New immunotherapy strategies in melanoma beyond PD1 inhibitors

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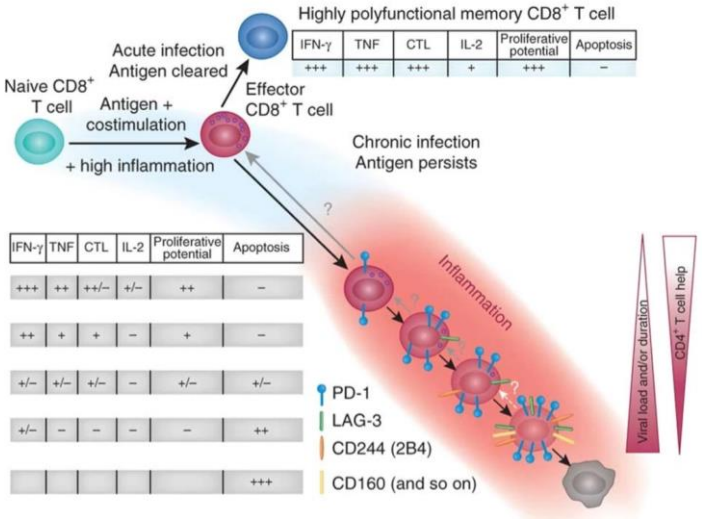
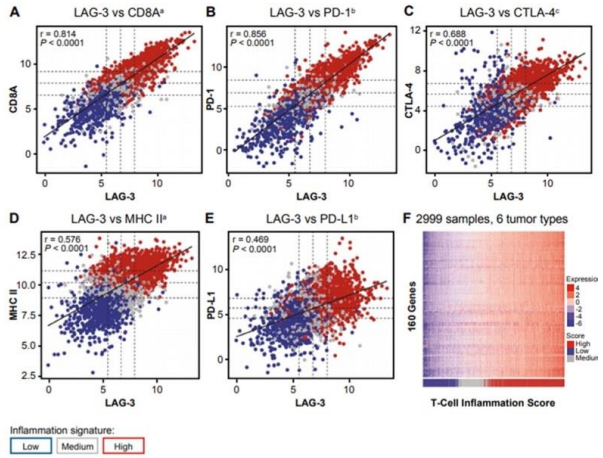
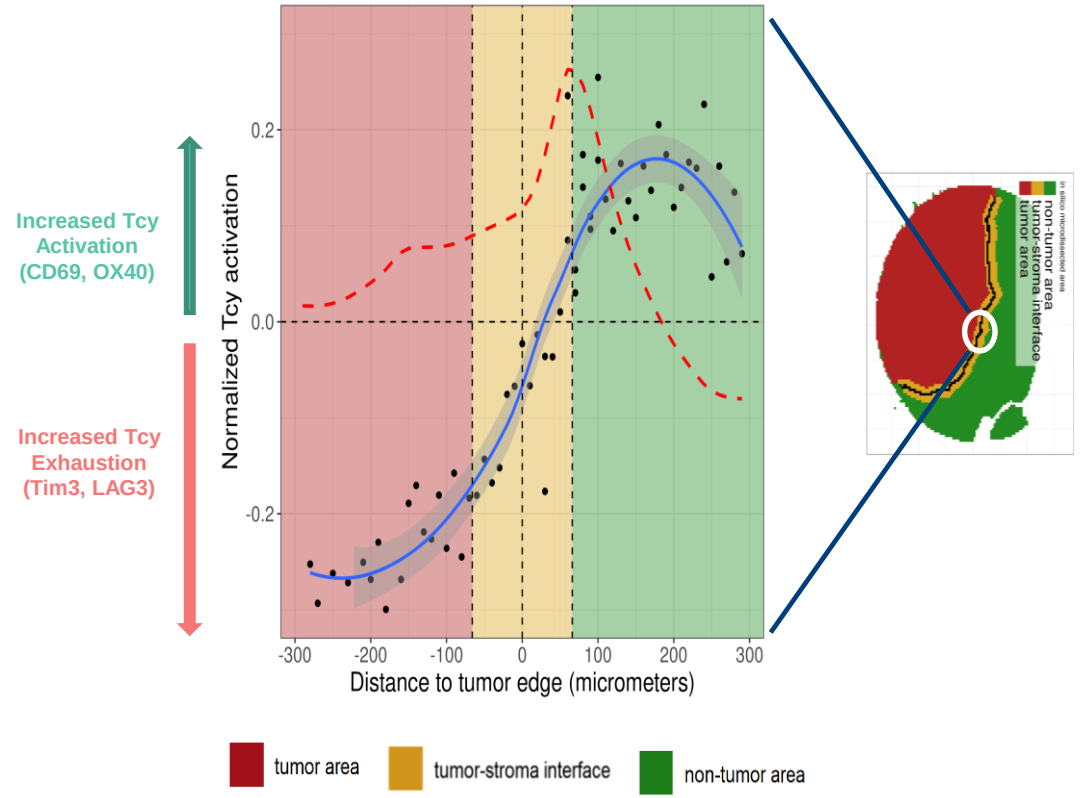
Outline

- Current treatment strategies entering the clinic, beyond anti-PD1 in melanoma mainly focus on combination therapies.
    - Lesser toxicity
    - Preserved efficacy
    - ➢ Anti-LAG3 and anti-IL6 in combination therapy
- Current strategies to overcome anti-PD1 resistance.
    - Challenging population of patients with a dismal prognosis.
    - Focus on impacting on the tumor microenvironment
    - ➢ Anti-angiogenic and anti-PD1 combination
    - ➢ Rewiring the TME with MDM2 inhibition

Expression of LAG3 is associated with a more exhausted state of CD8 cells





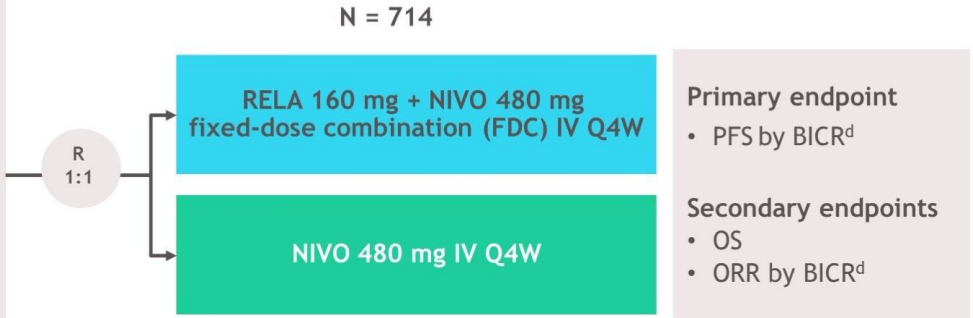


Wherry et al Nat. Immunol 2021

Relativity-047: A randomized double blinded phase 2/3 study comparing Relatinib+Nivo with Nivo in patients with malignant melanoma

Key eligibility criteria
- Previously untreated unresectable or metastatic melanoma[a]
- ECOG PS 0–1

Stratification factors
- LAG-3[b]
- PD-L1[c]
- *BRAF*
- AJCC v8 M stage



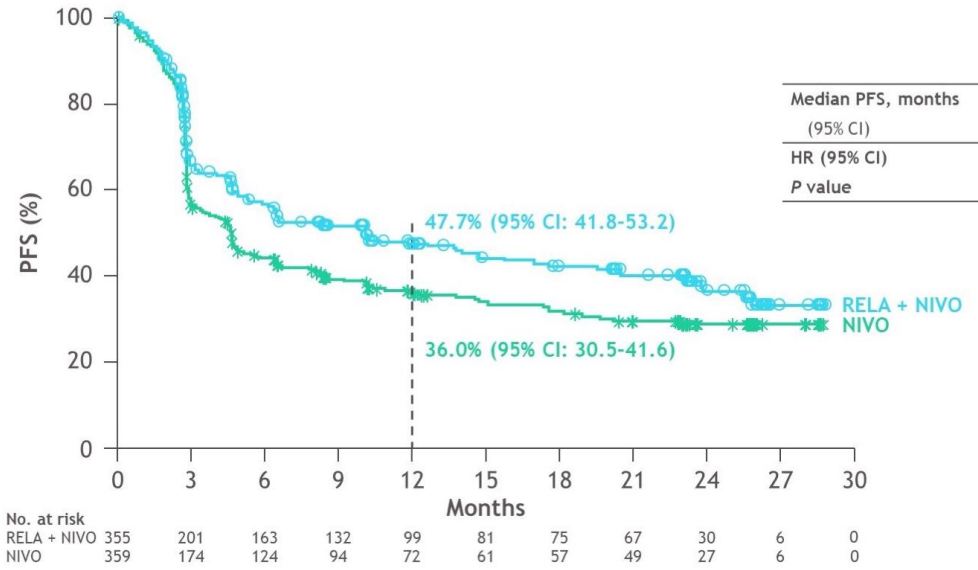
Primary endpoint
- PFS by BICR[d]

Secondary endpoints
- OS
- ORR by BICR[d]

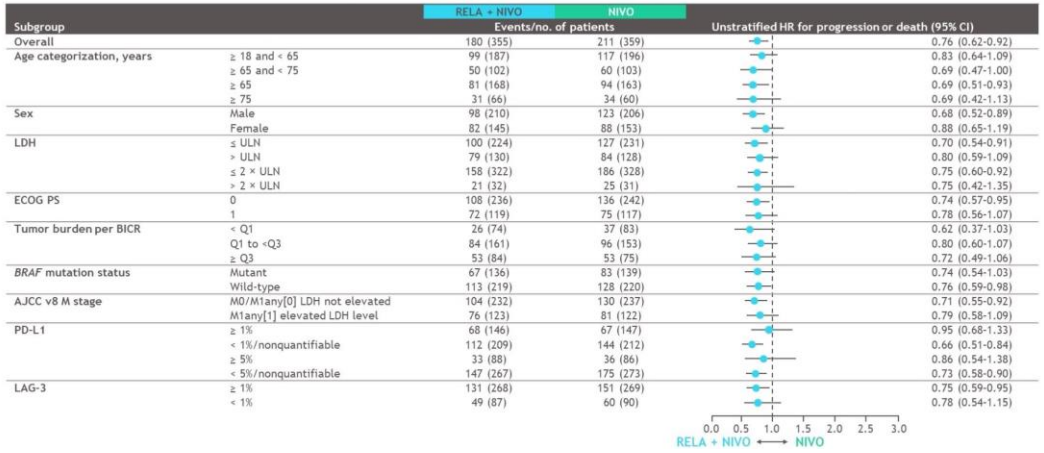
Baseline characteristics

Characteristic		RELA + NIVO (n = 355)	NIVO (n = 359)	Total (N = 714)
Median age, years		63	62	63
Female, n (%)		145 (40.8)	153 (42.6)	298 (41.7)
AJCC v8 M stage, n (%)	M1A	77 (21.7)	107 (29.8)	184 (25.8)
	M1B	85 (23.9)	88 (24.5)	173 (24.2)
	M1C	151 (42.5)	127 (35.4)	278 (38.9)
	M1D	6 (1.7)	11 (3.1)	17 (2.4)
ECOG PS, n (%)	0	236 (66.5)	242 (67.4)	478 (66.9)
	1	119 (33.5)	117 (32.6)	236 (33.1)
Serum LDH level, n (%)	> ULN	130 (36.6)	128 (35.7)	258 (36.1)
	> 2× ULN	32 (9.0)	31 (8.6)	63 (8.8)
Prior neoadjuvant/adjuvant[a], n (%)		33 (9.3)	27 (7.5)	60 (8.4)
Tumor burden[b], median (min.-max.), mm		59.0 (10-317)	54.5 (10-548)	
Stratification factor, n (%)				
LAG-3 expression	≥ 1%	268 (75.5)	269 (74.9)	537 (75.2)
	< 1%	87 (24.5)	90 (25.1)	177 (24.8)
PD-L1 expression	≥ 1%	146 (41.1)	147 (40.9)	293 (41.0)
	< 1%	209 (58.9)	212 (59.1)	421 (59.0)
BRAF mutation status	Mutant	136 (38.3)	139 (38.7)	275 (38.5)
	Wild-type	219 (61.7)	220 (61.3)	439 (61.5)
AJCC M stage	M0/M1any[0][c]	232 (65.4)	237 (66.0)	469 (65.7)
	M1any[1][d]	123 (34.6)	122 (34.0)	245 (34.3)

Relatinib+Nivo has superior PFS compared to Nivo



	RELA + NIVO (n = 355)	NIVO (n = 359)
Median PFS, months	10.12	4.63
(95% CI)	(6.37-15.74)	(3.38-5.62)
HR (95% CI)	0.75 (0.62-0.92)	
P value	0.0055	



Subgroup		RELA + NIVO Events/no. of patients	NIVO Events/no. of patients	Unstratified HR for progression or death (95% CI)
Overall		180 (355)	211 (359)	0.76 (0.62-0.92)
Age categorization, years	≥ 18 and < 65	99 (187)	117 (196)	0.83 (0.64-1.09)
	≥ 65 and < 75	50 (102)	60 (103)	0.69 (0.47-1.00)
	≥ 65	81 (168)	94 (163)	0.69 (0.51-0.93)
	≥ 75	31 (66)	34 (60)	0.69 (0.42-1.13)
Sex	Male	98 (210)	123 (206)	0.68 (0.52-0.89)
	Female	82 (145)	88 (153)	0.88 (0.65-1.19)
LDH	≤ ULN	100 (224)	127 (231)	0.70 (0.54-0.91)
	> ULN	79 (130)	84 (128)	0.80 (0.59-1.09)
	≤ 2 × ULN	158 (322)	186 (328)	0.75 (0.60-0.92)
	> 2 × ULN	21 (32)	25 (31)	0.75 (0.42-1.35)
ECOG PS	0	108 (236)	136 (242)	0.74 (0.57-0.95)
	1	72 (119)	75 (117)	0.78 (0.56-1.07)
Tumor burden per BICR	< Q1	26 (74)	37 (83)	0.62 (0.37-1.03)
	Q1 to <Q3	84 (161)	96 (153)	0.80 (0.60-1.07)
	≥ Q3	53 (84)	53 (75)	0.72 (0.49-1.06)
BRAF mutation status	Mutant	67 (136)	83 (139)	0.74 (0.54-1.03)
	Wild-type	113 (219)	128 (220)	0.76 (0.59-0.98)
AJCC v8 M stage	M0/M1any[0] LDH not elevated	104 (232)	130 (237)	0.71 (0.55-0.92)
	M1any[1] elevated LDH level	76 (123)	81 (122)	0.79 (0.58-1.09)
PD-L1	≥ 1%	68 (146)	67 (147)	0.95 (0.68-1.33)
	< 1%/nonquantifiable	112 (209)	144 (212)	0.66 (0.51-0.84)
	≥ 5%	33 (88)	36 (86)	0.86 (0.54-1.38)
	< 5%/nonquantifiable	147 (267)	175 (273)	0.73 (0.58-0.90)
LAG-3	≥ 1%	131 (268)	151 (269)	0.75 (0.59-0.95)
	< 1%	49 (87)	60 (90)	0.78 (0.54-1.15)

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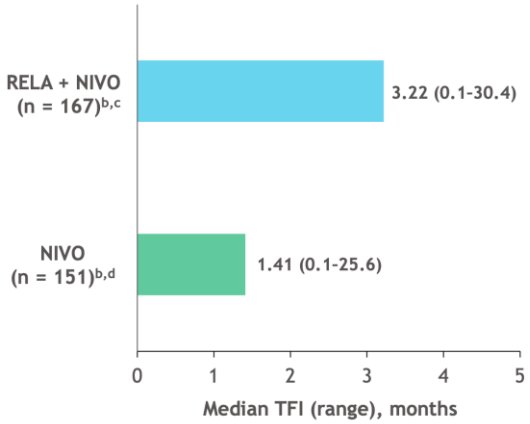
Treatment free interval and PFS2 in Rela+Nivo vs Nivo patients

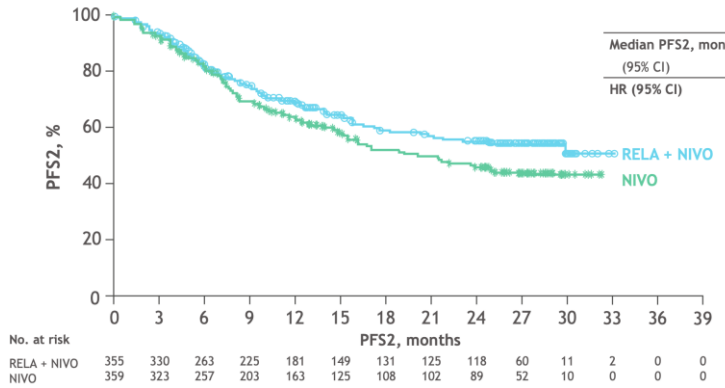
- Patients treated with RELA + NIVO who discontinued study therapy had a longer treatment-free interval versus NIVO alone

Off-treatment patients included in TFI analysis, n (%)	RELA + NIVO (n = 167)[b,c]	NIVO (n = 151)[b,d]
On study without subsequent systemic therapy	68 (40.7)	44 (29.1)
On study with subsequent systemic therapy	52 (31.1)	57 (37.7)
Off study with subsequent systemic therapy	47 (28.1)	50 (33.1)



- RELA + NIVO reduced the risk of progression after next line of systemic therapy, per investigator assessment, or death versus NIVO alone

	RELA + NIVO (n = 355)[b]	NIVO (n = 359)[c]
Median PFS2, months	NR	20.04
(95% CI)	(21.75-NR)	(15.44-25.13)
HR (95% CI)	0.77 (0.61-0.97)	



No. at risk													
RELA + NIVO	355	330	263	225	181	149	131	125	118	60	11	2	0	0
NIVO	359	323	257	203	163	125	108	102	89	52	10	0	0	0

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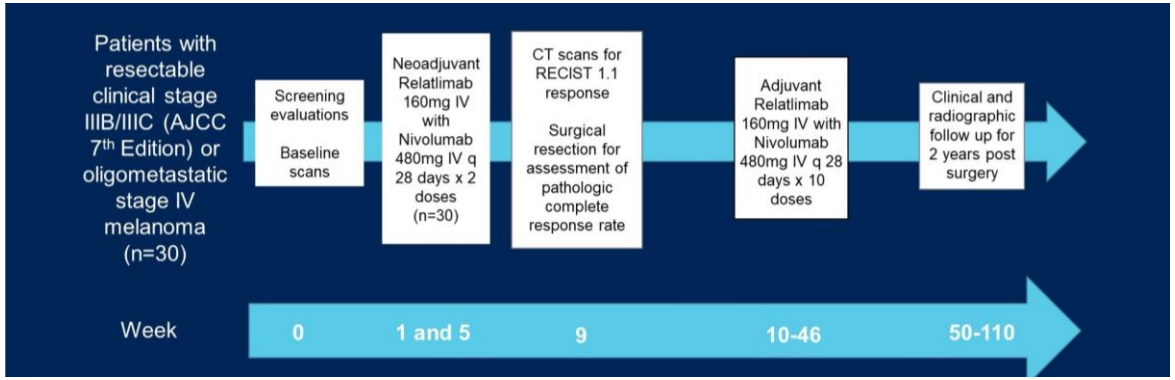
Hodi et al ESMO 2021

Neo-adjuvant/adjuvant Relatinib+Nivo in stage III melanoma



	Total cohort N=29
pCR	17 (59%)
Near pCR	2 (7%)
pPR	2 (7%)
pNR	8 (27%)

MPR: 66%

Any path response: 73%

Amaria et al ASCO 2021

Toxicity of Rela+Nivo vs Nivo compared to other combinations

AE, n (%)	RELA + NIVO (n = 355)		NIVO (n = 359)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any AE	345 (97.2)	143 (40.3)	339 (94.4)	120 (33.4)
TRAE	288 (81.1)	67 (18.9)	251 (69.9)	35 (9.7)
Leading to discontinuation	52 (14.6)	30 (8.5)	24 (6.7)	11 (3.1)
TRAE ≥ 10%				
Pruritus	83 (23.4)	0	57 (15.9)	2 (0.6)
Fatigue	82 (23.1)	4 (1.1)	46 (12.8)	1 (0.3)
Rash	55 (15.5)	3 (0.8)	43 (12.0)	2 (0.6)
Arthralgia	51 (14.4)	3 (0.8)	26 (7.2)	1 (0.3)
Hypothyroidism	51 (14.4)	0	43 (12.0)	0
Diarrhea	48 (13.5)	3 (0.8)	33 (9.2)	2 (0.6)
Vitiligo	37 (10.4)	0	35 (9.7)	0

	Nivo	Ipi3/Nivo1	Ipi1/Nivo3	Rela+Nivo
TRAE's G3/4	9.7%	55%	33.3%	18.9%
TRAE's leading to discontinuation	7.7%	35%	17.2%	8.5%

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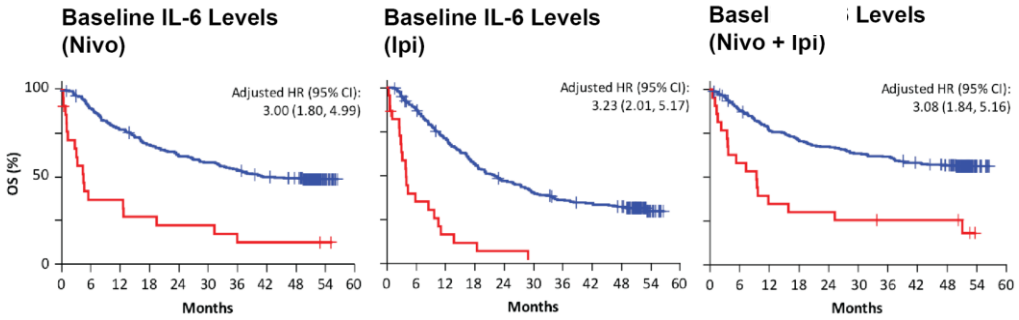
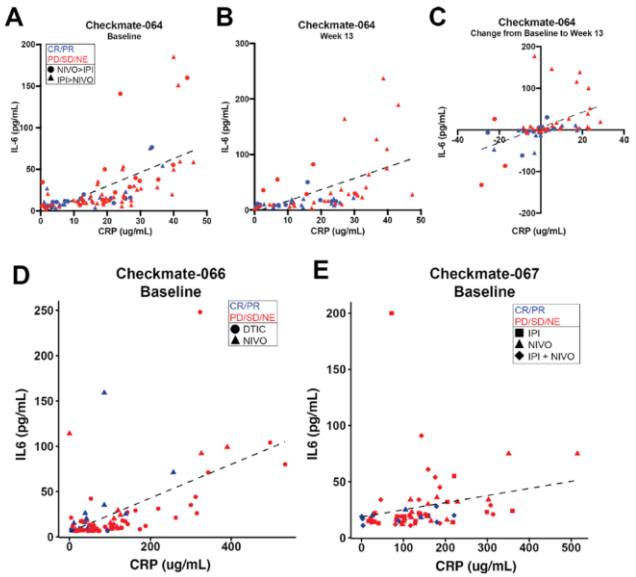
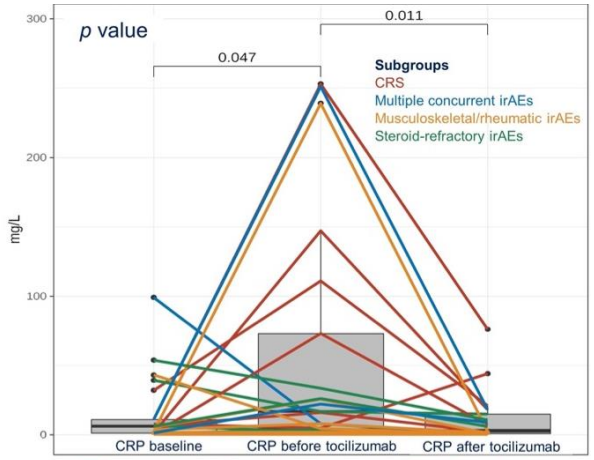
Hodi et al ESMO 2021 Lebbe et al JCO 2019 Wolchok et al NEJM 2017

IL6 is associated with irAE's and unfavourable outcome





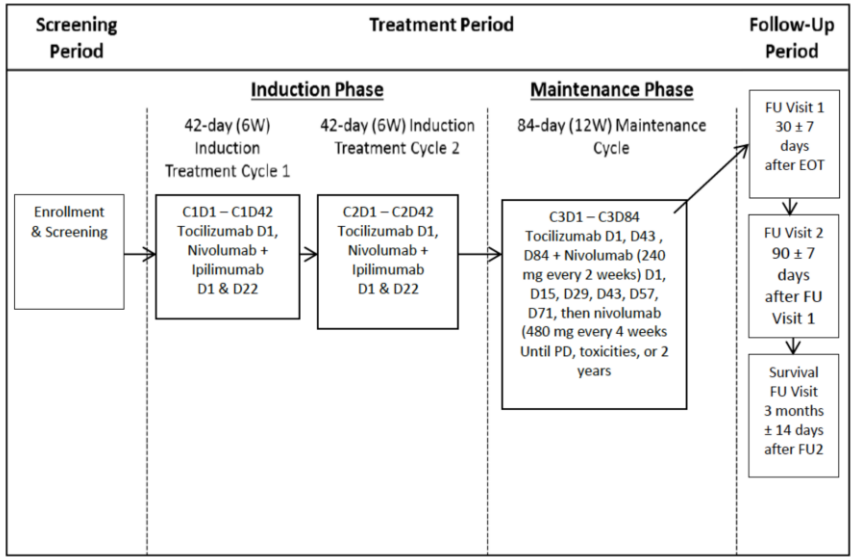


□ *CRP values after tocilizumab were measured within 1-2 weeks after tocilizumab administration.*

Events	*n*= 22
Outcome of irAE or underlying auto-immune disorder	
Resolved	14 (64%)
Resolved with sequalae	1 (5%)
Not resolved (but reduced immunosuppression)	4 (18%)
Not resolved[1]	1 (5%)
Not flared	2 (9%)
Tocilizumab toxicity	5 (23%)
Neutropenia	5 (23%)
Transaminitis	4 (18%)
Lymphopenia	1 (5%)
Bowel perforation	1 (5%)
Action taken to ICI	
Permanently discontinued	8 (36%)
Interrupted	4 (18%)
Median time to irAE onset after ICI start	48 days (range 8-786)
Median time from irAE onset to tocilizumab administration	32 days (range 1-192)
Median time to irAE resolution from tocilizumab administration	6.5 days (range 1-93)

Dimitriou et al ASCO 2021
Laino et al J Immunotherapy and Cancer 2020

Phase II trial of ipilimumab, nivolumab and tocilizumab for unresectable metastatic melanoma



Category	Distribution
Age all (patients)	Median 65.5 years
Gender (all patients)	24 males, 17 females
Stage (all patients)	IV: 38 III: 3
LDH > ULN: of those at week 12	10/29 = 34%
Liver metastases: of those at week 12	7/29 = 24%
Linear tumor measure at baseline, mean	8 cm
Failed adjuvant immunotherapy	2
Performance status of those at week 12	0 = 12 1 = 17
Treatment centers (all patients)	NYU – 18; Angeles Clinic – 14; Dana Farber – 6; MGH - 3

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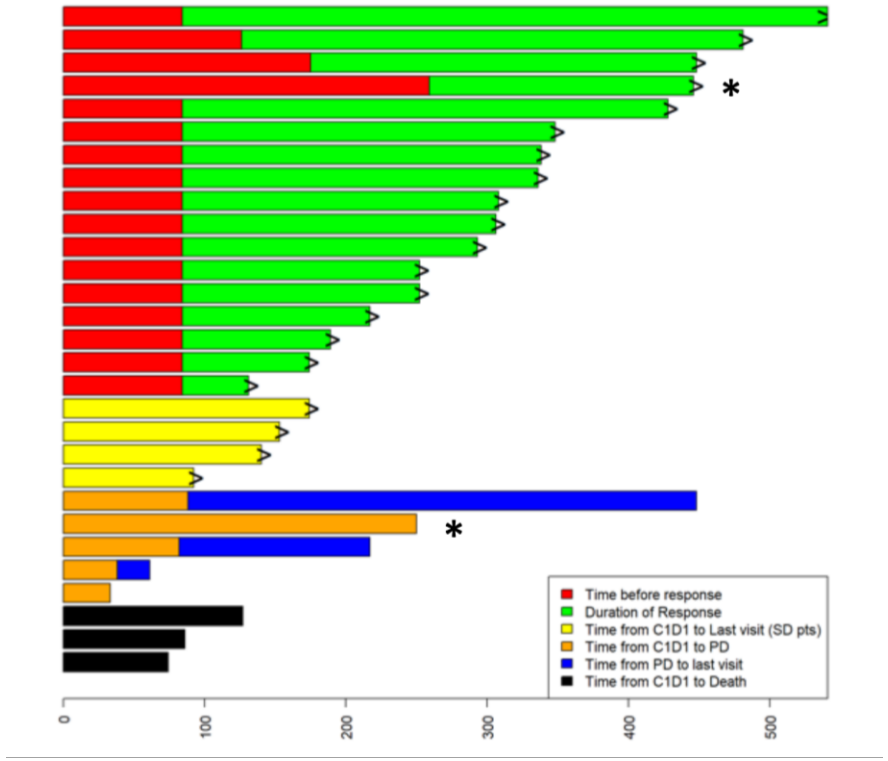
Phase II trial of ipilimumab, nivolumab and tocilizumab for unresectable metastatic melanoma

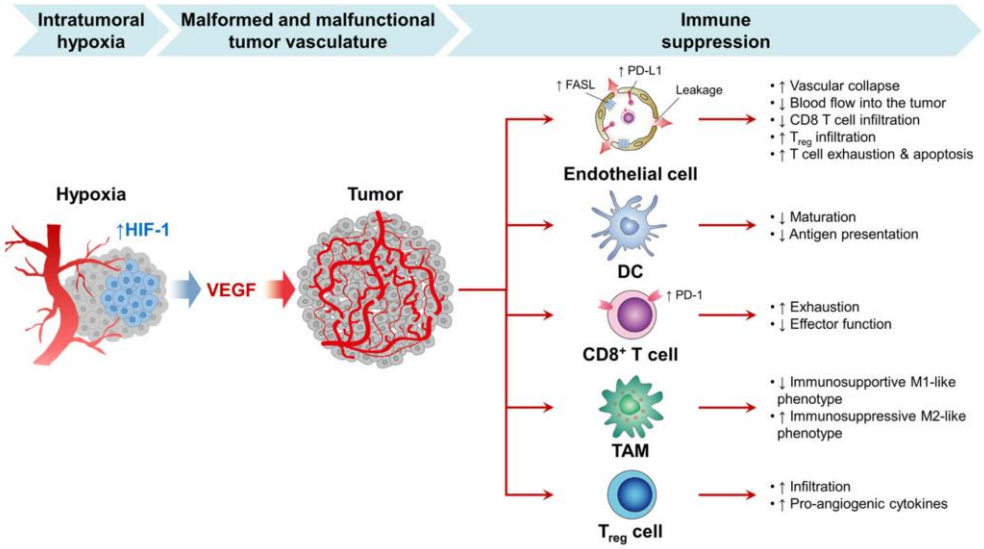
- **Median time of follow up: 8.2mo**
  - **17/29 ORR = 58%**
  - **5/29 SD = 17%**
  - **7/29 PD = 24%**
  - **mDOR: 7.2mo**
  - **mPFS: nr**

- **41 patients evaluable for toxicity**
  - **7/41 patients had G3/4 tox = 17%**
  - **6/41 patient had to discontinue due to tox = 14%**



Anti-angiogenic therapy in melanoma

- **Hypoxia and acidosis induces an immunosuppressive environment:**
  - ✓ **Increasing Treg presence.**
  - ✓ **Drives CD8 cells into exhaustion.**
  - ✓ **Increases immunosuppressive M2 macrophages.**
  - ✓ **Reduces DC antigen presentation.**



Single Agent*	ORR	DOR (mo)	PFS/TTP (mo)	Reference
Lenvatinib	9.7%	8.9	3.7	O'Day. ASCO. 2013
Axitinib	18.8%	5.9	3.9	Fruehauf. *Clin Can Res*. 2011
Aflibercept	7.5%	NA	3.7	Tarhini. *Clin Can Res*. 2011
Bevacizumab	17.0%	NR	7.7	Schuster. *Plos One*. 2012
Average	**13.3%**	**7.4**	**4.8**	

Lee et al Exp & Mol Medicine 2020

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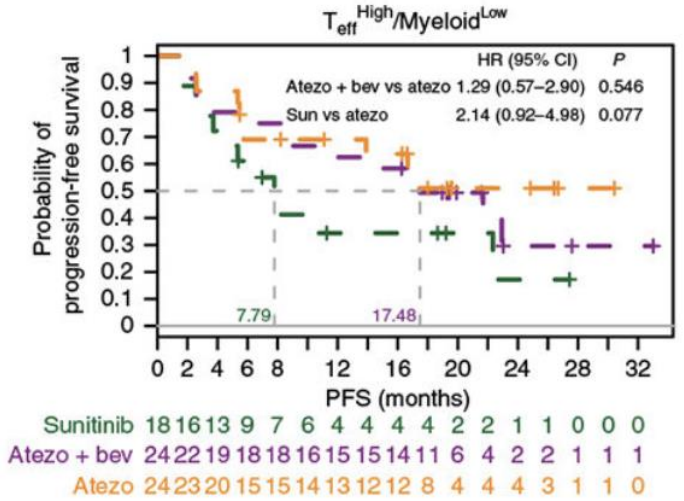
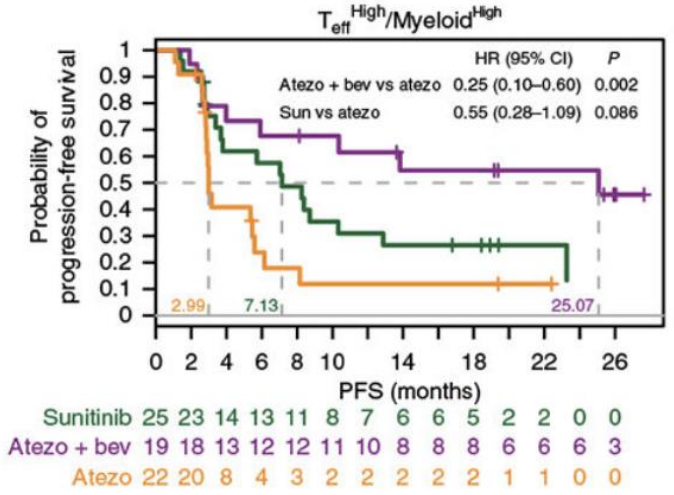
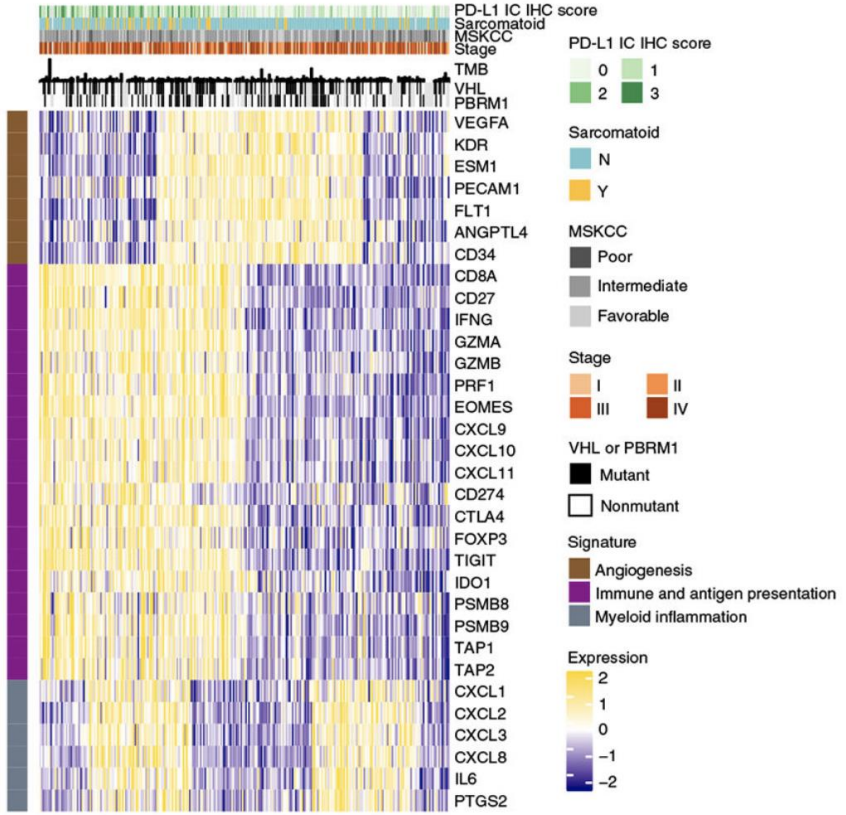
Anti-angiogenic/anti-PD1 therapy in RCC







McDermott et al. Nat. Med. 2018

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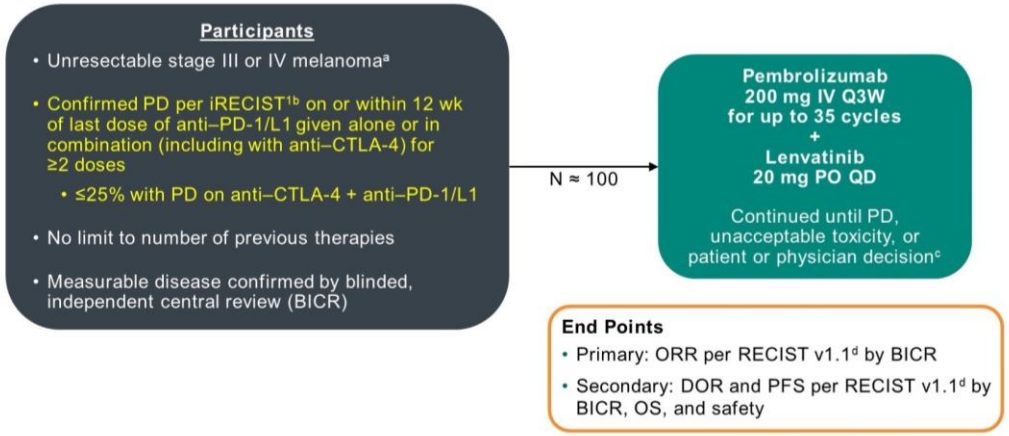
LEAP-004: Lenvatinbi plus pembrolizumab in anti-PD1 refractory melanoma



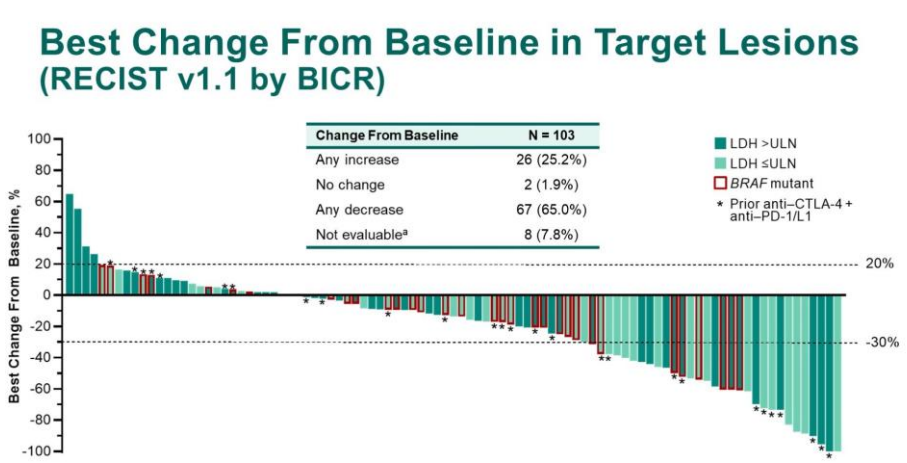
Characteristic, n (%)	N = 103
Age, median (range)	63 y (21-85)
Males	55 (53.4%)
ECOG PS 1	41 (39.8%)
LDH >ULN	57 (55.3%)
≥2 × ULN	21 (20.4%)
Brain metastasis (history of or current)	15 (14.6%)
Sum of target lesions, median (range)	95 mm (18-530)

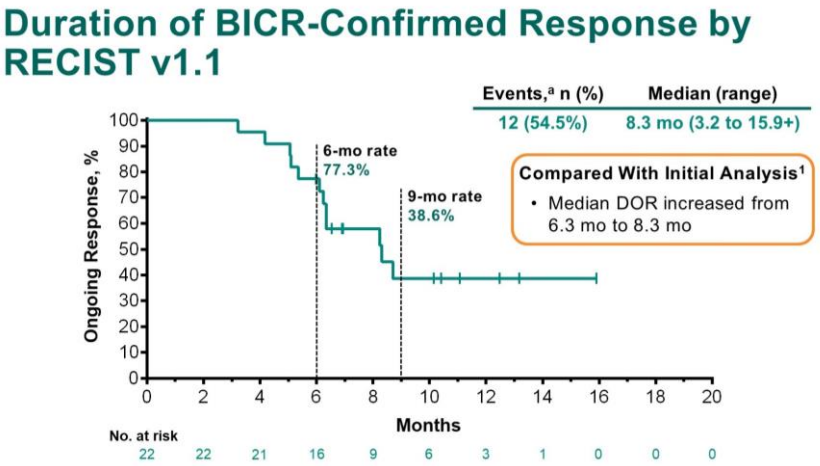
Characteristic, n (%)	N = 103
BRAF^{V600} mutation	38 (36.9%)
PD-L1 positive[a]	66 (64.1%)
Metastatic stage at enrollment	
M0, M1a, or M1b	33 (32.0%)
M1c or M1d	70 (68.0%)
No. of prior lines of therapy	
1	43 (41.7%)
2	26 (25.2%)
≥3	34 (33.0%)

LEAP-004: Lenvatinbi plus pembrolizumab in anti-PD1 refractory melanoma

Clinical efficacy

ORR: 21.4% *DCR: 66%* *PD: 29%*

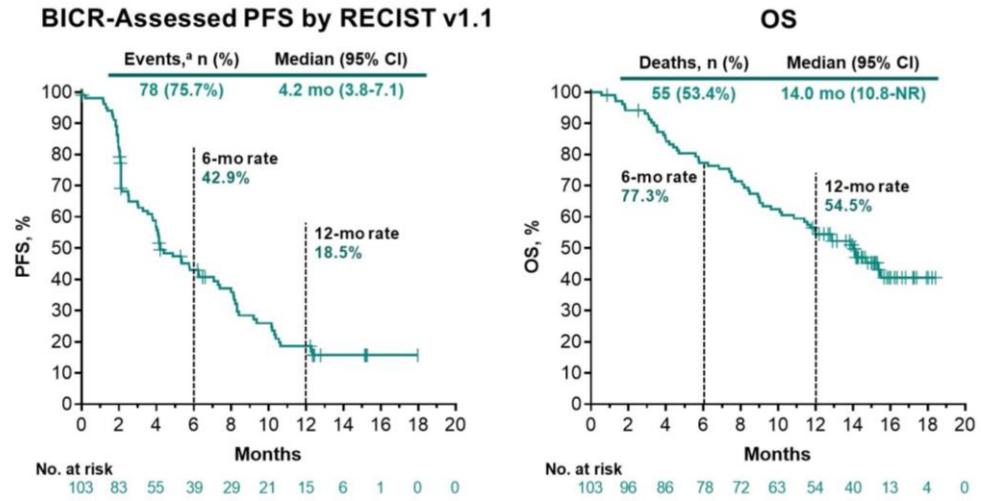




LEAP-004: Lenvatinbi plus pembrolizumab in anti-PD1 refractory melanoma

Outcome and Toxicity

Progression-Free and Overall Survival

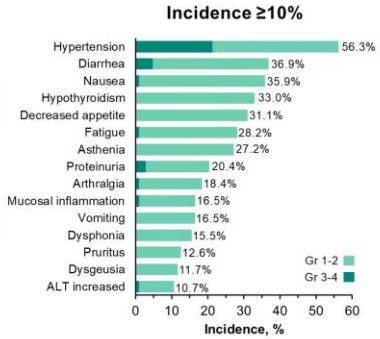


Treatment-Related Adverse Events

Summary

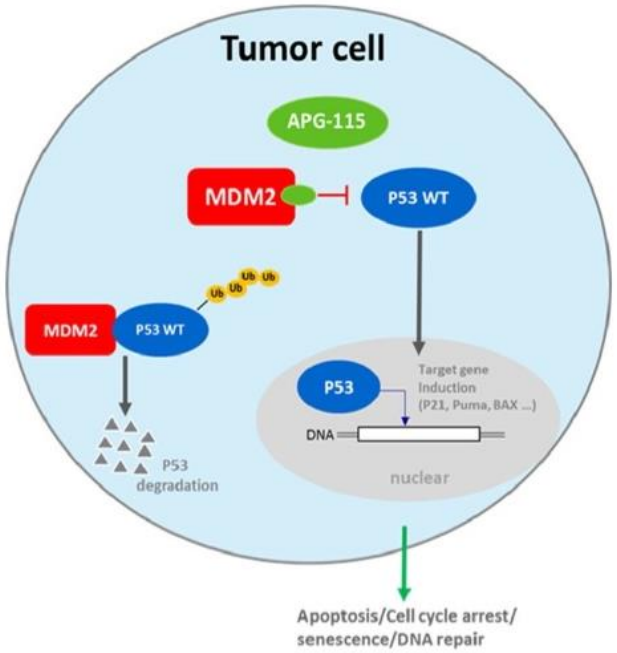
n (%)	N = 103
Any grade	99 (96.1%)
Grade 3-5	47 (45.6%)
Grade 3	42 (40.8%)
Grade 4	4 (3.9%)
Grade 5	1 (1.0%)[a]
Serious	19 (18.4%)
Led to discontinuation[b]	8 (7.8%)
Led to interruption[b]	61 (59.2%)
Led to len dose reduction	58 (56.3%)

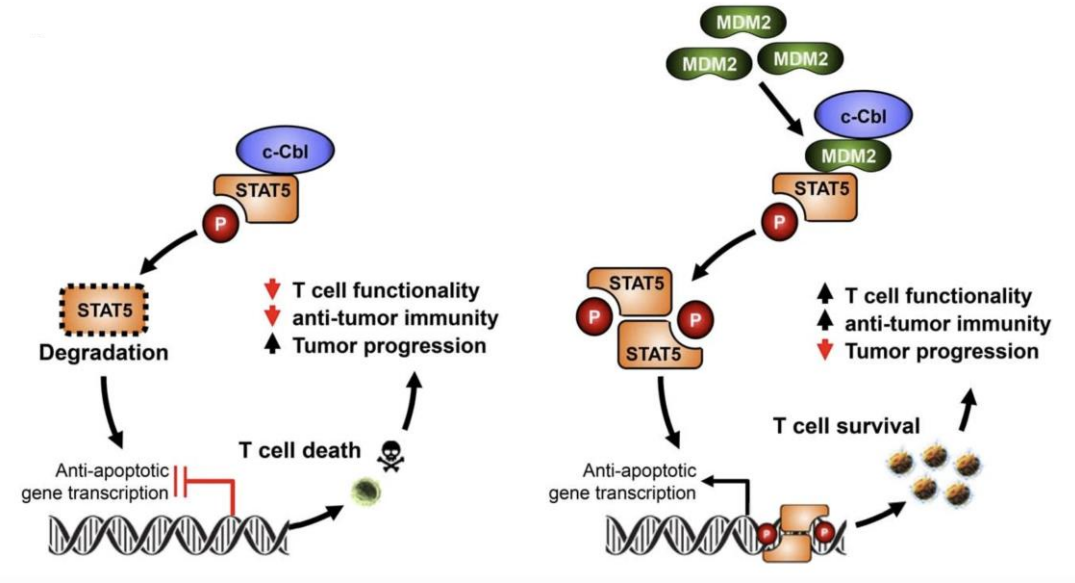
Median (range) duration of treatment
- 6.0 mo (0.1-18.2) for len
- 5.6 mo (1 day-18.2 mo) for pembro



[a]Platelet count decreased. [b]Includes participants who discontinued or interrupted both len and pembro, len alone, or pembro alone.
Data cutoff date: Sep 18, 2020.

Rewiring the TME via inhibition of MDM2





- Blocks MDM2-p53 interaction
- Restores p53 mediated apoptosis in wt and MDM2 expressing cells

- MDM2 inhibition leads to MDM2 abundance
- MDM2 blocks c-Cbl mediated STAT5 degradation
- p53/MDM2/c-MYC axis as a physiological 'brake' to the M2 polarization process

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Zhou et al Nat. Immunology 2021

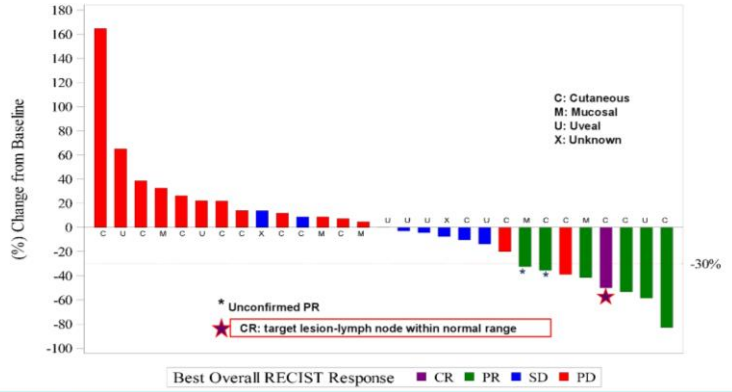
Fang et al J Immunother Cancer 2019

Preliminary results of a phase 2 study of Alrizomadlin (APG-115), a novel, small molecule MDM2 inhibitor in combination with pembrolizumab in patients with unresectable or metastatic melanoma or advanced solid tumors that have been resistant to immuno-oncology drugs

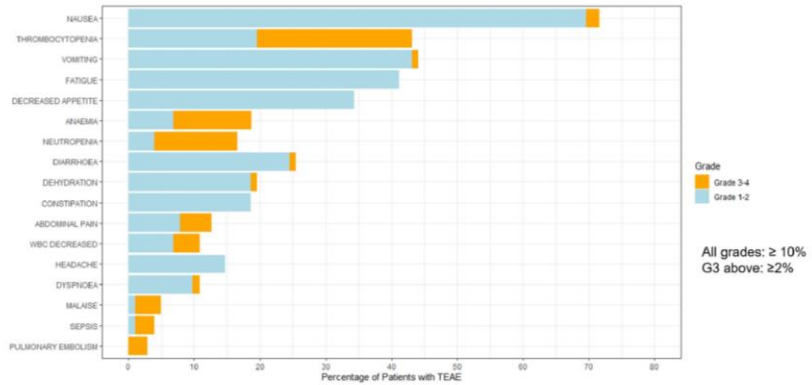
Efficacy in Patients with IO Resistant Melanoma

Response	Uveal (n = 8)	Mucosal (n = 5)	Cutaneous (n = 16)	Unknown primary (n = 3)	Total (N = 32)
ORR (CR + PR)	14.3% (1/7)	40% (2/5)	26.7% (4/15)	0	**24.1%** (7/29*)
DCR (CR+ PR+ SD)	71.4% (5/7)	40% (2/5)	46.7% (7/15)	100% (2/2)	**55.2%** (16/29)
Best overall RECIST or iRECIST response					
CR	0	0	1	0	**1**
PR	1	2 (1 unconfirmed)	3 (1 unconfirmed)	0	**6**
SD	4	0	3	2	**9**

Waterfall Plot: Best Overall Response for all Melanoma Subtypes



Safety: Treatment Emergent AEs (TEAEs)



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Summary

- Currently anti-PD1 based therapy remains the backbone of new immuno-oncology combinations.
- Anit-LAG3 and anti-IL6 appear to be effective with less toxicity compared to the Ipi/Nivo standard of care.
- The tumor microenvironment offers a new set of targets for of immune therapy combinations.
- Early efficacy data with anti-angiogenic and MDM2 inhibition are encouraging.

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