Immunotherapy I:
Targeting Checkpoint, Co-Stimulatory and Novel Immunomodulatory MOAs

March 17-18, 2015
New York, NY

Immunotherapy I: Targeting Checkpoint, Co-Stimulatory and Novel Immunomodulatory MOAs

Moderator:

Jeff Bockman, PhD, VP, Defined Health

Panelists:

- *Ada Braun, MD, PhD,* Chief Medical Officer, Biothera
- *Axel Hoos, MD, PhD*, VP, Oncology Research and Development, GlaxoSmithKline
- *Johanna Joyce, PhD*, Member, Memorial Sloan Kettering Cancer Center
- *Hy Levitsky*, MD, Adjunct Professor, Oncology, Medicine and Urology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine
- *Nils Lonberg, PhD*, SVP, Biologics Discovery, Bristol-Myers Squibb
- *Harlan Robins, PhD,* Co-Founder and Chief Scientific Officer, Adaptive Biotechnologies
- *Jedd Wolchok, MD, PhD*, Ludwig Center at Memorial Sloan Kettering Cancer Center

This Space Is Hot, Really Hot…

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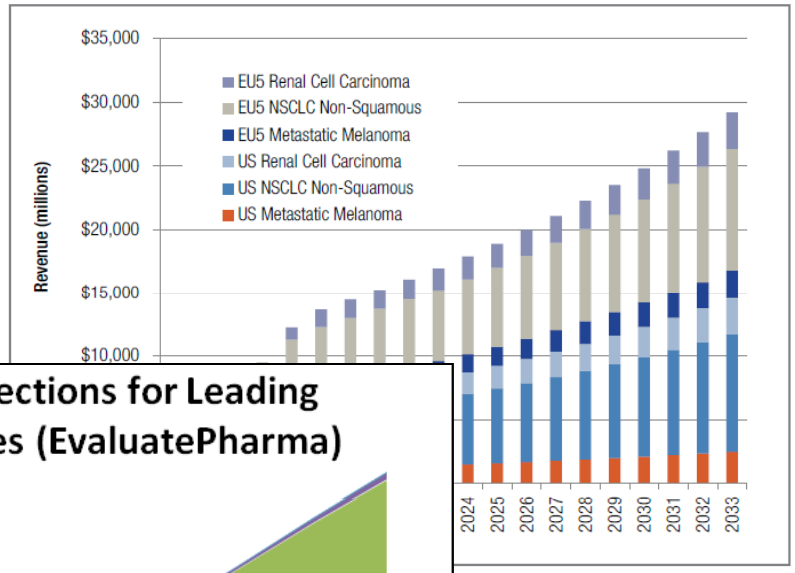
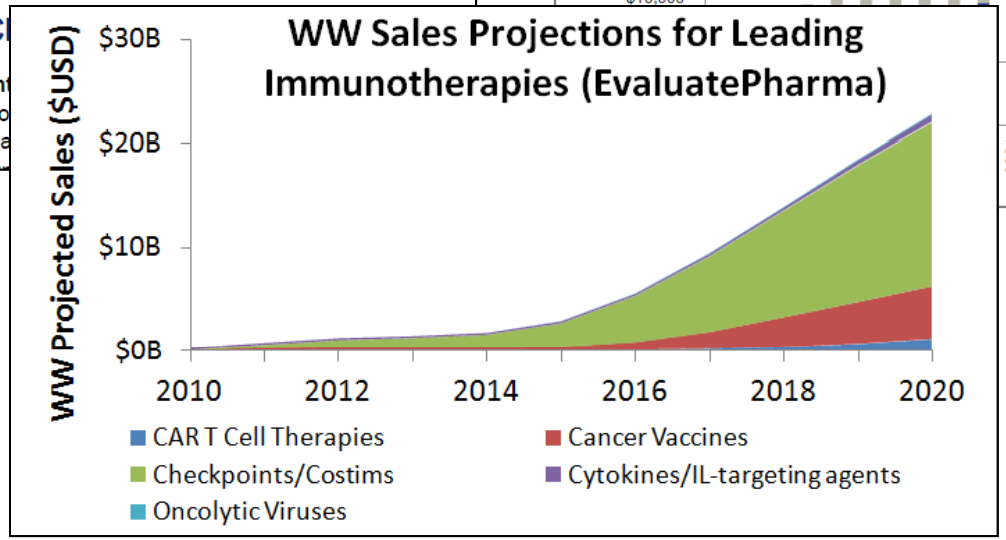
22 May 2013 | 52 pages

Immunotherapy – The Beginning of the End for Cancer.

Transforming Cancer into Cl

- Immunotherapies—$35bn potent
  backbone in up to 60% of cancers o
  The current explosion in all ongoing a





Citibank; Triangle Insights Group; EvaluatePharma

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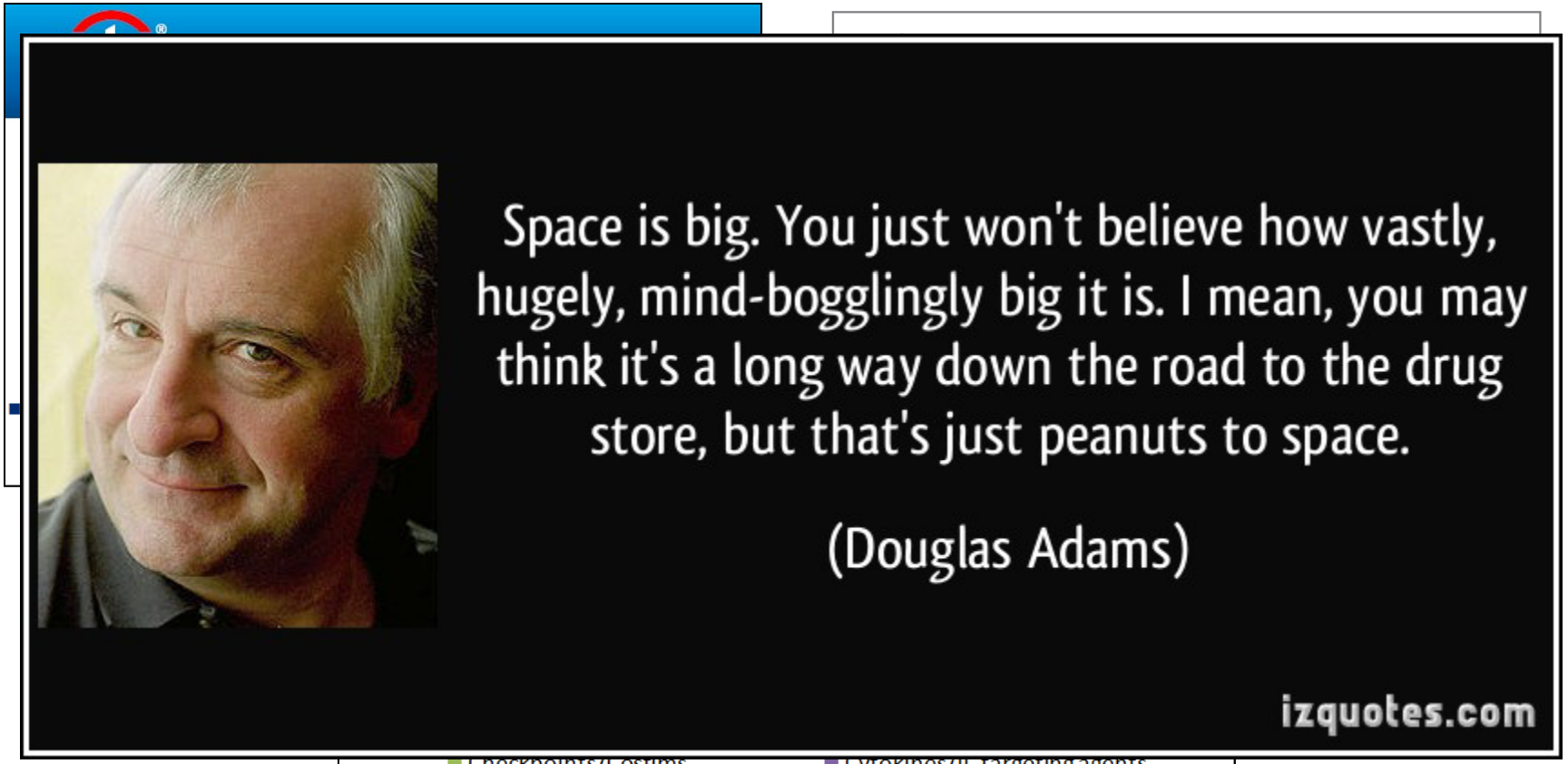

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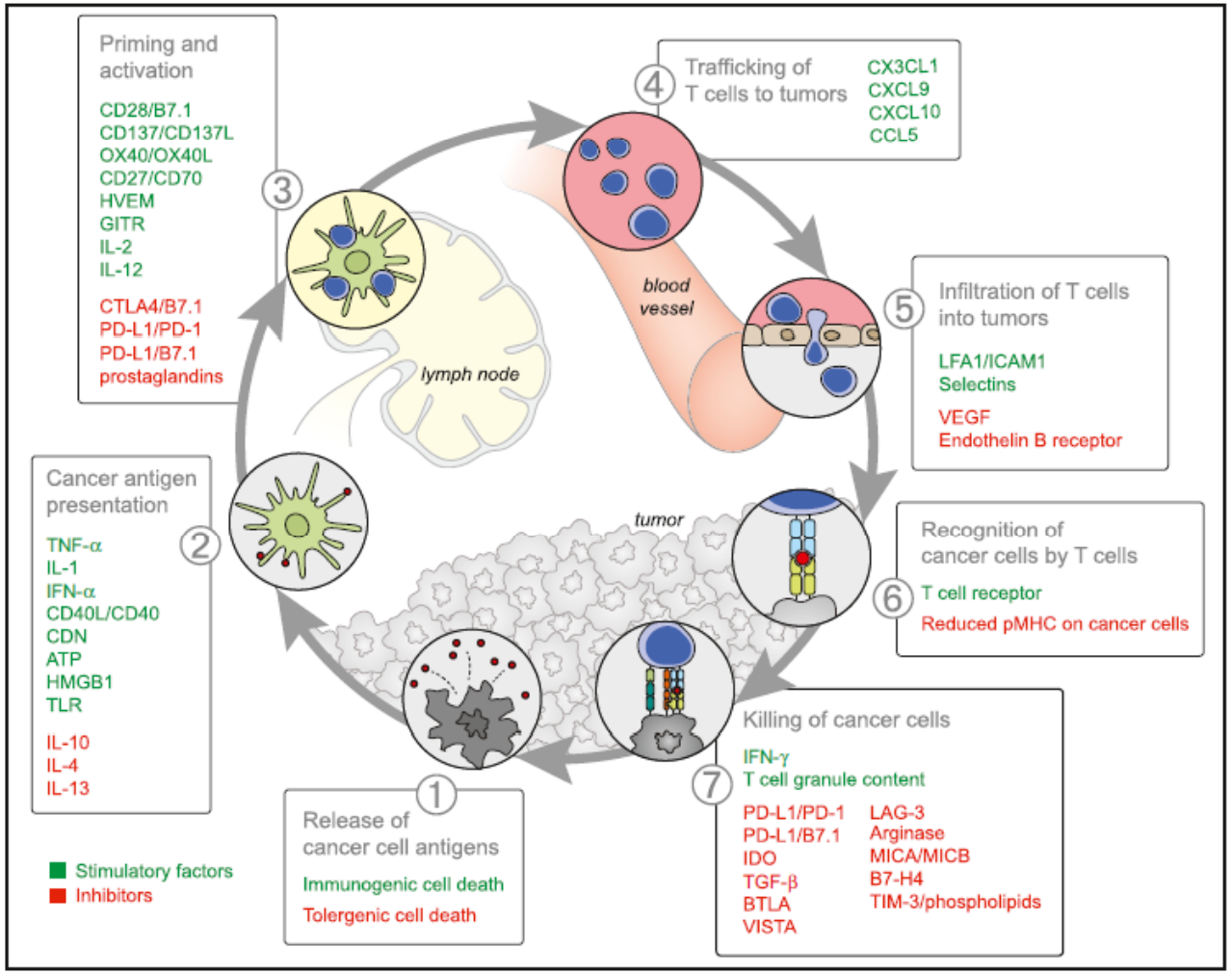
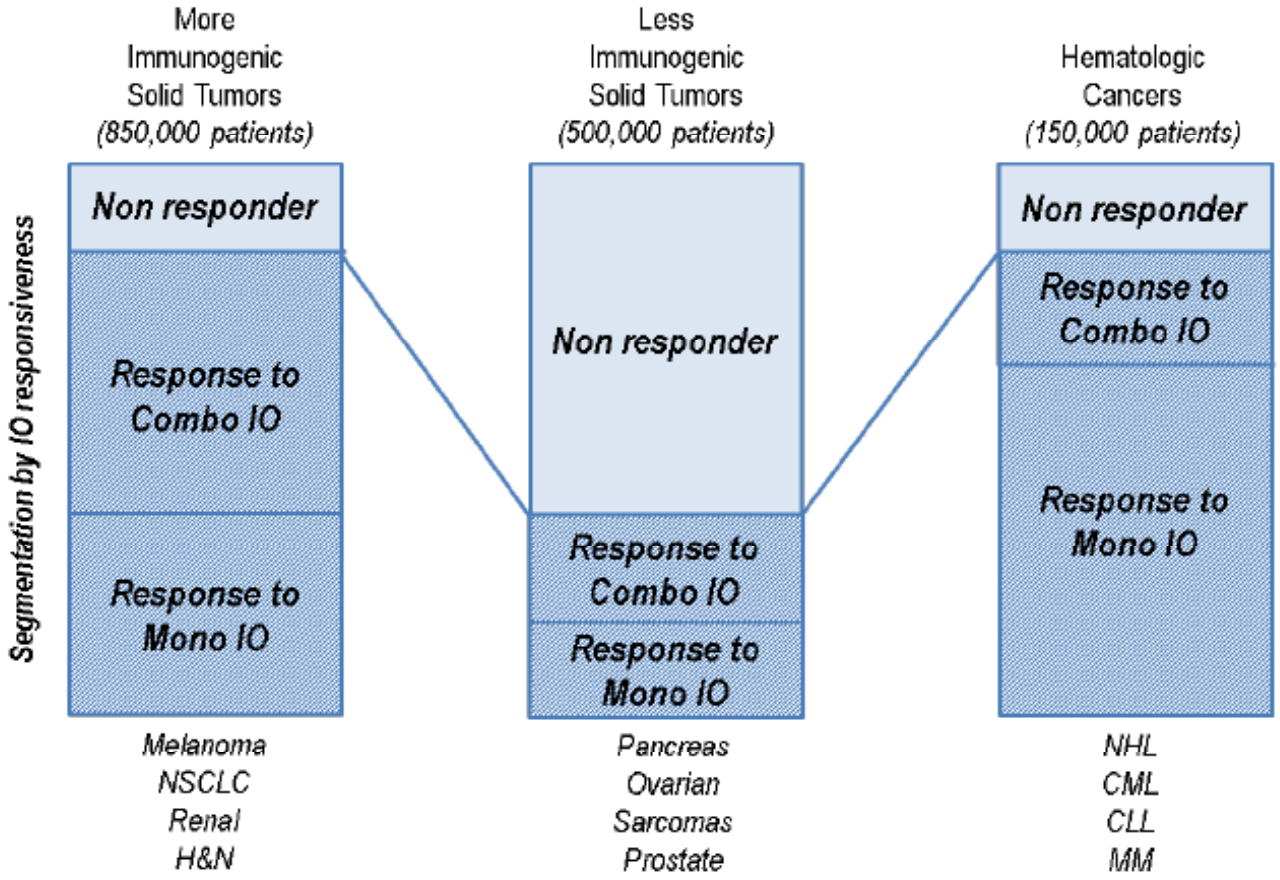
The Cancer Immunity Cycle Offers Multiple Points of Intervention



Abbreviations are as follows: IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; CDN, cyclic dinucleotide; ATP, adenosine triphosphate; HMGB1, high-mobility group protein B1; TLR, Toll-like receptor; HVEM, herpes virus entry mediator; GITR, glucocorticoid-induced TNFR family-related gene; CTLA4, cytotoxic T-lympocyte antigen-4; PD-L1, programmed death-ligand 1; CXCL/CCL, chemokine motif ligands; LFA1, lymphocyte function-associated antigen-1; ICAM1, intracellular adhesion molecule 1; VEGF, vascular endothelial growth factor; IDO, indoleamine 2,3-dioxygenase; TGF, transforming growth factor; BTLA, B- and T-lymphocyte attenuator; VISTA, V-domain Ig suppressor of T cell activation; LAG-3, lymphocyte-activation gene 3 protein; MIC, MHC class I polypeptide-related sequence protein; TIM-3, T cell immunoglobulin domain and mucin domain-3. Although not illustrated, it is important to note that intratumoral T regulatory cells, macrophages, and myeloid-derived suppressor cells are key sources of many of these inhibitory factors.

Immunity 39, July 25, 2013

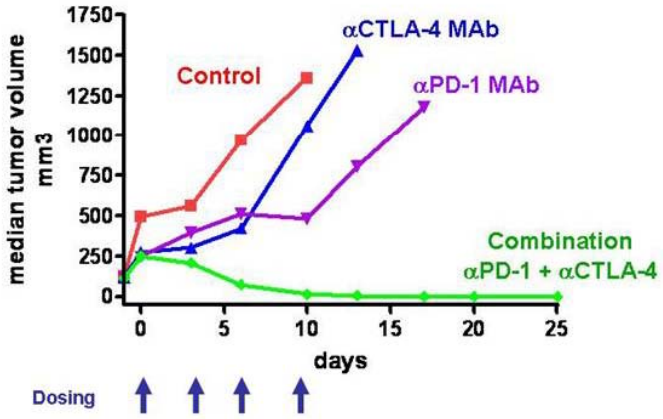
Expanding the Settings That Are Amenable to Immunotherapy…

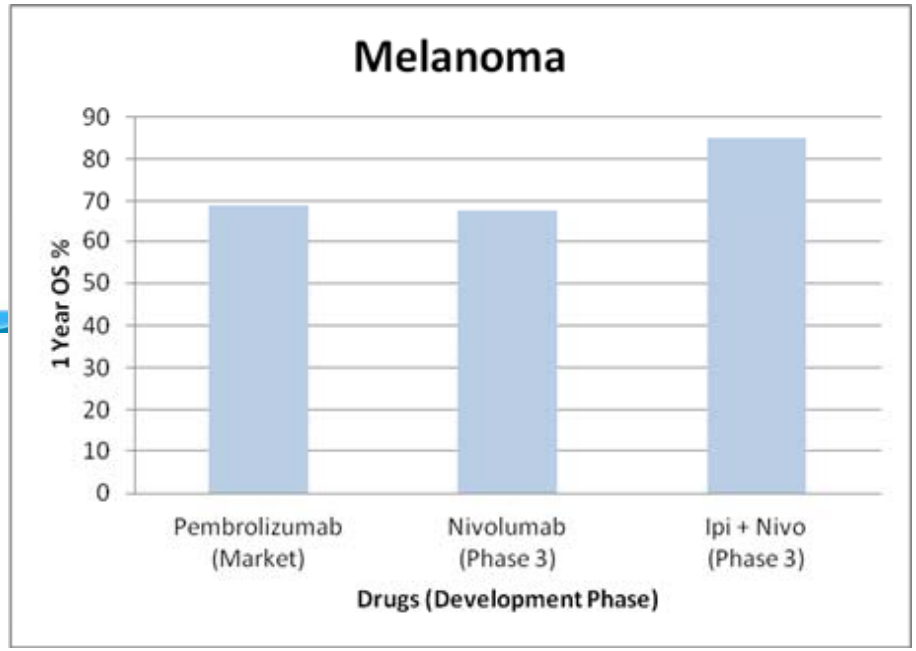


…By Combinations of Immuno-Oncology Agents & Every Other Possible Approach

Synergistic Activity with Anti-PD-1 and Anti-CTLA-4 Antibodies

Combination of Sub-Efficacious Doses of anti-PD1 and anti-CTLA-4 Antibodies is Efficacious in Mouse Model

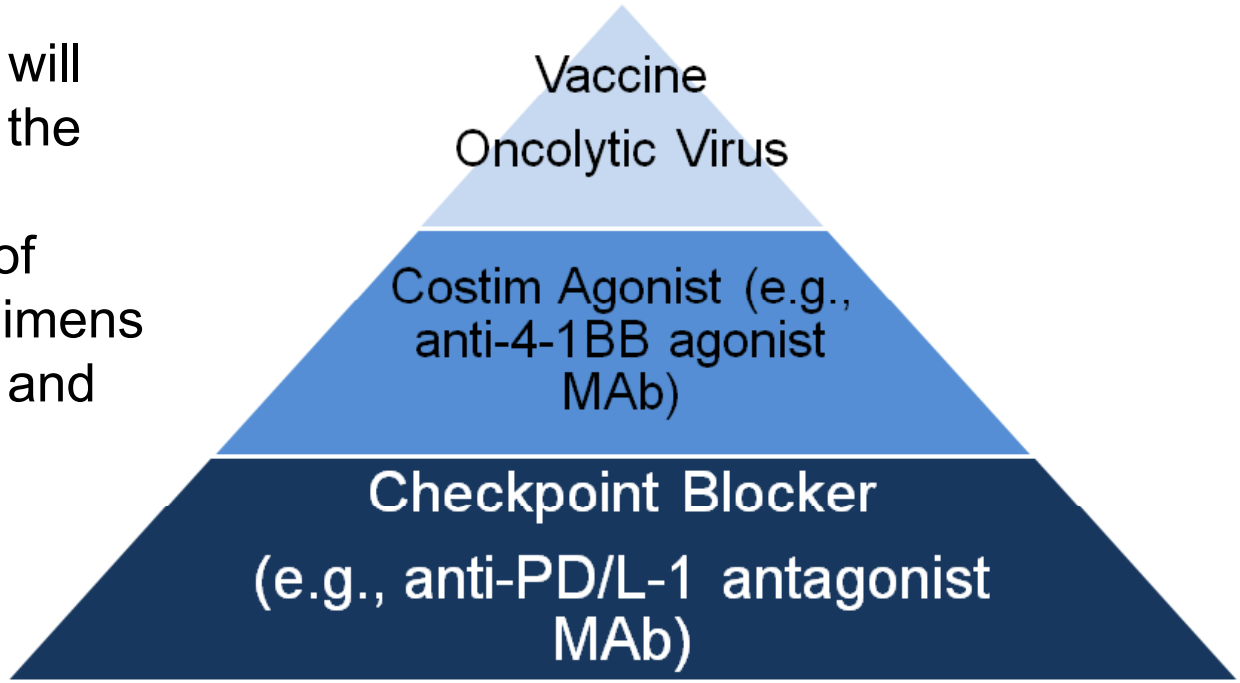




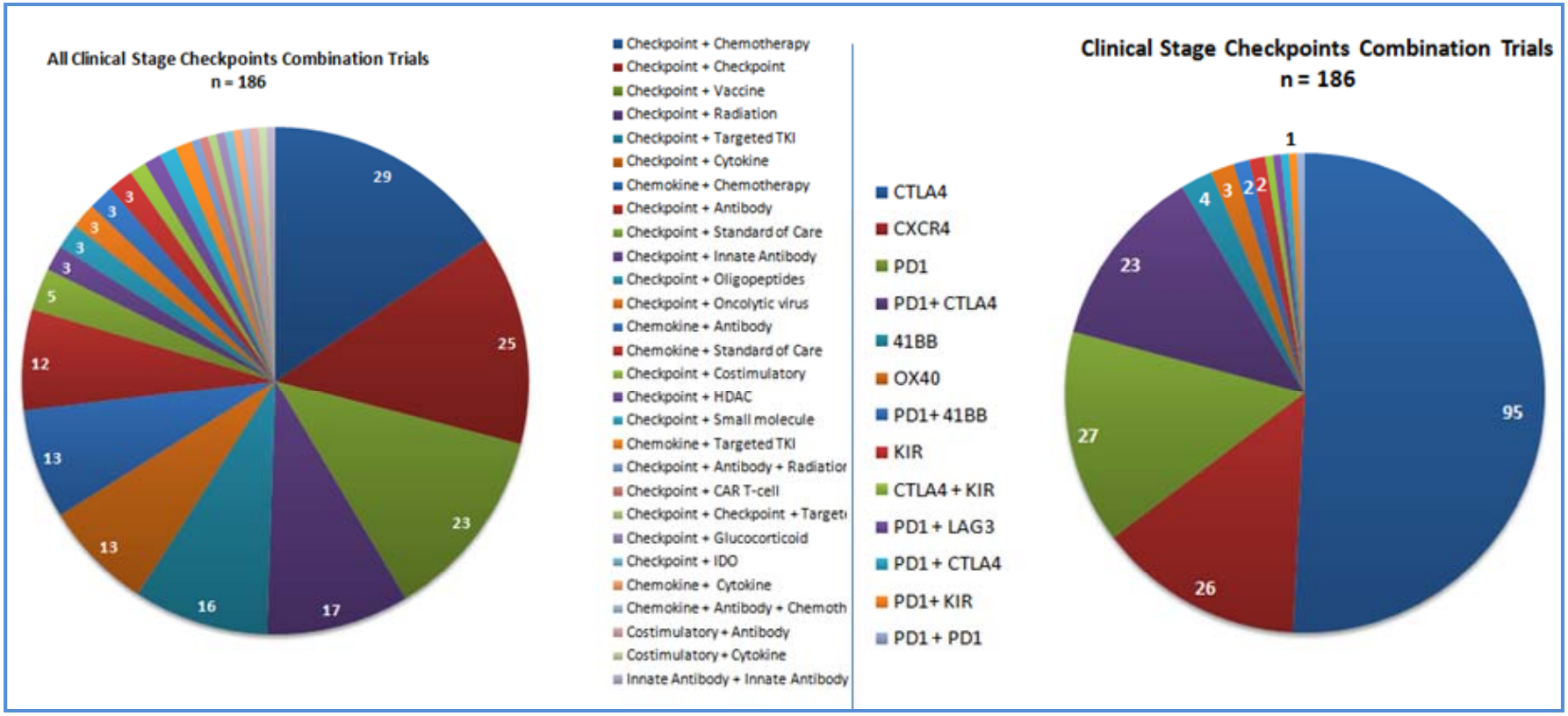
Medarex (JPMorgan 2007), Company data, Defined Health

Checkpoints Likely to Be Foundational

- Anti-PD/L-1 agents will be similar to that of the taxanes being the foundational piece of immunotherapy regimens across tumor types and lines of therapy.



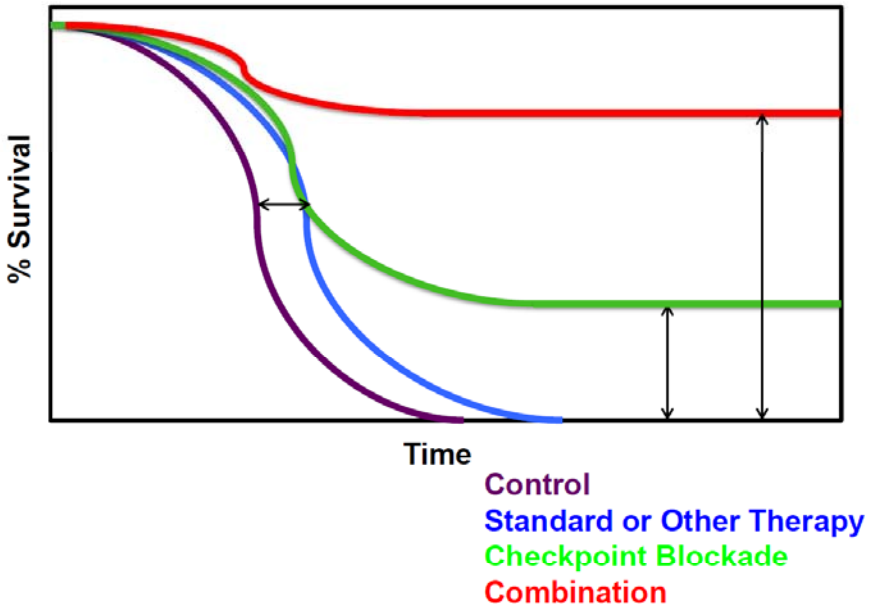
Combinations (& Permutations?)



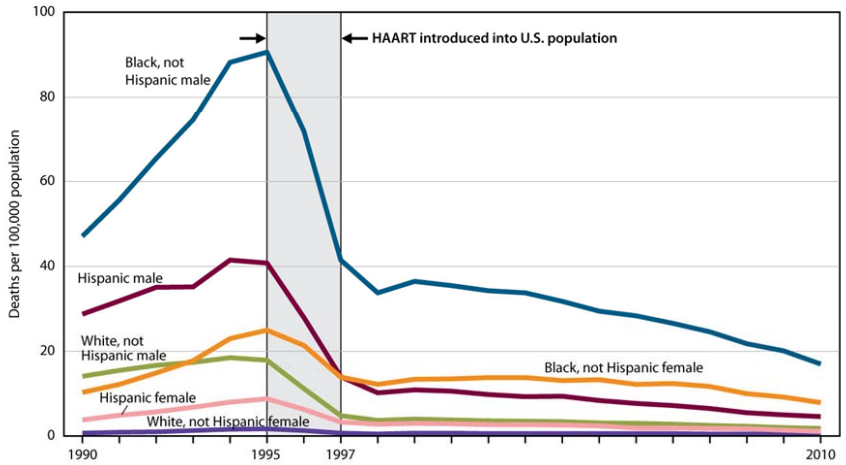
Clinicaltrials.gov, Defined Health

Cancer Progress Conference by Defined Health
March 4th – 5th, 2014, Conrad New York

Will We Be Able to Deflect the Growth Curve Enough to Effect a Functional Cure?



Death rates for HIV disease for all ages



NOTE: HAART is highly active antiretroviral therapy.
SOURCE: CDC/NCHS, Health, United States, 2013, Figure 24. Data from the National Vital Statistics System.

Drew Pardoll 2014; CDC Chartbook 2013 - http://www.cdc.gov/nchs/hus/chartbook.htm

2015 Deals (Industry-Industry Only)

Date	BMS	Originator	Platform/ Product	Phase	Terms
1/5/2015	Amgen	Kite	ACT: CART	Pre	Kite to Receive a $60 Million Upfront Payment From Amgen and Eligible for up to $525 Million in Regulatory and Sales Milestone Payments per Amgen Program; Plus, Tiered High Single- to Double-Digit Royalties for Sales and License of Kite's Intellectual Property for CAR T Cell Products Amgen Eligible to Receive up to $525 Million in Milestone Payments per Kite Program; Plus, Tiered Single-Digit Sales Royalties
1/9/2015	Incyte	Agenus	Checpints and costims: GITR, OX40, LA G-3 and TIM-3	Pre	Agenus to receive $60 million comprised of a $25 million technology and program access fee under the collaboration plus $35 million equity investment in Agenus at $4.51/share Agenus eligible to receive up to $350 million in development, regulatory and commercial milestones across the four lead programs
1/12/2015	MedImmune	Omnis	OV -Genetically engineered strain of VSV	I	ND
1/21/2015	Celgene	Zymeworks	Bispecific	Pre	Zymeworks will receive an initial upfront payment, as well as an equity investment from Celgene. Zymeworks is eligible to receive clinical, regulatory, and commercial milestones on successful candidates totaling up to US $164M per therapeutic candidate. Additionally, Zymeworks will receive royalties on worldwide net sales. Further financial details are not disclosed.
1/27/2015	Janssen	Macrogenics	Bispecific T-cell engager	Pre	MacroGenics will receive a $50 million upfront license fee and Johnson & Johnson Innovation - JJDC, Inc. has invested $75 million with the purchase of 1,923,077 new shares of MacroGenics common stock at a price of $39.00 per share. Janssen will be fully responsible for developing MGD011 following submission of the IND, which is planned for 2015. Assuming successful development and commercialization, MacroGenics could receive up to an additional $575 million in clinical, regulatory and commercialization milestone payments. MacroGenics may elect to fund a portion of late-stage clinical development in exchange for a profit share in the U.S. and Canada. If commercialized, MacroGenics would be eligible to receive double-digit royalties on any global net sales and has the option to co-promote the molecule with Janssen in the U.S.

EvaluatePharma, Defined Health

2015 Deals (Industry-Industry Only)

Date	BMS	Originator	Platform/ Product	Phase	Terms
2/11/2015	Incyte	Advaxis	Vaccine: ADXS-HPV	II	Advaxis and Incyte will collaborate on a non-exclusive basis to evaluate the combination of ADXS-HPV with IDO1 inhibitor for the treatment of cervical cancer. The companies will collaboratively conduct and fund the study, which is expected to begin later this year. Results from the study will be used to determine whether further clinical development of this combination is warranted. Further details of the agreement were not disclosed.
2/23/2015	BMS	Rigel	TGF-beta kinase inhibitors	Pre	Bristol-Myers Squibb will obtain exclusive, worldwide rights to develop and commercialize small molecule therapeutics derived from Rigel's TGF beta library, including, but not limited to, those approved to treat cancer. Bristol-Myers Squibb will pay $30 million upfront and Rigel will be eligible to receive development and regulatory milestones that could total more than $309 million for a successful compound approved in multiple indications. Rigel will also be eligible to receive tiered royalties on the net sales of any products from the collaboration.
2/23/2015	BMS	Flexus	IDO1 inhibitors	Pre	$800 million upfront to gain control of a preclinical IDO1 immunotherapy that shows promise in treating cancer, buying out San Carlos, CA-based Flexus with another $450 million set aside for milestones.
3/4/2015	BMS	Bavarian Nordic	Vaccine: Prostvac		Up to $975 million: $80 million upon exercise of the option plus additional incremental payments starting at $50 million, but with a potential to exceed $230 million should the median overall survival benefit of PROSTVAC exceed the efficacy seen in Phase 2 results. Furthermore, Bavarian Nordic could receive regulatory milestone payments of $110 million, up to $495 million in sales milestones as well as tiered double-digit royalties on future sales of PROSTVAC.

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Immunotherapy I: Targeting Checkpoint, Co-Stimulatory and Novel Immunomodulatory MOAs

- Unique drug development challenges of IO
- Role of biomarkers, surrogates
- What endpoints function in a time frame to capture earliest possible signal?
- How to do in dynamic manner, monitor real-time?
- What is the level of evidence for combinations--what, when, where, in whom?
- Importance of neoantigens, how to discover?
- Endogenous anti tumor response, innate immunity and how to exploit to improve adaptive responses
- Role of SOC with IO such as chemo?
- Beyond checkpoints-next wave including costims, vaccines, oncolytic virus, bispecifics and ACT (separate panel)
- New targets especially countering immunosuppressive microenvironment
- What is the level of evidence for new targets?
- How to differentiate, even new targets--what endpoints, benchmarks? QoL?