IL-2 Combinations

Michael Hurwitz
Yale Cancer Center
November 8, 2019

Disclosure

Advisory Boards: Nektar Therapeutics, Janssen Pharmaceuticals, CRISPR Therapeutics

Research: Apexigen, Astellas, AstraZeneca, Bayer, Bristol Myer Squibb, Clovis, Corvus, Eli Lilly, Endocyte, Genentech, Genmab, Innocrin, Iovance, MedImmune, Merck, Nektar Therapeutics, Novartis, Pfizer, Progenics, Roche Laboratories, Sanofi Aventis, Seattle Genetics

Other: Gamida Cell

Talk outline

- Basic Interleukin-2 biology
- Current IL-2 combinations in trials
- Currently studied modified IL-2 combinations

IL-2: a master regulator of adaptive immunity

- 16 kDa monomeric cytokine
- IL-2 production
  - At resting conditions: $CD4^+$ Th cells primarily
  - On activation: $\alpha\beta^+$ and $\gamma\delta^+$ T, NK, NKT, DC, mast cells
  - Tregs do not produce IL-2 (for the most part)
- Overstimulation by IL-2 can lead to T cell exhaustion or Fas (CD95) mediated cell death
- IL-2 with polarizing cytokines facilitate differentiation of naïve Ts into different types of cells (see table)

IL-2 and T cell differentiation

IL-2 +	cell type
IL-12	Th1
IL-4	Th2
TGF-β	Treg
IL-6 + TGF-β	Th17
IL-6 + IL-21	follicular TH

the IL-2 receptor

Receptor	components	Affinity	cell specificity
Trimeric	$\alpha/\beta/\gamma$	high K_d ~10^{-11} M	Tregs, other T cells, ILC2, some endothelia, DCs
Dimeric	β/γ	low K_d ~10^{-9} M	T cells except Tregs

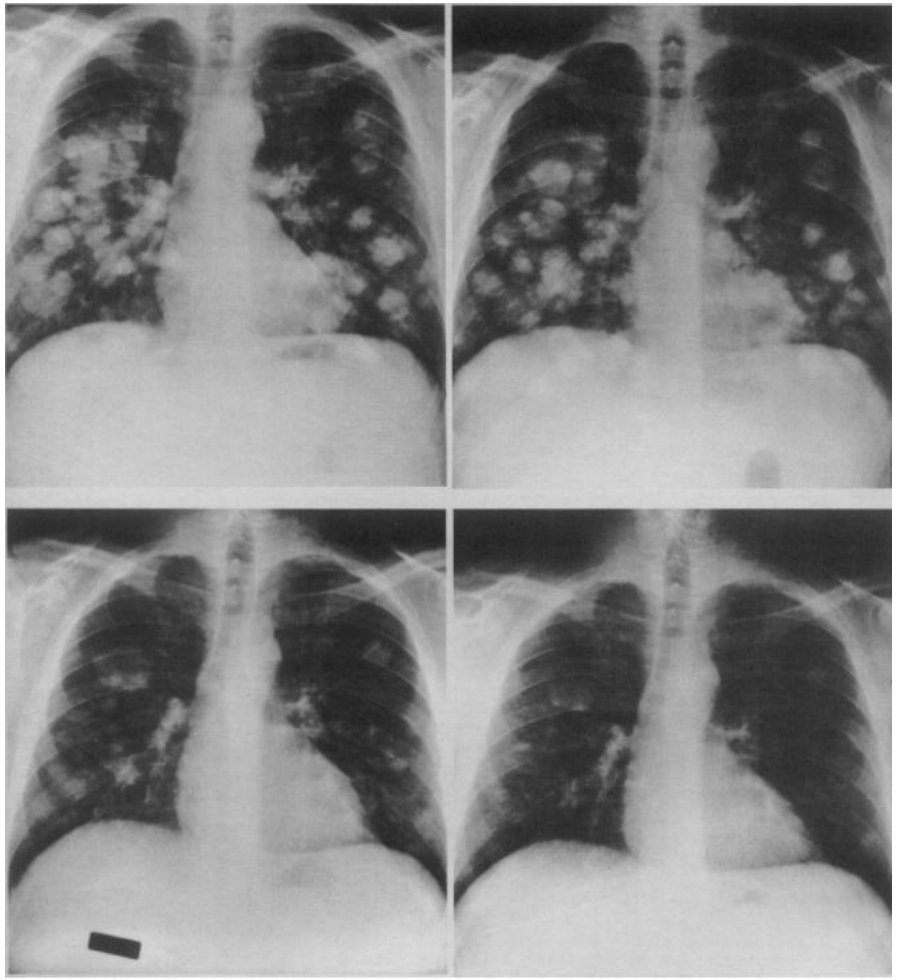
Component	Other name
IL-2Rα	CD25
IL-2Rβ	CD122
IL-2Rγ	γ_c/CD132

- Low levels of exogenous IL-2 signal through the high affinity trimeric receptor
- Only with high levels of IL-2 does signaling through low affinity dimeric receptor occur
- Activated T cells have ~2000 trimeric and ~11000 dimeric IL-2Rs

High Dose IL-2: The First FDA-Approved Cancer Immunotherapy

- First IL-2 response achieved in 1984
- Durable ‘curative’ responses in ~10%
- Approved 1992 for mRCC; 1998 for melanoma
- Challenges of high dose IL-2:
  - Highly toxic – requires hospitalization; only to be given at experienced centers

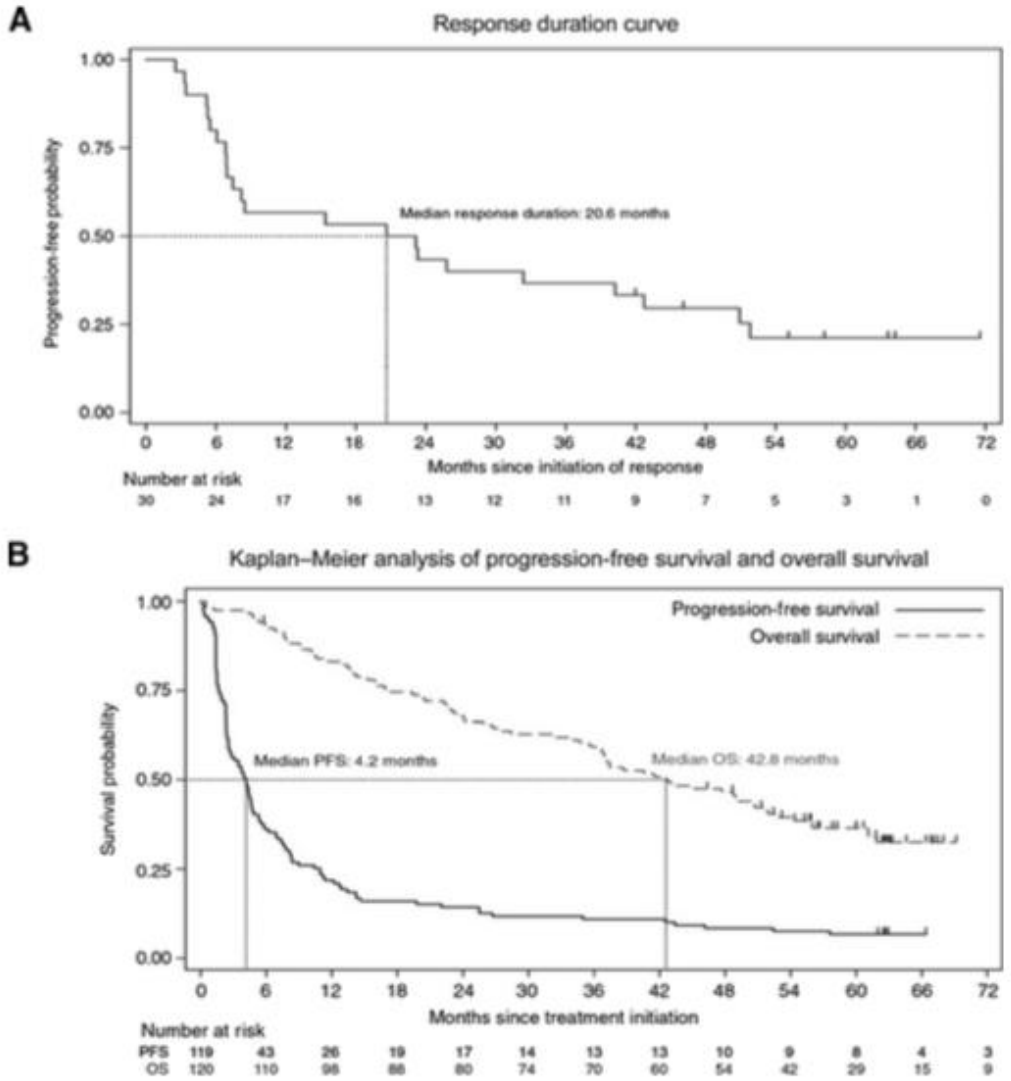
    Capillary leak syndrome
    Sepsis
    Hypotension
    renal failure
    Confusion/neurotoxicity
    Cardiac disease

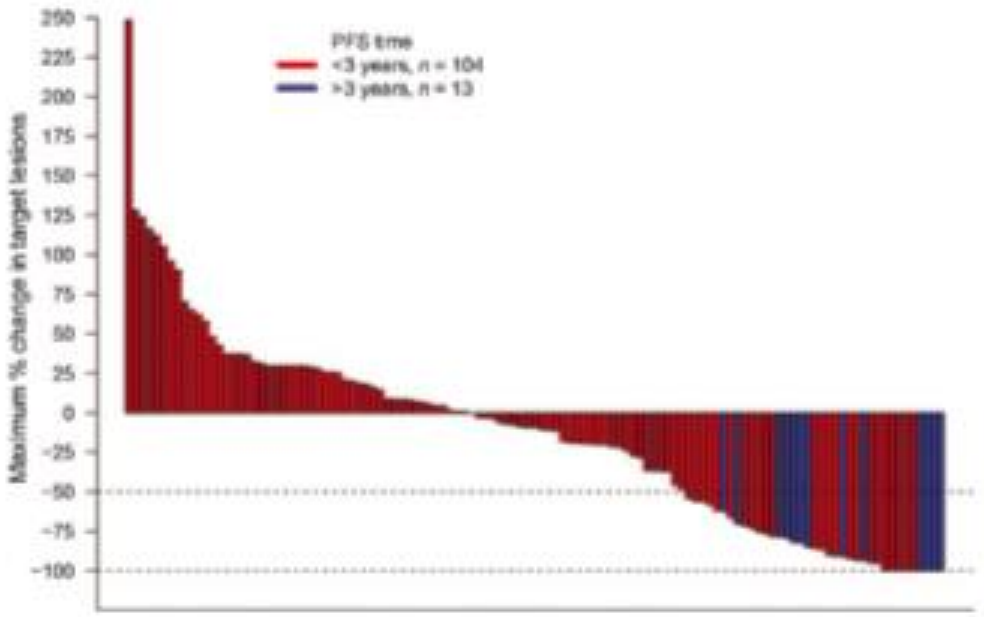


Buchbinder et al, 2016, JITC, Donskov et al, ASCO, 2010, Lotze et al, JAMA, 1986, Atkins et al, JCO, 1999, Klapper et al, Cancer, 2008

Slide adapted from Dr. Heather McArthur, ASCO 2018

High dose IL-2 in RCC





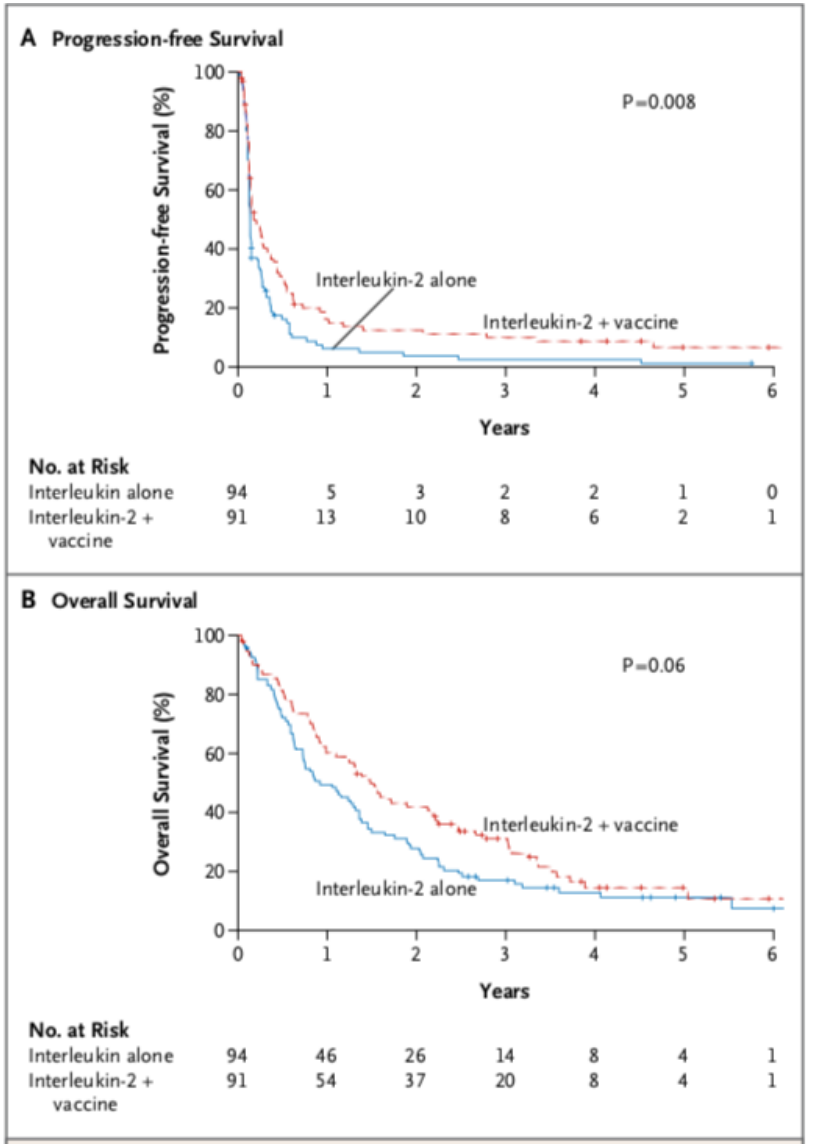
CWG Select trial

- ORR 25%
- 11% disease free at 3 years
- Many with ‘treatment free survival’

McDermott et al, Clin Cancer Res 2015; Regan et al, JCO 2019

Combinations: IL-2 + vaccines in metastatic melanoma

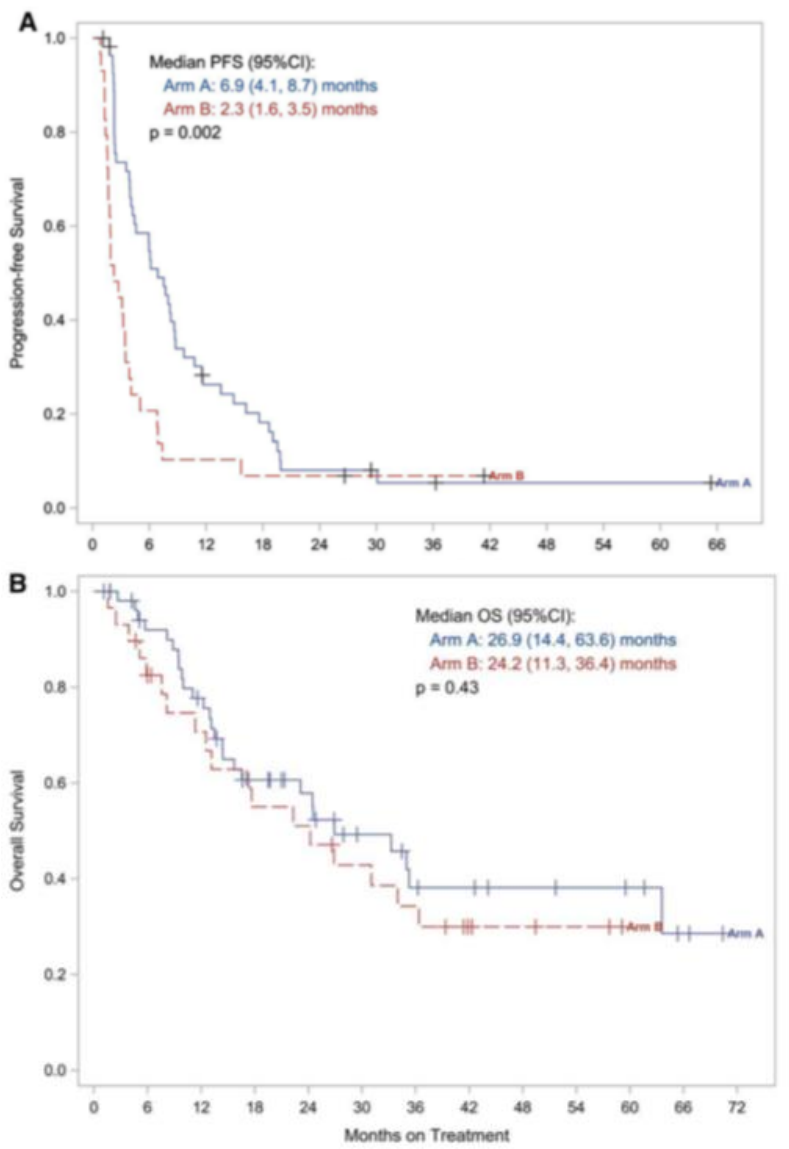
- Randomized phase III of HD IL-2 + gp100 vaccine in 185 pts, untreated:
  - ORR 16% vs 6% (p = 0.03)
  - PFS 2.2 mo vs 1.6 mo (p = 0.008)
  - OS 17.8 mo vs 11.1 mo (p = 0.06)
- Toxicities: same as HD IL-2 alone
- A more recent small trial (n = 16) using HD IL-2 + MAGE-A3/AS15 had 25% ORR



Schwartzentruber et al, NEJM 2011, McQuade et al, BMC Cancer 2018

Combinations: HD IL-2 +/- Ziv-aflibercept

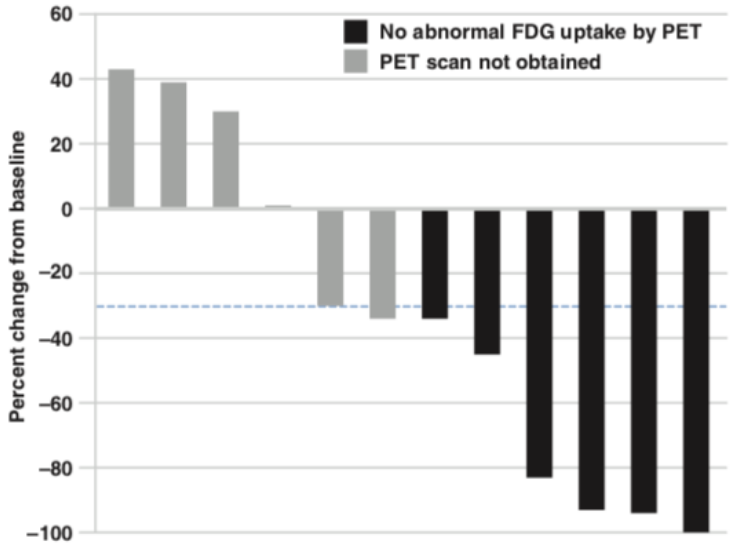
- Ziv-aflibercept is a VEGF trap
- VEGF signaling affects innate and adaptive immunity including:
  - Blocks DC maturation
  - Inhibits priming of T cell responses
- Randomized phase II in 89 patients with metastatic melanoma (≤ 2 prior treatments):
  - ORR 22% vs 17%
  - PFS 6.9 mo vs 2.3 mo ($p < 0.01$)
  - OS 26.9 mo vs 24.2 mo (NS)
- Toxicities: same as HD IL-2 and anti-VEGF rx

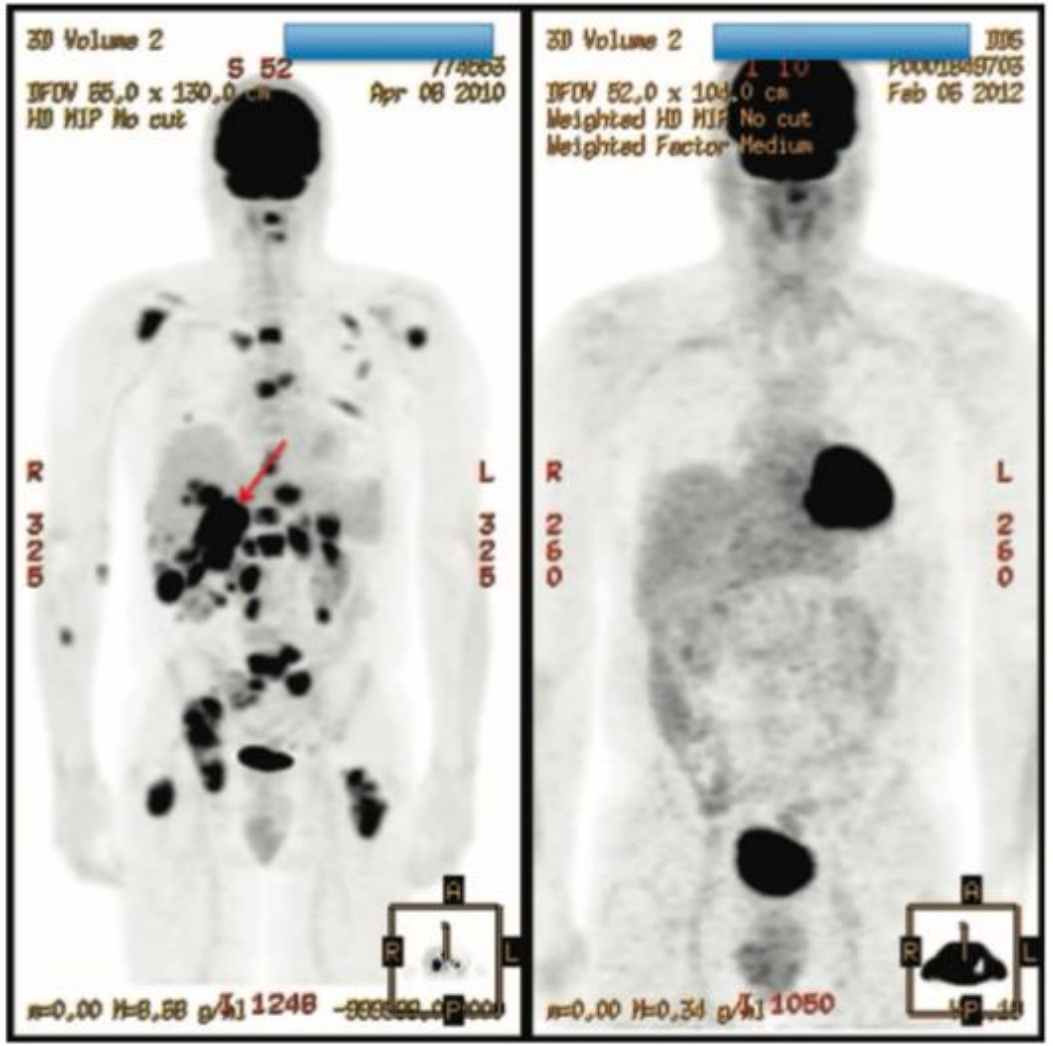


Tarhini et al, Cancer 2018

Combinations: HD IL-2 + SBRT

- 12 patients with untreated melanoma or RCC with at least 2 measurable lesions
- SBRT to 1 lesion followed by HD IL-2
- 1 CR and 7 PR in non-radiated lesions
- Toxicities: same as HD IL-2



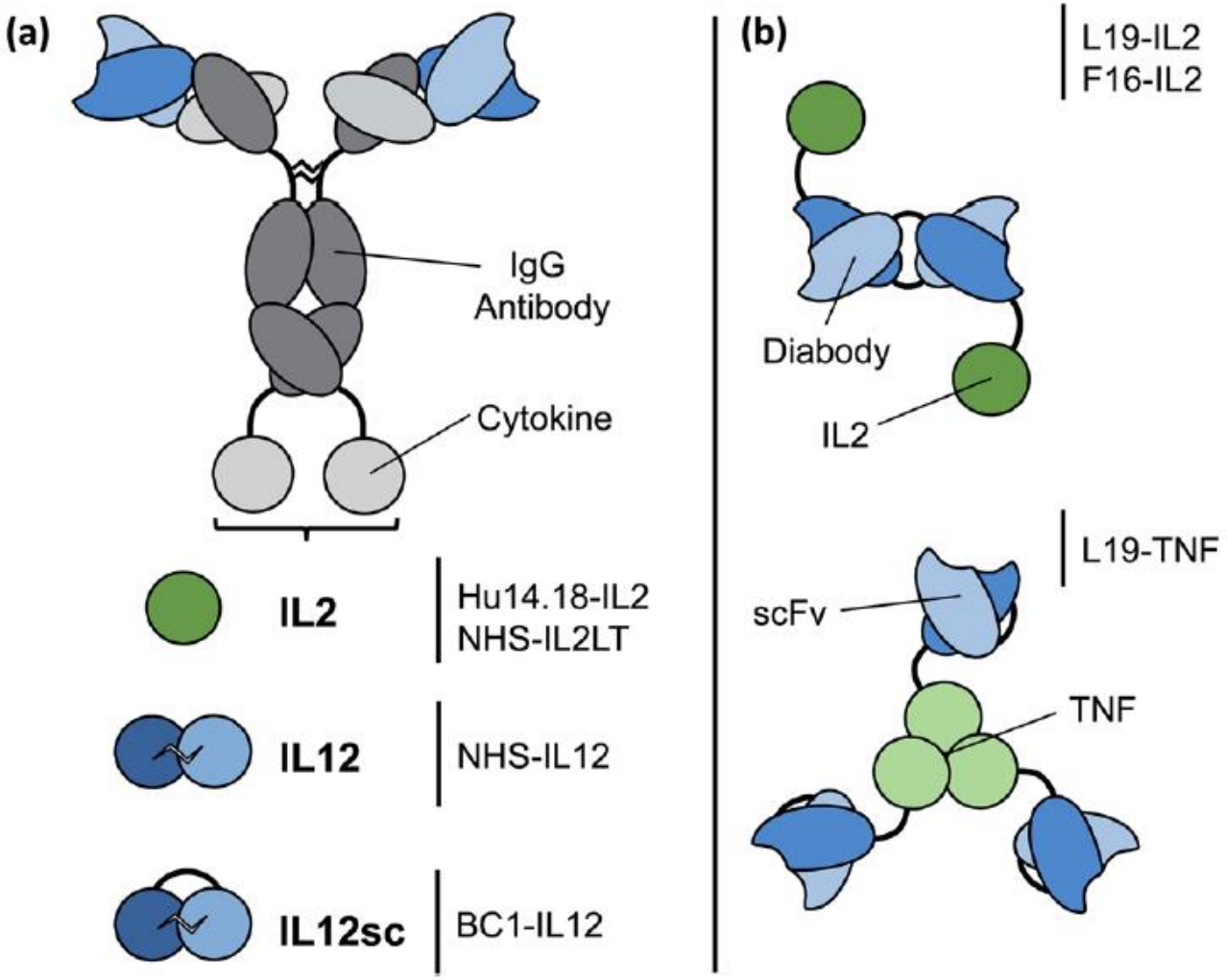


Seung et al, Science Trans Med 2012

IL-2 combinations: ongoing trials

	Other agents	Disease	notes
NCT03260504	pembrolizumab	RCC	low dose SQ IL-2
NCT03474497	pembrolizumab radiotherapy	NSCLC melanoma RCC H&N SCC	intralesional IL-2
NCT03991130	anti-PD-1	melanoma RCC	HD IL-2; in PD-1 refractory pts
NCT03501381	entinostat	RCC	randomized HD IL-2 ± entinostat (HDAC inhibitor)

modified IL-2 drugs: antibody conjugates

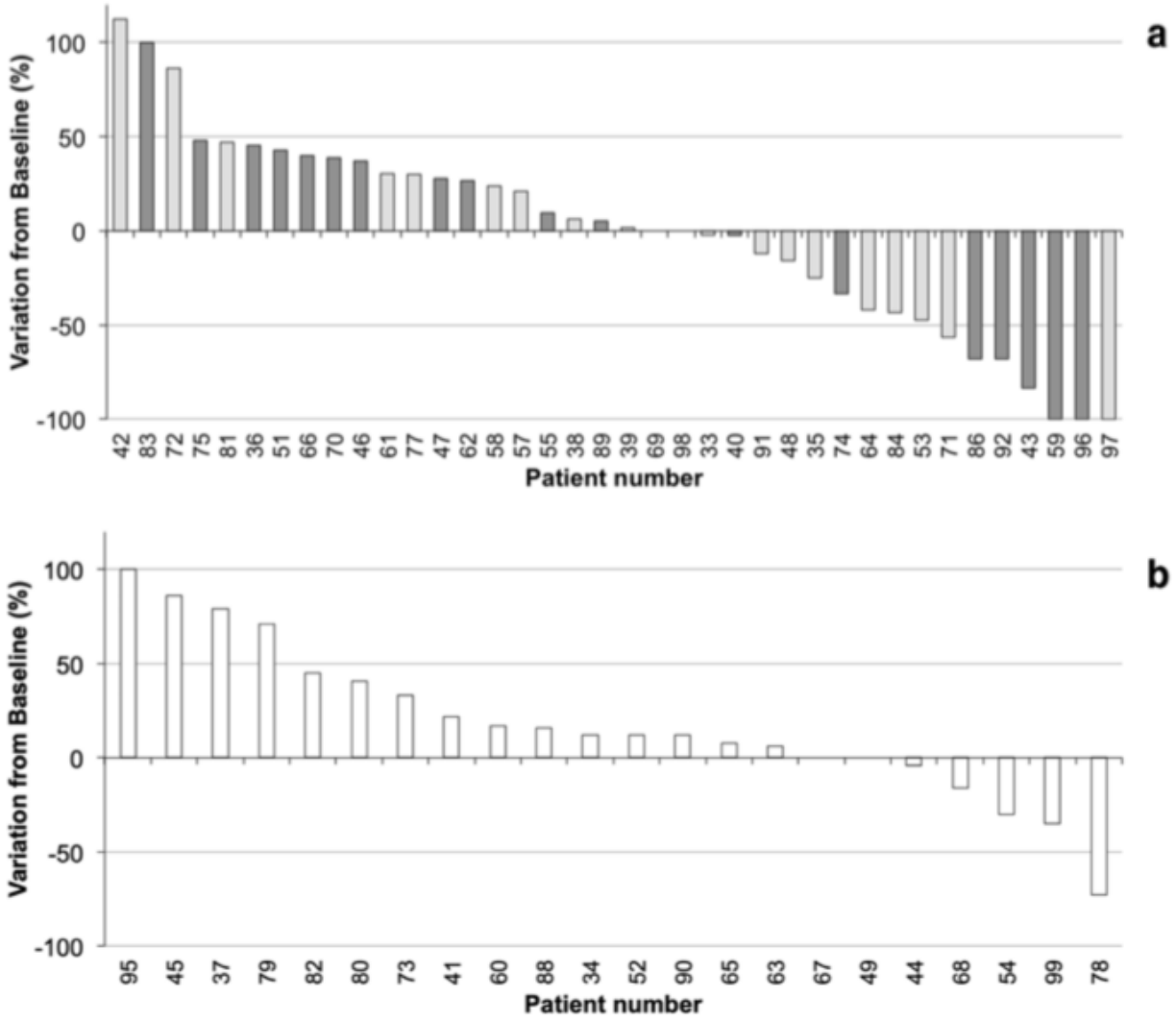


- Regular or modified IL-2
- Either antibody or antibody component
  - scFv: single chain variable fragment
  - Diabody: bi- or mono-specific antibody construct
- Can target IL-2 to tumor site

Hess et al, Med Chem Commun 2014

Combinations: DTIC ± L19IL-2

- L19 targets an angiogenesis-specific fibronectin domain upregulated in cancer
- Randomized phase 2
- ORR: 18.4% vs 4.5%
- PFS: no different
- OS: 419 d vs 325 d (p = 0.048)
- Toxicities: mild, few grade 3

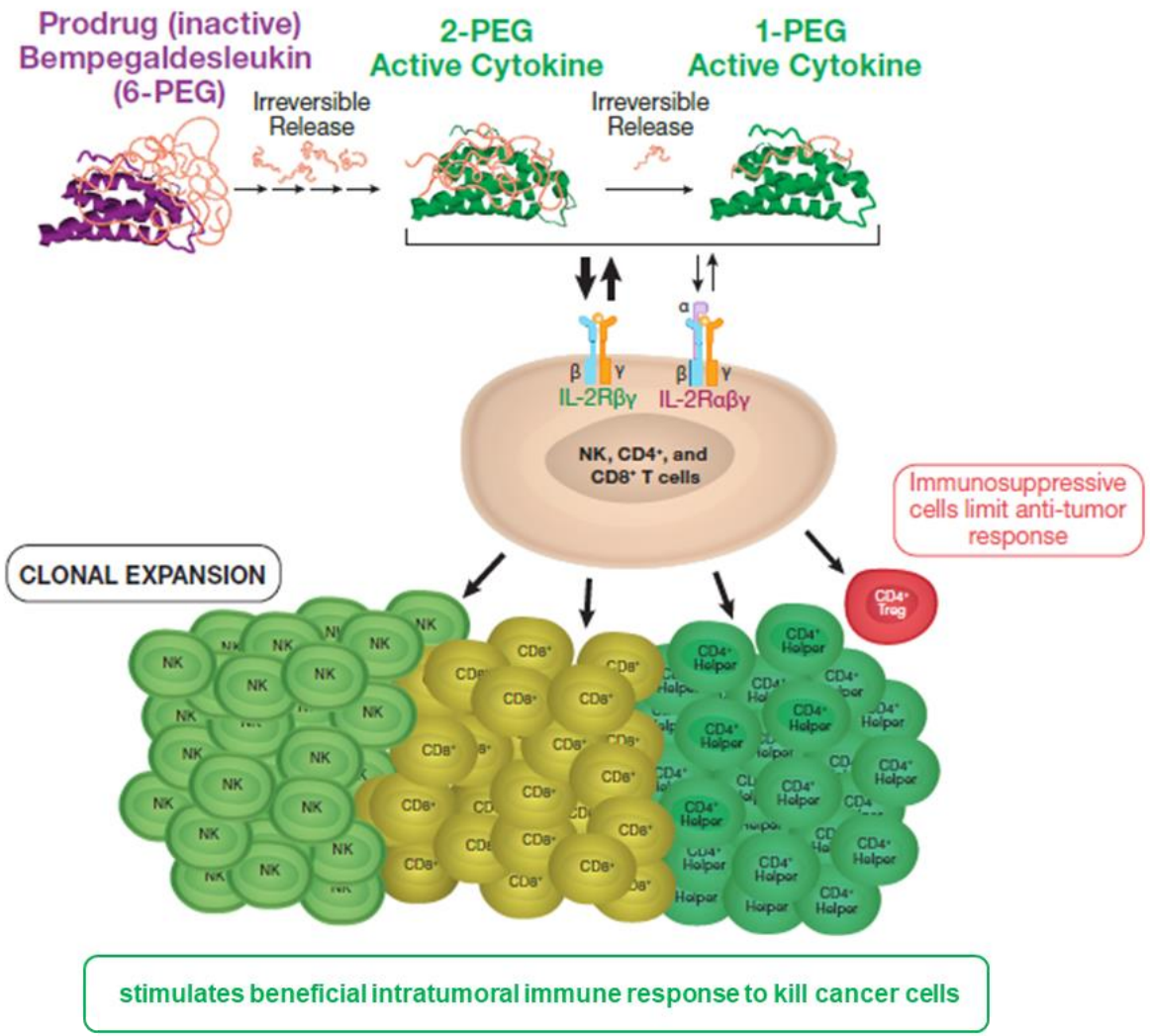


Weide et al, Cancer Immunology Immunotherapy 2019

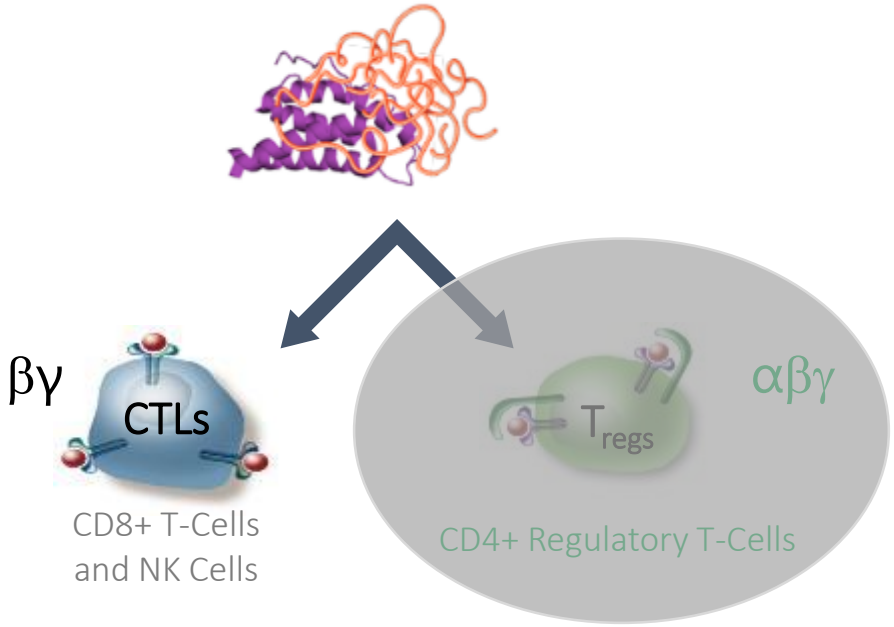
Modified IL-2 combinations: ongoing trials

	IL-2	Other agent	Disease	target
NCT02957019	L19IL2	Rituximab	lymphoma	angiogenesis-specific fibronectin domain (B-FN)
NCT03958383	Hu14.18-IL2	ipi/nivo + RT	melanoma	GD2: disialoganglioside
NCT03207191	F16IL2	BI836858 (anti-CD33)	relapsed AML	tenascin-C domain
NCT03861793	ALKS 4230	pembrolizumab	solid tumors	IL-2Rα/IL-2 -> activates dimeric IL-2R
NCT03875079	FAP-IL2 (RO6874281)	pembrolizumab	melanoma	fibroblast activation protein linked to IL-2R$\beta\gamma$-specific modified IL-2
NCT03063762	FAP-IL2	atezolizumab ± bevacizumab	RCC	
NCT02627274	FAP-IL2	Trastuzumab or Cetuximab	Breast H&N	

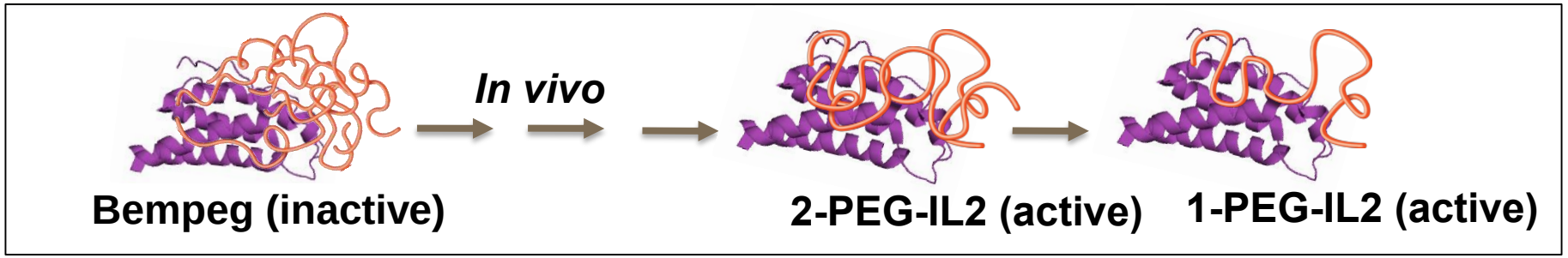
Bempegaldesleukin: preferential IL-2Rβγ binding

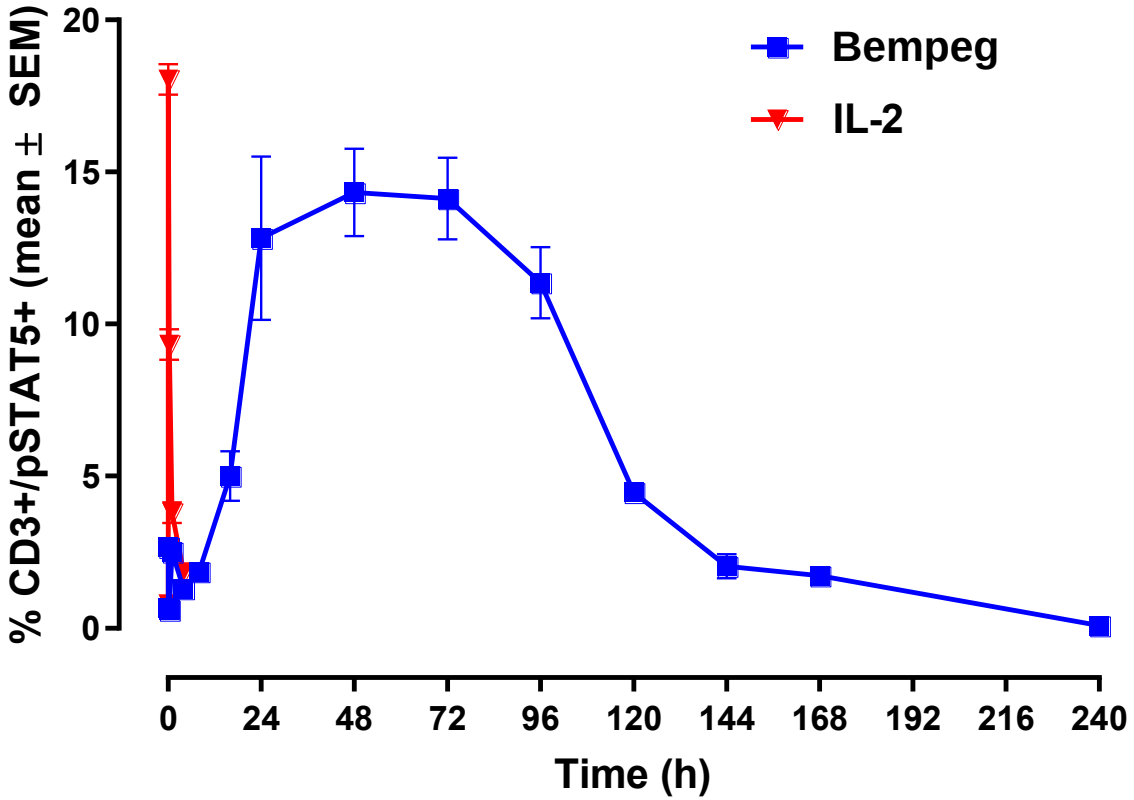


- Preferentially activates and expands effector T cells and NK cells over Tregs in the tumor microenvironment
- Received **Breakthrough Therapy Designation**, July 29th, 2019 from the FDA, for patients with previously untreated, unresectable or metastatic melanoma



Kinetics of Bempegaldesleukin in blood

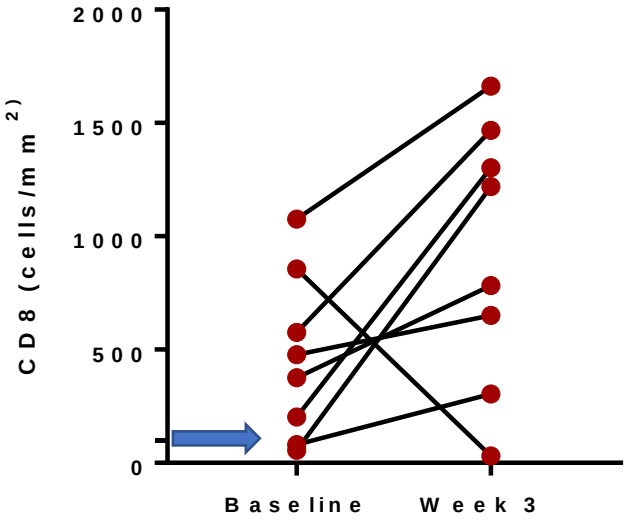




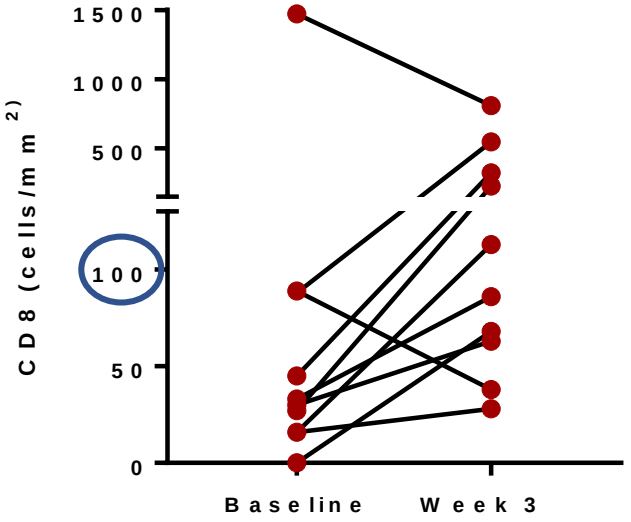
- IL-2 produces rapid signal burst that declines by 4 hours
- BEMPEG builds and sustains signal through 7 days
- Free IL-2 undetectable
- 3 week dosing possible

TIL Increase After Bempegaldesleukin + Nivo in 1L MEL and UC

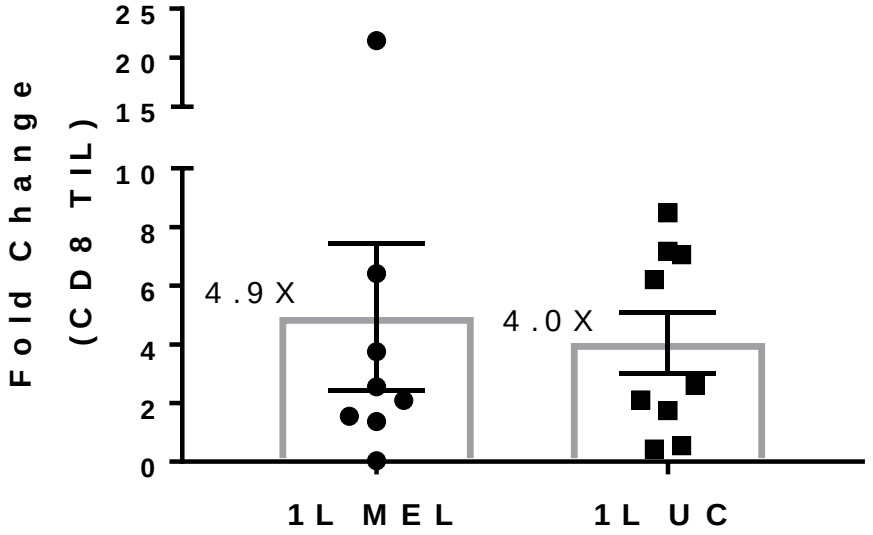
1L MEL
Change in CD8 Infiltrate
IHC Staining



1L UC
Change in CD8 Infiltrate
IHC Staining



Fold Change CD8 Infiltrate

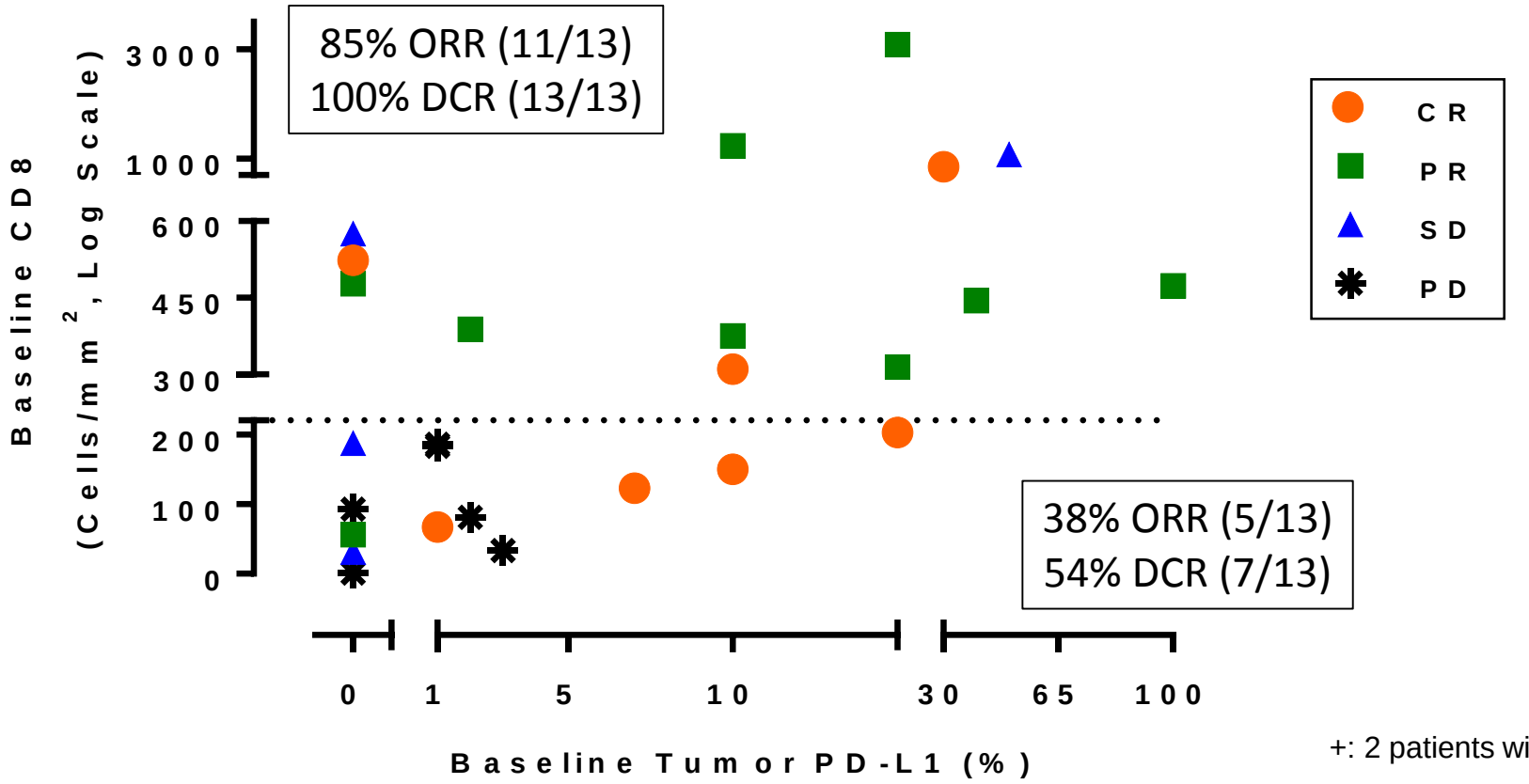


Source: Diab SITC 2018

- TIL increase is preferentially T effectors; T regs not increased after Bempeg
- New T cell clones are seen in tumors after Bempeg

IHC for CD8 was obtained by standard methods. All 1L MEL and 1L UC patients with matched Baseline and Week 3 biopsy were included in the analysis. Fold change was calculated from the Week 3 / Baseline values and is plotted with mean ± SEM.

Bempeg/Nivo active in tumors with low TIL and PD-L1

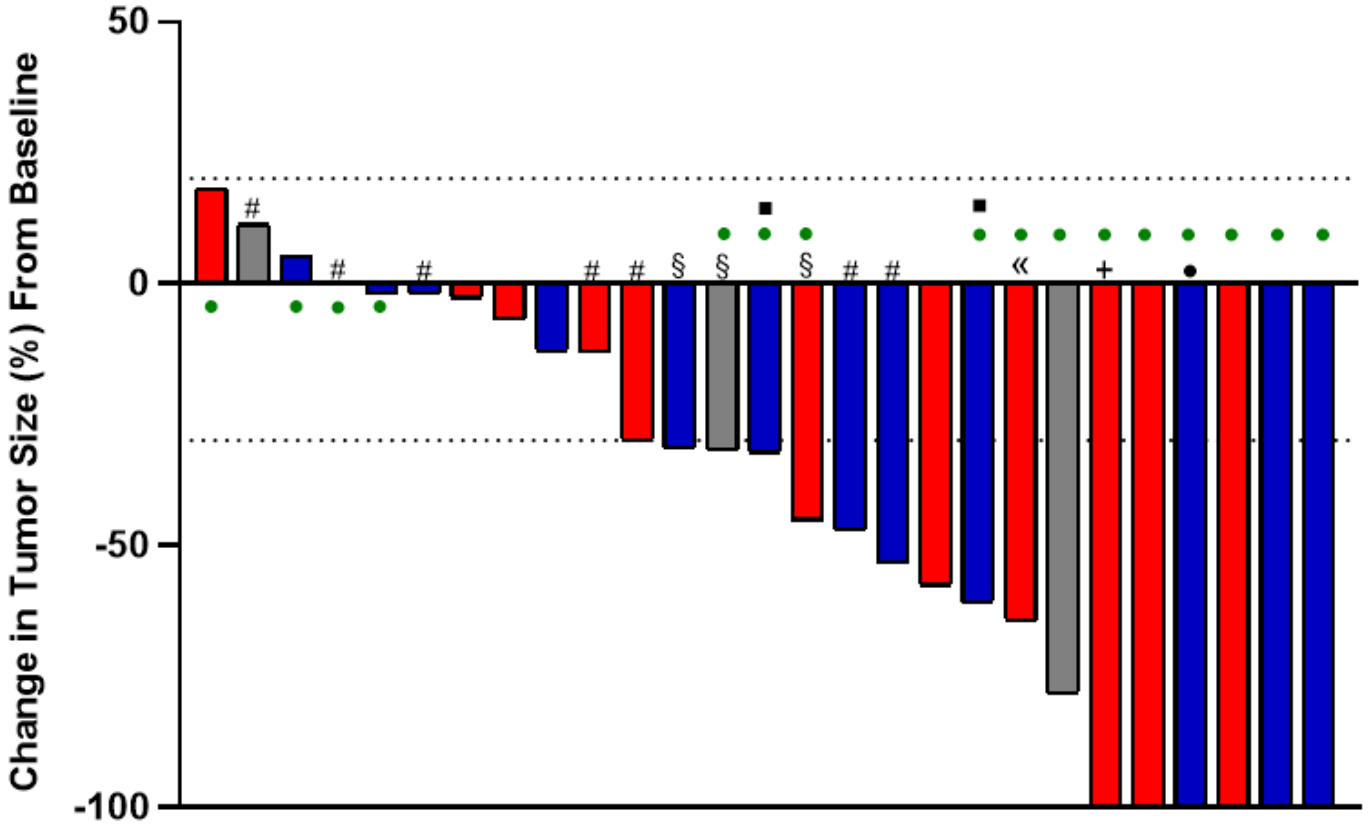


+: 2 patients with PD

Baseline tumor biopsies were evaluated by immunohistochemistry for CD8 cell counts (N=26), and PD-L1 expression (N=26) using the 28-8 method, or tumor mutation burden (TMB, N=12) using the Foundation TMB method. Each patient with matched baseline CD8 and %PD-L1 were plotted as x/y coordinates and correlated with BOR. Each symbol represents an individual patient (CR: N=7, PR: N=9, SD: N=4, and PD: N=6).

Hurwitz ASCO 2019

Bempegaldesleukin + nivolumab in 1L mUC

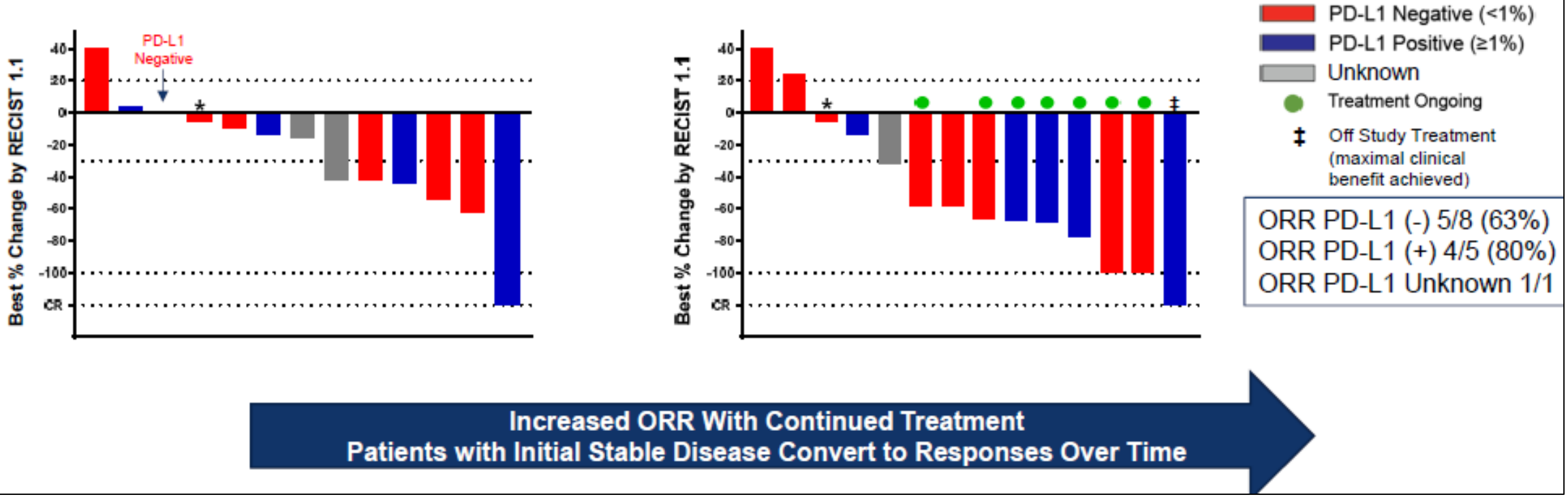


1L metastatic urothelial cancer (n=27 Efficacy Evaluable)	Overall Response Rate
ORR by RECIST*	13 (48%)
ORR by irRECIST	14 (52%)
Responses noted across all disease locations	
Visceral non-nodal metastases (n=15)	8 (53%)
Nodal metastases (n=11)	5 (46%)

Siefker-Radtke A, et al. *J Clin Oncol*. 2019;37 (suppl):388. (ASCO GU 2019)

Bempeg + nivolumab in 1L mRCC: deepened responses over time

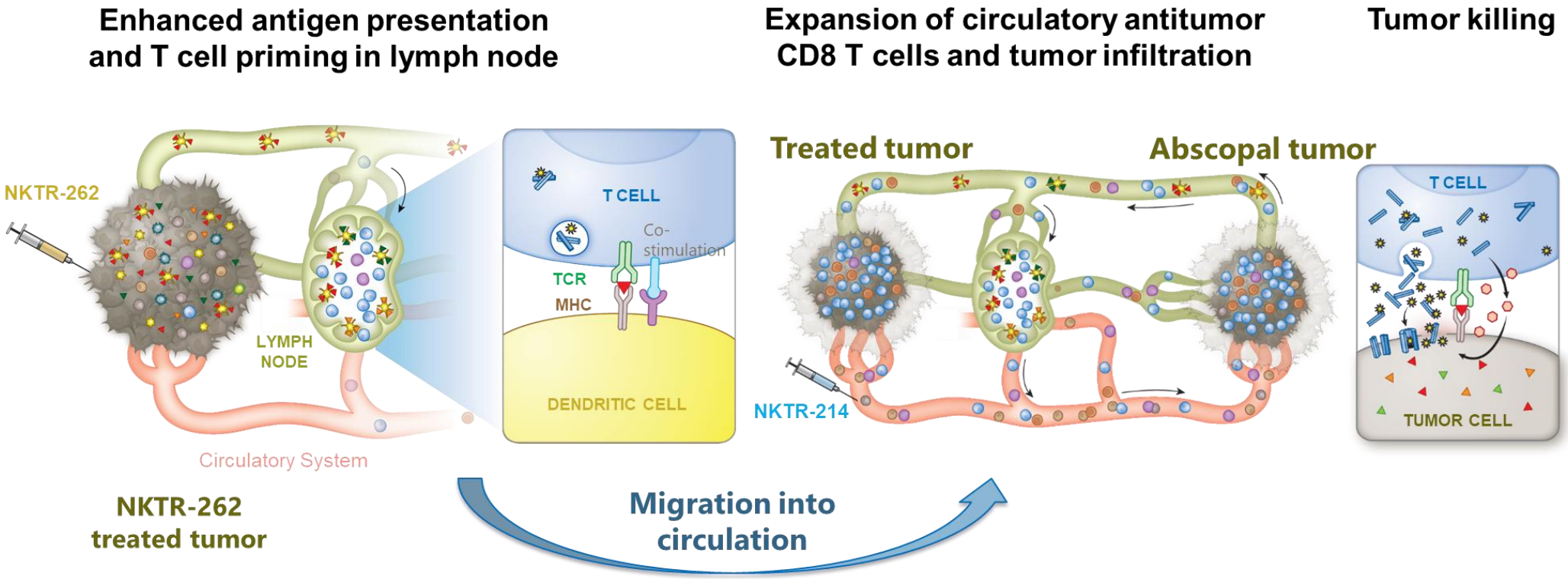
SITC 2017: ORR=6/13 (46%); DCR=11/13 (85%)
ASCO 2018: ORR=10/14 (71%); DCR=11/14 (79%)



1 Diab A, et al. Oral presentation at American Society of Clinical Oncology (ASCO) Annual Meeting; June 1–5, 2018; Chicago, IL, USA. Abstract 3006.

Horizontal dotted lines indicate the thresholds for PD, PR and CR response according to RECIST (version 1.1) criteria. *Best overall response is PD (SD for target lesions, PD per non-target lesions). “u”: Unconfirmed.

NKTR-262 plus Bempeg: Targeting Innate and Adaptive Immunity



- NKTR-262: small molecule PEGylated agonist of toll-like receptors (TLRs) 7/8.
- NKTR-262/bempeg combination resulted in abscopal responses in preclinical models[1]
- NCT03435640: Phase 1b/2 REVEAL study: NKTR-262 + bempegaldesleukin enrolling

1. Journal for ImmunoTherapy of Cancer 2017, 5(Suppl 2):P275

IL-2 combinations

- Multiple ongoing combination trials
  - High dose IL-2
  - modified/engineered IL-2 agents
- Question:
  - Will the modified IL-2 agents provide improved therapeutic window?

Immune Therapy in 2019

Thanks for your attention