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Advances in Cancer Immunotherapy Post-Program Webinar - Updates from the Field: Clinical Updates from SITC 2018

Monday December 10, 2018

1-2pm CST

Disclosures

- Nektar Therapeutics – Advisory Board/Honorarium

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SITC 2018 update

- Biomarkers and Immune Monitoring
- Cellular Metabolism and Antitumor Immunity
- Cellular Therapy Approaches
- Clinical Trials (completed)
- Clinical Trials (in progress)
- Combination Therapy

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Using assays together increases positive predictive value of responding to anti-PD(L)1 therapy

- Meta-analysis of 44 papers/abstracts examining the association between overall response rate to anti-PD(L)1 monotherapy and reported biomarkers including:
  - PD-L1 immunohistochemistry
  - Tumor mutation burden (TMB)
  - Gene expression profiling (GEP)
  - multiplex immunohistochemistry/immunofluorescence (mIHC/IF)

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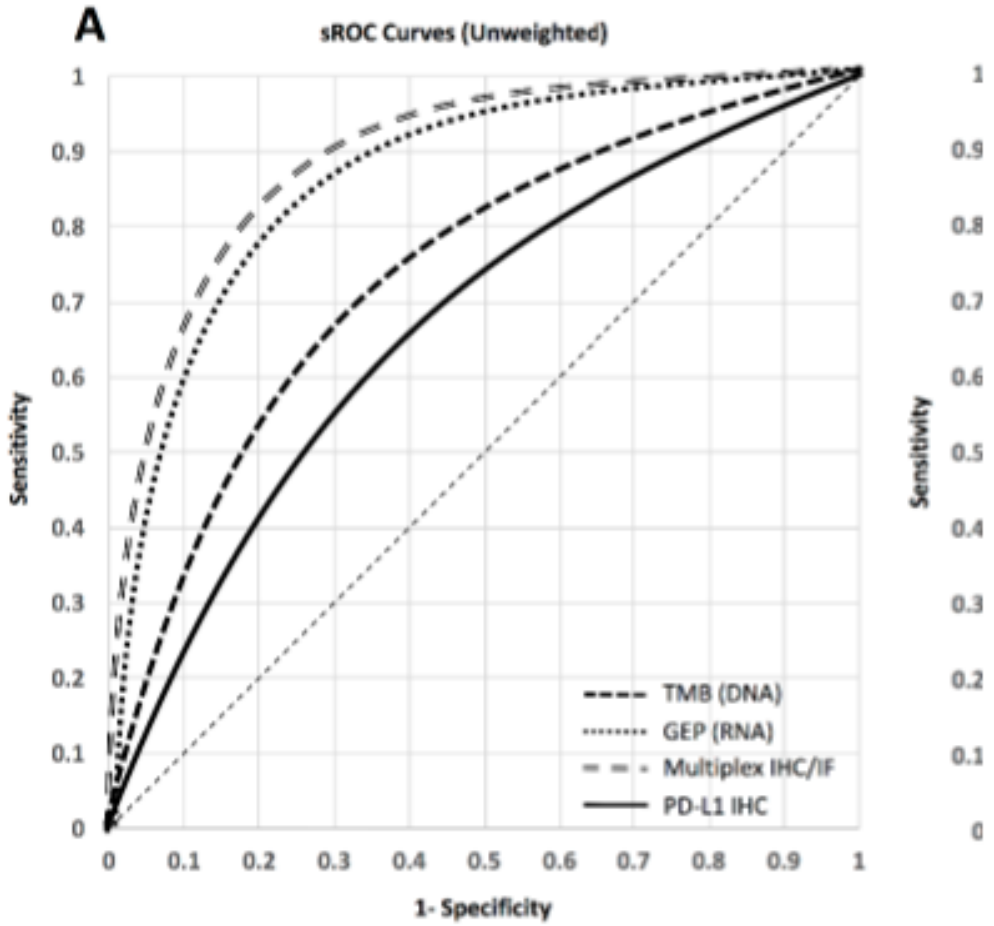
Abstract 6: Steve Lu et al. Comparison of biomarker assay modalities in anti-PD-(L)1 monotherapy: a meta-analysis

TMB has a modestly better performance relative to PD-L1 IHC, and newer approaches such as GEP and mIHC/IF may have improved sensitivity and specificity.



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Abstract 6: Steve Lu et al. Comparison of biomarker assay modalities in anti-PD-(L)1 monotherapy: a meta-analysis

B-cell signatures are prognostic and predictive factors for response to immune checkpoint blockade.

- Performed transcriptomic profiling on longitudinal blood specimens from a neoadjuvant immune checkpoint blockade trial in patients with high-risk, resectable melanoma (NCT02519322)
- Most differential gene expression over time in responders were B-cell related genes
  - MZB1, BTLA, and IGLL5 (NR)
- Findings were validated in a renal cell carcinoma cohort (NCT02210117) and the melanoma TCGA dataset, in which B lineage scores were predictive of response
- Assessment of tissue sections from tumor samples demonstrated co-localization of the B cells in tertiary lymphoid structures (TLS) with CD8 and CD4 T-cells and CD21 follicular dendritic cells.

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Abstract 5: Sangeetha Reddy et al. B-cells and tertiary lymphoid structures (TLS) predict response to immune checkpoint blockade

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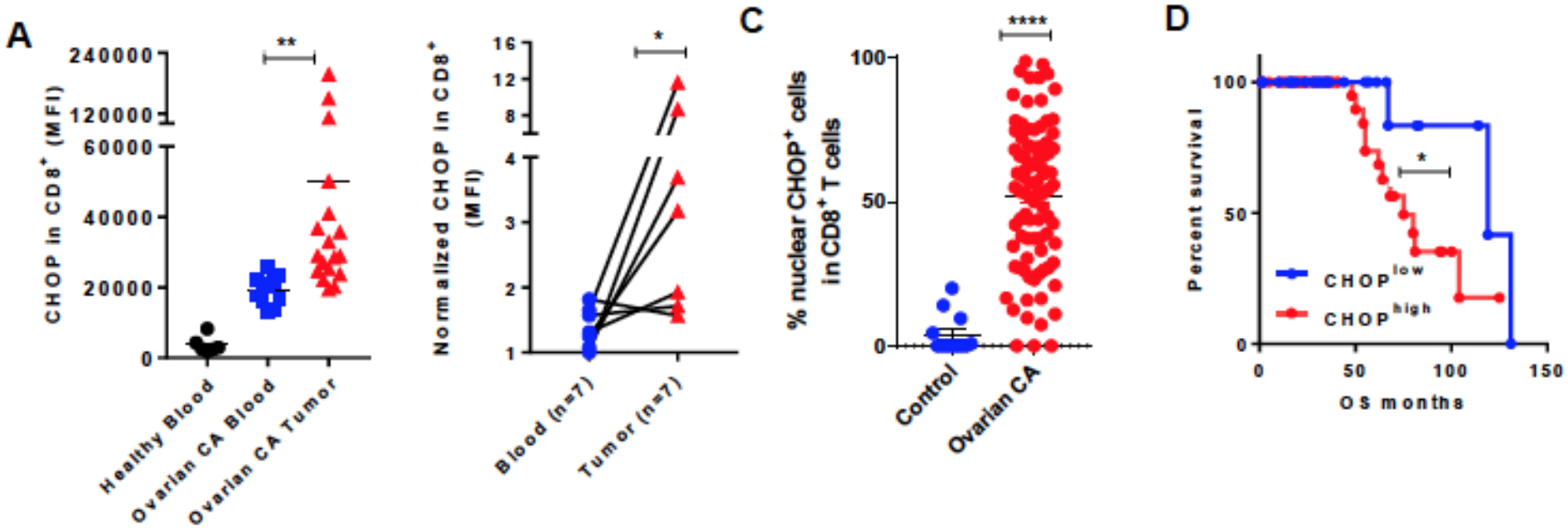
C/EBP homologous protein (Chop) represses Tbet, and abrogates effector T cell activity

- Chop is upregulated in tumor infiltrating CD8+ T cells from patients with advanced ovarian carcinoma



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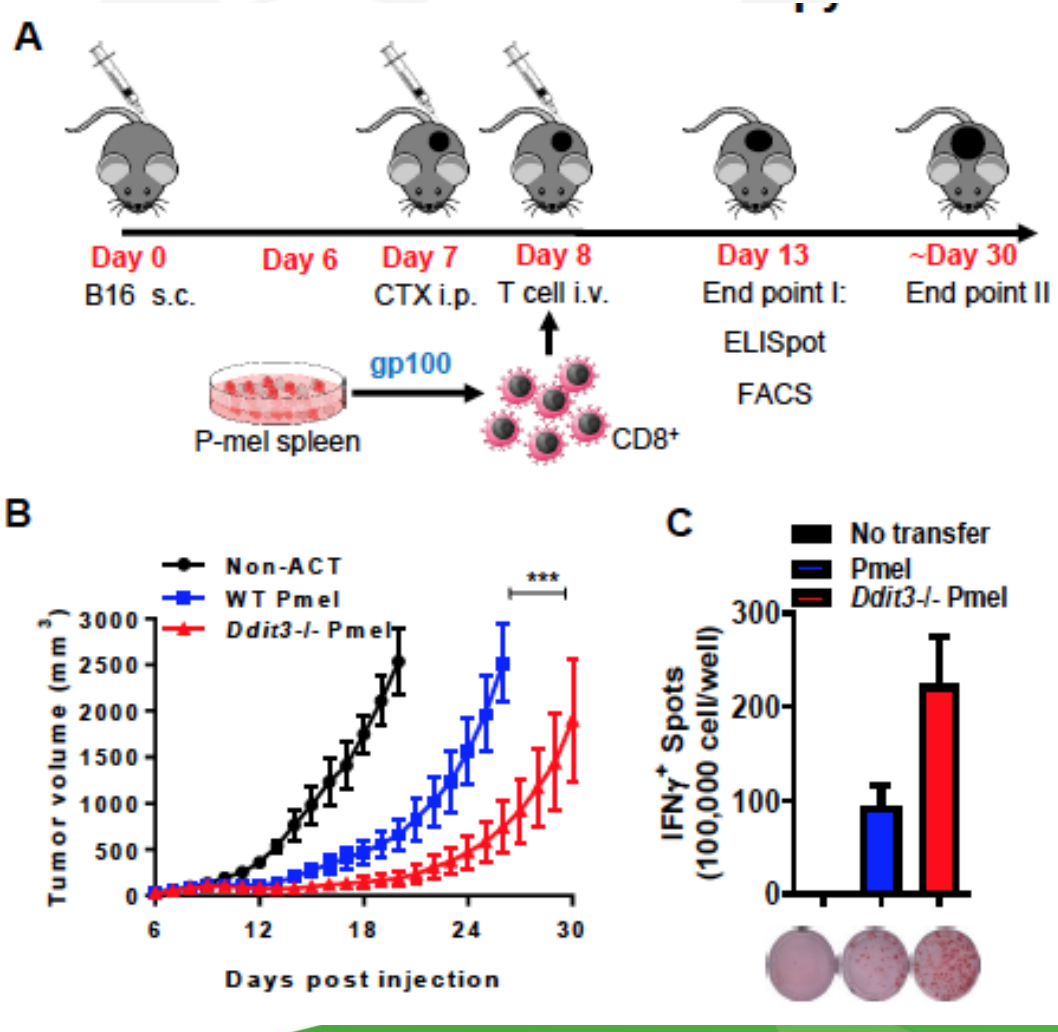
Abstract 9: Yu Cao et al. Endoplasmic reticulum stress-induced transcription factor C/EBP homologous protein (Chop) thwarts effector T cell activity in tumors through repression of T-bet

C/EBP homologous protein (Chop) represses Tbet, and abrogates effector T cell activity

- Chop deficient mice have reduced tumor growth
- Deletion of Chop in CD8+ T cells enhanced effector/cytotoxic pathways, promoted significant anti-tumor effects, and overcame tumor-induced T cell tolerance



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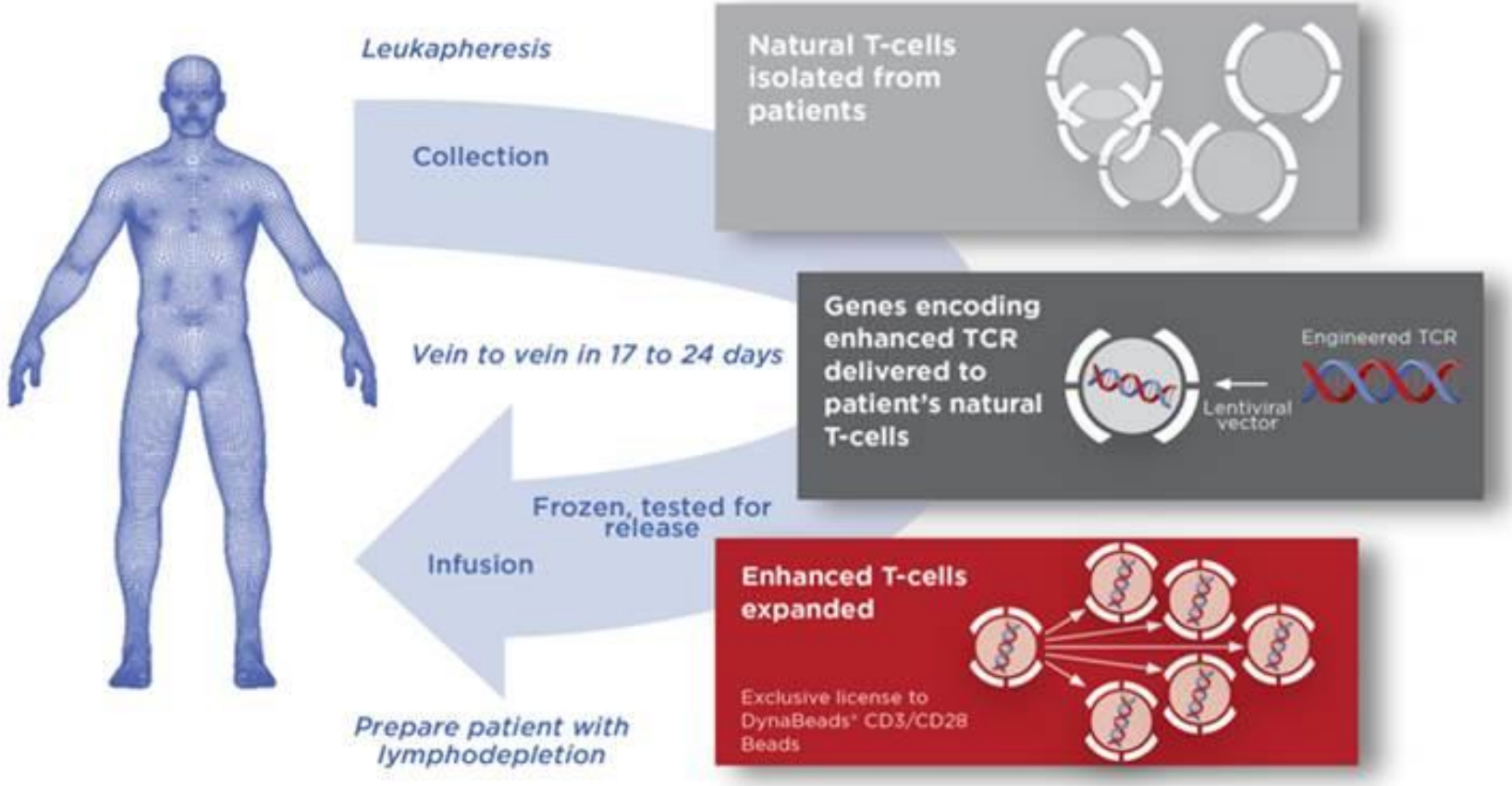
NY-ESO-1c259T-cells in myxoid/round cell liposarcoma (MRCLS) have an acceptable safety profile with potential antitumor effects.

- Open label phase I/II single arm pilot study evaluating affinity enhanced autologous NY-ESO-1c259T-cells (SPEAR T-cells) recognizing an NY-ESO-1-derived peptide complexed with HLA-A*02 in MRCLS (NCT02992743)



https://www.adaptimmune.com/technology/manufacturing

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Abstract 18: Sandra D'Angelo et al. Preliminary clinical data from a pilot study of NYESO-1c259T-cells in advanced myxoid/round cell liposarcoma

NY-ESO-1c259T-cells in myxoid/round cell liposarcoma (MRCLS) have an acceptable safety profile with potential antitumor effects.

- 1– 8 × 10^9 transduced T-cells are infused on day 1 after lymphodepletion with fludarabine and cyclophosphamide on d -7 to -5.
- Thirteen patients were enrolled, and 10 received the TCR therapy
- 4 of the 8 patients (50%) have achieved a confirmed partial response (PR) and 50% have stable disease (SD) as the best overall response.
  - Duration of responses varies from 4 weeks to greater than 5 months
  - AEs≥ grade 3 in these 8 patients include lymphopenia (6), neutropenia (5), leukopenia (5), thrombocytopenia (3), hypophosphatemia (2), anemia (1), cytokine release syndrome (1; SAE), pyrexia (1) and leukocytosis (1).

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Combining Mogamulizumab with either Durvalumab or Tremelimumab in solid tumors is tolerable and decreases eTregs in peripheral blood.

- Multicenter, Phase 1, open label, dose escalation/cohort expansion study of Mogamulizumab in combination with either Durvalumab or Tremelimumab in adult subjects with advanced solid tumors (NCT02301130).

T-cell subset	The dominant-type chemokine receptor
T_h1 cells	CXCR3
T_h2 cells	CCR4
T_{reg} cells	CCR4
CLA^+ skin-homing T cells	CCR4
$\alpha4\beta7^+$ intestine-homing T cells	CCR6
T_h17 cells	CCR6
Naive T cells	CCR7
Central memory T cells	CCR7
Skin resident T cells	CCR8
Intestine resident T cells	CCR9
Follicular helper T cells	CXCR5
Cytotoxic effector T cells	CX3CR1

Yoshie and Matsushima 2015 Int Immunol

Mogamulizumab

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Abstract 19: Dmitriy Zamarin et al. Phase 1 study using mogamulizumab (KW-0761) to deplete regulatory T cells in combination with checkpoint inhibitors durvalumab (MEDI4736) or tremelimumab in subjects with advanced solid tumors

Combining Mogamulizumab with either Durvalumab or Tremelimumab in solid tumors is tolerable and decreases eTregs in peripheral blood.

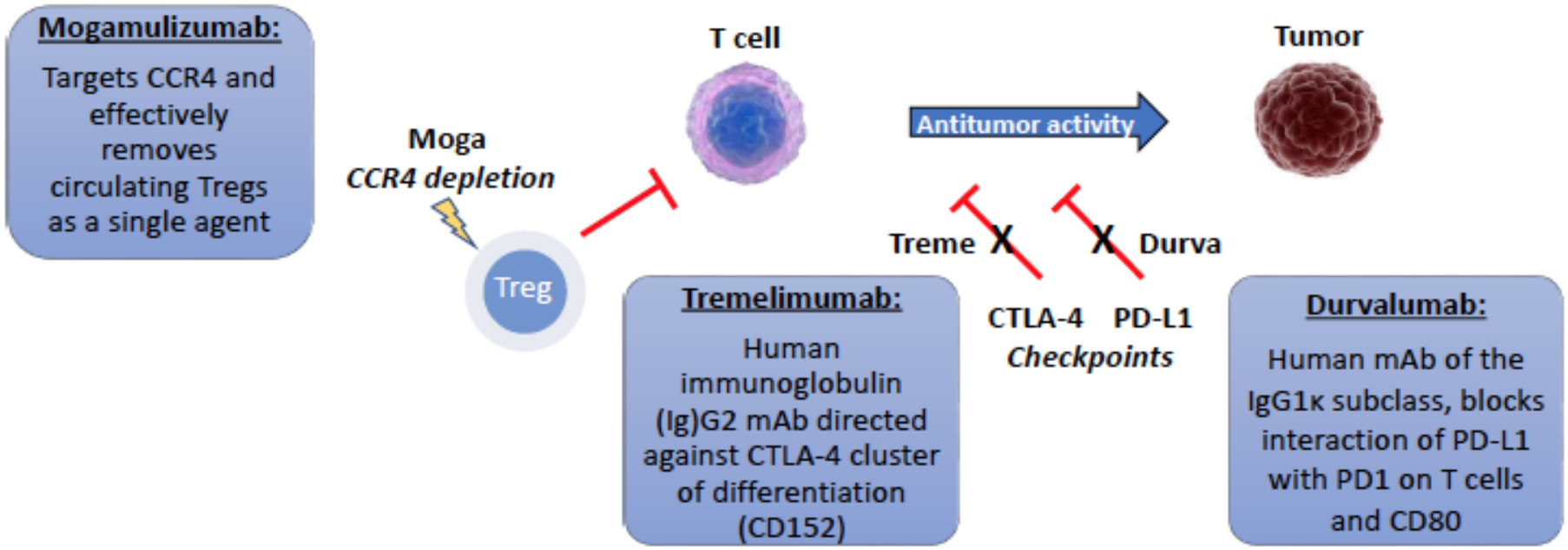

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Table 2.

A total of 64 subjects were enrolled and treated:
n=40 in Part 1 and n=24 in Part 2.

Dose escalations were completed in Part 1 without any dose-limiting toxicities, and combinations of 1 mg/kg Moga with 10 mg/kg of either Durva or Treme were used to treat an expansion cohort with pancreatic cancer in Part 2.

	Treatment A[a] (Moga+Durva)	Treatment B[a] (Moga+Treme)
Part 1 (Dose escalation) All dose cohorts	N=21	N=19
Any TEAE[b] (n, %)	21 (100.0)	19 (100.0)
≥Grade 3 (n, %)	15 (71.4)	15 (78.9
≥Grade 3, related to either IMP (n, %)	6 (28.6)	9 (47.4)
SAE (n, %)	12 (57.1)	9 (47.4)
SAE, related to either IMP (n, %)	4 (19.0)	5 (26.3)
Most common TEAEs (preferred term, %)	Fatigue 12 (57.1) Diarrhea 9 (42.9)	Diarrhea 10 (52.6) Fatigue 9 (47.4) Decr appetite 8 (42.1)
Part 2 (Dose expansion) Pancreatic cancer	N=12	N=12
Any TEAE[b] (n, %)	12 (100.0)	12 (100.0)
≥Grade 3 (n, %)	10 (83.3)	10 (83.3)
≥Grade 3, related to either IMP (n, %)	4 (33.3)	4 (33.3)
SAE (n, %)	10 (83.3)	8 (66.7)
SAE, related to either IMP (n, %)	3 (25.0)	1 (8.3)
Most common TEAEs (preferred term, %)	Fatigue 11 (91.7) Abdominal pain 9 (75.0) Constipation 6 (50.0) Nausea 6 (50.0)	Edema peripheral 6 (50.0) IRR 6 (50.0) Hyponatremia 6 (50.0)

a: In Part 2, Treatment A = 1 mg/kg Moga + 10 mg/kg Durva; Treatment B = 1mg/kg Moga + 10mg/kg Treme.
b: TEAEs during any cycle
Decr=decreased; IMP=investigational medicinal product; IRR=infusion-related reaction; Moga=muganulizumab; SAE=serious adverse event; Treme=tremelimumab

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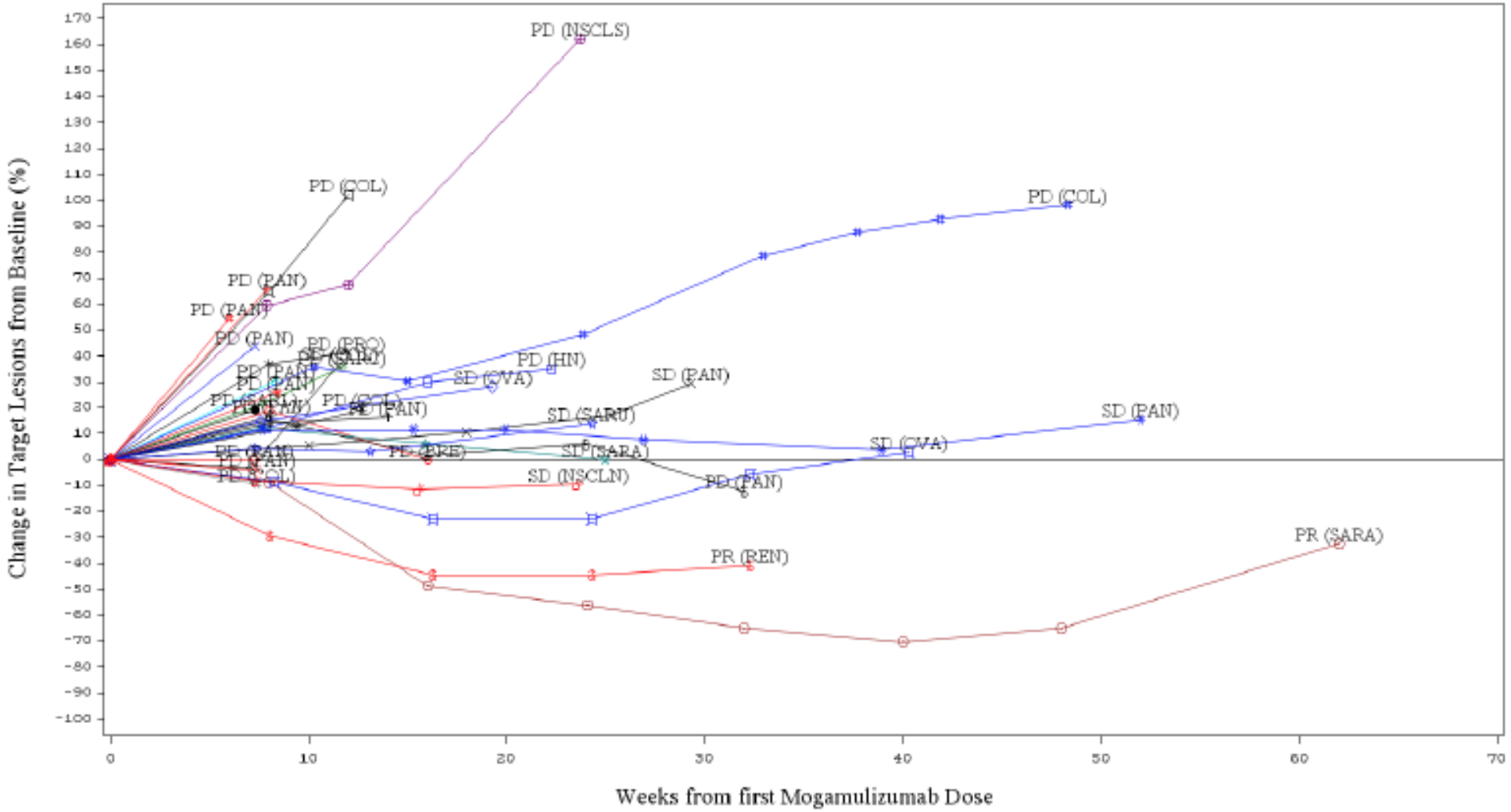
Change in Tumor Burden Over Time: Moga+Durva



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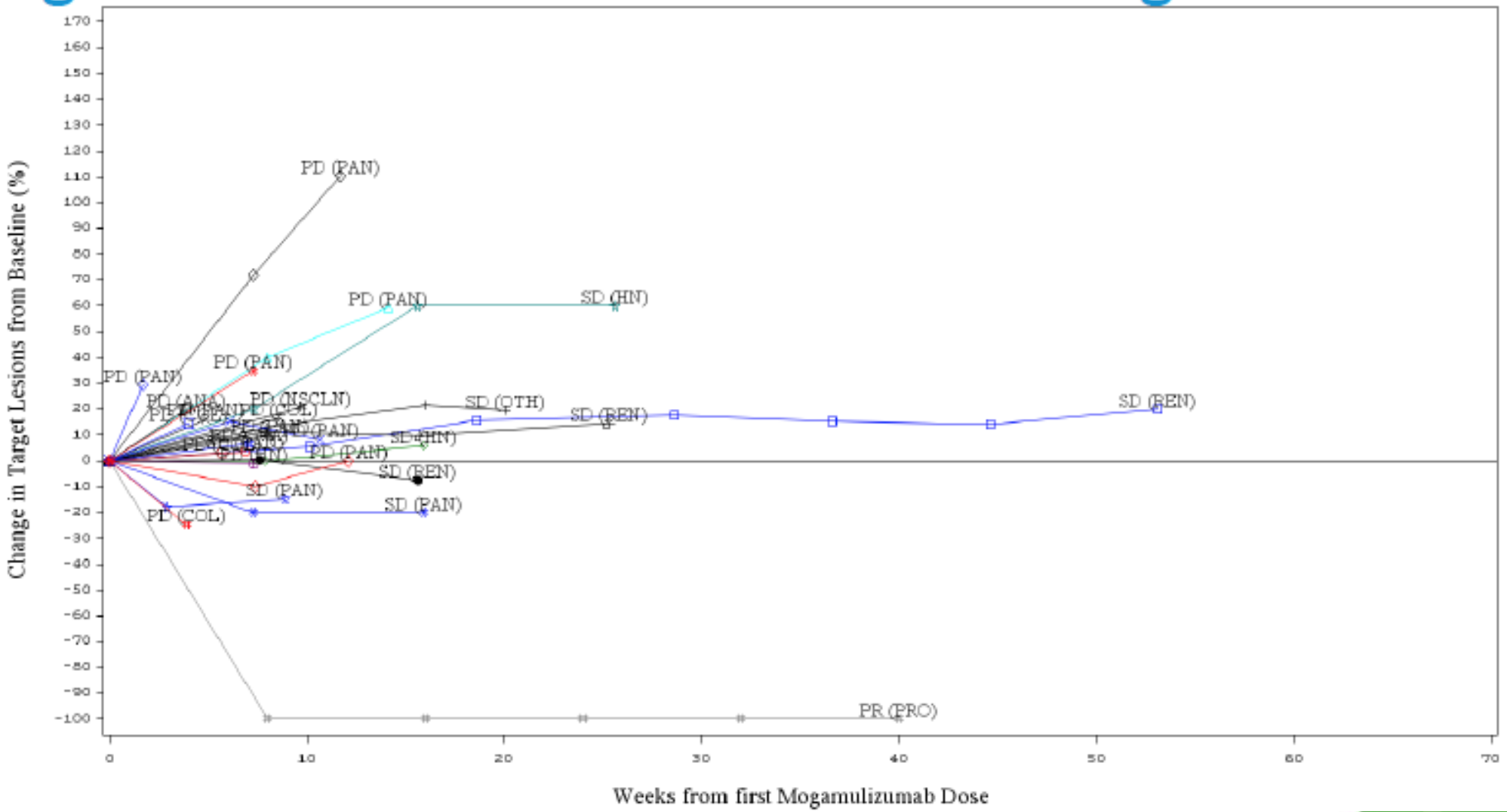
Change in Tumor Burden Over Time: Moga+Treme



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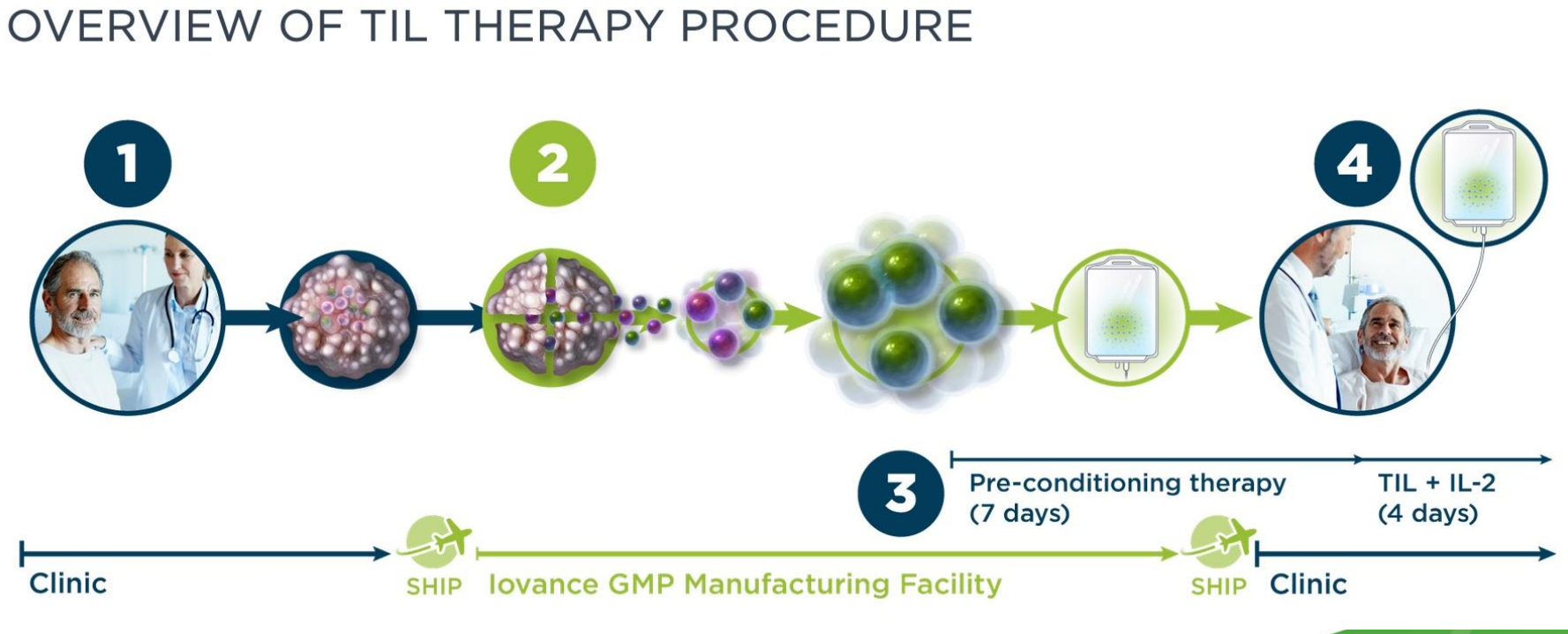
TIL therapy with lifileucel is an efficacious and well tolerated therapeutic option for metastatic melanoma

- Global phase 2, open-label, multicenter study of efficacy and safety of lifileucel (TIL) in patients with unresectable metastatic melanoma (NCT02360579)



http://www.iovance.com/clinical/c-144-01-metastatic-melanoma/

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Abstract 22: Amod Sarnaik et al. Safety and efficacy of cryopreserved autologous tumor infiltrating lymphocyte therapy (LN-144, lifileucel) in advanced metastatic melanoma patients following progression on checkpoint inhibitors tumors

TIL therapy with lifileucel is an efficacious and well tolerated therapeutic option for metastatic melanoma

- Patients receive one week of cyclophosphamide/fludarabine lymphodepletion, followed by a single infusion of lifileucel, plus up to 6 doses of intravenous IL-2 (600,000 IU/kg).

- ORR=33% (1 uCR, 7 PR, 2 uPR), DCR=73%, median follow-up of all patients was 6 months, median time to initial response 1.7 months (range: 1.6-4.4 months), and median DOR not reached (8 ongoing responders out of 10).
  - Median follow up for all responders was 4.5 months.

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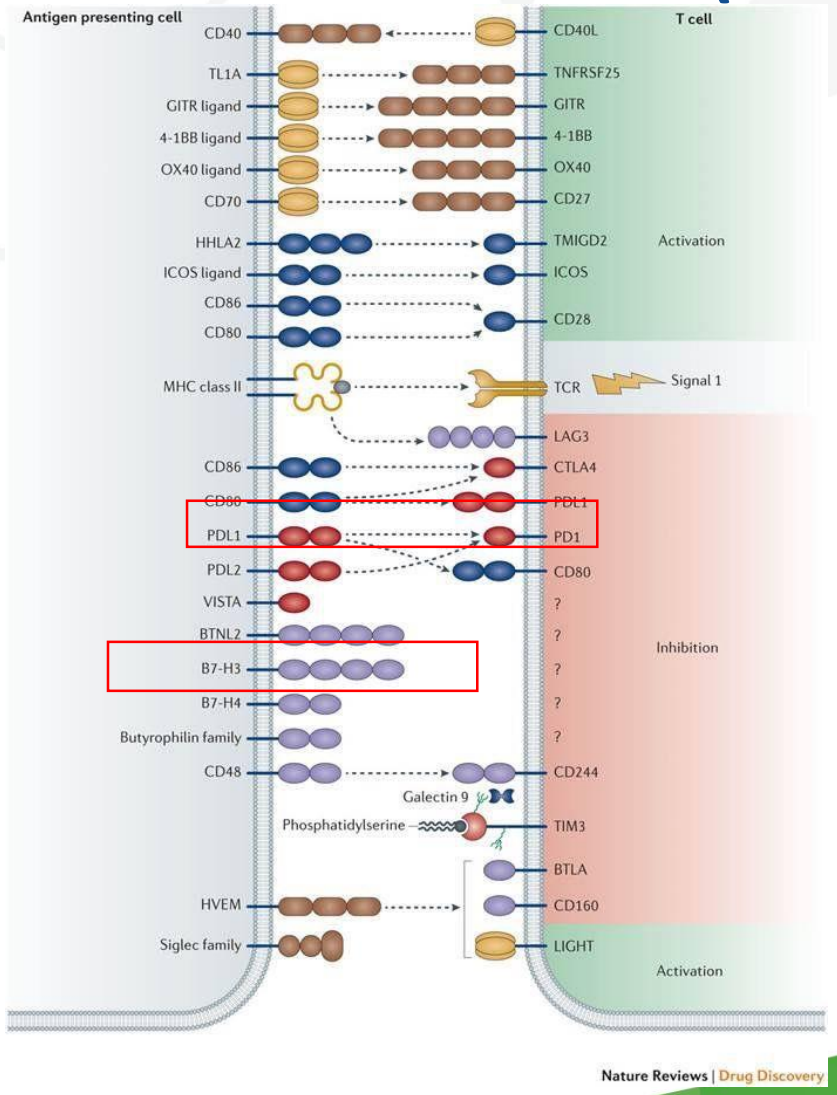
A phase 1, open-label, dose-escalation study of enoblituzumab (anti-B7-H3) in combination with pembrolizumab in patients with select solid tumors (NCT02475213)



Mahoney KM et al. 2015 Nat Rev Drug Discovery

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Abstract 24: Charu Aggarwal et al. A phase 1, open-label, dose-escalation study of enoblituzumab in combination with pembrolizumab in patients with select solid tumors.

Enoblituzumab+pembrolizumab combination demonstrated an acceptable safety profile and initial antitumor activity in patients with checkpoint-inhibitor-naïve head and neck cancer

- Treatment-related AE, (all grade) occurred in 85% of patients, with > G3 in 28%.

- ORR 6/18 (33%), including 4 confirmed and 2 unconfirmed PR

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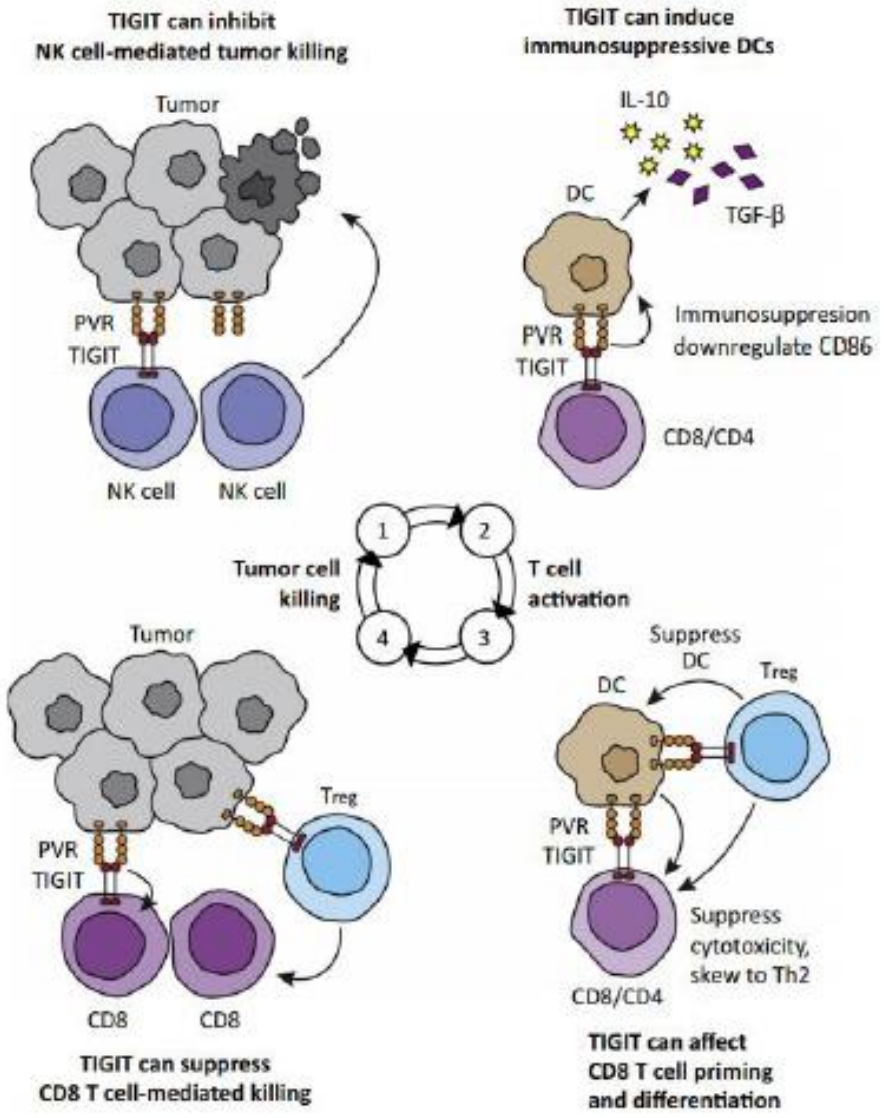
Abstract 24: Charu Aggarwal et al. A phase 1, open-label, dose-escalation study of enoblituzumab in combination with pembrolizumab in patients with select solid tumors.

Phase 1 dose-finding study of the anti–TIGIT antibody MK-7684 as monotherapy and in combination with pembrolizumab in patients with advanced solid tumors (NCT02964013)



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Abstract 25: Talia Golan et al. Phase 1 dose-finding study of the anti–TIGIT antibody MK-7684 as monotherapy and in combination with pembrolizumab in patients with advanced solid tumors.

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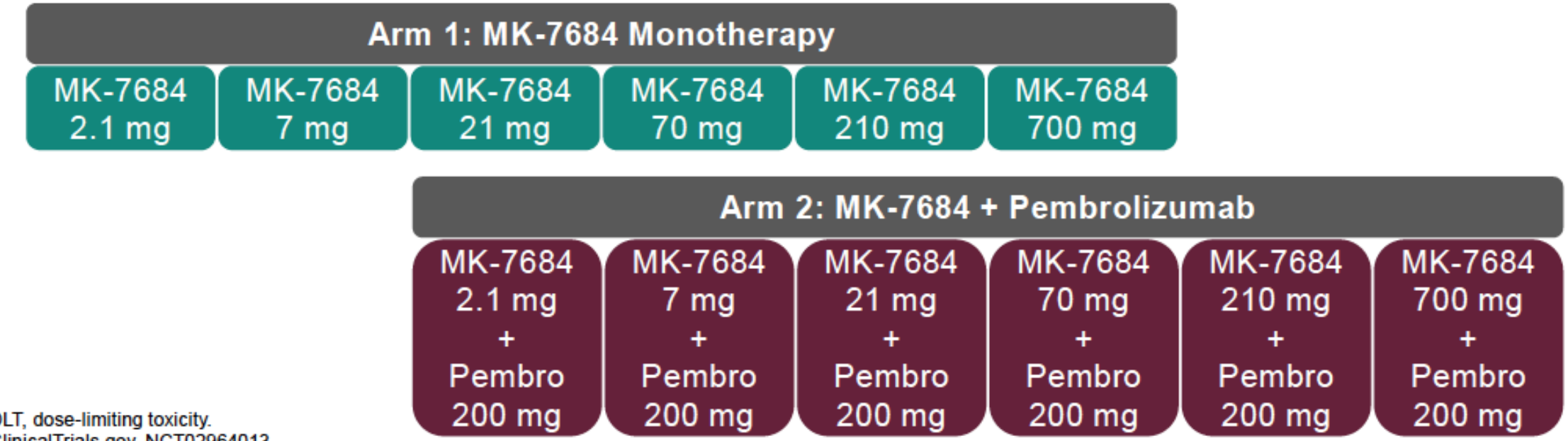

DLT, dose-limiting toxicity.
ClinicalTrials.gov, NCT02964013.

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Abstract 25: Talia Golan et al. Phase 1 dose-finding study of the anti–TIGIT antibody MK-7684 as monotherapy and in combination with pembrolizumab in patients with advanced solid tumors.

Anti-TIGIT (MK-7684) as monotherapy and in combination with pembrolizumab was well tolerated and across all dose levels.

- AEs occurred in 53% of monotherapy and 65% of combination therapy recipients (grade 3-5, 6% and 12%)

MK-7684 Monotherapy

Occurred in ≥2 patients, n (%)	N = 34
Fatigue	5 (15%)
Pruritus	4 (12%)
Anemia	3 (9%)
Infusion-related reaction	3 (9%)
Arthralgia	2 (6%)
Decreased appetite	2 (6%)
Dermatitis acneiform	2 (6%)
Diarrhea	2 (6%)
Headache	2 (6%)
Nausea	2 (6%)
Rash	2 (6%)
Rash maculopapular	2 (6%)

- 2 grade 3: anemia and diarrhea (n = 1 each)
- 0 grade 4 or 5

MK-7684 + Pembrolizumab

Occurred in ≥2 patients, n (%)	N = 47
Pruritus	10 (21%)
Fatigue	4 (9%)
Nausea	4 (9%)
Rash	4 (9%)
Decreased appetite	3 (6%)
Diarrhea	3 (6%)
ALT increased	2 (4%)
Dyspnea	2 (4%)
Hypophosphatemia	2 (4%)
Neuropathy peripheral	2 (4%)
Pyrexia	2 (4%)
Rash maculopapular	2 (4%)

- 5 grade 3: ALT increased, colitis, γGT increased, hypersensitivity, and rash maculopapular (n = 1 each)
- 0 grade 4 or 5

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Anti-TIGIT (MK-7684) as monotherapy and in combination with pembrolizumab was well tolerated and across all dose levels.

Response	MK-7684 Monotherapy N = 34	MK-7684 + Pembrolizumab N = 43[b]
ORR, % (95% CI)	3% (<1-15)	19% (8-33)
DCR, % (95% CI)	35% (20-54)	47% (31-62)
Best response, n (%)		
Complete response	0	0
Partial response	1 (3%)	8 (19%)
Stable disease	11 (32%)	12 (28%)
Progressive disease	13 (38%)	20 (47%)
Not assessed[c]	9 (26%)	3 (7%)

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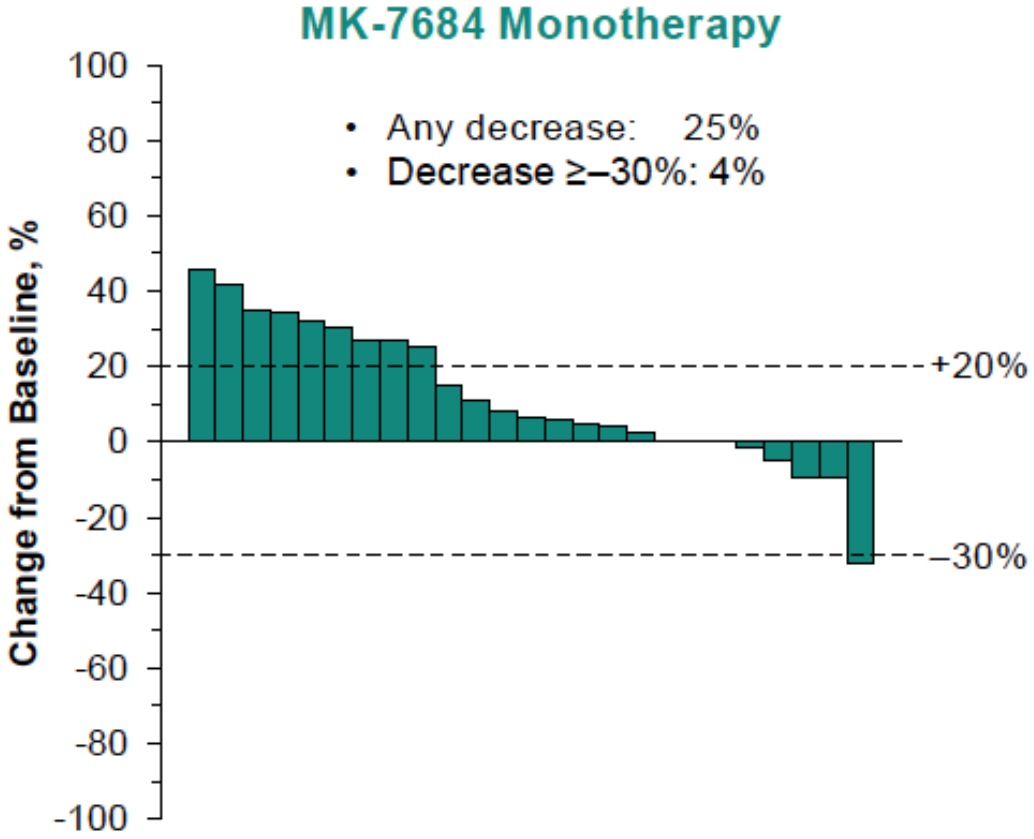

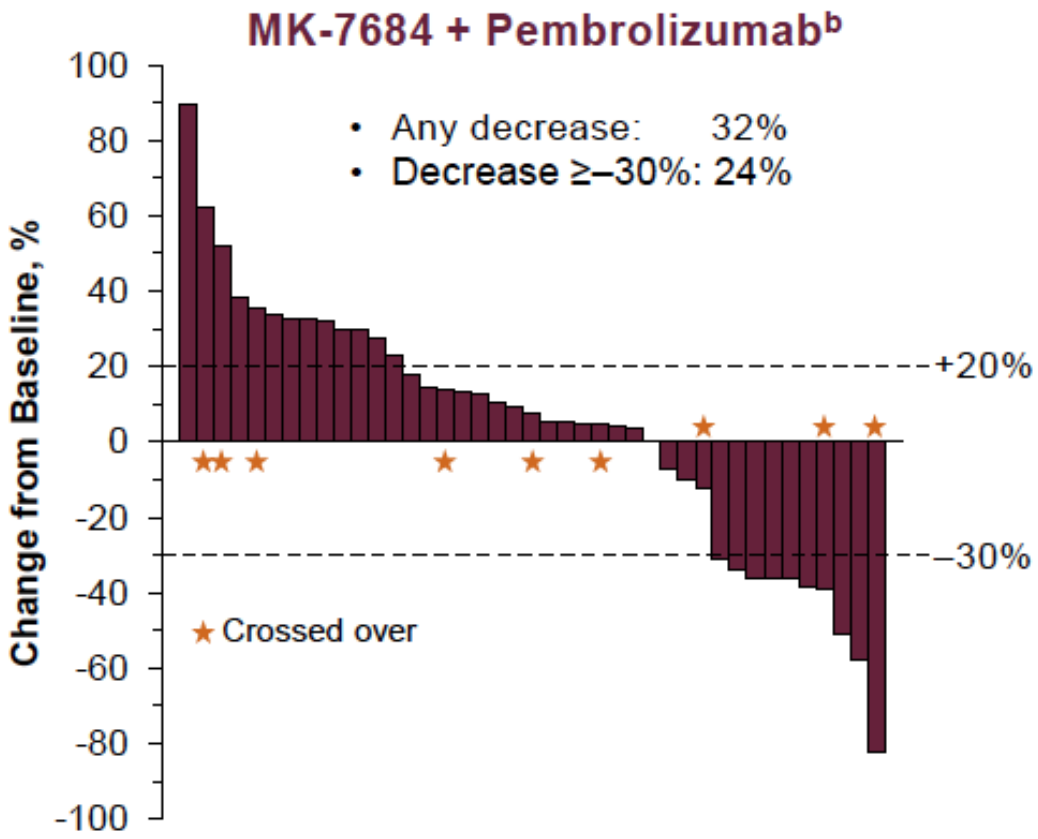

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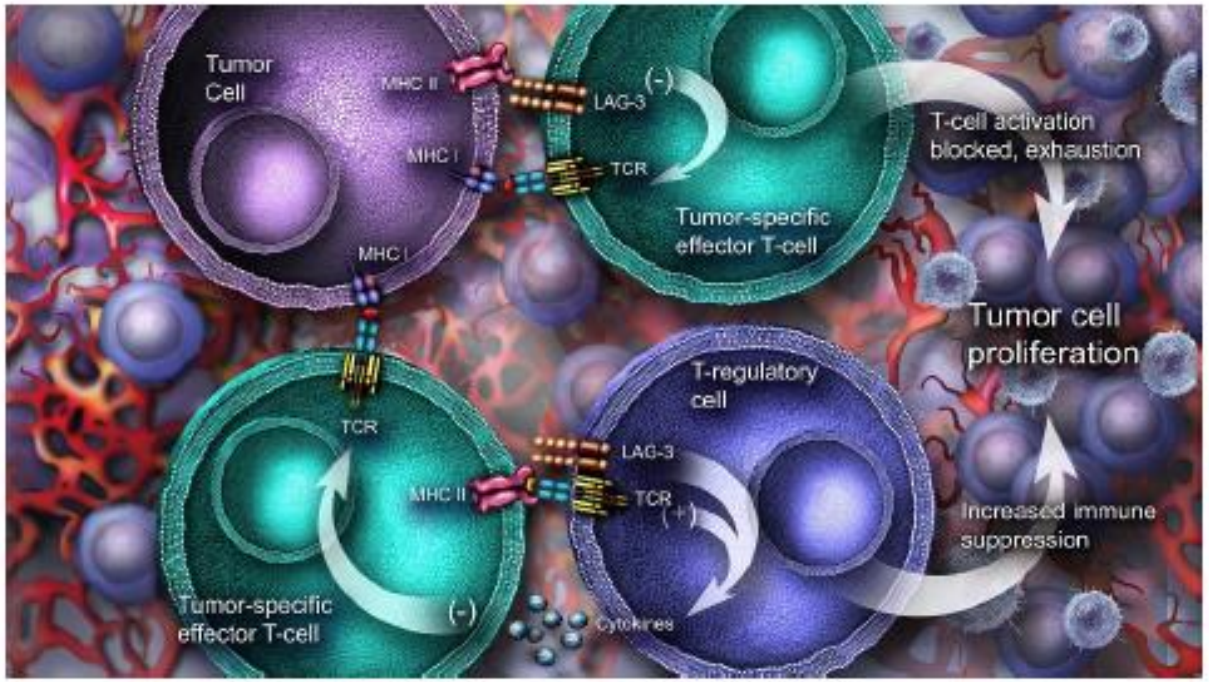
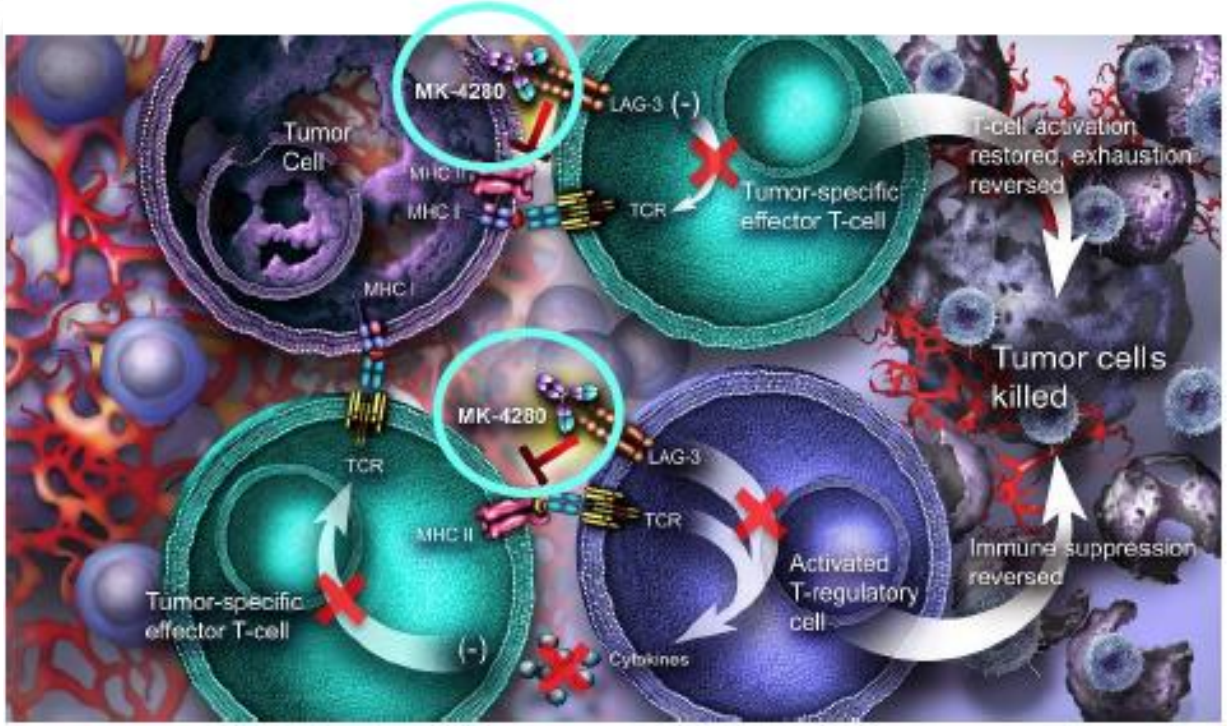
Abstract 25: Talia Golan et al. Phase 1 dose-finding study of the anti–TIGIT antibody MK-7684 as monotherapy and in combination with pembrolizumab in patients with advanced solid tumors.

The anti–LAG-3 antibody MK-4280 as monotherapy and in combination with pembrolizumab for advanced solid tumors: first-in-human phase 1 dose-finding studv (NCT02720068)





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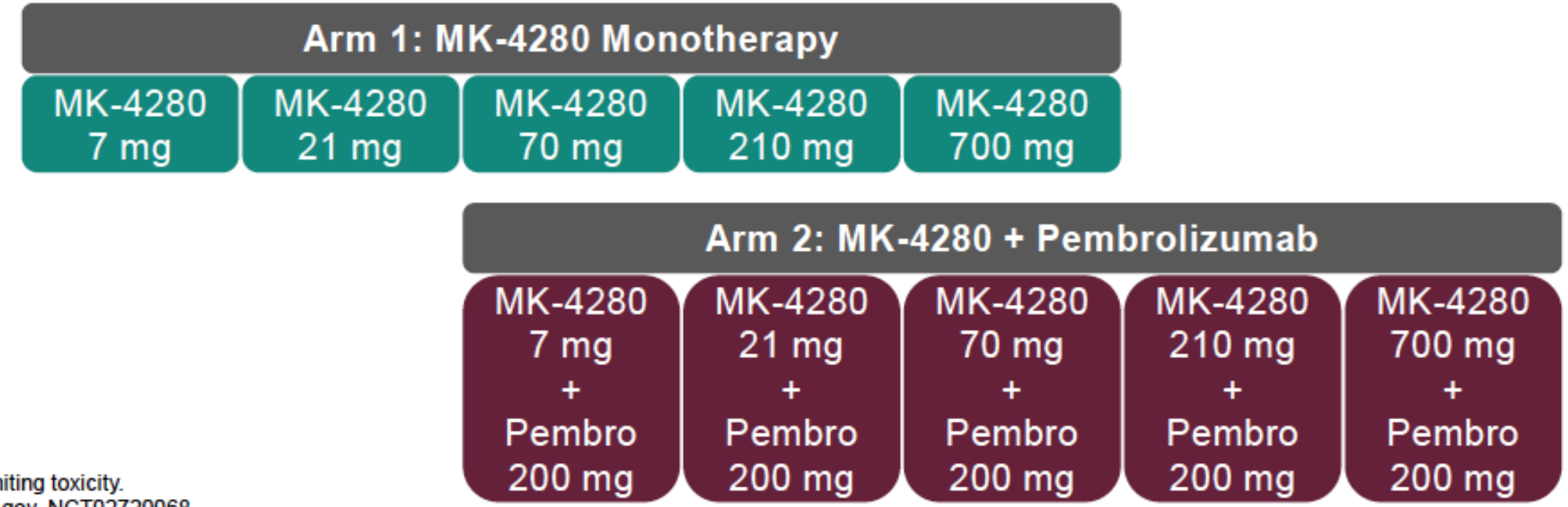
Abstract 26: Nehal Lakani et al. The anti–LAG-3 antibody MK-4280 as monotherapy and in combination with pembrolizumab for advanced solid tumors: first-in-human phase 1 dose-finding study

The anti–LAG-3 antibody MK-4280 as monotherapy and in combination with pembrolizumab for advanced solid tumors: first-in-human phase 1 dose-finding study (NCT02720068)



DLT, dose-limiting toxicity.
ClinicalTrials.gov, NCT02720068.

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Anti-LAG3 (MK-4280) as monotherapy and in combination with pembrolizumab was well tolerated and shows antitumor activity in combination.

- AEs occurred in 61% of monotherapy and 53% of combination therapy recipients, were of grade 3-4 toxicity in 6% and 20%

Adverse Event, n (%)	MK-4280 Monotherapy N = 18	MK-4280 + Pembrolizumab N = 15
Any attribution		
Any grade	17 (94%)	15 (100%)
Grade 3	9 (50%)	9 (60%)
Grade 4	0	0
Grade 5	0	0
Led to discontinuation	1 (6%)	3 (20%)
Treatment related		
Any grade	11 (61%)	8 (53%)
Grade 3	1 (6%)	3 (20%)
Grade 4	0	0
Grade 5	0	0
Led to discontinuation	1 (6%)	2 (13%)

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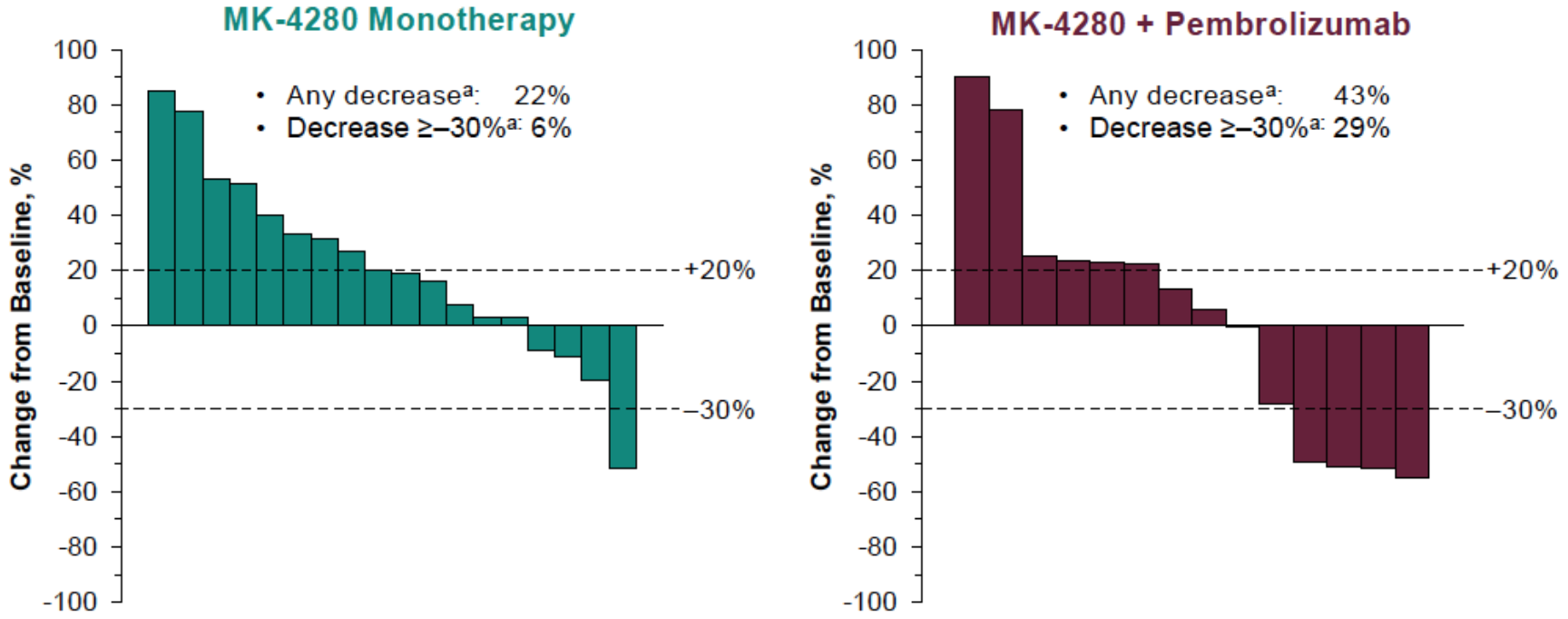
Abstract 26: Nehal Lakani et al. The anti–LAG-3 antibody MK-4280 as monotherapy and in combination with pembrolizumab for advanced solid tumors: first-in-human phase 1 dose-finding study

Anti-LAG3 (MK-4280) as monotherapy and in combination with pembrolizumab was well tolerated and shows antitumor activity in combination.

- ORR was 6% with monotherapy (1 PR) and 27% with combination therapy (4 PRs)



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Conclusions

- Biomarkers are sorely needed to predict who will respond to anti-PD1 therapy
  - There is a wide range of sensitivity and specificity with the currently available assays used to predict sensitive tumors, but they may work best in combination
  - B cell signature may be critical
- Cellular therapies continue to show favorable safety and efficacy profiles
  - TCR transduced T cells targeting NY-ESO-1 are safe and show response rates 50%
  - TILs + IL-2 are safe and show response rates 33%
- Combination therapies are proving to be tolerable and may show clinical activity
  - CCR4 + anti-PDL1 or anti-CTLA4
  - Anti-B7H3 + anti-PD1
  - Anti-TIGIT + anti-PD1
  - Anti-LAG3 + anti-PD1

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In a meta-analysis of 44 papers and abstracts, which of the following biomarkers was most effective in predicting overall response rate to PD-1/PD-L1 monotherapy?

A. PD-L1 immunohistochemistry
B. Tumor mutation burden
C. Gene expression profiling
D. Multiplex immunohistochemistry immunofluorescence

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Abstract O6: Steve Lu et al. Comparison of biomarker assay modalities in anti-PD-(L)1 monotherapy: a meta-analysis

In a meta-analysis of 44 papers and abstracts, which of the following biomarkers was most effective in predicting overall response rate to PD-1/PD-L1 monotherapy?

A. PD-L1 immunohistochemistry
B. Tumor mutation burden
C. Gene expression profiling
D. Multiplex immunohistochemistry immunofluorescence

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Abstract O6: Steve Lu et al. Comparison of biomarker assay modalities in anti-PD-(L)1 monotherapy: a meta-analysis

Checkpoint inhibitors target all of the following molecules EXCEPT:

- A. PD-1
- B. B7-H3
- C. CCR4
- D. TIGIT
- E. LAG3

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Checkpoint inhibitors target all of the following molecules EXCEPT:

- A. PD-1
- B. B7-H3
- C. CCR4
- D. TIGIT
- E. LAG3

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