Best of 2020 ASCO: Melanoma

June 19th, 2020

Annual Midwest Oncology ASCO Review

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Disclosures

- **Research support (to UW)**:

  BMS, EMD-Serono, Immune Design, Merck, Novartis, Oncosec, Nantkwest, Exicure, Nektar.

- **Advisory Board**:

  Genentech, BMS, EMD-Serono, Sanofi-Genzyme

Since 2011, multiple new drugs have been FDA-approved.

IMMUNOTHERAPY

Ipilimumab (2011)

Pembrolizumab (2014)

Nivolumab (2014)

Ipilumumab + Nivolumab (2015)

TVEC (2015)

CHEMOTHERAPY

Vemurafenib (2011)

Dabrafenib (2013)

Trametinib (2013)

Dabrafenib + Trametinib (2014)

Vemurafenib + Cobimetinib (2015)

Encorafenib + Binimetinib (2018)

IMMUNOTHERAPY

Anti-PD-1 agents (as monotherapy or in combination with ipilimumab) are regarded as the current standard-of-care for immunotherapy of metastatic melanoma.

- Pembrolizumab
- Nivolumab

Systemic immunotherapy: Outcomes in melanoma

	Response rate (%)	Grade 3 or higher IRAE (%)
Ipilimumab	19	27
Nivolumab	44	16
Ipi plus Nivo	58	**55**

[*Larkin J et al* NEJM *2015*]

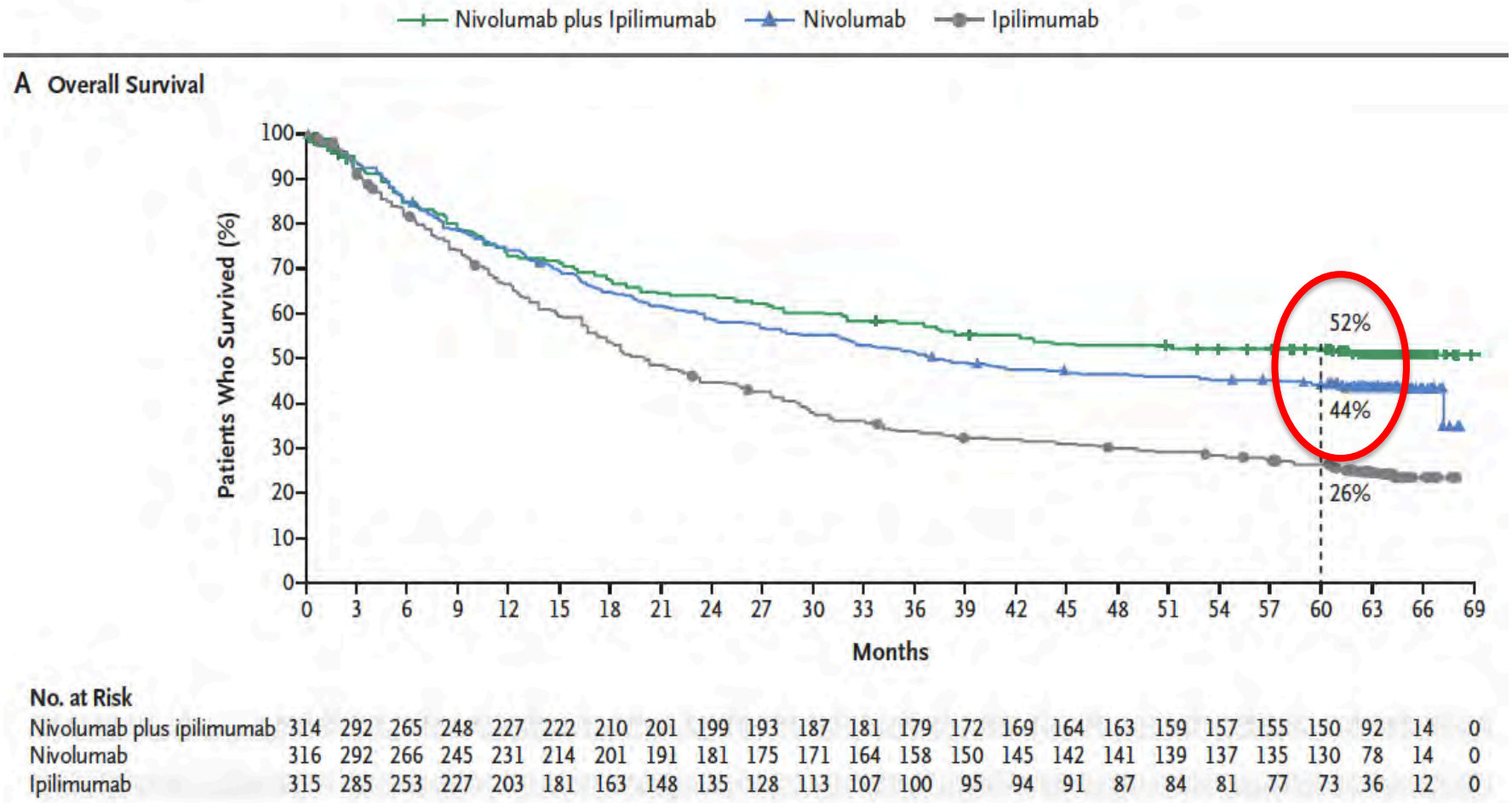
Ipilimumab *plus* Nivolumab combination

Combination was approved by the US FDA in **September 2015**

Approved dose is Ipilimumab 3 mg/kg plus Nivolumab 1 mg/kg administered IV every 3 weeks x 4 doses [**Induction**] followed by Nivolumab 3 mg/kg administered IV every 2 weeks [**Maintenance**].

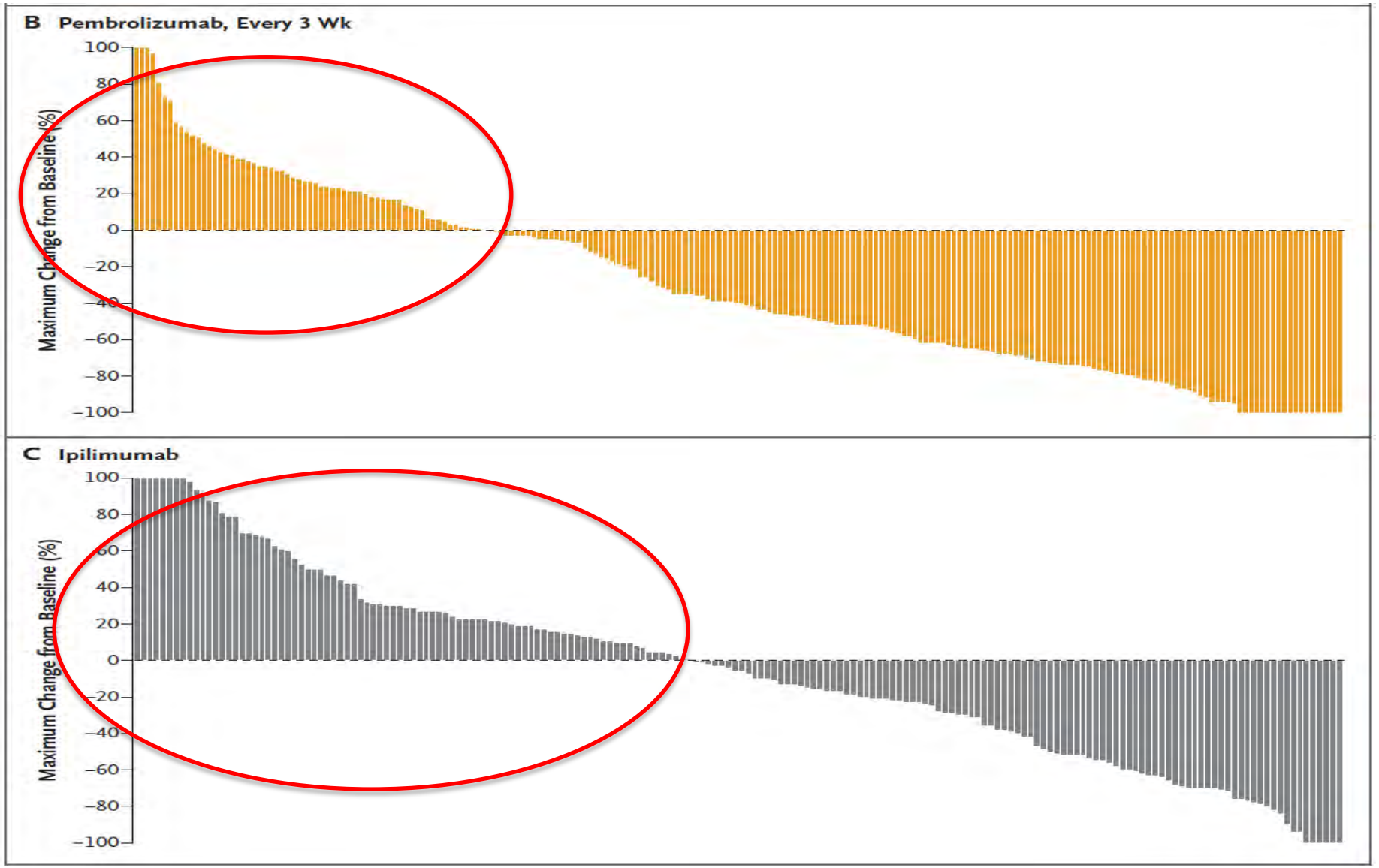
Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.-J. Grob, P. Rutkowski, C.D. Lao,



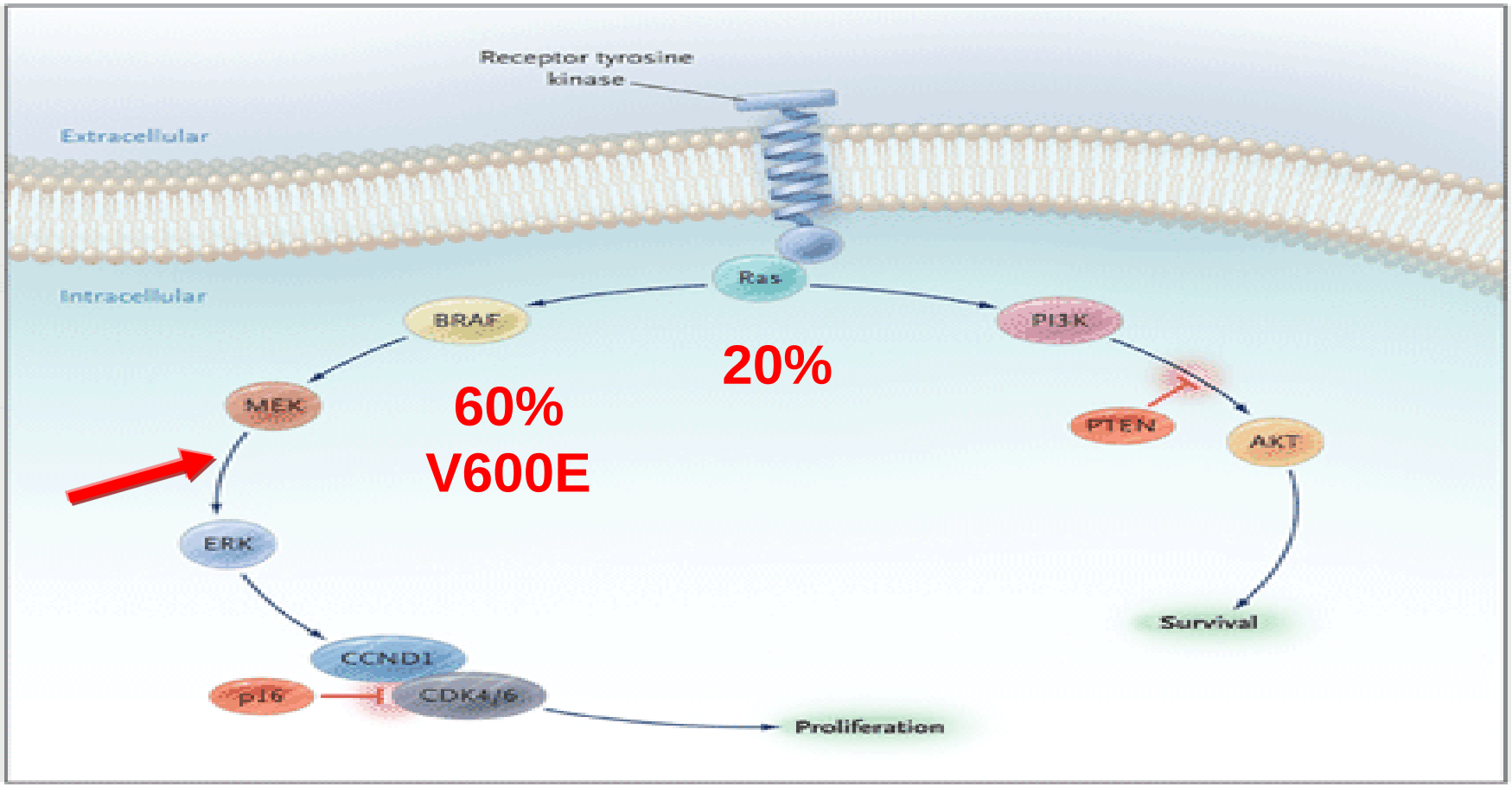
DOI: 10.1056/NEJMoa1910836

Immunotherapy does not work all the time



[Robert C et al. NEJM]

Mutations in BRAF and NRAS are frequent in cutaneous melanomas



[Curtin JA et al. NEJM 2005]

Multiple targeted agents are efficacious in BRAF-mutated melanoma

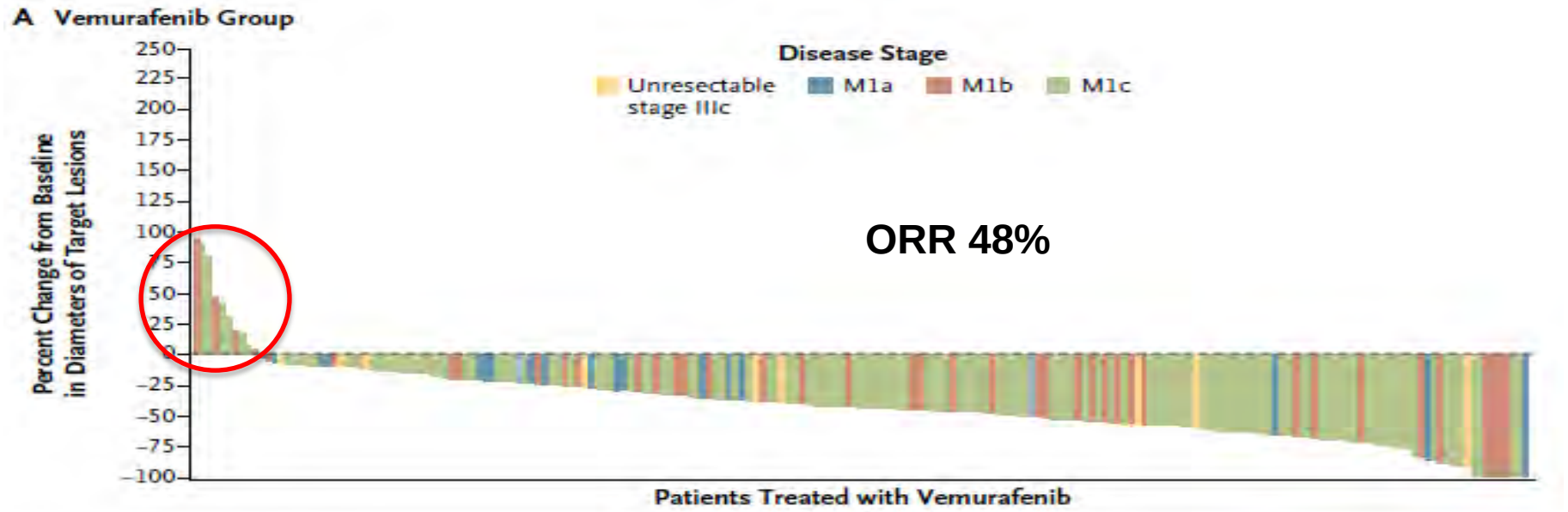
BRAFi

- Vemurafenib
- Dabrafenib
- Encorafenib

MEKi

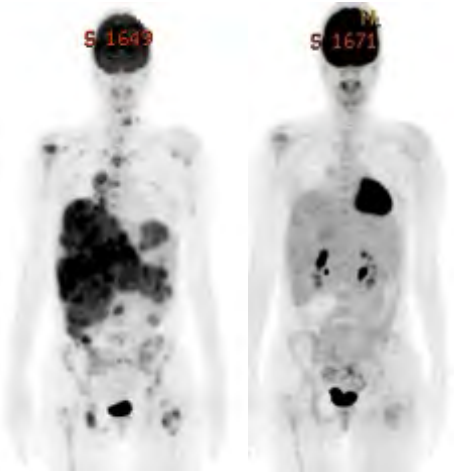
- Trametinib
- Cobimetinib
- Binimetinib

BRAFi (+/-MEKi) are associated with tumor regressions in **vast majority** of patients with BRAF-mutant melanoma

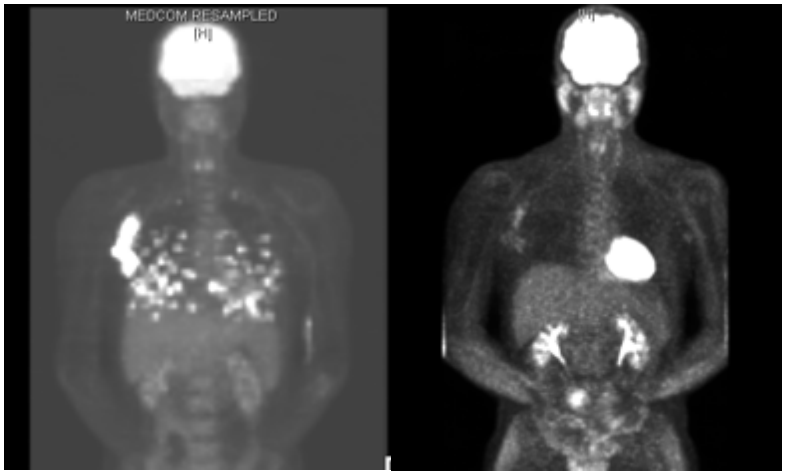


[Chapman P et al. NEJM. 2011]

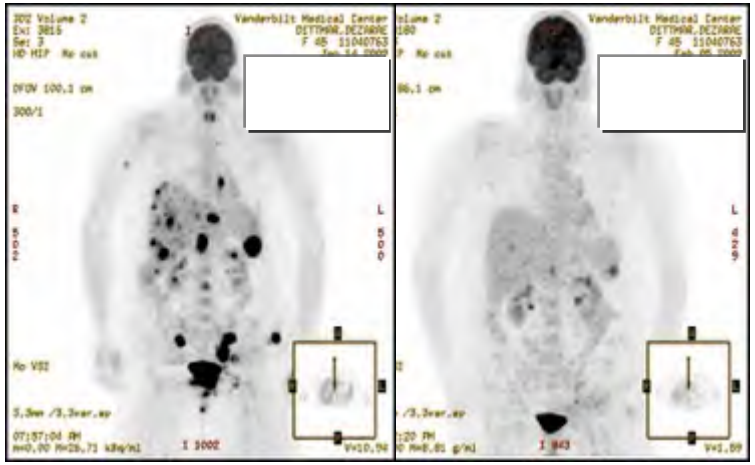
Onset of tumor regression is **fairly rapid** with BRAFi (median TTR ~6 weeks)

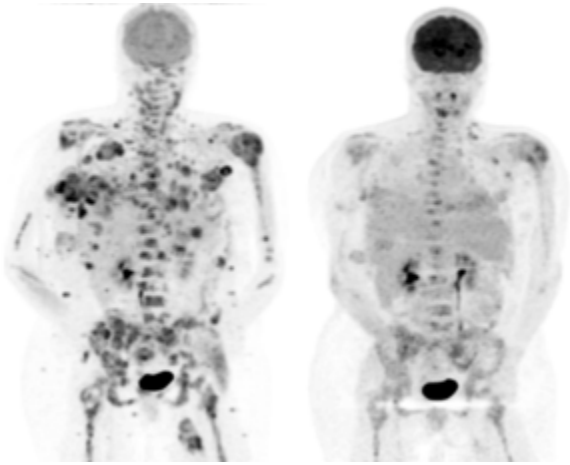


Baseline Day 15

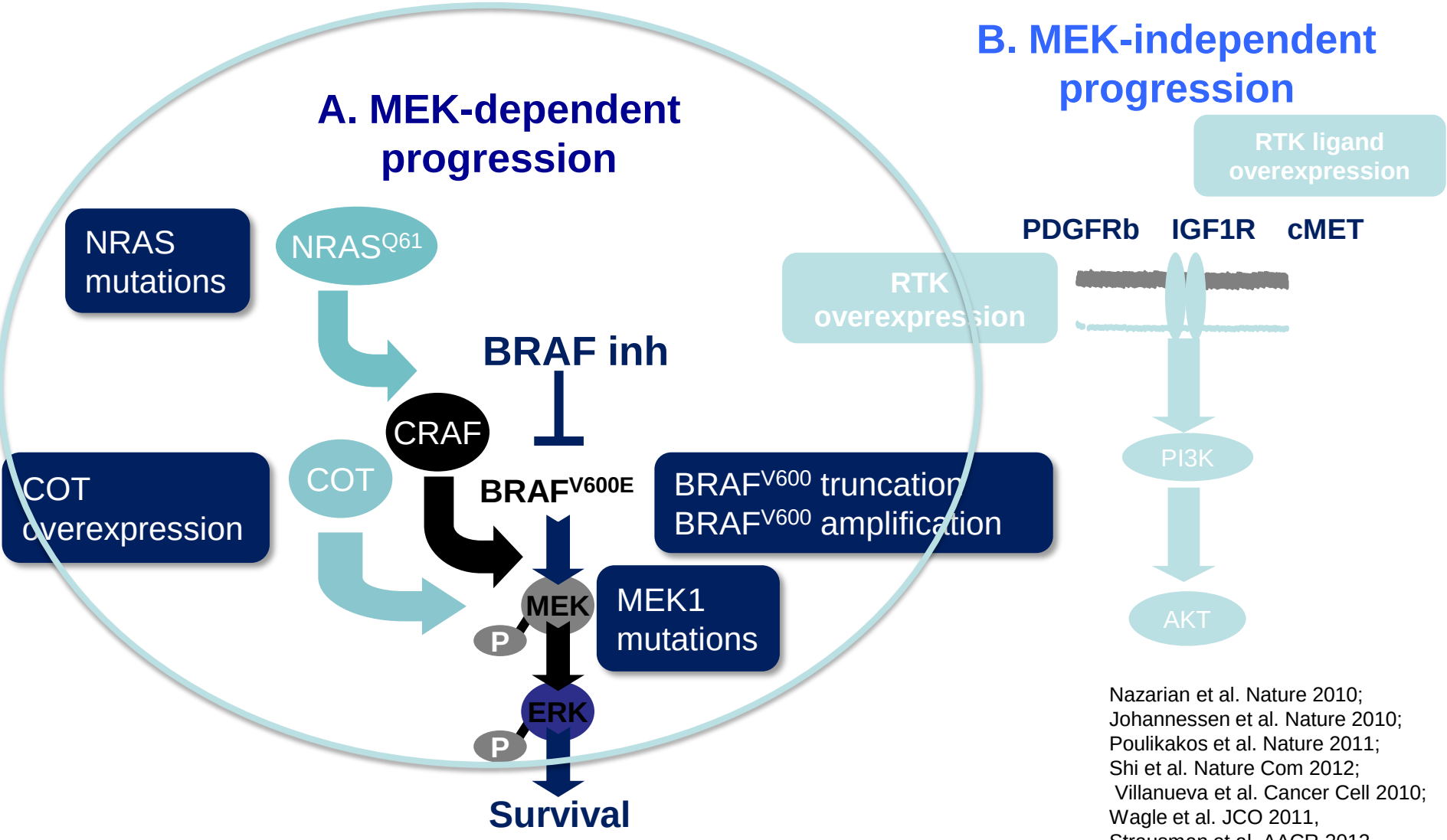


Baseline Day 15



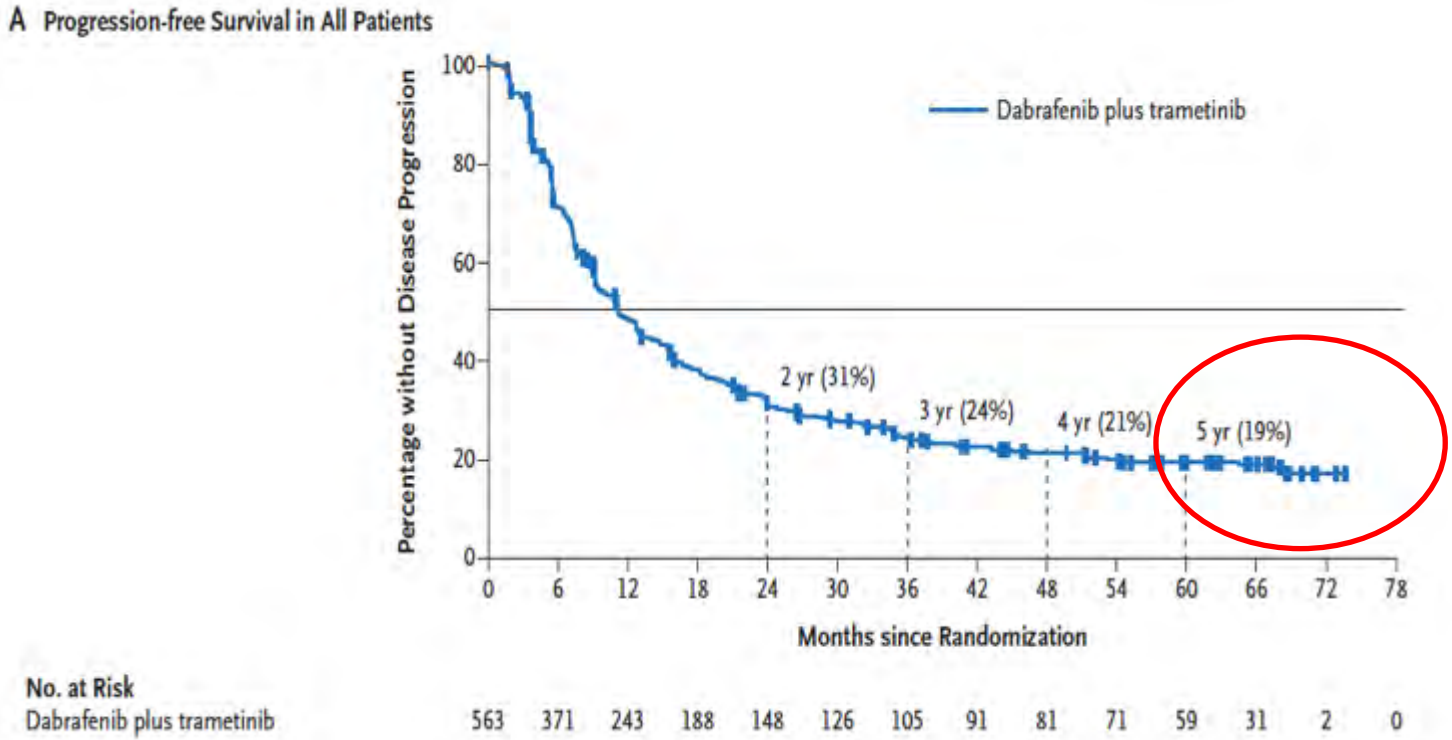


Unfortunately, resistance develops after initial benefit in the majority of patients



Nazarian et al. Nature 2010;
Johannessen et al. Nature 2010;
Poulikakos et al. Nature 2011;
Shi et al. Nature Com 2012;
Villanueva et al. Cancer Cell 2010;
Wagle et al. JCO 2011,
Strausman et al. AACR 2012

Durable PFS with BRAF-MEKi in some pts



88% (52/59) of patients, who were ongoing on trial and progression-free at 5-years, were **still receiving treatment (Dab or Tram or both).**

[Robert C et al. NEJM 2019]

Immunotherapy vs BRAF-MEKi: LTFU

	BRAF-MEKi (Combi-D and -V)	Ipi-Nivo (Checkmate 067)
ORR	**68%**	58%
CR	19%	21%
4-yr PFS	21%	37%
4-yr OS	37%	**62%**
Ongoing Study Treatment	**88%**	**11%**

How to choose amongst therapeutic options?

SB approach	BRAF wild type	BRAF mutated
Low Volume, Asymptomatic disease	**Immunotherapy** (anti PD-1 alone or in combination)	**Immunotherapy (preferred)** **BRAFi +/- MEKi (acceptable)**
Bulky disease, Symptomatic	**Immunotherapy** (anti PD-1 alone or in combination) **Chemotherapy**	**BRAFi +/- MEKi followed by Immunotherapy**

NCCN Guidelines v3.2020

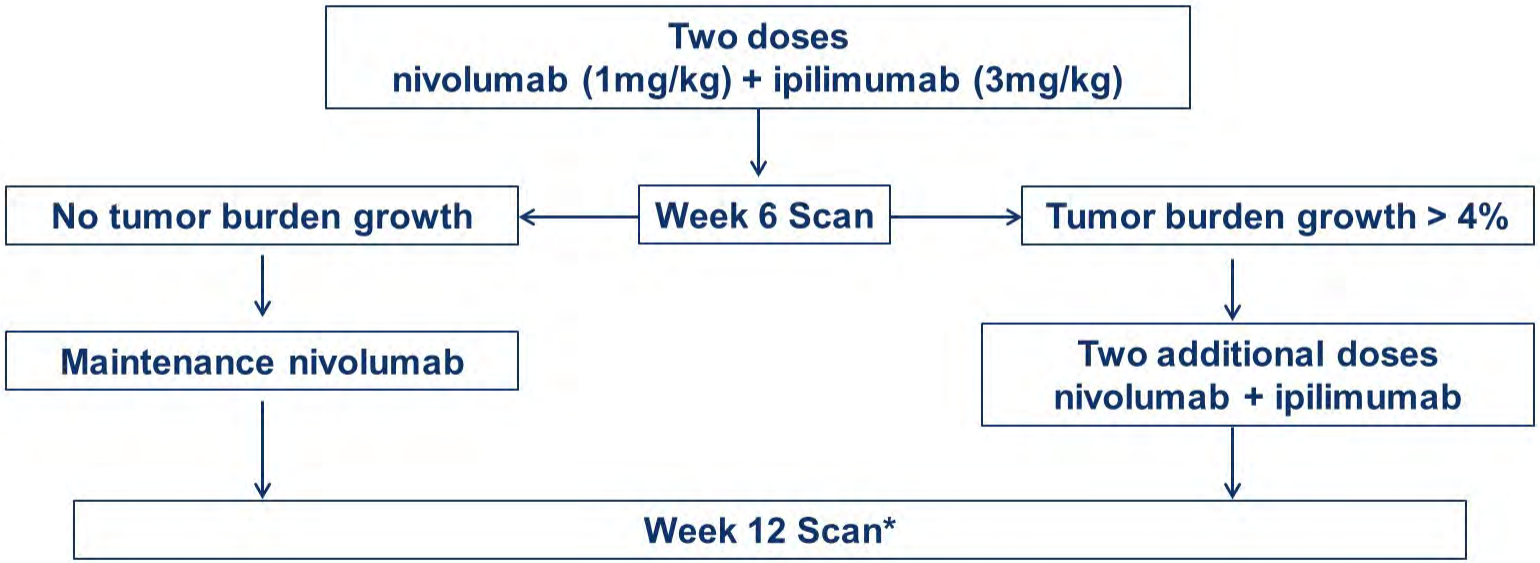
Question # 1

Optimizing frontline immunotherapy for metastatic melanoma?

A Phase II Study to Evaluate the Need for >2 Doses of Nivolumab + Ipilimumab Combination Immunotherapy in Patients with Unresectable Stage III/IV Melanoma

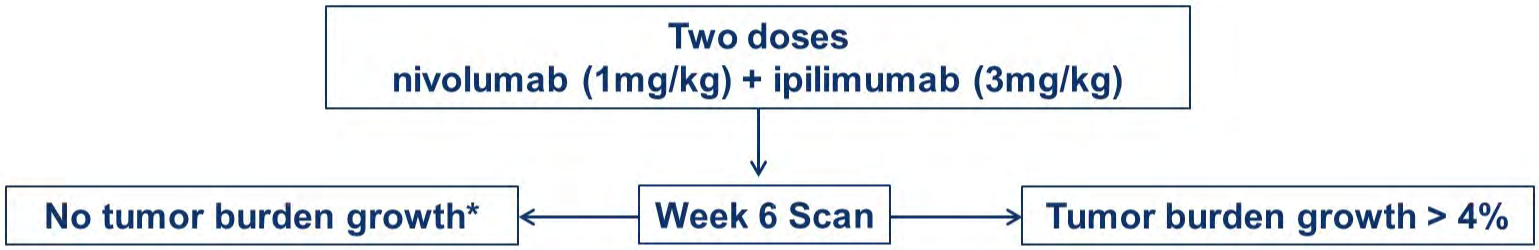
Michael A. Postow, Debra A. Goldman, Alexander N. Shoushtari, Allison Betof Warner, Margaret K. Callahan, Parisa Momtaz, Ellesa Naito, Omar Eton, Suresh G. Nair, Katherine S. Panageas, Jedd D. Wolchok, and Paul B. Chapman

Study Design



*If additional tumor growth was present, additional nivo + ipi was permitted

Most patients had tumor shrinkage or no growth at week 6 with ≤ 2 doses of nivo + ipi



68%
(41/60)

32%
(19/60)

Among the 19, no patients had subsequent RECIST response**

*7 patients only had 1 total dose of nivo + ipi

**12/19 patients received ≥3 total doses of nivo + ipi

Response Rates (RECIST 1.1)

	Week 6 N (%; 95%CI)	Week 12* N (%; 95%CI)	BORR N (%; 95%CI)
Overall Response	21 (35%; 23-48)	29 (48%; 35-62)	34 (57%; 43-69)
CR	0 (0)	3 (5)	11 (18)
PR	21 (35)	26 (43)	23 (38)
SD	26 (43)	11 (18)	13 (22)
PD	13 (22)	18 (30)	13 (22)

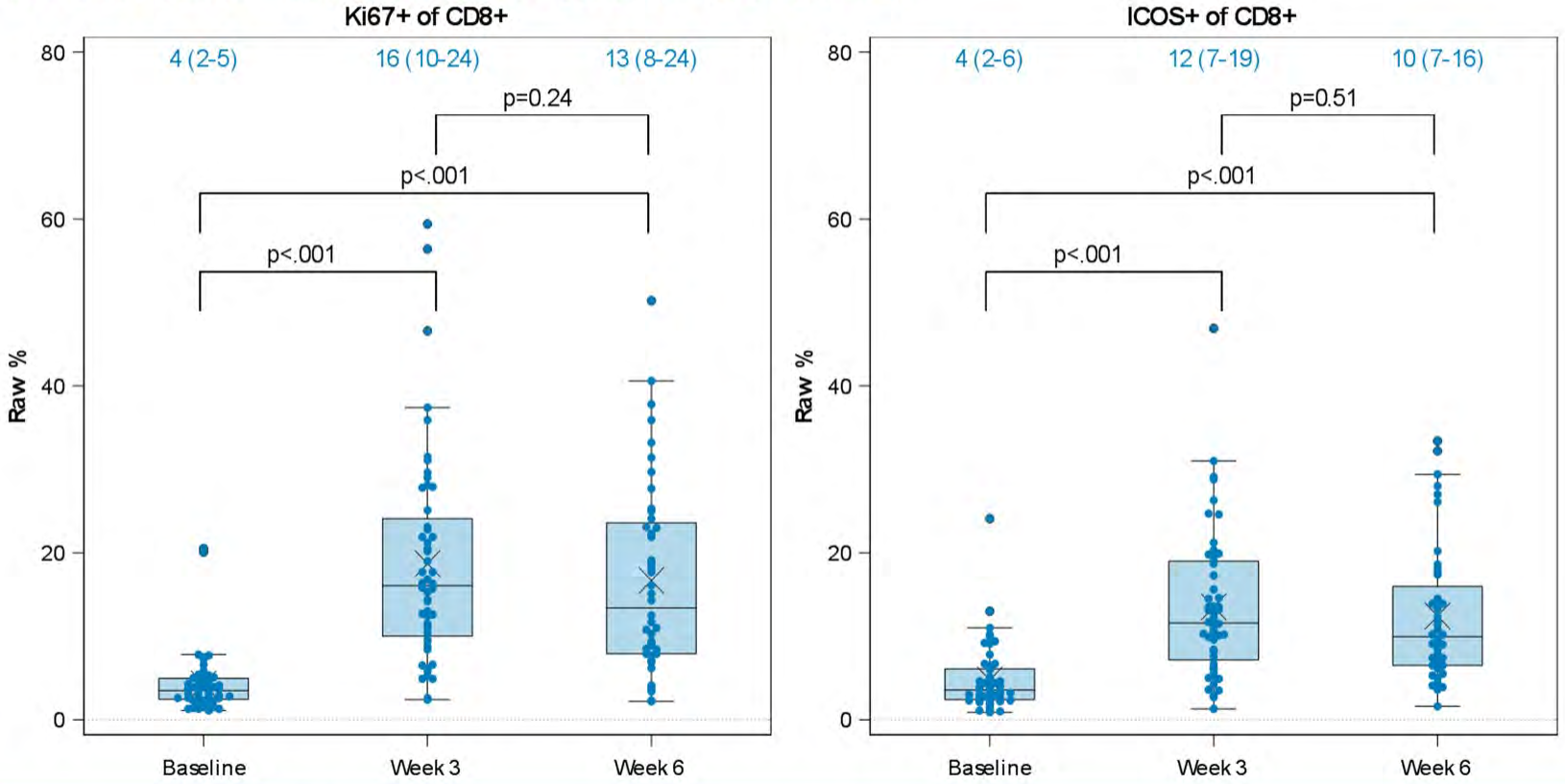
*Two patients with unknown Week 12 responses were included in denominator

Adverse Events

- 100% of patients had any grade treatment-related adverse events*
- 57% had grade 3-4 treatment-related adverse events*
- 3 patients died from treatment-related toxicity
  - 1 patient received 3 doses and developed secondary adrenal insufficiency and upper extremity DVT– died suddenly
  - 2 patients received only 1 dose– died from myocarditis

*Confounding issues prevent reporting of toxicity rates by # of doses received

Immunologic effects in blood occurred after dose 1 and did not further increase after dose 2



Presented By Michael Postow at TBD

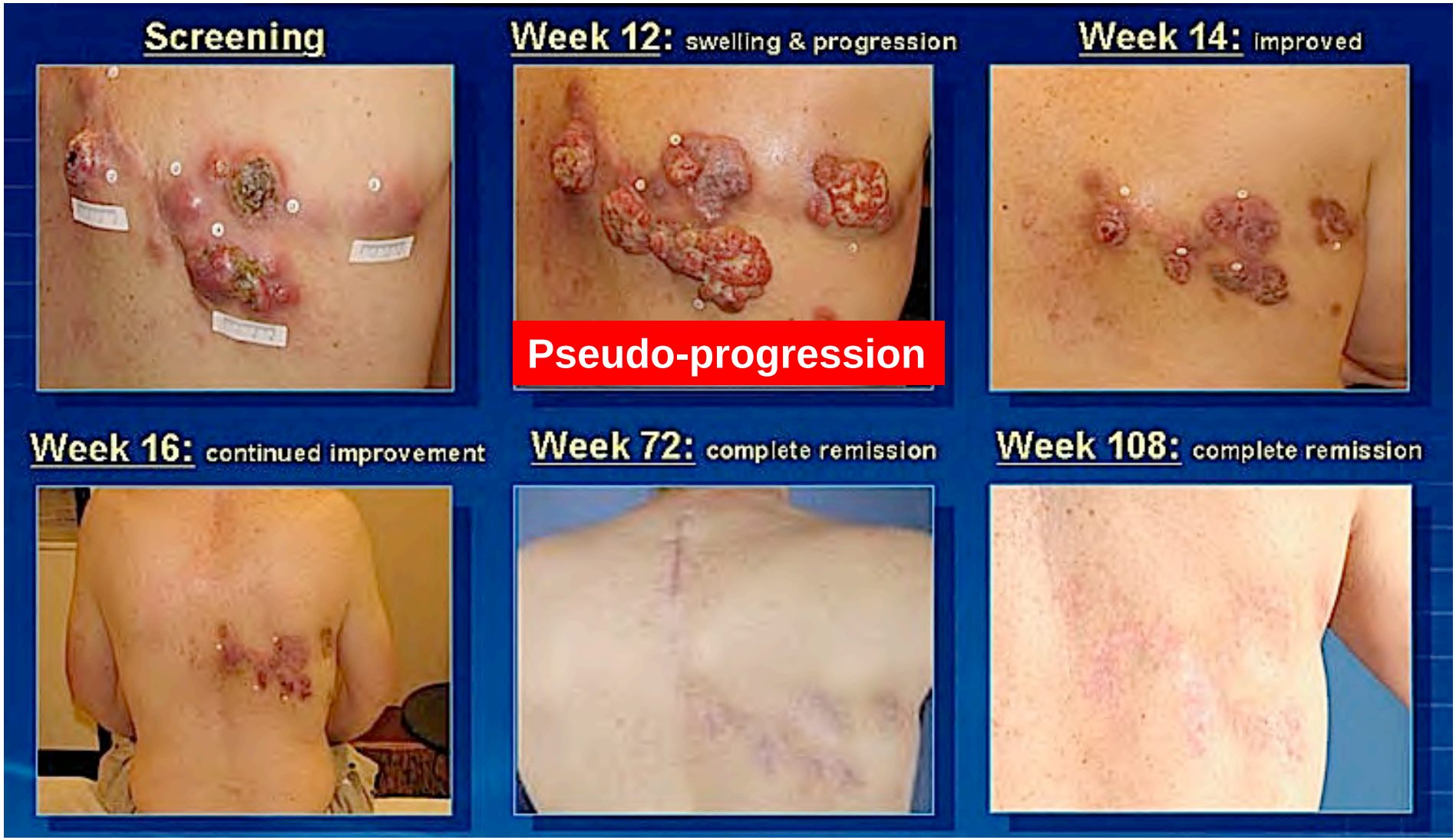
Conclusions

- The efficacy and adverse events of nivo + ipi appear mostly driven by the first 2 doses. Additional analyses of baseline factors and on treatment effects are needed to understand which patients are most likely to benefit from fewer doses.

- Although numbers were low, no patients with tumor burden growth at week 6 later had a RECIST response. Larger randomized studies are needed to determine whether this early interim assessment should be used for clinical management.

- Preliminary correlative data suggest immunologic effects occur after dose 1 and do not further increase after dose 2. Studies testing the efficacy and safety of 1 dose of nivo + ipi are needed.

Ipilimumab: Potential for Delayed responses



My conclusions

1. An early restaging scan at 6 weeks is (somewhat) predictive of the final outcome.

2. If major regression is seen at 6 weeks, an early switch to maintenance therapy is not entirely unreasonable (could avoid IRAEs and hence, use of immunosuppression).

3. If clear progression is seen at 6 weeks (especially PD that threatens clinical safety), this data may support proactive switching to another approach (such as BRAF-MEKi in BRAF mutant melanoma).

4. Small N limits generalizability of results at this time.

Evaluation of Two Dosing Regimens for Nivolumab in Combination With Ipilimumab in Patients With Advanced Melanoma: Results From the Phase IIIb/IV CheckMate 511 Trial

Celeste Lebbé, MD, PhD[1]; Nicolas Meyer, MD, PhD[2]; Laurent Mortier, MD, PhD[3]; Ivan Marquez-Rodas, MD, PhD[4]; Caroline Robert, MD, PhD[5]; Piotr Rutkowski, MD, PhD[6]; Alexander M. Menzies, MBBS, PhD[7], Thomas Eigentler, MD[8]; Paolo A. Ascierto, MD[9]; Michael Smylie, MD[10]; Dirk Schadendorf, MD[11,12]; Mazhar Ajaz, PhD, MRCP[13]; Inge Marie Svane, MD, PhD[14]; Rene Gonzalez, MD[15]; Linda Rollin, PhD[16]; Jennifer Lord-Bessen, PhD[16]; Abdel Saci, PhD[16]; Elena Grigoryeva, MD, PhD[16]; and Jacopo Pigozzo, MD[17]

Figure 1. CheckMate 511 study design

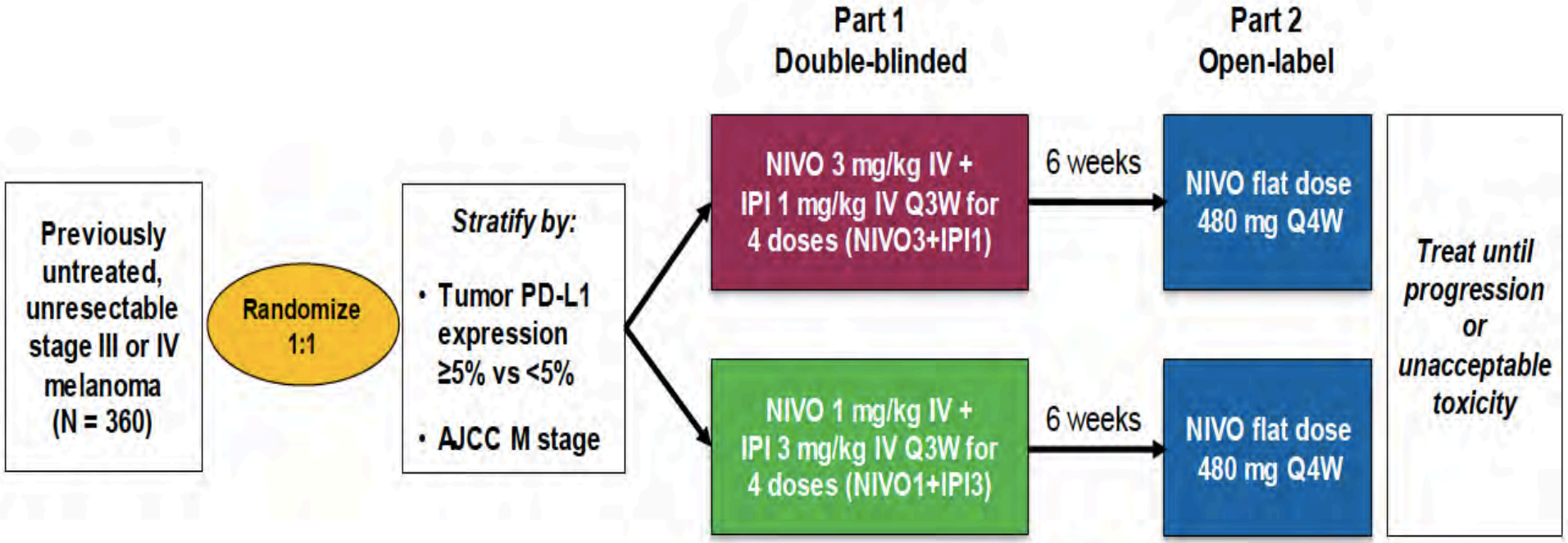
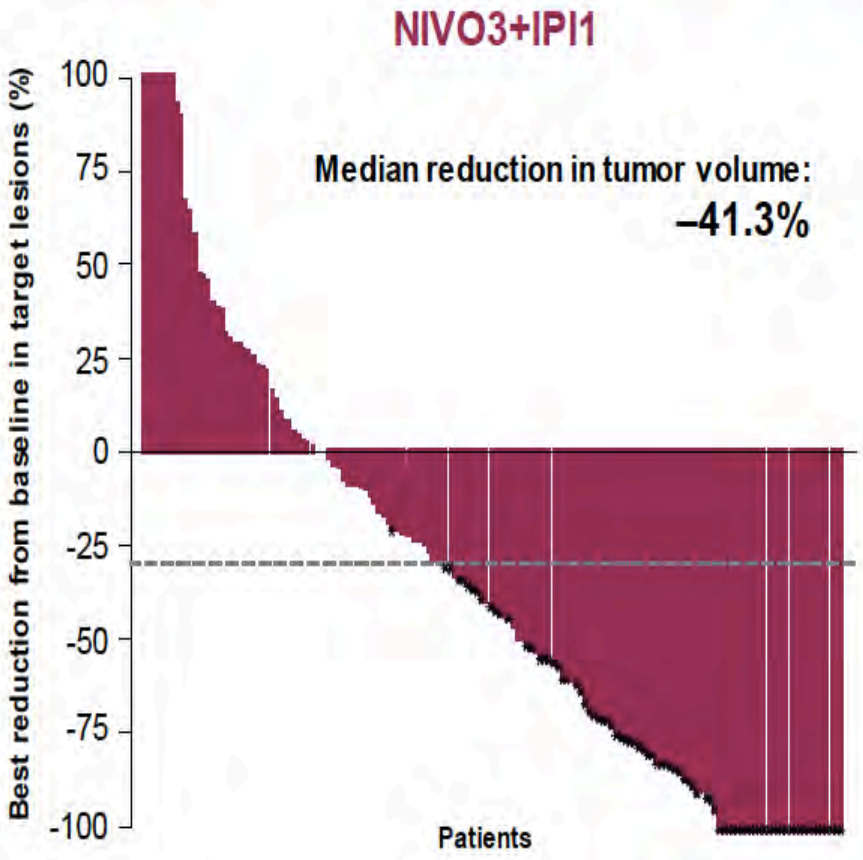


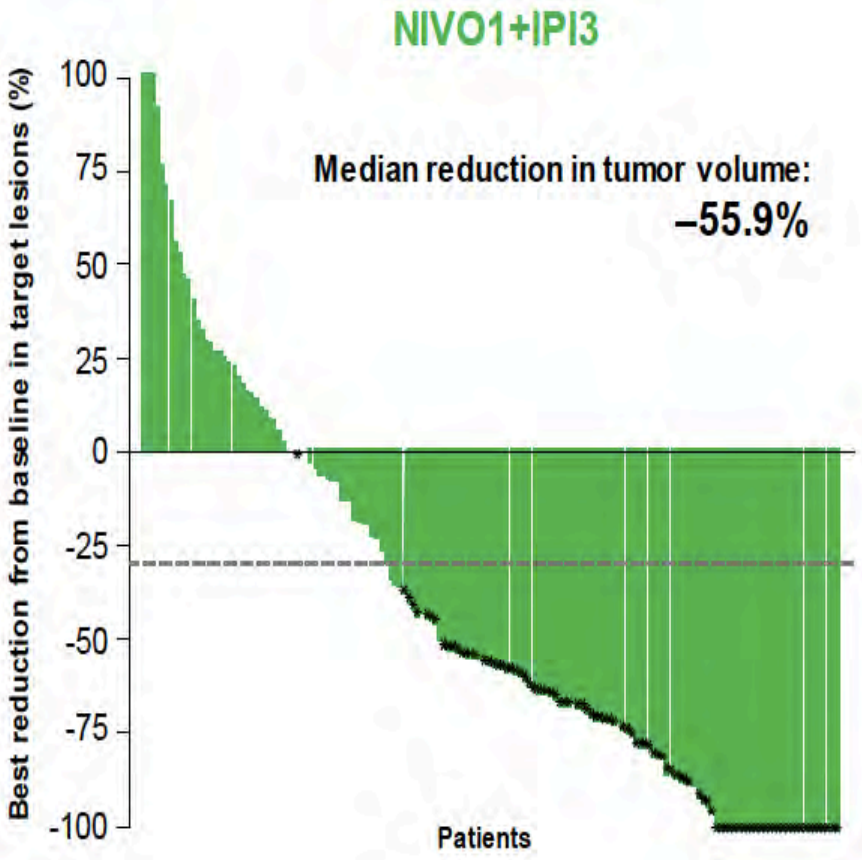
TABLE 4. Investigator-Assessed Response

Response	NIVO3+IPI1 (n = 180)		NIVO1+IPI3 (n = 178)
Best overall response, No. (%)			
Complete response	27 (15.0)		24 (13.5)
Partial response	55 (30.6)		66 (37.1)
Stable disease	21 (11.7)		21 (11.8)
Progressive disease	62 (34.4)		47 (26.4)
Unknown	15 (8.3)		20 (11.2)
ORR (95% CI), %	45.6 (38.1 to 53.1)		50.6 (43.0 to 58.1)
P		0.35	
Median time to response, months (range)	2.83 (2.0-17.9)		2.79 (2.3-10.5)
No. of ongoing responses/No. of responders (%)	63/82 (76.8)		68/90 (75.6)
Median duration of response, months	NR		NR

Abbreviations: NIVO1+IPI3, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg; NIVO3+IPI1, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg; NR, not reached; ORR, objective response rate.

Figure 2. Tumor burden change from baseline in target lesions[a]





[a]Based on investigator-assessed responses

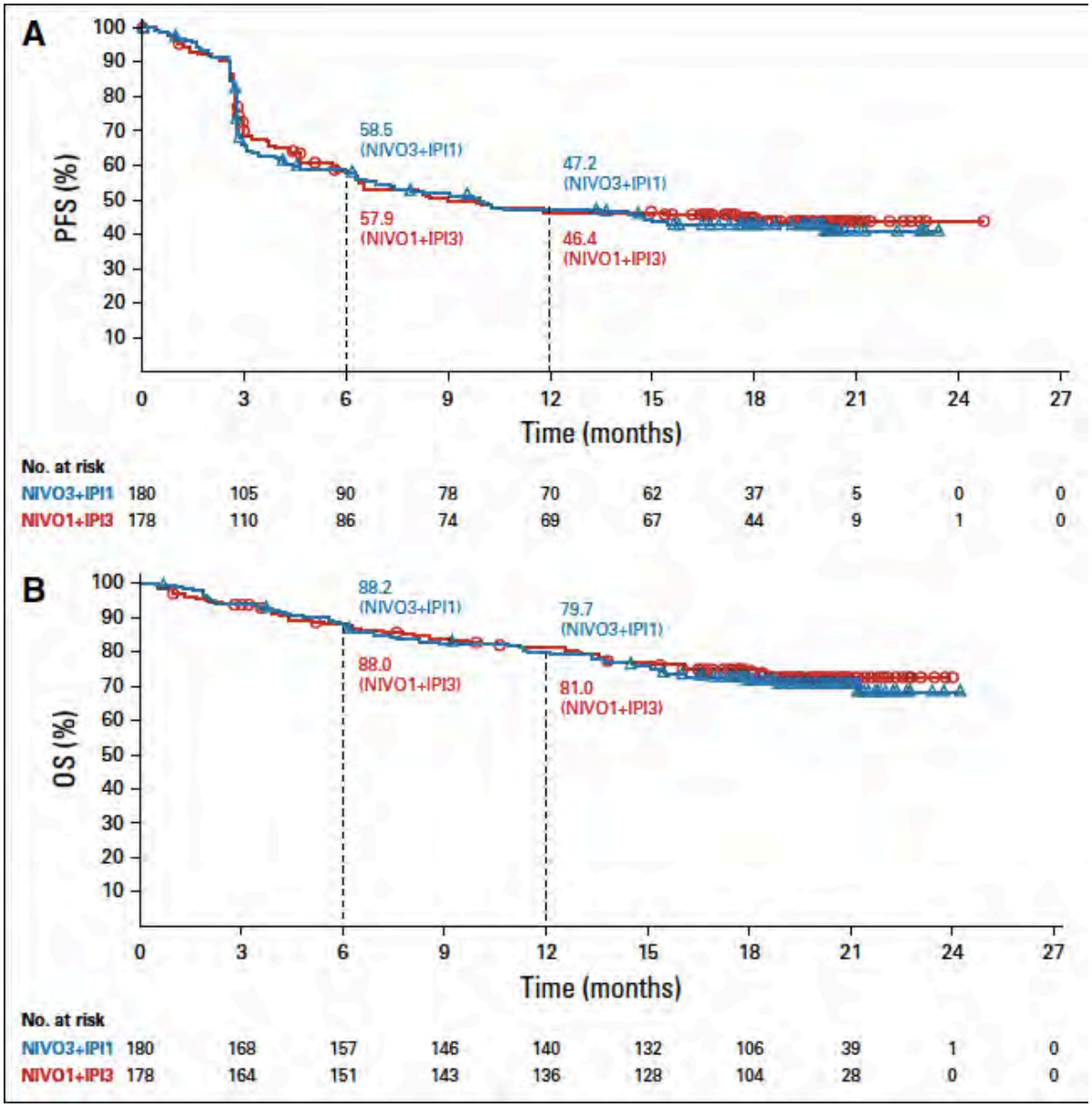

A
PFS (%)
100
90
80
70
60
50
40
30
20
10
58.5
(NIVO3+IPI1)
57.9
(NIVO1+IPI3)
47.2
(NIVO3+IPI1)
46.4
(NIVO1+IPI3)
0 3 6 9 12 15 18 21 24 27
Time (months)
No. at risk
NIVO3+IPI1 180 105 90 78 70 62 37 5 0 0
NIVO1+IPI3 178 110 86 74 69 67 44 9 1 0
B
OS (%)
100
90
80
70
60
50
40
30
20
10
88.2
(NIVO3+IPI1)
88.0
(NIVO1+IPI3)
79.7
(NIVO3+IPI1)
81.0
(NIVO1+IPI3)
0 3 6 9 12 15 18 21 24 27
Time (months)
No. at risk
NIVO3+IPI1 180 168 157 146 140 132 106 39 1 0
NIVO1+IPI3 178 164 151 143 136 128 104 28 0 0

Table 2. Safety summary[a]

	NIVO3+IPI1 (n = 180)	NIVO1+IPI3 (n = 178)
Rate of treatment-related grade 3-5 AEs, % (n/N) (95% CI)	**33.9%** (61/180) (27.0–41.3)	**48.3%** (86/178) (40.8–55.9)
Difference between treatment-related grade 3-5 AE rates (95% CI)	**-14.4%** (-24.5 to -4.3)	
***P* value**	**0.0059**	
Treatment-related AEs, %	85.6	93.8
Grade 3–4	33.3	48.3
Grade 5	0.6	0
All cause serious AEs, %	47.8	63.5
Grade 3–4	33.9	47.8
Grade 5	3.3	1.7
Treatment-related AEs leading to discontinuation, %	23.9	33.1
Grade 3–4	16.7	27.5
Grade 5	0.6	0

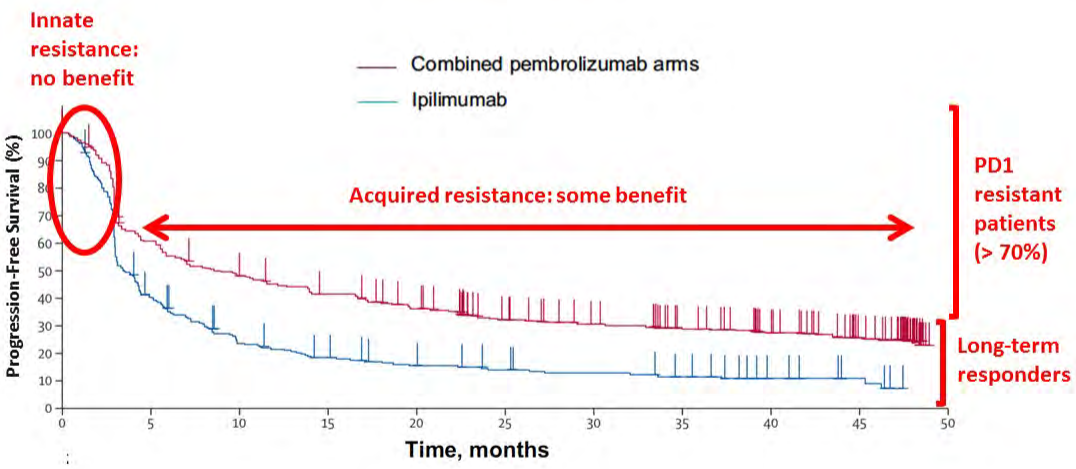
[a]Includes events reported between the first dose and 30 days after the last dose of study therapy

Question # 2

How should we treat PD-1 refractory melanoma?

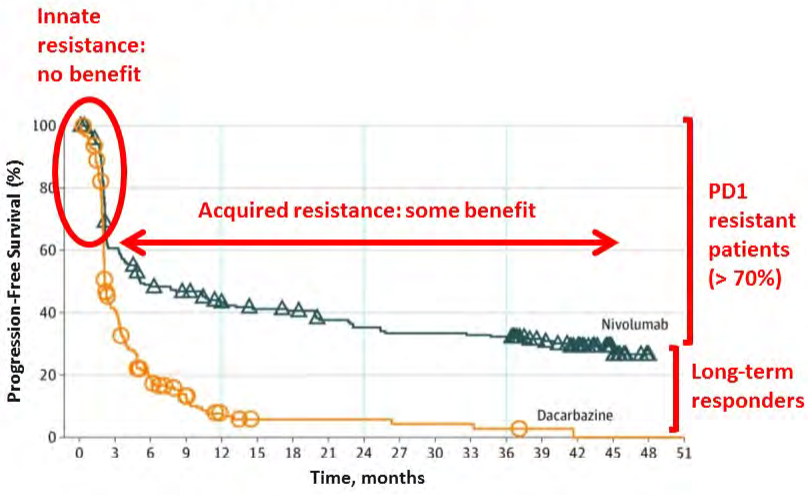
Background: 2/3 of advanced melanoma patients are resistant (innate or acquired) to PD1 monotherapy

KEYNOTE-006



Robert C, *et al*. The Lancet 2019

CheckMate-066



Robert C, *et al*. Lancet Oncol 2019

Presented By Ines Pires Da Silva at TBD

Ipilimumab (IPI) alone or in combination with anti-PD-1 (IPI+PD1) in patients (pts) with metastatic melanoma (MM) resistant to PD1 monotherapy

Ines Pires da Silva, Tasnia Ahmed, Serigne Lo, Irene LM Reijers, Alison Weppler, Allison Betof, James Randall Patrinely, Patricio Serra-bellver, Celeste Lebbe, Johanna Mangana, Khang Nguyen, Lisa Zimmer, Paolo Ascierto, Dan Stout, Megan Lyle, Olivier Klein, Camille Gerard, Christian U Blank, Alexander A Menzies, Georgina V Long

Melanoma Institute Australia

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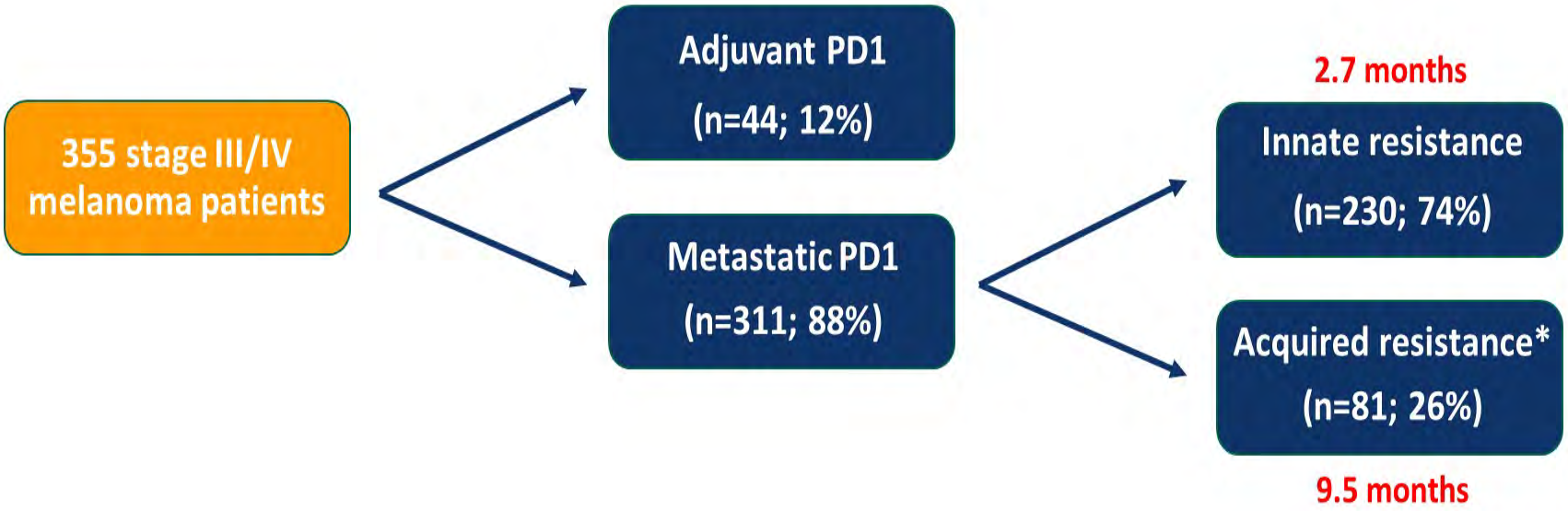
*Supported by **Friends and Family of Dr. and Mrs. Ronald Beller***

Presented By Ines Pires Da Silva at TBD

Cohort of PD1 resistant metastatic melanoma patients



Median time to PD1 progression 3 months (0.5 – 42.3)

*Acquired resistance: disease progression after initial CR, PR or SD ≥ 6 months

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Patient characteristics at start of IPI +/- PD1

	IPI + PD1 (n=193)	IPI (n=162)	*p-value*
Age, median (range)	61.0 (22.0, 91.0)	67.0 (21.0, 85.0)	0.0003
Sex, male (%)	124 (64.2%)	103 (63.6%)	0.8961
Geography			
Australia	93 (48.2%)	22 (13.6%)	<0.0001
Europe	55 (28.5%)	113 (69.8%)	
USA	45 (23.3%)	27 (16.7%)	
Mutational status			
BRAF mutant	70 (36.3%)	34 (21.0%)	0.0002
NRAS mutant	43 (22.3%)	26 (16.0%)	
BRAF & NRAS WT	80 (41.5%)	102 (63.0%)	
ECOG PS ≥ 1 (%)	58 (30.9%)	95 (59.7%)	<0.0001
Staging (M1C/M1D)	134 (69.4%)	121 (74.7%)	0.2723
Presence of liver metastases	56 (29.0%)	55 (34.0%)	0.3178
Presence of brain metastases	71 (36.8%)	43 (26.5%)	0.0395
LDH, > UNL (%)	67 (41.9%)	57 (37.5%)	0.4299

Presented By Ines Pires Da Silva at TBD

Response rate

	IPI + PD1 (n=193)	IPI (n=162)	*p-value*
Objective Response Rate (%)	61 (32%)	21 (13%)	**0.0021**
Response			**0.0076**
Complete response (%)	21 (11%)	3 (2%)	
Partial response (%)	40 (21%)	18 (11%)	
Stable disease (%)	17 (9%)	23 (14%)	
Progressive disease (%)	115 (59%)	118 (73%)	
Rate of Disease Control (%)	78 (41%)	44 (27%)	0.0519
Response Duration (95% CI) - months	11.6 (9.4 – 15.5)	9.0 (4.4 – 13.7)	**0.0467**

Median follow-up from start of IPI+/-PD1 of 22.2 months (18.4 - 25.6)

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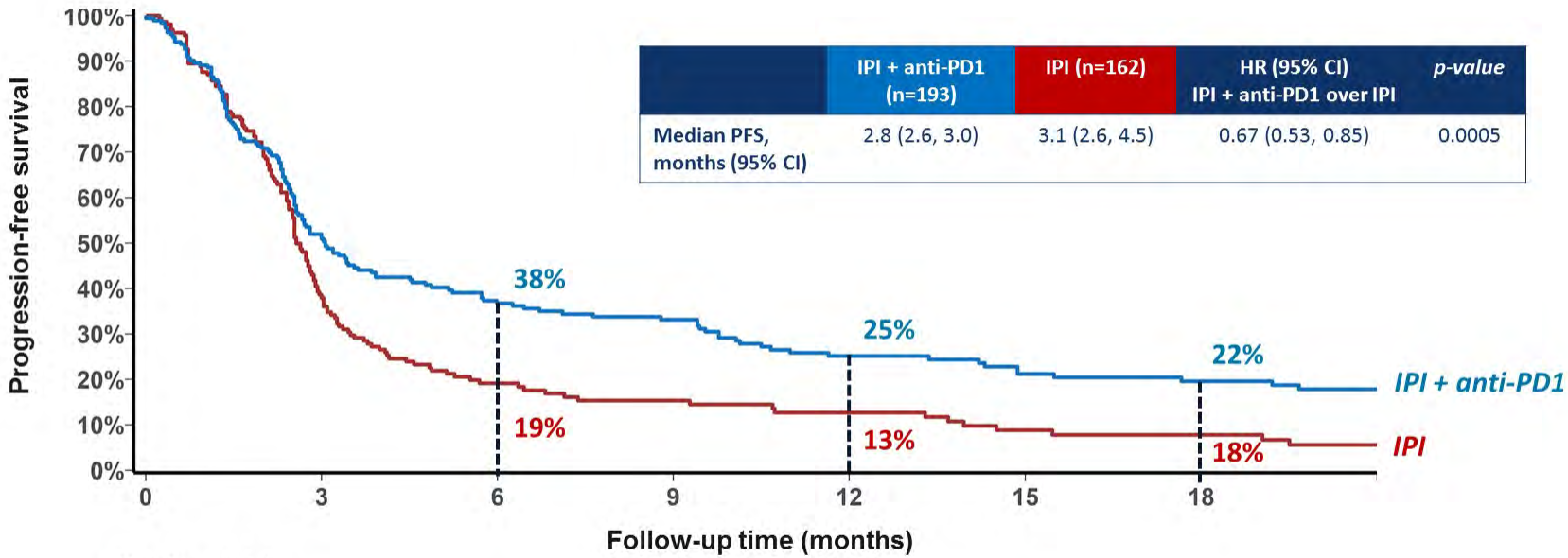
Progression-free survival

	IPI + anti-PD1 (n=193)	IPI (n=162)	HR (95% CI) IPI + anti-PD1 over IPI	*p-value*
Median PFS, months (95% CI)	2.8 (2.6, 3.0)	3.1 (2.6, 4.5)	0.67 (0.53, 0.85)	0.0005



Number at risk

IPI	162	60	25	20	13	9	7
IPI+anti-PD1	193	97	63	52	35	27	24

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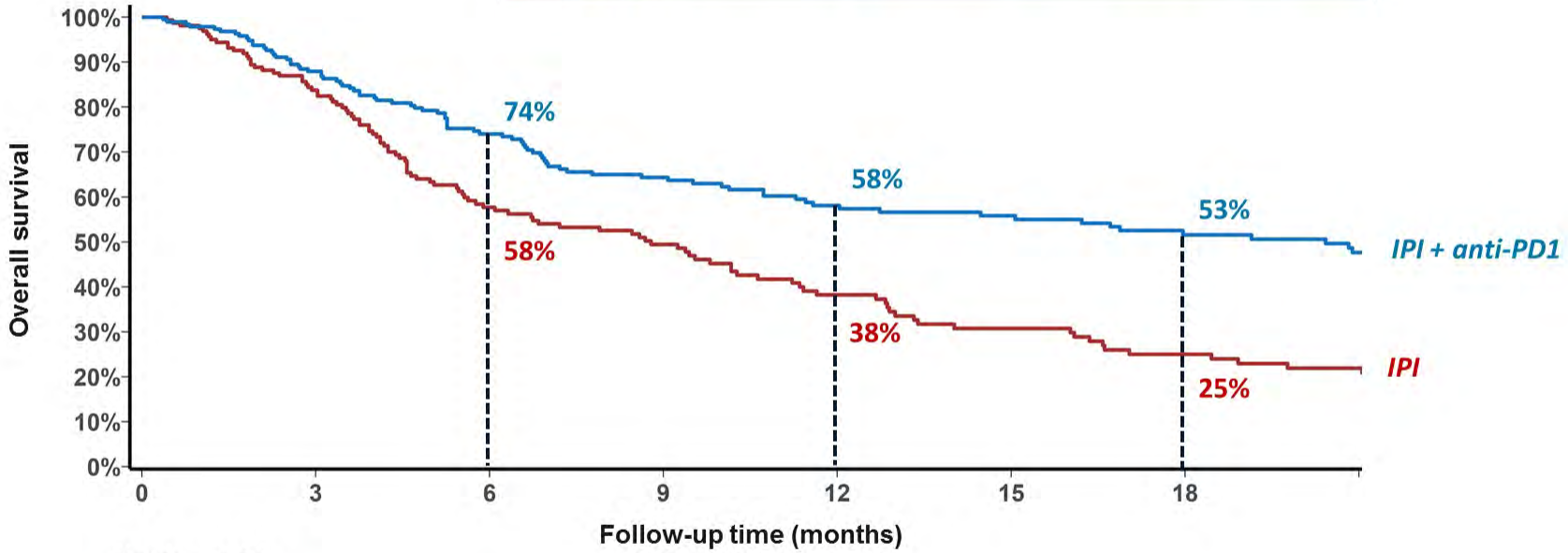
Overall survival

	IPI + anti-PD1 (n=193)	IPI (n=162)	HR (95% CI) IPI + anti-PD1 over IPI	*p-value*
Median OS, months (95% CI)	20.4 (12.7, 34.8)	8.8 (6.1, 11.3)	0.51 (0.38, 0.67)	<0.0001



Number at risk

IPI	162	131	79	63	43	33	26
IPI+anti-PD1	193	165	125	98	80	69	56

Presented By Ines Pires Da Silva at TBD

Safety

High Grade Adverse Events (≥ G3)	IPI + PD1 (n=193)	IPI (n=162)	p-value
Total	59 (31%)	54 (33%)	0.6474
Rash	3 (2%)	2 (1%)	0.9999
Diarrhoea / colitis	23 (12%)	33 (20%)	0.0401
Increased ALT/AST level	24 (12%)	15 (9%)	0.3960
Dyspnea / pneumonitis	2 (1%)	1 (1%)	0.9999
Nephritis	-	1 (1%)	0.4579
Endocrinopathies	3 (2%)	2 (1%)	0.9999
Others	9 (5%)	5 (3%)	0.5869

High grade (≥ G3) toxicity was not associated with response.

Presented By Ines Pires Da Silva at TBD

Conclusion

1. In patients resistant to PD1, IPI combined with PD1 has a higher response rate (32%) and longer PFS (25% at 12 months) and OS (58% at 12 months), yet similar high grade toxicity than IPI alone.

2. Predictive models of response and survival will help forecast patient outcomes when treated with IPI +/- PD1 after progressing on PD1 monotherapy.

Presented By Ines Pires Da Silva at TBD

Significant antitumor activity for low-dose ipilimumab (IPI) with pembrolizumab (PEMBRO) immediately following progression on PD1 Ab in melanoma (MEL) in a phase II trial

Daniel J. Olson[1], Jason J. Luke[2], Andrew S. Poklepovic[3], Madhuri Bajaj[4], Emily Higgs[1], Timothy C. Carll[1], Brian Labadie[1], Thomas Krausz[1], Yuanyuan Zha[1], Theodore Karrison[1], Jose Lutzky[5], Sigrun Hallmeyer[6], Bruce Brockstein[7], Vernon K. Sondak[8], Zeynep Eroglu[8], Thomas F. Gajewski[1], Nikhil I. Khushalani[8]

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AT THE FOREFRONT UChicago Medicine

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PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Daniel J. Olson (@DanielOlsonMD)

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Pembro + low-dose ipi after PD1 Ab failure: Study Design

Patient Criteria

- Unresectable or metastatic melanoma
- Confirmed progression on a PD1 Ab immediately prior, or within six months of adjuvant therapy
- Prior BRAF treatment allowed
- Uveal melanoma excluded
- ECOG 0 to 1
- Treated CNS disease allowed

Prior to study enrollment

PD1/L1 Ab or non-CTLA4 combination

Study day 1

Pembrolizumab 200mg IV Q3 weeks

ipilimumab 1mg/kg Q3 weeks x 4 doses

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Pembro + low-dose ipi after PD1 Ab failure: Patient demographics

Characteristic	Study patients receiving ≥ 1 dose (n=70)
Age (years)	
Median	64
Range	27 - 87
Sex	
M	47 (67%)
F	23 (33%)
BRAF Status	
Mutant (V600)	20 (29%)
Wild Type	50 (71%)
AJCC Stage	
IIIc (unresectable)	12 (17%)
IV	58 (83%)
M1a	15 (21%)
M1b	9 (13%)
M1c	27 (39%)
M1d	7 (10%)
Melanoma Subtypes	
Cutaneous	62 (89%)
Acral	7 (10%)
Mucosal	1 (1%)

Characteristic	Study patients receiving ≥ 1 dose (n=70)
Adjuvant PD1 Ab Progression	13 (19%)
Baseline LDH	
≤ ULN	50 (71%)
> ULN	15 (21%)
≥ 2x ULN	5 (7%)
History of Brain Metastases (treated)	
Yes	7 (10%)
No	53 (90%)
Liver Metastases	
Yes	17 (24%)
No	53 (76%)
Prior Lines Systemic Therapy (Mean = 1)	
PD1 Ab alone	60 (86%)
PD1 Ab combination (non-CTLA4 Ab)	10 (14%)
Prior BRAF directed therapy (pre-PD1 Ab)	5 (7%)

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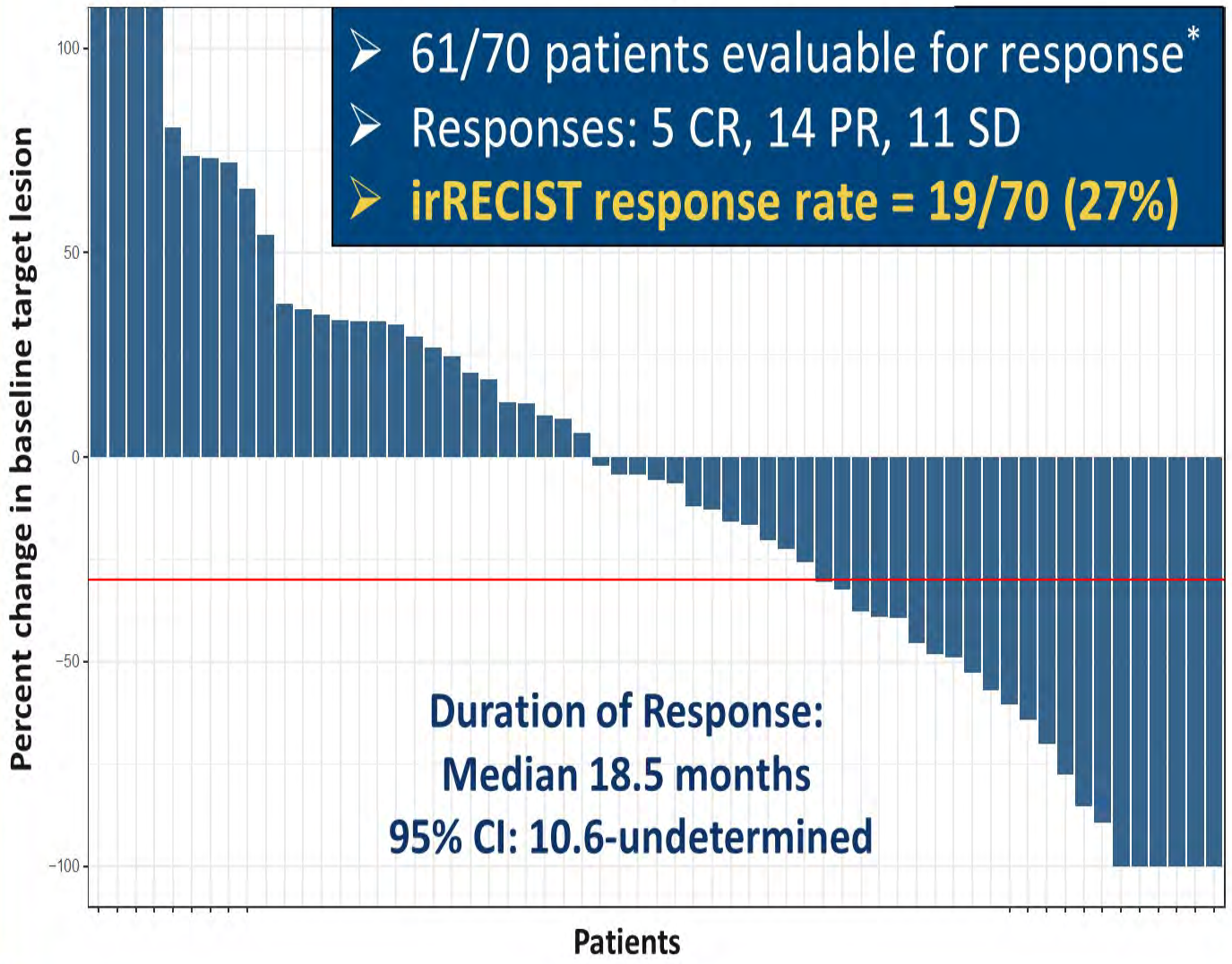
Best Overall Response



Lower high-grade irAE event rate with Pembro + low-dose ipi

Patients with toxicity at least possibly related to treatment - n (%)			
Grade 1	Grade 2	Grade 3	Grade 4
61/70 (87%)	40/70 (57%)	18/70 (26%)	1 (1%)

Possibly related toxicites occuring at > 10% of patients - n (%)	Grade 1	Grade 2	Grade 3
Pruritis	23 (33%)	5 (7%)	
Rash (maculo-papular, acneiform, papulopustular)	22 (31%)	3 (4%)	4 (6%)
Colitis/Diarrhea	21 (30%)	7 (10%)	6 (9%)
Fatigue	12 (17%)	11 (16%)	
Nausea	12 (17%)	5 (7%)	1 (1%)
Alanine/Aspartate aminotransferase increased	11 (16%)	3 (4%)	4 (6%)
Arthralgia	7 (10%)		
Anorexia	6 (9%)	8 (11%)	

Number of patients with ≥ grade 3 toxicity at least possibly related to study drug - n (%)*	Grade 3	Grade 4
Colitis/Diarrhea	6 (9%)	0
Rash (acneiform or maculopapular)	4 (6%)	0
AST and/or ALT elevation	4 (6%)	0
Lipase Elevation	2 (3%)	1 (1%)
Acute Kidney Injury	2 (3%)	0
Hyperglycemia	2 (3%)	0
Pancreatitis	1 (1%)	0
Skin and subcutaneous tissue disorders - Other, specify (vasculitis)	1 (1%)	0
Anemia	1 (1%)	0
Nausea	1 (1%)	0
Lymphocyte Count Decreased	1 (1%)	0
Lympocyte count increased	1 (1%)	0
Lung Infection	1 (1%)	0
Alkaline Phosphatase Elevation	1 (1%)	0

*Four patients experienced two grade 3+ toxicities; one patient experienced four

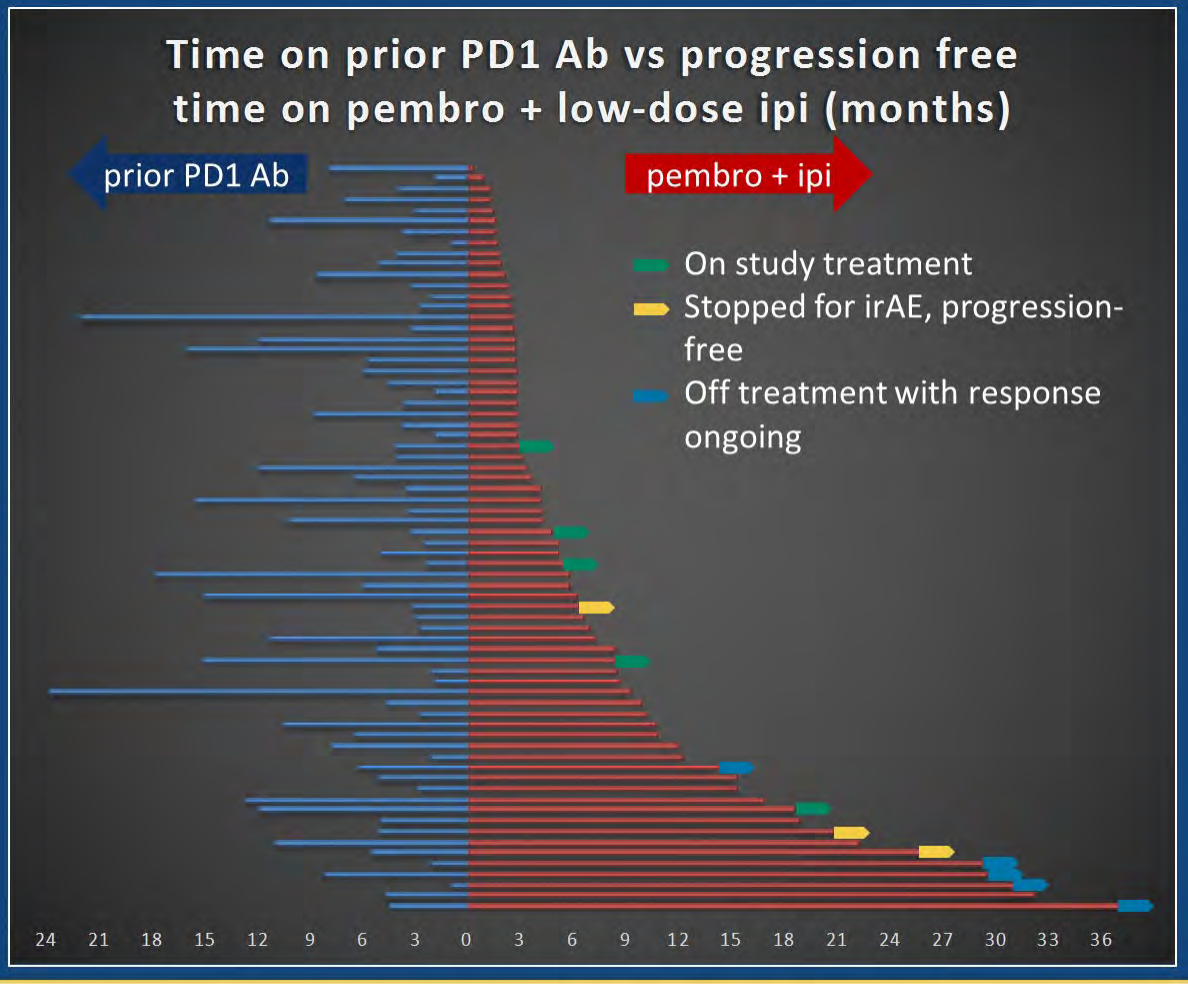
Median time to onset of all high-grade irAEs = 55 days

Weber JS et al. *Cancer 2013*

Pembro + low-dose ipi: study timeline

Median time on prior PD1 Ab = 4.8 months

Median PFS on Pembro + low-dose ipi = 5 months (95% CI: 2.8-8.3)



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Conclusions

- This is the largest prospective study of a PD1 Ab + CTLA4 Ab demonstrating antitumor activity and tolerability in melanoma post PD1 Ab
- The combination of pembro plus low-dose ipi generated an irRECIST response rate of 27%, higher than the 15% in historical controls with ipi alone
- Treatment-related G3-4 toxicity occurred in 27% of patients, comparing favorably to ipi 3mg/kg + nivolumab regimens in the front line (G3-4: 59%)
- Pembro + low-dose ipi can be effective in non-T cell-inflamed tumors

My conclusions

1. Ipilimumab (monotherapy or in combination with PD-1) can be an effective salvage therapy in a proportion of patients with PD-1 refractory melanoma

2. Response rates are low, but responses tend to be durable.

3. Toxicity rates may be similar with Ipilimumab monotherapy or Ipi-PD-1 combo in this setting.

NCCN Guidelines v3.2020

SECOND-LINE OR SUBSEQUENT THERAPY[l]

- **Systemic therapy**
  - **Preferred regimens**
    - ◊ **Anti PD-1 monotherapy[d,e]**
      - – **Pembrolizumab**
      - – **Nivolumab**
    - ◊ **Nivolumab/ipilimumab[d,e,f]**
    - ◊ **Combination targeted therapy if *BRAF* V600-activating mutation[i,j,k]**
      - ▪ **Dabrafenib/trametinib**
      - ▪ **Vemurafenib/cobimetinib**
      - ▪ **Encorafenib/binimetinib**
  - **Other regimens**
    - ◊ **Ipilimumab[d]**
    - ◊ **High-dose IL-2[m]**

Long-term follow up of lifileucel (LN-144) cryopreserved autologous tumor infiltrating lymphocyte therapy in patients with advanced melanoma progressed on multiple prior therapies

Amod Sarnaik, MD
H. Lee Moffitt Cancer Center, Tampa, FL, USA

Study Overview and Procedures

1 → 2 → 3 → 4 → 5 → 6

Patient Intake

Surgical Resection

The process begins with surgical resection of a tumor lesion (~1.5 cm in diameter). The tumor lesion is shipped to a Central GMP facility and undergoes a 22-day process that generates a cryopreserved TIL infusion product.

TIL were generated from **skin, lymph nodes, liver, lung, peritoneal, musculo-skeletal, breast, and other organs.**

NMA-LD

Patient undergoes nonmyeloablative lymphodepletion: Cyclophosphamide followed by fludarabine.

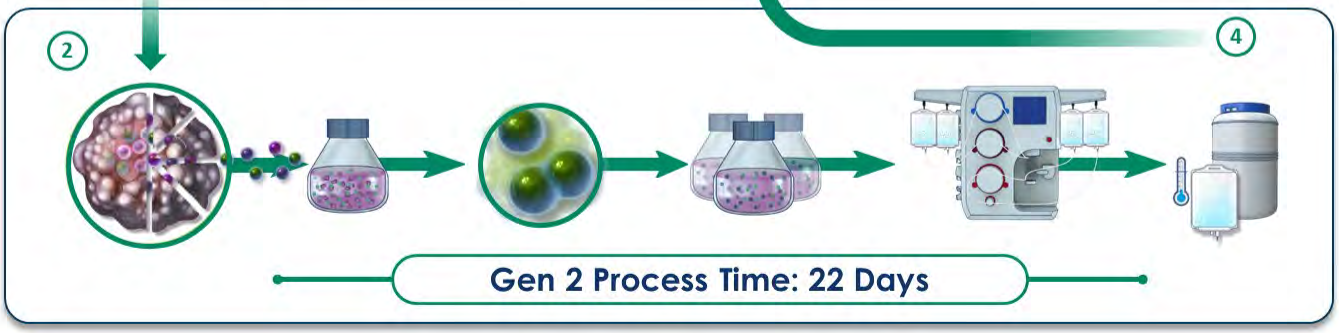
TIL Infusion

Patient receives one time treatment of expanded and activated lifileucel TIL product infusion.

IL-2 Infusions

Following lifileucel, patients complete a short course of up to 6 doses of interleukin-2 (IL-2) infusions, to enhance the antitumor activity of the TIL.

Recovery/Discharge



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C-144-01 Cohort 2 Patient Characteristics

CHARACTERISTIC	Cohort 2, N=66, (%)
Gender, n (%)	
Female	27 (41)
Male	39 (59)
Age, years	
Median	55
Min, Max	20, 79
Prior therapies, n (%)	
Mean # prior therapies	3.3
Anti-CTLA-4	53 (80)
Anti-PD-1	66 (100)
BRAF/MEK	15 (23)
Progressive Disease for at least 1 prior therapy	
Anti-CTLA-4	41 (77[(1)])
Anti-PD-1	65 (99)
Baseline ECOG score, n (%)	
0	37 (56)
1	29 (44)

CHARACTERISTIC	Cohort 2, N=66, (%)
BRAF Status, n (%)	
Mutated V600	17 (26)
Wild Type	45 (68)
Unknown	3 (5)
Other	1 (2)
Baseline LDH (U/L)	
Median	244
1-2 times ULN	19 (29)
> 2 times ULN	8 (12)
Target Lesions Sum of Diameter (mm)	
Mean (SD)	106 (71)
Min, Max	11, 343
Number of Target and Non-Target Lesions (at Baseline)	
>3	51 (77)
Mean (SD)	6 (2.7)
Patients with Baseline Liver and/or Brain Lesions	28 (42)

Cohort 2 patients have:

- 3.3 mean prior therapies, ranging from 1-9
- High tumor burden at baseline: 106 mm mean sum of diameters of the target lesions

[(1)] The denominator is the 53 patients who received prior anti-CTLA-4.

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Iovance C-144-01 Cohort 2 Safety:

Treatment Emergent Adverse Events (≥ 30%)

PREFERRED TERM	Cohort 2 (N=66)		
	Any Grade, n (%)	Grade 3/4, n (%)	Grade 5, n (%)
Number of patients reporting at least one Treatment-Emergent AE	66 (100)	64 (97.0)	2 (3.0)*
Thrombocytopenia	59 (89.4)	54 (81.8)	0
Chills	53 (80.3)	4 (6.1)	0
Anemia	45 (68.2)	37 (56.1)	0
Pyrexia	39 (59.1)	11 (16.7)	0
Neutropenia	37 (56.1)	26 (39.4)	0
Febrile neutropenia	36 (54.5)	36 (54.5)	0
Hypophosphatemia	30 (45.5)	23 (34.8)	0
Leukopenia	28 (42.4)	23 (34.8)	0
Fatigue	26 (39.4)	1 (1.5)	0
Hypotension	24 (36.4)	7 (10.6)	0
Lymphopenia	23 (34.8)	21 (31.8)	0
Tachycardia	23 (34.8)	1 (1.5)	0

*One death was due to intra-abdominal hemorrhage considered possibly related to TIL and one was due to acute respiratory failure assessed as not related to TIL per investigator assessment.
Patients with multiple events for a given preferred term are counted only once using the maximum grade under each preferred term.
Treatment-Emergent Adverse Events refer to all AEs starting on or after the first dose date of TIL up to 30 days.

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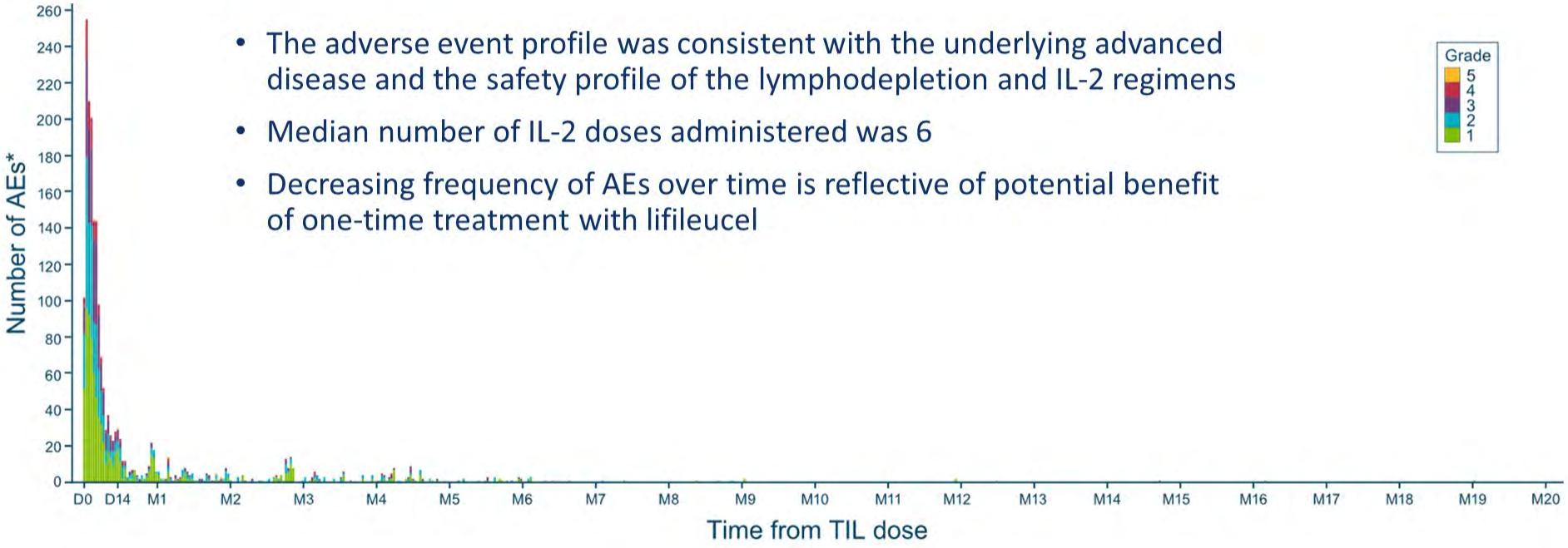
C-144-01 Cohort 2 Safety:

Adverse Events over Time



- The adverse event profile was consistent with the underlying advanced disease and the safety profile of the lymphodepletion and IL-2 regimens
- Median number of IL-2 doses administered was 6
- Decreasing frequency of AEs over time is reflective of potential benefit of one-time treatment with lifileucel

*The number of AEs is cumulative and represent the total number of patients dosed.

C-144-01 Cohort 2 Efficacy

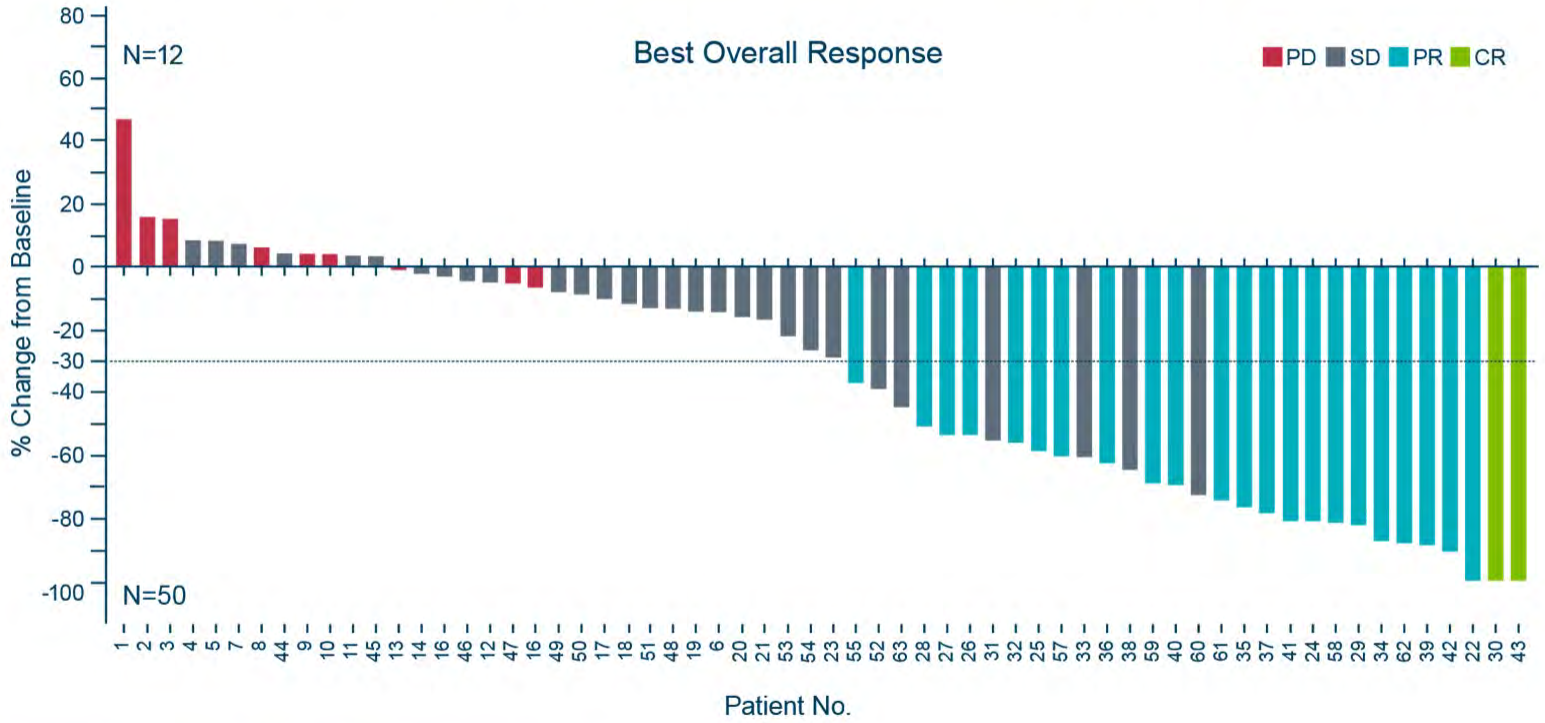
RESPONSE	PATIENTS, N=66 n (%)
Objective Response Rate	**24 (36.4)**
Complete Response	2 (3.0)
Partial Response	22 (33.3)
Stable Disease	29 (43.9)
Progressive Disease	9 (13.6)
Non-Evaluable[1]	4 (6.1)
Disease Control Rate	53 (80.3)
Median Duration of Response	**Not Reached**
Min, Max (months)	2.2, 26.9+

- After a median study follow-up of 18.7 months, median DOR was still not reached (range 2.2, 26.9+)
- Response was seen regardless of location of tumor resected
- Mean number of TIL cells infused: 27.3 x 10^9

[1] NE due to not reaching first assessment.

C-144-01 Cohort 2 Efficacy: Best Overall Response

81% (50/62) of patients had a reduction in tumor burden



Three subjects had no post TIL disease assessment due to early death, and one due to start of new anti-cancer therapy.

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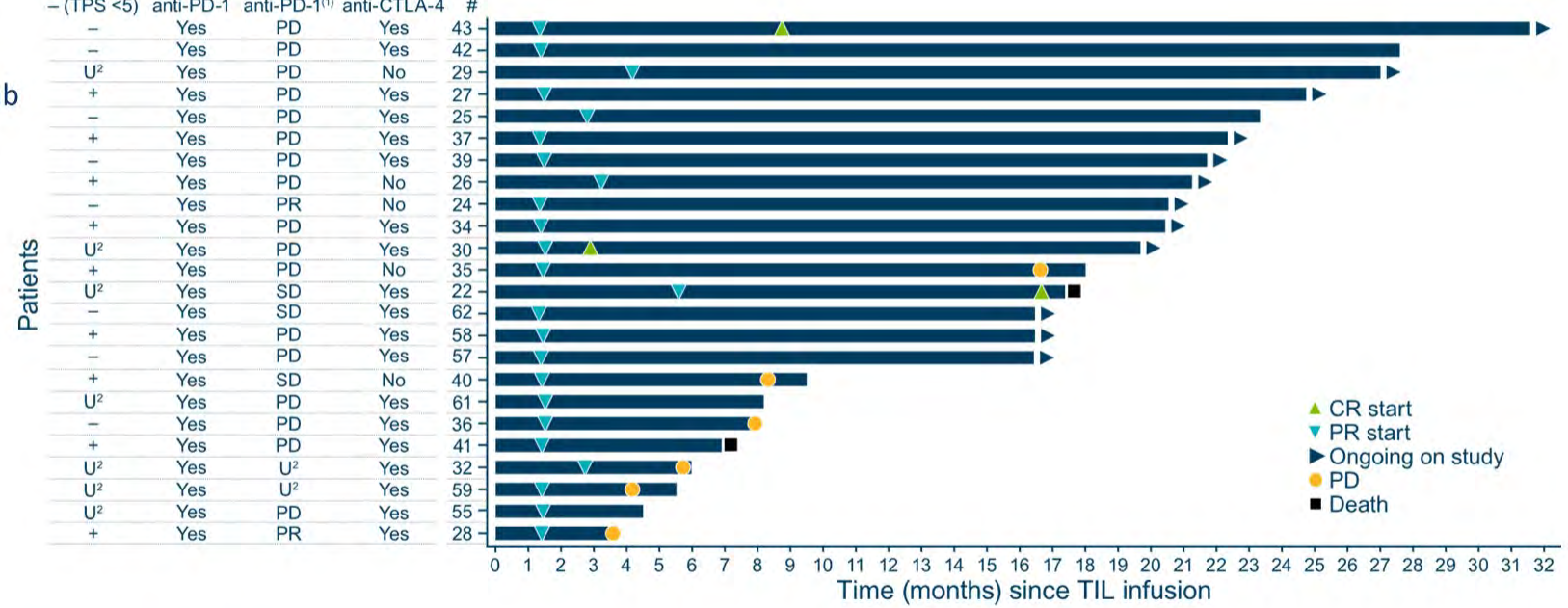
C-144-01 Cohort 2 Efficacy:

Time to Response for Evaluable Patients (PR or Better)

79% of responders had received prior ipilimumab

Responses deepen over time

PD-L1 + (TPS ≥5)/ – (TPS <5)	Prior anti-PD-1	BOR on Prior anti-PD-1[1]	Prior anti-CTLA-4	#
–	Yes	PD	Yes	43
–	Yes	PD	Yes	42
U[2]	Yes	PD	No	29
+	Yes	PD	Yes	27
–	Yes	PD	Yes	25
+	Yes	PD	Yes	37
–	Yes	PD	Yes	39
+	Yes	PD	No	26
–	Yes	PR	No	24
+	Yes	PD	Yes	34
U[2]	Yes	PD	Yes	30
+	Yes	PD	No	35
U[2]	Yes	SD	Yes	22
–	Yes	SD	Yes	62
+	Yes	PD	Yes	58
–	Yes	PD	Yes	57
+	Yes	SD	No	40
U[2]	Yes	PD	Yes	61
–	Yes	PD	Yes	36
+	Yes	PD	Yes	41
U[2]	Yes	U[2]	Yes	32
U[2]	Yes	U[2]	Yes	59
U[2]	Yes	PD	Yes	55
+	Yes	PR	Yes	28



[1] BOR is best overall response on prior anti-PD-1 immunotherapy
[2] U: unknown
[3] Patient 22 BOR is PR

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C-144-01 Cohort 2: Conclusions

- In heavily pretreated metastatic melanoma patients with high baseline disease burden who progressed on multiple prior therapies, including anti-PD-1 and BRAF/MEK inhibitors, if BRAFV600 mutant, lifileucel treatment results in:
  - 36.4% ORR
  - 80.3% DCR
  - Median DOR was still not reached at 18.7 months of median study follow up
- Responses deepen over time

Lifileucel has demonstrated potential efficacy and durability of response for patients with metastatic melanoma and represents a viable therapeutic option warranting further investigation

Cohort 4 in C-144-01 recently completed enrollment in support of lifileucel registration

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Neo-Adjuvant Immunotherapy in Stage III Melanoma

nature medicine

LETTERS

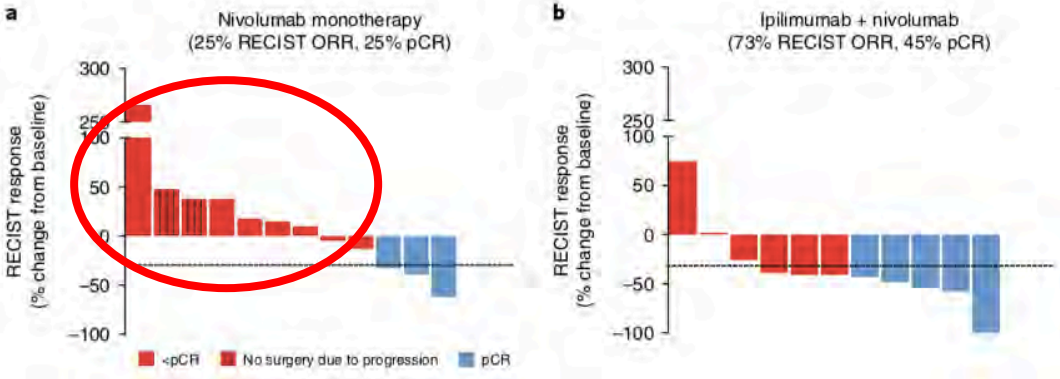
https://doi.org/10.1038/s41591-018-0197-1

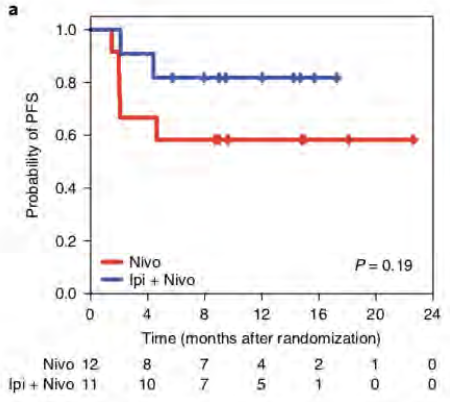
Corrected: Author Correction; Publisher Correction

NATURE MEDICINE | VOL 24 | NOVEMBER 2018 | 1649–1654 |

Neoadjuvant immune checkpoint blockade in high-risk resectable melanoma

Rodabe N. Amaria[1,12], Sangeetha M. Reddy[2,12], Hussein A. Tawbi[1], Michael A. Davies[1],



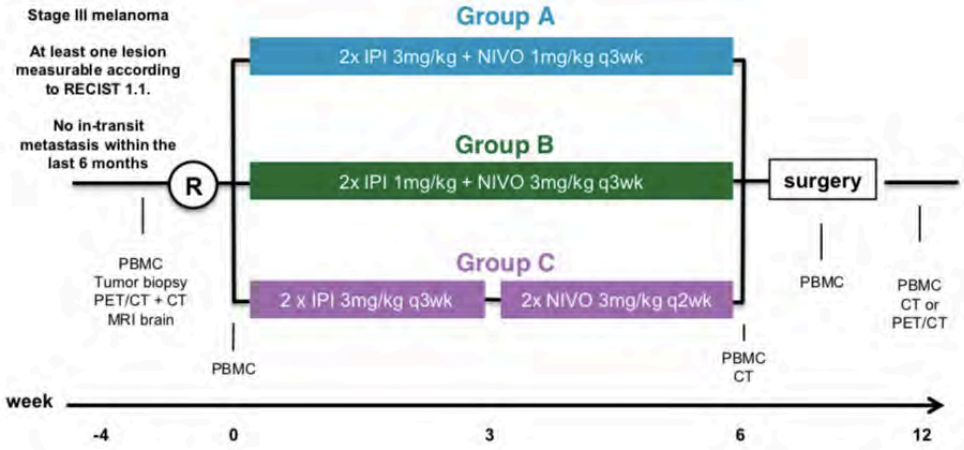


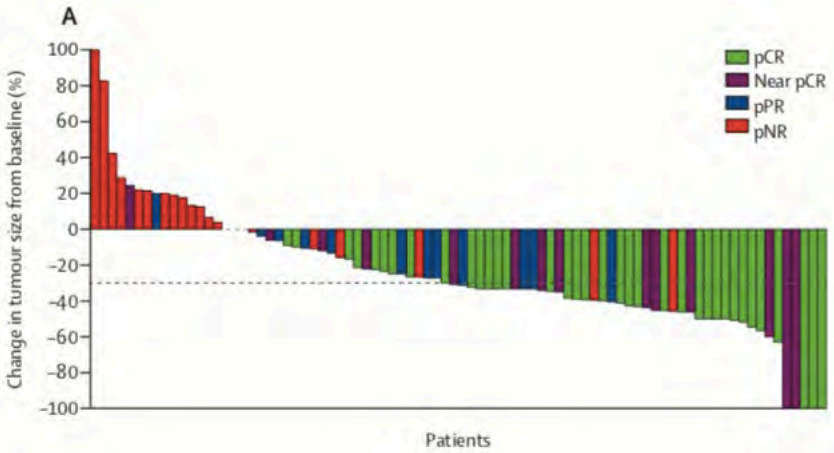
Regimen	N	ORR (8 wks)	pCR (8 wks)	IRAEs (Gr 3 +)	Comments
Nivo Q2wk x 4	**12**	25%	25%	8%	**17% PD**
Ipi 3 + Nivo 1 Q3wk x3	**11**	**73%**	**45%**	**73%**	**? Too toxic**

Identification of the optimal combination dosing schedule of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma (OpACIN-neo): a multicentre, phase 2, randomised, controlled trial

Lancet Oncol 2019; 20: 948–60

Elisa A Rozeman, Alexander M Menzies, Alexander C J van Akkooi, Chandra Adhikari, Carolien Bierman, Bart A van de Wiel, Richard A Scolyer,



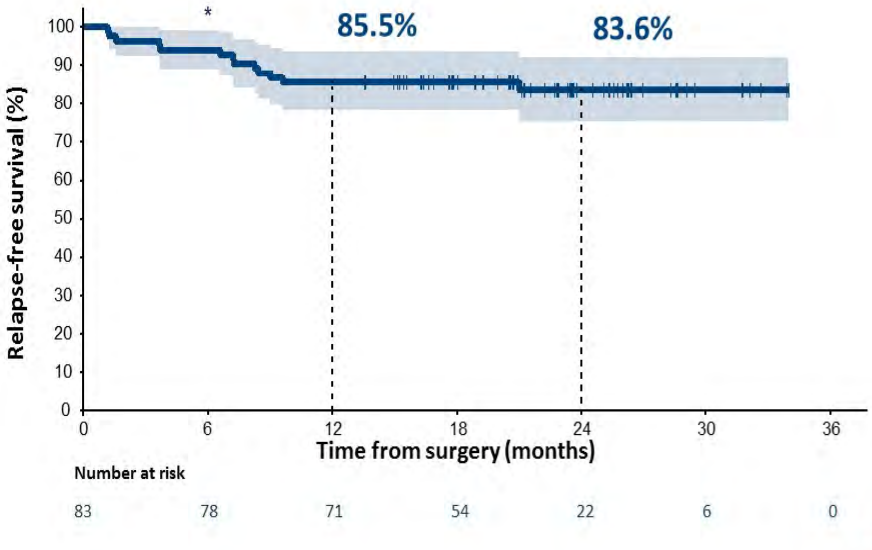


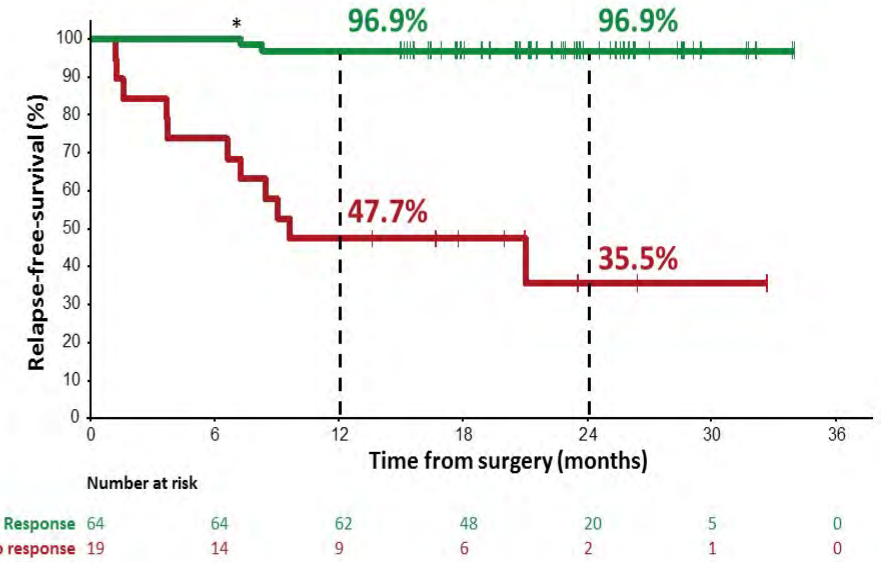
Regimen	N	ORR (6 wks)	pCR (6 wks)	pRR (pCR+PR)	IRAEs (Gr 3 +)
A: (Ipi 3 + Nivo 1) Q3w x 2	**30**	**64%**	47%	**80%**	**37%**
B: (Ipi 1 + Nivo 3) Q3w x 2	**30**	57%	**57%**	**77%**	**17%**

Abstract 10015

Promising RFS after 2 years follow-up and pathologic response predicts outcome

- **OpACIN-neo:** After a median follow-up of 24.6 months, only 1/64 (2%) patients with pathologic response has relapsed





(near-)pCR = (near) pathologic complete response, pPR = pathologic partial response, pNR = pathologic non-response

Rozeman et al., abstract 10015, ASCO 2020

* patient died due to toxicity without signs of melanoma relapse

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First safety and efficacy results of PRADO

A phase 2 study of Personalized Response-driven surgery and Adjuvant therapy after neoadjuvant ipilimumab and nivolumab in resectable stage III melanoma

CU Blank, ILM Reijers, T Pennington, JM Versluis, RPM Saw, EA Rozeman, E Kapiteijn, AAM van der Veldt, KPM Suijkerbuijk, GAP Hospers, WMC Klop, K Sikorska, JA van der Hage, DJ Grünhagen, A Spillane, RV Rawson, BA van de Wiel, AM Menzies, ACJ van Akkooi and GV Long

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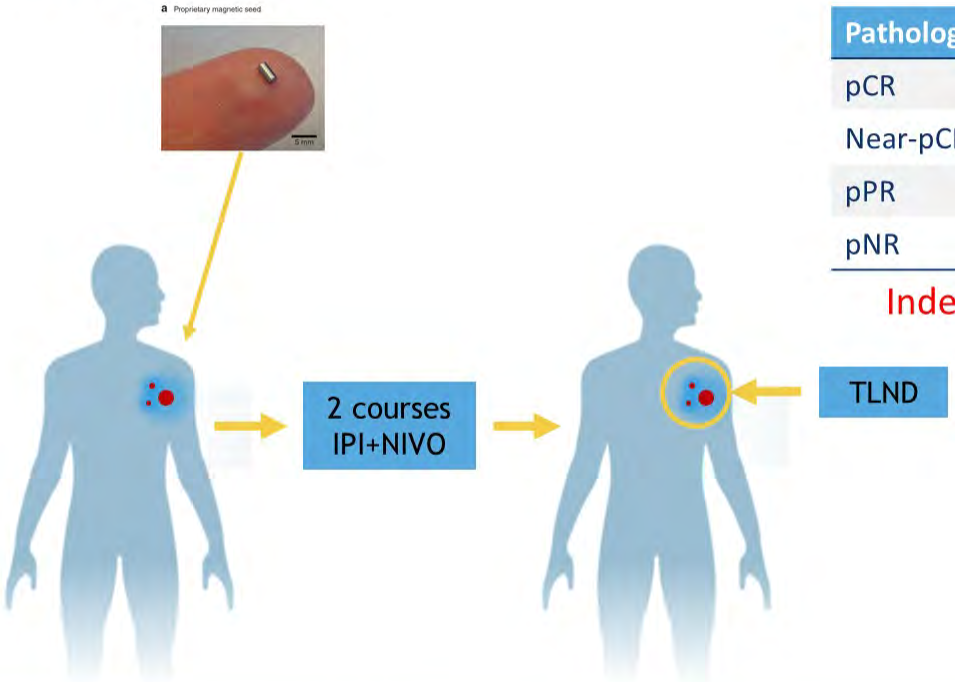
MeMaloc substudy of OpACIN-neo

The pathologic response in the largest lymph node (**index node**) represents the entire lymph node bed



Pathologic response	Index node	Total basin
pCR	7	7
Near-pCR	3	3
pPR	1	1
pNR	1	1

Index node congruent with total basin = 12/12 cases

Schermers et al., BJS 2019

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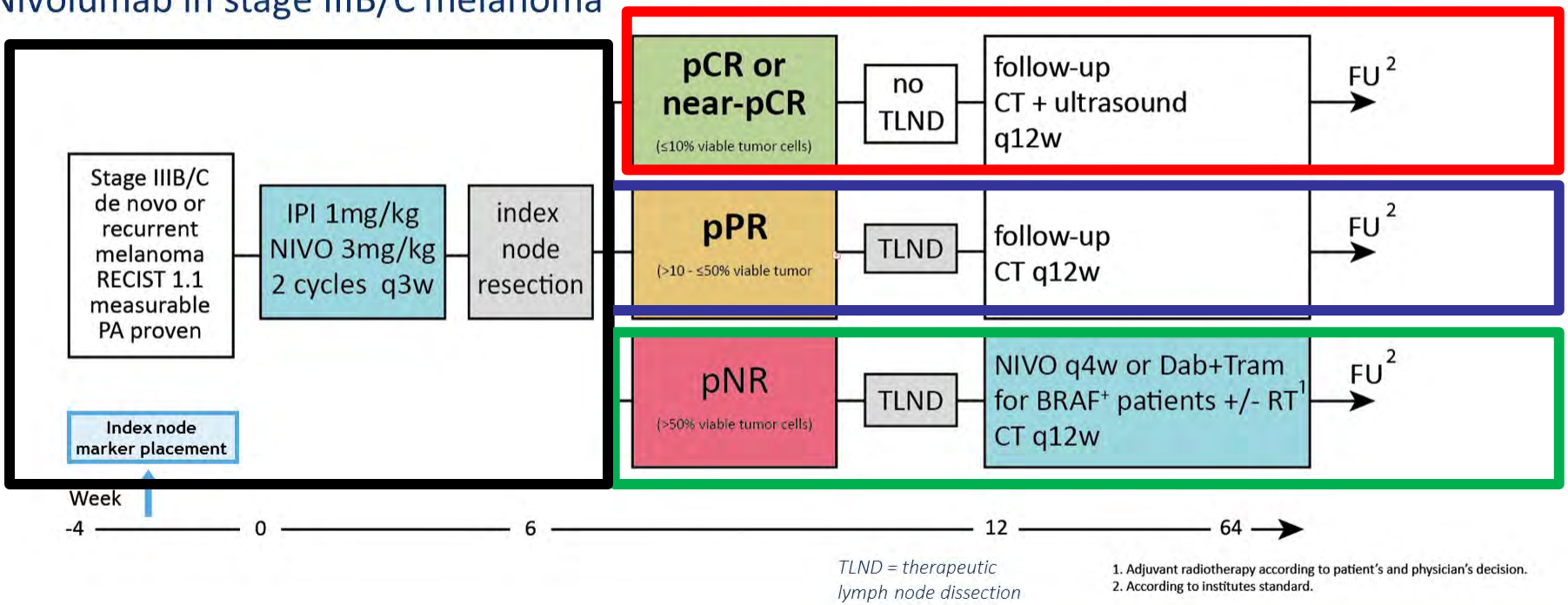
PRADO: study design

Personalized Response-driven Adjuvant therapy after Combination of Ipilimumab and Nivolumab in stage IIIB/C melanoma



TLND = therapeutic lymph node dissection

1. Adjuvant radiotherapy according to patient's and physician's decision.
2. According to institutes standard.

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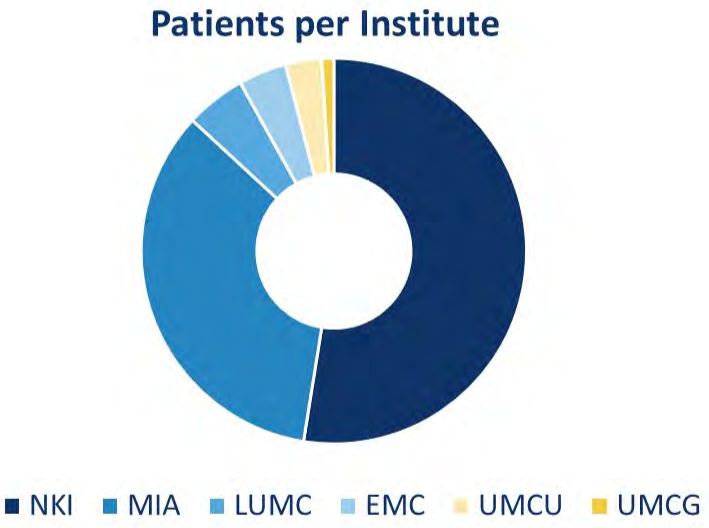
Baseline characteristics

	Total cohort (n=99)
Age, median (range)	58 (19-85)
Gender, male	65 (66)
WHO PS, 0	94 (95)
T stage at diagnosis	
T1a/b	17 (17)
T2a/b	26 (26)
T3a/b	20 (20)
T4a/b	21 (21)
Tx	2 (2)
Unknown primary	13 (13)
Positive nodes on baseline PET/CT	
1	57 (58)
2-3	33 (33)
>3	9 (9)
Ulceration, yes	20 (20)
BRAF V600E/K mutation, positive	50 (51)



Data are presented as n (%) unless stated otherwise

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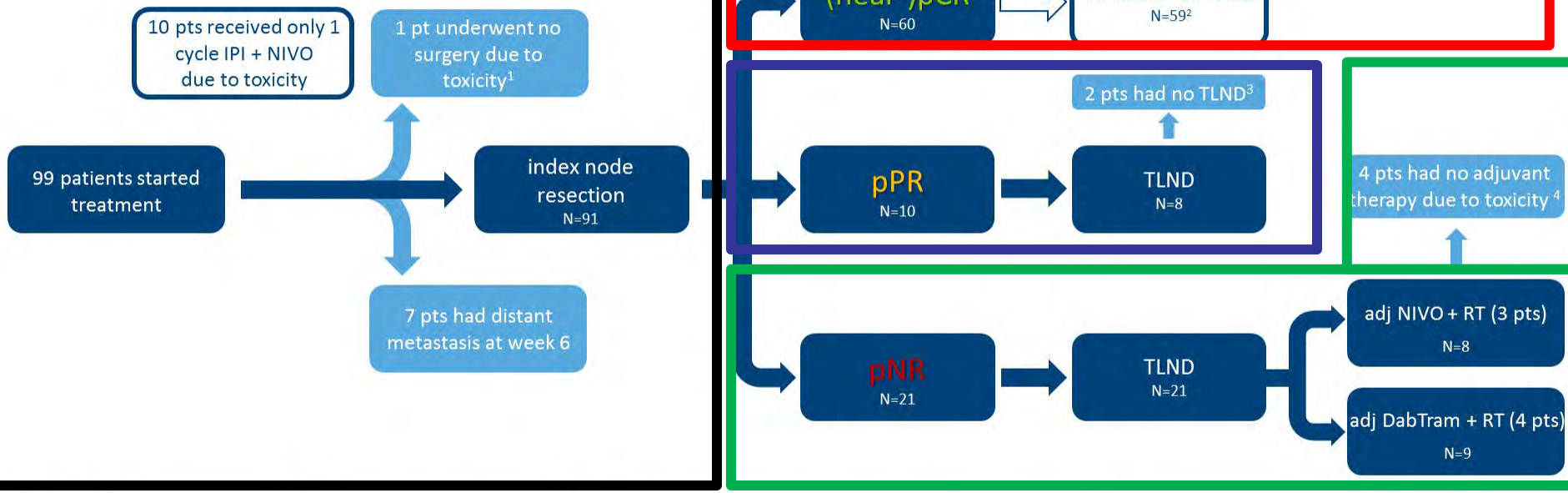
Study profile



1. One patient developed a myelitis transversa-like syndrome leading to constipation and colon perforation. This patient had a radiologic response.
2. One patient had surgery despite achieving a near-pCR due to unfavorable pathologic features in the index node.
3. Two patients did not want to undergo a CLND after achieving a pPR.
4. All patients were BRAF wildtype and did not receive adjuvant nivolumab due to an immunotherapy-related colitis, cholangitis, myocarditis and arthritis.

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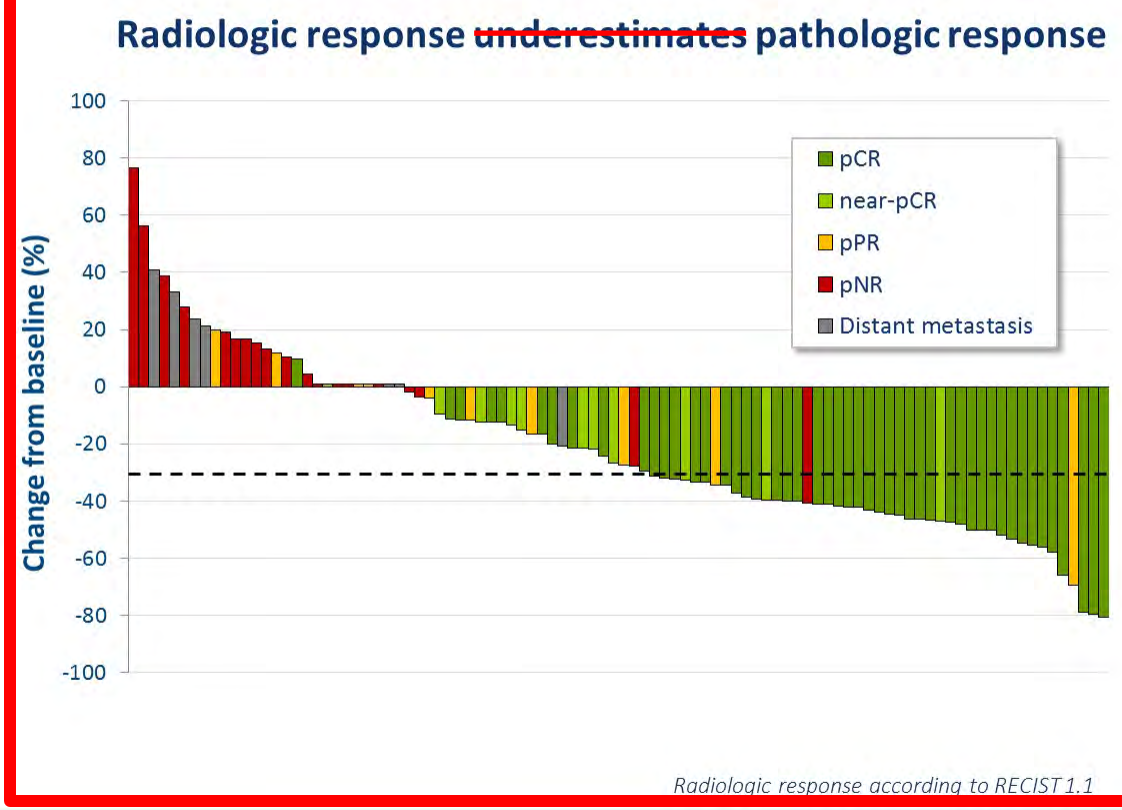
Radiologic response

PRADO	Total cohort (n=99)
ORR	45 (45%)
CR	14 (14%)
PR	31 (31%)
SD	38 (38%)
PD	13 (13%)
Not done [1]	3 (3%)

1. 3 patients did not have a week 6 CT-scan due toxicity.



Radiologic response according to RECIST 1.1

Presented By Christian Blank at TBD

Immune-related AEs within the first 12 weeks

Adverse event	All grade (%)	Grade 3-4 (%)
Any adverse event	**96 (97)**	**22 (22)**
Fatigue	54 (55)	–
Rash	47 (47)	3 (3)
Pruritus	27 (27)	–
Alanine aminotransferase increased	22 (22)	7 (7)
Hyperthyreoidism	22 (22)	–
Diarrhea	21 (21)	5 (5)
Aspartate aminotransferase increased	20 (20)	5 (5)
Nausea	18 (18)	1 (1)
Dry mouth	16 (16)	–
Hypothyreoidism	16 (16)	–
Arthralgia	15 (15)	–
Headache	13 (13)	1 (1)
Myalgia	10 (10)	–
Infusion related reaction	8 (8)	–

Adverse event	All grade (%)	Grade 3-4 (%)
Serum lipase increased	8 (8)	3 (3)
Dry skin	7 (7)	–
Fever	7 (7)	–
Colitis	6 (6)	4 (4)
Creatine kinase increased	6 (6)	1 (1)
Dry eye	6 (6)	–
Dyspnea	5 (5)	–
Serum amylase increased	4 (4)	1 (1)
Myocarditis	2 (2)	2 (2)
Ggt increased	2 (2)	1 (1)
Cholangitis	1 (1)	1 (1)
Confusion	1 (1)	1 (1)
Myelitis transversa-like syndrome	1 (1)	1 (1)

Adverse events that occurred in ≥ 5 patients or were grade 3-4 are displayed in the table

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Surgery-related adverse events

p<0.001

	Total cohort (n=96)[1]		Index node procedure only (n=63)[2]		Subsequent TLND (n=31)	
Adverse event	All grade (%)	Grade 3 (%)	All grade (%)	Grade 3 (%)	All grade (%)	Grade 3 (%)
Any adverse event	**52 (54)**	**6 (6)**	**26 (41)**	–	**25 (81)**	**6 (19)**
Seroma	30 (31)	–	17 (27)	–	13 (42)	–
Wound infection	11 (11)	3 (3)	4 (6)	–	7 (23)	3 (10)
Lymphedema	7 (7)	–	2 (3)	–	5 (16)	–
Wound dehiscence	6 (6)	–	1 (1)		5 (16)	–
Fever	3 (3)	–	–	–	3 (10)	–
Wound complication	1 (1)	1 (1)	–	–	1 (3)	1 (3)
Difficulty mobilizing	1 (1)	1 (1)	–	–	1 (3)	1 (3)
Dizziness	1 (1)	1 (1)	–	–	1 (3)	1 (3)
Postoperative hemorrhage	1 (1)	1 (1)	–	–	1 (3)	1 (3)

1. One patient did not undergo surgery because of toxicity, 2 patients because of distant metastases.
2. Two patients had an additional small surgery to remove 1-3 lymph nodes and were therefore excluded from the surgical subgroup analysis.

Adverse events that occurred in ≥3 patients or were grade 3-4 are displayed in the table

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Summary and conclusion

- PRADO **confirms the high pathologic response rate and safety** observed previously in OpACIN-neo arm B (ipilimumab 1mg/kg + nivolumab 3mg/kg)
  - Pathologic response rate = **71%**
  - Grade 3-4 irAE rate = **22%** in the first 12 weeks
- The radiologic response underestimates the pathologic response, but radiologic assessment has an added value in identifying patients progressing to stage IV disease pre-surgically
- TLND was omitted in 59 (**60%**) patients 58% pts had only 1 LN at baseline
- Index lymph node-only surgery reduced the surgical morbidity
  - Surgical-related adverse events in **41%** of patients with index node procedure only versus **81%** in patients with TLND
- Index LN only patients show **higher quality of life scores**
- First EFS and RFS data is planned to be presented at ESMO 2020

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My conclusions on Neo-adjuvant therapy

- Feasible and potentially promising outcomes.
- Goals of therapy, such as reducing surgical morbidity or avoiding unnecessary systemic therapy, must be defined beforehand for each patient.
- Benefits over standard therapy (Surgery plus adjuvant therapy) must be proven before routine incorporation in the clinical workflows.
- BRAFi vs Immunotherapy highly relevant in adjuvant/neo-adjuvant setting for BRAF-mutant patients

Thank you!!