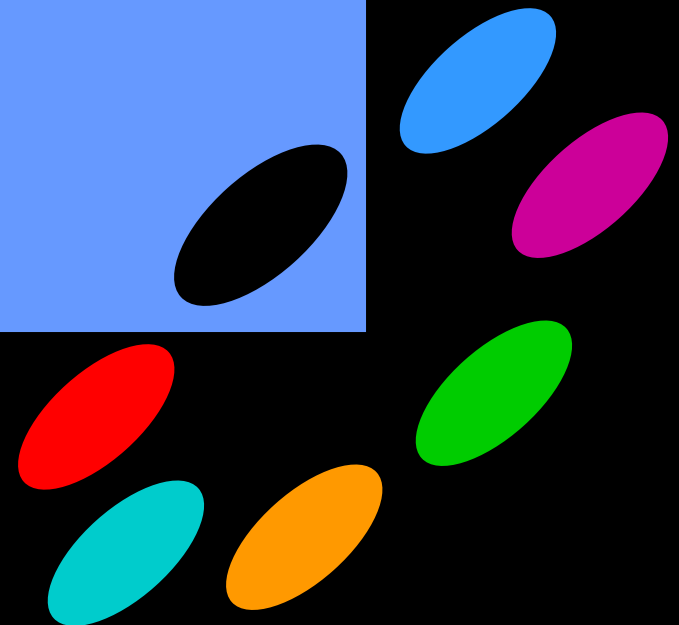


The Future of Immuno-Oncology: Perspectives from Academia and Industry

September 19, 2014

DefinedHealth
unconventional insight




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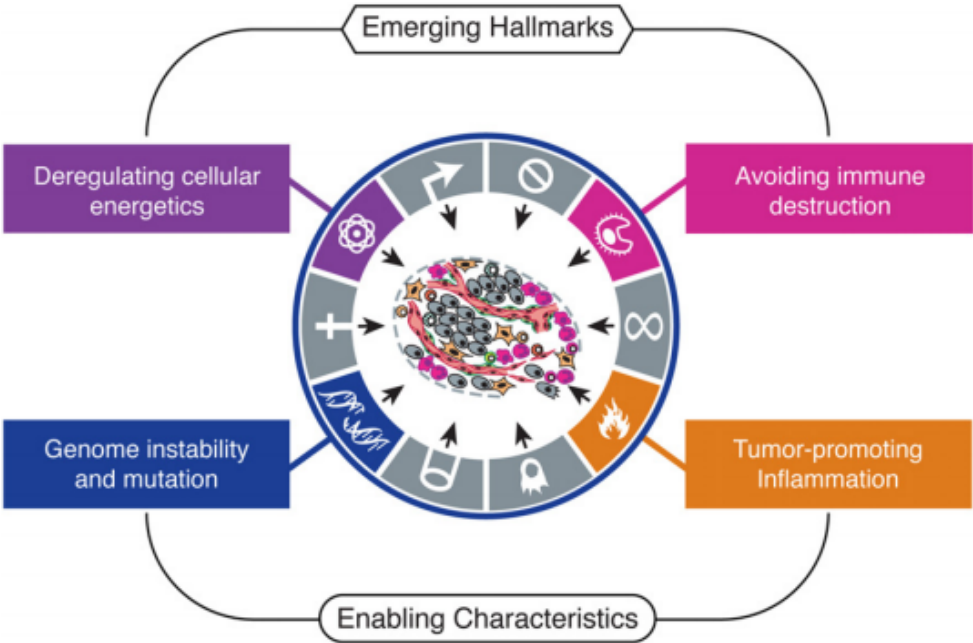
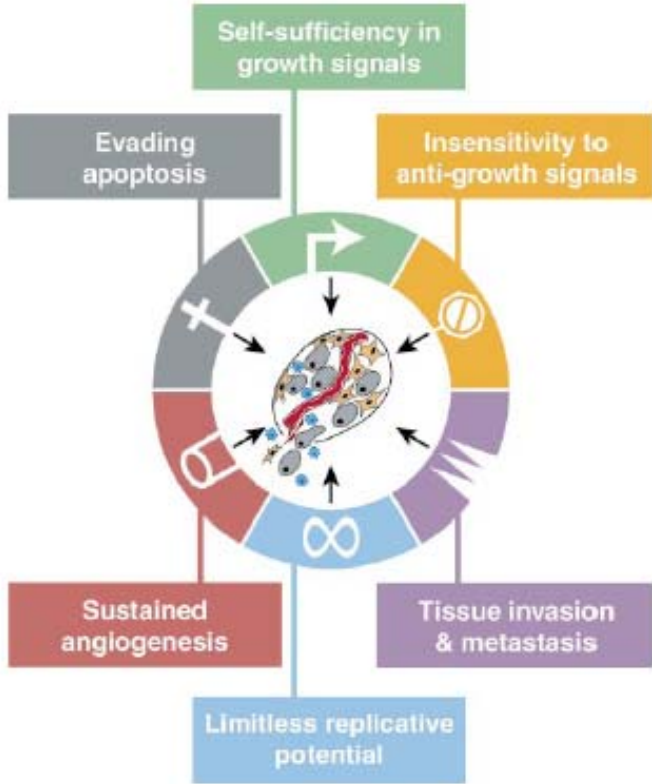
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Our Distinguished Panelists

- **Axel Hoos, Vice President of Oncology Research and Development at GSK**
- **Drew Pardoll, Abeloff Professorship of Oncology and Director of Cancer Immunology at Johns Hopkins University**
- **Moderated by Jeffrey M. Bockman, PhD, Vice President, Defined Health**

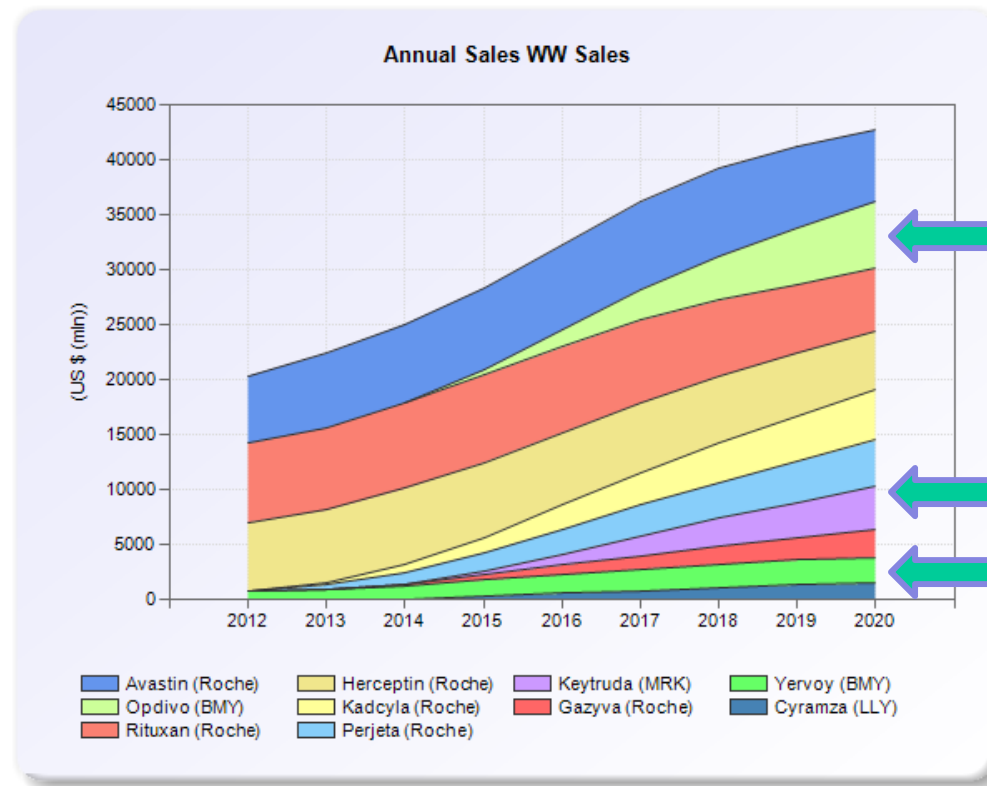
Because Cancers Under-Cut a Key Defense of the Host, Tumor Immunology Has Been a Longstanding Focus of Research



Cell, Vol. 100, 57–70, January 7, 2000; *Cell*, Vol.144, 646-674, March 4, 2011

The Commercial Market for Immuno-Oncology Products is Projected to Grow Significantly – Though How Quickly and by How Much is Not Clear

- Roughly 30% of the nearly \$43B in worldwide sales coming from the top 10 antibodies in oncology in 2020 will come from anti-PD1 and anti-CTLA4.¹
- A recent Citi report forecasts that in ten years, immunotherapy drugs of various sorts will be treating 60% of cancers and earning US\$35 billion per year.²

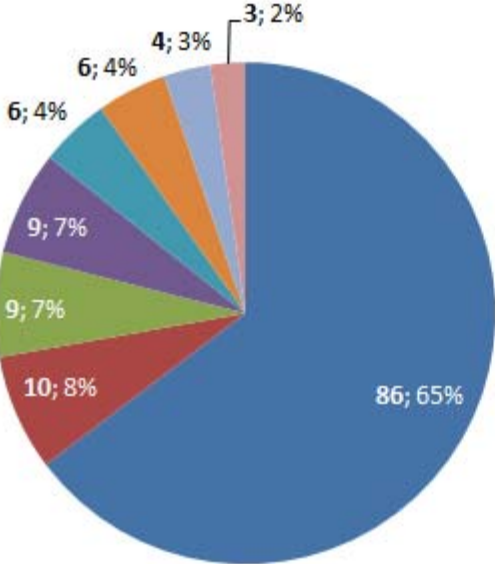


¹Evaluate Pharma; ²Nature 497, 544 (30 May 2013); Defined Health

The Field Has a Diversity of Platforms Currently in Mid-to-Late Stage Clinical Development

Comparison of Late-Stage Immuno-Oncology Products in Development (Phase II through Registration)

Products by Category



Phase	# of Drugs
Cancer vaccine	86
Antibody	10
Cytokine	9
Cell-therapy	9
Other	6
Gene therapy	6
Oncolytic virus	4
Small molecule	3

- Cancer vaccine
- Antibody
- Cytokine
- Cell-therapies
- Other
- Gene therapy
- Oncolytic virus
- Small molecule

Adis R&D Insight

Major Oncology Players Have Staked Out Their Positions, Primarily in Checkpoint and Costimulatory Antibodies and Adoptive Cell Therapies

Categories of major immunotherapeutic intervention include methods to increase the frequency of tumor antigen-specific effector T cells in the circulation, strategies to block or uncouple a range of immune suppressive mechanisms within the tumor microenvironment, and tactics to induce de novo immune inflammation within the tumor microenvironment.

	BMY	ROG	AZN	MRK	GSK	PFE	NOVN	LLY	MRCG	AMGN	CELG
Checkpoint blockers											
CTLA4	✓		✓			✓					
PD1	✓		✓	✓	✓						
PD-L1	✓	✓	✓						✓		
LAG-3	✓										
KIR	✓										
CSF1R		✓									
Checkpoint costimulators											
CD137	✓					✓					
CD40		✓				✓					
OX40			✓								
TGFβ								✓			
Chemokine Blockers											
	✓	✓		✓		✓					
Cell therapy											
							✓				✓
Therapeutic Vaccines											
		✓			✓				✓		

Citi, 14 February 2014, *Immunotherapy - The Beginning of the End for Cancer*

Principles for Combining Different Types of Immunotherapies With Each Other and Standard of Care

- The range of combinations are quite daunting and, as noted by KOLs, very difficult to gauge from preclinical data; therefore, to **increase optionality and reduce risk**, players must make multiple bets across the diverse range of platforms and approaches.

	(I) Increase of T-cell frequencies in circulation	(II) Blocking immune-inhibitory pathways within the tumor microenvironment				(III) De novo induction of immune inflammation in tumor site
		Inhibitory Molecules	Metabolic Dysregulation	Suppressive Cell Types	T-cell Anergy	
BLOCKING	αCTLA-4	PD-1/PDL-1 intervention αB7-H3 αB7-H4	IDO inhibitors Arginase inhibitors	CD25-dependant Treg depletion Depletion of MDSC	αLAG3 αTIM3 EGR2 inhibitors	Blocking inhibitory oncogene pathways (e.g., STAT 3) Blockade of MDSC function or depletion
ENGAGING	αCD28 Homeostatic cytokines Vaccines IL-2 therapy	N/A	N/A	TLR-mediated activation of MDSC	α4-1BB αOX40 Homeostatic cytokines	Induction of type I interferons TLR agonists Radiation TNF-like molecules (e.g., LIGHT)

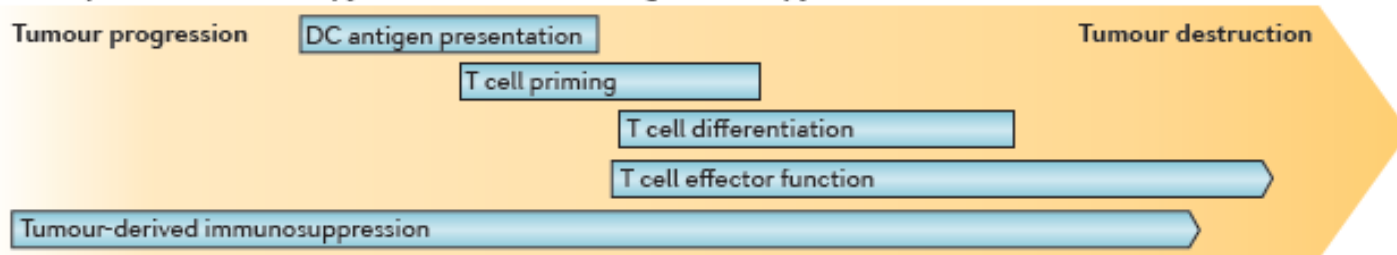
Figure 4 Categories of potential immunotherapeutic interventions for cancer and opportunities for combinations.

Journal for ImmunoTherapy of Cancer 2013, 1:16

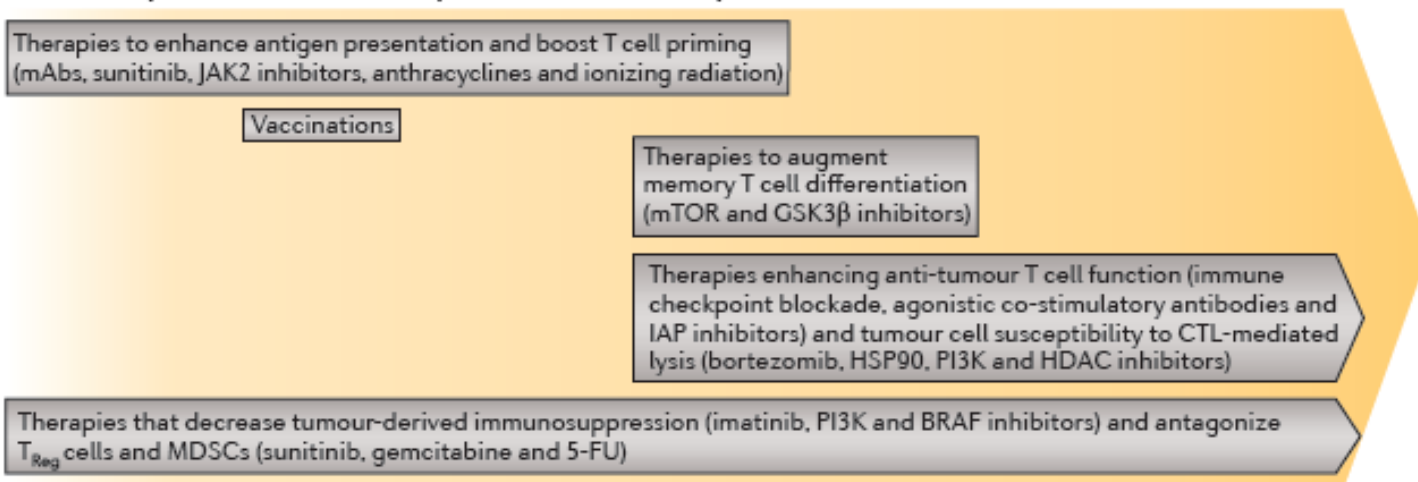
Principles of Combination with “Targeted” Therapies

- There are also many opportunities for franchise plays in combining immunotherapies with targeted therapies and other modalities.

a Principles of immunotherapy in combination with targeted therapy



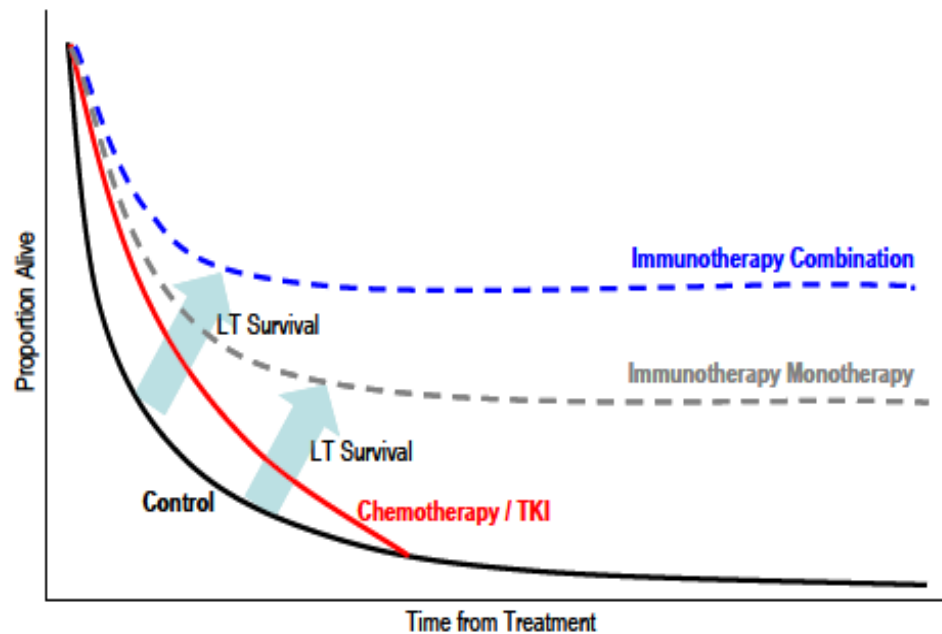
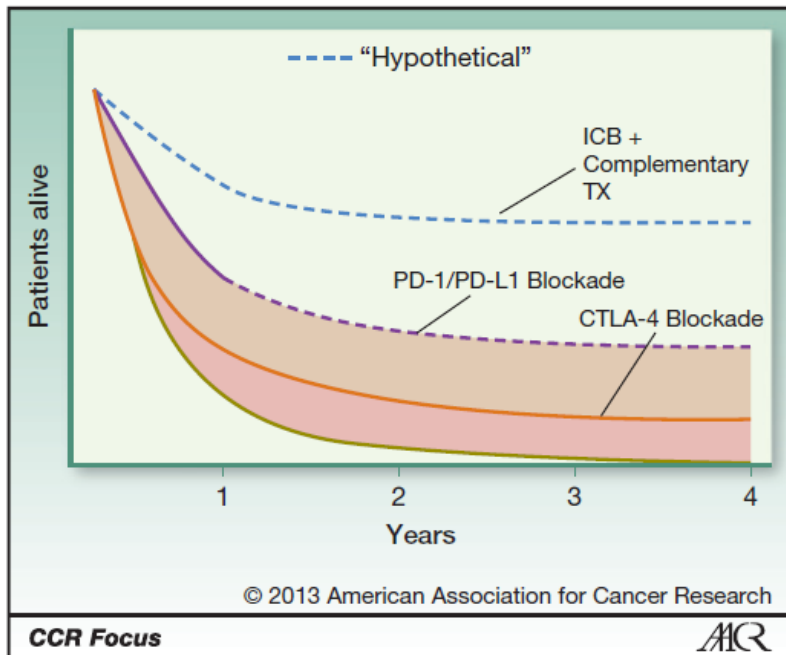
b Potential timing parameters of specific targeted therapies with the potential to enhance responses to immunotherapies



Nat Rev Cancer. 2012 Mar 22;12(4):237-5

The Potential of Immunotherapy, in Combination, and on Top of Standard of Care Regimens, to Shift Survival Towards Chronic Disease, or Even Cure

- Really for the first time, oncologists are talking about potentials for significant advances in survival, and even cures, using immunotherapies.



Clin Cancer Res 2013;19:5300-5309; Citi, 14 February 2014, *Immunotherapy - The Beginning of the End for Cancer*

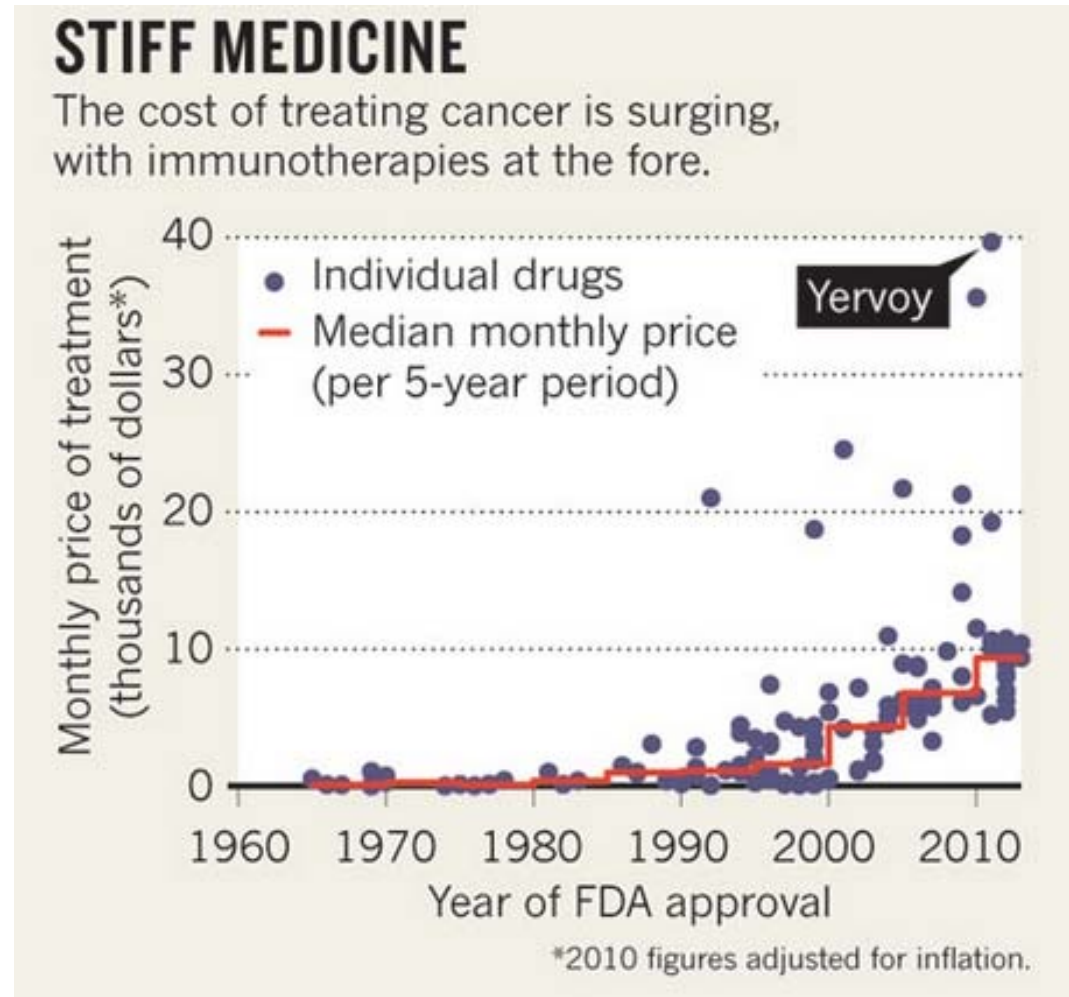
Seven of the Top 14 Deals Were Oncology – Five of These Were Immuno-Oncology...Plus Yesterday's (9/18) Deal

Buyer	Seller	Size (US \$ M)	Upfront (US \$M)	Subject	Stage	Primary Rx Area
Pfizer	Collectis	\$2,855	\$80	Allogeneic CAR-T immunotherapies with 15 Pfizer and 4 Collectis targets	Discovery	Cancer
Celgene	Giuliani/Nogra	\$2,575	\$710	GED-0301 oral oligonucleotide vs SMAD-7 for Crohn's disease and other gastrointestinal indications	Phase II complete	AI/Inflam
Merck	Ablynx	\$2,341	\$27	Nanobody technology to discover nanobody-based immunotherapies	Discovery	Cancer
Merck	Bayer	\$2,100	\$1,000	Adempas, BAY102 and other soluble guanylate cyclase (sGC) modulators for cardiovascular diseases	Approved	CV
Viking Therapeutics	Ligand	\$1,564	\$29M in Viking equity upon IPO	FBPase, SARM, TR-Beta, EPOR, DGAT-1 programs for type 2 diabetes, cancer cachexia, dyslipidemia, obesity	Phase II	Endo/Meta
BMS	CytomX	\$1,242	\$50	Probodyes against up to 4 immuno-oncology targets including CTLA-4	Discovery	Cancer
Biogen Idec	Eisai	\$1,100	\$100	E2609 BACE inhibitor and BAN2401 anti-Aβ ab for Alzheimers + option for 2 additional BIIB Alz ab	Phase II	Neurology
Novartis	Ophthotech	\$1,030	\$200	Fovista anti-PDGF for wet AMD worldwide ex-US	Phase III	Ophthalmic
Servier	Collectis	\$850	\$10	Option to UCART19 for leukemia + 5 CAR-Ts to undisclosed solid tumor targets	Preclinical	Cancer
Merck KGaA / EMD Serono	Mersana	\$792	CON	Fleximer technology to develop ADCs for multiple undisclosed targets	Not applicable (Technology)	Cancer
BMS	Five Prime	\$650	\$20M + \$21M equity	Discovery of targets in 2 undisc. immune checkpoint pathways to develop immune-oncology therapies	Discovery	Cancer
Regeneron	Avalanche	\$640	\$2M + \$5M preferred stock	8 gene therapies for ophthalmologic diseases	Phase II	Ophthalmic
Roche	Oryzon	\$521	CON	ORY-1001 small molecule inhibitor of LSD1 epigenetic modulator for AML + option to additional programs	Phase II	Cancer
Takeda	MacroGenics	\$502	\$15	MGD010 bi-specific DART vs. CD32B and CD79B	Preclinical	AI/Inflam
Boehringer Ingelheim	CureVac	\$556M	\$45M	CV9202 is a combination of mRNA molecules coding for six antigens overexpressed in lung cancer, designed to induce an immune response against the tumor.	Phase I	Cancer



As With Other Areas of Oncology, Combination Therapies Pose Additional Hurdles for Demonstrating Value – the Pharmacoeconomics of Pricing

- The challenges of developing and pricing immunotherapies are substantive.
- Such challenges are underscored by the scientific and clinical difficulty of showing synergy and acceptable tolerability.
- This may explain in part the number of clinical trial collaborations rather than strict licensing deals that are occurring.



Nature 497, 544 (30 May 2013); Peter Bach, Center for Health Policy & Outcomes, MSKCC, <http://www.mskcc.org/research/health-policy-outcomes>



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Featured Keynotes:

Peter Bach, MD, Memorial Sloan-Kettering Cancer Center

Clifford A. Hudis, MD, Memorial Sloan Kettering Cancer Center, 2013-2014
President, ASCO

Michael Kolodziej, MD, Aetna

Lee Newcomer, MD, MHA, United Healthcare

Lynda Chin, MD, MD Anderson Cancer Center



Our Featured Panelists

Peter C. Adamson, MD, The Children's Hospital of Philadelphia
Rafael Amado, MD, GlaxoSmithKline
Jeff Bockman, PhD, Defined Health
Renier J. Brentjens, MD, PhD, Memorial Sloan Kettering Cancer Center
Meredith K. Chuk, MD, FDA
Robert Cohen, MD, Calico Life Sciences
Barbara A. Conley, MD, National Institute of Health
Heather Cooper-Ortner, Dr. Susan Love Research Foundation
Lou DeGennaro, PhD, Leukemia & Lymphoma Society
Thomas O. Daniel, MD, Celgene Corporation
Kathleen A. Denis, PhD, The Rockefeller University
Kapil Dhingra, MD, KAPital Consulting LLC
James H. Doroshow, MD, National Cancer Institute
Thomas J. Farrell, Bellicum Pharmaceuticals
Stanley R. Frankel, MD, Amgen
Richard Brian Gaynor, MD, Eli Lilly and Company
Brad Gray, NanoStrings Technologies
William Grossman, MD, PhD, AbbVie
Ivan Horak, MD, Symphogen A/S
Axel Hoos, MD, PhD, GlaxoSmithKline
Johanna Joyce, PhD, Memorial Sloan Kettering Cancer Center
Thomas J. Kipps, MD, PhD, Moores UCSD Cancer Center
Michael Kolodziej, MD, Aetna
Amy Krie, MD, Avera Cancer Institute
Manfred Lehnert, MD, Takeda Pharmaceuticals International
Christoph Lengauer, MD, PhD, Blueprint Medicines
Ross Levine, MD, Memorial Sloan Kettering Cancer Center
Hy Levitsky, MD, Roche Pharmaceuticals
Brian Leyland-Jones, MD, Avera Cancer Institute

Nils Lonberg, PhD, Bristol-Myers Squibb
Patricia LoRusso, D.O., Smilow Cancer Center, Yale University
Susan Love, MD, Dr. Susan Love Research Foundation
Franziska Michor, PhD, Harvard School of Public Health
Ronnie Morris, MD, Champions Oncology
Larry Norton, MD, Memorial Sloan Kettering Cancer Center
Mike Rice, MS, MBA, Defined Health
Dr. Harlan Robins, PhD, Adaptive Biotechnologies
Carlos Rodriguez-Galindo, MD, Harvard Medical School
Noemi Rosa, MD, PhD, GlaxoSmithKline
Neal Rosen, MD, PhD, Memorial Sloan Kettering Cancer Center
Raphaël F. Rousseau, MD, PhD, Genentech Inc.
Eric Rowinsky, MD, Stemline Therapeutics
Rob Ruijtenbeek, PamGene BV
Prof. Dolores J. Schendel, PhD, Medigene
Jeffrey Settleman, PhD, Genetech
Angela Shen, MD, MBA, Novartis Pharmaceuticals Corp.
Ellen V. Sigal, PhD, Friends of Cancer Research
Mark J. Simon, Torrey Partners LLC
Eric Slosberg, PhD, Novartis Oncology
Malcolm A. Smith, MD, PhD, National Cancer Institute
John J. Sninsky, PhD, Quest Diagnostics
David Solit, MD, Memorial Sloan Kettering Cancer Center
Chris H. Takimoto, MD, PhD, Janssen Research & Development
Marc Theoret, MD, FDA
Alain Thibault, MD, arGEN-X N.V.
Jedd Wolchok, MD, PhD, Memorial Sloan-Kettering Cancer Center
Cassian Yee MD, MD Anderson Cancer Center

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