Update: Melanoma/Skin Cancers

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Overview

- Adjuvant therapy for melanoma
  - Practice clarifying data (Abstract #9500)
- Metastatic disease
  - Practice confirming data (Abstracts #9504, #9505)
- Brain metastasis
  - *Practice changing data* (Abstracts #9507, #9508)
- SCC update

Preliminary Safety and Efficacy of the Ipilimumab Arms in U.S. Intergroup E1609: A Phase III of Adjuvant Ipilimumab (3 or 10 mg/kg) vs. High-Dose Interferon α-2b for Resected High-Risk Melanoma

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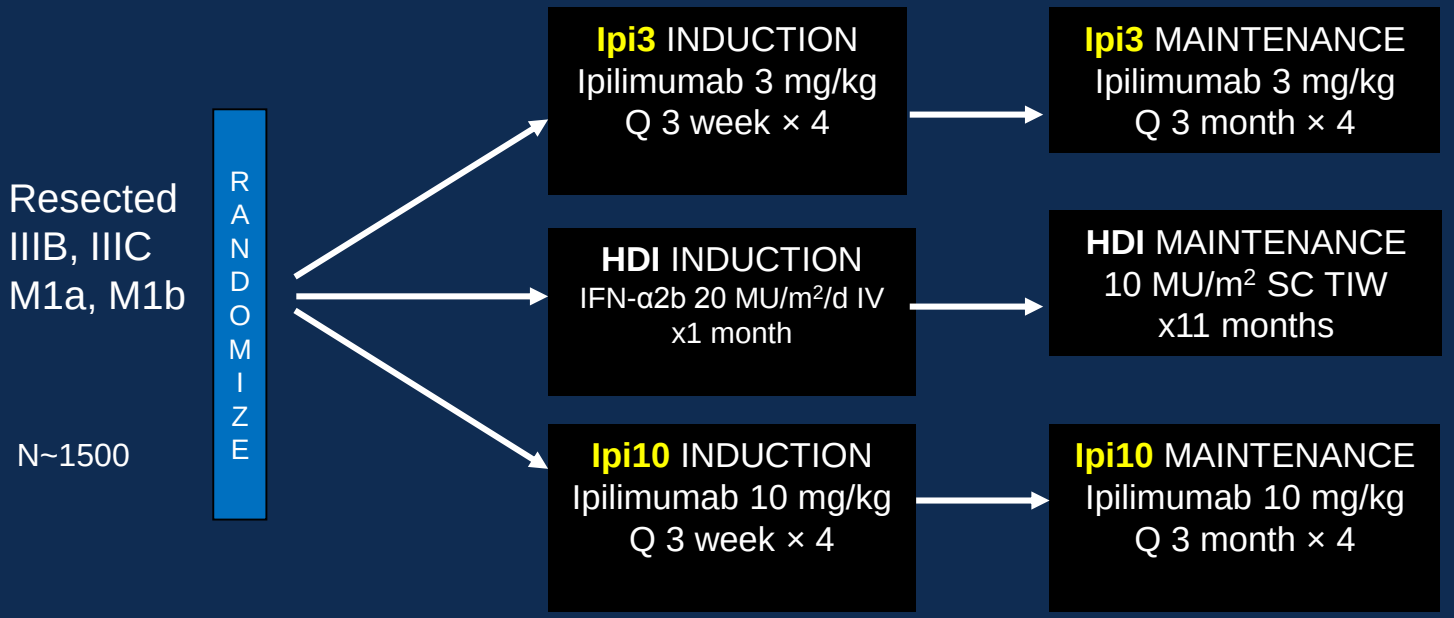
Presented by: Ahmad Tarhini, MD, PhD

Intergroup E1609: Study Design



- **Unscheduled interim analysis: Only RFS and safety Ipi 3 mg vs. Ipi 10 mg**
- **Stratification Factors: IIIB, IIIC, M1a, M1b**
- **Co Primary Endpoints: RFS and OS**

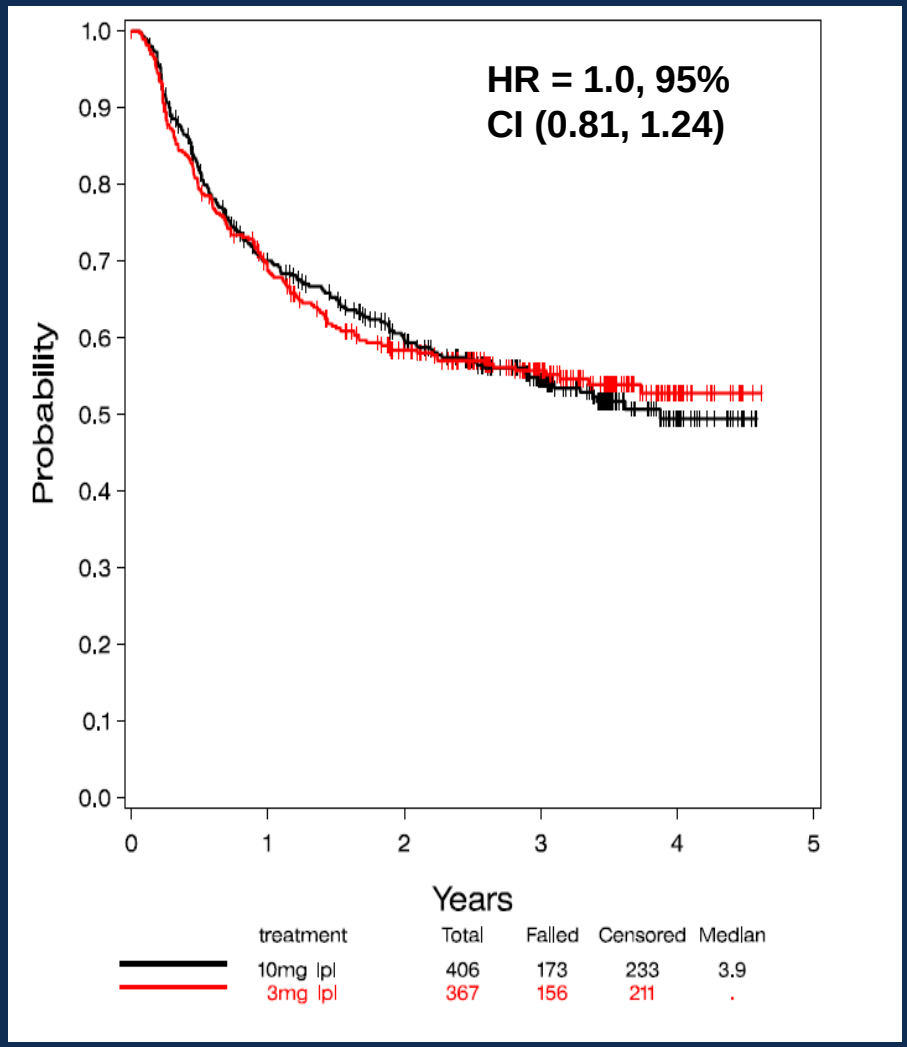
Unplanned analysis due to a critical need for more information

- Toxicity of ipilimumab is dose-dependent
  - 3 mg/kg dose approved for advanced disease
  - 10 mg/kg dose approved for adjuvant therapy based on randomized EORTC 18071 trial data
  - Grade 3/4 adverse events in 54% of patients treated with 10 mg/kg
  - 5 deaths due to ipi 10 mg/kg related AEs occurred on EORTC 18071
    - 3 colitis, 1 myocarditis, 1 mullti-organ failure with GB
- Following the regulatory approval of adjuvant ipi10, it has become urgent to evaluate the relative safety and efficacy of adjuvant ipilimumab at the 2 dose levels tested in E1609

RFS: Ipi10 vs. Ipi3

(Concurrently randomized patients)

- No difference in RFS for Ipi 10 mg/kg vs. Ipi 3 mg/kg
- Median follow up for patients included in this analysis: 3.1 years
- RFS events
  - Ipi10: 173 events / 406 patients (42.6%)
  - Ipi3: 156 events / 367 patients (42.5%)



Safety Summary

(Based on all toxicity data as of 3/2/17)

	Ipi3 (n = 516)		Ipi10 (n = 503)	
	Any Grade	Grade 3/4	Any grade	Grade 3/4
Any AE, %	98.4	53.3	100	65.4
Treatment-related AE, %	96.0	36.6	98.8	56.5
Treatment-related AE leading to discontinuation, %	34.9	25.0	53.7	42.9
Any immune-related AE, %	73.6	18.8	86.9	34.0

Treatment Related Deaths

Ipi3 (2 patients/516; 0.4%)
Colitis / Bowel perforation
Colitis / Death NOS (Colitis requiring steroids & infliximab. C-diff infection. D/C in stable condition. Withdrew consent. Death)

Ipi10 (8 patients/503; 1.6%)
Colitis
Colitis / Colonic perforation
Colitis
Colitis / Ventricular tachycardia (Gr4 Colitis, later rehab, DVT, pneumonia, VT)
Colitis / Nervous system disorder (GI toxicity with subsequent neurologic decline; 81 y.o.)
Pneumonitis
Thromboembolic event / Hypopituitarism
Cardiac arrest (Syncope, dehydration, UTI, sepsis, sudden death)

E1609 unplanned analysis Summary and Conclusions

- Adjuvant therapy for high-risk melanoma with ipilimumab 10 mg/kg is associated with significantly more toxicity and more treatment-related deaths compared to ipilimumab 3 mg/kg
- Unplanned exploratory analysis of concurrently randomized patients shows no difference in RFS for ipilimumab 10 mg/kg compared to ipilimumab 3 mg/kg at a median follow up of 3.1 years
- Analyses of the planned co-primary endpoints of RFS and OS for Ipi3 vs. HD-IFN await maturation of the trial

Adjuvant therapy take home points

- There is no clear standard of care; Options include:
  - Ipilimumab at the approved dose of 10 mg/kg
    - Very low threshold to stop for toxicity
  - Observation
  - Clinical trials
    - Neoadjuvant PD-1 clinical trial
    - Other PD-1 clinical trials
- Need to carefully discuss risks and potential benefit with patients when deciding on a plan of care
- Awaiting data from several completed trials

New Phase III Adjuvant Studies

Study Sponsor	Agents to be tested	Endpoint	Accrual (n)	Study Status
MSD	Pembro vs. HD IFN	OS	1400	Accrual completed
EORTC / MSD	Pembro vs. Observation	RFS	950	Accrual completed
BMS Checkmate 238	Nivo 3mg vs. Ipi 10mg	RFS	800	Accrual completed
BMS / DeCOG	Nivo + Ipi vs. Nivo vs. Observation	RFS	312	Started 2015
BMS CA209-915	Nivo 240 mg+ Ipi 1mg vs. Nivo 480mg vs. Ipi 10mg	RFS	1125	Started 2017
Genetech/ Roche	Vem 960 mg vs. placebo	DFS	725	Accrual completed
GSK / Novartis	Dabra (BRAFi) + Tram (MEKi) vs. no placebo	RFS	852	Accrual completed

Metastatic disease

Can we stop PD-1 Therapy?

Long-Term Outcomes in Patients With Ipilimumab-Naive Advanced Melanoma in the Phase 3 KEYNOTE-006 Study Who Completed Pembrolizumab Treatment

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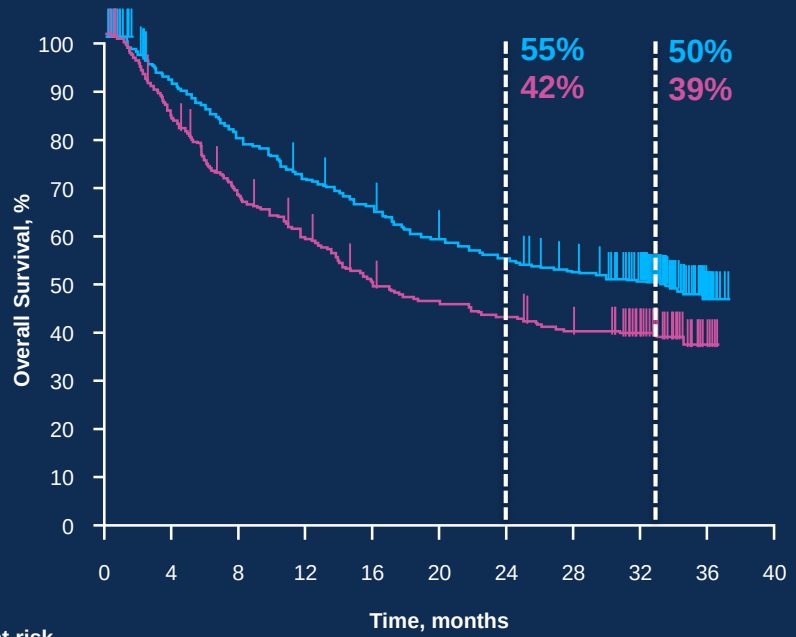
KEYNOTE-006 (randomized phase 3 trial)

- Pembrolizumab improved PFS, OS and ORR compared to ipilimumab in advanced melanoma
  - lower rate of grade 3-5 treatment-related AEs
- Objectives of the current analysis
  - Long-term outcomes (median follow-up, 33.9 months) in all patients
  - Outcomes in patients who stopped pembrolizumab per protocol-specified duration of treatment (2 years)

Kaplan-Meier Estimates of Survival in Total Population (Median Follow-Up, 33.9 mo)

OS

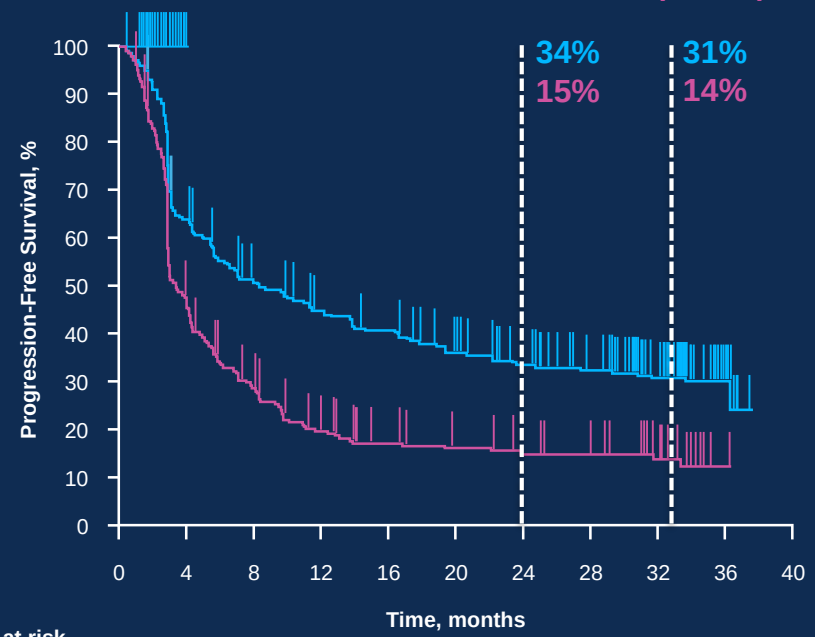
Arm	Events, n	HR (95% CI)	Median, mos (95% CI)
Pembrolizumab	278	0.70 (0.58-0.86)	32.3 (24.5-NR)
Ipilimumab	155	—	15.9 (13.3-22.0)



No. at risk											
Pembrolizumab	556	500	436	387	351	317	297	273	229	24	0
Ipilimumab	278	212	169	145	122	111	103	94	77	10	0

PFS per irRC by Investigator

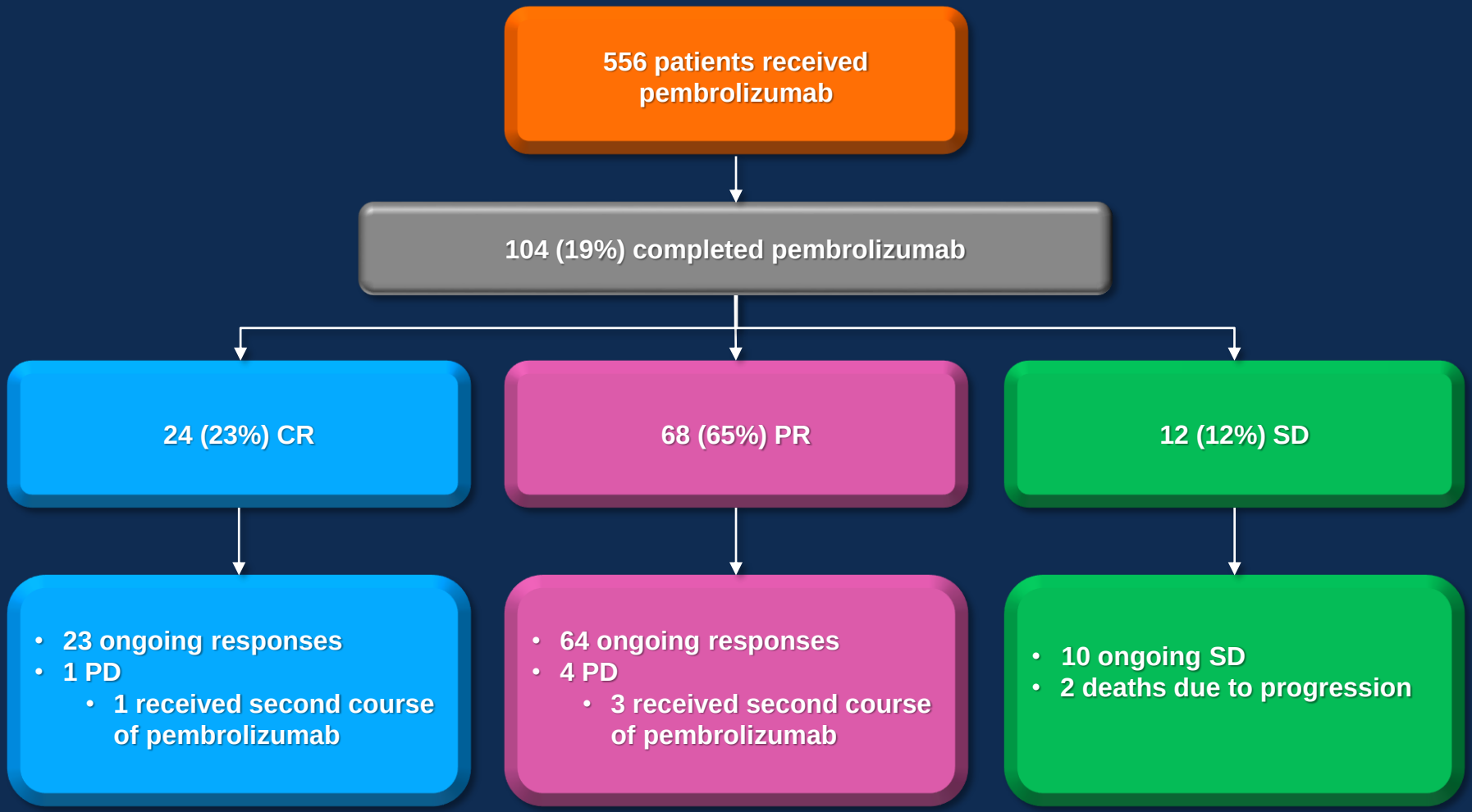
Arm	Events, n	HR (95% CI)	Median, mos (95% CI)
Pembrolizumab	369	0.56 (0.47-0.67)	8.3 (6.5-11.2)
Ipilimumab	204	—	3.3 (2.9-4.1)



No. at risk											
Pembrolizumab	556	347	269	231	211	182	155	138	88	12	0
Ipilimumab	278	110	64	40	32	27	23	20	14	2	0

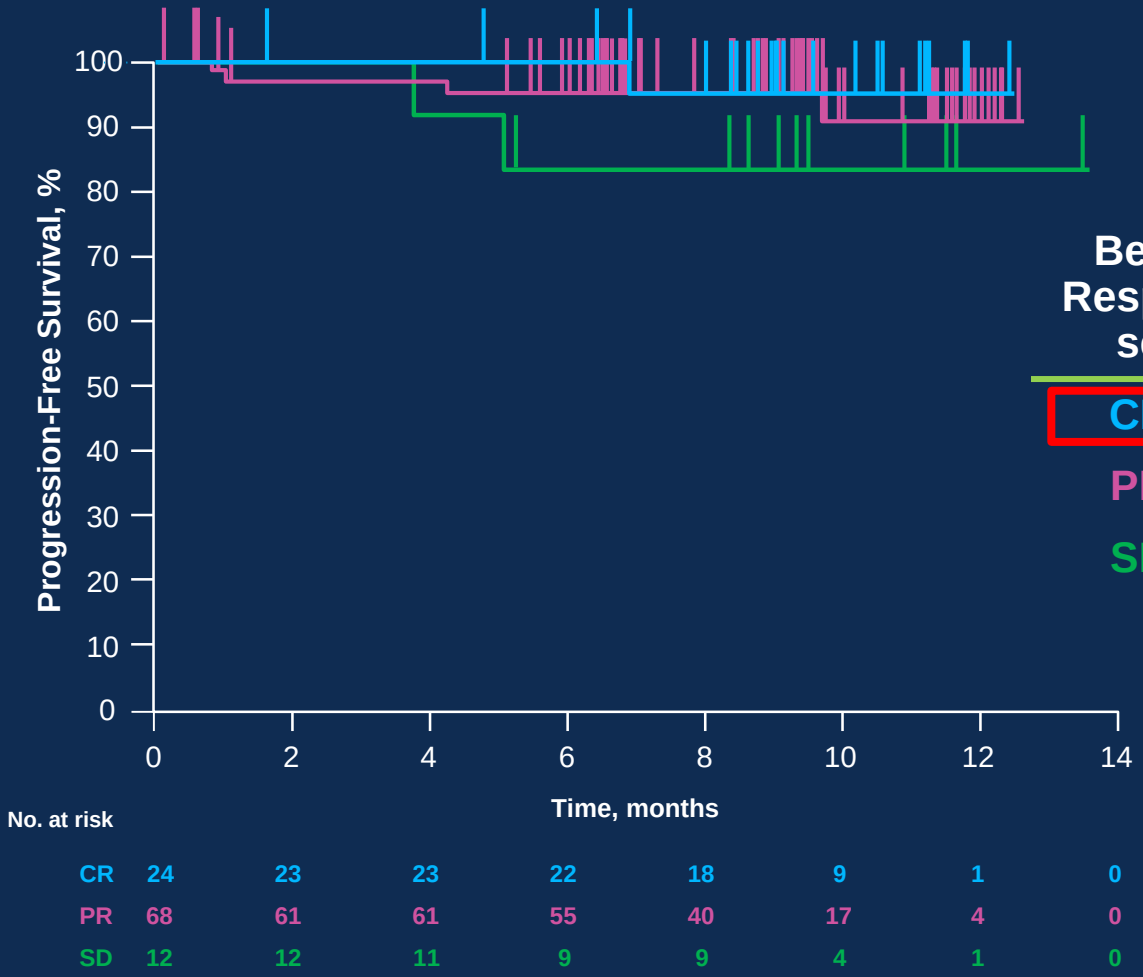
Study required treatment discontinuation at 2 years

Disposition of Patients Who Completed Protocol-Specified Time on Pembrolizumab[a] (median follow-up, 9.7 mo)



[a]Includes patients completing ≥21.6 months of treatment.

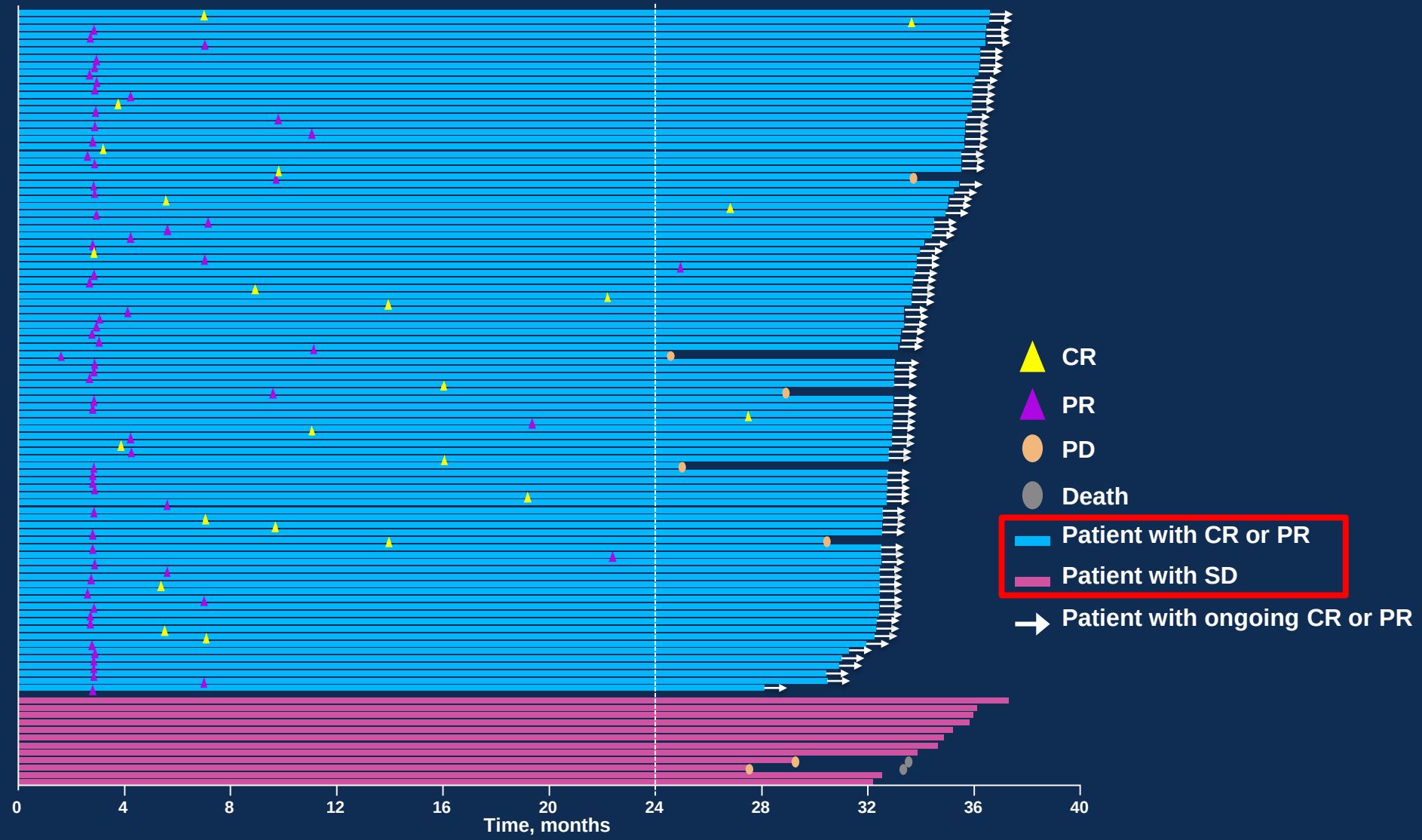
PFS (irRC, investigator) From Last Pembrolizumab Dose to PD or Death in Patients Who Completed Protocol-Specified Time on Pembrolizumab (n = 104)



Best Response	n	Estimated PFS, % (95% CI)	Median PFS
CR	24	95 (69-99)	NR
PR	68	91 (74-97)	NR
SD	12	83 (48-96)	NR

Data cutoff date: Nov 3, 2016.

Durable Responses in Patients Who Stopped Pembrolizumab (N=104)



KEYNOTE-006 Summary and Conclusions

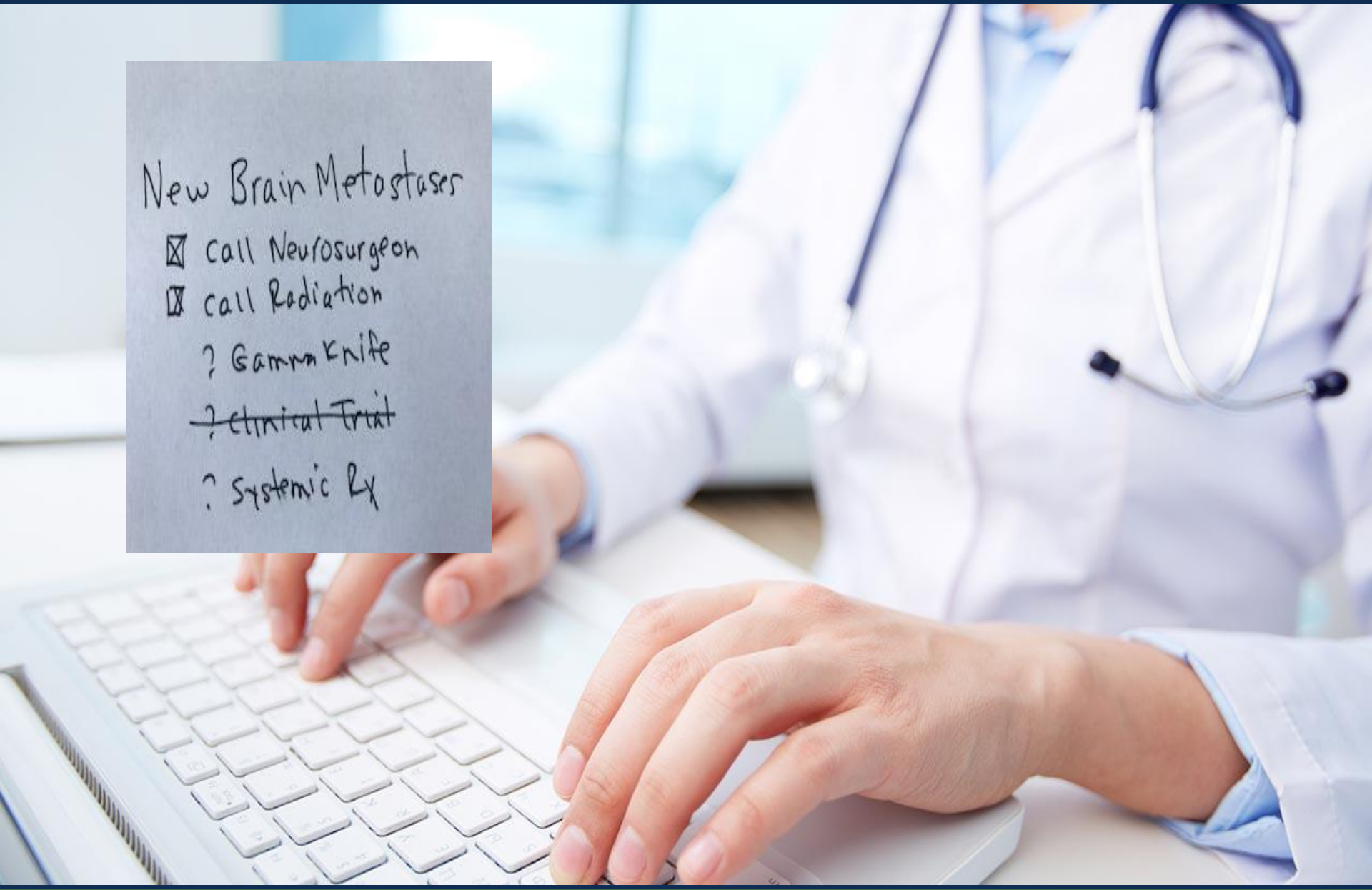
- After a median follow-up of nearly 3 years, superiority of pembrolizumab over ipilimumab was confirmed
  - Median OS: 32.3 vs 15.9 months
  - Median PFS: 8.3 vs 3.3 months
  - Favorable safety profile
- 91% of patients who completed 2 years of pembrolizumab treatment are progression free after a median follow-up of 9.7 months
  - ~96% for patients with complete responses
  - Consider stopping PD-1 blockade in patients with a confirmed complete response

Brain metastasis: Questions

How do we approach patients now?

What have learned from recent studies?

Are these results practice changing?



Latest study results

- 3 trials reported very promising results
- Patients with melanoma metastatic to the brain can potentially gain long term disease control with up front systemic therapy
  - Without local neurosurgery or radiation in select patients with asymptomatic brain metastasis

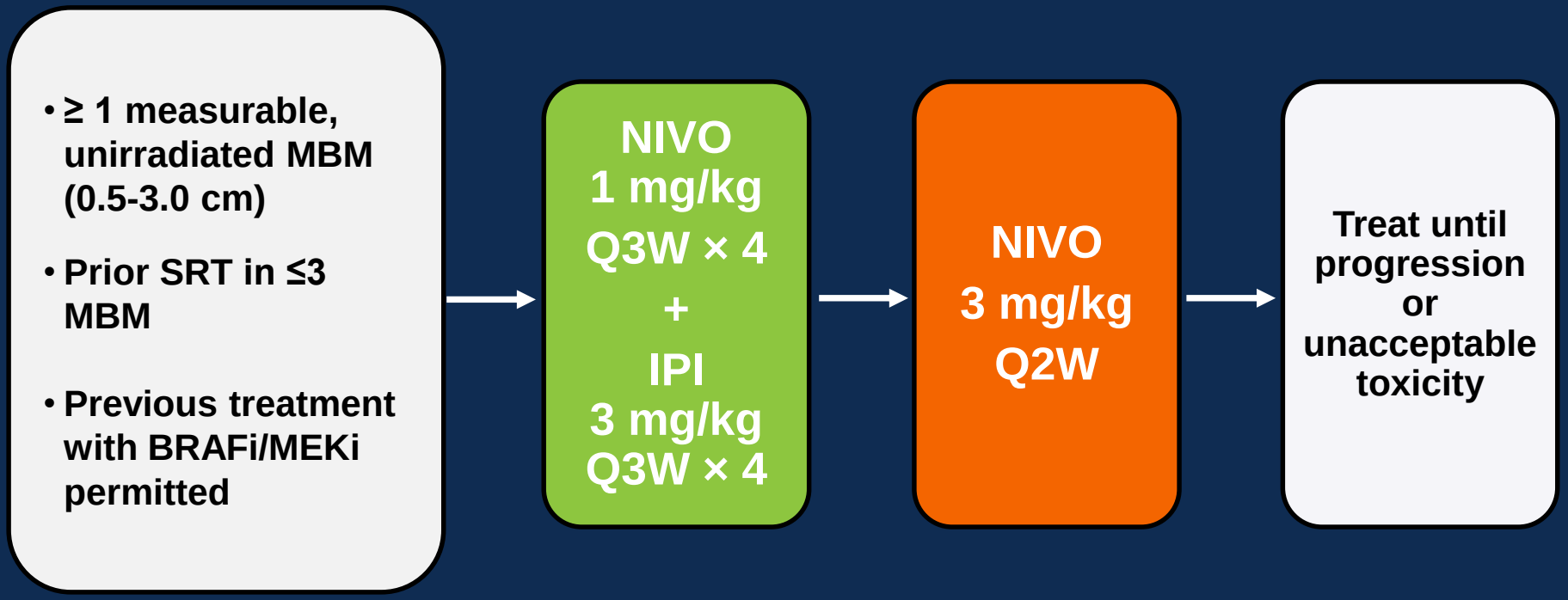
3 trials with promising results

Clinical Trial Title	Agents Tested	Patients	Response in brain (Complete or partial response or stable disease)
CheckMate 204 Study	Ipilimumab/ Nivolumab	75	60% (21% Complete)
ABC Study	Ipi/Nivo vs Nivolumab alone	75	Ipi/Nivo- 50% (15% Complete) Nivo- 24%
Combi MB Study	Dabrafenib/ Trametinib	125	75%-88%

Key findings

- High intracranial response rates, durable
  - Early results, short follow up
  - Many variables in patient selection
- No unexpected toxicities
- Safe to give immunotherapy with ipilimumab/nivolumab in patients with brain metastases
- In general, concordant responses- brain and extra-CNS disease

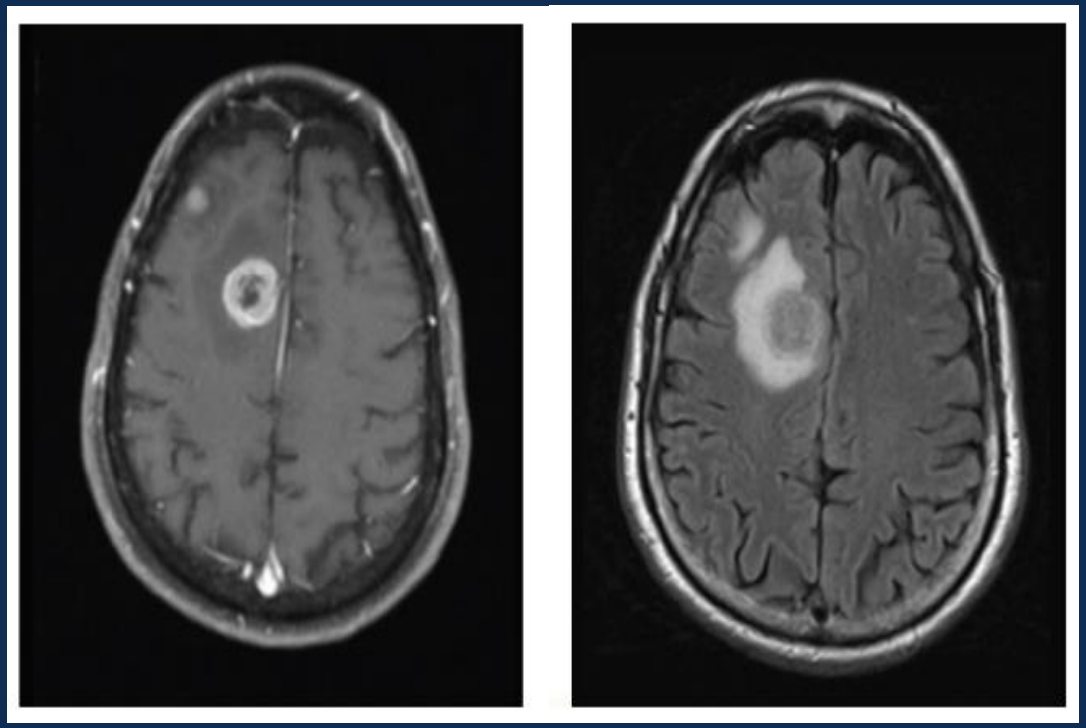
Checkmate 204: Trial design



- Exclusion criteria included neurological symptoms; steroids > 10 days; WBRT; prior treatment with checkpoint inhibitors; leptomeningeal disease

Checkmate 204: Patient example

71 year old man with *BRAF* V600E-mutated melanoma, ~7 brain mets, asymptomatic, no steroids or prior SRT

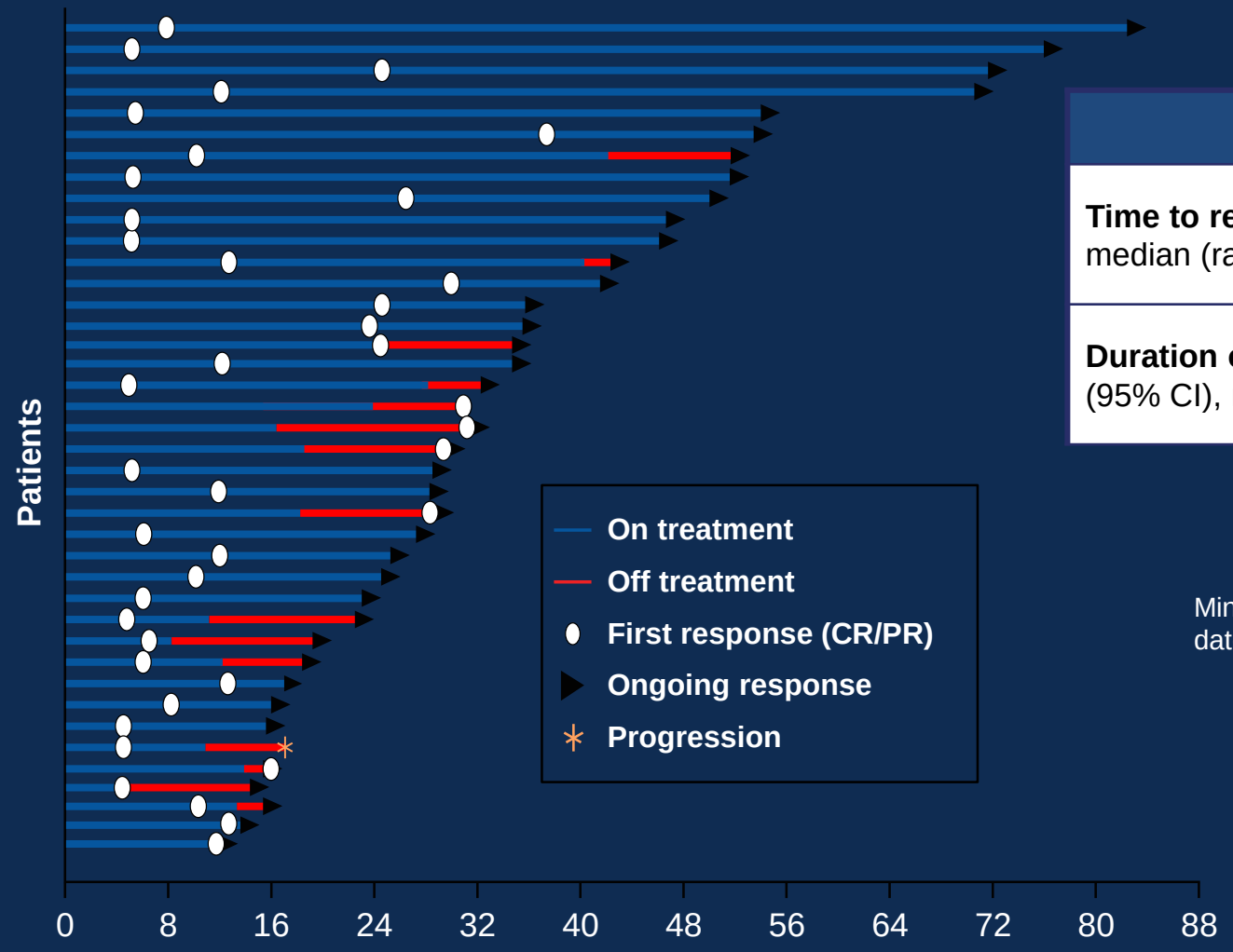


Patients with multiple sub-centimeter mets – another common pattern

Checkmate 204: Response rates

	Global	Intracranial	Extracranial
Best overall response, n (%)			
Complete response	4 (5)	16 (21)	5 (7)
Partial response	36 (48)	25 (33)	32 (43)
Stable disease	4 (5)	4 (5)	2 (3)
Progressive disease	18 (24)	18 (24)	16 (21)
Not evaluable	13 (17)	12 (16)	20 (27)
ORR, %, (95% CI)	53 (41–65)	55 (43–66)	49 (38–61)
Clinical benefit rate, (95% CI)	59 (47–70)	60 (48–71)	52 (40–64)

Checkmate 204: durable responses



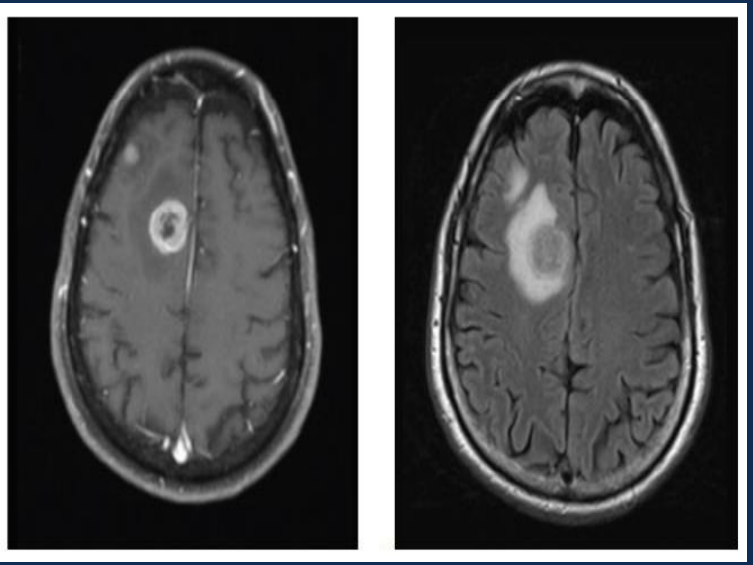
	N = 41
Time to response, median (range), months	2.8 (1.0–11.0)
Duration of response, median (95% CI), months	NR (NR-NR)

Minimum follow-up of 6 months from date of first dose

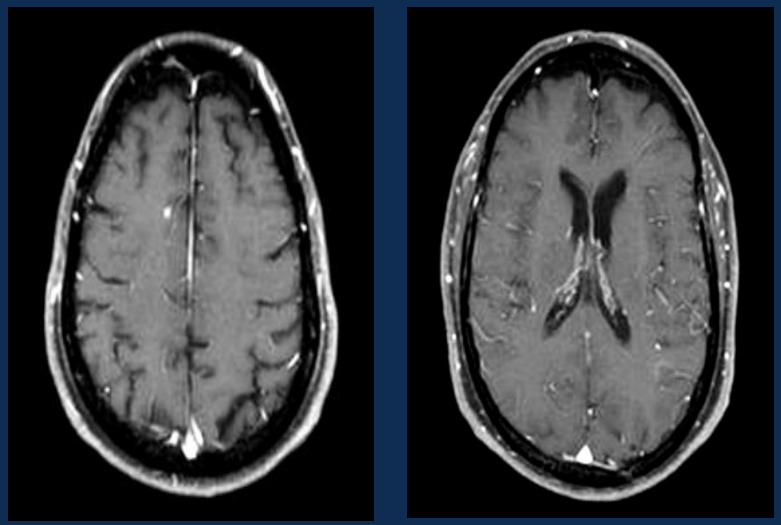
First tumor assessment was at 6 weeks (+/- 2 weeks)

Response – patient example

71 year old man with *BRAF* V600E-mutated melanoma, ~7 brain mets, no steroids or prior SRT



Baseline



1 year

Checkmate 204: Conclusions

- In patients with advanced melanoma and untreated brain metastases, NIVO+IPI demonstrates clinically meaningful efficacy, and can be considered a new treatment option in select patients with asymptomatic brain mets
- With over 9 months of follow-up, NIVO+IPI resulted in an intracranial ORR of 55%, with 21% of patients achieving a complete response

ABC Trial: Study design

- Melanoma Brain Metastases
  ≥ 5mm & < 40mm
- No previous
  Anti-CTLA-4
  Anti-PD-1 or -PD-L1 agents
- Previous BRAFi+MEKi allowed
- ECOG PS 0-2
- No serious autoimmune disease
- No corticosteroids
  (Cohort C < 10mg prednisone allowed)

R 1:1
up to n=53

A
No prior local brain Rx & asymptomatic
n=33
Rx = Nivolumab + Ipilimumab

B
No prior local brain Rx & asymptomatic
n=27
Rx = Nivolumab

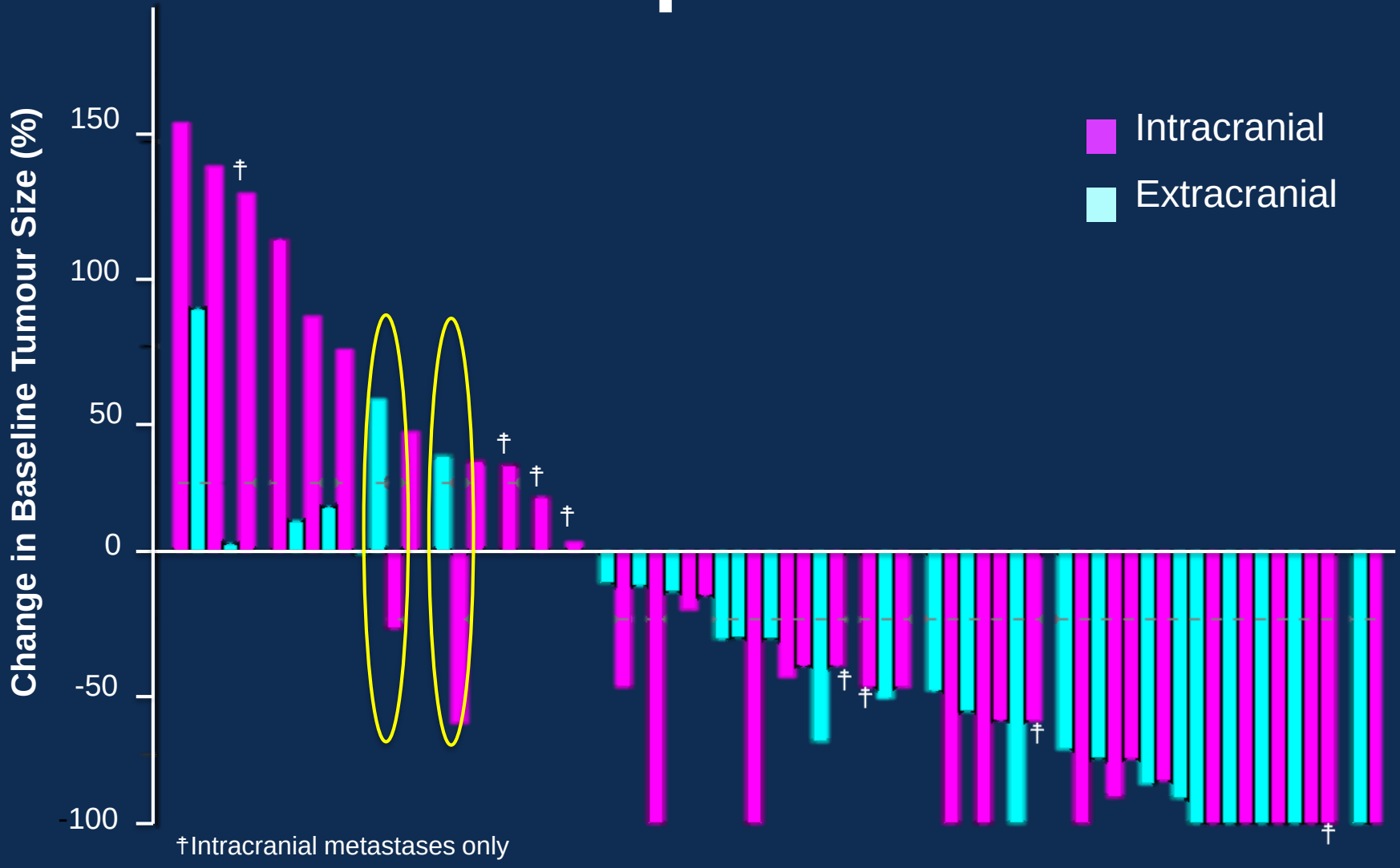
C
Previously treated or symptomatic or leptomeningeal, with MRI progression
n=16
Rx = Nivolumab

Total 76 Patients

ABC trial: response rates

	A: Ipi+Nivo N=20	B: Nivo N=19	C: Nivo† N=4
Intracranial Response, n (%)	**10 (50%)**	**4 (21%)**	**1 (25%)**
CR	3 (15%)	2 (11%)	0
PR	7 (35%)	2 (11%)	1 (25%)
SD	2 (10%)	1 (5%)	1 (25%)
PD	7 (35%)	13 (68%)	2 (50%)
NE	1 (5%)	1 (5%)	0

Concordant responses



BRAF/MEK in CNS: COMBI-MB results

- BRAF/MEK targeted therapy also has efficacy
- First report of a phase 2 trial evaluating BRAFi + MEKi in patients with melanoma brain metastases
  - Response rate of 58%
  - Duration of response was shorter than that observed in patients without melanoma brain metastases

Combining local and systemic therapy

Targeted Therapy 

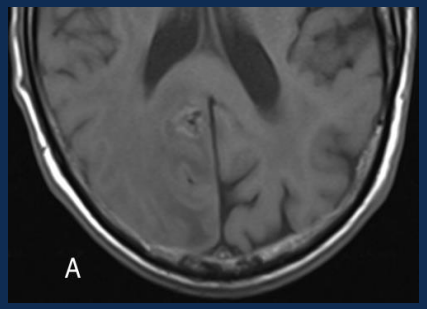
- Reports of CNS radiation necrosis when radiation is given concurrently with BRAF inhibitors.
- Recommendation is to hold targeted therapy several days prior to radiation.
- Hold targeted therapy prior to surgery.

Immunotherapy 

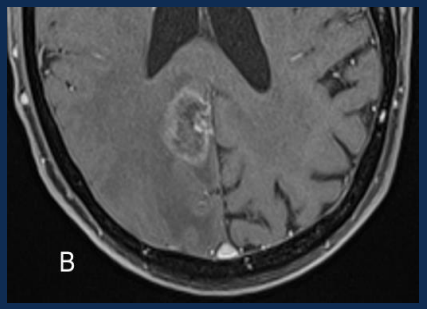
- In general appears safe when combined with radiation.
- Possible enhanced efficacy when radiation and immunotherapy combined.
- Concern about concurrent steroid use in limiting activity of immunotherapy
- Radionecrosis does occur

Radionecrosis in treated mets

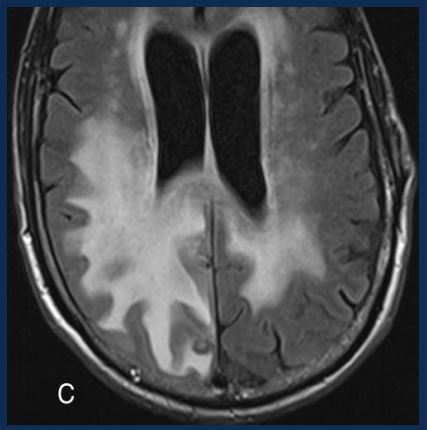
Patient 1



T1-weighted sequence demonstrates patchy high signal within the lesion

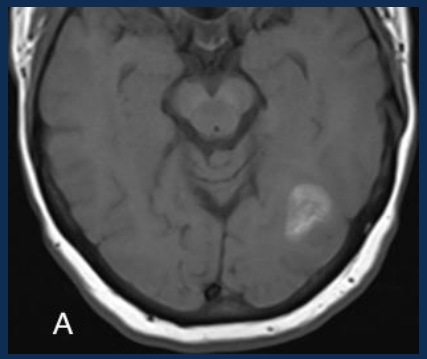


Post-gadolinium administration there is peripheral rim enhancement

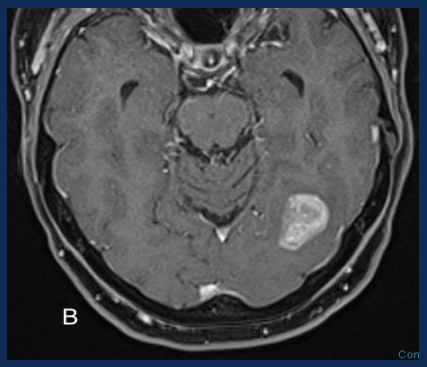


Extensive oedema is seen on the FLAIR sequence.

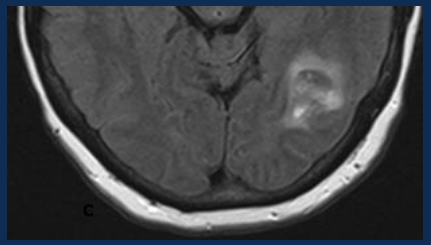
Patient 2



Intrinsic T1 high signal is seen



Even with the intrinsic high signal, contrast enhancement is identified post gadolinium administration



Perilesional oedema is present, however minimal, on FLAIR.

Radionecrosis diagnosed in 17% of patients in a study of 135 patients with RT and PD-1 blockade within 1 year

CNS disease: Summary

- High rates of durable responses in brain
- Responses are concordant
  - Implications for assessing response
    - Occasionally observe increased enhancement/edema with PD-1 blockade
    - Assess in context of therapy, clinical assessment, overall response
    - Imaging every 6 weeks initially if no local therapy
- Requires multi-disciplinary coordination of care between neurosurgery, radiation oncology, radiology and medical oncology

REGN2810, A Human Anti-PD-1 Monoclonal Antibody, for Patients with Unresectable Locally Advanced or Metastatic Cutaneous Squamous Cell Carcinoma (CSCC): Initial Safety and Efficacy

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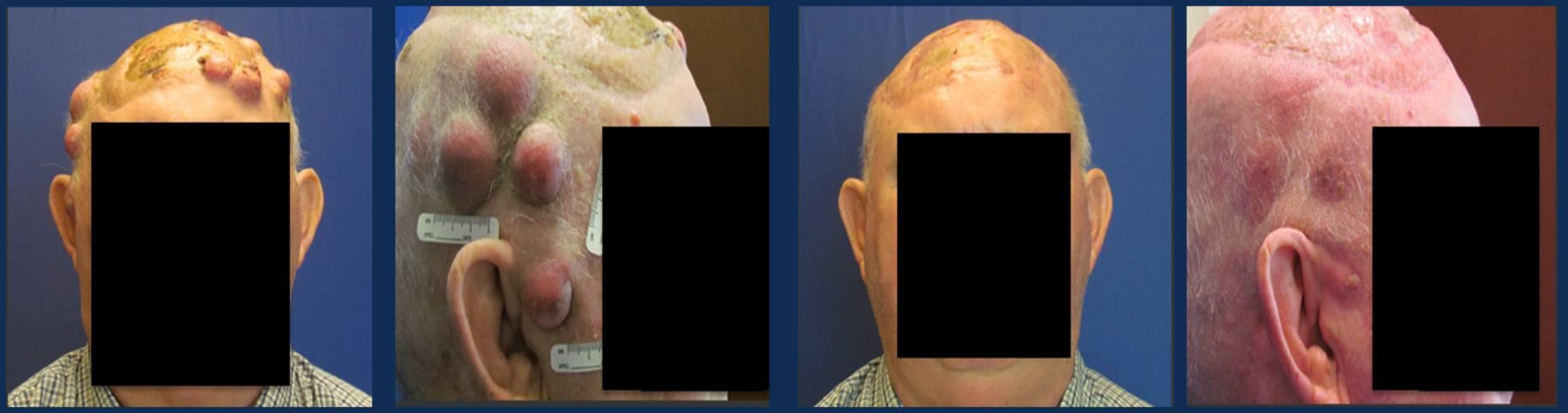
Presented by: Kyri Papadopoulos

Early Response to REGN2810 in a 62-Year Old Male with Locally Advanced CSCC

Screening

Response after 6 weeks of REGN2810



CSCC, cutaneous squamous cell carcinoma.

Investigator Assessed Preliminary Response Rate by RECIST 1.1 is 46.2% (ITT Population)

Investigator assessment	Metastatic (N=10), n (%)	Locally advanced (N=16), n (%)	Overall (N=26), n (%)
Complete response	0	2 (12.5)	2 (7.7)
Partial response	6 (60.0)†	4 (25.0)	10 (38.5)
Stable disease	1 (10.0)	5 (31.3)	6 (23.1)
Progressive disease	2 (20.0)	4 (25.0)	6 (23.1)
Not evaluated	1 (10.0)	1 (6.3)	2 (7.7)

ORR (CR + PR + one unconfirmed PR) = 46.2% (12/26 patients; 95% CI: 26.6–66.6)
DCR (ORR + SD) = 69.2% (18/26 patients; 95% CI: 48.2–85.7)

†Includes 5 confirmed partial responses and 1 unconfirmed partial response.
CR, complete response; DCR, disease control rate; ITT, intention-to-treat; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; RECIST, Response Evaluation Criteria In Solid Tumors.

Data cut-off date: 27 April 2017

Take home points

- Adjuvant therapy for melanoma – Clarification:
  - There is no clear standard of care (observe, ipilimumab)
  - Need to discuss risks and potential benefit with patients
  - Awaiting data from several completed trials
- Metastatic disease – Confirmation:
  - Need to discuss the data for stopping PD-1 blockade with patients who have confirmed complete responses
  - Longer follow up confirms OS, durability of responses
- Brain metastasis – Practice change:
  - Consider systemic therapy alone (without local therapy) in select patients with asymptomatic CNS disease