Instituto Nacional de Oncología y Radiobiología

1er Taller Anual Sobre Manejo del Melanoma

Melanoma: racional para las combinaciones de terapia dirigida e inmunoterapia. Nuevos ensayos en curso

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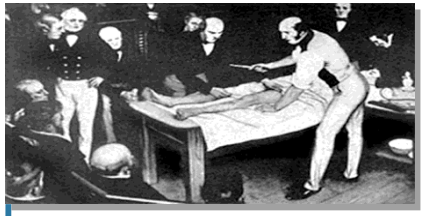
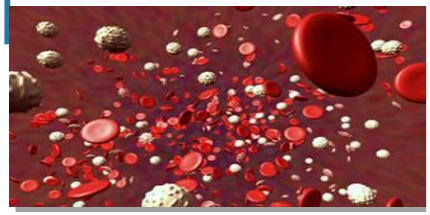


Surgery
1846

Chemotherapy
1946

Radiation Therapy
1901

Immunotherapy
Interferon-α 1995[a]
Interleukin-2 1998[a]



[a]Date of first approval in the United States or European Union. IPI, ipilimumab; NIVO, nivolumab.

1. DeVita VT Jr, et al. *Cancer Res*. 2008;68:8643-8653. 2. American Cancer Society. The history of cancer. http://www.cancer.org/cancer/cancerbasics/thehistoryofca[illegible]. 4. Mansh M. *Yale J Biol Med*. 2011;84:381-389. 5. Kirkwood JM, et al. *CA Cancer J Clin.* 2012;62:309-335. 6. NCI Cancer Drug Information. Vemurafenib. http://www.cancer.gov/cancertopics/druginfo/vemurafenib. 7. NCI Cancer Drug Information. Dabrafenib. http://www.cancer.gov/cancertopics/druginfo/dabrafenib. 8. NCI Cancer Drug Information. Trametinib. http://www.cancer.gov/cancertopics/druginfo/trametinib. 9. FDA Press Release. December 22, 2014 http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm427807.htm accessed 9 March, 2015. 10. FDA. Approved drugs: pembrolizumab. September 4, 2014. http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm412861.htm; 11. ASCO press release 10 Jan, 2014. 12. BMS Press Release 1 October, 2015.

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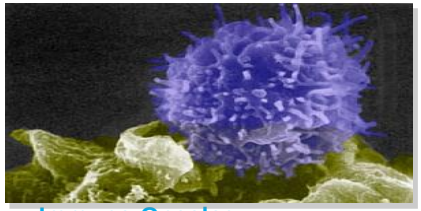
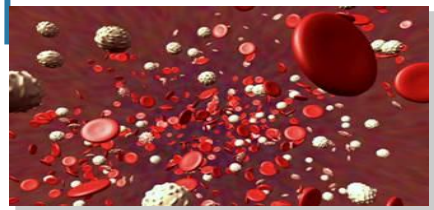


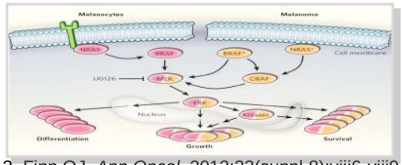
Immuno-Oncology
Ipilimumab 2011[a]
Nivolumab 2014[a]
Pembrolizumab 2014[a]
Nivolumab+ Ipilimumab 2015[a]

Radiation Therapy
1901

Immunotherapy
Interferon-α 1995[a]
Interleukin-2 1998[a]



Targeted Therapy
Vemurafenib 2011[a]
Trametinib 2013[a]
Dabrafenib 2013[a]
Dabrafenib + trametinib 2014[a]
Vemurafenib + Cobimetinib 2015
Encorafenib + Binimetinib 2018



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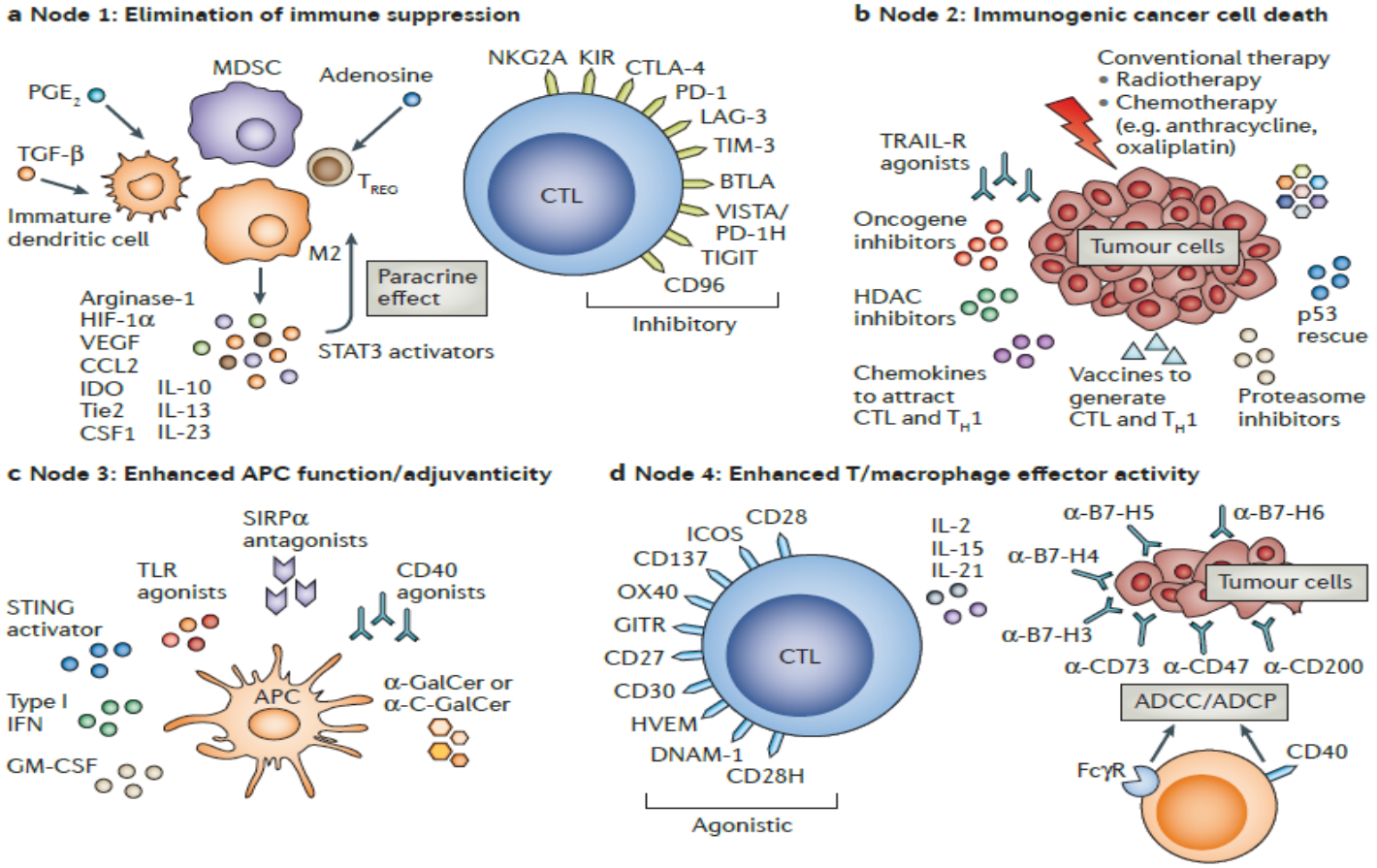

Estrategias para inducir inmunogenicidad

Smyth Nature Rev November 2015

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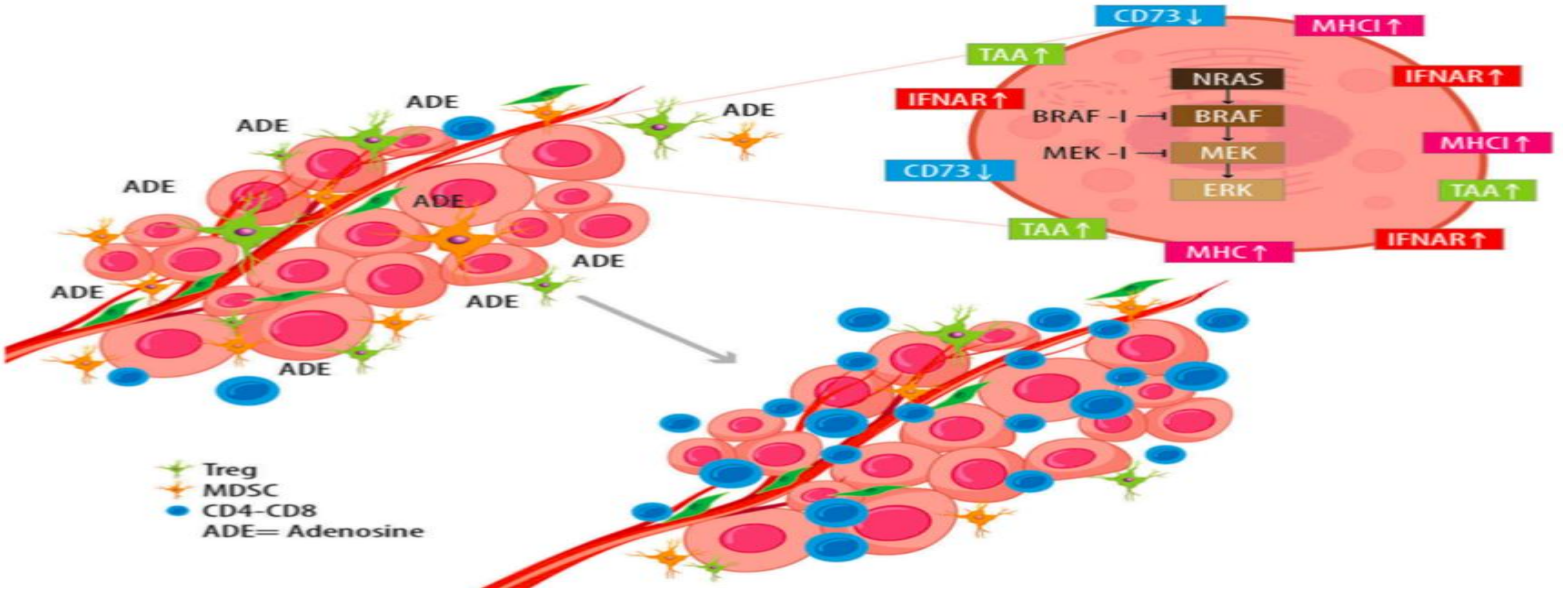
1er Taller Anual Sobre Manejo del Melanoma

Immunological effects of BRAF+MEK inhibition

Paolo A. Ascierto [a] and Reinhard Dummer[b]

[a]Unit of Melanoma, Cancer Immunotherapy and Development Therapeutics, Istituto Nazionale Tumori – IRCCS Fondazione "G. Pascale", Napoli, Italy; [b]Department of Dermatology, University Hospital Zürich Skin Cancer Center, Zürich, Switzerland



Ascierto OncoImmunology 2018

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1er Taller Anual Sobre Manejo del Melanoma

Immunomodulatory effects of BRAF and MEK inhibitors: Implications for Melanoma therapy

Marvin Kuske[a,d,e,1], Dana Westphal[a,b,d,1], Rebekka Wehner[c,d], Marc Schmitz[c,d], Stefan Beissert[a,d,e], Christian Praetorius[a,b,2], Friedegund Meier[a,d,e,2,*]

Immunological effects of BRAFi and MEKi.

effects			BRAFi BRAF-mutant	MEKi BRAF wild-type	BRAFi + MEKi BRAF-mutant
microenvironment	*in vitro*	immune stimulatory molecules and cytokines	↑ restoration of IL-12 and TNFα production of DCs [30]; ↑ i.a. CD40, CD70, CD83 [22]		↑ [22]
		immunosuppressive cytokines	↓ IL-1 A, IL-8 [22]; ↓ IL-6, IL-10 [30]		↓ [22]; ↓ GRO, IL-8 [36]
	in vivo	immunosuppressive cytokines	↓ [37]		↓ [37]
		Tregs and MDSCs	↓ [26,40,41]	↓ MDSC by ↓ differentiation MDSCs and ↓ osteopontin [42]	
		immune stimulatory molecules and cytokines and regulatory chemokine	↑ CD40 L, ↑ IFNγ [26]; ↓ CCL2 [39]		
		maturation of APCs	↑ [26], restoration of (IL-12 and TNFα) and surface marker expression (CD80, CD83, and CD86) in DCs [29]		
tumor infiltration of immune cells	*in vitro*	VEGF expression	↓ [30,36]	↓ VEGF [36]	↓ [36]
	in vivo	tumor T cell infiltrate	↑ [37,44,45,46,49]	↑ tumor-infiltrating $CD8^+$ T cells as a result of protection from death caused by chronic TCR stimulation [24]	↑ [37]
		VEGF expression	↓ [44]		
		NK cells	↑ [39]		
better recognition of melanoma cells	*in vitro*	melanoma antigen expression	↑ [21,37]	↑ [21,22]	
		expression of HLA I and/or HLA II	↑ [22,32]	↑ [22,48]	↑ [22]
	in vivo	melanoma antigen expression	↑ [37]		↑ [37]
improved activity of immune effector cells	*in vitro*	reactivity of T lymphocytes	↑ (measured by IFNγ release) [21,26]		
	in vivo	T cell cytotoxicity	↑ (perforin, granzyme B) [37]		↑ (perforin, granzyme B) [37]

Kuske Pharm Res 2018

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Immunomodulatory effects of BRAF and MEK inhibitors: Implications for Melanoma therapy

Marvin Kuske[a,d,e,1], Dana Westphal[a,b,d,1], Rebekka Wehner[c,d], Marc Schmitz[c,d], Stefan Beissert[a,d,e], Christian Praetorius[a,b,2], Friedegund Meier[a,d,e,2,*]

Synergistic effects of combining MAPK inhibitors with immune checkpoint inhibitors (preclinical data).

effect on		BRAFi +/- MEKi + Checkpoint-I BRAF-mutant	MEKi + Checkpoint-I BRAF wild-type
tumor regression (Superior to single agents)		yes [19,50]	yes [22]
microenvironment	immunosuppressive cytokines		↓ [22]
tumor infiltration of T cells	tumor T cell infiltrate	↑ [19,49]	↑ [22]
better recognition of melanoma cells	melanoma antigen expression	↑ [19]	
	HLA class II		↑ [22]
improved activity of effector T cells	T cell cytotoxicity	↑ [19]	
	reactivity of T lymphocytes	↑ production of granzyme B, IFNγ and TNFα [49]	

Kuske Pharm Res 2018

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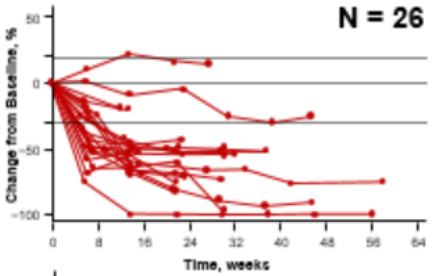
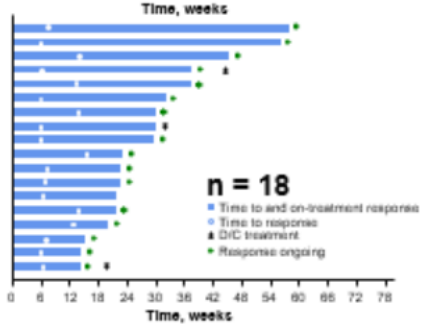
P3: 1804057580

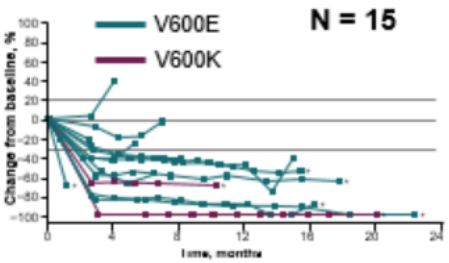
Clinical Trials Combining BRAFi + MEKi + Anti–PD-1/L1

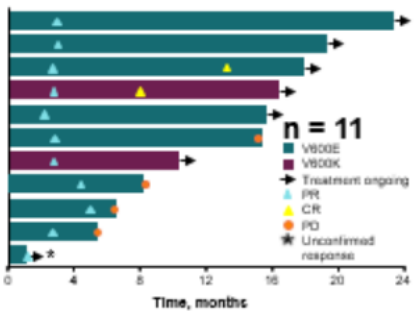
Dabrafenib + Trametinib + Durvalumab[1]



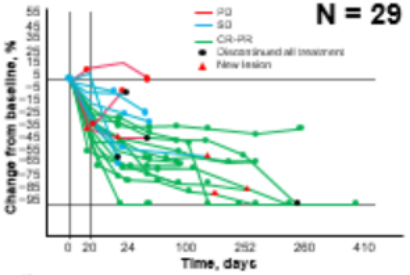


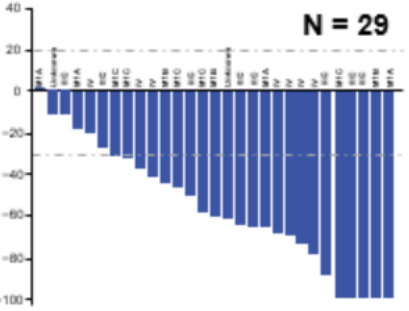
Dabrafenib + Trametinib + Pembrolizumab[2,3]



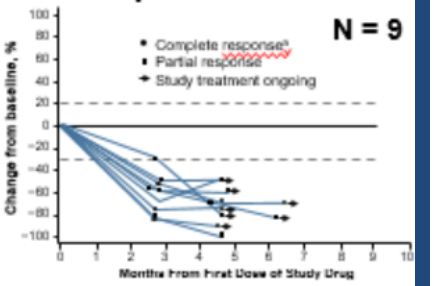


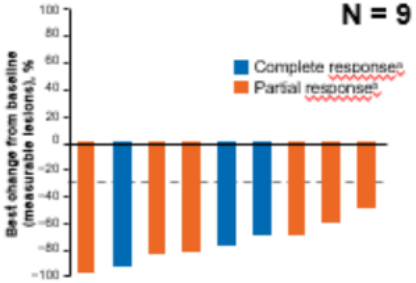
Vemurafenib + Cobimetinib + Atezolizumab[4]





Dabrafenib + Trametinib + Spartalizumab[5]





BRAFi, BRAF inhibitor; CR, complete response; D/C, discontinued; MEKi, MEK inhibitor; PD, progressive disease; PR, partial response; SD, stable disease; SLD, sum of lesion diameters. [a] Patients with CR and < 100% change in sum of diameters (SOD) have (a) 100% change in non-nodal target lesions and all nodal target lesions are < 10 mm and (b) CR for nontarget lesions. [b] Patients with PR and 100% change in SOD have (a) 100% change in all target lesions and (b) non-CR/non-PD response for nontarget lesions.

1. Ribas A, et al. *J Clin Oncol*. 2015; 33(suppl) [abstract 3003]; 2. Ribas A, et al. *J Clin Oncol*. 2016; 34(suppl) [abstract 3014]; 3. Ribas A, et al. *Ann Oncol*. 2017; 28(suppl 5) [abstract 1216O]; 4. Hwu P, et al. *Ann Oncol*. 2016; 27(suppl 6) [abstract 1109PD]; 5. Dummer, R, et al. *J Clin Oncol*. 2018;36(suppl 5S) [abstract 189].

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P3: 1804057580

The Anti–PD-1 Antibody Spartalizumab (PDR001) in Combination With Dabrafenib and Trametinib in Previously Untreated Patients With Advanced BRAF V600–Mutant Melanoma: First Efficacy, Safety, and Biomarker Findings From the Part 2 Biomarker Cohort of COMBI-i (NCT02967692)

Reinhard Dummer, Dirk Schadendorf, Paul Nathan, Hussein Tawbi, Caroline Robert, Paolo A. Ascierto, Antoni Ribas, Celeste Lebbé, Mario Mandala, Naoya Yamazaki, Erika Richtig, Wilson H. Miller Jr, Eduard Gasal, Mathilde Kaper, Jan C. Brase,
Bijoyesh Mookerjee, Georgina V. Long

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P3: 1804057580

COMBI-i Part 2: Biomarker Cohort

N ~ 20

- Unresectable or metastatic melanoma
- *BRAF* V600 mutation
- Previously untreated
- No active brain metastasis
- ECOG PS ≤ 2
- A total of ≥ 2 cutaneous or subcutaneous lesions or nodal lesions for tumor sample collection

Screening → **Spartalizumab (PDR001) 400 mg Q4W + dabrafenib 150 mg BID + trametinib 2 mg QD** → PD^{RECIST} or unacceptable toxicity

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

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

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

BID, twice daily; CD, cluster of differentiation; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FFPE, formalin-fixed, paraffin-embedded; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; S, screening.

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Sample Assays

- **Tissue:**
  - Immunohistochemistry: CD8, PD-L1 (Dako 28-8), LAG-3, TIM-3, CD163, FOXP3
    - PD-L1 assessed using MEL score (membrane staining in tumor and tumor-associated immune cells); MEL score ≥ 2 = PD-L1+
- **PBMC + plasma:**
  - Flow cytometry
    - Myeloid-derived suppressor cell (MDSC) panel
  - Plasma cytokine profiling
    - 45-marker Meso Scale Discovery (MSD) immunoassay panel

FOXP3, forkhead box protein P3; LAG-3; lymphocyte activation gene 3 protein; PBMC, peripheral blood mononuclear cells.

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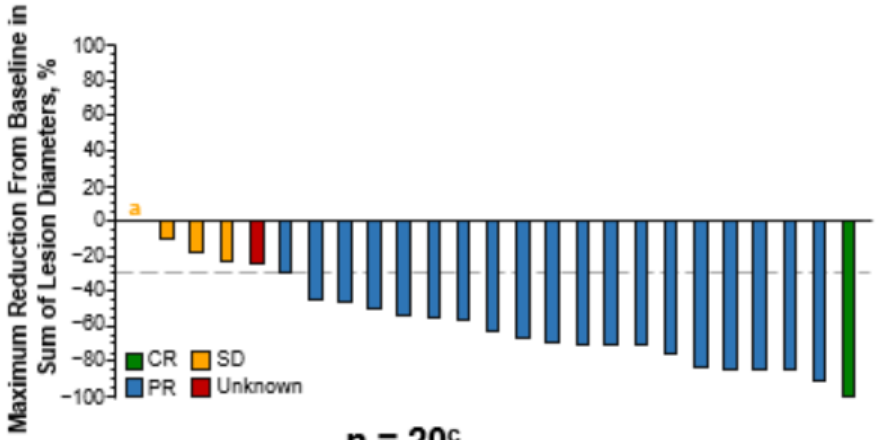
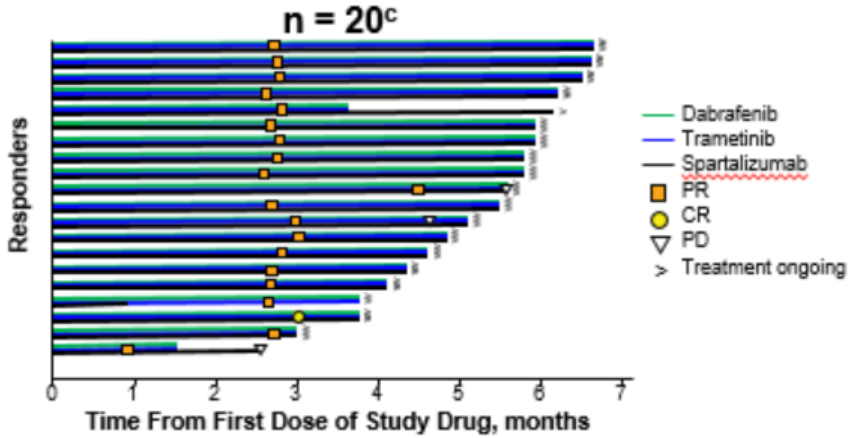
RECIST v1.1 Best Response (unconfirmed)





Evaluable for Analysis	N = 25[b]
Best response, n (%)	
CR	1 (4)
PR	19 (76)
SD	4 (16)
Unknown	1 (4)
PD	0
Overall response rate, %	**80**
95% CI	59-93

- At data cutoff, 14 patients had ≥ 2 post-baseline assessments (10 patients with confirmed response)

Dashed line at −30% represents cutoff for response per RECIST v1.1. [a] Patient had best change from baseline of 0%. [b] 2 patients without ≥ 1 postbaseline assessment were excluded from this analysis. [c] Includes patients with unconfirmed PR or CR.

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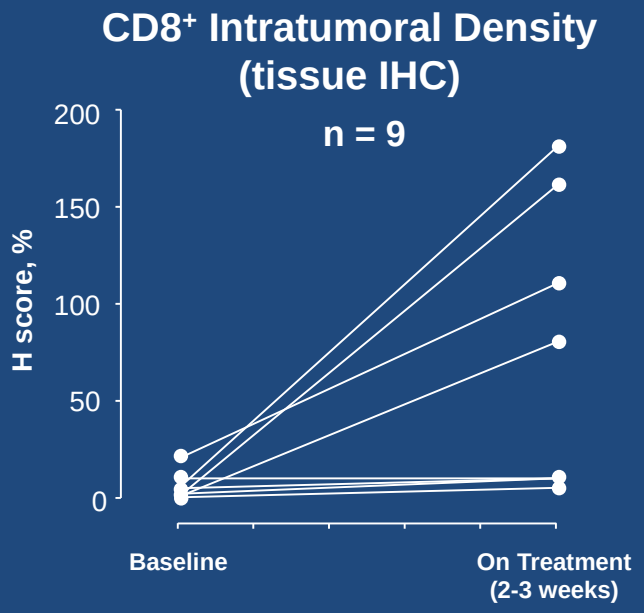
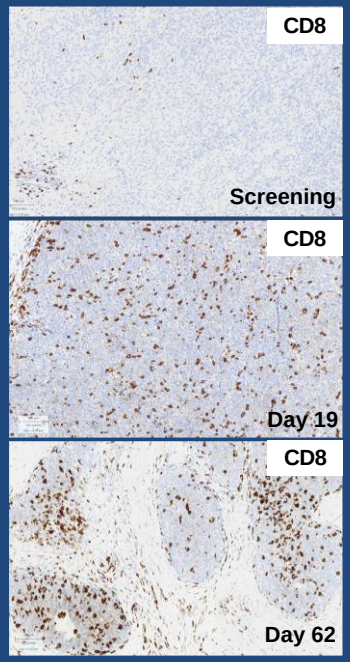
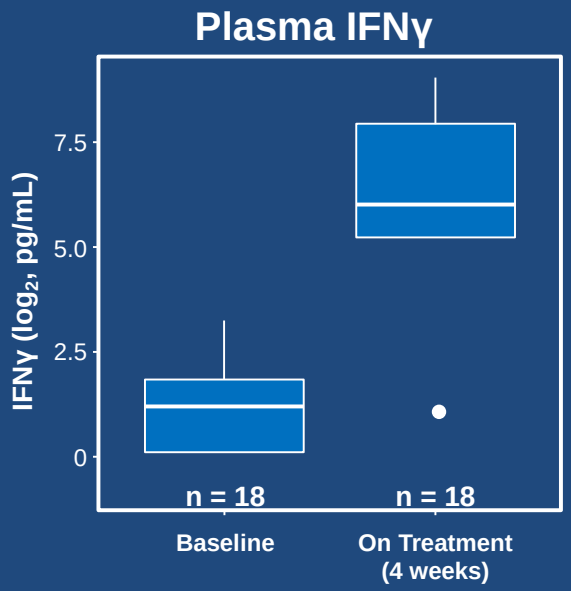
Evidence of Immune Activation After Treatment







- Increase in intratumoral CD8+ cells based on exploratory H-score analysis
- All patients showed elevated IFNγ levels in plasma upon treatment

IFNγ, interferon-gamma; IHC, immunohistochemistry.

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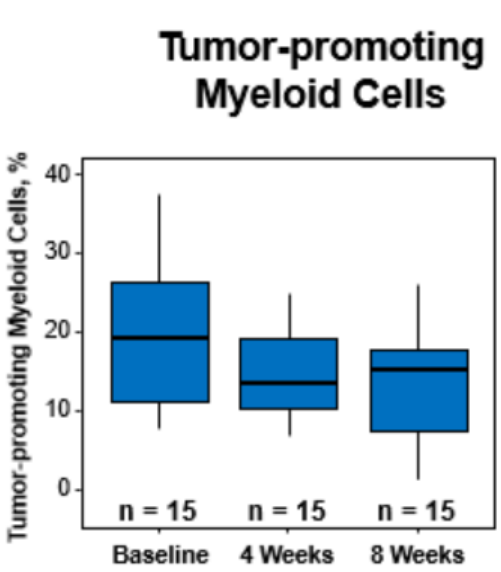
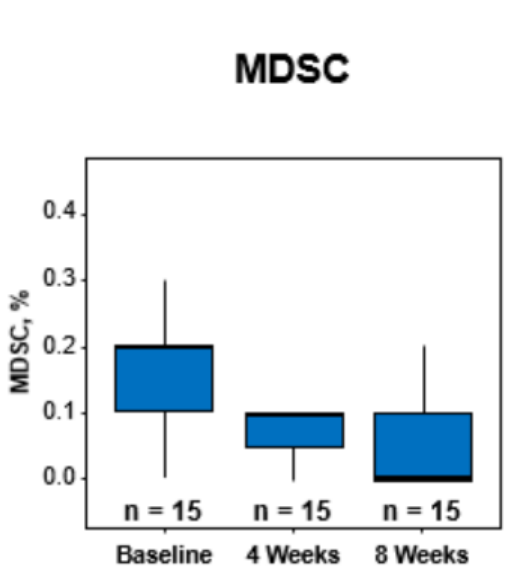
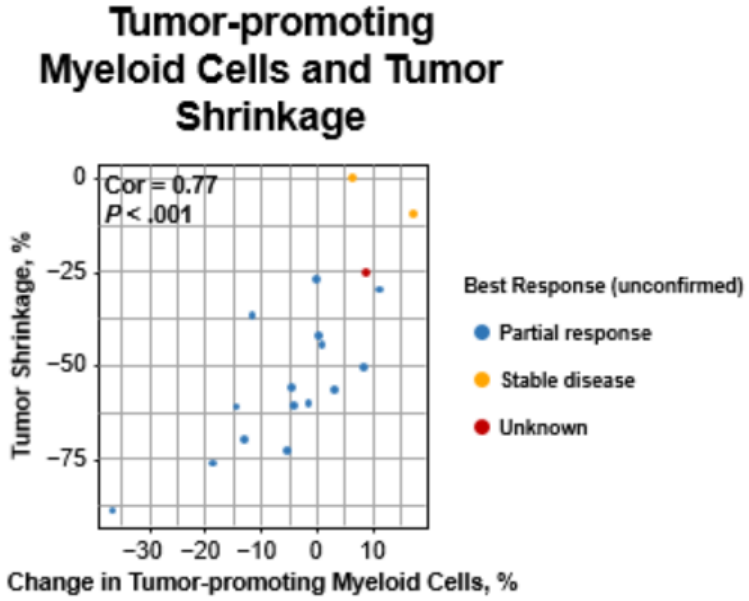
On-Treatment Modulation of Tumor-promoting Myeloid Cells/MDSC







- A decrease in tumor-promoting myeloid cells and MDSC ($Lin^{-}CD11b^{+}CD33^{+}$) was observed, indicating that the environment became less suppressive
- Changes in tumor-promoting myeloid cells following treatment were correlated with tumor shrinkage

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Summary of Adverse Events

Category, n (%)	N = 27 All Grades	N = 27 Grade ≥ 3
AE	27 (100)	13 (48)
Treatment related	27 (100)	9 (33)
SAE	10 (37)	5 (19)
Treatment related	9 (33)	4 (15)
AE leading to discontinuation		
All 3 study drugs	0	0
Spartalizumab only	2 (7)	2 (7)
Dabrafenib/trametinib only	3 (11)	2 (7)
AE leading to dose adjustment/interruption	24 (89)	12 (44)
Fatal AE[a]	1 (4)	1 (4)
Treatment related	0	0

- **2 patients discontinued spartalizumab only:**
  Grade 3 hepatic enzyme increased (onset, day 34; resolving); grade 3 rash (day 139; resolving)
- **3 patients discontinued dabrafenib and trametinib only:**
  Grade 2 acute kidney injury (day 113; not resolved); grade 3 rhabdomyolysis (day 27; resolving); grade 3 hepatic enzyme increased (day 111; resolved)

AE, adverse events; SAE, serious adverse events.
[a] 74-year-old man. Adverse events: septic shock, pseudomonas sepsis, cardiac arrest (fatal).

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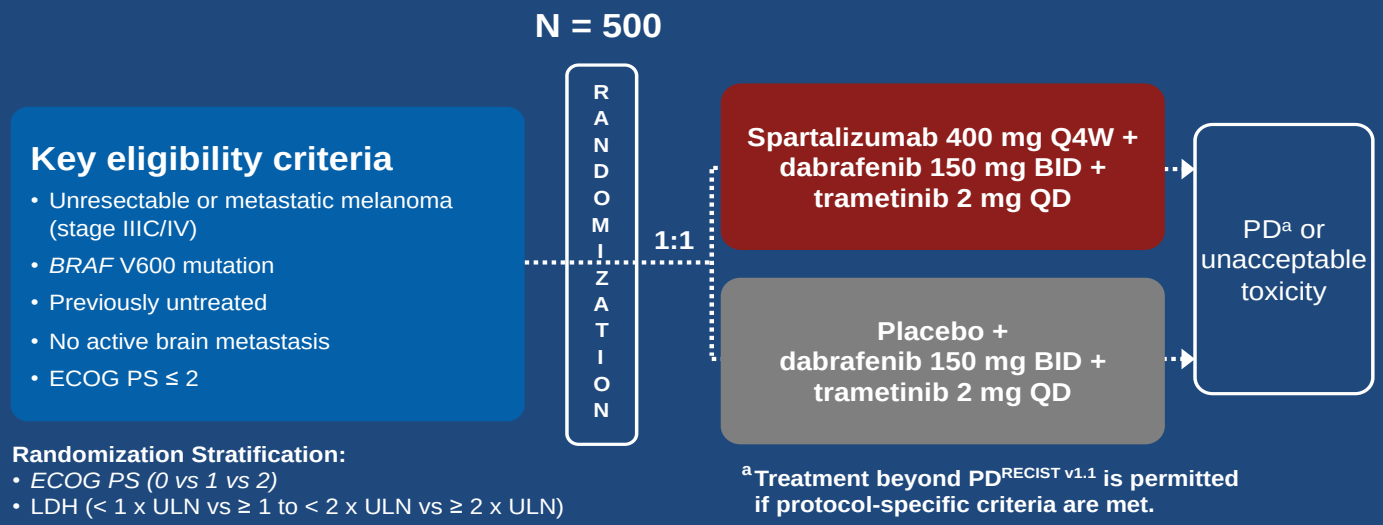
COMBI-i Part 3: Randomized, Double Blind, Placebo Controlled



Randomization Stratification:
- *ECOG PS (0 vs 1 vs 2)*
- LDH (< 1 x ULN vs ≥ 1 to < 2 x ULN vs ≥ 2 x ULN)

[a]**Treatment beyond PD$^{RECIST\ v1.1}$ is permitted if protocol-specific criteria are met.**

Primary endpoint: PFS$^{RECIST\ v1.1}$

Secondary endpoints: OS, ORR, DOR, DCR, safety, PRO, PK

PRO, patient-reported outcomes; ULN, upper limit of normal.

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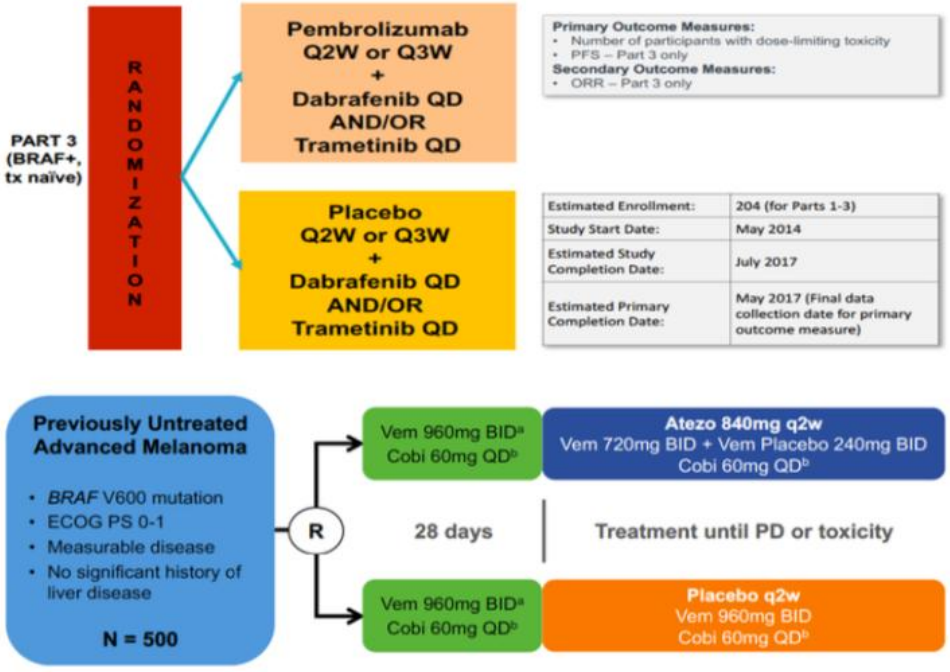
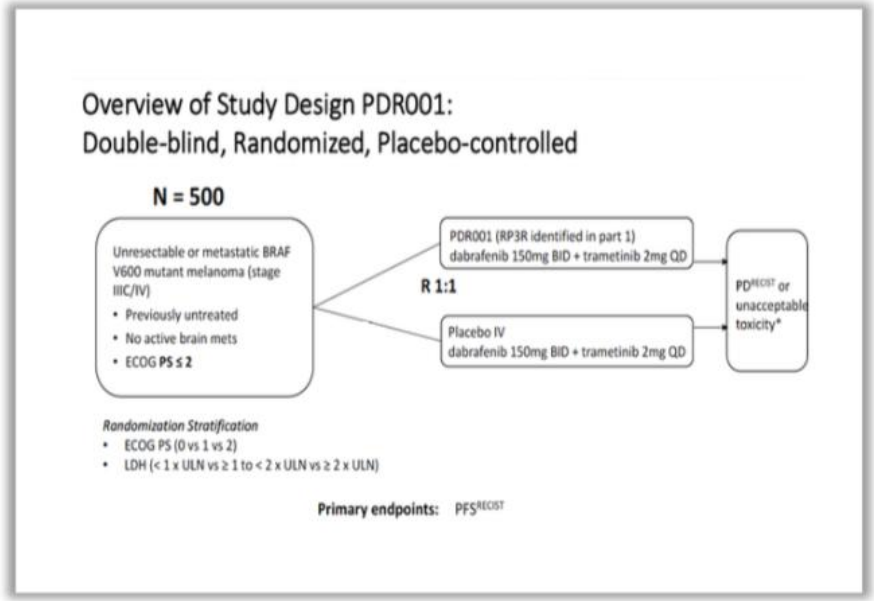
Phase II-III clinical trials BRAF/MEKi + Anti-PD-1/PDL-1





- **Key study objectives**
  - Primary: investigator-assessed PFS
  - Secondary: PFS (IRF-assessed), OS, ORR, DOR, Safety, PK

A Phase III, Open-Label, Multicenter, Two Arm, Randomized Study to Investigate the Efficacy and Safety of Cobimetinib Plus Atezolizumab Versus Pembrolizumab in Patients With Previously Untreated Advanced BRAF V600 Wild-Type Melanoma

P3: 1810061949

KEYNOTE-022 Part 3 Study Design (NCT02130466)

Patients

- Histologically confirmed unresectable or metastatic stage IV *BRAF*$^{V600E/K}$-mutant melanoma
- No prior therapy
- Measurable disease
- ECOG PS 0/1

Stratification factors[a]

- ECOG PS (0 vs 1)
- LDH level (>1.1 × ULN vs ≤1.1 × ULN)

R (1:1)
N = 120

N = 60 → Pembrolizumab 2 mg/kg Q3W + Dabrafenib 150 mg BID + Trametinib 2 mg QD

N = 60 → Placebo Q3W + Dabrafenib 150 mg BID + Trametinib 2 mg QD

- Primary end point: PFS
- Secondary end points: ORR, duration of response, and OS
- Data cutoff: Feb 15, 2018

[a]Owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.

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Baseline Characteristics

	Pembro + D + T N = 60	Placebo + D + T N = 60
Age, median (range), y	54 (18-82)	58 (21-83)
Male, n (%)	33 (55)	36 (60)
ECOG PS, n (%)		
0	48 (80)	48 (80)
1	12 (20)	12 (20)
LDH, n (%)		
≤1.1 × ULN	33 (55)	34 (57)
>1.1 × ULN	27 (45)	26 (43)
BRAF mutation, n (%)		
V600E	52 (87)	49 (82)
V600K	8 (13)	11 (18)
PD-L1 status,[a] n (%)		
Positive	47 (78)	44 (73)
Negative/missing	10 (17)/3 (5)	12 (20)/4 (7)

[a]Defined as ≥1% staining in tumor and adjacent immune cells as assessed by IHC (22C3 antibody).
Data cutoff: Feb 15, 2018.

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Baseline Characteristics (cont)

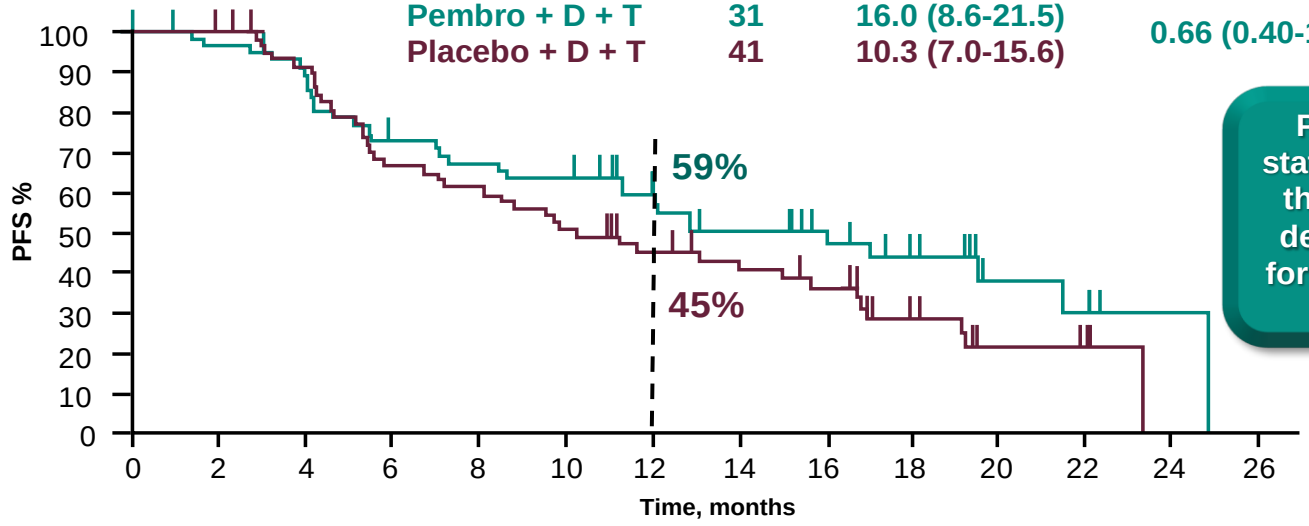
	Pembro + D + T N = 60	Placebo + D + T N = 60
Stage at entry, n (%)		
IIIB	1 (2)	1 (2)
IIIC	0 (0)	2 (3)
IV	59 (98)	57 (95)
Metastatic stage, n (%)		
M1a	2 (3)	10 (17)
M1b	8 (13)	9 (15)
M1c	49 (82)	38 (63)
No brain metastases, n (%)	59 (98)	59 (98)
No prior radiation, n (%)	51 (85)	54 (90)
Prior therapy, n (%)		
Adjuvant	8 (13)	5 (8)
Neoadjuvant	1 (2)	1 (2)
No prior therapy	51 (85)	54 (90)

Data cutoff: Feb 15, 2018.

P3: 1810061949

Progression-Free Survival

	Events, n	Median,[a] mo (95% CI)	HR[b] (95% CI)[b]	*P* Value[c]
Pembro + D + T	31	16.0 (8.6-21.5)	0.66 (0.40-1.07)	0.04287
Placebo + D + T	41	10.3 (7.0-15.6)		



PFS did not reach statistical significance threshold per study design (required HR for significance ≤0.62, $P \leq 0.025$)

No. at risk

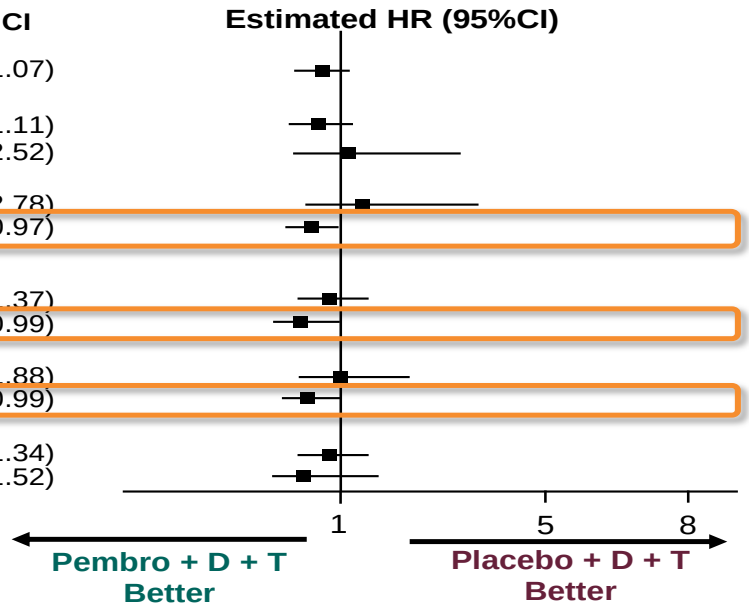
Pembro + D + T	60	55	49	39	36	34	27	21	17	12	5	4	1	0
Placebo + D + T	60	59	52	38	35	29	23	20	16	9	4	3	0	0

[a]Based on Kaplan-Meier estimate of PFS, per investigator assessment.
[b]Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (LDH >1.1 × ULN vs =1.1 × ULN); owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.
[c]One-sided *P* value based on stratified log-rank test.
Data cutoff: Feb 15, 2018.

P3: 1810061949

Progression-Free Survival[a] by Subgroups

Subgroup		Event, n/N	HR	95% CI
Overall		72/120	0.66	(0.40-1.07)
Age				
	<65 Years	47/81	0.61	(0.33-1.11)
	≥65 Years	25/39	1.02	(0.41-2.52)
Sex				
	Female	25/51	1.22	(0.53-2.78)
	Male	47/69	0.53	(0.29-0.97)
ECOG Status				
	0	55/96	0.79	(0.46-1.37)
	1	17/24	0.37	(0.14-0.99)
LDH				
	LDH ≤1.1 × ULN	33/67	0.93	(0.46-1.88)
	LDH >1.1 × ULN	39/53	0.51	(0.26-0.99)
PD-L1				
	PD-L1 positive	54/91	0.76	(0.44-1.34)
	PD-L1 negative	13/22	0.44	(0.13-1.52)



[a]Based on Kaplan-Meier estimate of PFS, by investigator assessment per RECIST v1.1.
Data cutoff: Feb 15, 2018.

[a]Based on Kaplan-Meier estimate of PFS, per investigator assessment.
[b]Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (LDH >1.1 × ULN vs =1.1 × ULN); owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.
[c]One-sided *P* value based on stratified log-rank test.
Data cutoff: Feb 15, 2018.

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P3: 1810061949

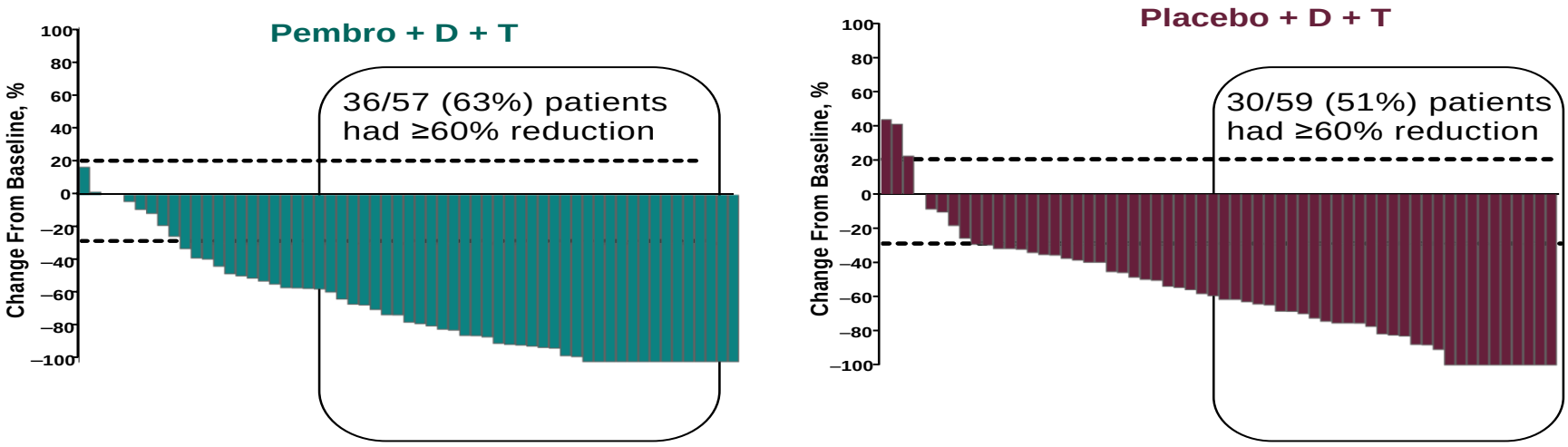
Best Overall Response (investigator review[a], RECIST v1.1)

	Pembro + D + T, n (%) N = 60	Placebo + D + T, n (%) N = 60	Difference in rate[b] % (95% CI)[b]	*P* Value[c]
ORR	38 (63.3)	43 (71.7)	–7.9 (–24.2 to 8.9)	0.3549
CR	11 (18.3)	8 (13.3)	5.4 (–8.2 to 18.8)	0.4229
PR	27 (45.0)	35 (58.3)	–13.2 (–30.4 to 4.7)	0.1477
DCR	51 (85.0)	56 (93.3)	–7.9 (–20.1 to 3.5)	0.1624
SD	13 (21.7)	13 (21.7)	0 (–14.9 to 15.0)	—
PD	5 (8.3)	3 (5.0)	3.0 (-7.0 to 13.6)	—
Nonevaluable	2 (3.3)	0	3.4 (–2.7 to 11.7)	—
No assessment	2 (3.3)	1 (1.7)	1.5 (–6.0 to 9.6)	—

[a]Responses are based on investigator best assessment across time points per RECIST v1.1 with confirmation.
[b]Based on Miettinen and Nurimen method stratified by ECOG PS (0 vs 1) and LDH (>1.1 × ULN vs ≤1.1 × ULN); owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.
[c]*P* values are provided for descriptive purposes only, no multiplicity adjustment was made.
Data cutoff: Feb 15, 2018.

P3: 1810061949

Best Percentage Change From Baseline in Target Lesion Size[a]

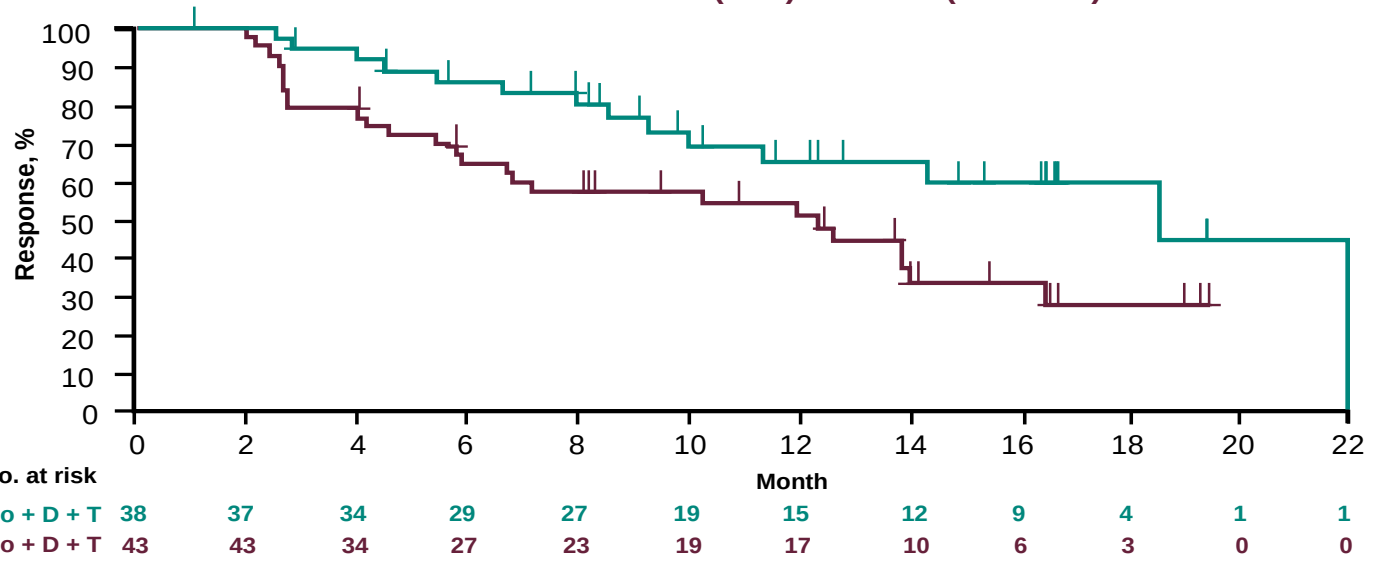


[a]Maximum percentage change in target lesion size based on investigator assessment in patients with post-baseline values.
Data cutoff: Feb 15, 2018.

P3: 1810061949

Kaplan-Meier Analysis of Duration of Response[a]

DOR	DOR[b] ≥18 mo n (%)	Median (range),[b] mo
Pembro + D + T	4 (59.8)	18.7 (1.9+-22.1)
Placebo + D + T	3 (27.8)	12.5 (2.1-19.5+)



No. at risk												
Pembro + D + T	38	37	34	29	27	19	15	12	9	4	1	1
Placebo + D + T	43	43	34	27	23	19	17	10	6	3	0	0

[a]Confirmed response based on investigator assessment per RECIST v1.1.
[b]From Kaplan-Meier method for censored data.
+ indicates there was no progressive disease at last disease assessment.
Data cutoff: Feb 15, 2018.

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P3: 1810061949

Oncologic Therapies After Discontinuing Study Treatment

n (%)	Pembro + D + T N = 60	Placebo + D + T N = 60
≥1 New systemic therapy	21 (35.0)	34 (56.7)
BRAF/MEK inhibitor[a]	14 (23.3)	7 (11.7)
Dabrafenib	8 (13.3)	8 (13.3)
Vemurafenib	8 (13.3)	1 (1.7)
Trametinib	7 (11.7)	5 (8.3)
Cobimetinib	8 (13.3)	1 (1.7)
Chemotherapy[b]	1 (1.7)	2 (3.3)

n (%)	Pembro + D + T N = 60	Placebo + D + T N = 60
Immunotherapy	9 (15.0)	29 (48.3)
Pembro	7 (11.7)	21 (35.0)
Nivolumab	0 (0)	10 (16.7)
Ipilimumab	2 (3.3)	8 (13.3)
Other		
Exemestane	0 (0)	1 (1.7)
Tamoxifen	0 (0)	1 (1.7)

[a]Includes BRAF inhibitors or MEK inhibitors.
[b]Carboplatin, paclitaxel, and 1 unspecified chemotherapy.

P3: 1810061949

Summary of Adverse Events

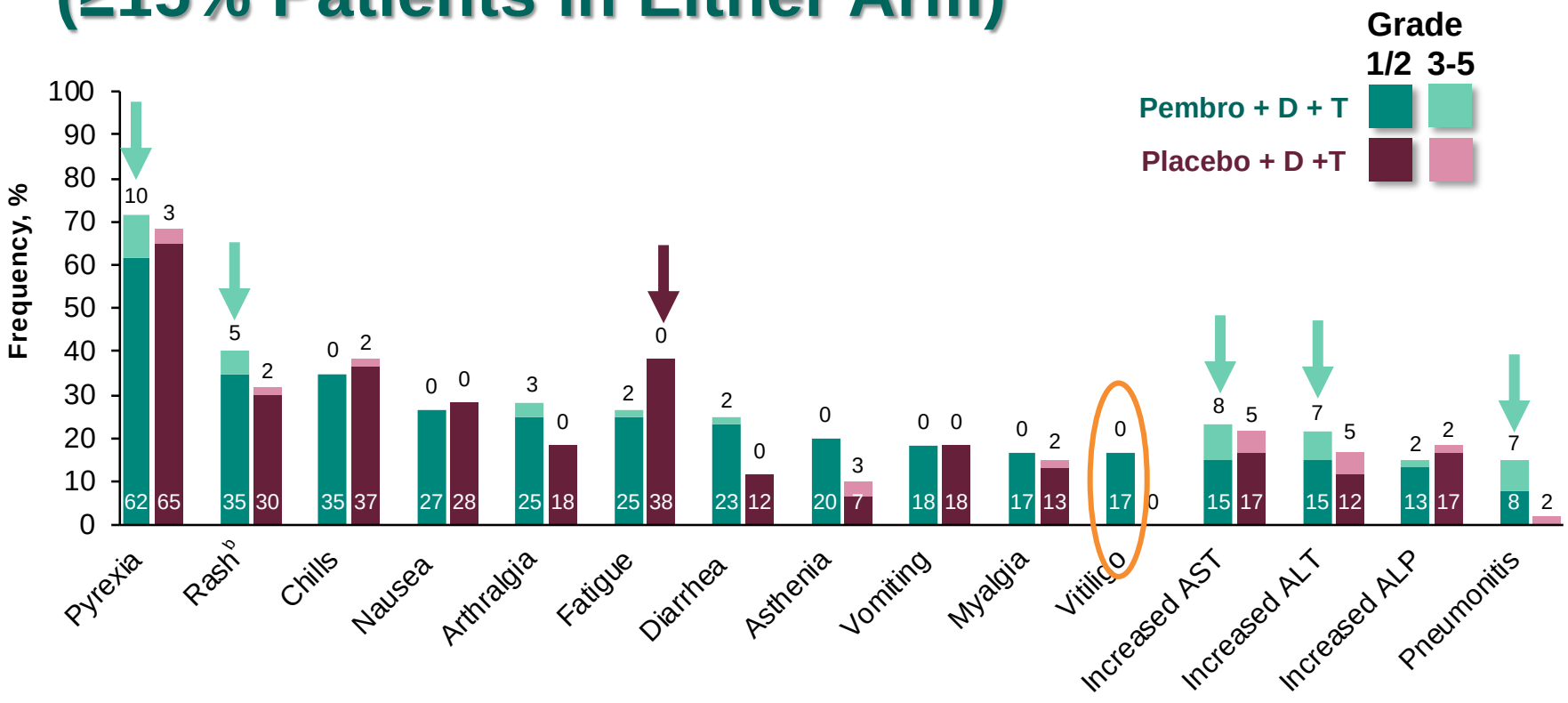
	Pembro + D + T n (%) N = 60	Placebo + D + T n (%) N = 60
Any-grade AE	59 (98)	58 (97)
Grade 3-4	40 (67)	27 (45)
Led to death[a]	2 (3)	0 (0)
Led to discontinuation	25 (42)	13 (22)
Led to discontinuation of all 3 study drugs	15 (25)	9 (15)
Treatment-related AE	57 (95)	56 (93)
Grade 3-4	34 (57)	16 (27)
Led to death	1 (2)	0 (0)
Led to discontinuation of ≥1 study drug	24 (40)	12 (20)

[a]One patient died due to treatment-related pneumonitis and one died of unknown cause.
Data cutoff: Feb 15, 2018.

Median follow-up: 9.6 months (range, 2.7-23.4 months)

P3: 1810061949

Treatment-Related Adverse Events[a] (≥15% Patients in Either Arm)



[a]Frequency indicated at the base of columns for grade 1/2 treatment-related adverse events, on top of the column for grade 3-5 events.
[b]Rash and maculopapular rash.
Data cutoff: Feb 15, 2018.

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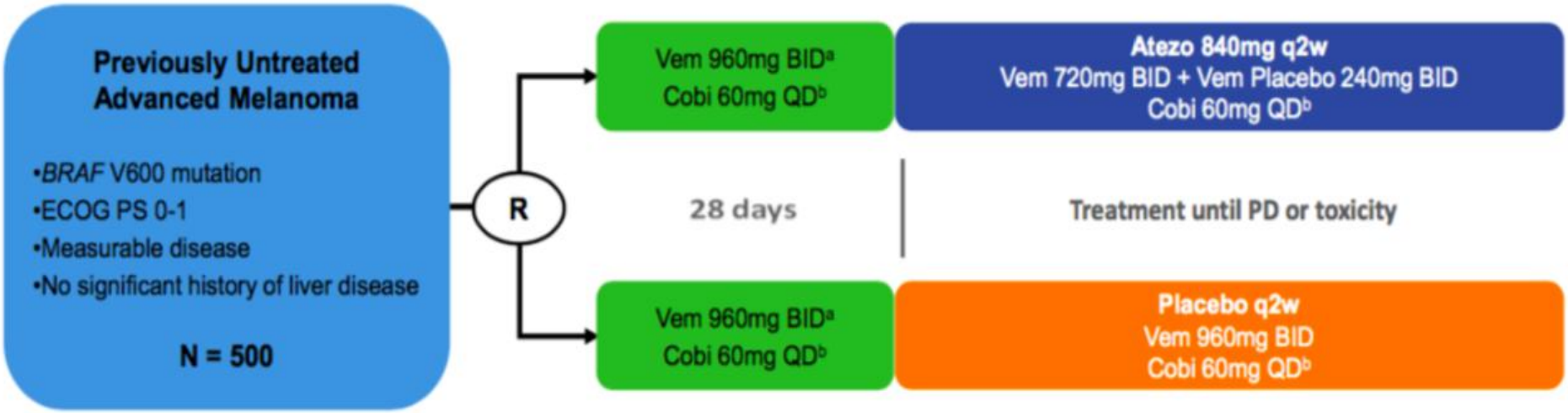
Phase III Study of Atezo + Cobi + Vem in *BRAF* V600 Mutant Melanoma (NCT02908672)

- A Phase III study evaluating atezo + cobi + vem vs placebo + cobi + vem in patients with ***BRAF* V600 mutant** advanced melanoma is planned



- **Key study objectives**
  - Primary: investigator-assessed PFS
  - Secondary: PFS (IRF-assessed), OS, ORR, DOR, Safety, PK

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TRICOTEL study

Atezolizumab, cobimetinib and vemurafenib in metastatic melanoma

Key inclusion criteria:
- ≥18 years of age
- Unresectable stage IIIC/IV metatstatic melanoma
- Documented *BRAF*^{V600} status of melanoma tumour tissue
- No prior WBRT
- Radiologically confirmed CNS metastases
- Adequate organ function
- ECOG PS 0–2

N=120

Study entry

Cobimetinib + atezolizumab *BRAF*wt

Cobimetinib + vemurafenib + atezolizumab *BRAF*mut

Progression

Primary endpoint:
- Intracranial response rate as per IRC

Secondary endpoints:
- PFS, DOR, CBR, OS, PRO, safety

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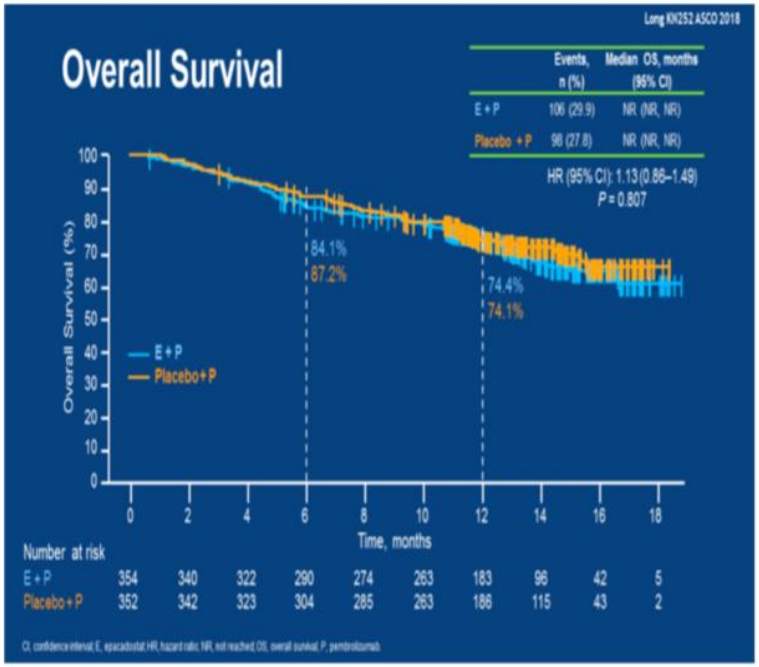
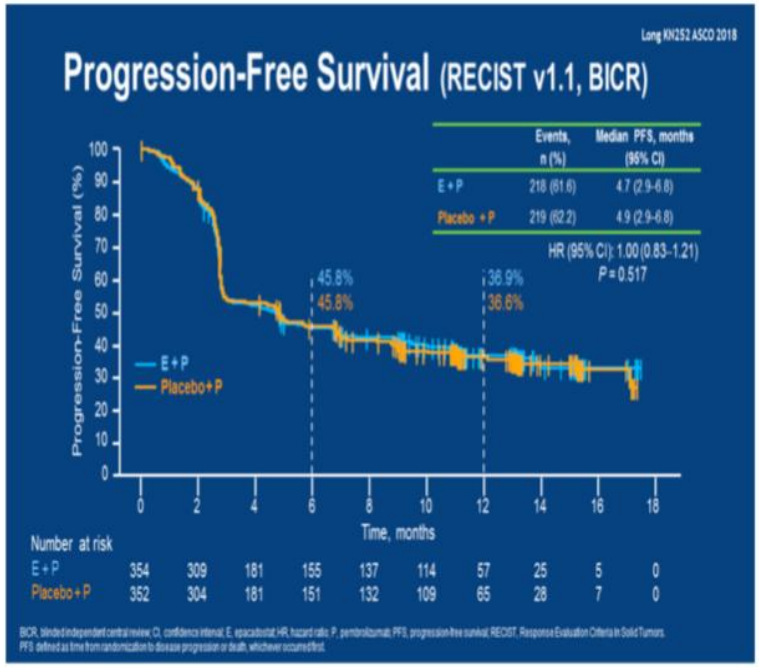
Pembrolizumab +/- Epacadostat / Placebo: Keynote 252





Long G, et al. ASCO 2018

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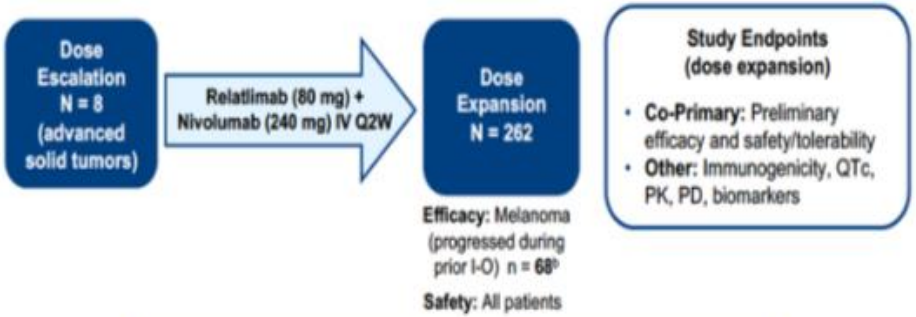
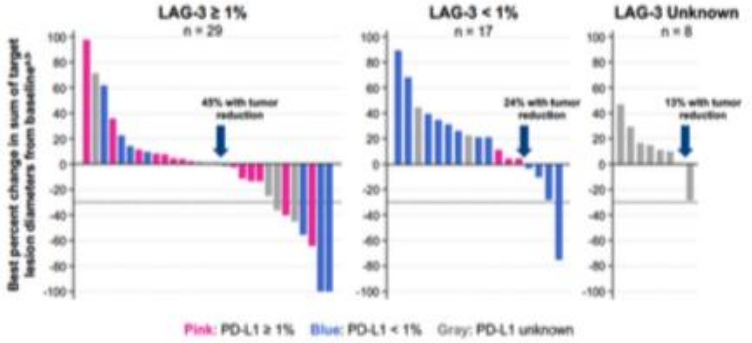
Anti-LAG3 and Nivolumab



	Mel Prior PD-(L)1[a]	
	All n = 61	LAG-3 ≥ 1%[b] n = 33
ORR, n (%)[c] 95% CI	7 (11.5)[d] 4.7, 22	6 (18)[d] 7, 35.5
BOR, n (%)[e]		
CR	1 (1.6)	1 (3.0)
PR	6 (9.8)[e]	5 (15)[e]
SD	23 (38)	15 (45)
PD	25 (41)	8 (24)
Clinical progression[e]	6 (9.8)	4 (12)
DCR (CR + PR + SD), n (%)[c] 95% CI	30 (49) 36, 62	21 (64) 45, 80

	All Patients[a] N = 270	
	Any Grade n (%)	Grade 3–4 n (%)
Any TRAE[b]	137 (51)	27 (10)
TRAEs in ≥ 5% of patients		
Fatigue	30 (11)	0
Pruritus	19 (7.0)	0
Diarrhea	18 (6.7)	3 (1.1)
Arthralgia	17 (6.3)	0
Infusion-related reaction	15 (5.6)	0
Any serious TRAE[b]	18 (6.7)	12 (4.4)
Serious TRAEs in > 1 patient		
Colitis	4 (1.5)	3 (1.1)
Pneumonitis	2 (0.7)	2 (0.7)
Myocarditis[c]	2 (0.7)	0
Pyrexia	2 (0.7)	0
Any TRAE leading to discontinuation[b]	11 (4.1)	8 (3.0)

Best change in target lesion size by LAG-3 and PD-L1 expression



Ascierto PA, et al. ESMO 2017

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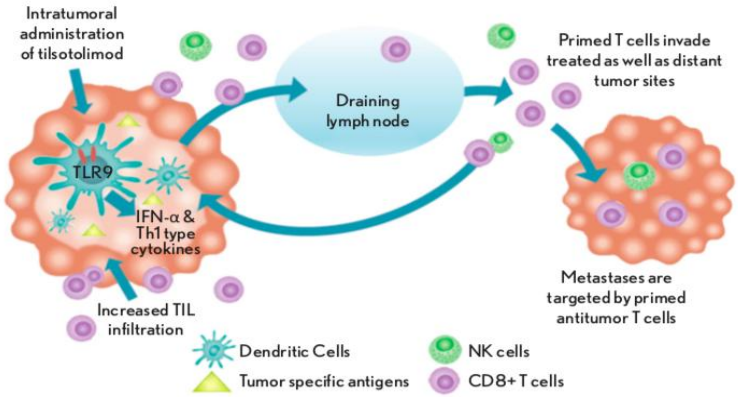
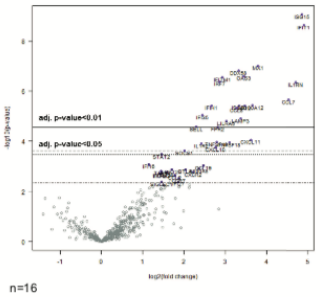
The safety and efficacy of intratumoral injection of the TLR9 agonist tilsotolimod (IMO-2125) in combination with ipilimumab in patients with PD-1 inhibitor refractory metastatic melanoma: An analysis of efficacy in injected and uninjected lesions

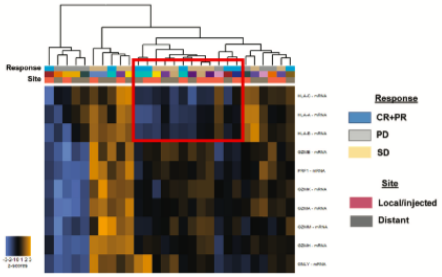


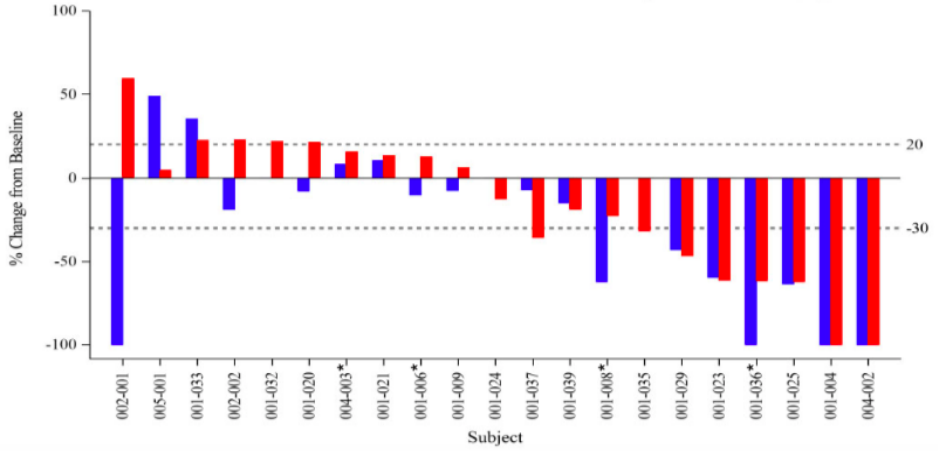
Best overall tumor response	Response rate (RECIST v1.1)
Complete response (CR)*	2 (10%)
Partial response (PR)	6 (29%)
Stable disease (SD)	7 (33%)
Progressive disease (PD)	6 (29%)
Overall response rate (CR, uCR, or PR)	8 (38%)
Disease control rate (CR, uCR, PR, or SD)	15 (71%)

Induction of type 1 IFN response gene signature at 24 hours after tilsotolimod



Responses seen in HLA-ABC neg/low tumors at baseline (indicated by red box)





Adi Diab ESMO 2018

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1er Taller Anual Sobre Manejo del Melanoma

Abstract: 1306TiP

A randomized phase 3 comparison of IMO-2125 with ipilimumab versus ipilimumab alone in subjects with anti-PD-1 refractory melanoma

Illuminate 301 Study Design (N=308)

308 adult subjects with unresectable or metastatic melanoma with confirmed radiologic progression during or after PD-1 inhibitor therapy who

- were ≥21 days from the most recent anti-PD-1 treatment and underwent no intervening systemic treatment
- underwent no prior ipilimumab treatment except adjuvant
- underwent no BRAF+ treatment or else declined it
- had no ocular melanoma

1:1 randomization stratification:

- Anti-PD-1 therapy for ≥12 or <12 wk
- Stage M1c or other metastasis
- BRAF mutation status and prior targeted therapy: wild type, mutation positive with targeted therapy, or mutation positive with no prior targeted therapy
- No crossover

Arm A

Ipilimumab 3 mg/kg (4 doses: wk 1, 4, 7, 10)

Disease assessments

- Baseline
- Week 12
- Every 8 wk during first year, then
- Every 12 wk

Arm B

Ipilimumab 3 mg/kg (4 doses: wk 2, 5, 8, 11)

plus

Intratumoral tilsotolimod 8 mg (9 doses: wk 1, 2, 3, 5, 8, 11, 16, 20, 24)

Active follow-up if there is no disease progression or new cancer treatment

Survival follow-up if there is disease progression or new cancer treatment

Active follow-up if there is no disease progression or new cancer treatment

Survival follow-up if there is disease progression or new cancer treatment

Primary endpoints

- Overall survival (HR, 0.63)
- Overall response rate*

*Using Response Evaluation Criteria in Solid Tumors (RECIST), v1.1

Ascierto ESMO 2018

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CONCLUSIONES

- INHIBIDORES BRAF y MEK EFECTO INMUNOGÉNICO EN MM BRAF +
- ENSAYOS FASE 1 COMBOS TKI + INMUNO FACTIBILIDAD, EFICACIA Y ACTIVACIÓN INMUNITARIA
- ENSAYO FASE 2 KEYNOTE-022 NEGATIVO PARA ENDPOINT PRIMARIO
- ENSAYOS FASE 3 TRICOTEL Y COMBI-i DILUCIDARÁN PAPEL COMBOS PRIMERA LÍNEA DE TRATAMIENTO
- MÚLTIPLES COMBINACIONES DIFERENTES EN INVESTIGACIÓN