Meet The Professor
Management of BRAF-Mutant Melanoma

Jason J Luke, MD
Director of the Cancer Immunotherapeutics Center
UPMC Hillman Cancer Center
Associate Professor of Medicine
University of Pittsburgh
Pittsburgh, Pennsylvania

Commercial Support

This activity is supported by educational grants from Novartis and Pfizer Inc.

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Dr Love — Disclosures

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

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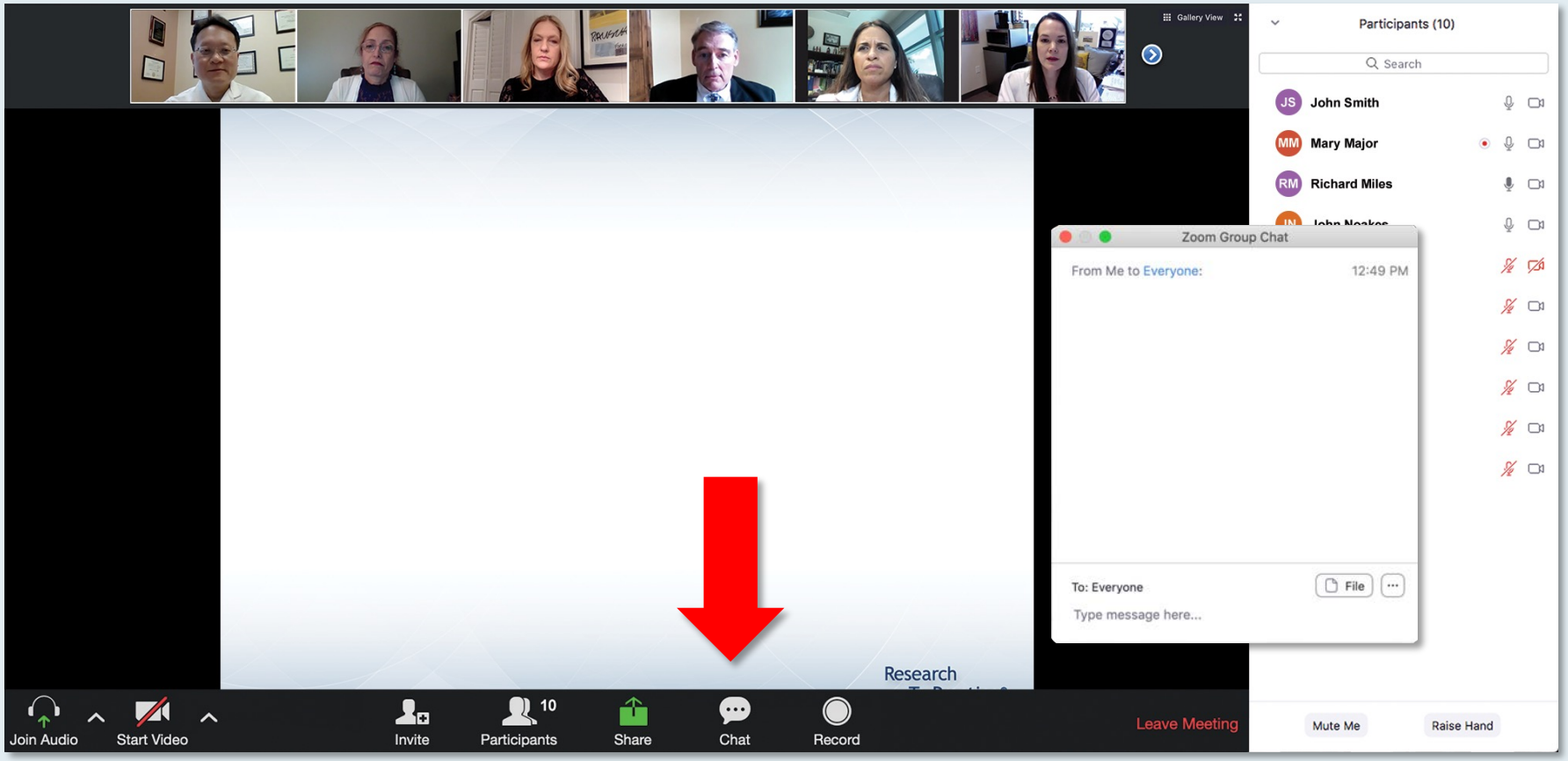

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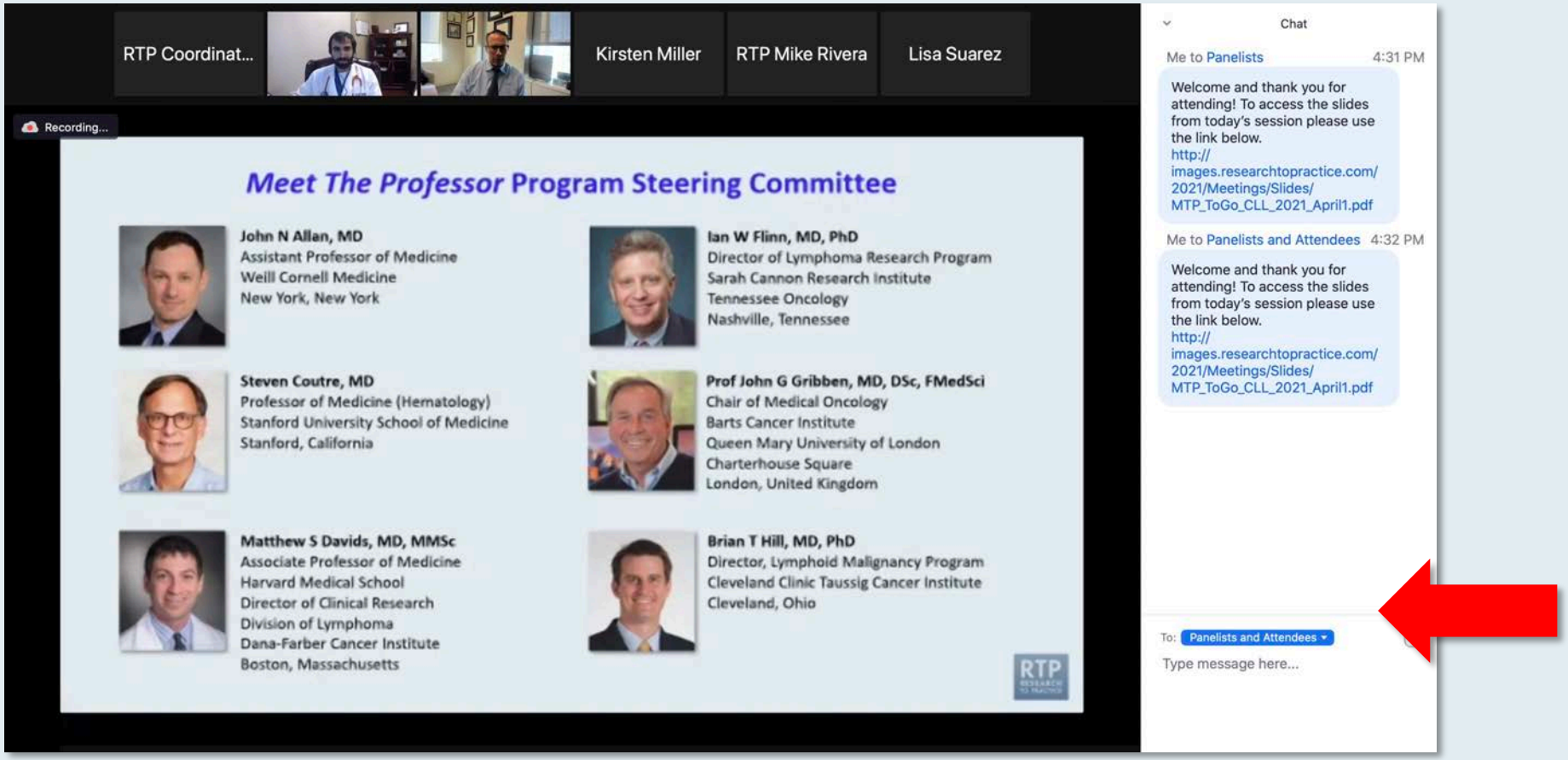

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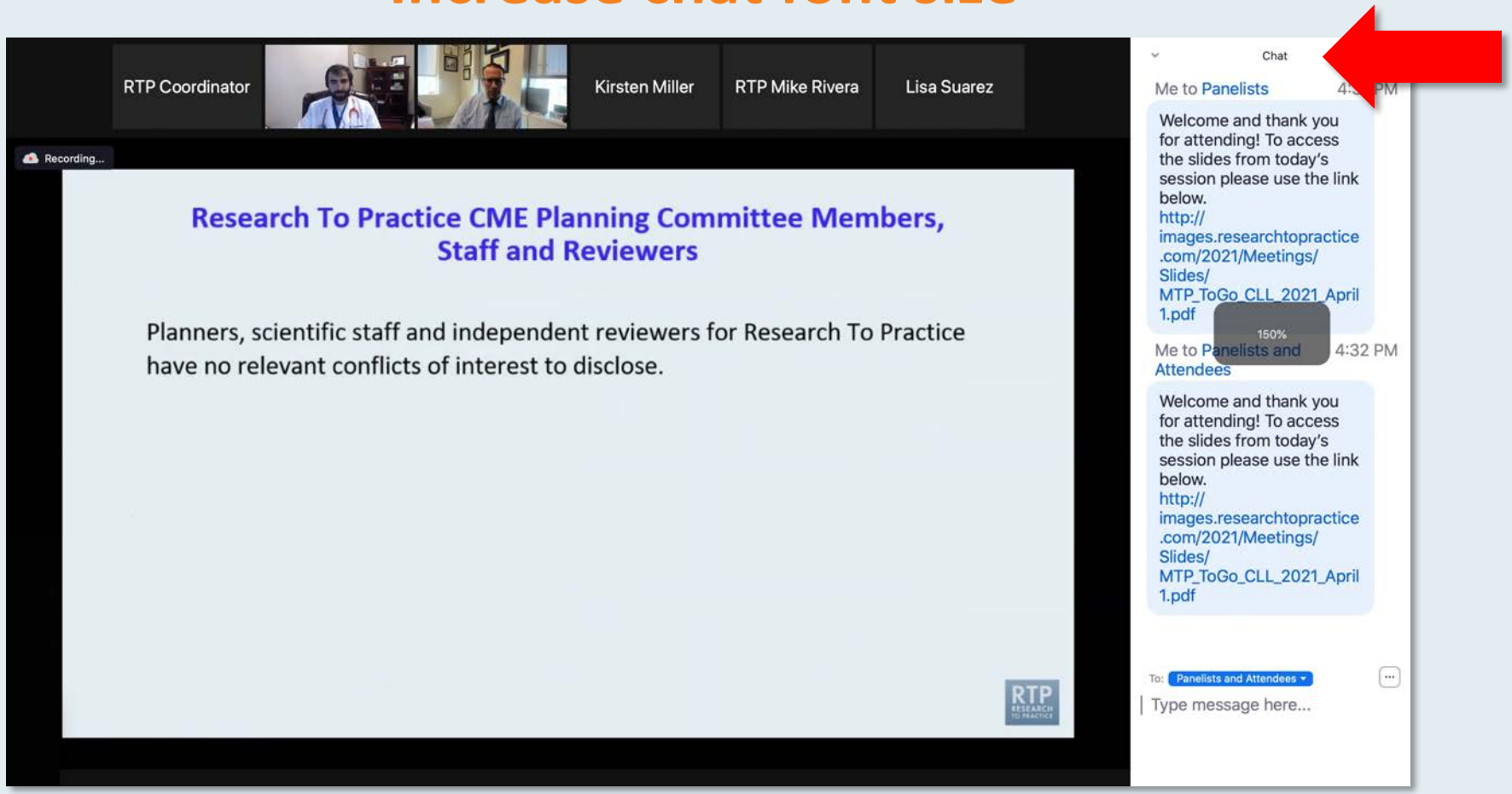

Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

ONCOLOGY TODAY

WITH DR NEIL LOVE

Management of HER2-Low Breast Cancer

DR IAN KROP

DANA-FARBER CANCER INSTITUTE

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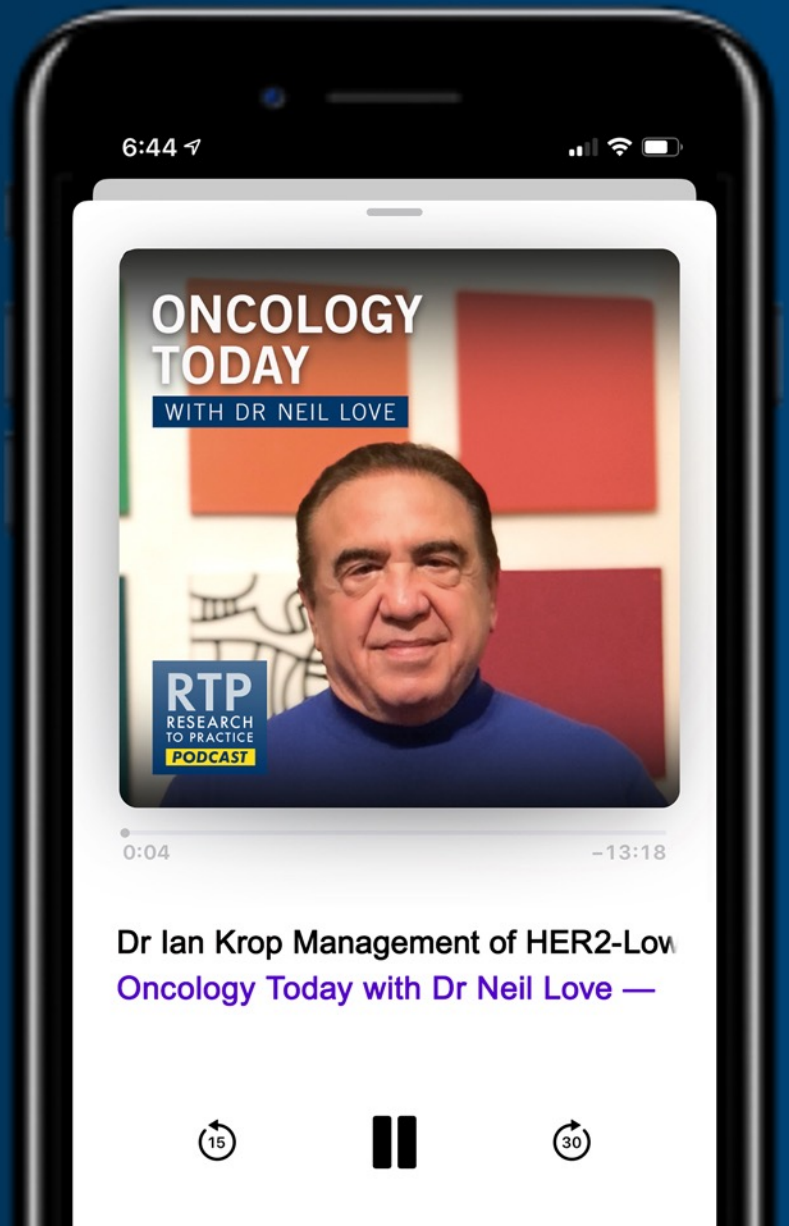

Meet The Professor

Optimizing the Management of Metastatic Castration-Resistant Prostate Cancer

Tuesday, November 30, 2021
5:00 PM – 6:00 PM ET

Faculty

A Oliver Sartor, MD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Management of Acute Myeloid Leukemia

Wednesday, December 1, 2021
5:00 PM – 6:00 PM ET

Faculty

Andrew H Wei, MBBS, PhD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with HER2-Positive Breast Cancer

Thursday, December 2, 2021
5:00 PM – 6:00 PM ET

Faculty

Hope S Rugo, MD

Moderator

Neil Love, MD

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

Tuesday, December 7, 2021
8:00 PM – 9:45 PM ET

Faculty

Aditya Bardia, MD, MPH
Joyce O'Shaughnessy, MD
Kevin Kalinsky, MD, MS

Moderator

Erika Hamilton, MD

RTP RESEARCH TO PRACTICE

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

Wednesday, December 8, 2021
8:00 PM – 10:00 PM ET

Faculty

Carey K Anders, MD
Virginia F Borges, MD, MMSc
Sara Hurvitz, MD
Ian E Krop, MD, PhD

Moderator

Lisa Carey, MD

RTP RESEARCH TO PRACTICE

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

Thursday, December 9, 2021
8:00 PM – 9:45 PM ET

Faculty

Rita Nanda, MD
Melinda Telli, MD
Peter Schmid, FRCP, MD, PhD

Moderator

Hope S Rugo, MD

RTP RESEARCH TO PRACTICE

What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Chronic Lymphocytic Leukemia

Friday, December 10, 2021
7:30 AM – 9:30 AM ET

Faculty

Nitin Jain, MD
Anthony R Mato, MD, MSCE
John M Pagel, MD, PhD
Jennifer Woyach, MD

Moderator

John N Allan, MD

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What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Hodgkin and Non-Hodgkin Lymphoma

Friday, December 10, 2021
11:30 AM – 1:30 PM ET

Faculty

Jeremy Abramson, MD
Martin Dreyling, MD, PhD
Loretta J Nastoupil, MD
Gilles Salles, MD, PhD

Moderator

Ann S LaCasce, MD, MMSc

RTP RESEARCH TO PRACTICE

What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Multiple Myeloma

Friday, December 10, 2021
3:15 PM – 5:15 PM ET

Faculty

Larry D Anderson Jr, MD, PhD
Morie A Gertz, MD, MACP
Irene M Ghobrial, MD
Peter Voorhees, MD

Moderator

Robert Z Orlowski, MD, PhD

RTP RESEARCH TO PRACTICE

What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Acute Myeloid Leukemia and Myelodysplastic Syndromes

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Alice S Mims, MD, MSCR
Alexander Perl, MD
Richard M Stone, MD
Geoffrey L Uy, MD

Moderator

Harry Paul Erba, MD, PhD

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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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Meet The Professor Program Participating Faculty

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Moderator
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Research To Practice
Miami, Florida

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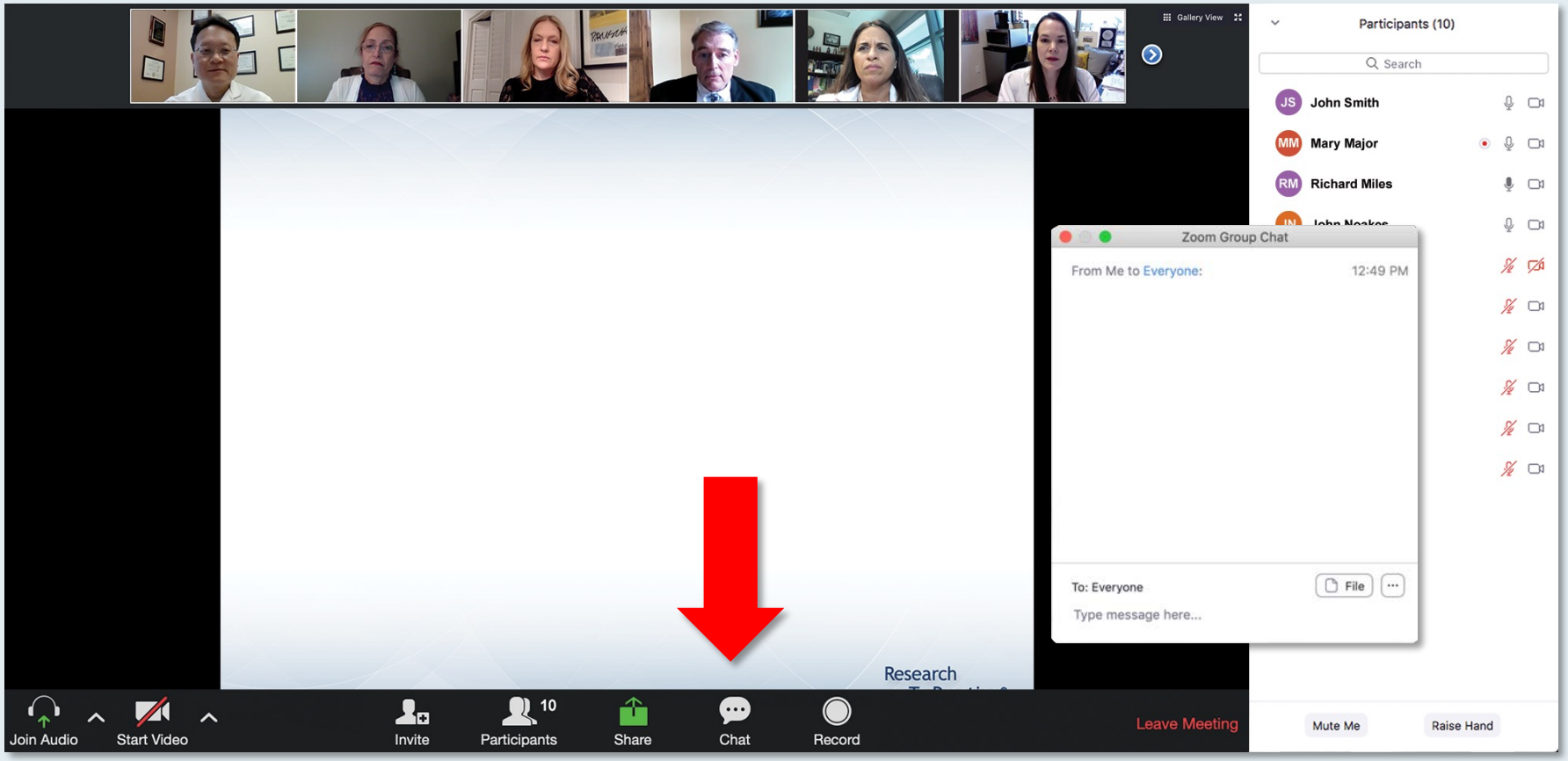

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Deland, Florida

Elizabeth Guancial, MD
Florida Cancer Specialists and Research Institute
FSU College of Medicine
Sarasota, Florida

Syed F Zafar, MD
Florida Cancer Specialists and Research Institute
Lee Health
Fort Myers, Florida

Evan J Lipson, MD
The Sidney Kimmel Comprehensive Cancer Center
Baltimore, Maryland

What would you generally recommend as first-line treatment for a symptomatic younger patient with extensive BRAF-mutant metastatic melanoma?

 Dr Hamid	BRAF/MEK → switch to ipilimumab/nivolumab	 Dr Pavlick	Nivolumab/ipilimumab
 Prof Long	Nivolumab/ipilimumab	 Dr Sznol	Nivolumab/ipilimumab
 Dr Luke	Nivolumab/ipilimumab	 Dr Weber	Encorafenib/ binimetinib x 8 wk, then switch to IO

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Meet The Professor with Dr Luke

Introduction: DREAMseq Phase III Study

MODULE 1: Case Presentations

- Dr Lipson: A 55-year-old woman with metastatic melanoma and a BRAF V600K mutation
- Dr Shameem: A 66-year-old man with metastatic melanoma and a BRAF V600E mutation
- Dr Zafar: A 69-year-old man with metastatic melanoma and a BRAF V600K mutation
- Dr Guancial: A 79-year-old man with melanoma and a history of transient ischemic attacks
- Dr Lipson: A man in his late 40s with resectable melanoma
- Dr Freedman: A 54-year-old man with metastatic melanoma and a BRAF mutation

MODULE 2: Journal Club with Dr Luke

MODULE 3: Beyond the Guidelines

MODULE 4: Appendix – Key Data Sets

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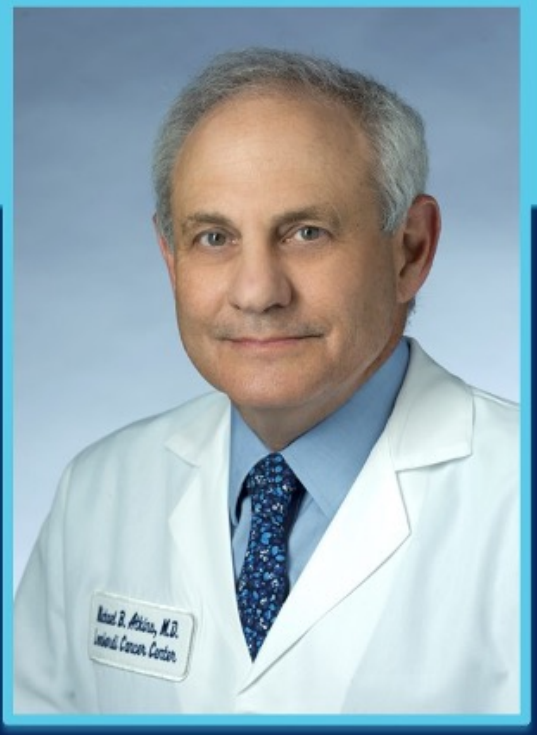
ASCO Plenary Series

2021

Abstract 356154

DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing) a Phase III Trial: ECOG-ACRIN EA6134



Michael Atkins, MD
Georgetown Lombardi Comprehensive Cancer Center

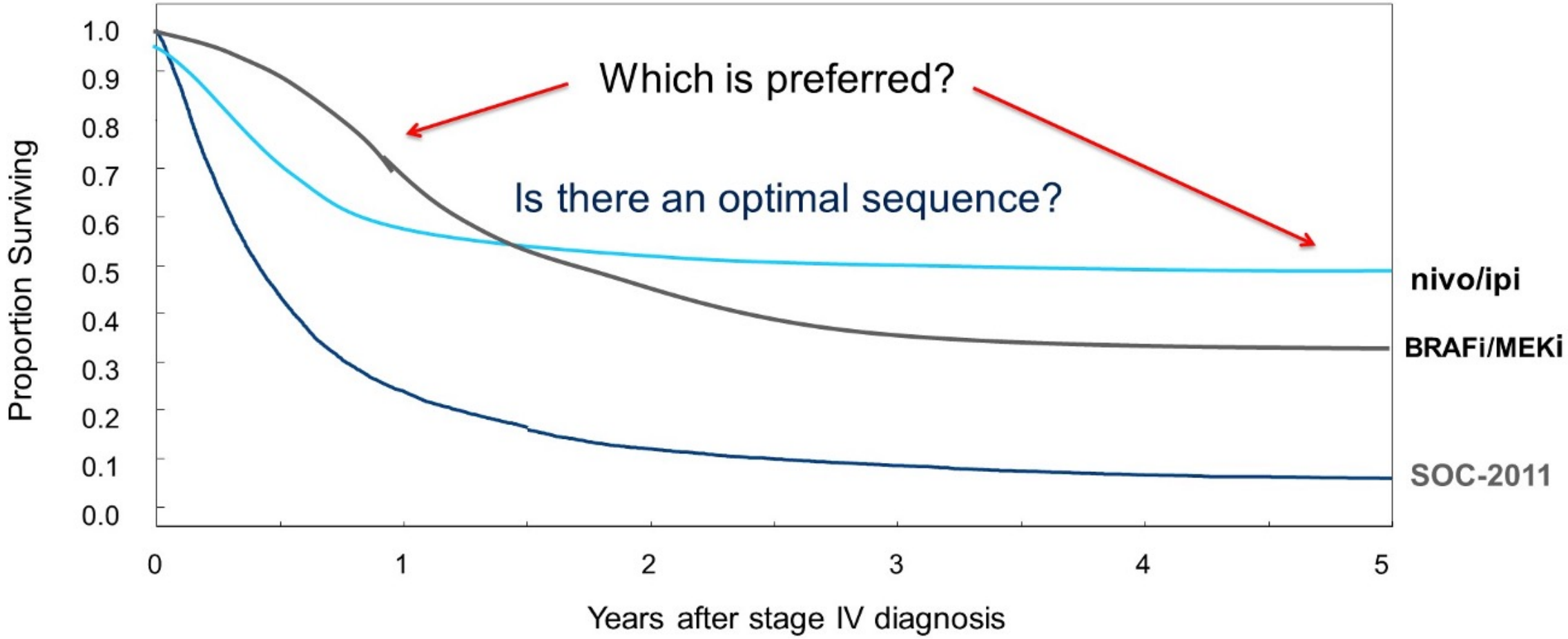
ASCO Plenary Series

Discussion

Discussion of Abstract 356154

Keith Flaherty, MD
Dana-Farber Cancer Institute/Harvard Medical School/Massachusetts General Hospital

Treatment for BRAF Mutant Melanoma-2015



Atkins M et al. ASCO 2021 Plenary Series;Abstract 356154.

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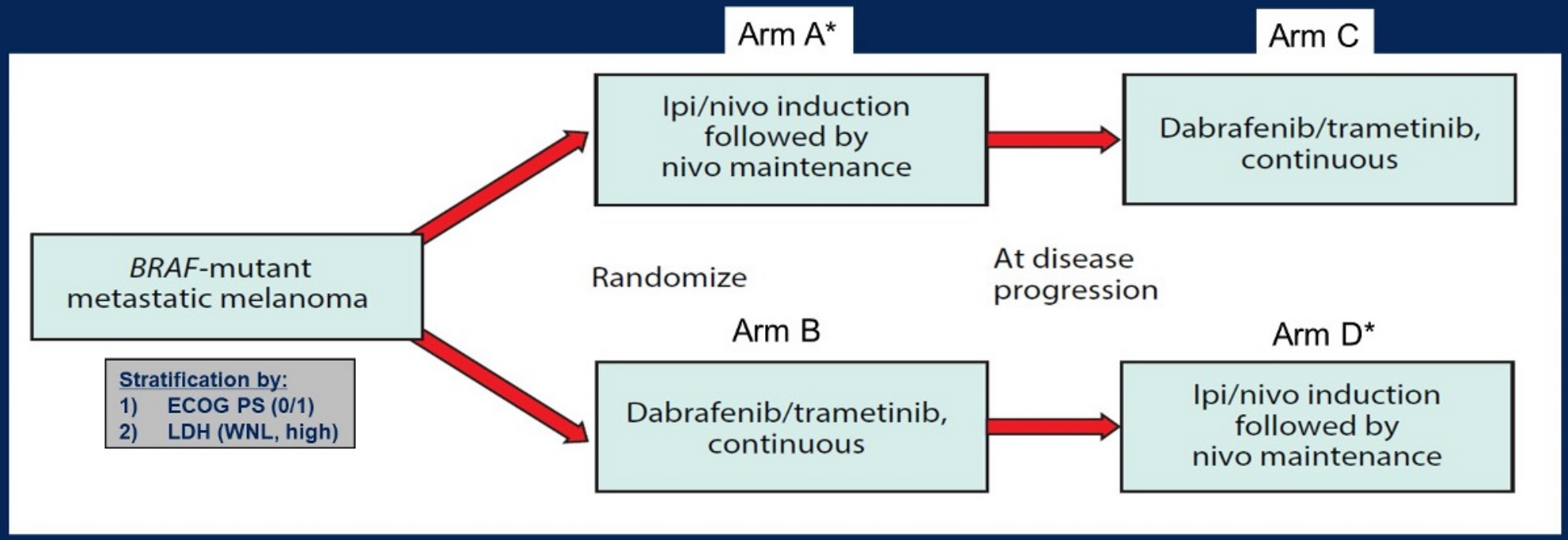
DREAMseq Trial Treatment Schema



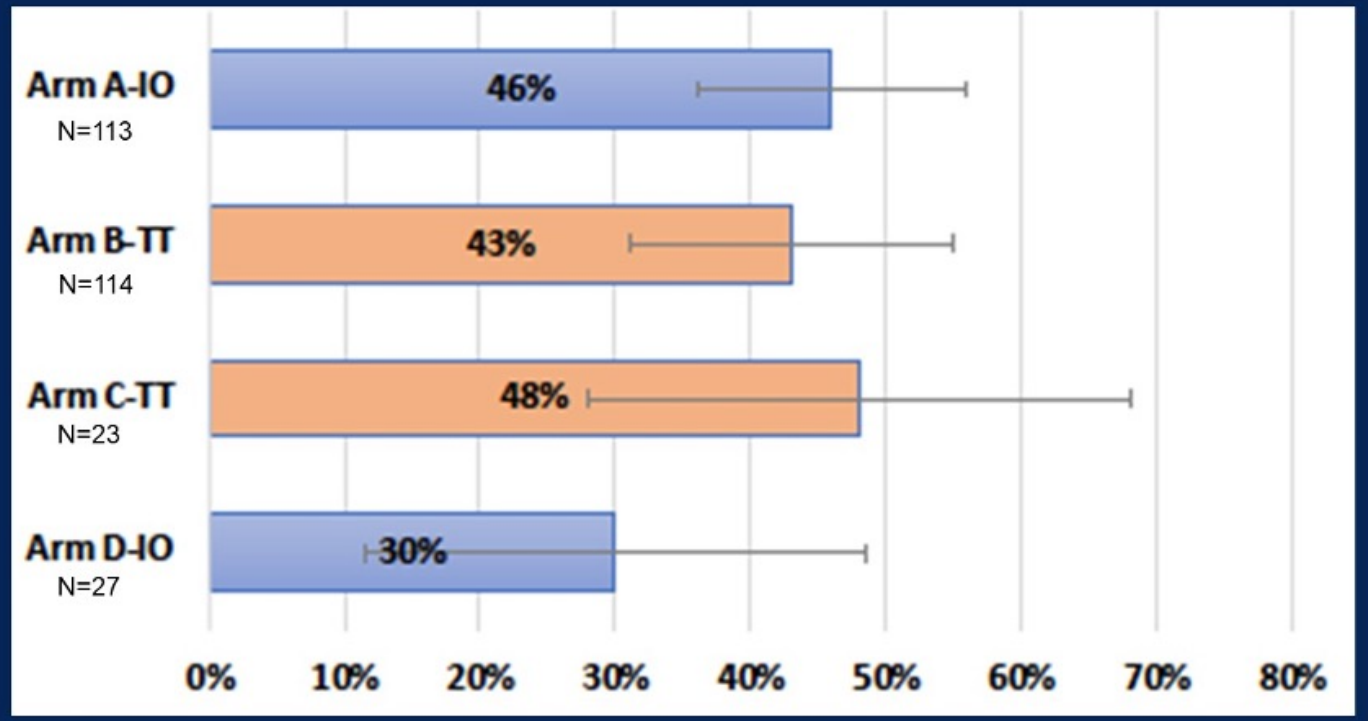
*Nivo/Ipi Induction = 12 wks; nivo maintenance = 72 wks

PRESENTED BY: Michael B. Atkins, MD

ORR (%) By Treatment Arm*

Step 1

Step 2



*Bars represent 95% CI

Data missing on ~ 15% of pts

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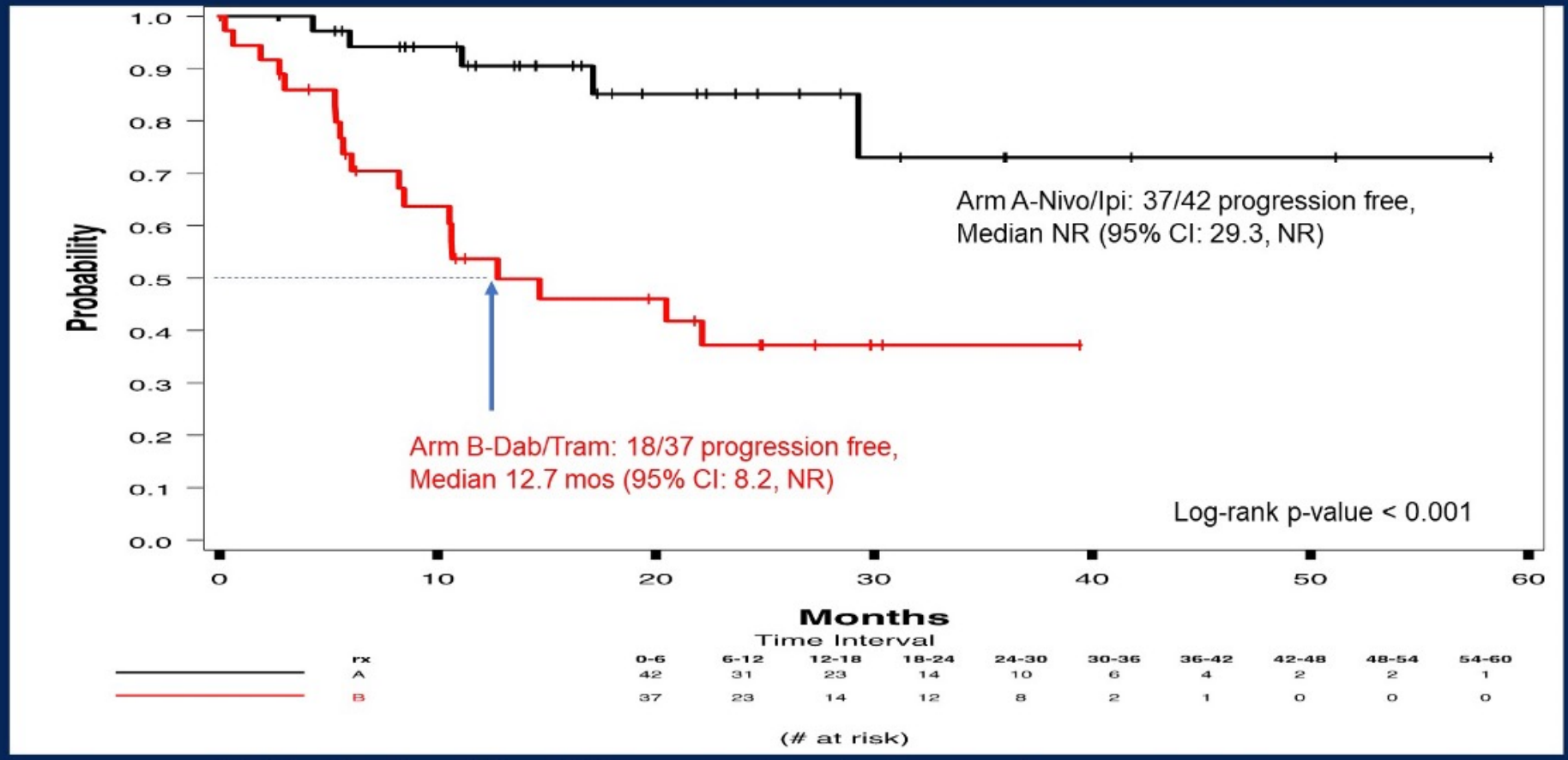
Duration of Response (DOR)*: Step1

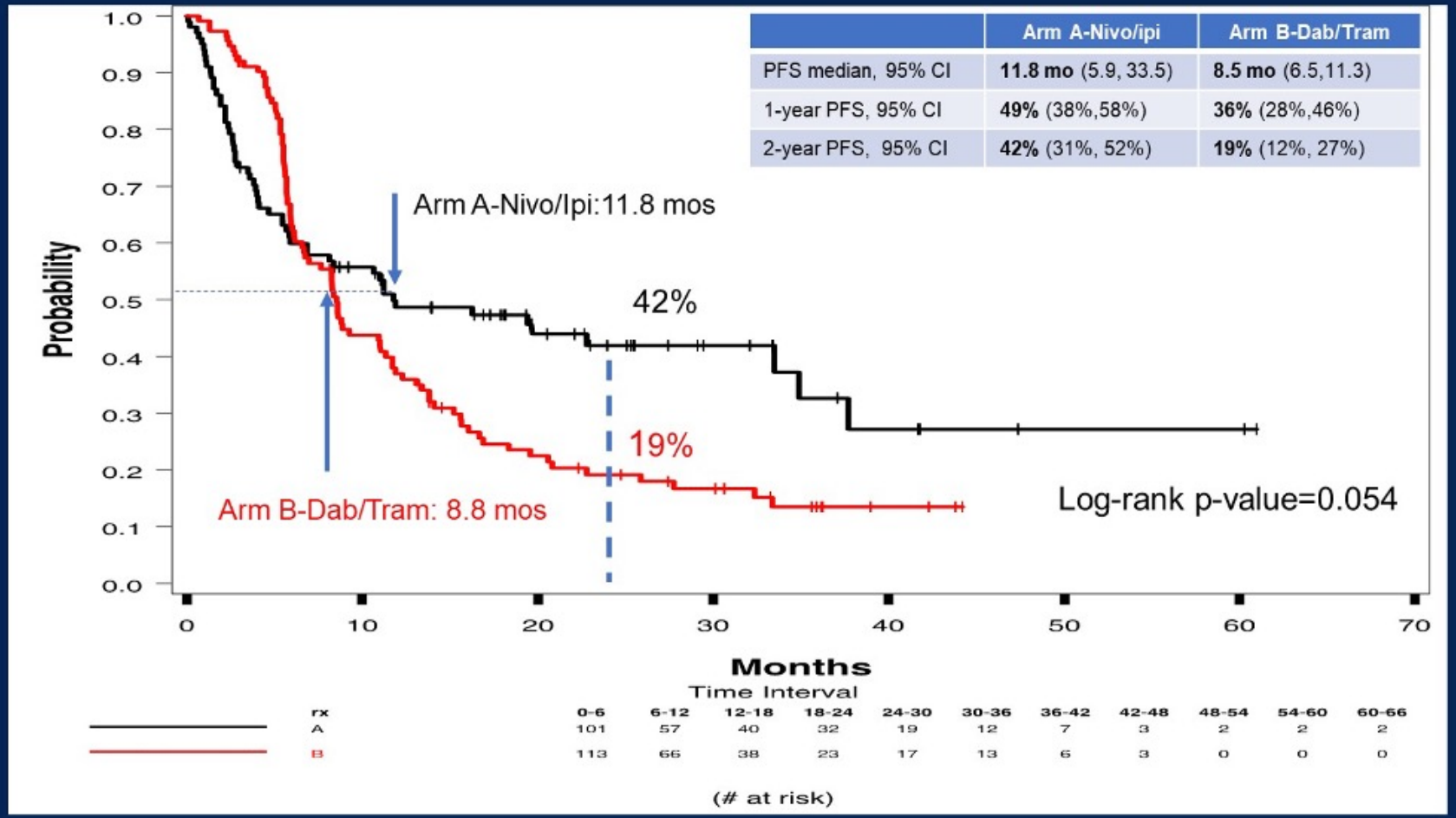


*DOR = time from PR or CR to progression or last assessed

PRESENTED BY: Michael B. Atkins, MD

Progression Free Survival (PFS): Step1 (n=214)

	Arm A-Nivo/ipi	Arm B-Dab/Tram
PFS median, 95% CI	**11.8 mo** (5.9, 33.5)	**8.5 mo** (6.5,11.3)
1-year PFS, 95% CI	**49%** (38%,58%)	**36%** (28%,46%)
2-year PFS, 95% CI	**42%** (31%, 52%)	**19%** (12%, 27%)



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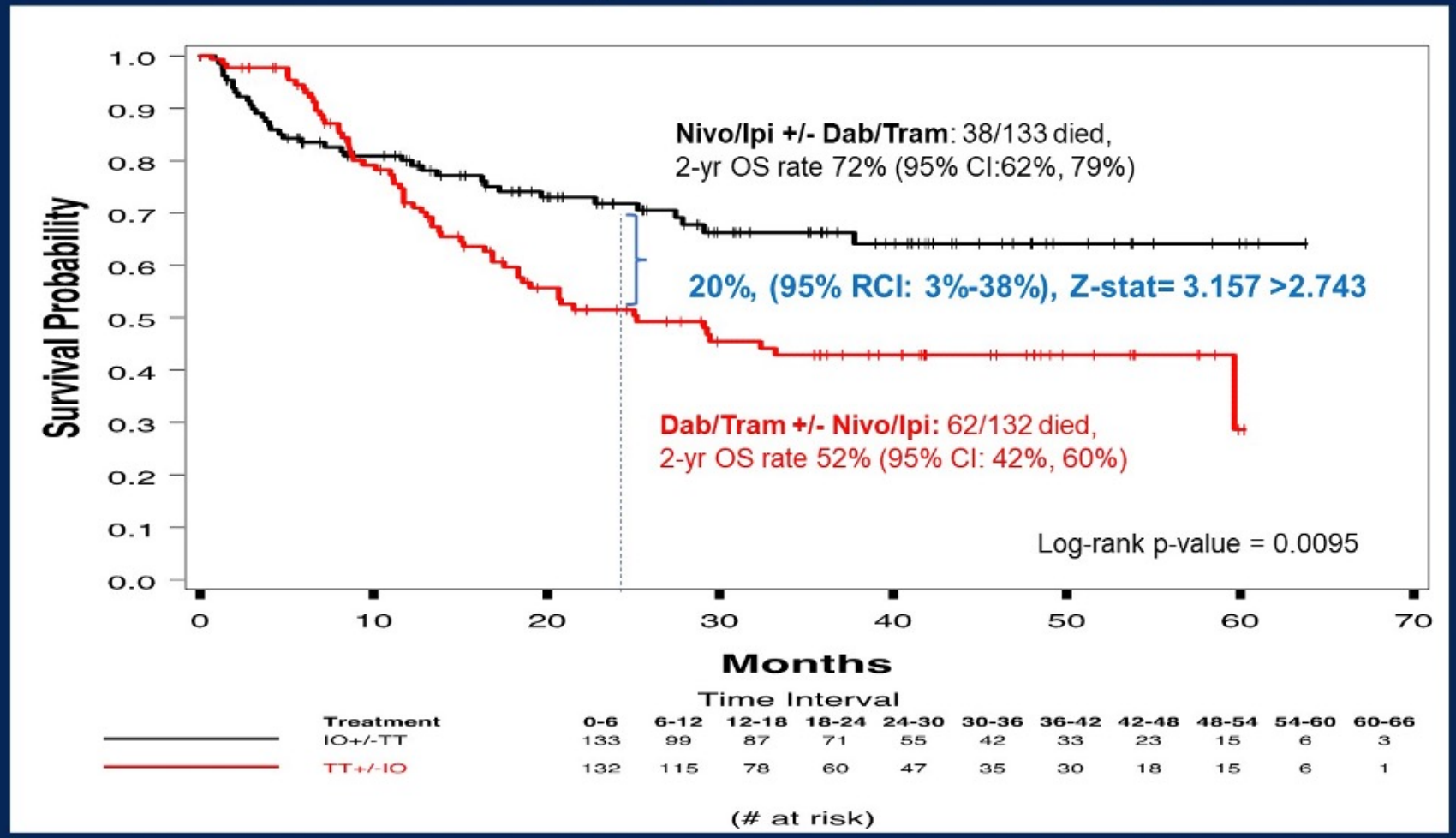
Overall Survival (OS): Step 1 +/- Step 2



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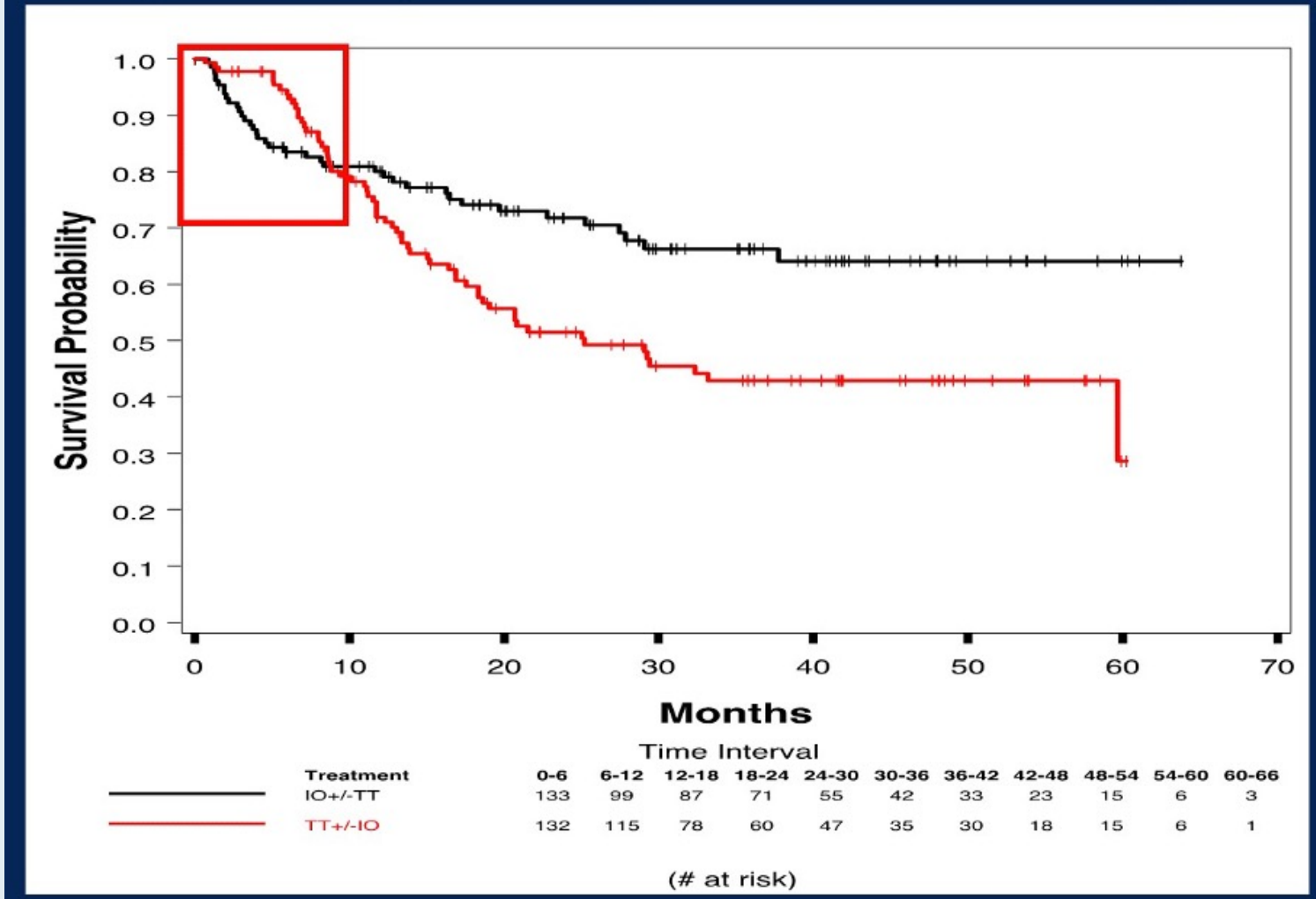
Early Deaths (<10 mos) on Arm A-Nivo/ipi; N=24



Med OS: 3 mos (0.9-8.4 mos)

PS 1 (42%); **LDH-high** (58%);
Stage M1c (71%)

Median Rx Duration < 6 weeks

Off Rx Reason

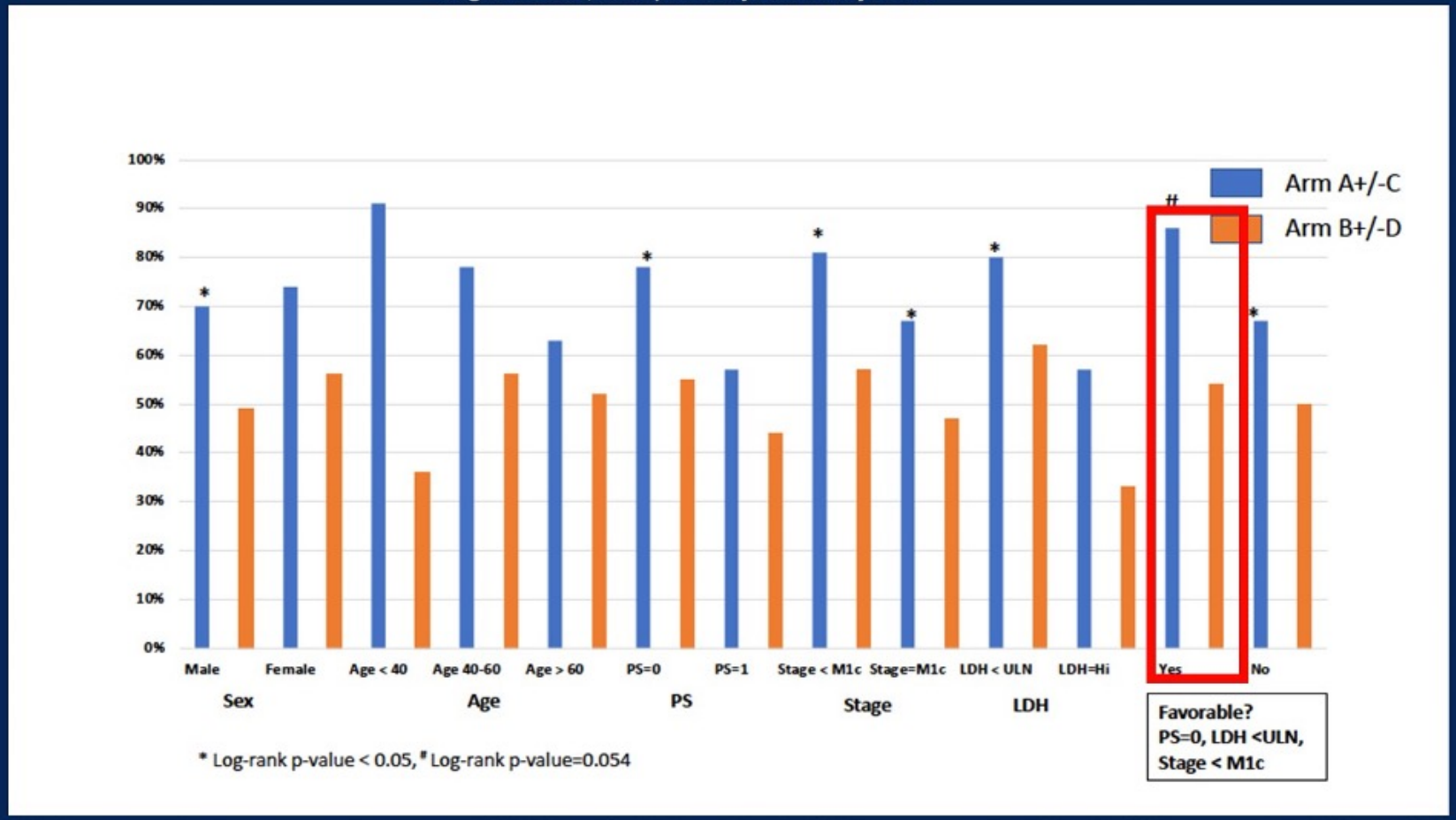
- PD= 39%
- AE = 30%
- Death= 26%
- Other= 4%

Crossover to Arm C-TT = 0

PRESENTED BY: Michael B. Atkins, MD

2-yr OS Rate Subgroup Analyses by Sequence

Log-rank test, multiple analysis not adjusted



All favor the sequence of Nivo/ipi to Dab/Tram over Dab/Tram to Nivo/ipi

PRESENTED BY: Michael B. Atkins, MD

Toxicity By Treatment Arm

	Step 1		Step 2	
	Arm A-IO (n=126)	Arm B-TT (n=130)	Arm C-TT (n=26)	Arm D-IO (n=42)
Grade 3+ TRAEs (95% CI)	60% (51%, 69%)	52% (43%, 61%)	54% (33%, 73%)	50% (34%, 66%)
Grade 5 AEs (CTEP)^	11	10	3	3
Grade 5 TRAE	2*	0	1#	0

*Myocarditis, GI
Thromboembolic-CVA

^CTEP Grade 5 AEs = death from any cause within 30 days of last treatment

PRESENTED BY: Michael B. Atkins, MD

Meet The Professor with Dr Luke

Introduction: DREAMseq Phase III Study

MODULE 1: Case Presentations

- Dr Lipson: A 55-year-old woman with metastatic melanoma and a BRAF V600K mutation
- Dr Shameem: A 66-year-old man with metastatic melanoma and a BRAF V600E mutation
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MODULE 2: Journal Club with Dr Luke

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Case Presentation – Dr Lipson: A 55-year-old woman with metastatic melanoma and a BRAF V600K mutation

Dr Evan Lipson

- PMH: inflammatory bowel disease
- Diagnosed with Stage IV melanoma
- Low LDH
- Low metastatic tumor burden
- Mutation analysis: BRAF V600K-mutation positive

Question:

- What treatment would you recommend?

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Case Presentation – Dr Shameem: A 66-year-old man with metastatic melanoma and a BRAF V600E mutation

Dr Raji Shameem

- 2001: Cutaneous melanoma, s/p resection and adjuvant interferon
- 3/2021: Presents to the hospital with ataxic gait → MRI brain: Right cerebellar mass and surrounding vasogenic edema
- CT: Pulmonary nodules, osseous lesion, mediastinal adenopathy and soft tissue masses
- US-guided biopsy: Metastatic melanoma, V600E mutation
- Resection of cerebellar mass and brain RT

Case Presentation – Dr Shameem: A 66-year-old man with metastatic melanoma and a BRAF V600E mutation (continued)

Dr Raji Shameem

- 2001: Cutaneous melanoma, s/p resection and adjuvant interferon
- 3/2021: Presents to the hospital with ataxic gait → MRI brain: Right cerebellar mass and surrounding vasogenic edema
- CT: Pulmonary nodules, osseous lesion, mediastinal adenopathy and soft tissue masses
- US-guided biopsy: Metastatic melanoma, V600E mutation
- Resection of cerebellar mass and brain RT
- ***Nivolumab/ipilimumab, with excellent response***
- ***Subsequent brain re-imaging: Negative***

Questions

- ***How do you decide between immunotherapy versus BRAF/MEK inhibitor therapy for patients with brain metastases?***
- ***If you decide on a BRAF/MEK combination, how do you decide which doublet to use?***
- ***What has been your experience with encorafenib/binimetinib, especially with regard to pyrexia?***

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Atezolizumab/vemurafenib/cobimetinib triplet combination; vemurafenib-associated photosensitivity; “Brain fog” with BRAFi/MEKi combination therapy

Dr Evan Lipson

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Case Presentation – Dr Zafar: A 69-year-old man with metastatic melanoma and a BRAF V600K mutation

Dr Syed Zafar

- 9/2017: Stage IIIB melanoma of the scalp, with positive lymph nodes and BRAF V600K mutation, s/p resection
- Adjuvant dabrafenib/trametinib x 6, stopped by patient due to fevers, malaise, asthenia, EKG issues
- 2018: Recurrent, locally advanced disease but no metastatic disease
- Pembrolizumab, without response, PD
- Encorafenib/binimetinib, with PR → PD

Question

- In a patient with metastatic melanoma and a BRAF V600K mutation, what are your thoughts about subsequent lines of therapy?

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Case Presentation – Dr Guancial: A 79-year-old man with Stage IIIC melanoma with a BRAF V600E mutation

Dr Elizabeth Guancial

- PMH: Atrial fibrillation, TIA
- 9/2020: Stage IIIC melanoma, BRAF V600E mutation, s/p resection and bilateral SLNB
- Adjuvant nivolumab, with PD after a couple of months

Question

- How do you choose between adjuvant immunotherapy versus a targeted therapy?

Case Presentation – Dr Lipson: A man in his late 40s with resectable melanoma

Dr Evan Lipson

- Presents with a large melanoma tumor on his left upper extremity
- BRAF mutation

Questions

- How would you approach initial treatment for this patient? Would you use a neoadjuvant therapy approach?
- Do you believe that immunotherapy or targeted therapy would be a better option?

RTP
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TO PRACTICE

Case Presentation – Dr Freedman: A 54-year-old man with metastatic melanoma and a BRAF mutation

Dr Allan Freedman

- 2003: Stage III superficial spreading melanoma (1.6 mm, Clark IV, no ulceration), s/p wide excision with no residual disease but 1 sentinel lymph node) → Lymphadenectomy and adjuvant interferon
- 3/2018: Biopsy-proven metastatic melanoma in axillary nodes, s/p ALND (11/30 nodes positive)
- 7/2018: Nivolumab x 3 months → New neck mass biopsy-proven melanoma (33/39 nodes positive)
- Dabrafenib/trametinib, with intermittent fevers, myalgias, headaches and fatigue

Questions

- Would it be reasonable to try a different BRAF/MEK combination in light of his fevers?
- How do you choose among the three BRAF/MEK combination regimens? Do the side effect profiles influence your choice?

RTP RESEARCH TO PRACTICE

Counseling patients with Stage IIIA melanoma about the risks and benefits of adjuvant immunotherapy; Risks and benefits of immunotherapy versus targeted therapy for high-risk melanoma

Dr Evan Lipson

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RESEARCH
TO PRACTICE

Meet The Professor with Dr Luke

Introduction: DREAMseq Phase III Study

MODULE 1: Case Presentations

- Dr Lipson: A 55-year-old woman with metastatic melanoma and a BRAF V600K mutation
- Dr Shameem: A 66-year-old man with metastatic melanoma and a BRAF V600E mutation
- Dr Zafar: A 69-year-old man with metastatic melanoma and a BRAF V600K mutation
- Dr Guancial: A 79-year-old man with melanoma and a history of transient ischemic attacks
- Dr Lipson: A man in his late 40s with resectable melanoma
- Dr Freedman: A 54-year-old man with metastatic melanoma and a BRAF mutation

MODULE 2: Journal Club with Dr Luke

MODULE 3: Beyond the Guidelines

MODULE 4: Appendix – Key Data Sets

RTP RESEARCH TO PRACTICE

Multi-Center Phase I/II Open Label Study to Evaluate Safety and Efficacy in Participants with Metastatic BRAF-Mutant Melanoma Treated with Encorafenib with and without Binimetinib in Combination with Nivolumab and Low-dose Ipilimumab (QUAD 01: Quadruple Therapy in Melanoma)

Jameson-Lee M et al.

ASCO 2021;Abstract TPS9596.

QUAD 01 Trial Eligibility Criteria

KEY INCLUSION CRITERIA:

Cohort 1: Brain Metastases

- Metastatic melanoma involving brain (excluding leptomeningeal disease)
- ECOG ≤ 2
- CAN be on 4mg of dex if stable/decreasing dose
- No SRT or surgery w/in 3 weeks
- No seizures 10 days
- Prior whole-brain radiation excluded

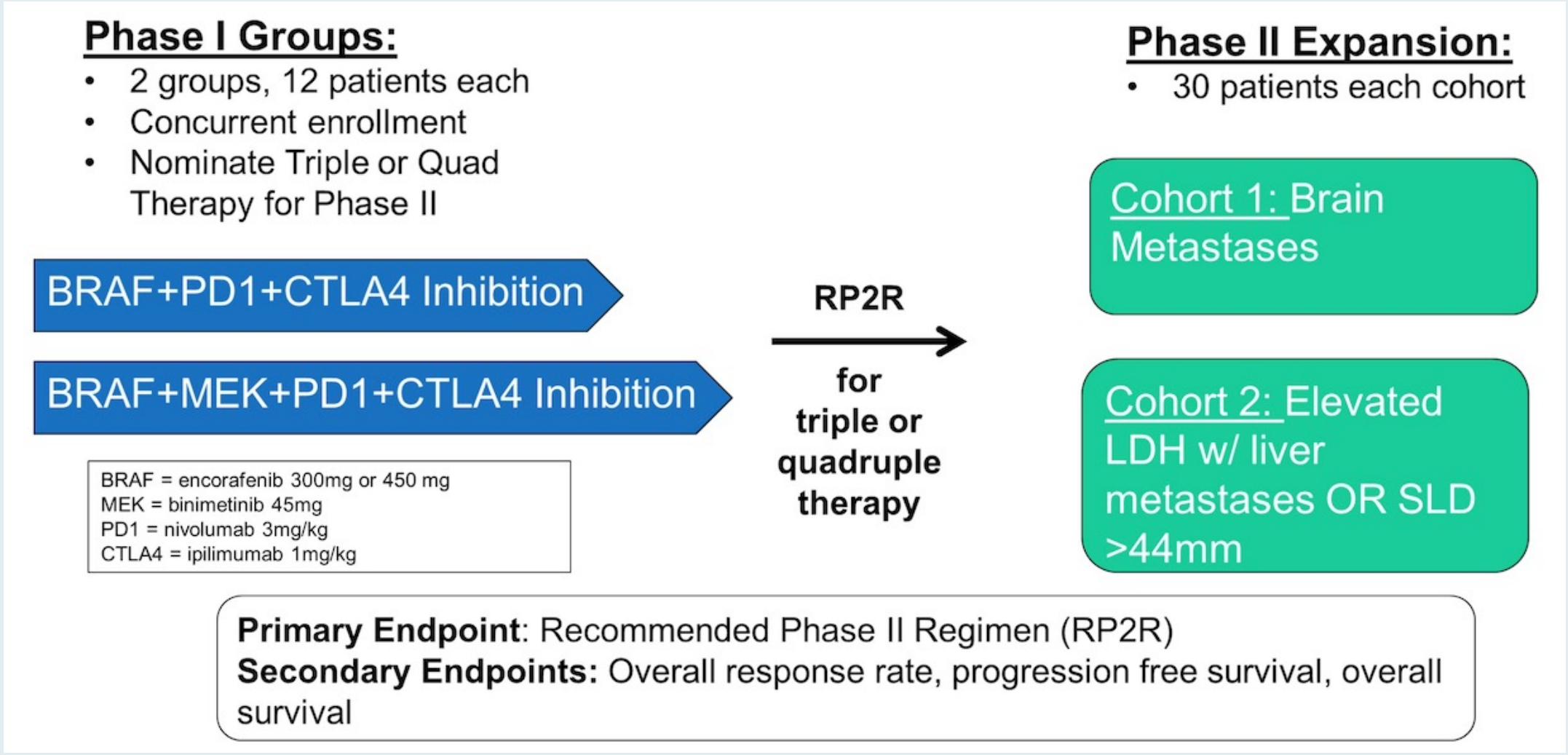
Cohort 2: Elevated LDH with Liver Mets OR Bulky Disease

- ECOG ≤ 1
- LDH > 1x ULN with a) liver metastases OR b)SLD >44mm

- Histologically confirmed metastatic or unresectable *BRAF*$^{V600E/K}$ mutant melanoma
- Greater than 6 months from adjuvant therapy (if any given) and/or have recently started treatment with up to 6 weeks of targeted therapy

Jameson-Lee M et al. ASCO 2021;Abstract TPS9596.

QUAD 01 Trial Schema



Jameson-Lee M et al. ASCO 2021;Abstract TPS9596.

Meet The Professor with Dr Luke

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Have you administered or would you administer neoadjuvant BRAF-targeted therapy to a patient with borderline-resectable BRAF-mutant melanoma outside of a clinical trial setting?

 Dr Hamid	I have	 Dr Pavlick	I have not and would not
 Prof Long	I have not and would not	 Dr Sznol	I have not but would for the right patient
 Dr Luke	I have not and would not	 Dr Weber	I have

RTP RESEARCH TO PRACTICE

What is your usual approach to adjuvant systemic treatment, if any, for a 35-year-old patient who is s/p complete surgical resection of Stage IIIB primary melanoma with a BRAF V600E mutation and 3 positive axillary nodes?

 Prof Long	Nivolumab or pembrolizumab	 Dr Sznol	Dabrafenib/trametinib
 Dr Luke	Nivolumab	 Dr Weber	Nivolumab
 Dr Pavlick	Nivolumab		

What is your usual approach to adjuvant systemic treatment, if any, for an 80-year-old patient who is s/p complete surgical resection of Stage IIIB primary melanoma with a BRAF V600E mutation and 3 positive axillary nodes?

 Prof Long	Nivolumab or pembrolizumab if fit and well*	 Dr Sznol	Dabrafenib/trametinib
 Dr Luke	Nivolumab	 Dr Weber	Nivolumab
 Dr Pavlick	Nivolumab		

*Active surveillance if red flags

RTP RESEARCH TO PRACTICE

What is your usual approach to adjuvant systemic treatment, if any, for a 35-year-old patient who is s/p complete surgical resection of Stage IIC primary melanoma with a BRAF V600E mutation?

Have you administered or would you administer either encorafenib/binimetinib or vemurafenib/cobimetinib as adjuvant therapy to a patient with BRAF-mutant melanoma outside of a clinical trial setting?

 Dr Hamid	I have not but would for the right patient	 Dr Pavlick	I have not and would not
 Prof Long	I have not and would not	 Dr Sznol	I have
 Dr Luke	I have not and would not	 Dr Weber	I have not but would for the right patient

RTP RESEARCH TO PRACTICE

What would you generally recommend as first-line treatment for an asymptomatic, clinically stable younger patient with BRAF-mutant metastatic melanoma?

 Dr Hamid	Nivolumab/ipilimumab	 Dr Pavlick	Nivolumab/ipilimumab
 Prof Long	Nivolumab/ipilimumab	 Dr Sznol	Nivolumab/ipilimumab
 Dr Luke	Nivolumab/ipilimumab	 Dr Weber	Nivolumab/ipilimumab

RTP RESEARCH TO PRACTICE

What would you generally recommend as first-line treatment for a symptomatic younger patient with extensive BRAF-mutant metastatic melanoma?

 Dr Hamid	BRAF/MEK → switch to ipilimumab/nivolumab	 Dr Pavlick	Nivolumab/ipilimumab
 Prof Long	Nivolumab/ipilimumab	 Dr Sznol	Nivolumab/ipilimumab
 Dr Luke	Nivolumab/ipilimumab	 Dr Weber	Encorafenib/ binimetinib x 8 wk, then switch to IO

RTP RESEARCH TO PRACTICE

What would you generally recommend as initial treatment for an asymptomatic younger patient with BRAF-mutant melanoma with systemic metastases and multiple bilateral, small brain metastases that would require whole-brain radiation therapy?

 Dr Hamid	Nivolumab/ipilimumab	 Dr Pavlick	Nivolumab/ipilimumab
 Prof Long	Nivolumab/ipilimumab	 Dr Sznol	Nivolumab/ipilimumab
 Dr Luke	Nivolumab/ipilimumab	 Dr Weber	Nivolumab/ipilimumab

RTP RESEARCH TO PRACTICE

An asymptomatic younger patient with BRAF-mutant melanoma is receiving first-line encorafenib/binimetinib and develops a new solitary brain metastasis with no evidence of disease progression elsewhere. What would you generally recommend?

 Dr Hamid	Switch to nivolumab/ipilimumab	 Dr Pavlick	Continue treatment, manage brain met with local therapy
 Prof Long	Continue treatment, manage brain met with local therapy	 Dr Sznol	Switch to nivolumab/ipilimumab and GKRT for brain mets
 Dr Luke	Continue treatment, manage brain met with local therapy	 Dr Weber	Continue treatment, manage brain met with local therapy

GKRT = Gamma Knife® radiation therapy

For a patient with metastatic BRAF-mutant melanoma to whom you have decided to administer a BRAF/MEK inhibitor combination, in general, do you have a preference as to which one?

 Dr Hamid	Yes, encorafenib/ binimetinib	 Dr Pavlick	Yes, encorafenib/ binimetinib
 Prof Long	Yes, encorafenib/ binimetinib	 Dr Sznol	Encorafenib/ binimetinib
 Dr Luke	Yes, encorafenib/ binimetinib	 Dr Weber	Yes, encorafenib/ binimetinib

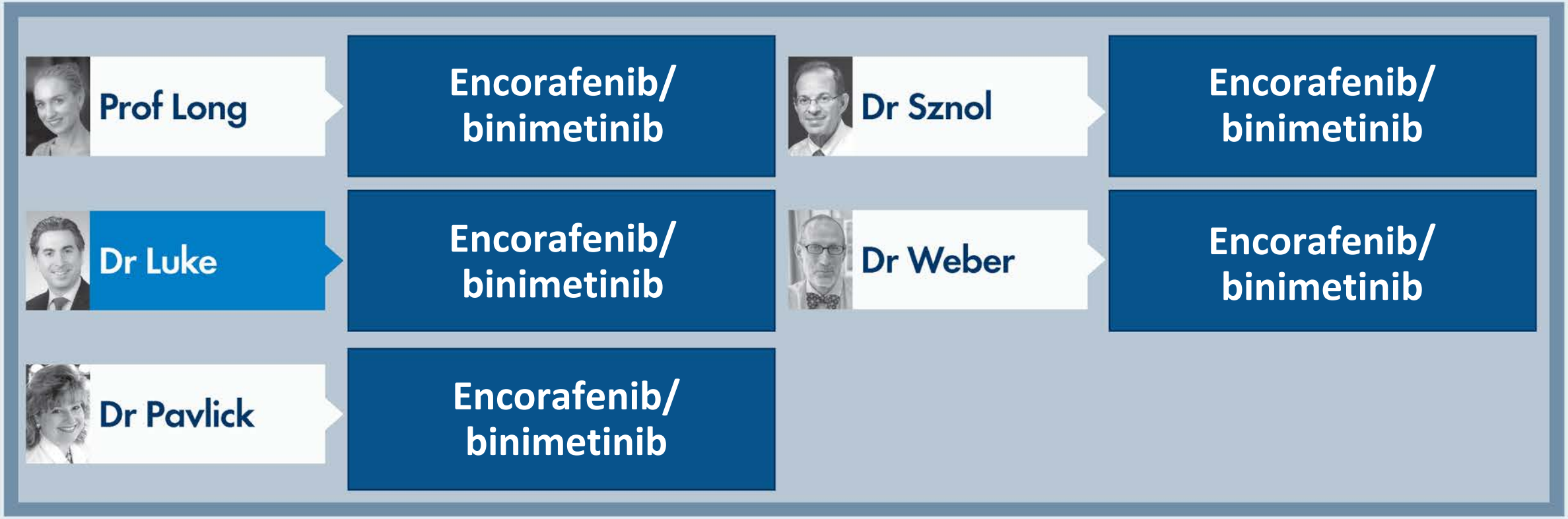
RTP RESEARCH TO PRACTICE

Based on current clinical trial data and your personal experience, how would you compare the rapidity of response observed with BRAF/MEK inhibitor combination therapy to that of anti-PD-1 monotherapy in patients with metastatic melanoma?

 Dr Hamid	BRAF/MEK inhibitor combination yields more rapid responses	 Dr Pavlick	BRAF/MEK inhibitor combination yields more rapid responses
 Prof Long	BRAF/MEK inhibitor combination yields more rapid responses	 Dr Sznol	BRAF/MEK inhibitor combination yields more rapid responses
 Dr Luke	About the same	 Dr Weber	BRAF/MEK inhibitor combination yields more rapid responses

RTP RESEARCH TO PRACTICE

What is your most likely second-line treatment recommendation for a patient with BRAF-mutant metastatic melanoma who experiences mildly symptomatic disease progression on first-line nivolumab/ipilimumab?



What is your most likely treatment recommendation for a patient who undergoes resection of localized BRAF-mutant melanoma and receives an adjuvant anti-PD-1 antibody but presents with highly symptomatic metastatic disease 2 years later?

 Dr Hamid	Vemurafenib/cobimetinib + atezolizumab	 Dr Pavlick	Encorafenib/ binimetinib
 Prof Long	Nivolumab/ipilimumab	 Dr Sznol	Nivolumab/ipilimumab
 Dr Luke	Nivolumab/ipilimumab	 Dr Weber	Encorafenib/ binimetinib

RTP RESEARCH TO PRACTICE

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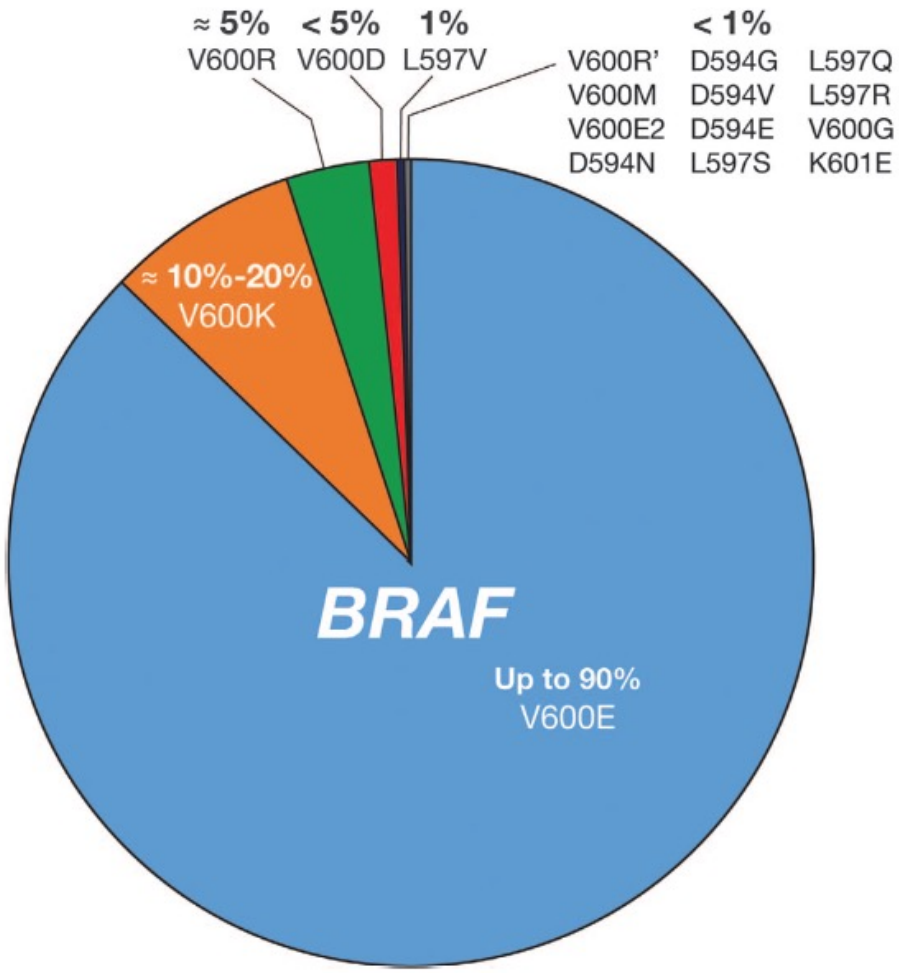
Localized Disease

Incidence and Types of BRAF Mutation in Melanoma



BRAF *mutation*	*Mutation at codon 600 of* BRAF *gene*	*Incidence in* BRAF-*mutant melanoma, %*
Common BRAF *mutations*		
V600E	Valine → glutamic acid	84.6
V600K	Valine → lysine	7.7
Other BRAF *mutations*		
V600R	Valine → arginine	1
V600M	Valine → leucine	0.3
V600D	Valine → aspartic acid	0.1
Non-V600 mutations (eg, K601E, D594N)	—	< 1

Cheng L et al. *Modern Pathology* 2017.

RTP RESEARCH TO PRACTICE

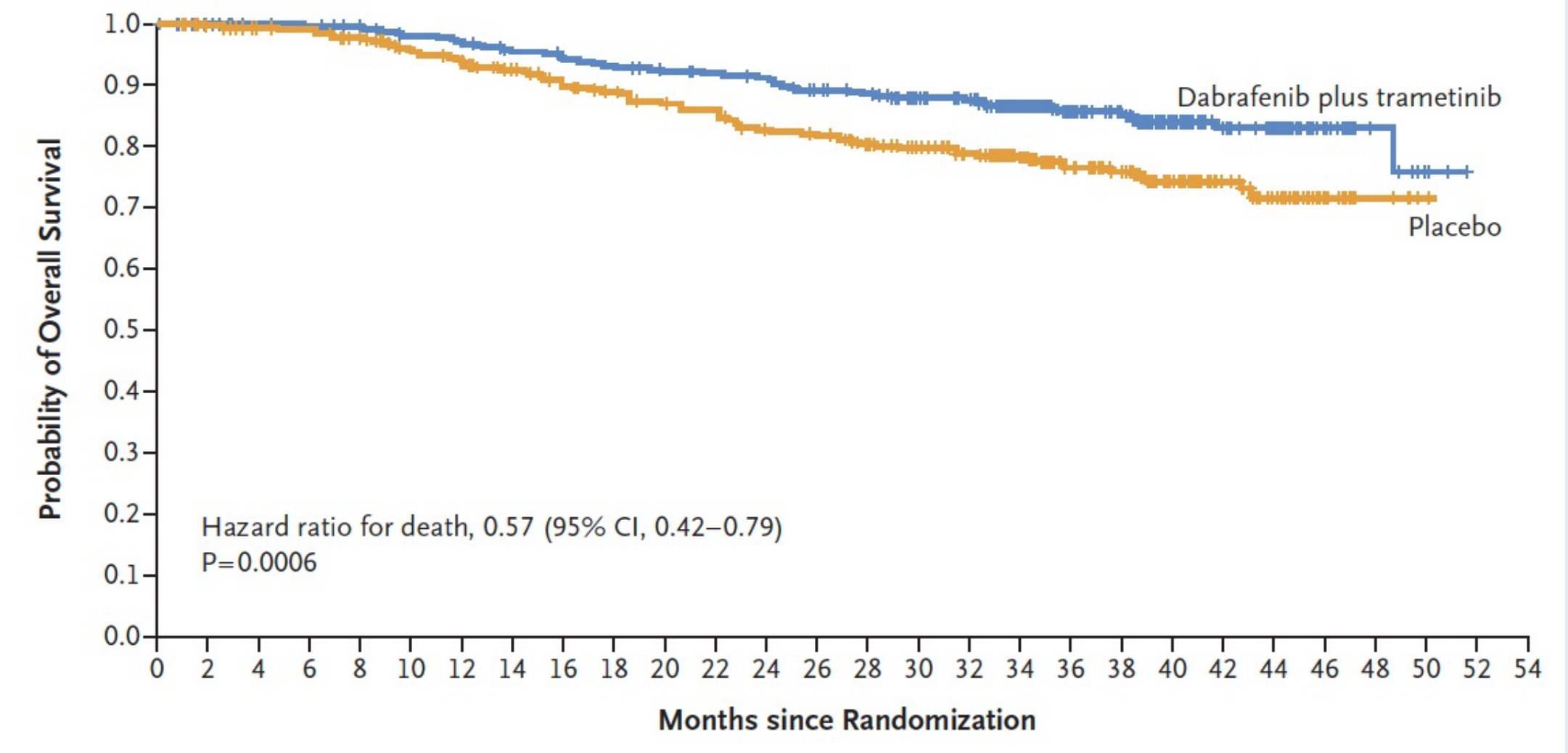
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 9, 2017 VOL. 377 NO. 19

Adjuvant Dabrafenib plus Trametinib in Stage III *BRAF*-Mutated Melanoma

G.V. Long, A. Hauschild, M. Santinami, V. Atkinson, M. Mandalà, V. Chiarion-Sileni, J. Larkin, M. Nyakas, C. Dutriaux, A. Haydon, C. Robert, L. Mortier, J. Schachter, D. Schadendorf, T. Lesimple, R. Plummer, R. Ji, P. Zhang, B. Mookerjee, J. Legos, R. Kefford, R. Dummer, and J.M. Kirkwood

COMBI-AD: Three-Year Overall Survival



Long GV et al. *N Engl J Med* 2017;377(19):1813-23.

COMBI-AD: Tolerability

	Dabrafenib/trametinib (N = 435)	Placebo (N = 432)
Discontinuation due to AE	26%	3%
Dose reduction due to AE	38%	3%
Dose interruption due to AE	66%	15%

AE = adverse event

Long GV et al. *N Engl J Med* 2017;377(19):1813-23.

N Engl J Med 2020;383:1139-48

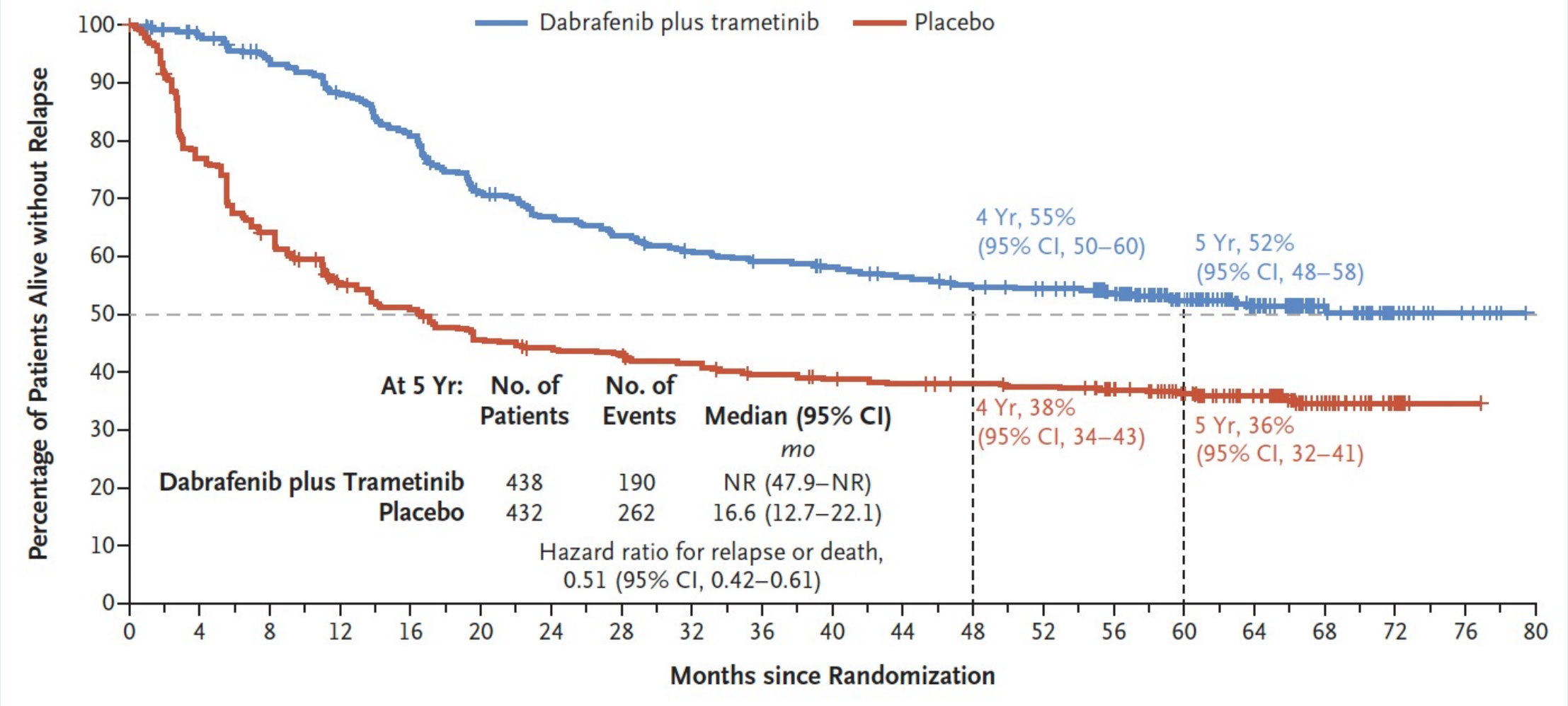
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Five-Year Analysis of Adjuvant Dabrafenib plus Trametinib in Stage III Melanoma

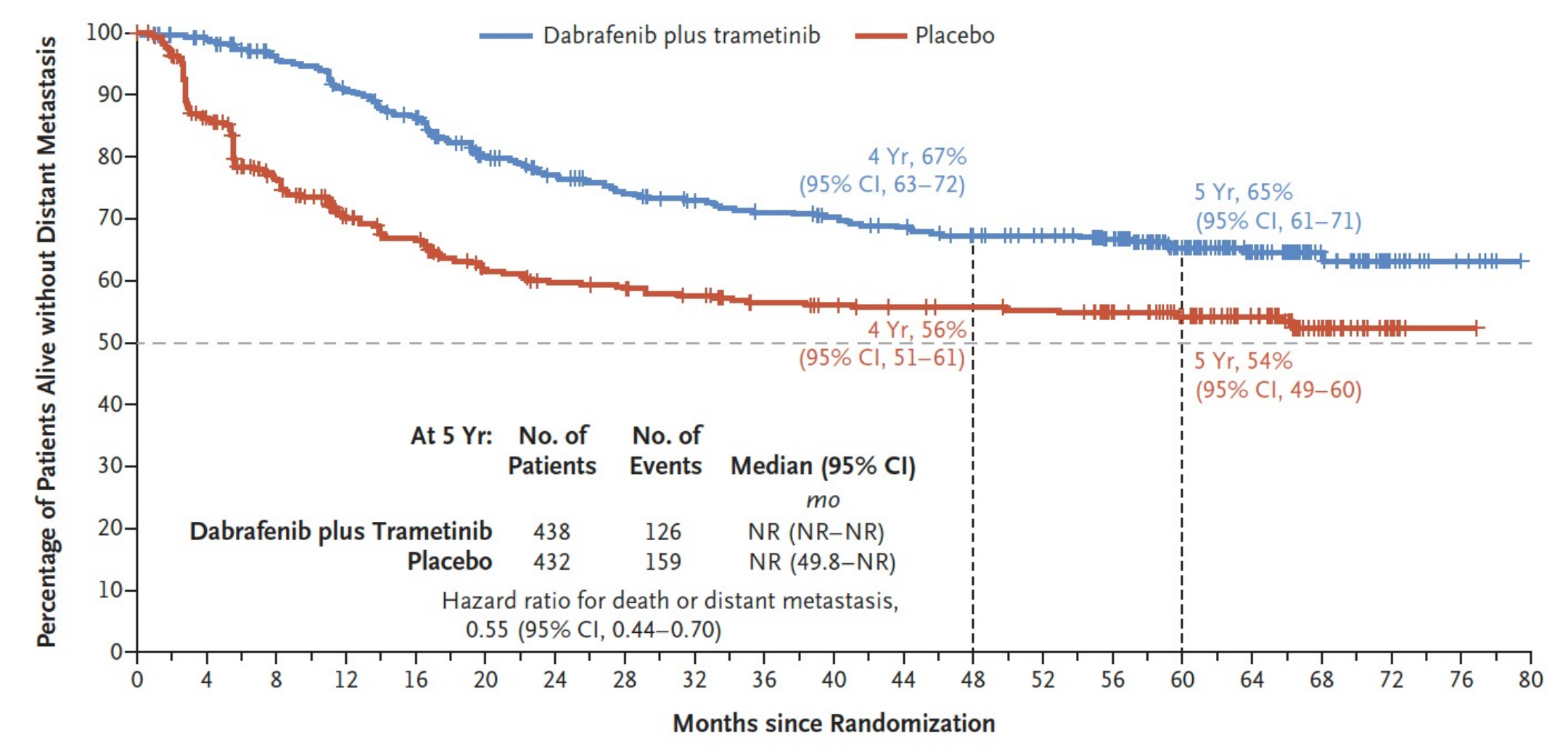
R. Dummer, A. Hauschild, M. Santinami, V. Atkinson, M. Mandalà, J.M. Kirkwood, V. Chiarion Sileni, J. Larkin, M. Nyakas, C. Dutriaux, A. Haydon, C. Robert, L. Mortier, J. Schachter, T. Lesimple, R. Plummer, K. Dasgupta, E. Gasal, M. Tan, G.V. Long, and D. Schadendorf

COMBI-AD: Five-Year Analysis of Relapse-Free Survival



Dummer R et al. *N Engl J Med* 2020;383(12):1139-48.

COMBI-AD: Five-Year Analysis of Survival without Distant Metastases



Dummer R et al. *N Engl J Med* 2020;383(12):1139-48.

FDA-Approved Adjuvant Immunotherapy Options for Melanoma

Monotherapy	FDA approval	Pivotal study	BRAF status	HR (RFS)			Treatment discontinuation
				ITT	BRAF wt	BRAF mutant	
Pembrolizumab	2/14/19	KEYNOTE-054	All comers	0.59	0.61	0.59	14%
Nivolumab	12/20/17	CheckMate 238	All comers	0.71	0.69	0.79	10%
Ipilimumab	10/28/15	EORTC-18071	All comers	0.75	NR	NR	53%

RFS = relapse-free survival; NR = not reported

Eggermont AMM et al. *N Engl J Med* 2018; *Eur J Cancer* 2019;. *N Engl J Med* 2021; Ascierto PA et al. *Lancet Oncol* 2020; Bai X et al. *Br J Dermatol* 2021.

Metastatic Disease

FDA-Approved BRAF/MEK Combination Options for First-Line Therapy for Melanoma with a BRAF V600 Mutation

Combination regimen	FDA approval	N	Pivotal study	Median OS	HR (OS)
Encorafenib + binimetinib vs vemurafenib	6/27/2018	276	COLUMBUS[1]	34.7 vs 21.4 mo	0.64
Dabrafenib + trametinib	11/20/2015	211 352	COMBI-d[2] COMBI-v[2]	4-y OS: 37% 5-y OS: 34%	NR
Cobimetinib + vemurafenib vs vemurafenib	11/10/2015	495	coBRIM[3]	22.5 vs 17.4 mo 5-y OS: 31% vs 26%	0.80

OS = overall survival

[1] Dummer R et al. ASCO 2021;Abstract 9507. [2] Robert C et al. *N Engl J Med* 2019;381(7):626-36. [3] Ascierto PA et al. *Clin Cancer Res* 2021; [Online ahead of print].

RTP RESEARCH TO PRACTICE

Select Any-Grade Adverse Events with BRAFi/MEKi Doublet Regimens

	COMBI-V Dabrafenib/trametinib (N = 350)	CoBRIM Vemurafenib/cobimetinib (N = 209)	COLUMBUS Encorafenib/binimetinib (N = 192)
AE leading to discontinuation	16%	15%	13%
Rash	24%	41%	14%
Photosensitivity reactions	4%	34%	4%
Cutaneous SCC	1%	4%	3%
Basal cell carcinoma	1%	6%	2%
Diarrhea	34%	61%	36%
Pyrexia	55%	29%	18%
ALT/AST increase	26%	51%	19%
Blood CPK increase	3%	35%	23%
Cardiovascular*	39%	32%	17%
Ocular events	6%	24%	19%

*QT interval prolongation, ejection fraction decrease, hypertension

Heinzerling L et al. *ESMO Open* 2019;4:e000491.

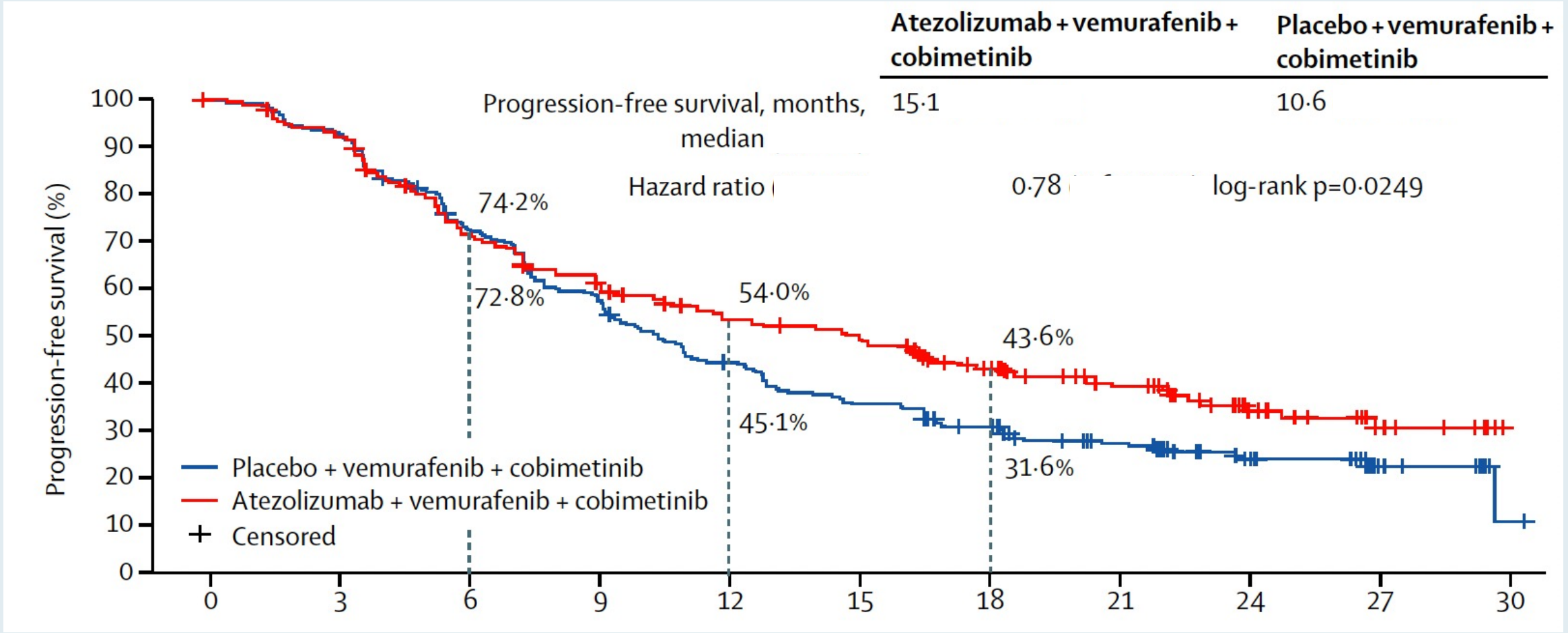
RTP RESEARCH TO PRACTICE

Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced *BRAF*^{V600} mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial

Ralf Gutzmer, Daniil Stroyakovskiy, Helen Gogas, Caroline Robert, Karl Lewis, Svetlana Protsenko, Rodrigo P Pereira, Thomas Eigentler, Piotr Rutkowski, Lev Demidov, Georgy Moiseevich Manikhas, Yibing Yan, Kuan-Chieh Huang, Anne Uyei, Virginia McNally, Grant A McArthur, Paolo A Ascierto**

***Lancet* 2020;395:1835-44**

IMspire 150: Investigator-Assessed PFS (ITT)



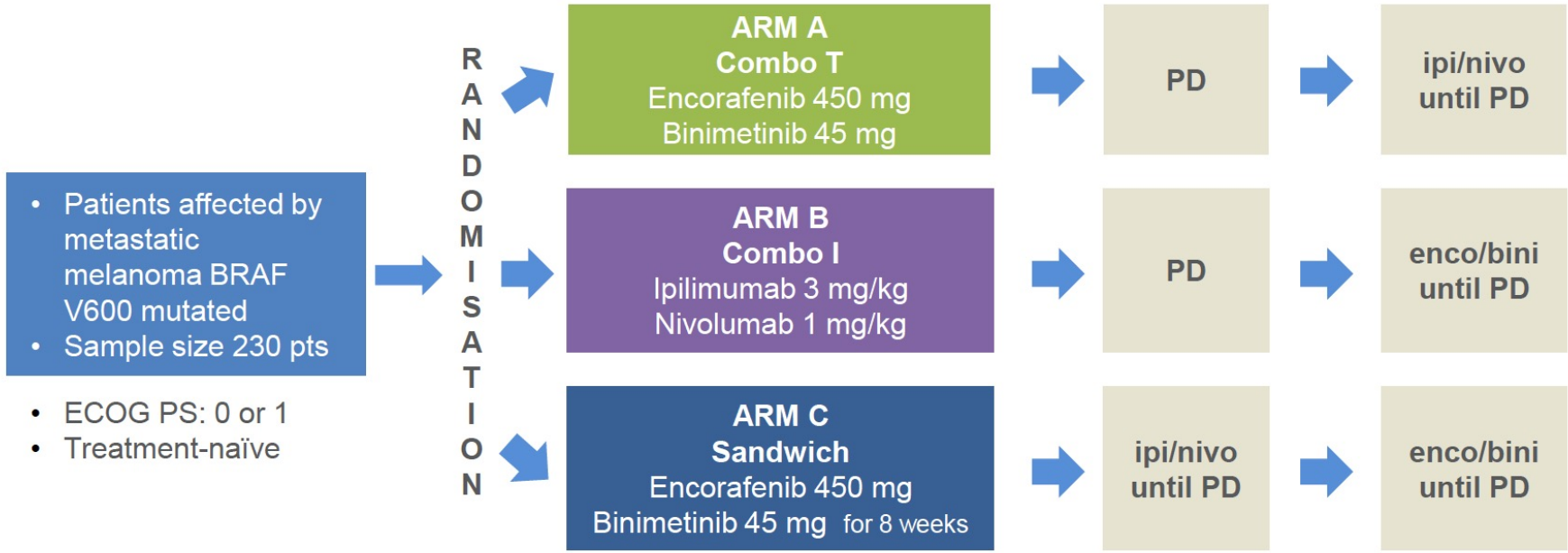
Gutzmer R et al. *Lancet* 2020;395:1835-44.

IMspire150: Selected Adverse Events

Adverse events (AEs)	Atezolizumab/ vemurafenib/ cobimetinib (n = 230)	Placebo/ vemurafenib/ cobimetinib (n = 281)
Grade 3 or 4 AEs	79%	73%
Increased blood creatine phosphokinase	20%	15%
Increased aminotransferase	8%	4%
Increased amylase	10%	7%
Increased aspartate aminotransferase	8%	4%
Immune-related AEs requiring steroids	63%	51%
Discontinuation of treatment due to AEs	13%	16%

Gutzmer R et al. *Lancet* 2020;395:1835-44.

SECOMBIT Phase II Study Design



Primary endpoint:
- OS

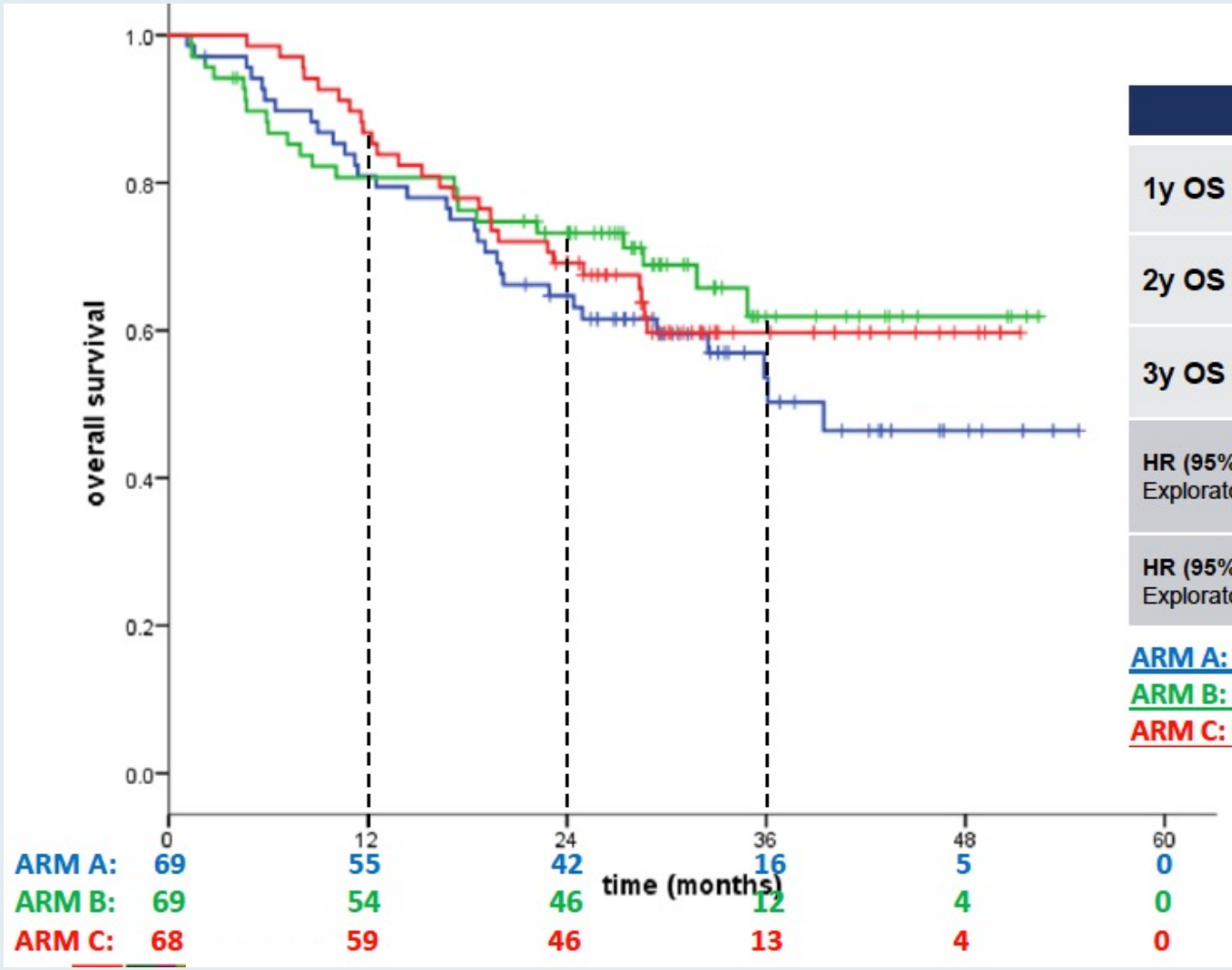
Secondary endpoints:
- PFS
- Total PFS
- Time to second progression
- % patients alive at 2–3 years
- Best ORR
- DOR

Stratification Factors:
- IIIb/c – M1a – M1b
- M1c with LDH ≤ 2ULN
- M1c with elevated LDH > 2 ULN

Current analysis: First patient randomized November 2016. Database lock 31st May 2021: 24- and 36-months PFS rate, total PFS at 24- and 36 months, OS at 24- and 36 months, Safety report. Duration of follow-up: the median follow-up estimated with the reverse Kaplan-Meier method is **32.2 months** (IQR= 27.9-41.6).

Ascierto PA et al. ESMO 2021;Abstract LBA1997.

SECOMBIT: Overall Survival



	Arm A	Arm B	Arm C
1y OS (95% CI)	**81%** (72-90)	**81%** (72-90)	**87%** (69-95)
2y OS (95% CI)	**65%** (54-76)	**73%** (62-84)	**69%** (58-80)
3y OS (95% CI)	**54%** (41-67)	**62%** (48-76)	**60%** (58-72)
HR (95% CI) Arm B vs A Exploratory analysis	**0.73** (0.42-1.26)	-	-
HR (95% CI) Arm C vs A Exploratory analysis	**0.81** (0.48-1.37)	-	-

ARM A: Enco/Bini PD → Ipi/Nivo
ARM B: Ipi/Nivo PD → Enco/Bini
ARM C: Enco/Bini (8 weeks) → Ipi/Nivo PD → Enco/Bini

Ascierto PA et al. ESMO 2021;Abstract LBA1997.

SECOMBIT: Safety Overview

	ARM A (n = 69)		ARM B (n = 69)		ARM C (n = 68)	
Patients reporting event	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Any Adverse Event n, (%)	65 (94)	41 (59)	68 (99)	51 (74)	59 (87)	35 (51)
Treatment-related AE*, n, (%)	**60 (87)**	**27 (39)**	**63 (91)**	**41 (59)**	**57 (84)**	**26 (38)**
Treatment-related AE* leading to discontinuation, n, (%)	**7 (10)**		**7 (10)**		**6 (9)**	

* Certain, Probable, Possible relation only

- No new safety signals were observed as compared to the established safety profile of IPI+NIVO and ENCO+BINI respectively.
- No Treatment-related deaths

Ascierto PA et al. ESMO 2021;Abstract LBA1997.

SECOMBIT: Adverse Events

	ARM A (69 pts)		ARM B (69 pts)		ARM C (68 pts)	
	Any Grade	G3-G4	Any Grade	G3-G4	Any Grade	G3-G4
Fatigue/Asthenia n, (%)	30 (43)	1 (1)	21 (30)	4 (6)	20 (29)	2 (3)
CPK increase n, (%)	26 (38)	6 (9)	7 (10)	1 (1)	8 (12)	0
Diarrhoea n, (%)	22 (32)	3 (4)	28 (41)	4 (6)	20 (29)	4 (6)
Fever n, (%)	13 (19)	0	14 (20)	0	9 (13)	2 (3)
Nausea n, (%)	21 (30)	1 (1)	7 (10)	1 (1)	10 (15)	0
Pruritus n, (%)	6 (9)	0	19 (27)	0	17 (25)	0
Rash n, (%)	8 (11)	1 (1)	16 (23)	2 (3)	19 (28)	1 (1)
Hypothyroidism, n (%)	8 (11)	0	18 (26)	0	9 (13)	0
Transaminases increase n, (%)	21 (30)	3 (4)	12 (17)	10 (14)	16 (23)	5 (7)
Hyperthyroidism, n (%)	5 (7)	0	14 (20)	2 (3)	7 (10)	0
Myalgia/Arthralgia n, (%)	11 (16)	0	9 (13)	2 (3)	6 (9)	1 (1)
Blurred vision n, (%)	13 (19)	0	7 (10)	1 (1)	5 (7)	0
Lipase increase n, (%)	8 (11)	2 (3)	14 (20)	5 (7)	9 (13)	8 (12)

Ascierto PA et al. ESMO 2021;Abstract LBA1997.

FDA-Approved First-Line Immunotherapy-Based Therapies for Melanoma

	FDA approval	Pivotal studies	BRAF status for study entry	HR (PFS)		
				ITT	BRAF wt	BRAF mutant
Pembrolizumab	9/4/14 12/18/15	KEYNOTE-001 KEYNOTE-006	All comers	0.58	0.57	0.44*
Nivolumab	9/4/14 12/20/17	CheckMate 037 CheckMate 067	All comers	0.53	0.47	0.71
Nivolumab + ipilimumab	9/30/15 1/23/16	CheckMate 067	All comers	0.42	0.41	0.44
Atezolizumab + cobimetinib and vemurafenib	7/30/20	IMspire150	BRAF V600 mutation	0.78	N/A	0.78

* No prior BRAF inhibitor; pembro q3wk

Robert C et al. *N Engl J Med* 2015; Larkin J et al. *N Engl J Med* 2015; Wolchok JD et al. ASCO 2021;Abstract 9506; Gutzmer R et al. *Lancet* 2020.

Meet The Professor

Optimizing the Management of Metastatic Castration-Resistant Prostate Cancer

Tuesday, November 30, 2021
5:00 PM – 6:00 PM ET

Faculty

A Oliver Sartor, MD

Moderator

Neil Love, MD

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Thank you for joining us!

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

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