2019 AIOM REVIEW: FROM CHICAGO TO VERONA

JUNE 14-15 2019

Verona,
Palazzo della Gran Guardia
Piazza Bra, 1

Università degli Studi di Bari '*Aldo Moro*'
Dipartimento di Scienze Biomediche e Oncologia Umana
UO Oncologia Medica Universitaria
Direttore: Prof. Franco Silvestris

POSTER REVIEW
MELANOMA SESSION

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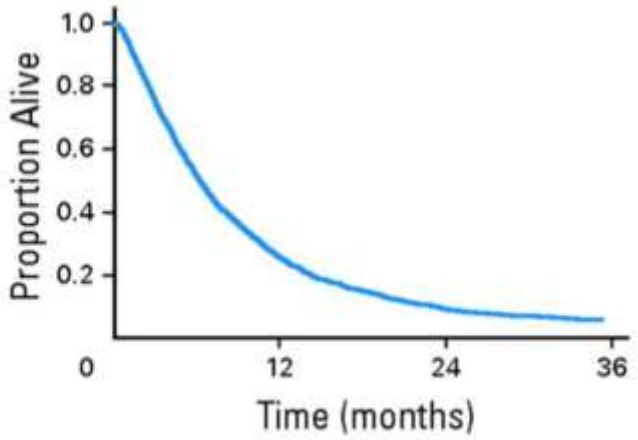
IMI GIOVANI

14 giugno 2019

Contents

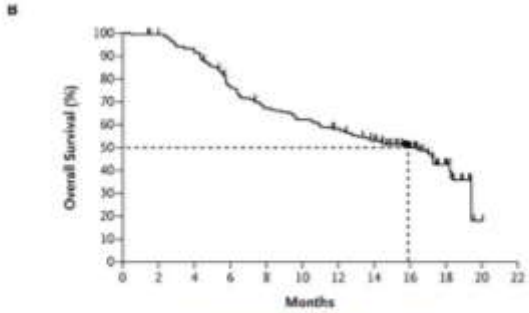
THE OLD DAYS…



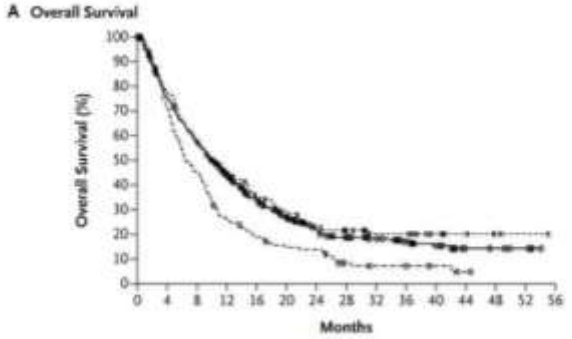
Korn et al, JCO 2008

Long-term survival: non existent

GLIMMERS OF HOPE



Sosman et al, NEJM 2012 - Vemurafenib



Hodi et al. NEJM 2011 - Ipilimumab

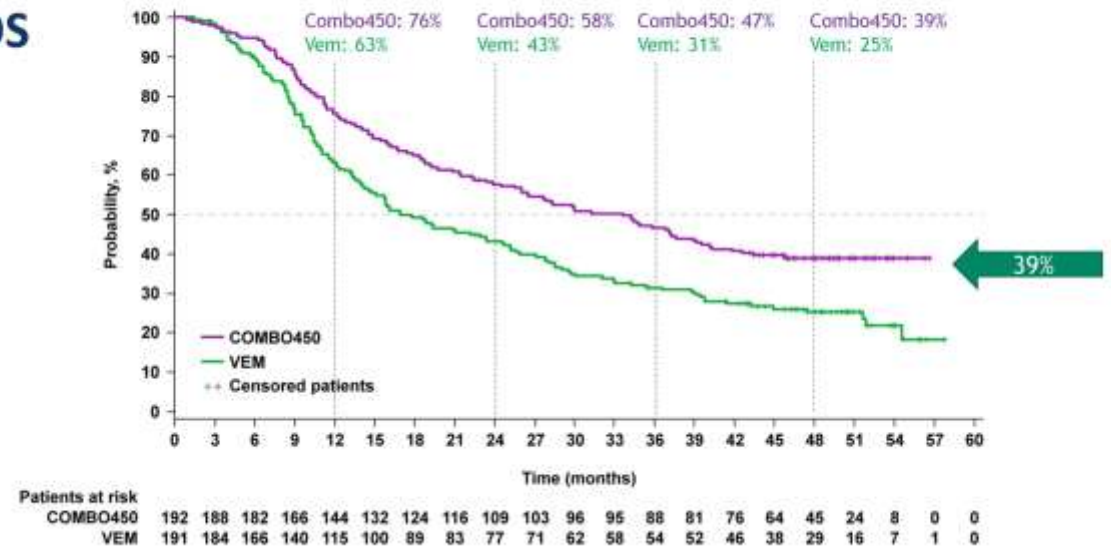
Long-term survival: rare (10-20%)

The modern era

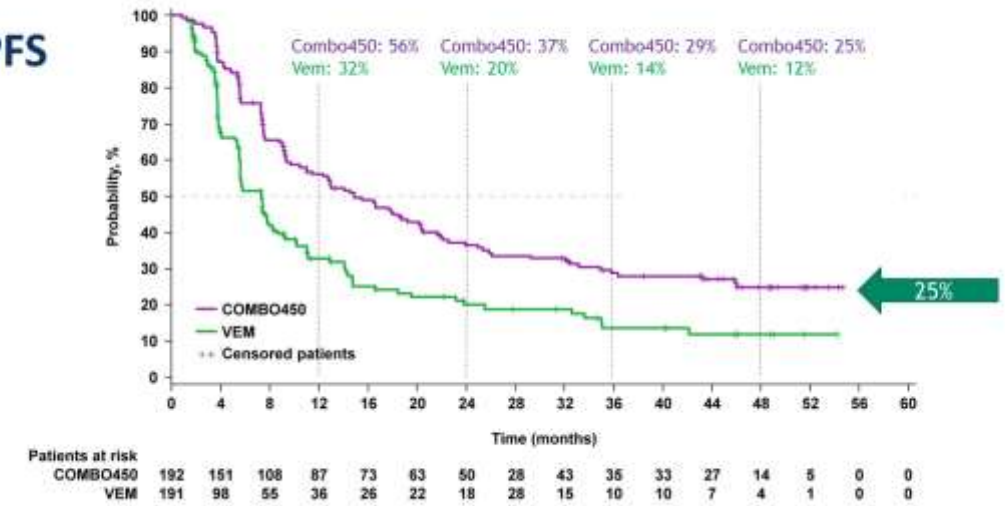
Long-term survival: rare (40-50%)

Median follow up of about 48 months

OS



PFS



Improved outcomes with combination therapy
Plateau on survival curves (durable responses)

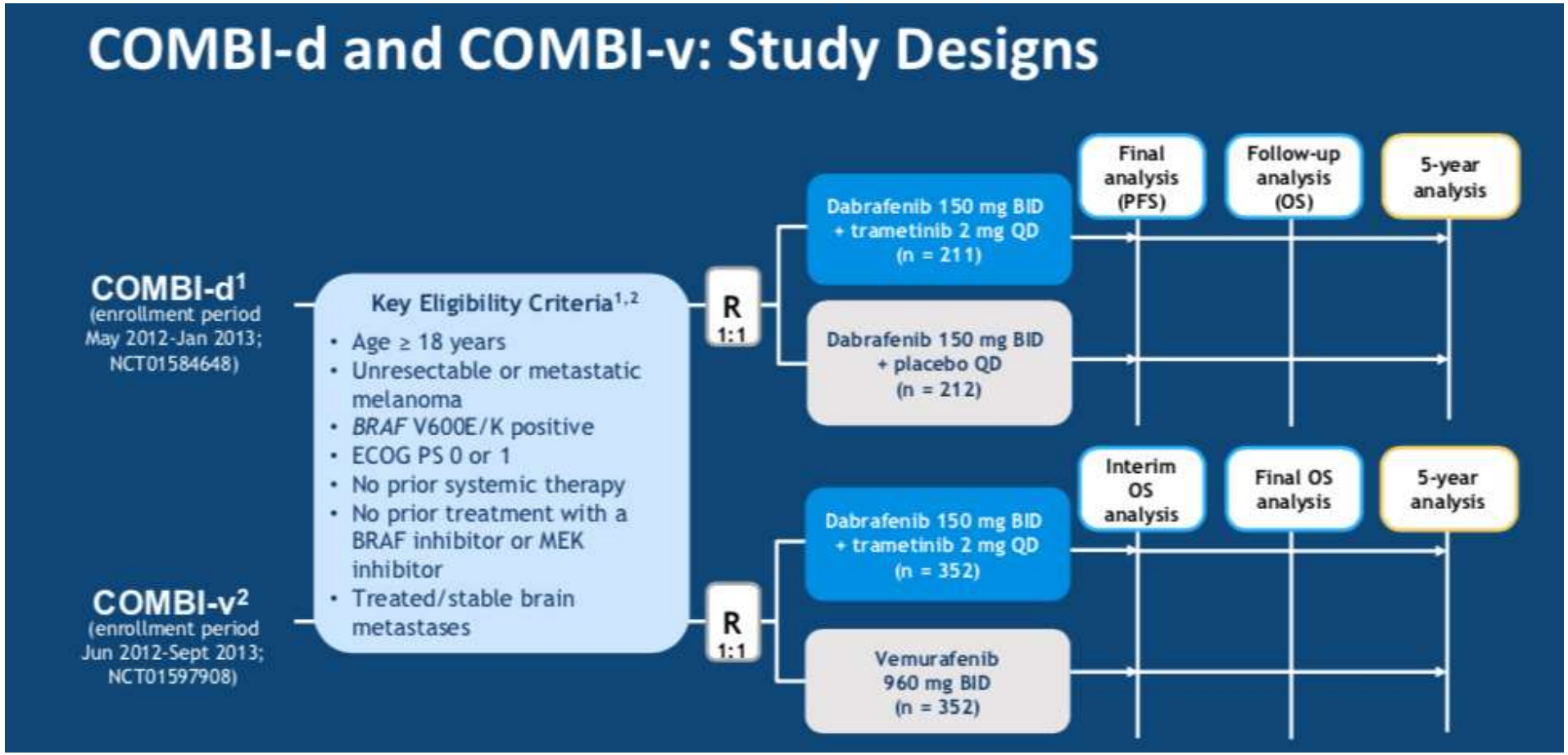
About 20% of the combination treated patients are actually still receiving therapy

Question raises: Do response persist?
Chronic toxicities?
Responses to subsequent therapies
Who can stop therapy

Litzay et al. abstract 9512 (Encorafenib+binimetinib)

The modern era

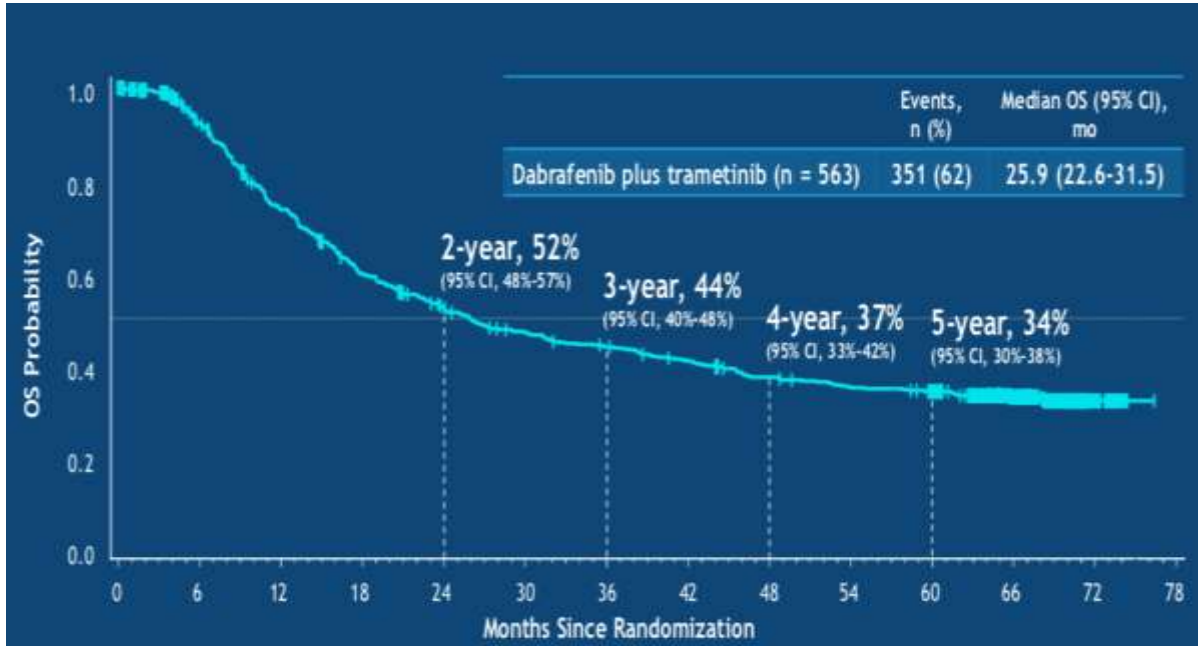
Five-Year Analysis of Dabrafenib Plus Trametinib in Patients with BRAF V600–Mutant Unresectable or Metastatic Melanoma



Nathan et al. ASCO 2019

The modern era

Five-Year Analysis of Dabrafenib Plus Trametinib in Patients with BRAF V600–Mutant Unresectable or Metastatic Melanoma



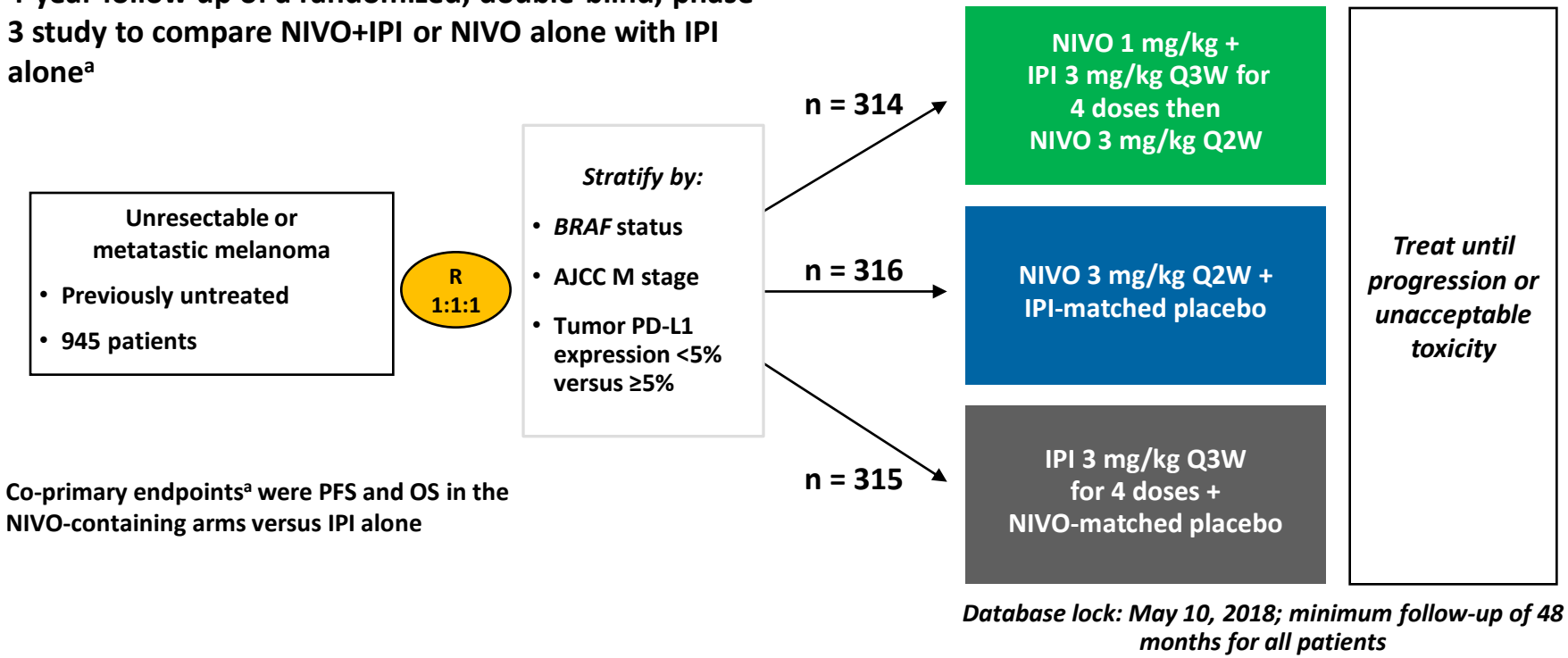
Lower baseline tumor burden and less-aggressive tumor biology were associated with prolonged PFS and OS

Nathan et al. ASCO 2019

CA209-067: Study Design

Randomized, double-blind, phase III study to compare NIVO+IPI or NIVO alone to IPI alone

4-year follow up of a randomized, double-blind, phase 3 study to compare NIVO+IPI or NIVO alone with IPI alone[a]

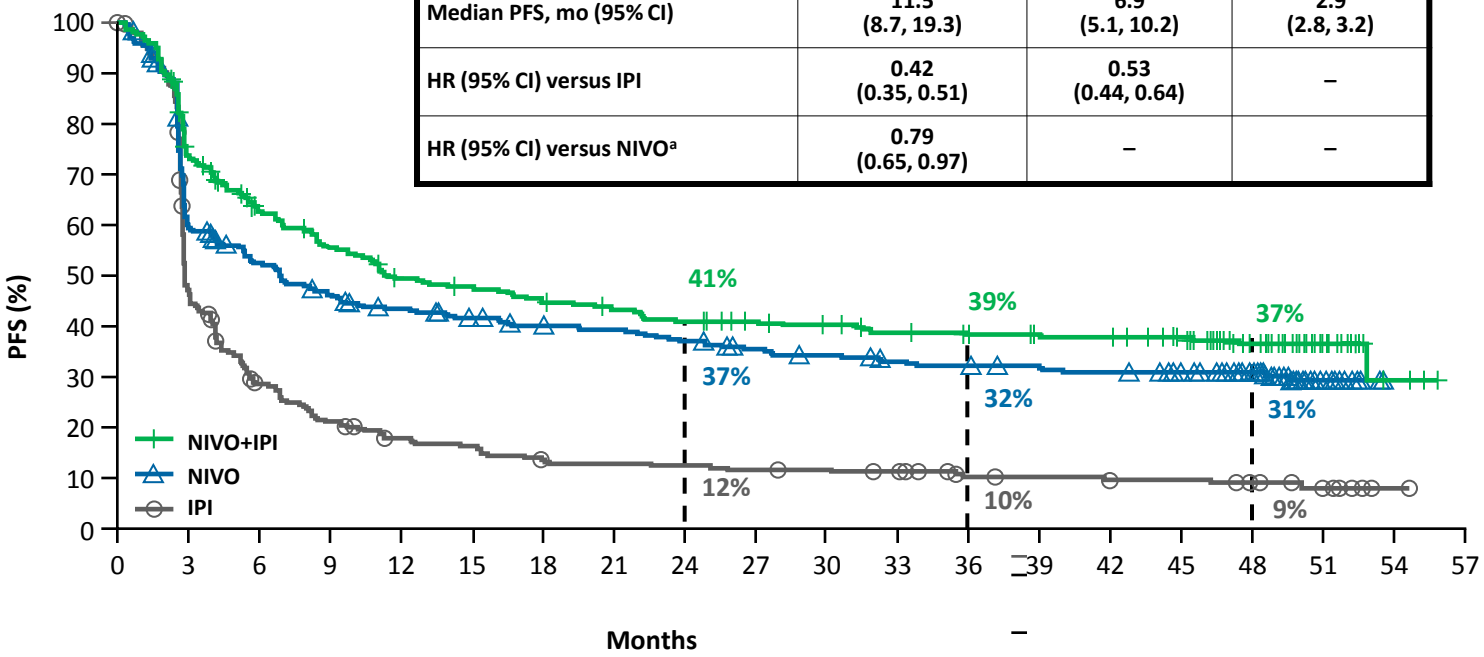


Co-primary endpoints[a] were PFS and OS in the NIVO-containing arms versus IPI alone

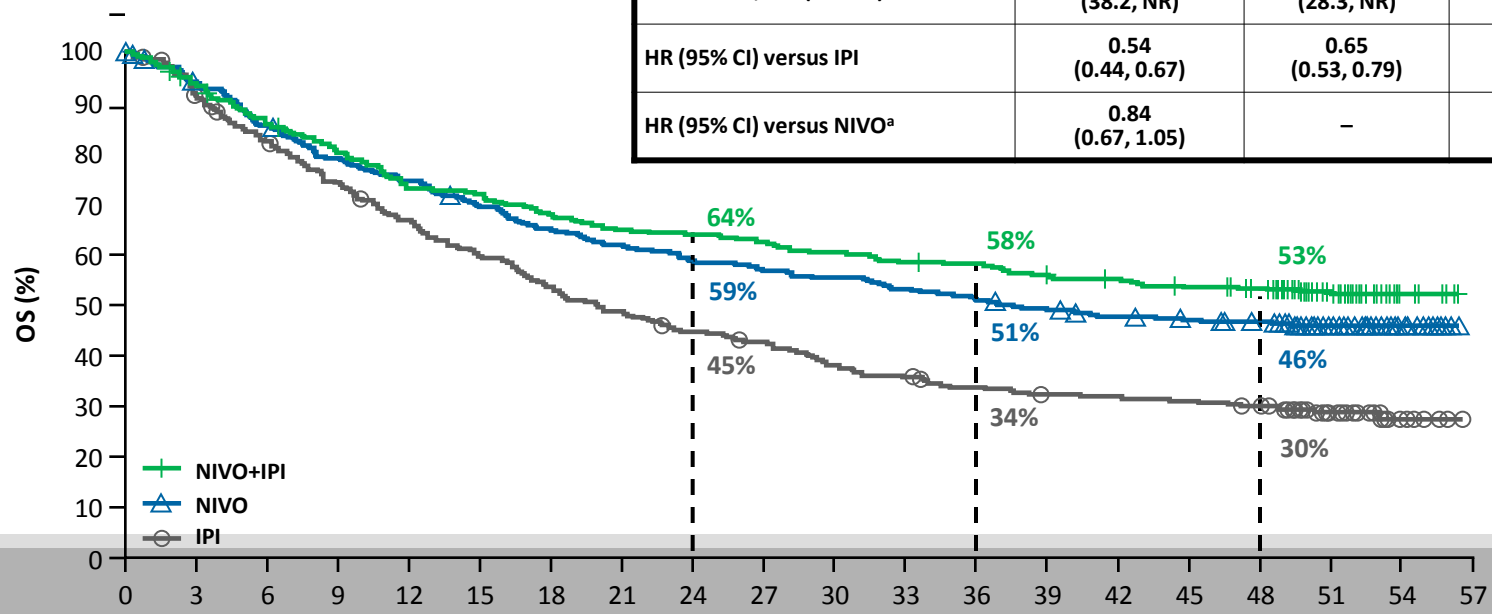
Database lock: May 10, 2018; minimum follow-up of 48 months for all patients

UPDATE OF PFS AND OS

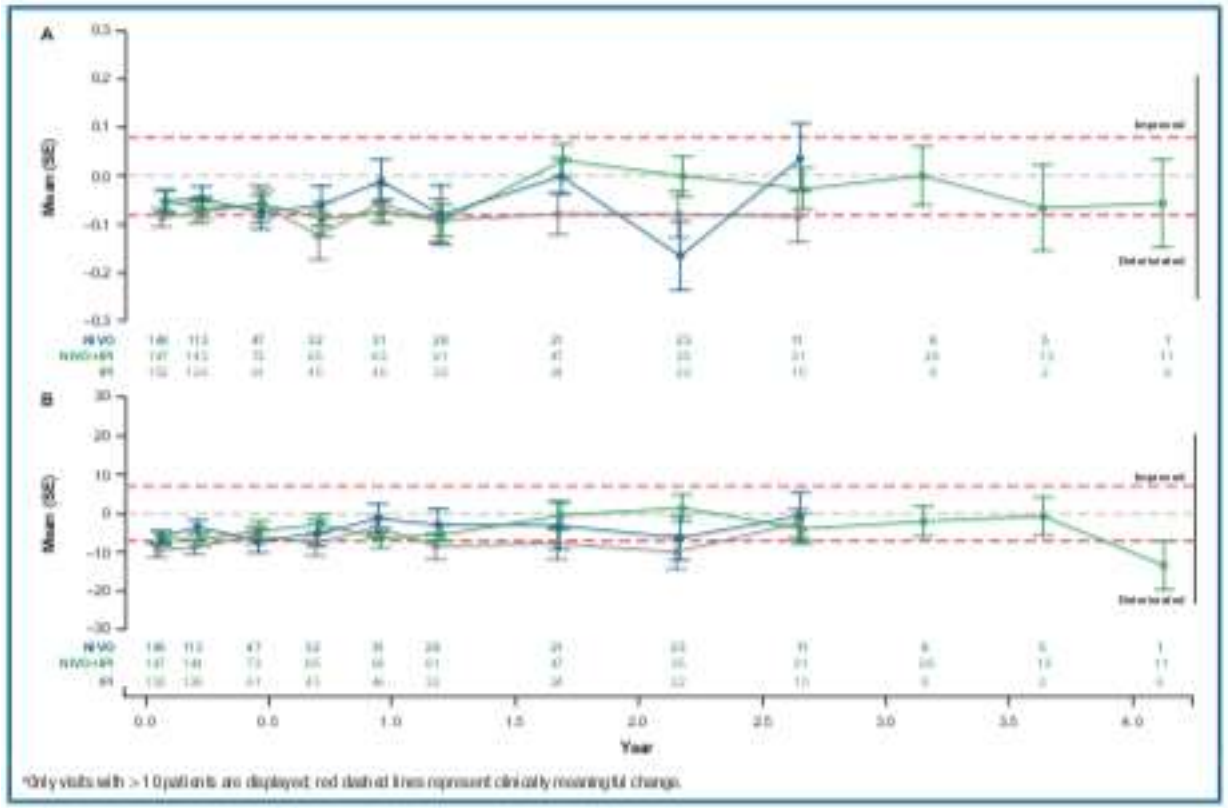
	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median PFS, mo (95% CI)	11.5 (8.7, 19.3)	6.9 (5.1, 10.2)	2.9 (2.8, 3.2)
HR (95% CI) versus IPI	0.42 (0.35, 0.51)	0.53 (0.44, 0.64)	–
HR (95% CI) versus NIVO[a]	0.79 (0.65, 0.97)	–	–

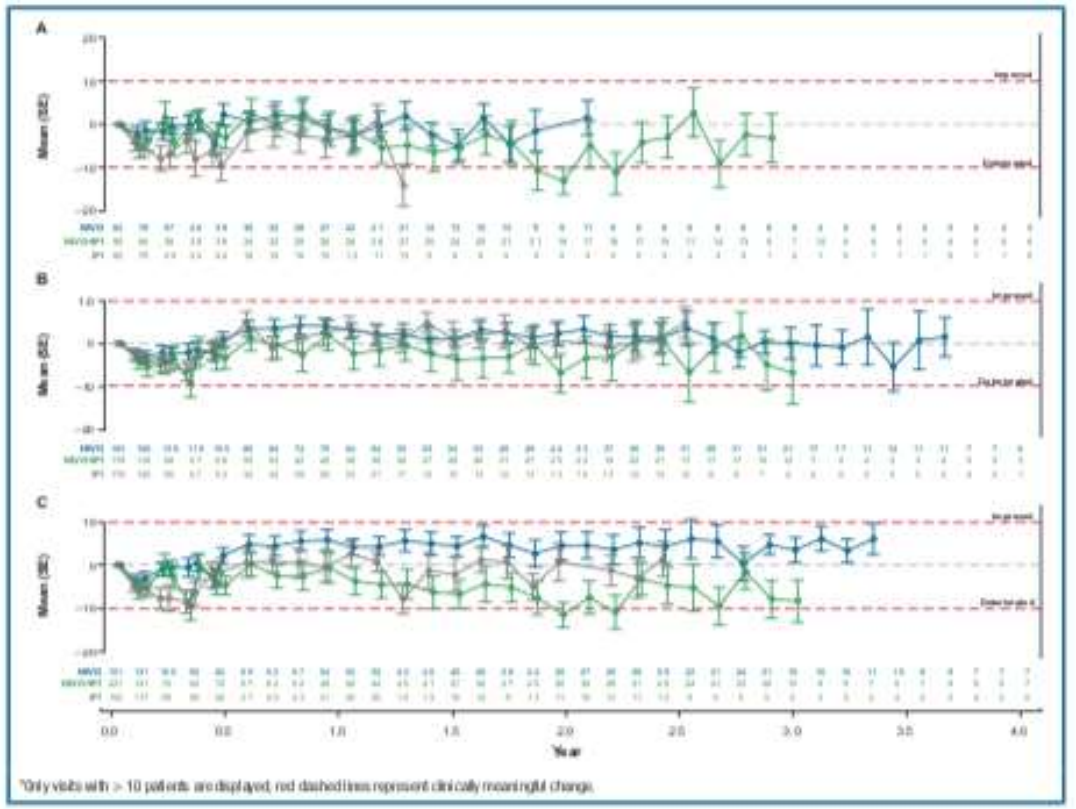


	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2, NR)	36.9 (28.3, NR)	19.9 (16.9, 24.6)
HR (95% CI) versus IPI	0.54 (0.44, 0.67)	0.65 (0.53, 0.79)	–
HR (95% CI) versus NIVO[a]	0.84 (0.67, 1.05)	–	–



Quality of life: 4-year data from checkmate 067





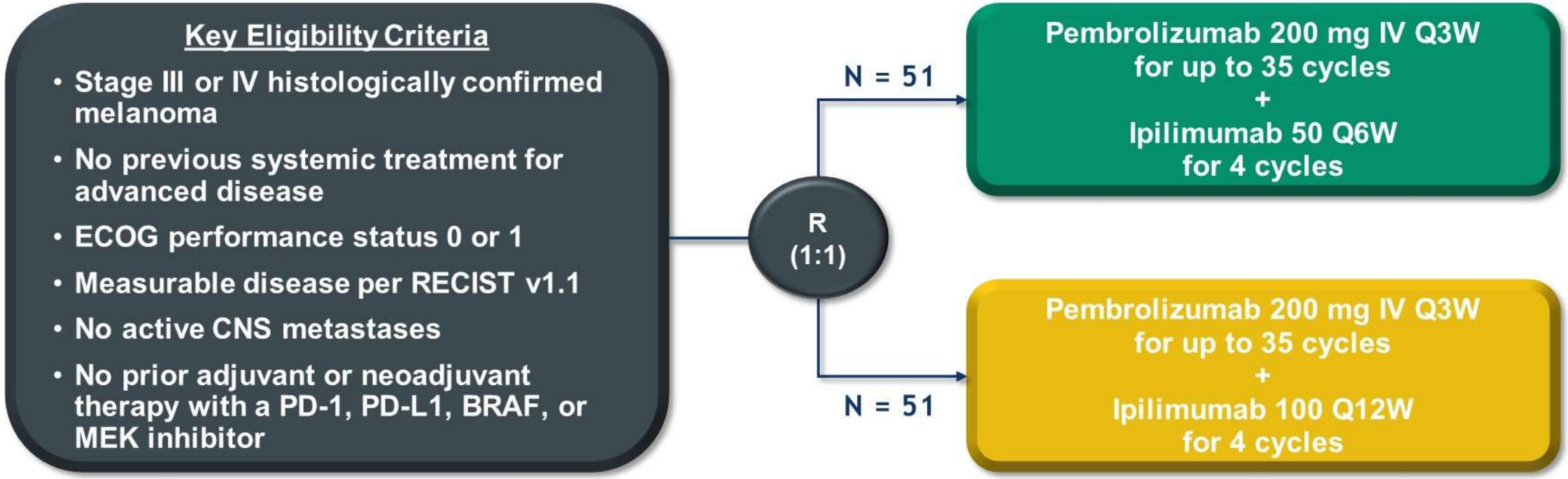
NIVO+IPI and NIVO maintained HRQoL with no deterioration over the time period

HRQoL was maintained in patient subgroups irrespective of *BRAF* mutation status

The difference in any grade 3 or 4 AEs reported across the treatment arms in CheckMate 067 did not translate into a clinically meaningful difference i
HRQoL

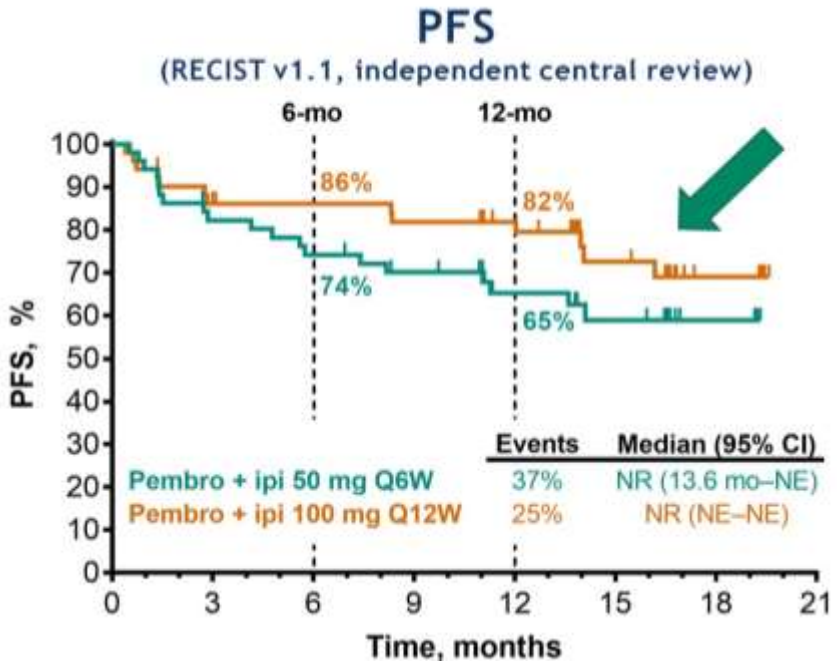
Shadendorf et al. Abstract 9551

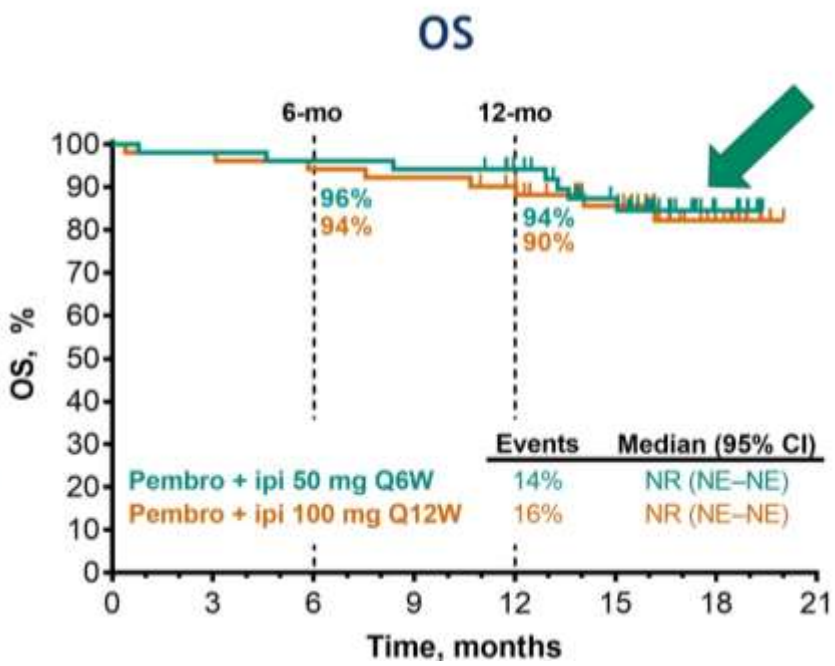
Combo-immune strategies



- **Primary end points:** grade 3-5 treatment-related AE rate and ORR[a]
- **Secondary end points:** PFS,[a] DOR,[a] OS

Survival curves and safety





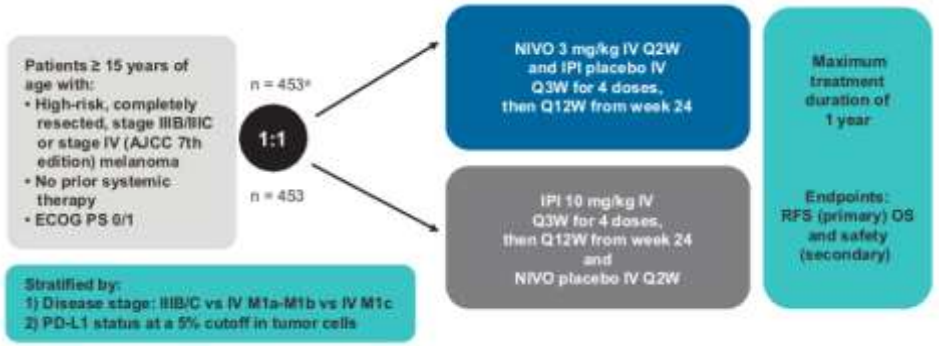
MORE ACTIVITY AND MORE TOXICITY

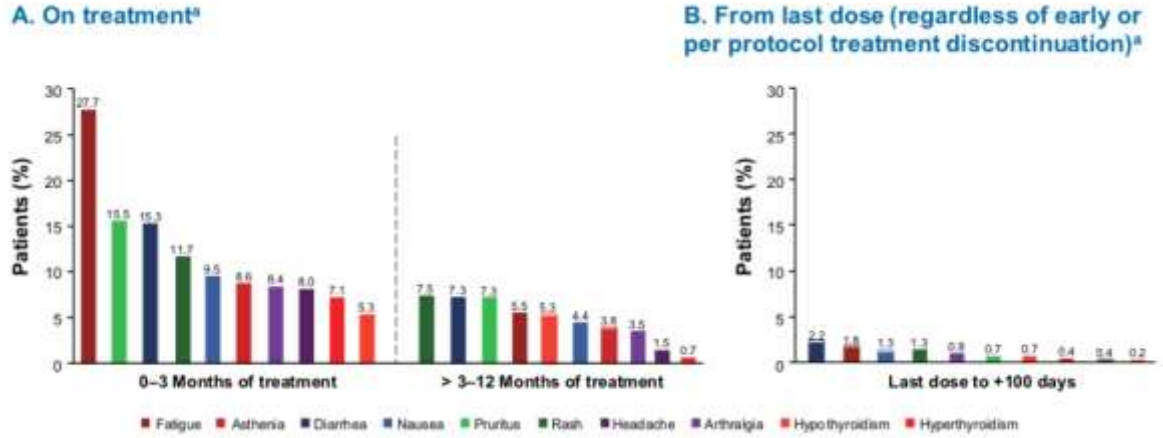
Ipi 50 mg:
55% response rate, 78% disease control rate
Ipi 100 mg:
61% response rate, 86% disease control rate

	Treatment Related		Immune-Mediated and Infusion Reactions[a]	
Event, n (%)	Pembro + Ipi 50 mg Q6W (N = 51)	Pembro + Ipi 100 mg Q12W (N = 51)	Pembro + Ipi 50 mg Q6W (N = 51)	Pembro + Ipi 100 mg Q12W (N = 51)
Any grade	51 (100%)	49 (96%)	21 (41%)	28 (55%)
Grade 3-5	12 (24%)	20 (39%)	5 (10%)	11 (22%)
Led to death	1 (2%)[b]	0	1 (2%)[d]	0
Led to discontinuation	8 (16%)	9 (18%)	3 (6%)	8 (16%)

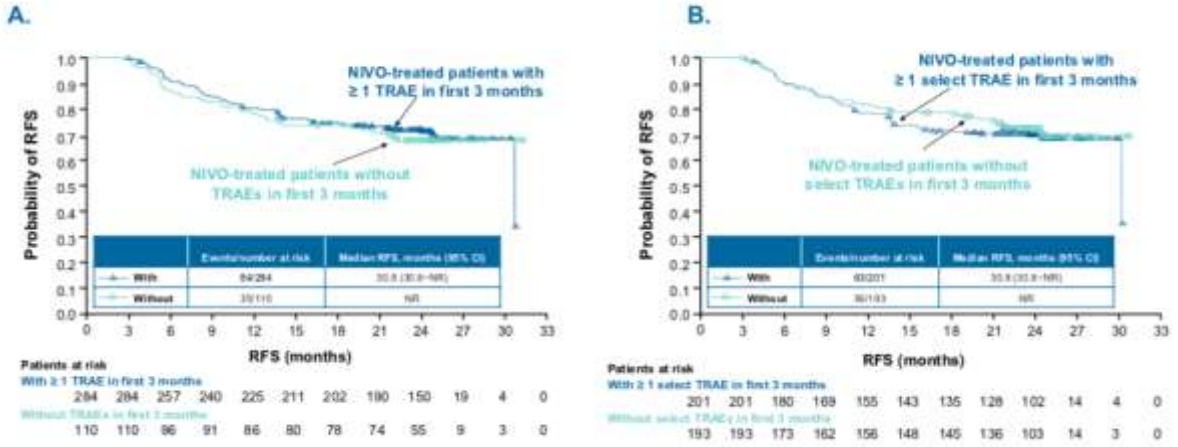
Adiuvant treatment with anti-PD1 and IRAEs

An Analysis of Nivolumab-Mediated Adverse Events and Association With Clinical Efficacy in Resected Stage III or IV Melanoma (CheckMate 238)





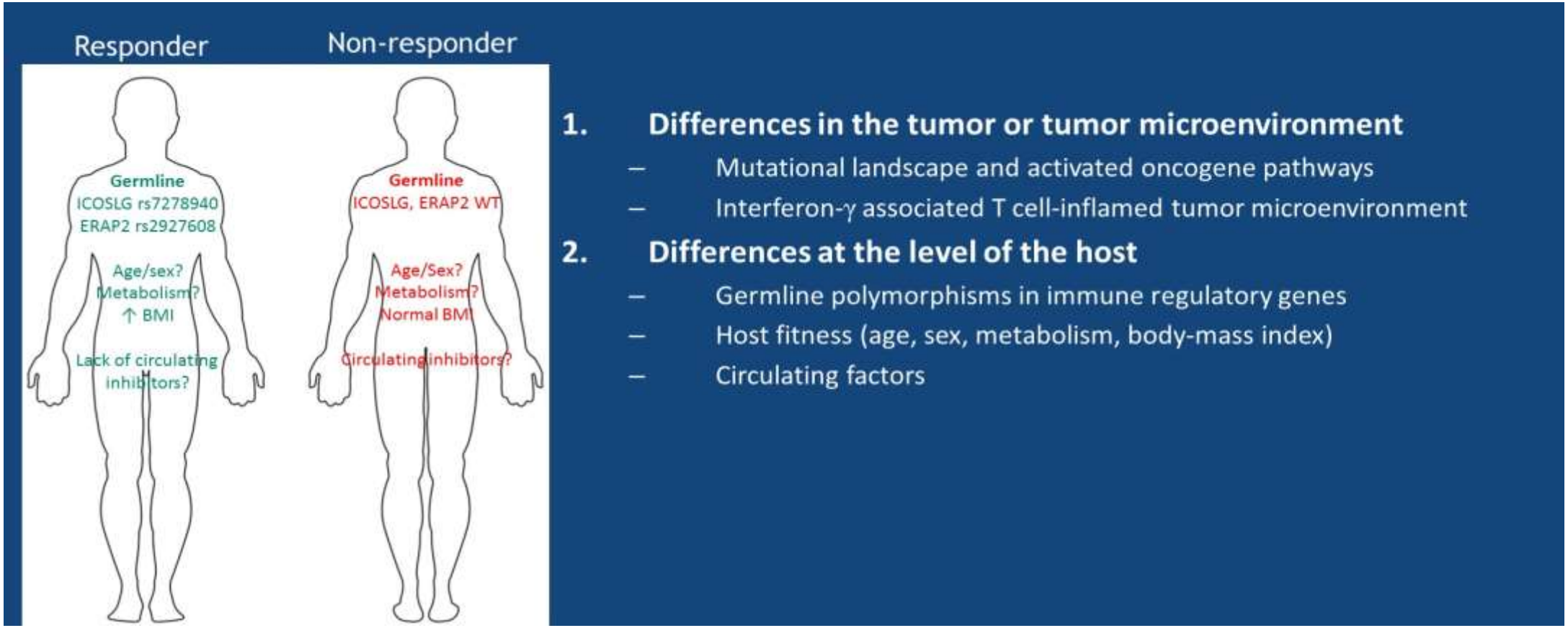
NO ASSOCIATION WAS OBSERVED BETWEEN EARLY TRAES AND RFS



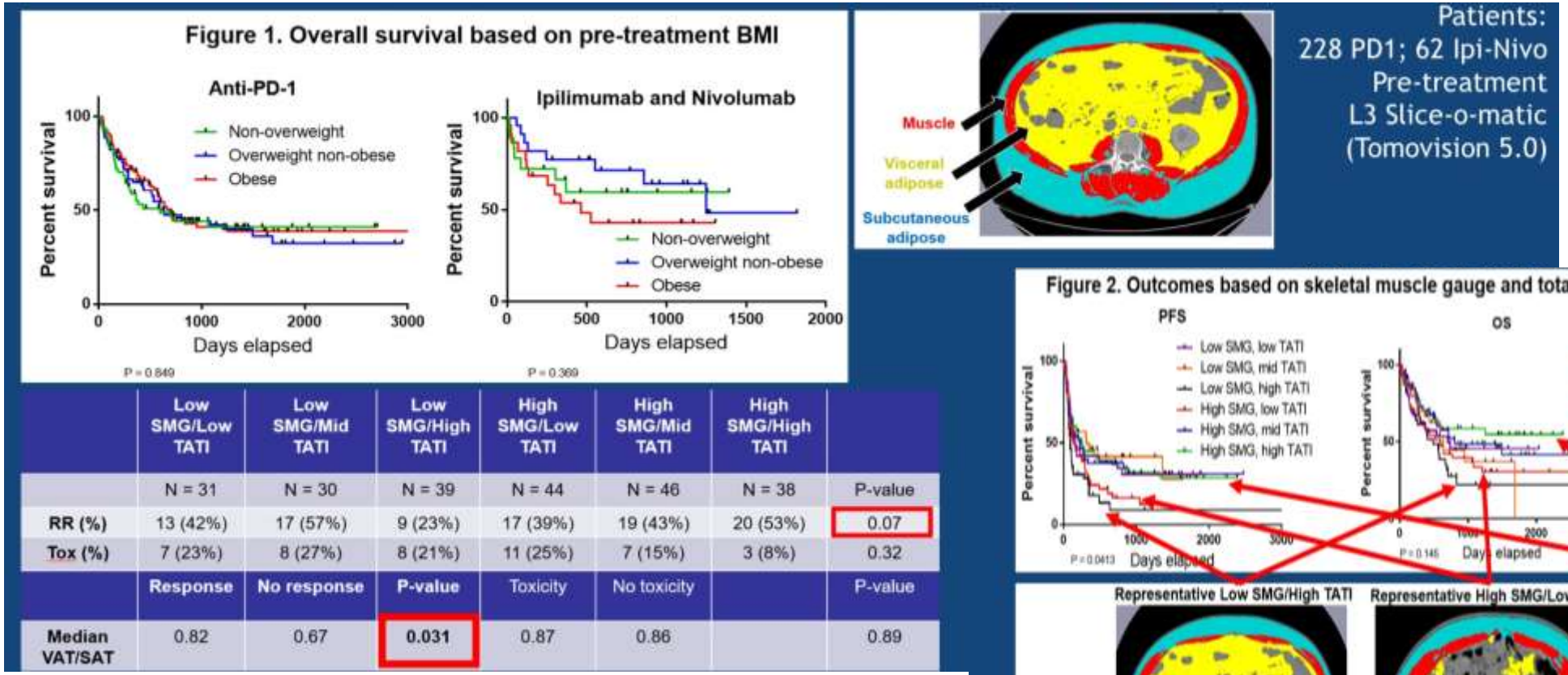
THE MAJORITY OF FIRST-OCCURRENCE TRAES WITH ADJUVANT NIVO OCCURRED EARLY DURING TREATMENT (0–3 MONTHS)

Mandalà M. et al.Abstract 9584 –ASCO 2019

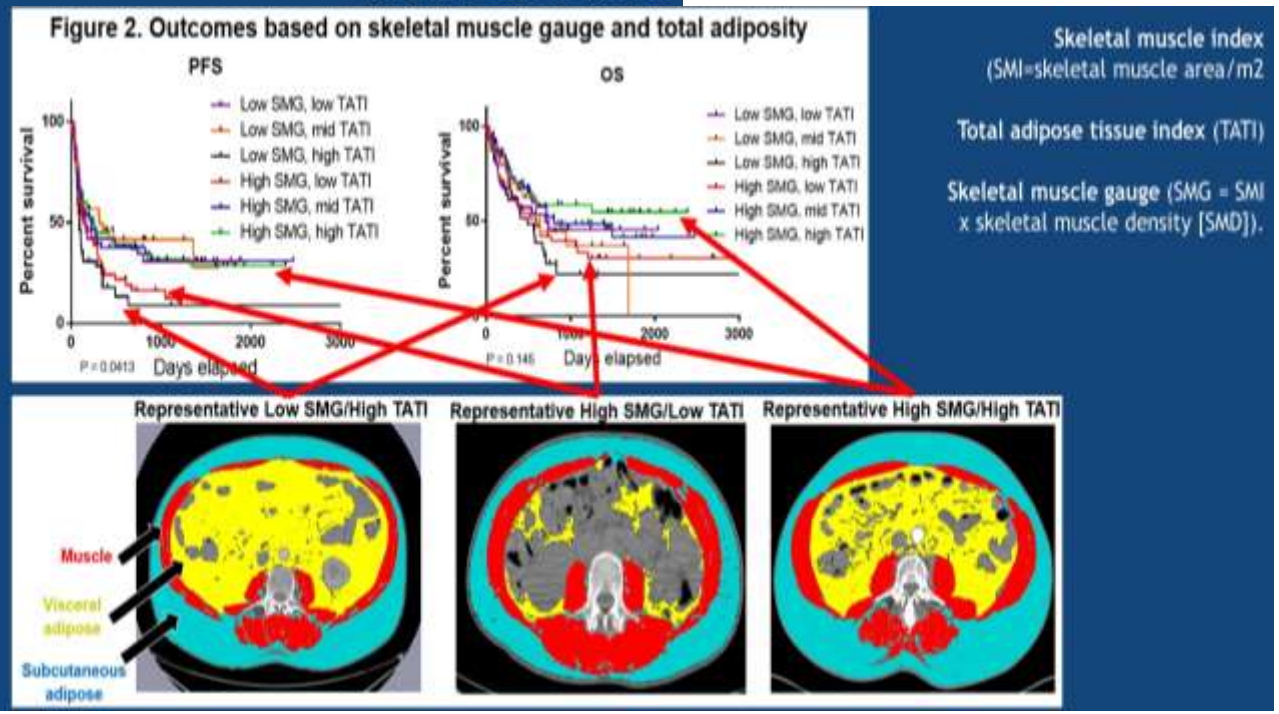
Predictive factors of immunotherapy response



Impact of BMI on outcomes from anti-PD1 treatment



	Low SMG/Low TATI	Low SMG/Mid TATI	Low SMG/High TATI	High SMG/Low TATI	High SMG/Mid TATI	High SMG/High TATI	
	N = 31	N = 30	N = 39	N = 44	N = 46	N = 38	P-value
RR (%)	13 (42%)	17 (57%)	9 (23%)	17 (39%)	19 (43%)	20 (53%)	0.07
Tox (%)	7 (23%)	8 (27%)	8 (21%)	11 (25%)	7 (15%)	3 (8%)	0.32
	Response	No response	P-value	Toxicity	No toxicity		P-value
Median VAT/SAT	0.82	0.67	0.031	0.87	0.86		0.89



BMI or sarcopenia was not associated with clinical outcome

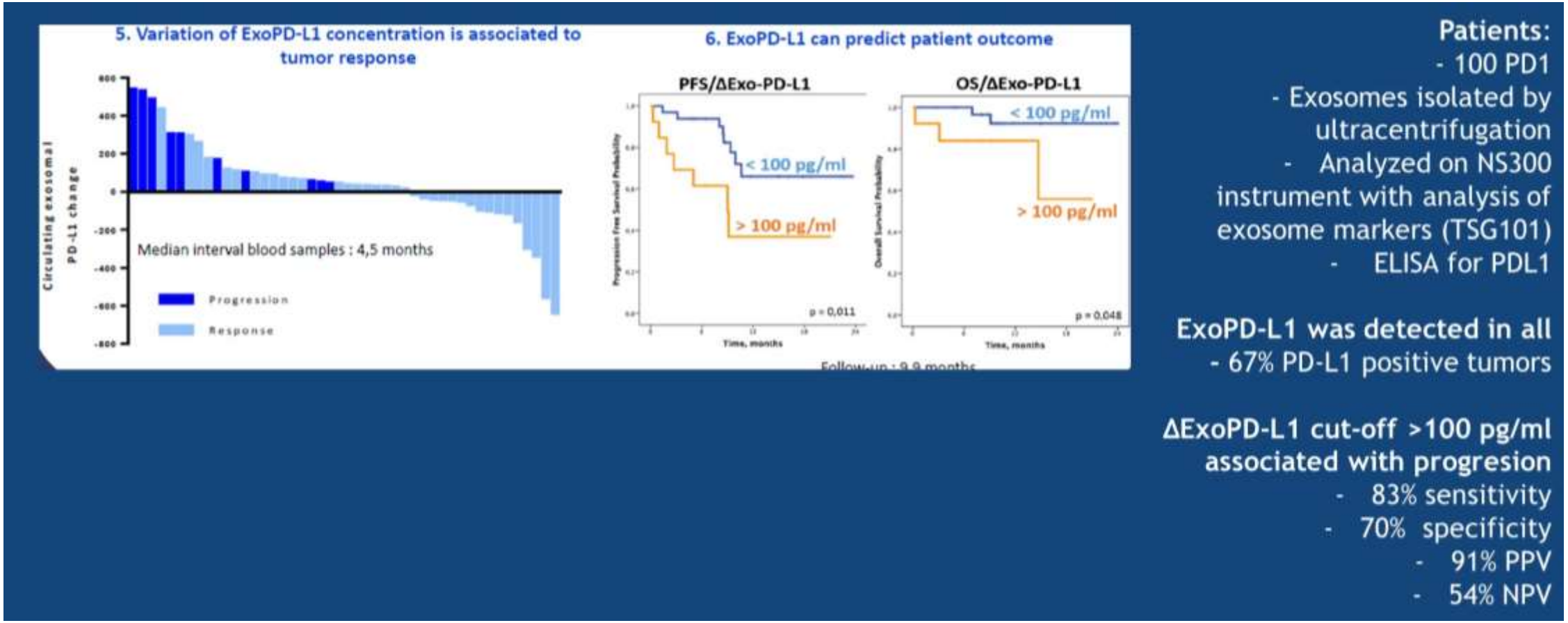
Multiple measures of body composition showed differences in clinical outcomes

Increased median VAT/SAT was associated with improved response

Young et al. .Abstract 9516 –ASCO 2019

Circulating factors as biomarkers

Exosomes PDL-1 positive

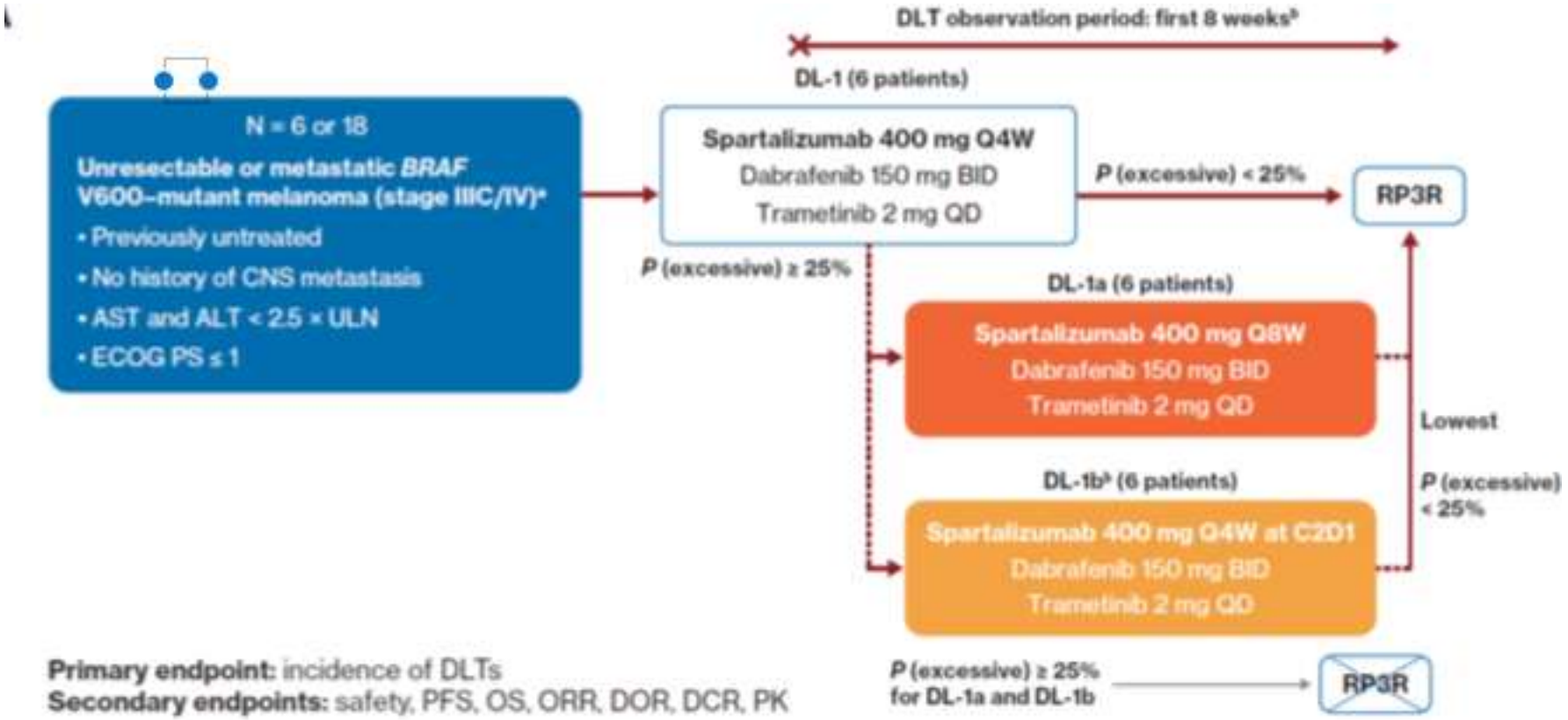


Are the isolation techniques for this sort of a technology, are they stable and reproducible? And are they clinically relevant?
Could these biomarkers monitor on treatment responses ahead of radiographic progression?

Cordonner et al. Abstract 9517

Circulating factors as biomarkers

Tumor microenvironment, longitudinal biomarker changes and clinical outcome in pts with advanced BRAF-mutant melanoma treated with first line spartalizumab +dabrafenib+trametenib

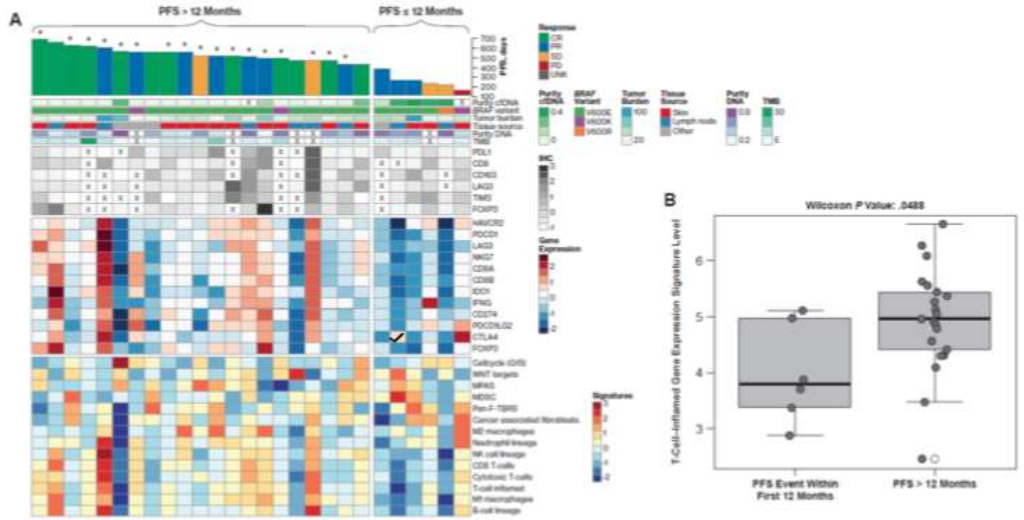


Long G et al. ASCO 2019

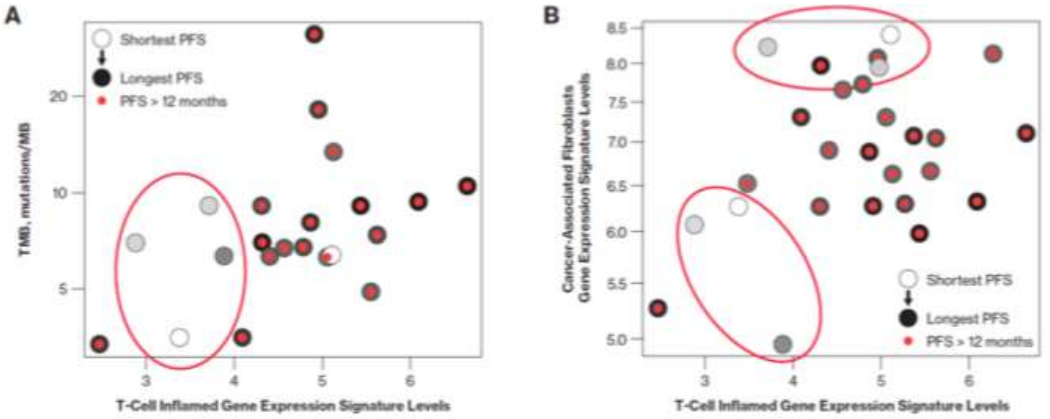
Dummer et al. Abstract 9515

Circulating factors as biomarkers

Baseline Biomarker Results (A) and T-Cell–Inflamed Gene Expression Signature (B) By PFS

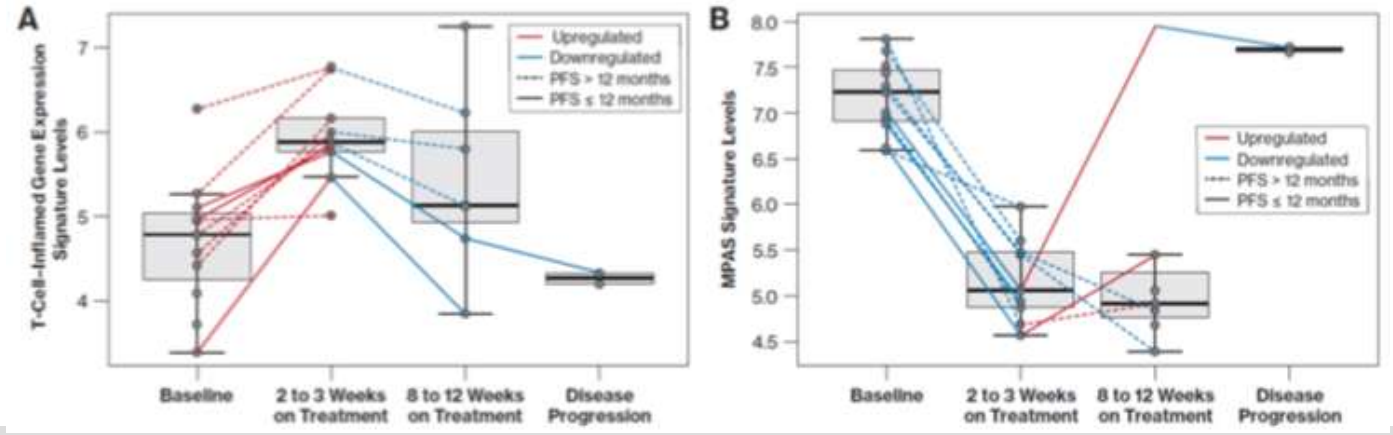


Patients With Progression Events in the First 12 Months Had Low TMB/Low T-Cell–Inflamed Gene Expression Signature Levels (A) or Increased Immunosuppressive TME Signatures (eg, cancer-associated fibroblasts) (B)



THE MAJORITY OF PFS EVENTS OCCURRED IN THE TMB-LOW/TI-GEP-LOW SUBGROUP

Modulation in T-Cell Inflamed Gene Expression Signature Levels (A) and MPAS (B) Upon Treatment

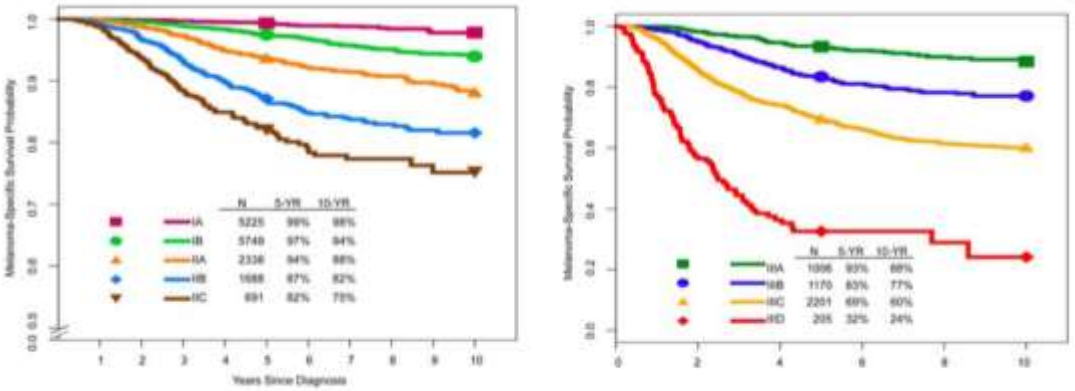


INCREASE IN TI-GEPS AND DECREASE IN MAPK PATHWAY ACTIVITY SCORE (MPAS) FROM BL TO BIOPSY AT 2-3 WK IN ALL PTS

Dummer et al. Abstract 9515

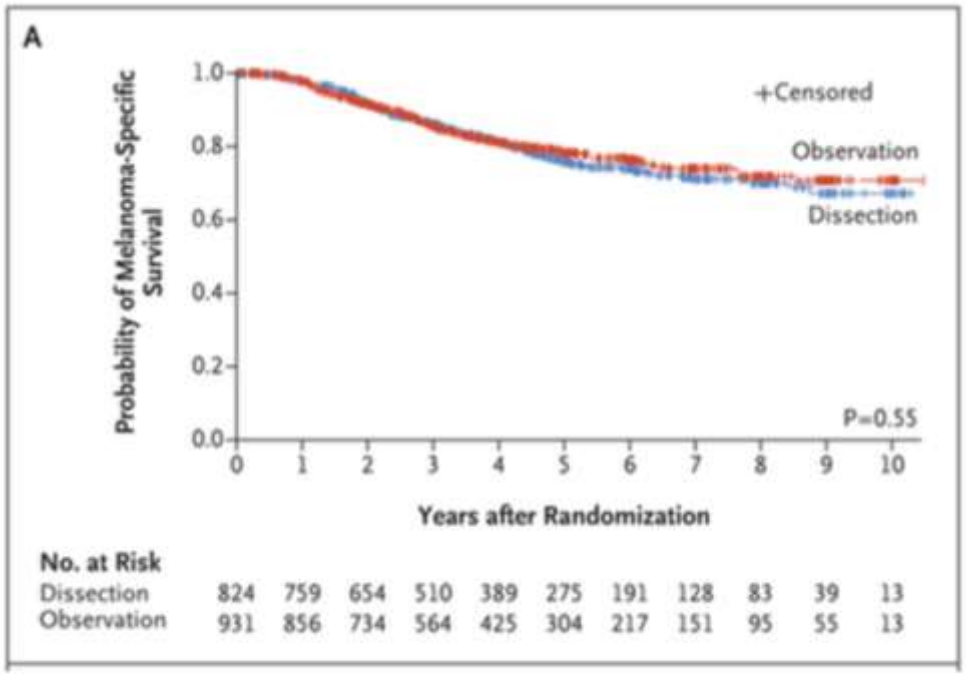
Prognostic biomarkers in melanoma

AJCC 8° EDITION



A Cancer J Clin. 2017 November ; 67(6): 472-492. doi:10.3322/caac.21409

MSLT-II



N Engl J Med. 2017 June 08; 376(23): 2211–2222. doi:10.1056/NEJMoa1613210.

Stage 1B have a 6% mortality rate at 10 years
Stage 2C have a 25% mortality rate at 10 years
Stage III includes heterogeneous population

9518

Clinical validation of a prognostic 11-gene assay in prospectively collected FFPE tissue of patients with AJCC v8 stage II cutaneous melanoma

Claus Garbe,[1] Tobias Sinnberg,[1] Heike Niessner,[1] Heiko Sülberg,[2] Thomas Eigentler,[1] and Teresa Amaral[1]

[1]Center for Dermatooncology, Department of Dermatology, Eberhard Karls University of Tuebingen, Tuebingen; [2]Wissenschaftlicher Service Pharma (WISP) Research Institute, Langenfeld; both in Germany

- Study Aim:
  - single center study to clinically validate a prognostic 11-gene GEP score for AJCC stage II melanoma patients.

- Methods:
  - Formalin-fixed paraffin-embedded (FFPE) primaries of AJCC stage II CMs from the Central Malignant Melanoma Registry (CMMR) of Germany archived in Tuebingen
  - Based upon a previously published algorithm, GEP score was calculated

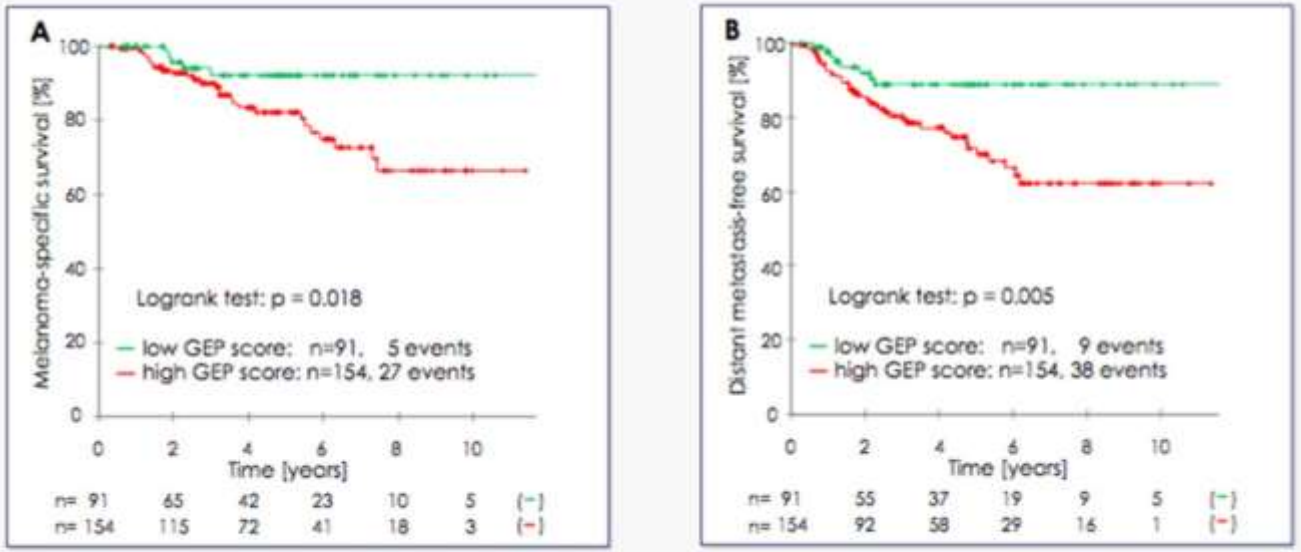


Figure 4: Kaplan-Meier MSS curves (A) and DMFS curves (B)

Three year survival outcomes in a prospective cohort evaluating a prognostic 31 gene expression profile (31-GEP) test for cutaneous melanoma

Eddy C. Hsueh, M.D.[1], James R. DeBloom, M.D.[2], Robert W. Cook, Ph.D.[3], Kelly M. McMasters, M.D., Ph.D.[4]
[1]Dept. of Surgery, St. Louis University, St. Louis, MO, [2]South Carolina Skin Cancer Center, Greenville, SC [3]Castle Biosciences Inc, Friendswood, TX, [4]Dept. of Surgical

Figure 1. Schematic of study objectives and analysis

Is the 31-GEP a consistent predictor of metastatic risk in a multi-center, prospective cohort of 342 patients?

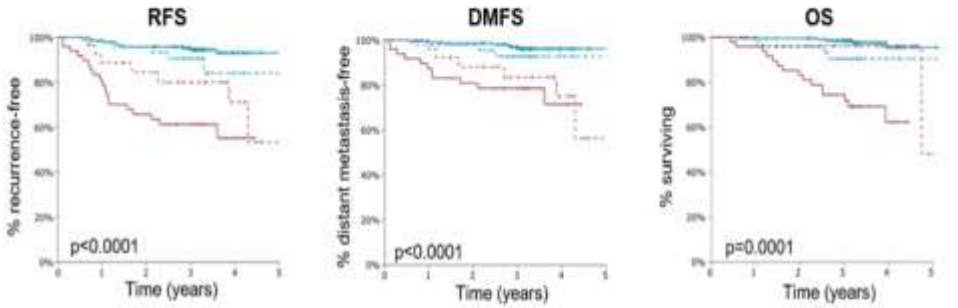
- Estimate 3-year RFS, DMFS, and OS and compare to previously published studies.

Do the outcomes of T1/T2 melanoma patients with Class 1A results support the previously published utility for SLNB guidance?[18]

- Evaluate survival of T1/T2 patients with Class 1A results and compare to previously published studies

Does the 31-GEP add prognostic value beyond AJCC staging?

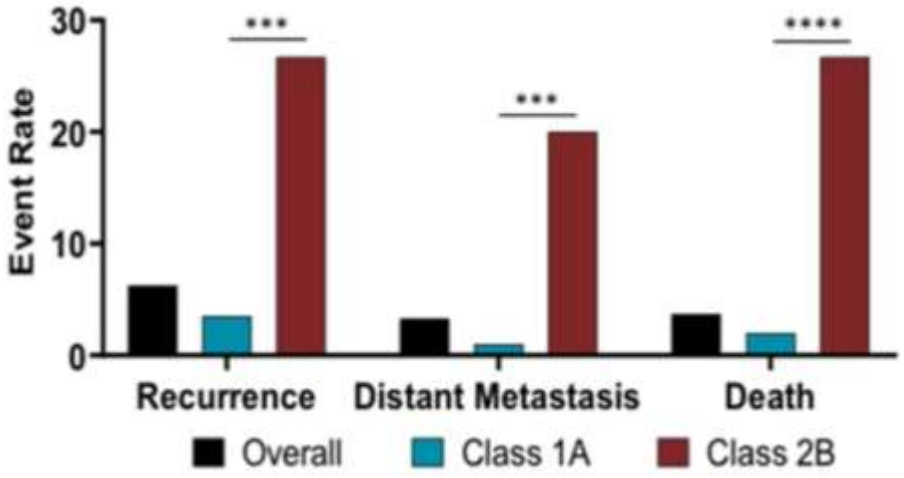
- Evaluate prognostic value of 31-GEP in Cox multivariate regression including AJCC risk categories



31 GEP Class	3-yr RFS (95% CI)	Events (%)
Class 1A (n=219)	95% (92-98%)	12 (5%)
Class 1B (n=47)	91% (82-100%)	5 (11%)
Class 2A (n=27)	80% (66-97%)	7 (26%)
Class 2B (n=49)	61% (49-77%)	19 (39%)

31 GEP Class	3-yr DMFS (95% CI)	Events (%)
Class 1A (n=219)	97% (94-99%)	7 (3%)
Class 1B (n=47)	93% (85-100%)	3 (6%)
Class 2A (n=27)	84% (70-100%)	6 (22%)
Class 2B (n=49)	79% (68-91%)	11 (22%)

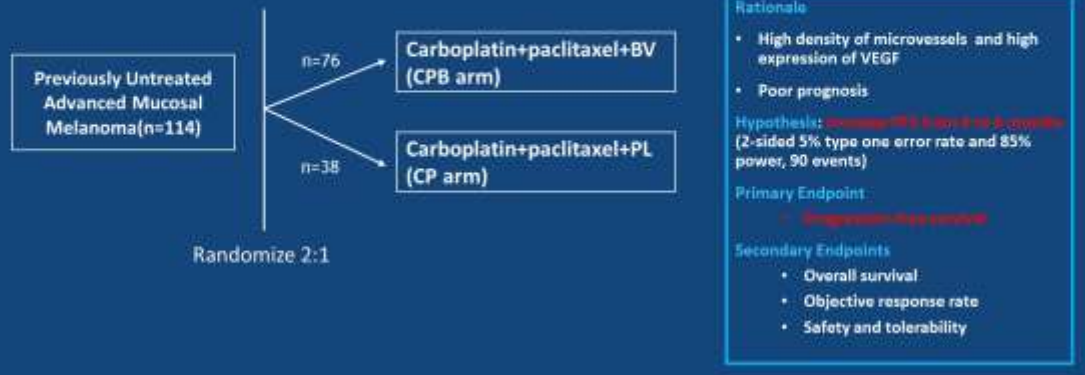
31 GEP Class	3-yr OS (95% CI)	Events (%)
Class 1A (n=219)	99% (97-100%)	5 (2%)
Class 1B (n=47)	90% (82-100%)	4 (9%)
Class 2A (n=27)	96% (89-100%)	2 (7%)
Class 2B (n=49)	74% (63-88%)	15 (31%)



Hsueh E. et al. Abstract 9519

Rare melanomas

Abstract 9521: A randomized phase II study evaluating the activity of bevacizumab in combination with carboplatin plus paclitaxel in patients with previously untreated advanced mucosal melanoma (NCT02023710).
Dr X. Yan et al.



Rationale
- High density of microvessels and high expression of VEGF
- Poor prognosis

Hypothesis: [redacted] (2-sided 5% type one error rate and 85% power, 90 events)

Primary Endpoint
- [redacted]

Secondary Endpoints
- Overall survival
- Objective response rate
- Safety and tolerability

Bevacizumab(BV) or placebo(PL) was administered 5 mg/kg q2w with carboplatin (AUC=5) plus paclitaxel (175 mg/m2) q4w by intravenous infusion.

Abstract 9522: Phase II study of ipilimumab and nivolumab in metastatic uveal melanoma
Dr M. Pelster et al.

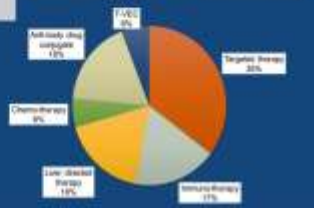
Patients
Metastatic uveal melanoma, any number of prior tx
Excluded: ECOG PS >1, second primary cancer, auto-immune disease
[redacted]

Treatment
Induction
Nivolumab 1mg/kg plus ipilimumab 3mg/kg Q3W x 4 doses
Maintenance
Nivolumab 3mg/kg IV Q2 W for up to 2 years
[redacted]

Endpoints
Primary: best ORR by investigator-assessed irRC
Secondary: PFS, OS, 1-y OS, adverse events
[redacted]

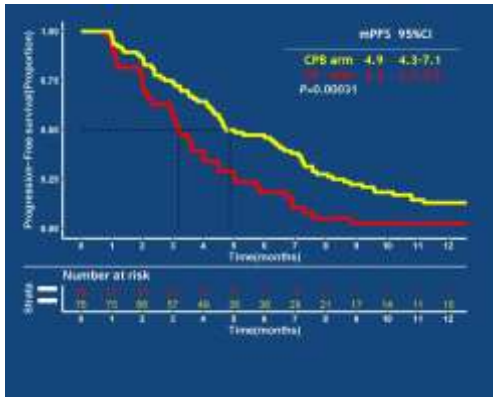
	N (%)
Total	35 (100%)
Sex	
Female	23 (66%)
Male	12 (34%)
Age, years, median (range)	62 (30-76)
Gene expression profile	
Class 1A	2 (6%)
Class 1B	3 (9%)
Class 2	8 (23%)
Not tested	22 (63%)
Mutation status	
GNAQ mutated	16 (46%)
GNA11 mutated	5 (15%)
GNAQ, GNA11 WT	1 (3%)
Not tested	13 (37%)

Baseline LDH, units/L, median (range)	558 (359 - 6145)
LDH ≤ ULN	20 (57%)
LDH > ULN	15 (43%)
Sites of metastases	
Hepatic	11 (31%)
Extra-hepatic only	7 (20%)
Both	17 (48%)
Metastatic stage	
M1a (LD ≤ 3.0cm)	17 (49%)
M1b (LD 3.1-8.0cm)	14 (40%)
M1c (LD ≥ 8.1cm)	4 (11%)
Prior lines of therapy	
0	20 (57%)
1	10 (29%)
2	3 (9%)
3	0 (0%)
4	2 (6%)

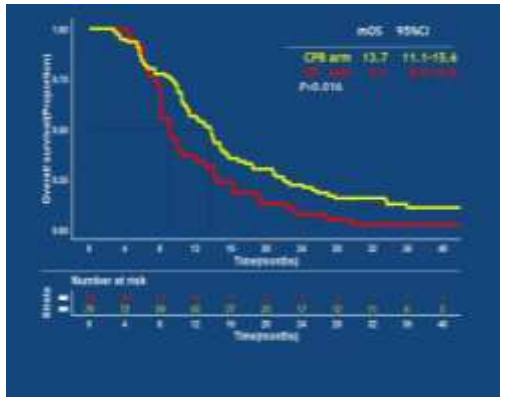


Primary endpoint: [redacted] (irRC)
Secondary endpoints: PFS, median OS, 1-year OS
Statistical methods: [redacted] with a null hypothesis of a 5% ORR
Target enrollment: 27 patients, giving 80% power with a type I error of 0.05
Scans at baseline, Week 12, and every 12 weeks thereafter

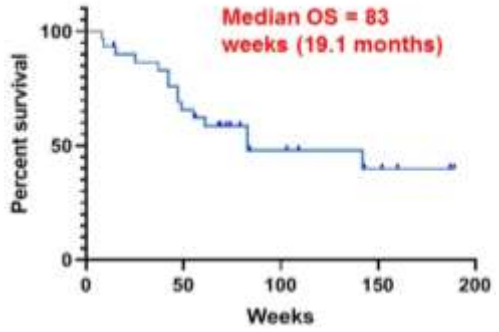
PFS



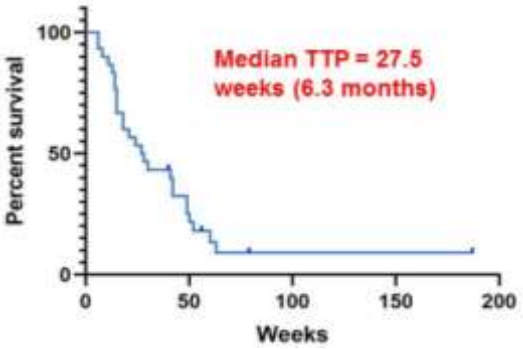
OS



Overall Survival



Time to Progression



Working Group IMI (intergruppo melanoma italiano) giovani Under 40

A patologo

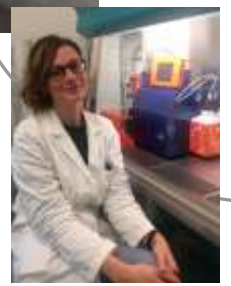
Genetista

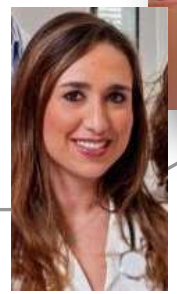
Radioterapista

Oncologo Medico

Dermatologo

Chirurgo





IMI

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