3 KEYNOTE-716** study. ASCO 2023;Abstract LBA9505.
- Long G et al. **Adjuvant** therapy with **nivolumab** versus **placebo** in patients with **stage IIB/C** melanoma (**CheckMate 76K**). Society for Melanoma Research 2022.

Key Data Sets – Localized Melanoma

Evan J Lipson, MD (continued)

- Patel SP et al. **Neoadjuvant-adjuvant** or **adjuvant-only pembrolizumab** in advanced melanoma. *N Engl J Med* 2023;388(9):813-23.
- Panella TJ et al. A **phase 3** trial comparing **fianlimab (anti–LAG-3)** plus **cemiplimab (anti–PD-1)** to **pembrolizumab** in patients with **completely resected high-risk** melanoma. ASCO 2023;Abstract TPS9598.
- Van Akkooi ACJ et al. **Phase III** study of **adjuvant encorafenib** plus **binimetinib** versus **placebo** in fully **resected stage IIB/C BRAFV600-mutated** melanoma: **COLUMBUS-AD** study design. ASCO 2023;Abstract TPS9601.
- Khattak MA et al. Distant metastasis-free survival results from the randomized, phase 2 **mRNA-4157-P201/KEYNOTE-942 trial.** ASCO 2023;Abstract LBA9503.

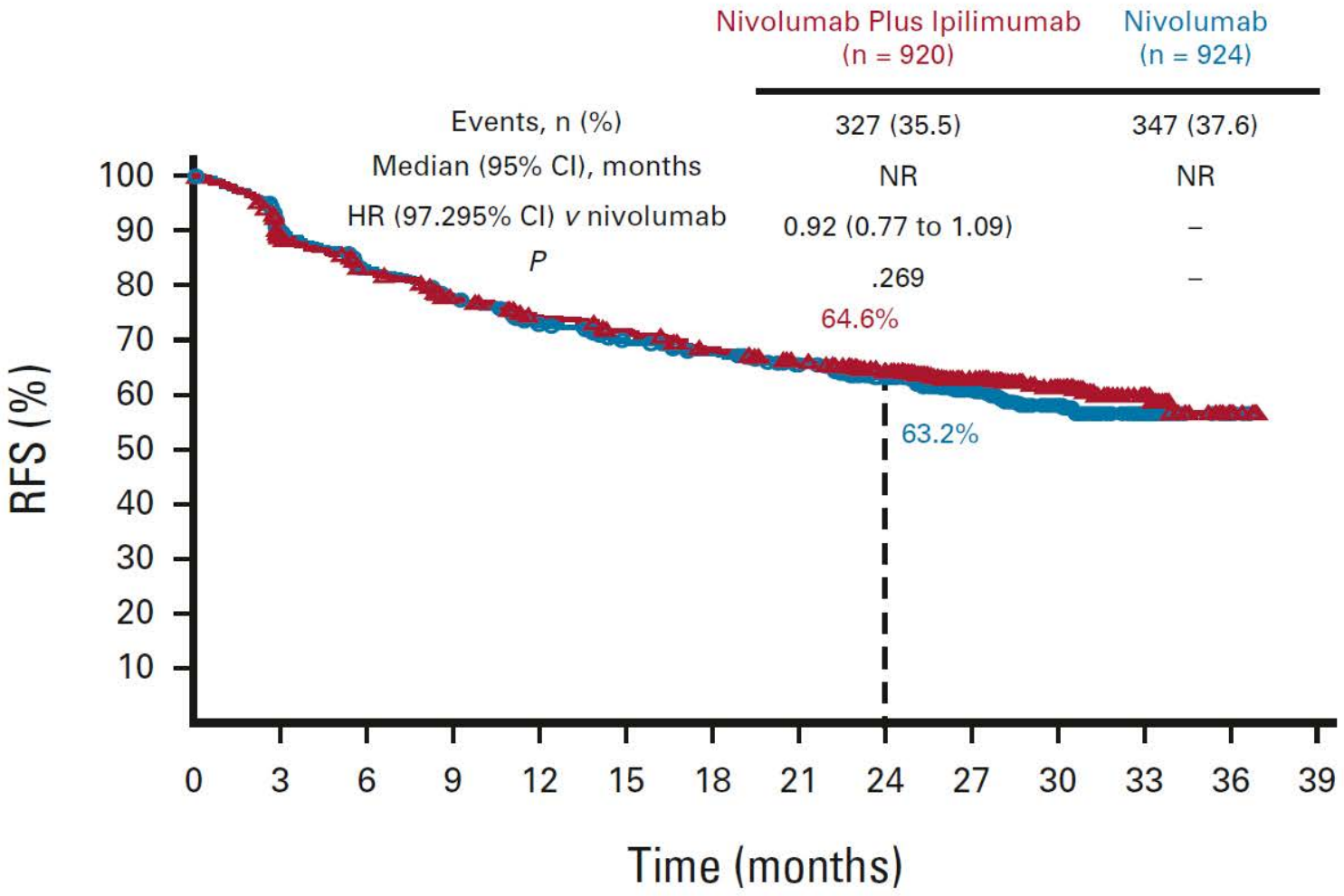
Adjuvant Therapy of Nivolumab Combined With Ipilimumab Versus Nivolumab Alone in Patients With Resected Stage IIIB-D or Stage IV Melanoma (CheckMate 915)

Jeffrey S. Weber, MD, PhD[1]; Dirk Schadendorf, MD[2]; Michele Del Vecchio, MD[3]; James Larkin, PhD, FRCP[4]; Victoria Atkinson, MD[5]; Michael Schenker, MD[6]; Jacopo Pigozzo, MD[7]; Helen Gogas, MD, PhD[8]; Stéphane Dalle, MD, PhD[9]; Nicolas Meyer, MD, PhD[10]; Paolo A. Ascierto, MD[11]; Shahneen Sandhu, MBBS[12]; Thomas Eigentler, MD[13]; Ralf Gutzmer, MD[14]; Jessica C. Hassel, MD[15]; Caroline Robert, MD, PhD[16]; Matteo S. Carlino, MBBS, PhD[17]; Anna Maria Di Giacomo, MD, PhD[18]; Marcus O. Butler, MD[19]; Eva Muñoz-Couselo, MD[20]; Michael P. Brown, MBBS, PhD[21]; Piotr Rutkowski, MD[22]; Andrew Haydon, MD[23]; Jean-Jacques Grob, MD[24]; Jacob Schachter, MD, PhD[25]; Paola Queirolo, MD[26,27]; Luis de la Cruz-Merino, MD[28]; Andre van der Westhuizen, MBChB, MMed[29]; Alexander M. Menzies, MBBS, PhD[30]; Sandra Re, MD[31]; Tuba Bas, PhD[31]; Veerle de Pril, MSc[31]; Julia Braverman, PhD[31]; Daniel J. Tenney, PhD[31]; Hao Tang, PhD[31]; and Georgina V. Long, MBBS, PhD[30]

Weber JS et al. J Clin Oncol 2023;41(3):517-27.

Courtesy of Evan J Lipson, MD

CheckMate 915: No difference in recurrence-free survival (RFS) among ~1800 patients with resected stage IIIB-D or IV melanoma randomized to nivolumab + ipilimumab 1mg/kg q6W vs nivolumab alone



Weber JS et al. J Clin Oncol 2023;41(3):517-27.

Courtesy of Evan J Lipson, MD

Conclusions

- **Critical finding(s):** No difference in recurrence-free survival among ~1800 patients with resected stage IIIB-D or IV melanoma randomized to nivolumab + ipilimumab 1mg/kg q6W vs nivolumab alone, regardless of PD-L1 status.
- Treatment-related grade 3-4 adverse events were reported in 32.6% of patients in the combination group and 12.8% in the nivolumab group. Treatment-related deaths were reported in 0.4% of patients in the combination group and in no nivolumab-treated patients.

- **Clinical implication(s):** These results support administration of adjuvant anti-PD-1 monotherapy for patients with high-risk resected melanoma.

- **Research relevance:** Could other combinations (e.g., anti-PD-1 + anti-LAG-3) provide benefit over anti-PD-1 alone in this patient population?

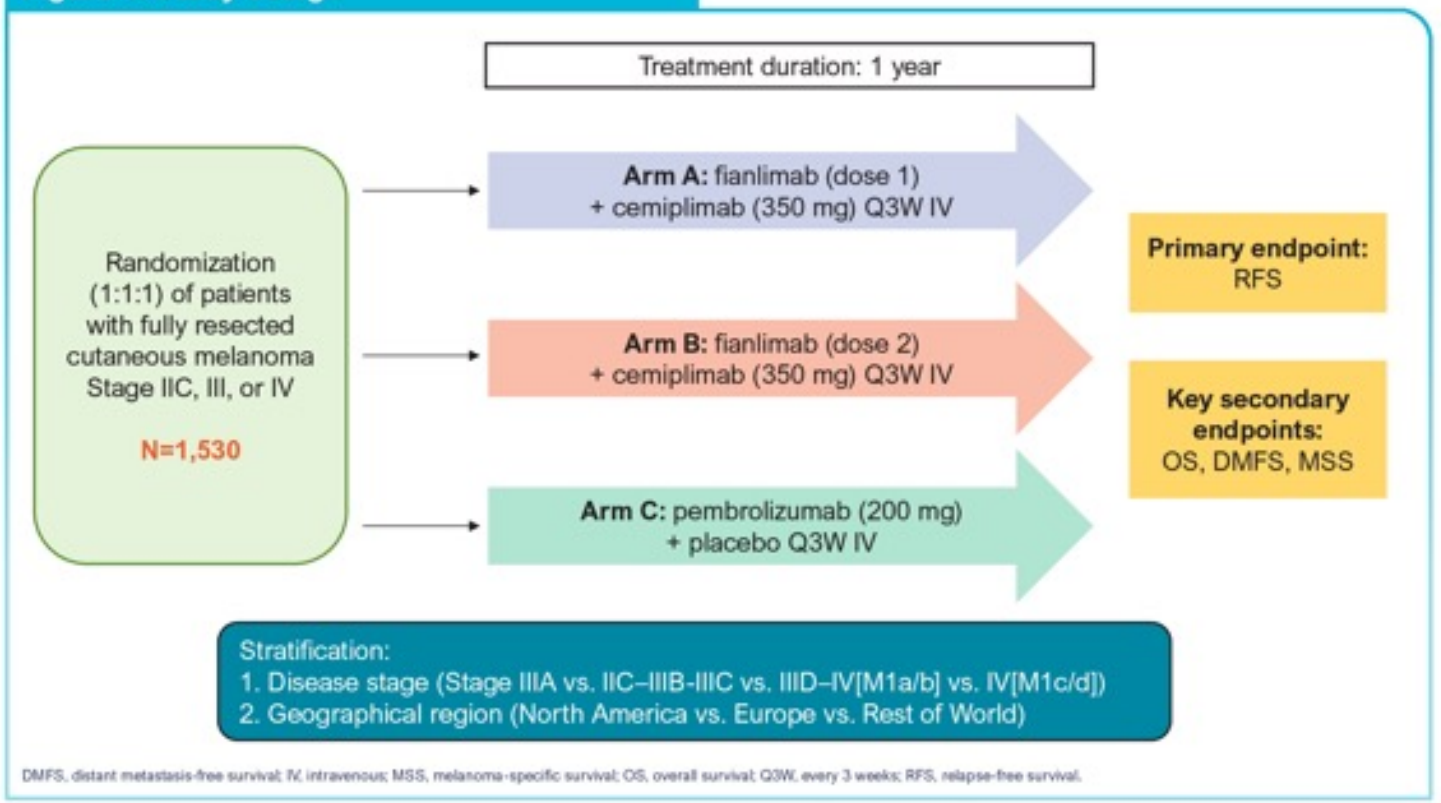
Courtesy of Evan J Lipson, MD

Abstract TPS9598: A Phase 3 trial comparing fianlimab (anti-LAG-3) plus cemiplimab (anti-PD-1) to pembrolizumab in patients with completely resected high-risk melanoma

Timothy J Panella,[1] Sajeve S Thomas,[2] Meredith McKean,[3] Kim Margolin,[4] Ryan Weight,[5] Jayakumar Mani,[6] Shraddha Patel,[6] Priya Desai,[6] Rossella Marullo,[6] Mark Salvati,[6] Israel Lowy,[6] Matthew G Fury,[6] Giuseppe Gullo[6]

[1]University of Tennessee Medical Center, Knoxville, TN, USA; [2]Orlando Health Cancer Institute, Lake Mary, FL, USA; [3]Sarah Cannon Research Institute/Tennessee Oncology PLLC, Nashville, TN, USA; [4]Saint John's Cancer Institute, Santa Monica, CA, USA; [5]The Melanoma And Skin Cancer Institute, Denver, CO, USA; [6]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

Figure 1. Study design



Panella TJ et al. ASCO 2023;Abstract TPS9598.

Courtesy of Evan J Lipson, MD

Conclusions

Abstract TPS9598: A Phase 3 trial comparing fianlimab (anti-LAG-3) plus cemiplimab (anti-PD-1) to pembrolizumab in patients with completely resected high-risk melanoma

Timothy J Panella,[1] Sajeve S Thomas,[2] Meredith McKean,[3] Kim Margolin,[4] Ryan Weight,[5] Jayakumar Mani,[6] Shraddha Patel,[6] Priya Desai,[6] Rossella Marullo,[6] Mark Salvati,[6] Israel Lowy,[6] Matthew G Fury,[6] Giuseppe Gullo[6]

[1]University of Tennessee Medical Center, Knoxville, TN, USA; [2]Orlando Health Cancer Institute, Lake Mary, FL, USA; [3]Sarah Cannon Research Institute/Tennessee Oncology PLLC, Nashville, TN, USA; [4]Saint John's Cancer Institute, Santa Monica, CA, USA; [5]The Melanoma And Skin Cancer Institute, Denver, CO, USA; [6]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

- **Critical finding(s):** This is a phase 3 trial comparing recurrence-free survival among patients with resected stage IIC, III or IV melanoma who receive pembrolizumab or cemiplimab+fianlimab (anti-PD-1 + anti-LAG-3).

- **Clinical implication(s):** If successful, this trial could introduce a combination adjuvant immunotherapy option for patients with resected high-risk melanoma.

- **Research relevance:** Phase 3 trial in progress.

Courtesy of Evan J Lipson, MD

2023 ASCO ANNUAL MEETING

Distant Metastasis-Free Survival Results From the Randomized, Phase 2 mRNA-4157-P201/ KEYNOTE-942 Trial

Adnan Khattak,[1,2] Jeffrey S. Weber,[3] Tarek Meniawy,[4] Matthew H. Taylor,[5] George Ansstas,[6] Kevin B. Kim,[7] Meredith McKean,[8] Georgina V. Long,[9] Ryan J. Sullivan,[10] Mark B. Faries,[11] Thuy Tran,[12] C. Lance Cowey,[13] Theresa M. Medina,[14] Jennifer M. Segar,[15] Victoria Atkinson,[16] Geoffrey T. Gibney,[17] Jason J. Luke,[18] Elizabeth I. Buchbinder,[19] Robert S. Meehan,[20] Matteo S. Carlino,[9,21] Moderna Author's Group[20]

[1]Hollywood Private Hospital, Nedlands, Australia; [2]Edith Cowan University, Perth, Australia; [3]NYU Langone Medical Center, New York, NY; [4]Saint John of God Subiaco Hospital, Subiaco, Australia; [5]Earle A. Chiles Research Institute, Portland, OR, USA; [6]Washington University School of Medicine, St Louis, MO, USA; [7]California Pacific Medical Center Research Institute, Oakland, CA, USA; [8]Sarah Cannon Research Institute, Nashville, TN, USA; [9]Melanoma Institute Australia, Wollstonecraft, Australia; [10]Massachusetts General Hospital, Boston, MA, USA; [11]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [12]Yale-New Haven Hospital, New Haven, CT, USA; [13]Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [14]University of Colorado, Aurora, CO, USA; [15]The University of Arizona Cancer Center, Tucson, AZ, USA; [16]Princess Alexandra Hospital, Woolloongabba, Australia; [17]Lombardi Cancer Center, Washington, DC, USA; [18]UPMC Hillman Cancer Center, Pittsburg, PA, USA; [19]Dana-Farber Cancer Institute, Boston, MA, USA; [20]Moderna Inc., Cambridge, MA, USA; [21]Westmead Hospital, Westmead, Australia.

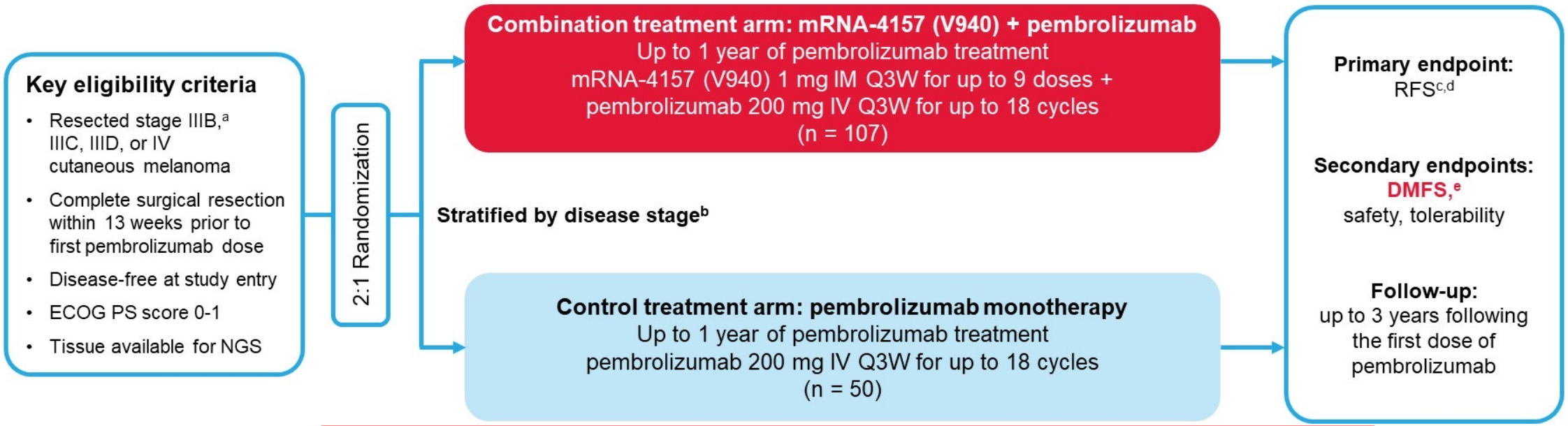
Sponsored by Moderna, Inc., in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Khattak MA et al. ASCO 2023;Abstract LBA9503.

Courtesy of Evan J Lipson, MD

mRNA-4157-P201/KEYNOTE-942 (NCT03897881) Study Design

Randomized, phase 2, open-label study in adjuvant resected melanoma patients at high risk of recurrence



Designed with 80% power to detect an HR of 0.5 with ≥40 RFS events (with a 1-sided alpha of 0.1)
DMFS analysis was prespecified for testing following positive RFS in the ITT population[f]
Median follow-up[g]: 23 months for mRNA-4157 (V940) + pembrolizumab
24 months for pembrolizumab monotherapy

[a]Patients with stage IIIB disease were eligible only if relapse occurred within 3 months of prior surgery of curative intent. [b]According to the 8th edition of the American Joint Committee on Cancer Staging Manual. [c]The primary endpoint was investigator-assessed RFS (defined as the time from first dose of pembrolizumab until the date of first recurrence [local, regional, or distant metastasis], a new primary melanoma, or death from any cause) in the intention-to-treat population. [d]The primary analysis for RFS was specified to occur after all patients completed ≥12 months on study and ≥40 RFS events were observed. Descriptive analysis was specified to occur when ≥51 RFS events were observed. [e]Investigator-assessed DMFS was defined as the time from first dose of pembrolizumab until the date of first distant recurrence or death from any cause. [f]The stratified log-rank test was used for comparison. [g]Time of database cutoff was November 14, 2022.

Khattak MA et al. ASCO 2023;Abstract LBA9503.

Courtesy of Evan J Lipson, MD

Conclusions

- **Critical finding(s):** Compared to pembrolizumab alone, mRNA-4157 (V940) + pembrolizumab led to a 44% reduction in the risk of recurrence or death and a 65% reduction in the risk of distant metastasis or death among patients with resected stage IIIB-IV melanoma.
- **Clinical implication(s):** Further testing needed. Sample size was relatively small and statistical outcomes are borderline, requiring additional investigation.
- **Research relevance:** Phase 3 trial opening soon.

Courtesy of Evan J Lipson, MD

Agenda

Introduction: Immunology of Melanoma

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- Sequencing of BRAF-targeted agents and immunotherapy for BRAF-mutant metastatic melanoma
- Choice of first-line immunotherapy for metastatic melanoma
- Adjuvant treatment of localized melanoma

MODULE 2: Cutaneous Squamous Cell Carcinoma

MODULE 3: Basal Cell Carcinoma and Merkel Cell Carcinoma

MODULE 4: Novel Agents and Strategies

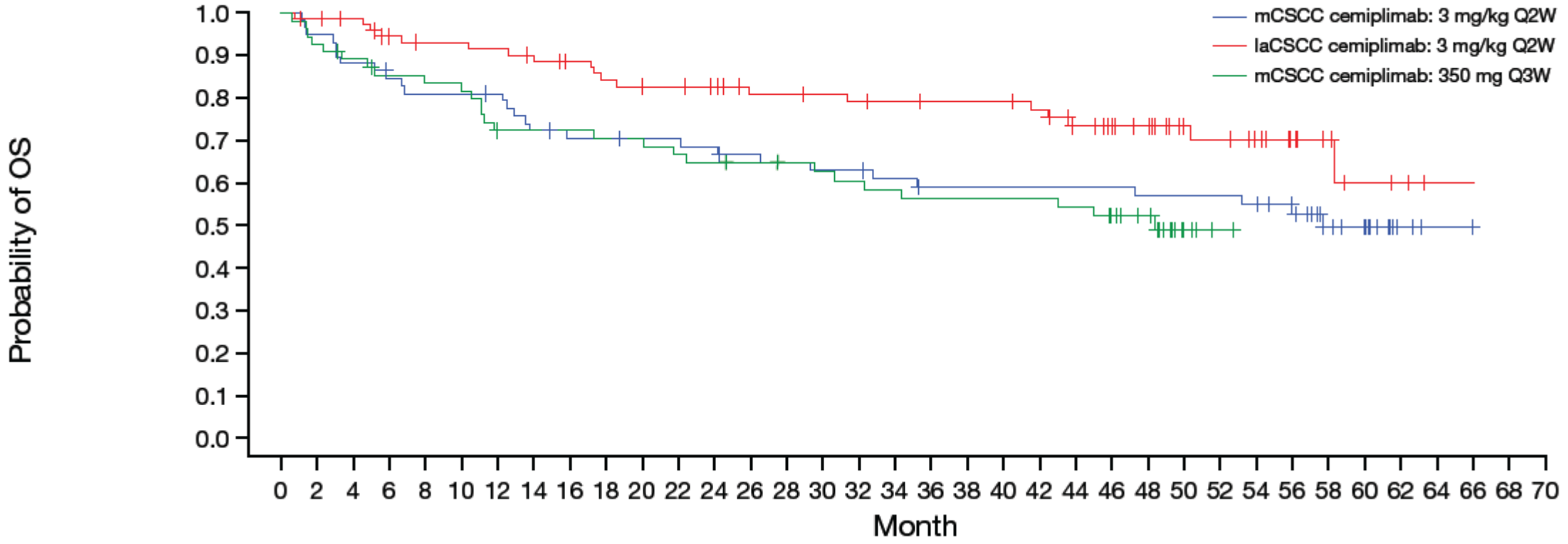
Key Data Sets – Cutaneous Squamous Cell Carcinoma

Evan J Lipson, MD (continued)

- Migden MR et al. Phase II study of **cemiplimab** in patients with advanced **cutaneous squamous cell carcinoma** (CSCC): Final analysis from **EMPOWER-CSCC**-1 groups 1, 2 and 3. ESMO 2022;Abstract 814P.
- Gross ND et al. **Neoadjuvant cemiplimab** for **Stage II to IV cutaneous squamous-cell carcinoma**. *N Engl J Med* 2022;387(17):1557-68.
- Hanna et al. **Cemiplimab** for **kidney organ transplant** recipients with advanced **cutaneous squamous** cell carcinoma: **CONTRAC-1**. ASCO 2023;Abstract 9519.
- Zuur CL et al. Towards **organ preservation** and **cure** via **2 infusions of immunotherapy** only, in patients normally undergoing extensive and mutilating curative surgery for **cutaneous squamous cell carcinoma:** An investigator-initiated randomized phase II trial—The **MATISSE** trial. ASCO 2023;Abstract 9507.

Phase 2 study of cemiplimab in patients with advanced cutaneous squamous cell carcinoma (CSCC): Final analysis from EMPOWER-CSCC-1 Groups 1, 2 and 3

Michael R Migden,[1] Chrysalyne D Schmults,[2] Nikhil I Khushalani,[3] Alexander Guminski,[4] Anne Lynn S Chang,[5] Karl D Lewis,[6] George Ansstas,[7] Samantha Bowyer,[8] Brett G Hughes,[9] Dirk Schadendorf,[10] Badri Modi,[11] Lara A Dunn,[12] Lukas Flatz,[13] Axel Hauschild,[14] Suk-Young Yoo,[15] Jocelyn Booth,[15] Frank Seebach,[15] Israel Lowy,[15] Matthew G Fury,[15] Danny Rischin[16]



Migden MR et al. ESMO 2022;Abstract 814P.

Courtesy of Evan J Lipson, MD

Conclusions

- **Critical finding(s):** 193 patients with advanced cutaneous squamous cell carcinoma received cemiplimab. Median duration of follow up was 15.7 months.
  - Median PFS = 22.1 months
  - Median duration of response = 41.3 months
  - Median OS not reached; Kaplan–Meier estimated probability of OS at 48 months was 61.8%

- **Clinical implication(s):** This study confirms the efficacy, durability, and safety profile of cemiplimab in patients with advanced CSCC.

- **Research relevance:** Could other combinations (e.g., anti-PD-1 + anti-LAG-3) provide benefit over anti-PD-1 alone in this patient population?

Courtesy of Evan J Lipson, MD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

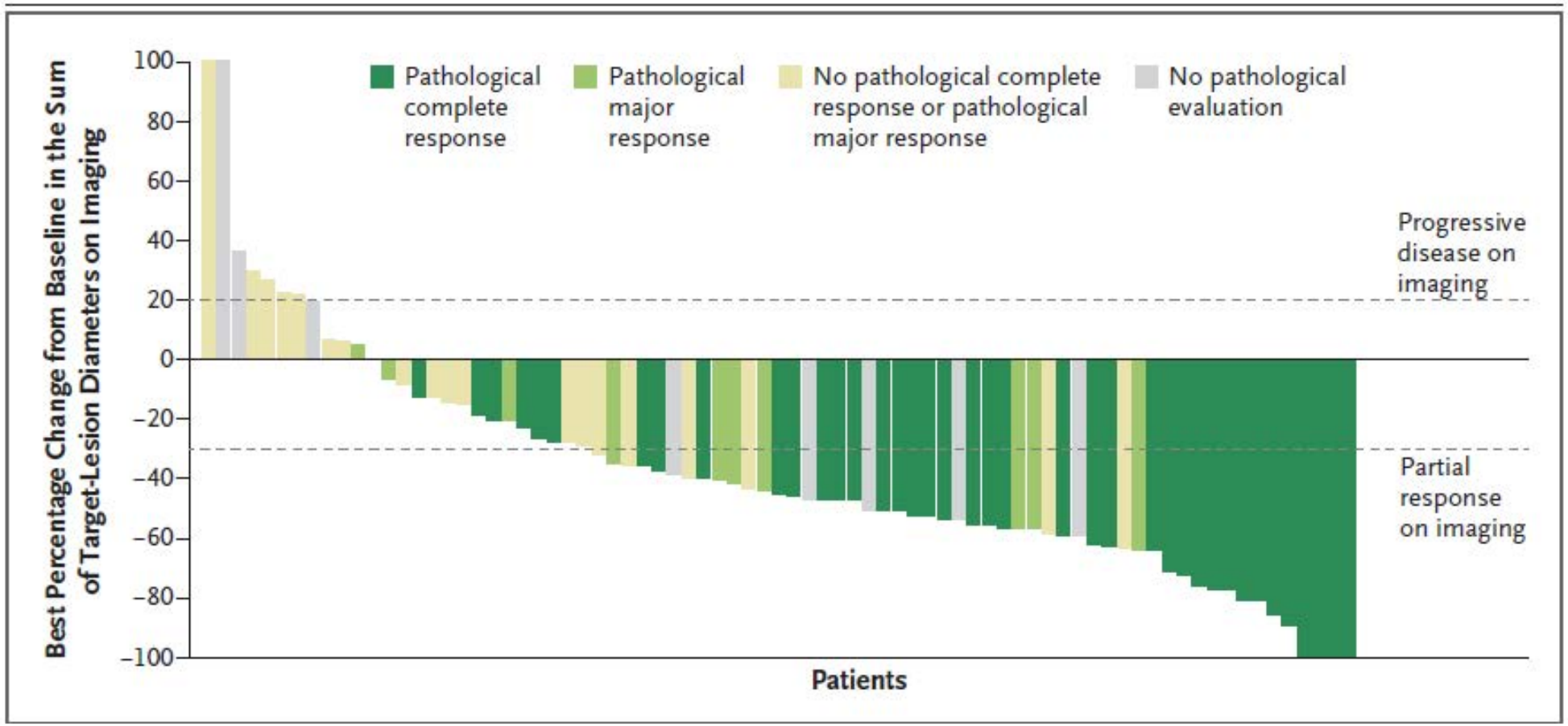
Neoadjuvant Cemiplimab for Stage II to IV Cutaneous Squamous-Cell Carcinoma

N.D. Gross, D.M. Miller, N.I. Khushalani, V. Divi, E.S. Ruiz, E.J. Lipson, F. Meier, Y.B. Su, P.L. Swiecicki, J. Atlas, J.L. Geiger, A. Hauschild, J.H. Choe, B.G.M. Hughes, D. Schadendorf, V.A. Patel, J. Homsi, J.M. Taube, A.M. Lim, R. Ferrarotto, H.L. Kaufman, F. Seebach, I. Lowy, S.-Y. Yoo, M. Mathias, K. Fenech, H. Han, M.G. Fury, and D. Rischin

Gross ND et al. N Engl J Med 2022;387(17):1557-68.

Courtesy of Evan J Lipson, MD

Among 79 patients with advanced CSCC who received neoadjuvant cemiplimab, complete or major pathological response was observed in 64%. Objective response on imaging was observed in 68%.



Gross ND et al. N Engl J Med 2022;387(17):1557-68.

Courtesy of Evan J Lipson, MD

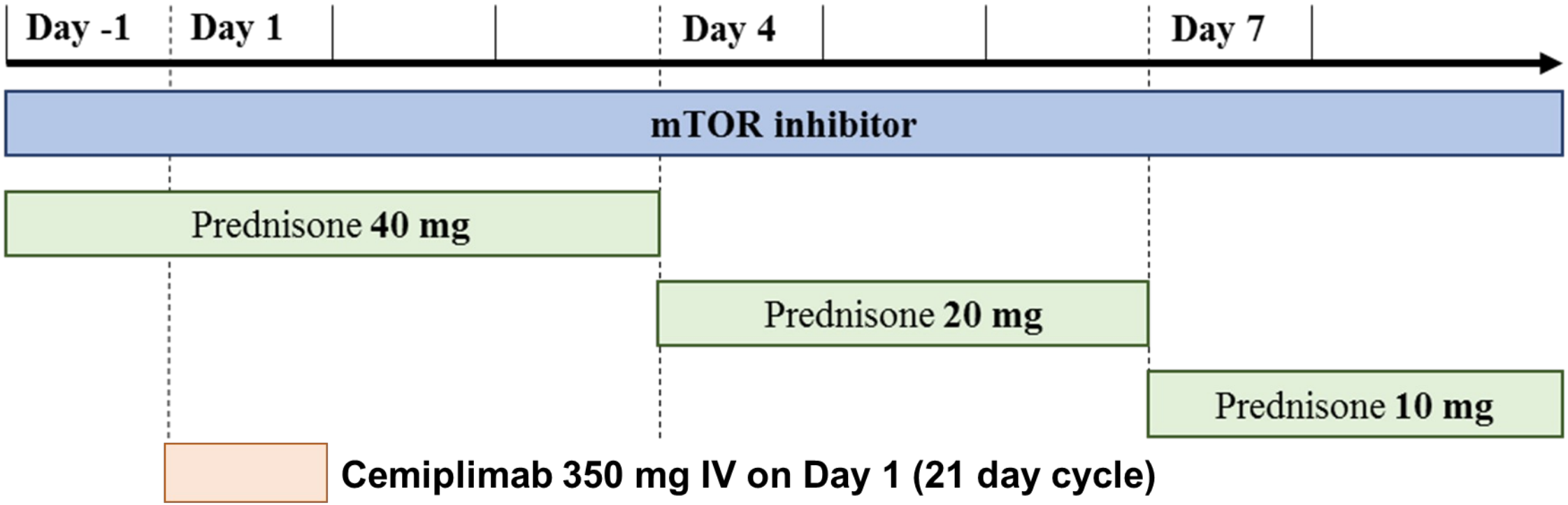
Conclusions

- **Critical finding(s):** Among 79 patients with resectable stage II, III, or IV (M0) CSCC who received neoadjuvant cemiplimab x 12 weeks, complete or major pathological response was observed in 64%. Objective response on imaging was observed in 68%.
- **Clinical implication(s):** Neoadjuvant immunotherapy is becoming standard-of-care for patients with locally-advanced resectable CSCC.
- **Research relevance:** Which regimen is best, for how long, and are surgery and/or adjuvant therapy needed, particularly in the setting of substantial tumor regression or a pathologic complete response? Larger trials addressing these questions are in process.

Courtesy of Evan J Lipson, MD

Cemiplimab for Kidney Organ Transplant Recipients with Advanced Cutaneous Squamous Cell Carcinoma (**CONTRAC-1**)

Glenn J. Hanna, M.D., Harita Dharaneeswaran, Anita Giobbe-Hurder, John J. Harran, Zixi Liao, Lori Pai, M.D., Vatche Tchekmedyian, M.D., Emily S. Ruiz, M.D., Abigail Waldman, M.D., Chrysalyne D. Schmults, M.D., Patrick Lizotte, Ph.D., Cloud Paweletz, Ph.D., Leonardo V. Riella, M.D., Ph.D., Naoka Murakami, M.D., Ph.D., Ann W. Silk, M.D.



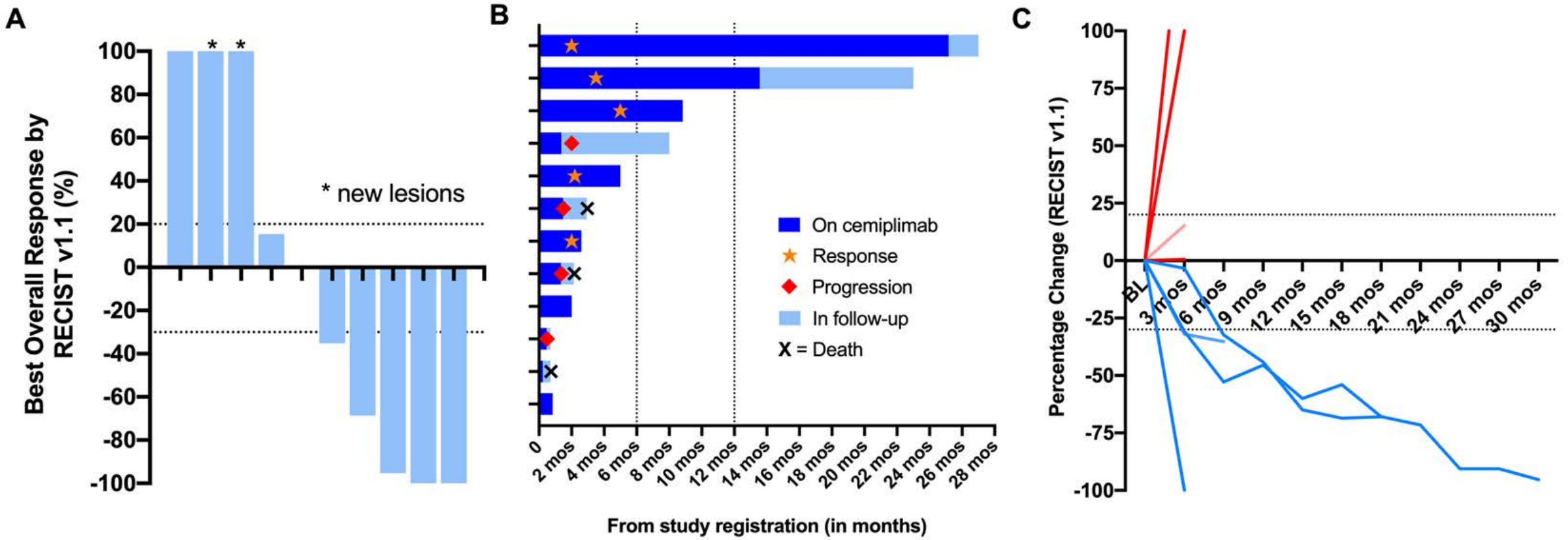
Hanna et al. ASCO 2023

Courtesy of Evan J Lipson, MD

Cemiplimab for Kidney Organ Transplant Recipients with Advanced Cutaneous Squamous Cell Carcinoma (**CONTRAC-1**)

Glenn J. Hanna, M.D., Harita Dharaneeswaran, Anita Giobbe-Hurder, John J. Harran, Zixi Liao, Lori Pai, M.D., Vatche Tchekmedyian, M.D., Emily S. Ruiz, M.D., Abigail Waldman, M.D., Chrysalyne D. Schmults, M.D., Patrick Lizotte, Ph.D., Cloud Paweletz, Ph.D., Leonardo V. Riella, M.D., Ph.D., Naoka Murakami, M.D., Ph.D., Ann W. Silk, M.D.

Figure 1. Efficacy Measurements



Hanna et al. ASCO 2023

Courtesy of Evan J Lipson, MD

Conclusions

- **Critical finding(s):** Among 12 patients, no kidney rejection observed. ORR= 50% (5/10 patients); some responses were durable (>2 years in 2/10 patients)
- **Clinical implication(s):** To date, mTor inhibition + pulsed prednisone is the regimen associated with the lowest risk of organ rejection that does not preclude responses to Cemiplimab in kidney transplant recipients with cutaneous squamous cell carcinoma.
- **Research relevance:** Larger trials are planned to further test combinatorial regimens that can activate anti-tumor immunity and maintain allograft tolerance.

Courtesy of Evan J Lipson, MD

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Key Data Sets – Basal Cell Carcinoma and Merkel Cell Carcinoma

Evan J Lipson, MD (continued)

- Lewis KD et al. Health-related **quality of life** in patients with **metastatic basal cell carcinoma** treated with **cemiplimab**: Analysis of a Phase 2 open-label clinical trial. EADO 2023;Abstract HSR23-097.
- Bhatia S et al. Non-comparative, open-label, international, multicenter phase I/II study of **nivolumab (NIVO) ± ipilimumab (IPI)** in patients (pts) with recurrent/metastatic **merkel cell carcinoma** (MCC) (CheckMate 358). ASCO 2023;Abstract 9506.

HSR23-097: Health-Related Quality of Life in Patients With Metastatic Basal Cell Carcinoma Treated With Cemiplimab: Analysis of a Phase 2 Open-Label Clinical Trial

Authors: Karl D. Lewis MD, Timothy J. Inocencio PharmD, PhD, Ruben G.W. Quek PhD, Patrick R. LaFontaine PharmD, PhD, Zeynep Eroglu MD, Anne Lynn S. Chang MD, Cristina Ivanescu PhD, LNMB, Alexander J. Stratigos PhD, Ketty Peris MD, Aleksandar Sekulic MD, PhD, Matthew G. Fury MD, PhD, and Chieh-I Chen MPH

Lewis KD et al. EADO 2023;Abstract HSR23-097.

Courtesy of Evan J Lipson, MD

- Phase 2 Trial of Cemiplimab in patients with metastatic basal cell carcinoma who progressed on or were intolerant to hedgehog inhibitor (HHI) treatment

- Objective response rate = 24.1%

- This analysis evaluated health-related quality of life data using validated questionnaires (European Organisation for Research and Treatment of Cancer Quality of Life-Core 30 and Skindex-16).

- Baseline scores showed moderate to high levels of functioning and low symptom burden. Responder analysis showed clinically meaningful improvement or maintenance of functioning and symptoms in 76–88% of patients at week 3 that were generally maintained at ~6 months.

Lewis KD et al. EADO 2023;Abstract HSR23-097.

Courtesy of Evan J Lipson, MD

Conclusions

- **Critical finding(s):** Most patients with metastatic BCC treated with cemiplimab reported maintenance in global health status/quality of life and functioning while maintaining low symptom burden.

- **Clinical implication(s):** Cemiplimab remains a standard-of-care therapy for patients with metastatic basal cell carcinoma who previously received a hedgehog inhibitor (HHI) or for whom a HHI is not appropriate.

- **Research relevance:** Response rates of BCC to anti-PD-1 after HHI seem low compared to tumors with similar tumor mutation burdens (CSCC, Merkel cell). An ongoing front-line anti-PD-1 study reports response rates of ~50% in patients with treatment-naïve BCC.

Courtesy of Evan J Lipson, MD

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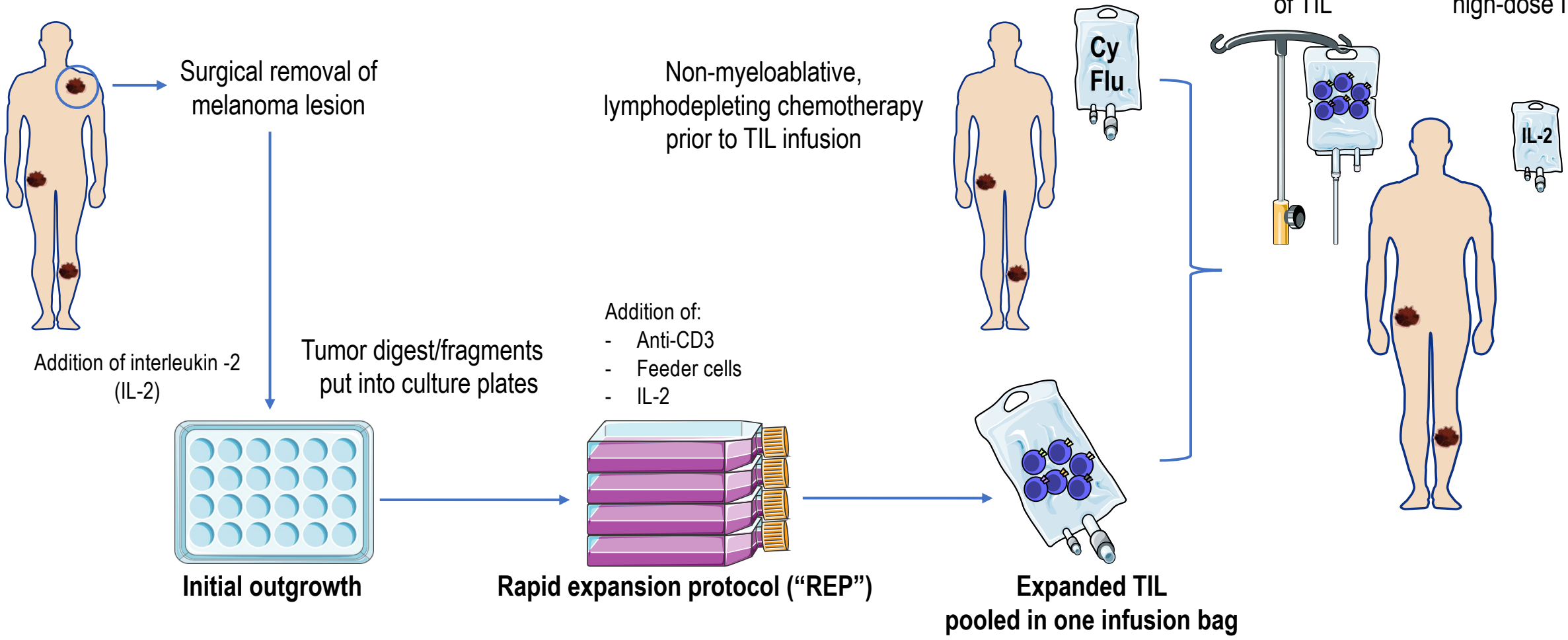
Key Data Sets – Metastatic Melanoma
Tumor-Infiltrating Lymphocytes

Omid Hamid, MD (continued)

- Haanen J et al. Treatment with tumor-infiltrating lymphocytes (**TIL**) versus **ipilimumab** (IPI) for advanced melanoma: Results from a multicenter, randomized **phase III** trial. ESMO 2022;Abstract LBA3.
- Rohaan MW et al. **Tumor-infiltrating lymphocyte therapy** or **ipilimumab** in advanced melanoma. *N Engl J Med* 2022;387(23):2113-25.
- Sarnaik A et al. **Lifileucel TIL cell monotherapy** in patients with advanced melanoma after **progression** on immune checkpoint inhibitors **(ICI)** and targeted therapy: Pooled analysis of consecutive cohorts (**C-144-01 study**). SITC 2022;Abstract 2409.
- Olson D et al. A **phase 3** study **(TILVANCE-301)** to assess the efficacy and safety of **lifileucel**, an autologous tumor-infiltrating lymphocyte cell therapy, in combination **with pembrolizumab** compared with **pembrolizumab alone** in patients with **untreated** unresectable or metastatic melanoma. ASCO 2023;Abstract TPS9607.
- O'Malley D et al. Phase 2 efficacy and safety of autologous tumor-infiltrating lymphocyte **(TIL)** cell therapy in combination with **pembrolizumab** in immune **checkpoint inhibitor-naïve** patients with advanced cancers. SITC 2021;Abstract 492.

Tumor-infiltrating lymphocytes (TIL)

Preparation and treatment



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Haanen, JBAG et al ESMO 2022

Courtesy of Omid Hamid, MD

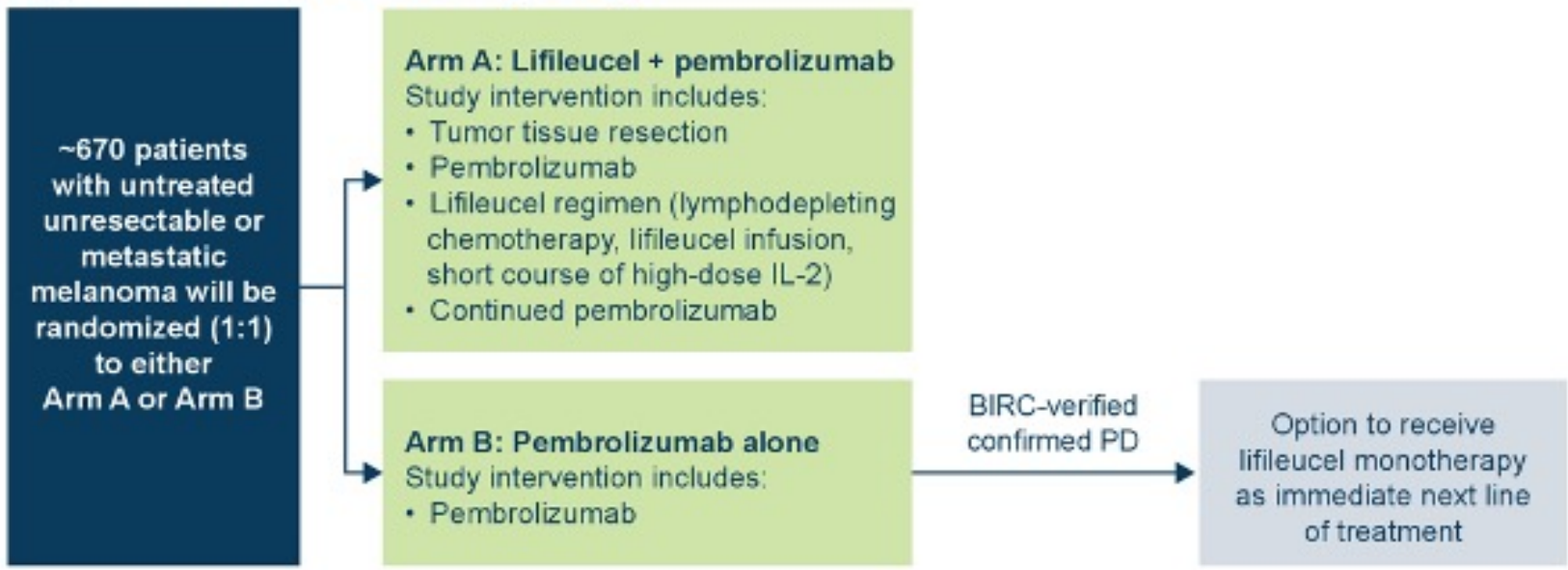
Trial in Progress: A Phase 3 Study (TILVANCE-301) to Assess the Efficacy and Safety of Lifileucel, an Autologous Tumor-Infiltrating Lymphocyte (TIL) Cell Therapy, in Combination With Pembrolizumab Compared With Pembrolizumab Alone in Patients With Untreated Unresectable or Metastatic Melanoma

Daniel Olson, MD[1]; Young Hong, MD, MPH[2]; Sajeve Thomas, MD[3]; Juan Martin-Liberal, MD, PhD[4]; Friedrich Graf Finckenstein, MD[5]; Xiao Wu, PhD[5]; Giri Sulur, PhD[5]; Wen Shi, MD, PhD[5]; James Larkin, PhD, FRCP, F Med Sci[6]

[1]University of Chicago, Chicago, IL, USA; [2]Cooper University Hospital, Camden, NJ, USA; [3]Orlando Health Cancer Institute, Orlando, FL, USA; [4]ICO L'Hospitalet – Hospital Duran i Reynals, Barcelona, Spain; [5]Iovance Biotherapeutics Inc, San Carlos, CA, USA; [6]The Royal Marsden NHS Foundation Trust, London, UK

Corresponding author: Wen Shi, wen.shi@iovance.com

Figure 1. TILVANCE-301 Study Design



Study Endpoints

- **Dual primary efficacy endpoints**
  - ORR as assessed by BIRC per RECIST v1.1
  - PFS as assessed by BIRC per RECIST v1.1
- **Key secondary efficacy endpoint**
  - OS
- **Additional secondary endpoints**
  - BIRC-assessed CR rate, DOR, EFS per RECIST v1.1
  - Investigator-assessed ORR, PFS, CR rate, DOR, EFS PFS2 per RECIST v1.1
  - Safety (characterized by severity and seriousness of TEAEs, and relationship to study drug)
- **The study will enroll globally**

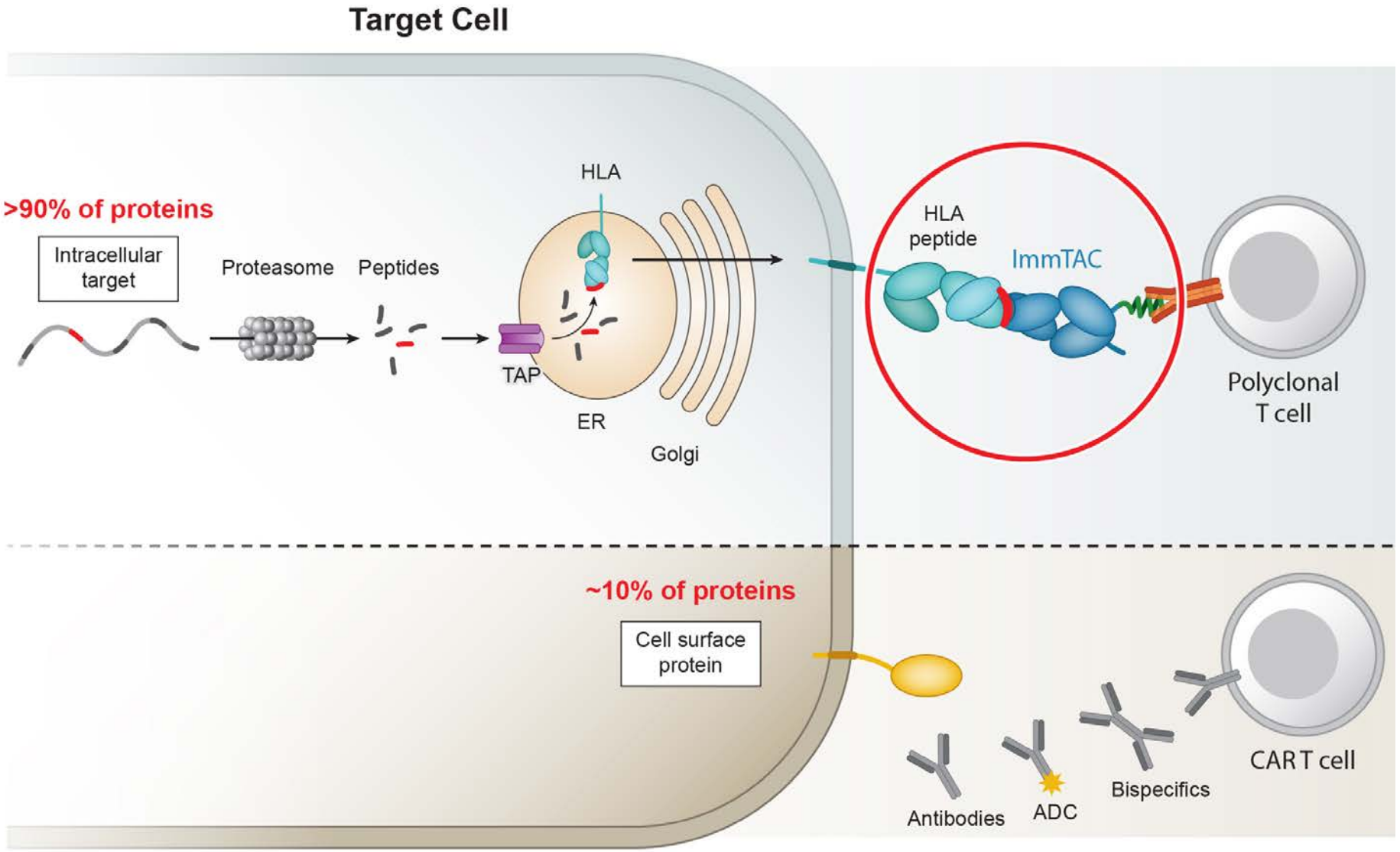
Courtesy of Omid Hamid, MD

Key Data Sets – Metastatic Melanoma
Bispecific T-Cell Engagers and Vaccines

Omid Hamid, MD (continued)

- Middleton MR et al. Updated overall survival (OS) data from the phase 1b study of **tebentafusp** (tebe) as **monotherapy** or combination therapy with **durvalumab** (durva) and/or **tremelimumab** (treme) in **metastatic cutaneous melanoma** (mCM). ASCO 2022;Abstract 104.
- Seth R et al. Systemic therapy for melanoma: ASCO guideline rapid recommendation update. *J Clin Oncol* 2022;40(21):2375-7.
- Carvajal RD et al. Clinical and molecular response to **tebentafusp** in **previously treated** patients with **metastatic uveal** melanoma: A phase 2 trial. *Nat Med* 2022;28(11):2364-73.
- Hamid O et al. Results from phase I dose escalation of **IMC-F106C**, the first PRAME × CD3 ImmTAC **bispecific** protein in solid tumors. ESMO 2022;Abstract 728O.
- Kjeldsen JW et al. A phase 1/2 trial of an **immune-modulatory vaccine** against IDO/PD-L1 in combination with **nivolumab** in metastatic melanoma. *Nat Med* 2021;27(12):2212-23.

ImmTAC: T cell receptor (TCR) bispecifics target intracellular proteins



ImmTAC target >90% of proteome via soluble TCR

Antibody bispecifics target 10% of proteome

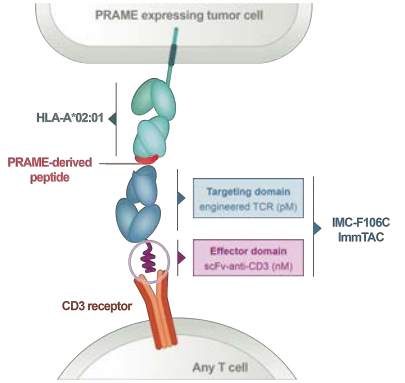
ImmTAC, Immune mobilizing T cell receptor Against Cancer

Middleton MR et al. ASCO 2022;Abstract 104

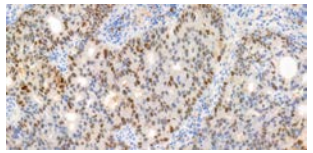
Courtesy of Omid Hamid, MD

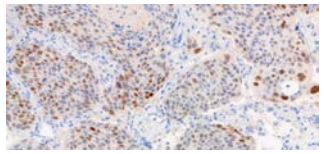
IMC-F106C: ImmTAC targeting HLA-A2-presented peptide from PRAME (PRAME × CD3)

- TCR bispecific proteins redirect polyclonal T cells to target intra- or extra-cellular cancer proteins (>90% of proteome)
- ImmTAC molecules are validated by tebentafusp (gp100 × CD3) with OS benefit in uveal melanoma (HR 0.51)[1]



PRAME: most broadly expressed cancer-testis antigen in several tumor types but with minimal normal tissue expression





Tumor	Prevalence of PRAME expression
Melanoma, endometrial, NSCLC, TNBC, SCLC, ovarian	
RCC, esophageal, SCCHN, cervical	
Bladder, HCC, gastric	

LOW — HIGH

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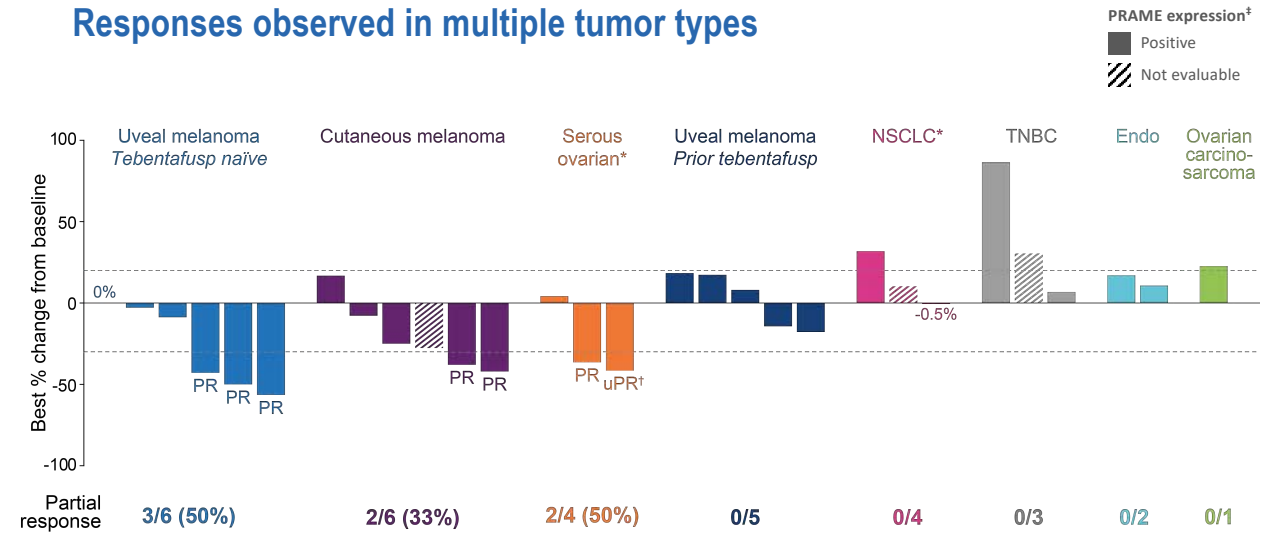
ImmTAC, Immune mobilizing T cell receptor Against Cancer; TCR, T cell receptor

1. Nathan P, et al. N Engl J Med 2021;385:1196-206;

Responses observed in multiple tumor types



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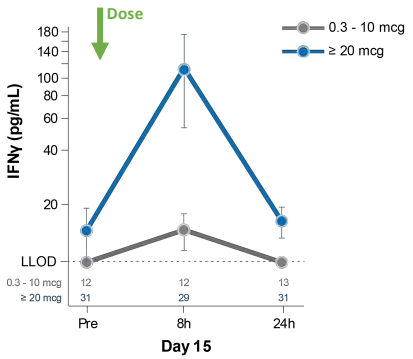
* Two patients (1 with NSCLC, 1 serous ovarian) discontinued treatment due to PD with scan data not available at DCO
† Ovarian cancer patient with unconfirmed PR (uPR) remains on treatment and eligible for confirmation
‡ PRAME expression assessed by IHC H-score
Two PRAME-negative patients both had PD (not shown)

Strong and Consistent Pharmacodynamic Activity at ≥20 mcg IMC-F106C

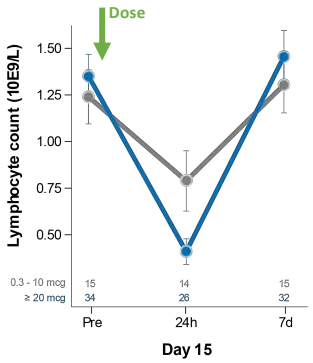
Interferon γ induction

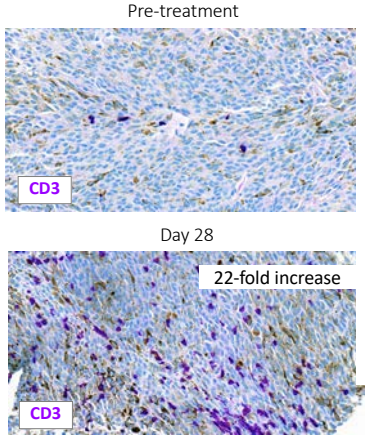
Peripheral blood



T cell trafficking

Peripheral blood ⇢ Tumor





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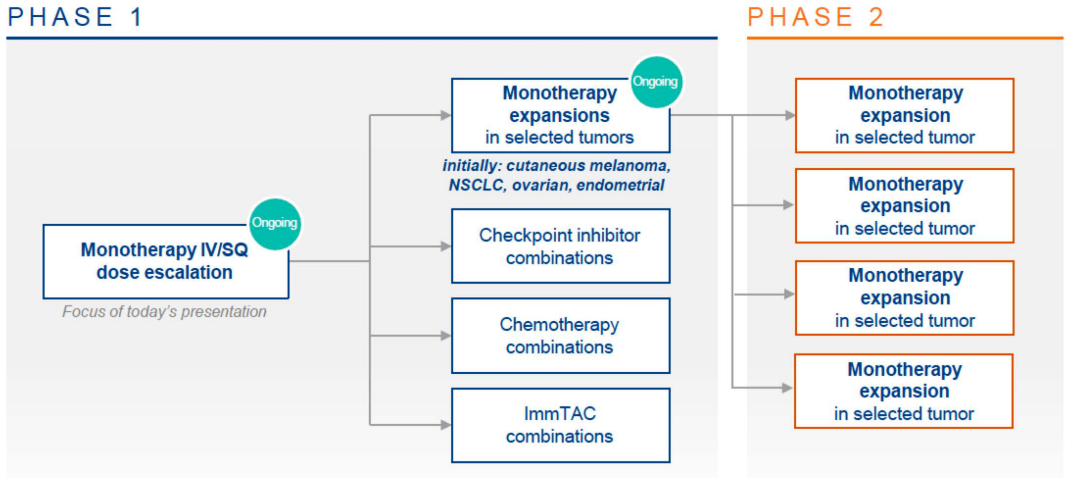
Results plotted as mean ± SEM

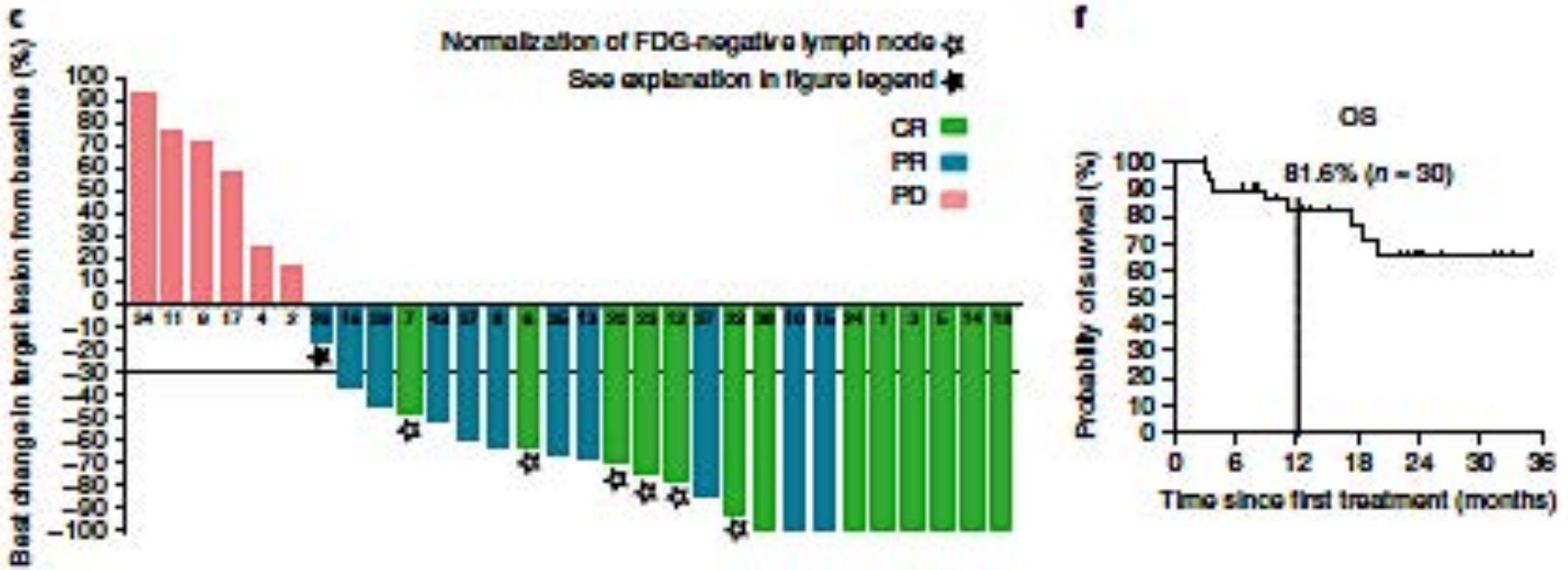
IMC-F106C-101 designed as an adaptive Phase 1/2 study



Courtesy of Omid Hamid, MD

ARTICLES
https://doi.org/10.1038/s41591-021-01544-x
nature medicine
Check for updates

A phase 1/2 trial of an immune-modulatory vaccine against IDO/PD-L1 in combination with nivolumab in metastatic melanoma



Kjeldsen JW et al. *Nat Med.* 2021;27(12):2212-2223.

Courtesy of Omid Hamid, MD

APPENDIX

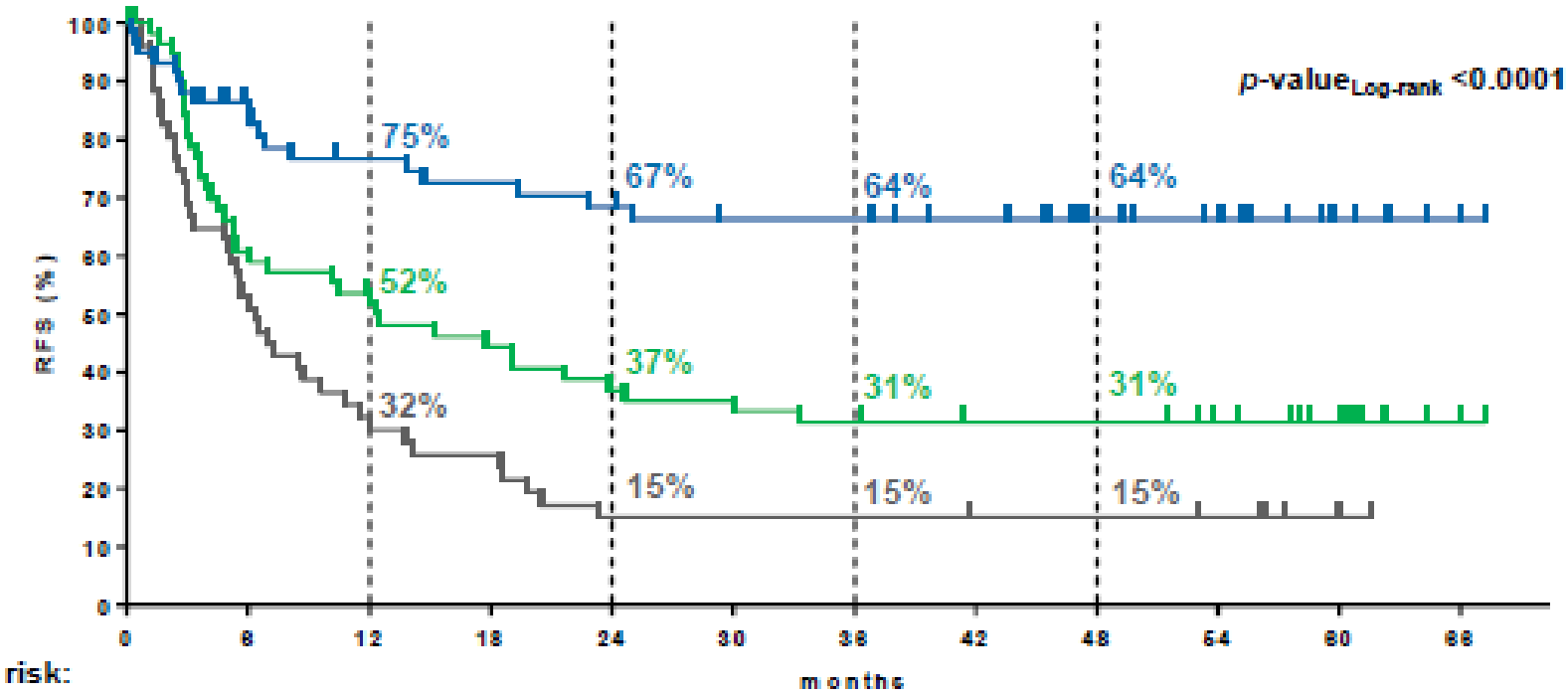
THE IMMUNED STUDY

Primary endpoint: RFS in all patients

Data cut-off date Sep 23, 2021
Median follow-up time: 49.2 months

	NIVO+IPI (n=56)	NIVO (n=59)	Placebo (n=52)
Median RFS, mo (95% CI)	NR[1] (25.0, NR)	12.3 (5.3, 23.9)	6.3 (3.3, 9.6)
HR (97.5% CI) vs placebo	0.25 (0.13, 0.48)	0.60 (0.36, 1.00)	-
HR (97.5% CI) vs NIVO	0.41 (0.22, 0.78)	-	-

[1]NR: not reached



Patients at risk:

NIVO + IPI	56	40	35	32	30	27	27	27	24	11	4	1
NIVO	59	34	28	24	20	19	17	15	15	12	7	2
Placebo	52	25	15	12	7	7	7	6	6	5	1	-

Schadendorf D et al. ESMO 2022;Abstract 784O

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Link: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)01654-3/fulltext

Courtesy of Omid Hamid, MD

Data cut-off date Sep 23, 2021
Median follow-up time: 49.2 months

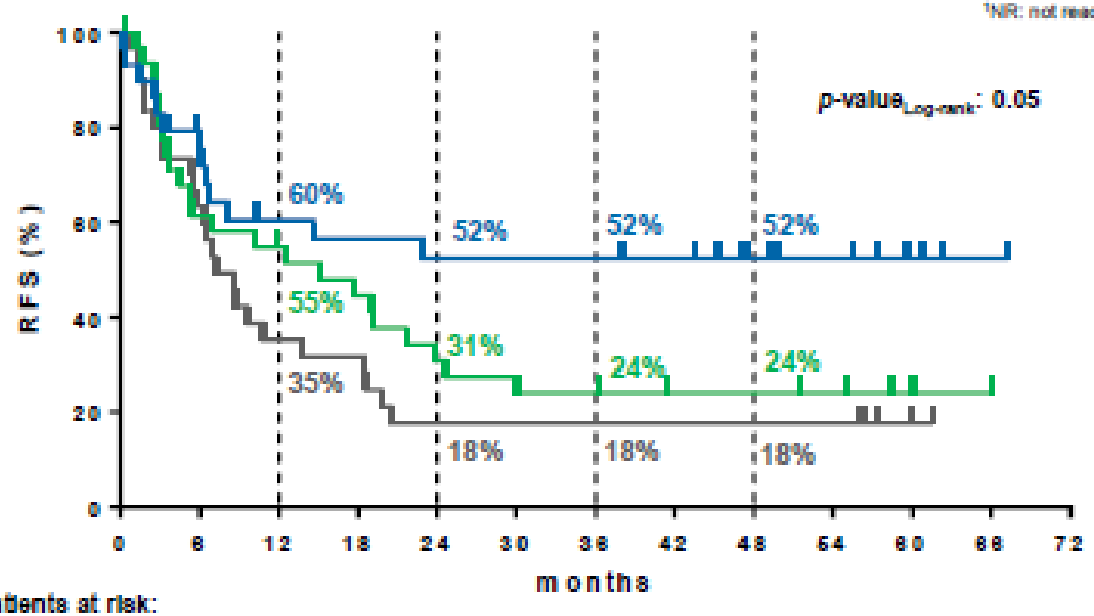
THE IMMUNED STUDY

RFS by BRAF mutation status

BRAF wildtype

	NIVO+IPI (n=29)	NIVO (n=32)	Placebo (n=31)
Median, mo (95% CI)	NR[1] (8.5, NR[1])	16.2 (4.6, 23.8)	7.3 (5.5, 13.8)
HR (95% CI) vs.placebo	0.46 (0.23, 0.89)	0.78 (0.43, 1.36)	–
HR (95% CI) vs. NIVO	0.58 (0.28, 1.11)	–	–

[1]NR: not reached.



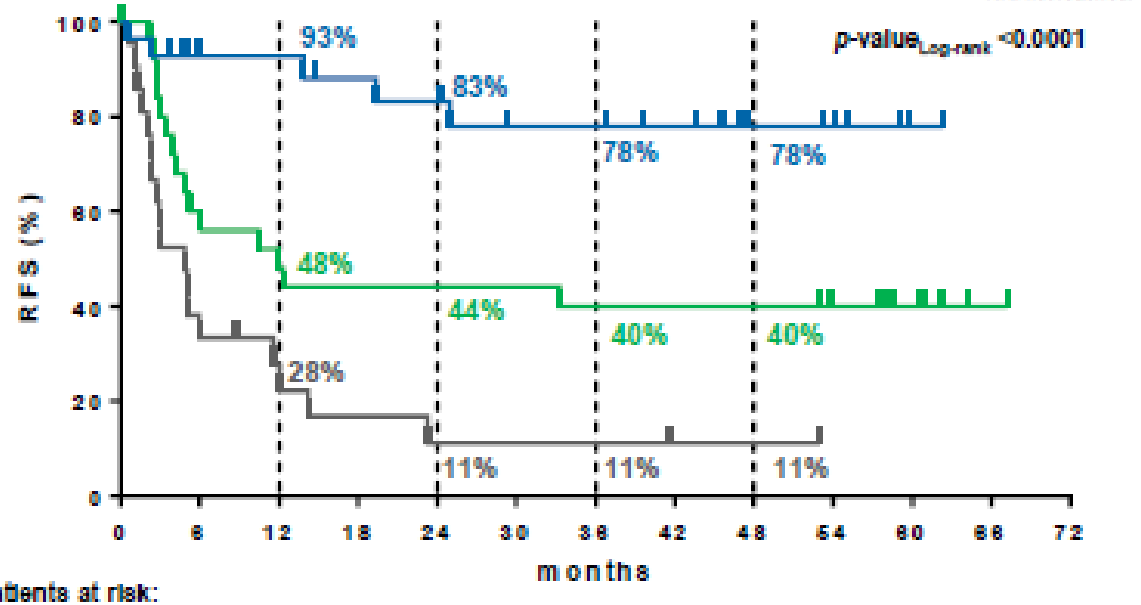
Patients at risk:

NIVO + IPI	29	20	15	14	13	13	13	12	8	6	3	1
NIVO	32	19	16	13	9	8	7	5	5	4	2	1
Placebo	31	18	10	9	5	5	5	5	5	5	1	-

BRAF mutated

	NIVO+IPI (n=27)	NIVO (n=27)	Placebo (n=21)
Median, mo (95% CI)	NR (NR[1])	11.9 (4.1, NR[1])	4.9 (2.3, 11.5)
HR (95% CI) vs.placebo	0.11 (0.04, 0.30)	0.46 (0.22, 0.90)	–
HR (95% CI) vs. NIVO	0.25 (0.09, 0.70)	–	–

[1]NR: not reached.



Patients at risk:

NIVO + IPI	27	20	20	18	17	14	14	12	6	5	1	-
NIVO	27	15	12	11	11	11	10	10	10	8	5	1
Placebo	21	7	5	3	3	2	2	1	1	-	-	-

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Link: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)01654-3/fulltext

Schadendorf D et al. ESMO 2022;Abstract 784O

Courtesy of Omid Hamid, MD

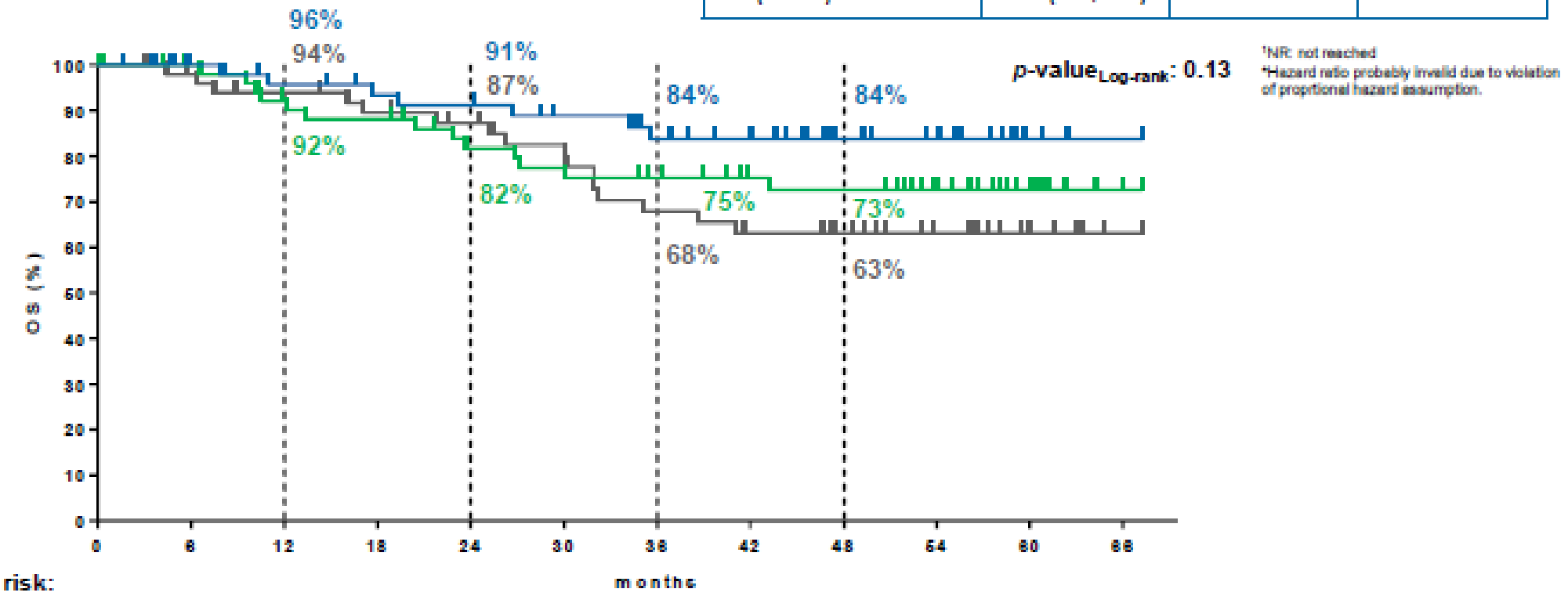
THE IMMUNED STUDY

Key secondary endpoint: OS in all patients

Data cut-off date Sep 23, 2021
Median follow-up time: 49.2 months

	NIVO+IPI (n=56)	NIVO (n=59)	Placebo (n=52)
Median OS, mo (95% CI)	NR[1]	NR[1]	NR[1] (38.59,NR)
HR (95% CI) vs placebo	0.41 (0.17, 0.99)	0.75 (0.36, 1.56)*	-
HR (95% CI) vs NIVO	0.55 (0.22, 1.38)	-	-

[1]NR: not reached
*Hazard ratio probably invalid due to violation of proportional hazard assumption.



Patients at risk:

NIVO + IPI	56	48	44	41	40	36	32	29	16	13	4	1
NIVO	59	51	46	44	38	36	33	28	27	20	10	2
Placebo	52	48	44	41	38	33	28	23	20	14	6	2

Schadendorf D et al. ESMO 2022;Abstract 784O

- 36 events (22%) within 167 patients of the intention-to-treat population

Link: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)01654-3/fulltext

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Courtesy of Omid Hamid, MD

Pembrolizumab Versus Placebo as Adjuvant Therapy in Stage IIB or IIC Melanoma: Final Distant Metastasis-Free Survival Analysis in the Phase 3 KEYNOTE-716 Study

Jason J. Luke[1]; Paolo A. Ascierto[2]; Muhammad A. Khattak[3]; Luis de la Cruz Merino[4]; Michele Del Vecchio[5]; Piotr Rutkowski[6]; Francesco Spagnolo[7]; Jacek Mackiewicz[8]; Vanna Chiarion-Sileni[9]; John M. Kirkwood[1]; Caroline Robert[10]; Jean-Jacques Grob[11]; Federica de Galitiis[12]; Dirk Schadendorf[13]; Matteo S. Carlino[14]; Xi Lawrence Wu[15]; Mizuho Fukunaga-Kalabis[15]; Clemens Krepler[15]; Alexander M. M. Eggermont[16]; Georgina V. Long[17]

[1]UPMC Hillman Cancer Center and University of Pittsburgh, Pittsburgh, PA, USA; [2]Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy; [3]Fiona Stanley Hospital and Edith Cowan University, Perth, WA, Australia; [4]Hospital Universitario Virgen Macarena, Seville, Spain; [5]Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; [6]Maria Sklodowska–Curie National Research Institute of Oncology, Warsaw, Poland; [7]IRCCS San Martino Polyclinic Hospital, Genoa, Italy; [8]Poznan University of Medical Sciences and Greater Poland Cancer Center, Poznan, Poland; [9]Istituto Oncologico Veneto, IOV-IRCCS, Padova, Italy; [10]Gustave Roussy, Villejuif, and Paris-Saclay University, Paris, France; [11]AP-HM Hospital, Aix-Marseille University, Marseille, France; [12]Dermopathic Institute of the Immaculate IDI-IRCCS, Rome, Italy; [13]University Hospital Essen and German Cancer Consortium Partner Site, Essen, Germany; [14]Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia, and Westmead and Blacktown Hospitals, Sydney, NSW, Australia; [15]Merck & Co., Inc., Rahway, NJ, USA; [16]University Medical Center Utrecht and Princess Máxima Center, Utrecht, Netherlands, and Comprehensive Cancer Center Munich, Munich, Germany; [17]Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia

Luke JJ et al. ASCO 2023;Abstract LBA9505.

Courtesy of Evan J Lipson, MD

Adjuvant therapy with nivolumab versus placebo in patients with resected stage IIB/C melanoma (CheckMate 76K)

Treatment naive patients ≥ 12 y with

- Completely resected stage IIB/C melanoma with standard wide local excision
- Negative sentinel lymph node biopsy

N = 790

R 2:1

Stratify by T category

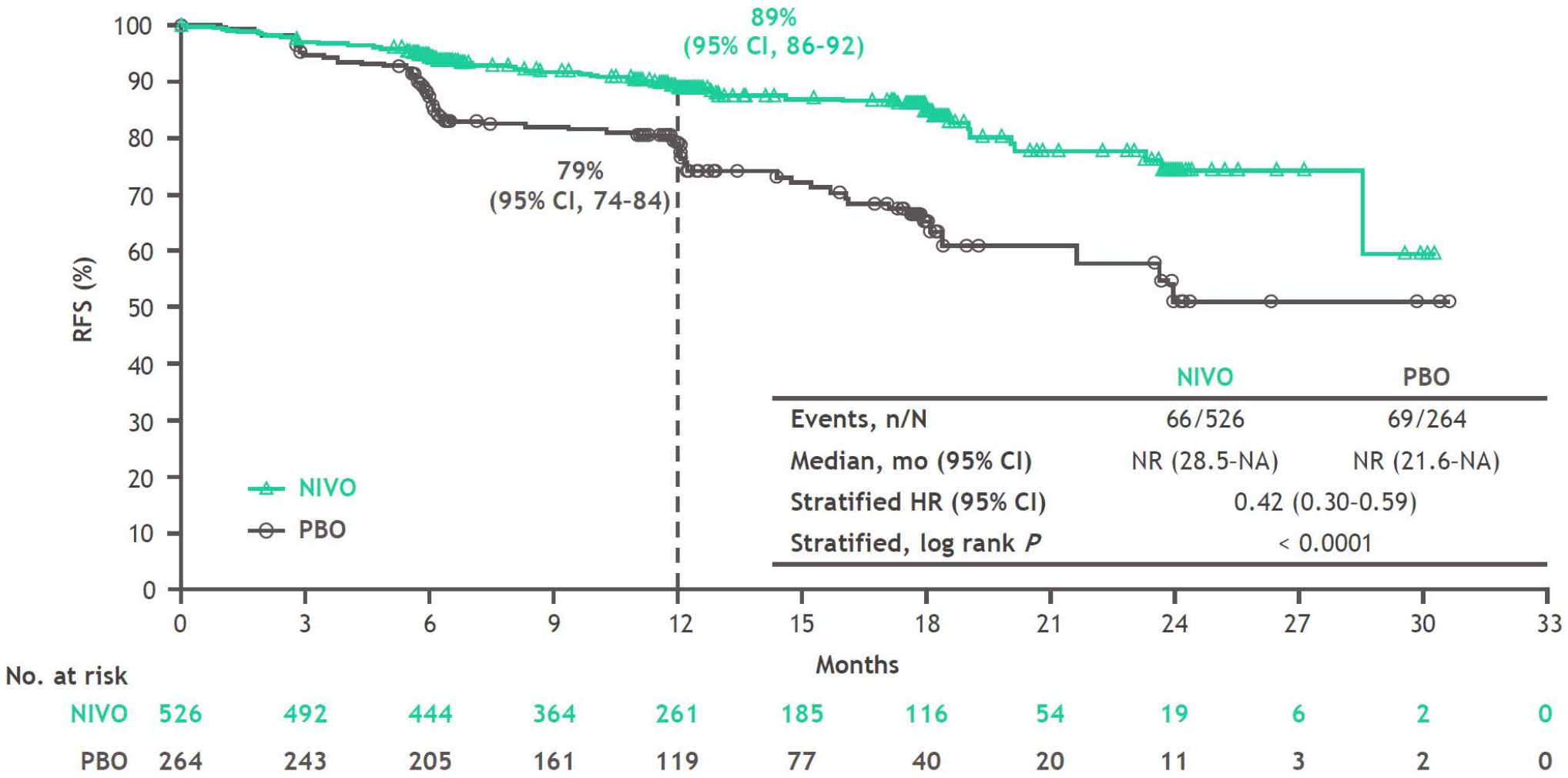
NIVO IV 480 mg Q4W for 12 months n = 526

PBO IV Q4W for 12 months n = 264

Long G et al. Society for Melanoma Research 2022.

Courtesy of Evan J Lipson, MD

CheckMate 76K: In patients with resected stage IIB/C melanoma, recurrence-free survival (RFS) improved with adjuvant nivolumab (NIVO) vs. placebo (PBO)



	NIVO	PBO
Events, n/N	66/526	69/264
Median, mo (95% CI)	NR (28.5-NA)	NR (21.6-NA)
Stratified HR (95% CI)	0.42 (0.30-0.59)	
Stratified, log rank *P*	< 0.0001	

NA, not available; NR, not reached.

Long G et al. Society for Melanoma Research 2022.

Courtesy of Evan J Lipson, MD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neoadjuvant–Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma

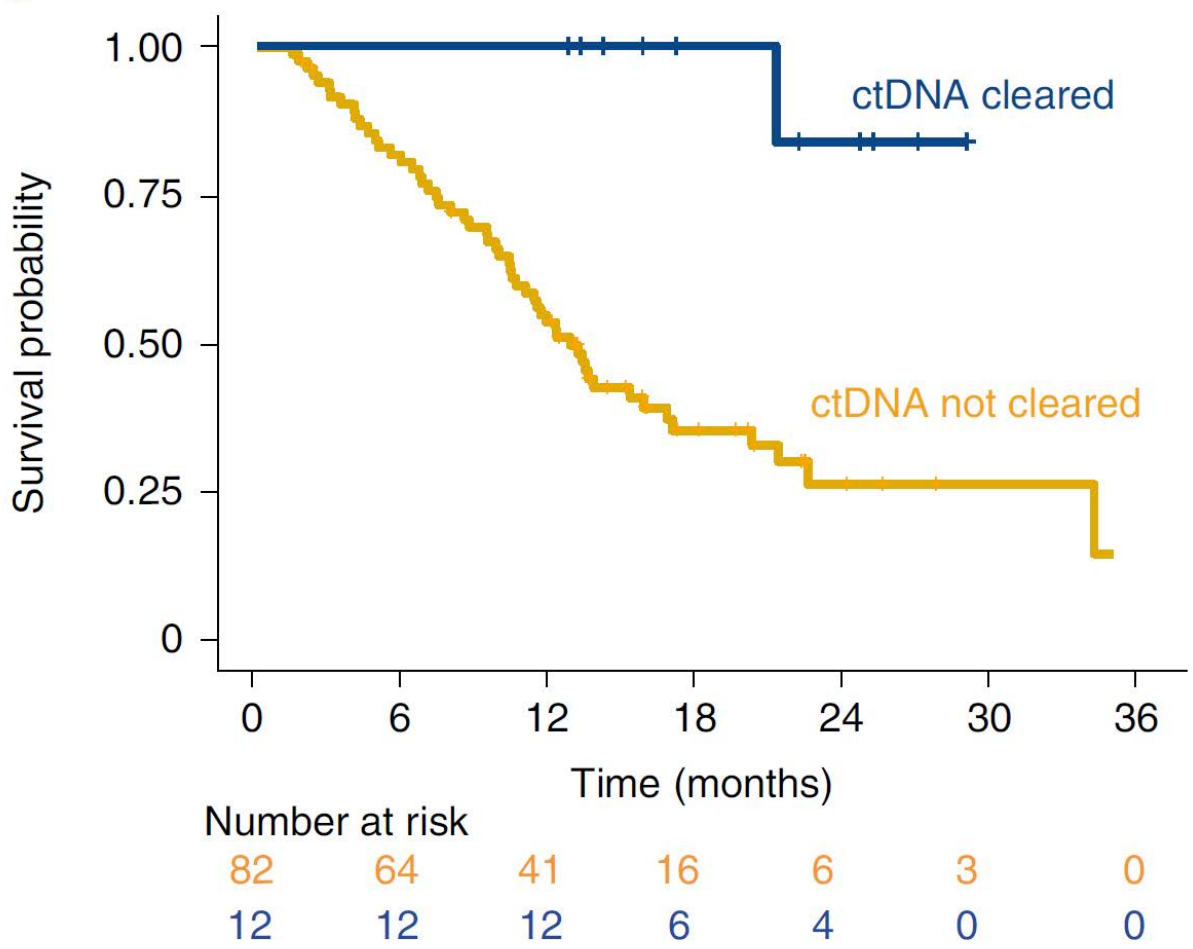
S.P. Patel, M. Othus, Y. Chen, G.P. Wright, Jr., K.J. Yost, J.R. Hyngstrom, S. Hu-Lieskovan, C.D. Lao, L.A. Fecher, T.-G. Truong, J.L. Eisenstein, S. Chandra, J.A. Sosman, K.L. Kendra, R.C. Wu, C.E. Devoe, G.B. Deutsch, A. Hegde, M. Khalil, A. Mangla, A.M. Reese, M.I. Ross, A.S. Poklepovic, G.Q. Phan, A.A. Onitilo, D.G. Yasar, B.C. Powers, G.C. Doolittle, G.K. In, N. Kokot, G.T. Gibney, M.B. Atkins, M. Shaheen, J.A. Warneke, A. Ikeguchi, J.E. Najera, B. Chmielowski, J.G. Crompton, J.D. Floyd, E. Hsueh, K.A. Margolin, W.A. Chow, K.F. Grossmann, E. Dietrich, V.G. Prieto, M.C. Lowe, E.I. Buchbinder, J.M. Kirkwood, L. Korde, J. Moon, E. Sharon, V.K. Sondak, and A. Ribas

Patel SP et al. N Engl J Med 2023;388(9):813-23.

Courtesy of Evan J Lipson, MD

Tebentafusp may improve OS compared to historical controls. Early on-treatment reduction in circulating tumor DNA was associated with overall survival, even in patients with radiographic progression.

	Historical controls	Tebentafusp
1-year OS rate (%)	37	62
Median OS (mos)	7.8	16.8



Carvajal RD et al. Nat Med 2022;28(11):2364-73.

Courtesy of Evan J Lipson, MD

Conclusions

- **Critical finding(s):** 127 patients with previously treated metastatic uveal melanoma received tebentafusp (T cell receptor bispecific (gp100×CD3))
  - Despite an overall response rate of only 5%, 1-year overall survival rate was 62% and median overall survival was 16.8 months, suggesting benefit beyond traditional imaging-based response criteria.
  - In an exploratory analysis, early on-treatment reduction in circulating tumor DNA was strongly associated with overall survival, even in patients with radiographic progression.

- **Clinical implication(s):** In patients with metastatic uveal melanoma who had previously received immunotherapy, chemotherapy, targeted therapy, radiotherapy, liver-directed therapy, and/or surgery, tebentafusp demonstrated promising clinical activity. ctDNA appears to be an early indicator of clinical benefit.

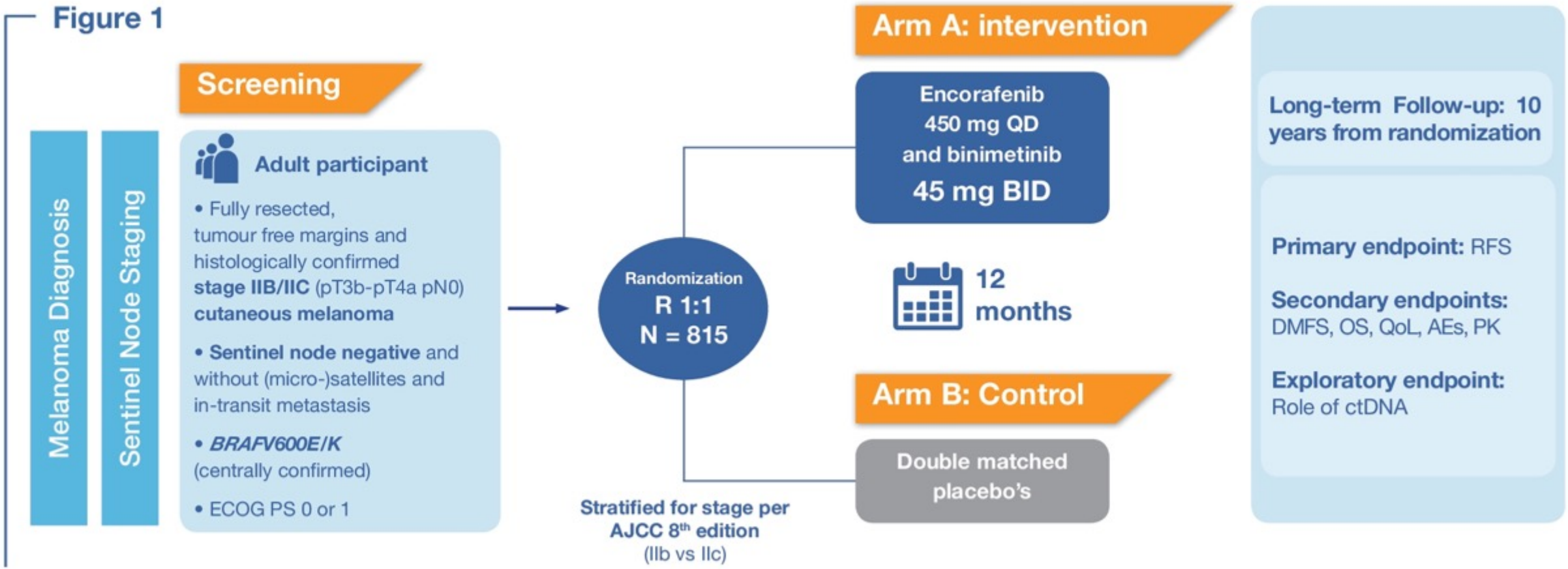
- **Research relevance:** The findings above need validation in a randomized trial.

Courtesy of Evan J Lipson, MD

Phase III Study of Adjuvant Encorafenib Plus Binimetinib Versus Placebo In Fully Resected Stage IIB/C *BRAFV600*-Mutated Melanoma : COLUMBUS-AD Study Design

Alexander C. J. van Akkooi[1], Axel Hauschild[2], Georgina V. Long[3], Mario Mandala[4] Michal Kicinski[5], Anne-Sophie Govaerts[5], Isabelle Klauck[6], Monia Ouali[6], Paul C. Lorigan[7], Alexander M. M. Eggermont[8]

[1]Melanoma Institute Australia, the University of Sydney, and Mater and Royal Hospitals, Sydney, NSW, Australia; [2]Department of Dermatology, University Hospital (UKSH), Kiel, Germany; [3]Melanoma Institute Australia, the University of Sydney, and Mater and Royal North Shore Hospitals, Sydney, NSW, Australia; [4]University of Perugia, Ospedale Santa Maria della Misericordia, Perugia, Italy; [5]EORTC Headquarters, Brussels, Belgium; [6]Pierre Fabre, France; [7]Christie NHS Foundation Trust, Manchester, United Kingdom; [8]University Medical Center Utrecht, Utrecht, the Netherlands.



Van Akkooi ACJ et al. ASCO 2023;Abstract TPS9601.

Courtesy of Evan J Lipson, MD

IOV-4001 First-in-Human Study: IOV-GM1-201

Phase 1/2, Open-label Study of PD-1 Knockout Tumor-infiltrating Lymphocytes (IOV-4001) in Participants With Unresectable or Metastatic Melanoma or Stage III or IV Non-small-cell Lung Cancer (NCT05361174)

Phase 1 / 2 study to investigate the efficacy and safety of an infusion of IOV-4001 in adult participants with unresectable or metastatic melanoma or advanced non-small-cell lung cancer (NSCLC). N=53

Cohort 1: Unresectable or metastatic melanoma
Post-anti-PD-1/L1, post-BRAF/MEK inhibitor in patients with BRAF mutations

Cohort 2: Stage III or IV non-small-cell lung cancer
Post -anti-PD-1/L1 or
Post targeted therapy and either chemotherapy or anti-PD-1/L1

Endpoints

- Phase I: Safety
- Phase 2: Objective Response Rate (ORR) per RECIST v1.1 as assessed by the investigator
- Secondary endpoints include complete response (CR) rate, duration of response (DOR), disease control rate (DCR), progression free survival (PFS), overall survival (OS), safety and tolerability, feasibility

Study Updates

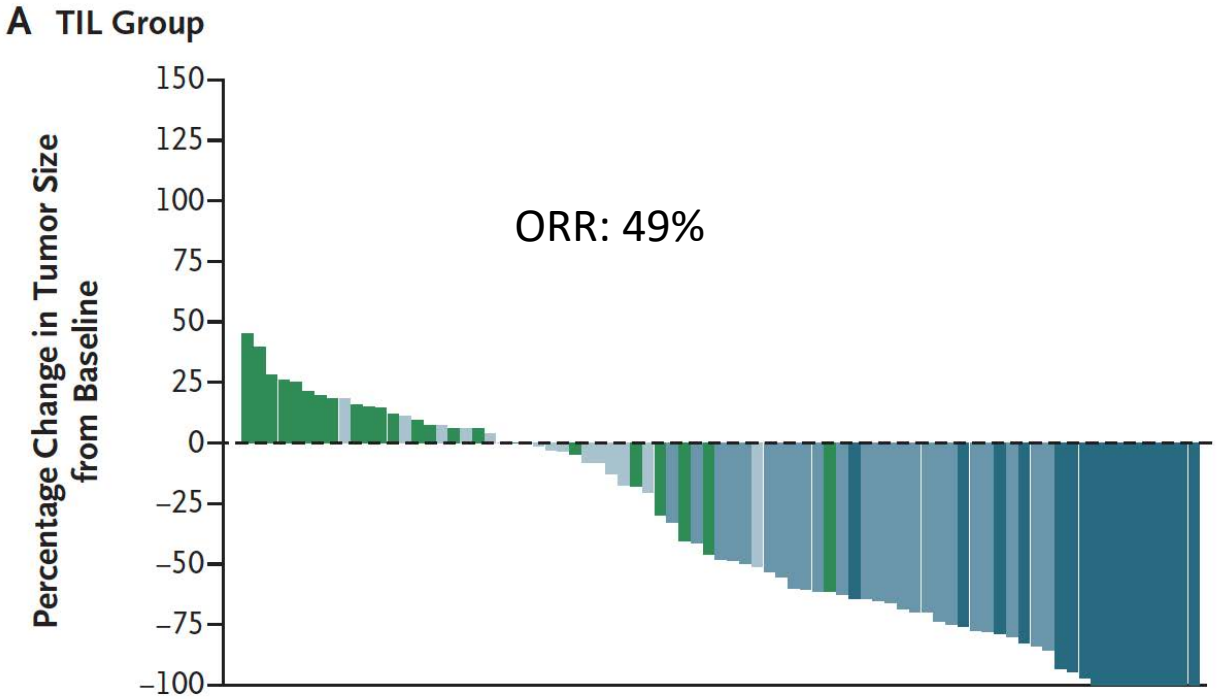
- Investigational New Drug (IND) Allowance March 2022

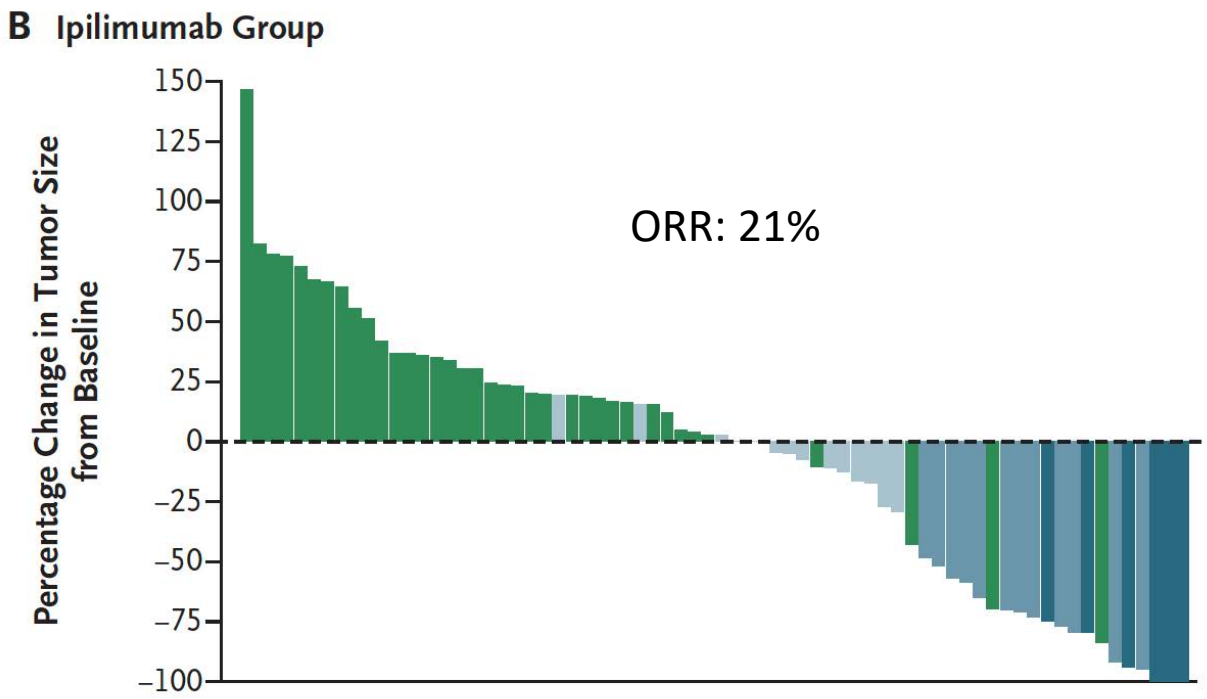
clinicaltrials.gov/NCT05361174

Courtesy of Omid Hamid, MD

TIL Versus Ipilimumab

Phase III trial in patients (PS 0-1) with unresectable or metastatic melanoma
At least 1 prior line of systemic therapy, excluding ipilimumab



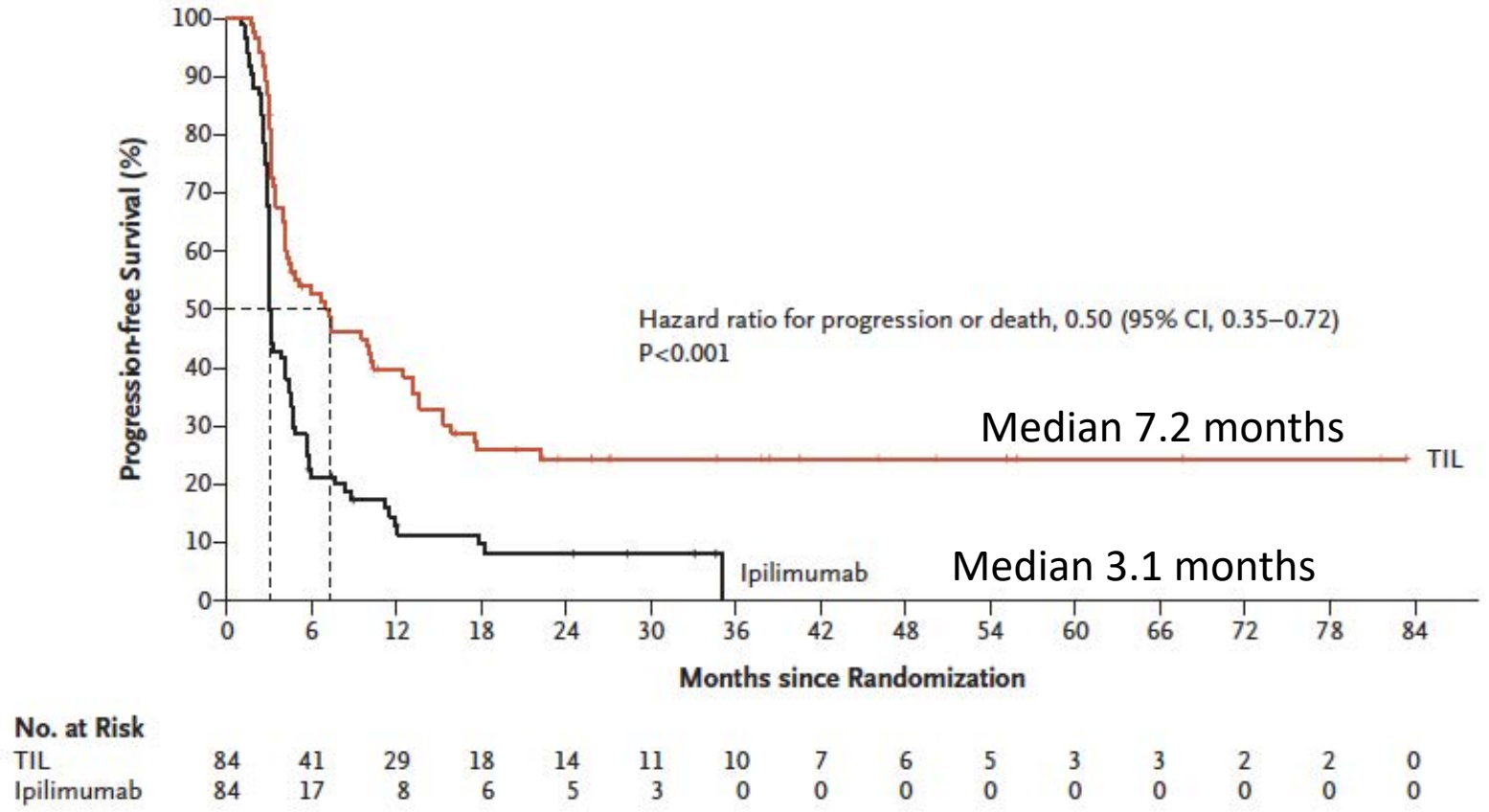


Rohaan MW et al. *N Engl J Med* 2022;387(23):2113-25.

Courtesy of Omid Hamid, MD

TIL Versus Ipilimumab

Phase III trial in patients (PS 0-1) with unresectable or metastatic melanoma
At least 1 prior line of systemic therapy, excluding ipilimumab



PFS @ 6 months

TIL	52.7%
Ipilimumab	21.4%

Median OS

TIL	25.8 months
Ipilimumab	18.9 months
HR 0.82	

2-year OS

TIL	54.3%
Ipilimumab	44.1%

Rohaan MW et al. *N Engl J Med* 2022;387(23):2113-25.

Courtesy of Omid Hamid, MD

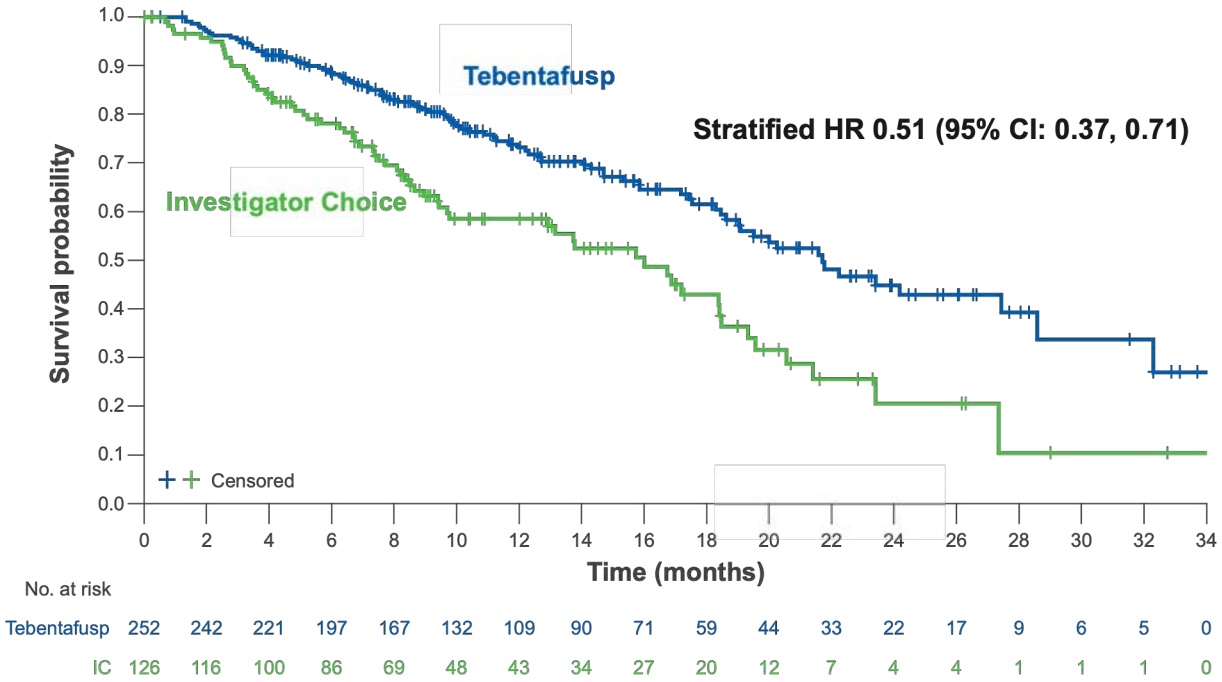
OS best captures benefit from tebentafusp (uveal melanoma)

Phase 3, first-line study (IMCgp100-202)[1]

RECIST response rate and PFS underestimate OS

	Tebentafusp vs Investigator Choice (IC)
RECIST response rate	9% vs 5%
Tumor shrinkage*	39% vs 24%
PFS (HR)	0.73 (95% CI: 0.58, 0.94)

Statistically and clinically significant OS benefit



* In phase 2, any tumor shrinkage (44%)[2] and ctDNA reduction (70%)[3] were associated with OS

1. Nathan P, et al. *N Engl J Med* 2021;385:1196-206; 2. Sacco JJ, et al. *Ann Oncol* 2020;31:S1442–43; 3. Shoushtari A et al. *Ann Oncol* 2021;32:S1210

Middleton MR et al. ASCO 2022;Abstract 104

Courtesy of Omid Hamid, MD

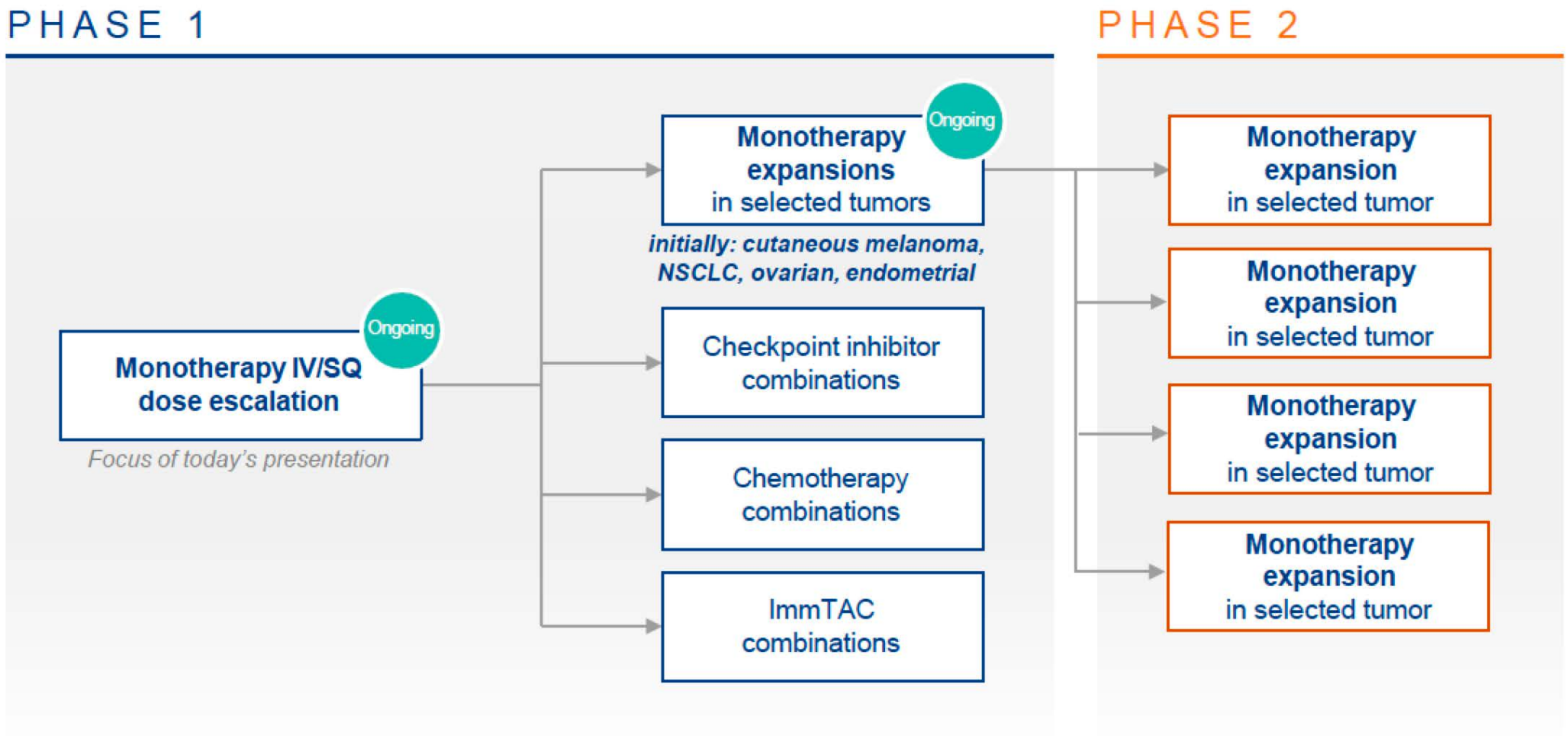
Similar associations with OS between mUM and mCM

	IMCgp100-201	IMCgp100-202
Population	Previously treated mCM (n=52)	Previously untreated mUM (n=230)†
Treatment	Tebentafusp + durvalumab	Tebentafusp
RECIST response rate (%)	10%	12%
Patients with tumor decrease (%)	37%*	40%*
Alive at 1 yr (%)	89%	85%
Patients with tumor increase (%)	60%*	54%*
Alive at 1 yr (%)	58%	64%

* 3% and 6% of patients in Study 201 and Study 202, respectively, had no change in tumor size
† April 2022 data cut off for survival data. Tumor shrinkage and increase for IMCgp100-202 (N=230)

Middleton MR et al. ASCO 2022;Abstract 104

IMC-F106C-101 designed as an adaptive Phase 1/2 study



Courtesy of Omid Hamid, MD

2022 ASCO® ANNUAL MEETING

Updated overall survival (OS) data from Phase 1b study of tebentafusp (tebe) as monotherapy or combination therapy with durvalumab (durva) and/or tremelimumab (treme) in metastatic cutaneous melanoma (mCM)

Authors: M.R. Middleton[1], O. Hamid[2], A.N. Shoushtari[3], F.E. Meier[4], T.M. Bauer[5], A.K.S. Salama[6], J.M. Kirkwood[7], P.A. Ascierto[8], P. Lorigan[9], C. Mauch[10], M.M. Orloff[11], T. R.J Evans[12], S.E. Abdullah[13], Y. Yuan[13], J. Mitchell[13], J.C. Hassel[14]

[1]University of Oxford, Oxford, UK; [2]The Angeles Clinic and Research Institute, A Cedars-Sinai Affiliate, Los Angeles, CA, USA; [3]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [4]University Hospital Carl Gustav Carus at the TU Dresden, Germany; [5]Tenessee Oncology, Nashville, TN, USA; [6]Duke University, Durham, NC, USA; [7]University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [8]IRCCS National Cancer Institute Pascale Foundation, Naples, Italy; [9]The Christie NHS Foundation Trust, Manchester, UK; [10]University of Cologne, Cologne, Germany; [11]Thomas Jefferson University Hospitals, Philadelphia, PA, US; [12]Beatson West of Scotland Cancer Centre, Glasgow, UK; [13]Immunocore Ltd, Abingdon, UK; [14]Heidelberg University Hospital, Heidelberg, German

Abstract #104

Courtesy of Omid Hamid, MD

nature medicine

Article

https://doi.org/10.1038/s41591-022-02015-7

Clinical and molecular response to tebentafusp in previously treated patients with metastatic uveal melanoma: a phase 2 trial

Carvajal RD et al. Nat Med 2022;28(11):2364-73.

Courtesy of Evan J Lipson, MD

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of nonmelanoma skin cancer

Ann W Silk ,[1] Christopher A Barker,[2] Shailender Bhatia ,[3] Kathryn B Bollin,[4] Sunandana Chandra,[5] Zeynep Eroglu ,[6] Brian R Gastman,[7] Kari L Kendra,[8] Harriet Kluger,[9] Evan J Lipson ,[10] Kathleen Madden,[11] David M Miller ,[12] Paul Nghiem ,[13] Anna C Pavlick,[14] Igor Puzanov ,[15] Guilherme Rabinowits,[16] Emily S Ruiz,[17] Vernon K Sondak,[6] Edward A Tavss,[18] Michael T Tetzlaff,[19] Isaac Brownell [20]

Silk AW et al. J Immunother Cancer 2022;10(7):e004434.

Courtesy of Evan J Lipson, MD

Conclusions

- **Critical finding(s):** With the goal of improving patient care by providing expert guidance to the oncology community, the Society for Immunotherapy of Cancer (SITC) convened a multidisciplinary panel of experts to develop a clinical practice guideline for treating patients with basal, cutaneous squamous and Merkel cell carcinomas.

- The expert panel drew on the published literature as well as their own clinical experience to develop recommendations for healthcare professionals on important aspects of immunotherapeutic treatment for these patients, including staging, biomarker testing, patient selection, therapy selection, post-treatment response evaluation and surveillance, and patient quality of life considerations.

- **Clinical implication(s):** The evidence- and consensus-based recommendations in this clinical practice guideline are intended to provide guidance to cancer care professionals treating patients with non-melanoma skin cancers.

- **Research relevance:** Some of the evidence- and consensus-based recommendations included in the clinical practice guideline are undergoing formal testing in clinical trials.

Courtesy of Evan J Lipson, MD

2023 ASCO ANNUAL MEETING

Towards organ preservation and cure via two infusions of immunotherapy only, in patients normally undergoing extensive and mutilating curative surgery for cutaneous squamous cell carcinoma (CSCC)

The MATISSE trial, NCT04620200

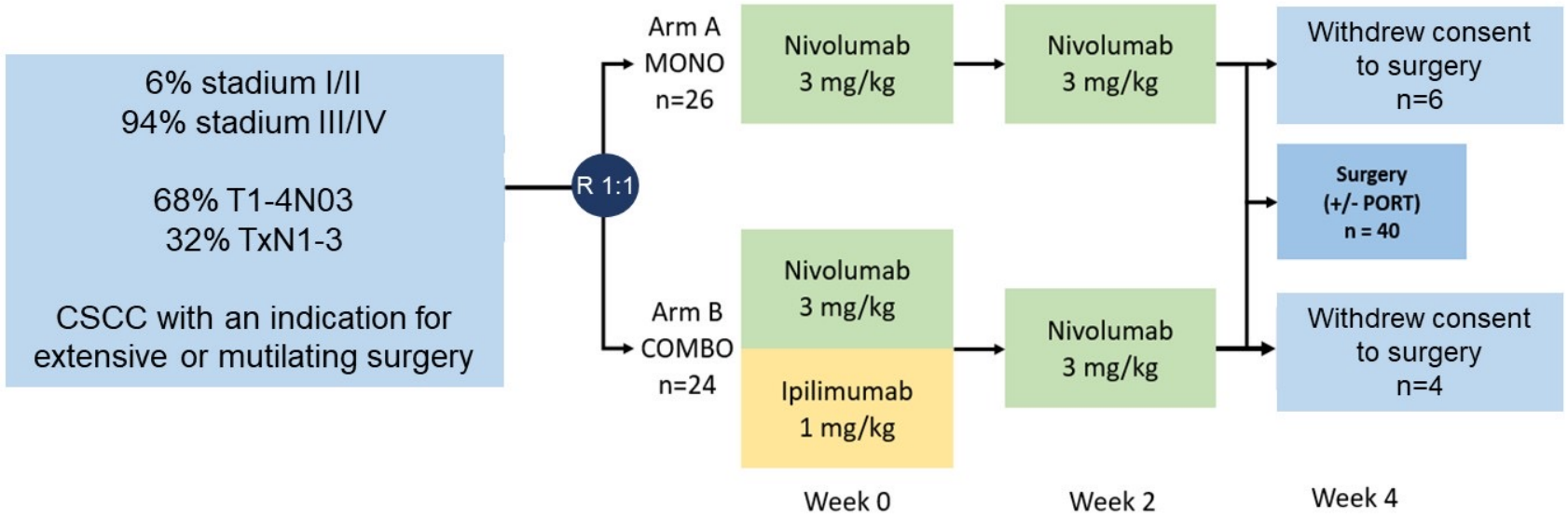
Charlotte (Lotje) Zuur, MD PhD, Head and Neck Surgeon, c.zuur@nki.nl

The Netherlands Cancer Institute, Amsterdam, The Netherlands.

Zuur CL et al. ASCO 2023;Abstract 9507.

Courtesy of Evan J Lipson, MD

MATISSE: Included patients



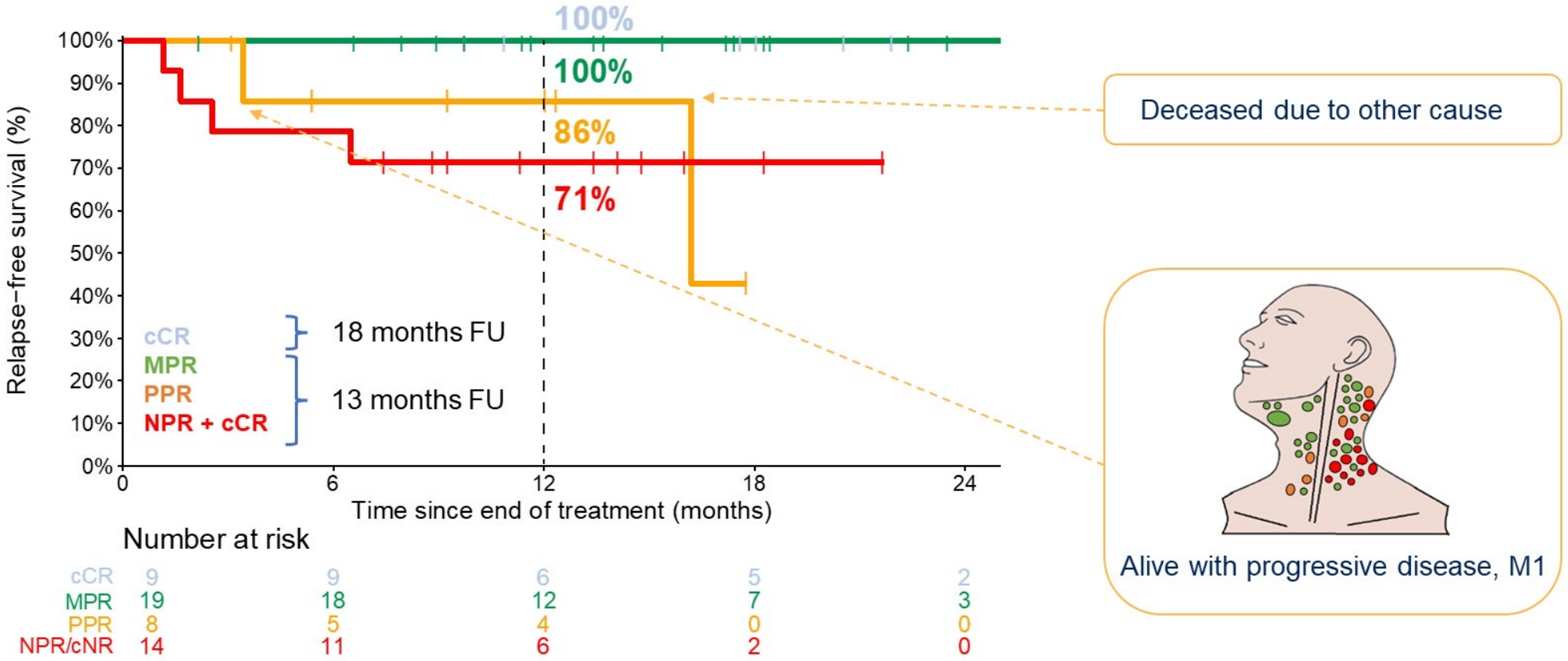
10 patients withdrew consent to surgery w/wo adjuvant RT and were 'not evaluable' according to the primary endpoint of the trial >> accrual of 10 extra patients

9/10 patients refused surgery w/wo RT as they themselves noticed remission of their cancer upon 2 infusions of immunotherapy only.

Zuur CL et al. ASCO 2023;Abstract 9507.

Courtesy of Evan J Lipson, MD

MATISSE, RFS:



Excellent clinical outcome in patients with an **MPR** or **CCR**,
at an overall median Follow-Up of 14 months.

PRESENTED BY: Charlotte (Lotje) Zuur, MD PhD, Head and Neck Surgeon, The Netherlands Cancer Institute, Amsterdam, The Netherlands.

Zuur CL et al. ASCO 2023;Abstract 9507.

Courtesy of Evan J Lipson, MD

Conclusions

- **Critical finding(s):** Among 40 patients with locally-advanced cutaneous squamous cell carcinoma who received NIVO or IPI+NIVO, major pathologic response rates were 40% and 53%, respectively.

- 9 pts declined surgery because of self-reported substantial clinical remission upon neoadjuvant immunotherapy. These clinical responses were confirmed via FDG-PET evaluation in week 4. All 9 pts were “cancer free” at median follow-up of 12 months (range 4 to 27) with superior quality-of-life compared to MATISSE pts undergoing standard of care surgery.

- **Clinical implication(s):** Neoadjuvant immunotherapy is becoming standard-of-care for patients with locally-advanced resectable CSCC. In the setting of substantial tumor regression, it remains unclear whether surgical resection is necessary.

- **Research relevance:** Which regimen is best, for how long, and are surgery and/or adjuvant therapy needed, particularly in the setting of substantial tumor regression or a pathologic complete response?

Courtesy of Evan J Lipson, MD

2023 ASCO® ANNUAL MEETING

Non-comparative, open-label, international, multicenter phase 1/2 study of nivolumab (NIVO) ± ipilimumab (IPI) in patients (pts) with recurrent/metastatic Merkel cell carcinoma (MCC) (CheckMate 358)

Shailender Bhatia,[1] Suzanne L. Topalian,[2] William Sharfman,[2] Tim Meyer,[3] Christopher D. Lao,[4] Lorena Fariñas-Madrid,[5] Lot A Devriese,[6] Raid Aljumaily,[7] Robert L. Ferris,[8] Yoshitaka Honma,[9] Tariq Aziz Khan,[10] Anjaiah Srirangam,[10] Charlie Garnett-Benson,[10] Michelle Lee,[10,11] Paul Nghiem[12]

[1]Division of Medical Oncology, University of Washington and Fred Hutchinson Cancer Center, Seattle, WA, USA; [2]Johns Hopkins Bloomberg-Kimmel Institute for Cancer Immunotherapy and Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA; [3]Department of Oncology, University College London Cancer Institute, London, UK; [4]Michigan Medicine, Rogel Cancer Center, Ann Arbor, MI, USA; [5]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [6]Department of Medical Oncology, Cancer Center, University Medical Center Utrecht, Utrecht, the Netherlands; [7]Stephenson Cancer Center at the University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; [8]Department of Otolaryngology, University of Pittsburgh, Pittsburgh, PA, USA; [9]Department of Head and Neck, Esophageal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; [10]Bristol Myers Squibb, Princeton, NJ, USA; [11]Syneos Health, Morrisville, NC, USA; [12]University of Washington Medical Center, Seattle, WA, USA

Presentation number 9506

Bhatia S et al. ASCO 2023;Abstract 9506.

Courtesy of Evan J Lipson, MD

Efficacy: all treated patients

- In this non-randomized trial, ORR appeared to be similar in the two cohorts
- NIVO + IPI combination appeared to be associated with shorter DOR, PFS, and OS

	NIVO (n = 25)	NIVO + IPI (n = 43)
ORR,[a] % (95% CI)	60.0 (38.7-78.9)	58.1 (42.1-73.0)
n	15	25
CR, n (%)	8 (32.0)	8 (18.6)
PR, n (%)	7 (28.0)	17 (39.5)
SD, n (%)	5 (20.0)	4 (9.3)
PD, n (%)	3 (12.0)	10 (23.3)
NE, n (%)	2 (8.0)	4 (9.3)
Median PFS, months (95% CI)	21.3 (9.2-62.5)	8.4 (3.7-24.3)
Median OS, months (95% CI)	80.7 (23.3-NA)	29.8 (8.5-48.3)

	NIVO (n = 25)	NIVO + IPI (n = 43)
Median DOR, months (95% CI)	60.6 (16.7-NA)	25.9 (10.4-NA)
Patients with DOR of at least:		
12 months, n (%)	12 (80.0)	17 (68.0)
18 months, n (%)	8 (53.3)	15 (60.0)
24 months, n (%)	6 (40.0)	13 (52.0)

Database lock: November 28, 2022. [a]ORR and PFS were investigator-assessed.
CR, complete response; DOR, duration of response; IPI, ipilimumab; NA, not applicable; NE, not evaluable; NIVO, nivolumab; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Bhatia S et al. ASCO 2023;Abstract 9506.

Courtesy of Evan J Lipson, MD

Conclusions

- **Critical finding(s):** This multicenter, international phase 1 /2 study investigated NIVO ± IPI 1 mg/kg Q6W in patients with advanced MCC, some treatment-naïve, some previously treated.
  - Both NIVO and NIVO + low-dose IPI were associated with frequent and durable responses.
  - While the non-randomized trial design limits comparisons between cohorts, results do not suggest additional efficacy (ORR, PFS, OS) in the combination arm.

- **Clinical implication(s):** Although this study does not support administration of IPI+NIVO to patients with advanced Merkel cell carcinoma, reports from other groups suggest some benefit associated with this combination. For now, anti-PD-(L)1 monotherapy remains the standard of care for this patient population, though the addition of ipilimumab might be considered in patients with refractory MCC.

- **Research relevance:** Further research is needed to assess a potential role for combination immune checkpoint inhibitor therapy in this patient population.

Courtesy of Evan J Lipson, MD

Inside the Issue: Integrating Bispecific Antibodies into the Management of Multiple Myeloma — Patient Selection and Toxicity Management

A CME/MOC-Accredited Live Webinar

Tuesday, July 18, 2023
5:00 PM – 6:00 PM ET

Faculty

Hans Lee, MD
Saad Zafar Usmani, MD, MBA

Moderator

Neil Love, MD

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