Meet The Professor
Management of BRAF-Mutant Melanoma

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Co-Medical Director
Professor of Medical Oncology and Translational Research
Melanoma Institute Australia
Wollstonecraft, Australia

Commercial Support

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

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Dr Love — Disclosures

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Prof Long — Disclosures

Consultant Advisor	Aduro Biotech, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Evaxion Biotech A/S, Hexal AG, Highlight Therapeutics SL, Merck Sharp & Dohme Corp, Novartis, OncoSec Medical, Pierre Fabre, QBiotics, Regeneron Pharmaceuticals Inc, SkylineDx, Specialised Therapeutics

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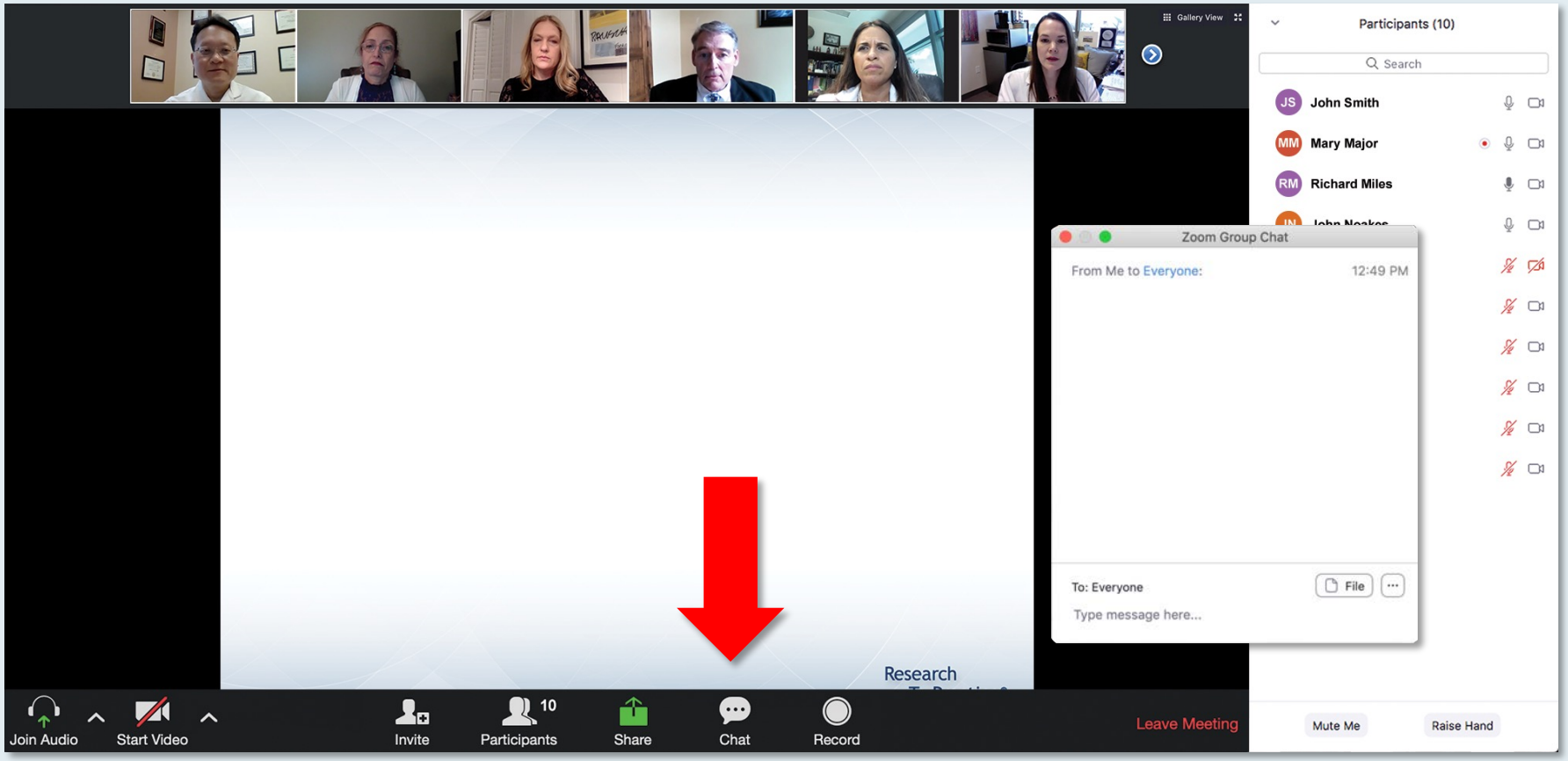

Feel free to submit questions now before the program begins and throughout the program.

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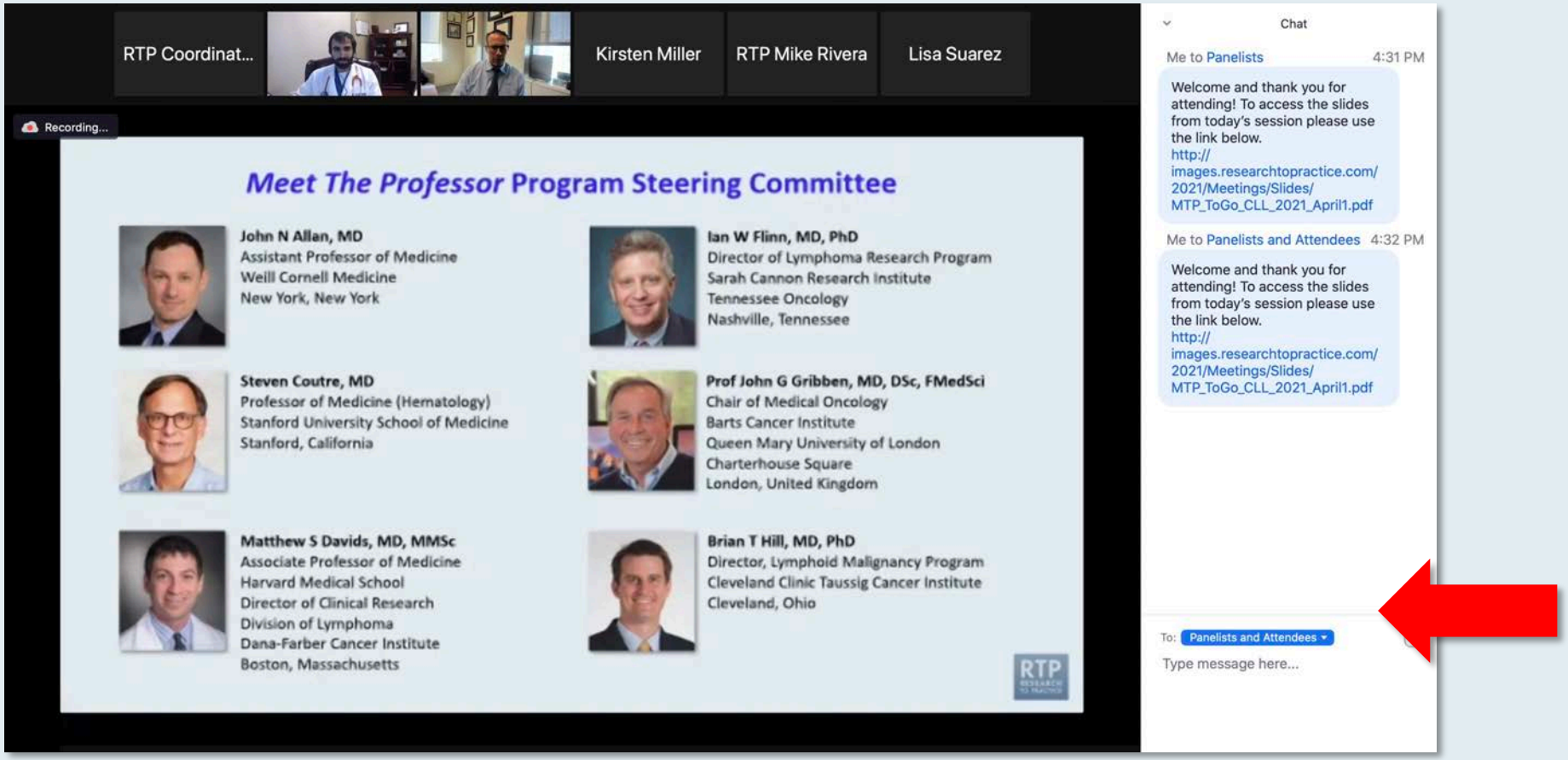
Expand chat submission box



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

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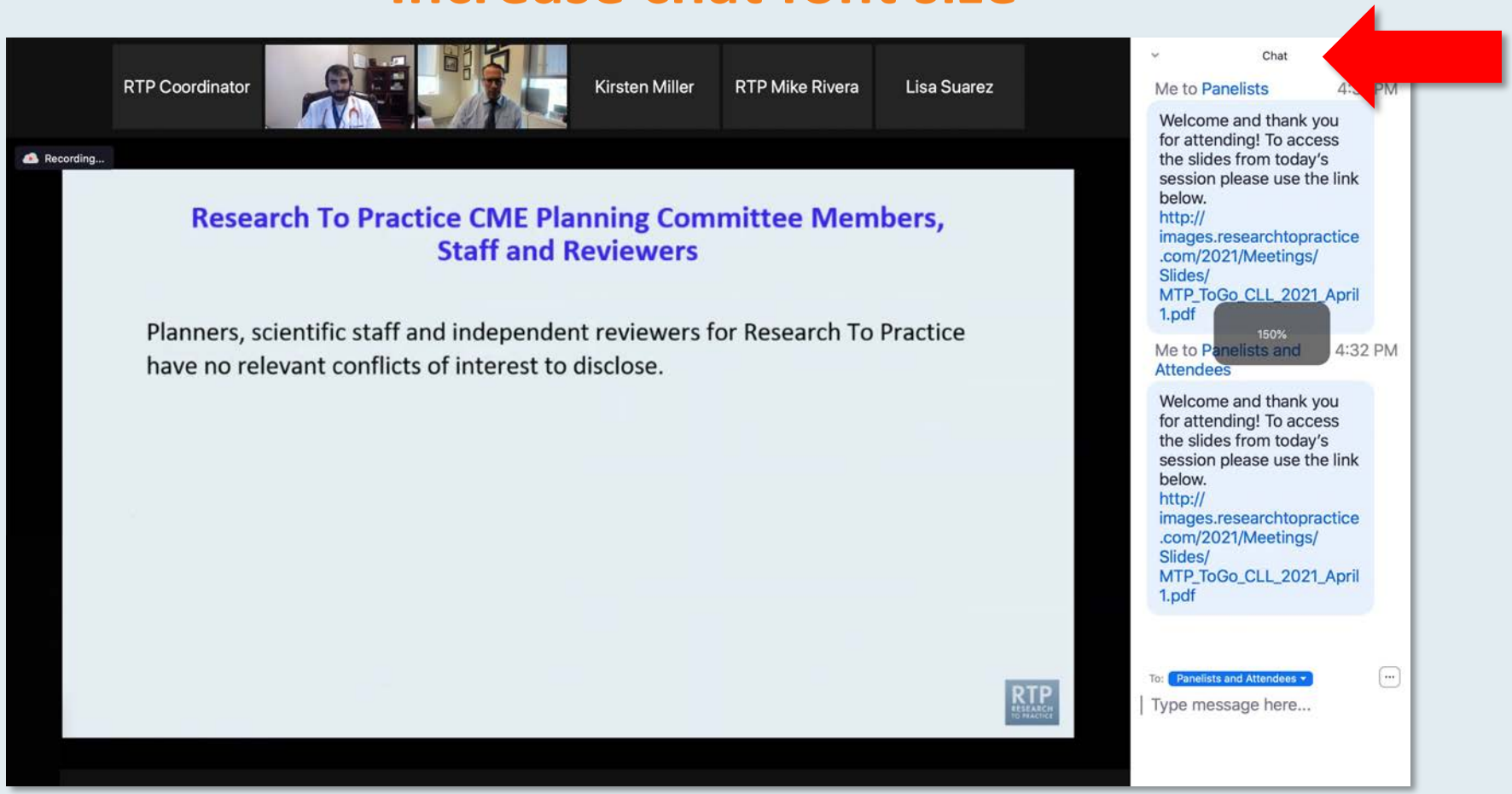
Increase chat font size



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

ONCOLOGY TODAY

WITH DR NEIL LOVE

Management of HER2-Low Breast Cancer

DR IAN KROP

DANA-FARBER CANCER INSTITUTE

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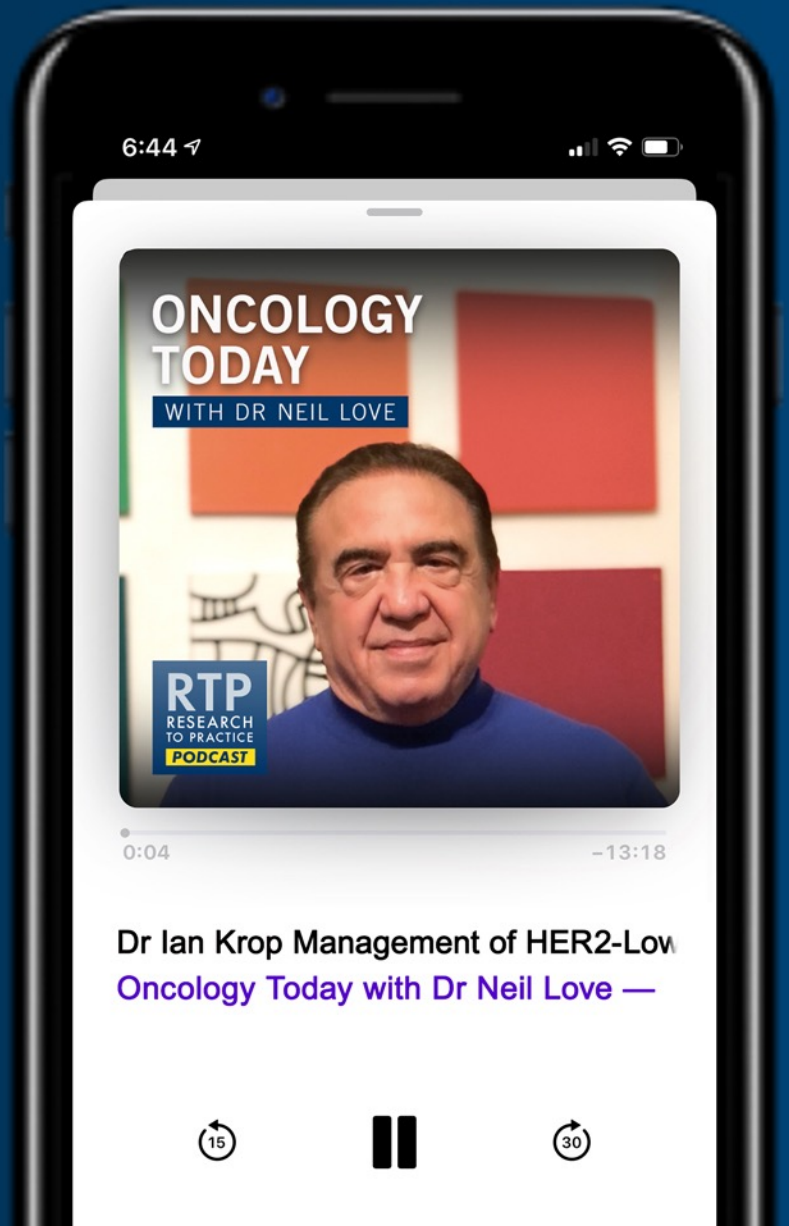
Listen on Google Podcasts



Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with Urothelial Bladder Carcinoma

Tuesday, November 2, 2021
5:00 PM – 6:00 PM ET

Faculty

Andrea Apolo, MD

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

Wednesday, November 3, 2021
5:00 PM – 6:00 PM ET

Faculty

Adam M Brufsky, MD, PhD

Moderator

Neil Love, MD

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

A CME/MOC-Accredited Virtual Event

Thursday, November 4, 2021
5:00 PM – 6:00 PM ET

Faculty

Anne Chiang, MD, PhD
David R Spigel, MD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Management of Acute Myeloid Leukemia

Monday, November 8, 2021
5:00 PM – 6:00 PM ET

Faculty
Keith W Pratz, MD

Moderator
Neil Love, MD

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Meet The Professor

Optimizing the Management of Metastatic Castration-Resistant Prostate Cancer

Tuesday, November 9, 2021
5:00 PM – 6:00 PM ET

Faculty

Simon Chowdhury, MD, PhD

Moderator

Neil Love, MD

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VIRTUAL MOLECULAR TUMOR BOARD
Optimizing Biomarker-Based Decision-Making for Patients with Non-Small Cell Lung Cancer with EGFR Mutations or with Other Oncogene-Addicted Lung Cancers

A 2-Part CME/MOC-Accredited Webinar Series

Thursday, November 11, 2021
5:00 PM – 6:00 PM ET

Faculty

Marc Ladanyi, MD
Andrew J McKenzie, PhD
Helena Yu, MD

Moderator

Neil Love, MD

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RESEARCH TO PRACTICE

Meet The Professor

Optimizing the Clinical Management of Hodgkin and Non-Hodgkin Lymphomas

Monday, November 15, 2021
5:00 PM – 6:00 PM ET

Faculty

Christopher R Flowers, MD, MS

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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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Melanoma Institute Australia
Wollstonecraft, Australia

Meet The Professor Program Participating Faculty

Prof Georgina Long, AO, BSc, PhD, MBBS
Co-Medical Director
Professor of Medical Oncology and
Translational Research
Melanoma Institute Australia
Wollstonecraft, Australia

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

Mario Sznol, MD
Professor, Internal Medicine
Leader, Melanoma Program
Co-Leader, Cancer Immunology Program
Yale Cancer Center
New Haven, Connecticut

Jeffrey S Weber, MD, PhD
Deputy Director
Laura and Isaac Perlmutter Cancer Center
(NCI-Funded Comprehensive Cancer Center)
Professor of Medicine
NYU Grossman School of Medicine
New York, New York

Moderator
Neil Love, MD
Research To Practice
Miami, Florida

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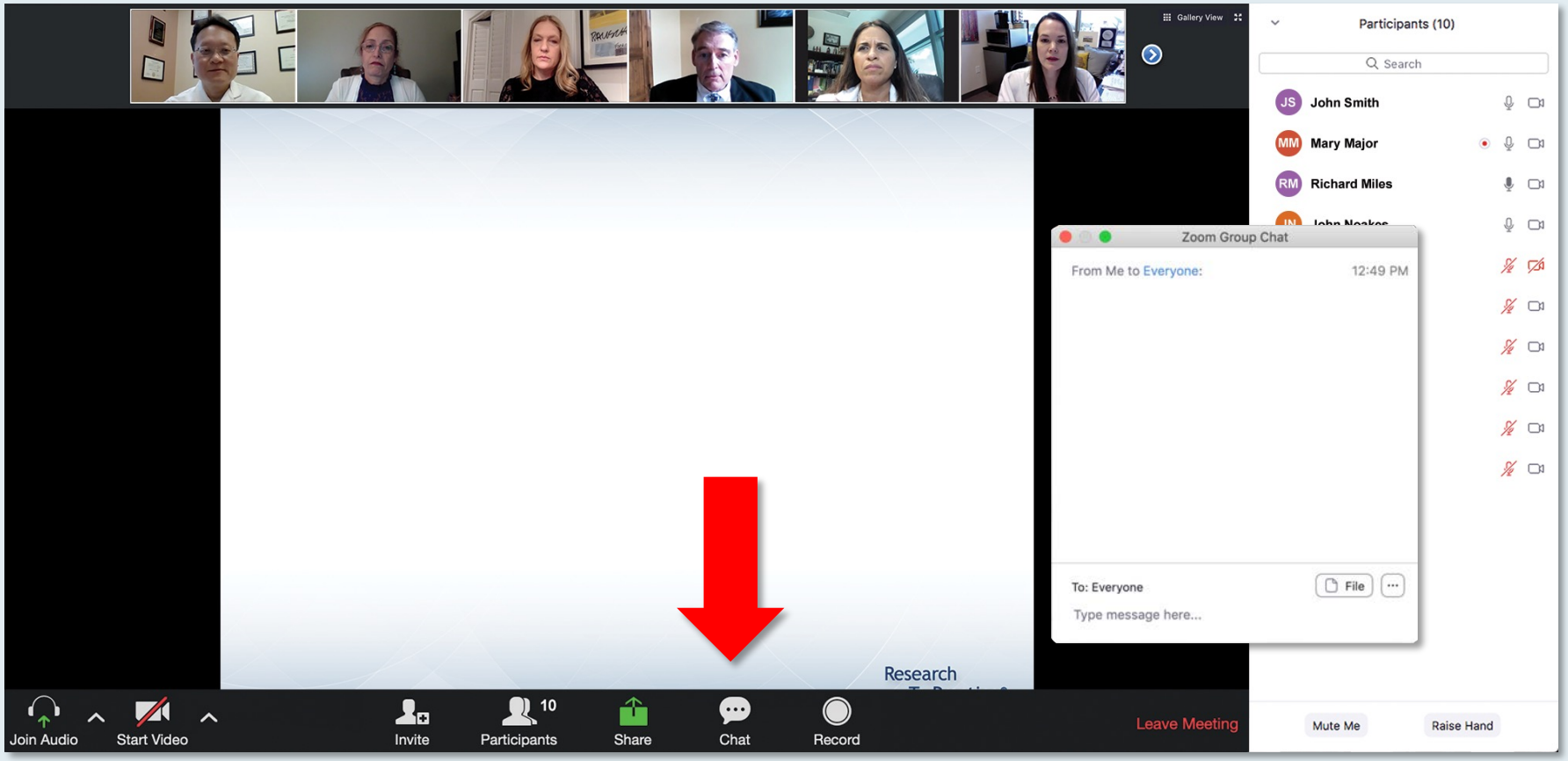

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Mamta Choksi, MD
Florida Cancer Specialists and Research Institute
New Port Richey, Florida

Allan Freedman, MD
Physician with Suburban Hematology-Oncology Associates
Snellville, Georgia

Elizabeth Guancial, MD
Florida Cancer Specialists and Research Institute
Clinical Associate Professor at FSU College of Medicine
Sarasota, Florida

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

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Meet The Professor with Prof Long

Introduction

MODULE 1: Making Progress Against Melanoma — A Historical Perspective

MODULE 2: Management of BRAF Inhibitor-Related Pyrexia

MODULE 3: Cases

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- Dr Choksi: An 84-year-old woman with metastatic melanoma
- Dr Lipson: A 48-year-old man with a large, resectable BRAF-mutant melanoma
- Dr Freedman: A 57-year-old man with metastatic melanoma with a BRAF V600E mutation

MODULE 4: Journal Club

MODULE 5: Beyond the Guidelines

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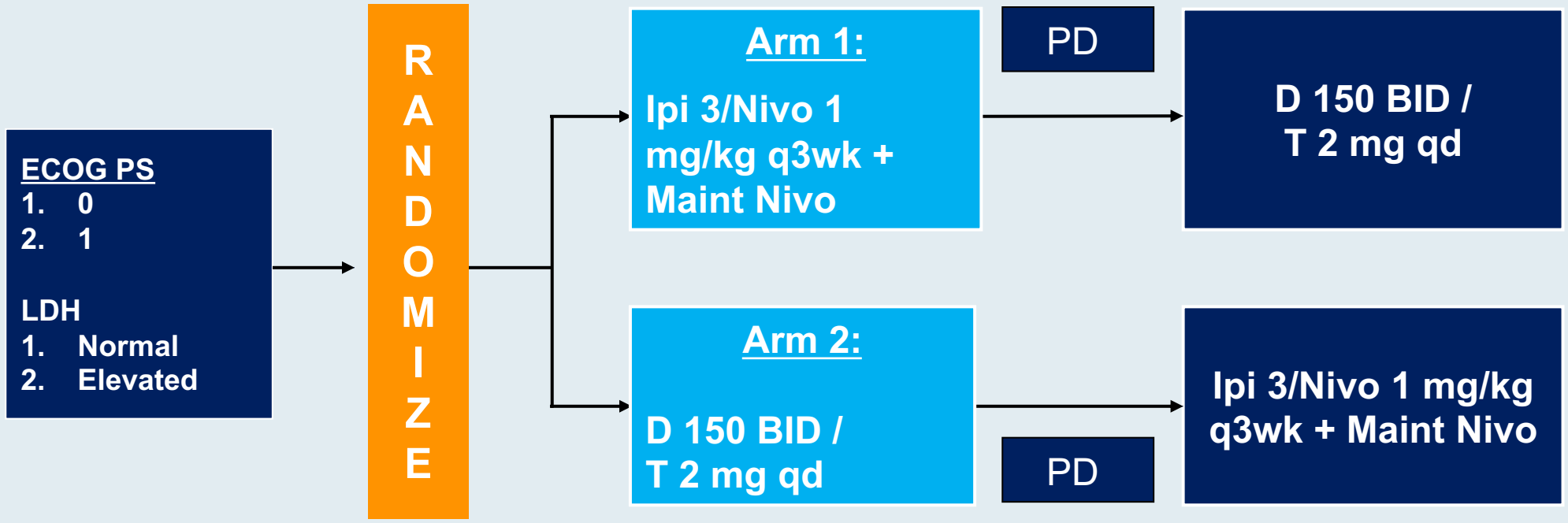
DREAMseq (ECOG-EA6134) Phase III Trial Schema



D = dabrafenib; T = trametinib

www.clinicaltrials.gov. NCT02224781. Accessed October 2021.

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2021 ASCO ANNUAL MEETING

MAKING PROGRESS AGAINST MELANOMA: HISTORICAL PERSPECTIVE

Georgina V Long

Melanoma Institute Australia

The University of Sydney

Royal North Shore & Mater Hospitals

June 2021

THE UNIVERSITY OF SYDNEY

Melanoma Institute Australia

Long G. ASCO 2021 Education Session.

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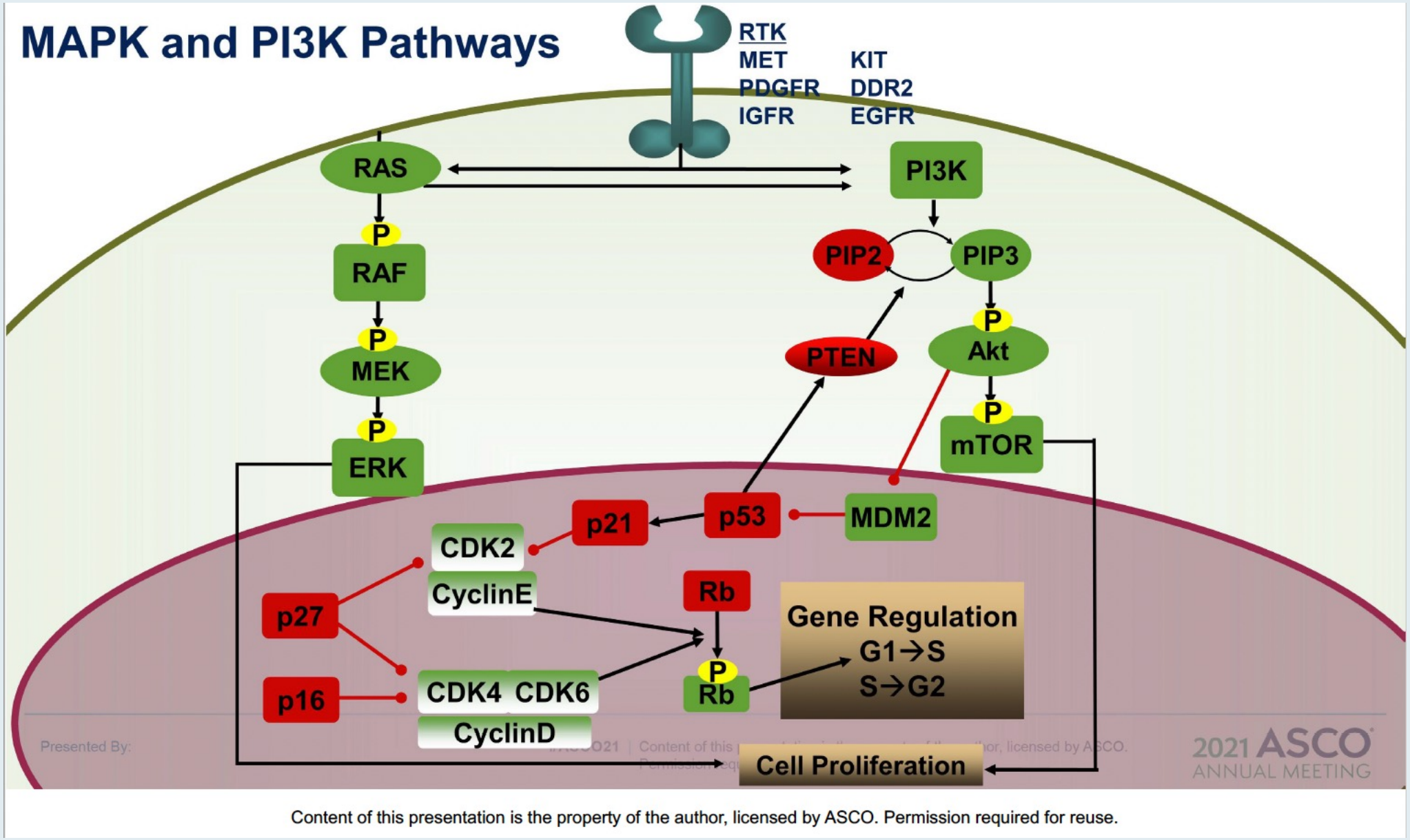
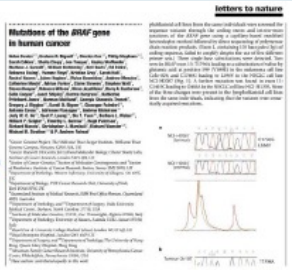
Long G. ASCO 2021 Education Session.

Long G. ASCO 2021 Education Session.



Long G. ASCO 2021 Education Session.

MAPK Pathway in Cancer



1839 Schleiden & Schwann
Birth of Modern Biology
Modern Cell Theory

1970 SRC Identified
First Oncogene identified

1980s ERK1/2 exist
'Extracellular signal regulated kinases' a.k.a MAPK3/1

1982 RAS
Mutated in Cancer

1983 RAF
Identified

1990 BRAF
Coding seq identified

2002 Davies H et al Nature
BRAF mutated in melanoma

2010 Dabrafenib + Trametinib
Ph 1 starts

2011 CRISPR
Genome editing tool
Doudna & Charpentier

1600-1800s | 1900s | 2000s

1665 Hooke
Conceptualised Cells in plants using microscope

1858 Virchow
Cells come from pre-existing cells

1951 HeLa Cell Line Est.
Break through for cell biology research

1971 Knudson
Two hit hypothesis & Tumour Suppressor Genes

1975 Western Blot

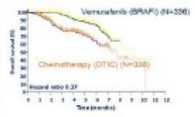
1980s-1990s
Identified the components of MAPK pathway

1983 Mullis
PCR invented

1990&1991 ERKs cloned
Boulton + others

2000-2010 Sorafenib Trials
2000 Ph 1 starts
2005 Ph 3 starts carbo+pacl+/- sorafenib recruited - negative

2006 PLX4032/ vemurafenib
Ph 1 starts



2020 MAPK
Ongoing targeting RAS, ERK & other MAPK components

Presented By: **Georgina V Long** @ProfGLongMIA

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2021 ASCO ANNUAL MEETING

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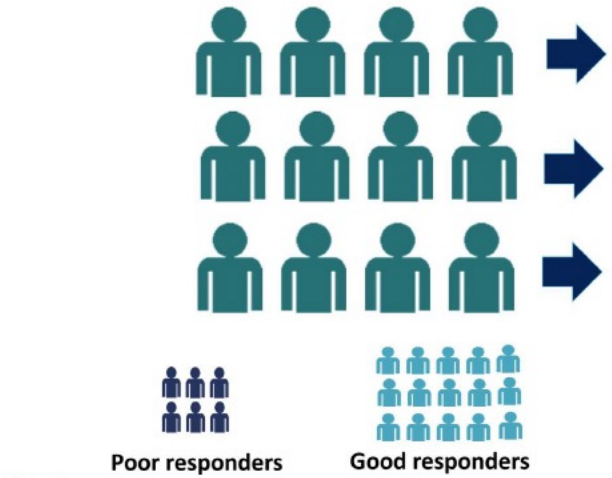
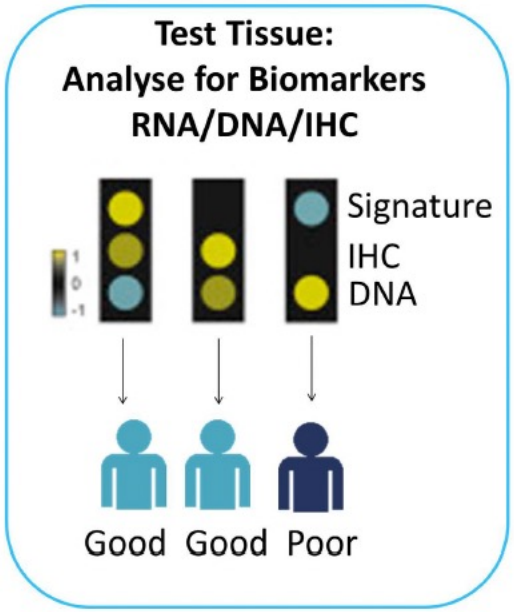
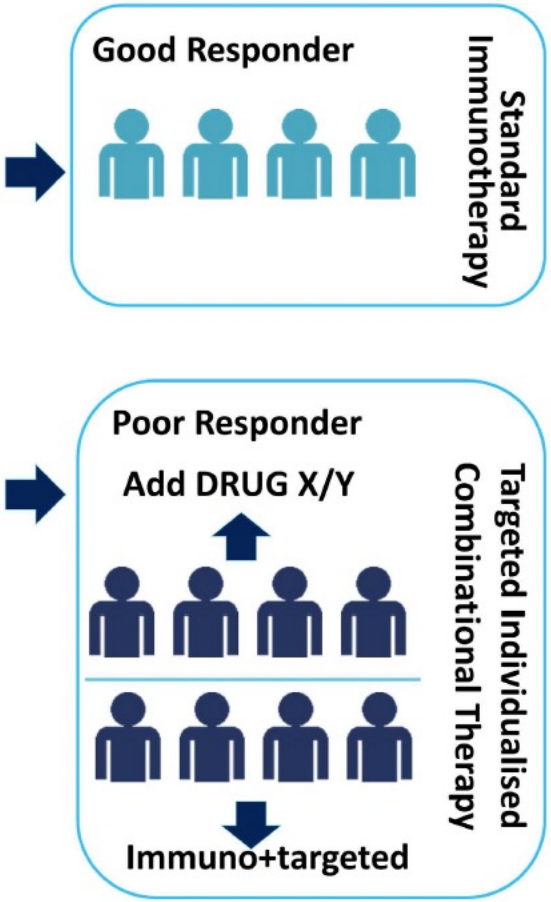
Match the Therapy to the Individual







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European Journal of Cancer 153 (2021) 234–241

Available online at www.sciencedirect.com

ScienceDirect

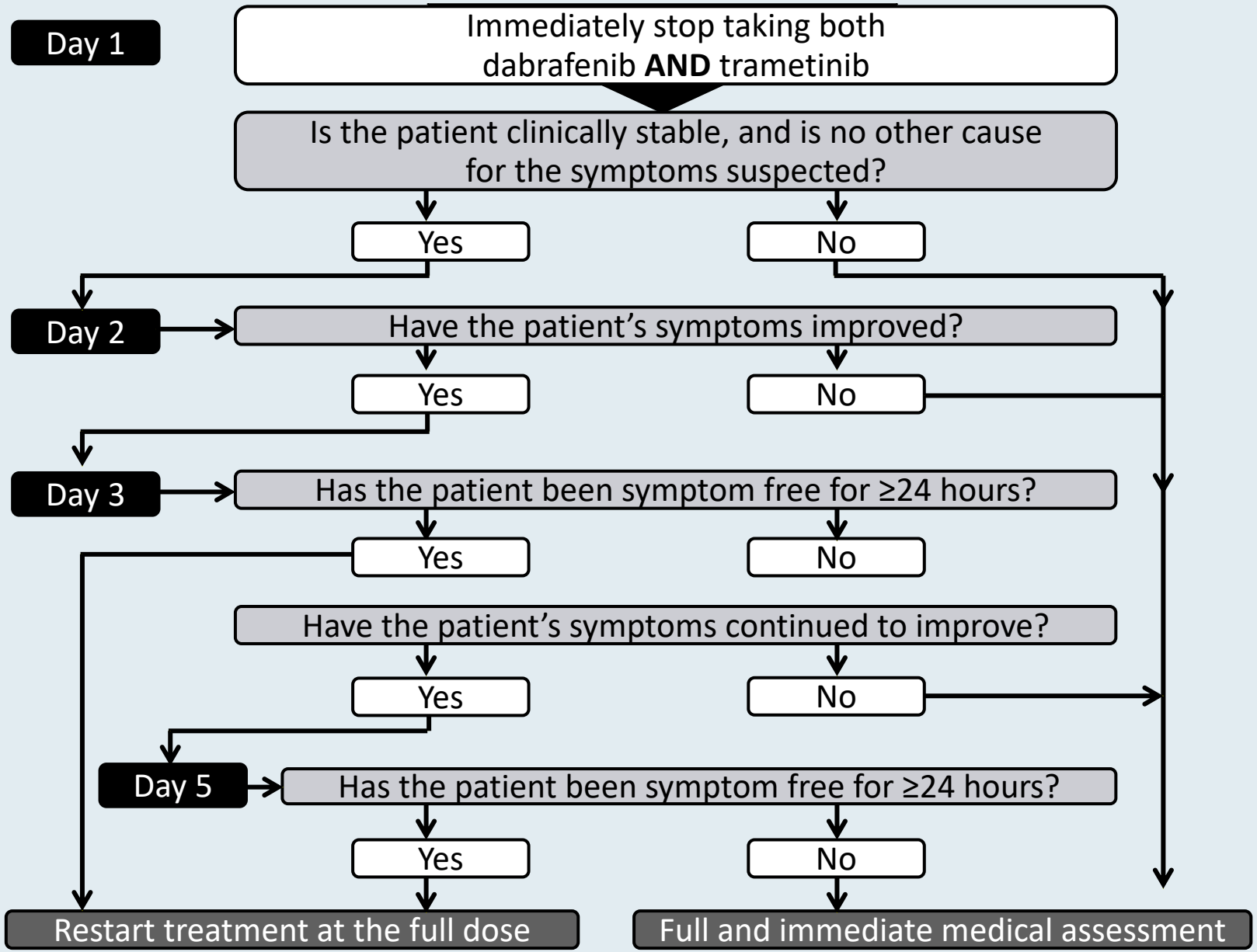
journal homepage: www.ejcancer.com

Original Research

Pyrexia in patients treated with dabrafenib plus trametinib across clinical trials in *BRAF*-mutant cancers

Dirk Schadendorf [a,b,*], Caroline Robert [c,d], Reinhard Dummer [e], Keith T. Flaherty [f], Hussein A. Tawbi [g], Alexander M. Menzies [h], Hiya Banerjee [i], Mike Lau [j], Georgina V. Long [h]

Modified Pyrexia Syndrome Management Algorithm



Schadendorf D et al. *Eur J Cancer* 2021;153:234-41.

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Pyrexia-Related Outcomes Upon Application of an Adapted Pyrexia Management Algorithm in Patients (pts) with BRAF V600: Mutant Unresectable or Metastatic Melanoma Treated with Dabrafenib plus Trametinib (DabTram) in the COMBI-i Trial

Ascierto PA et al.

ASCO 2021;Abstract 9560.

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Case Presentation – Dr Guancial: A 79-year-old man with melanoma and a history of transient ischemic attacks

Dr Elizabeth Guancial

- PMH: TIA, atrial fibrillation controlled with medication
- Presented with palpable mass in right groin and skin lesion on right lower extremity
- Diagnosed with Stage IIIC melanoma with a BRAF V600E mutation post resection; bilateral sentinel lymph node biopsy
- Adjuvant nivolumab x 6 → residual right groin palpable adenopathy
- Biopsy of of right groin node confirms melanoma

Question

- How do you choose between adjuvant immunotherapy and targeted therapy for patients such as this man?

Case Presentation – Dr Guancial: A 79-year-old man with melanoma and a history of transient ischemic attacks (continued)

Dr Elizabeth Guancial

- 9/2020: Stage IIIC melanoma with a BRAF V600E mutation post resection; bilateral sentinel lymph node biopsy
- Adjuvant nivolumab x 6 with right groin palpable adenopathy
- ***Patient switched to encorafenib/binimetinib with rapid response***
  - ***Blood work monitored every 2 weeks***
- ***Admitted to hospital: Fatigue, muscle weakness, confusion, kidney failure and symptomatic rhabdomyolysis***
  - ***Brain imaging shows no signs of metastases***
- ***Treatment held, patient still recovering***

Case Presentation – Dr Lipson: A 59-year-old woman with metastatic melanoma and asymptomatic brain metastases

Dr Evan Lipson

- Diagnosed with Stage IV melanoma
- Workup reveals brain metastases
- She is asymptomatic from brain metastases
- Mutation analysis: BRAF V600E-mutation positive

Questions

- How do you think about the management of a patient with brain metastases when you have immunotherapy and targeted agents at your disposal?
- How do you integrate stereotactic radiosurgery or other forms of radiotherapy into the treatment of patients with melanoma and brain metastases?
- In patients with metastatic BRAF V600-mutant melanoma who have brain metastases, if you're going to use targeted agents, how do you choose which combination to use to treat brain metastases?
- In patients who present with widely metastatic melanoma, when is it appropriate to get a brain MRI?

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Case Presentation – Dr Choksi: An 84-year-old woman with metastatic melanoma

Dr Mamta Choksi

- PMH: anemia, chronic kidney disease, uterine carcinoma, and melanoma (15 years ago)
- 1/2020: Presented during routine annual follow-up with a palpable 4.4-cm mass in left axilla
- Workup revealed at least 1 large necrotic mass (~4.9 cm) and several other small left axillary lymph nodes; biopsy confirmed malignant melanoma
- Cellulitis developed in left axilla post-biopsy – entire area was red, erythematous and swollen
- Antibiotics given outpatient – no improvement
- Admitted to hospital for IV antibiotics – very minimal response
- BRAF IHC – positive

Case Presentation – Dr Choksi: An 84-year-old woman with metastatic melanoma (continued)

Dr Mamta Choksi

- PMH: anemia, chronic kidney disease, uterine carcinoma, and melanoma
- Diagnosed with metastatic malignant myeloma
- Cellulitis developed in left axilla post-biopsy – entire area red, erythematous and swollen
- Admitted to hospital for IV antibiotics – very minimal response
- BRAF IHC – positive
- ***Encorafenib/binimetinib → redness and tenderness resolved in 2-3 weeks, residual 3-cm palpable mass***
- ***Presented with jerky facial movements and further workup revealed 5 mm focus in left frontal lobe of brain***
- ***MRI at 3 months demonstrated resolution of brain focus and restaging workup showed significant improvement of her melanoma in terms of the lymphadenopathy in the left axillary region***

Question

- ***What is your experience for how long patients' disease responds to BRAF/MEK-targeted therapy before progression?***

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Counseling patients on the risks of long-term toxicities associated with adjuvant immunotherapy; use of adjuvant encorafenib/binimetinib during the COVID-19 pandemic

Dr Evan Lipson

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Case Presentation – Dr Lipson: A 48-year-old man with a large, resectable BRAF-mutant melanoma

Dr Evan Lipson

- Large, resectable BRAF-mutated melanoma on the upper extremity
- Discussed option of neoadjuvant therapy with either BRAF/MEK inhibitors or with immunotherapy

Question

- How would you approach a patient such as this, and would neoadjuvant targeted therapy or immunotherapy be a better option for him?

Case Presentation – Dr Freedman: A 57-year-old man with metastatic melanoma with a BRAF V600E mutation

Dr Allan Freedman

- 2014: Superficial spreading melanoma, Breslow 1.35, Clark IV, ulceration present, 1 mitosis/mm^2
- Wide excision with no residual disease, 0/5 sentinel nodes; no adjuvant therapy
- 4/2020: Thigh, T2 vertebral body and atrial metastases; BRAF V600E mutation
- MRI brain: Three metastases, none greater than 4-mm
- His wife indicated that patient was having issues with his memory
- Nivolumab/ipilimumab, but treatment held and high-dose steroids initiated for rash, diarrhea, anorexia
- Nivolumab continued, ipilimumab discontinued, with near CR
  - Brain metastases regressed but new lesion in the temporal lobe → Brain RT

Case Presentation – Dr Freedman: A 57-year-old man with metastatic melanoma with a BRAF V600E mutation (continued)

Dr Allan Freedman

- 2014: Superficial spreading melanoma, Breslow 1.35, Clark IV, ulceration present, 1 mitosis/mm^2
- Wide excision with no residual disease, 0/5 sentinel nodes; no adjuvant therapy
- 4/2020: Thigh, T2 vertebral body and atrial metastases; BRAF V600E mutation
- MRI brain: Three metastases
- Nivolumab/ipilimumab, but treatment held and high-dose steroids initiated for rash, diarrhea, anorexia
- Nivolumab continued, ipilimumab discontinued, with near CR
  - Brain metastases regressed but new lesion in the temporal lobe → Brain RT

Questions

- ***Is there a preferred sequence in treating CNS melanoma with regard to radiotherapy or systemic therapy? What is our current state of knowledge regarding the relative efficacy of immunotherapy versus targeted therapy for BRAF-mutated CNS metastases in melanoma?***
- ***If steroids are needed for cerebral edema, how will those affect the activity of immunotherapy?***
- ***What are your thoughts about pharmacologic therapy for immune-mediated colitis? Will that reduce the efficacy of immunotherapy? What about non-absorbable steroids or infliximab?***

Integration of the triplet regimen of atezolizumab/vemurafenib/cobimetinib

Dr Evan Lipson

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Efficacy of COVID-19 vaccinations in patients

Dr Evan Lipson

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Introduction

MODULE 1: Making Progress Against Melanoma — A Historical Perspective

MODULE 2: Management of BRAF Inhibitor-Related Pyrexia

MODULE 3: Cases

- Dr Guancial: A 79-year-old man with melanoma and a history of transient ischemic attacks
- Dr Lipson: A 59-year-old woman with metastatic melanoma and asymptomatic brain metastases
- Dr Choksi: An 84-year-old woman with metastatic melanoma
- Dr Lipson: A 48-year-old man with a large, resectable BRAF-mutant melanoma
- Dr Freedman: A 57-year-old man with metastatic melanoma with a BRAF V600E mutation

MODULE 4: Journal Club

MODULE 5: Beyond the Guidelines

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Journal Club with Prof Long

- Ferrucci PF et al; KEYNOTE-022 International Team. **KEYNOTE-022 part 3: A randomized, double-blind, phase 2 study of pembrolizumab, dabrafenib, and trametinib in BRAF-mutant melanoma.** *J Immunother Cancer* 2020;8(2):e001806.
- Hong AM et al. **Management of melanoma brain metastases: Evidence-based clinical practice guidelines by Cancer Council Australia.** *Eur J Cancer* 2021;142:10-7.
- Tawbi HAH et al. **Treatment outcomes in patients (pts) with melanoma brain metastases (MBM) treated with systemic therapy: A systematic literature review (SLR) and meta-analysis.** ASCO 2021;Abstract 9561.
- Li AT et al. **Survival outcomes of salvage metastasectomy after failure of modern-era systemic therapy for melanoma.** *Ann Surg Oncol* 2021;28(11):6109-23.
- Brase JC et al. **Role of tumor-infiltrating B cells in clinical outcome of patients with melanoma treated with dabrafenib plus trametinib.** *Clin Cancer Res* 2021; 27(16):4500-10.

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Journal Club with Prof Long (Continued)

- Cho KK et al. **Metastatic acral melanoma treatment outcomes: A systematic review and meta-analysis.** *Melanoma Res* 2021;31(5):482-6.
- Rabbie R et al. **The mutational landscape of melanoma brain metastases presenting as the first visceral site of recurrence.** *Br J Cancer* 2021;124(1):156-60.
- Syeda MM et al. **Circulating tumour DNA in patients with advanced melanoma treated with dabrafenib or dabrafenib plus trametinib: A clinical validation study.** *Lancet Oncol* 2021;22(3):370-80.

RTP RESEARCH TO PRACTICE

Meet The Professor with Prof Long

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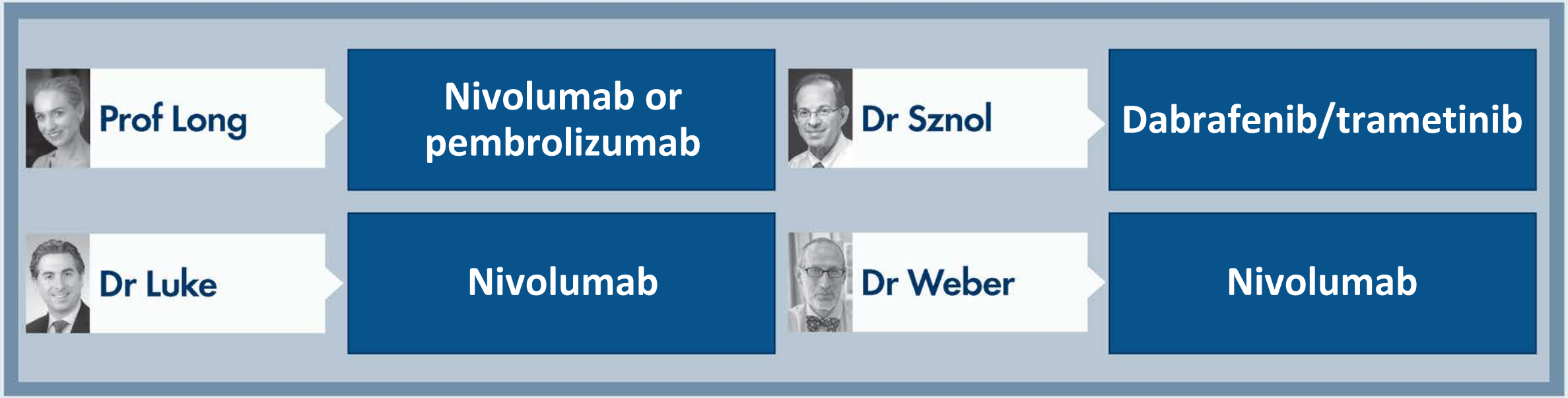
What type of assay do you generally use to test for BRAF mutation status in your patients with melanoma?

Do you generally offer multiplex genomic testing such as next-generation sequencing to your patients with melanoma?

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?

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?



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

*Active surveillance if red flags.

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?

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 IIC primary melanoma with a BRAF V600E mutation?

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 and a liver transplant 2 weeks ago who is willing to try any approach to decrease the risk of disease recurrence?

 Prof Long	None	 Dr Sznol	Consult with transplant team first, possibly dabrafenib/trametinib
 Dr Luke	None	 Dr Weber	None

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Based on current clinical trial data and your personal experience, how would you compare the efficacy of adjuvant dabrafenib/ trametinib to that of anti-PD-1 monotherapy when used as adjuvant therapy for high-risk melanoma with a BRAF V600E mutation?

 Prof Long	Not enough data at this time	 Dr Sznol	About the same
 Dr Luke	About the same	 Dr Weber	About the same

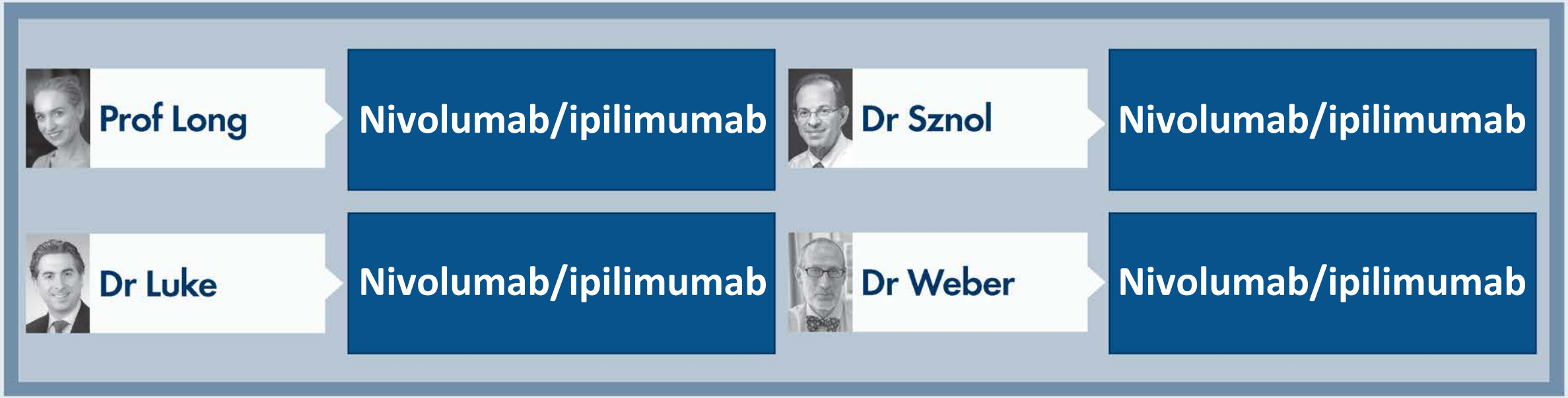
RTP RESEARCH TO PRACTICE

Based on current clinical trial data and your personal experience, how would you compare the global tolerability/toxicity of adjuvant dabrafenib/trametinib to that of anti-PD-1 monotherapy when used as adjuvant therapy for high-risk 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?

Do you consider PD-L1 levels when attempting to decide on first-line therapy for patients with metastatic melanoma?

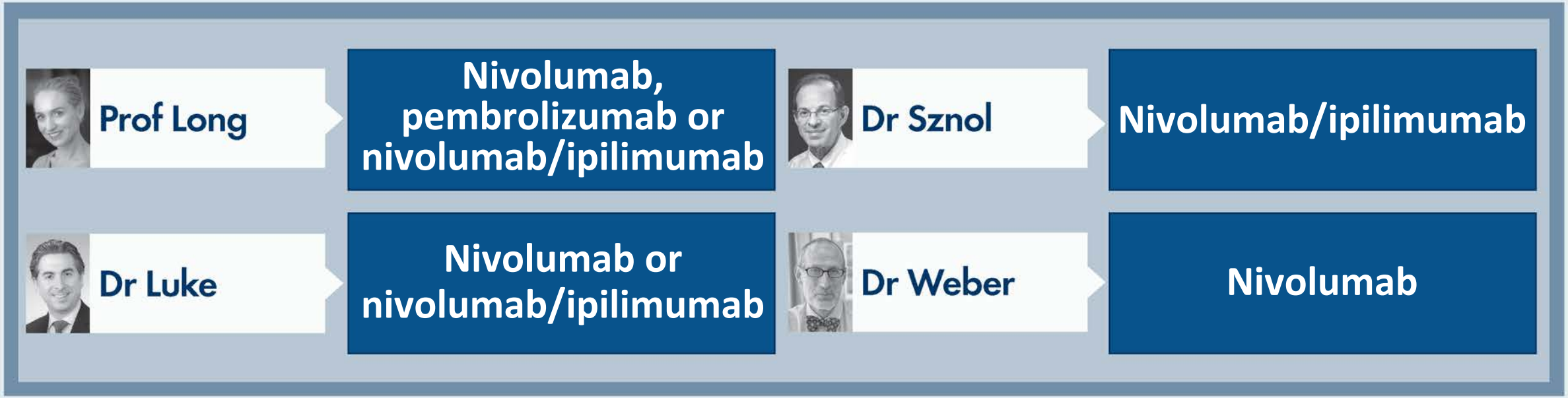
What would you generally recommend as first-line treatment for an asymptomatic, clinically stable younger patient with BRAF-mutant metastatic melanoma?



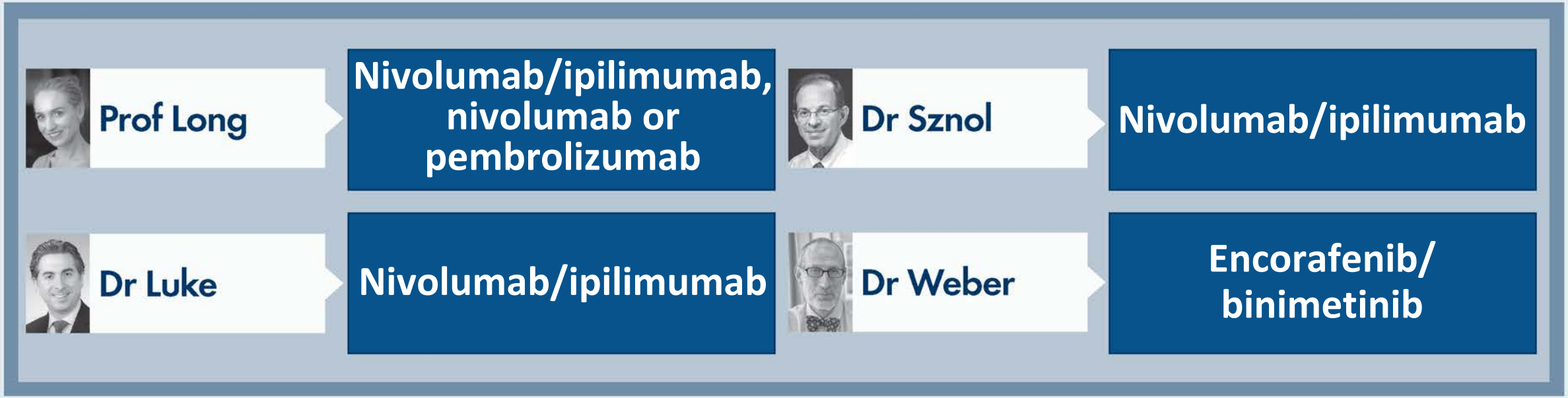
What would you generally recommend as first-line treatment for a symptomatic younger patient with extensive BRAF-mutant metastatic melanoma?

 Prof Long	Nivolumab/ipilimumab	 Dr Sznol	Nivolumab/ipilimumab
 Dr Luke	Nivolumab/ipilimumab	 Dr Weber	Encorafenib/ binimetinib x 8 wks, then switch to IO

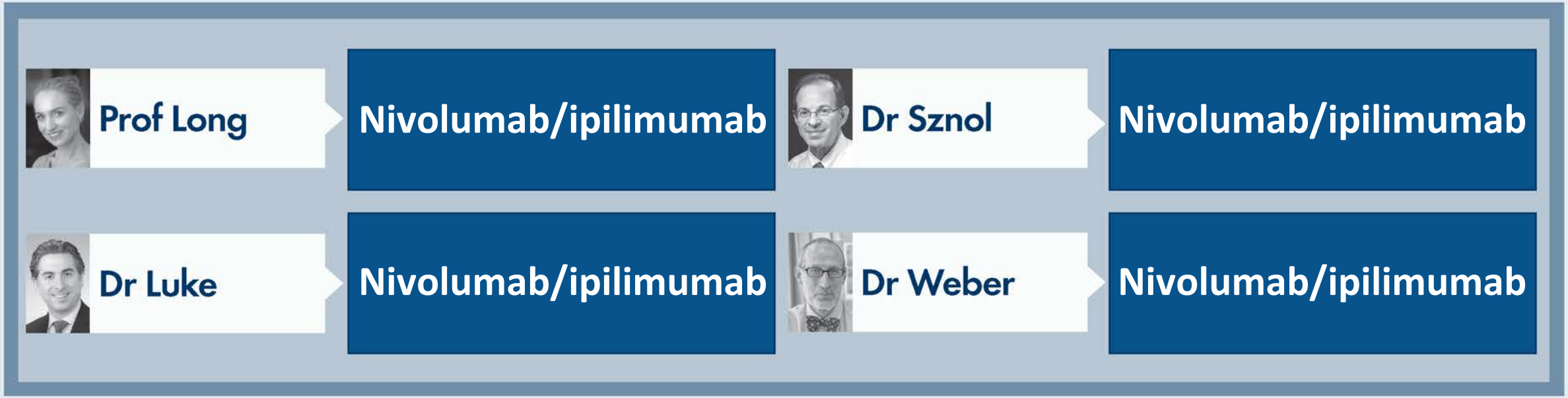
What would you generally recommend as first-line treatment for an asymptomatic, clinically stable 80-year-old patient with BRAF-mutant metastatic melanoma?



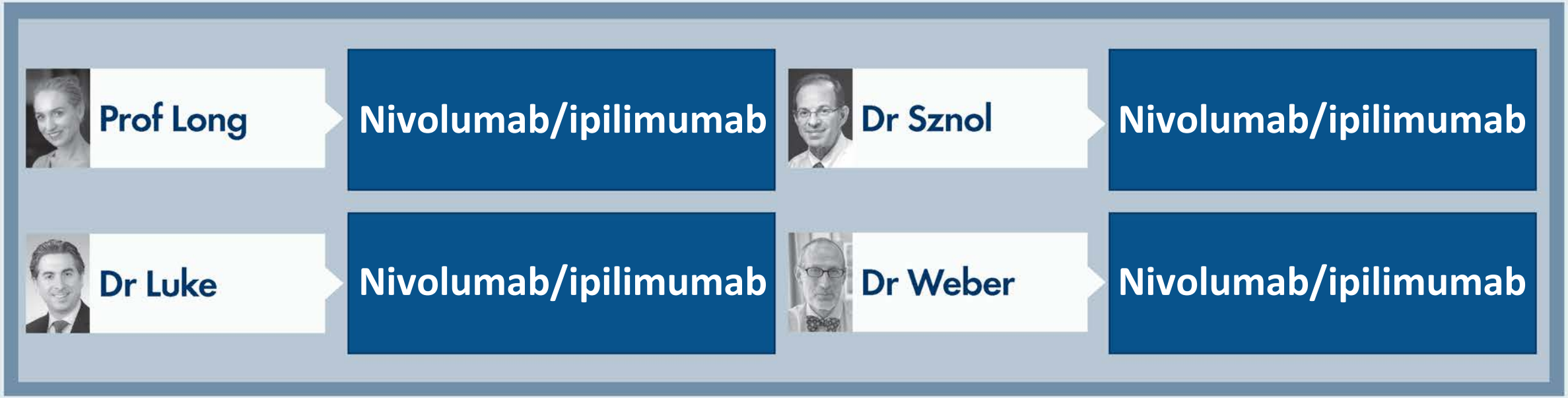
What would you generally recommend as first-line treatment for a symptomatic 80-year-old patient with extensive BRAF-mutant metastatic melanoma?



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?



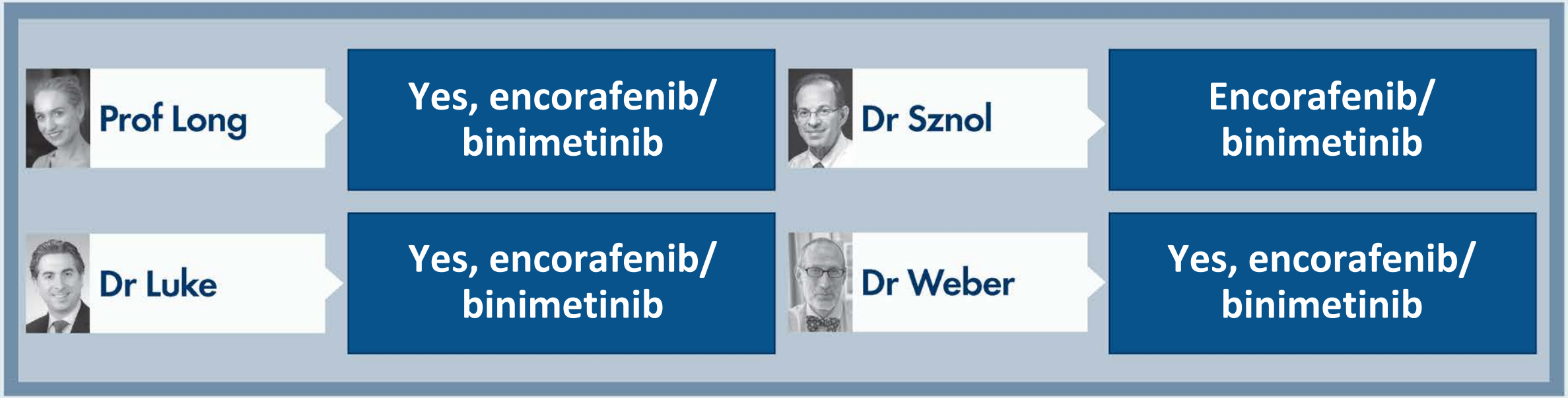
What would you generally recommend as initial treatment for an asymptomatic younger patient with BRAF-mutant melanoma with systemic metastases and several small brain metastases that would be amenable to stereotactic radiation therapy?



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?

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?



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?

 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

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 nivolumab/ipilimumab in patients with metastatic melanoma?

 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

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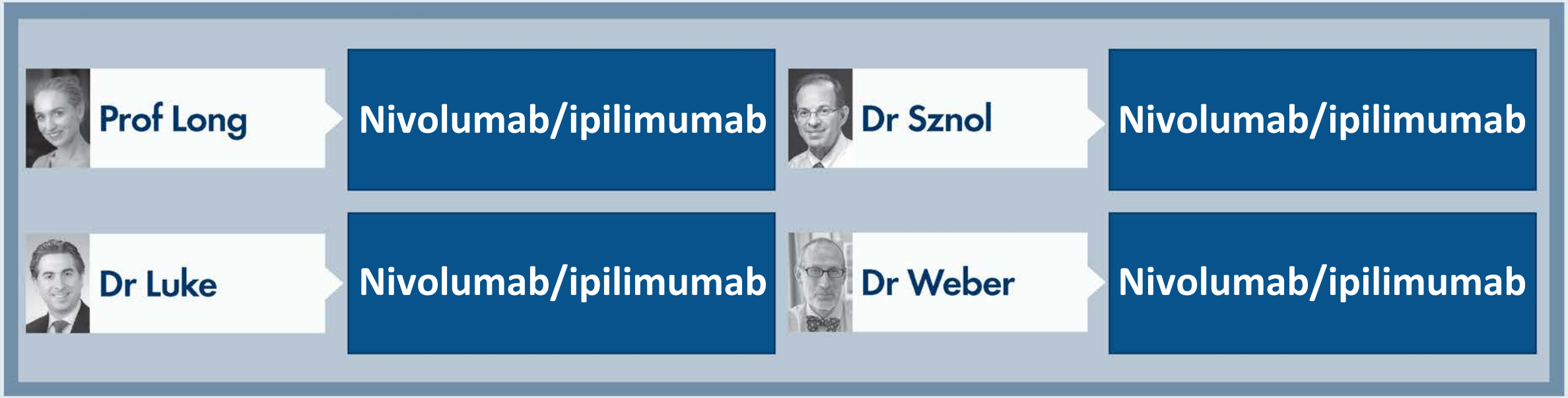
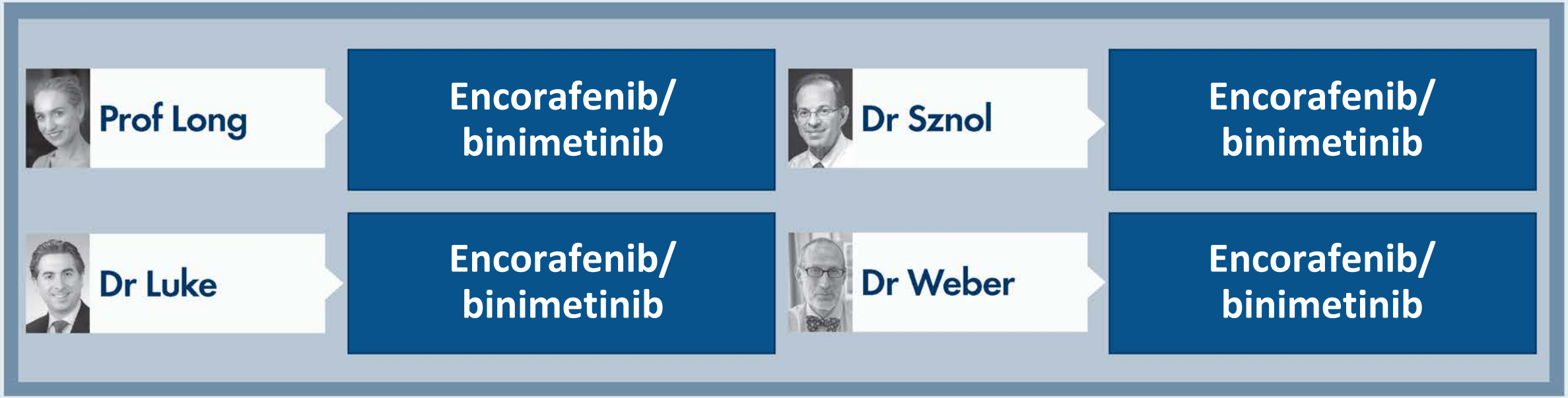
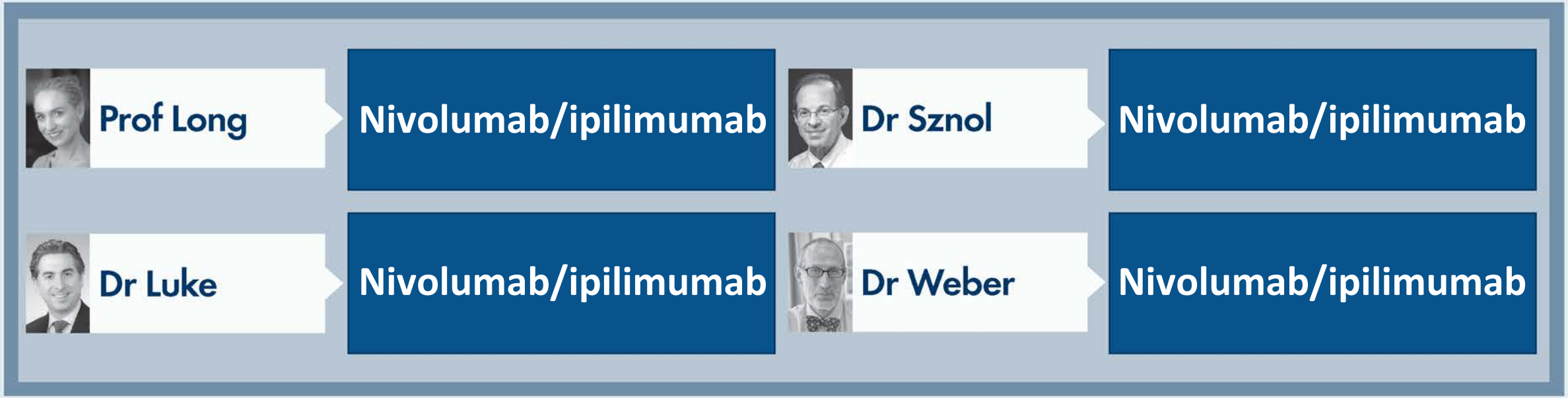
What is your most likely second-line treatment recommendation for a patient with BRAF-mutant metastatic melanoma who experiences mildly symptomatic disease progression on first-line anti-PD-1 monotherapy?



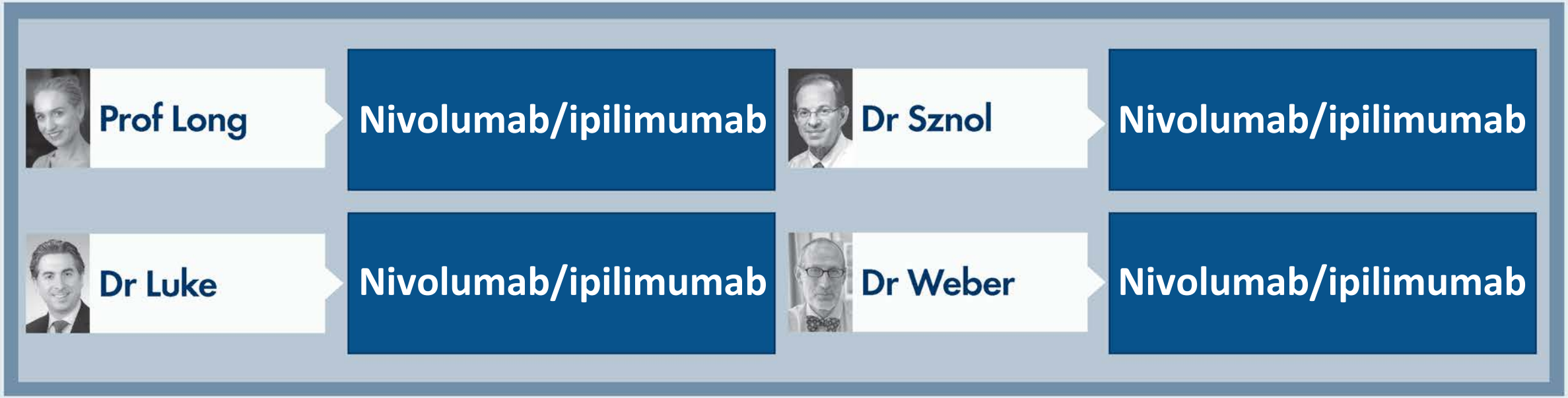
What is your most likely second-line treatment recommendation for a patient with BRAF-mutant metastatic melanoma who experiences mildly symptomatic disease progression on first-line nivolumab/ipilimumab?



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



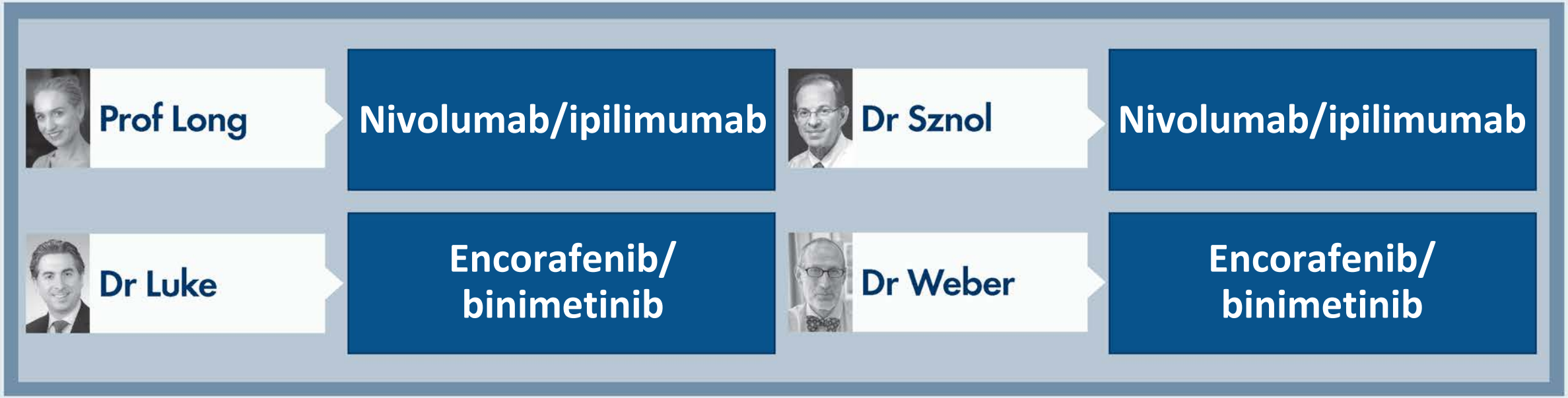
What is your most likely second-line treatment recommendation for a patient with BRAF-mutant metastatic melanoma who experiences mildly symptomatic disease progression on first-line vemurafenib/cobimetinib + atezolizumab?



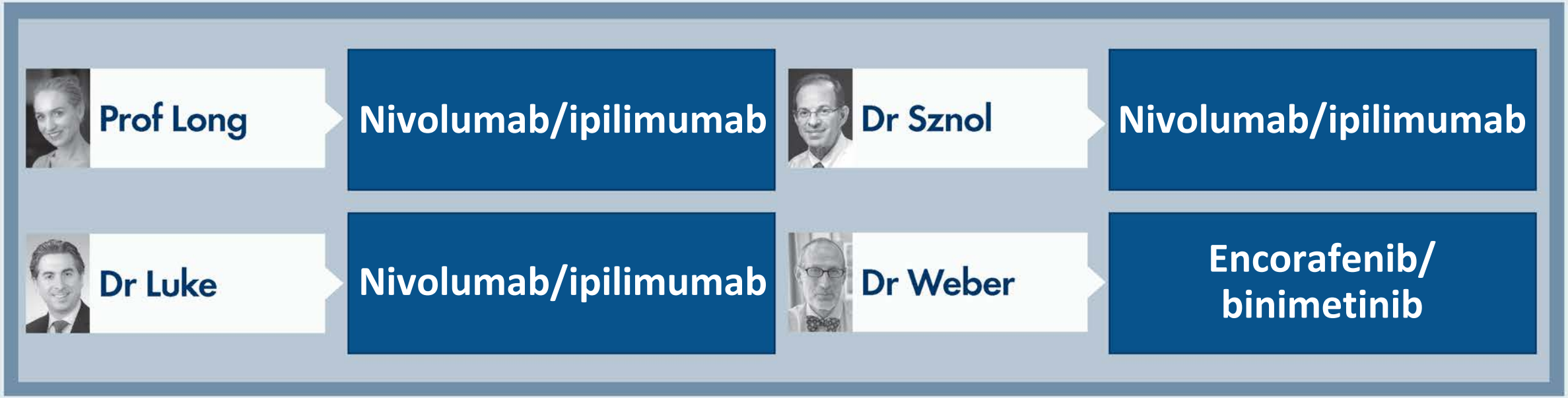
What is your most likely treatment recommendation for a patient who undergoes resection of localized BRAF-mutant melanoma and receives an adjuvant anti-PD-1 antibody but presents with highly symptomatic metastatic disease 2 years later?

 Prof Long	Nivolumab/ipilimumab	 Dr Sznol	Nivolumab/ipilimumab
 Dr Luke	Nivolumab/ipilimumab	 Dr Weber	Encorafenib/ binimetinib

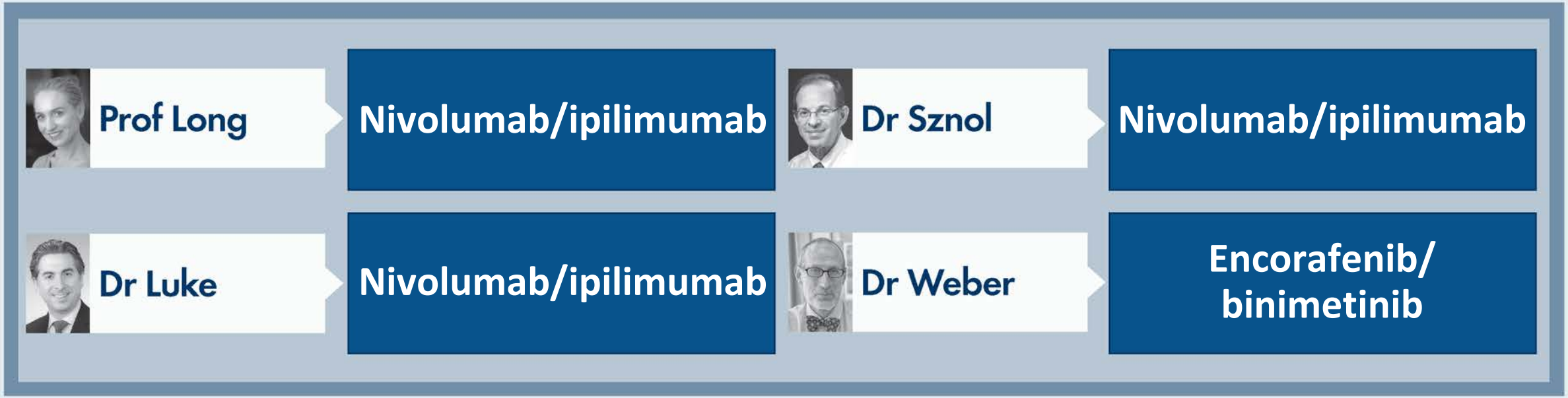
What is your most likely treatment recommendation for a patient who undergoes resection of localized BRAF-mutant melanoma and receives an adjuvant anti-PD-1 antibody but presents with highly symptomatic metastatic disease 6 months later?



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



What is your most likely treatment recommendation for a patient who undergoes resection of localized BRAF-mutant melanoma and receives adjuvant dabrafenib/trametinib but presents with highly symptomatic metastatic disease 6 months later?



For a patient with BRAF-mutant metastatic melanoma who has experienced disease progression on BRAF/MEK inhibitor treatment, have you considered or would you consider administering the same or a different targeted therapy combination at some point?

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Have you administered or would you administer BRAF-targeted therapy to a patient with metastatic melanoma with a rarer BRAF V600 mutation (eg, V600R/M/D/G) outside of a clinical trial setting?

RTP RESEARCH TO PRACTICE

Have you administered or would you administer BRAF-targeted therapy to a patient with metastatic melanoma with a non-V600 mutation (eg, BRAF L597, K601) outside of a clinical trial setting?

Based on current clinical trial data and your personal experience, how would you compare the global tolerability/toxicity of dabrafenib/trametinib, vemurafenib/cobimetinib and encorafenib/binimetinib for metastatic melanoma?

Do you recommend regular ophthalmologic examinations to your patients with metastatic melanoma receiving BRAF/MEK inhibitor combination therapy?

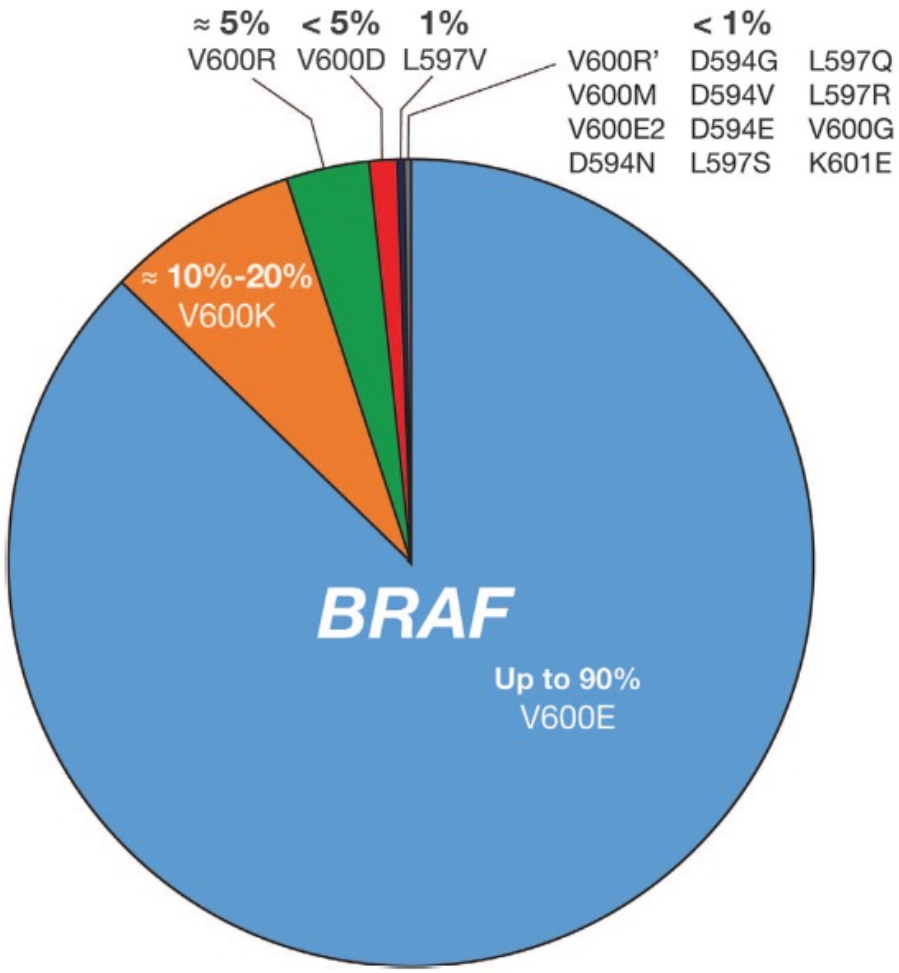
Have any of your patients receiving BRAF/MEK inhibitor combination therapy for metastatic melanoma developed cutaneous squamous cell carcinoma?

What would you generally recommend for a patient with metastatic melanoma who is experiencing a good response to BRAF/MEK inhibitor combination therapy but cannot tolerate treatment despite dose adjustment and/or appropriate supportive care measures?

Appendix

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.

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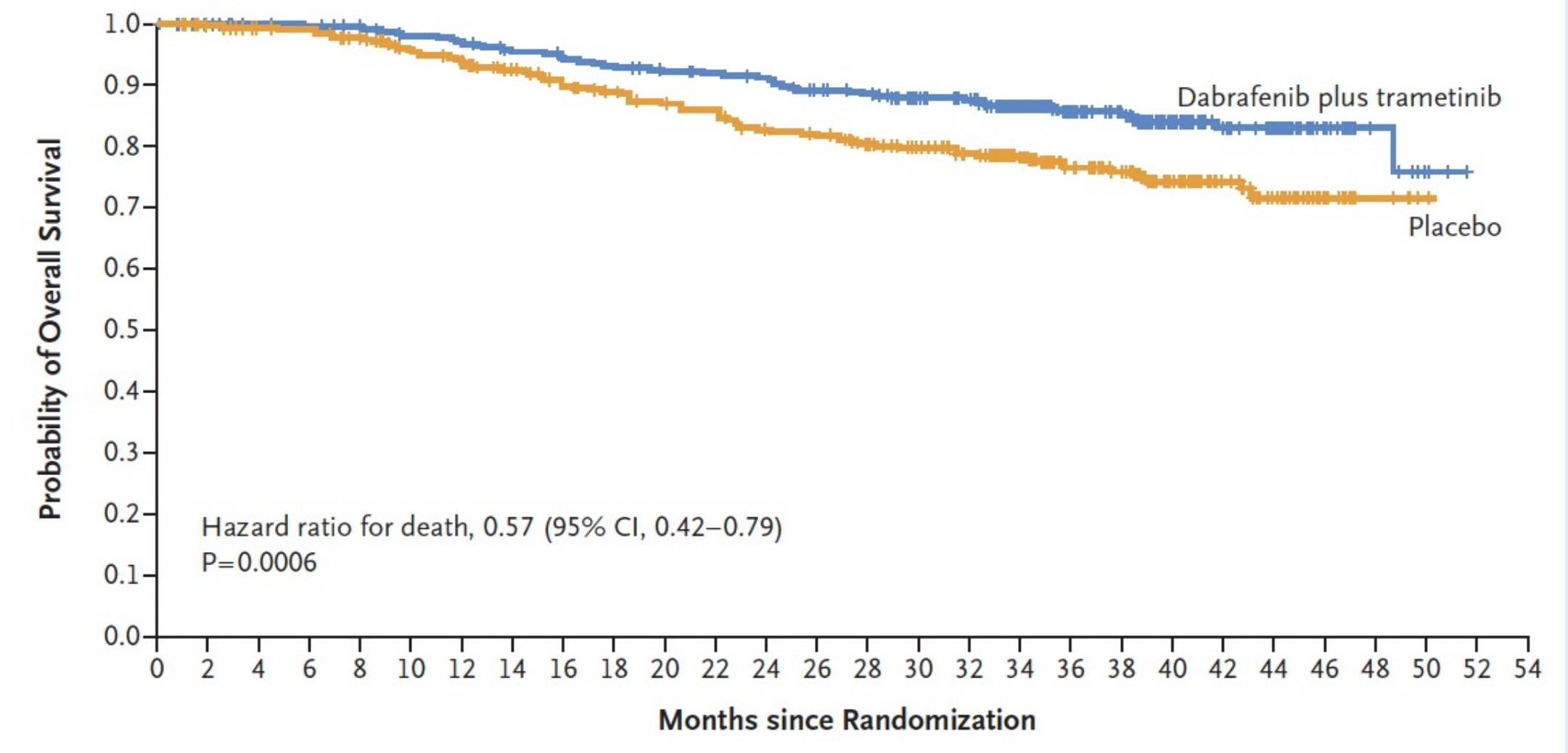
The NEW ENGLAND JOURNAL of MEDICINE

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

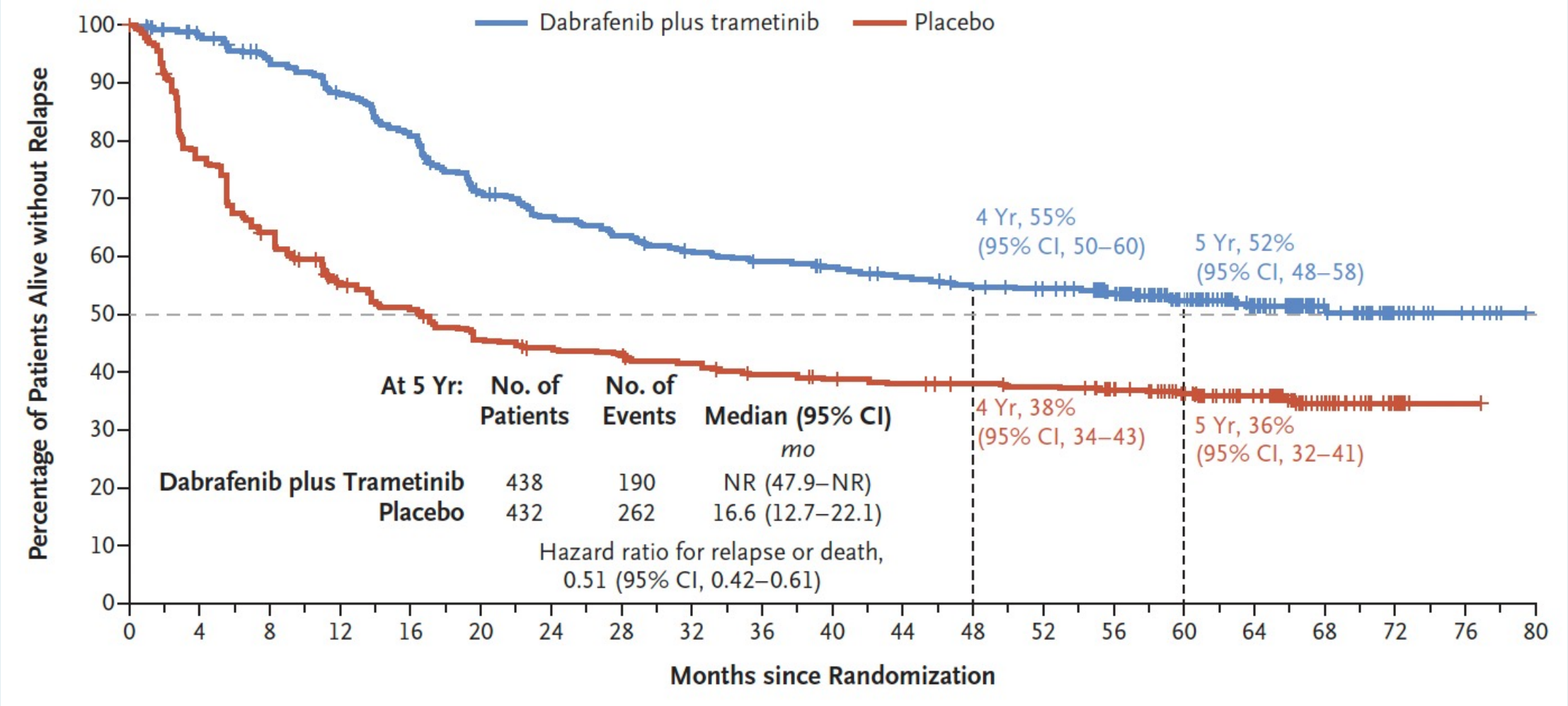
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

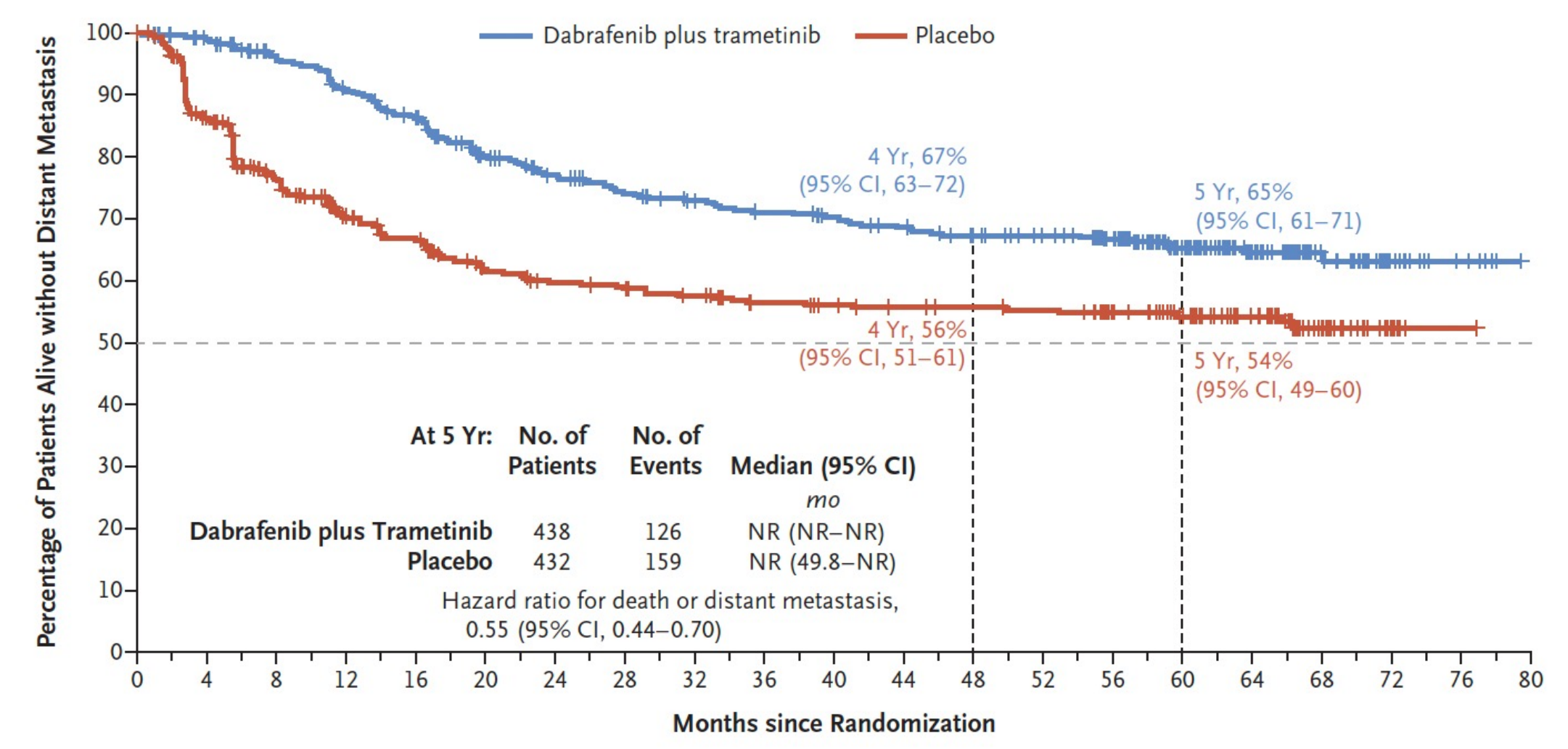
R. Dummer, A. Hauschild, M. Santinami, V. Atkinson, M. Mandalà, J.M. Kirkwood, V. Chiarion Sileni, J. Larkin, M. Nyakas, C. Dutriaux, A. Haydon, C. Robert, L. Mortier, J. Schachter, T. Lesimple, R. Plummer, K. Dasgupta, E. Gasal, M. Tan, G.V. Long, and D. Schadendorf

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].

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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.

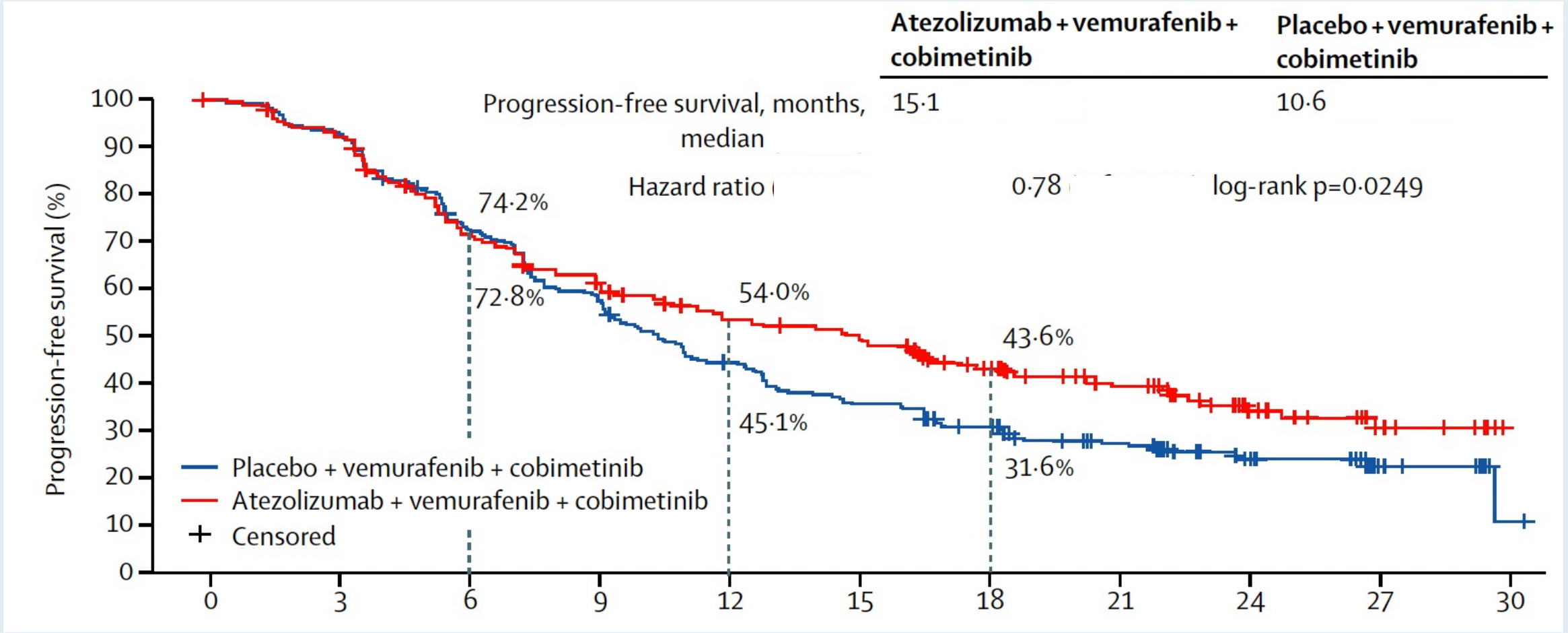
RTP RESEARCH TO PRACTICE

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)



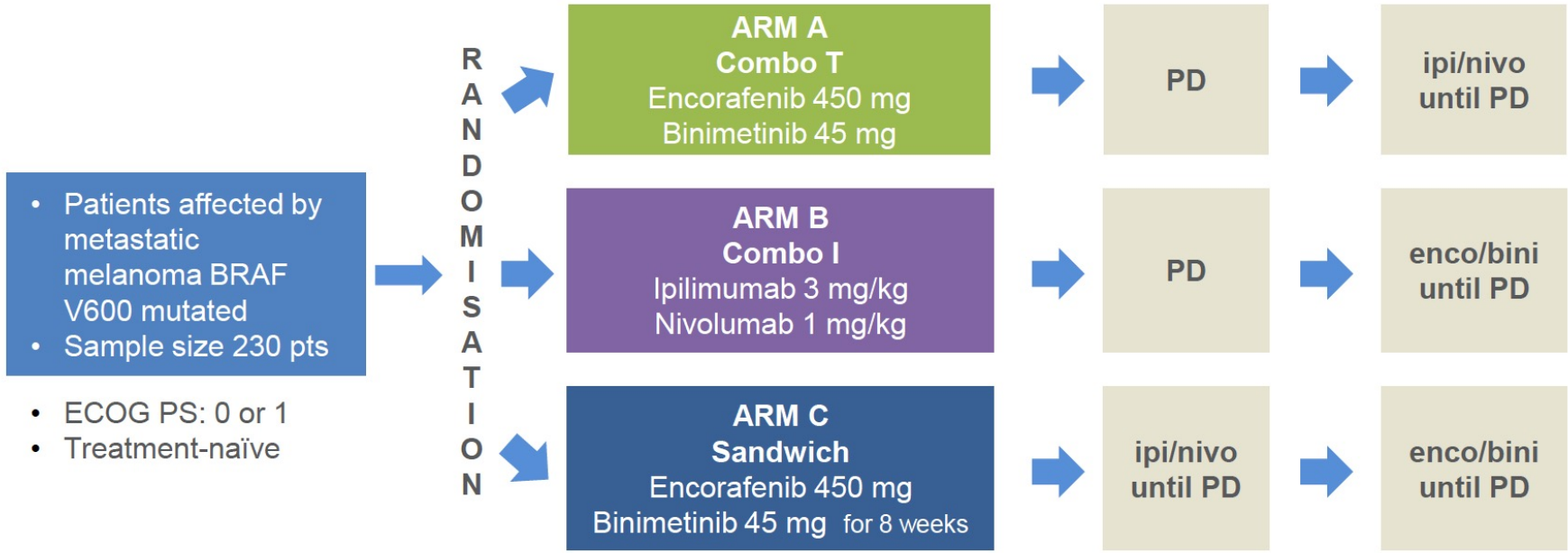
Gutzmer R et al. *Lancet* 2020;395:1835-44.

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

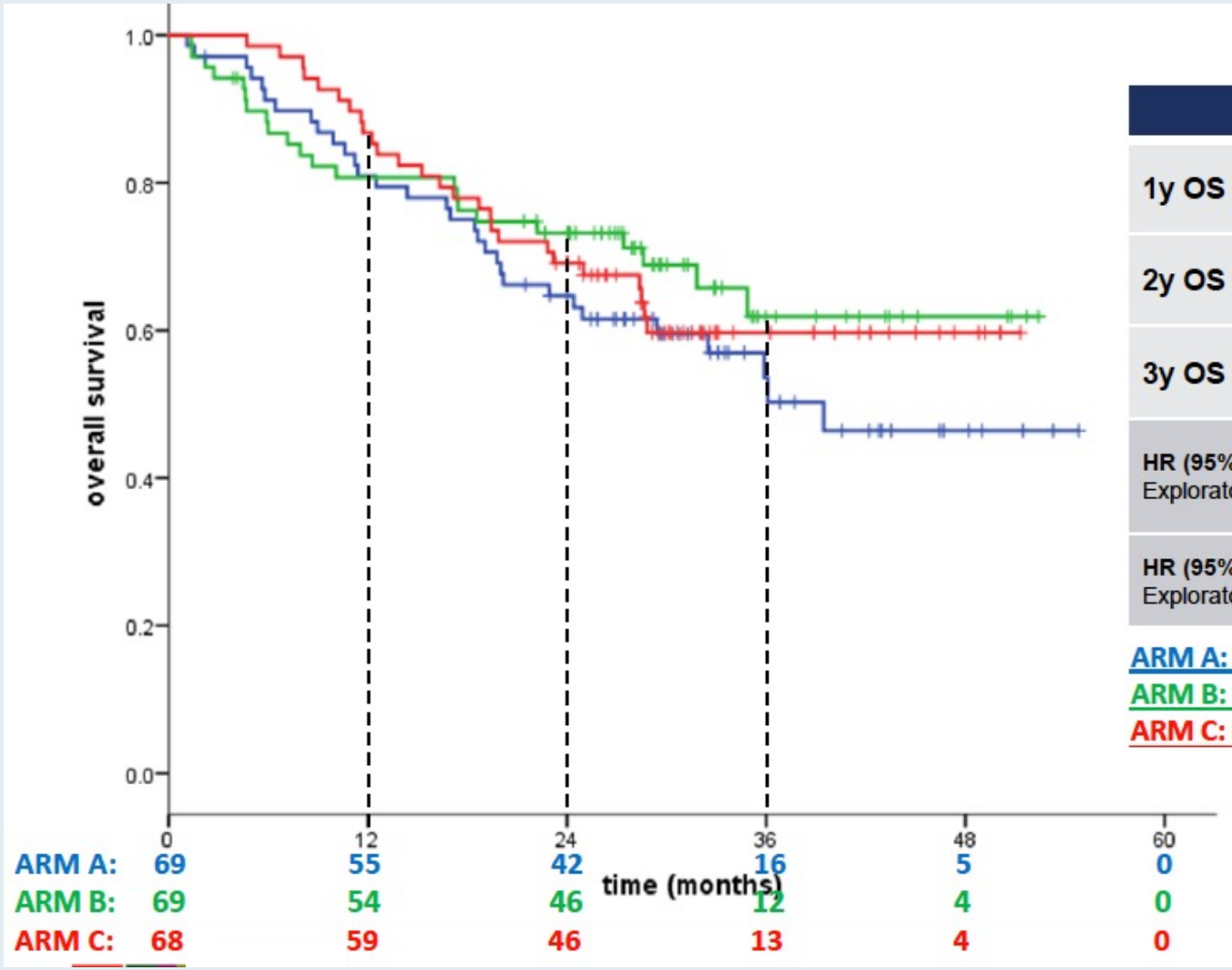
Secondary endpoints:
- PFS
- Total PFS
- Time to second progression
- % patients alive at 2–3 years
- Best ORR
- DOR

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 Selection and Sequencing of Therapy for Patients with Urothelial Bladder Carcinoma

Tuesday, November 2, 2021
5:00 PM – 6:00 PM ET

Faculty

Andrea Apolo, 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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