EMORY
WINSHIP
CANCER
INSTITUTE
National Cancer Institute-Designated
Comprehensive Cancer Center

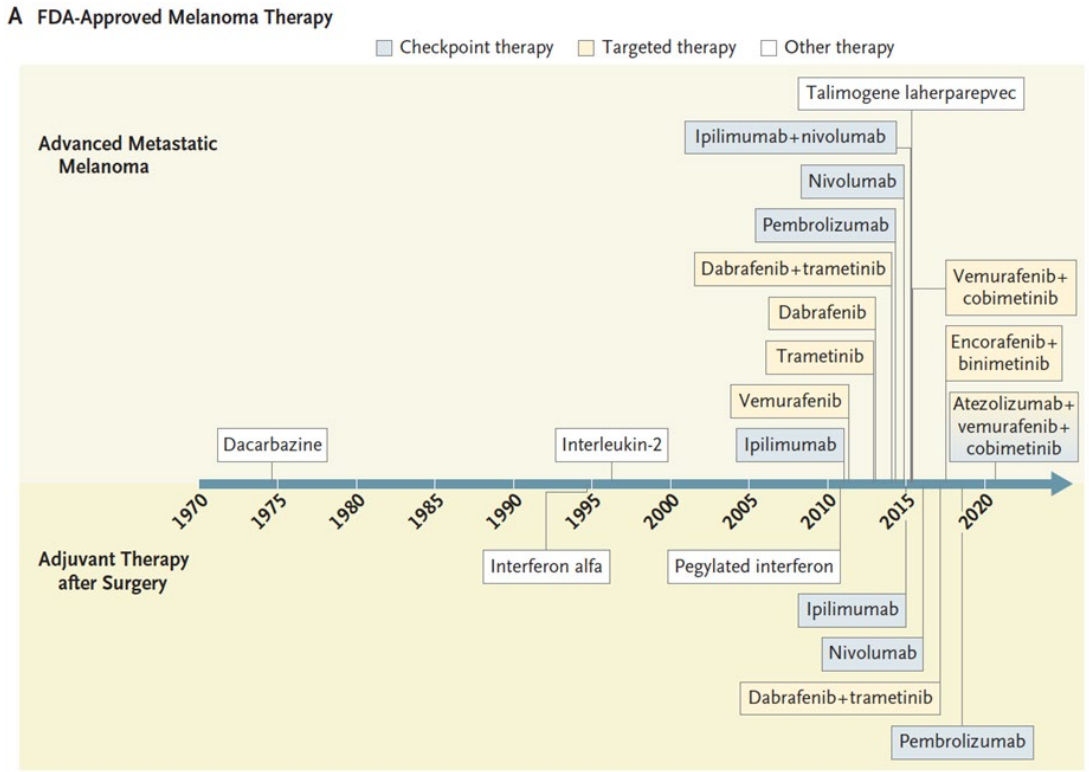
Treatment of PD-1 Refractory Melanoma

Melinda L. Yushak, MD MPH
Winship Cancer Institute

Management of PD-1 Refractory Melanoma

- Background
- BRAF Mutated
- Immune Combinations
- Future Directions

Therapy for Melanoma



BD Curti, MB Faries. N Engl J Med 2021;384:2229-2240

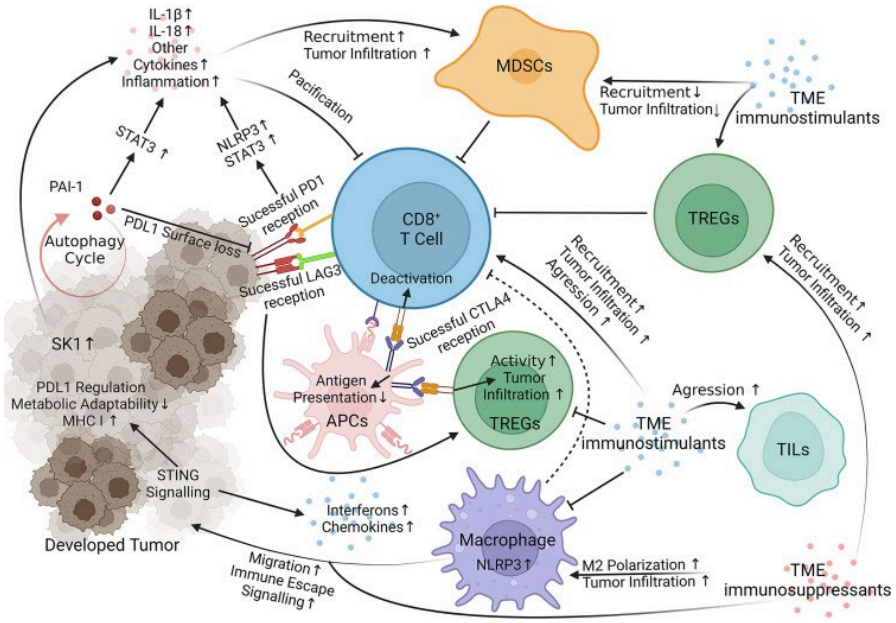
Clinical Scenario

- 52 year old man with a stage IIIC melanoma of the right forearm on adjuvant nivolumab presents for cycle 10 with imaging concerning for new lung and liver lesions and is BRAF V600E mutated

- 63 year old woman with metastatic melanoma who progressed on pembrolizumab and is BRAF WT

PD-1 Refractory Disease

- Primary or acquired resistance
- TME plays role in immunosuppression
- Unmet need



Front Oncol. 2022; 12: 880876.

BRAF Mutated Melanoma

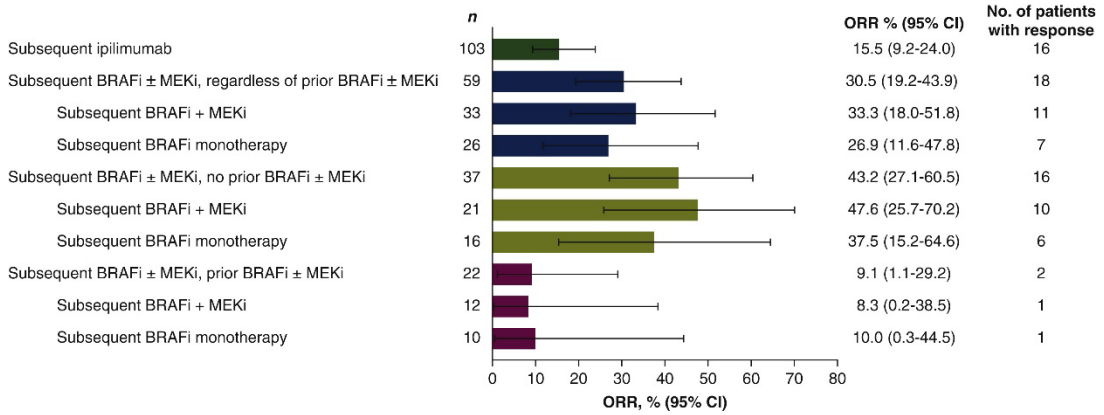
- Approximately 40% of patients

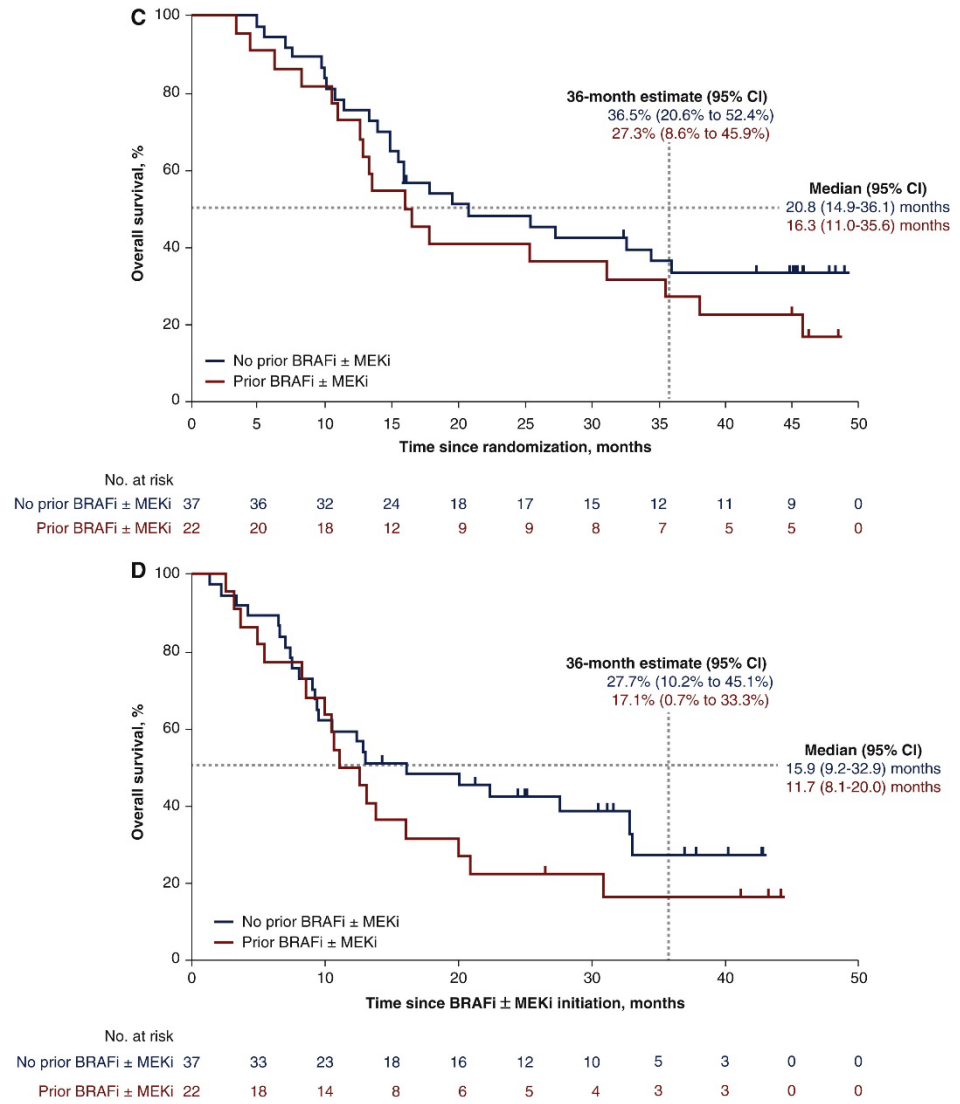
- Many of these patients have prior immunotherapy

BRAF inhibitors after Pembrolizumab

- Keynote-006 post hoc analysis
- Unresectable stage III/IV melanoma
- Pembrolizumab 10 mg/kg every 2 or 3 weeks

BRAF inhibitors after Pembrolizumab





Ann Oncol. 2022 Feb;33(2):204-215.

BRAF inhibitors after Ipi/Nivo

- DREAMseq
- Patients who progressed on Ipilimumab and nivolumab received dabrafenib and trametinib
- ORR 47.8%
- N=23

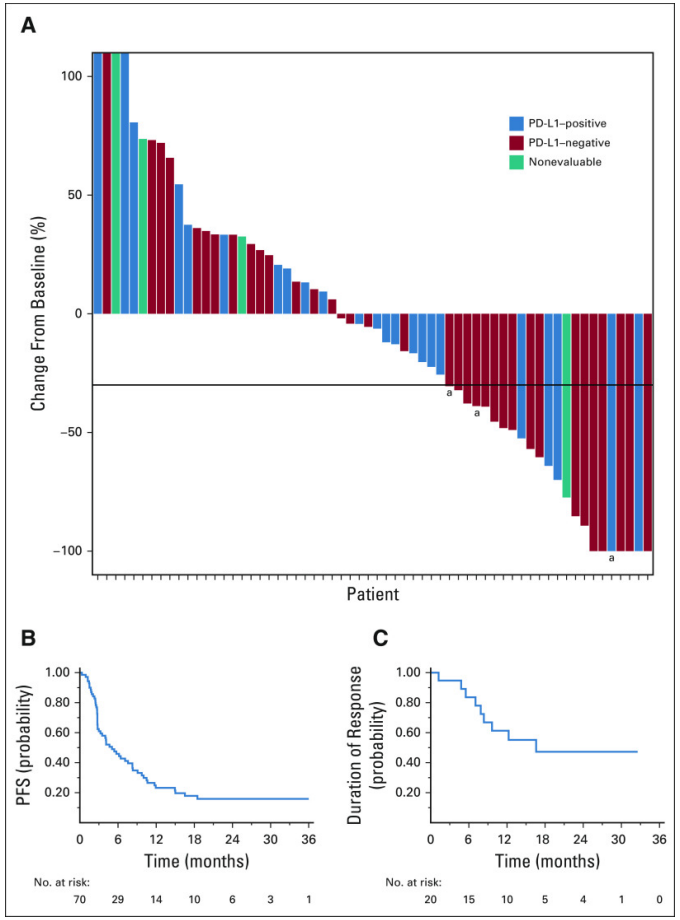
Journal of Clinical Oncology 41, no. 2 (January 10, 2023) 186-197.

What about non BRAF mutated patients?

- Nivolumab or Pembrolizumab
- Nivolumab and Ipilimumab
- Nivolumab and Relatlimab

Addition of Ipilimumab to anti PD-1

- Ipilimumab (1 mg/kg) and pembrolizumab after anti PD-1/L1 failure
- RR 29%
- Median PFS 5 months
- Median OS 24.7 months
- Median duration of response was 16.6 months



J Clin Oncol. 2021 Aug 20; 39(24): 2647–2655.

Ipilimumab and Nivolumab vs. Ipilimumab after anti PD-1 alone

- S1616
- Patients with metastatic or unresectable melanoma without an objective response to anti PD-1 monotherapy
- Patients randomized to ipilimumab and nivolumab vs. ipilimumab
- Hazard ratio for PFS 0.63 favoring ipi/nivo (p=0.04)

	Ipi and Nivo	Ipi alone
ORR	28% (CI 17-40%)	9% (CI 3-34%)
12 month OS	63% (CI 52-72%)	57% (CI 38-71%)

Cancer Res (2022) 82 (12_Supplement): CT013.

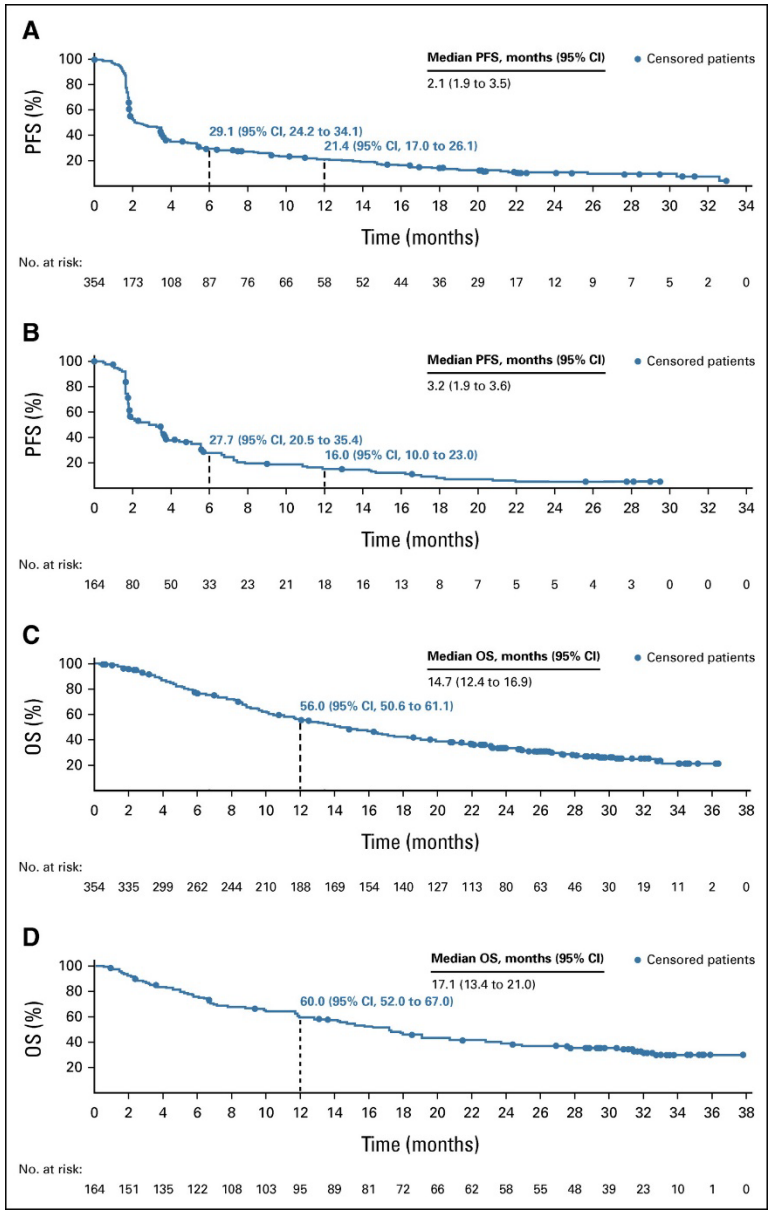
Nivolumab-Relatlimab

- Heavily pretreated patients (46% had >=3 lines of therapy)
- Nivolumab 240 mg and Relatlimab 80 my every 2 weeks
- ORR 11.5%
- DCR 49%

J Clin Oncol 35, 2017 (suppl 15; abstr 9520)

Nivolumab-Relatlimab

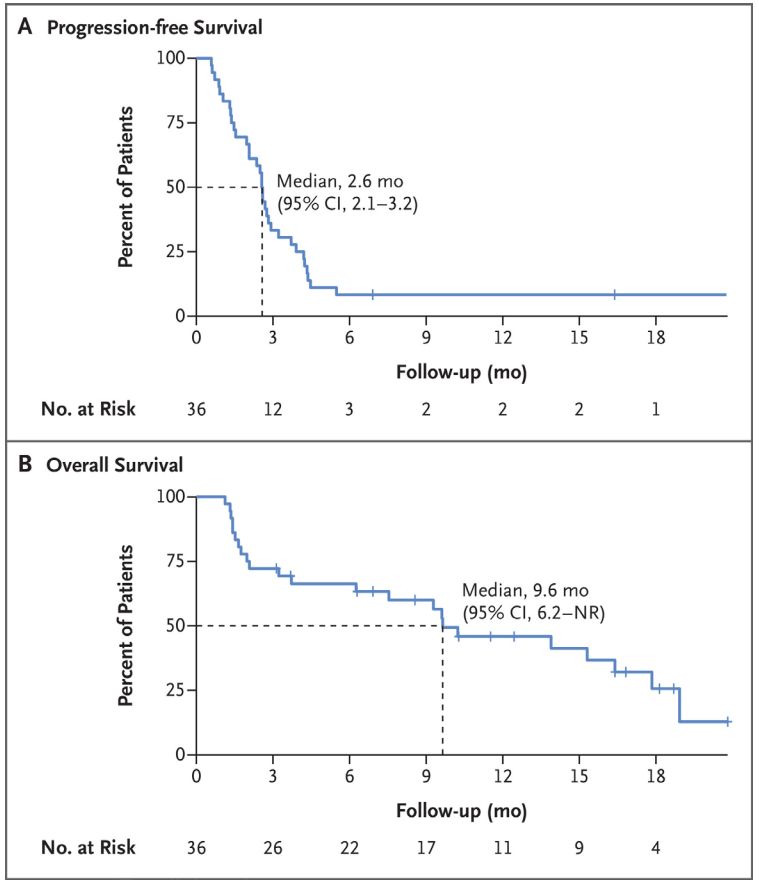
- RELATIVITY-020
- Patients had progressed on PD-1 or PD-1/CTLA-4
- Objective response rate 12%
- PFS at 6 months was 20 percent



J Clin Oncol. 2023 May 20;41(15):2724-2735.

Progression after Nivo-Rela

- Retrospective pooled data from 5 centers
- 36 patients with progression on nivolumab-relatlimab
- Patients received anti CTLA-4 alone or in combination with anti PD-1 antibody
- Objective response in 11%
- Median PFS 2.6 months
- One year OS 46%



N Engl J Med 2022; 386:1668-1669

Second Line Therapy from Relativity-047

RELATIVITY-047

Efficacy on 2L systemic therapy following progression

Investigator reported

Subsequent 2L therapy	NIVO + RELA arm			NIVO arm		
	NIVO + IPI (n = 16)	IPI (n = 9)	BRAFi/MEKi (n = 43)	NIVO + IPI (n = 16)	IPI (n = 14)	BRAFi/MEKi (n = 45)
BOR on subsequent 2L therapy, n (%)	4 (25)	2 (22)	7 (16)	3 (19)	0	7 (16)
CR	2 (12)	0	2 (5)	0	0	0
PR	2 (12)	2 (22)	5 (12)	3 (19)	0	7 (16)
SD	4 (25)	0	1 (2)	0	1 (7.1)	9 (20)
Unk/not reported/UTD[a]	4 (25)	3 (33)	24 (56)	7 (44)	2 (14)	17 (38)
Median time to next treatment, months (range)	8.1 (1.8-18.1)	4.2 (2.1-38.1)	9.7 (0.6-46.4)	4.5 (1.1-30.2)	5.3 (2.5-37.6)	10.6 (<0.1-46.5)
Median PFS,[b] months (95% CI)	8.4 (3.0-NA)	3.4 (1.7-22.3)	15.4 (6.9-NA)	2.9 (1.9-11.6)	2.9 (1.9-3.7)	10.6 (6.0-14.9)
6-month PFS, %	54	33	71	28	7	65
12-month PFS, %	45	22	56	21	0	43

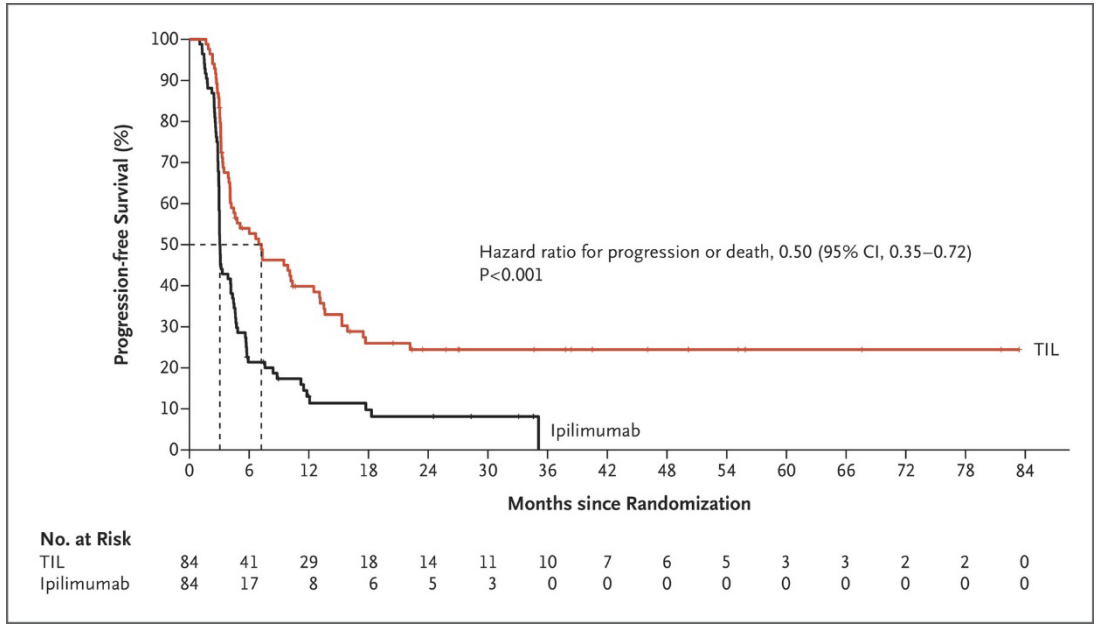
RELATIVITY-047 (NCT03470922). Median follow-up: 25.3 months.
Response on 2L systemic therapy was a post hoc exploratory analysis. Efficacy outcomes on 2L therapy were as reported by the investigator. [a]Responses were unknown, not reported, or unable to be determined. [b]Defined as PFS from the start of 2L therapy to reported PD or death by the investigator.

Tawbi et al. Oral Presentation at ASCO Annual Meeting; June 2-6, 2023; Chicago, IL. Abstract 9502

Future Directions

Tumor Infiltrating Lymphocyte Therapy (TIL)

- Phase III trial of TIL vs. Ipilimumab
- Patients could have received one prior therapy (89%)
  - 24% adjuvant anti PD-1
  - 62% first line anti PD-1
- PFS 7.2 vs. 3.1 months
- OS 25.8 vs. 18.9 months



N Engl J Med 2022; 387:2113-2125

Lifileucel

- Autologous TIL product
- Centrally manufactured with Good Manufacturing Practices
- 22 day process
- Not yet FDA approved, but PDUFA November 2023

Lifileucel

- Unresectable/Metastatic melanoma
- Prior progression on immunotherapy and BRAF/MEK (if applicable)
- At least 1 resectable lesion
- Nonmyeloablative lymphodepleting regimen with cyclophosphamide (60 mg/kg) for 2 days then fludarabine (25 mg/m^2) for 5 days
- One dose of lifileucel (1 x 10^9- 150 x 10^9 cells)
- IL-2 (600,000 IU/kg) every 8-12 hours for up to 6 doses

Outcomes

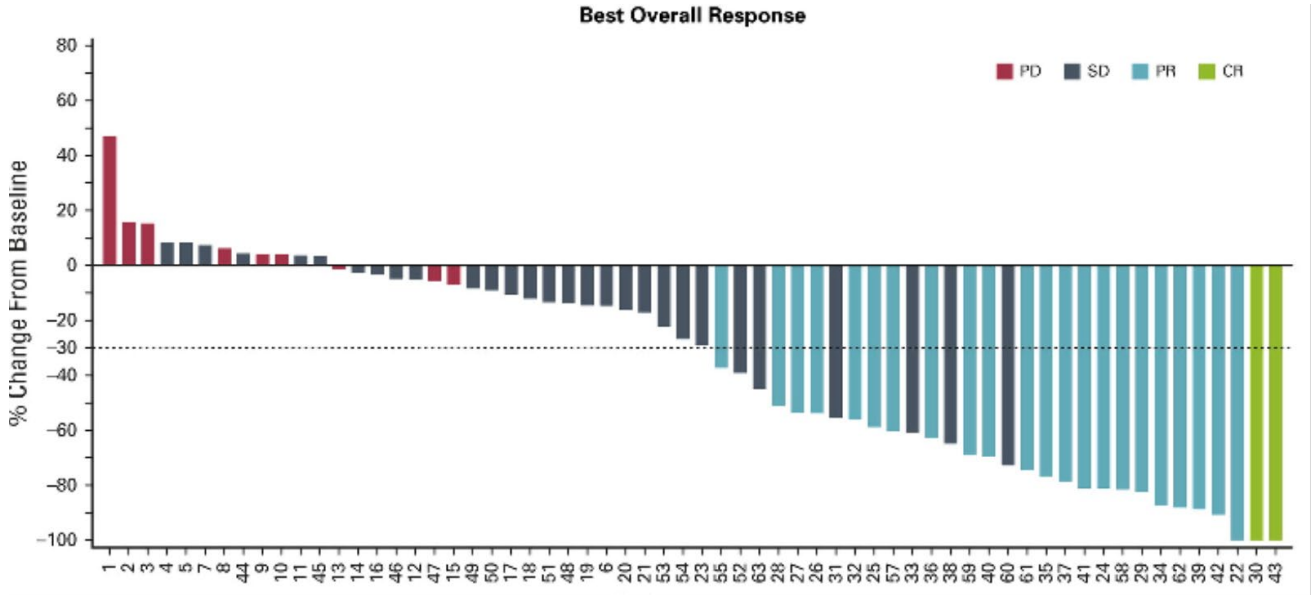


TABLE 2. Efficacy Outcomes by Investigator Assessment

Response (RECIST v1.1)	Cohort 2 (N = 66)
ORR, No. (%) (95% CI)	24 (36) (25 to 49)
DCR, No. (%) (95% CI)	53 (80) (69 to 89)
Best overall response, No. (%)	
CR	2 (3)
PR	22 (33)
SD	29 (44)
PD	9 (14)
Nonevaluable	4 (6)
Median DOR, months (range)	Not reached (2.2-26.9+)

NOTE. +, censored.

Abbreviations: CR, complete response; DCR, disease control rate; DOR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

DOI: 10.1200/JCO.21.00612 *Journal of Clinical Oncology*

Lifileucel

- ORR to patients who failed ipilimumab and nivolumab therapy was similar regardless of receiving treatment frontline or subsequent (33 vs. 32%)

- ORR 35% vs. 27% for primary vs. acquired resistance

Conclusions

- No standard approach for PD-1 refractory melanoma
- Combination therapy is promising for those receiving prior single agent
- New options on the horizon