

What's New in Cancer Immunotherapy?

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**Daisy M. Skinner President's Chair in Cancer Immunology
University of Texas Health San Antonio**

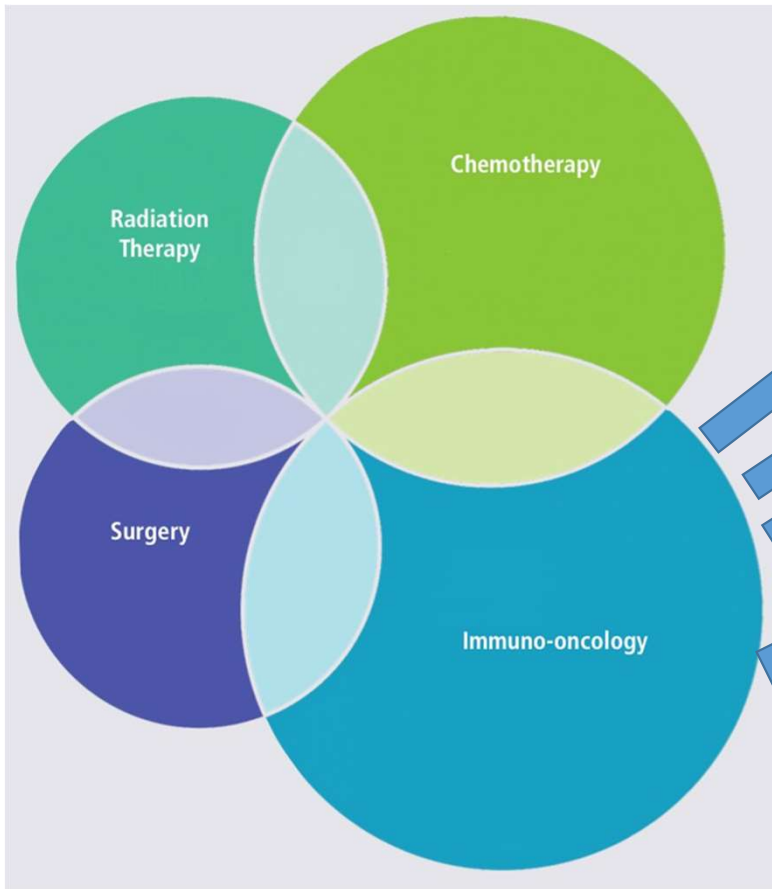
Disclosures

- **Consulting fees:** Agenus, Dr. Reddy, Gilead, Xencor
- **Stock or options:** Agenus, Faron, ImVax, Mythic, Xencor
- **Lab research support:** Agenus
- I will be discussing non-FDA approved indications during my presentation.

Educational Takeaways

- **Understand comprehensive immunotherapy approaches**
- **Understand rationale for new immune checkpoint targets**
- **Become familiar with new concepts such as bi-targeting molecules, engineered cytokines, metabolic targeting**
- **Become familiar with advances in adoptive cell strategies**
- **Understand major technological advances**

Look for Multi-Multi Modal Approaches



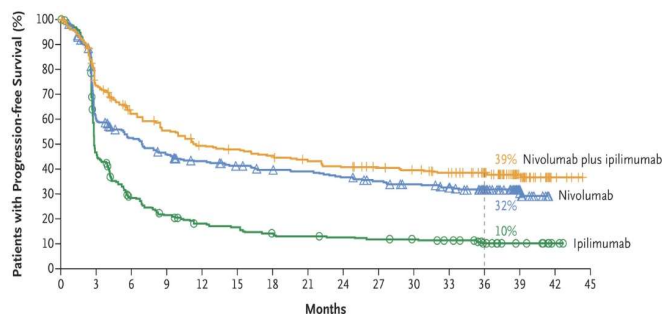
Checkpoint inhibitors
Bi-specifics
Engineered cytokines
Adoptive cells
Other approaches

Galon and Bruni, *Nat Rev Drug Discovery* 2019 18:197Galon and Bruni, *Nat Rev Drug Discovery* 2019 18:197

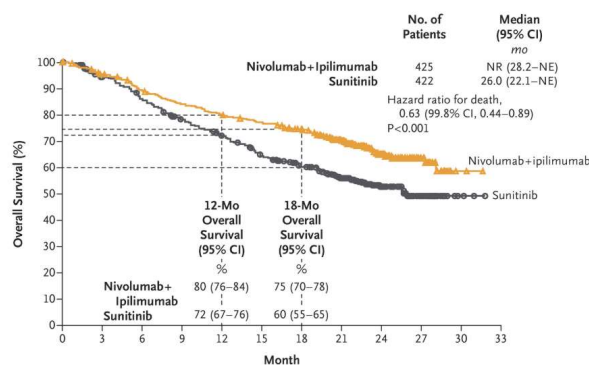
- [illegible]

Combos with ICB and chemo are FDA approved, with more coming soon

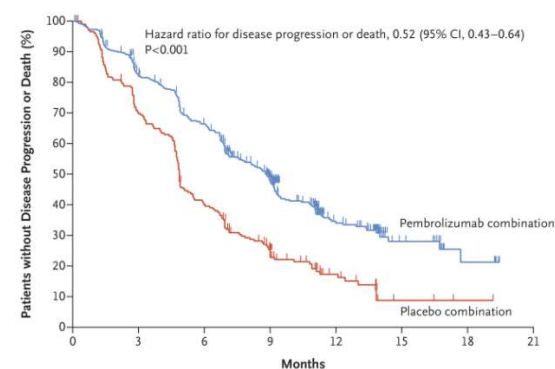
Melanoma: α PD-1 + α CTLA-4



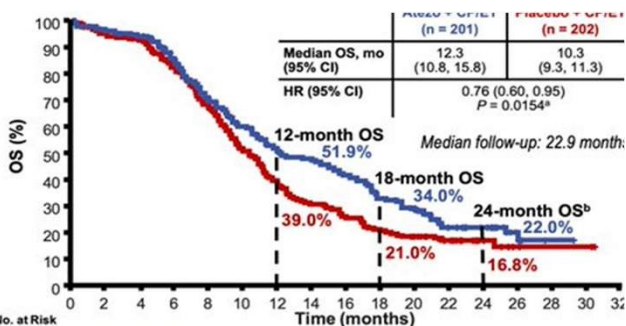
RCC: α PD-1 + α CTLA-4



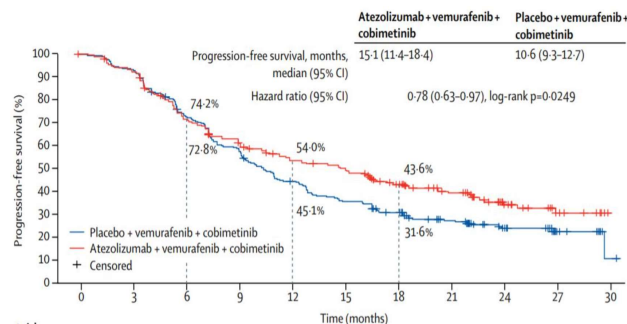
NSCLC: α PD-1 + chemo



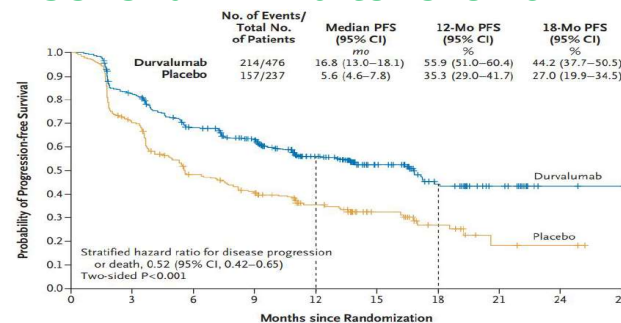
ES-SCLC α PD-L1 + chemo



Melanoma: BRAFi+MEKi+ α PD-L1

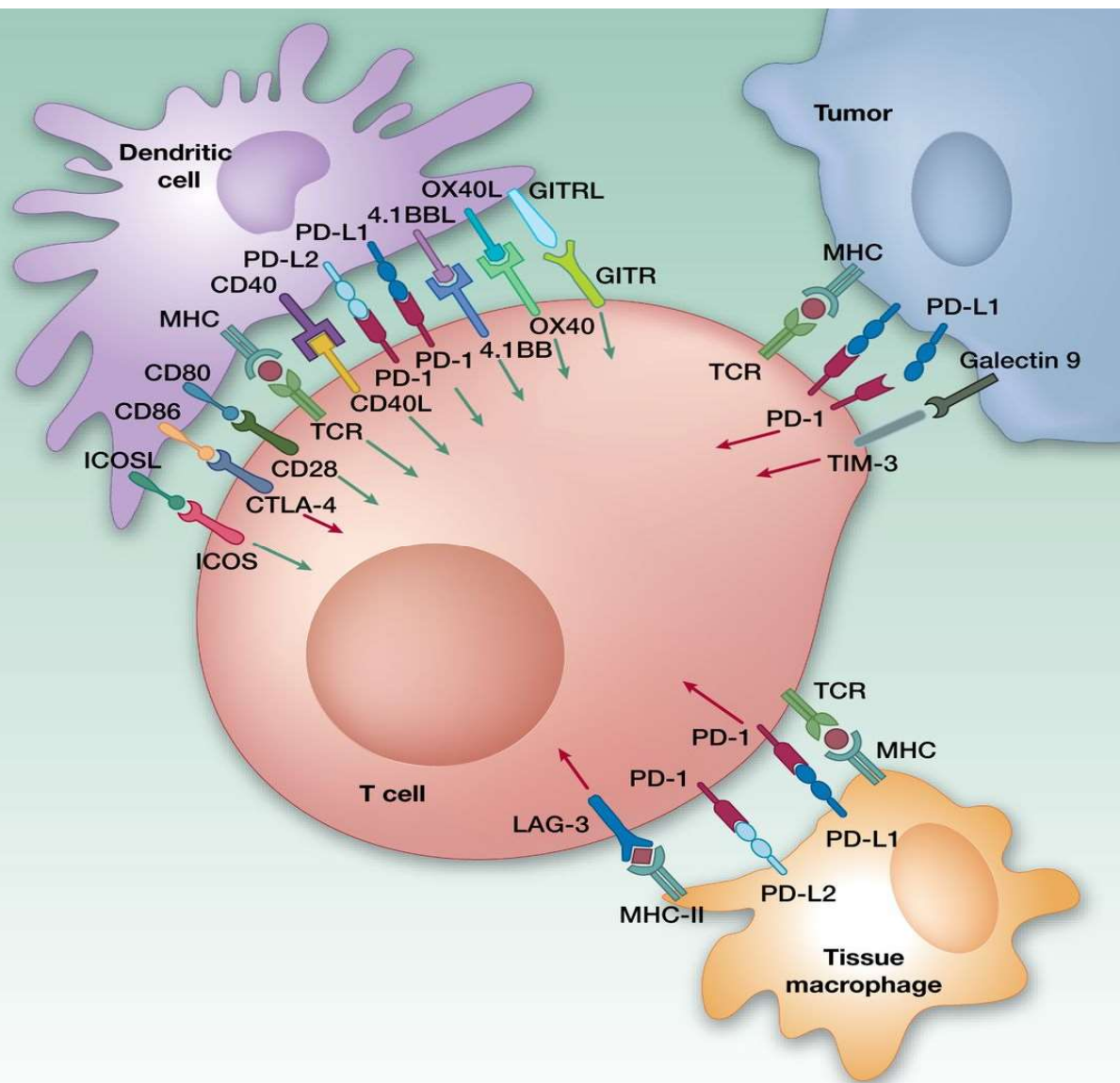


NSCLC: α PD-L1 after chemoRT



Wolchok *et al.* NEJM 2017; Horn, *et al.*, NEJM 2018; Gutzmer *et al.* Lancet. 2020; Motzer *et al.* NEJM 2018; Rini *et al.* NEJM 2019; Ghandi *et al.* NEJM 2018; Antonia *et al.* NEJM 2017

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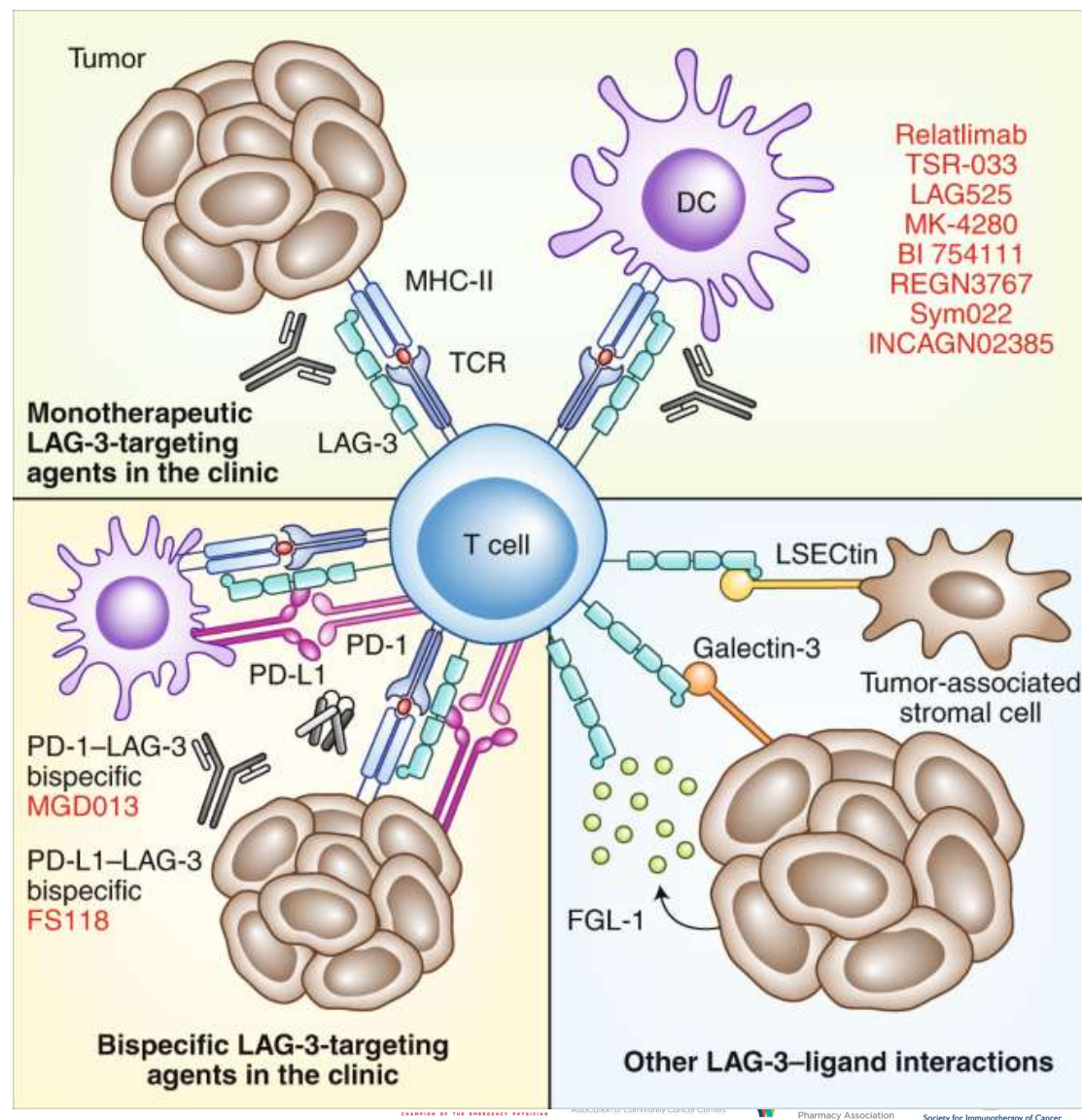


**Many new
checkpoint blockade
antibodies in the
clinic now**

LAG3 actions and antagonists

Lawrence P. Andrews,
 Hiroshi Yano &
 Dario A. A. Vignali

Nature Immunology 20, 1425–1434 (2019)



αLAG3 alone and with αPD-1

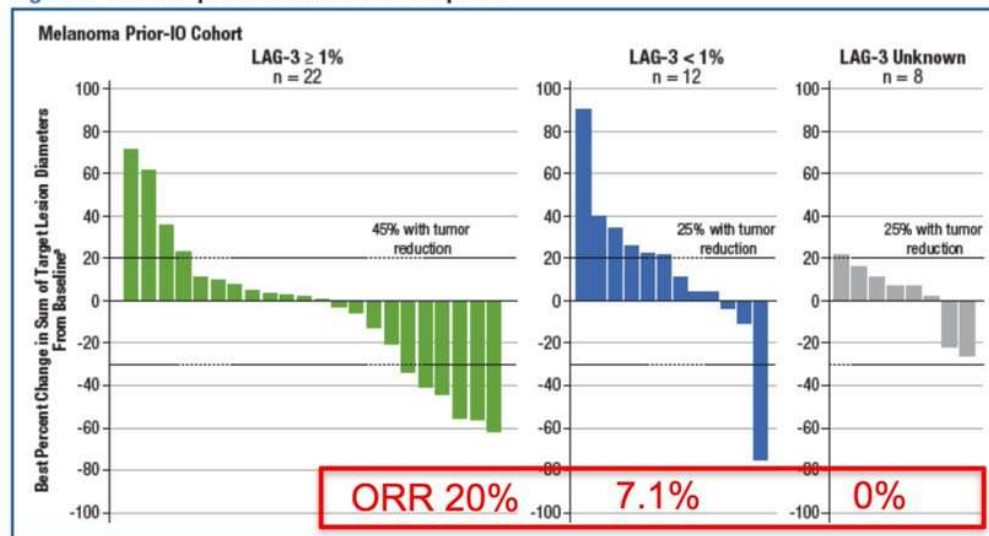
**Phase 2/3 study of
 nivolumab +/-
 relatlimab (αLAG3) in
 frontline melanoma**

NCT03470922

**Ends accrual in Jan
 2021**

Anti-Tumor Activity

Figure 3. LAG-3 Expression Enriches for Response



- Related grade 3/4 AEs 9.4%
- Results support ongoing phase I/II investigation in melanoma and other LAG-3+ tumors

Data presented by Paolo Ascierto, MD, ASCO 2017.

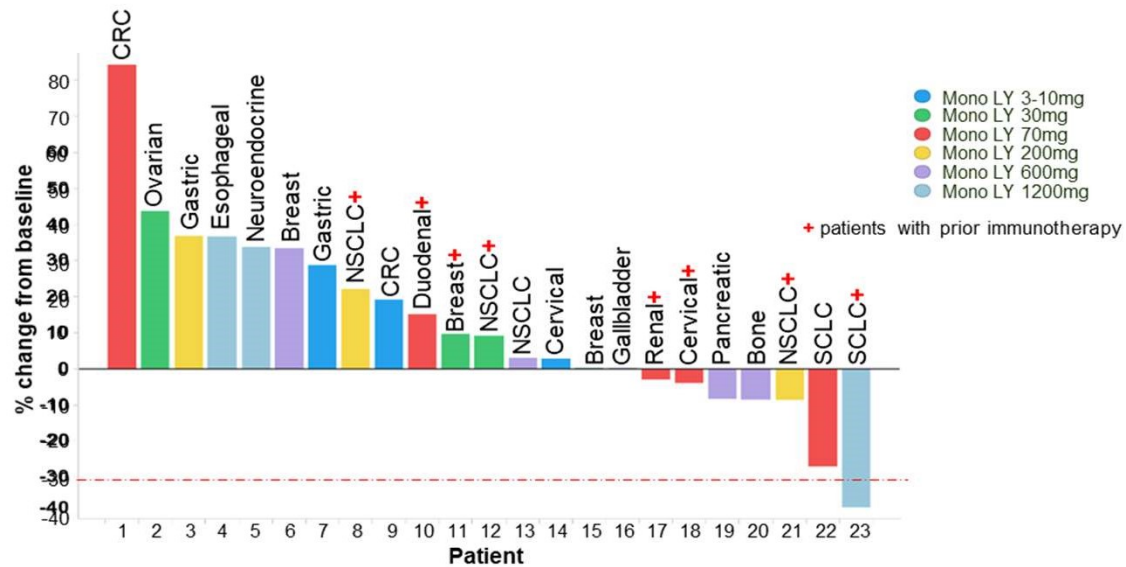
PRESENTED AT: ASCO-SITC CLINICAL IMMUNO-ONCOLOGY SYMPOSIUM | #ImmunoOnc18

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Presented by: Katy K. Tsai, MD

Wang *et al.* Cell 2019; Ascierto *et al.* ASCO 2017

Tim3 actions and antagonists

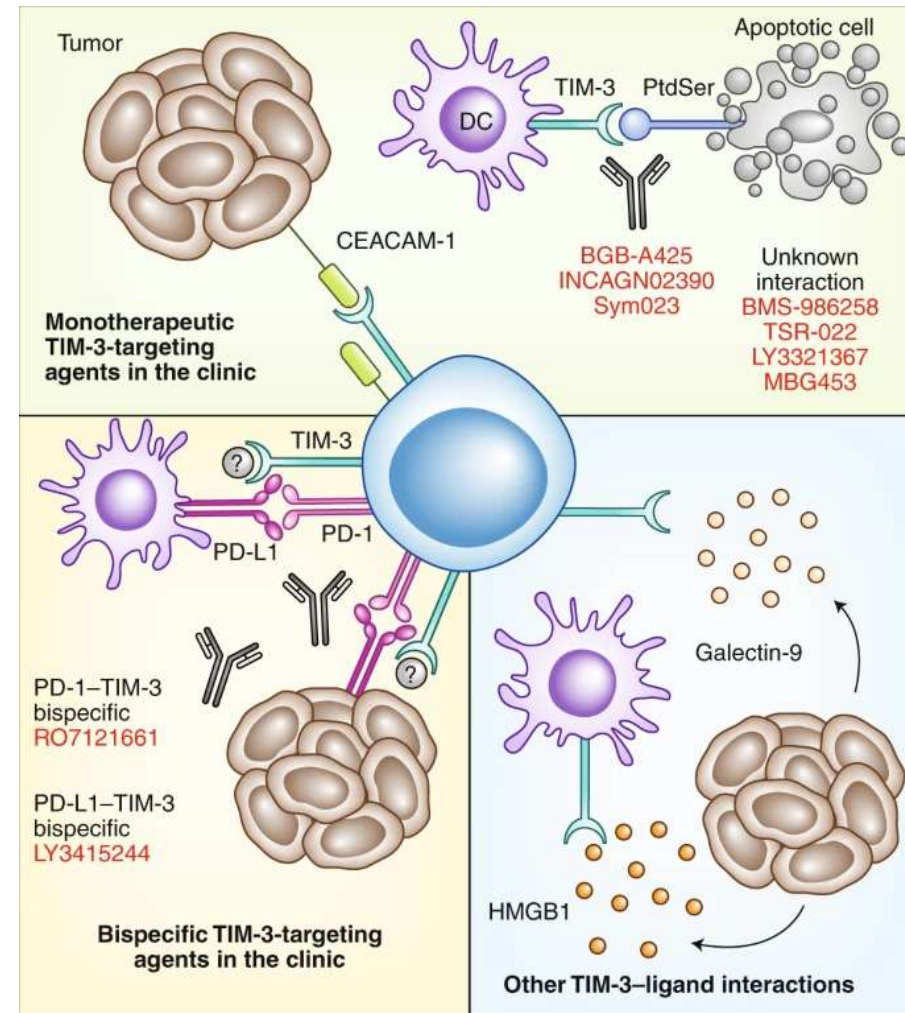


Wolf et al. Nat Rev Immuno 2019

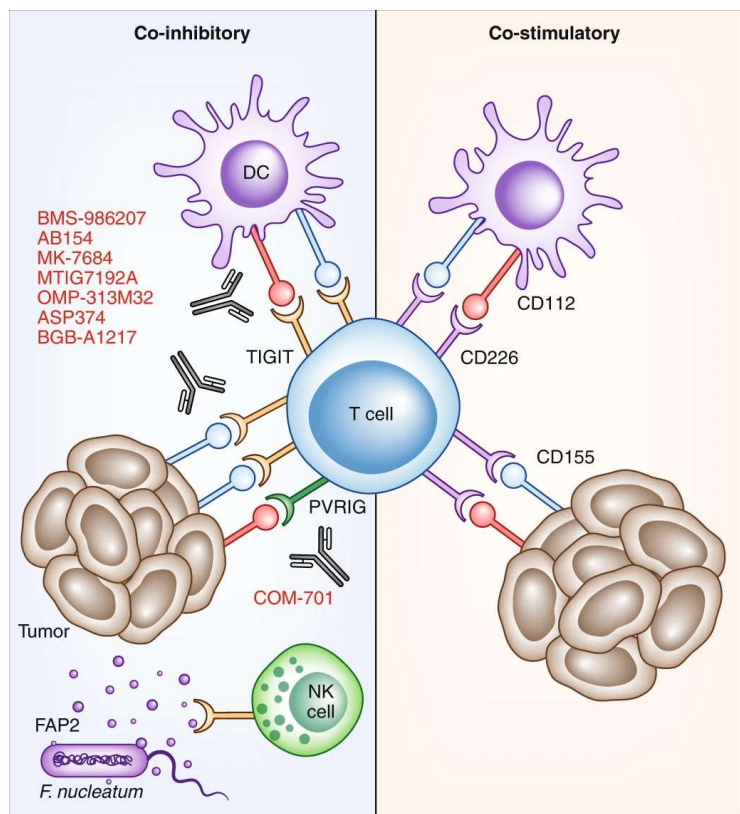
Davar et al., SITC 2018

Harding et al., ASCO-SITC 2019

Andrews, Yano & Vignali
***Nature Immunology* 20, 1425–1434 (2019)**



TIGIT antagonists

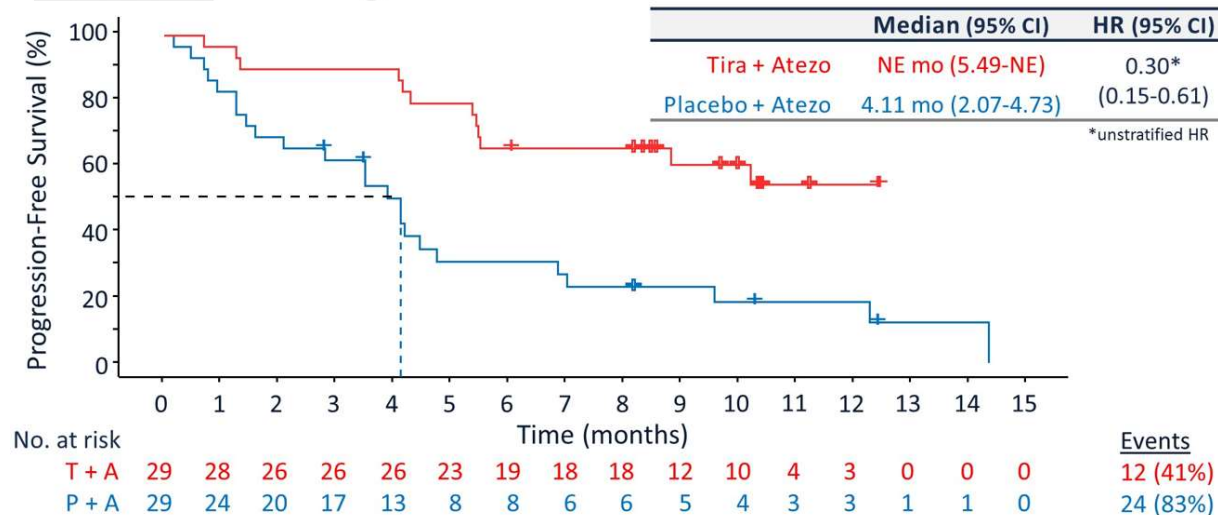


Andrews, Yano & Vignali

***Nature Immunology* 20, 1425–1434 (2019)**

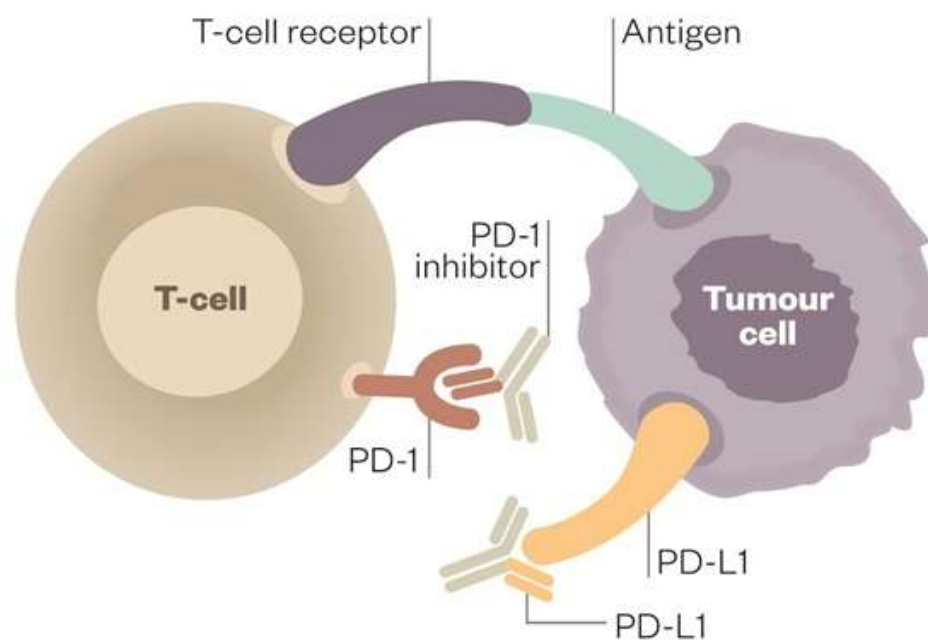
@jasonlukemda | Society for Immunotherapy of Cancer

Updated Investigator-Assessed PFS: PD-L1 TPS ≥ 50%



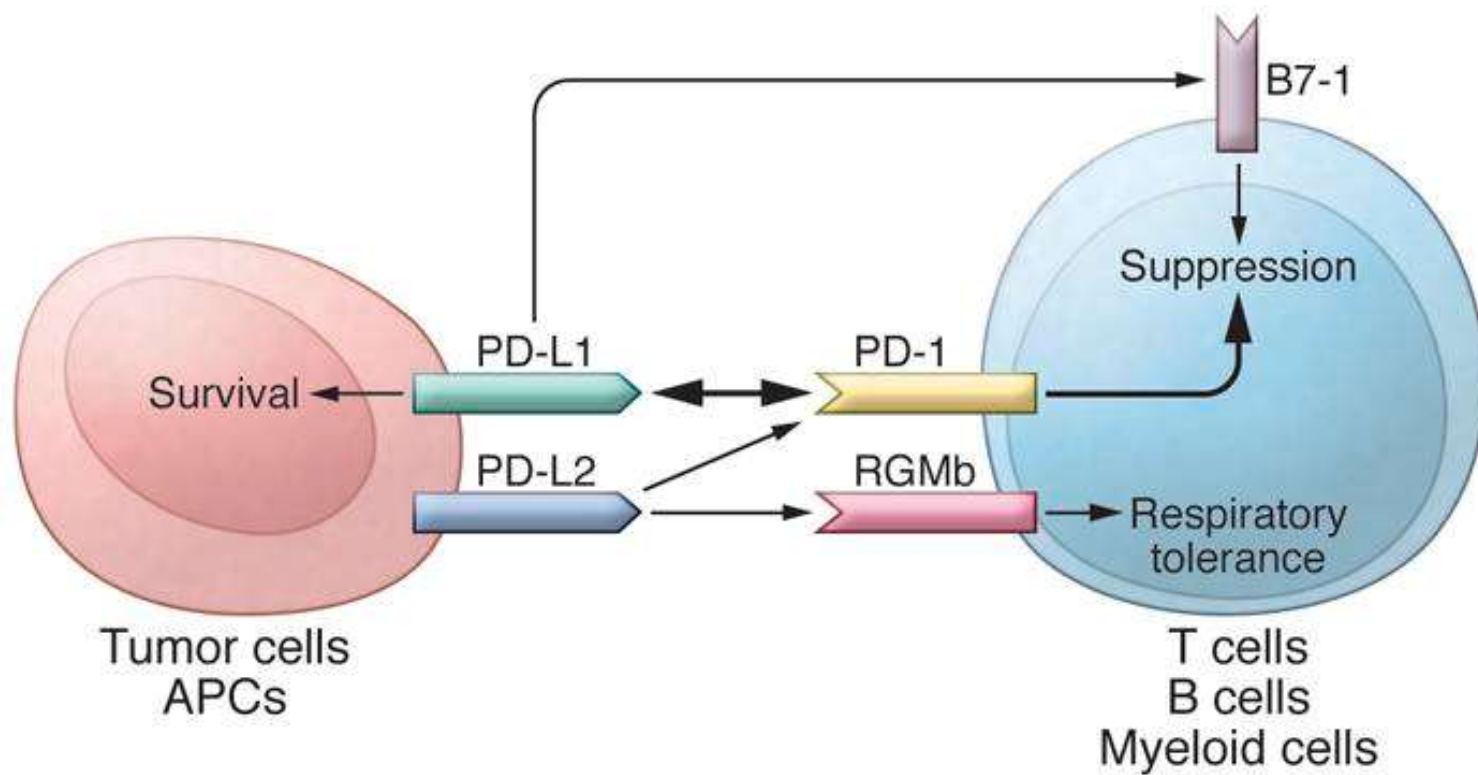
Rodriguez-Abreu, *et al.* PD-L1-selected NSCLC (CITYSCAPE) ASCO Virtual Meeting, 29-31 May 2020, Abstract 9503

Blocking PD-L1 versus PD-1 looks symmetrical...

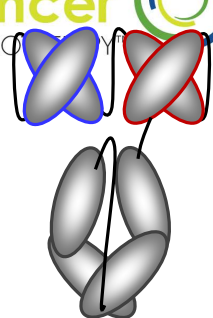


...but it is not

Biotech/Pharma missed α PD-L2 but they are racing now



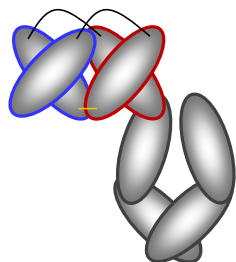
Many platforms for dual-targeting



HLE-BiTE

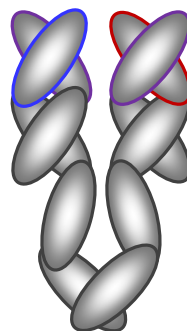
Amgen

Blinatumomab (CD3 x CD19)

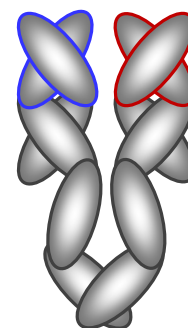


Fc-DART

Macrogenics



Common light chain
(Both Fabs use same light chain)
OR
Common heavy chain
Regeneron, Merus, Novimmune

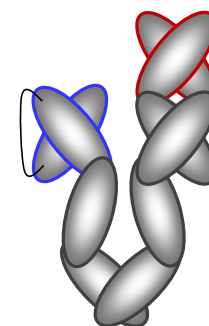


Crossmab

Roche

or

Duobody
Genmab

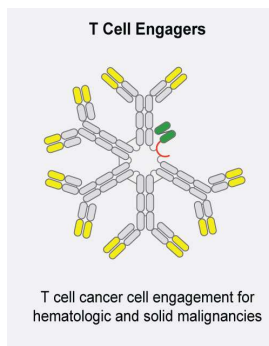


scFv-Fab-Fc

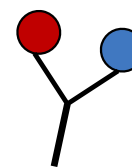
Xencor

Zymeworks

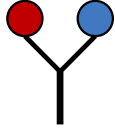
IgM
bio



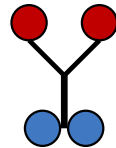
There are many others!



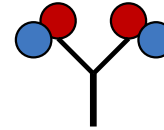
Cartoon bispecific



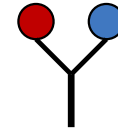
MEDI5752
Medimmune



AK104
Akeso



MGD019
Macrogenics

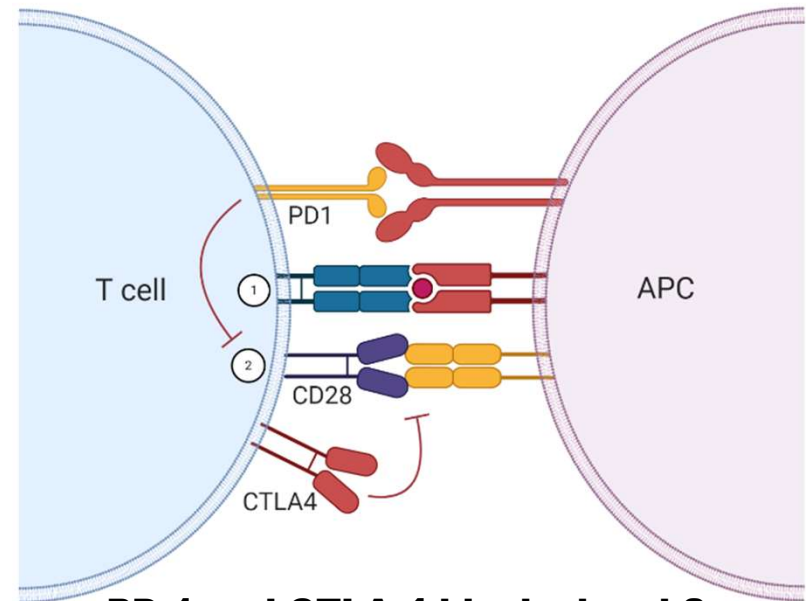


XmAb20717
Xencor

General Goals:

- **Block both PD-1 and CTLA-4**
- **Improve therapeutic index compared to α PD-1 + α CTL-A-4 (e.g., nivo + ipi)**
- **Inactive Fc domains**

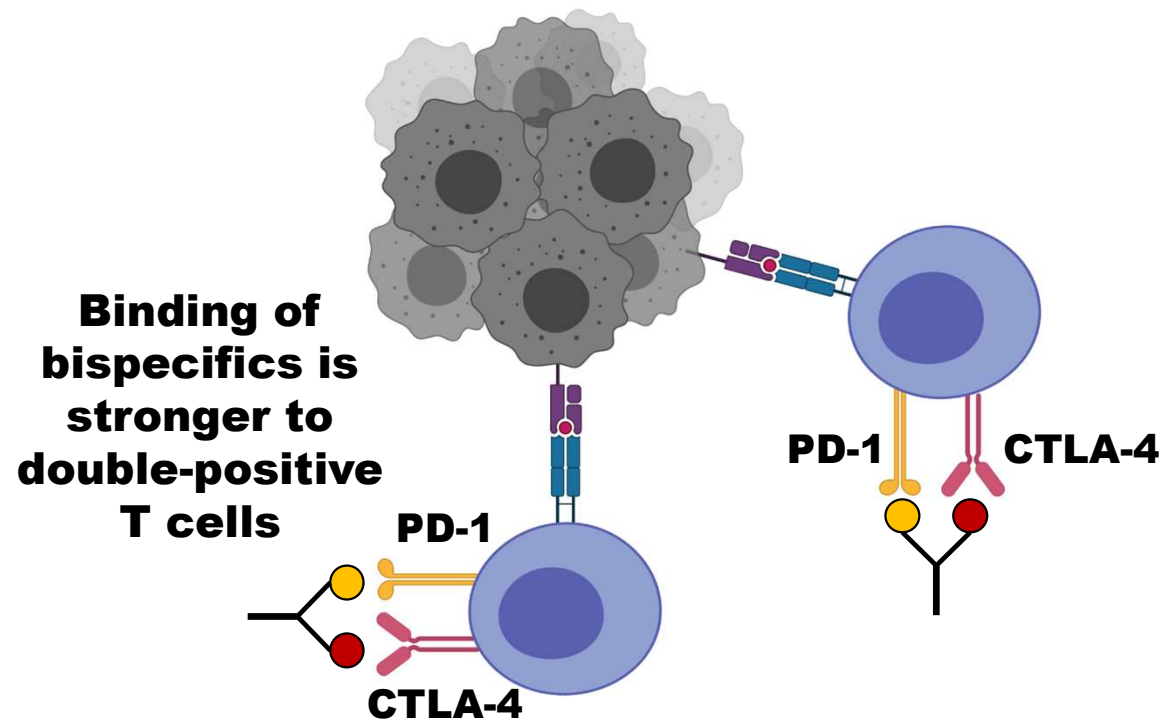
Courtesy: John Desjarlais, PhD Xencor



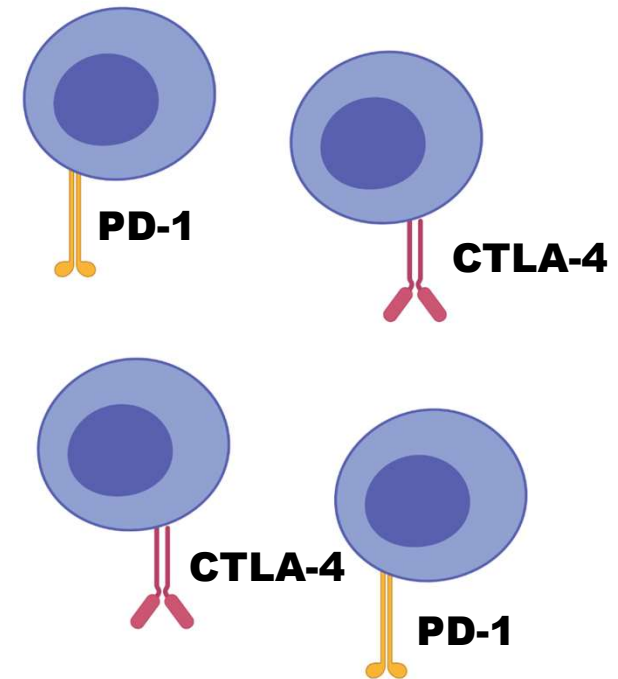
PD-1 and CTLA-4 block signal 2

PD-1 x CTLA-4 bispecifics preferentially activate PD-1⁺CTLA-4⁺ T cells

Tumor-reactive TILs express multiple checkpoints
PD-1 x CTLA-4 bispecifics can selectively activate them

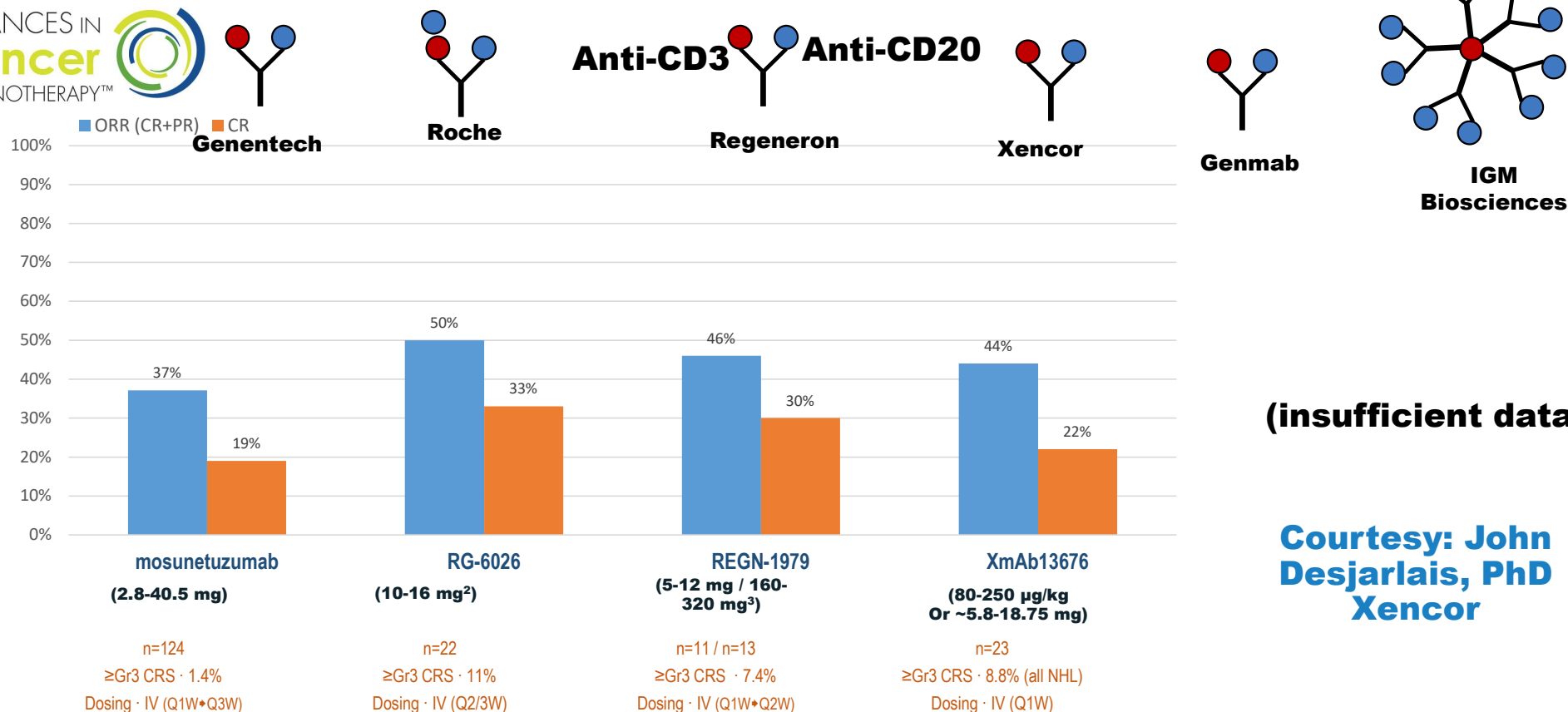


Peripheral T cells



Courtesy: John Desjarlais, PhD Xencor

CD20 x CD3 Bispecific antibodies highly active in R/R DLBCL



¹ Data Source: | mosunetuzumab · ASH Dec'19 | RG-6026 · ICML Jun'19 | REGN-1979 · ASH Dec'19 | XmAb13676 · Jun 24, 2020

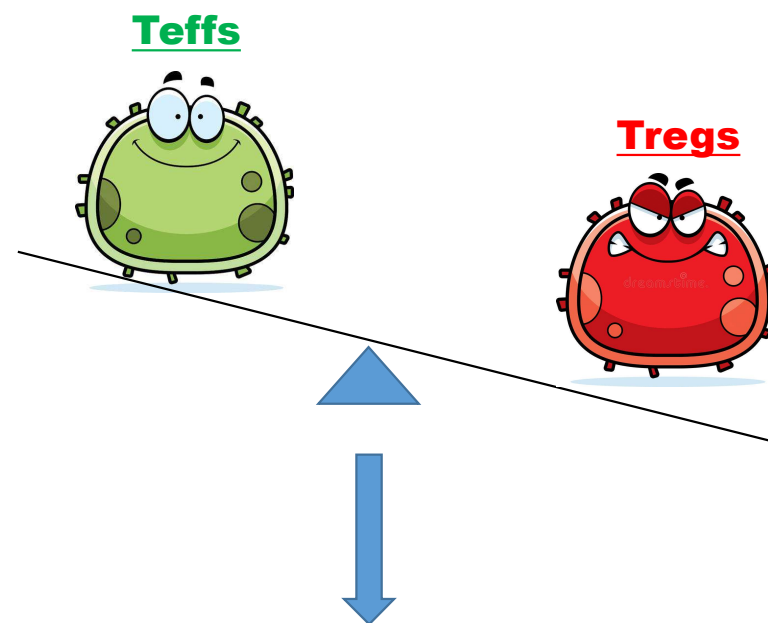
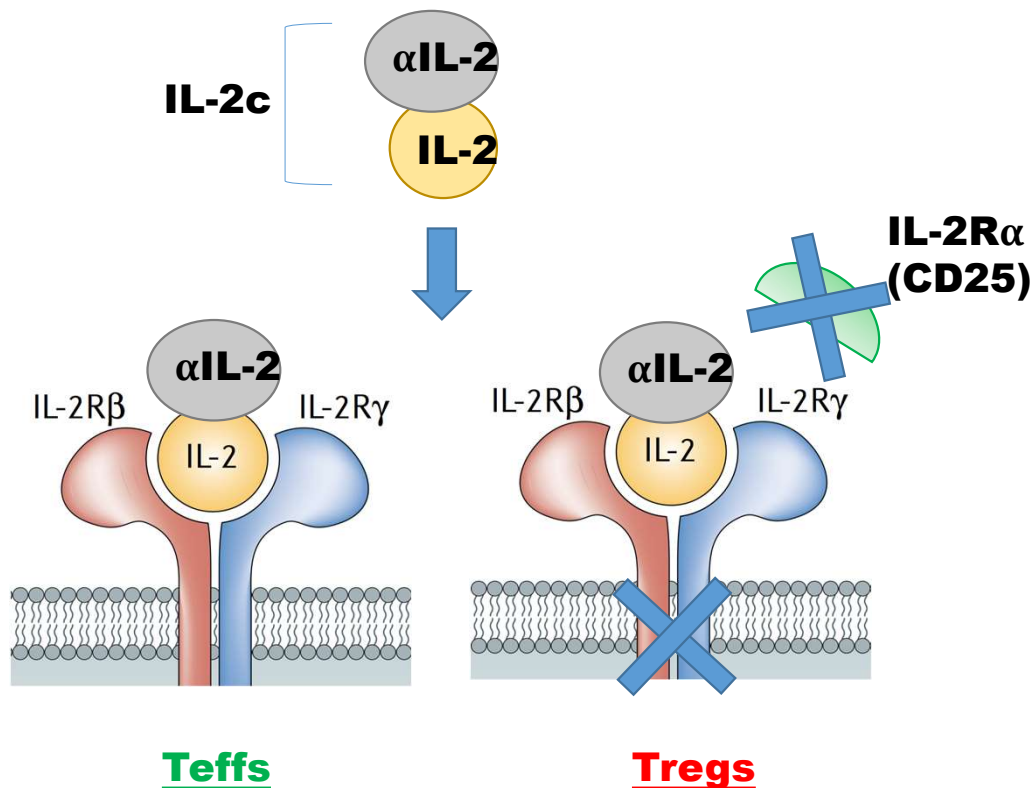
² | 25 mg RG-6026 monotherapy cohort terminated due to DLT; pursuing combinations w/ obinutuzumab and atezolizumab

³ 160mg is their selected dose for Ph 2 study

ORR: Overall Response Rate | CR: Complete Response | DoR: Duration of Response | NR: Not Reached | NA: Not Available | CRS: Cytokine Release Syndrome | TEAE: Treatment-emergent adverse events | Tx: Therapy | BR: Bendamustine + Rituximab

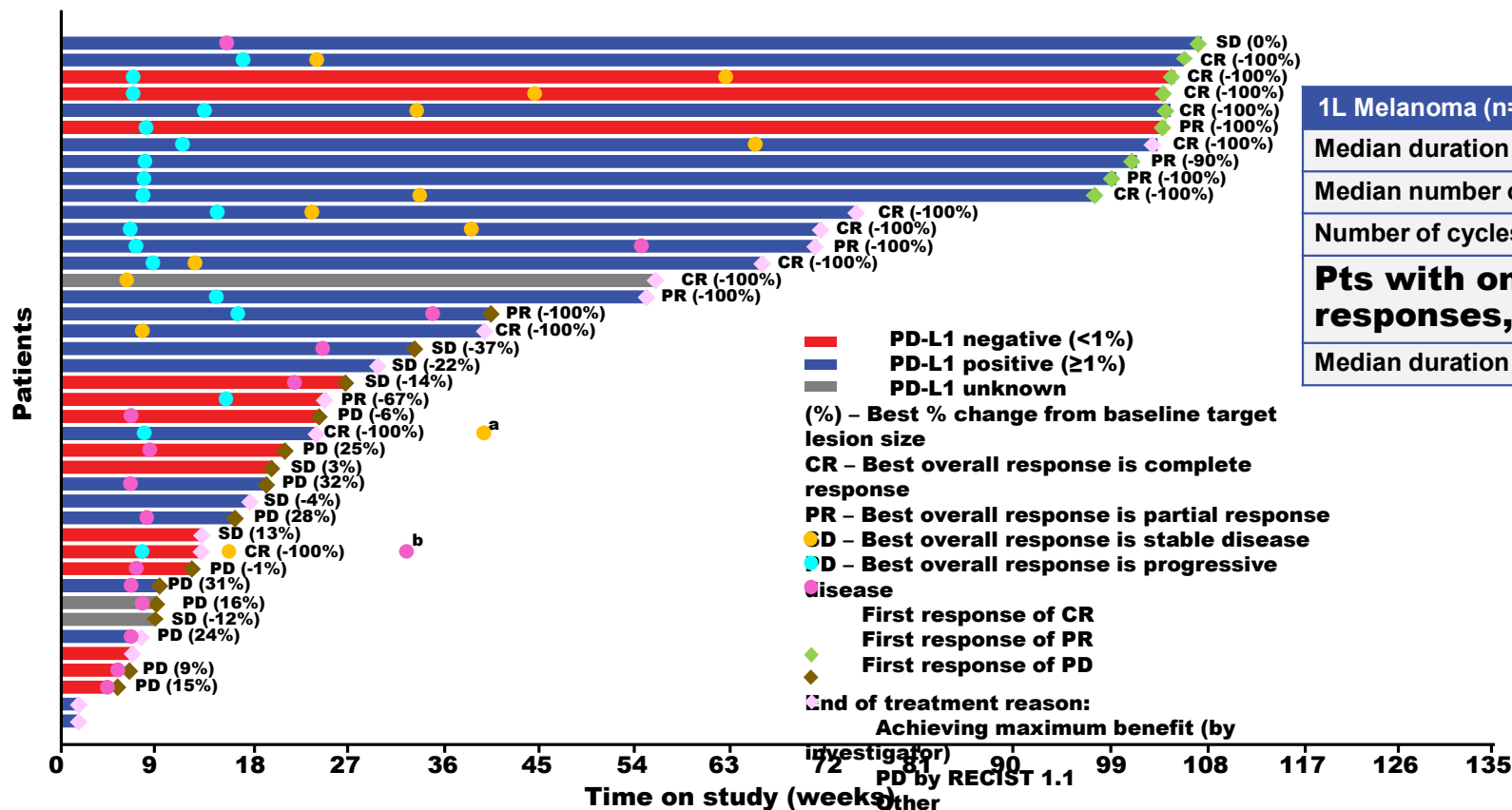
Engineered cytokines

CD122-selective IL-2 complexes (IL-2c)



Better Tumor control
Cancer Res Drerup, et al., 2020;80: 5063

Responses durable with bempegaldesleukin + nivolumab Deepened over time: Stage IV 1L melanoma: ORR 53% CR 34%

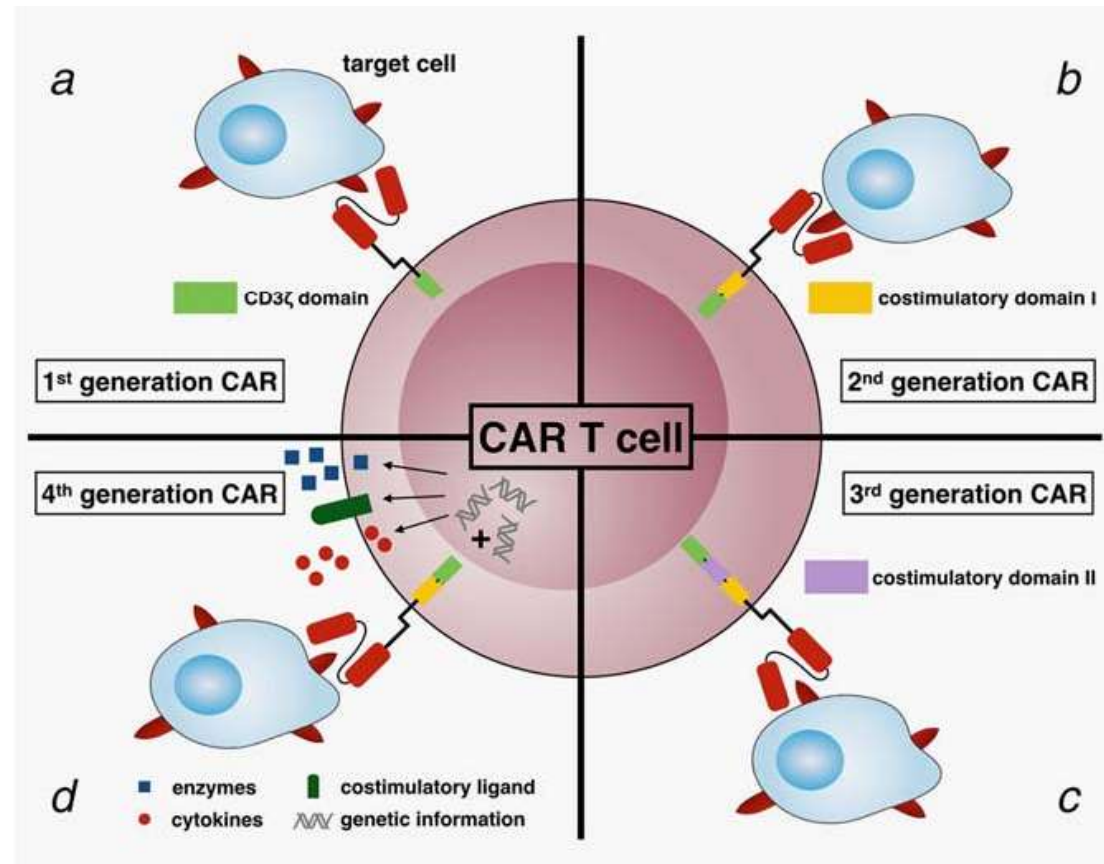


1L Melanoma (n=38 Efficacy Evaluable)	
Median duration of follow-up (months)	29.0
Median number of cycles (range)	9 (1–35)
Number of cycles ≥6, n (%)	29 (70.7)
Pts with ongoing responses, n (%)	16 (80.0)
Median duration of response (months)	NE

Data cutoff: 1SEPT2020. ^aPatient achieved PR in Mar 2018; EoT in Jul 2018; achieved CR in Oct 2018. ^bPatient achieved PR in Mar 2018; EoT in May 2018 due to patient decision (QoL issues); achieved CR in May 2018; disease relapse in Sept 2018 due to new lesion (brain). EoT, end of treatment; NE, not estimable; PD-L1, programmed death-ligand 1.

Fourth generation CAR immune cells: T cells, NK cells, NK T cells and $\gamma\delta$ T cells

- **Mesothelin CAR T** inducing remission in metastatic pancreatic cancer
- **Next generation CARs** with better safety, harder to suppress, off-the-shelf engineering, armored CAR, new targets



Advantages of NK cells over T cells for CAR therapy

CAR-T

- **Autologous Product**
 - **Production time**
 - **Cost**
 - **1 patient, 1 product**
- **If allogeneic: GVHD Risk**
- **Toxicity: cytokine release syndrome; neurotoxicity (50% need ICU care)**
- **CAR-mediated killing**

CAR-NK

- **Allogeneic Product**
 - **“Off the shelf”**
 - **Potential low cost**
 - **1 cord, > 100 doses**
- **Low/absent GVHD**
- **CAR + NK Receptor mediated**

ORIGINAL ARTICLE

Use of CAR-Transduced Natural Killer Cells in CD19-Positive Lymphoid Tumors

Enli Liu, M.D., David Marin, M.D., Pinaki Banerjee, Ph.D.,
Homer A. Macapinlac, M.D., Philip Thompson, M.B., B.S., Rafet Basar, M.D.,
Lucila Nassif Kerbaui, M.D., Bethany Overman, B.S.N., Peter Thall, Ph.D.,
Mecit Kaplan, M.S., Vandana Nandivada, M.S., Indresh Kaur, Ph.D.,
Ana Nunez Cortes, M.D., Kai Cao, M.D., May Daher, M.D., Chitra Hosing, M.D.,
Evan N. Cohen, Ph.D., Partow Kebriaei, M.D., Rohtesh Mehta, M.D.,
Sattva Neelapu, M.D., Yago Nieto, M.D., Ph.D., Michael Wang, M.D.,
William Wierda, M.D., Ph.D., Michael Keating, M.D., Richard Champlin, M.D.,
Elizabeth J. Shpall, M.D., and Katayoun Rezvani, M.D., Ph.D.

***N Engl J Med* 2020;382:545-53 2020**

Patient 5 Achieved Complete Response in Richter's ($1 \times 10^6/\text{kg}$)

Pre-admission



Day 30 post CAR NK

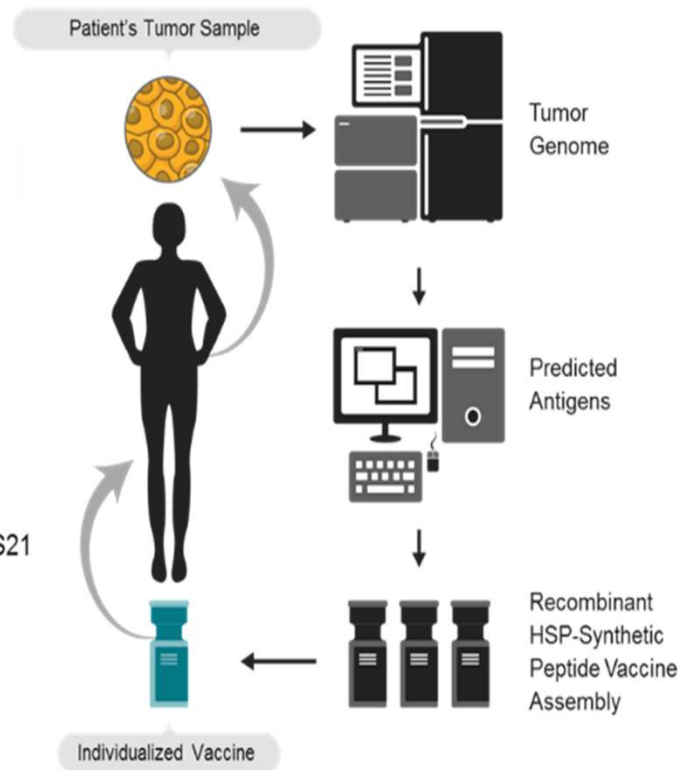


Courtesy Katy Rezvani, MD, PhD
MDACC

Personalized cancer vaccines

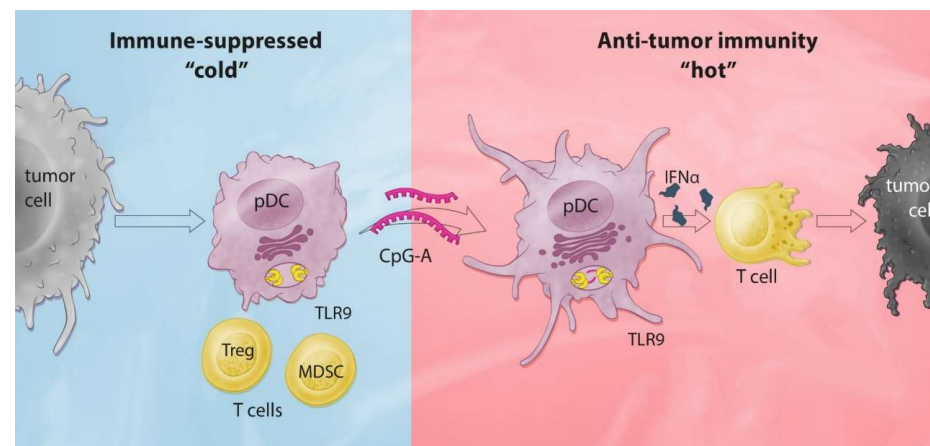
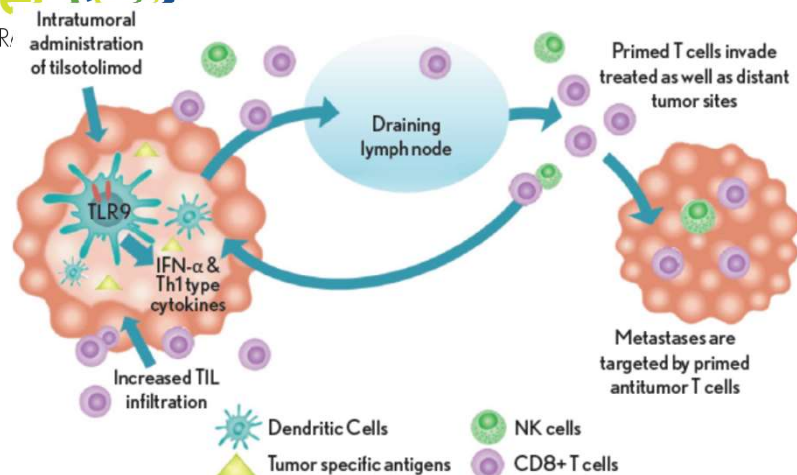
ASV™ Concept

- Synthetic individualized cancer vaccine designed to impart an immune response against tumor-specific mutations
- Exploits cutting-edge NGS and bioinformatics technologies, rapid peptide synthesis and rh-Hsc70/QS21 vaccine platform



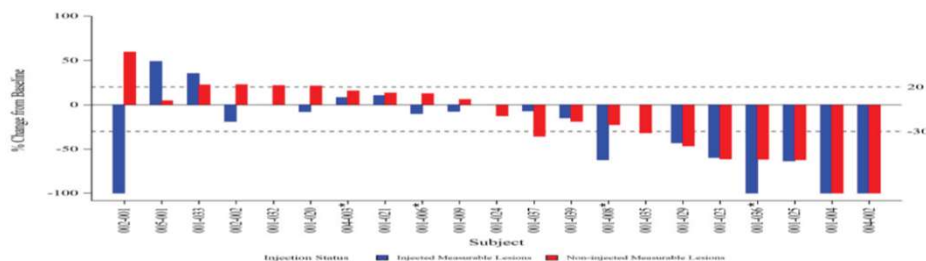
Three companies have personalized cancer vaccines in trials

Innate activation of via TLR9 agonism can overcome checkpoint inhibitor resistance

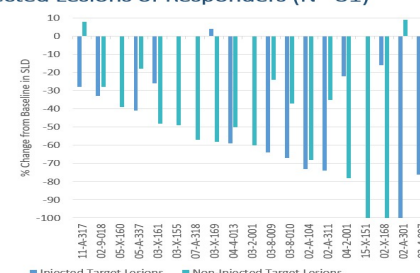
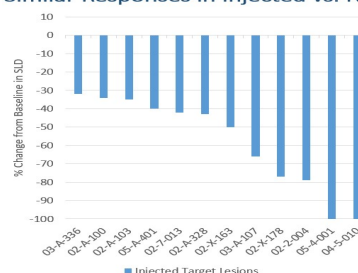


CMP-001 + Pembrolizumab in Anti-PD-1 Refractory Melanoma

Similar Responses in Injected vs. Non-Injected Lesions of Responders (N= 31)

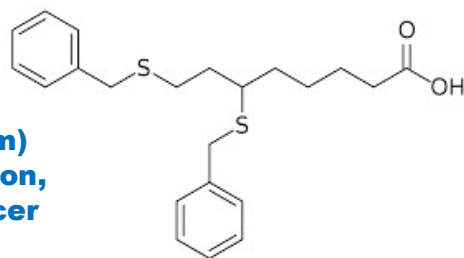


*Subjects were previously treated with ipilimumab in the metastatic setting.

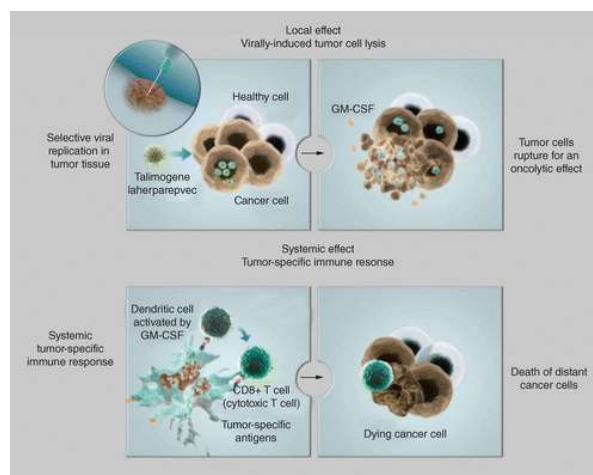


2020 SITC update: ORR of 23.5% median response duration 19.9 mos in αPD-1 failure

Miscellaneous other approaches

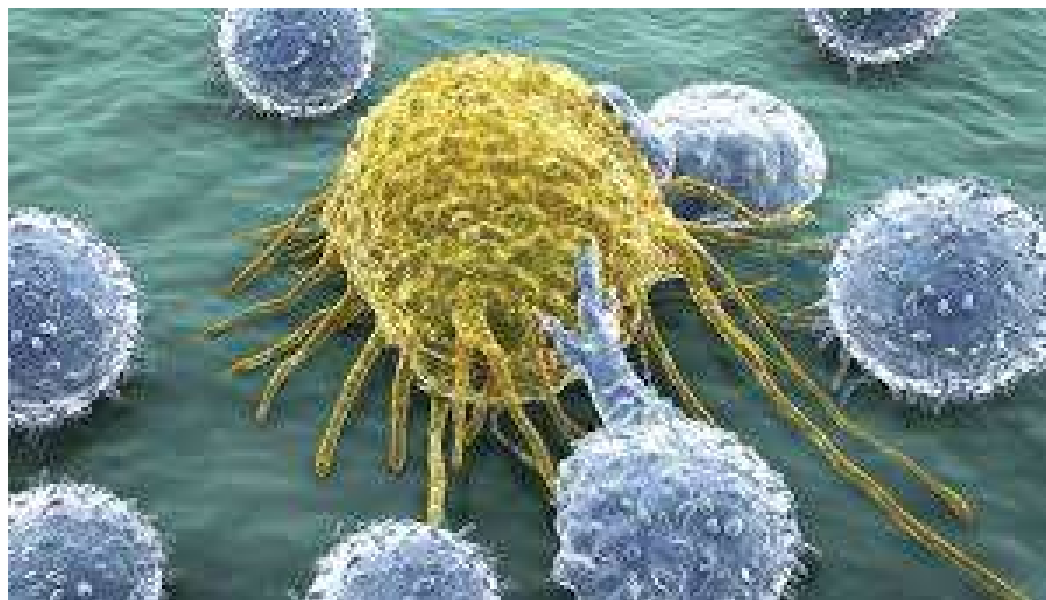


- **Metabolic disruption**
 - **Devimistat (lipid metabolism)** gets FDA Fast Track designation, in Phase 3 for pancreatic cancer
- **Altering the metabolome**
 - **Specific gut microbes alter ICB outcomes**
 - **McQuade JL:** [2020 ASCO-SITC Clinical Immuno-Oncology Symposium](#).
- **Engineered viruses**
 - **Engineered Herpesvirus**
FDA-approved (Talimogene laherparepvec)
- **Nanoparticles**
- **Re-directed drugs**
 - **PARP inhibitors**



Summary of What's New Cancer Immunotherapy in 2020

- **A world beyond just immune checkpoint blockade and CAR-T cells**
- **Many new agents coming very soon**
- **Lots of combinations, especially with chemo and each other**
- **As the pace of basic discovery quickens, expect many new insights**
- **Consider clinical trials**



Curiel Team

- **Vincent Hurez, PhD, DVM**
- **Rob Svatek, MD, MSc**
- **Álvaro Padrón, PhD**
- **Curtis Clark, PhD**
- **Harshita Gupta, PhD**
- **Ryan Reyes**
- **Yilun Deng, PhD**
- **Suresh Kari, PhD**
- **Hailian Shen, PhD**

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**Larry Turka, Arlene
Sharpe**

Dartmouth

MJ Turk

Moffitt

José Conejo-Garcia

International

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FR), Kathrin Thedieck (U.
Groningen, Netherlands),
Sirpa Halonen (U. Turku,
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John Desjarlais Xencor
Jason Luke Univ.
Pittsburgh**

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OCRFA**

**Skinner endowment
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Center**

Clayton Foundation



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