ASCO 2019: HIGHLIGHTS IN MELANOMA

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2019 AIOM Review: from Chicago to Verona

HIGHLIGHTS IN MELANOMA

Metastatic Setting:

- Five-Year Analysis of Dabrafenib Plus Trametinib in Patients with *BRAF* V600–Mutant Unresectable or Metastatic Melanoma.
- The Anti–PD-1 Antibody Spartalizumab in Combination With Dabrafenib and Trametinib in Previously Untreated Patients With Advanced *BRAF* V600–Mutant Melanoma: Updated Efficacy and Safety From Parts 1 and 2 of COMBI-i.

Neo-Adjuvant or Adjuvant Setting:

- Pathological Response and Survival with Neoadjuvant Therapy in Melanoma: a Pooled Analysis From the International Neoadjuvant Melanoma Consortium (INMC).
- A Phase III Study of Adjuvant Ipilimumab (3 or 10 mg/kg) vs High-Dose IFN-alfa2 for Resected High-Risck Melanoma.

Biomarkers:

- Circulating Tumor DNA Kinetics Predict Survival in Patients With Unresectable or Metastatic Melanoma Treated With Dabrafenib or Dabrafenib + Trametinib.
- Tumor Microenvironment, Longitudinal Biomarker Changes, and Clinical Outcome in Patients With Advanced *BRAF* V600-Mutant Melanoma Treated With First-Line Spartalizumab + Dabrafenib + Trametinib.
- IL-6 and C-Reactive Protein as Potential Biomarkers for Checkpoint Inhibition

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

Paul Nathan, Caroline Robert, Jean-Jacques Grob, Daniil Stroyakovskiy, Boguslawa Karaszewska, Axel Hauschild, Eugeny Levchenko, Vanna Chiarion Sileni, Jacob Schachter, Claus Garbe, Igor Bondarenko, Michael A. Davies, Antoni Ribas, Keith Flaherty, Paul Burgess, Monique Tan, Eduard Gasal, Dirk Schadendorf, Georgina V. Long

See the Manuscript in *New England Journal of Medicine*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Five-Year Outcomes with Dabrafenib plus Trametinib in Metastatic Melanoma

C. Robert, J.J. Grob, D. Stroyakovskiy, B. Karaszewska, A. Hauschild, E. Levchenko, V. Chiarion Sileni, J. Schachter, C. Garbe, I. Bondarenko, H. Gogas, M. Mandalá, J.B.A.G. Haanen, C. Lebbé, A. Mackiewicz, P. Rutkowski, P.D. Nathan, A. Ribas, M.A. Davies, K.T. Flaherty, P. Burgess, M. Tan, E. Gasal, M. Voi, D. Schadendorf, and G.V. Long

Open access available for a limited time:

Robert C, et al. *N Engl J Med*. 2019 June 4. doi: 10.1056/NEJMoa1904059.

COMBI-d and COMBI-v: Study Designs

Objectives

- To determine long-term survival in previously untreated patients who received dabrafenib plus trametinib
- To confirm baseline factors predictive of long-term survival based on previous regression-tree and multivariate analyses

COMBI-d[1]
(enrollment period May 2012-Jan 2013; NCT01584648)

(n = 563)

COMBI-v[2]
(enrollment period Jun 2012-Sept 2013; NCT01597908)

Key Eligibility Criteria[1,2]

- Age ≥ 18 years
- Unresectable or metastatic melanoma
- *BRAF* V600E/K positive
- ECOG PS 0 or 1
- No prior systemic therapy
- No prior treatment with a BRAF inhibitor or MEK inhibitor
- Treated/stable brain metastases

R 1:1

- Dabrafenib 150 mg BID + trametinib 2 mg QD (n = 211)
- Dabrafenib 150 mg BID + placebo QD (n = 212)

Final analysis (PFS) → Follow-up analysis (OS) → 5-year analysis

R 1:1

- Dabrafenib 150 mg BID + trametinib 2 mg QD (n = 352)
- Vemurafenib 960 mg BID (n = 352)

Interim OS analysis → Final OS analysis → 5-year analysis

BID, twice daily; QD, once daily; R, randomized.

1. Long GV, et al. *N Engl J Med*. 2014;371:1877-1888; 2. Robert C, et al. *N Engl J Med*. 2015;372:30-39.

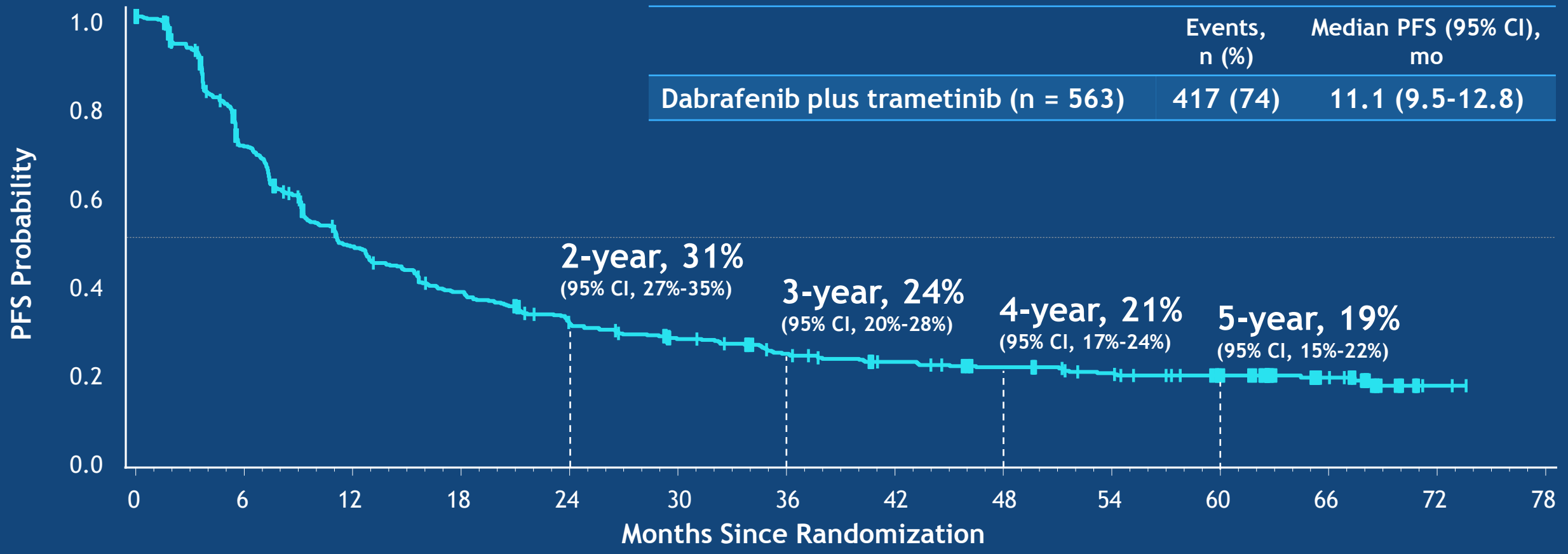
Best Overall RECIST Response

	Pooled COMBI-d/v n = 561[a]
Best overall response, n (%)	
Complete response	109 **(19)**
Partial Response	274 **(49)**
Stable disease	130 **(23)**
Progressive disease	31 **(6)**
Not evaluable	17 **(3)**
Objective response rate, n (%) [95% CI]	383 **(68)** [64-72]

RECIST, Response Evaluation Criteria in Solid Tumors.
[a] Two patients are excluded from the table because they had no measurable disease at baseline.

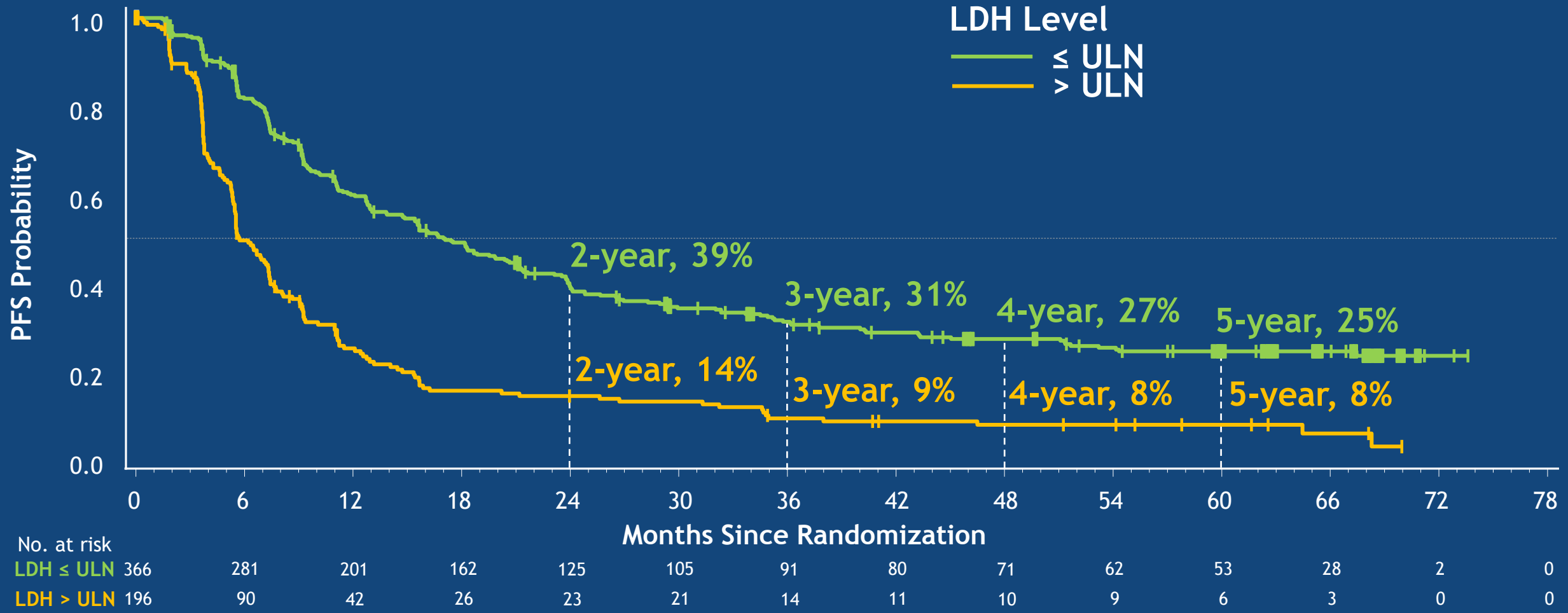
Dab + Tram: 5-Year PFS

	Events, n (%)	Median PFS (95% CI), mo
Dabrafenib plus trametinib (n = 563)	417 (74)	11.1 (9.5-12.8)



No. at risk	563	371	243	188	148	126	105	91	81	71	59	31	2	0

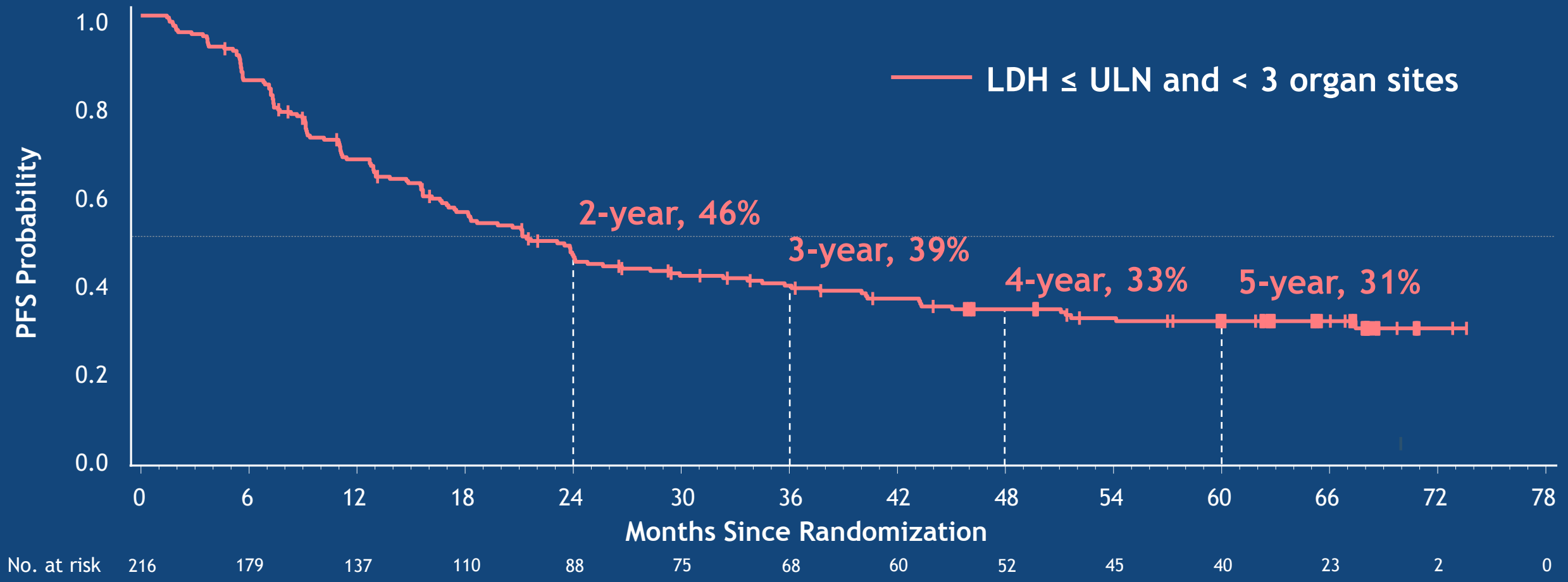
Dab + Tram: PFS by Baseline LDH Level



No. at risk

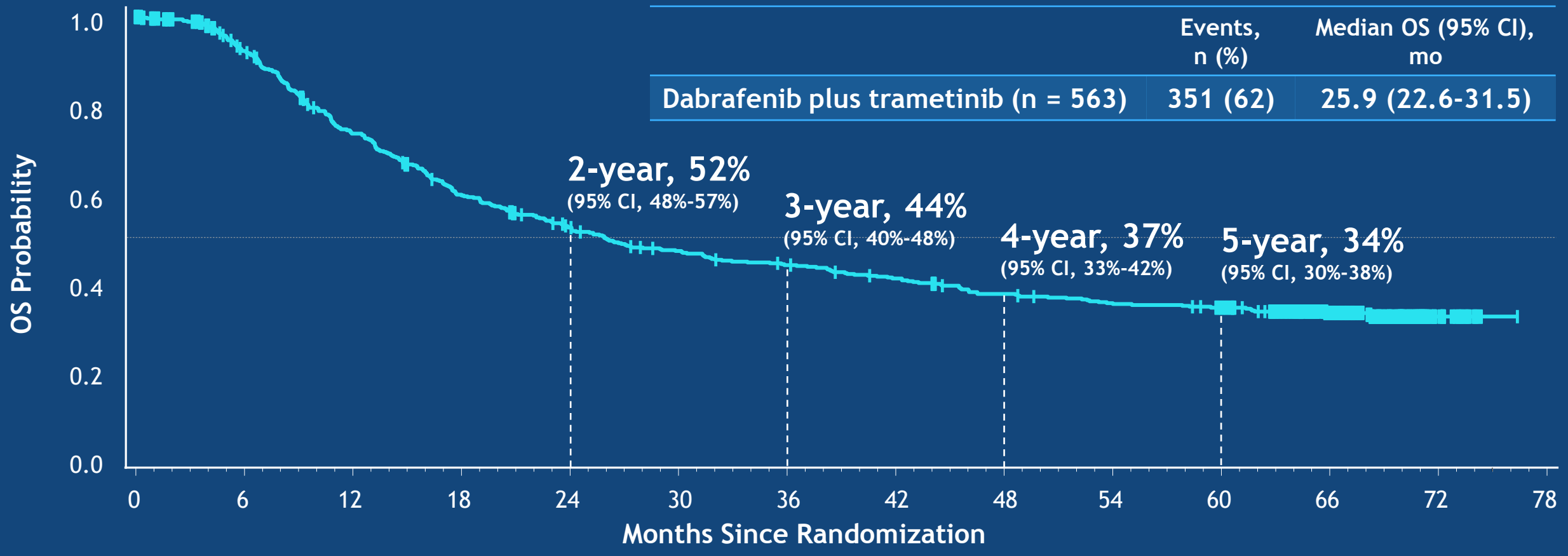
LDH ≤ ULN	366	281	201	162	125	105	91	80	71	62	53	28	2	0
LDH > ULN	196	90	42	26	23	21	14	11	10	9	6	3	0	0

Dab + Tram: PFS in Pts With Normal LDH and <3 Organ Sites



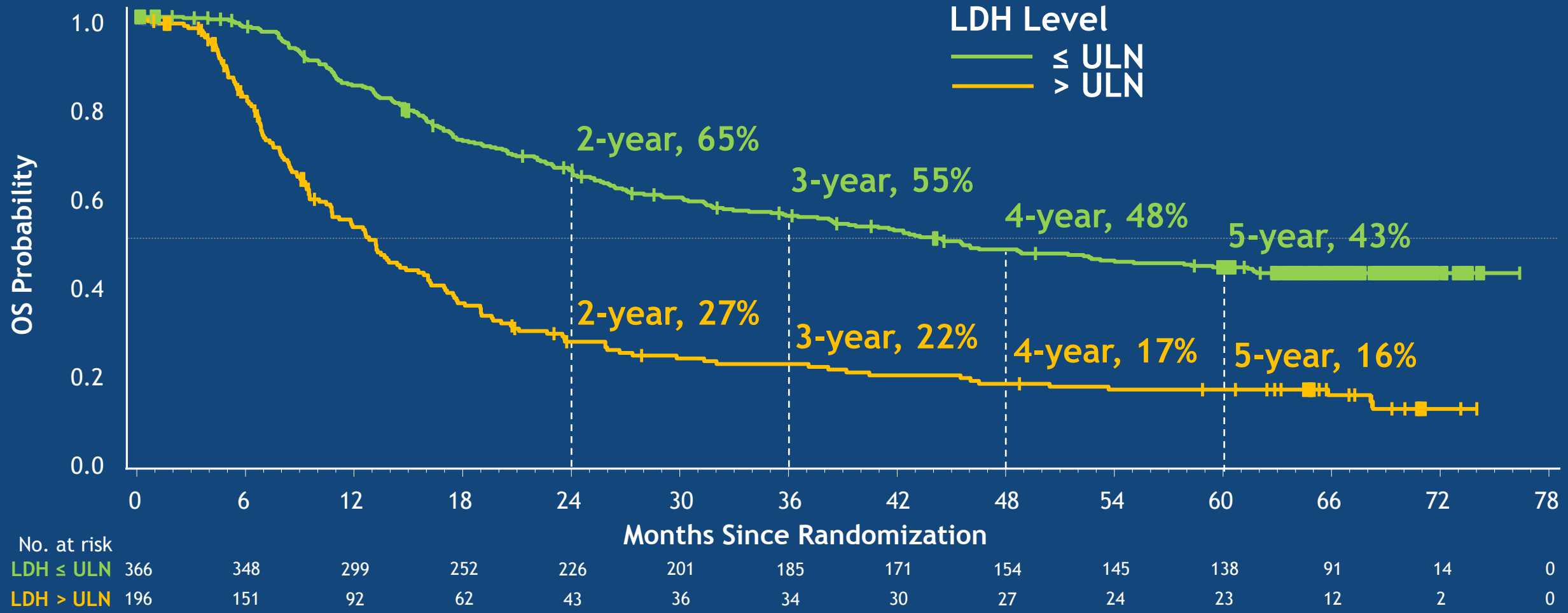
Dab + Tram: 5-Year OS

	Events, n (%)	Median OS (95% CI), mo
Dabrafenib plus trametinib (n = 563)	351 (62)	25.9 (22.6-31.5)



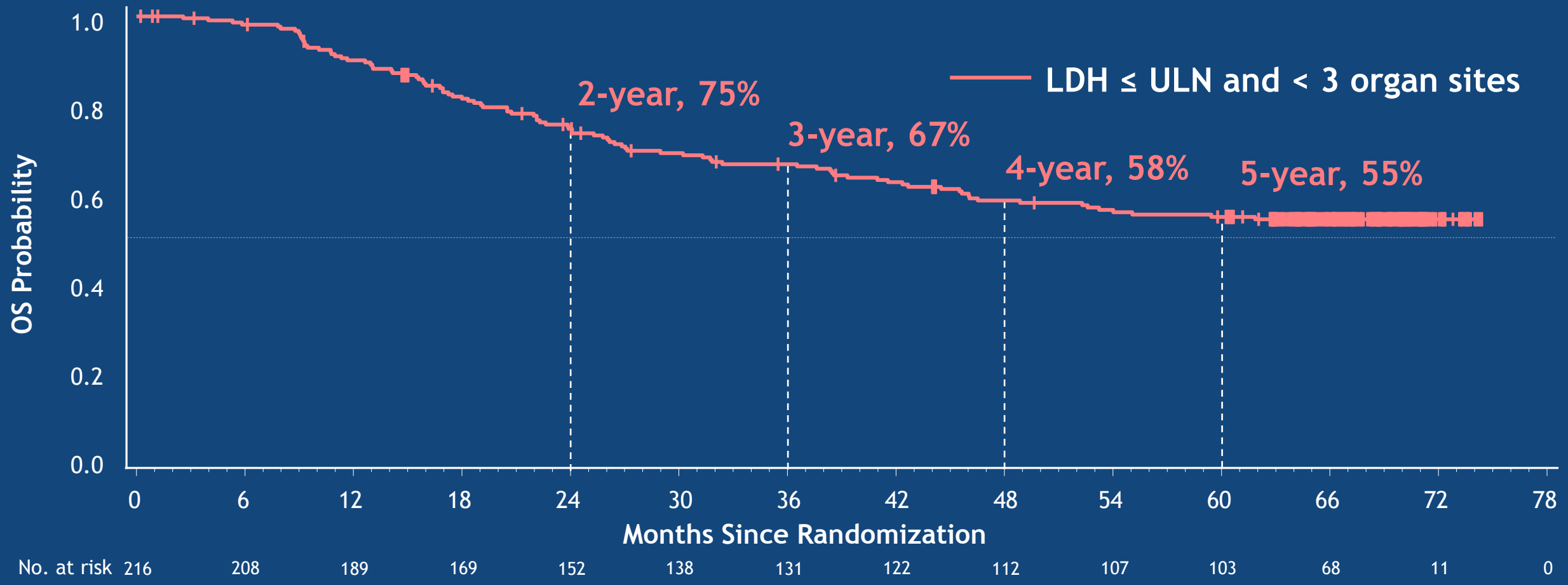
No. at risk	563	499	391	314	269	237	219	201	181	169	161	103	16	0

Dab + Tram: OS by Baseline LDH Level

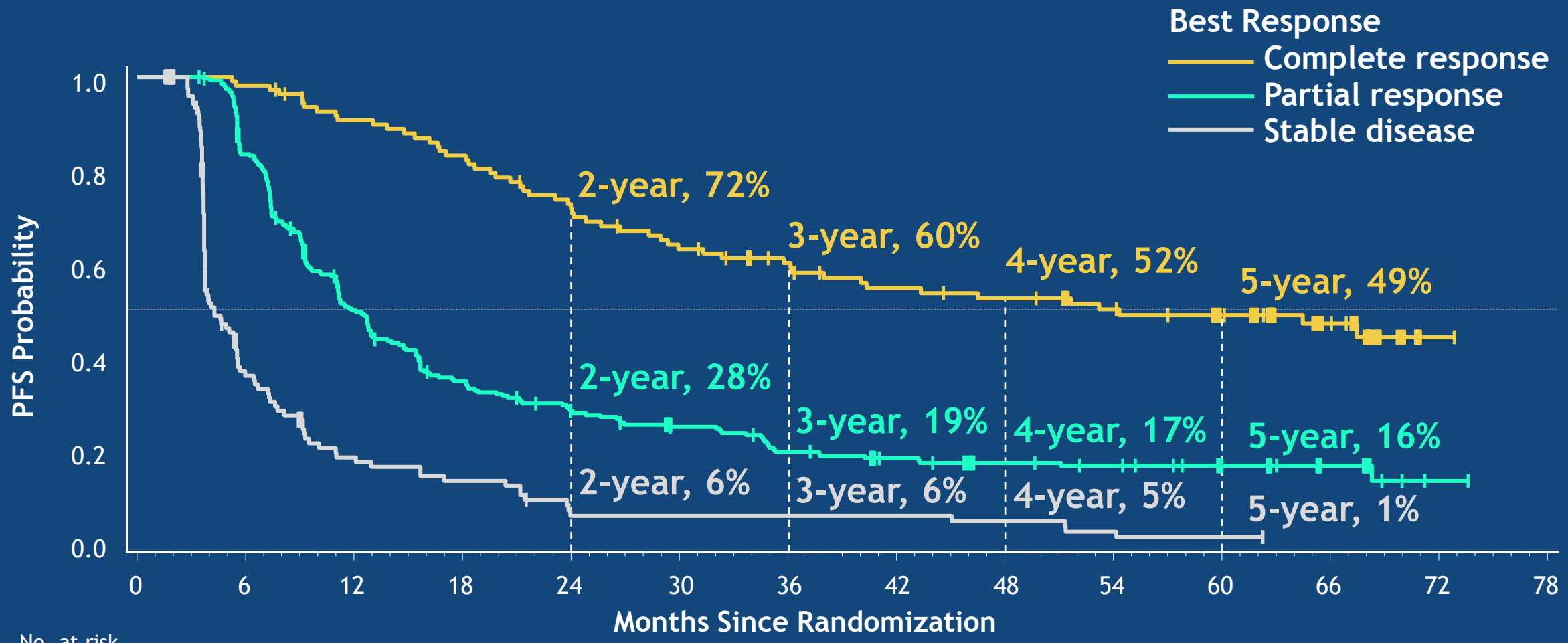


No. at risk													
LDH ≤ ULN	366	348	299	252	226	201	185	171	154	145	138	91	14	0
LDH > ULN	196	151	92	62	43	36	34	30	27	24	23	12	2	0

Dab + Tram: OS in Pts With Normal LDH and <3 Organ Sites



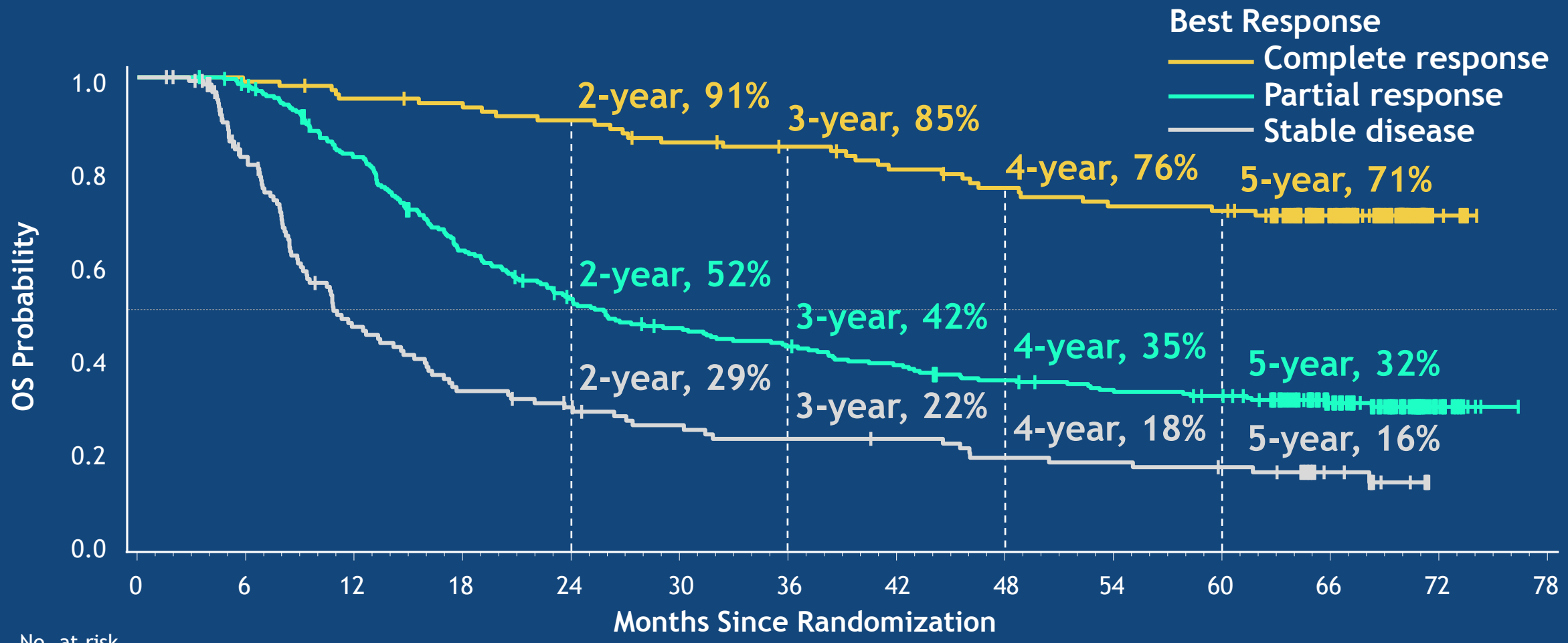
Dabrafenib Plus Trametinib: PFS by Best Response



No. at risk

Complete response	109	107	96	88	75	65	57	50	47	42	37	20	1	0
Partial response	274	224	129	87	68	56	43	36	30	27	21	11	1	0
Stable disease	130	38	18	13	5	5	5	5	4	2	1	0	0	0

Dabrafenib Plus Trametinib: OS by Best Response



No. at risk													
Complete response	109	108	103	101	97	91	88	82	77	73	72	48	4	0
Partial response	274	266	220	165	134	116	106	95	85	78	73	46	11	0
Stable disease	130	99	54	38	32	26	23	22	18	17	15	8	0	0

Summary

- This is the largest data set and longest follow-up in previously untreated patients with *BRAF* V600–mutant unresectable or metastatic melanoma treated with BRAF plus MEK inhibitors
- Dabrafenib plus trametinib led to 5-year disease control in approximately one-fifth of patients and 5-year survival in approximately one-third
- Complete response appears to strongly predict long-term benefit
- Lower baseline tumor burden and less-aggressive tumor biology were associated with prolonged PFS and OS
- These results suggest that first-line treatment with dabrafenib plus trametinib provides long-term survival benefit in a sizeable cohort of patients

Circulating Tumor DNA Kinetics Predict Survival in Patients With Unresectable or Metastatic Melanoma Treated With Dabrafenib or Dabrafenib + Trametinib

Mahrukh M. Syeda,[1] Jennifer M. Wiggins,[1] Broderick Corless,[1] Georgina V. Long,[2] Keith Flaherty,[3] Dirk Schadendorf,[4] Paul D. Nathan,[5] Caroline Robert,[6] Antoni Ribas,[7] Michael Davies,[8] Jean-Jacques Grob,[9] Eduard Gasal,[10] Matthew Squires,[11] Mahtab Marker,[10] Jan C. Brase,[11] David Polsky[1]

[1]NYU Langone Medical Center, New York, NY; [2]Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia; [3]Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA; [4]University Hospital Essen, Essen, and German Cancer Consortium, Heidelberg, Germany; [5]Mount Vernon Cancer Centre, Northwood, United Kingdom; [6]Gustave Roussy and Paris-Sud-Paris-Saclay University, Villejuif, France; [7]University of California, Los Angeles, CA; [8]The University of Texas MD Anderson Cancer Center, Houston, TX; [9]Aix-Marseille University, Marseille, France; [10]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [11]Novartis Pharma AG, Basel, Switzerland

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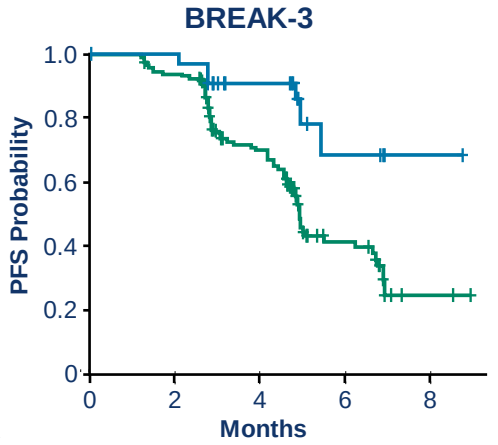
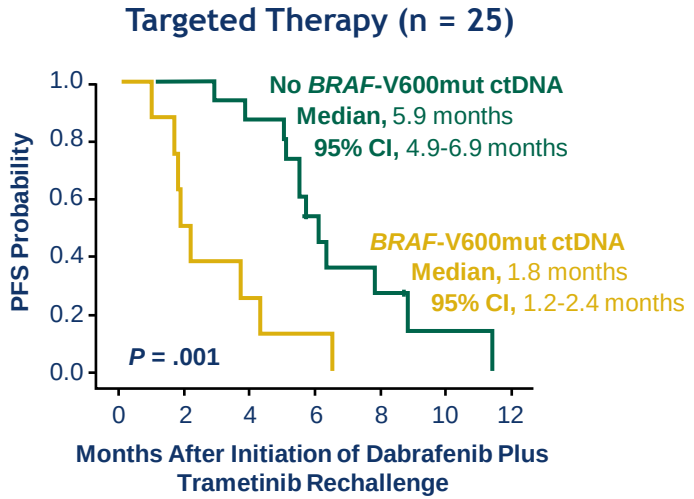
ctDNA as a Potential Biomarker in Melanoma

Baseline ctDNA indicates poor prognosis in patients treated with BRAF inhibitors, immune checkpoint blockade, or chemotherapy[1,2]

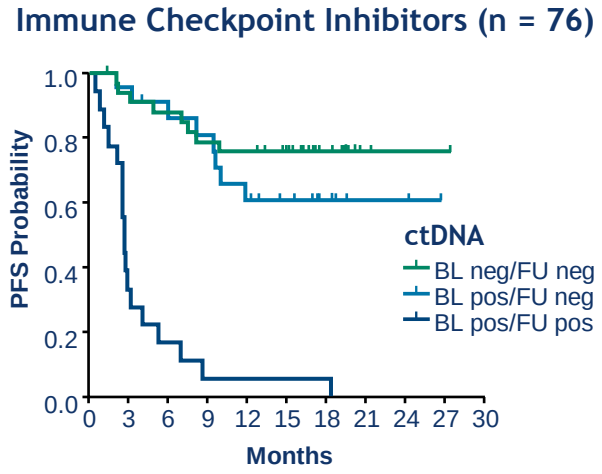


Reprinted from Santiago-Walker A, et al. *Clin Cancer Res*. 2016;22(3):567-574, with permission from AACR.

- Small case series observed associations between on-treatment ctDNA levels and clinical outcomes after immune checkpoint blockade and targeted therapy[3,4,a]
- Various detection methods for *BRAF*-mutant ctDNA in patients with metastatic disease
- Sensitivities range between 53% and 91%



Schreuer M, et al. *Lancet Oncol*. 2017;18(4):464-472, Copyright 2017, with permission from Elsevier.



Lee JH, et al. *Ann Oncol*. 2017;28(5):1130-1136 by permission of Oxford University Press.

BL, baseline; ctDNA, circulating tumor DNA; ddPCR, droplet digital PCR; FU, follow-up; mut, mutant; PFS, progression-free survival.

[a] Patient inclusion criteria and treatments received varied within and between studies.

1. Santiago-Walker A, et al. *Clin Cancer Res.* 2016;22(3):567-574; 2. Schreuer M, et al. *J Transl Med.* 2016;14:95; 3. Schreuer M, et al. *Lancet Oncol.* 2017;18(4):464-472; 4. Lee JH, et al. *Ann Oncol.* 2017;28(5):1130-1136.

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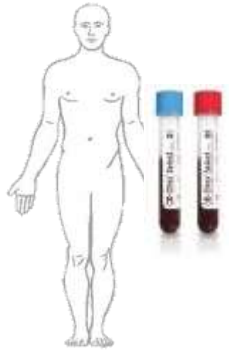
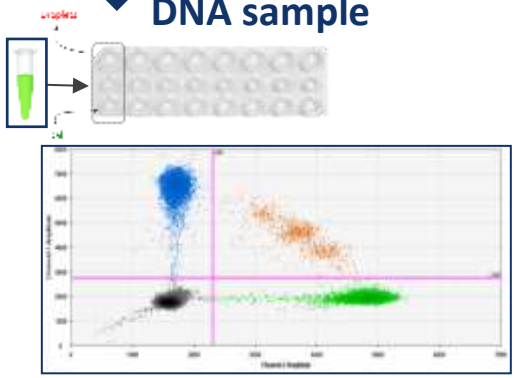
Analytic Validation of ddPCR Assays for Melanoma Hot-Spot Mutations[a]

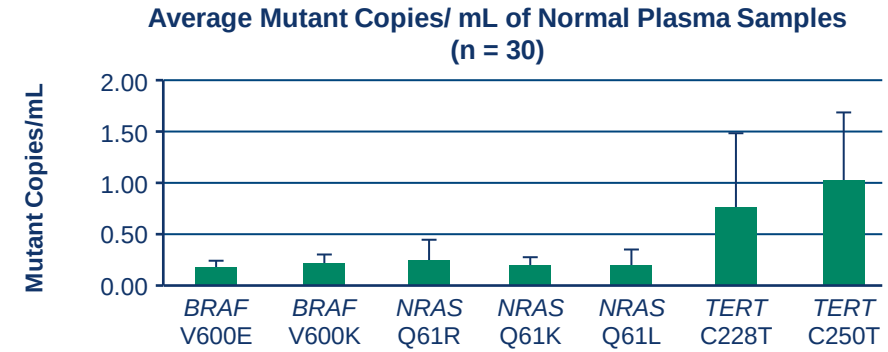


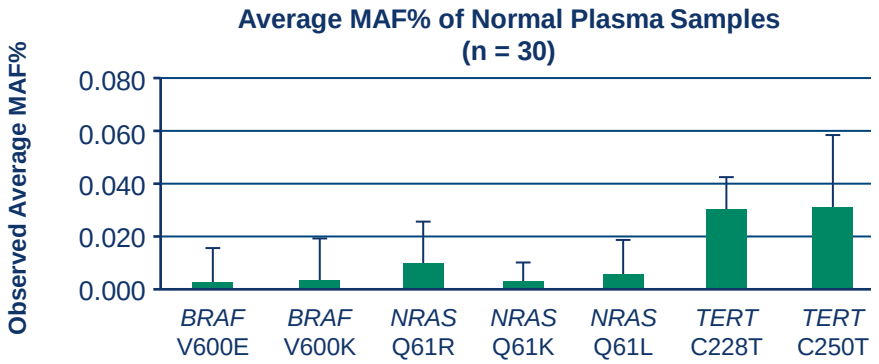
5 mL of Plasma

DNA sample



ddPCR





Mutant Copies/mL (n = 30)	
***BRAF* V600E**	0.24
***BRAF* V600K**	0.29
***NRAS* Q61R**	0.44
***NRAS* Q61K**	0.28
***NRAS* Q61L**	0.34
***TERT* C228T**	1.50
***TERT* C250T**	1.68

Fractional Abundance (n = 30)	
***BRAF* V600E**	0.016%
***BRAF* V600K**	0.019%
***NRAS* Q61R**	0.026%
***NRAS* Q61K**	0.010%
***NRAS* Q61L**	0.018%
***TERT* C228T**	0.043%
***TERT* C250T**	0.058%

ddPCR, droplet digital polymerase chain reaction.
[a] *BRAF*, *NRAS*, *TERT* promoter.

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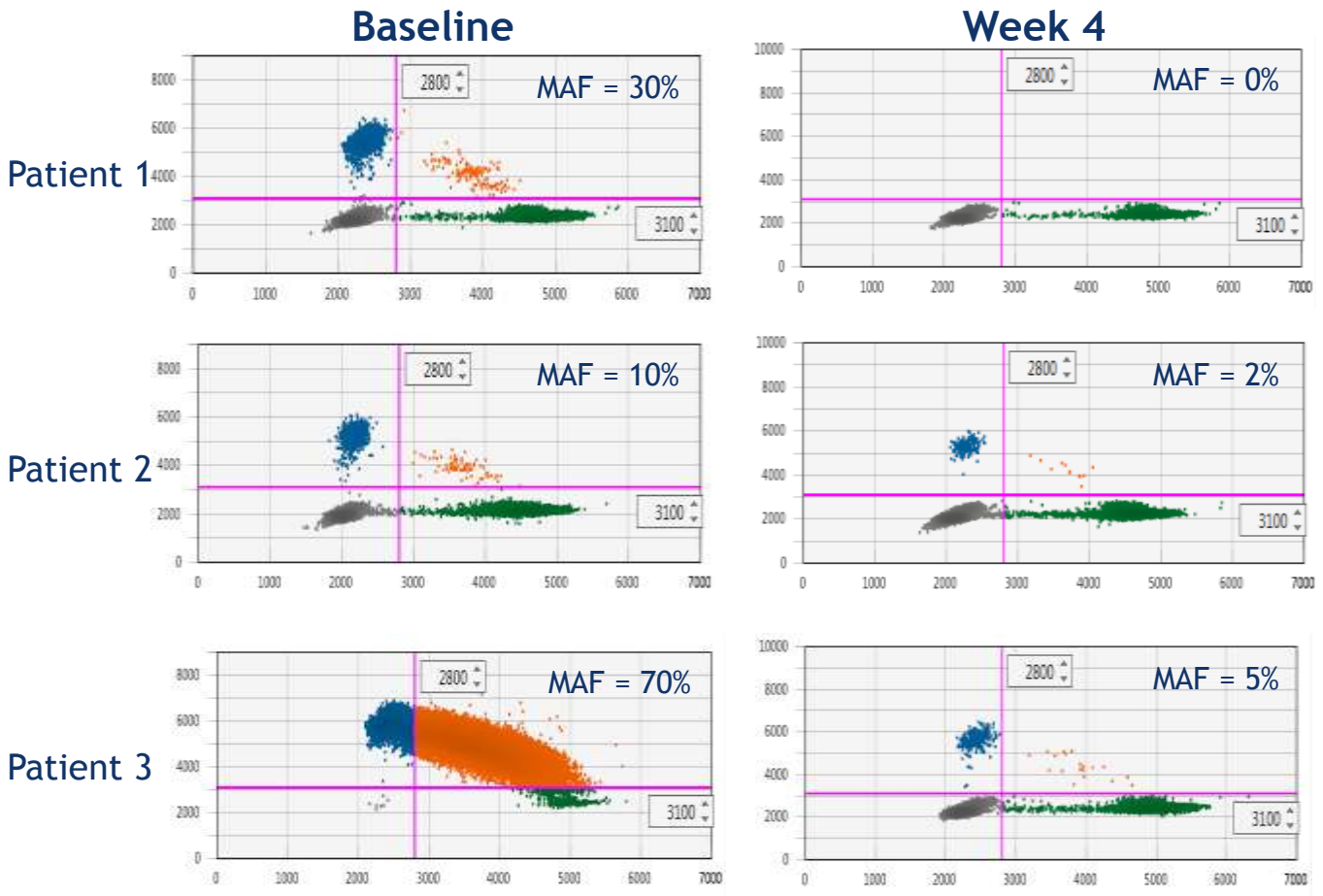
Study Design: ctDNA Biomarker Analysis and Example Results

Methods

Patients: large-scale, randomized, phase 3 trial (COMBI-d)

Plasma analysis: analytically validated digital droplet PCR (ddPCR) *BRAF* V600E/K

Patients and Samples Analyzed[a]	
Baseline, n/N (%)	345/423 (82)
Paired weeks 1 and 4, n/N (%)	224/423 (53)
Sample volume, median	3.6 mL
cfDNA recovered, range	< 1-5990 ng
cfDNA recovered, median	28.6 ng
ctDNA mutant fraction, range	0%-79%



cfDNA, cell-free DNA; ctDNA, circulating tumor DNA; MAF, mutant allele fraction.

[a] Equal portions of dabrafenib and dabrafenib + trametinib.

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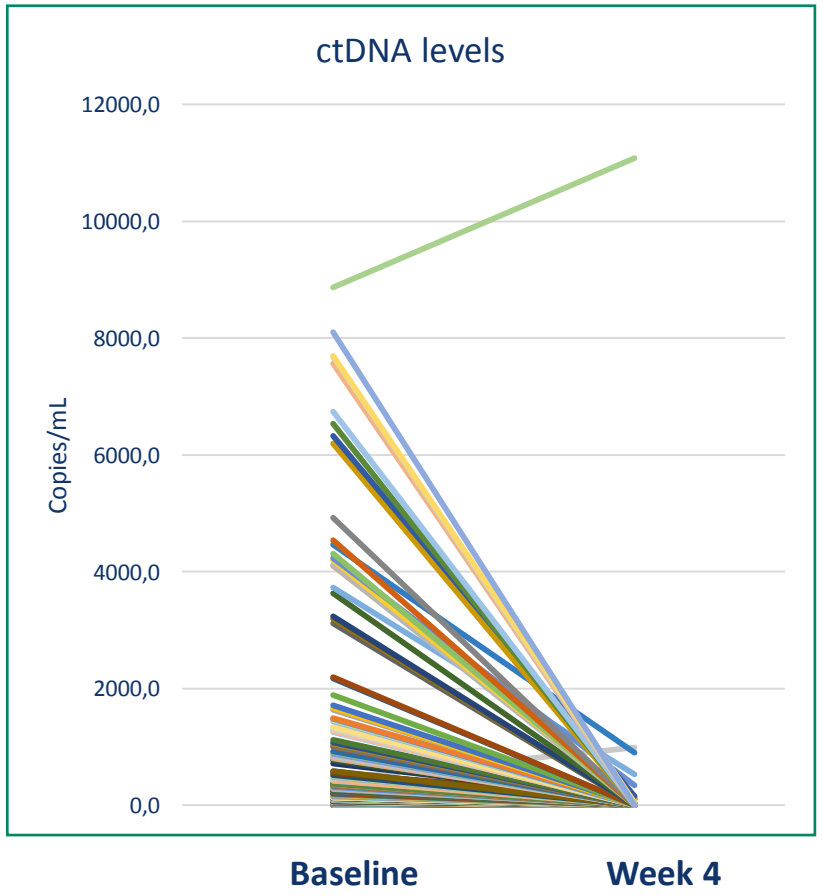
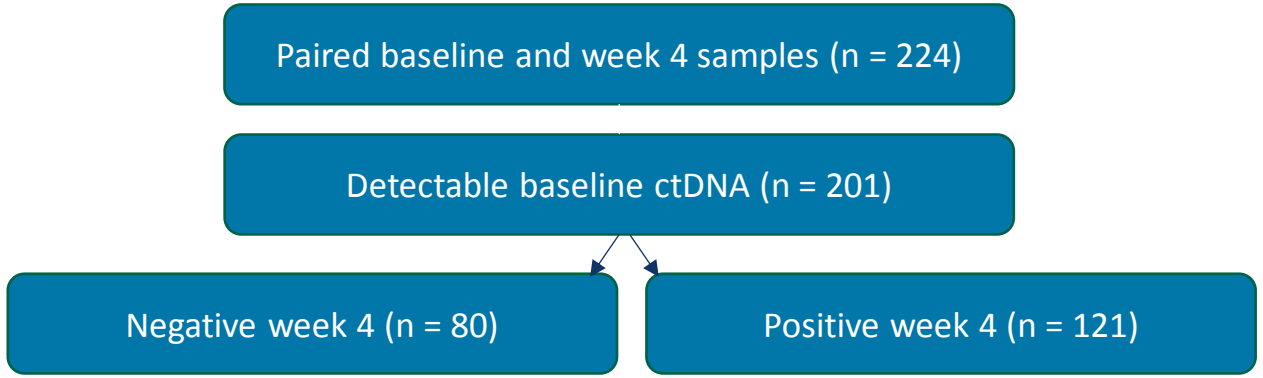
BRAF-Mutant ctDNA Was Detectable in 93% of Baseline Samples and 60% of Week 4 Samples





	Baseline (n = 345)	Week 4 (n = 224)
Median copies/mL (range)	66.7 (0-266,902)	0.55 (0-11,078)
Median mutant fraction % (range)	3.1 (0-79.3)	0.02 (0-47)

ctDNA, circulating tumor DNA.

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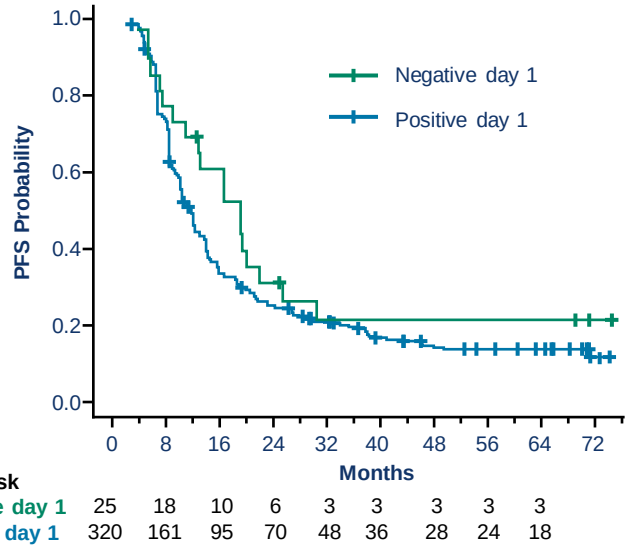
Elevated ctDNA at Baseline Was Associated With Survival as a Continuous Variable Not as a Categorical Variable

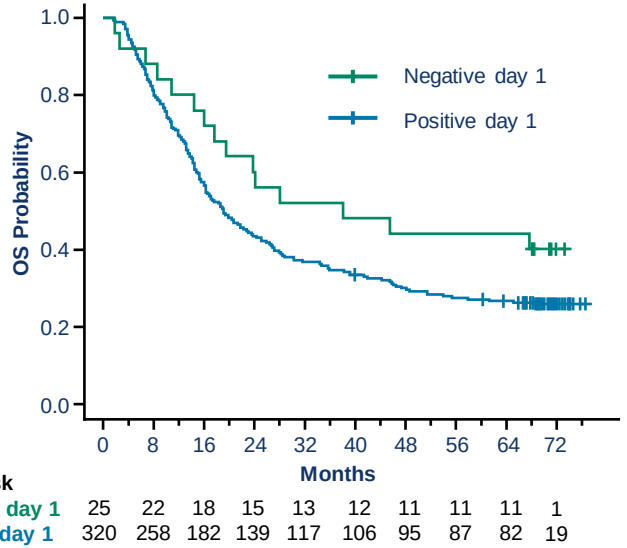
Positive/Negative

PFS



No. at risk										
Negative day 1	25	18	10	6	3	3	3	3	3	
Positive day 1	320	161	95	70	48	36	28	24	18	

OS



No. at risk											
Negative day 1	25	22	18	15	13	12	11	11	11	1	
Positive day 1	320	258	182	139	117	106	95	87	82	19	

		Events	Median (95% CI)	HR (95% CI), months	*P*
PFS	Negative (n = 25)	18	15.41 (9.13-21.75)	1.34 (0.83-2.16)	.23
	Positive (n = 320)	253	9.03 (7.36-10.25)		
OS	Negative (n = 25)	15	38.11 (17.64-NA)	1.52 (0.9-2.57)	.11
	Positive (n = 320)	237	19.09 (16.26-23.03)		

ctDNA, circulating tumor DNA; HR, hazard ratio; NA, not available; OS, overall survival; PFS, progression-free survival.

Continuous Variable

	Log(ctDNA) HR (95% CI)	
	PFS	OS
Unstratified	1.08 (1.04-1.12) *P* < .001	1.13 (1.09-1.18) *P* < .001
Stratified	1.03 (0.99-1.08) *P* = .012	1.08 (1.03-1.13) *P* = .002

- Cox analysis demonstrated that continuous ctDNA levels at baseline were associated with PFS and OS (higher ctDNA = worse clinical outcome)

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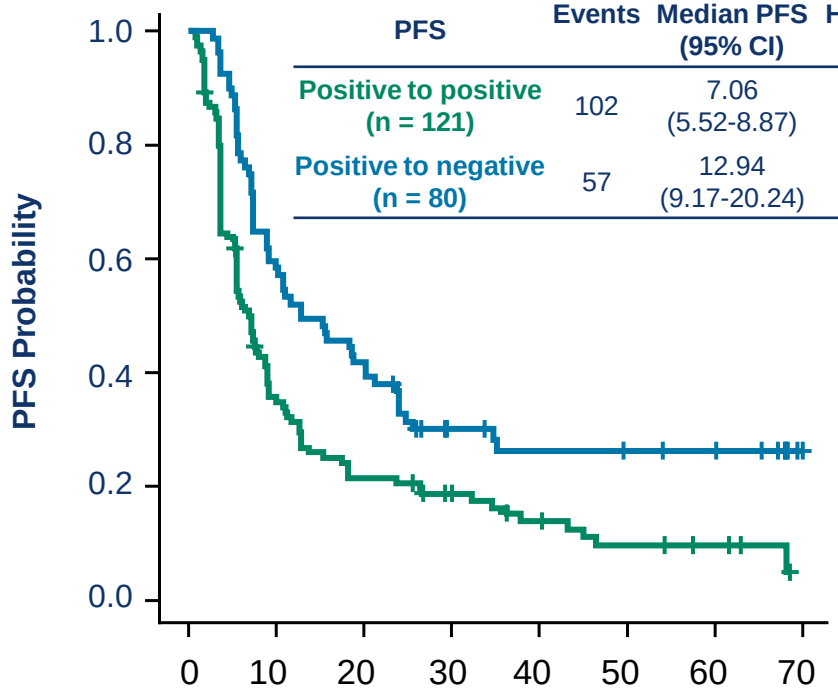
Achieving Undetectable ctDNA at Week 4 Was Associated With Extended PFS and OS

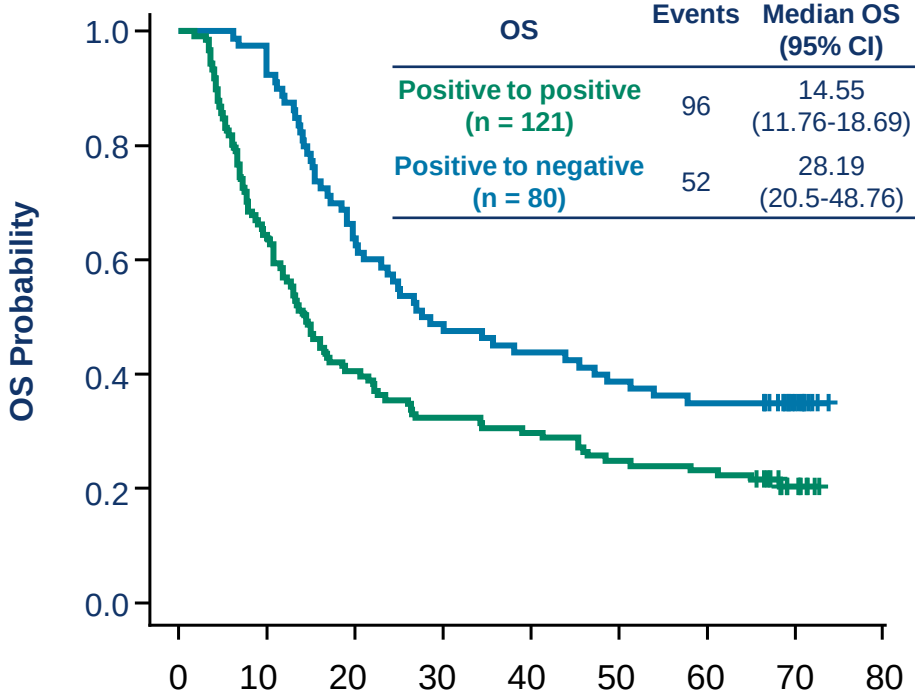
Differences were more evident in pts with elevated LDH

PFS	Events	Median PFS (95% CI)	HR (95% CI), months	*P*
Positive to positive (n = 121)	102	7.06 (5.52-8.87)	0.55 (0.39-0.76)	.00028
Positive to negative (n = 80)	57	12.94 (9.17-20.24)		



No. at risk							
Positive to positive	121	40	24	17	11	7	5
Positive to negative	80	47	33	17	14	13	12

OS	Events	Median OS (95% CI)	HR (95% CI), months	*P*
Positive to positive (n = 121)	96	14.55 (11.76-18.69)	0.56 (0.4-0.79)	.00086
Positive to negative (n = 80)	52	28.19 (20.5-48.76)		



No. at risk				
Positive to positive	121	49	36	28
Positive to negative	80	51	35	28

HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; ULN, upper limit of normal.

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Conclusions

- Pretreatment *BRAF* V600-mutant ctDNA was detectable in 93% of patients with unresectable or metastatic melanoma
- Elevated pretreatment levels were associated with shorter survival outcomes
- Undetectable ctDNA at week 4 was significantly associated with extended PFS and OS, especially in patients with elevated LDH levels
- Analysis of additional on-treatment time points may improve predictive accuracy
- On-treatment ctDNA monitoring may inform clinical decision-making

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The Anti–PD-1 Antibody Spartalizumab in Combination With Dabrafenib and Trametinib in Previously Untreated Patients With Advanced *BRAF* V600–Mutant Melanoma: Updated Efficacy and Safety From Parts 1 and 2 of COMBI-i

Georgina V. Long,[1] Celeste Lebbé,[2] Victoria Atkinson,[3] Mario Mandalà,[4] Paul D. Nathan,[5] Ana Arance,[6] Erika Richtig,[7] Naoya Yamazaki,[8] Caroline Robert,[9] Dirk Schadendorf,[10] Hussein Abdul-Hassan Tawbi,[11] Paolo Antonio Ascierto,[12] Antoni Ribas,[13] Keith Flaherty,[14] Dung-Yang Lee,[15] Aisha Masood,[15] Eduard Gasal,[15] Reinhard Dummer[16]

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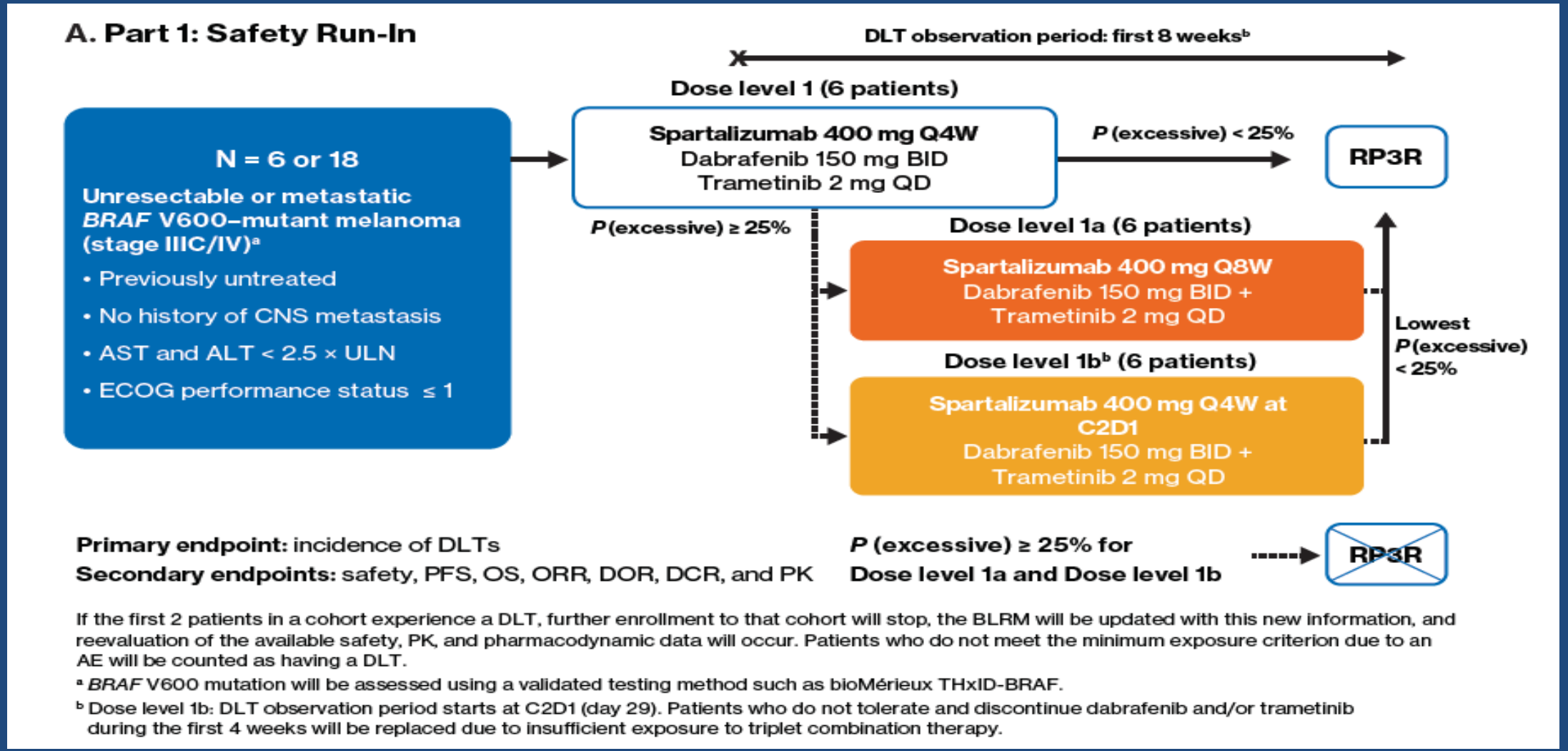
PRESENTED AT ASCO 2019.

Background

- Treatment with targeted therapy has improved outcomes in patients with *BRAF*-mutant, unresectable or metastatic melanoma; however, many patients experience disease progression, and new treatment strategies are needed to further improve their outcomes[1-3]
- It is hypothesized that combining anti–programmed death-1 (PD-1) antibodies with BRAF and MEK inhibitors could delay progression in patients with *BRAF* V600–mutant melanoma[4]
- Spartalizumab binds to an overlapping region of PD-1 with similar binding affinity compared with other anti–PD-1 agents[1-4]
  - In preclinical studies, the combination of an anti–PD-1 receptor monoclonal antibody with dabrafenib (D) + trametinib (T) demonstrated superior antitumor activity compared with D+T[5]
  - In a phase 1/2 study in advanced solid tumors, spartalizumab was well tolerated and showed preliminary anti-tumor activity in melanoma and non-small cell lung carcinoma[5]
  - Spartalizumab + D + T has demonstrated a higher response rate compared with previous trials of D+T alone in patients with *BRAF* V600–mutated unresectable or metastatic melanoma[6-9]
- We report updated analyses for 36 patients enrolled in part 1 (safety run-in cohort) and part 2 (biomarker cohort) of COMBI-i (NCT02967692), a phase 3 study evaluating the safety and efficacy of spartalizumab in combination with the approved doses of D+T in previously untreated *BRAF* V600–mutant unresectable or metastatic melanoma

1. Nathan PD, et al. ASCO 2019 [abstract 9531]; 2. Robert C, et al. AACR 2019 [abstract CT188]; 3. Hodi FS, et al. *Ann Oncol*. 2018;29(suppl 8):viii735; 4. McArthur GA, Ribas A. *J Clin Oncol*. 2013;31:499-506; 5. Hu-Lieskovan S, et al. *Sci Transl Med*. 2015;7:279ra41; 6. Long GV et al. *J Clin Oncol*. 2016; 34:871-878; 7. Dummer, R, et al. *J Clin Oncol*. 2018;36(suppl 5S) [abstract 189]; 8. Dummer R, et al. AACR 2018 [abstract CT182]; 9. Robert C, et al. ESMO 2016 [abstract LBA40].

Study Schemata for COMBI-i (A) Part 1: Safety Run-In, (B) Part 2: Biomarker Cohort, and (C) Part 3: Randomized Phase 3 Portion



If the first 2 patients in a cohort experience a DLT, further enrollment to that cohort will stop, the BLRM will be updated with this new information, and reevaluation of the available safety, PK, and pharmacodynamic data will occur. Patients who do not meet the minimum exposure criterion due to an AE will be counted as having a DLT.

[a] *BRAF* V600 mutation will be assessed using a validated testing method such as bioMérieux THxID-BRAF.

[b] Dose level 1b: DLT observation period starts at C2D1 (day 29). Patients who do not tolerate and discontinue dabrafenib and/or trametinib during the first 4 weeks will be replaced due to insufficient exposure to triplet combination therapy.

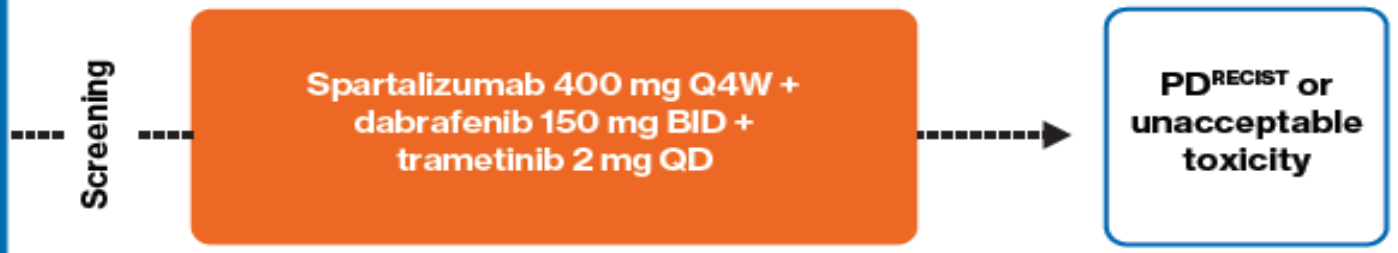
Study Schemata for COMBI-i (A) Part 1: Safety Run-In, (B) Part 2: Biomarker Cohort, and (C) Part 3: Randomized Phase 3 Portion

B. Part 2: Biomarker Cohort

Primary objective: to evaluate changes in PD-L1 levels and CD8+ cells following treatment with spartalizumab 400 mg Q4W in combination with D 150 mg BID and T 2 mg QD

N ≈ 20

- Unresectable or metastatic melanoma
- *BRAF* V600 mutation
- Previously untreated
- No active brain metastasis
- ECOG performance status ≤ 2
- ≥ 2 cutaneous, subcutaneous, or nodal lesions for tumor sample collection



	S	Day 1	2-4 weeks	8-12 weeks	PD
Tumor biopsy (FFPE) for biomarker analysis	×		×	×	×
Blood/plasma for biomarker analyses	×	×	×	×	×

Primary endpoint: change in PD-L1 levels and CD8+ cells upon treatment

Secondary endpoints: safety, PFS, OS, ORR, DOR, DCR, and PK

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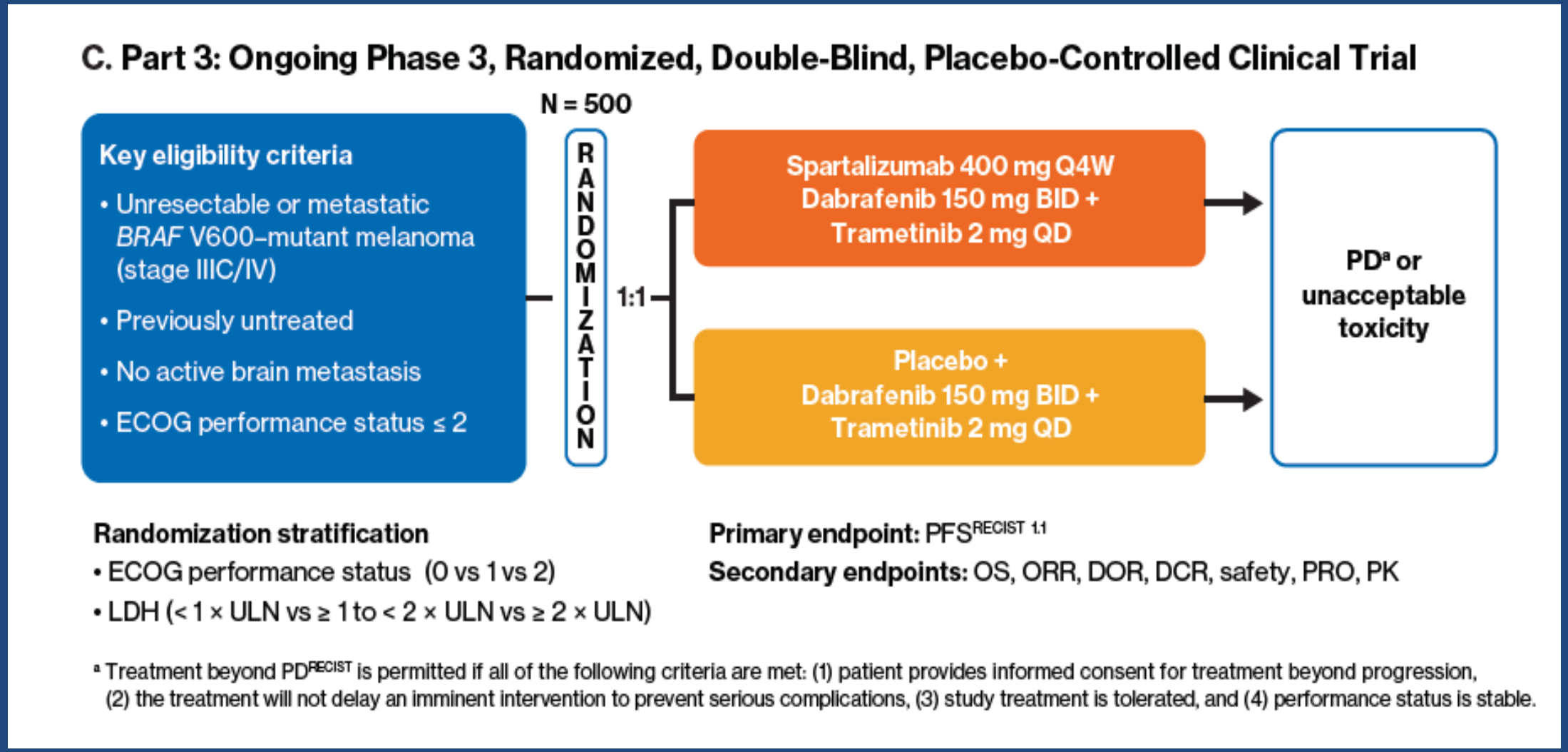
Study Schemata for COMBI-i (A) Part 1: Safety Run-In, (B) Part 2: Biomarker Cohort, and (C) Part 3: Randomized Phase 3 Portion



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Results

Patient Factors and Baseline Disease Characteristics

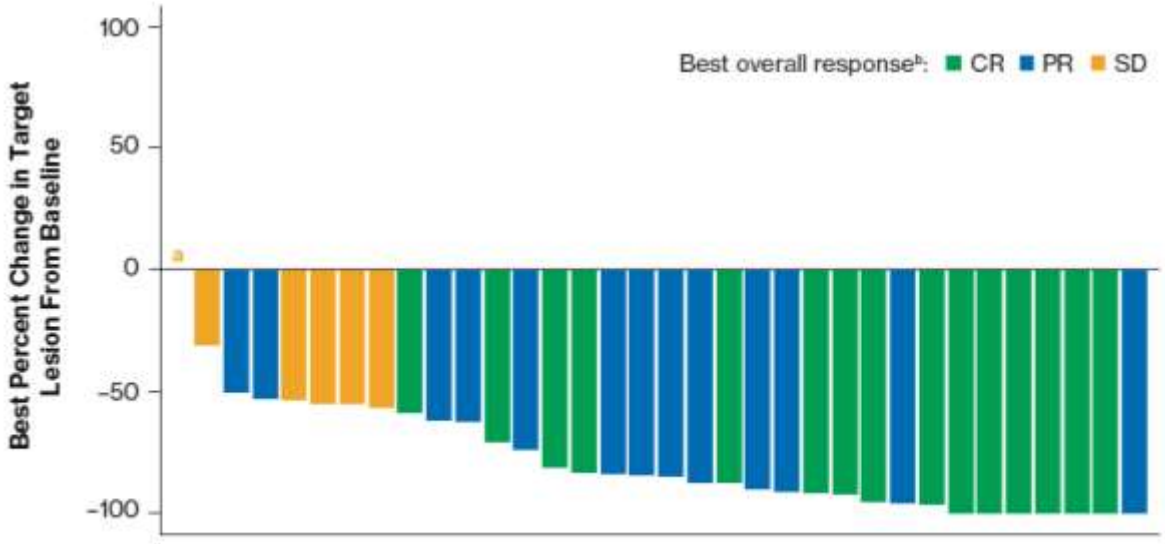
	Part 1 (n = 9)	Part 2 (n = 27)	Part 1 and 2 (N = 36)
Median age (range), years	45 (35-69)	61 (23-76)	55.5 (23-76)
Age < 65 years/≥ 65 years, n (%)	7 (78)/2 (22)	18 (67)/9 (33)	25 (69)/11 (31)
Male/female, n (%)	7 (78)/2 (22)	15 (56)/12 (44)	22 (61)/14 (39)
White, n (%)	9 (100)	24 (89)	33 (92)
ECOG PS, n (%)			
0	7 (78)	18 (67)	25 (69)
1	2 (22)	8 (30)	10 (28)
AJCC 7 stage, n (%)			
IIIC	0	2 (7)	2 (6)
IV M1a	2 (22)	6 (22)	8 (22)
IV M1b	3 (33)	3 (11)	6 (17)
IV M1c with elevated LDH levels	2 (22)	11 (41)	13 (36)
IV M1c with normal LDH levels	2 (22)	5 (19)	7 (19)
LDH levels, n (%)[a]			
LDH < 1 × ULN	6 (67)	13 (48)	19 (53)
LDH ≥ 1 to < 2 × ULN	3 (33)	6 (22)	9 (25)
LDH ≥ 2 × ULN	0	6 (22)	6 (17)
Median sum of diameters (range), mm	42 (10-133)	61 (10-255)	57 (10-255)
No. of organ sites with disease, n (%)			
< 3	4 (44)	12 (44)	16 (44)
≥ 3	5 (56)	15 (56)	20 (56)

AJCC 7, American Joint Committee on Cancer, 7th edition; PS, performance status.
[a] LDH levels from 2 patients were not available.

Results: Efficacy

ORR of 78% by investigator assessment and a complete response rate of 42%. Of the pts with a CR, 20% (3 of 15) had elevated baseline LDH levels, and 40% (6 of 15) had stage IV M1c disease

Patients With Measurable Disease at Baseline	N = 36
Best overall response, n (%)	
CR	15 (42)
PR	13 (36)
SD	6 (17)
PD	1 (3)
Unknown	1 (3)
Confirmed ORR (CR + PR), n (%) [95% CI]	28 (78) [61-90]
DCR (CR + PR + SD), n (%) [95% CI]	34 (94) [81-99]



PR, partial response; SD, stable disease.

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Results: Efficacy

- The Median Duration of Response was 20.7 months with 8 of 28 (29%) responders experiencing subsequent progression
- Median PFS was 23.7 months
  - In patients with elevated baseline LDH, the median PFS was 10.7 months (95% CI, 4.6 months-NE), with events in 10 of 15 (67%) patients
- At the data cutoff, 8 of 36 (22%) patients had died. The median OS was NE
  - The median OS was NE in patients with elevated baseline LDH levels, with events in 7 of 15 (47%) patients

	(N = 36)
DOR, median (95% CI), mo	**20.7 (16.8-NE)**
12-month DOR rate (95% CI), %	80.3 (59-91)
Median in patients with elevated baseline LDH levels (95% CI), mo	NE (3.9-NE)
Median in patients with stage IV M1c disease (95% CI), mo	NE (9.2-NE)
PFS, median (95% CI), mo	**23.7 (12.0-NE)**
12-month PFS rate (95% CI), %	66.7 (49-80)
Median in patients with elevated baseline LDH levels (95% CI), mo	10.7 (4.6-NE)
Median in patients with stage IV M1c disease (95% CI), mo	12.9 (6.6-NE)
OS, median (95% CI), mo	**NE (NE-NE)**
12-month OS rate (95% CI), %	86.1 (70-94)
Median in patients with elevated baseline LDH levels (95% CI), mo	NE (7.0-NE)
Median in patients with stage IV M1c disease (95% CI), mo	NE (11.2-NE)

Results: Safety

- All patients experienced ≥ 1 any-grade AE, and serious AEs occurred in 23 (64%) patients
  - The most common serious AEs were pyrexia in 8 patients and pancreatitis (grade ≥ 3), cellulitis, pneumonia, and decrease in ejection fraction in 2 patients each
- AEs leading to discontinuation of all 3 study drugs occurred in 6 (17%) patients and included increased γ-glutamyltransferase, increased AST or ALT, dermatitis, hyperkalemia, paresthesia, immune-mediated hepatitis, and interstitial lung disease
- Pyrexia was the most common AE and occurred in 32 (89%) patients

Category, n (%)	N = 36	
	Any Grade	Grade ≥ 3
AEs	36 (100)	28 (78)
Treatment-related	36 (100)	26 (72)
Serious AEs	23 (64)	18 (50)
Treatment-related	19 (53)	13 (36)
AEs leading to dose adjustment/interruption	36 (100)	
AEs leading to treatment discontinuation of any study drug	17 (47)	
Spartalizumab + D + T	6 (17)	
Treatment-related deaths[a]	0	

Conclusions

- More than 40% of patients treated with spartalizumab + D + T had a confirmed CR
  - At the time of data cutoff, CRs were ongoing in 67% (10 of 15) of patients
  - Of the patients with a CR, 20% (3 of 15) had elevated baseline LDH levels
- The median PFS was 23.7 months (95% CI, 12.0 months-NE) overall and 10.7 months (95% CI, 4.6 months-NE) in patients with elevated baseline LDH levels
- No new safety signals were observed; AEs were consistent with the individual toxicity profiles of each study drug
- Grade ≥ 3 AEs occurred in 78% of patients, and AEs leading to discontinuation of all 3 study drugs occurred in 6 (17%) patients
- The global, placebo-controlled, randomized part 3 of COMBI-i is ongoing

Tumor Microenvironment, Longitudinal Biomarker Changes, and Clinical Outcome in Patients With Advanced *BRAF* V600-Mutant Melanoma Treated With First-Line Spartalizumab + Dabrafenib + Trametinib

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PRESENTED AT ASCO 2019.

BACKGROUND

- Patients with both low tumor mutational burden (TMB) and low T-cell–inflamed gene expression signature levels in the tumor usually have poor outcomes with anti–PD-1 therapy[1]
- An analysis in the adjuvant melanoma setting suggested that these patients benefited from adjuvant dabrafenib + trametinib therapy[2]
- TMB and T-cell–inflamed gene expression signatures have not been analyzed in patients receiving a combination of anti–PD-1 and BRAF/MEK inhibitors
- We present an analysis of TMB, T-cell–inflamed gene expression signatures, and other biomarkers in patients enrolled in the safety run-in (part 1) and biomarker cohort (part 2,) of the COMBI-i trial; a 3-part phase 3 study investigating the concomitant use of spartalizumab every 4 weeks (Q4W) with dabrafenib and trametinib to treat unresectable or metastatic *BRAF* V600–mutant melanoma (NCT02967692)[3]

1. Cristescu R, et al. *Science.* 2018;362(6411); 2. Long GV, et al. *Ann Oncol.* 2018;29(suppl_8) [LBA 43]; 3. ClinicalTrials.gov. A study of the anti-PD1 antibody PDR001, in combination with dabrafenib and trametinib in advanced melanoma (COMBI-i). https://clinicaltrials.gov/ct2/show/NCT02967692. Accessed April 20, 2019.

METHODS

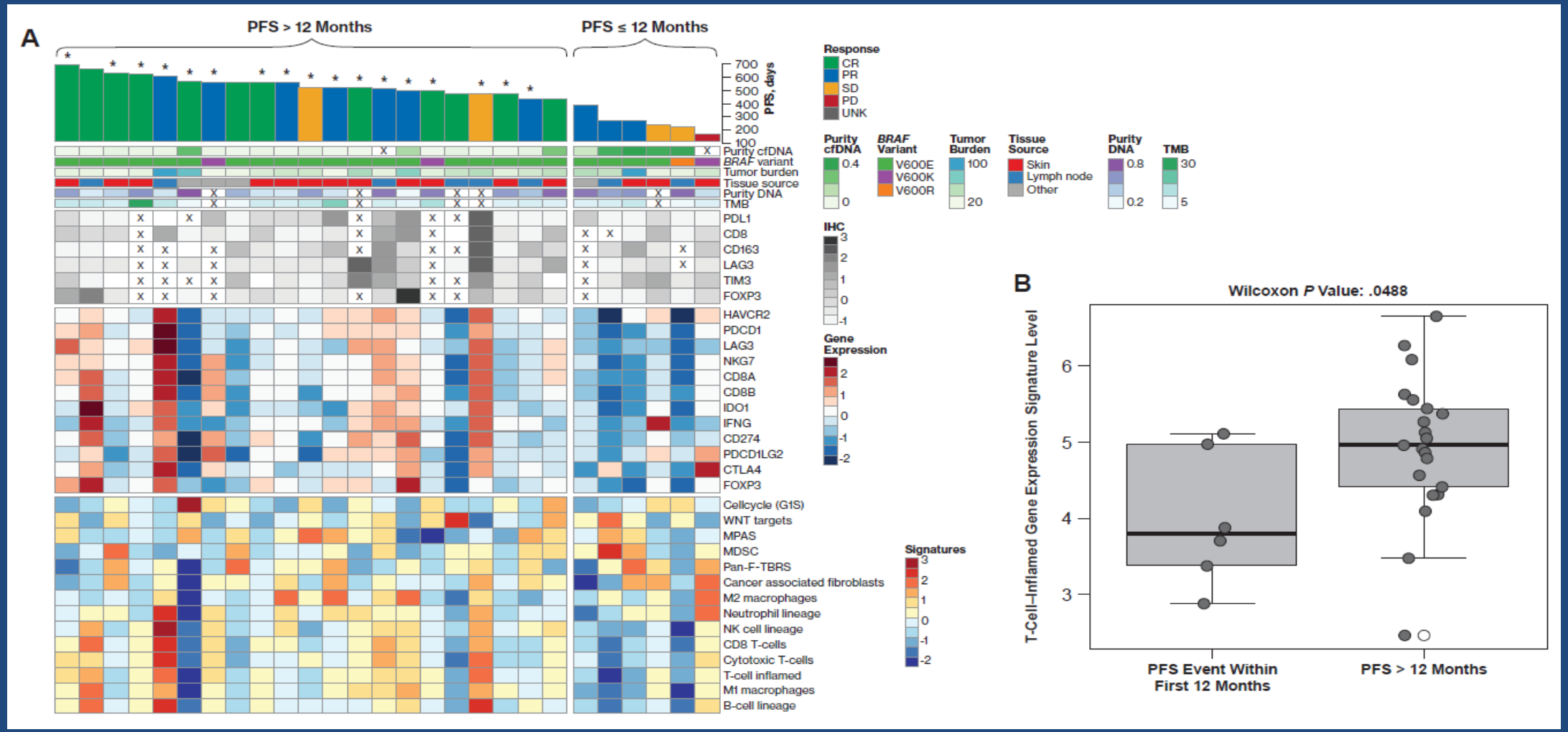
- Blood and tissue samples were collected at baseline, on treatment after 2 to 3 weeks and 8 to 12 weeks, and at disease progression for patients enrolled in part 1 (optional on-treatment/progression sample collection) and part 2 (mandatory on-treatment/progression sample collection)
- Tissue samples were prepared as FFPE slides, and the DNA/RNA was coextracted from each available sample using the AllPrep RNA/DNA extraction from FFPE tissue kit (Qiagen)
- TMB/circulating tumor DNA (ctDNA) and gene expression levels were examined by targeted DNA-seq (≈ 1.5-Mb coding sequence) and RNA-seq, respectively

RESULTS

- Patients with a PFS event prior to 12 months had relatively cold tumors (eg, low T-cell, interferon γ signature levels) compared with patients with a PFS >12 months
- Patients with a PFS event in the first 12 months had significantly lower T-cell–inflamed gene expression signature levels in the tumor
- At the time of the data cut (April 8, 2019) 5 of 22 patients with DNA- and RNA-seq data available had a PFS event within the first 12 months
- At baseline, tumor samples of these patients were characterized by either low TMB, low T-cell inflamed gene expression signature levels (4 of 5) or high levels of immunosuppressive tumor microenvironment (TME) signatures (eg, cancer-associated fibroblast)

Results

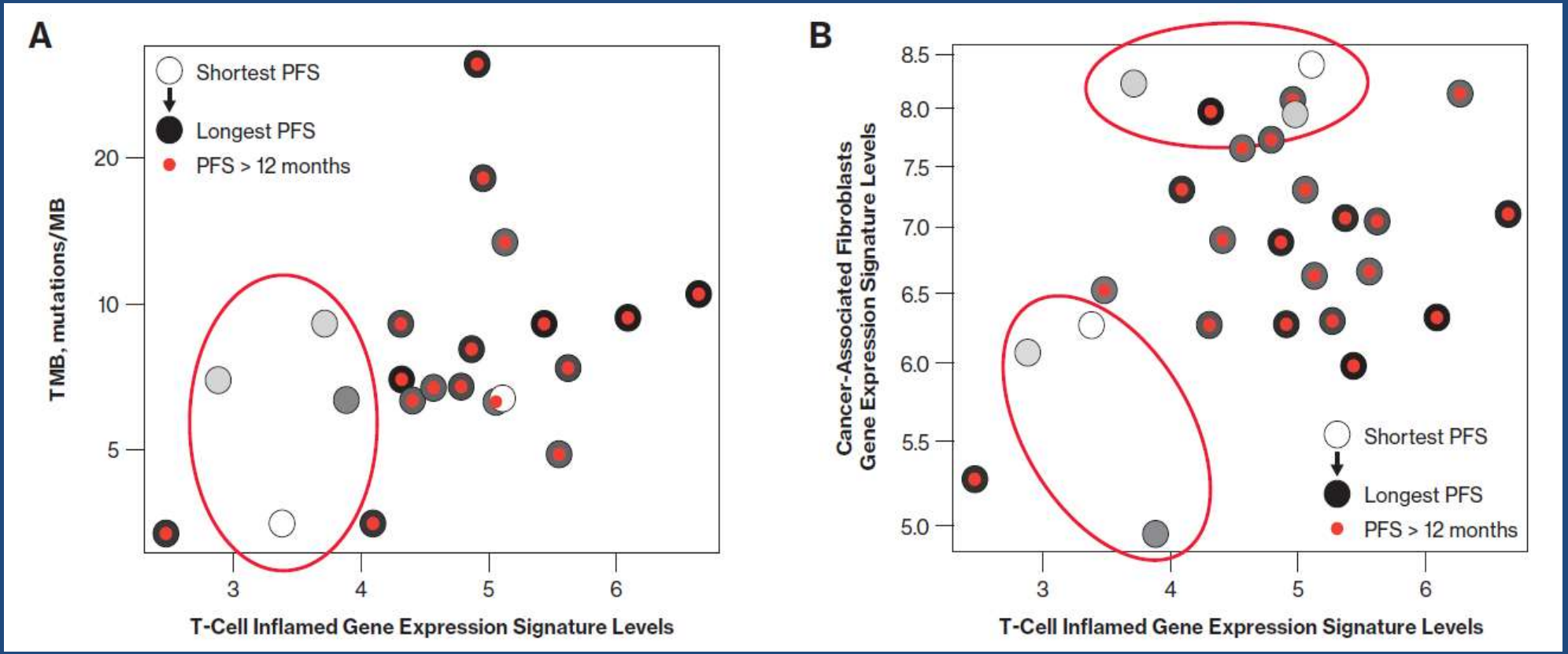
Baseline Biomarker Results (A) and T-Cell–Inflamed Gene Expression Signature (B) By PFS



cfDNA, cell-free DNA; IHC, immunohistochemistry; UNK, unknown.
* Patient was censored for PFS.

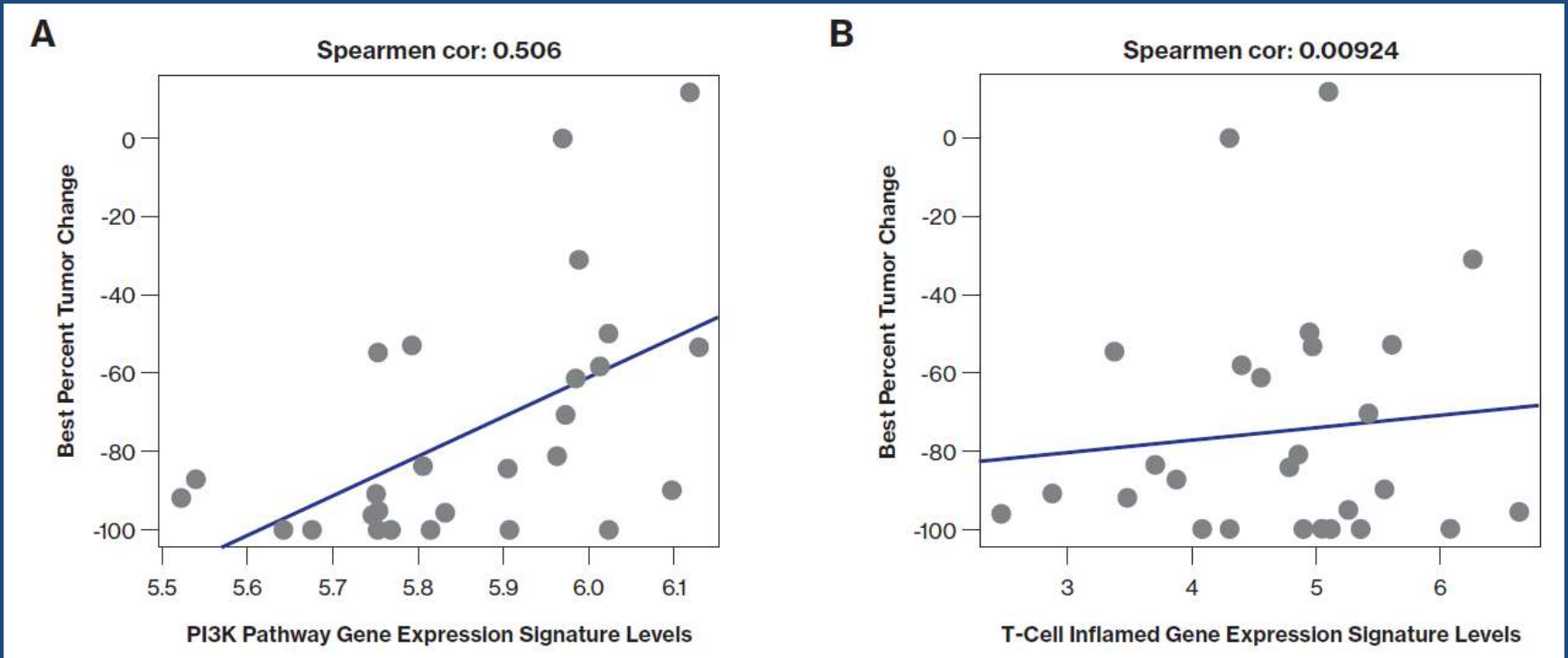
Results

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)



Results

- In an unbiased correlative analysis of gene expression signatures and tumor shrinkage after spartalizumab + dabrafenib and trametinib therapy, phosphoinositide 3-kinase (PI3K) signaling was identified as one of the most activated pathways in tumors with low tumor reduction.
- In contrast, the T-cell–inflamed gene expression signature was not associated with best tumor change, suggesting that a compensatory signaling mechanism to mitogen-activated protein kinase (MAPK) inhibition may be of relevance for early tumor responses.

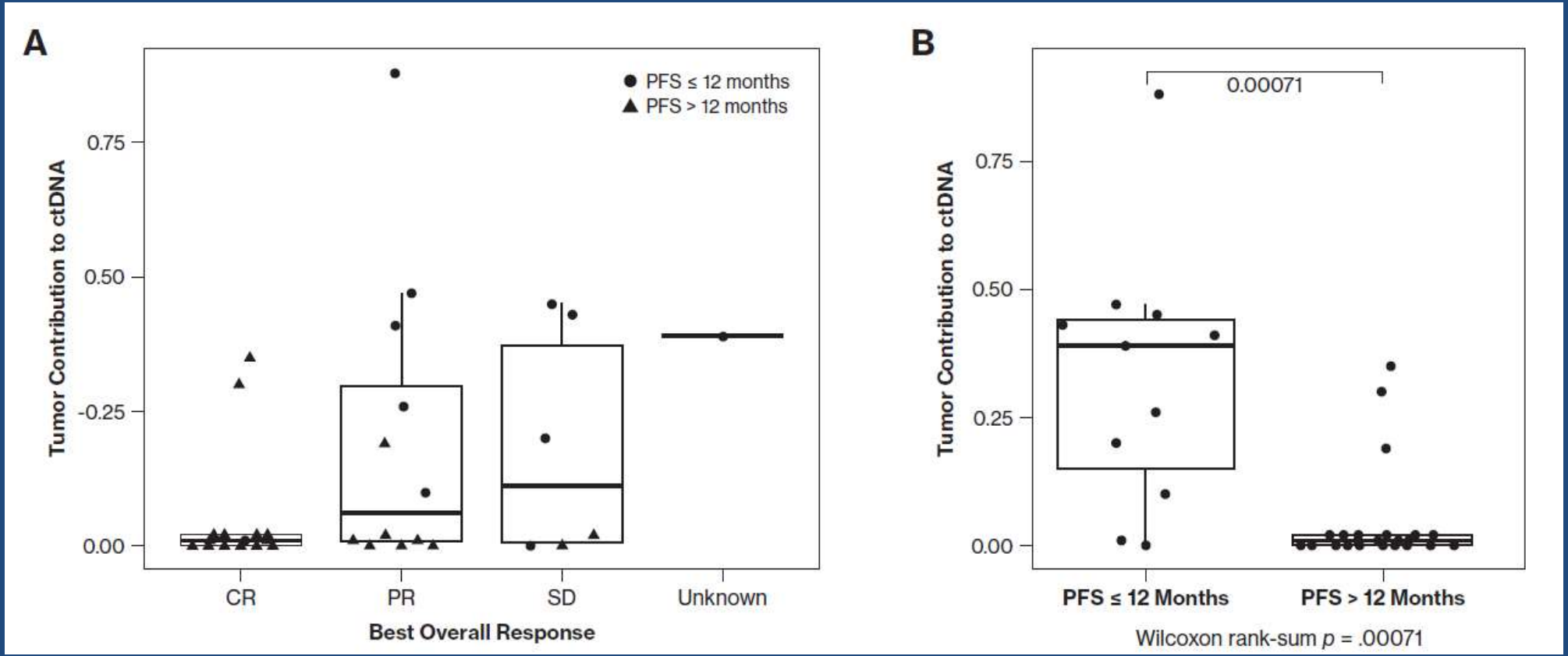


Results

ctDNA Detected Prior to Therapy vs Best Overall Response (A) and PFS (B)

Most patients with a CR had low or no detectable ctDNA at baseline

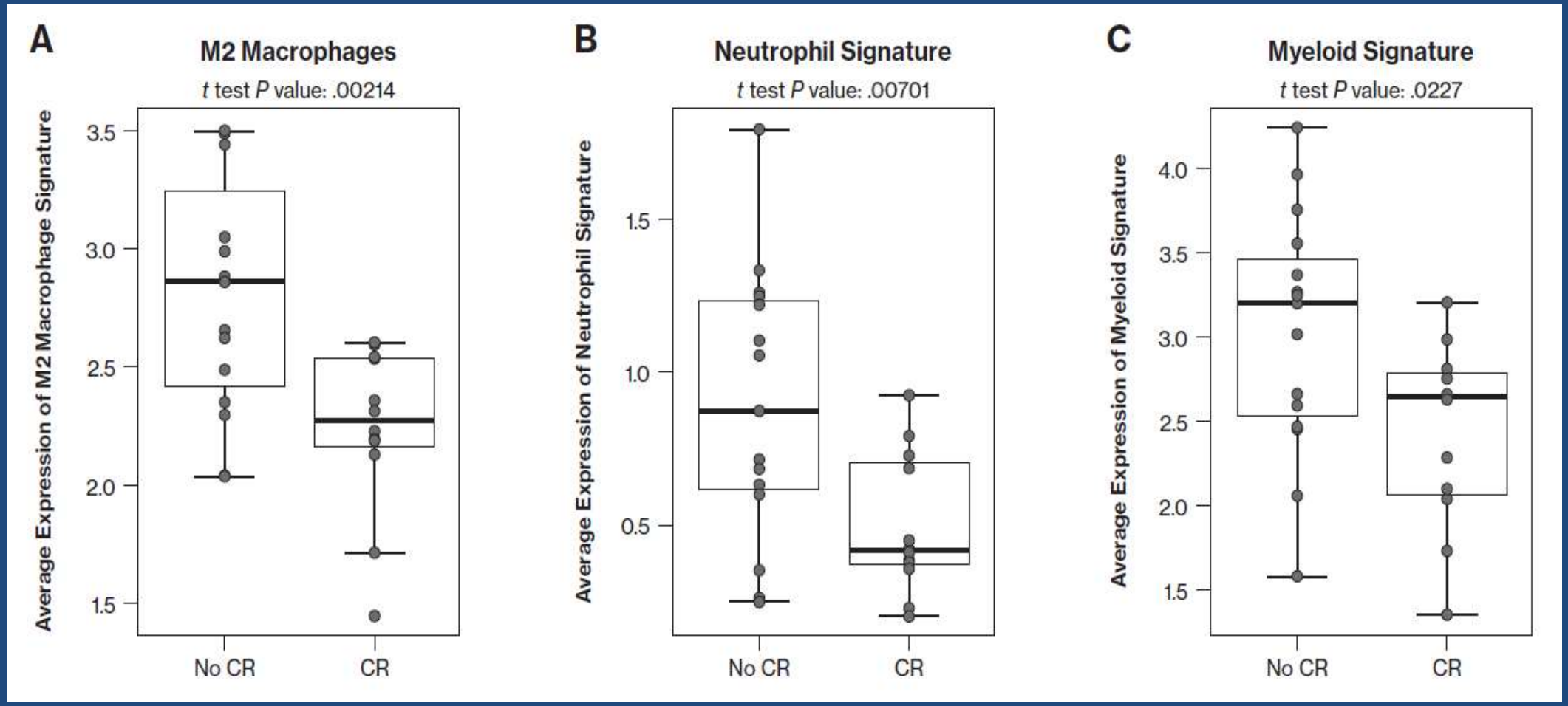
Elevated ctDNA level was significantly associated with PFS events in the first 12 months (*P* <.001)



Results

M2 Macrophages (A), Neutrophils (B), and Myeloid Cells (C)

Patients with a CR while receiving spartalizumab + dabrafenib and trametinib had significantly lower levels of baseline immunosuppressive TME signatures than patients without a CR



Conclusions

- These results suggest that treatment with spartalizumab in combination with dabrafenib and trametinib had an early impact on tumor cells and the TME, potentially promoting antitumor activity
- The majority of PFS events in the first 12 months occurred in patients with low TMB and low T-cell–inflamed gene expression signature levels and/or high levels of immunosuppressive TME factors
- An immunosuppressive TME might preclude early CRs
- The predictive implications of coupling TMB and T-cell–inflamed gene expression signature subgroups with other TME marker subgroups needs further validation
- The randomized placebo-controlled part 3 of COMBI-i is ongoing

Serum IL-6 and CRP Are Prognostic Factors in Melanoma Patients Receiving Single Agent and Combination Checkpoint Inhibition

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Introduction

- The inflammatory biomarker C-reactive protein (CRP) is synthesized predominantly in the liver in response to stimuli, such as interleukin-6 (IL-6), that sustain chronic inflammation[1–3]
- Elevated levels of IL-6 and CRP have been associated with poor prognosis and poor outcome after anti–programmed death-1 (PD-1)/ programmed death ligand 1 (PD-L1) therapy in melanoma and other cancers[1–3]
- In murine models of melanoma and pancreatic cancer, combined treatment with anti–IL-6 and anti–PD-1/PD-L1 antibodies enhances antitumor immune responses and efficacy[3,4]

1. Fang S, et al. *J Clin Oncol* 2015;33:1389–1396; 2. Thomsen M, et al. *Oncotarget* 2016;7:75013–75022; 3. Tsukamoto H, et al. *Cancer Res* 2018;78:5011–5022; 4. Mace TA, et al. *Gut* 2018;67:320–332.

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Objectives

- To evaluate the association of IL-6 and/or CRP levels with clinical outcome in patients with melanoma treated with nivolumab (NIVO) or ipilimumab (IPI) alone and in combination
- Explore the associations of immune response with CRP *in vitro* to elucidate mechanisms that may lead to a poor prognosis

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Analyses Used to Determine the Association of IL-6 and CRP With Clinical Outcomes and Prognosis

- Exploratory, post-hoc analyses of baseline levels of IL-6 and CRP in sera of patients from CheckMate 064, 066, and 067 were conducted (using Luminex® multiplex panels, Thermo Fisher Scientific)
- Associations between IL-6/CRP levels and OS were determined by Kaplan-Meier analysis
  - IL-6/CRP high or low groups were defined based on the median or lower limit of quantification (LLOQ) value for the study population, depending on assay sensitivity and the number of patients with levels at LLOQ
- For patients from CheckMate 064, marker levels were assessed at baseline and at week 13, when the switch in treatment occurred
  - Associations between IL-6/CRP levels and best overall response (BOR) were determined by Student's t-test (two-tailed, $P < 0.05$) or Wilcoxon rank sum test

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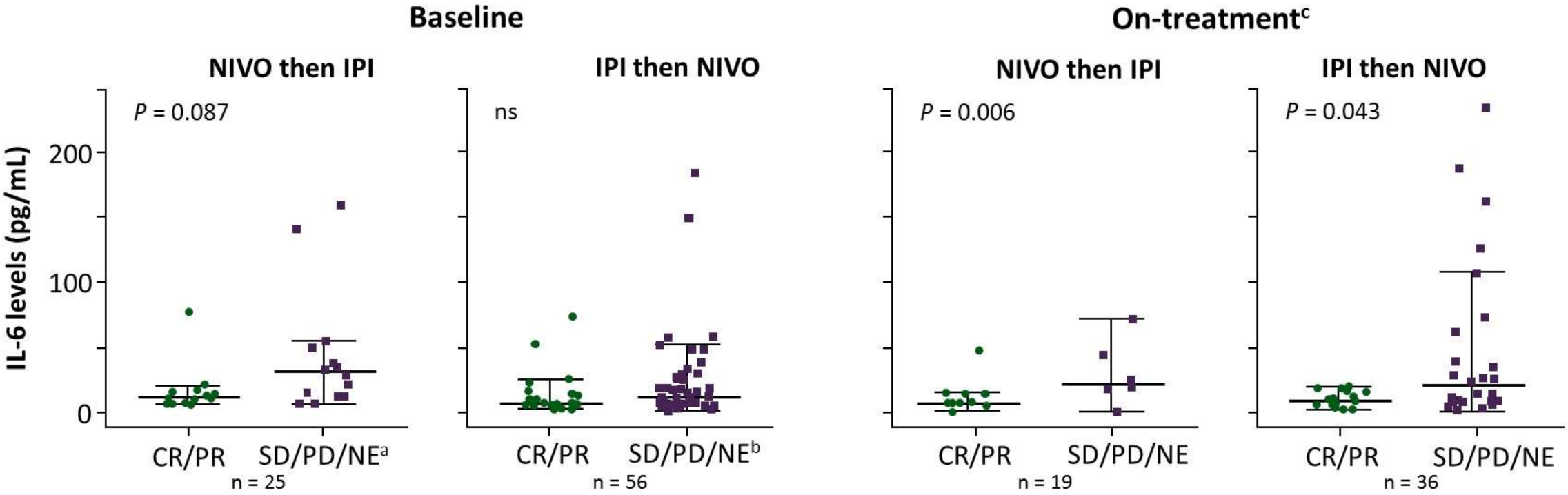
CheckMate 064: Association of Baseline and On-Treatment IL-6 Levels With BOR



Lower baseline and on-treatment IL-6 levels were observed in patients with CR/PR vs SD/PD/NE

Data include non-evaluable (NE) classified as non-responders if OS < 3 months, [a]n = 2, [b]n = 9. [c]On-treatment at week 13; switch in treatment occurred at week 13.
P values based on Wilcoxon rank sum test. CR, complete response; ns, not significant; PD, progressive disease; PR, partial response; SD, stable disease.

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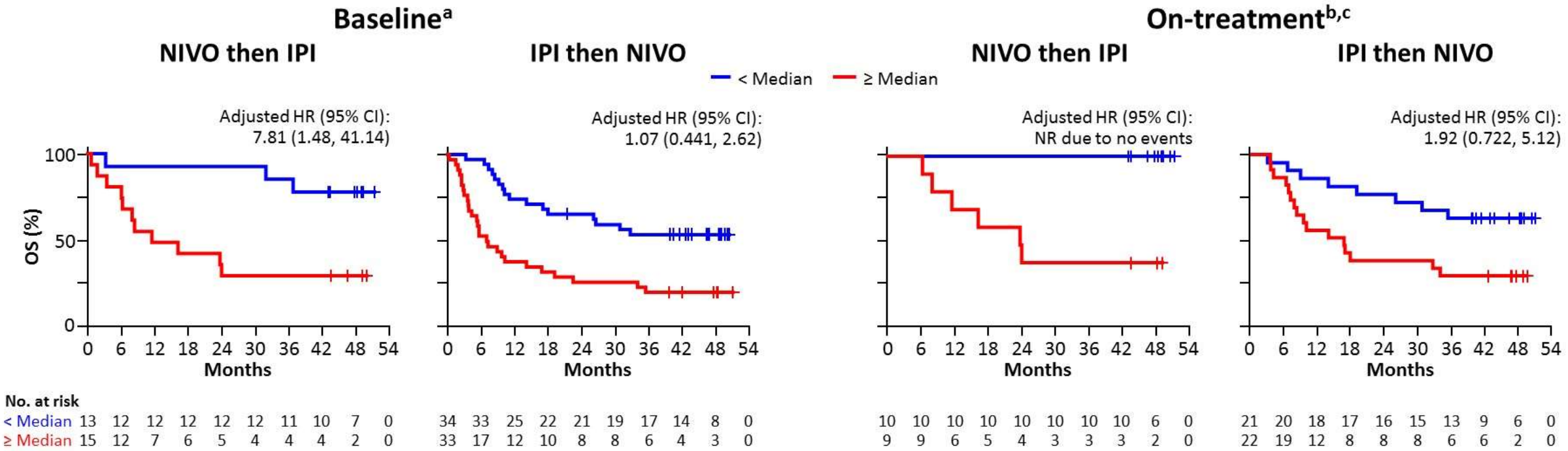
CheckMate 064: Association of Baseline and On-Treatment IL-6 Levels With OS Across Treatment Arms



High baseline and on-treatment IL-6 levels were associated with shorter OS

[a]Median IL-6 at week 0: 13.3 pg/mL; [b]Median IL-6 at week 13: 13.6 pg/mL; [c]On-treatment at week 13; switch in treatment occurred at week 13.
HR adjusted for The Eastern Cooperative Oncology Group performance status (ECOG), *BRAF* status, M stage, and baseline lactate dehydrogenase (LDH). NR, not relevant.

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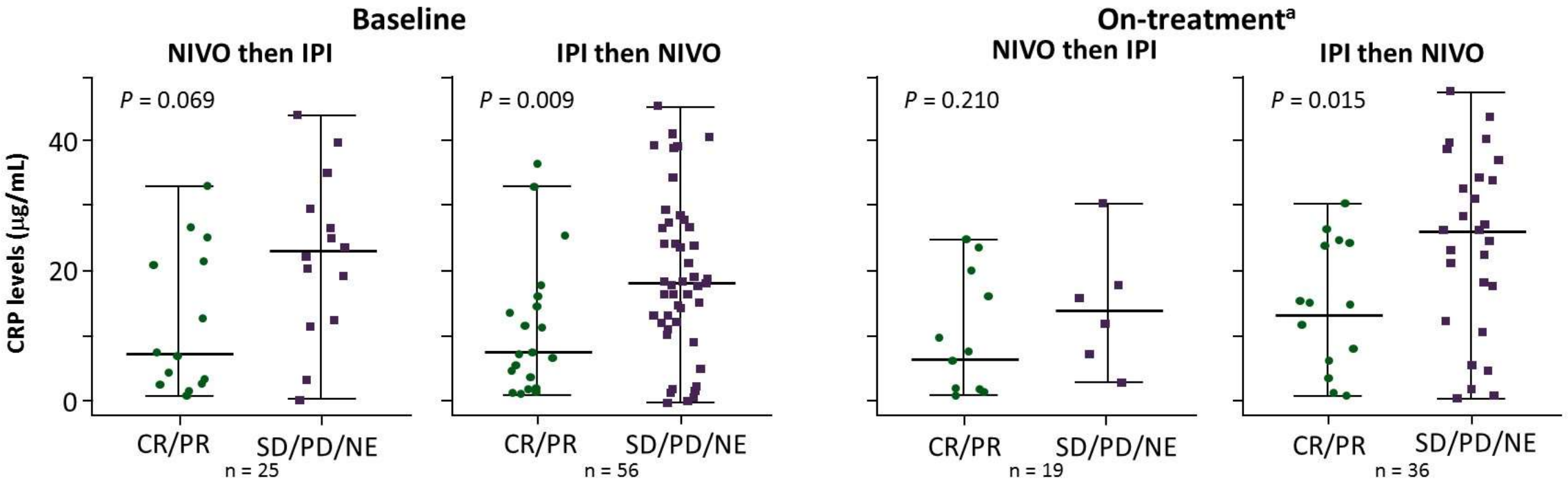
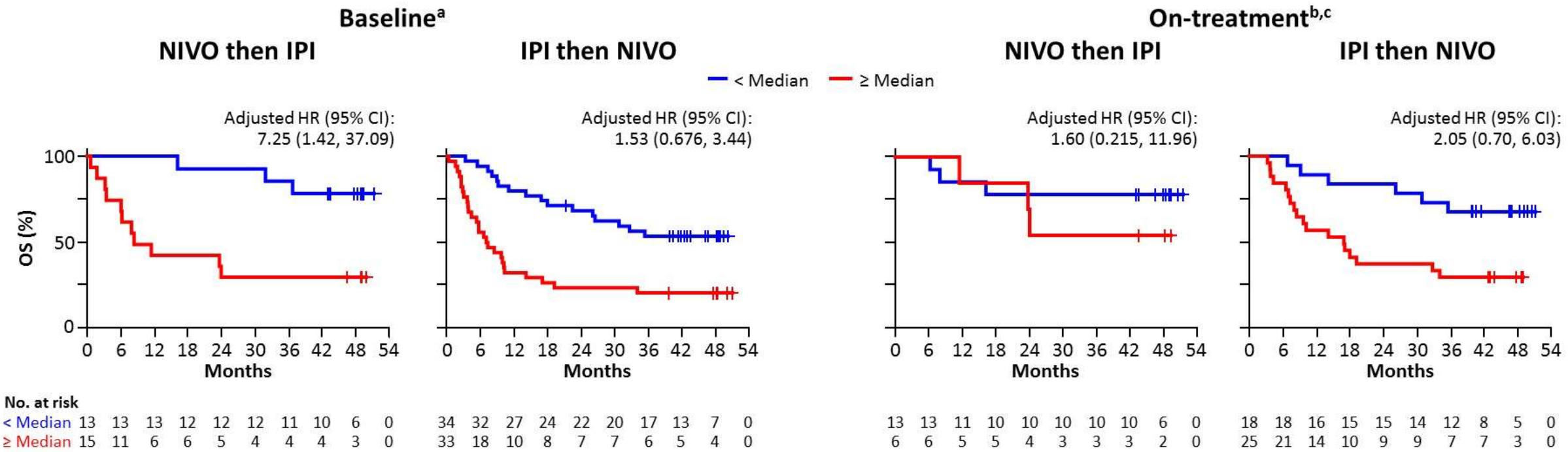
CheckMate 064: Association of Baseline and On-Treatment CRP Levels With BOR



Lower baseline and on-treatment CRP levels were observed in patients with CR/PR vs SD/PD/NE

Data include non-evaluable (NE) classified as non-responders if OS < 3 months. [a]On-treatment at week 13; switch in treatment occurred at week 13. *P* values based on Wilcoxon rank sum test.

CheckMate 064: Association of Baseline and On-Treatment CRP Levels With OS



High baseline and on-treatment CRP levels were associated with shorter OS

[a]Median CRP at week 0: 17.0 µg/mL; [b]Median CRP at week 13: 15.8 µg/mL; [c]On-treatment at week 13; switch in treatment occurred at week 13.
HR adjusted for ECOG, *BRAF*, M stage, and baseline LDH.

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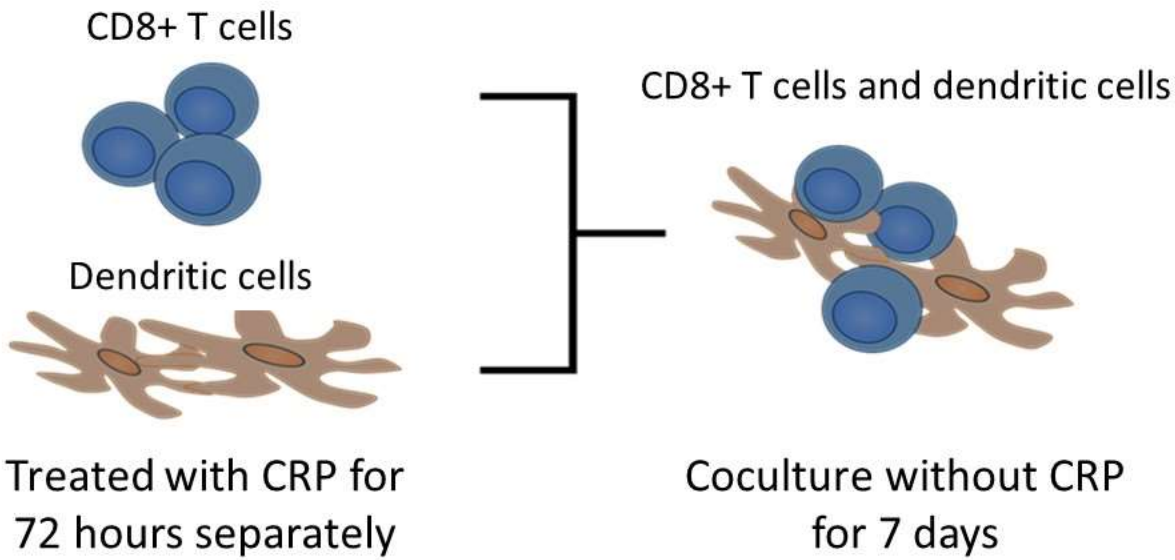
In Vitro Studies to Examine Impact of Exogenous CRP on T-Cell Function

To examine the immune effects and mechanisms by which CRP might inhibit immunity, the impact of purified endotoxin/azide-free CRP was tested *in vitro* using human T cells generated against melanoma antigens



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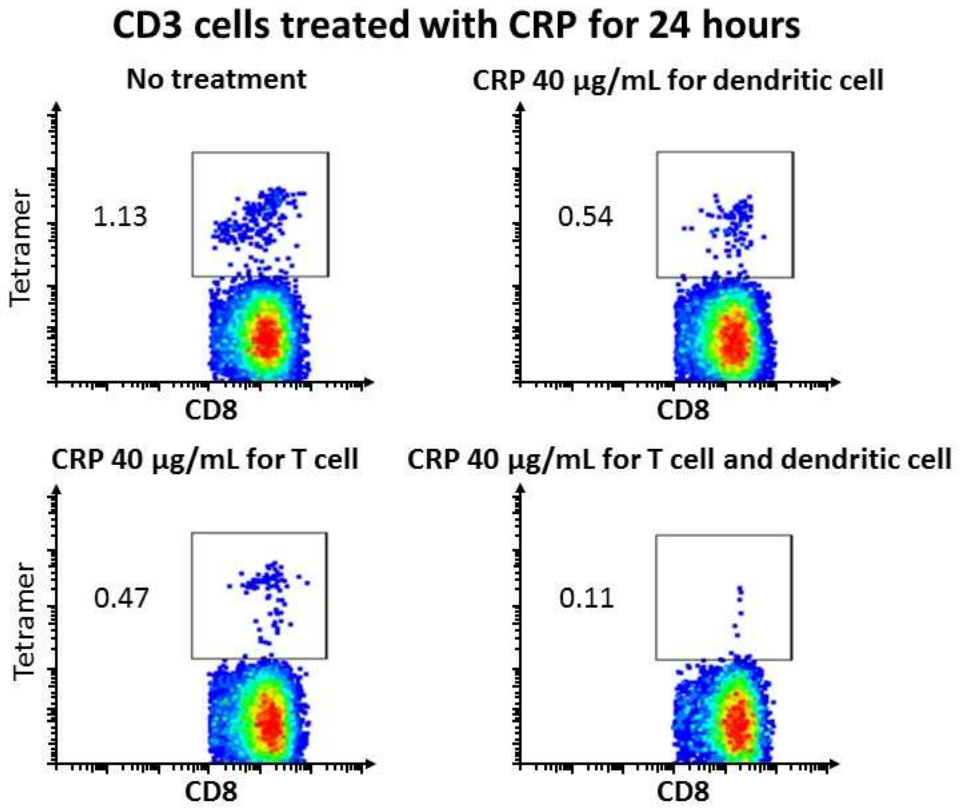
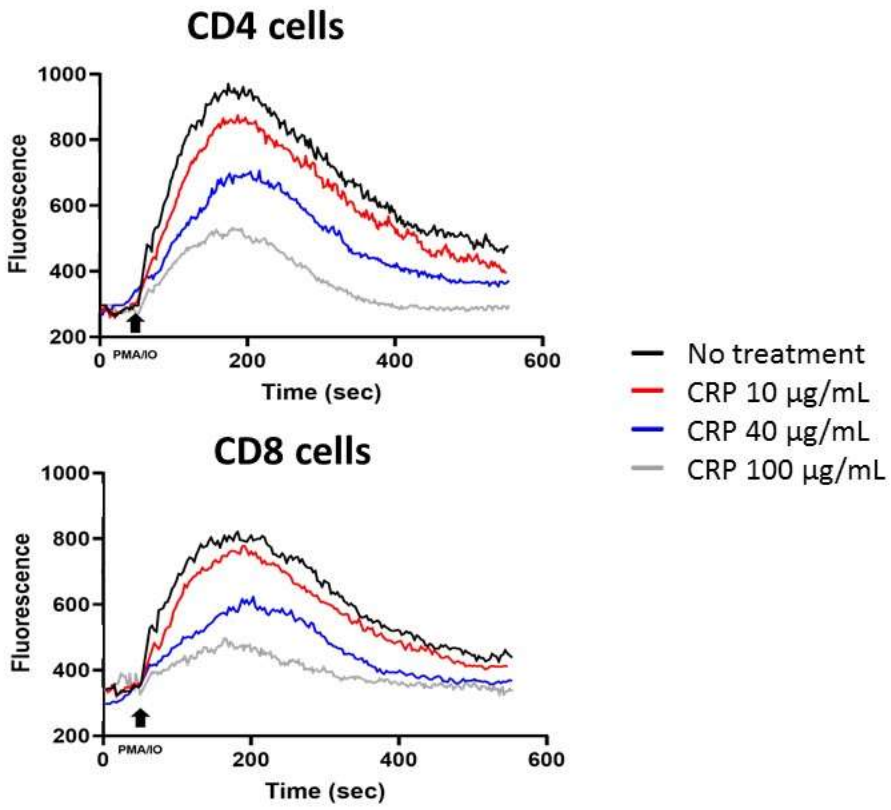
T-Cell Function After Exposure to CRP





CRP suppressed T-cell and dendritic-cell function, decreased generation of antigen-specific T cells, and inhibited calcium influx in T cells

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Conclusions

- High levels of IL-6 and/or CRP were associated with shorter OS in patients treated with NIVO, NIVO+IPI, IPI, or dacarbazine
  - High CRP levels dampened antitumor immune responses *in vitro*
- IL-6 and CRP may be prognostic factors for immune checkpoint inhibitor therapies in patients with melanoma
  - In multivariate analyses (including LDH, ECOG performance status, and M stage) from CheckMate 066 and 067, IL-6 appeared to be a potent prognostic factor
- Blockade of IL-6 and CRP synthesis and/or activity in combination with immune checkpoint therapies may enhance responses and survival rates in patients with different malignancies, including melanoma

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GRAZIE PER L'ATTENZIONE
…APPUNTAMENTO AD ESMO 2019