Thank you for joining us.
The program will commence momentarily.

Recent Advances in Medical Oncology: Melanoma

Wednesday, July 22, 2020

5:00 PM – 6:00 PM ET

Faculty

Michael B Atkins, MD
Professor Georgina Long, AO, BSc, PhD, MBBS
Jason J Luke, MD

Moderator

Neil Love, MD

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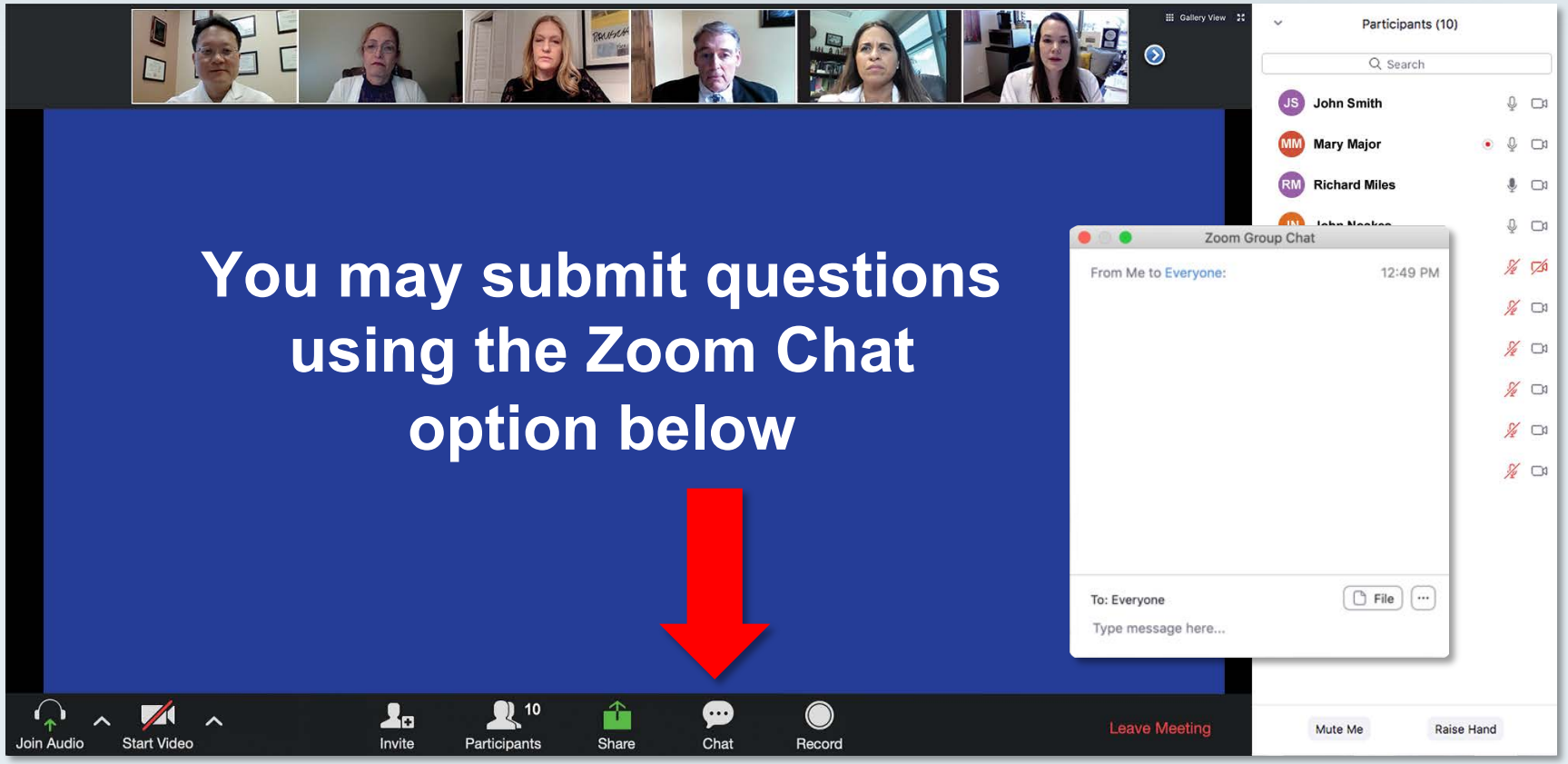
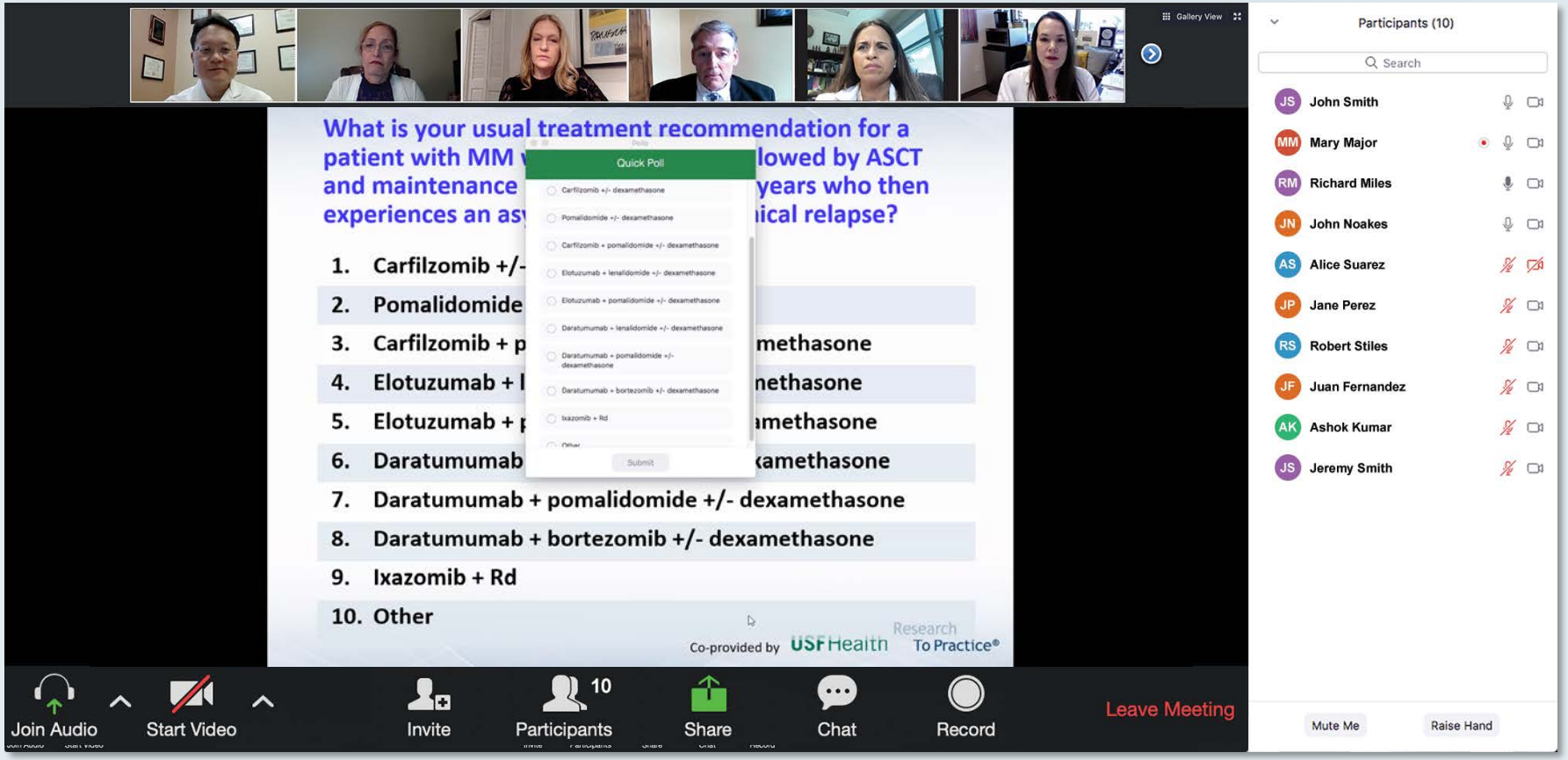
Dr Love and Faculty Encourage You to Ask Questions



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

Familiarizing yourself with the Zoom interface
How to answer poll questions



When a poll question pops up, click your answer choice from the available options. Results will be shown after everyone has answered.

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Upcoming Live Webinars

Thursday, July 23, 2020
12:00 PM – 1:00 PM ET

MEET THE PROFESSOR Current Questions and Controversies in the Management of Lung Cancer

Faculty
Joel W Neal, MD, PhD

Moderator
Neil Love, MD

Monday, July 27, 2020
5:00 PM – 6:30 PM ET

Recent Advances in Medical Oncology: Colorectal and Gastric Cancer

Faculty
Johanna Bendell, MD
Crystal Denlinger, MD
Luis A Diaz, MD
Axel Grothey, MD

Moderator
Neil Love, MD

Upcoming Live Webinars

Wednesday, July 29, 2020
5:00 PM – 6:00 PM ET

Recent Advances in Medical Oncology: Ovarian Cancer

Faculty
Mansoor Raza Mirza, MD
Kathleen Moore, MD
Shannon N Westin, MD, MPH

Moderator
Neil Love, MD

Thursday, July 30, 2020
12:00 PM – 1:00 PM ET

Clinical Investigator Perspectives on the Current and Future Management of Multiple Myeloma

Faculty
Rafael Fonseca, MD

Moderator
Neil Love, MD

Upcoming Live Webinars

Friday, July 31, 2020
9:00 AM – 10:00 AM ET

Virtual Molecular Tumor Board: Role of Genomic Profiling for Patients with Solid Tumors and the Optimal Application of Available Testing Platforms

Faculty
Andrew McKenzie, PhD
Bryan P Schneider, MD
Milan Radovich, PhD

Moderator
Neil Love, MD

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Deputy Director, Georgetown Lombardi Comprehensive Cancer Center
William M Scholl Professor and Vice-Chair
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Professor of Medicine
Georgetown University Medical Center
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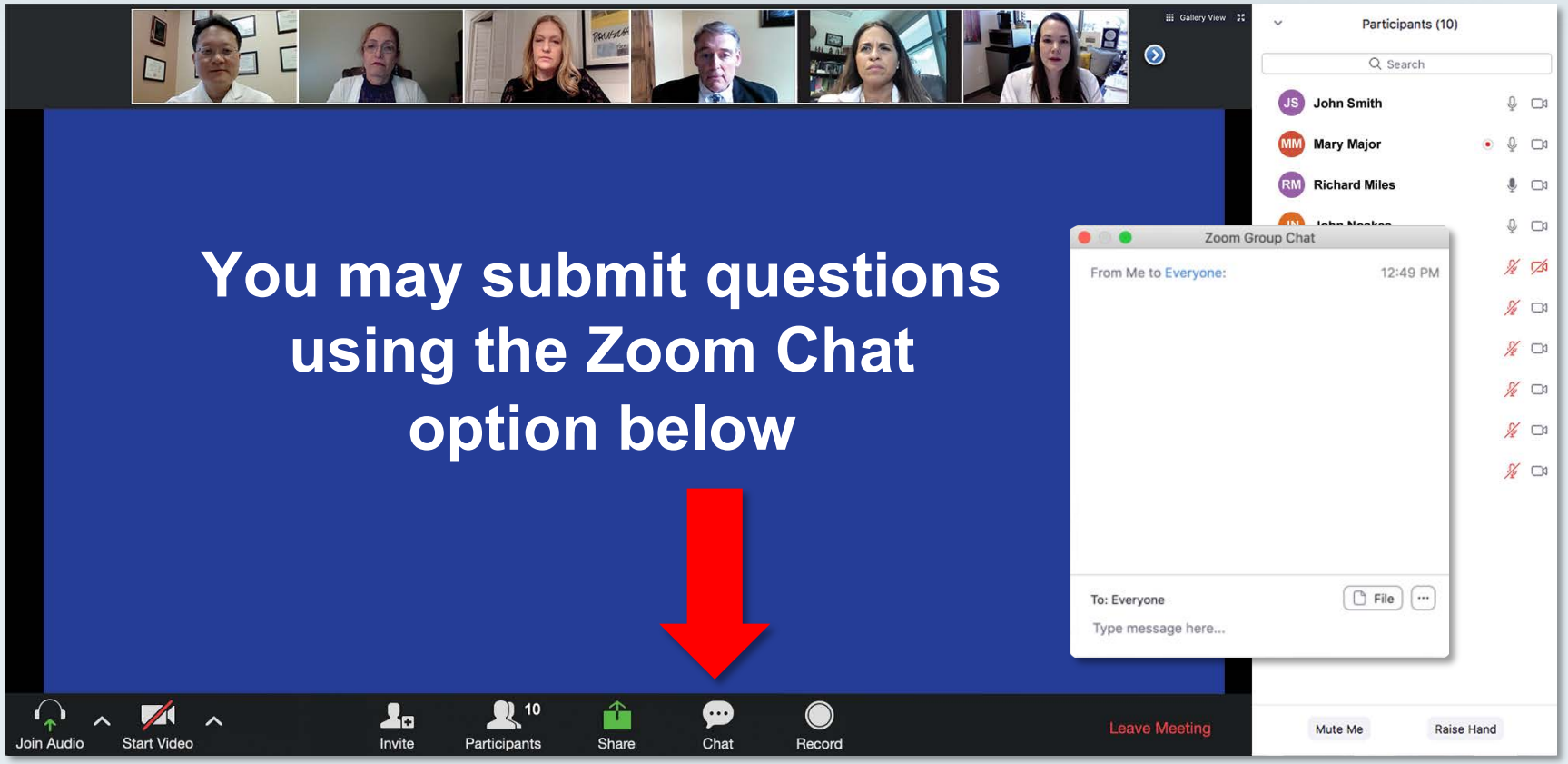
Associate Professor and Director of the Cancer Immunotherapeutics Center
University of Pittsburgh Medical Center and Hillman Cancer Center
Pittsburgh, Pennsylvania

Professor Georgina Long, AO, BSc, PhD, MBBS
Co-Medical Director of Melanoma Institute Australia
Chair of Melanoma Medical Oncology and Translational Research
Melanoma Institute Australia and Royal North Shore Hospital
The University of Sydney
Sydney, Australia

Dr Love and Faculty Encourage You to Ask Questions



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Agenda

Module 1: Management of Metastatic Melanoma with BRAF Mutation — Dr Luke

Module 2: Case from the Community

Module 3: Adjuvant and Neoadjuvant Treatment — Prof Long

Module 4: Current and Future Use of Checkpoint Inhibition — Dr Atkins

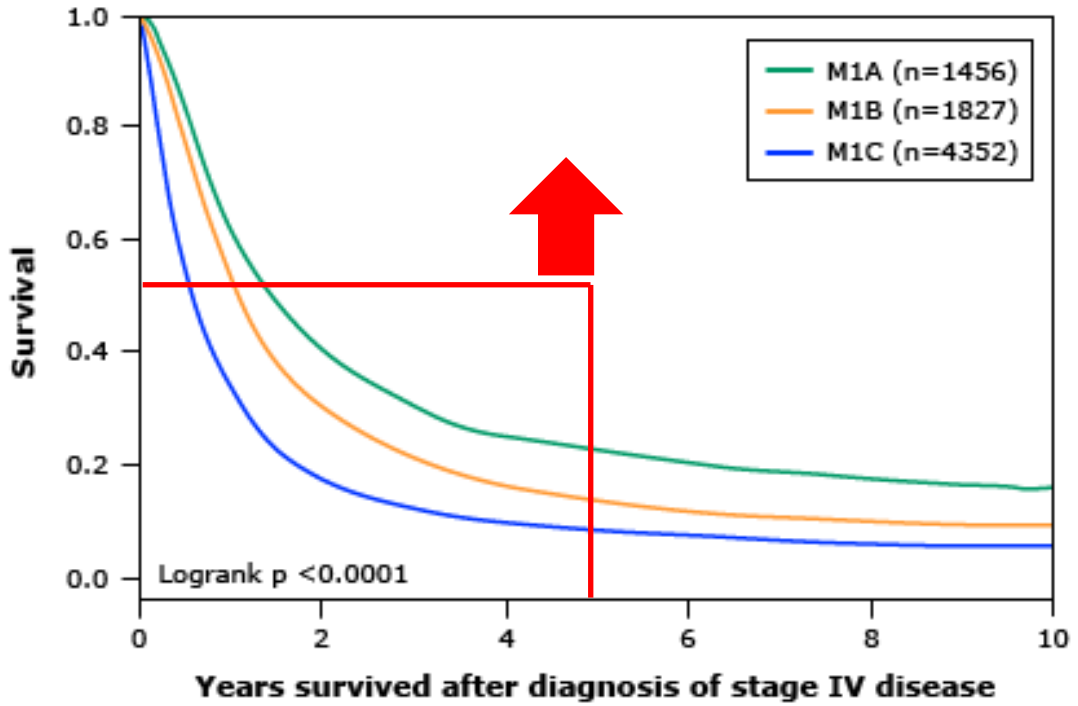
Agenda

Module 1: Management of Metastatic Melanoma with BRAF Mutation — Dr Luke

Enormous Change in Treatment for Melanoma

- Before 2011:
  - **Chemotherapy**
  - **Interleukin-2** (fit patients)
- In 2020:
  - Targeted therapy
    - BRAF
      - **Encorafenib+Binimetinib**
      - **Dabrafenib+Trametinib**
      - **Vemurafenib+Cobimetinib**
    - KIT
      - **Imatinib**
  - Immunotherapy
    - **Ipilimumab**
    - **Pembrolizumab**
    - **Nivolumab**
    - **Ipilimumab + Nivolumab**
  - Virotherapy
    - **Talimogene laherparepvec (TVEC)**

Impact of distant metastases on survival in metastatic melanoma – AJCC 7th Ed.



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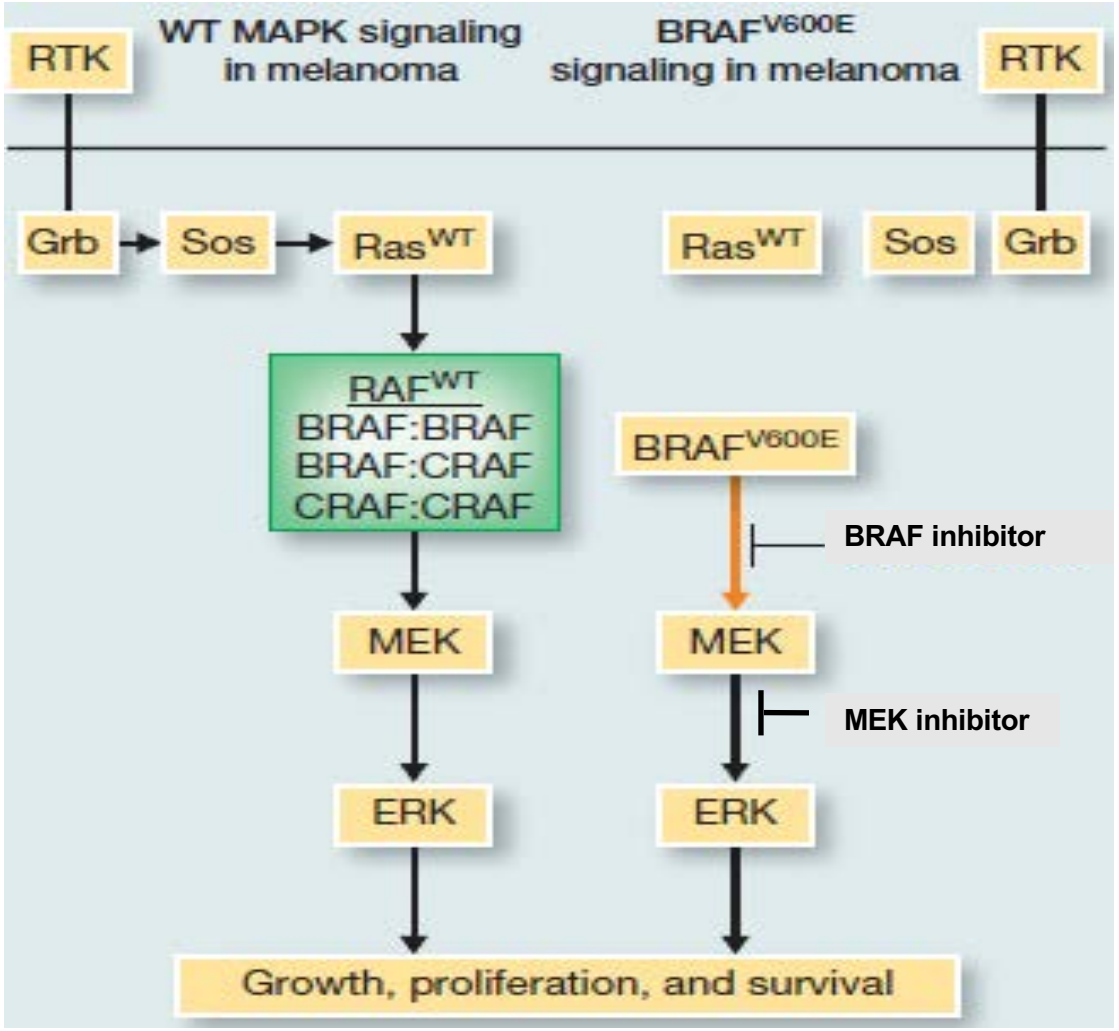
AJCC Cancer Staging Manual, 7th Ed (2010), Springer New York, Inc.

Courtesy of Jason J Luke, MD

Canonical and BRAF mutant MAPK signaling

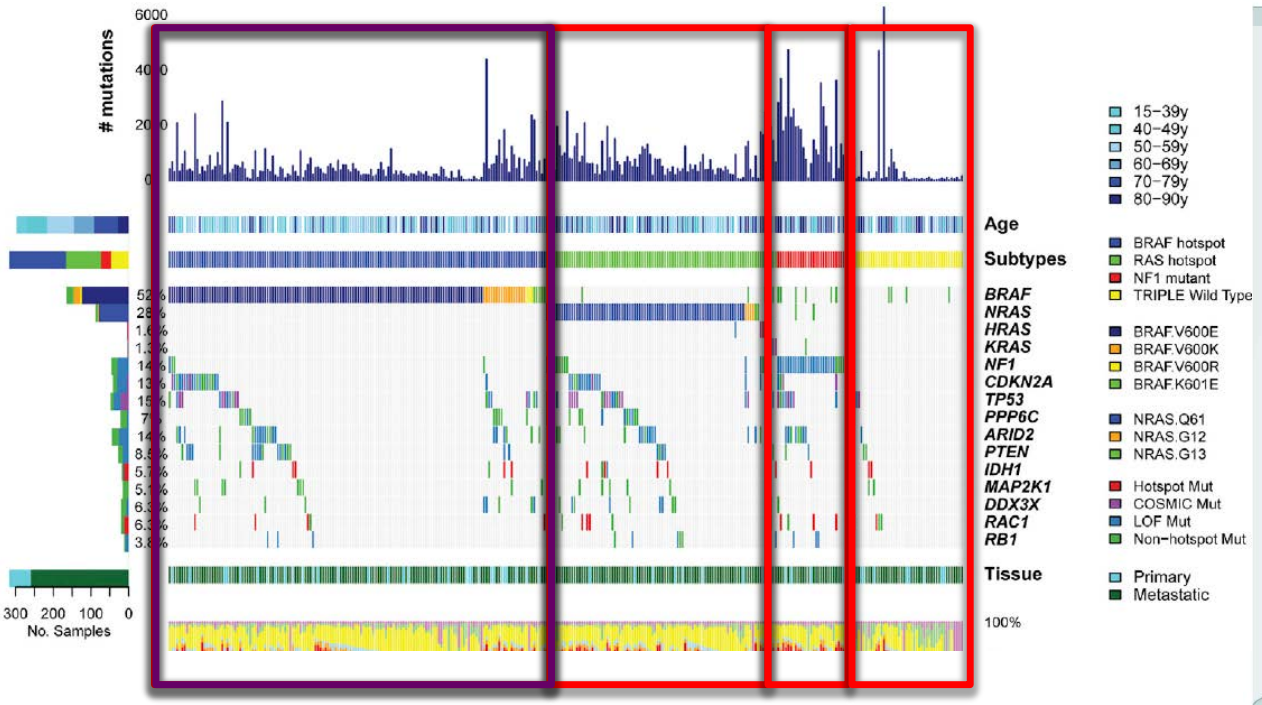
BRAF Targeted Therapy:

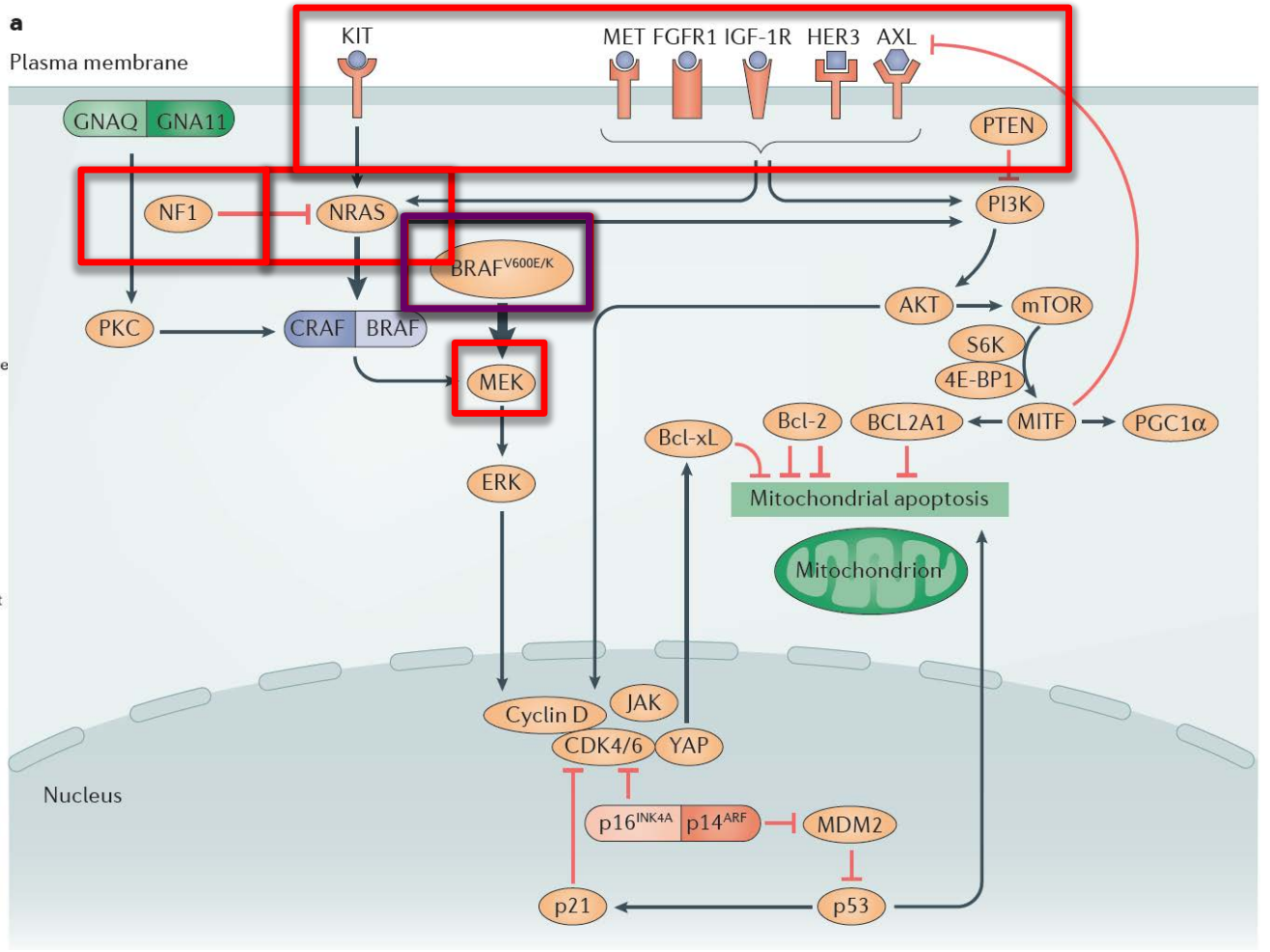


Luke *et al*. *Clin Cancer Res*. 2012

Courtesy of Jason J Luke, MD

Melanoma signaling networks





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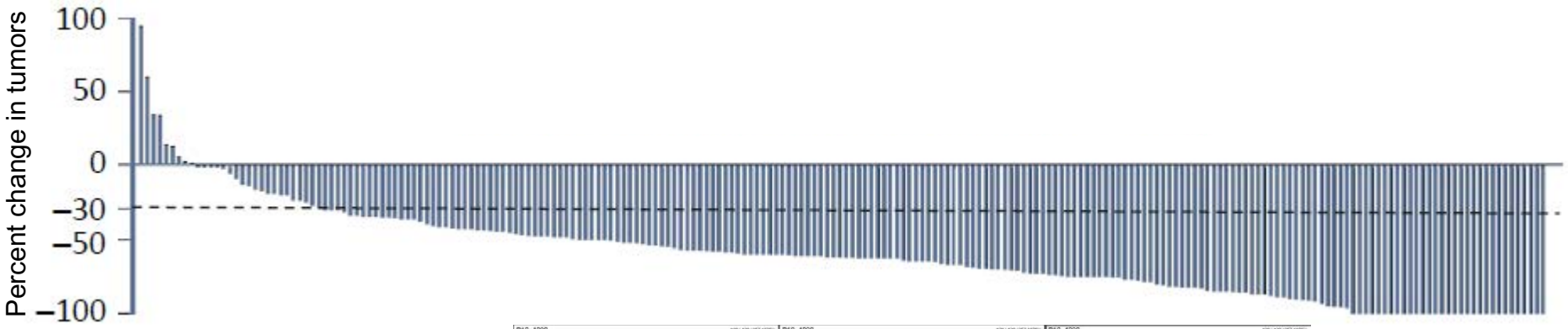
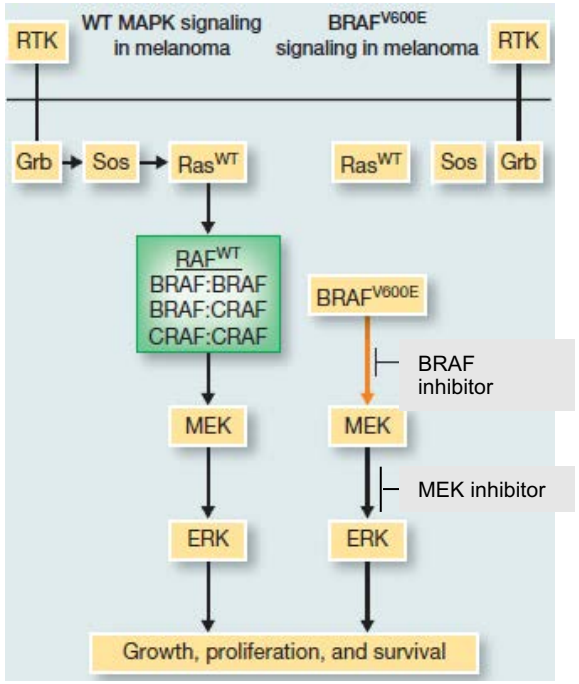
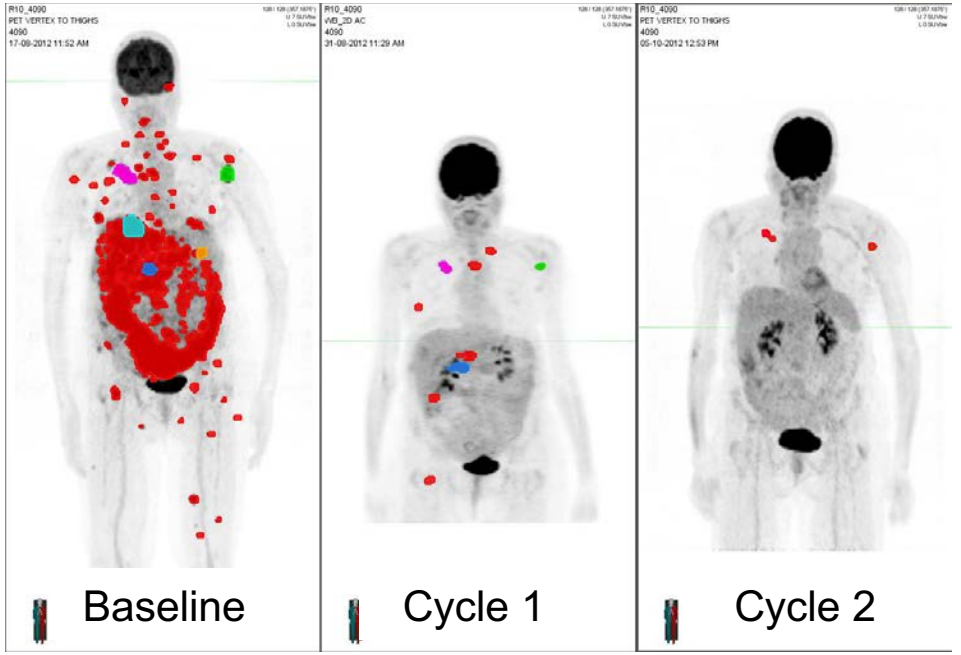
TCGA. *Cell*. 2015; Luke *et al*. *Nat Rev Clin Oncol*. 2017

Courtesy of Jason J Luke, MD

BRAF + MEK inhibitor treatment response







Example of patient with high disease burden achieving substantial metabolic response

Luke et al. Clin Can Res 2012
Larkin et al. J Clin Oncol 33, 2015 (suppl; abstr 9006)

Courtesy of Jason J Luke, MD

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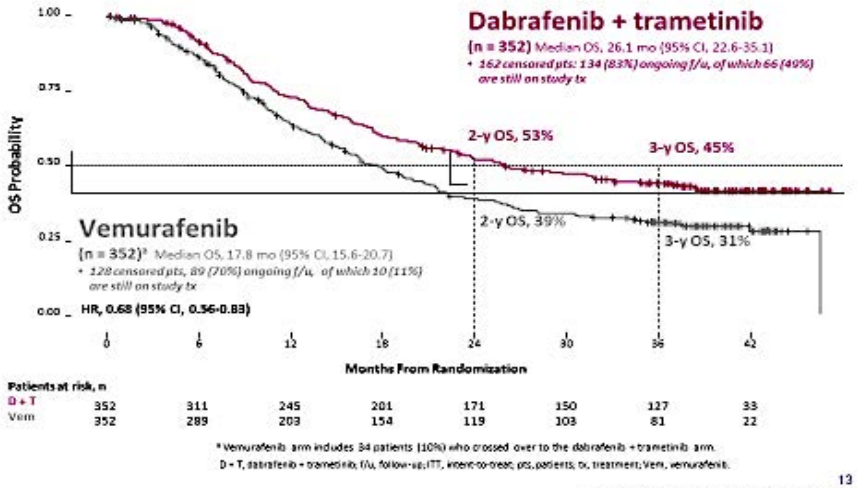
Improved Overall Survival Targeting BRAF

COMBI-v: Overall Survival (ITT Population)



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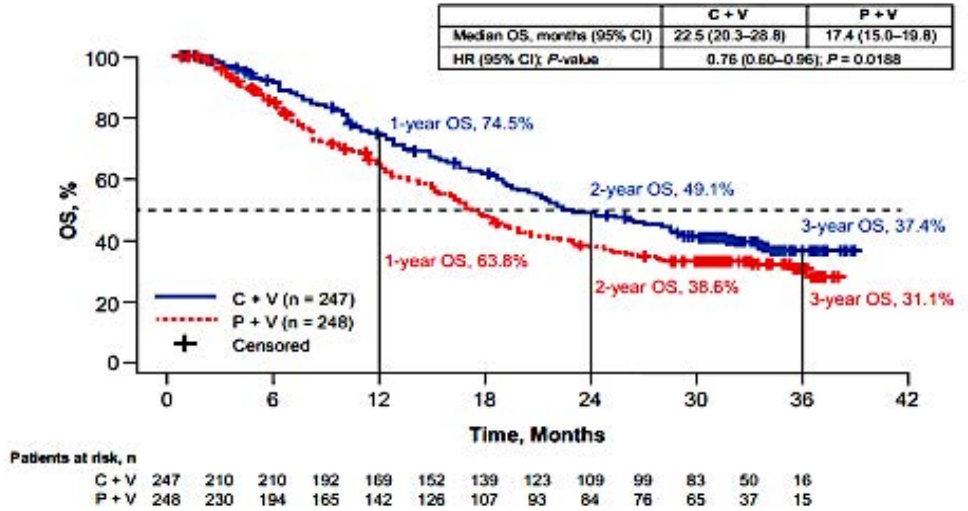
Robert et al, *ESMO*, 2016 Abstract 1140P

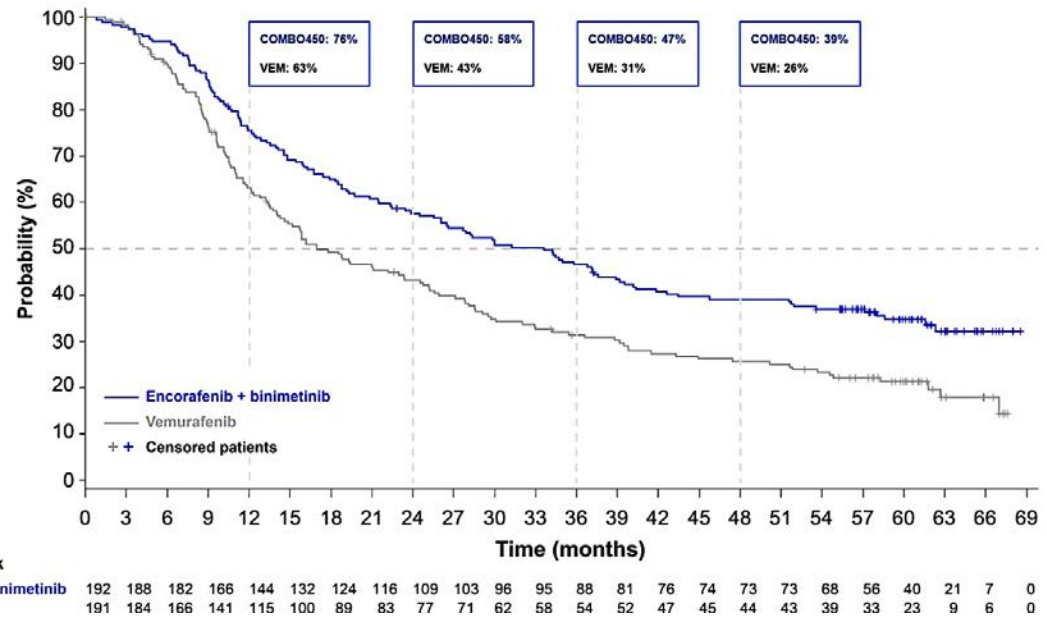
BRAF+MEK Inhibition

CoBRIM: Overall Survival (ITT Population)



McArthur et al, *SMR*, 2016

14



Gogas *et al*. ASCO 2020 abst 10012

Courtesy of Jason J Luke, MD

@jasonlukemd

Toxicities of BRAF and MEK Inhibitors

Dabrafenib + Trametinib	Vemurafenib + Cobimetinib	Encorafenib + Binimetinib
Pyrexia	Rash	Nausea
Fatigue	Diarrhea	Diarrhea
Nausea	Nausea	Vomiting
Headache	Arthralgia	Fatigue
Chills	Fatigue	Arthralgia
Diarrhea	Photosensitivity	Elevated creatinine phosphokinase
Vomiting	Pyrexia	Blurred vision
Arthralgia	ALT, GGT, AST increase	Headache
Rash	Decreased appetite	Asthenia
	Alopecia	Pyrexia
	Hyperkeratosis	Abdominal pain

@jasonlukemd

Long *et al*. *N Engl J Med*. 2017; Ascierto *et al*. *Lancet Oncol*. 2016; Dummer *et al*. *Lancet Oncol*. 2018

Courtesy of Jason J Luke, MD

Conclusions

- **BRAF-MEK inhibition is a standard of care in melanoma**
- **ECOG <1, normal LDH, disease in <3 sites, without brain metastasis do best with BRAF-MEK inhibition**
- **Three BRAF-MEK regimens with slightly different toxicity profiles**
- **Future will include combinations of BRAF-MEK with PD-1/L1 vs IO combos!**

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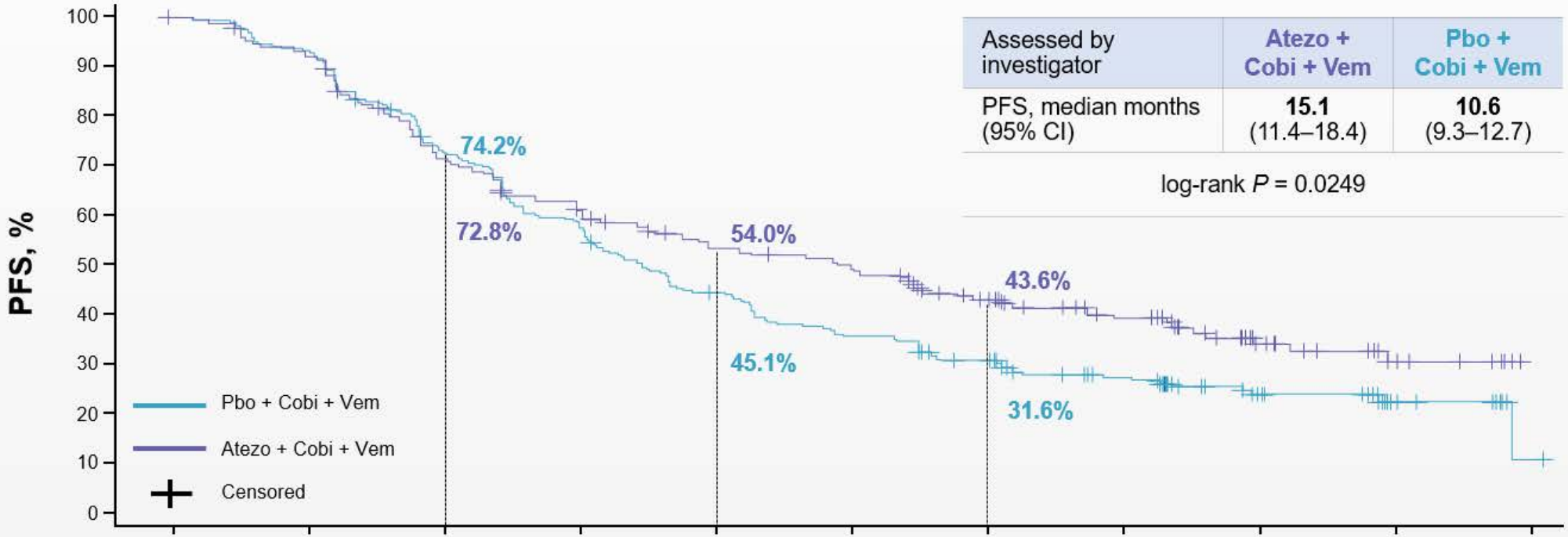
Triplet BRAF+MEK+PD-1/L1 combos

IMspire150: Primary Endpoint: Investigator-Assessed PFS



Assessed by investigator	Atezo + Cobi + Vem	Pbo + Cobi + Vem
PFS, median months (95% CI)	**15.1** (11.4–18.4)	**10.6** (9.3–12.7)

log-rank $P = 0.0249$

Patients remaining at risk

Pbo + Cobi + Vem	258	230	179	143	107	86	71	51	27	11	1
Atezo + Cobi + Vem	256	229	174	149	123	114	90	66	34	11	

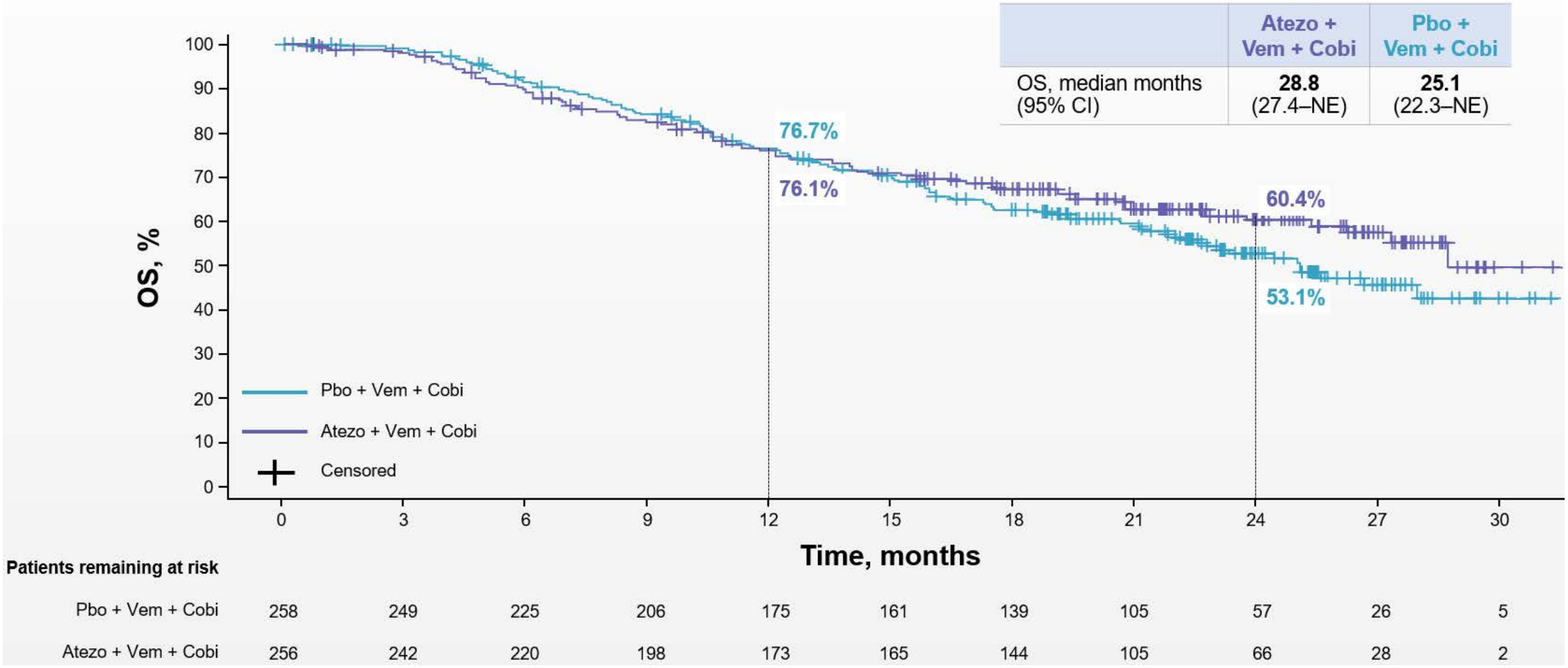
@jasonlukemd

McArthur *et al*. AACR. 2020

Courtesy of Jason J Luke, MD

Overall survival atezo+vem+cobi

IMspire150: Overall Survival



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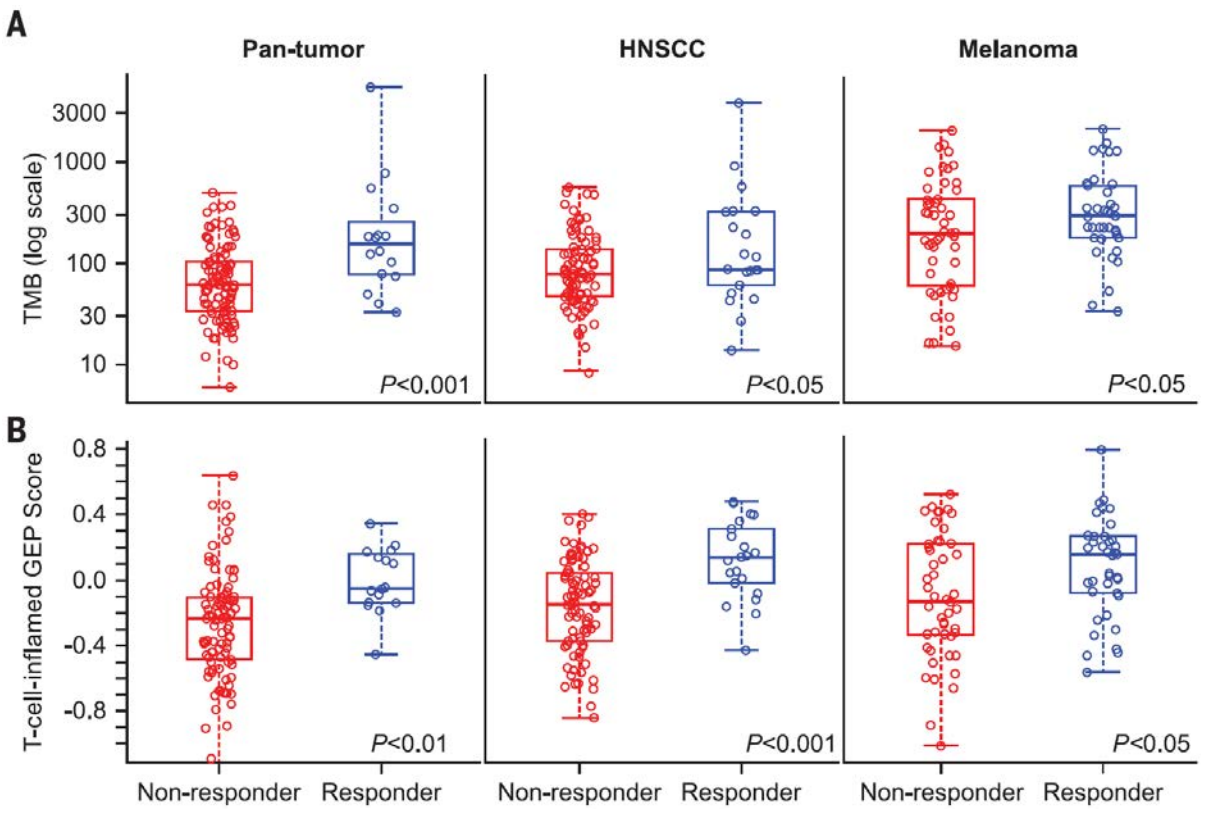
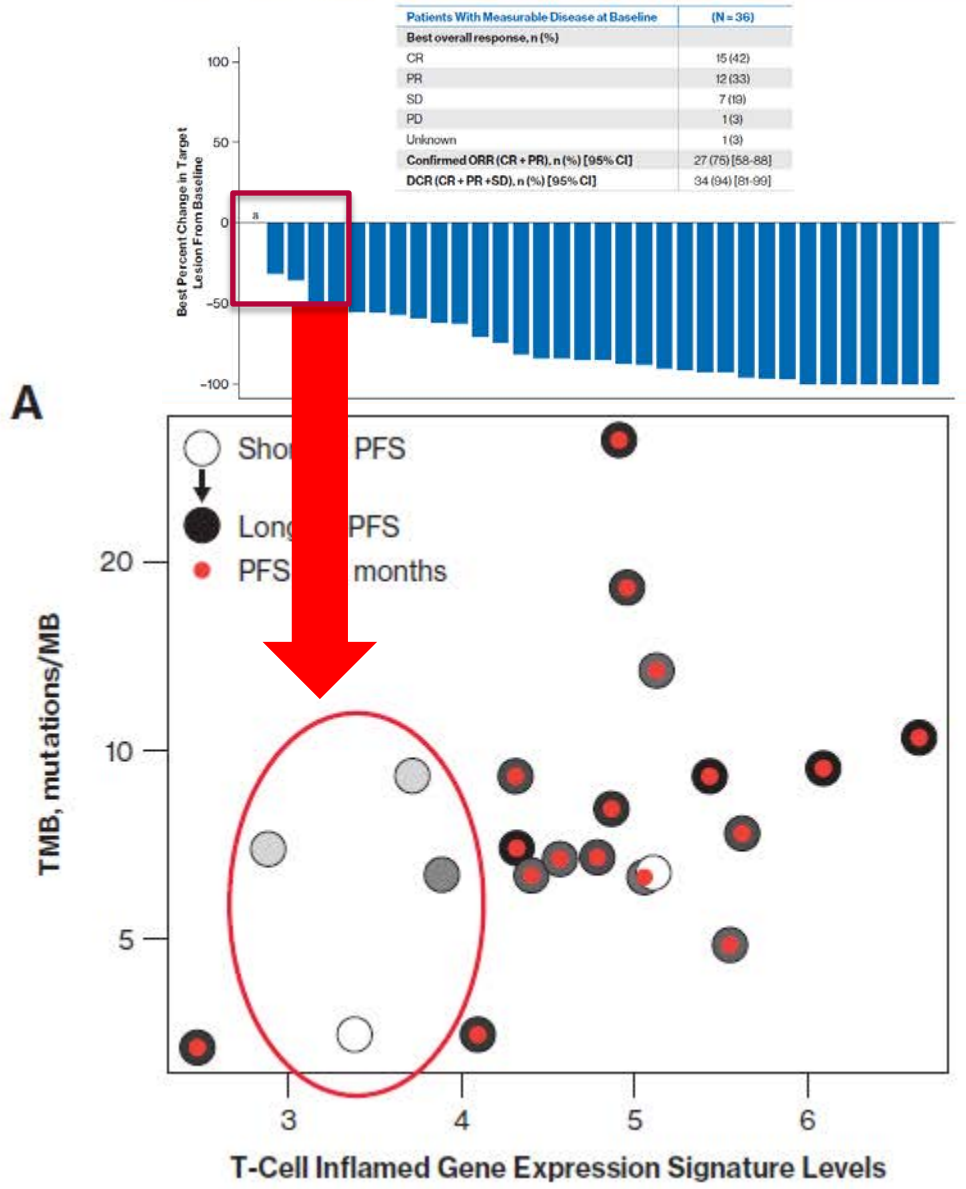
McArthur *et al*. AACR. 2020

Courtesy of Jason J Luke, MD

Is BRAF+MEK+PD-1/L1 triplet adequate for all patients?





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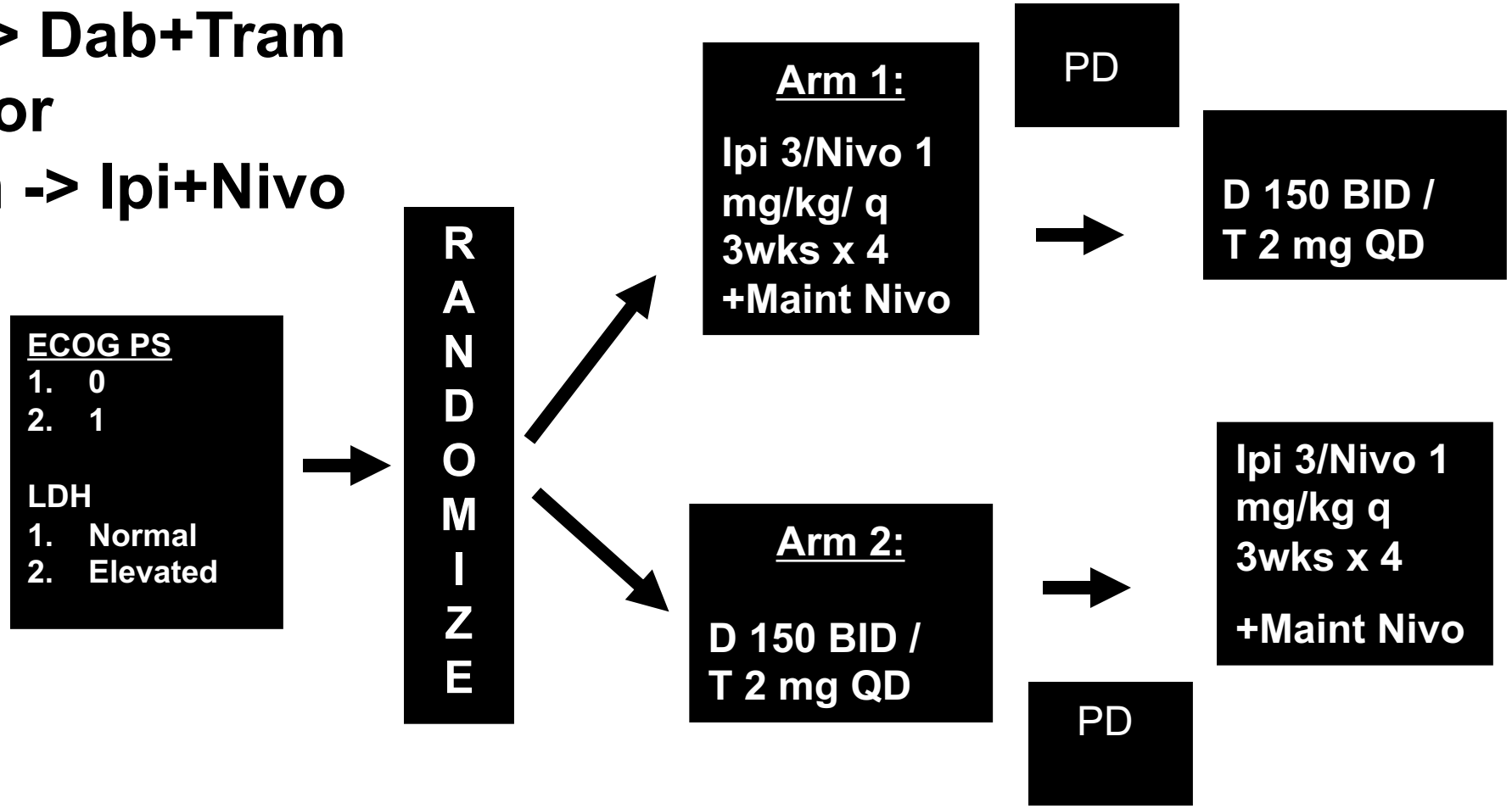
Cristescu *et al*. *Science* 2018; Dummer *et al*. ASCO 2019

Courtesy of Jason J Luke, MD

Optimal sequence of targeted & immunotherapy?

EA6134 Trial (DREAM-seq):

Ipi+Nivo -> Dab+Tram
or
Dab+Tram -> Ipi+Nivo

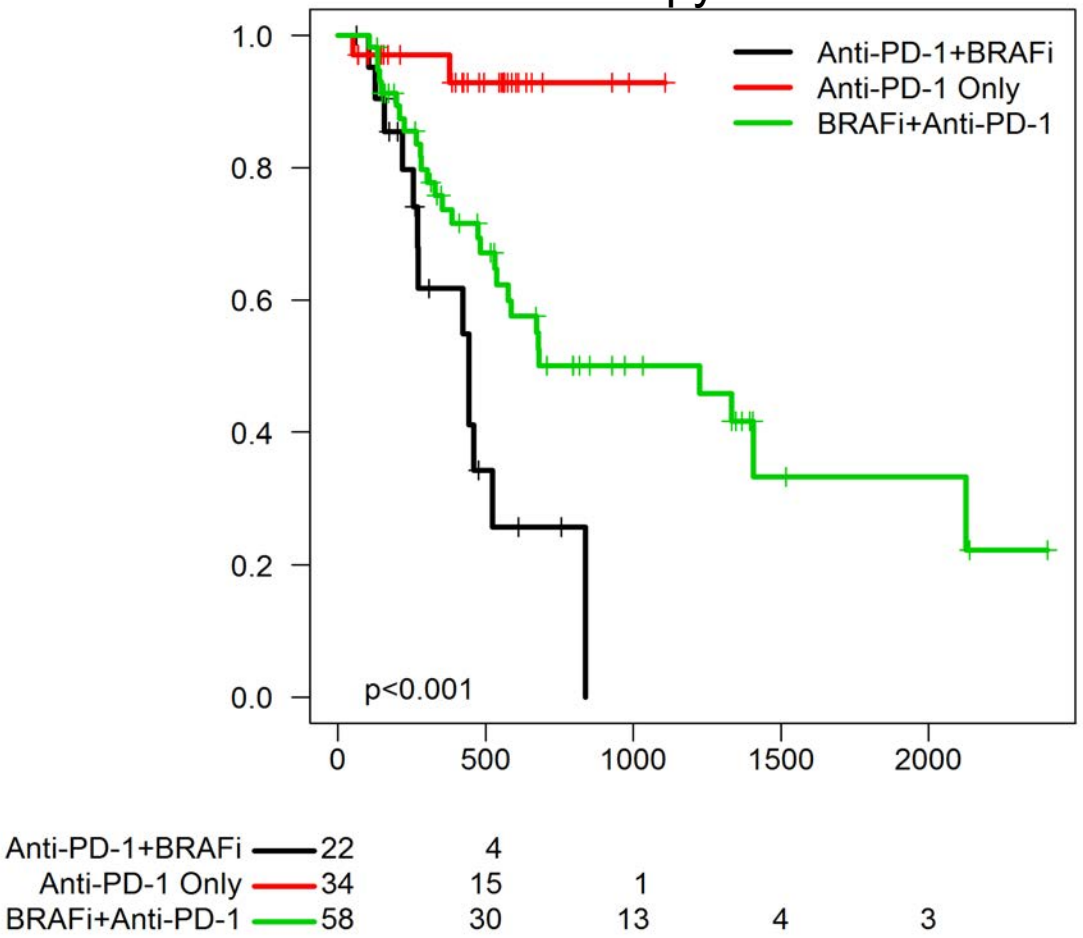


D = dabrafenib; T = trametinib; PD = disease progression

Courtesy of Jason J Luke, MD

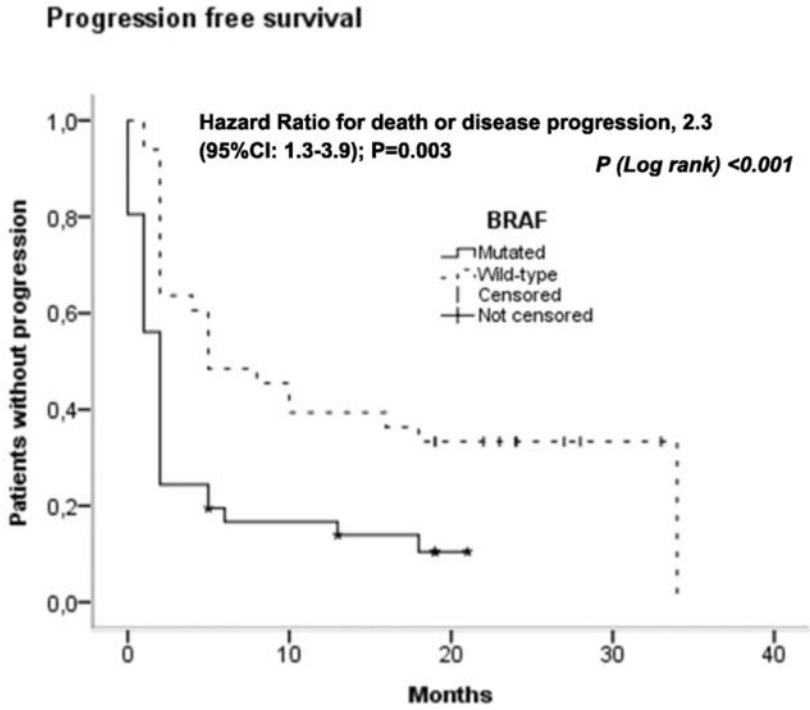
Sequencing BRAF-IO

Anti-PD-1 therapy then BRAF



BRAF then anti-PD-1 therapy

	Wild-type BRAF	Mutated BRAF	p
	n = 33	n = 41	
Objective Response Rate, n (%)	15 (45.5)	5 (12.2)	0.003
Disease Control Rate, n (%)	19 (57.6)	10 (24.4)	0.008
Progressive Disease, n (%)	14 (42.4)	31 (42.4)	
Median Progression-Free Survival, months [95%CI]	5 [0.2–9.8]	2 [1.6–2.4]	< 0.001
Median Overall Survival, months [95%CI]	20 [5.4–34.6]	7 [4.0–10.0]	< 0.001



2nd line therapy not as good as first line…

@jasonlukemd

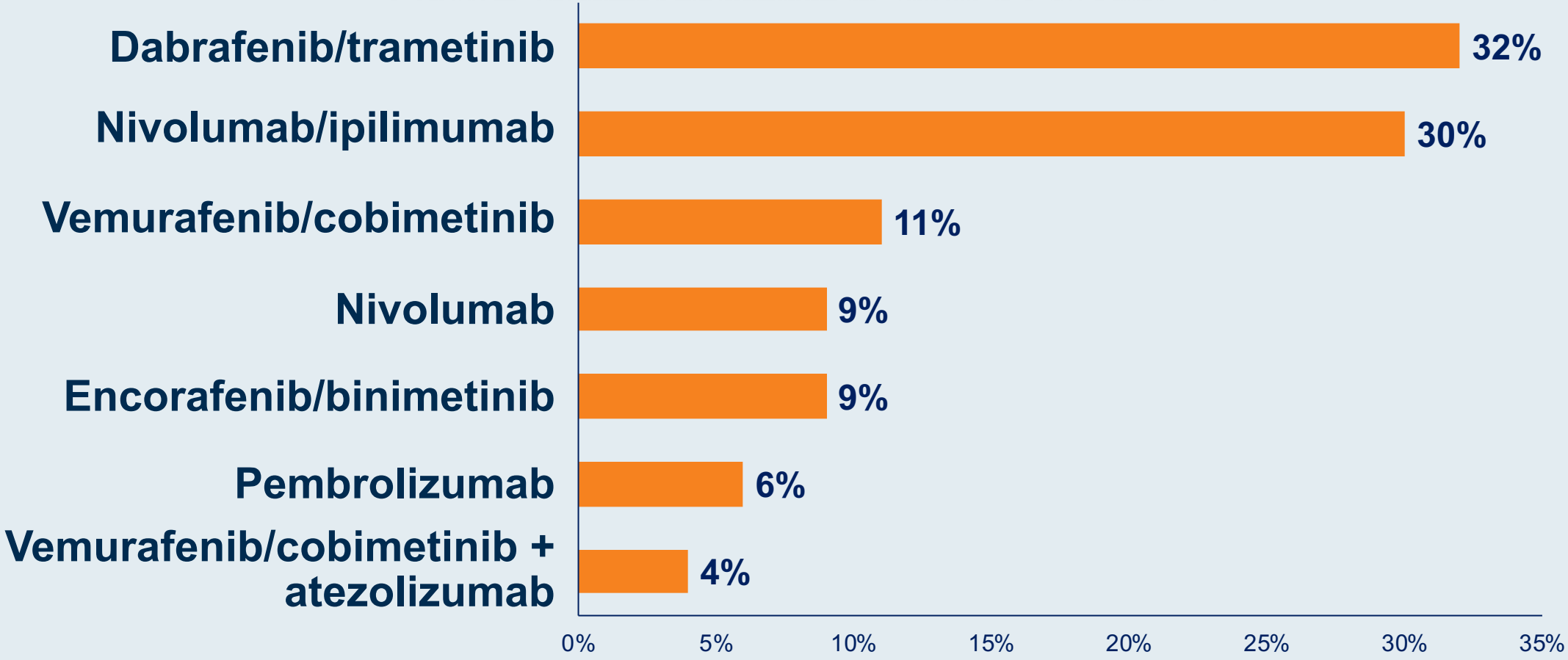
Johnson *et al*. *J Immunother*. 2017; Amini-Adle *et al*. *BMC Cancer*. 2018

Courtesy of Jason J Luke, MD

Regulatory and reimbursement issues aside, what would you recommend as first-line treatment for an asymptomatic, clinically stable younger patient with BRAF-mutant metastatic melanoma?

a. Nivolumab
b. Nivolumab/ipilimumab
c. Pembrolizumab
d. Vemurafenib/cobimetinib
e. Dabrafenib/trametinib
f. Encorafenib/binimetinib
g. Vemurafenib/cobimetinib + atezolizumab
h. Other (please specify)

Regulatory and reimbursement issues aside, what would you recommend as first-line treatment for an asymptomatic, clinically stable younger patient with BRAF-mutated metastatic melanoma?

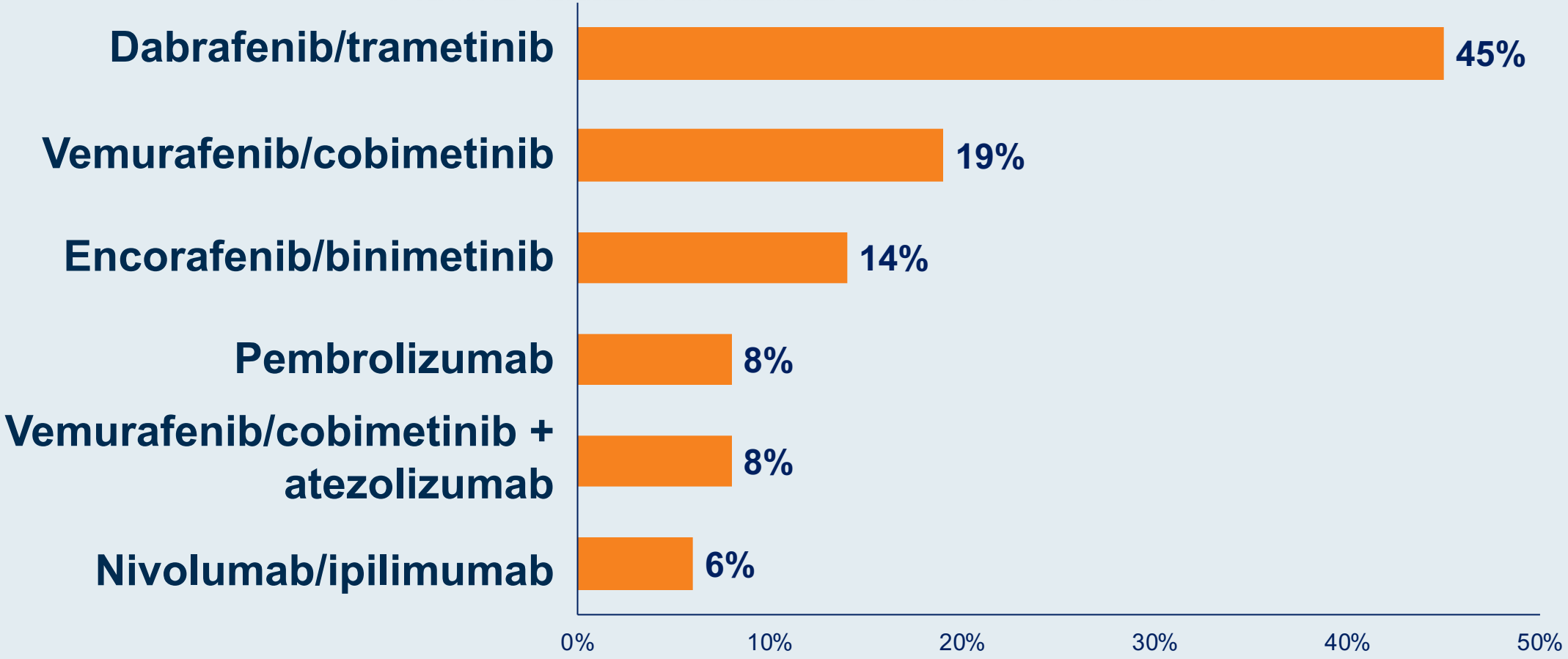


Survey of 48 US-based medical oncologists

Regulatory and reimbursement issues aside, what would you recommend as first-line treatment for a symptomatic younger patient with extensive BRAF-mutant metastatic melanoma?

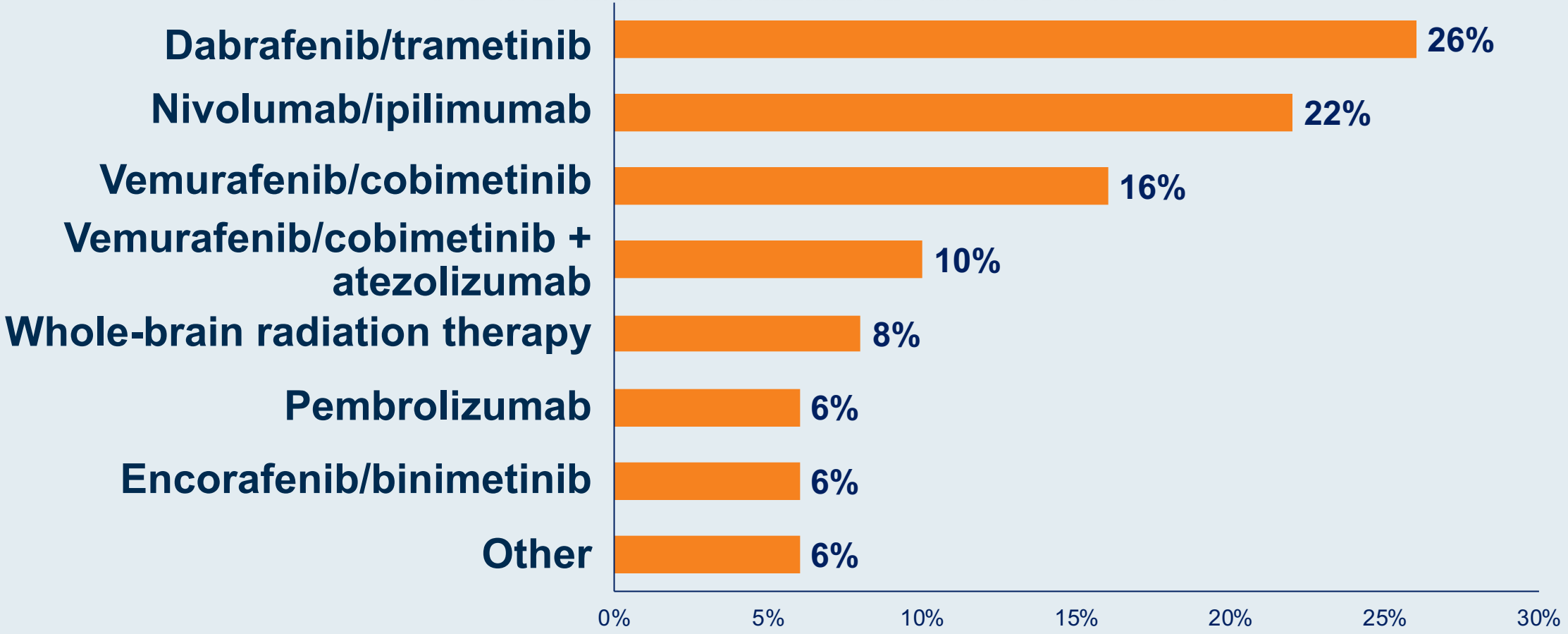
a. Nivolumab
b. Nivolumab/ipilimumab
c. Pembrolizumab
d. Vemurafenib/cobimetinib
e. Dabrafenib/trametinib
f. Encorafenib/binimetinib
g. Vemurafenib/cobimetinib + atezolizumab
h. Other

Regulatory and reimbursement issues aside, what would you recommend as first-line treatment for a symptomatic younger patient with extensive BRAF-mutated metastatic melanoma?



Survey of 49 US-based medical oncologists

Regulatory and reimbursement issues aside, what would you recommend as initial treatment for an asymptomatic younger patient with BRAF-mutated metastatic melanoma including multiple bilateral brain metastases?



Survey of 50 US-based medical oncologists

Case Presentation – Dr Luke: A 53-Year-Old Woman with Stage IIIB Melanoma and a BRAF V600E Mutation

- 53 year old woman with stage IIIB melanoma on her left arm
  - Wide local excision and sentinel node but deferred completion dissection
  - BRAF testing showing V600E mutation
- Received adjuvant nivolumab but developed severe fatigue by month 8
  - Check TSH which was WNL
- Restaging imaging showing disease in lung and liver
- Started on encorafenib + binimetinib
- MRI delayed due to COVID-19 but shows multiple small brain lesions
- Nivolumab added to regimen for BRAF-MEK-anti-PD-1 combo

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@jasonlukemd

Case Presentation – Dr Luke: A 42-Year-Old Man with Stage IIIC Melanoma and a BRAF V600E Mutation

- 42 year old man with stage IIIC melanoma on right leg
  - Wide local excision, sentinel node with completion dissection due to palpable disease in right groin
  - BRAF testing showing V600E mutation
- Received adjuvant dabrafenib + trametinib
  - Had 1 treatment delay due to pyrexia
- Had recurrence with bone and lung mets 1 year after stopping BRAF-MEK inhibitor
- Treated with ipilimumab + nivolumab with resolution of lung mets but new bone mets
- Started on encorafenib + binimetinib with resolution of pain

UPMC | HILLMAN CANCER CENTER

NCI Designated Comprehensive Cancer Center

@jasonlukemd

Agenda

Module 2: Case from the Community

Hi Dr Love,

I am encountering a challenging case this week and wondering if I could get some opinions from investigators in the field about further management. 69 yr old gentleman presented with small amt of penile bleeding / found to have a small distal urethral nodule and a small skin pigmented lesion - path from urethral biopsy - melanoma. BRAF WT
PET focal uptake in distal penis and no other abn.
Underwent partial penectomy - path showed distal urethral mucosal melanoma (1.6 x 1.1 x 0.9cm) and a small satellite lesion on skin (0.6cm)
Margins widely neg
No SLN or lymphadenectomy done
Debating on role of immunotherapy
Because of skip lesion, that would be stage 3
Would there be a role for adj immunotherapy? Would they have done surgical ln eval?
Thanks for your time.

P Mallidi

Agenda

Module 3: Adjuvant and Neoadjuvant Treatment — Prof Long

The NEW ENGLAND JOURNAL of MEDICINE

Melanoma Institute Australia

ORIGINAL ARTICLE

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

G.V. Long, A. Hauschild, M. S
V. Chiarion-Sileni, J. Larkin, M. Ny
L. Mortier, J. Schachter, D. Schadendc
B. Mookerjee, J. Legos, R. Keff

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV M

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

12 Months of Treatment

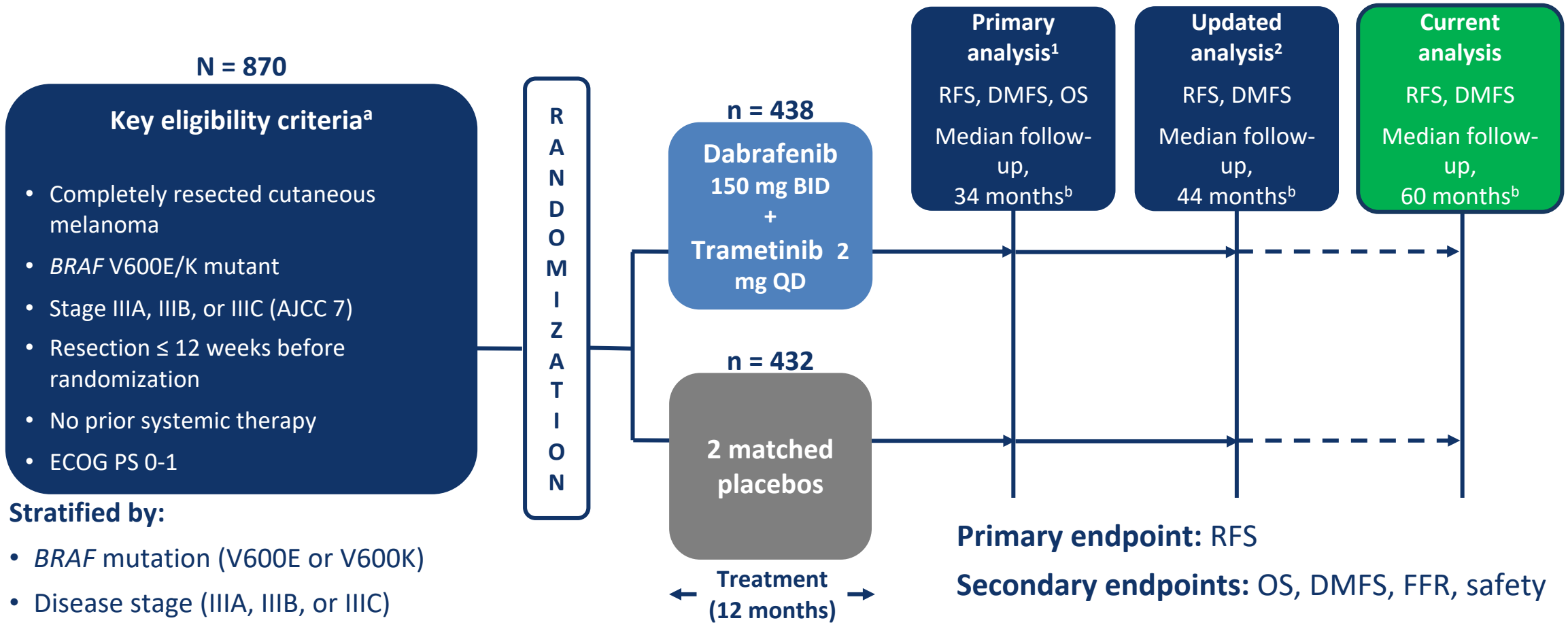
~50% reduction in risk of recurrence vs placebo

James Larkin, M.D., Susana Puig, M.D., Ph.D., Paolo A. Ascierto, M.D.,
Piotr Rutkowski, M.D., Dirk Schadendorf, M.D., Ph.D., Rutger Koornstra, M.D.,
Leonel Hernandez-Aya, M.D., Michele Maio, M.D., Ph.D.,
Alfonsus J.M. van den Eertwegh, M.D., Ph.D., Jean-Jacques Grob, M.D., Ph.D.,
Ralf Gutzmer, M.D., Rahima Jamal, M.D., Paul Lorigan, M.D., Nageatte Ibrahim, M.D.,
Sandrine Marreaud, M.D., Alexander C.J. van Akkooi, M.D., Ph.D., Stefan Suciu, Ph.D.,
and Caroline Robert, M.D., Ph.D.

Courtesy of Georgina V Long, MD

Phase 3 COMBI-AD

Dabrafenib + Trametinib vs Placebo Resected Stage III Melanoma
AJCC 7th edn: IIIA (>1mm in LN), IIIB, IIIC



1. Long GV, et al. *N Engl J Med*. 2017;377:1813-1823; 2. Hauschild A, et al. *J Clin Oncol*. 2018;4:1382-1388.

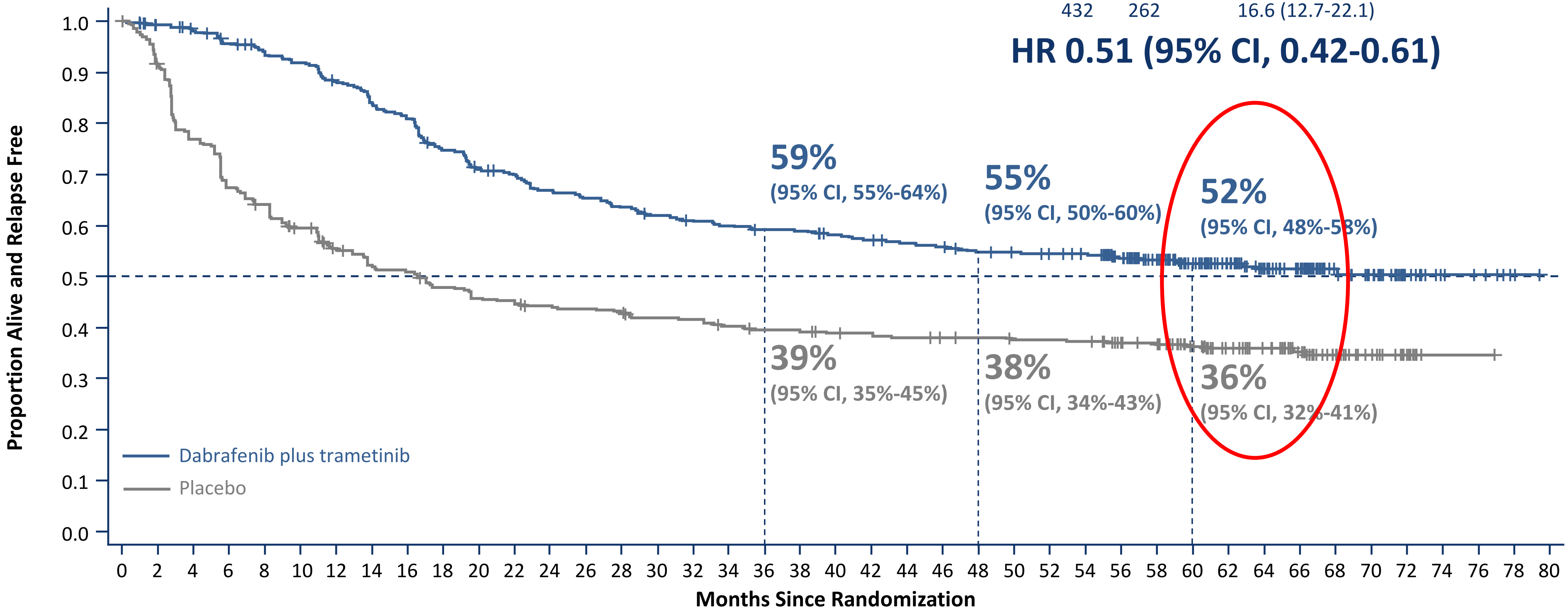
Courtesy of Georgina V Long, MD

Phase 3 COMBI-AD
Dabrafenib + Trametinib vs Placebo Resected Stage III Melanoma
AJCC 7th edn: IIIA (>1mm in LN), IIIB, IIIC

Melanoma Institute Australia

	n	Events	Median (95% CI), mo
Dabrafenib plus trametinib	438	190	NR (47.9-NR)
Placebo	432	262	16.6 (12.7-22.1)

HR 0.51 (95% CI, 0.42-0.61)



No. at risk

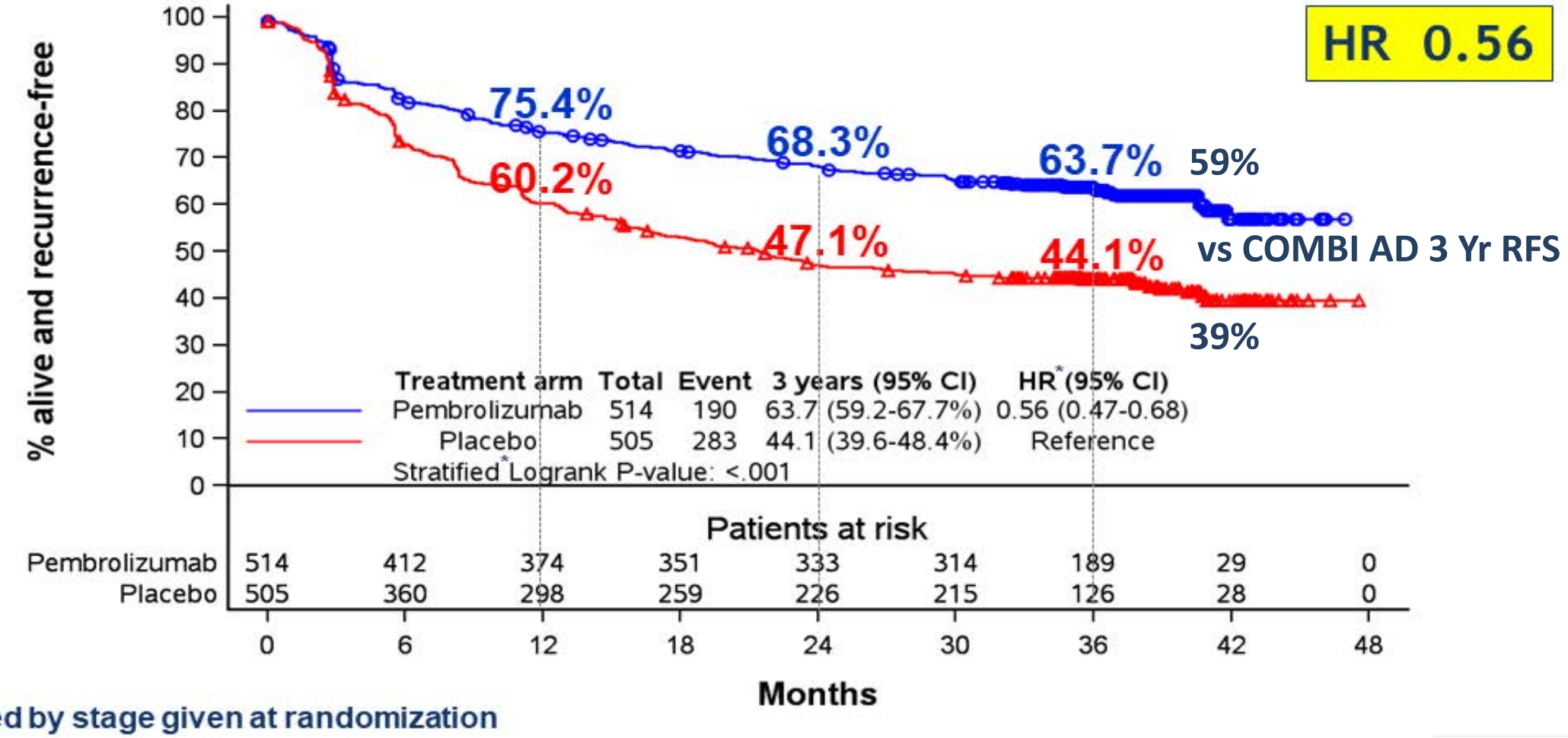
Months	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54	56	58	60	62	64	66	68	70	72	74	76	78	80
Dabrafenib plus trametinib	438	413	405	391	381	372	354	335	324	298	281	275	262	256	249	242	236	233	229	228	221	217	213	210	204	202	199	195	176	156	133	109	92	80	45	38	17	8	6	2	0
Placebo	432	387	322	280	263	243	219	204	199	185	178	175	168	166	164	158	157	151	147	146	143	140	139	137	136	133	133	132	121	115	99	80	69	56	35	26	13	1	1	0	0

Med Follow up 60 months

Courtesy of Georgina V Long, MD

Hauschild et al. ASCO 2020

Phase 3 EORTC 1325 - KEYNOTE-054
Pembrolizumab vs Placebo Resected Stage III Melanoma
AJCC 7th edn: IIIA (>1mm in LN), IIIB, IIIC

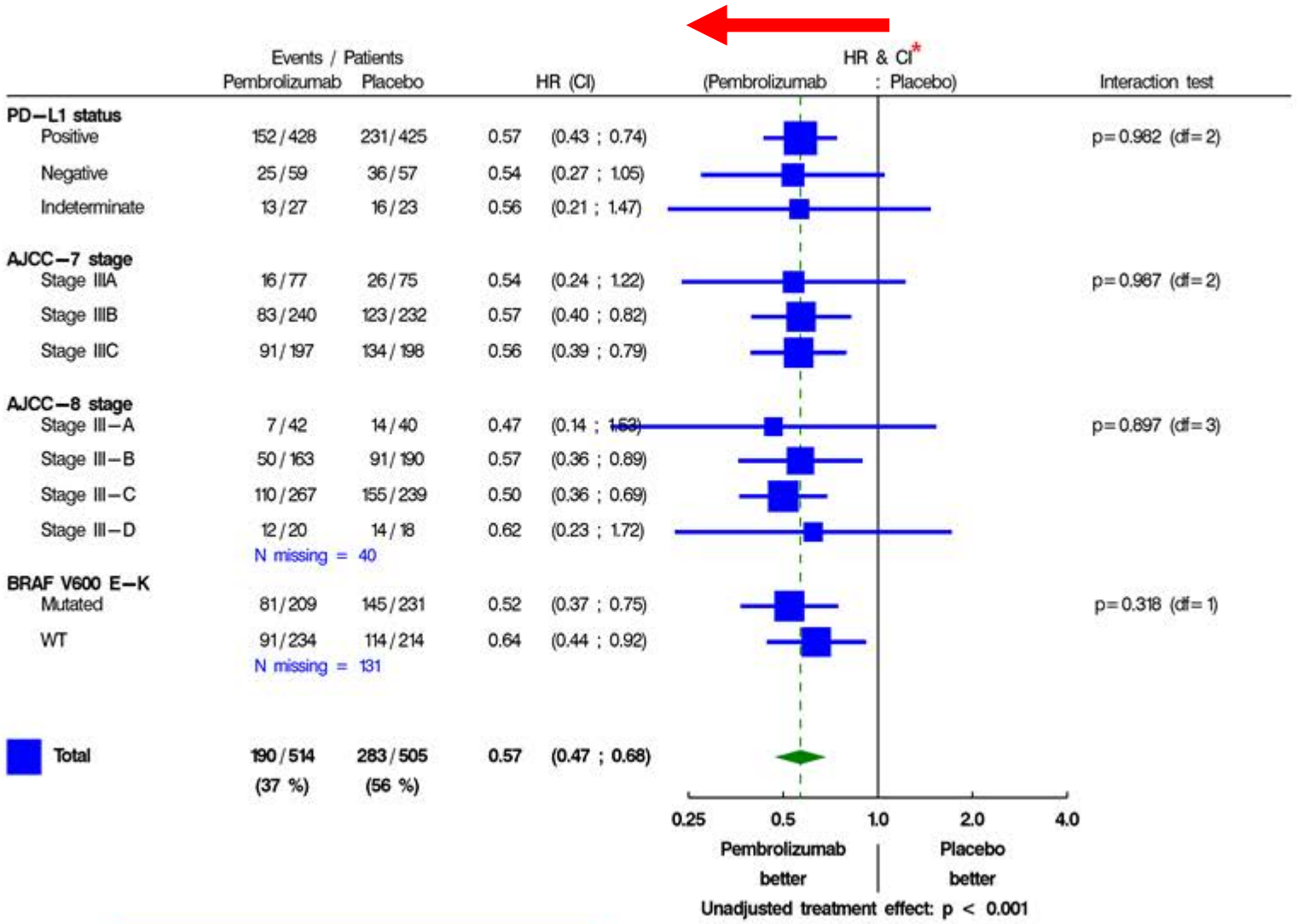


Med Follow up 36 months

Courtesy of Georgina V Long, MD

Eggermont A et al ASCO 2020

EORTC 1325 - KN-054 RFS: Every Subgroup Benefits



*95% CI for total, 99% CI for subgroups

Unstratified analysis by stage given at randomization

Courtesy of Georgina V Long, MD

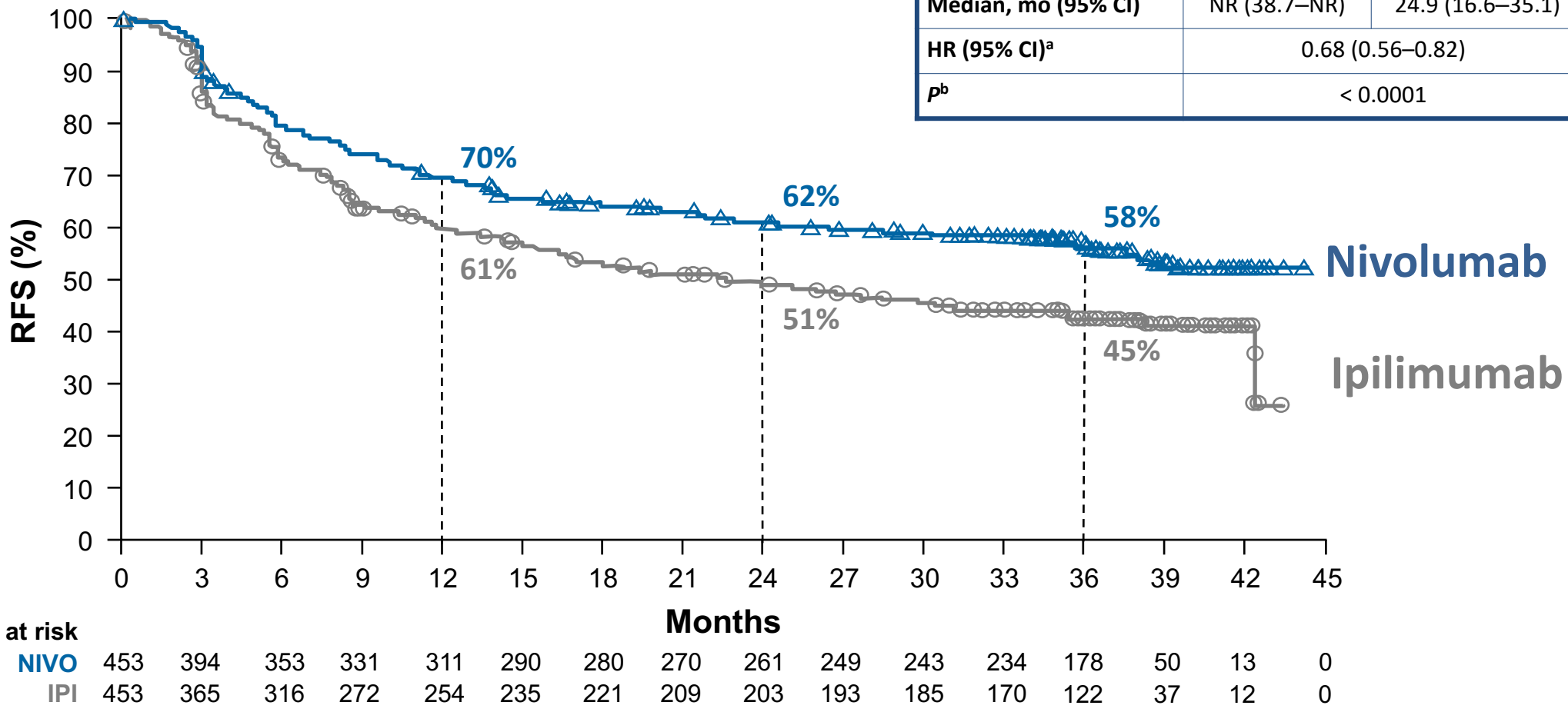
Eggermont A et al ASCO 2020

Phase 3 CheckMate 238

Nivolumab vs Ipilimumab Resected Stage III/IV Melanoma

AJCC 7th edn: IIIB, IIIC, IV

	NIVO (n = 453)	IPI (n = 453)
Events, n	188	239
Median, mo (95% CI)	NR (38.7–NR)	24.9 (16.6–35.1)
HR (95% CI)[a]	0.68 (0.56–0.82)	
***P*[b]**	< 0.0001	



Minimum follow-up: 36 months

[a]Stratified; [b]Log-rank test. NR, not yet reached.

Weber et al ESMO 2019

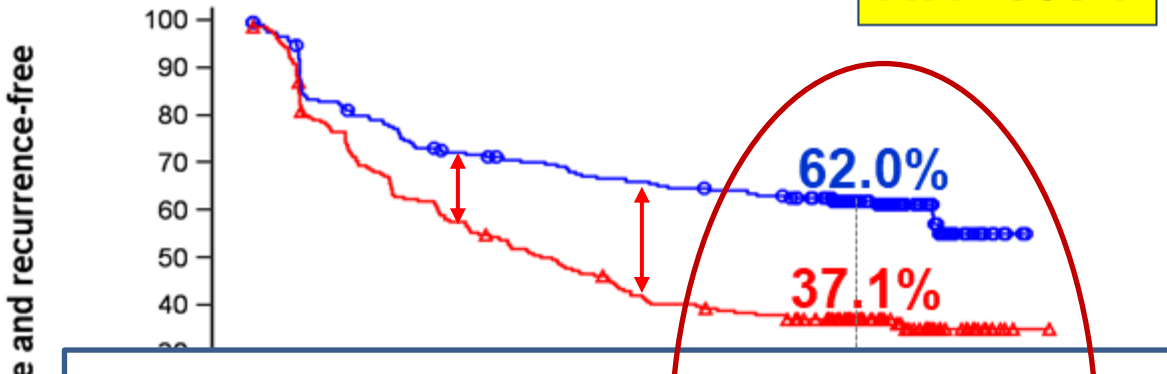
Courtesy of Georgina V Long, MD

Phase 3 EORTC 1325 - KEYNOTE-054 (Pembrolizumab vs Placebo Resected Stage III Melanoma)

Compared to Phase III COMBI-AD (Dabrafenib/Trametinib vs Placebo)

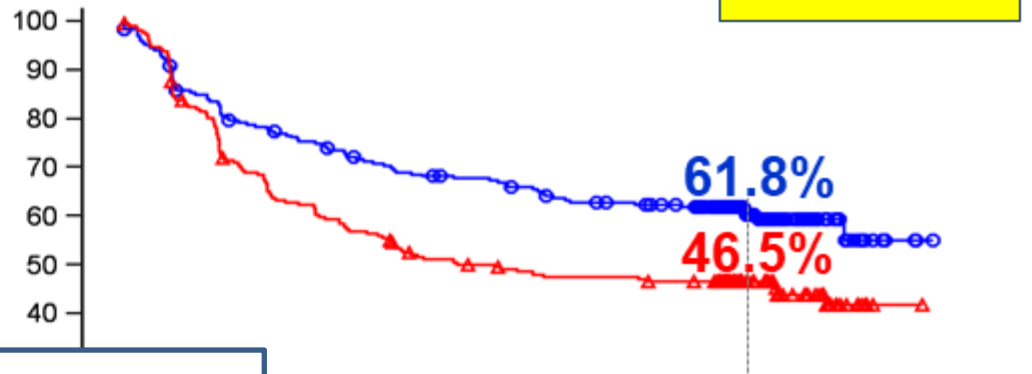
V600E/K BRAF mutated

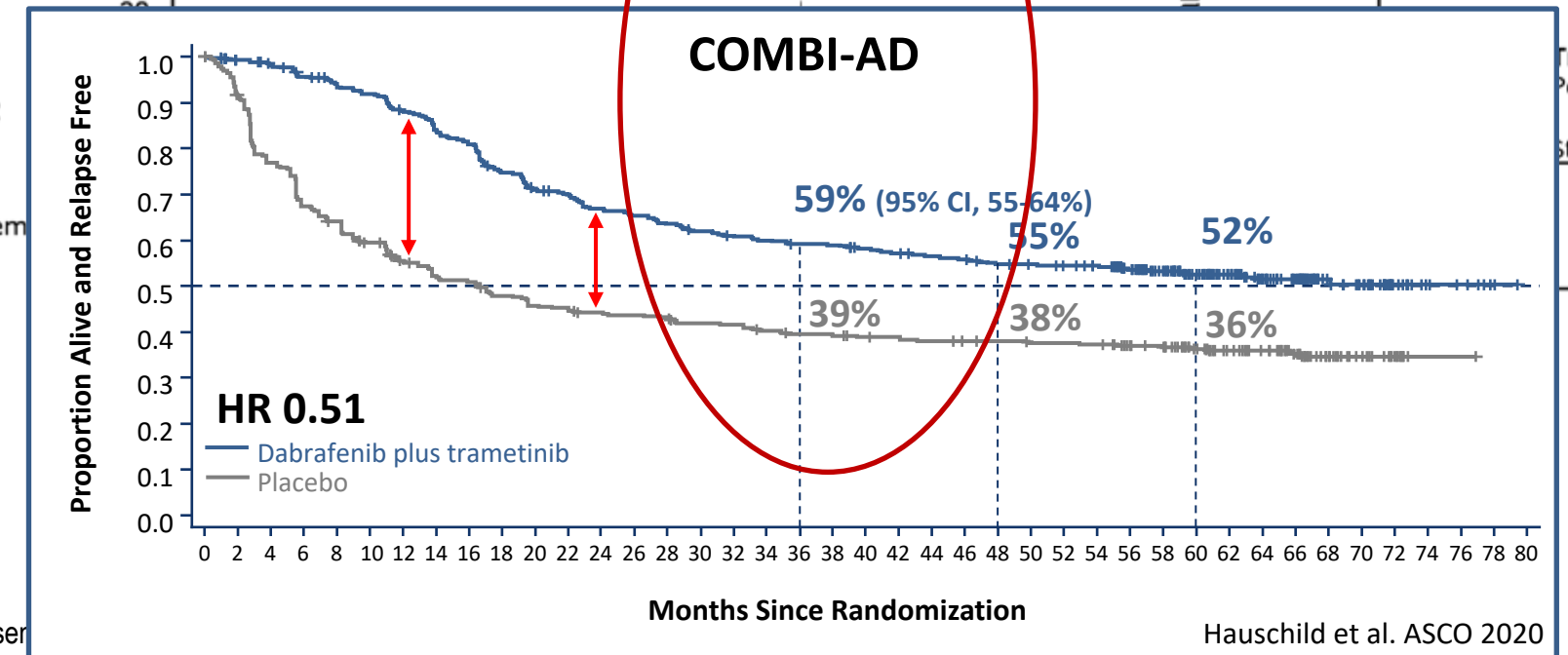
HR 0.51



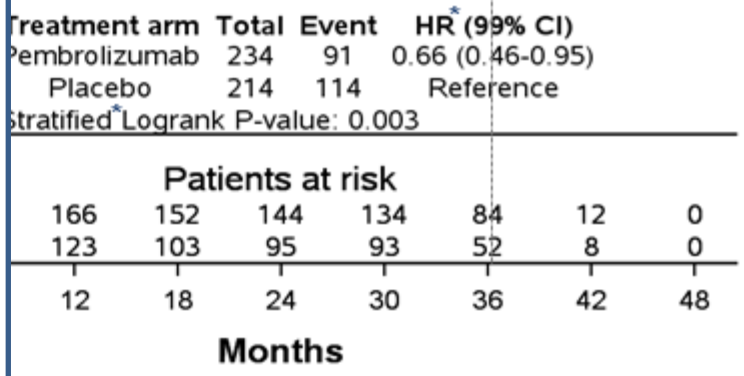
BRAF wildtype

HR 0.66





Hauschild et al. ASCO 2020



Eggermont A et al ASCO 2020

Courtesy of Georgina V Long, MD

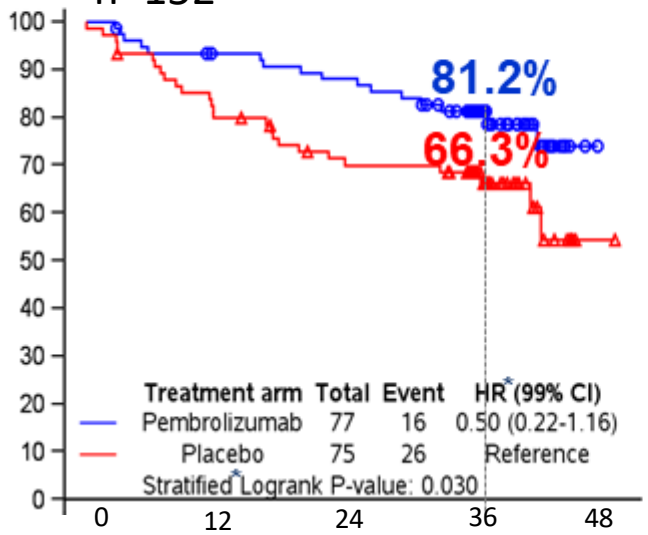
KEYNOTE-054 vs COMBI-AD: Relapse-Free Survival by AJCC Stage (7th edn)

Melanoma Institute Australia

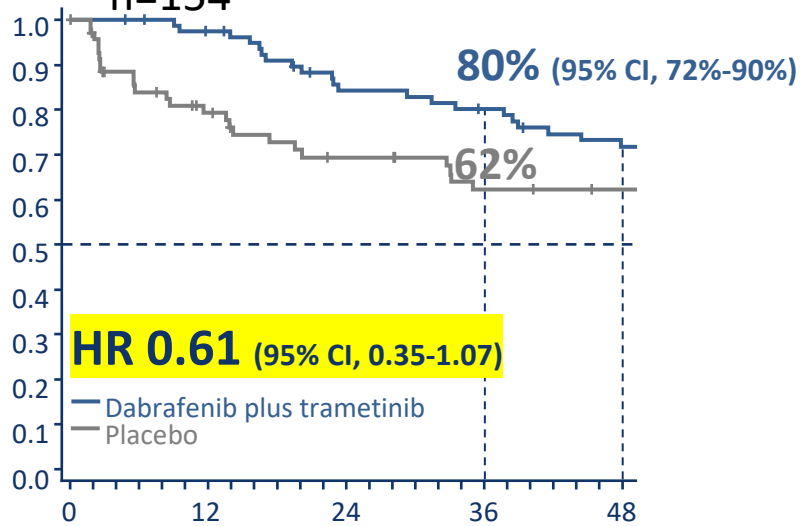
Stage IIIA

HR 0.50

n=152



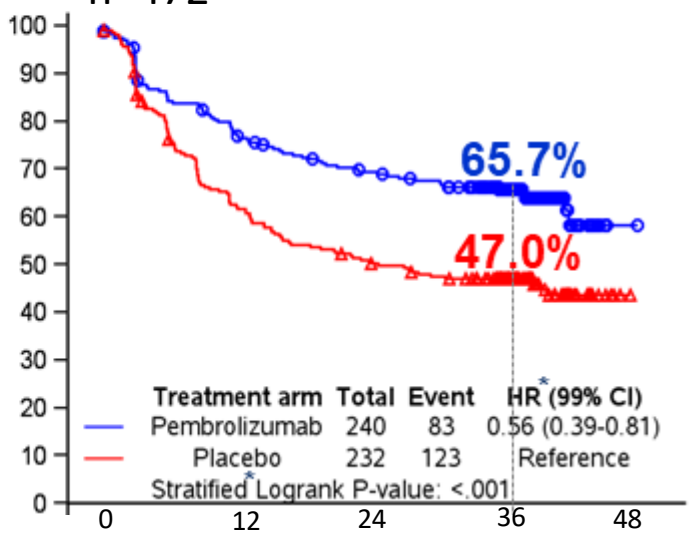
n=154



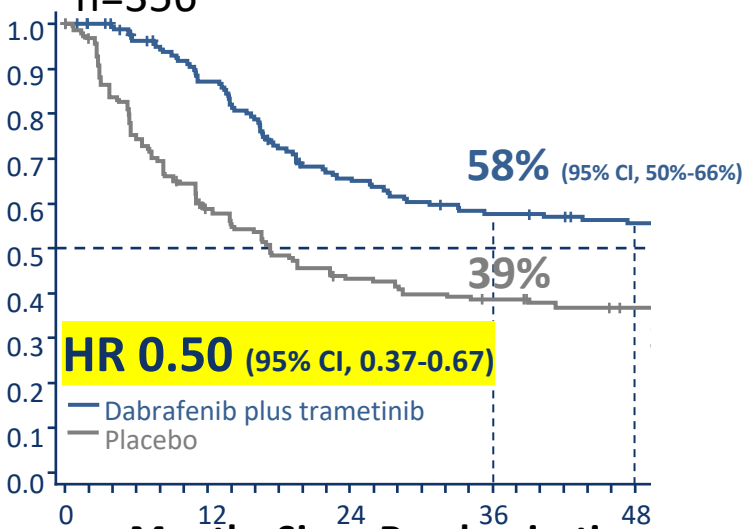
Stage IIIB

HR 0.56

n=472



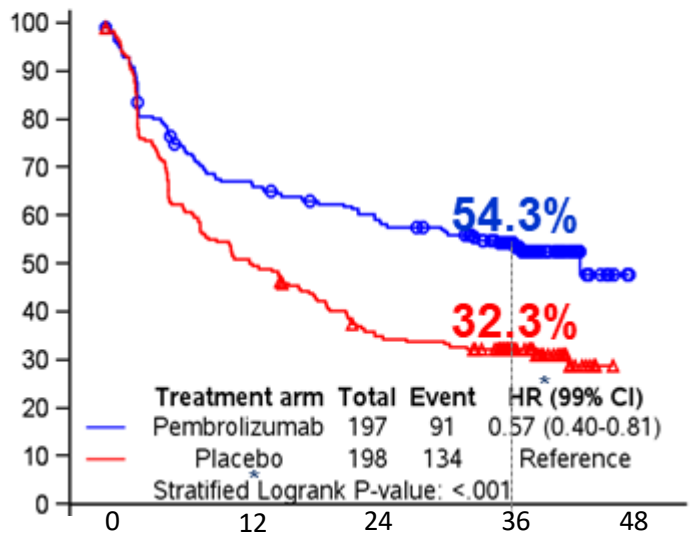
n=356



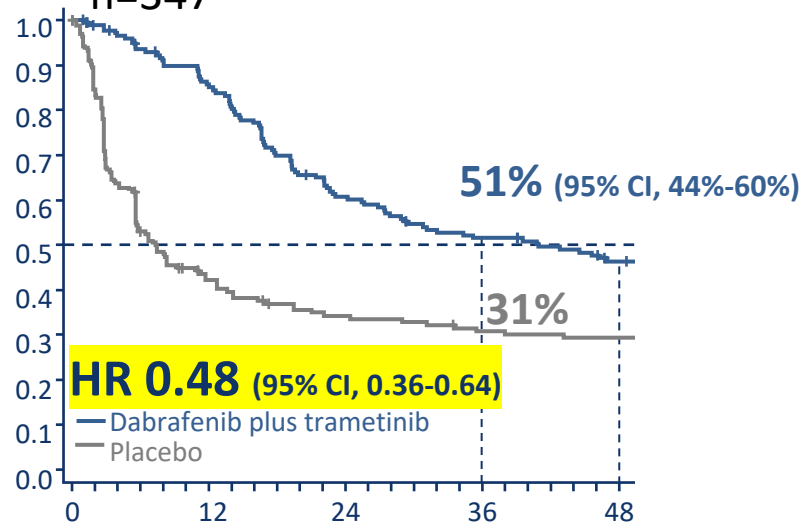
Stage IIIC

HR 0.57

n=395



n=347



% alive and recurrence-free

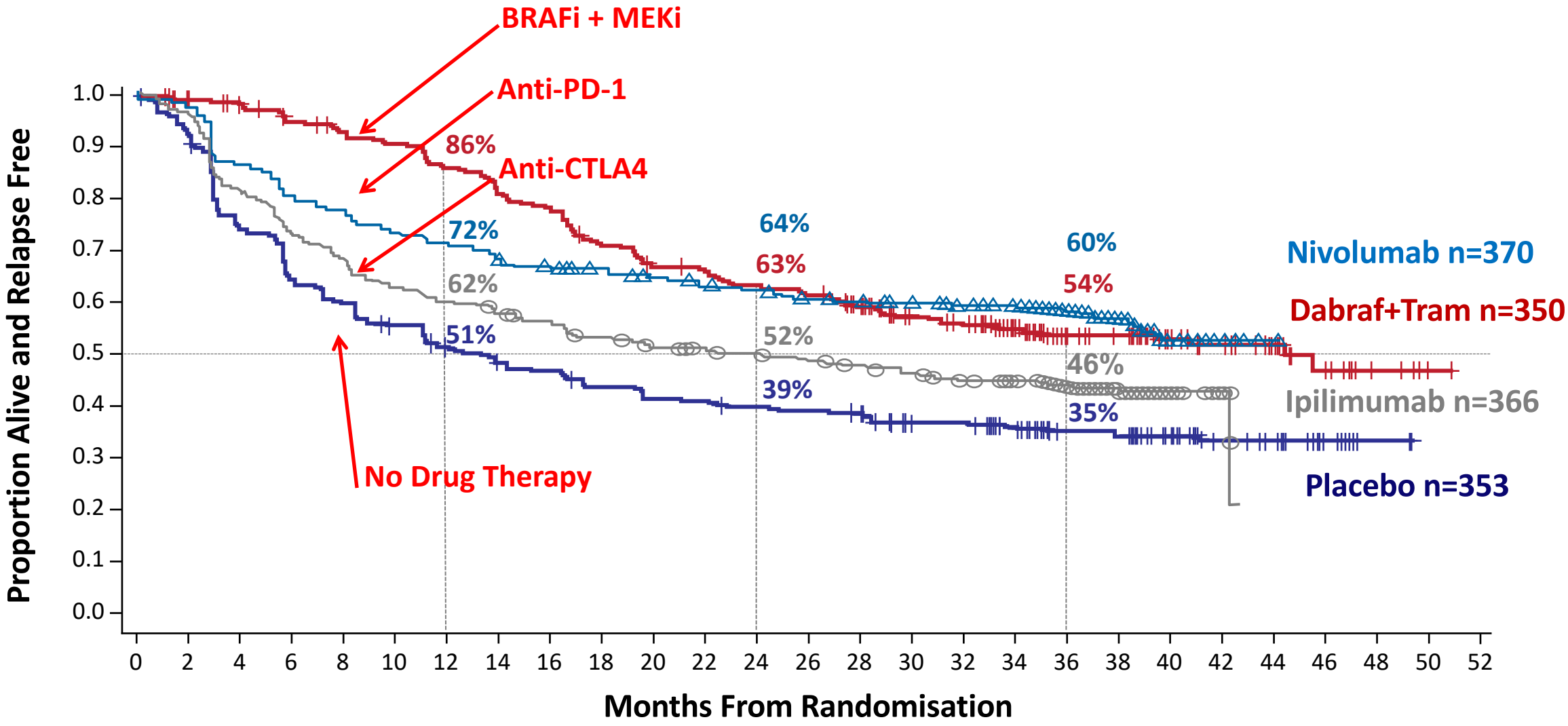
Proportion Alive and Relapse Free

Months Since Randomization

Presented by Georgina V Long @ProfGLongMIA

Courtesy of Georgina V Long, MD

COMBI-AD[1] and CheckMate 238[2]
Relapse Free Survival: Stage IIIB and IIIC



1. Long GV et al SMR 2017; 2. Weber et al ESMO 2019

Presented by Georgina V Long @ProfGLongMIA

Courtesy of Georgina V Long, MD

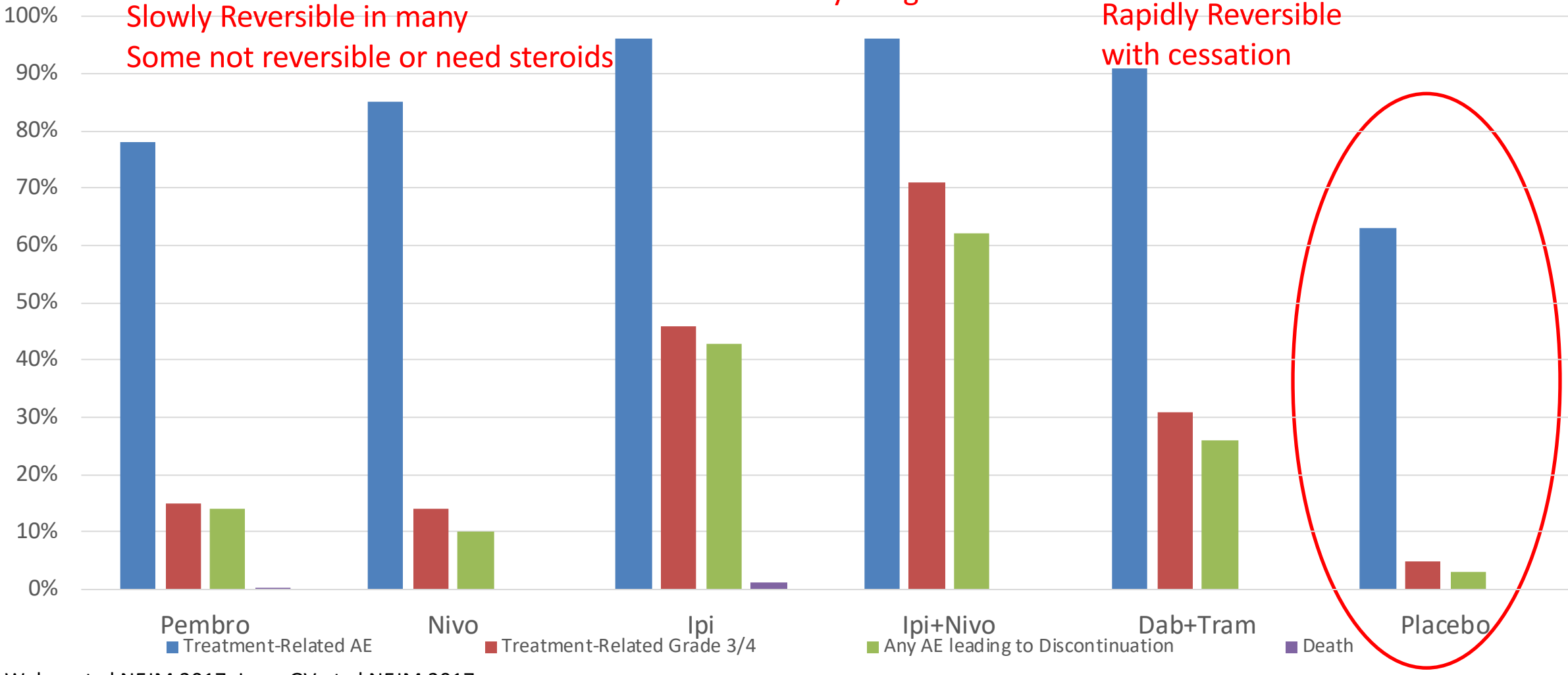
Adjuvant Studies - Toxicity

Melanoma Institute Australia

Slowly Reversible in some
May not be reversible or need steroids
~1% very dangerous

Slowly Reversible in many
Some not reversible or need steroids

Rapidly Reversible
with cessation



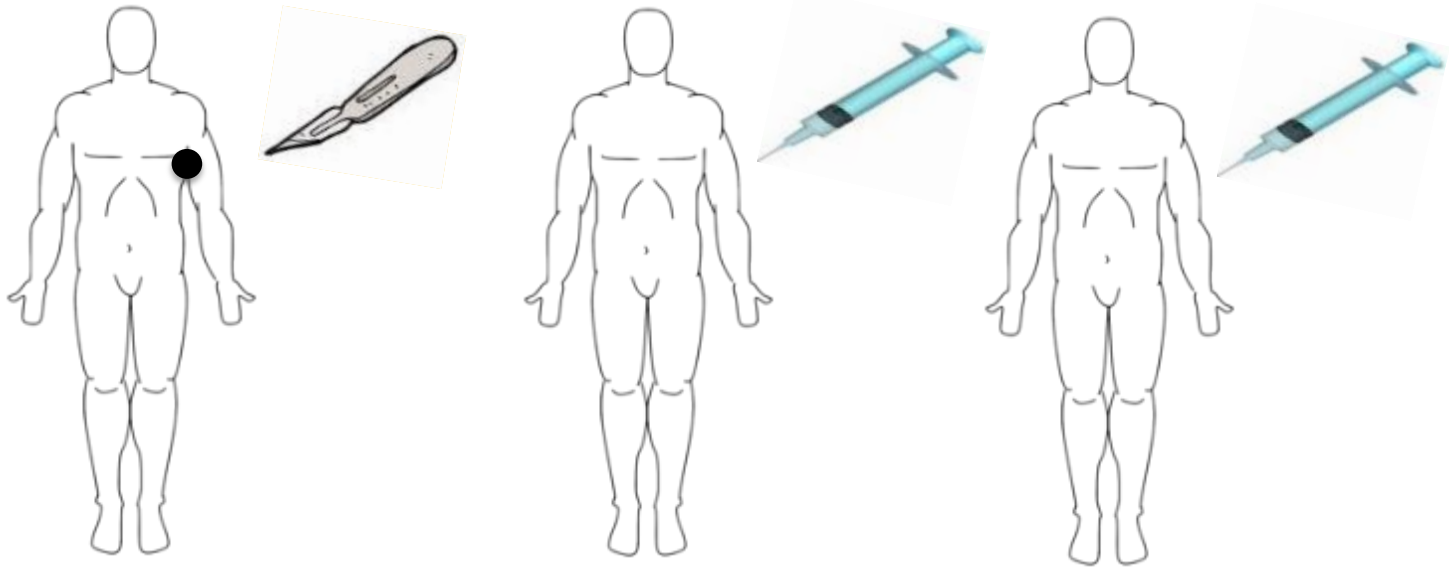
Weber et al NEJM 2017; Long GV et al NEJM 2017;
Eggermont A et al NEJM 2018; Schadendorf D et al ESMO 2019

Presented by Georgina V Long @ProfGLongMIA

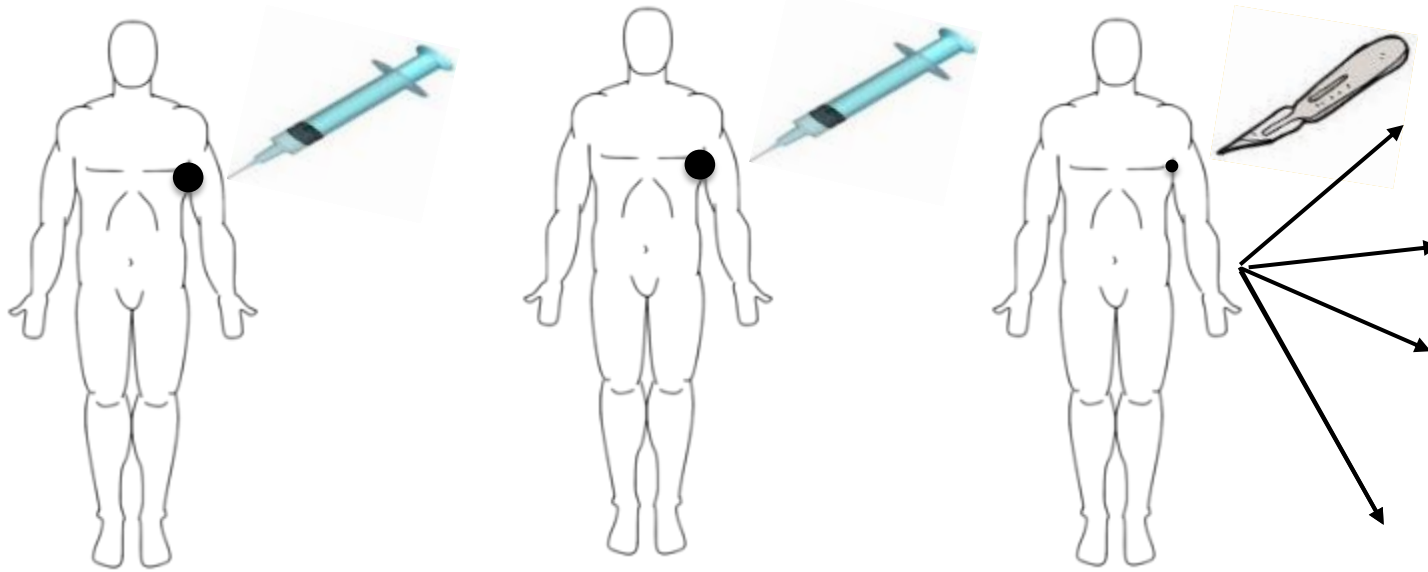
Courtesy of Georgina V Long, MD

Melanoma Institute Australia

Adjuvant



NeoAdjuvant

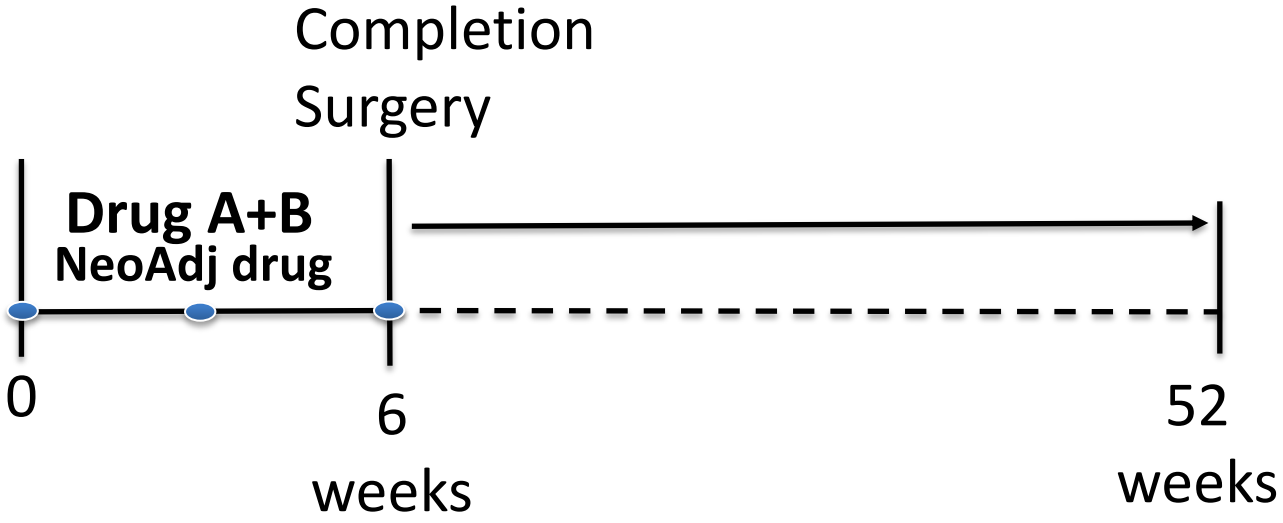


- **Pathological Complete Response**
- **Pathological Near Complete Response**
- **Pathological Partial Response**
- **No Pathological Response**

Courtesy of Georgina V Long, MD

6 Weeks Neoadjuvant Therapy: The Perfect Model

	pCR	pCR+near pCR
Ipi + Nivo	~50-60%	~65-70%
Dabraf + Tram	~50%	-
Pembro	~20%	~30%
TVEC	17%	-

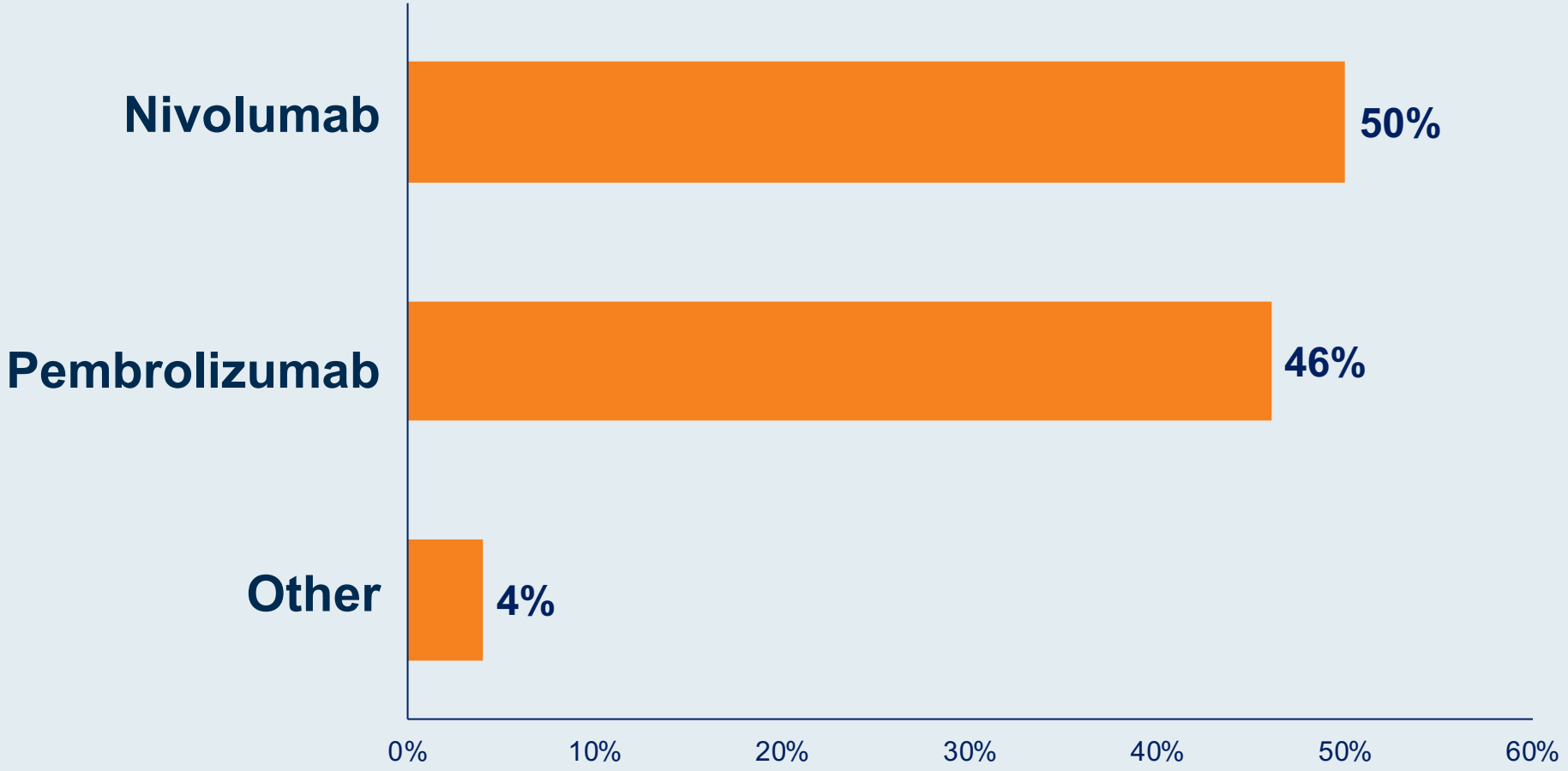


Path CR rate?

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 BRAF wild-type primary melanoma with 1 positive axillary node?

a. None
b. Nivolumab
c. Pembrolizumab
d. Ipilimumab
e. Other

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 BRAF wild-type primary melanoma with 1 positive axillary node?

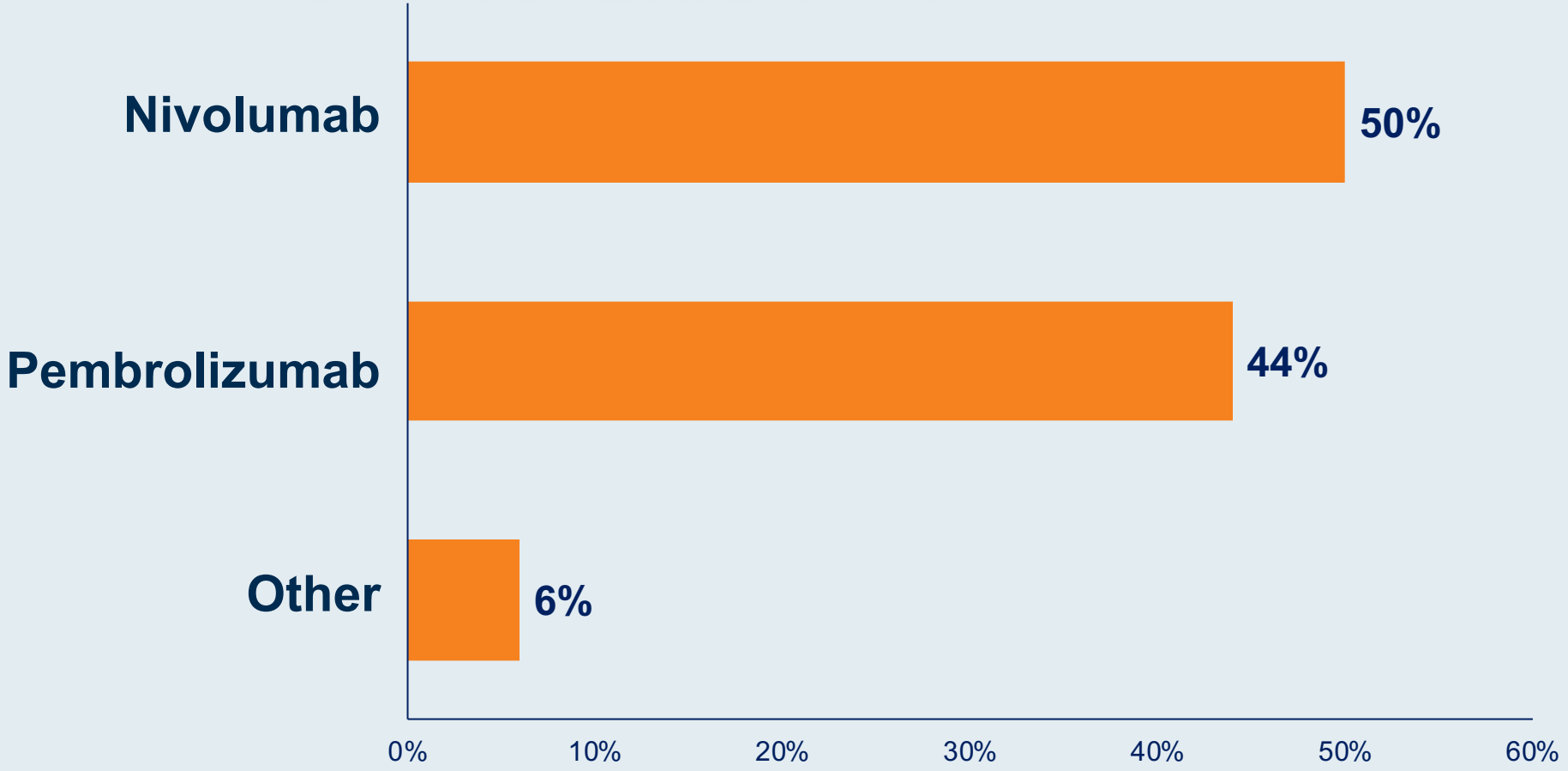


Survey of 50 US-based medical oncologists

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 BRAF wild-type primary melanoma with 1 positive axillary node?

a. None
b. Nivolumab
c. Pembrolizumab
d. Ipilimumab
e. Other

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 BRAF wild-type primary melanoma with 1 positive axillary node?

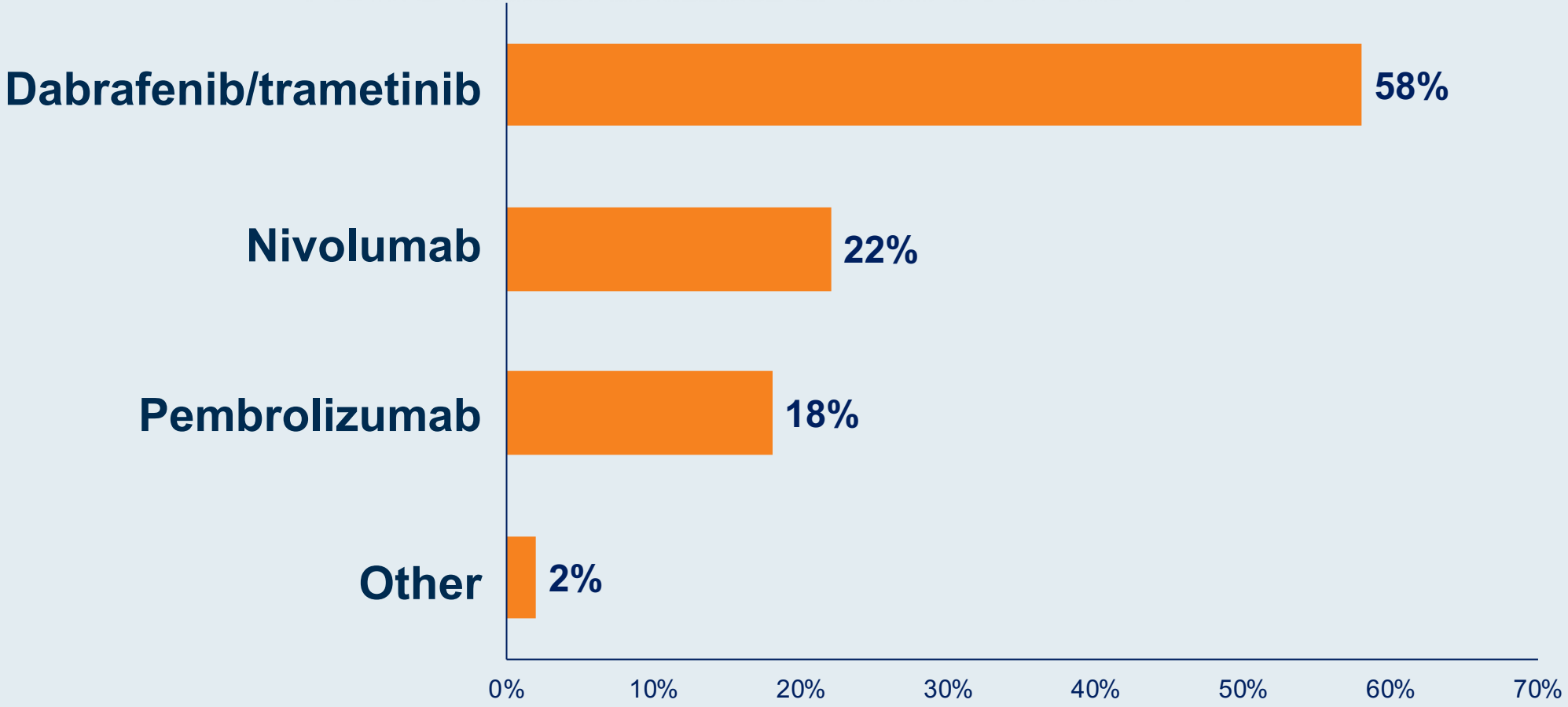


Survey of 50 US-based medical oncologists

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 BRAF V600E-mutant primary melanoma with 1 positive axillary node?

a. None
b. Nivolumab
c. Pembrolizumab
d. Ipilimumab
e. Dabrafenib/trametinib
f. Other

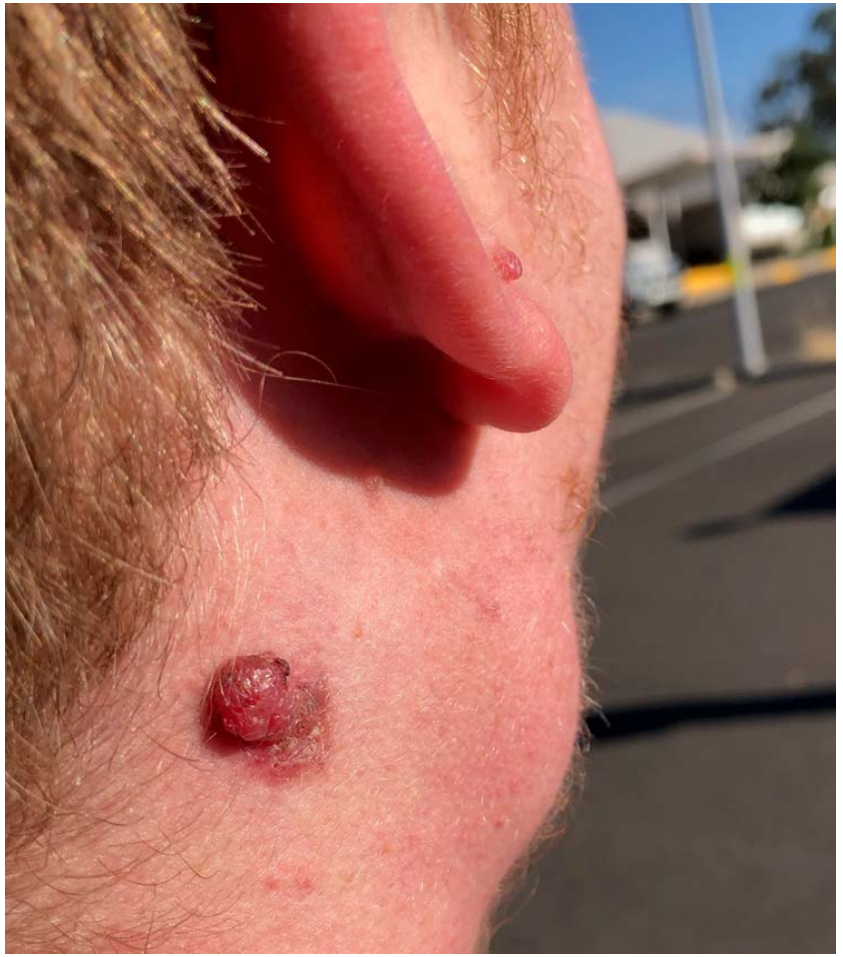
What is your usual approach to adjuvant systemic treatment, if any, for a 35-year-old patient who is s/p complete surgical resection of Stage IIIB primary melanoma with a BRAF V600E mutation and 1 positive axillary node?



Survey of 50 US-based medical oncologists

Case Presentation – Prof Long: A 19-Year-Old Male with Stage IIIC Melanoma

- 19 yo male
- Significant developmental delay
- Regional Australia (4h from major city)
- Presents to family doctor with
  - Mass in parotid
  - Lesion right post auricular
- Referred to general surgeon
- Height of COVID pandemic



Case Presentation (continued)

- Excision biopsy post-auricular lesion:
  - 6.5mm
  - Ulcerated
  - 2 mitosis/mm^2
  - Involved margin
- Right superficial parotidectomy + resection 2 neck lymph nodes
  - Intra-parotid lymph node involved with melanoma
  - Extra-nodal extension
  - Involved margin
  - 0/2 neck lymph nodes involved with melanoma

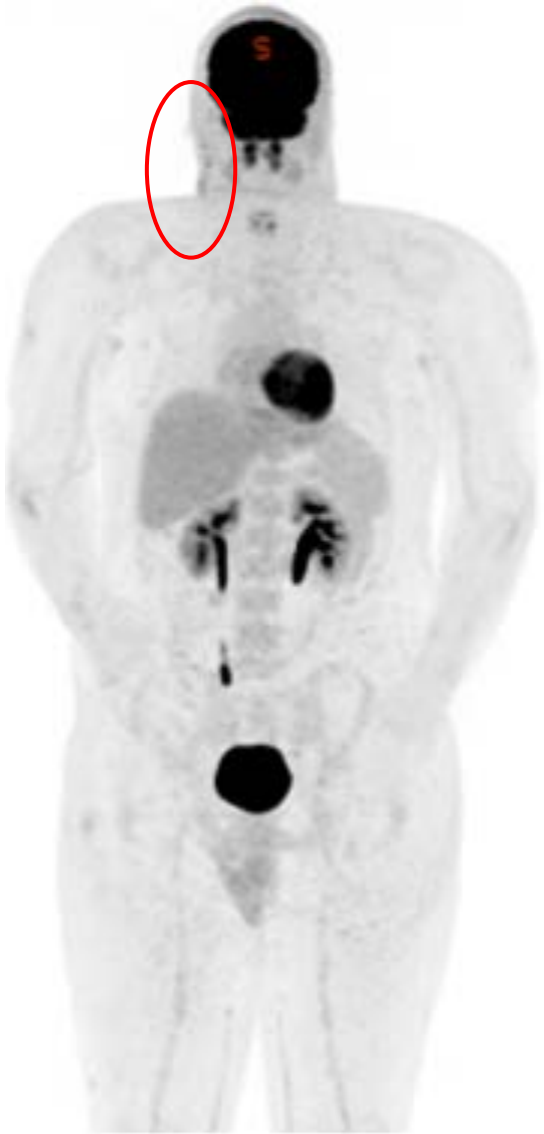
Case Presentation (continued)

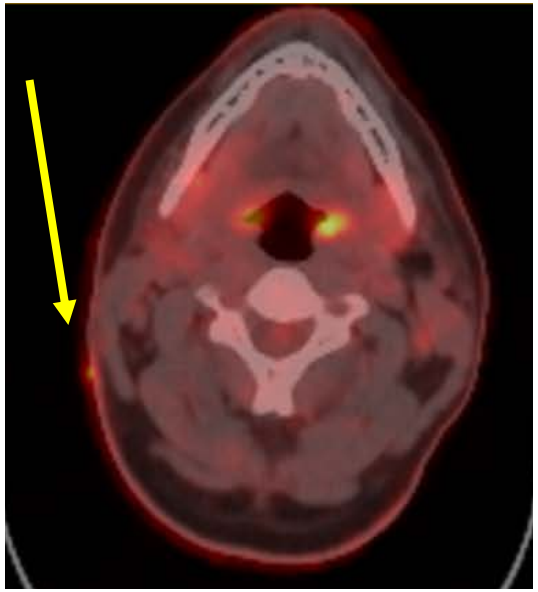
- COVID-pandemic
- 4 weeks later → Wider local Excision of Primary Site
  - Melanoma
  - Margins clear

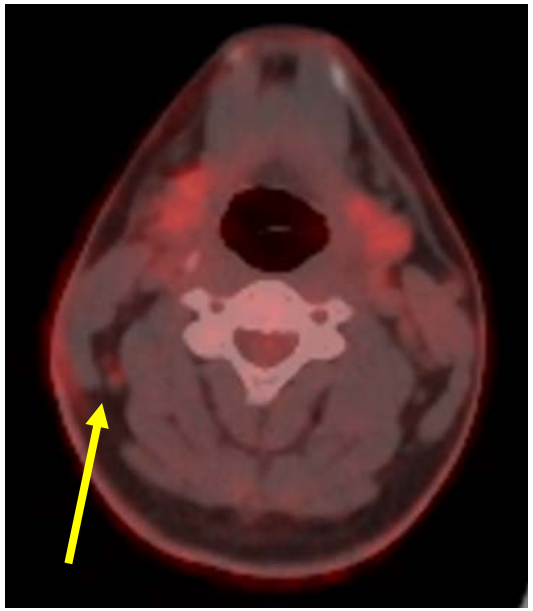
AJCC Staging - T4b N1b

Case Presentation (continued)

- Management
  - Referred to medical oncologist
  - Staging
  - MRI Brain clear
  - Referred to quaternary centre

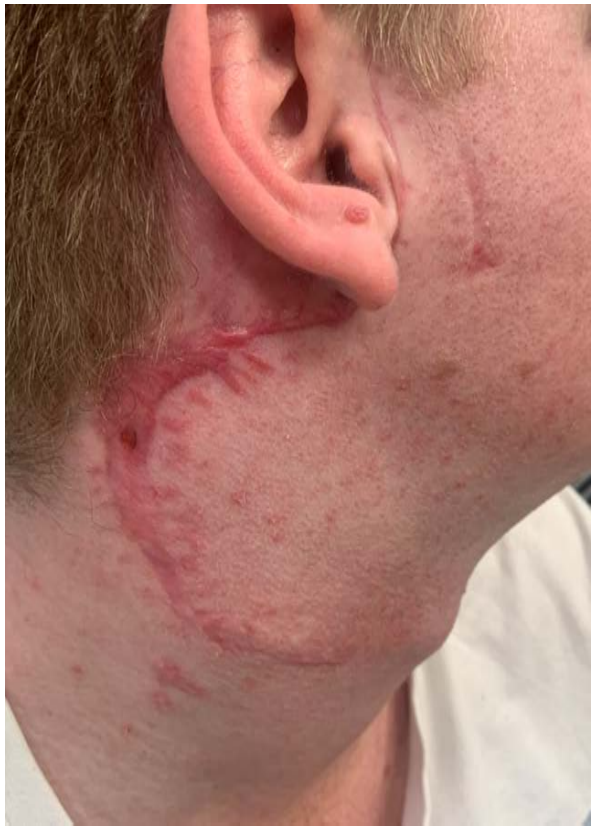


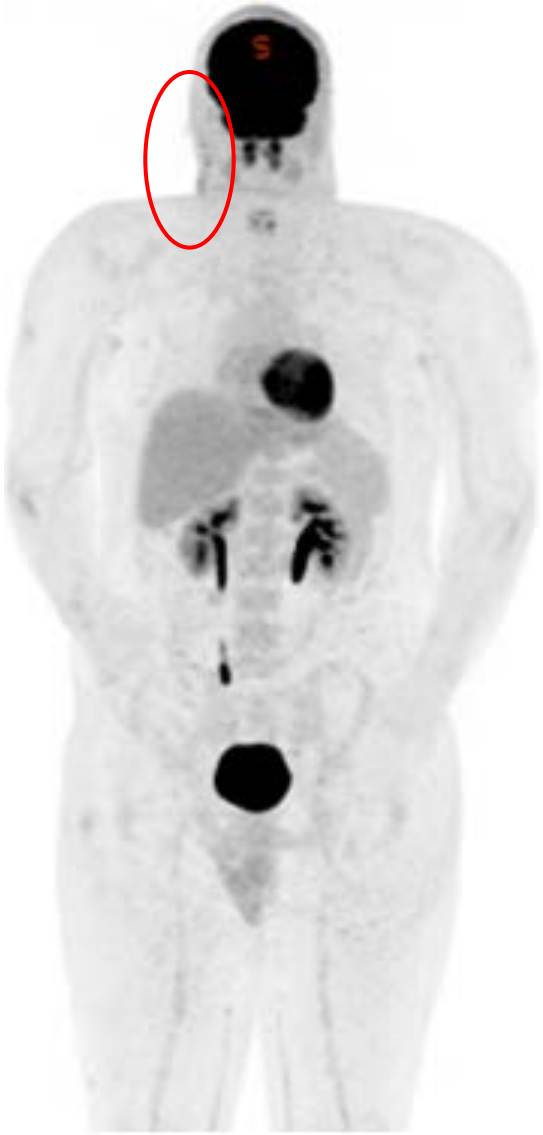


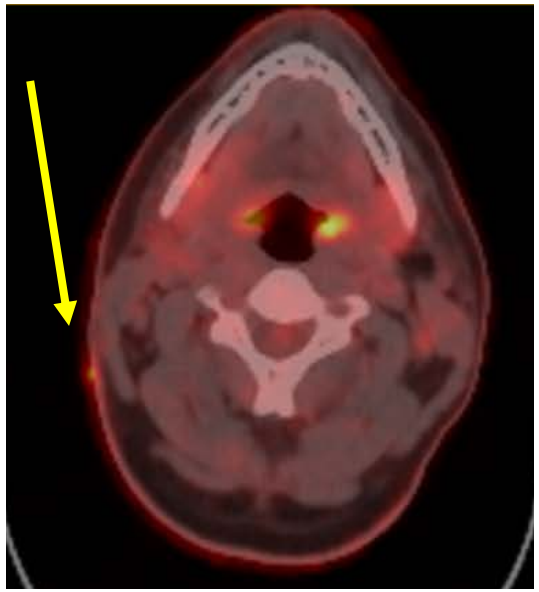


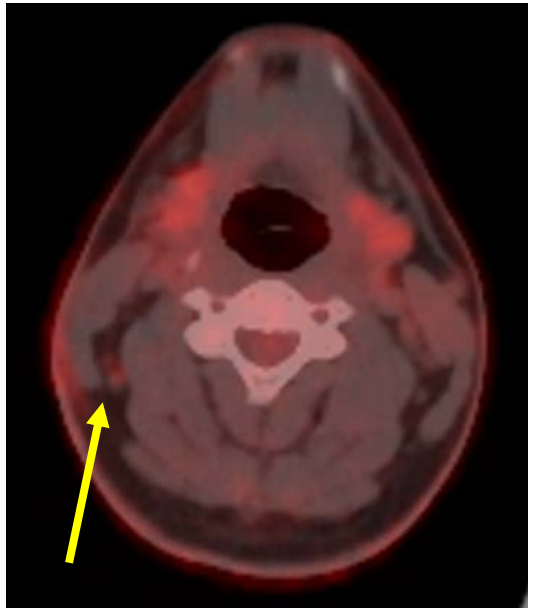
Case Presentation (continued)

- Management









High resolution Ultra Sound R neck – nil evidence of recurrence

T4b N1b M0 – Stage IIIC (AJCC 8th edn)

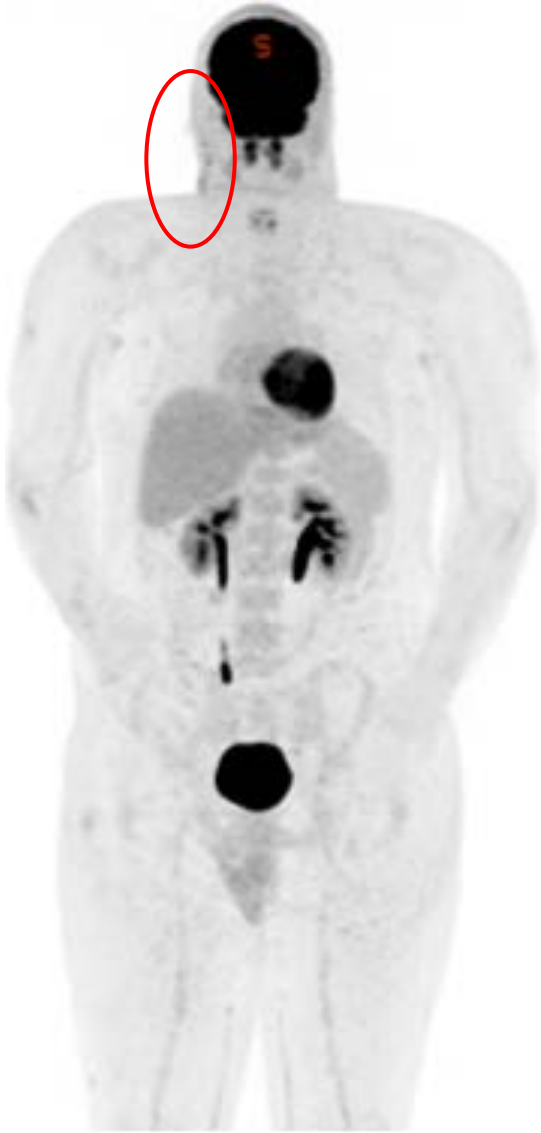
Risk of Recurrence[2] ~ 60-70%

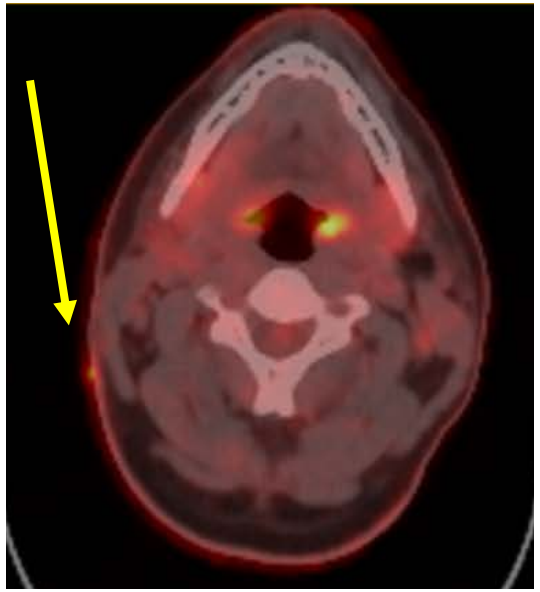
2 Long GV et al COMBI-AD NEJM 2017; Hauschild A et al COMBI-AD JCO 2019

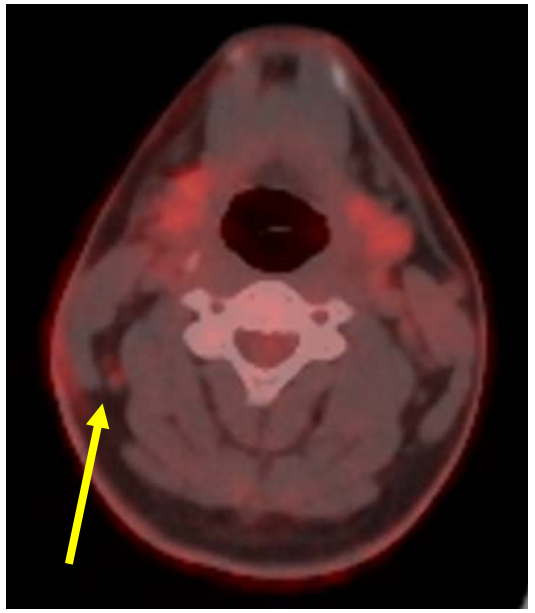
Case Presentation (continued)

- Management
  - Discussed adjuvant drug options
    - Anti-PD1 vs BRAFi+MEKi
    - Fear of **irreversible** toxicity in develop'l delay
    - Needle phobia
    - Dabrafenib dissolvable
    - Trametinib small
    - Better long term outcome IIIC?
  - Further Surgery?
  - Role for radiotherapy?

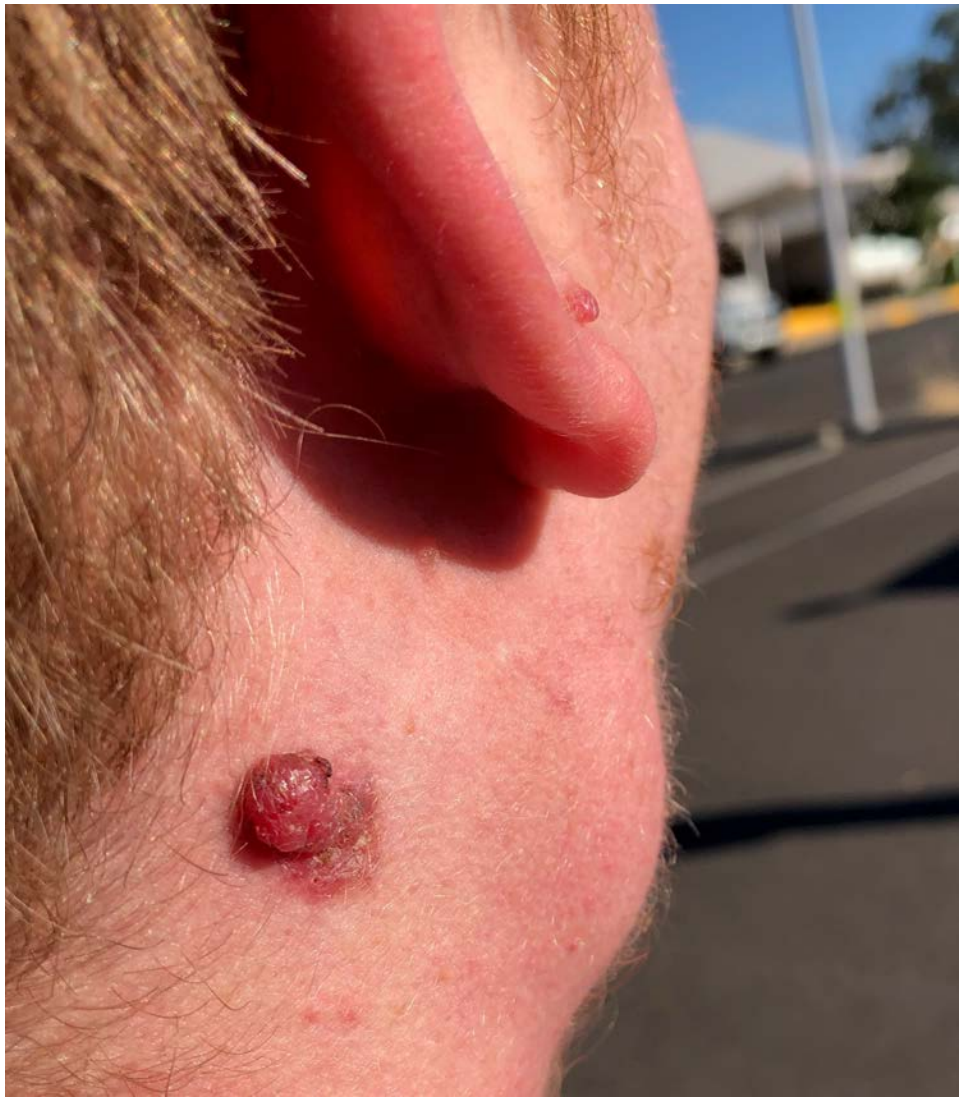
Tumour Board Discussion







Alternative: Neoadjuvant therapy at diagnosis?



Agenda

Module 4: Current and Future Use of Checkpoint Inhibition — Dr Atkins

Topics

- CheckMate 067 combination vs monotherapy
- IMMUNED study
  - Less Ipi
- IO Treatment of CNS metastases
- Optimal treatment for patients with BRAF WT Disease progressing after adjuvant anti-PD-1 therapy
- Novel IO approaches
  - PIVOT-02
  - Relatlimab

Courtesy of Michael Atkins, MD

Who should get Nivo/ipi vs Single Agent?

- Patients with aggressive/advanced disease
  - PS ≥ 1, elevated LDH, or stage IVC-D
- Lacking significant co-morbidities
  - No autoimmune conditions, need for steroids, or inability to tolerate grade 3 toxicity of HD steroids
- Other
  - BRAF Mutant, PD-L1 negative
  - Mucosal or acral primary
  - Prior adjuvant or BRAF/MEK inhibitor Rx

Courtesy of Michael Atkins, MD

My Approach

- Goal of Immunotherapy is to cure patients
- Those relapsing after adjuvant anti-PD-1 therapy (whether on treatment, within 6 months or after 6 months) can't be cured with single agent anti-PD-1 therapy
- Therefore, a different approach is needed – guided by stage IV disease data

Courtesy of Michael Atkins, MD

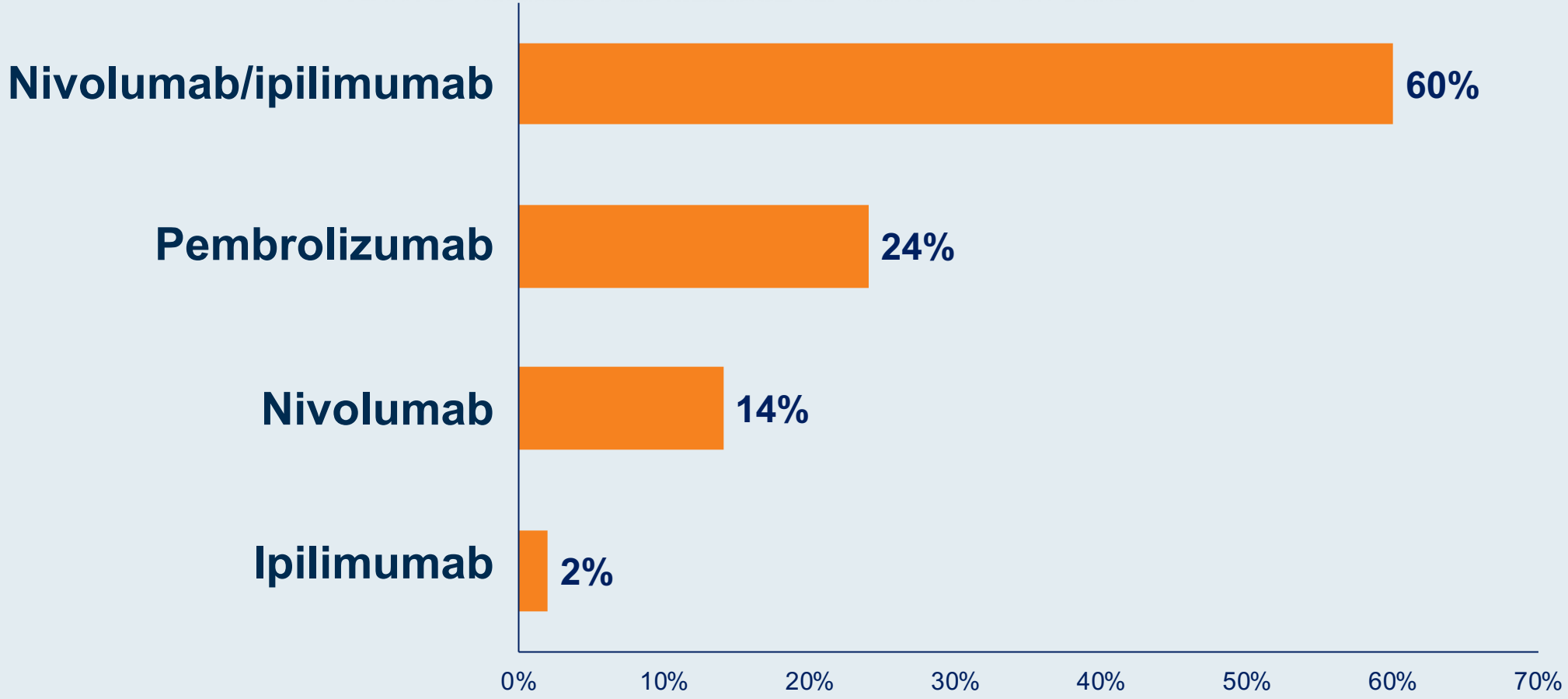
Novel Combinations

- Nivo + NKTR 214 (bempegaldesleukin) or anti-LAG-3 (relatlimab) show some promising activity in small phase II trials
- Lack of single agent activity or activity of combo in anti-PD-1 failures for bempegaldesleukin is concerning
- Relatlimab activity in anti-PD-1 failures and link to a biomarker is encouraging but may have limited application
- Phase III trials underway compared to nivo monotherapy

- Unlikely to produce better results than nivo/ipi combos

Courtesy of Michael Atkins, MD

What is your usual first-line treatment for an asymptomatic, clinically stable younger patient with BRAF wild-type metastatic melanoma?



Survey of 50 US-based medical oncologists

Case Presentation – Dr Atkins:
A 51-year-old man with metastatic BRAF WT melanoma to liver and axilla

History (1)

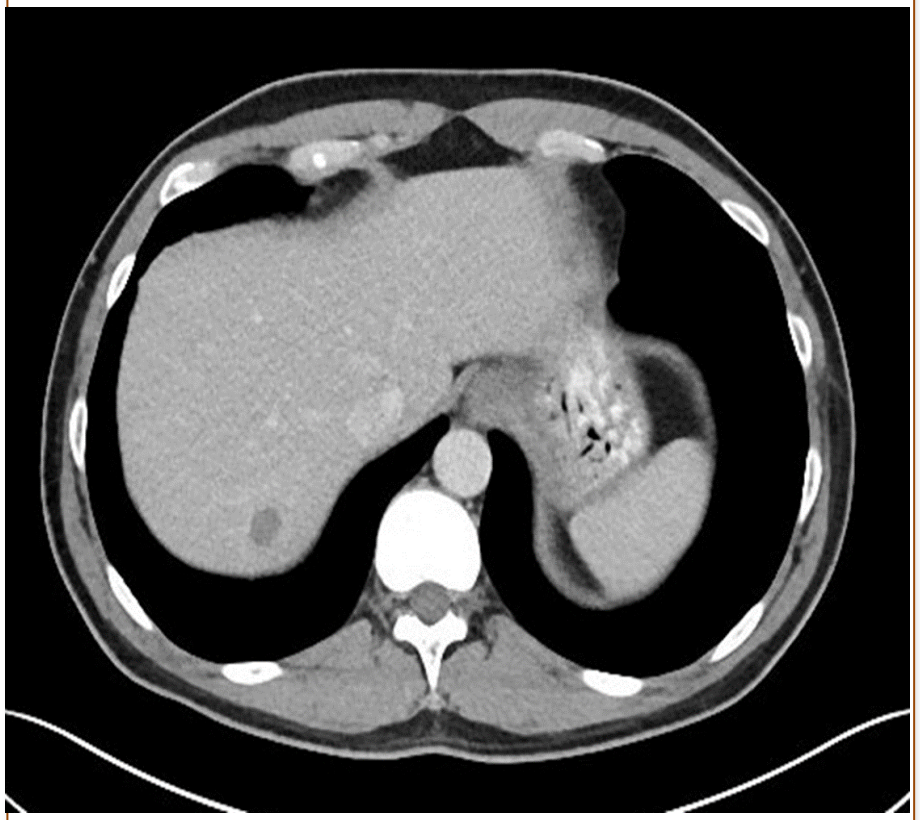
- 2014: Noted changing mole R arm
- 2017: bx = 1.5 mm thick mel, no ulceration, 7 mitoses/mm2
- WLE neg, SLN bx + micromet
- Stage IIIA, declined adjuvant Rx
- 2018: R axillary nodes, Scan with liver met.
- Bx = mel; BRAF WT.
- Brain MRI: no mets

History (2)

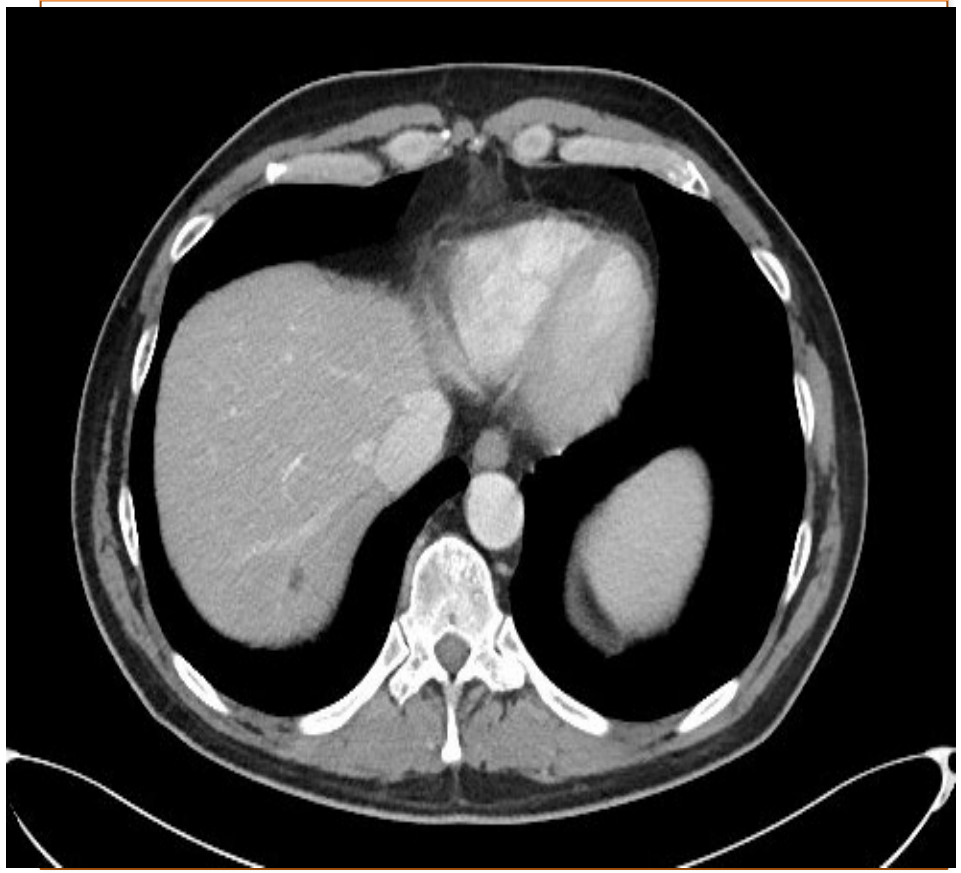
- Treatment plan: Nivo 1/ipi 3 x 4 doses to be followed by nivo 480 mg q 4 weeks
- Developed fevers after dose 1, treated with NSAIDs
- Developed grade 3 LFTs at week 5. Treated with steroids, then MMF taking 3 months to taper off.
- Scans at week 12 show PR.

Imaging (1)

Pre-Treatment Scan Dec 2018



Post-Treatment Scan March 2019 (3 months)



History (3)

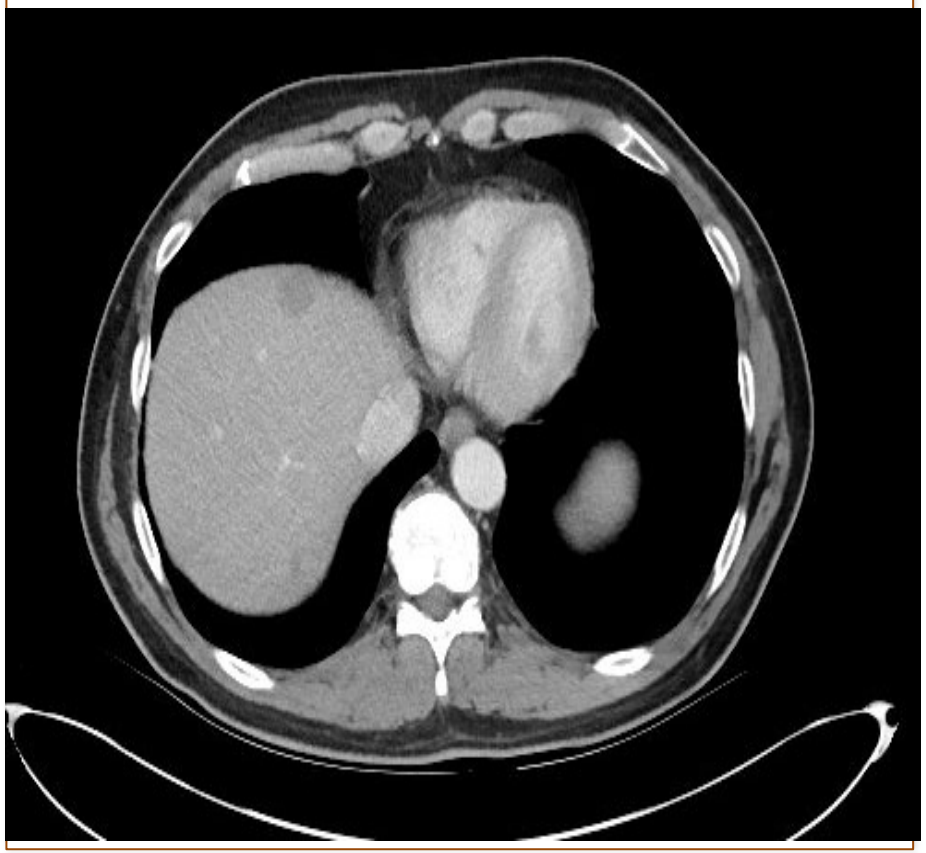
- Scan 6 months shows regrowth of R axillary adenopathy and new liver mets.
- Patient c/o fatigue and R axillary pain

History (4)

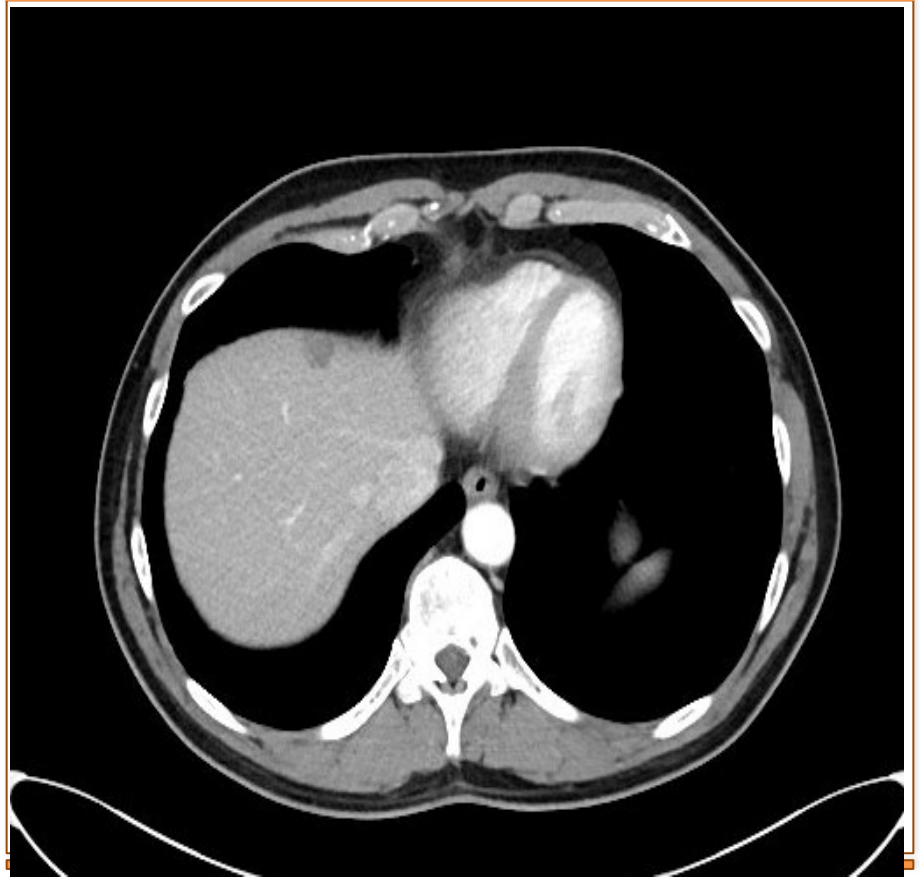
- Started on nivo 480 mg q 4 weeks
- Week 8 grade 2 fatigue
- Labs: Grade 2 LFTs, low cortisol and NA+
- Begun on hydrocortisone replacement. Nivo continued.
- Fatigue and LFTs improve
- Liver and axillary lesions shrink.
- Returns to PS 0
- 6/2020- PET-CT No liver uptake

Imaging 2

Treatment Scan : June 2019 (6 months)



Treatment Scan: December 2019 (12 months)



Take Home Messages

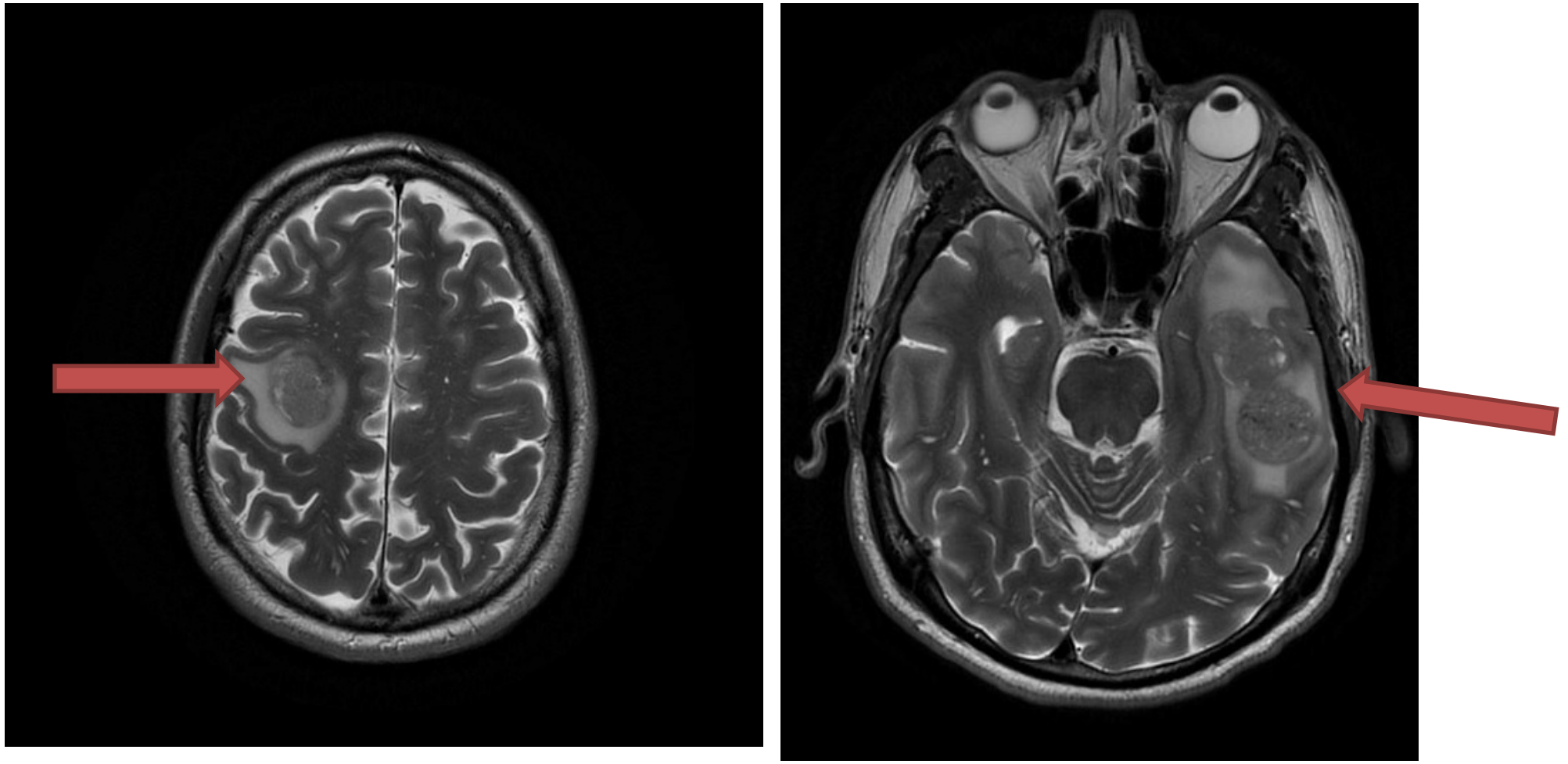
- Ipi 3/Nivo 1 is the treatment of choice for patients with stage IVC met melanoma
- Toxicity is common and prolonged Immunosuppressive treatment may blunt response
- Worth considering maintenance Nivo monotherapy in a responding patient with relapse after induction therapy-related toxicity

Case Presentation – Dr Atkins: A 66-year-old man presenting with large CNS Metastases

History (1)

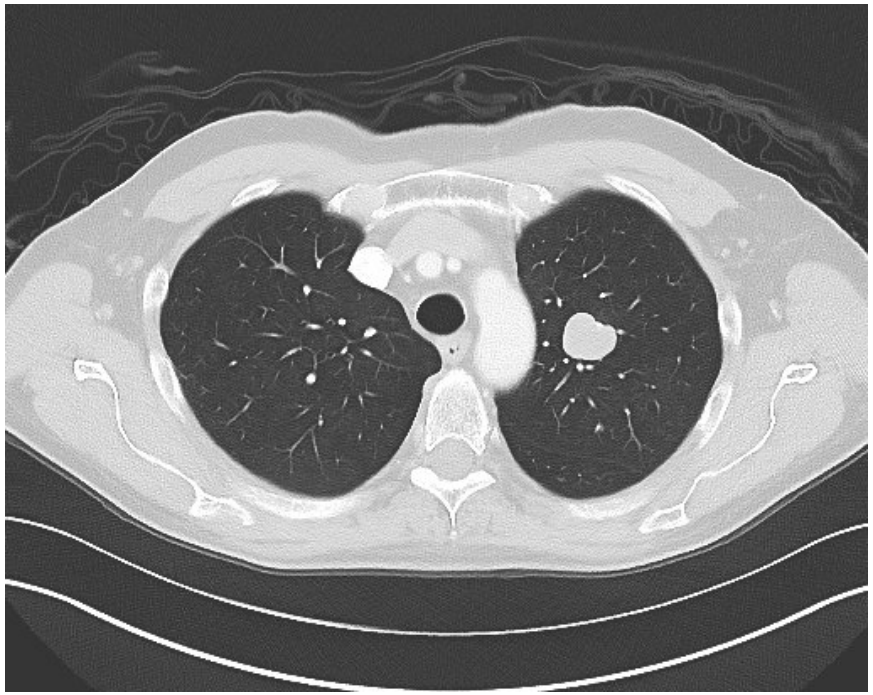
- 66 yo otherwise healthy male presents in February 2016, with pigmented lesion on scalp. Derm bx showed melanoma.
- Staging CT scans showed bilateral lung nodules, largest 3.2cm and a right paracolic mass measuring 1.7cm
- Brain showed 6 intracranial lesions with surrounding vasogenic edema. The two largest lesions were in the left temporal and right frontal areas and measured 2.5 and 2 cm.

Baseline MRI Brain



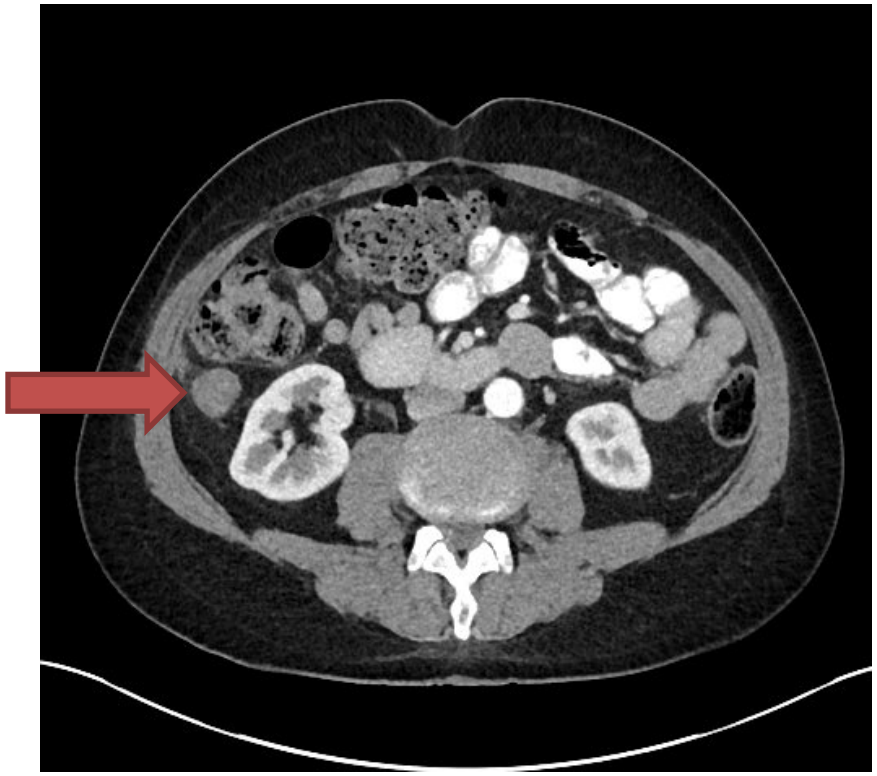
LUL nodule

Baseline 3/2017



Right paracolic mass

Baseline 3/2017

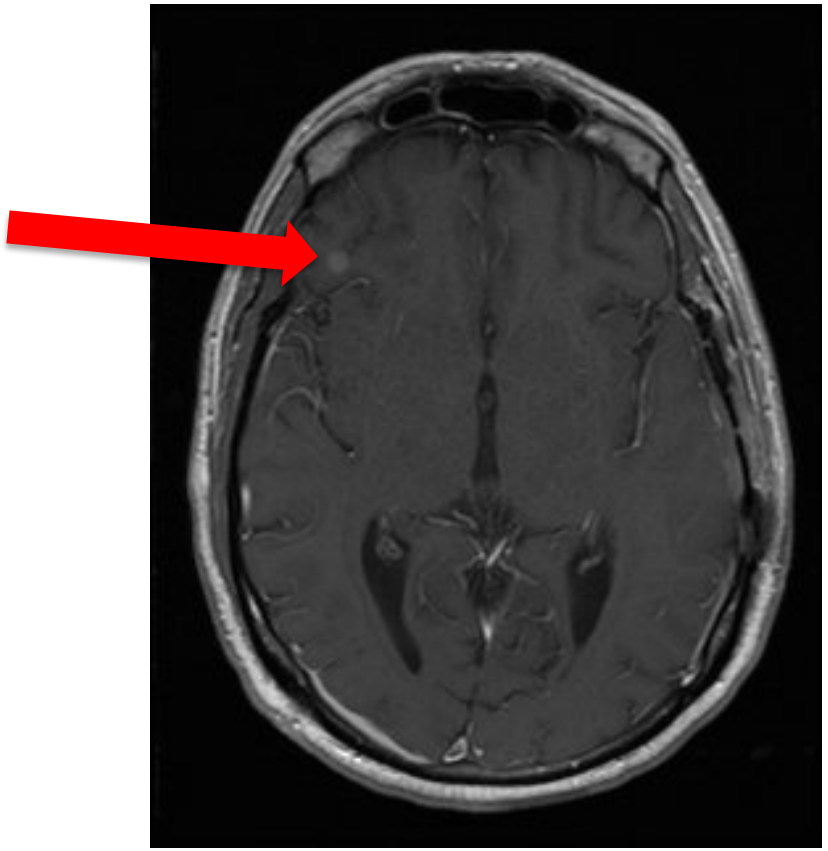


History (2)

- He underwent L temporal and R frontal craniotomies with resection of lesions
- Path confirmed to be melanoma, BRAF WT
- Patient referred to Med Onc
- Taking dexamethasone 4 mg BID for cerebral edema

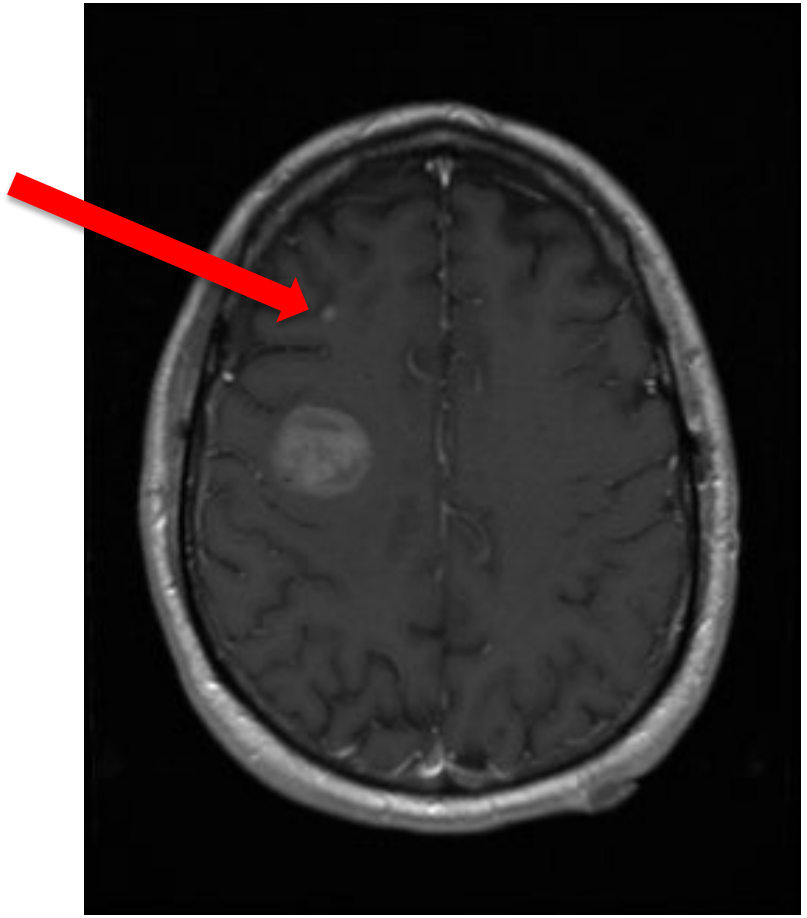
Post-Craniotomy Presentation

Post-surgical scan- 3/29/17
R frontal lesion 5x5 mm



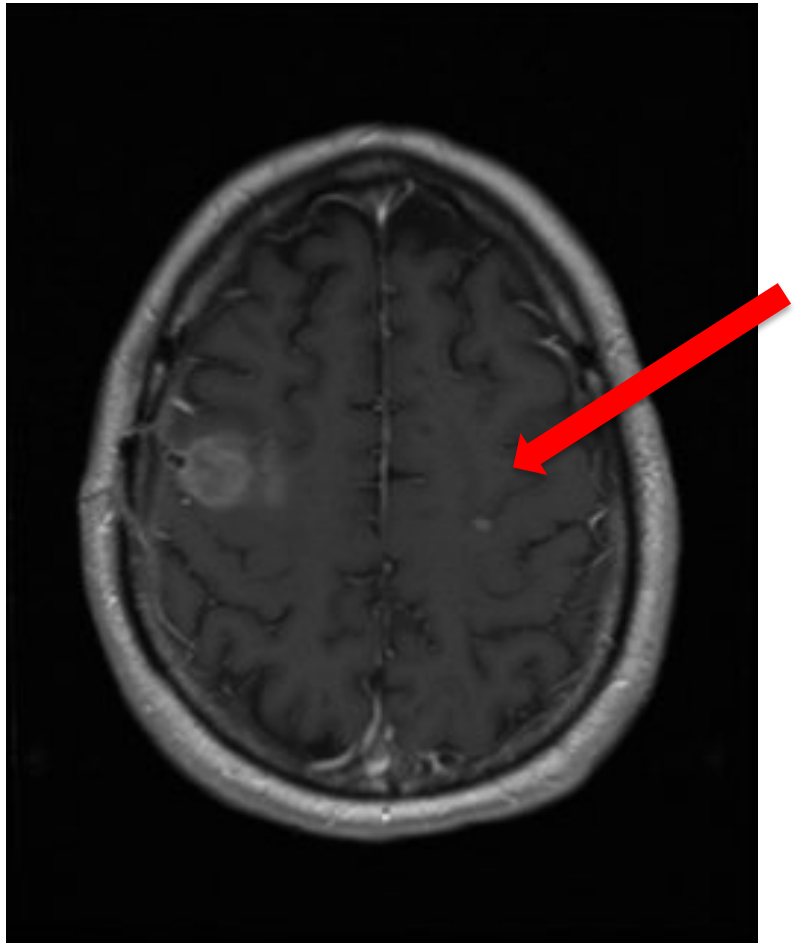
Post-Craniotomy Presentation

3/29/17: Post-surgical R posterior frontal lesion; R frontal lesion 3X4 mm



Post-Craniotomy Presentation

Post-surgical 3/29/17:
left parietal lesion- 4 x 3 mm

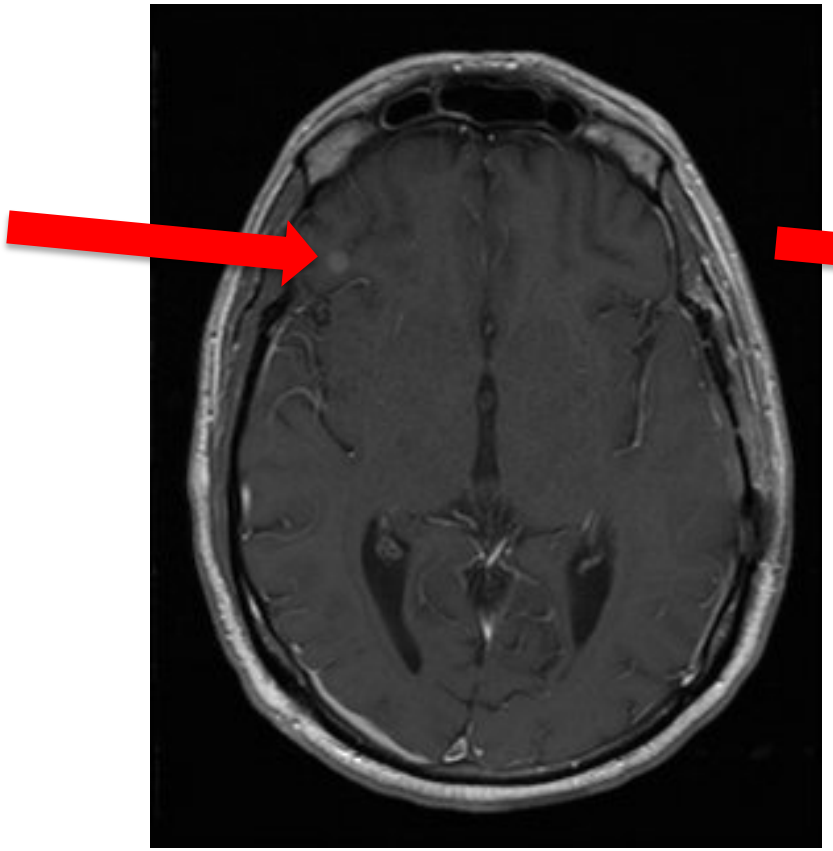


History (3)

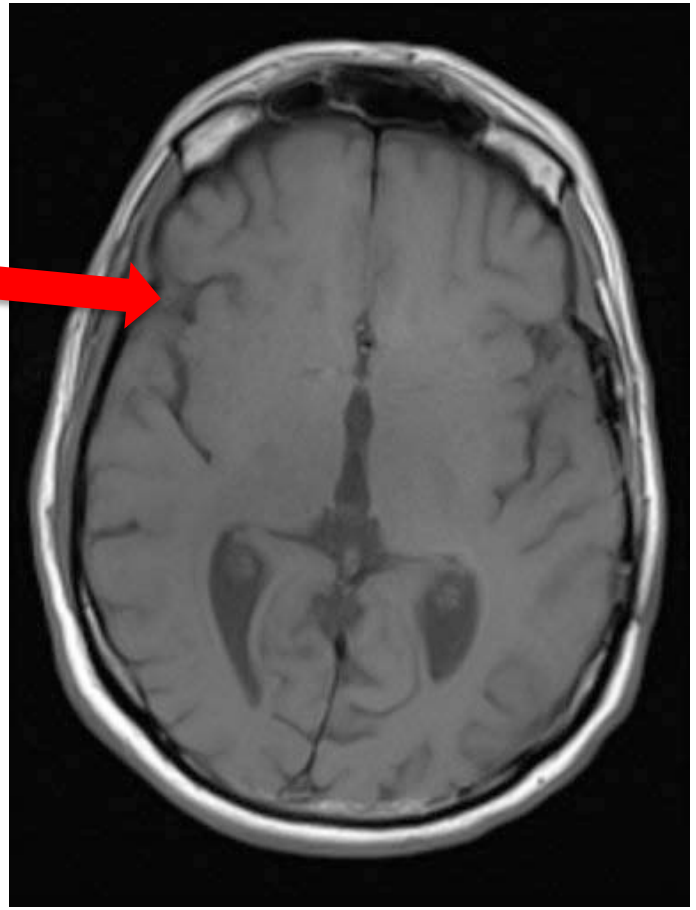
- Weaned off steroids and started immediately on nivo/ipi brain met study (CheckMate 204) Cohort B
- Week 6 CT scans and brain MRI showed improvement of systemic and CNS mets
- Week 13 scans showed continued response
- Week 24 scans showed systemic PR, CR in brain
- Week 48 scans showed continued CNS CR, systemic PR

One year Post-treatment Initiation

Post-surgical scan- 3/29/17
R frontal lesion 5x5 mm

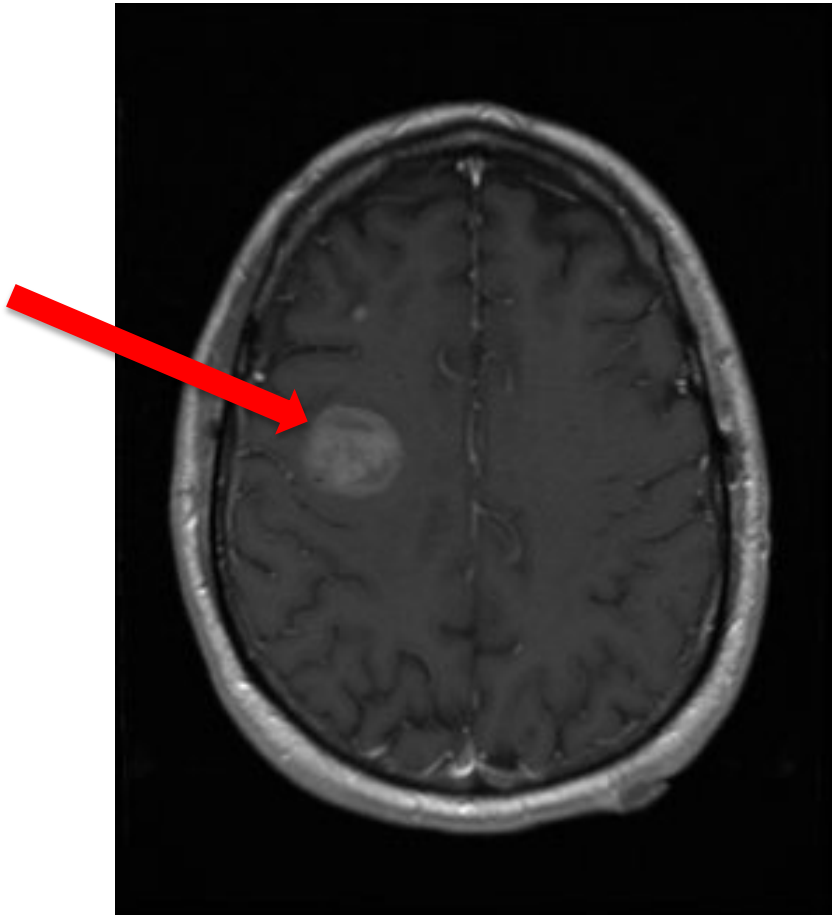


CR of R frontal lesion

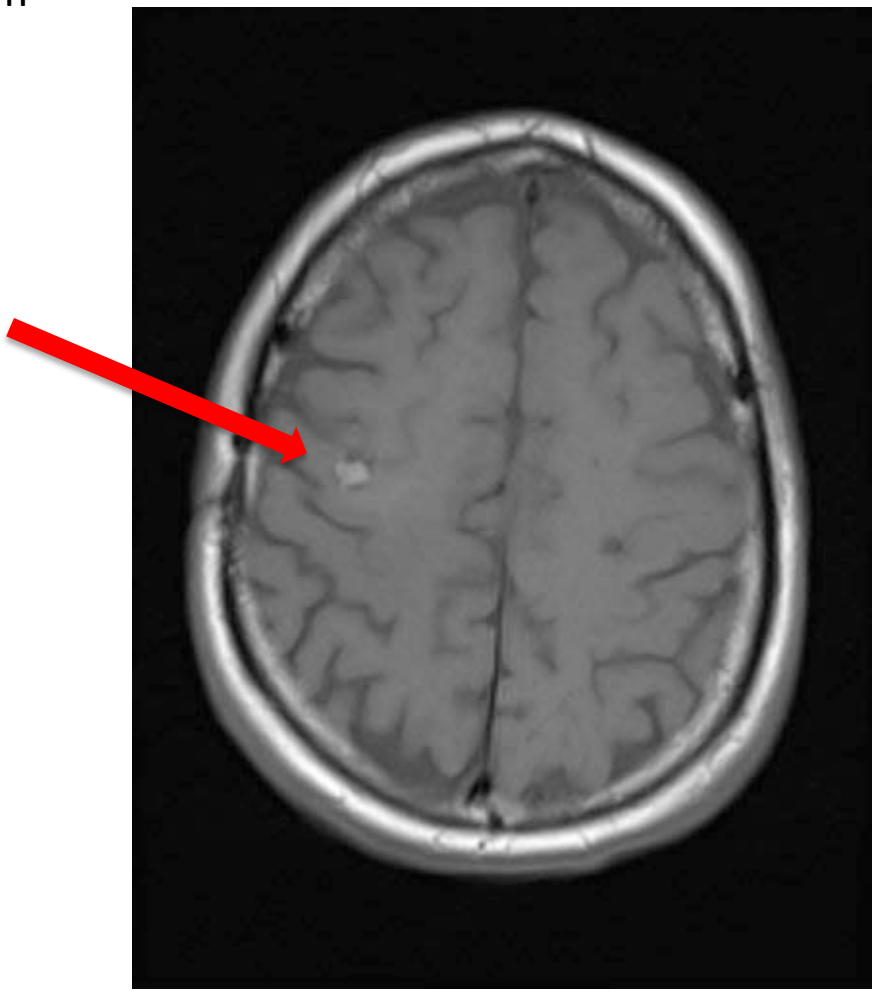


One year post treatment initiation

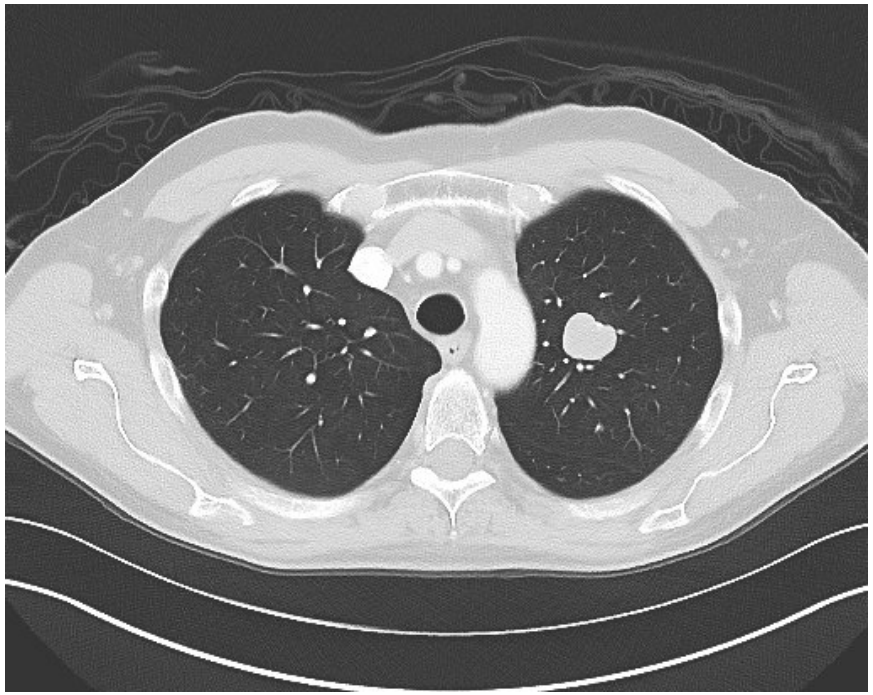
3/29/17: Post-surgical R posterior frontal lesion; R frontal lesion 3X4 mm

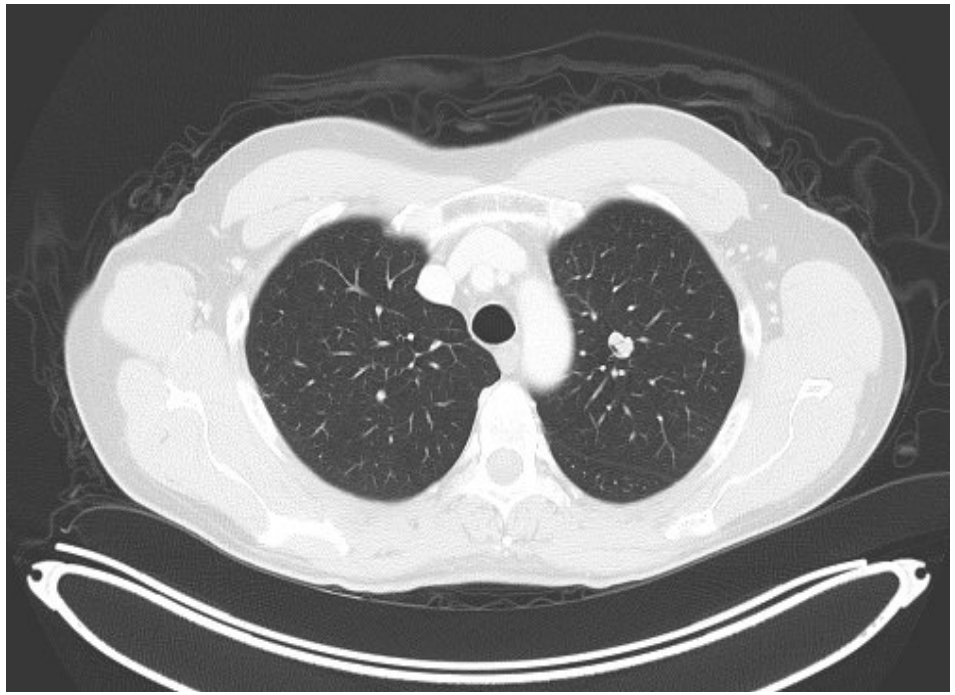


Resolving R posterior frontal resection cavity; absent R frontal lesion

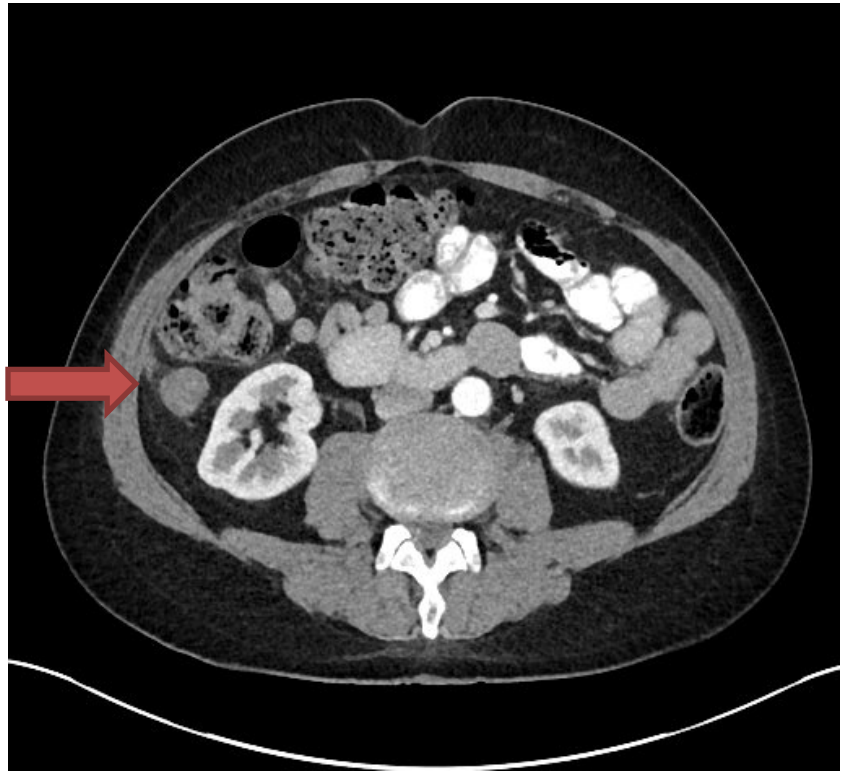


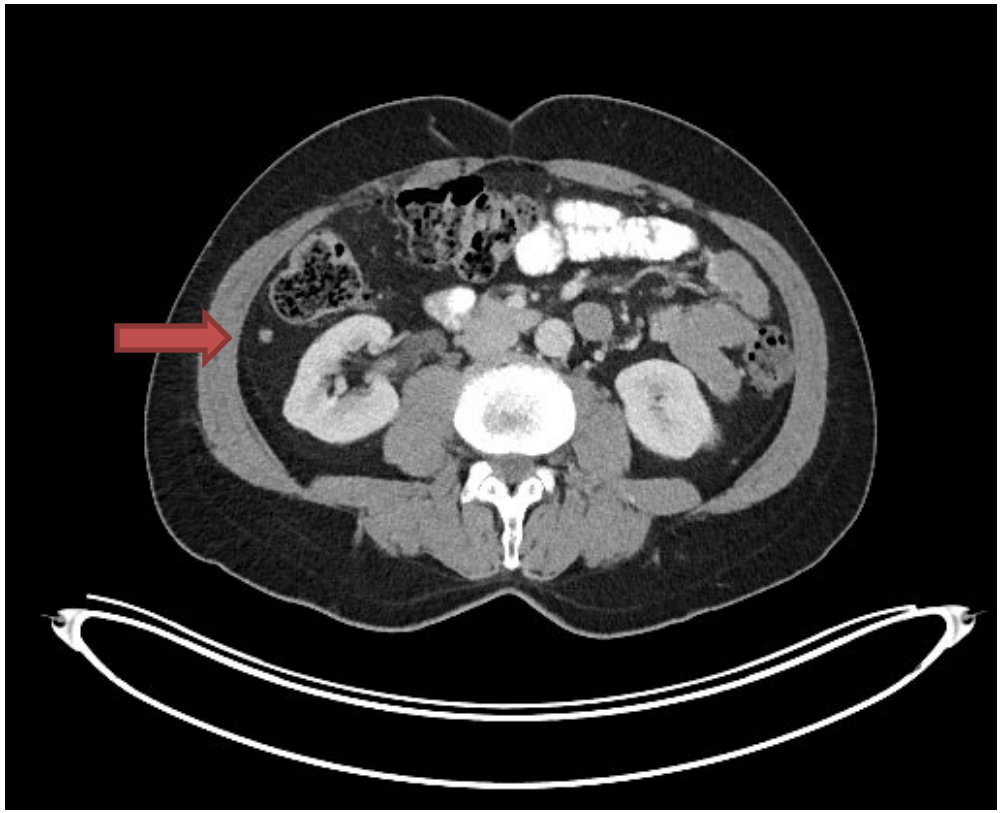
One year post treatment
LUL nodule





One year post Treatment
Right peritoneum





History (4)

- PET-CT was performed which showed no active disease
- Treatment was stopped 4/2018
- Currently remains free of disease progression

- Patient has taken up biking and rides his bike in for clinic appointments

Take Home Messages

- Large melanoma brain mets should be resected if this will allow patients to come off steroids and receive systemic therapy
- Asymptomatic patients with small CNS mets can be treated with ipi/nivo instead of SRS
- IO therapy can eliminate CNS disease
- Stopping IO therapy at 1 year in CT or PET-CT based CRs appears safe and can turn survivors into thrivers

Meet The Professors

Current Questions and Controversies in the Management of Lung Cancer

Thursday, July 23, 2020

12:00 PM – 1:00 PM ET

Faculty

Joel W Neal, MD, PhD

Moderator

Neil Love, MD

RTP
RESEARCH TO PRACTICE

Thank you for joining us!

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