Next Generation cytokines IL-2Memitics

Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

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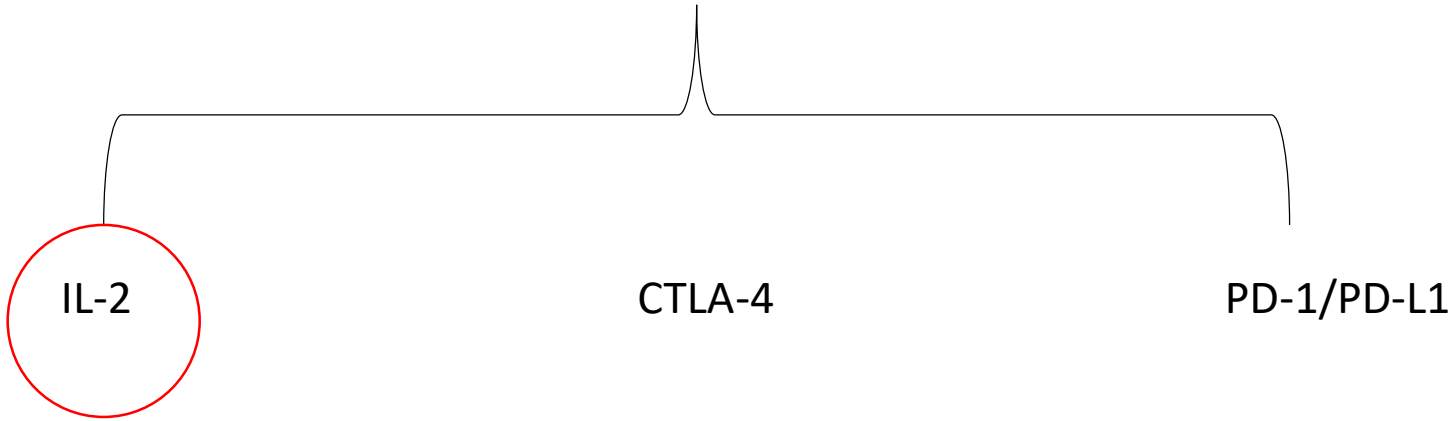
Presenter Disclosure Information

Adi Diab, MD, The University of Texas MD Anderson Cancer Center

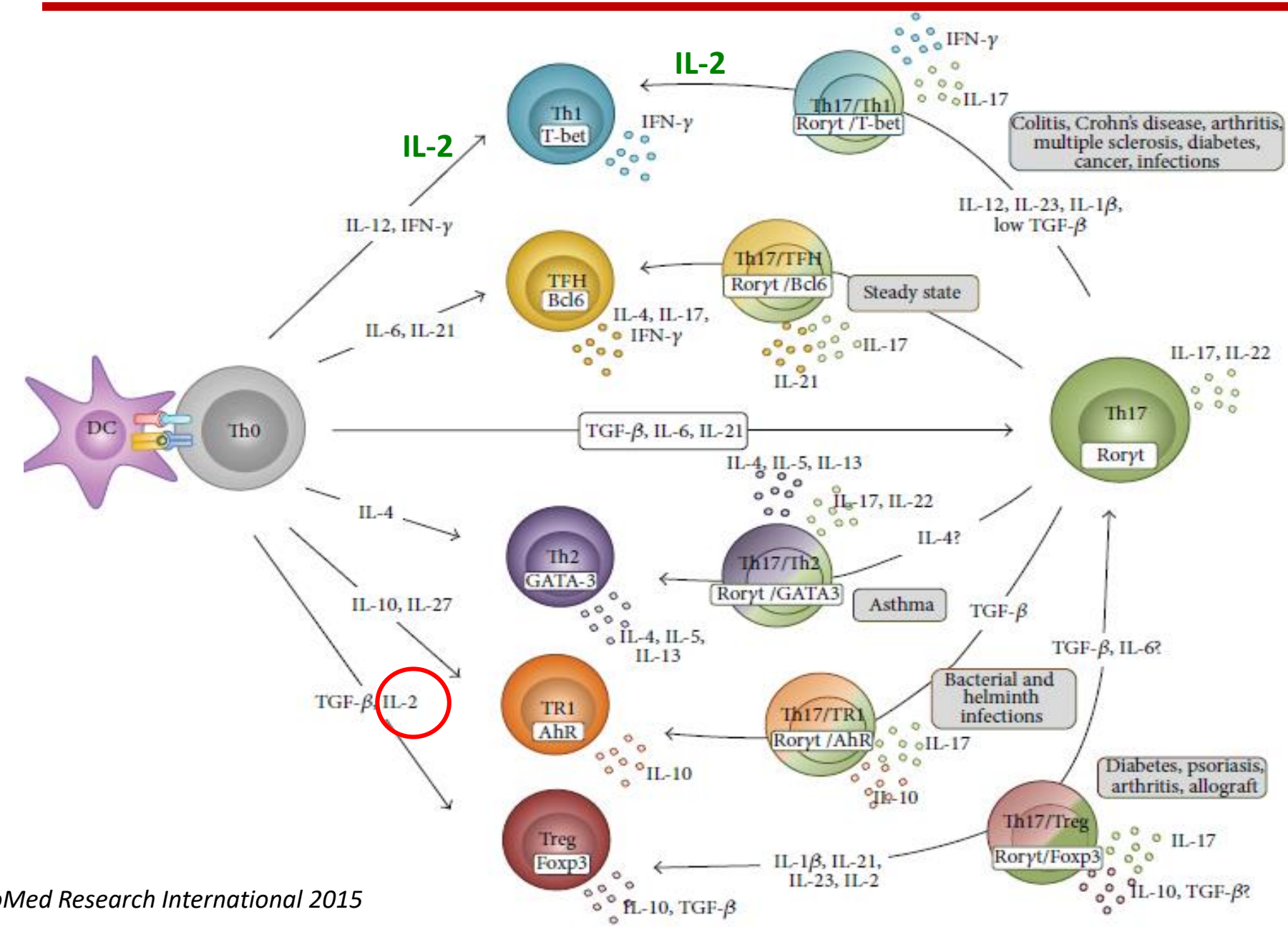
- No Relevant financial relationships to disclose

Validated Pathways of therapeutic Immunotherapy



1. Nemvaleukin/Alkermes
2. THOR707/Synthrox-SANOFI
3. **Bempegaldesleukin/Nektar**

Cytokines Role in the Plasticity of T-cells

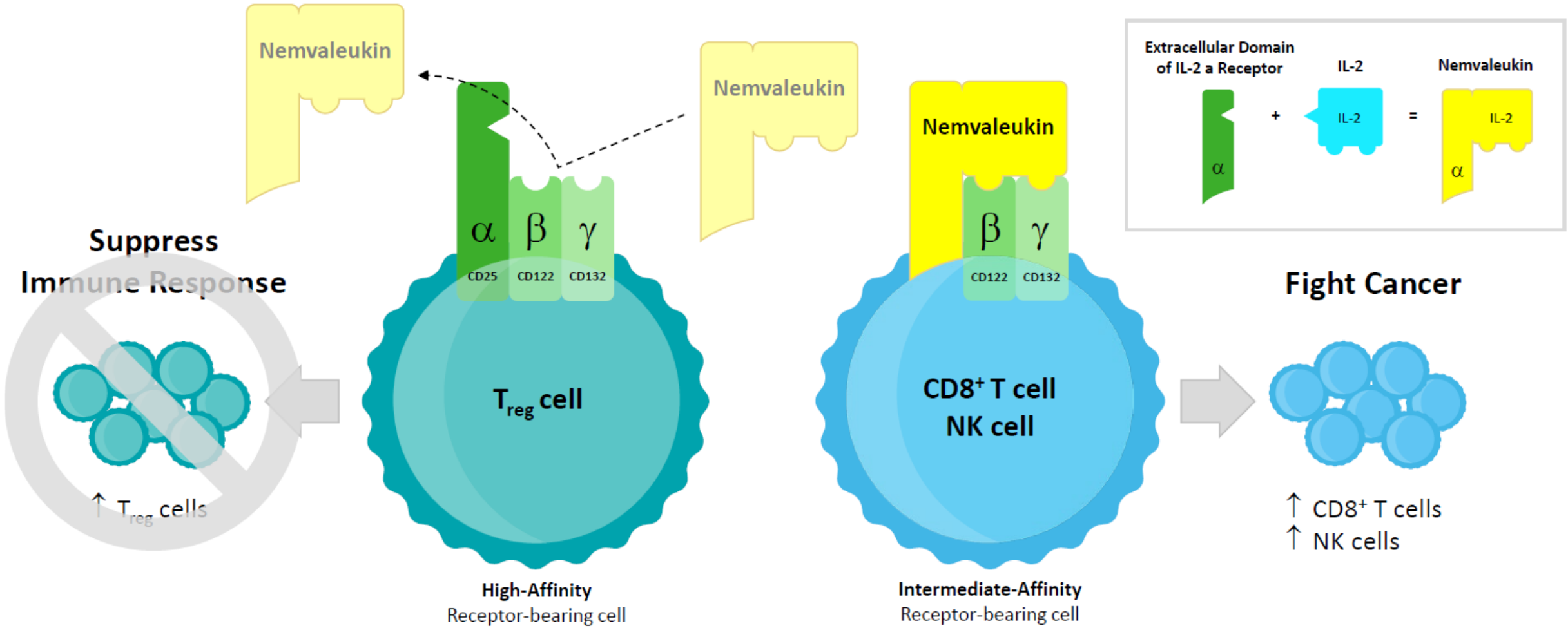


Guery L et al BioMed Research International 2015

Nemvaleukin/ALKS4230

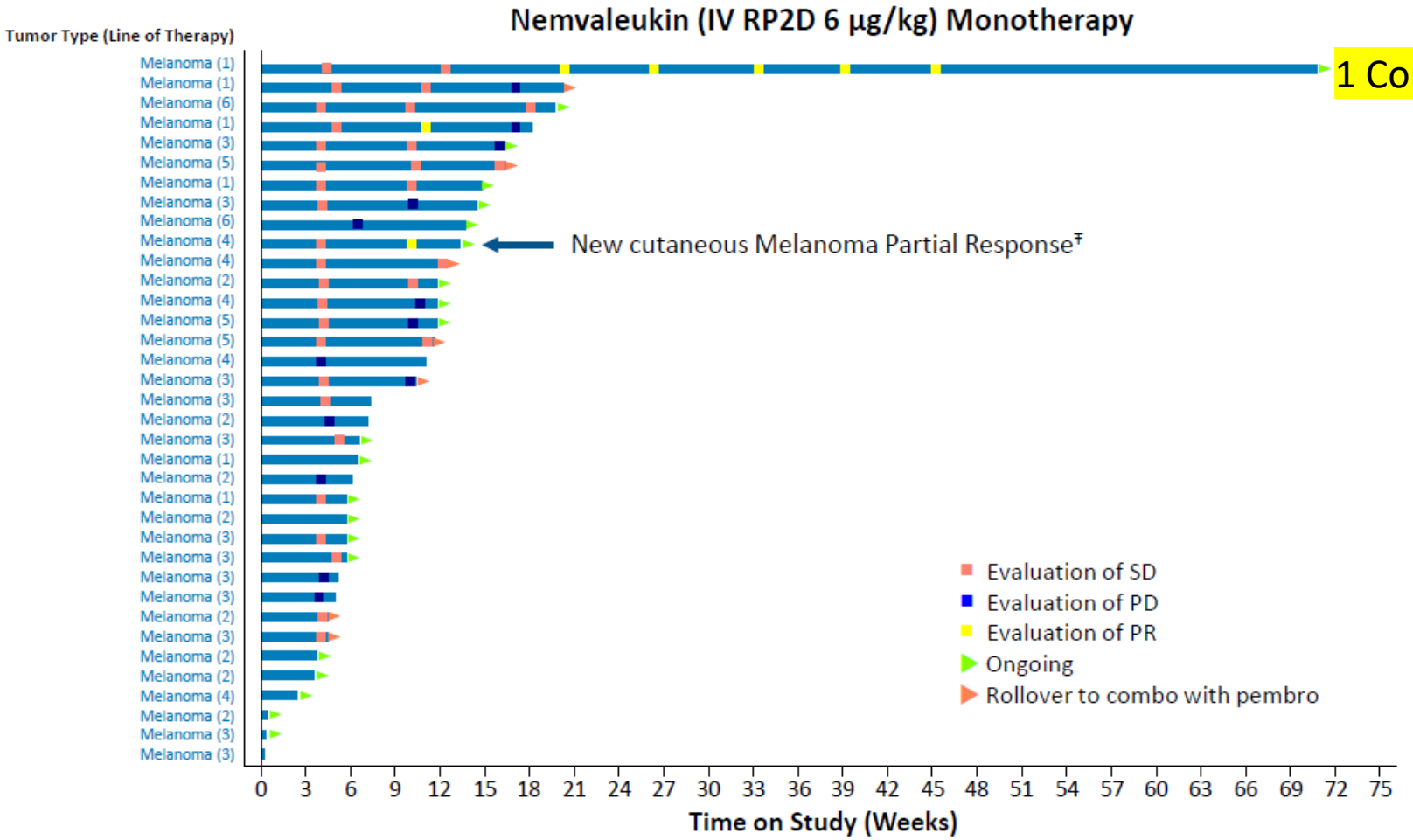
Alkermes

Nemvaleukin is Sterically Occluded From Binding to the High-Affinity IL-2 Receptor



For illustrative purposes only; T_{reg}: regulatory T cell; NK cell: natural killer cell

ARTISTRY-1: Nemvaleukin Monotherapy
Responses in CPI-Experienced Melanoma Patients



- Preliminary data (ongoing study):
  - Out of 28 evaluable patients (with ≥ 1 scans):
  - Total 3 responses observed, with tumor shrinkage
    - 2 mucosal melanoma and 1 cutaneous melanoma
  - Majority of patients are ongoing as of March 15, 2021 data cut

CPI = Checkpoint Inhibitors, IV,=Intravenous, PD=Progressive Disease, PR=Partial Response, RP2D=Recommended Phase 2 Dose, SD=Stable Disease.
‡Reported after the data cut off and awaiting confirmation.

Data cut off March 15, 2021

ALKS 4230 Safety Overview

Part B: ALKS 4230 Monotherapy

Preferred Term[a]	Overall (n = 15)
AE summary, n (%)	
Any TEAE	15 (100)
Grade 1-2 TRAE	15 (100)
Grade ≥ 3 TRAE	7 (46.7)
TEAEs leading to discontinuation[c]	1 (6.7)
Death	0
TEAEs in ≥ 3 patients overall, n (%)	
Chills	11 (73.3)
Pyrexia	7 (46.7)
Nausea	6 (40.0)
Hypotension	5 (33.3)
Tachycardia	5 (33.3)
Headache	5 (33.3)
Fatigue	4 (26.7)
Diarrhea	4 (26.7)
Neutrophil count decreased	4 (26.7)
Vomiting	4 (26.7)
Abdominal pain	3 (20.0)
Constipation	3 (20.0)
Hypertension	3 (20.0)
Decreased appetite	3 (20.0)
Lymphocyte count decreased	3 (20.0)
Rash	3 (20.0)
Hyperhidrosis	3 (20.0)
Grade ≥ 3 TRAEs in ≥ 2 patients overall , n (%)	
Neutrophil count decreased	3 (20.0)

Part C: ALKS 4230 + Pembrolizumab

Preferred Term[a]	Overall[b] (n = 79)
AE summary, n (%)	
Any TEAE	76 (96.2)
Grade 1-2 TRAE	73 (92.4)
Grade ≥ 3 TRAE	32 (40.5)
TEAEs leading to discontinuation[d]	9 (11.4)
Death[e]	2 (2.5)
TEAEs in ≥ 20% patients overall, n (%)	
Chills	51 (64.6)
Pyrexia	47 (59.5)
Nausea	34 (43.0)
Fatigue	29 (36.7)
Hypotension	25 (31.6)
Vomiting	23 (29.1)
Tachycardia	21 (26.6)
Constipation	18 (22.8)
Decreased appetite	18 (22.8)
Anemia	17 (21.5)
Grade ≥ 3 TRAEs in ≥ 2 patients overall, n (%)	
Lymphocyte count decreased	7 (8.9)
Anemia	5 (6.3)
Fatigue	5 (6.3)
Neutrophil count decreased	3 (3.8)
Alanine aminotransferase increased	2 (2.5)
Aspartate aminotransferase increased	2 (2.5)
Muscular weakness	2 (2.5)
Hypertension	2 (2.5)
Infusion-related reaction	2 (2.5)

[a]AEs coded using MedDRA version 19.0.
[b]Overall data based on all patients enrolled in Part C of the trial (all cohorts).
[c]One participant discontinued due to abdominal pain (assessed as not related to ALKS 4230).
[d]Discontinuations due to ALKS 4230 as assessed by the investigator include fatigue, pneumonitis, and infusion-related reaction.
[e]Two deaths occurred in pancreatic cancer patients; one was due to the underlying cancer and assessed by the investigator as not related to treatment, the other was due to inanition and assessed by the investigator as related to both study drugs; the latter occurred after the data cutoff date of 24 Jul 2020.
TEAE, treatment-emergent AE; TRAE, treatment-related AE.

Vaishampayan U et al ESMO 2020

Data as of 24 Jul 2020[e]

ARTISTRY-1 Safety Summary

- Safety profile of nemvaleukin in combination with pembrolizumab generally consistent with monotherapy profile
- In combination, no emerging evidence of additive toxicities to those already established for pembrolizumab alone

Monotherapy (Part B only; n=42)

- Chills, pyrexia, nausea & hypotension are most frequently (>30%) reported treatment-related adverse events (TRAEs); anticipated effects of cytokine administration
  - Transient, majority Grade ≤2 in severity
- Most frequent (>10%) Grade 3-4 TRAE was neutropenia
- No discontinuations due to treatment-related AEs
- No deaths due to treatment-related AEs

Combination with Pembrolizumab (Part C only; n=111)

- Chills, pyrexia & fatigue are most frequently (>30%) reported treatment-related AEs; anticipated effects of cytokine administration
  - Transient, all Grade ≤2 in severity
- Most frequent (>10%) Grade 3-4 TRAE was neutrophil count decrease
- Discontinuation due to treatment-related AEs included: fatigue, pneumonitis, infusion-related reaction, inanition
- Two deaths in pancreatic cancer patients (reported at ESMO 2020)
  - One death due to inanition and assessed by the investigator as related to nemvaleukin
  - One death due to underlying cancer and assessed as unrelated to treatment

Data as of December 2020

Phase 1/2 Study of Subcutaneously Administered ALKS 4230, a Novel Engineered Cytokine, as Monotherapy and in Combination With Pembrolizumab, in Patients With Advanced Solid Tumors: ARTISTRY-2

John Powderly,[1] Bradley Carthon,[2] Marc S. Ernstoff,[3] Anthony J. Olszanski,[4] John Wrangle,[5] Anthony F. Shields,[6] Sarina A. Piha-Paul,[7] Kelly K. Curtis,[8] Ilda Bidollari,[9] Yangchun Du,[9] Lei Sun,[9] Emily Putiri,[9] Yan Wang,[9] Heather C. Losey,[9] Bruce J. Dezube,[9] David Cohan,[9] Ulka N. Vaishampayan[10]

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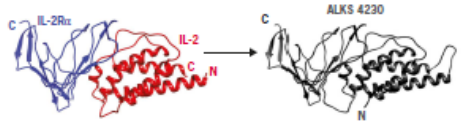
Poster 671

INTRODUCTION

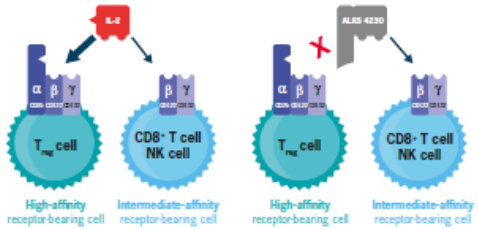
- ALKS 4230 is a novel engineered cytokine designed to selectively expand natural killer (NK) and cytotoxic CD8+ T cells by activating the intermediate-affinity IL-2 receptor (IL-2R) (Figure 1).
- High doses of IL-2 are required to induce the activation of the intermediate-affinity IL-2R for antitumor activity; however, this also leads to activation of the high-affinity IL-2R, which is associated with regulatory T cell (T_{reg}) expansion and may lead to life-threatening acute toxicities.[1]
- Intravenous (IV) dosing of ALKS 4230 has shown encouraging antitumor activity and acceptable tolerability, as monotherapy and in combination with pembrolizumab, in patients with advanced solid tumors (ARTISTRY-1, NCT02799095; see Poster 689).[2]
- Subcutaneous (SC) dosing may provide an alternative administration option for patients.

Figure 1: ALKS 4230 Structure and Activity

A. ALKS 4230 is a fusion protein of circularly permuted IL-2 and IL-2Rα.



B. ALKS 4230 is designed to selectively bind only to the intermediate-affinity IL-2R complex.



RESULTS

Patient Characteristics

- 43 patients have been treated with ALKS 4230 across 8 assigned dose escalation cohorts, with SC doses ranging from 0.3 mg to 10 mg across both dosing regimens (Table 1).
  - The median (range) number of prior therapies was 4 (0-17).
  - 42% of patients were previously treated with immunotherapy.
  - Median (range) age at study entry was 61.0 (28-82) years.
  - 16 patients (37.2%) are male.
- Patient tumor indications were mixed; the most common tumor types included colon cancer (n = 8), ovarian cancer (n = 5), and lung cancer (n = 4).
- 30 patients (69.8%) completed lead-in monotherapy and initiated combination therapy.

Safety and Tolerability

- The maximum tolerated dose and RP2D for SC administration have not yet been determined.
  - 6 mg q7d, 6 mg q21d, and 10 mg q21d cohorts are ongoing.
- Overall, across both treatment periods, injection site reactions (ISRs) were the most commonly reported adverse events (AEs).
- AEs, regardless of causality, occurred in 42 (97.7%) patients during the monotherapy lead-in period and in 28 (65.1%) during the combination period (Table 1).
- Overall, across both treatment periods, 16 patients (37.2%) experienced grade ≥ 3 AEs assessed by the investigator as being related to ALKS 4230, with lymphopenia (25.6%) as the only AE reported in ≥ 2 patients.
- 1 patient experienced dose-limiting AEs while receiving 10 mg q21d ALKS 4230 (grade 3 nausea, vomiting, and fatigue).
- Additionally, 1 patient experienced a treatment-related serious AE (SAE) (grade 3 tumor flare manifesting as a colonic obstruction).

Table 1: Summary of AEs

Patients With an AE, n (%)	q7d 0.3 mg (n = 7)	q7d 0.6 mg (n = 3)	q7d 1 mg (n = 7)	q7d 3 mg (n = 7)	q7d 6 mg (n = 3)	q21d 1 mg (n = 4)	q21d 3 mg (n = 4)	q21d 10 mg (n = 8)	q7d + q21d Overall (N = 43)
Overall, both treatment periods									
Any AE	7 (100)	3 (100)	7 (100)	7 (100)	3 (100)	4 (100)	4 (100)	7 (87.5)	42 (97.7)
Grade ≥ 3 TRAEs	1 (14.3)	0	4 (57.1)	4 (57.1)	2 (66.7)	1 (25.0)	1 (25.0)	3 (37.5)	16 (37.2)
Related ISR AEs[a]	5 (71.4)	1 (33.3)	3 (42.9)	5 (71.4)	1 (33.3)	3 (75.0)	3 (75.0)	6 (75.0)	27 (62.8)
Monotherapy lead-in period									
Any AE	7 (100)	3 (100)	7 (100)	7 (100)	3 (100)	4 (100)	4 (100)	7 (87.5)	42 (97.7)
AEs occurring in ≥ 20% of the overall population									
Pyrexia	3 (42.9)	0	2 (28.6)	4 (57.1)	0	0	4 (100)	4 (50.0)	17 (39.5)
Fatigue	4 (57.1)	1 (33.3)	2 (28.6)	2 (28.6)	1 (33.3)	0	2 (50.0)	3 (37.5)	15 (34.9)
Chills	3 (42.9)	0	2 (28.6)	3 (42.9)	1 (33.3)	0	2 (50.0)	4 (50.0)	15 (34.9)
Nausea	3 (42.9)	0	2 (28.6)	3 (42.9)	1 (33.3)	0	1 (25.0)	4 (50)	14 (32.6)
Lymphopenia	1 (14.3)	0	3 (42.9)	3 (42.9)	0	1 (25.0)	1 (25.0)	2 (25.0)	11 (25.6)
Combination period									
Any AE	7 (100)	2 (66.7)	6 (85.7)	3 (42.9)	0	3 (75.0)	3 (75.0)	4 (50.0)	28 (65.1)
AEs occurring in ≥ 15% of the overall population									
Lymphopenia	0	0	3 (42.9)	1 (14.3)	0	2 (50.0)	0	2 (25.0)	8 (18.6)
Fatigue	3 (42.9)	0	2 (28.6)	1 (14.3)	0	1 (25.0)	0	0	7 (16.3)

[a]ISRs include the following preferred terms: injection site reaction, injection site erythema, injection site pain, injection site pruritus, injection site swelling, injection site discoloration, injection site inflammation, injection site irritation, and injection site warmth. TRAE, treatment-related AE.

Clinical Results

- Median (range) duration of treatment was 65 (1-562) days.
- 23 of 33 evaluable patients treated in the study so far achieved stable disease.
  - 1 patient with ovarian cancer (low-grade Mullerian mesenchymal tumor) has been receiving study treatment for > 6 months (number of prior therapies was 1).
  - 1 patient with head and neck squamous cell carcinoma (malignant neoplasm of lacrimal gland and duct) has been receiving study treatment for > 12 months (number of prior therapies was 4).

Pharmacokinetics/Pharmacodynamics

- Systemic exposure to ALKS 4230 increased with increasing dose (Figure 3), resulting in a dose-dependent increase in circulating NK and CD8+ T cells, with minimal impact on T_{regs} (Figure 4).
  - Accompanying dose-dependent transient elevation of serum IFNγ and, to a lesser extent, IL-6 concentrations were also observed (Figure 3).
  - Relative to IV ALKS 4230, there was a greater increase in serum IFNγ and a smaller increase in serum IL-6 concentrations.

Figure 3: Serum Concentrations After the First Dose in Monotherapy Lead-In Period

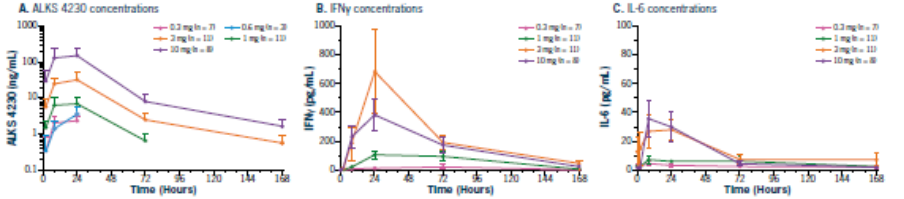
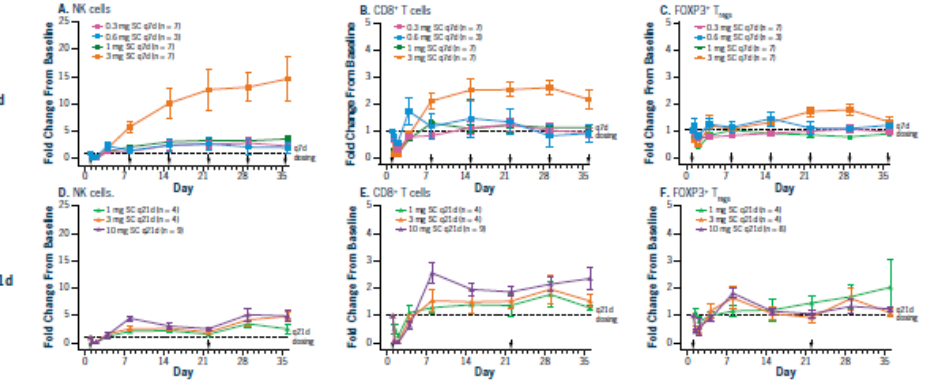


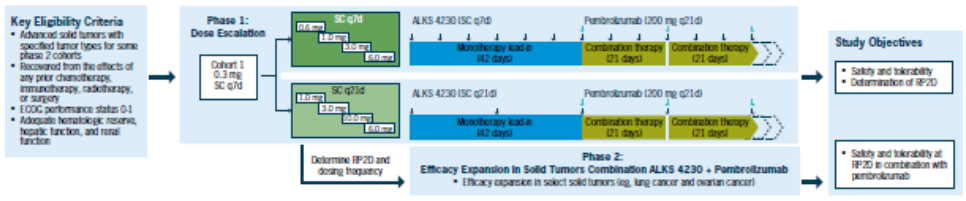
Figure 4: ALKS 4230 Pharmacodynamics by Dosing Regimen



METHODS

- ARTISTRY-2 (NCT03861793) is an ongoing phase 1/2 study of SC ALKS 4230 ± pembrolizumab.
- Phase 1 is an ongoing dose escalation during which cohort-specific doses of SC ALKS 4230 are administered.
- Each patient assigned to a given cohort receives ALKS 4230 at a single dose level and on a schedule of either every 7 days (q7d) or every 21 days (q21d).
  - Intrapatient dose escalation is allowed.
- The dosing schedule included a 6-week lead-in monotherapy period followed by combination with IV pembrolizumab 200 mg q21d (Figure 2).
- Safety, tolerability, and pharmacokinetic/pharmacodynamic data from dose escalation up to a dose of 10 mg, as of 9/29/2020, are reported in his poster.

Figure 2: Study Design and Dosing Schedule



ECOG, Eastern Cooperative Oncology Group; RP2D, recommended phase 2 dose.

CONCLUSIONS

- ALKS 4230 is a promising investigational agent for the treatment of advanced solid tumors.
- Subcutaneously administered ALKS 4230 in the doses studied has an acceptable safety and tolerability profile consistent with the anticipated pharmacological effect and what is observed with IV ALKS 4230.
- Pharmacodynamic results show dose-dependent increases in NK cell and CD8+ T cell activation and minimal increase in immunosuppressive markers, such as FOXP3+ T_{regs}.
- Clinical benefit is noted, even in immunotherapy-pretreated patients; 11 patients continued on therapy past 6 months.
- The study, including dose escalation, is ongoing.
- Maximum tolerated dose and RP2D for SC ALKS 4230 have not yet been determined.

REFERENCES AND ACKNOWLEDGMENTS

References

1. Lopes J, et al. *J Immunother Cancer*. 2020;8:e000673.
2. Vaishampayan UN, et al. *Ann Oncol*. 2020;30:suppl 4:iv708-iv709.

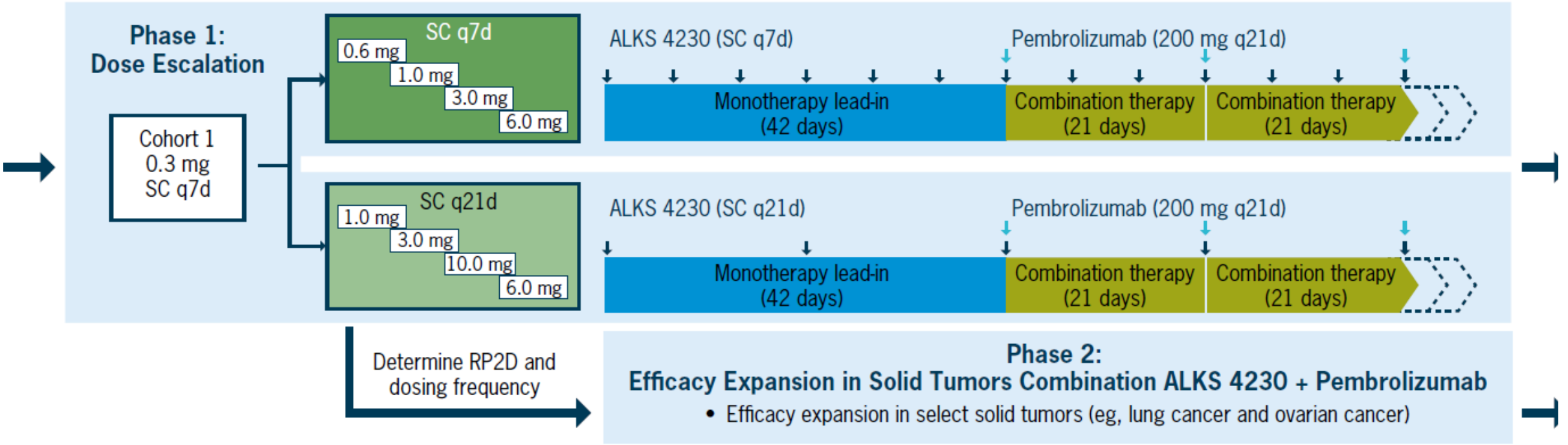
Acknowledgments

The authors would like to thank all of the patients who are participating in this trial and their families. Many thanks to all the investigators and site personnel for their participation in the study. The trial is sponsored by Alkermes, Inc. Medical writing and editorial support was provided by Parexel and funded by Alkermes, Inc.

ARTISTRY

Alkermes Patient Inspired

ARTISTRY-2 RP2D



Group; RP2D, recommended phase 2 dose.

Powderly J et al SITC 2020

Safety Profile of SC Nemvaleukin Consistent With Mechanism of Action and IV Nemvaleukin

RP2D Regimens Selected

SC **3 mg q7d** declared as RP2D based on totality of data

- 6 mg q21d dose may offer additional flexibility in treating certain tumor types and/or in combination settings in the future
- Maximum tolerated doses (MTD) for SC nemvaleukin were determined to be 6 mg q7d and 10 mg q21d

No additional toxicities were reported in combination with pembrolizumab

Most Commonly Reported TEAEs at RP2D Monotherapy

3 mg q7d (n=7):

- Chills, pyrexia, fatigue, nausea, lymphopenia, injection site reactions, AST/ALT increase are most frequently (>30%) reported treatment-related adverse events (AEs); majority anticipated effects of cytokine administration
  - Transient, majority Grade ≤2 in severity
- Most frequent (>10%) Grade 3-4 TRAE was neutropenia
- No treatment-related SAE, discontinuations or deaths

6 mg q21d (n=8):

- Safety profile was consistent with 3mg q7
- Most frequent (>10%) Grade 3-4 TRAE was AST/ALT increase (1 patient)
- No treatment-related SAE, discontinuations or deaths

DLTs at MTD

Three DLTs reported at MTDs of 6 mg q7d and 10 mg q21d

- DLTs were manageable with either dose interruption, discontinuation and/or standard of care treatment
  - Atypical Capillary Leak Syndrome, without hypotension (Grade 3)
  - Injection site reaction (Grade 3)
  - Transient fatigue, nausea, vomiting (Grade 3)

TRAEs = Treatment-related adverse events; DLTs = Dose-limiting-toxicities; MTD = Maximum tolerated dose, RP2D = Recommended phase 2 dose, SAE = Serious Adverse Event, SC = Subcutaneous, IV = Intravenous

Data as of 02 Mar 2020

THOR 707

Synthorx/SANOFI

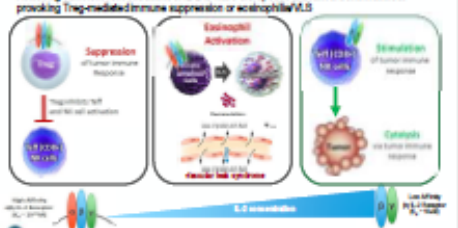
THOR-707 (SAR444245), a Novel Not-alpha IL-2 as Monotherapy and in Combination With Pembrolizumab in Advanced / Metastatic Solid Tumors: Interim Results From HAMMER, an Open-label, Multicenter Phase 1/2 Study

F Janku,[1] R Abdul-Karim,[2] A Azad,[3] J Bendell,[4] G Falchook,[5] HK Gan,[6] T Tan,[7] JS Wang,[8] CE Chee,[9] L Ma,[10] J Mooney,[10] N Marina,[10] G Abbadessa,[11] M Milla,[10] T Meniawy,[12]

[1]Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX, [2]NEXT Oncology, Texas Oncology, San Antonio, TX, [3]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia, [4]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, [5]Sarah Cannon Research Institute at HealthONE, Denver, CO, [6]Olivia Newton-John Cancer Center, Austin Health, Melbourne, Victoria, Australia, [7]Division of Medical Oncology, National Cancer Centre Singapore, [8]Florida Cancer Specialists/Sarah Cannon Research Institute/Sarasota Memorial Hospital, Sarasota FL, [9]Division of Medical Oncology, National University Cancer Institute Singapore, [10]Synthorx, a Sanofi Company, La Jolla, CA, [11]Sanofi, Cambridge, MA, [12]Linear Clinical Research, Nedlands, Western Australia, Australia.

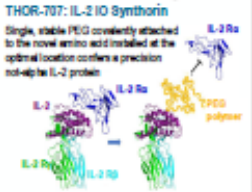
INTRODUCTION

Dual Pharmacology of IL-2 is Explained by αβγ and βγ Receptor Engagement



THOR-707: IL-2 IO Synthorin

Single, stable PEG covalently attached to the novel amino acid installed at the optimal location confers a precision not-alpha IL-2 protein

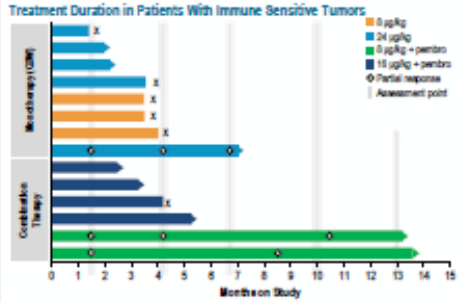


IL-2 binds to the αβγ receptor form with high affinity because of 3 chain

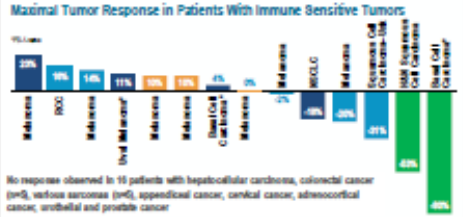
Targeted pegylation of THOR-707 at the novel amino acid blocks α chain engagement

RESULTS

Treatment Duration in Patients With Immune Sensitive Tumors



Maximal Tumor Response in Patients With Immune Sensitive Tumors



No response observed in 16 patients with hepatocellular carcinoma, colorectal cancer (n=9), various sarcomas (n=6), appendiceal cancer, cervical cancer, adrenocortical cancer, urothelial and prostate cancer

RESULTS

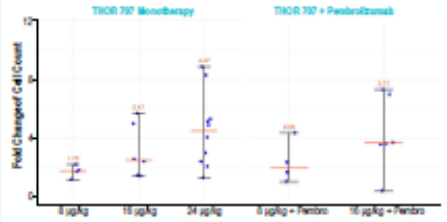
Responses Across Patients Receiving Q3W Monotherapy and Combination With Pembrolizumab

59 yo, male; HNSCC (BRCA2, PIK3CA, MSS, TMB-low)	50 yo male; basal cell carcinoma	73 yo male; squamous cell carcinoma, unk orig.	62 yo male; prostate adenocarcinoma	59 yo male; non-small cell lung cancer
Dose: 8 µg/kg Q3W + pembro	Dose: 8 µg/kg Q3W + pembro	Dose: 24 µg/kg Q3W	Dose: 16 µg/kg Q3W	Dose: 16 µg/kg Q3W
Time on Therapy: 18 cycles +	Time on Therapy: 17 cycles +	Time on Therapy: 7 cycles +	Time on Therapy: 10 cycles, off due to rising PSA	Time on Therapy: 6+ cycles
Prior Treatment: 4 lines of systemic therapy including 2 anti-PD-1s (best response to anti-PD1: SD)	Prior Treatment: Surgeries, radiation therapy	Prior Treatment: 2 lines of systemic therapy including anti-PD-1 (best response on anti-PD-1: SD)	Prior Treatment: Surgeries; radiation therapy; 9 systemic therapies	Prior Treatment: 2 systemic therapies including anti-PD-1 (best response to anti-PD-1: SD)
Best Response: Confirmed PR (31% decrease after 8 cycles)	Best Response: Confirmed PR (50% decrease after 2 cycles; 80% after 8	Best Response: Confirmed PR (31% decrease after 2 cycles)	Best Response: SD (24% decrease after 2 cycles)	Best Response: SD (17.9% decrease after 5 cycles)

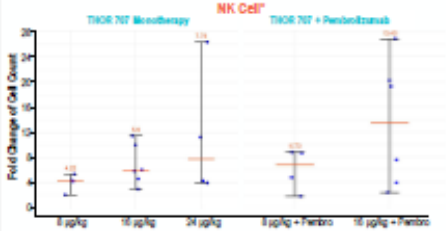
Clinical Pharmacodynamic Effect Consistent With Not-Alpha Profile for THOR-707 Q3W +/- Pembrolizumab

Pharmacodynamic Markers of Immune Activity

CD8+ Effector T-Cell*

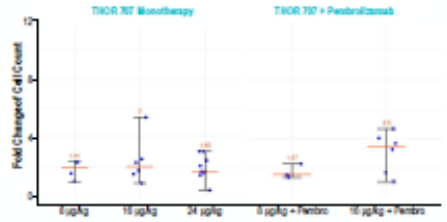


NK Cell*

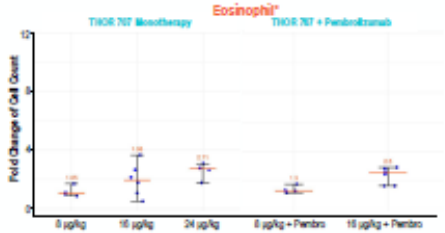


Pharmacodynamic Markers of Not-Alpha Selectivity

CD4+ Regulatory T-Cell*



Eosinophil*



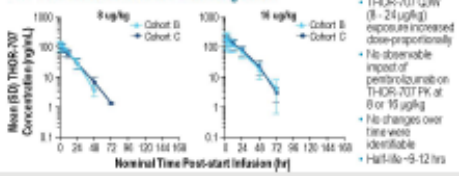
*Post peripheral expansion post THOR-707 first dose

	IL-6, serum pg/mL Mean (range)	IL-6, serum pg/mL Mean (range)	CD8+ Teff, cells/µL Median (range)	NK cells/µL Median (range)	CD4+ Treg, cells/µL Median (range)	Eosinophil, cells/µL Median (range)
8 µg/kg THOR 707	8.8	5.0 (1.3 – 94.4)	201.7 (56.0-328.9)	172.1 (56.8-283.1)	37.8 (29.3-42.9)	129.05 (44.3-317.7)
8 µg/kg THOR 707 + pembro	8.8	5.8 (1.3 – 70.8)	314.9 (56.9-632.2)	241.8 (183.3-658.6)	44.3 (26.1-62.5)	237.5 (181.3-285.4)
16 µg/kg THOR707	8.8	26.9 (1.3 – 275)	186.6 (23.9-659.1)	613.71 (82.7-1848.4)	50.1 (7.5-93.2)	199.3 (15.9-1078.5)
16 µg/kg THOR 707 + pembro	8.8	35.8 (1.3 – 503.4)	102.7 (41.2-1369.0)	503.0 (206.7-1131.8)	33.8 (18.2-76.8)	117.7 (67.5-368.0)
24 µg/kg THOR 707	9.0 (8.8 – 12.1)	97.3 (1.3 – 1100)	218.0 (83.8-626.5)	542.0 (352.3-772.3)	41.0 (14.5-83.2)	194.1 (152.4-218.5)

*EOS>5

PHARMACOKINETICS

PK Profile Consistent Across Escalating Doses



- THOR-707 Q3W (8 - 24 µg/kg) exposure increased dose-proportionally
- No observable impact of pembrolizumab on THOR-707 PK at 8 or 16 µg/kg
- No changes over time were identifiable
- Half-life ~9-12 hrs

SAFETY

Adverse Events (PT), n (%)	TEAEs (N=38)	THOR-707 Q3W Monotherapy TEAEs (N=26)	THOR-707 + Pembrolizumab TEAEs (N=10)
Anemia	7 (23.3%)	5 (25%)	2 (20%)
Influenza-Like Illness	17 (56.7%)	13 (65%)	4 (40%)
Pyrexia	16 (53.3%)	10 (50%)	6 (60%)
Chills	11 (36.7%)	7 (35%)	4 (40%)
Fatigue	10 (33.3%)	5 (25%)	5 (50%)
Nausea	13 (43.3%)	11 (55%)	2 (20%)
Vomiting	13 (43.3%)	11 (55%)	2 (20%)
ALT Increase	10 (33.3%)	6 (30%)	4 (40%)
AST Increase	12 (40%)	8 (40%)	4 (40%)
Decreased Appetite	6 (20%)	5 (25%)	1 (10%)
Hypophosphatemia	8 (26.7%)	5 (25%)	3 (30%)
Lymphocyte Count Decreased	7 (23.3%)	5 (25%)	2 (20%)
Hypotension	7 (23.3%)	4 (20%)	3 (30%)

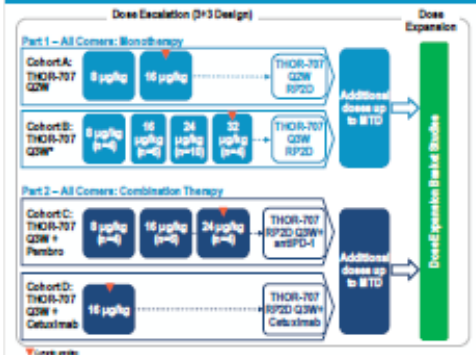
Adverse Events ≥5 pts, n (%)	Related Grade 3/4 Events (N=38)	In Monotherapy (N=28)	In Combination (N=10)
Cytokine Release Syndrome	5.0% (1 G2; 1 G4)	1G4 (24 µg/kg)	1G2
ALT	5.0% (2 G3)	2G3 (16 µg/kg, 24 µg/kg)	--
AST	10% (2 G3; 1 G4)	2G3 (16µg/kg; 24µg/kg); 1G4 (16 µg/kg)	--
Lymphocyte Count Decrease	10.7% (1 G3; 4 G4)	3G4 (16 µg/kg,24 µg/kg)	1G3, 1G4

- TRAEs mostly consisted of flu-like symptoms, nausea, or vomiting, were transient and managed with supportive care in doses tested; 1 TEAE resulted in a drug discontinuation (G4 CRS); 2 patients dose reduced due CRS (1 at C3D1 and 1 C4D1)
- All TRAEs coded as CRS based on clinical symptoms did not correspond to increases in IL-6, or progression, and resolved without need for tocilizumab
  - G4 CRS (fever, chills, rigor + hypotension, concentration impairment at 4hr; symptoms resolved <1hr with supportive care incl. narcotics, steroids + tocilizumab; transient, IL-6 increase at discharge (at 24 hr)
  - G3 CRS (fever + hypotension requiring pressors; had baseline orthostatic hypotension)
  - G2 CRS (fever + hypoxia; had baseline hypoxia, SPO2 91%, oxygen need at night)
- No reports of VLS or eosinophilia; IL-6 levels remain at or below lowest level of detection

CONCLUSIONS

- Tolerability and biomarker findings further confirm not-alpha IL-2 profile seen preclinically
  - No elevations of IL-6, reports of VLS, or AEIAs observed in any patient
  - No cumulative toxicity or end organ toxicity was observed, no QTc prolongation, or other cardiac toxicity
  - AEs of fever, hypotension, and hypoxia did not correlate with IL-6/IL-6 cytokine elevation
  - Treatment-related adverse events were transient and resolved with accepted SOC
- No DLTs observed at doses up to 24 µg/kg as monotherapy; 16 µg/kg with pembro
- THOR-707 dose escalation has progressed beyond projected monotherapy RP2D dose of 24 µg/kg Q3W to 32 µg/kg Q3W to further characterize the upper bounds of the dose range
- Initial efficacy at 8 and 16 µg/kg, both mono and combo

OVERALL STUDY DESIGN AND PATIENT CHARACTERISTICS



Patients

- Adults ≥ 18 years of age
- Advanced and/or metastatic solid tumors
- ECOG PS of 0 or 1
- Not eligible for standard of care or standard therapy
- Adequate organ function and laboratory parameters

Primary Objectives

- Safety and tolerability of THOR-707 alone and in combination with a checkpoint inhibitor
- MTD and/or the RP2D of THOR-707 alone and in combination with a checkpoint inhibitor

Secondary Objectives

- ORR by RECIST v1.1
- TTR, DOR, RFS, OS and DCR of THOR-707 alone and in combination with a checkpoint inhibitor

Biomarkers Endpoints

- CD8+ Teff and NK cell counts
- CD4+ Treg cell counts
- Eosinophil counts and levels of IL-5 and IL-6
- Ki67 expression levels in peripheral blood immune cells

We report the findings from Cohort B (8, 16, and 24 µg/kg) n = 20 and Cohort C (8 and 16 µg/kg) n=10

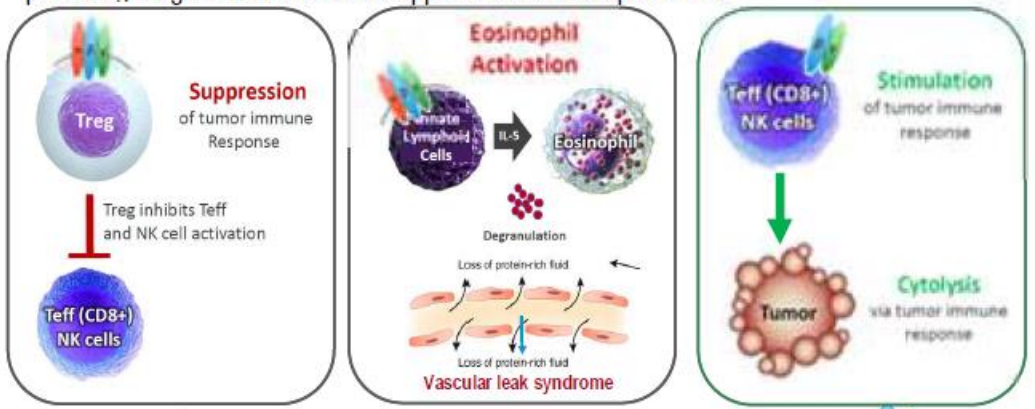
Baseline Characteristics	N=42
Median age (range), years	62 (37-78)
Sex, male, n (%)	24 (57.1)
Race, Caucasian, n (%)	37 (88.1)
Metastatic disease, n (%)	38 (90.5)
ECOG, n (%)	
0	16 (38.1)
1	25 (59.5)
Median prior lines of therapy, n (range)	4 (1 to >5)
Tumor type, n (%)	
Colorectal	7 (24.0)
Melanoma	4 (16.0)
Sarcoma	3 (12.0)
Prostate	1 (4.0)
Other	8 (32.0)

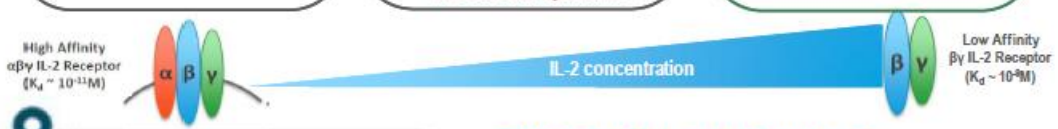
Janku F et al.. AACR 2021

Dual Pharmacology of IL-2 is Explained by αβγ and βγ Receptor Engagement

The Alpha Problem

Achieving sufficient concentrations of IL-2 to have therapeutic anticancer benefit without provoking Treg-mediated immune suppression or eosinophilia/VLS





At low concentrations, IL-2 activates a trimeric IL-2R that includes α, β, and γ subunits

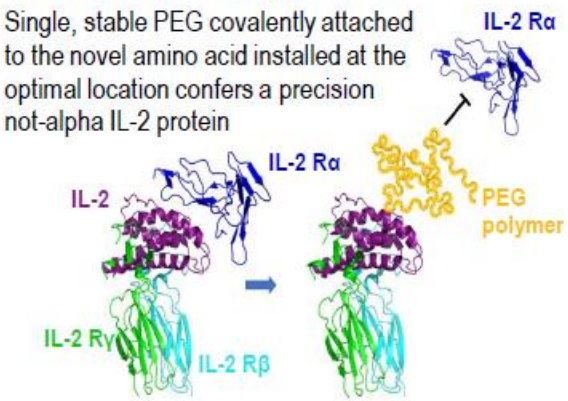
- Trimeric IL-2R are expressed on Treg cells and innate lymphoid cells

At higher concentrations, IL-2 activates a dimeric IL2R that includes only the β and γ subunits

- Dimeric IL-2R is expressed by Teff and NK cells

THOR-707: IL-2 IO Synthorin

Single, stable PEG covalently attached to the novel amino acid installed at the optimal location confers a precision not-alpha IL-2 protein

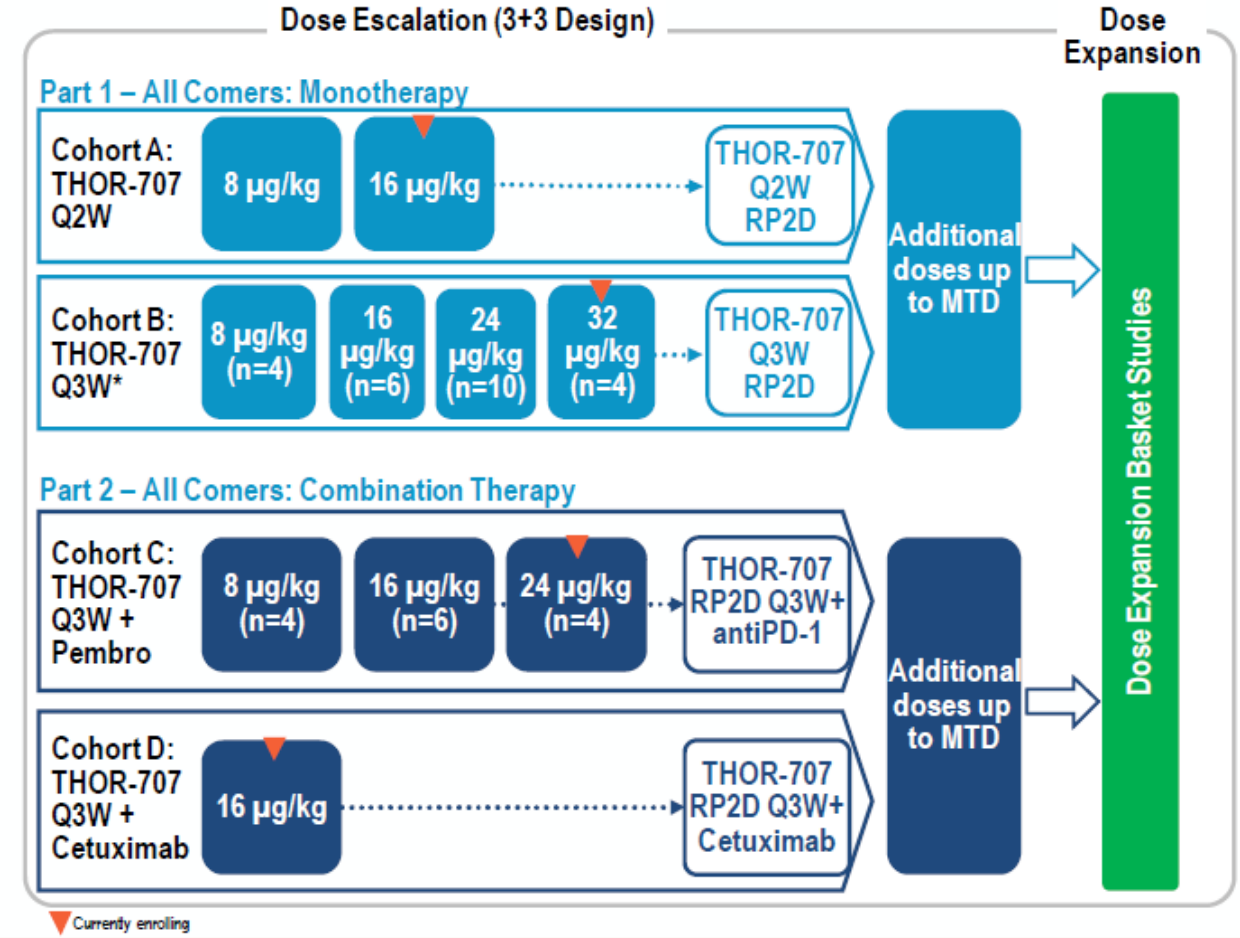


IL-2 binds to the αβγ **receptor form** with high affinity because of α chain

Targeted pegylation of THOR-707 at the novel amino acid blocks α chain engagement

1. Van Gool F, et al. *Blood*. 2014;124(24):3572-3576. 2. Todd JA, et al. *PLoS Med*. 2016; 13(10):e1102139. 3. Siddell E, et al. *Kidney Int*. 2017; 92(1):p37-p46.

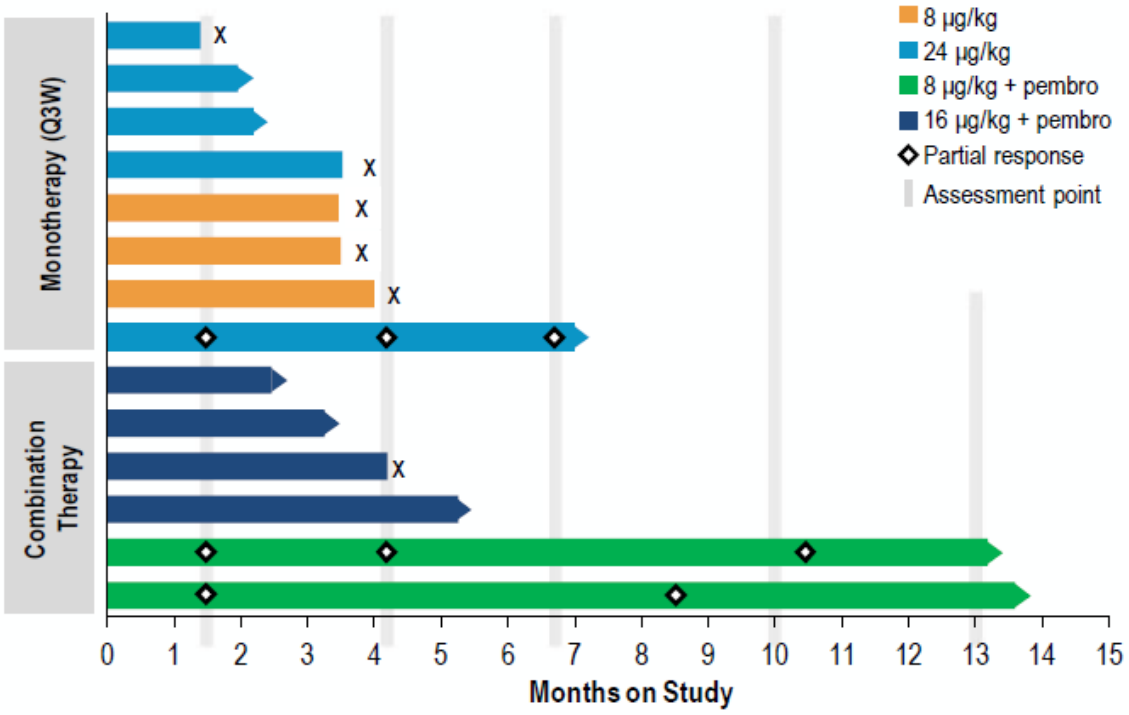
OVERALL STUDY DESIGN AND PATIENT CHARACTERISTICS



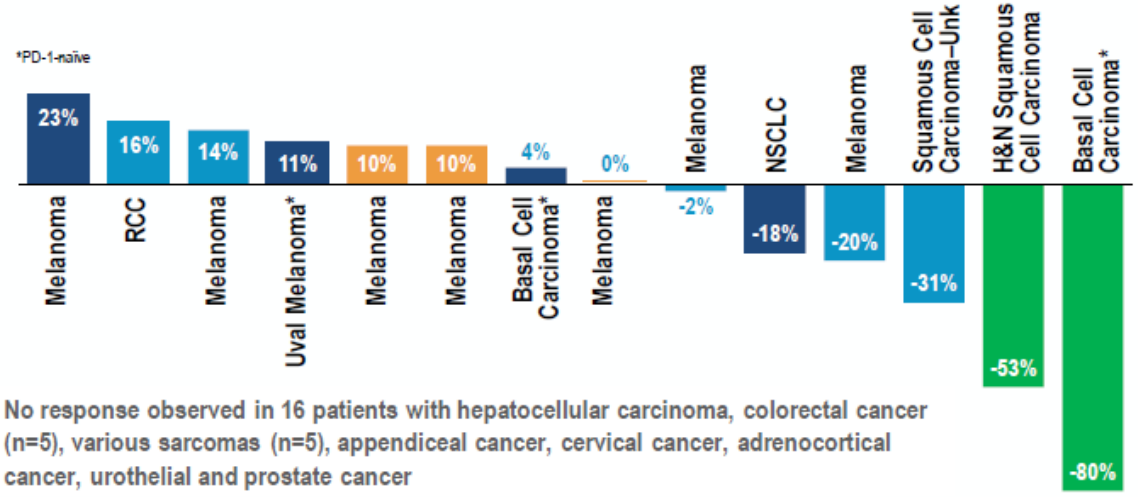
Janku F et al.. AACR 2021

RESULTS

Treatment Duration in Patients With Immune Sensitive Tumors



Maximal Tumor Response in Patients With Immune Sensitive Tumors



No response observed in 16 patients with hepatocellular carcinoma, colorectal cancer (n=5), various sarcomas (n=5), appendiceal cancer, cervical cancer, adrenocortical cancer, urothelial and prostate cancer

SAFETY

Adverse Events (PT), n (%)	TEAEs (N=30)	THOR-707 Q3W Monotherapy TEAEs (N=20)	THOR-707 + Pembrolizumab TEAEs (N=10)
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AST Increase	12 (40%)	8 (40%)	4 (40%)
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Hypophosphatemia	8 (26.7%)	5 (25%)	3 (30%)
Lymphocyte Count Decreased	7 (23.3%)	5 (25%)	2 (20%)
Hypotension	7 (23.3%)	4 (20%)	3 (30%)

Adverse Events >2 pts, n (%)	Related Grade 3/4 Events (N=30)	In Monotherapy (N=20)	In Combination (N=10)
Cytokine Release Syndrome	6.6% (1 G3; 1 G4)	1G4 (24 µg/kg)	1G3
ALT	6.6% (2 G3)	2G3 (16 µg/kg, 24 µg/kg)	--
AST	10% (2 G3; 1 G4)	2G3 (16µg/kg, 24µg/kg); 1G4 (16 µg/kg)	--
Lymphocyte Count Decrease	16.7% (1 G3; 4 G4)	3G4 (16 µg/kg,24 µg/kg)	1G3, 1G4

- TRAEs mostly consisted of flu-like symptoms, nausea, or vomiting, were transient and managed with supportive care in doses tested; 1 TEAE resulted in a drug discontinuation (G4 CRS); 2 patients dose reduced due CRS (1 at C3D1 and 1 C4D1)
- All TRAEs coded as CRS based on clinical symptoms did not correspond to increases in IL-6, or progression, and resolved without need for tocilizumab
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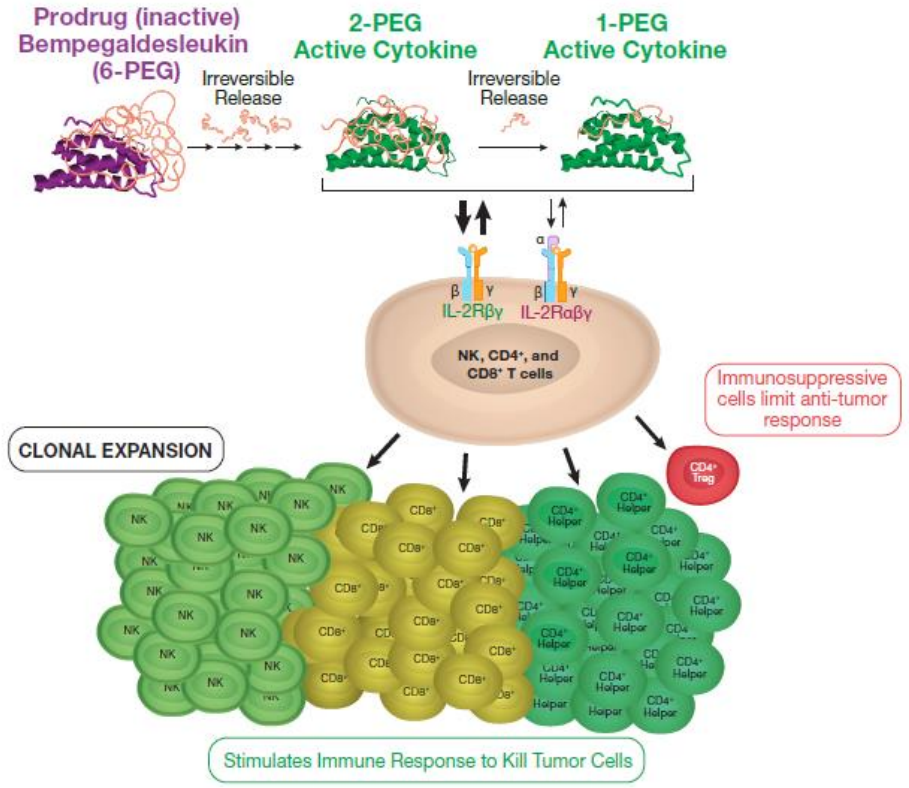
  - G2 CRS (fever + hypoxia; had baseline hypoxia, SP02 91%, oxygen need at night)
- No reports of VLS or eosinophilia; IL-5 levels remain at or below lowest level of detection

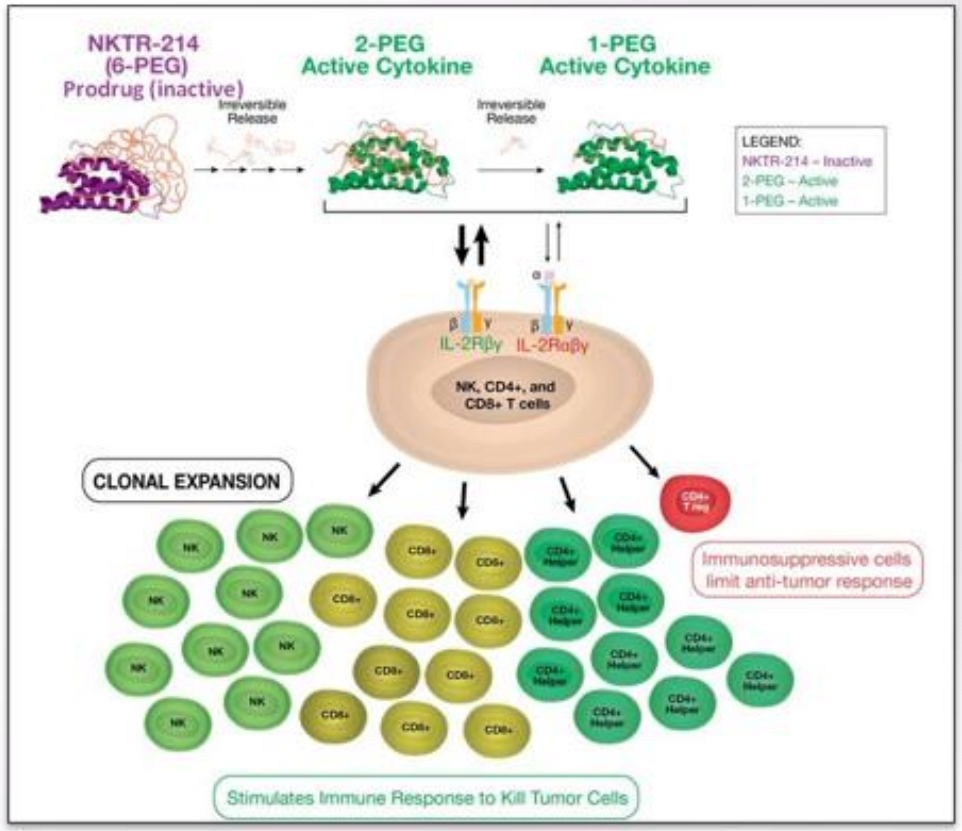
Bempegaldesleukin/NKTR214

Nektar Therapeutics



Bempegaldesleukin (NKTR-214), a CD122-preferential IL-2 pathway agonist, stimulates the immune response to kill tumor cells

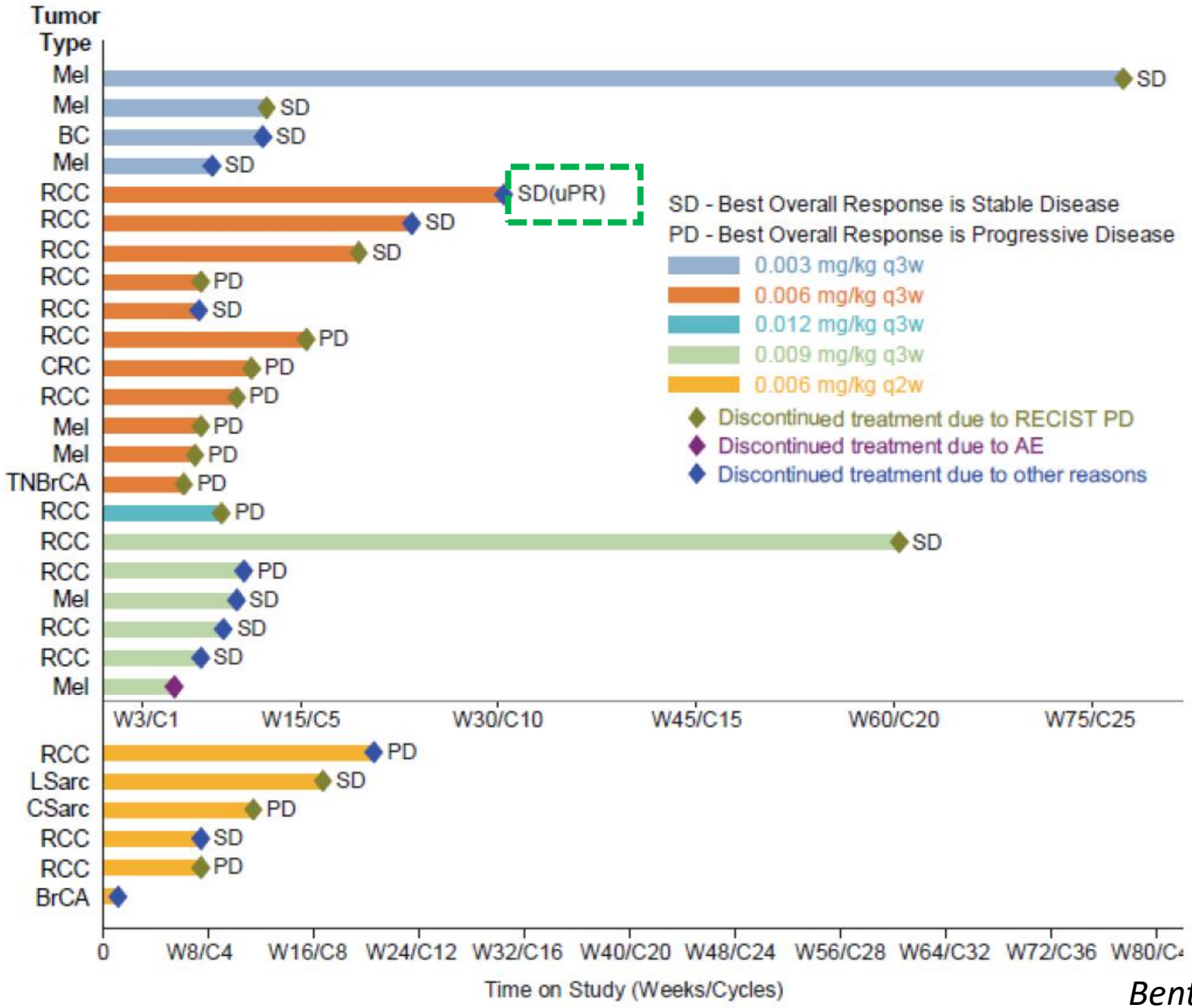
- While CPIs are effective in several tumor types, only a subset of patients derive durable response[1]
  - Low levels of baseline TILs and T-cell inflammation, and low tumor PD-L1 expression can predict poor response to CPIs[2,3]
- Bempegaldesleukin provides sustained signaling through the IL-2 receptor pathway via CD122 (IL-2Rβγ)[4]
  - Monotherapy increases TILs (NK and CD8+ T cells) and the expression of PD-1[5]
- The mechanism of action of bempegaldesleukin provides a rationale for combining with the CPI nivolumab



CPI, checkpoint inhibitor; NK, natural killer; TILs, tumor-infiltrating lymphocytes.

1. Haslam A, et al. *JAMA Netw Open* 2019;2:e192535; 2. Daud AI, et al. *J Clin Oncol* 2016;34:4102–4109; 3. Daud AI, et al. *J Clin Invest* 2016;126:3447–3452; 4. Charych DH, et al. *Clin Cancer Res* 2016;22:680–690; 5. Bentebibel S-E, et al. *Cancer Discov* 2019;9:711–721.

Bempeg (NKTR214) Monotherapy:Efficacy

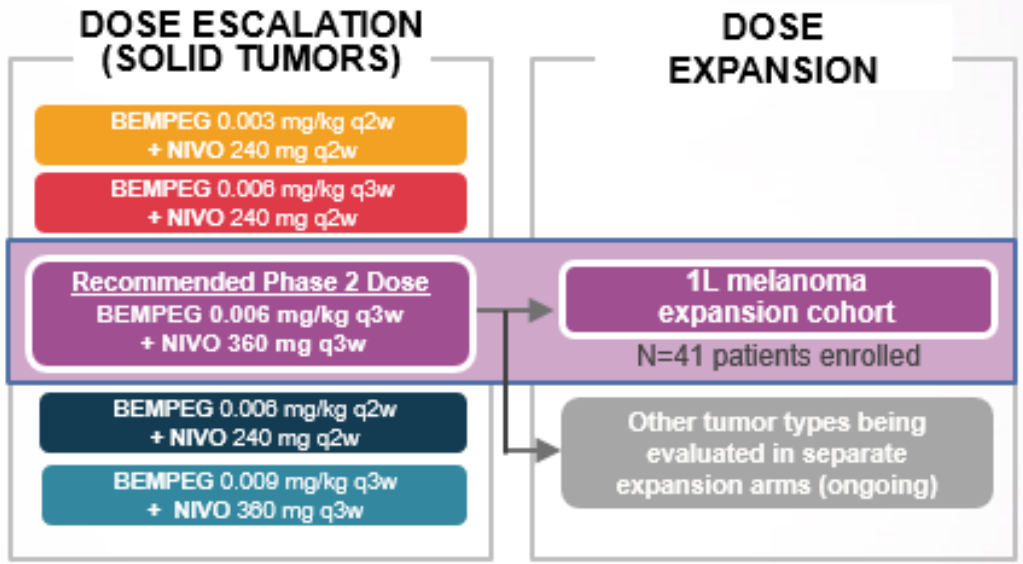


Bentebible S et al. Cancer Discovery 2019

PIVOT-02 1L Melanoma: Dose-expansion Study of BEMPEG Plus NIVO (NCT02983045)

KEY ELIGIBILITY CRITERIA

- Unresectable or metastatic melanoma (with known PD-L1 and *BRAF* status)
- No prior treatment
- Measurable disease per RECIST v1.1
- ECOG PS 0 or 1



Primary endpoints

- Safety and tolerability
- ORR per RECIST assessed every 8 weeks*

Selected secondary and exploratory endpoints

- PFS
- OS
- Duration of response
- Clinical benefit rate
- Biomarkers in blood and tumor

- 41 patients with unresectable or metastatic melanoma were enrolled and received ≥1 dose of BEMPEG plus NIVO
- As of data cutoff: 38 patients were efficacy evaluable, defined by the protocol as patients with ≥1 post-baseline scan (3 patients discontinued prior to first scan due to an unrelated TEAE [n=1] and patient decision [n=2]); all patients are now off treatment

Data cutoff: September 1, 2020.
*Tumors were assessed by BICR and local investigator. BICR was used for the primary analysis, which required radiologic imaging scans to be submitted to a central location and reviewed by independent radiologists who were not involved in the treatment of the patients.
1L, first line; BEMPEG, bempegaldesleukin; BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; NIVO, nivolumab; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TEAE, treatment-emergent adverse event.
Diab A, et al. *Cancer Discov* 2020;10:1158–1173.

PIVOT-02 1L Melanoma: Demographics and Baseline Characteristics

Baseline Characteristics	
Median age, years (IQR)	63.0 (52–70)
Male, n (%)	24 (58.5)
ECOG PS 0/1*, n (%)	32 (78.0) / 9 (22.0)
Liver metastases present at baseline, n (%)	11 (26.8)
PD-L1 status†, n (%)	
Negative <1%	14 (34.1)
Positive ≥1%	24 (58.5)
Unknown	3 (7.3)
Serum lactate dehydrogenase, n (%)	
Normal	29 (70.7)
>1–<2 × ULN	4 (9.8)
≥2–<3 × ULN	4 (9.8)
≥3 × ULN	4 (9.8)
Stage (AJCC v7), n (%)	
M1a	5 (12.2)
M1b	16 (39.0)
M1c	20 (48.8)
BRAF mutation status, n (%)	
V600E/K BRAF mutation	13 (31.7)
Other BRAF mutation	2 (4.9)
Wildtype	25 (61.0)
Unknown	1 (2.4)

Diab A et al. JCO 2021

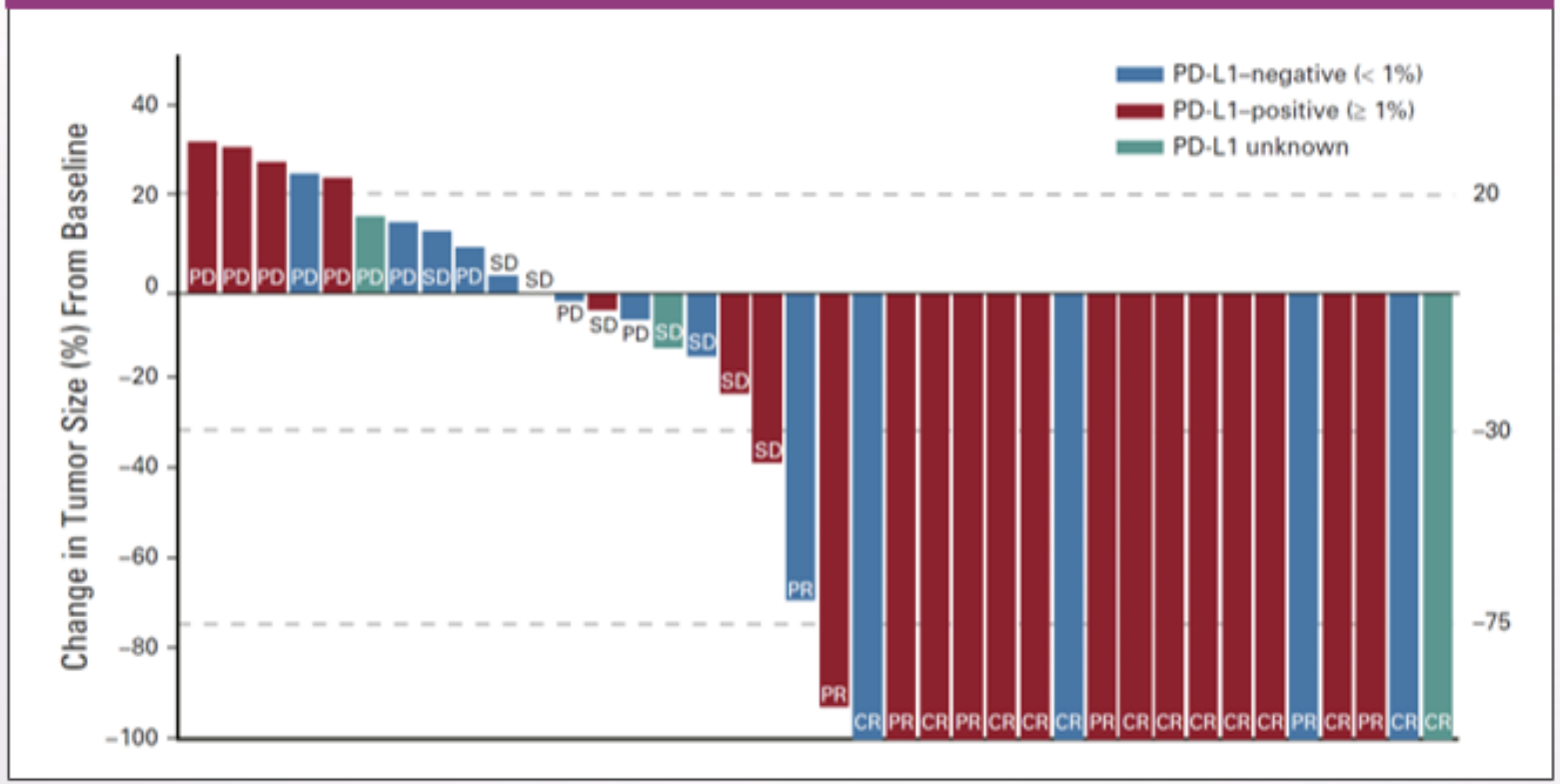
Safety of BEMPEG Plus NIVO was Consistent With Previous Reports

Preferred Term[a], n (%)	Total (N=41)
Grade 3/4 treatment-related AEs	7 (17.1)[b]
Acute kidney injury	2 (4.9)
Atrial fibrillation[c]	2 (4.9)
Dizziness, dyspnea, hyperglycemia, hypernatremia, hypoxia	1 each (2.4)
Grade 1/2 treatment-related AEs (>30% listed below)	
Flu-like symptoms[d]	33 (80.5)
Rash[e]	29 (70.7)
Fatigue	27 (65.9)
Pruritus	20 (48.8)
Nausea	19 (46.3)
Arthralgia	19 (46.3)
Decreased appetite	15 (36.6)
Myalgia	15 (36.6)
Any imAE (Grade ≥3) (Nephritis and renal dysfunction, diabetes mellitus/hyperglycemia treated with insulin)	2 (4.9)
Patients who discontinued BEMPEG or NIVO due to a treatment-related AE (Blood creatinine increased, cerebrovascular accident, malaise, peripheral edema, pharyngitis)	5 (12.2)
Treatment-related deaths	**0**

Diab A, et al. *J Clin Oncol* 2021; July 13 [epub]

PIVOT-02 1L Melanoma: Best Overall Response by Independent Radiology

Waterfall Plot of the Maximum Change in Tumor Size with BEMPEG Plus NIVO (n=38)



- **Median duration of follow-up: 29.0 months** (IQR: 15.7–32.3 months)
- **Confirmed ORR** by BICR: **52.6%** (95% CI: 35.8–69.0; 20/38)
  - **CR rate: 34.2%** (13/38)
- Median change in target lesion size from baseline was **–78.5%**
  - **90%** (18/20) of responding patients achieved 100% reduction in target lesions from baseline

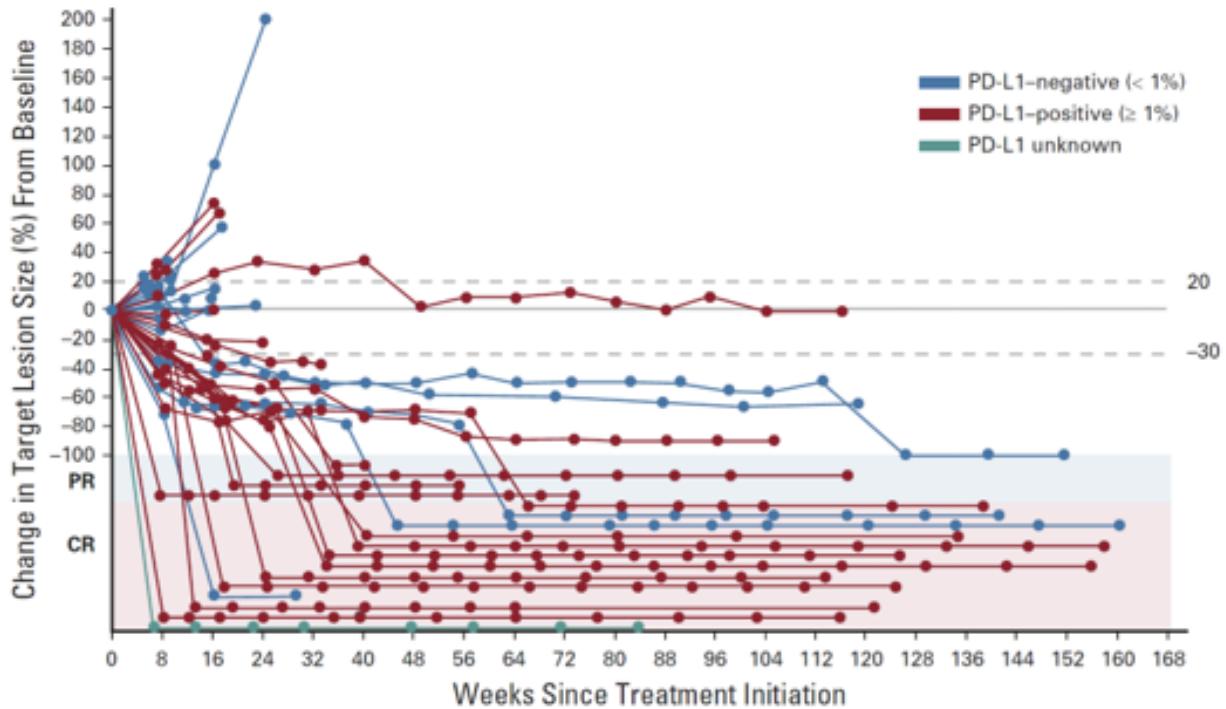
Data cutoff: September 1, 2020. Response-evaluable population (n=38).
Response-evaluable population includes eligible patients with measurable disease (BICR per RECIST v1.1) at baseline and at least one post-baseline assessment of tumor response.
All objective responses are confirmed.
1L, first line; BEMPEG, bempegaldesleukin; BICR, blinded independent central review; CR, complete response; IQR, interquartile range; NIVO, nivolumab; ORR, objective response rate; PD, progressive disease (due to non-target lesion progression or presence of new lesion); PD-L1, programmed death-ligand 1; PR, partial response (complete response for target lesion; non-target lesion

Diab A et al. JCO 2021

Diab A, et al. *J Clin Oncol* 2021; July 13 [epub]

PIVOT-02 1L Melanoma: Median Duration of Response Was Not Reached

Percent Change in Target Lesion Size Over Time with BEMPEG Plus NIVO (n=38)



- **Median time to response:**
  - First response: **2.0 months** (range: 1.5–4.1 months)
  - CR: **7.9 months** (range: 1.5–15.2 months)
- At cutoff, **80%** of patients (16/20) had an ongoing objective response
- Responses lasted for:
  - ≥6 months in **90%** (18/20 patients)
  - ≥12 months in **80%** (16/20 patients)

Data cutoff: September 1, 2020. Response-evaluable population (n=38).
Response-evaluable population includes eligible patients with measurable disease (BICR per RECIST v1.1) at baseline and at least one post-baseline assessment of tumor response. All objective responses are confirmed.
1L, first line; BEMPEG, bempegaldesleukin; CR, complete response; NIVO, nivolumab; PD-L1, programmed death-ligand 1; PR, partial response (complete response for target lesion; non-target lesion

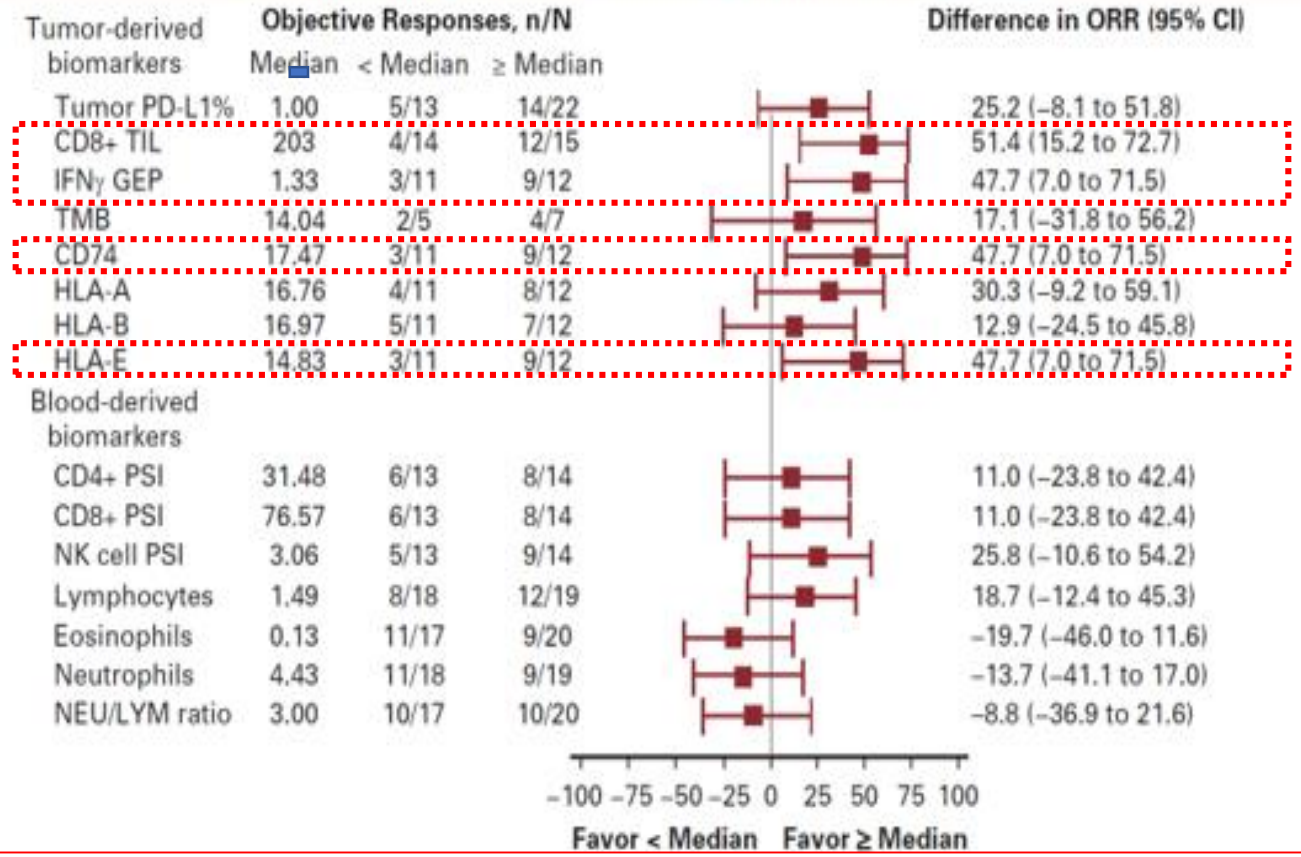
Diab A, et al. *J Clin Oncol* 2021; July 13 [epub]

PIVOT-02 1L Melanoma: Relationship Between Baseline Biomarkers and Response

Baseline tumor biomarkers were associated with objective response to BEMPEG plus NIVO*†

- High CD8+ TIL, high IFN-γ GEP, high CD74, and high HLA-E in baseline tumor biopsies were associated with a higher ORR
- Baseline tumor PD-L1 expression and TMB were not associated with objective response

Relationship Between Baseline Biomarkers and ORR



Diab A et al. JCO 2021

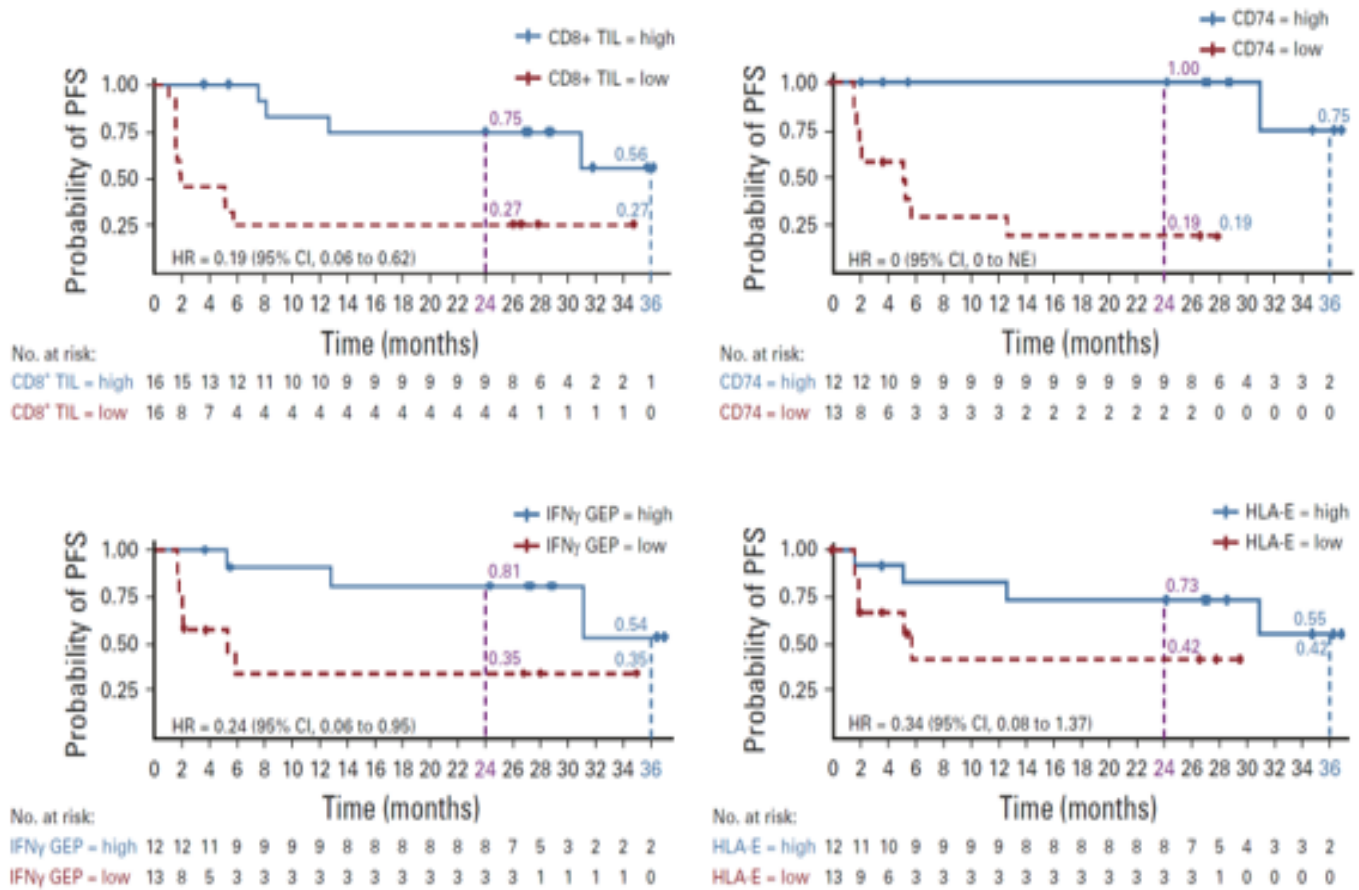
Diab A, et al. *J Clin Oncol* 2021; July 13 [epub]

PIVOT-02 1L Melanoma: Relationship Between Baseline Biomarkers and Response

Baseline tumor biomarkers were associated with longer PFS*

- High **CD8+ TIL**, high **IFN-γ GEP**, high **CD74**, and high **HLA-E** in baseline tumor biopsies were associated with a longer PFS

Relationship Between Selected Baseline Tumor Biomarkers and PFS



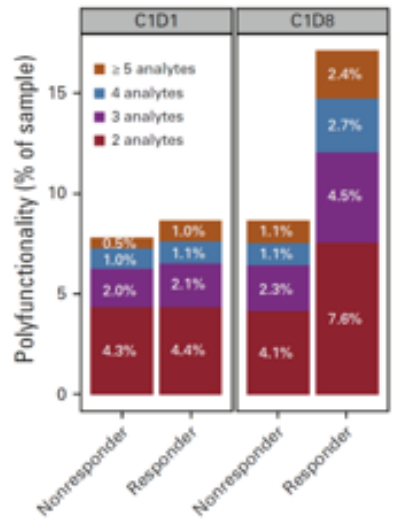
Diab A et al. JCO 2021

Diab A, et al. *J Clin Oncol* 2021; July 13 [epub]

PIVOT-02 1L Melanoma: Single-cell Cytokine Analysis of CD8+ T cells in the Blood On treatment by Response

- Robust upregulation of polyfunctional CD8+ T cells in the blood of patients with an objective response was observed
- The heatmap shows an increase in polyfunctional CD8+ T-cell subsets that co-produce combination cytokines
- Treatment elicited an ~2.2-fold increase in the PSI of CD8+ T cells in patients with an objective response
- Increase in polyfunctional response in responders on treatment appeared to be driven by cytokines with effector functions

Change in Polyfunctionality of CD8+ T Cells on Treatment by Response

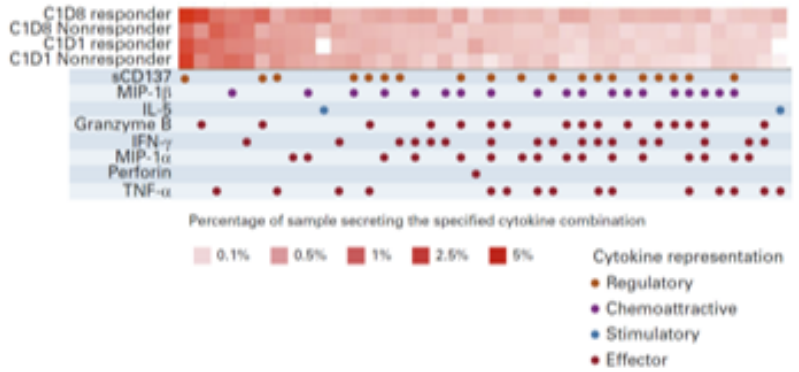


Data cutoff: September 1, 2020.

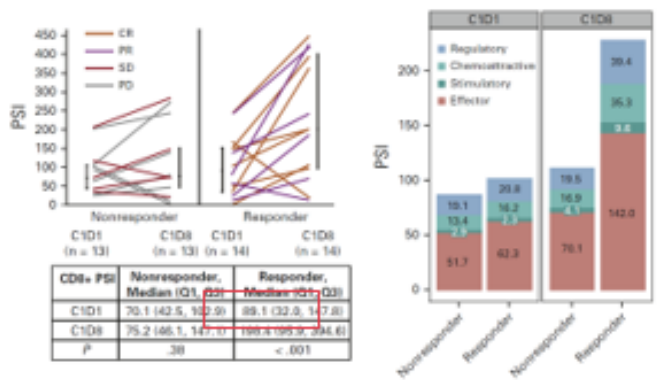
*Each column corresponds to a specific cytokine or combination of cytokines, and the red squares represent the frequency at which the group was secreted by the corresponding sample. Cytokine groups are ordered by overall frequency across all the samples.

1L, first line; C1D1, cycle 1 day 1 (baseline); C1D8, cycle 1 day 8 (on treatment); IFN, interferon; MIP, macrophage inflammatory protein; Polyfunctionality, co-secretion of two or more cytokines per cell; TNF, tumor necrosis factor.

Single-cell Polyfunctional Heatmap Illustrating the Single-cell Cytokine Combinations Secreted by Each Sample*



Change in Single-cell PSI on Treatment by Response and Cytokine Representation



CD8+ PSI	Nonresponder, Median (Q1, Q3)	Responder, Median (Q1, Q3)
C1D1	70.1 (42.5, 102.9)	89.1 (32.0, 147.8)
C1D8	75.2 (46.1, 147.1)	198.4 (95.9, 394.6)
P	.38	<.001

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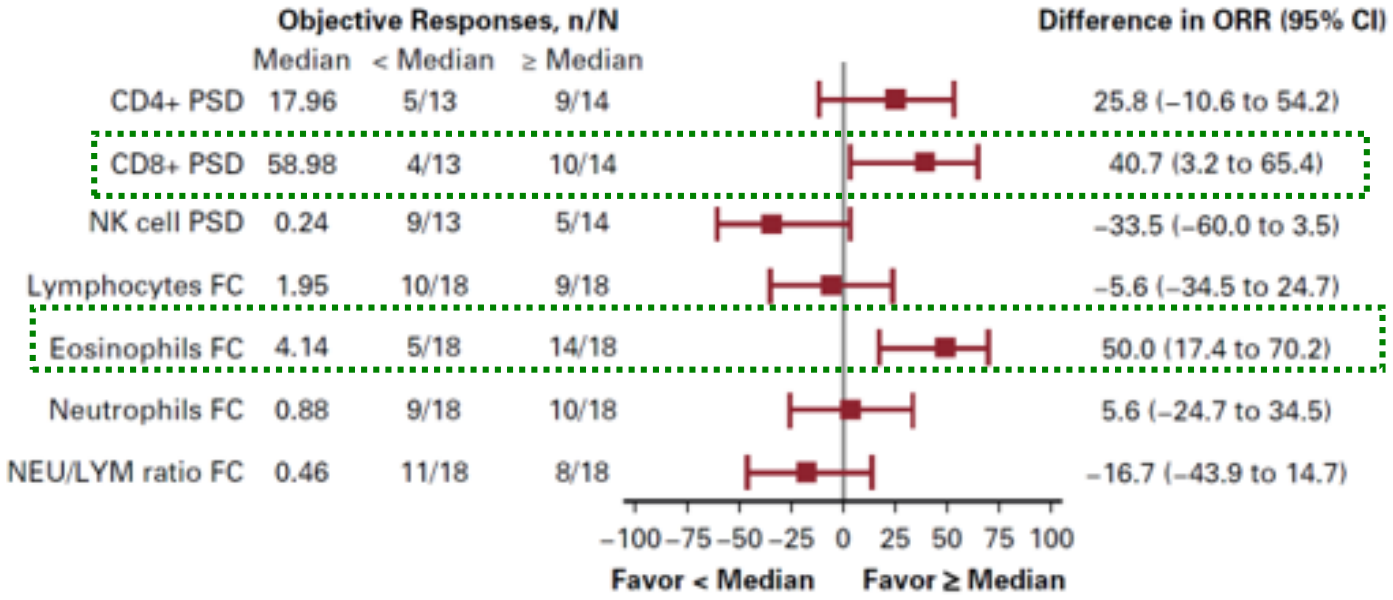
PIVOT-02 1L Melanoma: Relationship Between On-treatment Blood Biomarkers in Matched Samples and Response

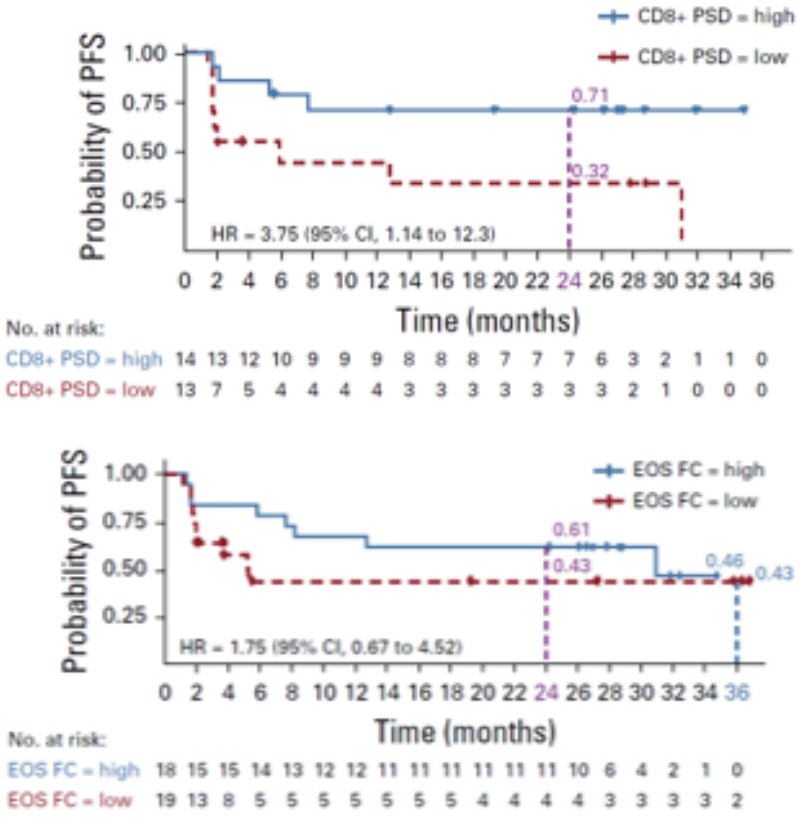
Changes in the Median Values of Blood Biomarkers in Paired Samples on Treatment vs Baseline and Relationship with ORR*†

Increased CD8+ PSD and eosinophil FC was associated with higher ORR

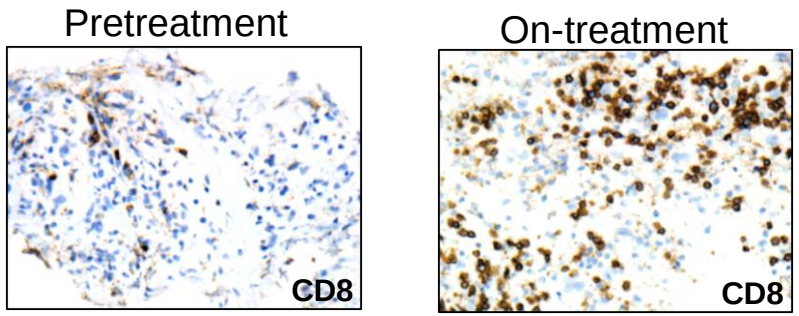


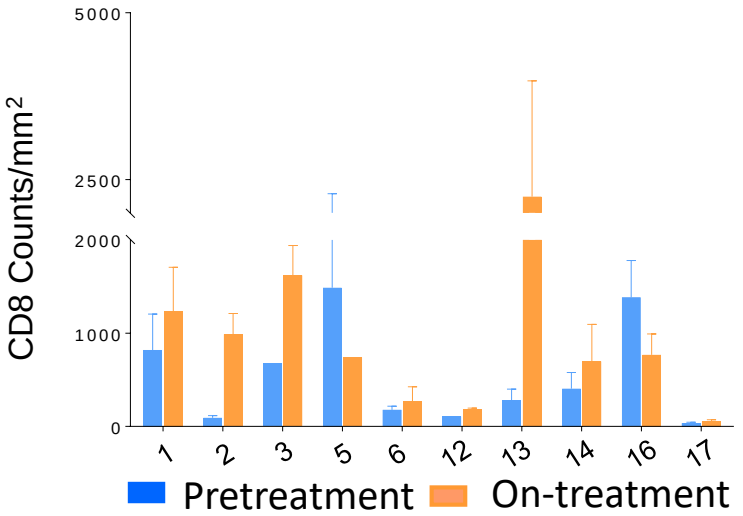
Relationship Between CD8+ PSD and Eosinophil FC and PFS

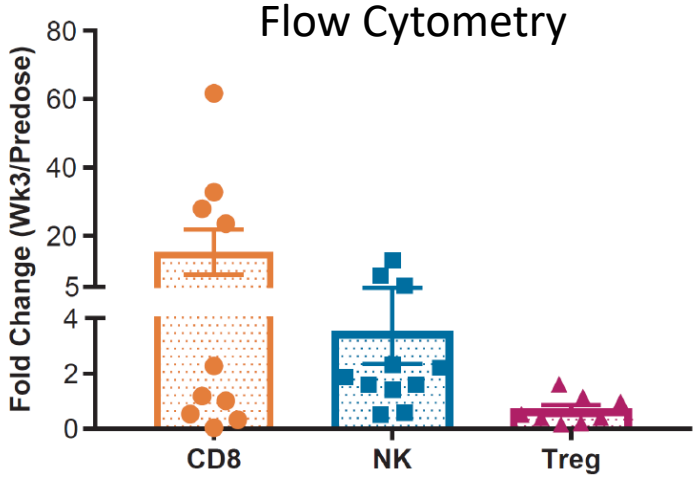
Increased CD8+ PSD, but not eosinophil FC, was associated with longer PFS



Bempeg Monotherapy







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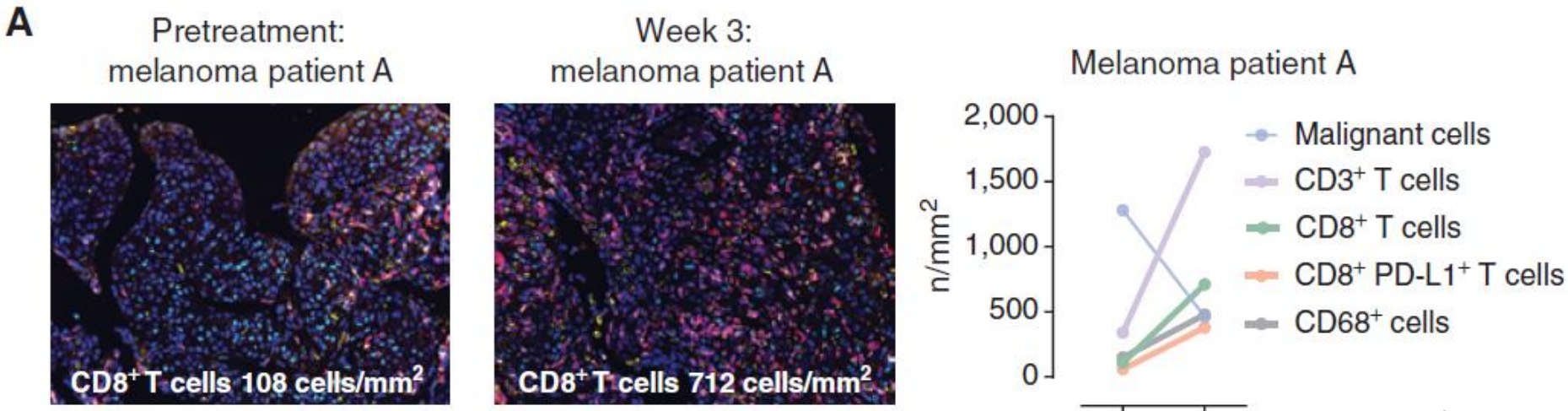
BEMPEG plus Nivolumab in Advanced Solid Tumors (PIVOT-02)

RESEARCH ARTICLE



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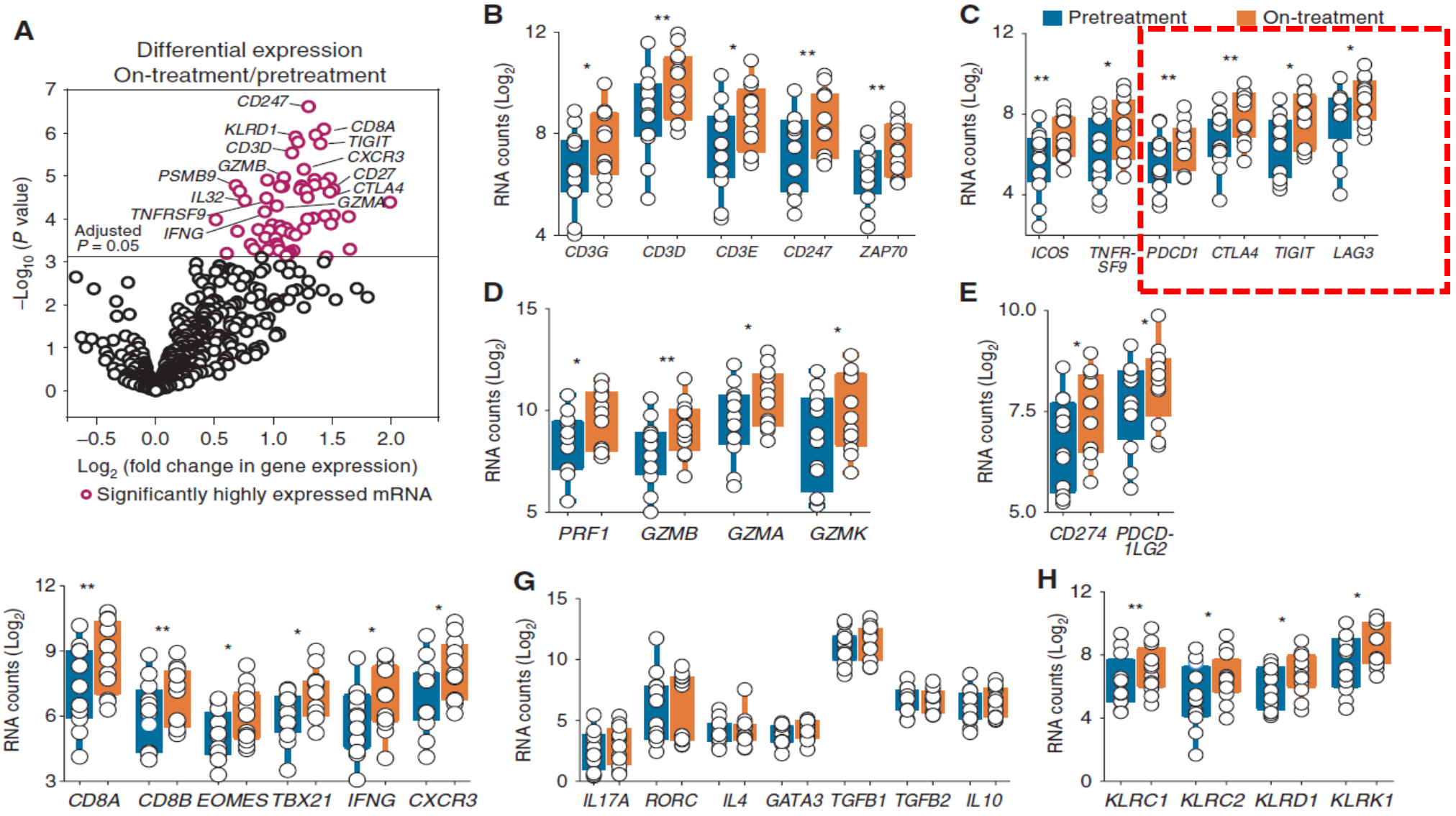
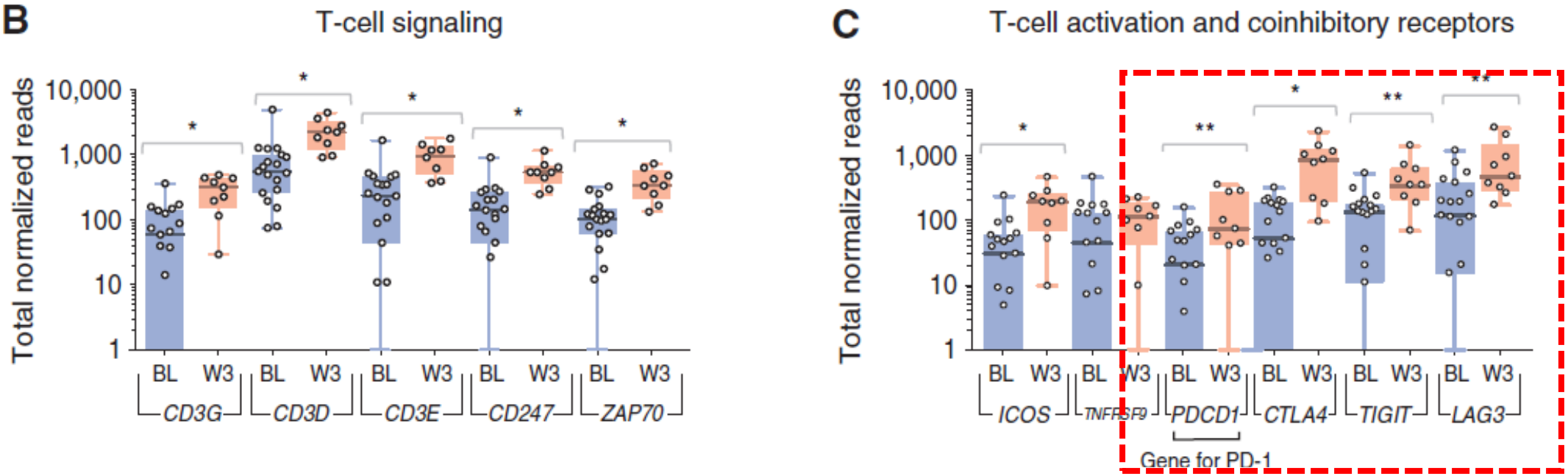
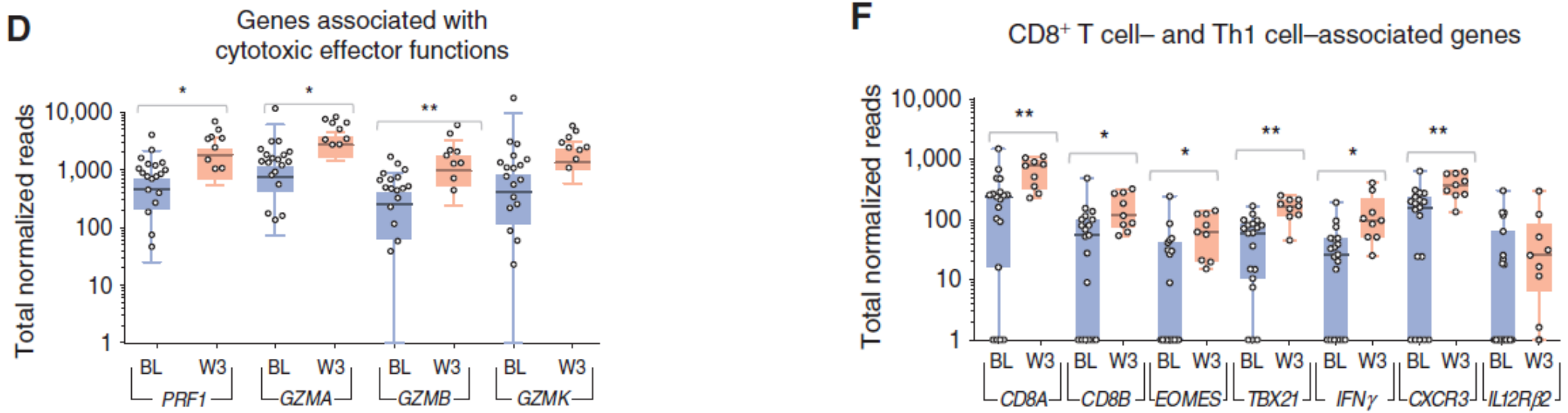
Bempeg (NKTR214) Monotherapy



Bentebible S et al. Cancer Discovery 2019





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BEMPEG + NIVO vs. NIVO in 1L Unresectable or Metastatic Melanoma (Phase 3 Registrational Trial)

PIVOT IO 001 (CA045-001) is a phase 3, randomized, open-label study of BEMPEG + NIVO vs. NIVO monotherapy in patients with treatment-naïve, unresectable or metastatic melanoma[1,2]

N=764

Population

- Treatment-naïve
- Unresectable or metastatic melanoma

Stratification factors:[2]

- PD-L1 status[a]
- *BRAF* status[b]
- AJCC stage (8th edition)[c]

R 1:1

Treatment

- **BEMPEG 0.006 mg/kg IV Q3W + NIVO 360 mg IV Q3W**
- **NIVO 360 mg IV Q3W**

Primary endpoints:

- Objective response rate by BICR
- Progression-free survival by BICR
- Overall survival

Key secondary endpoints:

- Clinical benefit rate, duration of response, time to response
- Safety and tolerability

Updates on Key Milestones

- Enrollment Completed: 4Q21
- Top Line Results: 1Q22
- Anticipating Filing: 2H22

Summary

- Safety :Agents has similar safety Profile from the preliminary data) not detailed comparison-- CRS observed at high doses (dose limiting toxicity
- Efficacy: All 3 has evidence of clear but very limited single agent activity
- All provided peripheral blood PD data of CD8-T/NK cells enhancement over T-regulatory cells
- Tumor tissue evidence(Bempeg) of enhanced T-effector cells without Tregs proliferation
- Promising Phase 2 data(Bempeg) in combination with Nivolumab
- Randomized Phase 3 Bempeg plus Nivo versus Nivo alone ,active and accruing
- Need for more combination trials beyond PD-1→ CTLA-4,Lag-3 , ACT, Cytokine-Cytokine combination like il-6/IL-1 blockade