Melanoma: What is after immunotherapy? More immunomodulation?

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Current Status of First-line Therapy

- BRAF Mutated
  - Targeted therapy
    - Combo BRAF/MEK
    - Combo anti-PD1/targeted (triple therapy)
  - Immunotherapy
    - Single agent anti-PD1
    - Combo anti-PD1/CTLA-4 (Ipi/Nivo)
    - Combo anti-PD1/LAG-3 (Nivo/Relatlimab)

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  - Immunotherapy
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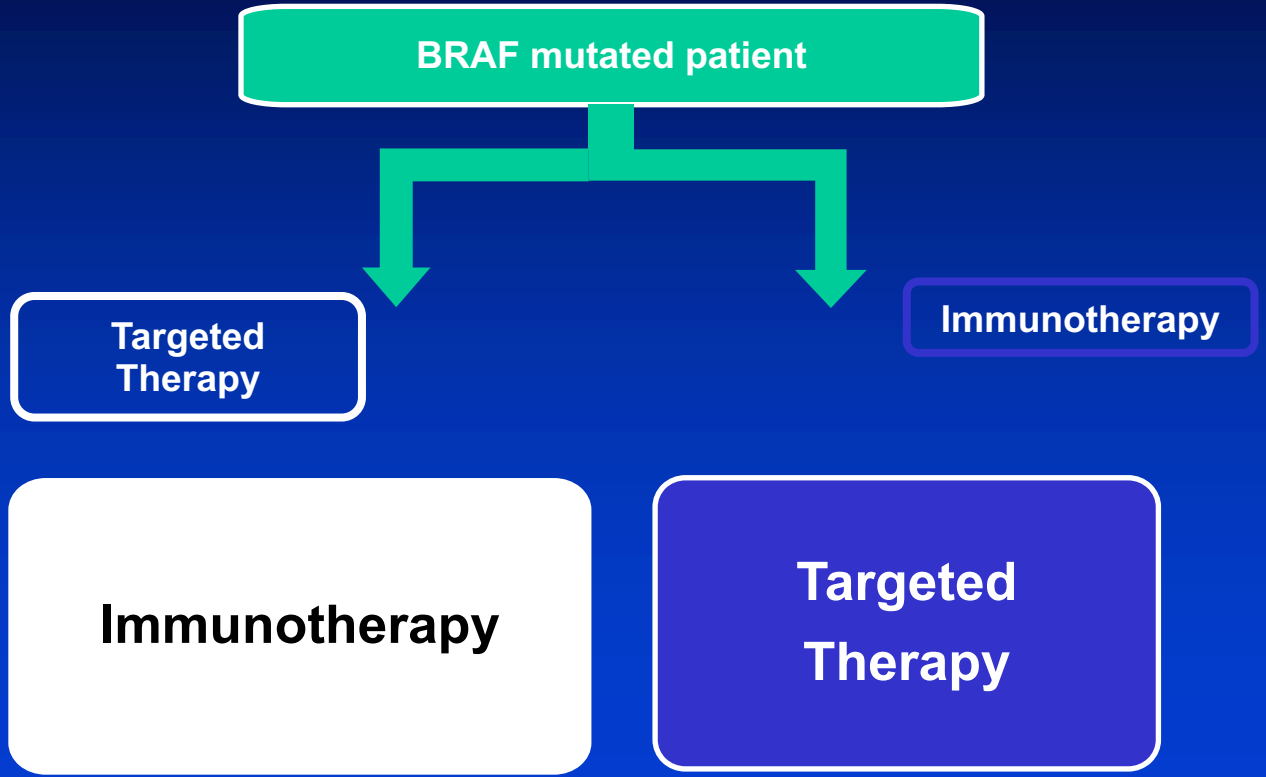
    - Combo anti-PD1/CTLA-4 (Ipi/Nivo)
    - Combo anti-PD1/LAG-3 (Nivo/Relatlimab)

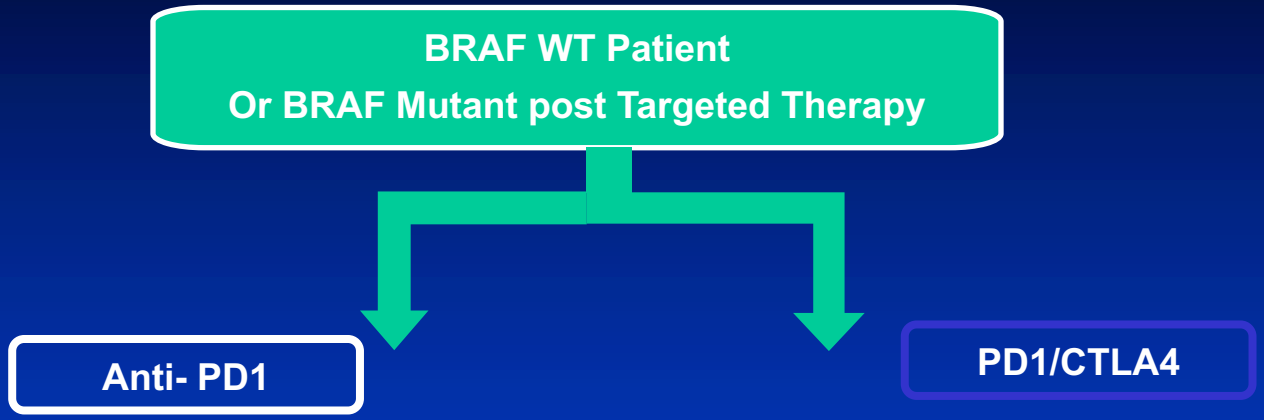
Clinical Issue

- Immunotherapy is most likely going to be used in all patients with advanced melanoma
- What to do after immunotherapy is an important clinical question

Previous Therapy



Previous Therapy



Add Ipi
Switch to Ipi
Other

Unmet Need

After Failure of Combo Immunotherapy

- LAG-3 plus PD-1
- Cellular Therapy
- Lenvatinib + PD-1
- Epigenetic Modification

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LAG3 + PD-1 is Minimally Effective in PD-(L)1 Refractory Melanoma

Relatlimab + Nivolumab 11.5% ORR (n=61) [1]

Fianlimab + Cemiplimab 13.3% ORR (n=15) [2]

[1] Ascierto et al. ESMO 2017
[2] Hamid et al. ESMO 2022

Study design: three serial expansion cohorts in advanced melanoma setting

Treatment:
Fianlimab 1600 mg + cemiplimab 350 mg IV every 3 weeks, for up to 51 weeks*

Initial cohort MM1# (n=40)
1L or 2L advanced melanoma patients who have never received anti-PD-(L)1

Confirmatory cohort MM2# (n=40)
1L advanced melanoma patients who have never received anti-PD-(L)1

PD-1 experienced cohort MM3# (n=18)
1L advanced melanoma patients with prior (neo)adjuvant systemic therapy†, including 13/18 patients who received anti-PD-1

Primary endpoint

- ORR per RECIST 1.1 criteria

Secondary endpoints

- PFS
- DoR
- DCR
- Safety
- PK

Key inclusion criteria

- Metastatic or inoperable locally advanced non-uveal melanoma
- ≥18 years of age
- ECOG PS of 0 or 1
- At least one lesion measurable by RECIST 1.1

Key exclusion criteria

- Uveal melanoma
- Prior treatment with a LAG-3 targeting agent
- Radiation therapy within 2 weeks prior to enrollment

MM1#, Cohort 6; MM2#, Cohort 15; MM3#, Cohort 16. *With an option for an additional 51 weeks; †Prior exposure to (neo)adjuvant systemic treatment (including anti-PD-1) with recurrence >6 months after adjuvant therapy.
1L, first line; 2L, second line; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance score; IV, intravenous; LAG-3, lymphocyte activation gene-3; MM, metastatic melanoma; NHL, non-Hodgkin lymphoma; ORR, objective response rate; PD-(L)1, programmed cell death-(ligand)1; PFS, progression-free survival; PK, pharmacokinetics; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Tumor response by cohort

Response endpoints	Initial cohort MM1# (n=40)	Confirmatory cohort MM2# (n=40)	PD-1 experienced cohort MM3# (n=18)*
Median follow-up (IQR), months	**20.8 (11.2–30.8)**	**11.5 (8.9–13.9)**	**9.7 (4.8–14.1)**
Treatment exposure, median (IQR), weeks	**37 (20–81)**	**35 (15–51)**	**23 (12–37)**
ORR, (n)	**63% (25)**	**63% (25)**	**56% (10)**
95% CI for ORR	(46–77)	(46–77)	(31–79)
DoR, median (95% CI), months	**NR (12–NE)**	**NR (NE–NE)**	**NR (6–NE)**
DCR, (n)	**80% (32)**	**80% (32)**	**67% (12)**
95% CI for DCR	(64–91)	(64–91)	(41–87)
Best overall response, (n)			
CR	15% (6)	13% (5)	6% (1)
PR	48% (19)	50% (20)	50% (9)
SD	18% (7)	18% (7)	11% (2)
PD	15% (6)	15% (6)	28% (5)
NE	5% (2)	5% (2)	6% (1)
KM-estimated PFS, median (95% CI), months	**24 (4–NE)**	**15 (7–NE)**	**12 (1–NE)**

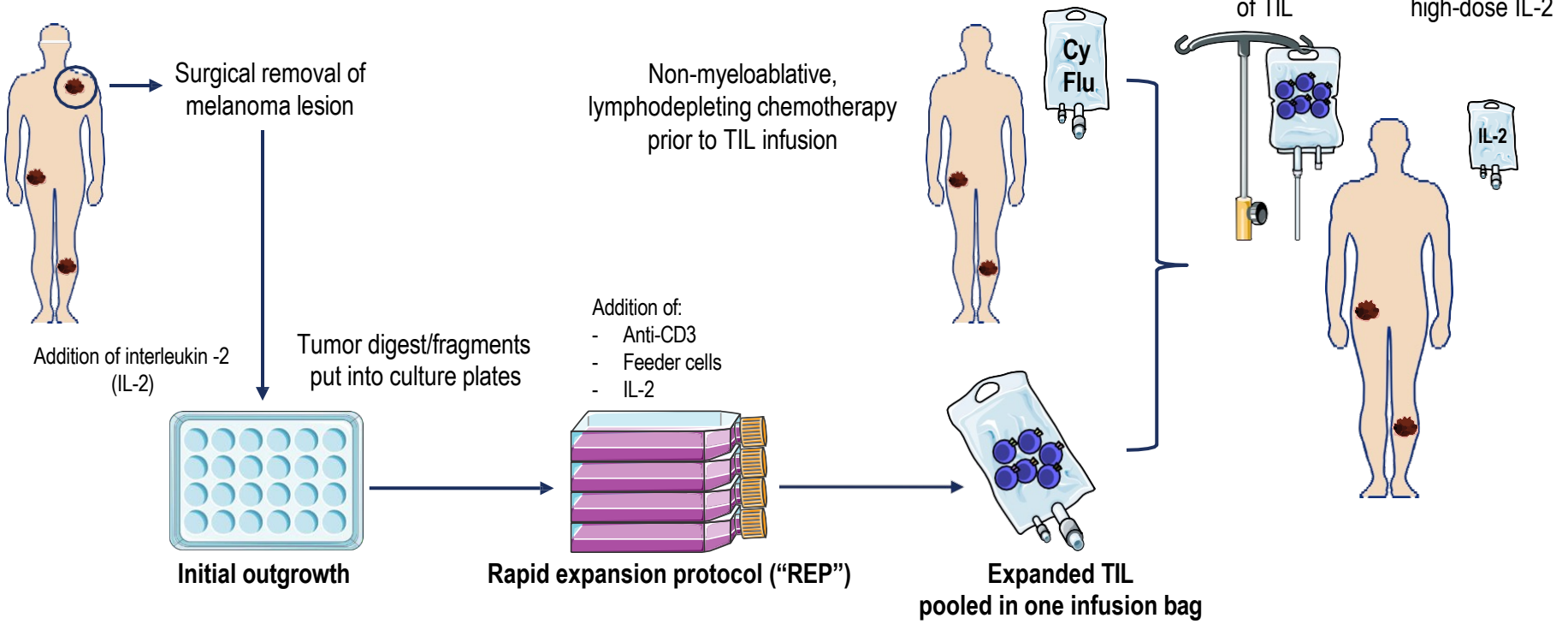
MM1#, Cohort 6; MM2#, Cohort 15; MM3#, Cohort 16. *17 patients in cohort MM3 received prior adjuvant therapy and 1 patient in cohort MM3 received prior neoadjuvant and adjuvant therapy.
CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; IQR, interquartile range; KM, Kaplan-Meier; MM, metastatic melanoma; n, number; NE, not estimated; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

After Failure of Combo Immunotherapy

- LAG-3 plus PD-1
- Cellular Therapy
- Lenvatinib + PD-1
- Epigenetic Modification

Tumor-infiltrating lymphocytes (TIL)

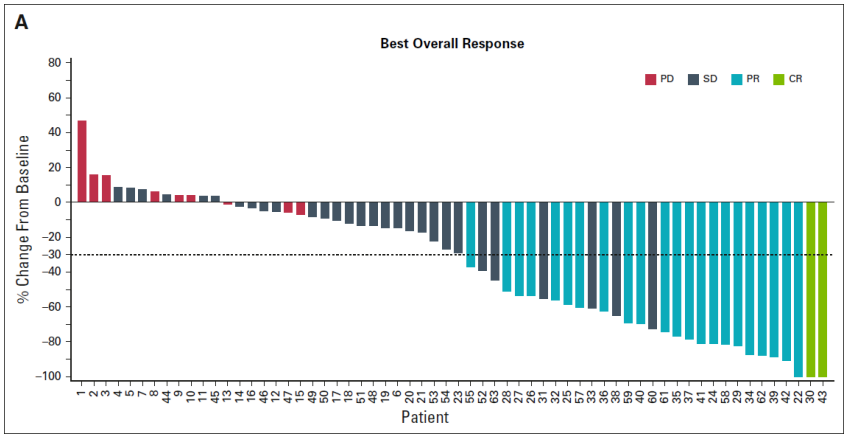
Preparation and treatment



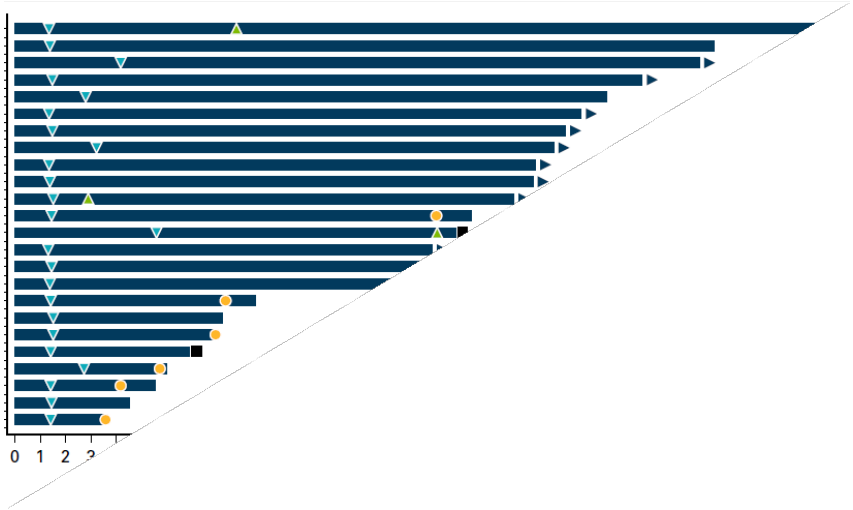
TIL therapy in aPD1 resistant melanoma patients

Clinical efficacy of cryopreserved TIL product - Lifileucel

Response rate 36 % CR 3%

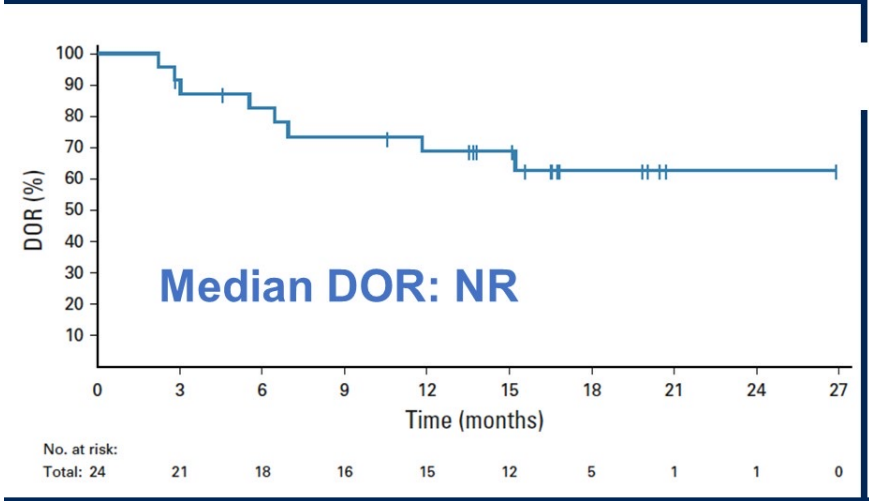


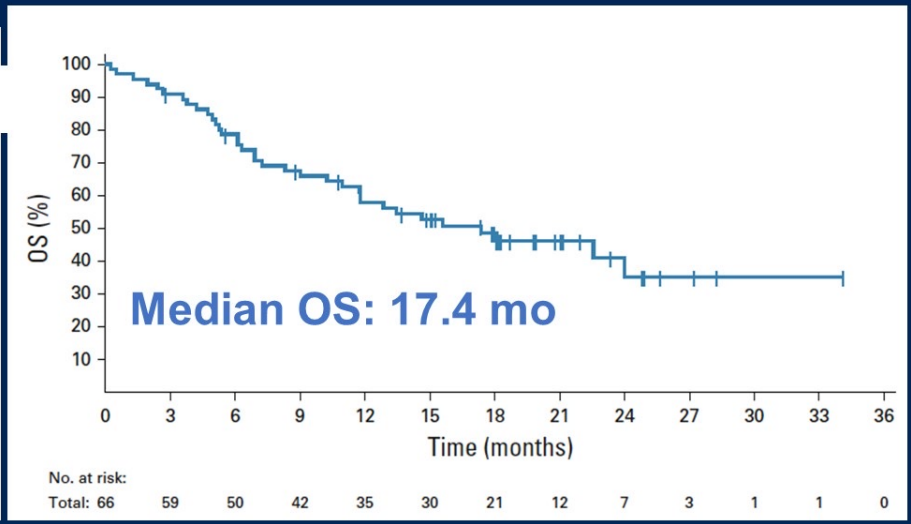
Durability of response



Lifileucel cryopreseved TIL product from Iovance
Production time 22 days.

Progression after anti-PD-1: TIL Therapy with Lifileucel

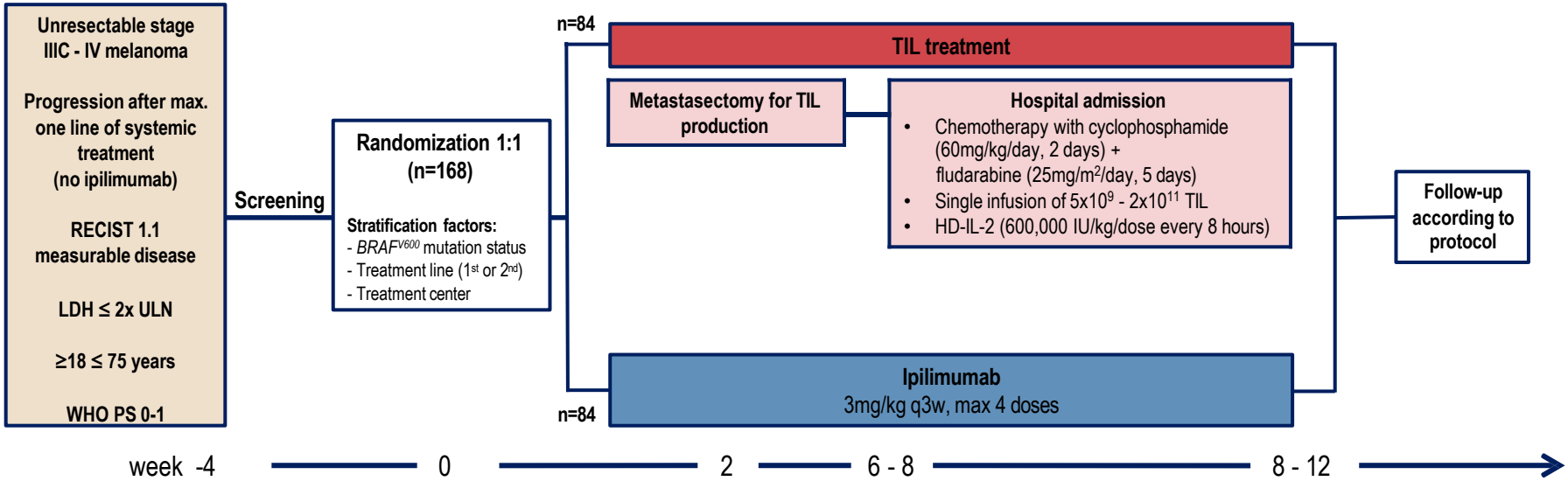




PRESENTED BY:

(Sarnaik et al. *J Clin Oncol* 2021)

Trial design

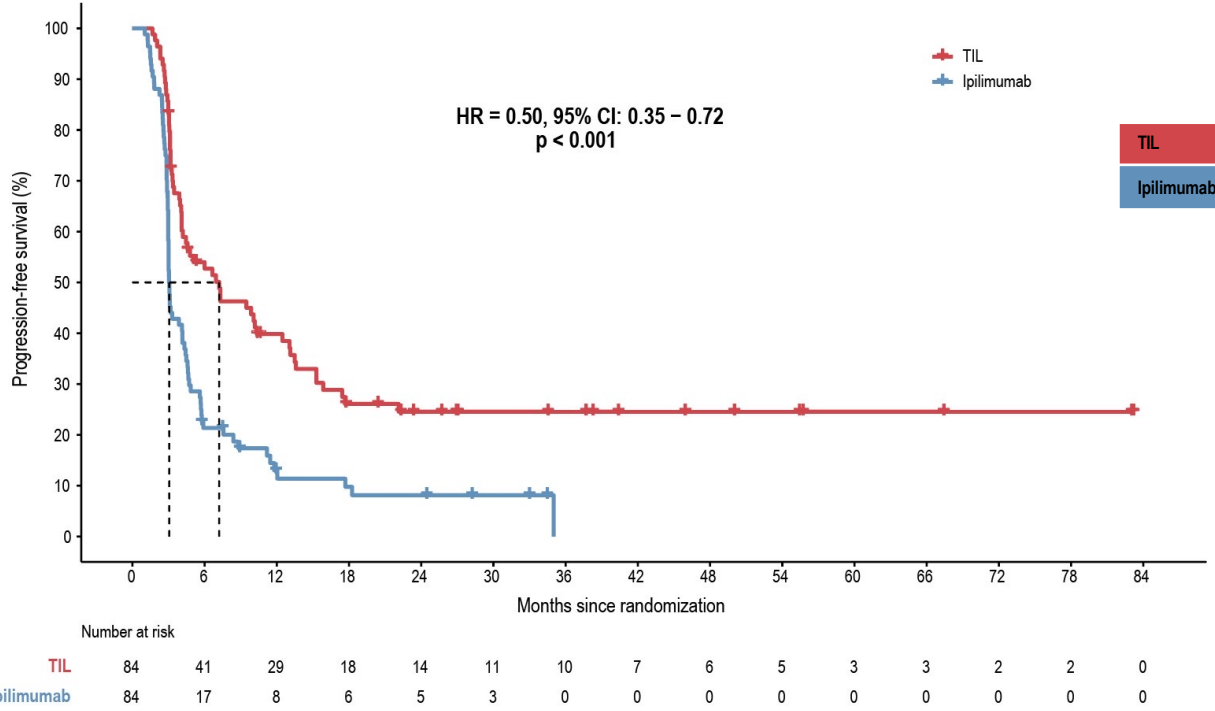


Primary endpoint: Progression-free survival (PFS) according to RECIST 1.1 per investigator review in the intention-to-treat population (ITT)*

*Using the stratified (unweighted) log-rank test and the stratified cox regression model. The study was considered to be positive when PFS after TIL is significantly longer than ipilimumab, based on the log-rank test with a two-sided p-value below 0.05.

Results (1)

Progression-free survival according to RECIST 1.1 in the ITT population



	Median follow-up (months)	Median PFS (months)	95% CI	6 month PFS (%)	95% CI
TIL	33.5	7.2	4.2 - 13.1	52.7	42.9 - 64.7
Ipilimumab	33.0	3.1	3.0 - 4.3	21.4	14.2 - 32.2

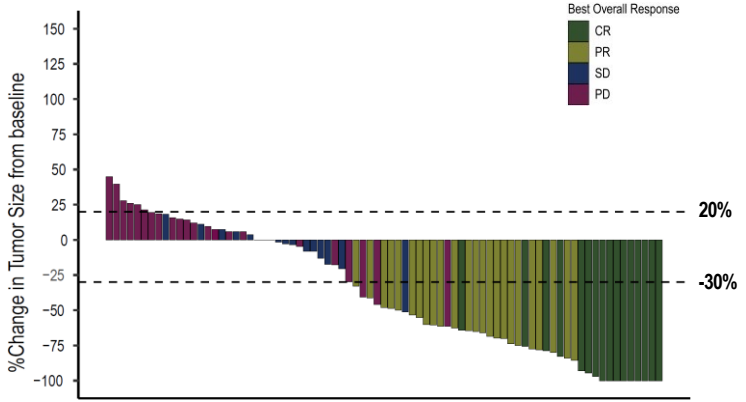
Results (2)

Best overall response according to RECIST 1.1*

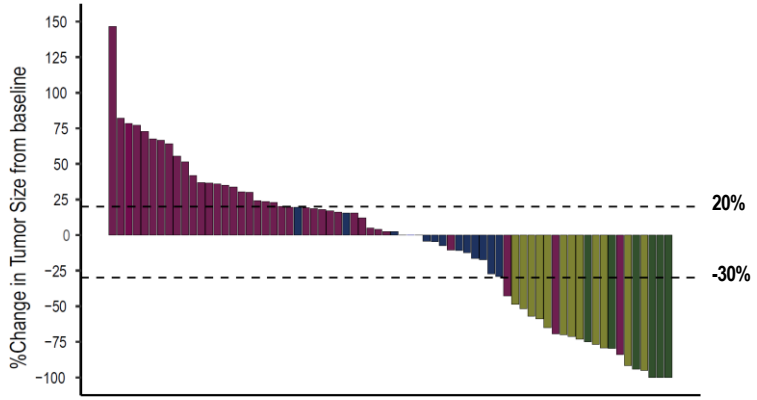
	TIL (n=84)	Ipilimumab (n=84)
Best overall response	**n (%)**	**n (%)**
Complete response	17 (20.2)	6 (7.1)
Partial response	24 (28.6)	12 (14.3)
Stable disease	16 (19.1)	15 (17.9)
Progressive disease	24 (28.6)	40 (47.6)
Not evaluable/done[#]	3 (3.6)	11 (13.1)
Overall response[†]	41 (48.8)	18 (21.4)
Clinical benefit[‡]	57 (67.9)	33 (39.3)

*In the intention-to-treat population. [#]In 3 (3.6%) and 11 (13.1%) of TIL and ipilimumab treated patients, respectively, best radiologic response could not be evaluated or was not done due to an event (death or need to start subsequent anticancer therapy) before the moment of first response evaluation or due to unevaluable target lesions in follow-up. [†]Defined as CR plus PR and [‡]CR, PR plus SD according to RECIST 1.1.

TIL treatment

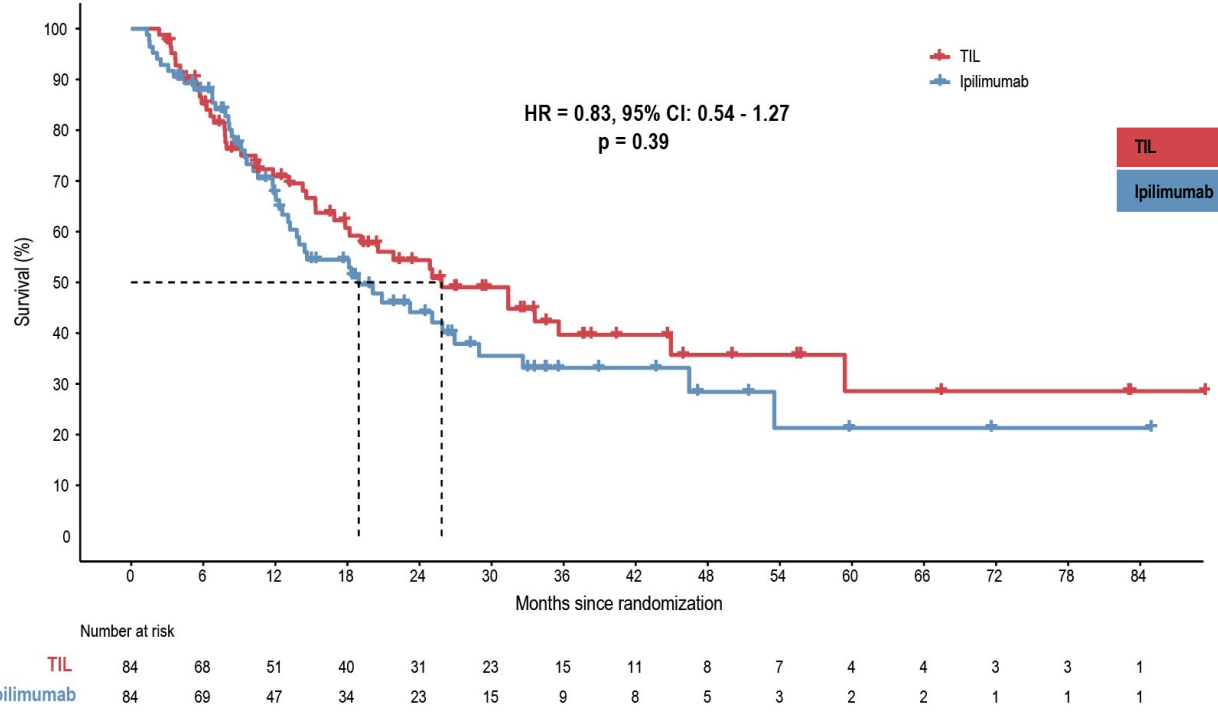


Ipilimumab treatment



Results (3)

Overall survival in the ITT population



	Median overall survival (months)	95% CI	2 year overall survival (%)	95% CI
TIL	25.8	18.2 – NR	54.4	44.0 – 67.3
Ipilimumab	18.9	13.8 – 32.6	44.1	33.7 – 57.8

Next-generation strategies

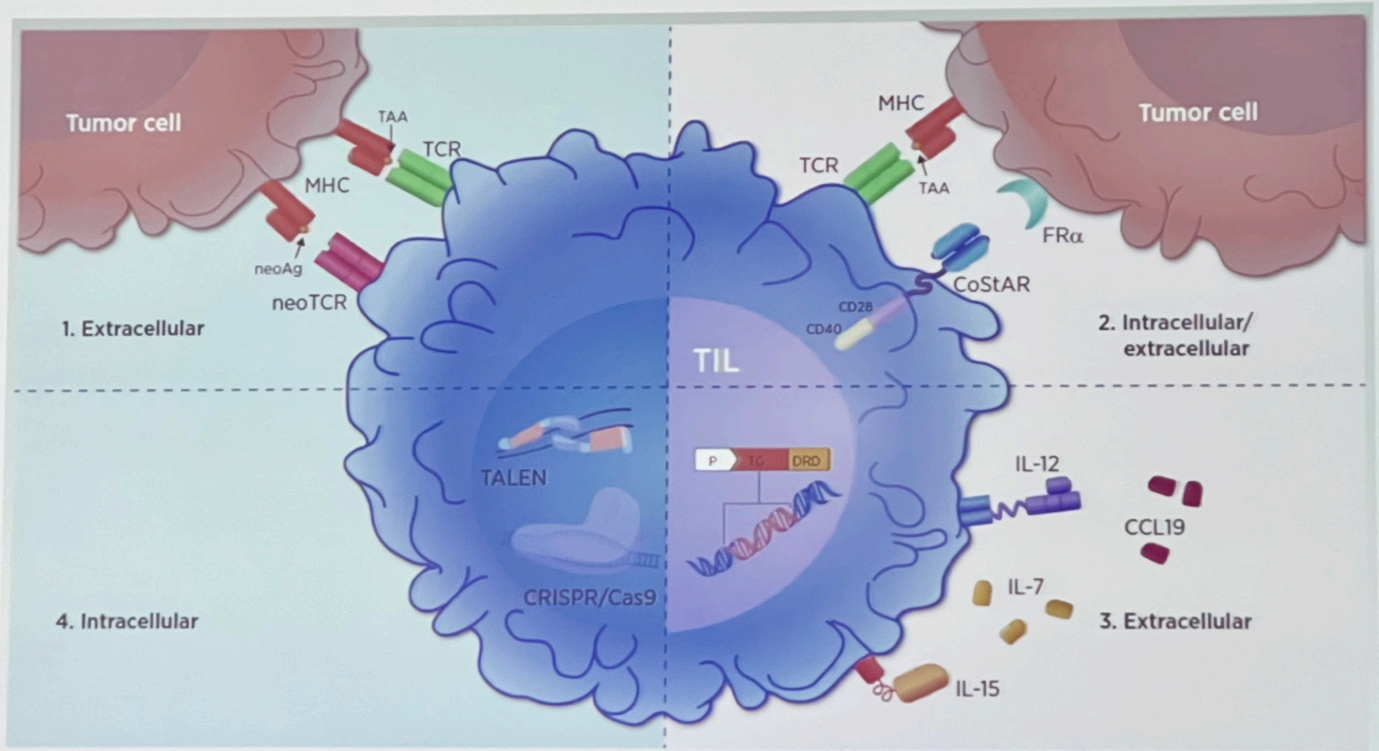
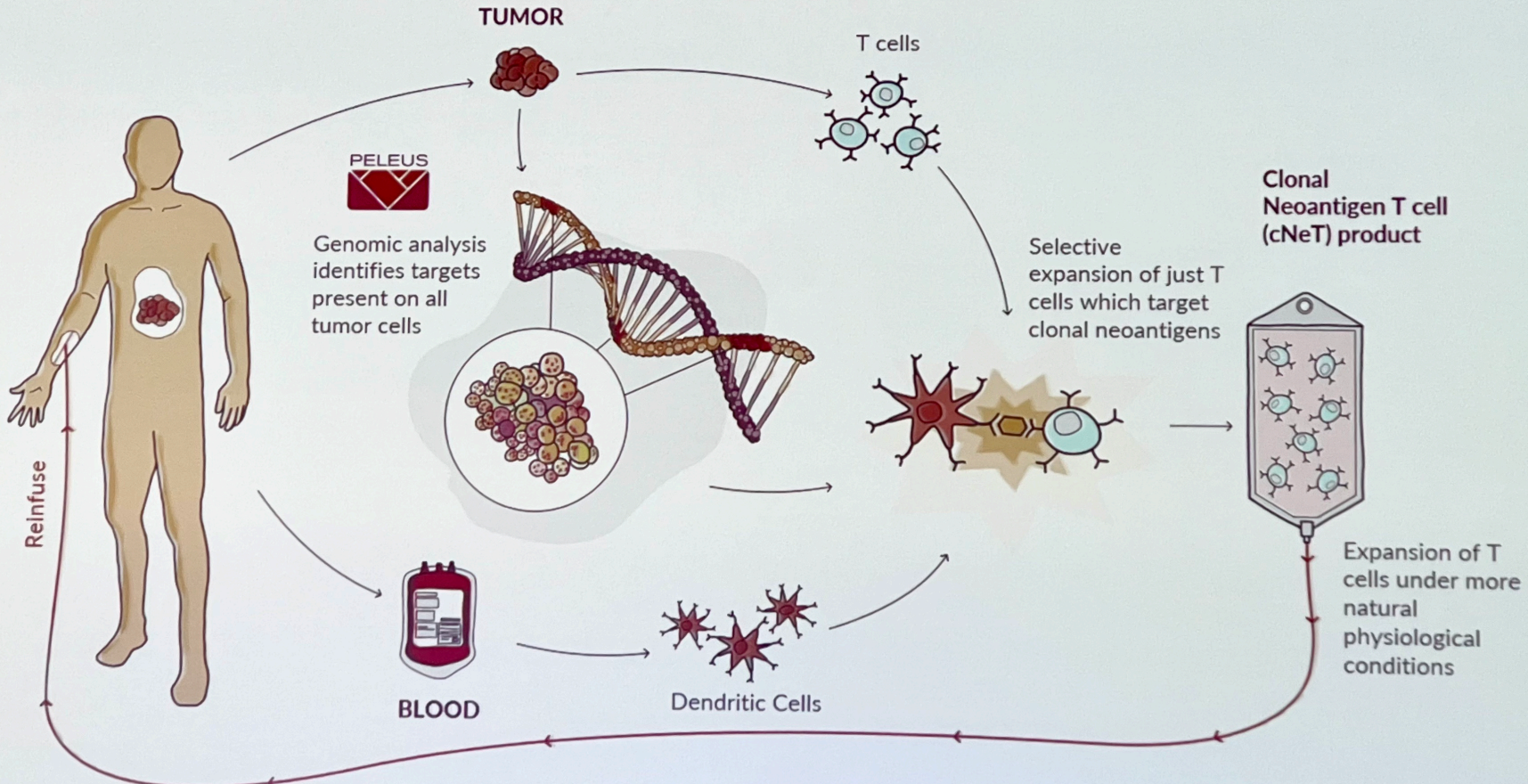


Figure 2.
Strategies to optimize T-cell activation in next-generation TIL. Immune-modulation strategies involve improvements in intracellular and extracellular signaling.

‘Precision’ TIL therapy - targeting clonal neoantigens



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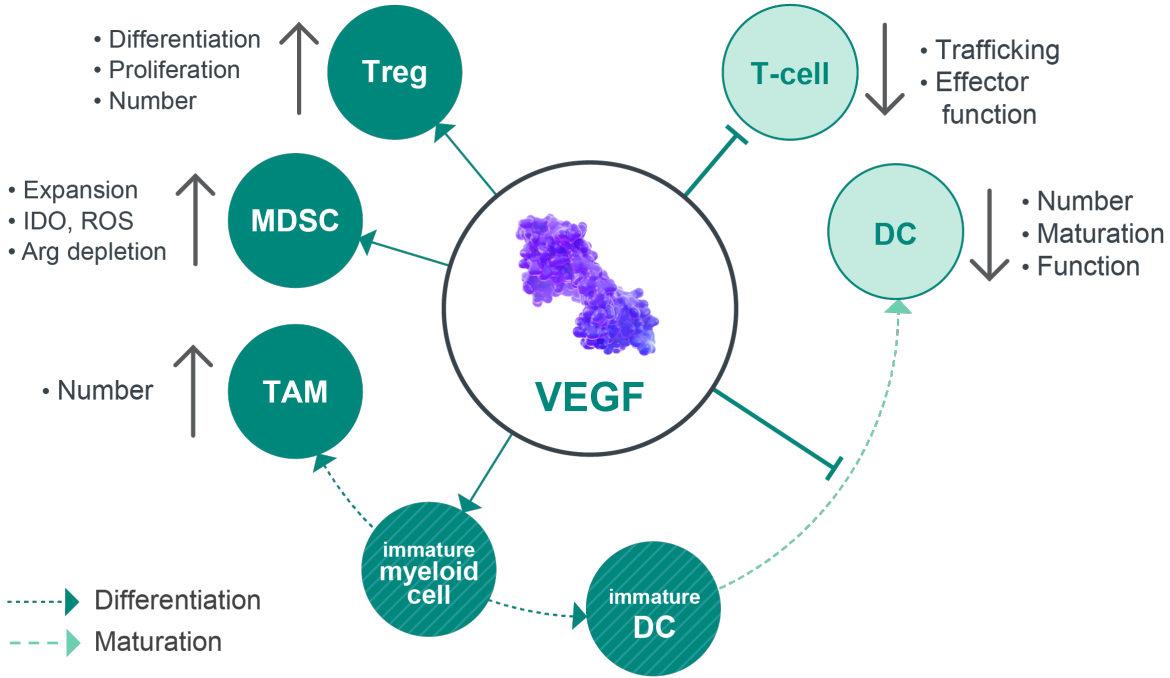
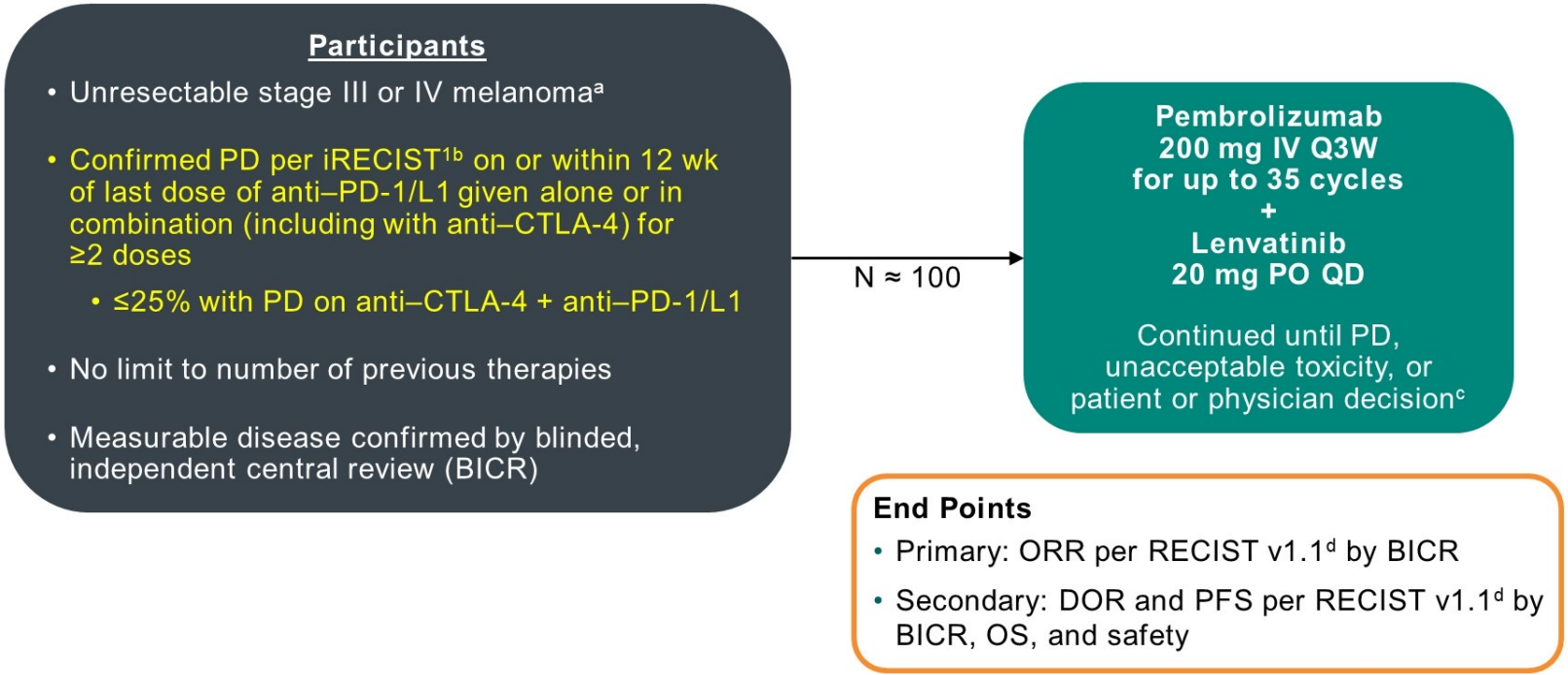
VEGFR Signaling Can Lead to an Immunosuppressive State in the Tumor Microenvironment



- VEGF modulates the function of T-cells, suppressive immune cells, and stroma in the tumor microenvironment
- Early studies in metastatic melanoma suggest a rationale for combining VEGF inhibitors with immune checkpoint inhibitors

Ott PA et al. Front Oncol. 2015;5:202.

LEAP-004 Study Design (NCT03776136)



[a]Per AJCC 8th edition. [b]In the absence of rapid clinical progression, initial evidence of radiologic PD required confirmation by a second assessment performed ≥4 weeks from first documented radiographic PD. [c]Eligible patients deriving clinical benefit can be treated beyond PD. Participants with CR can discontinue study treatment if they have received it for ≥24 weeks. [d]Modified to follow ≤10 target lesions total and ≤5 target lesions per organ. 1. Seymour L et al. *Lancet Oncol* 2017;18:e143-52.

BICR-Confirmed Response by RECIST v1.1

	Total Population N = 103
ORR, % (95% CI)	**21.4% (13.9-30.5)**
DCR, % (95% CI)	66.0% (56.0-75.1)
Best overall response, n (%)	
CR	3 (2.9%)
PR	19 (18.4%)
SD	46 (44.7%)
PD	30 (29.1%)
Not assessed[a]	5 (4.9%)

Compared With Initial Analysis[1]

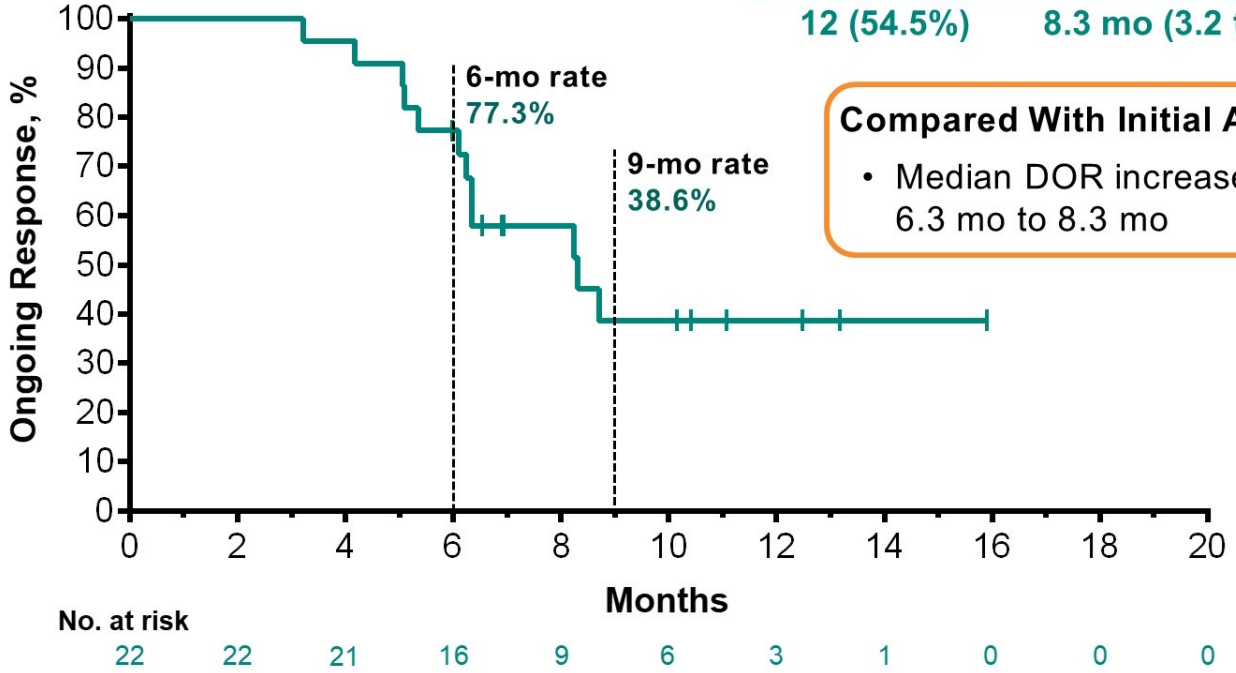
- ORR remained the same
  - 1 additional CR
- DCR increased from 65.0% to 66.0%
  - 1 additional SD

[a]Participants who had no post-baseline imaging assessments. Data cutoff date: Sep 18, 2020.

1. Arance A et al. *Ann Oncol* 2020;31(suppl_4): S1142-S1215 [Abstr LBA44].

Duration of BICR-Confirmed Response by RECIST v1.1

Events,[a] n (%)	Median (range)
12 (54.5%)	8.3 mo (3.2 to 15.9+)



Compared With Initial Analysis[1]

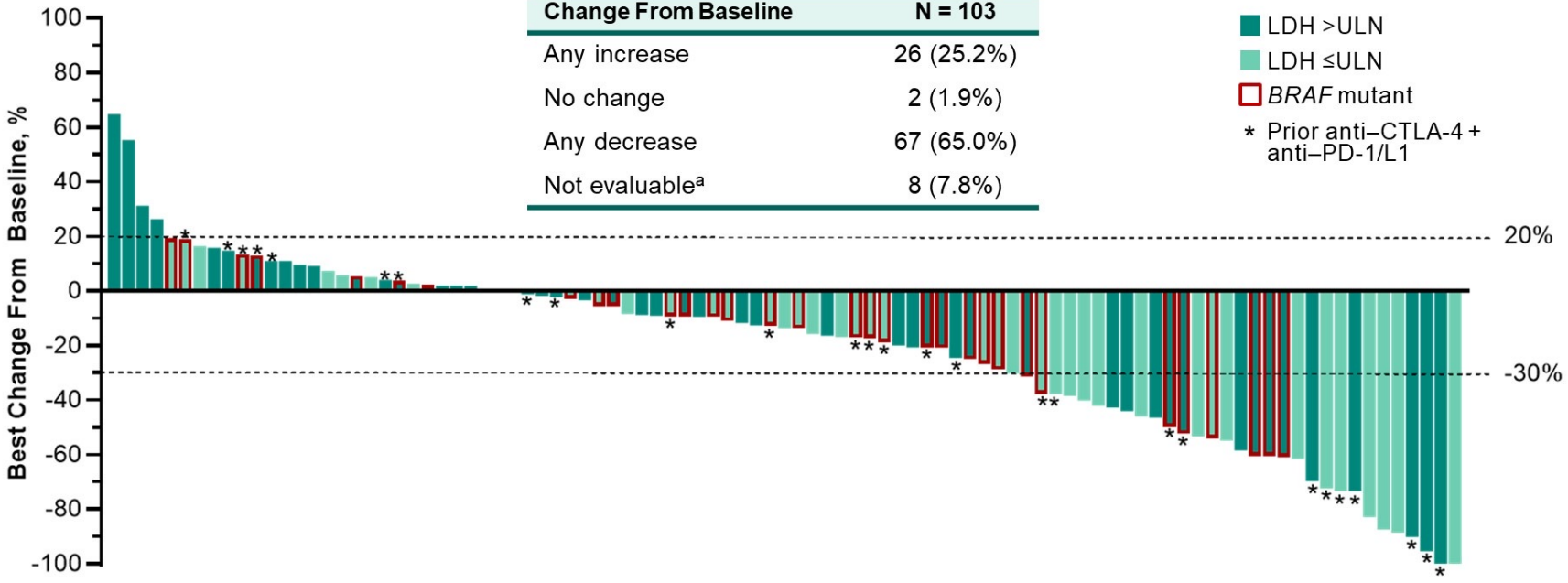
- Median DOR increased from 6.3 mo to 8.3 mo

[a]Patients who died or had PD. Data cutoff date: Sep 18, 2020.

1. Arance A et al. *Ann Oncol* 2020;31(suppl_4): S1142-S1215 [Abstr LBA44].

Best Change From Baseline in Target Lesions (RECIST v1.1 by BICR)

Change From Baseline	N = 103
Any increase	26 (25.2%)
No change	2 (1.9%)
Any decrease	67 (65.0%)
Not evaluable[a]	8 (7.8%)



[a]The 8 participants who did not have ≥1 post-baseline imaging assessment evaluable for change from baseline in target lesions are excluded from the graph.
Data cutoff date: Sep 18, 2020.

After Failure of Combo Immunotherapy

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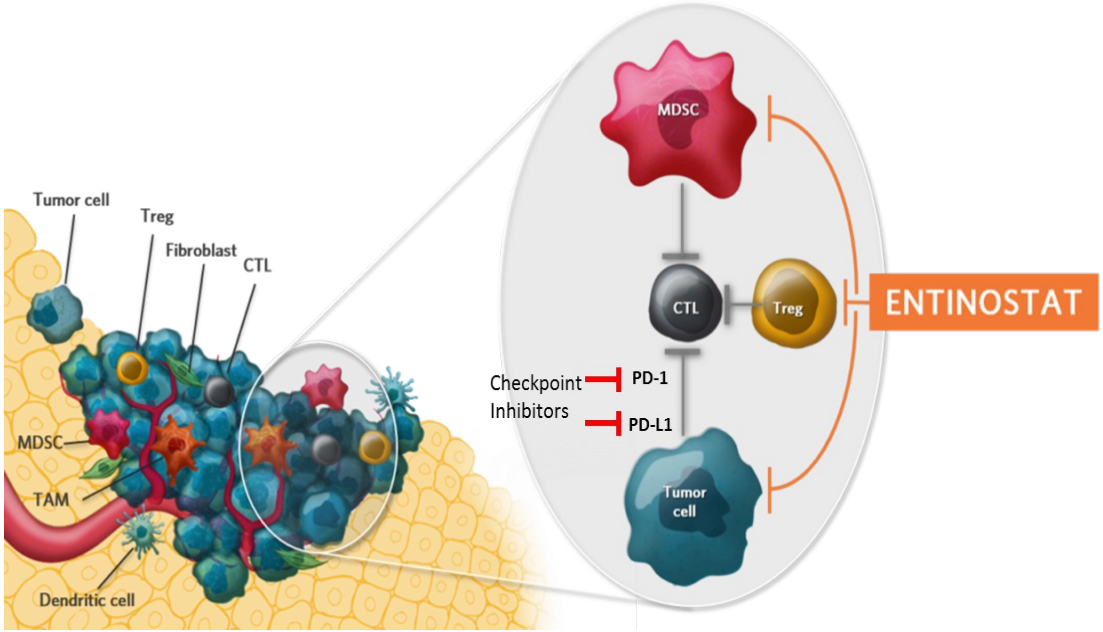
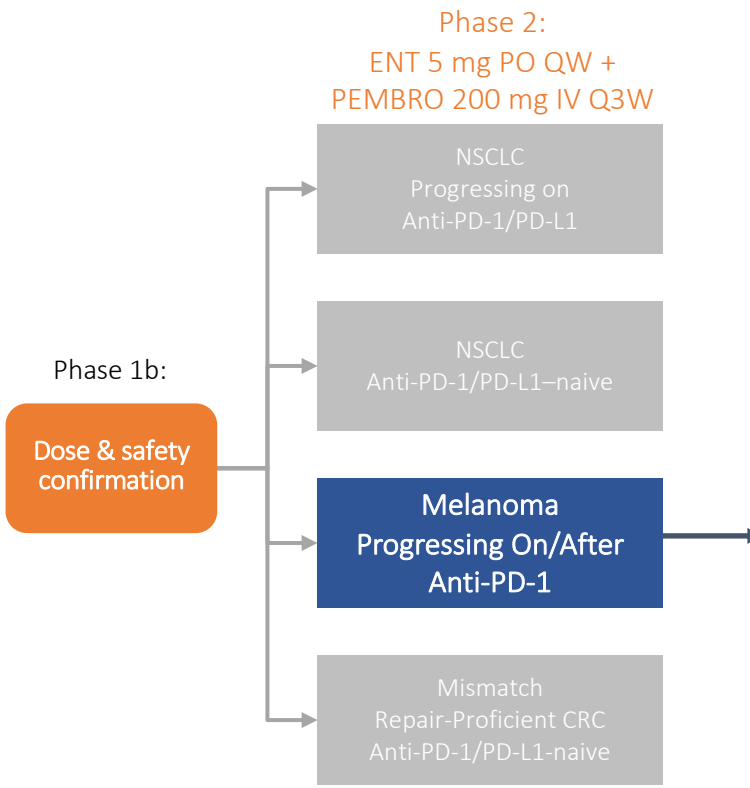
Proposed MOA of HDAC inhibition as IO

- Entinostat (ENT) is an oral class I-selective histone deacetylase inhibitor
- ENT reduces MDSC and Treg number & function
- ENT induces pro-inflammatory cascade in TME
- ENT enhances antigen presentation
- Additional beneficial effects on Teff & NK cells
- Synergy with anti-PD1 inhibition in preclinical models



ENCORE-601: Open-Label Study Evaluating ENT + PEMBRO in Patients With Recurrent or Metastatic Melanoma and Prior Progression On or After Anti-PD-1 Therapy



- Inclusion Criteria:
  - Recurrent or metastatic melanoma, measurable by RECIST 1.1
  - Prior progression on or after anti-PD-(L)1 treatment
  - Prior BRAF treatment if indicated
  - ECOG Performance Status < 2
  - Willingness to participate in baseline and on-treatment biopsy and blood samples

Primary Endpoint

- ORR (irRECIST)

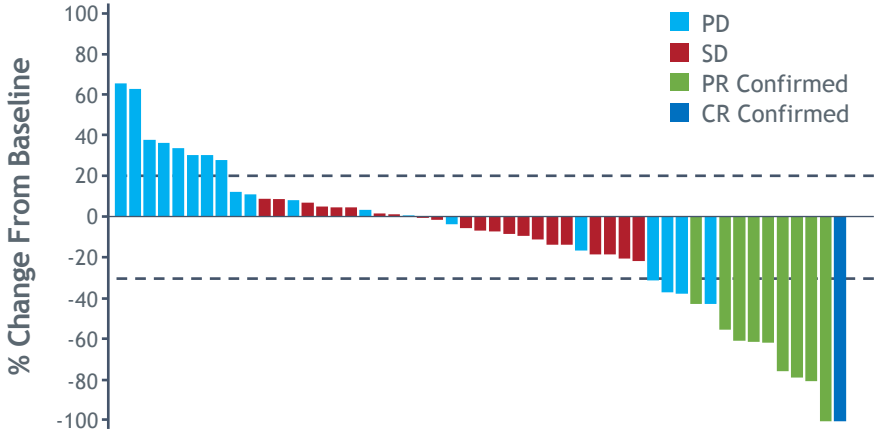
Secondary Endpoints

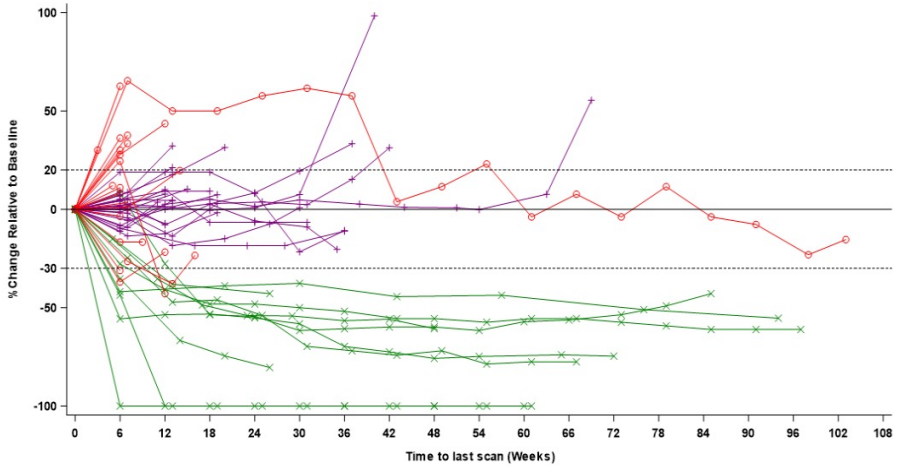
- CBR, PFS, OS, safety & tolerability

53 patients enrolled, last patient enrolled April 2018

Sullivan, Agarwala, et al. AACR 2019

ENT plus pembro is associated with durable responses in patients who previously progressed on anti-PD-1 therapy





- 10 confirmed responses of 53 treated [19% ORR (95% CI: 9%-32%)]
  - 1 CR, 9 PRs
- Median duration of response: 13 months (range 3-20)
  - 4 responders ongoing
- An additional 9 patients have had SD for >6 months
  - 36% CBR (95% CI: 23%-50%)

Sullivan, Agarwala, et al. AACR 2019

There’s a Lot Going On!

ANTI-LAG-3 DEVELOPMENT

Drug	Study phase	Cancer type	Combination
relatlimab	Phase 1,2, and 3	Solid tumors Haematological malignancies	nivolumab
LAG525/ Ieramilimab	Phase 1, 2	Solid tumors Haematological malignancies	spartalizumab
MK4280	Phase 1	Solid tumors	pembrolizumab
REGN3767	Phase 1	Solid tumors	cemiplimab (anti-PD-1)
MGD013	Phase 1	Solid tumors Haematological malignancies	-
TSR-033	Phase 1	Solid tumors	Anti-PD-1
BI754111	Phase 1	Solid tumors	BI754091 (anti-PD-1)
INCAGN02385	Phase 1	Solid tumors	Solid tumors
IMP321/ Eftilagimod alpha	Phase 1,2	Solid tumors	pembrolizumab, chemotherapy
LBL-007	Phase 1	Melanoma	Toripalimab
IBI110	Phase 1	Solid tumors	Sintilimab (anti-PD-1)

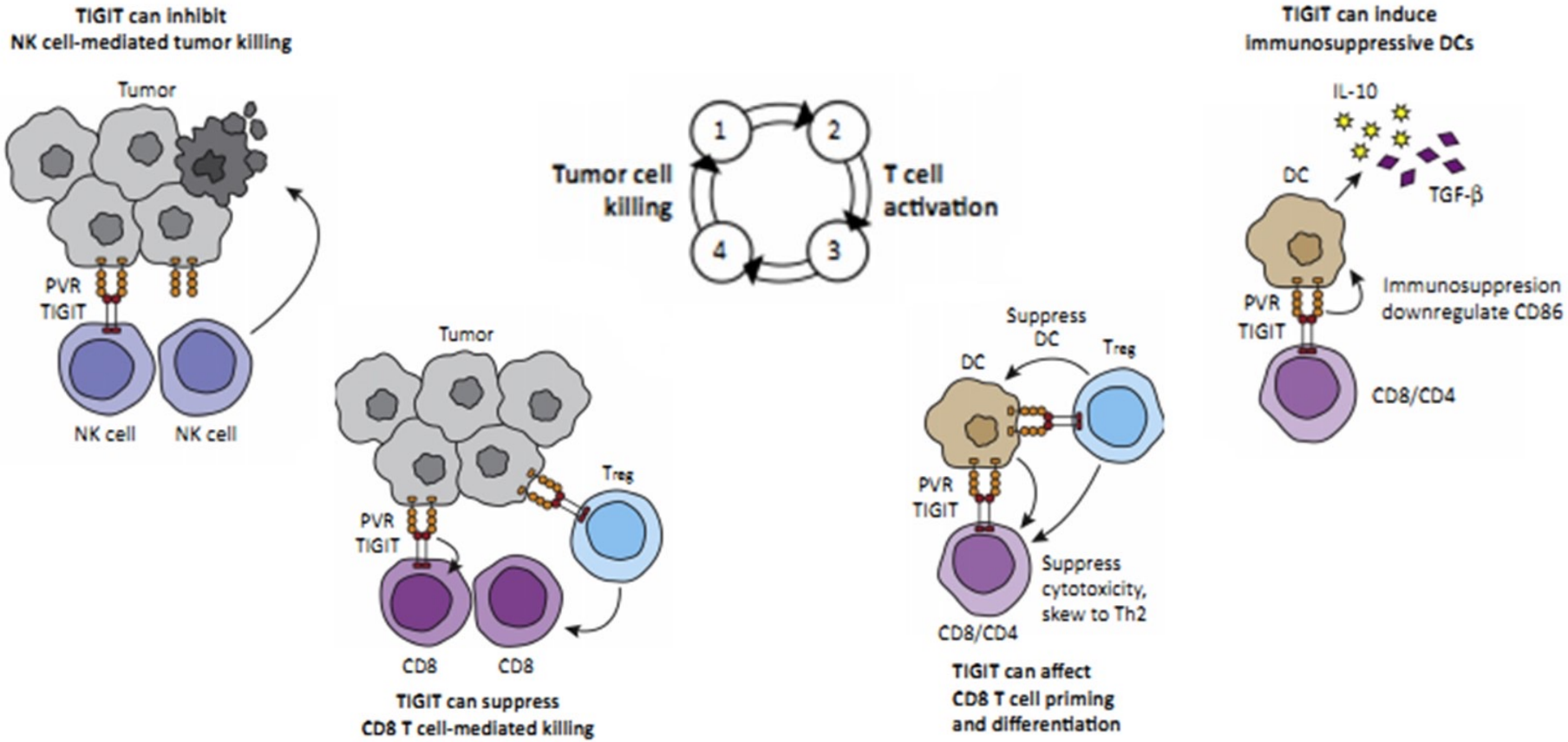
Clinical Development of Novel Anti–CTLA-4 Antibodies

Trial number	Drug name	Trial description	Study endpoints	Patients
CA022-001[1]	BMS-986218	Phase 1/2a first-in-human study of anti–CTLA-4 NF monoclonal antibody alone and in combination with nivolumab in advanced solid tumors	Safety, PK, PD, preliminary antitumor activity	Advanced solid tumors, including metastatic melanoma and NSCLC after anti–PD-1/PD-L1 therapy[2]
CA030-001[3,4]	BMS-986249	Phase 1/2 first-in-human study of anti–CTLA-4 PB alone and in combination with nivolumab in advanced solid tumors	Safety, PK, PD, preliminary antitumor activity	Advanced solid tumors, including metastatic melanoma, HCC, CRPC, TNBC
CA043-001[5]	BMS-986288	Phase 1/2 first-in-human study of anti–CTLA-4 NF PB alone and in combination with nivolumab in advanced malignant tumors	Safety, PK, PD, preliminary antitumor activity	Advanced solid tumors

Probody is a US registered trademark of CytomX Therapeutics, Inc.

1. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT03110107. Accessed February 4, 2021; 2. Friedman C, et al. Poster presented at the SITC 2020 Annual Virtual Meeting; November 9–14, 2020; 3. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT03369223. Accessed February 4, 2021; 4. CytomX Therapeutics. Press release. https://www.globenewswire.com/news-release/2020/06/22/2051270/0/en/CytomX-Therapeutics-Announces-Preclinical-Data-from-anti-CTLA-4 -Probody-Therapeutic-Programs-Presented-by-Partner-Bristol-Myers-Squibb-at-AACR-Annual-Meeting.html. June 22, 2020. Accessed February 4, 2021; 5. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT03994601. Accessed February 4, 2021.

TIGIT: T-Cell Immunoreceptor with Ig and ITIM domains



Manieri et al., *Trends in Immunol* 2017

CAR-T Trials in Melanoma

Target antigen	Disease	Modification	Country	ClinicalTrials.gov identifier	Status
c-Met	melanoma, breast cancer	4-1BBζ CAR	United States	NCT03060356	recruiting
CD70	melanoma, pancreatic cancer, renal cell cancer, breast cancer, ovarian cancer	NA	United States	NCT02830724	recruiting
GD2	melanoma, sarcoma, osteosarcoma, neuroblastoma	28OX40ζ + ICD9 CAR	United States	NCT02107963	completed
VEGFR2	metastatic cancer, melanoma, renal cancer	NA	United States	NCT01218867	completed

4-1BBζ CAR, chimeric antigen receptor with 4-1BB co-stimulatory domain; 28OX40ζ CAR, chimeric antigen receptor with CD28 and OX40 co-stimulatory domains; ICD9, caspase dimerization domain; NA, not available.

What's After Immunotherapy?

Clinical Trials!