Optimizing Cancer Immunotherapy: Combining and Sequencing Antibodies, Antigens and Cell Based Modalities

August 23, 2012, Defined Health Insight Briefing - Webinar

Jeffrey M. Bockman, PhD – Vice President, Defined Health

Joel Sandler, PhD – Consultant, Defined Health

Defined Health is pleased to present…

March 5 – 6, 2013 | **Conrad New York**
www.cancerprogressbyDH.com

BioEurope Spring | **March 11 – 13, 2013**
Barcelona, Spain
www.therapeuticinsight.com

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ICAAC | September 9 - 12, 2012 | San Francisco
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IDSA | October 17 - 21, 2012 | San Diego
US Japan Health Sciences Dialogue 2012 | November 27 - 28, 2012 | Philadelphia
ASH | December 8-11, 2012 | Atlanta

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24th ANNUAL CANCER PROGRESS CONFERENCE

"The Premier Cancer Conference for Healthcare Executives"

March 5th - 6th, 2013
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THERAPEUTIC INSIGHT

Cancer Progress, in its 24th year, has an outstanding reputation as the premier annual oncology conference that affords a unique dialogue between experts in the cancer field. Scientific and clinical opinion leaders and industry executives offer valuable insights and candid assessments of key issues impacting oncology research, development and commercialization.

Cancer Progress fosters direct interactions between top cancer researchers, leading clinical investigators and senior executives from the pharmaceutical, biotechnology, payer and investment arenas. Pivotal topics, frank discussions, vigorous debate, lively audience participation and generous networking combine to make this a highly impactful conference. We invite you to join us in New York City on March 5-6th, 2013 for the 24th Annual Cancer Progress Conference, where continuing progress on the cancer front is the focus of an important dialogue among stakeholders in research and development, industry, public and private finance and government.

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THERAPEUTIC INSIGHT

Topics include:

- Translational Oncology
- Cancer Metabolism
- Diagnosis with Next Generation Sequencing
- Chemoprevention
- Cancer Stem Cells
- Leukemia
- Epigenetics
- Growing a Cancer-Focused Biotech
- Pharmacoeconomics of Cancer
- Next Generation Biologics

2013 Keynote Speakers:

- Giulio Draetta, PhD, MD, MD Anderson Cancer Center
- Sir Michael Rawlins, MD, NICE

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Panelists to date include:

- J. Carl Barrett, PhD, AstraZeneca
- Stephen B. Baylin, MD, The Johns Hopkins University
- Scott Biller, PhD, Agios Pharmaceuticals
- Jeff Bockman, PhD, Defined Health
- Robert Cohen, Genentech
- George Q. Daley, MD, PhD, Dana-Farber Cancer Institute
- Keith E. Dionne, PhD, Constellation Pharmaceuticals
- Kirsten Drejer, PhD, Symphogen A/S
- Hans-Peter Gerber, PhD, Pfizer
- Jeremy Goldberg, JPG Healthcare LLC
- Robert J. Gould, PhD, Epizyme
- John Haurum, MD, f-Star Biotech
- Colin Hill, GNS Healthcare
- Gary Kelloff, MD, National Cancer Institute
- John M. Lambert, Ph.D, ImmunoGen, Inc.
- Patrick J. Mahaffy, Clovis Oncology
- Tak Mak, PhD, Ontario Cancer Institute; University of Toronto
- James S.J. Manuso, PhD, Astex Pharmaceuticals, Inc.
- Michael Morrissey, PhD, Exelixis, Inc.
- Perry Nisen, MD, PhD, GlaxoSmithKline
- Takashi Owa, PhD, Eisai
- Greg Plowman, MD, PhD, ImClone Systems
- Michael B. Sporn, MD, Dartmouth Medical School
- Chris H. Takimoko, MD, PhD, Janssen, Pharmaceutical
- Christoph Westphal, MD, PhD, Verastem, Inc.
- Christian Zahnd, PhD, Molecular Partners AG

The information in this report has been obtained from what are believed to be reliable sources and has been verified whenever possible. Nevertheless, we cannot guarantee the information contained herein as to accuracy or completeness. All expressions of opinion are the responsibility of Defined Health, and though current as of the date of this report, are subject to change.

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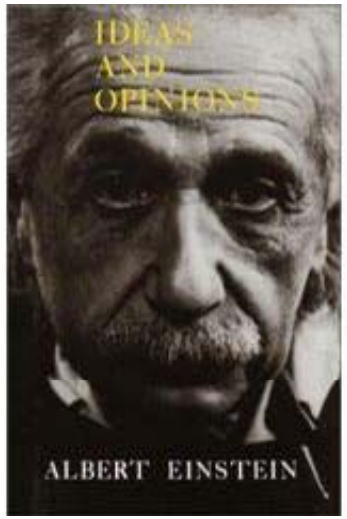
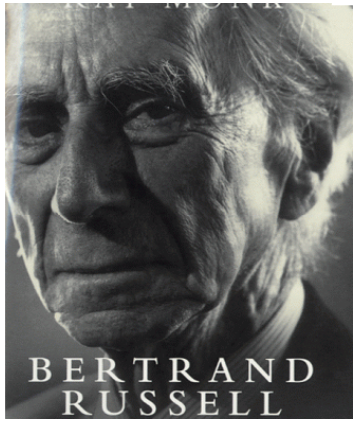
"Things should be made as simple as possible, but not simpler."



"The point of philosophy is to start with something so simple as not to seem worth stating, and to end with something so paradoxical that no one will believe it".



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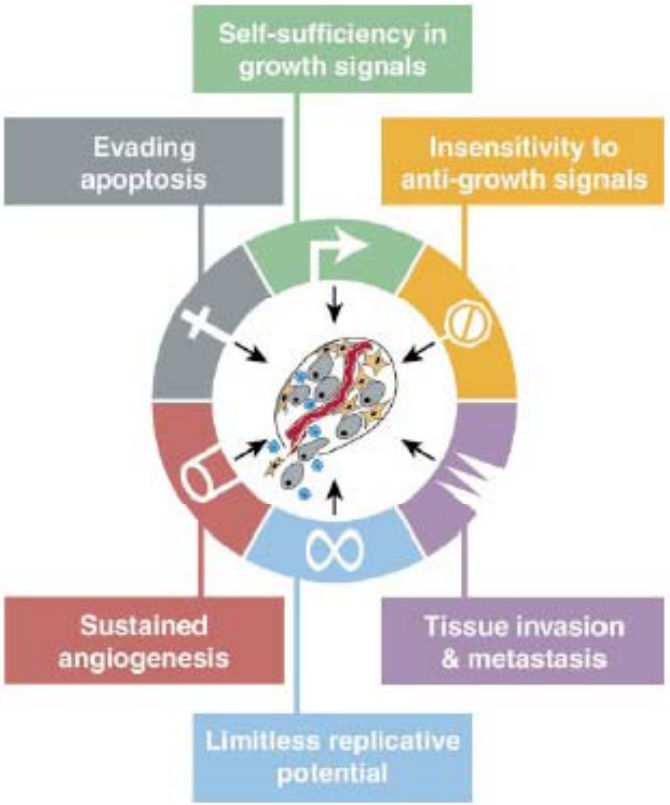
Discriminating Self From Non-Self

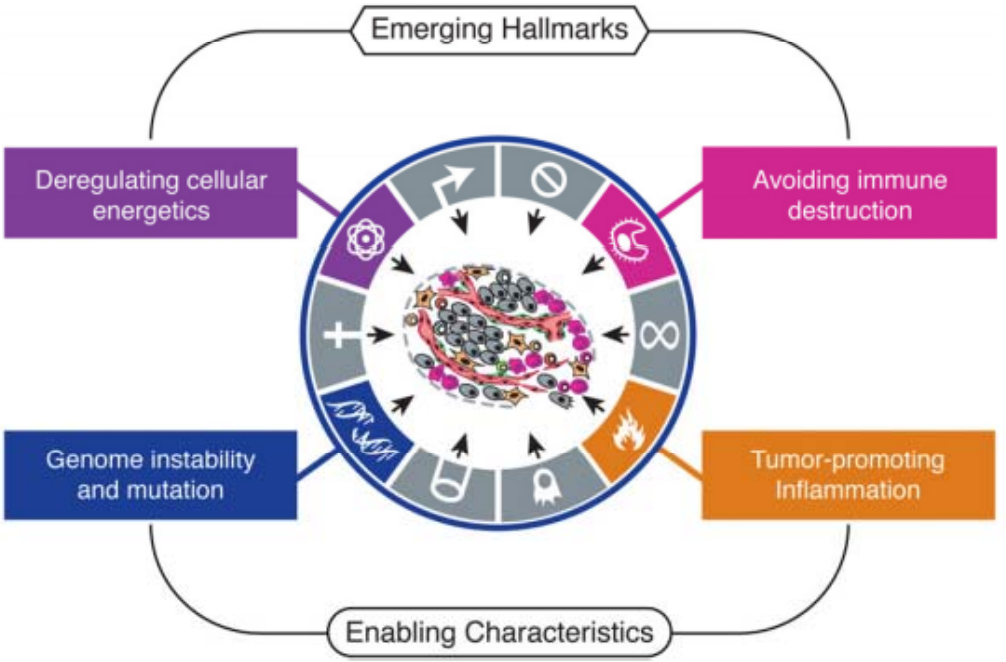
Peter Doherty (1940 -) and Rolf Zinkernagel (1944 -)

Introduction

Hallmarks of Cancer – A Decade of Learning



Cell, Vol. 100, 57–70, January 7, 2000,



Cell, Vol.144, 646-674, March 4, 2011

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Hitting Multiple Targets – We've Known This, But Have Yet to Fully Exploit the Knowledge

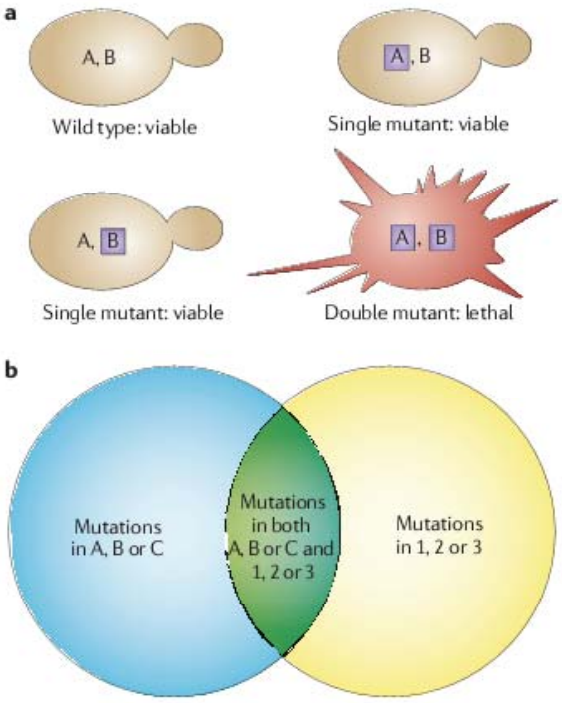
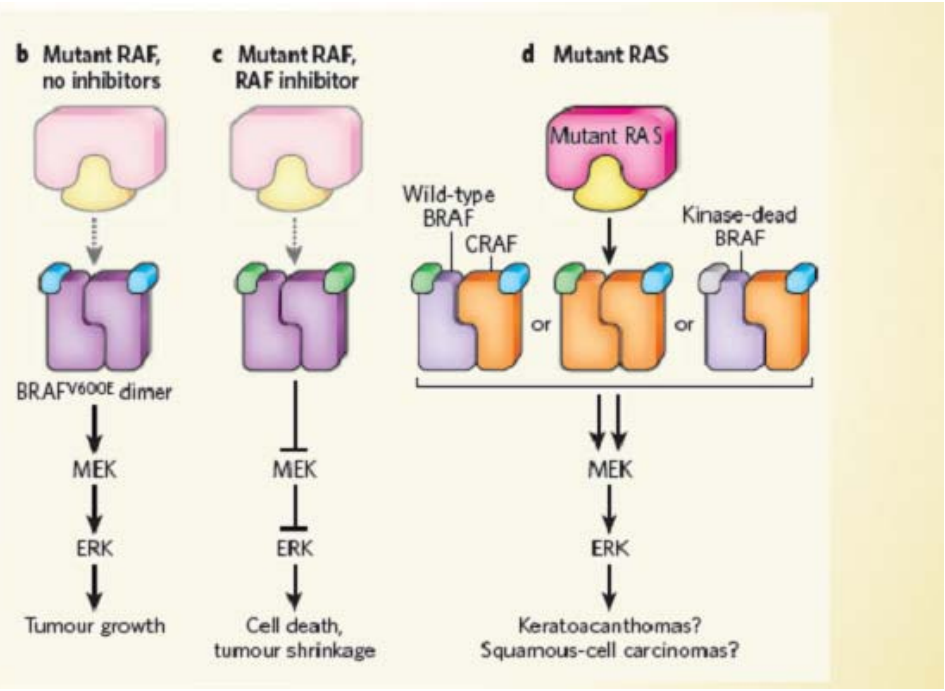


Figure 1 | **Synthetic lethality. a** | Organismal view. In model organisms, synthetic lethality describes the genetic interaction between two genes. If either gene is mutated by itself, the organism remains viable. The combination of a mutation in both genes is incompatible with viability and results in lethality. **b** | Pathway view. Two genes are considered to be synthetic lethal when they contribute to an essential process. For example, when either gene 'A', 'B' or 'C', or gene '1', '2' or '3' is mutated, the organism or cell remains viable. However, the combination of these mutations ('A', 'B' or 'C' with '1', '2' or '3') results in death.



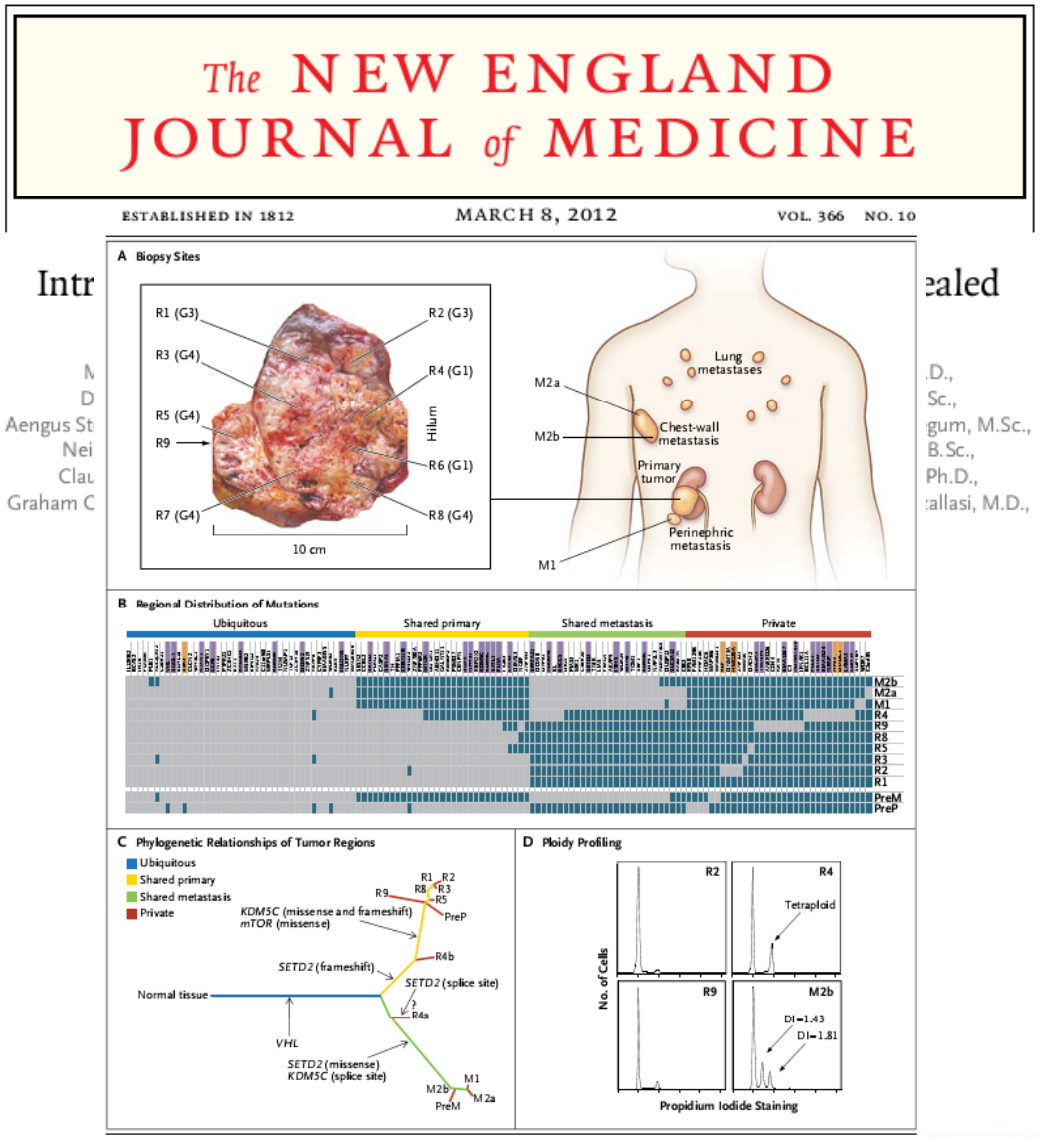
GSK Announces Submissions in the EU and US for Dabrafenib and Trametinib

GlaxoSmithKline (GSK) plc today announced regulatory submissions in the European Union and United States (US) related to single-agent use of its BRAF inhibitor dabrafenib and MEK inhibitor trametinib to treat patients with BRAF V600 mutation positive metastatic melanoma. (PhamaLive, Aug 3, 2012)

Nature Reviews Drug Discovery 10, 351-364 (May 2011); FierceMarkets Webinar, June 12, 2012 – Getting the most PoC data in Phase I cancer studies – Jamie Freedman, MD, PhD, VP Cancer Research, GSK

Challenges of Conventional Targeted Therapy

- Intra-tumor heterogeneity can lead to underestimation of the tumor genomics landscape portrayed from single tumor-biopsy samples and may present major challenges to personalized-medicine and biomarker development. Intra-tumor heterogeneity, associated with heterogeneous protein function, may foster tumor adaptation and therapeutic failure through Darwinian selection.



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And Yet Why Do We Keep Hitting the Same Targets…Again, and Again, and Again?

- I could cite myself in several previous Insight Briefings, but I will defer to Bruce Booth's timely *Forbes* blog from this year's ASCO: 8 targets are addressed by >20% of pipeline projects, each of which has more than 24 projects in clinical development

Forbes

Bruce Booth, Contributor
Early stage life science VC
+ Follow (76)

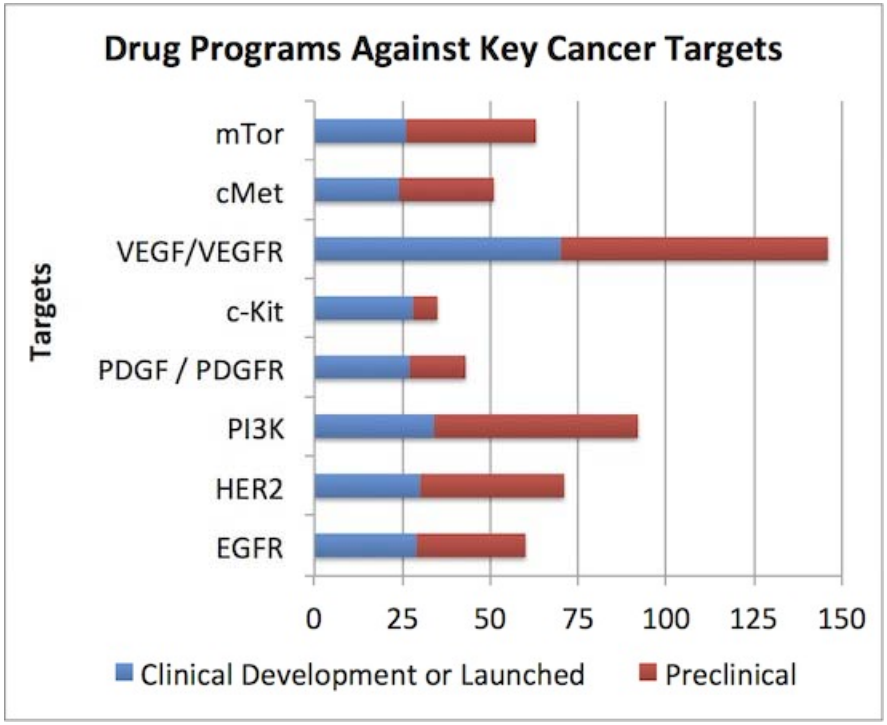
PHARMA & HEALTHCARE | 6/07/2012 @ 4:11PM | 6,457 views

Cancer Drug Targets: The March of the Lemmings

4 comments, 1 called-out + Comment now

Just in time for the annual ASCO cancer circus, PhRMA released a new report listing the nearly 1000 projects in the industry's pipeline for oncology – it's an impressively long list against a whole range of cancers. And this should be celebrated: we're working on big problems and throwing lots of drug candidates, time, and money after solving them.

But the lemming behavior revealed by this list is frightening: a significant percentage of these programs are chasing the same targets.

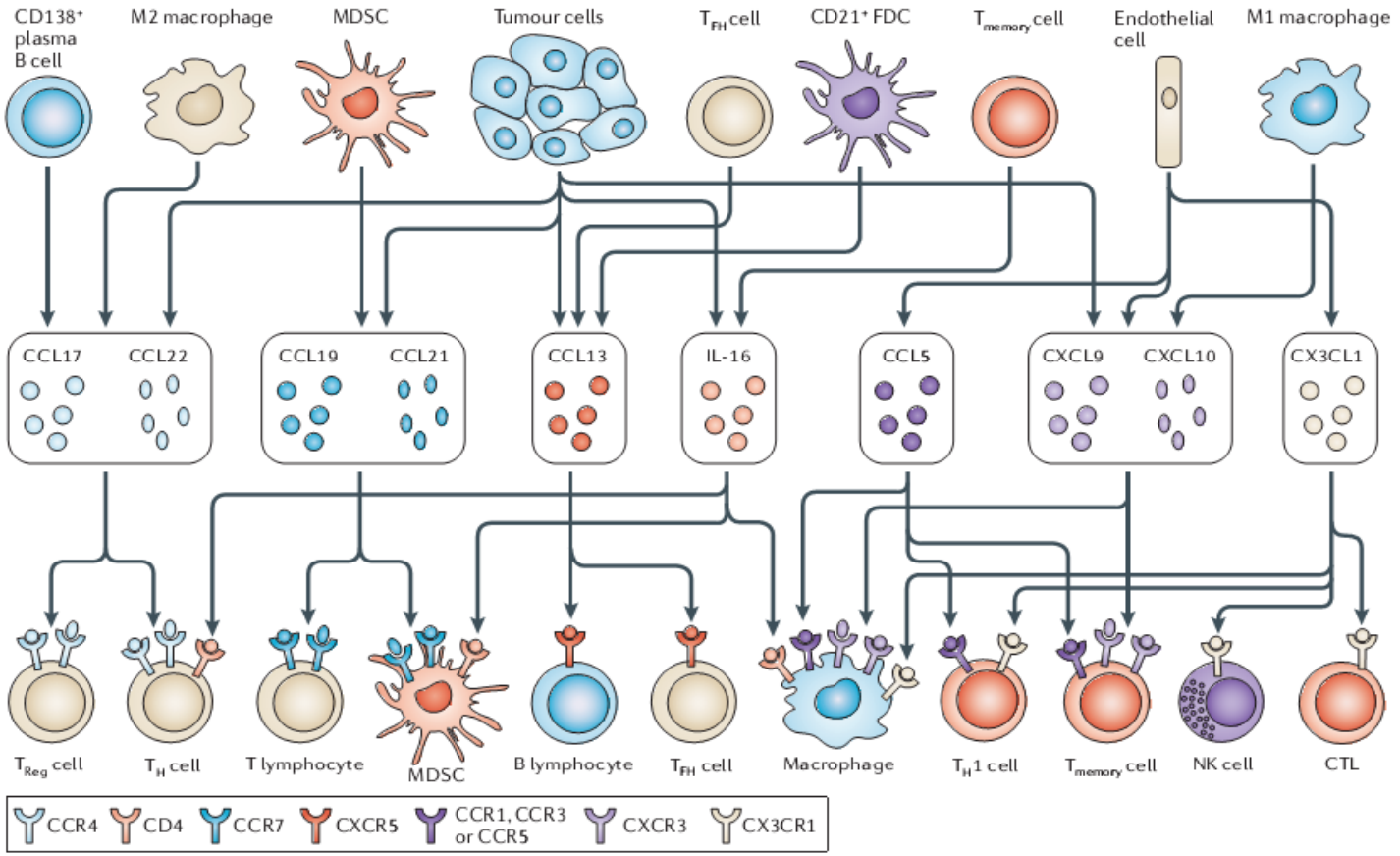


Forbes, Pharma & Healthcare 6/07/2012 (using Thomson Pipeline)

When We Have So Many Exciting New Targets, Especially for Immunotherapy

- "Water, water, every where,
  Nor any drop to drink." --Coleridge, *Rime of the Ancient Mariner*

Cells and chemokines that coordinate the tumor micro-environment



Nat Rev Cancer 12, 298-306 , April 2012

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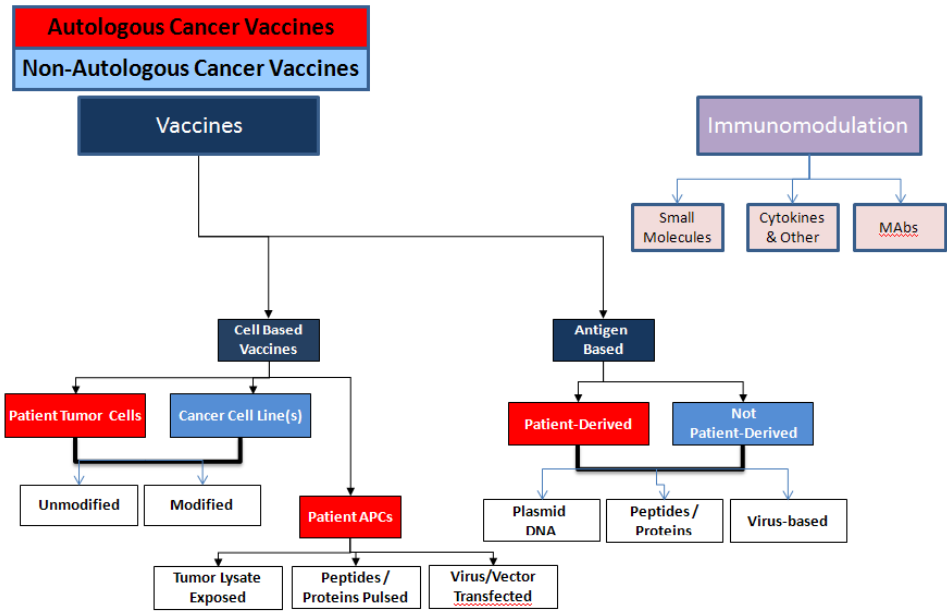
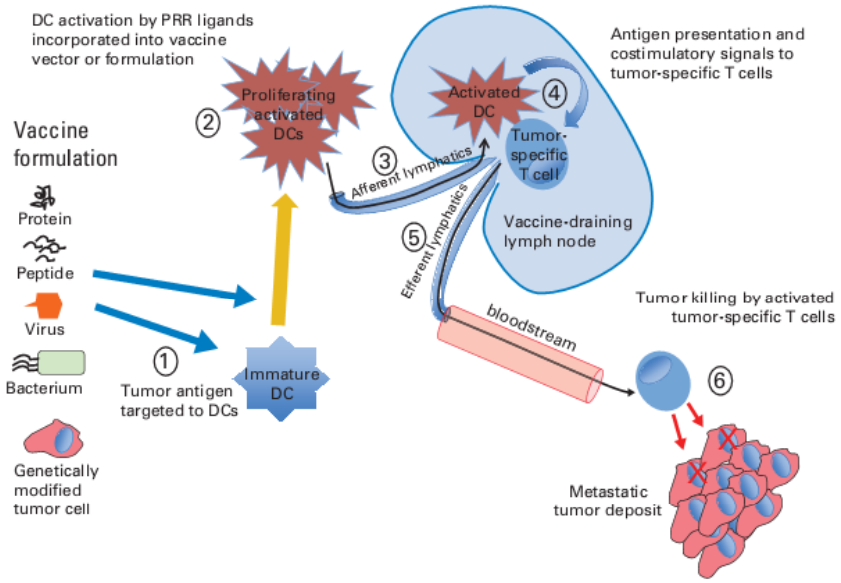
Diverse Options for Combinations with SOC, and Combinations with Each Other

- Cancer immunotherapy consists of a diverse range of therapeutic approaches, directed at harnessing the both the tremendous specificity and diversity of the **adaptive immune system** (T cells and antibodies) and **innate immunity**. Immunotherapeutic approaches **include antitumor monoclonal antibodies**, **cancer vaccines**, **adoptive transfer of ex vivo activated DCs, T-cells and NK cells**, and **immune checkpoint targets** where administration of antibodies or recombinant proteins either co-stimulate immune cells or block immune inhibitory pathways.
- **Combination approaches of two or more of the above** to suppress tumor-derived inhibitors of immune response, to activate co-stimulatory signals, to engage both adaptive (cellular and humoral sides) and innate arms of the immune system by providing antigen, APC signals, etc., are all viable approaches in theory – notwithstanding logistical, regulatory and cost considerations!



Source: Defined Health



Source: *J Clin Oncol* 29:4828-4836, Dec 2011

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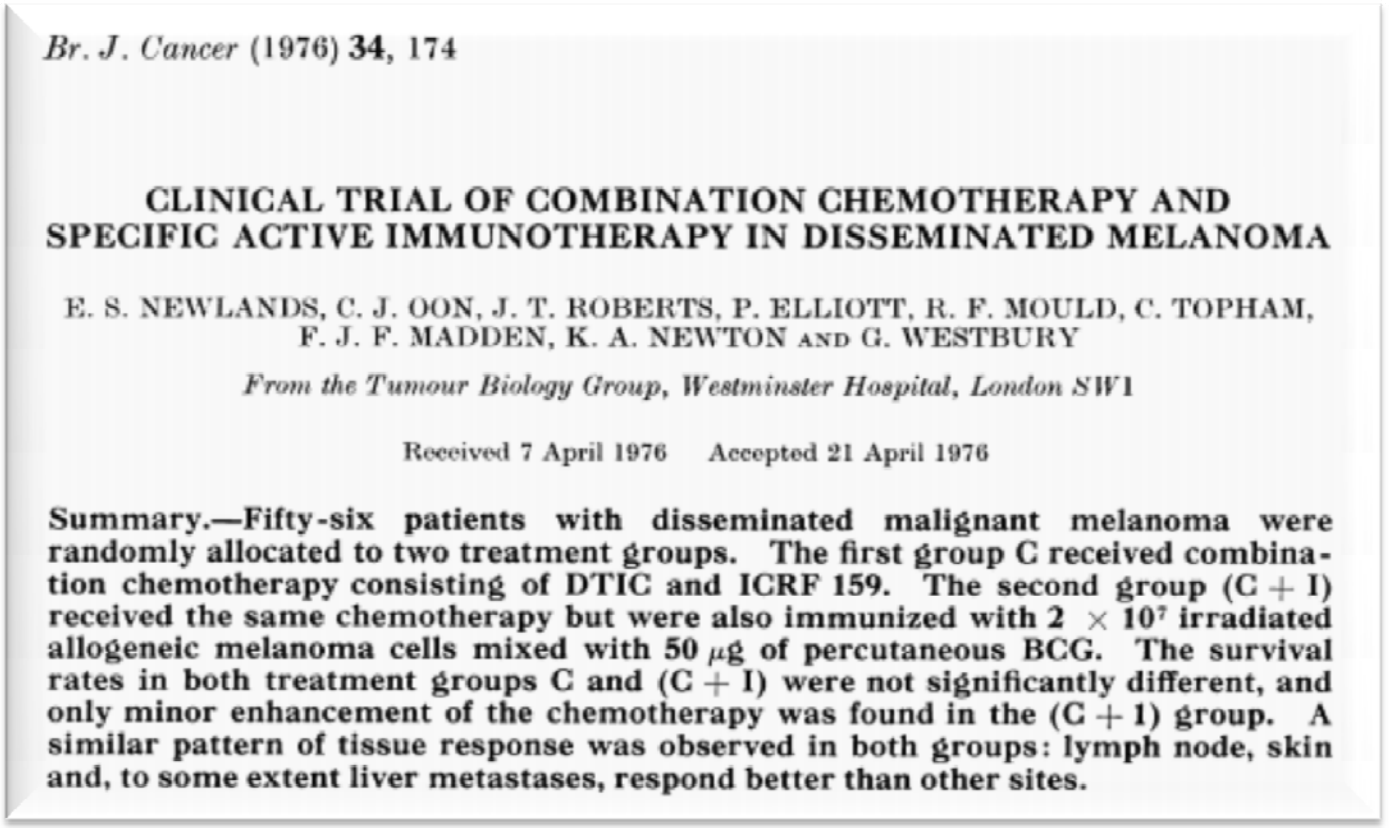
Not Surprisingly, This Is Not a New Concept



Br. J. Cancer (1976) **34**, 174

CLINICAL TRIAL OF COMBINATION CHEMOTHERAPY AND SPECIFIC ACTIVE IMMUNOTHERAPY IN DISSEMINATED MELANOMA

E. S. NEWLANDS, C. J. OON, J. T. ROBERTS, P. ELLIOTT, R. F. MOULD, C. TOPHAM, F. J. F. MADDEN, K. A. NEWTON AND G. WESTBURY

From the Tumour Biology Group, Westminster Hospital, London SW1

Received 7 April 1976 Accepted 21 April 1976

Summary.—Fifty-six patients with disseminated malignant melanoma were randomly allocated to two treatment groups. The first group C received combination chemotherapy consisting of DTIC and ICRF 159. The second group (C + I) received the same chemotherapy but were also immunized with 2 × 10^7 irradiated allogeneic melanoma cells mixed with 50 μg of percutaneous BCG. The survival rates in both treatment groups C and (C + I) were not significantly different, and only minor enhancement of the chemotherapy was found in the (C + 1) group. A similar pattern of tissue response was observed in both groups: lymph node, skin and, to some extent liver metastases, respond better than other sites.

Immune Re-Engagement: Why Combination Approaches Should Be Necessary

- Basic immunology has advanced our understanding of the complex mechanisms of immune regulation.
- At the same time, our understanding of cancer **immune surveillance** has been confirmed in animal models and supports the idea that immune evasion by aberrant cells is key in the development and progression of tumors.

Table 1 | Types of immune responses and regulatory mechanisms

Innate immune response

- Nonspecific
- Lacks memory
- Comprised of inflammatory cytokines, the complement system and phagocytes, such as macrophages, neutrophils and dendritic cells

Adaptive immune response

- Highly specific
- Development of memory cells
- Comprised of B and T lymphocytes, specifically $CD8^+$ cytotoxic T lymphocytes and $CD4^+$ T helper lymphocytes (T_H1 and T_H2 cells)

Activation of T cell responses

- Antigen-presenting cells (APCs), such as dendritic cells, can take up foreign antigens and process the antigens, which are then bound to major histocompatibility complex (MHC) molecules for presentation to T cells
- T cells interact with MHC and MHC-bound antigen through the T cell receptor; the signalling that results from this interaction is known as signal 1
- T cells become activated in the presence of signal 1 and co-stimulatory signals, which are known as signal 2
- Activated T cells can directly kill tumour cells that express the antigen for which the T cell has specificity
- Activated T cells can kill indirectly by producing cytokines that act to initiate apoptotic pathways in tumour and/or surrounding stromal cells
- Activated T cells can also kill indirectly by secreting cytokines to recruit other cells, such as macrophages; these recruited cells act in a nonspecific manner to destroy surrounding tumour and/or stromal cells

Regulation and suppression of T cell responses

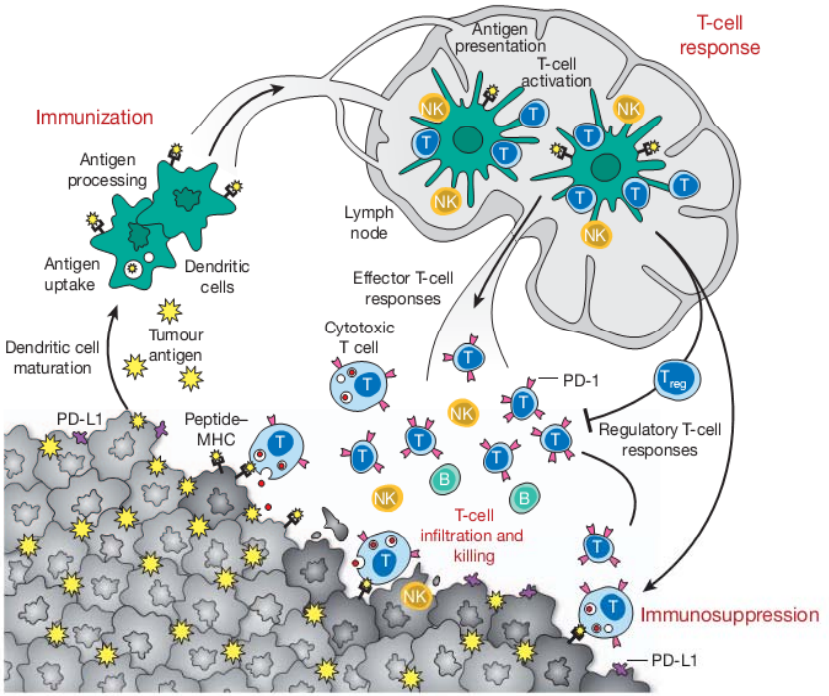
- Regulatory mechanisms can be intrinsic to T cells; examples are inhibitory immune-checkpoint molecules, such as cytotoxic T lymphocyte-associated protein 4 (CTLA4) and programmed cell death 1 (PD1)
- Regulatory mechanisms can also be extrinsic to T cells; examples are certain cytokines (such as IL-10), regulatory T cells and myeloid-derived suppressor T cells (MDSCs)

Nature Reviews Cancer 11, 805-812 (November 2011)

Immune Re-Engagement: Why Combination Approaches ARE Necessary

- The relationship between the immune system and human cancer is dynamic and complex.
- Individual human tumors harbor multiple somatic mutations and epigenetically dysregulated genes, with these all potentially recognizable as foreign antigens that are tumor-specific or tumor-selective.
- **However, by the time of frank cancer (and certainly much earlier), the balance of power between the patient's immune system and the growing cancer has been tipped in favor of the latter, with the consequent manifestation being immune tolerance.**

Generation and regulation of antitumor immunity



- Growing cancers contain tumor-infiltrating lymphocytes (TILs), which are ineffective at tumor elimination in vivo but can exert specific functions (eg, proliferation, cytokine secretion, cytolysis) out-side the immunosuppressive and toleragenic tumor microenvironment. This is because the tumor milieu contains suppressive elements including regulatory T cells and myeloid-derived suppressor cells; soluble factors such as interleukin 6 (IL-6), IL-10, vascular endothelial growth factor, and transforming growth factor beta; and ligands for coinhibitory receptors that down-modulate TIL activity.

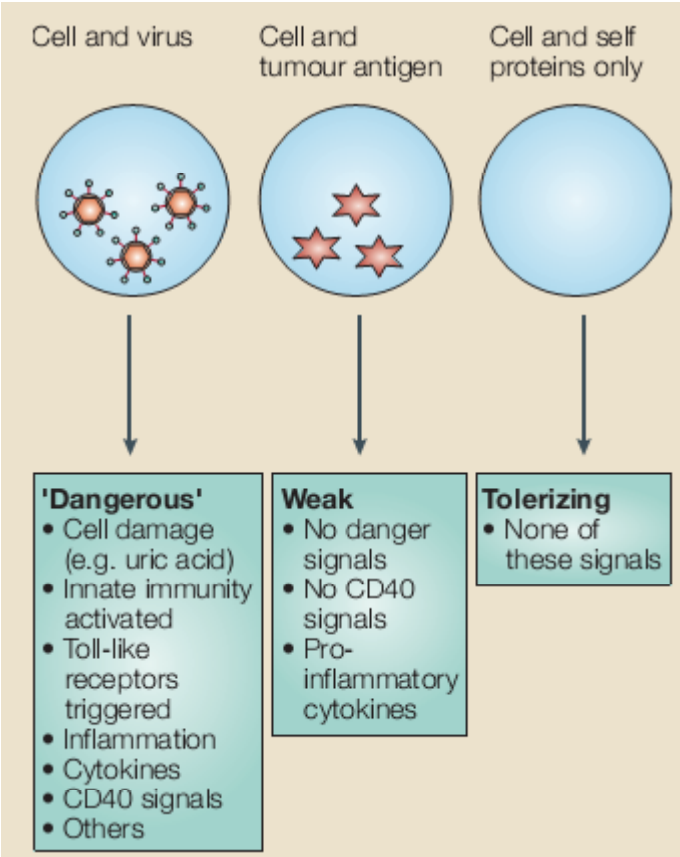
J Clin Oncol 29:4828-4836 ; Nature, 2011 Dec 21;480(7378):480-9

Does Immunotherapy Offer a Broader Acting Alternative for Tackling Cancer?

- **The inherent nature of the cancer cell (heterogeneity and genetic plasticity) limits the effectiveness of therapies that have been developed or that arguably can be developed.**
  - Being of host origin, cancer cells share features of the host that make effective treatment difficult due to side effects that limit the therapeutic window.
  - Their genetic plasticity makes tumors readily resistant to clinical regimens of radiotherapy and chemotherapy.
  - Even when the vast majority of cancer cells are killed by a cytotoxic chemotherapeutic drug, a small number of residual cells that are resistant to the agent (inherently or through selection – including CSCs) can be sufficient to seed the re-establishment of the tumor.
- Countering these obstacles includes:
  - **Redirecting the focus of therapeutic intervention away from the tumor cell itself to the microenvironment**, such as by depriving tumors of blood supply via anti-angiogenic therapies can indirectly kill cancer cells (e.g., *Avastin*); however, due to their passive nature, such therapies are still prone to circumvention through tumor cell evolution.
  - Engaging or reactivating the patient's own immunity which **may offer the advantage of being responsive to the complex initial state and evolving tumor heterogeneity**; also, the immune system may be particularly well suited to targeting the residual tumor cells (dormant cells or cancer stem cells) that may be poorly eradicated by radiotherapy and chemotherapy, which could help lengthen remission periods.

Alerting the Immune System: Difference, Dose, Danger and Duration

- We have learned a lot in the two decades of fraught and frustrating efforts around cancer immunotherapy.
- Were it not for the many failures – experiments, trials and companies – we would not have gotten where we are today.

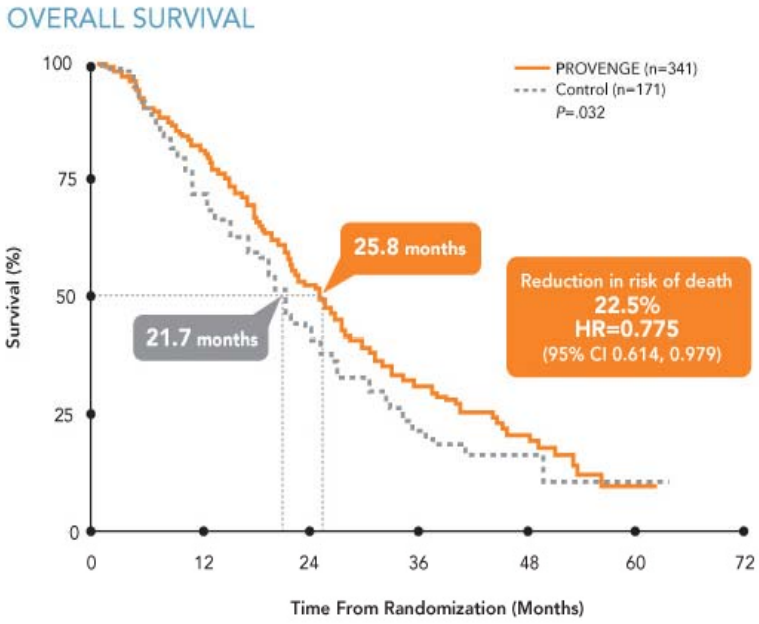


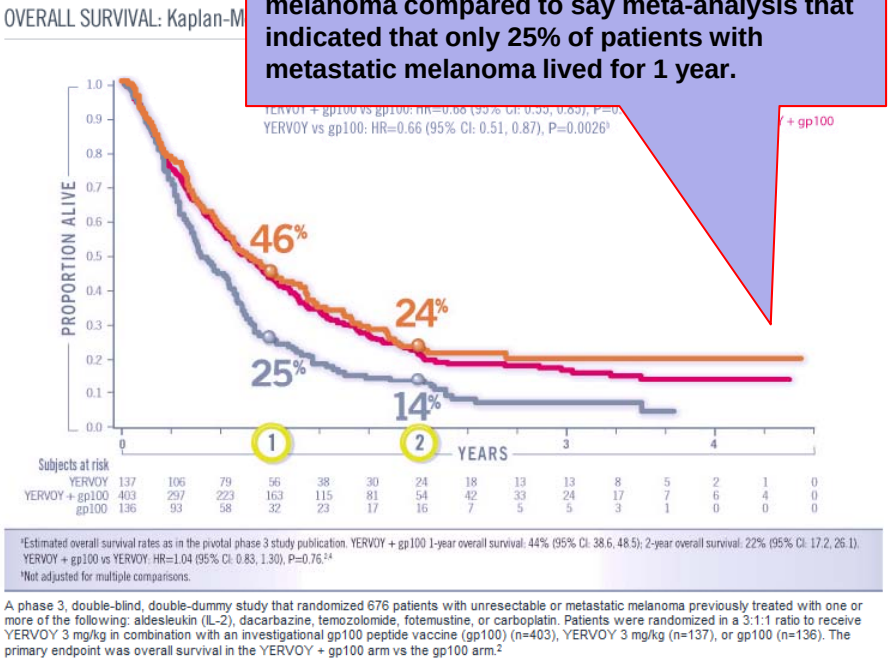
Nature Reviews Cancer 5, 397-405 (May 2005)

The Promise & The Challenge

- Durable tumor regression and improved outcomes can be achieved in selected situations of metastatic solid cancers by various immune approaches including cytokine therapy (e.g., *Leukine*), dendritic cell-based vaccines (e.g., *Provenge*), and immune-modulating antibodies (e.g., *Yervoy*).
- But there is still room for improvement...For example, the clinical benefit of Provenge is relatively small and only 15-20% of melanoma patients obtain durable benefits from ipi.

45% of ipilimumab-treated patients were alive after 1 year, 24% of patients were alive after 2 years, and some patients had a durable clinical benefit that lasted for the 4.5 years of follow-up. This was a dramatic improvement in the survival of patients with metastatic melanoma compared to say meta-analysis that indicated that only 25% of patients with metastatic melanoma lived for 1 year.





Source: Provenge and Yervoy product web sites

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Phase III Trials Are Almost All Combinations, And as Expected Mostly on Top of SOC

- But many of these are simply adding on the vaccine as one would any other new agent, on top of the standard of care rather than head-to-head.
- **What is probably a fair generalization is that such combinations, dosing and timing/sequencing are not optimized**.

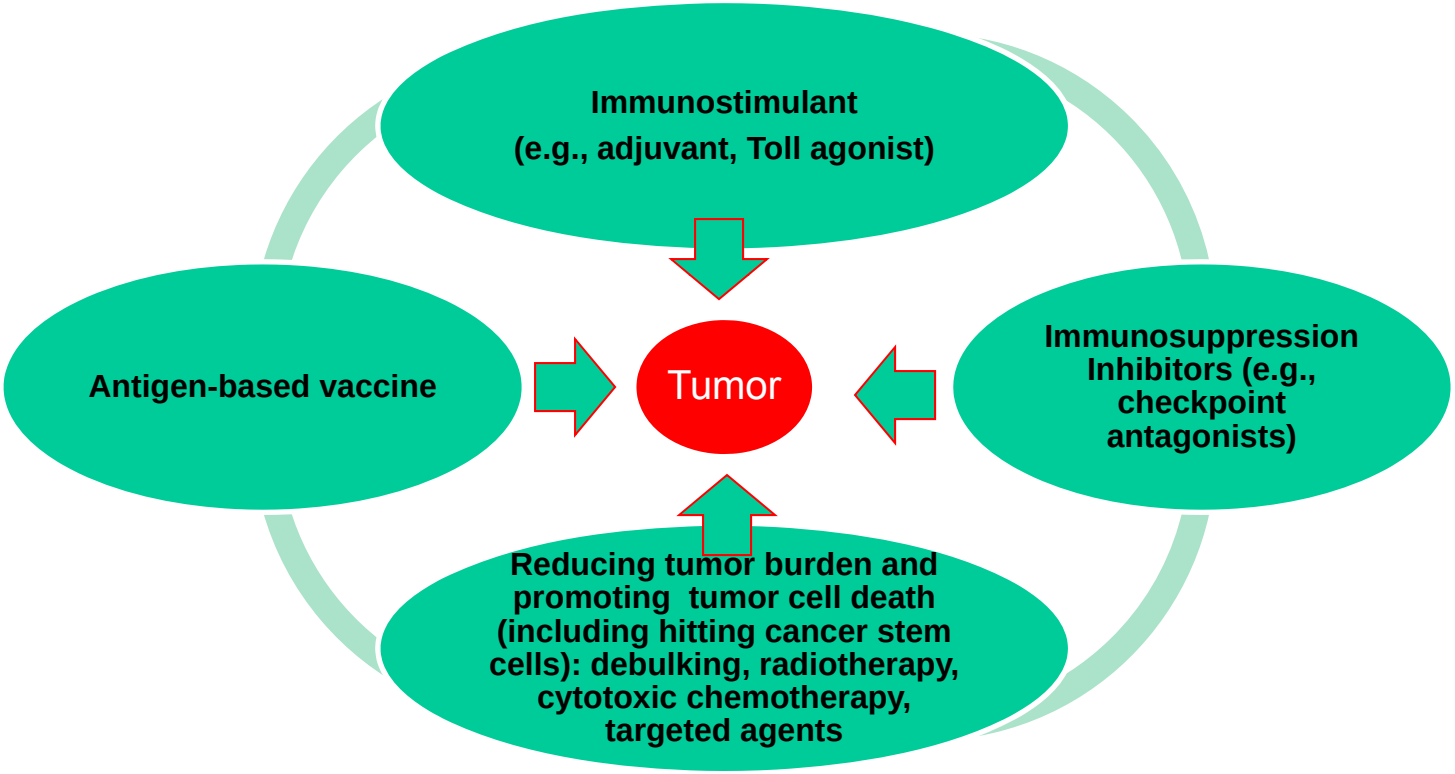
10 Phase III	vaccine+GCSF	breast
	vaccine +/- GMCSF	prostate
	vaccine+radiation	prostate
	vaccine + RT + chemo	GBM
	vaccine+chemo or chemoradiation	pancreatic
	vaccine+chemo	myeloma
	vaccine+MTKI	kidney
	vaccine alone	melanoma
	immunostimulant+Mab	colon
	vaccine+chemo	GBM

Source: Clinicaltrials.gov, Defined Health

Higher Bar to Satisfy Clinicians, Regulators & Payers?

- Trial design – controlled, randomized, head-to-head vs. single arm; combinations versus monotherapy
- Immune-based biomarkers, surrogate endpoints – **predictive biomarkers**
- Companion diagnostics
- Importance of OS benefit versus RR – “tail effect”
- Evidence of cost-effectiveness, individually and in combination

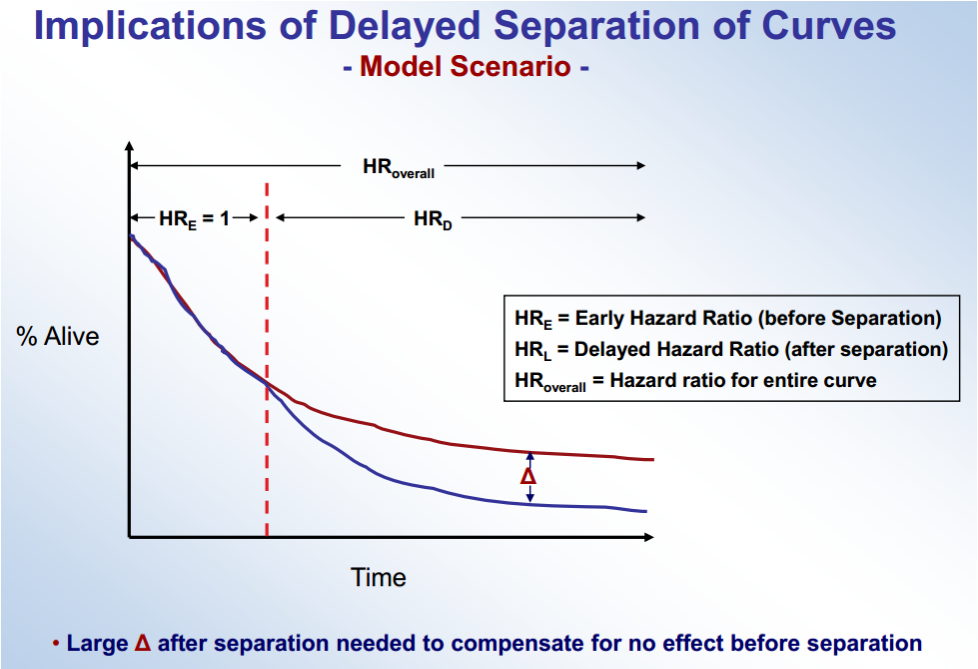
The Challenge & The Promise



Source: Defined Health

The Key Observation(s)

- One of the key benefits, and key challenges to clinical development, with immunotherapy is that short-term treatment with some of these immunotherapy approaches – whether antigen-based vaccine or immunomodulatory antibody – can provide disease control for extended periods after treatment stops, and in fact the **delayed effect** has likely confounded many past studies.
  - And on the other hand, apparent progression and increase in tumor volume due to immune infiltration.

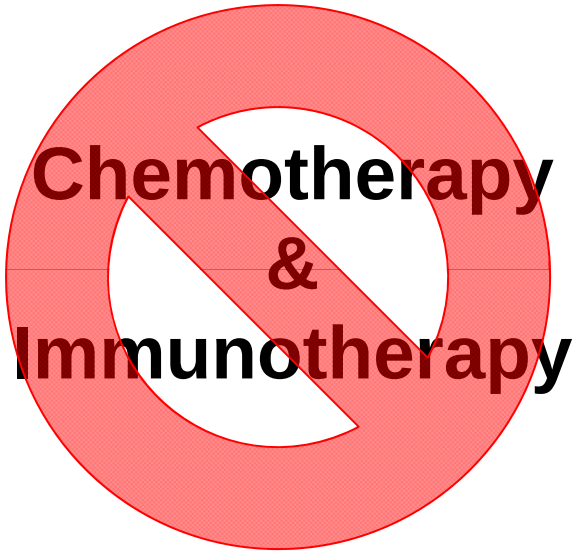


Source: Cancer Research Institute (CRI) and Cancer Immunotherapy Consortium (CIC): Immuno-Oncology: Creating the Framework for a New Era of Cancer Therapy,
Axel Hoos, MD, PhD
Co-Chair, CIC Executive Committee
Medical Lead, Ipillimumab Program, Bristol-Myers Squibb

Immunotherapy & Chemotherapy – Challenging the Dogma

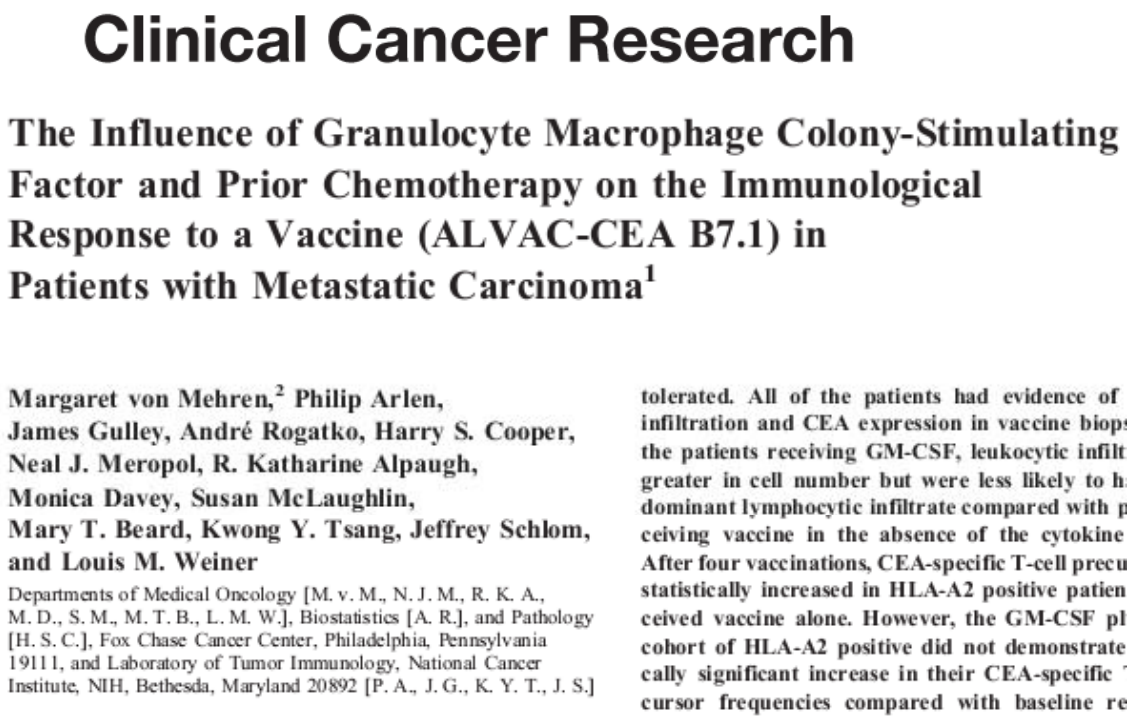
The Dogma

- Two *a priori* assumptions have contributed to this state of affairs.
- First, most chemotherapies kill target cells by **apoptosis** and this mode of cell death has been regarded immunologically as either **non-stimulatory** or **inducing immune tolerance** — a state where T cells can no longer respond to the presented antigen by mounting an immune response.
- Second, lymphopenia is a common side effect of many anticancer drugs and this has also been assumed to be detrimental to any potential immune response.



Just an Example of the Data Underpinning the Old Conceptual Framework

- "The number of prior chemotherapy regimens was negatively correlated with the generation of a T-cell response, whereas there was a positive correlation between the number of months from the last chemotherapy regimen and the T-cell response."
- **What this really says is not that chemotherapy and immunotherapy don't mix but that it is all in the timing.**



Clinical Cancer Research

The Influence of Granulocyte Macrophage Colony-Stimulating Factor and Prior Chemotherapy on the Immunological Response to a Vaccine (ALVAC-CEA B7.1) in Patients with Metastatic Carcinoma[1]

Margaret von Mehren,[2] Philip Arlen, James Gulley, André Rogatko, Harry S. Cooper, Neal J. Meropol, R. Katharine Alpaugh, Monica Davey, Susan McLaughlin, Mary T. Beard, Kwong Y. Tsang, Jeffrey Schlom, and Louis M. Weiner

Departments of Medical Oncology [M. v. M., N. J. M., R. K. A., M. D., S. M., M. T. B., L. M. W.], Biostatistics [A. R.], and Pathology [H. S. C.], Fox Chase Cancer Center, Philadelphia, Pennsylvania 19111, and Laboratory of Tumor Immunology, National Cancer Institute, NIH, Bethesda, Maryland 20892 [P. A., J. G., K. Y. T., J. S.]

tolerated. All of the patients had evidence of infiltration and CEA expression in vaccine biops the patients receiving GM-CSF, leukocytic infilt greater in cell number but were less likely to h dominant lymphocytic infiltrate compared with p ceiving vaccine in the absence of the cytokine After four vaccinations, CEA-specific T-cell precu statistically increased in HLA-A2 positive patien ceived vaccine alone. However, the GM-CSF pl cohort of HLA-A2 positive did not demonstrate cally significant increase in their CEA-specific cursor frequencies compared with baseline re

Clin Cancer Res. 2001 May;7(5):1181-9

Some Specific Ways That Chemotherapy May Augment Anticancer Immune Responses

- Different chemotherapies kill tumor cells in different ways and in the process they can modulate the host immune system with consequences that have yet to be elucidated.

How chemotherapy could augment immunotherapy

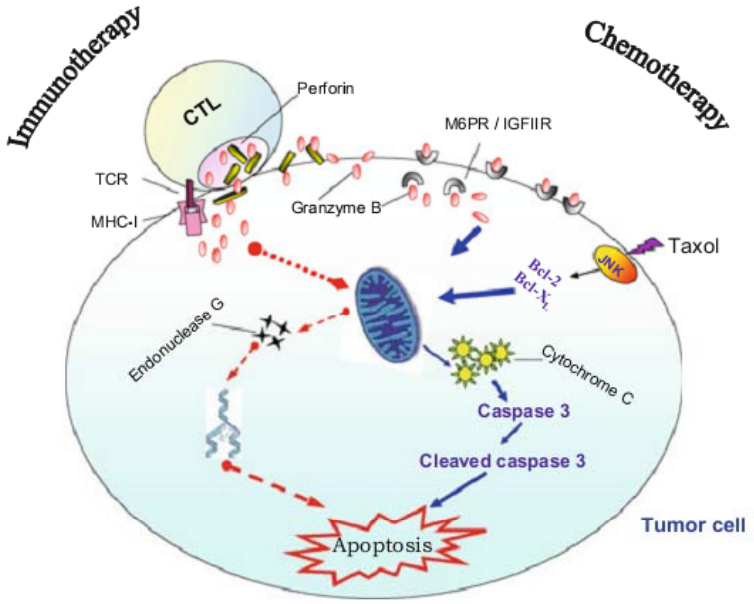
Essential steps in the induction of an antitumour immune response	Potential effects of chemotherapy on the capacity of immunotherapy to destroy tumours
Antigen threshold	Delivery of a broader range of different tumour antigens
Antigen presentation	Increased antigen cross-presentation
	Partial activation of dendritic cells
	Priming of APCs for CD40 signal
	Killing subsets of APC
T-cell response	No tolerance induction by apoptotic tumour cells
	Lymphopaenia-related proliferation increases tumour-specific T-cell response
T-cell traffic	Increased T-cell accumulation within tumour
Target destruction	Increased local tumour-antigen cross-presentation (permitting CD8 re-stimulation)
	Tumour debulking (less systemic suppression, smaller target, less chance for escape variants etc.)
	Partial sensitization of tumour cells for CTL lysis
Generation of memory	Promotion of long-term antigen-independent memory
External regulation of these steps	Increased delivery of exogenous antigen
	Increased CD4 help (for example, delivery of CD40 signals)
	Reduction in function of negative regulatory cells
	Induction of homeostatic proliferation

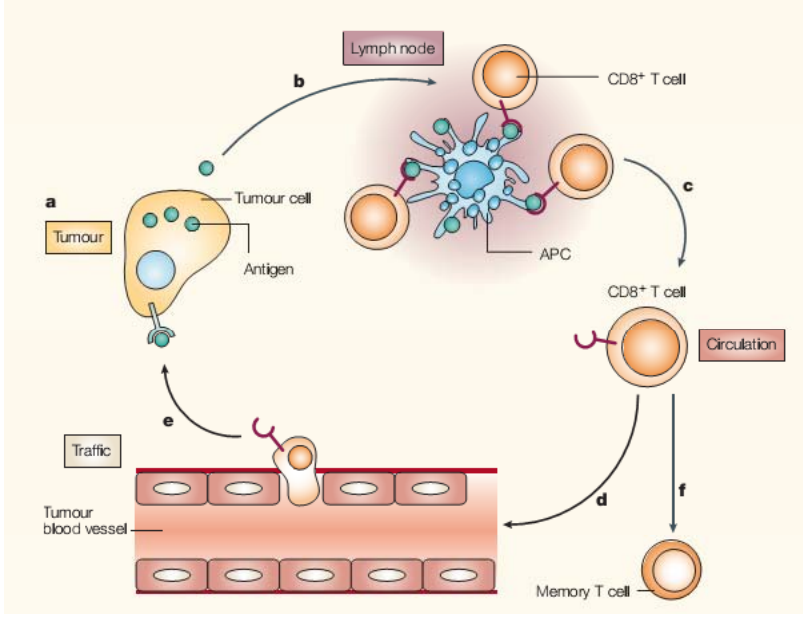
*Not yet demonstrated in tumour models. APC, antigen-presenting cell; CTL, cytotoxic T lymphocyte

Nature Reviews Cancer 5, 397-405

Chemotherapy May Augment Anticancer Immune Responses Through Activating CTLs

- Chemotherapy causes the disruption of tumor stroma that allows more CTLs to penetrate into tumor site. It also may inhibit negative regulatory network inside the tumor by eliminating MDSC and Treg and by decreasing production of immune suppressive cytokines by tumor cells.
- In addition, chemotherapy up-regulates expression of multi-functional cation-independent mannose 6-phosphate receptor (CI-MPR) on tumor cells. As a result granzyme B (GrzB being the most studied and arguably most important member of this family of pore-forming serine proteases) that is released by activated CTLs can be picked up by a large number of neighboring tumor cells.
- Thus, a relatively small number of CTLs can cause apoptosis in large numbers of tumor cells manifesting in a clinically evident antitumor effect.





Cancer Immunology Immunotherapy (2010) 60:419-423; *Nature Reviews Cancer* 5, 397-405

Chemotherapy Plus Immunotherapy: Prostate Cancer Ongoing Trials

- Most advancing trials in prostate cancer, for example, are studying vaccines concurrent with standard of care docetaxel.

Vaccine	Description	Study Protocol	Results	Source
rV-PSA/rF-PSA	A combination of recombinant pox viruses expressing either PSA or the B7.1 costimulatory molecule. A vaccinia-based vaccine is given once and then boosted with monthly PSA fowlpox recombinant virus. Each vaccination is given with GM-CSF.	Vaccine recipients with CRPC (N=28) received concurrent standard-dose docetaxel/dexamethasone or vaccine alone. Those on vaccine alone switched to docetaxel/ dexamethasone alone at disease progression.	The median increase in PSA-responsive T-cell precursors was 3-fold in both trial arms at month 3. Patients also developed responses to other prostatic antigens. Patients on the vaccine-alone arm had a median time-to-progression of 1.8 months, whereas the combination recipients had a median PFS of 3.2 months. Patients who switched from vaccine alone to docetaxel alone then had a median PFS of 6.1 months. The median PFS in a historic docetaxel-treated control was 3.7 months.	Arlen et al, 2006[42]
Sipuleucel-T	Autologous dendritic cells cultured ex vivo with recombinant PAP linked to GM-CSF for increased cell activation. The cells are reinfused to their donor 3 times, 2 weeks apart.	Postimmunization standard-dose docetaxel in progressing CRPC (N=82)	Improved survival with sipuleucel-T followed by docetaxel (see Table 1)	Petrylak et al, 2007[6]
Prostate GVAX	A polyvalent vaccine that includes irradiated whole cells from 2 standardized prostate cancer lines. 1 androgen-dependent and 1 androgen-independent. The cells also produce GM-CSF due to a transduced gene.	Patients with symptomatic metastatic CRPC, N=408. Two trial arms: 1) Docetaxel (75 mg/ m^2 q3w for 10 cycles) plus GVAX (q3w for 10 cycles). 2) Docetaxel (75 mg/m^2 q3w for 10 cycles) plus prednisone (10 mg/day)	Median overall survival: 12.2 months vs. 14.1 months in the GVAX and control arms, respectively (HR=1.70; 95% CI. 1.15–2.53; *P*=.0076) The trial was discontinued early due to excess deaths in the GVAX arm	Small et al, 2009[44]
PSA-TRICOM	Recombinant vaccinia or fowlpox expressing PSA plus 3 T-cell costimulatory molecules. The vaccinia-based vaccine is given once and then boosted with further immunizations with PSA fowlpox recombinant virus.	CRPC patients with visceral metastases and no current treatment (N=144) Two trial arms: 1) Vaccinia-TRICOM on day 1 and then 4 biweekly fowlpox TRICOM immunizations. Standard docetaxel/prednisone starting on day 85. 2) Standard docetaxel/ prednisone	Trial is ongoing	ClinicalTrials.gov (NCT01145508)

CI=confidence interval; CRPC=castrate-resistant prostate cancer; GM-CSF=granulocyte/macrophage-colony stimulating factor; GVAX=granulocyte-macrophage colony-stimulating factor (GM-CSF) gene-transfected tumor cell vaccine; HR=hazard ratio; PAP=prostatic acid phosphatase; PFS=progression-free survival; PSA=prostate-specific antigen.

Clinical Advances in Hematology & Oncology, Volume 10, Issue 2, pp. 90-100, February 2012

But Let's Not Minimize the Complexities of Combining Chemotherapy & Immunotherapy

- In prostate cancer, there is considerable evidence that tumors promote immune tolerance starting early in the disease. In theory, therefore, by suppressing tumors and activating immune system homeostatic mechanisms, chemotherapy may help overcome this tumor-induced immune tolerance. **However, data has been mixed and likely reflects the realities, that is the complexities, of sequencing/timing of chemotherapy and immunotherapies.**
- Sipuleucel-T/*Provenge*, which has recently been approved in the United States, is an active immunotherapy that triggers T-cell responses against prostate cancer.
  - **An exploratory analysis of phase III trial participants found a substantial survival benefit to receiving docetaxel some months after sipuleucel-T**.
  - **However, VITAL-2, a phase III trial investigating a prostate cancer therapeutic vaccine plus concurrent docetaxel versus standard docetaxel therapy in advanced prostate cancer, observed lower overall survival with the vaccine regimen.**

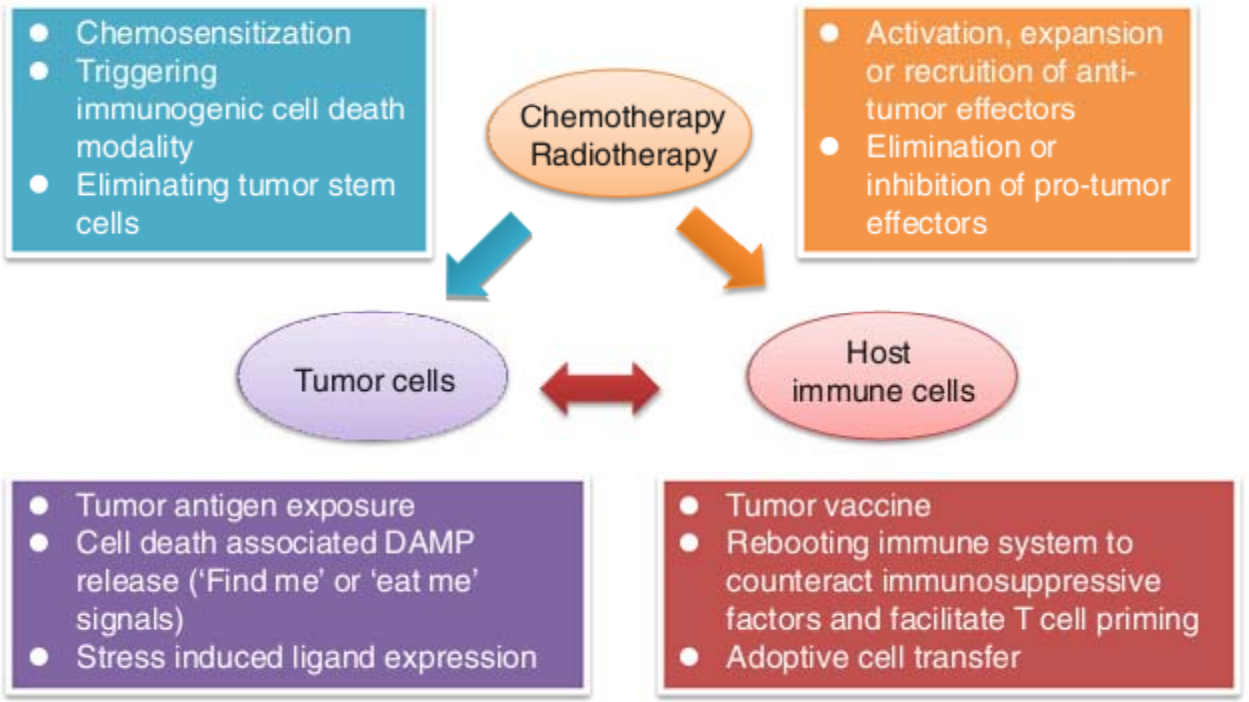
Group	Number of patients	Observed median overall survival (months)	Predicted median overall survival† (months)	Survival HR, sipuleucel-T vs combined placebo groups
Sipuleucel-T → Docetaxel	51	34.5	20.9	HR=1.90, *P*=.023 (log rank)
Placebo → APC8015F* → Docetaxel	21	25.7	20.3	
Placebo → Docetaxel	10	20.2	19.1	Adjusted HR=2.53, *P*=.006‡

*Antigen-primed autologous dendritic cell vaccine product similar to sipuleucel-T (APC8015) but produced from frozen cells.
†As calculated using the Halabi nomogram.[30]
Adjusted for the following baseline risk factors: lactate dehydrogenase, prostate-specific antigen, number of bone metastases, localization of disease, and weight.
HR=hazard ratio.

Clinical Advances in Hematology & Oncology, Volume 10, Issue 2, pp. 90-100, February 2012

Strategies to Improve Immunogenicity of Chemotherapy & Radiotherapy

- Effective antitumor therapy will need to induce sufficient tumor cell death in order to release tumor antigen as well as danger signals attracting phagocytes/APCs for uptake and presentation of tumor antigen. Proper cell death should be triggered in tumor cells, tumor stem cell, as well as probably stromal cells.

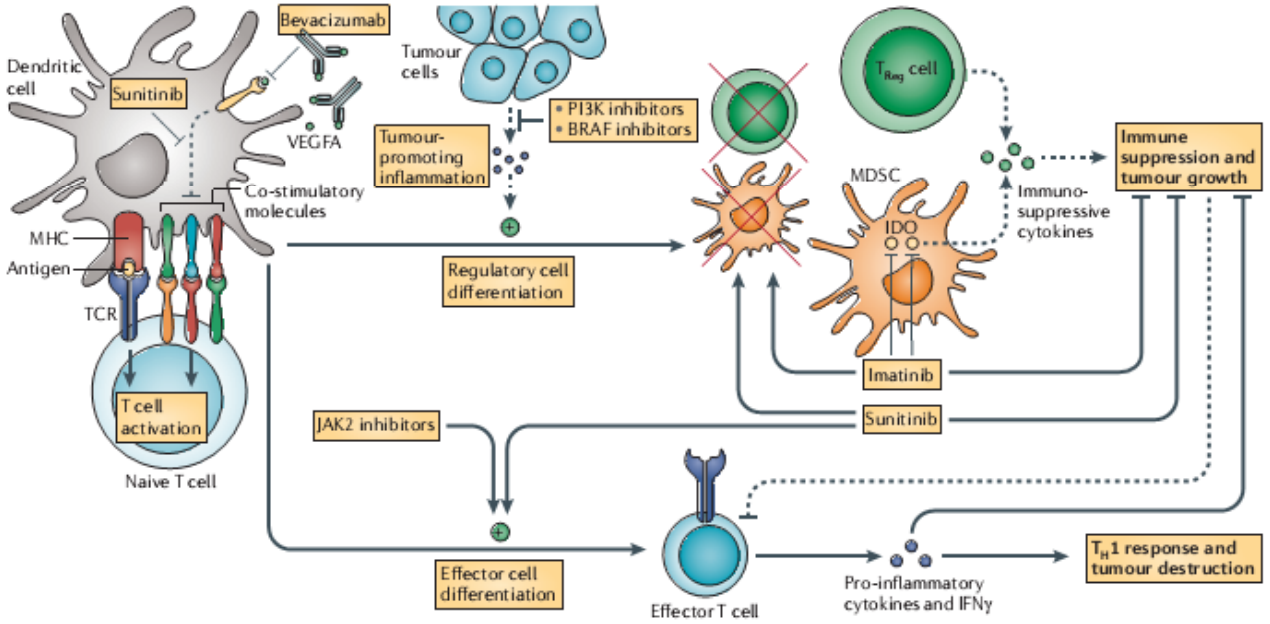


Cancer Metastasis Rev (2011) 30:71–82

Immunotherapy & “Targeted” Therapies

Mechanism-Based Therapeutics Meets Immunotherapeutics

- Targeted agents and immunotherapy might have complementary roles. But is this just a variation on the role of conventional cytotoxics or is something else potentially at work here?



Targeted agents may antagonize immunosuppression in the tumor microenvironment. Multiple factors within tumors promote immune tolerance and curb the anti-tumor immune response. tumor cells secrete vascular endothelial growth factor A (VEGFA), and VEGF signaling decreases dendritic cell (DC) co-stimulatory molecule expression and T cell priming, and also encourages the formation of myeloid-derived suppressor cells (MDSCs). VEGF antagonists, either as a monoclonal antibody (mAb) — such as bevacizumab — or as small-molecule inhibitors — for example, sunitinib — reverse these deleterious effects and promote the formation of potent anti-tumor T cells. Tumor cells also produce inflammatory mediators that promote tumorigenesis, as well as encourage suppressor cell formation, and these can be inhibited with PI3K and BRAF inhibitors, respectively. Regulatory T (TReg) cells and MDSCs are two immunosuppressive cell types that dampen immune responses. Treg cells secrete immunosuppressive cytokines; whereas, MDSCs use indoleamine-pyrrole 2,3-dioxygenase (IDO) to deplete tryptophan and to kill effector T cells. Sunitinib and imatinib both decrease the number and effectiveness of these suppressor cell types. Imatinib also directly inhibits IDO, decreasing MDSC suppressive capacity. Sunitinib and janus kinase 2 (JAK2) inhibitors also block the signal transducer and activator of transcription 3 (STAT3) pathway, which is an immunosuppressive pathway favouing differentiation into regulatory cells and tumor growth. Decreasing STAT3 signaling diminishes the formation of Treg cells and promotes the formation of effector T helper 1 (TH1) cells secreting interferon-γ(IFNγ).

Nature Reviews Cancer 12, 237-251 (April 2012)

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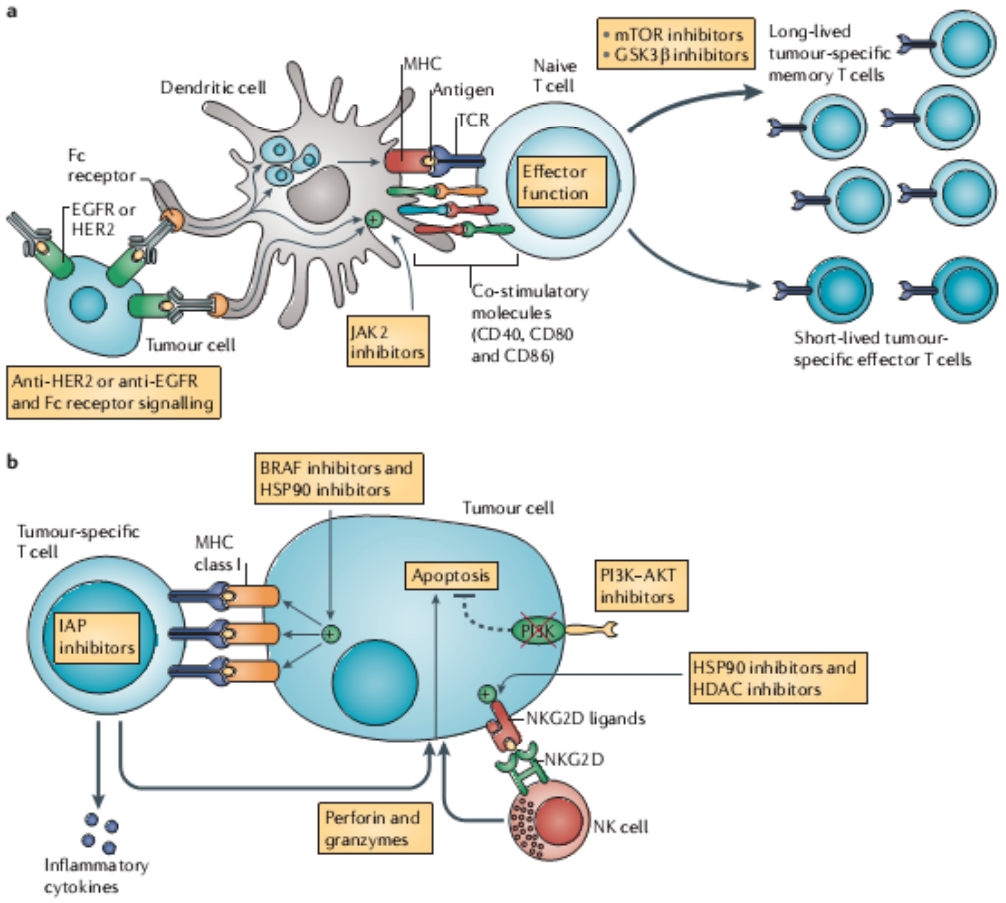
Targeted Plus Immune Therapies: Potential for Near- & Long-Term Tumor Destruction

- As cytostatic agents, these compounds might allow time for the immune system to “kick-in” and in combination with chemotherapy induced tumor regression might decrease tumor-associated immunosuppression.
- Also, targeted therapies might potentiate anti-tumor immune responses by breaking *oncogene addiction* and in turn triggering tumor cell senescence and clearance by T cells.
- Finally, the release of large amounts of antigenic debris from tumor cell death (whether apoptotic, necrotic or other) may, as with chemotherapy, lead to DC activation.



Nature Reviews Cancer 12, 237-251 (April 2012)

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Targeted Agents: Not Just Direct Anticancer Effects But Also Immunomodulatory Effects

- For example:
  - the anti–VEGF monoclonal antibody bevacizumab, in addition to its effect on tumor vasculature, may decrease VEGF–induced inhibition of DC and T-cell function;
  - drugs that target epigenetic mechanisms, such as the demethylating agents and the histone deacetylase inhibitors, have multiple effects on gene transcription and can up-regulate MHC and tumor antigen expression, induce ‘‘stress’’ molecules recognizable by NK-activating receptors such as NKG2D, and increase expression of surface death receptors.

Drug	Effect on tumour	Effect on the immune system	Current and experimental immunotherapy combinations
Sunitinib	Blocks multiple tumour-associated tyrosine kinases, including VEGFR and PDGFR	Blocks STAT3, decreases numbers and effectiveness of MDSCs and T_{Reg} cells, and blocks VEGF signalling	• Preclinical trial of adoptive T cell transfer plus sunitinib in HCC and RCC • Preclinical trial of combination of sunitinib, agonistic anti-CD137 plus IL-12 in colon adenocarcinoma
Imatinib	Blocks multiple tumour-associated tyrosine kinases, including ABL and KIT	Blocks IDO, decreases numbers and effectiveness of T_{Reg} cells, promotes DC cell–NK cell crosstalk, and increases the numbers of B-1 B cells and the amount of 'natural' anti-tumour carbohydrate antibodies	• Phase III trial of IFN–alfa 2A and imatinib in CML. Phase II trial of imatinib plus BCR-ABL vaccine in CML • Preclinical trial of imatinib plus anti-CTLA4 in GIST
Vemurafenib	Blocks BRAF-V600E	Increases expression of gp100, MART1 and other antigens, and decreases tumour secretion of immunosuppressive cytokines	Phase I trial of vemurafenib plus ipilimumab (NCT01400451)
Trastuzumab	Blocks growth signalling through HER2	Primes anti-tumour CTLs, and boosts NK cell secretion of IFNγ and ADCC	• Phase II trial of trastuzumab plus HER2 peptide vaccine • Phase I trial of trastuzumab plus IL-12 plus paclitaxel in HER2+ breast cancer • Preclinical trial of anti-HER2 plus anti-PD1 • Preclinical trial of anti-HER2 plus 4-1BB agonistic antibody
Bevacizumab	Neutralizing antibody against VEGF: blocks angiogenesis	Increases DC maturation, shifts DC differentiation towards mature DCs instead of MDSCs and increases DC priming of T cells	• Phase III trial of bevacizumab plus IFN–alfa 2A in metastatic RCC • Phase I trial of bevacizumab plus ipilimumab (NCT00790010) • Preclinical trial of anti-VEGF plus adoptive T cell transfer therapy
Cetuximab	Neutralizing antibody against EGFR: blocks growth signals	• Immune activating: complement fixation, ADCC, increases MHC class I and MHC class II expression and augments DC priming of tumour-specific CTLs • Immunosuppressive: activates M2 macrophages	Phase II trial of cetuximab plus EGFR vaccine (NCT00305760)
Temsirolimus, rapamycin and other mTOR inhibitors	Blocks mTOR pathway	• Immunostimulatory: enhances $CD8^+$ T cell activation and IFNγ production, augments $CD8^+$ T cell differentiation into memory T cells, impairs the homeostasis of T_{Reg} cells and decreases IDO expression • Immunosuppressive: augments the responsiveness of T_{Reg} cells to antigen	• Preclinical trial of temsirolimus plus HSP90 and tumour-specific antigen vaccines in melanoma and RCC • Preclinical trial of temsiroliums plus agonistic CD40 antibody in RCC
Bortezomib	Blocks 26S subunit of the proteasome	Sensitizes tumour cells to CTL-mediated lysis, sensitizes tumour cells to NK cell-mediated lysis by downregulating MHC class I molecule expression and boosts antigen-specific T cell response to vaccination	Preclinical trial of bortezomib plus vaccination with DNA encoding a tumour-specific protein
JAK2 inhibitors	Block JAK2 signalling in tumour cells	Enhances DC maturation, bolsters DC-mediated antigen presentation and T cell priming, decreases immunosuppressive STAT3 signalling, decreases IAP expression and decreases tumour cell PDL1 expression	Preclinical trial of JAK2 inhibitor plus DC vaccines
PI3K–AKT inhibitors	Decreases PI3K–AKT signalling in tumour cells	Increases tumour susceptibility to perforin and granzyme-mediated lysis (mediated by CTLs and NK cells), decreases pro-survival signalling and decreases tumour-promoting inflammation	Preclinical trial of AKT inhibitor plus vaccine
Lenalidomide	Not well understood	Pleiotropic: increases co-stimulatory molecules on tumour cells, modulates SOCS1 expression to increase cytokine secretion, decreases PDL1 expression on tumour cells, increases NK cell cytotoxicity and cytokine secretion, and increases NKG2D ligand expression	• Phase II trial of lenalidomide as maintenance after BMT • Preclinical trial of lenalidomide plus KIR antibody • Preclinical trial of lenalidomide plus CD38 antibody (daratumomab)

Clin Cancer Res. 2008 Jul 15;14(14):4385-9; *Nat Rev Cancer*. 2012 Mar 22;12(4):237-51

Early BMS-Roche Partnership: Mutual Franchise Benefit

Cancer Research

Selective BRAF^{V600E} Inhibition Enhances T-Cell Recognition of Melanoma without Affecting Lymphocyte Function

Andrea Boni, Alexandria P. Cogdill, Ping Dang, Durga Udayakumar, Ching-Ni Jenny Njauw, Callum M. Sloss, Cristina R. Ferrone, Keith T. Flaherty, Donald P. Lawrence, David E. Fisher, Hensin Tsao, and Jennifer A. Wargo

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Abstract

Targeted therapy against the BRAF/mitogen-activated protein kinase (MAPK) pathway is a promising new therapeutic approach for the treatment of melanoma. Treatment with selective BRAF inhibitors results in a high initial response rate but limited duration of response. To counter this, investigators propose combining this therapy with other targeted agents, addressing the issue of redundancy and signaling through different oncogenic pathways. An alternative approach is combining BRAF/MAPK-targeted agents with immunotherapy. Preliminary evidence suggests that oncogenic BRAF (BRAF^{V600E}) contributes to immune escape and that blocking its activity via MAPK pathway inhibition leads to increased expression of melanocyte differentiation antigens (MDA). Recognition of MDAs is a critical component of the immunologic response to melanoma, and several forms of immunotherapy capitalize on this recognition. Among the various approaches to inhibiting BRAF/MAPK, broad MAPK pathway inhibition may have deleterious effects on T lymphocyte function. Here, we corroborate the role of oncogenic BRAF in immune evasion by melanoma cells through suppression of MDAs. We show that inhibition of the MAPK pathway with MAPK/extracellular signal-regulated kinase kinase (MEK) inhibitors or a specific inhibitor of BRAF^{V600E} in melanoma cell lines and tumor digests results in increased levels of MDAs, which is associated with improved recognition by antigen-specific T lymphocytes. However, treatment with MEK inhibitors impairs T lymphocyte function, whereas T-cell function is preserved after treatment with a specific inhibitor of BRAF^{V600E}. These findings suggest that immune evasion of melanomas mediated by oncogenic BRAF may be reversed by targeted BRAF inhibition without compromising T-cell function. These findings have important implications for combined kinase-targeted therapy plus immunotherapy for melanoma. Cancer Res; 70(13); OF1–7. ©2010 AACR.

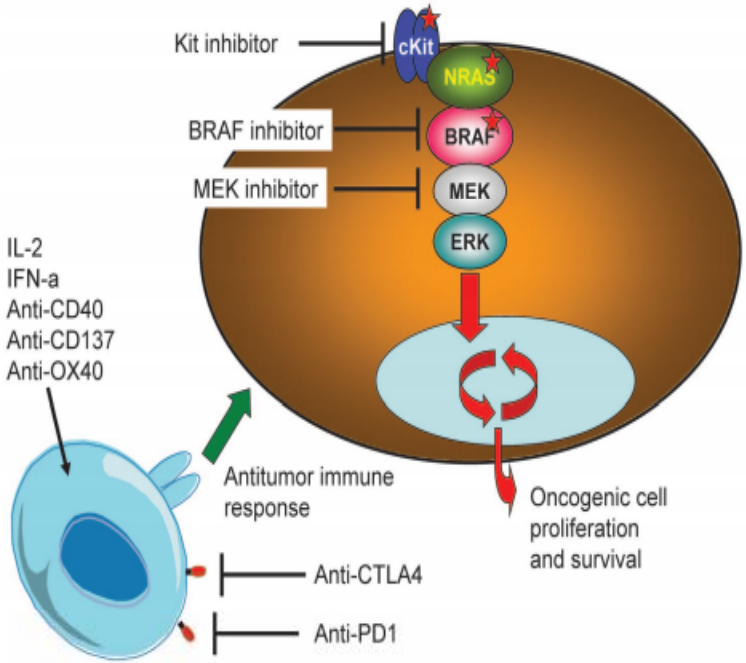

Fig. 1. Schematic of the mechanism of action of new treatments demonstrating patient benefit in advanced melanoma. The majority of melanomas demonstrate a constitutively active mitogen-activated protein kinase (MAPK) pathway leading to uncontrolled cell proliferation and avoidance of apoptosis, which is to the result of the presence of mutually exclusive activating mutations in the receptor tyrosine kinase cKit, in NRAS or BRAF (red stars). Inhibitors of oncogenic driver mutations blocking cKit or BRAF result in high response rates, and this oncogenic pathway can also be blocked with MEK inhibitors. Melanoma can also be treated by activating an antitumor immune response, either by turning it on against cancer cells by the immune activating cytokines interleukin-2 (IL2) or interferon, or the immune activating antibodies to CD40, CD137 or OX40, or by administering antibodies blocking negative costimulatory signaling through CTLA4 or PD1.

Cancer Research 70(13); OnlineFirst 1–7, June 15, 2010;
Antoni Ribas, Combination Therapies Building on the Efficacy of CTLA4 and BRAF Inhibitors for Metastatic Melanoma
http://www.asco.org/ASCOv2/Home/Education%20&%20Training/Educational%20Book/PDF%20Files/2012/zds00112000675.PDF

Early BMS-Roche Partnership: Mutual Franchise Benefit - If AEs Do Not Limit

Ph I/II Ipilimumab Vemurafenib Combo

This study is currently recruiting participants.
Verified November 2011 by Bristol-Myers Squibb

First Received on July 21, 2011. Last Updated on April 30, 2012 History of Changes

Sponsor:	Bristol-Myers Squibb
Collaborator:	Roche-Genentech
Information provided by (Responsible Party):	Bristol-Myers Squibb
ClinicalTrials.gov Identifier:	NCT01400451

Vemurafenib Sensitivity Skin Reaction after Ipilimumab

Table 1. Patients with Stage IV Melanoma Harboring a *BRAF V600E* Mutation Treated with Vemurafenib after Receiving Ipilimumab.

Patient No.	Age	Stage of Metastasis	Ipilimumab Dose	No. of Doses of Ipilimumab	Immune-Related Adverse Event with Ipilimumab	No. of Days from Last Dose of Ipilimumab to Start of Vemurafenib	Rash	No. of Days to Onset of Rash
	yr		*mg/kg*					
1	63	M1c	3	4	Yes	20	Grade 3	6
2	25	M1c	3	4	No	24	Grade 3	8
3	72	M1c	3	6	No	28	Grade 3	8
4	44	M1c	3	1	Yes	36	No	
5	61	M1c	3	4	No	51	Grade 1	Not reported
6	51	M1c	10	1	Yes	76	No	
7	46	M1c	3	4	Yes	83	Grade 1	2
8	31	M1c	3	4	No	117	Grade 1	15
9	39	M1c	3	11	No	147	Grade 1	13
10	49	M1c	10	1	Yes	168	No	
11	50	M1c	10	3	Yes	247	Grade 3	7
12	59	M1a	10	4	Yes	294	Grade 1	28
13	65	M1b	10	5	Yes	955	No	

clinicaltrials.gov; *N Engl J Med* 366:866-868, March 1, 2012

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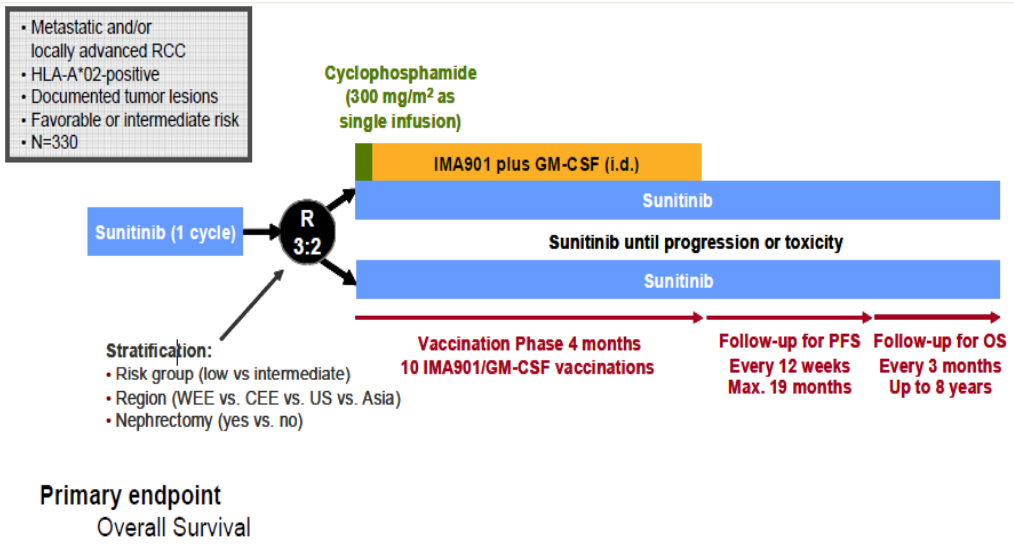
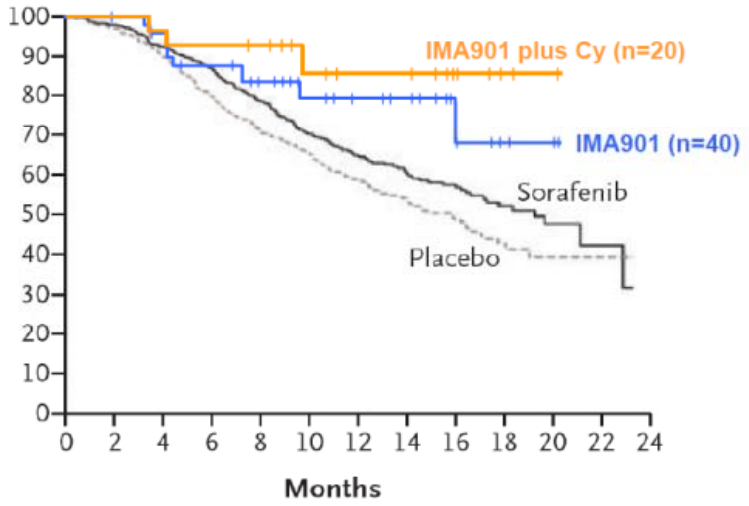
A Multi-Peptide Vaccine Combined with an MTKI in RCC: Phase III And Counting…





Drug	Effect on tumour	Effect on the immune system	Current and experimental immunotherapy combinations
Sunitinib	Blocks multiple tumour-associated tyrosine kinases, including VEGFR and PDGFR	Blocks STAT3, decreases numbers and effectiveness of MDSCs and T_{Reg} cells, and blocks VEGF signalling	• Preclinical trial of adoptive T cell transfer plus sunitinib in HCC and RCC • Preclinical trial of combination of sunitinib, agonistic anti-CD137 plus IL-12 in colon adenocarcinoma

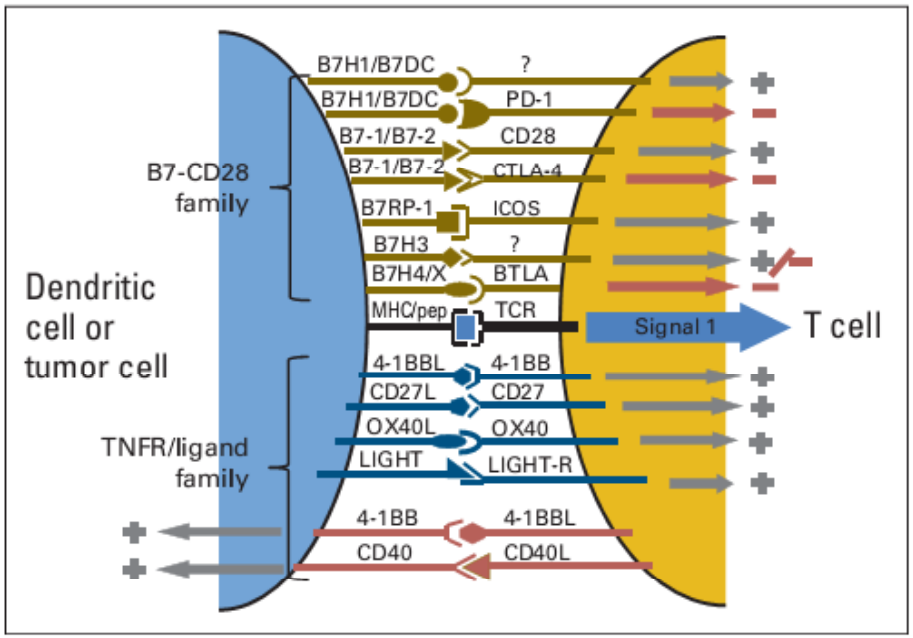
Immatics Corporate presentation, JPMorgan, Jan 2011; *Nat Rev Cancer*. 2012 Mar 22;12(4):237-51

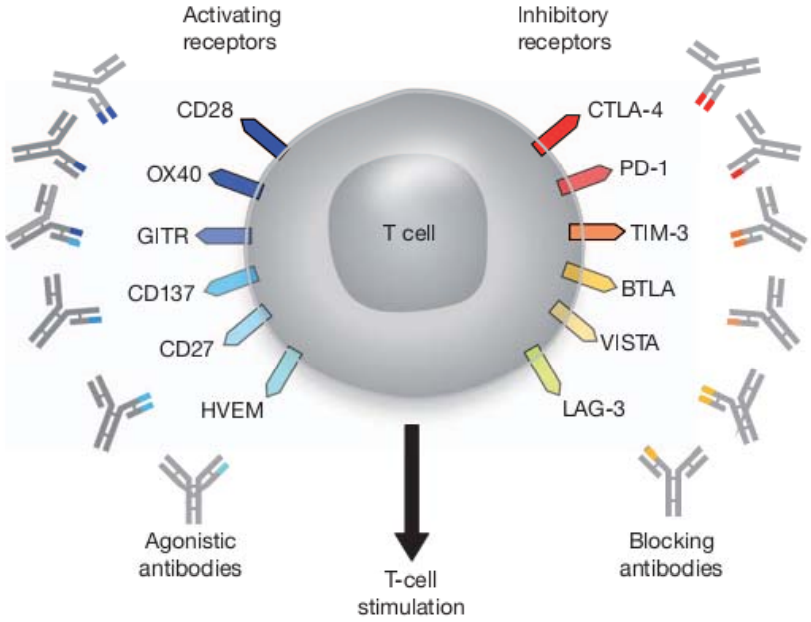
Immunotherapy & Immunotherapy

Checkpoint & Co-Stimulatory Combinations

The “Immune Synapse”

- Target recognition by T cells is two-step process. Specific interaction of T-cell receptor (TCR) with major histocompatibility complex (MHC) –peptide complexes displayed by tumor cells or antigen-presenting cells (APCs; e.g., dendritic cells) provides first signal for T-cell recognition. Second event is co-regulatory signal that determines whether T cell will become activated or anergic (nonreactive). T-cell co-receptors transmitting stimulatory or inhibitory signals on engagement of specific ligands expressed by tumor cells or APCs are depicted.





J Clin Oncol Vol. 29:4828-4836, Dec 2011; *Nature* 480, 480–489 (22 December 2011)

Cancer Immunotherapy Agents:
Phase 2 – Marketed

Mechanism (Technology)	Drug	Company	Phase	Tumor Types	Comments
CTLA-4 antagonist (mAb)	Ipilimumab	Bristol-Myers Squibb	Marketed (melanoma); Phase I-III (several cancers)	Malignant melanoma; other cancers	• Demonstrated survival advantage in metastatic melanoma in a Ph3 study (10.0 vs. 6.4 months in 2nd-line mets pts [n=676] receiving IPI+gp100 vs. gp100 alone) • Gr.3/4 immune-related AEs in 10-15% of IPI-treated patients (vs. 3% treated with gp100 alone) • No PFS benefit over carbo-tax alone in Ph2 NSCLC study
PD-1 antagonist (mAb)	Nivolumab (BMS-936558)	Bristol-Myers Squibb	Phase-II	Metastic melanoma, NSCLC, RCC, HRPC, CRC	• Objective response rate of 33% is better than Ipi' s 10% – 15% for a similar metastatic melanoma patient population, and with somewhat less severe overall side-effects • Two Ph1 dose-ranging studies in advanced cancers (metastatic melanoma, NSCLC, RCC, HRPC, CRC) have demonstrated clean safety (MTD not reached, absence of immune-related AEs) and high/durable response rates (15/46 [33%] mets melanoma, 7/19 [37%] RCC) • **Ph1 combination study with Ipi currently underway**
PD-1 antagonist (mAb)	CT 011	CureTech/ Teva	Phase-II	Hematological malignancies	• Ph1 study in advanced heme malignancies (AML, NHL, HL, MM) demonstrated clean safety profile and early evidence of clinical activity in 6/17 (35%) • Additional combination studies with gem (pancreatic), p53 vaccine (advanced solid), and rituximab (lymphoma)
4-1BB agonist (mAb)	Urelumab (BMS-663513)	Bristol-Myers Squibb	Phase-II	Malignant melanoma, NSCLC	• Among the 83 patients receiving IV urelumab 0.3 - 15 mg/kg every 3 weeks, 3 patients with melanoma experienced a partial response and 4 had stable disease • AEs included fatigue (26%; grade 3-4, 3%), reversible transaminitis grade 3-4 (11%), grade 3-4 neutropenia (5%)
CTLA-4 antagonist (mAb)	Tremelimumab	Pfizer/Astra Zeneca	Phase-II	Metastic melanoma, HCC, metastatic CRC	• TREM monotherapy failed to demonstrated survival benefit (11.8 vs. 10.7 months) over chemo in Ph3 metastatic melanoma study • Failure of TREM attributed to dosing, scheduling, and trial design rather than MOA despite subtle isotype differences • Licensed by Medimmune in October 2011

Adis R&D Insight; Thomson Pharma Partnering; clinicaltrials.gov

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Cancer Immunotherapy Agents:
Preclinical – Phase 1

Mechanism (Technology)	Drug	Company	Phase	Tumor Types	Comments
PD-1 antagonist (Fc-fusion)	AMP 224	Amplimmune/ GSK	Phase-I	Solid tumors	• Fusion protein blocks the interaction between PD-1, B7-H1 • Ph1 dose-escalation study in refractory cancer underway
OX40 receptor agonist (mAb)	Anti OX40	AgonOx/ AstraZeneca	Phase-I	HRPC, metastatic melanoma	• Currently enrolling for Ph1 dose-ranging HRPC study in combination with cyclophosphamide and radiation • Ph2 study planned for metastatic melanoma
B7-H3 antagonist (mAb)	MGA 271	MacroGenics/ Servier	Phase-I	Solid tumors	• Ph1 open-label dose-escalation study in cancer, including melanoma and glioblastoma, that overexpress B7-H3 (companion diagnostic)
4-1BB agonists (mAb)	PF-05082566	Pfizer	Phase-I	Cancer, NHL	• Open-label, Ph1 study initiated in patients with solid tumors, B-cell lymphoma or NHL, in combination with rituximab
PD-L2 antagonist (mAb)	rHIgM12B7	Mayo Foundation	Phase-I	Malignant melanoma	• Purified antibody from patient serum activates immature and mature DC in vitro and induces potent anti-melanoma response in animal model • Ph1 study in St.IV melanoma currently ongoing
PD-L1 antagonist (mAb)	BMS-936559	Bristol-Myers Squibb	Phase-I	Solid tumor	• Ph1 trial in in advanced or recurrent solid tumors ongoing • Two additional studies (heme malignancies, metastatic melanoma) withdrawn prior to enrollment in 12/2011
PD-L1 antagonist (mAb)	RG-7446	Roche	Phase-I	Solid tumor	• Open-label, dose-escalation, phase I study initiated in patients with locally advanced or metastatic solid tumors
PD-1 antagonist (mAb)	MK-3475	Merck & Co.	Phase-I	Advanced melanoma	• SD, unconfirmed PR and unconfirmed CR observed in 5, 2, and 1 patient, respectively (n=19), based on the Immune-Related Response Criteria (primary endpoint) at week 12
B7-H3 antagonist (mAb)	8H9 MAb	United Therapeutics	Phase-I	Metastatic brain cancer	• Currently in early development for brain metastases originating from other tissues in the body
4-1BB agonists (mAb)	anti-CD137	GTC Bio-therapeutics	Preclin	Cancer	• licensed from Mayo Clinic
CTLA-4 antagonist (mAb)	anti-CTLA-4 monoclonal	Aida Pharma-ceuticals	Preclin	Cancer	• Development is at the preclinical stage in China
OX40 agonist (Fc-fusion)	OX40 agonists	AgonOx/ AstraZeneca	Preclin	Cancer	• Immunoglobulin fusion of OX40 ligand (OX40L), complexes OX40L trimers to agonize OX40 receptor

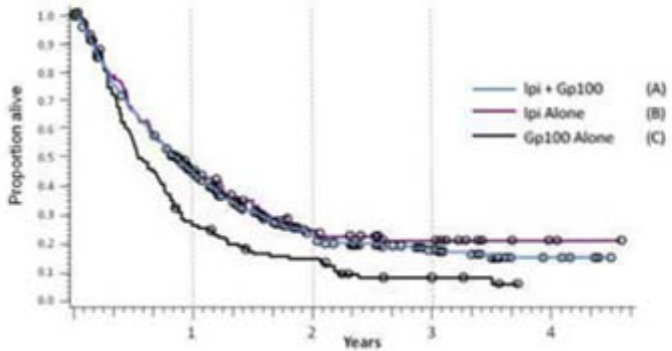
Adis R&D Insight; Thomson Pharma Partnering; clinicaltrials.gov

Yervoy Produces Long-Term Durable Responses, but in Small Number of Patients

"The tails on the survival curves go out beyond five years or more for the 10-20% of responders, which albeit is low and something to improve upon."

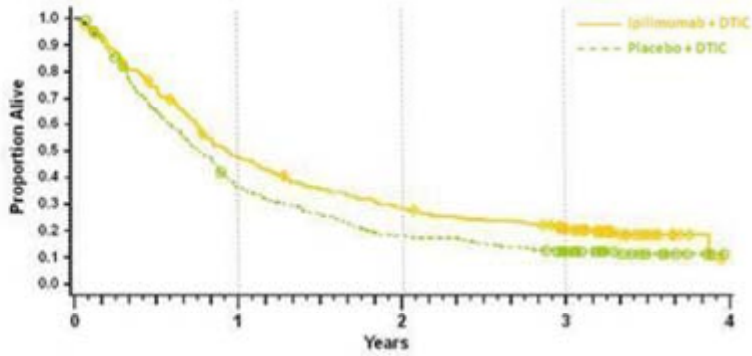
- Carsten Reinhart, CMO, immatics (Biocentury, 6/18/12)

MDX010-020 study
modified from Hodi et al. *N Engl J Med.* 2010



Survival Rate	Ipi + gp100 N=403	Ipi + pbo N=137	gp100 + pbo N=136
1 year	44%	46%	25%
2 year	22%	24%	14%

Ca184-024 study
modified from Robert et al. *N Engl J Med.* 2011



Survival Rate	1 Year	2 Year	3 Year
Ipilimumab + DTIC n=250	47.3	28.5	20.8
Placebo + DTIC n=252	36.3	17.9	12.2

Figure 1 Comparison between the Overall Survival curves of the studies MDX010-20 and CA184-024.

J.Transl.Med. 2011 Nov 13;9:196.

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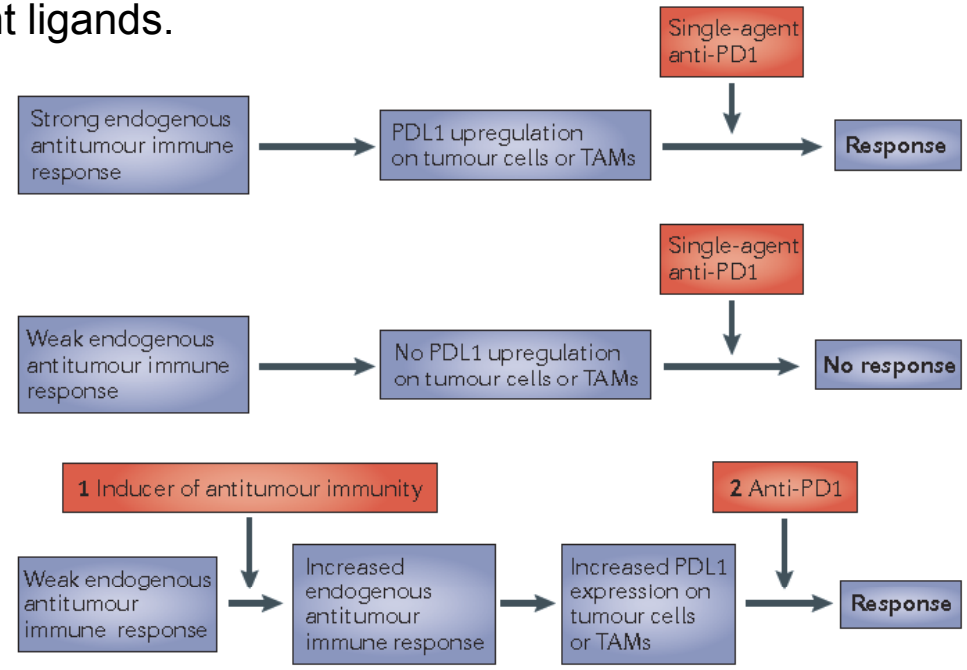
Multiple Immunostimulatory Approaches Needed to Maximize Tumor Regression?

- **Unleashing the immune system on cancer growth may require both checkpoint inhibition and vaccine-mediated immunostimulation:**
  - Blockade of an immune-checkpoint will only induce tumor regressions when there is a pre-existing antitumor immune response to be 'unleashed'
  - On the other hand, vaccine-mediated activation of an antitumor immune response may be ineffective if tumors respond by upregulating immune-checkpoint ligands.

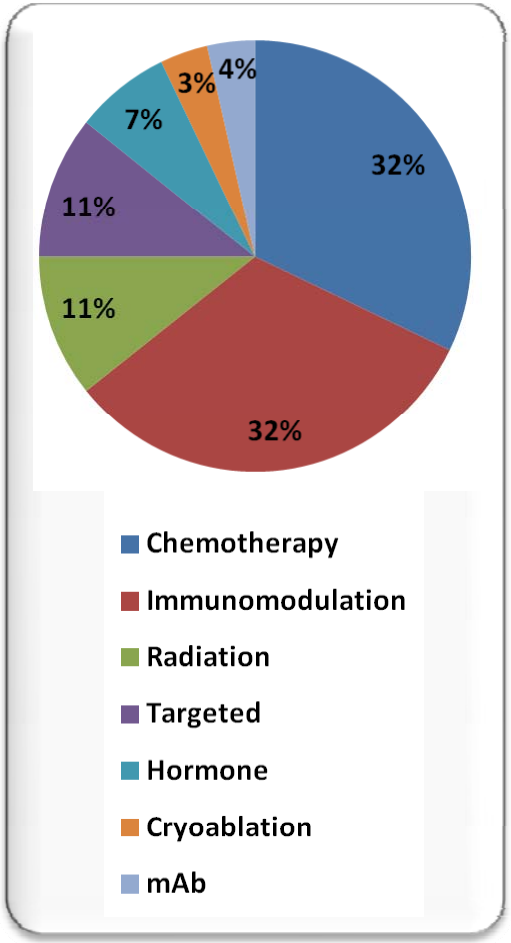


Nat.Rev.Cancer 2012 Mar 22;12(4):252-64.

Ipilimumab Combination Studies* (n=28)

Sponsor/Collaborators	Phase (n)	Condition	Intervention + Ipi
BMS	3 (912)	SCLC	Etoposide, cisplatin, carboplatin
NCI, ECOG	3 (1500)	Melanoma	PegIFNα-2b
BMS	3 (920)	NSCLC	Paclitaxel, carboplatin
BMS, MSKCC	2 (39)	Melanoma	Melphalan, Dactinomycin
BMS, MDACC	2 (20)	Prostate	Leuprolide
BMS, MDACC	2 (48)	Prostate	Leuprolide, goserelin, degarelix
BMS, MDACC	2 (64)	Melanoma (mets)	Temozolomide
UCSF	2 (43)	Melanoma (mets)	GM-CSF
University of Brussels	2 (39)	Melanoma (III/IV)	TriMix-DC
BMS	2 (330)	SCLC, NSCLC	Paraplatin
BMS, Hoosier Oncology	2 (36)	Urothelial	gemcitabine, cisplatin
NCI, ECOG	2 (220)	Melanoma	GM-CSF
BMS, Roche	1/2 (50)	Melanoma	Vemurafenib (BRAF inhibitor)
FHCRC, NCI	1/2 (10)	Melanoma (rel/IV)	alloSCT
Incyte	1/2 (136)	Melanoma (mets)	INCB024360 (IDO1 inhibitor)
UPenn	1/2 (40)	Melanoma (mets)	Stereotactic Body Radiation
DFCI, Roche, BMS	1 (46)	Melanoma	Bevacizumab
BMS	1 (15)	NSCLC	Paclitaxel, carboplatin
Northwestern	1 (28)	Pancreatic (III/IV)	Gemcitabine
Sidney Kimmel	1 (30)	Pancreatic	pcDNA-1 neo vaccine
Institut Gustave Roussy	1 (30)	Melanoma	Radiation
Merck, H. Lee Moffitt	1 (36)	Melanoma	PegIFNα-2b
BMS	1 (120)	Melanoma	BMS-908662 (BRAF inhibitor)
BMS, Ono	1 (64)	Melanoma	MDX1106-04 (anti-PD1 mAb)
BMS	1 (60)	Melanoma (adv.)	Carbo-tax, dacarbazine
NCI, UCSF	1 (36)	Prostate Cancer	GM-CSF

Adis R&D Insight; clinicaltrials.gov



*Clinical trials reported in *www.clinicaltrials.gov* that are active or recruiting patients

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BMS's Ipi + Anti-PD1 Trial: The Test Case

- **BMS is currently conducting an open-label phase I trial to assess safety and efficacy of multiple doses of nivolumab (BMS-936558) in combination with ipilimumab in patients with malignant melanoma (est. completion: 8/2014).**

A Phase 1b, Open-label, Multicenter, Multidose, Dose-escalation Study of BMS-936558 (MDX-1106) in Combination With Ipilimumab in Subjects With Unresectable Stage III or Stage IV Malignant Melanoma

Study Arm	Assigned Interventions	Study Endpoints	Study Population (est. n=64)
C1	BMS-936558 (0.3 mg/kg) + Ipilimumab (3 mg/kg)	1°: Safety assessments 2°: • PK peak and trough concentration • Blood samples to test immunogenicity • Tumor response evaluations	• Histologic diagnosis of malignant melanoma • Measurable unresectable Stage III or IV melanoma • ECOG performance status score of 0 or 1 • subjects treated with ≤3 prior systemic standard treatments
C2	BMS-936558 (1 mg/kg) + Ipilimumab (3 mg/kg)		
C3	BMS-936558 (3 mg/kg) + Ipilimumab (3 mg/kg)		
C4	BMS-936558 (3 mg/kg) + Ipilimumab (10 mg/kg)		
C5	BMS-936558 (10 mg/kg) + Ipilimumab (10 mg/kg)		
C6	BMS-936558 (1 mg/kg)		
C7	BMS-936558 (3 mg/kg)		

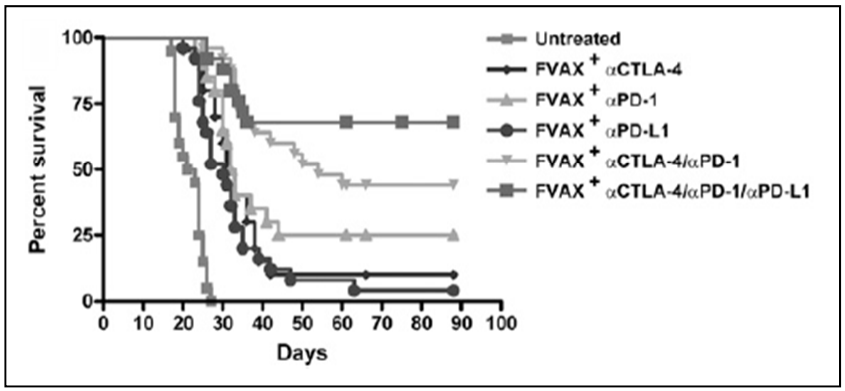
Clinicaltrials.gov

- Nivolumab is a PD-1 inhibitor touted as a safer and possibly more efficacious means of targeting the immune checkpoint relative to anti-CTLA4, and combining the two approaches could have a synergistic effect that can not be achieved at the MTD of either agent alone. **The challenge for this or any combination regimen will be balancing clinical benefit with toxicity.**

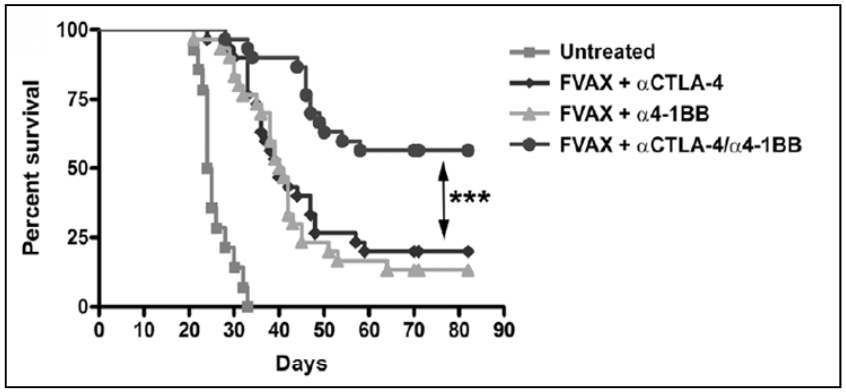
Preclinical Combinatorial Studies:
Dual Checkpoint Inhibition and/or Costimulation

- **Simultaneous activation and inhibition of co-stimulatory and immune checkpoint pathways, respectively, could be necessary to prevent compensatory adaptation and maximize efficacy of CTLA-4 inhibition.**
- Murine data suggest that combinations* of CTLA-4 and PD-1/PD-L1 blockade, or CTLA-4 blockade and 4-1BB activation, act synergistically in extending survival.

αCTLA-4 ± αPD-1/αPD-L1:



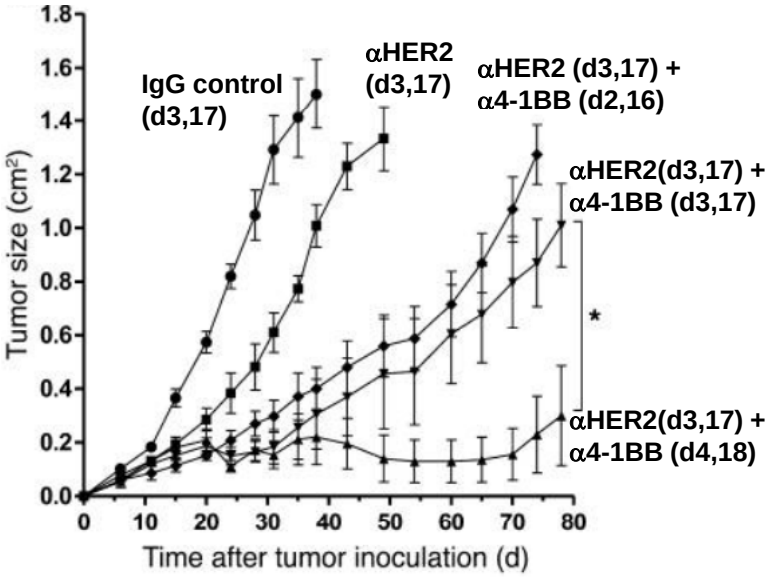
αCTLA-4 ± α4-1BB:



Proc Natl Acad Sci U S A. 107(9):4275-80. March 2010; PLoS One. 2011 Apr 29;6(4):e19499
*Studies were conducted in combination with a vaccine consisting of irradiated B16 melanoma cells expressing Flt3-ligand (Fvax)

Preclinical Combinatorial Studies:
Costimulation + Targeted mAb

- **Costimulatory agonist (α4-1BB agonist mAb) augments clinical efficacy of anti-HER2 mAb trastuzumab (Herceptin).**



Since maximal upregulation of 4-1BB requires 24 hours of NK cell exposure to trastuzumab-coated cells in vitro, injection sequence and timing was crucial for optimizing tumor regression

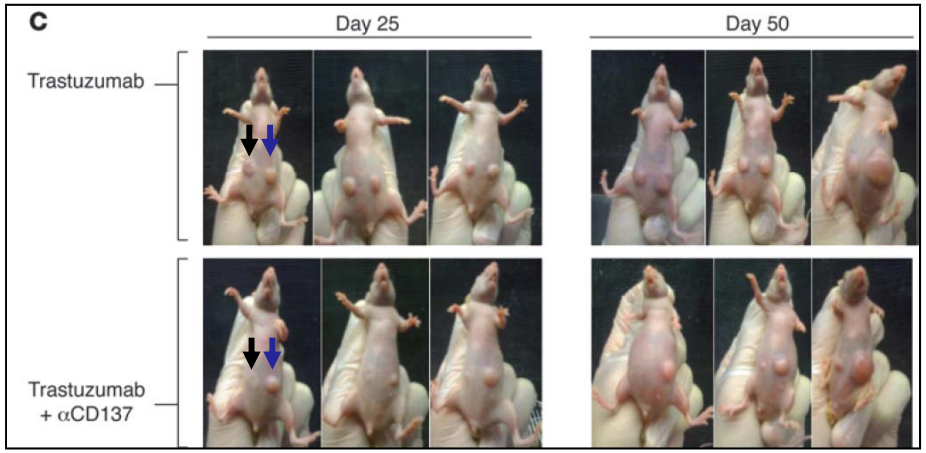
J.Clin.Invest. 2012 Mar 1;122(3):1066-75

Research article

Stimulation of natural killer cells with a CD137-specific antibody enhances trastuzumab efficacy in xenotransplant models of breast cancer

Holbrook E. Kohrt,[1] Roch Houot,[1,2,3] Kipp Weiskopf,[1] Matthew J. Goldstein,[1] Ferenc Scheeren,[4] Debra Czerwinski,[1] A. Dimitrios Colevas,[1] Wen-Kai Weng,[1] Michael F. Clarke,[4] Robert W. Carlson,[1] Frank E. Stockdale,[1] Joseph A. Mollick,[1] Lieping Chen,[5] and Ronald Levy[1]

[1]Department of Medicine, Division of Oncology, Stanford University, Stanford, California, USA. [2]Service d'Hématologie Clinique, Centre Hospitalier Universitaire de Rennes, Rennes, France. [3]INSERM U917, Université de Rennes 1, Rennes, France. [4]Institute for Stem Cell Biology and Regenerative Medicine, Stanford University, Stanford, California, USA. [5]Department of Immunobiology, Yale Cancer Center, New Haven, Connecticut, USA.



Anti-CD137 agonistic mAb enhances anti–breast cancer activity of trastuzumab in vivo while retaining HER2 specificity against HER2-overexpressing breast cancer cell lines and a primary breast tumor. Mice were inoculated with HER18 breast tumor cells (HER2+) on the left flank (black arrow) and MCF7 breast tumor cells (HER2-) on the right flank (blue arrow), followed by treatment with either trastuzumab alone (top panels) or trastuzumab + anti-CD137 antibody (bottom panels).

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Preclinical Combinatorial Studies:
Costimulation + Oncolytic Virus

- **Combinatorial approach to enhance the antitumor efficacy of an oncolytic virus.**

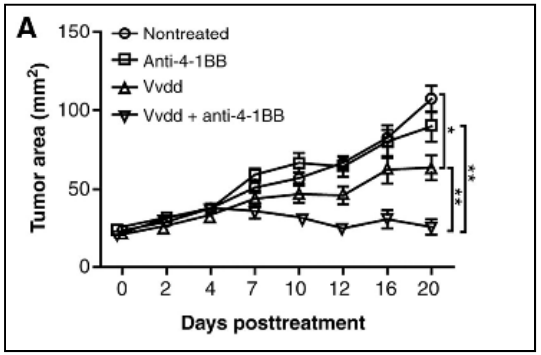
Cancer Res. 2012 Apr 1;72(7):1651-60. Epub 2012 Feb 7.

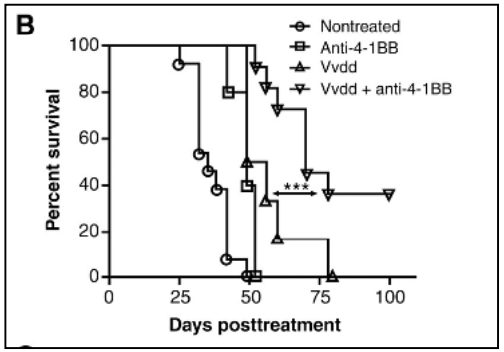
Oncolytic virus and anti-4-1BB combination therapy elicits strong antitumor immunity against established cancer.

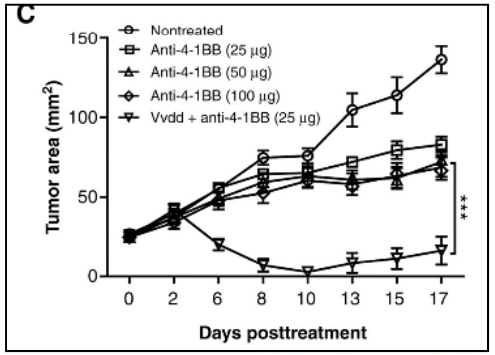
John LB, Howland LJ, Flynn JK, West AC, Devaud C, Duong CP, Stewart TJ, Westwood JA, Guo ZS, Bartlett DL, Smyth MJ, Kershaw MH, Darcy PK.
Cancer Immunology Program, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia.

Abstract

Oncolytic virotherapy using vaccinia virus (Vv) has shown some encouraging antitumor responses in mouse models and patients, but the breadth of efficacy in clinical trials has been somewhat limited. Given that antitumor effects have correlated with increased host immune responses, we hypothesized that improved therapeutic outcomes may be achieved by using oncolytic virus (OV) in combination with a potent immune agonist reagent. In this study, we carried out a preclinical evaluation of a genetically engineered strain of oncolytic vaccinia virus (Vvdd) for its capacity to induce antitumor responses when combined with an agonist antibody (Ab) specific for the costimulatory molecule 4-1BB (CD137). In immune-competent syngeneic mouse models of cancer, this combination therapy significantly reduced the growth of established subcutaneous tumors relative to either treatment alone. Importantly, the development of pulmonary metastatic lesions was also reduced. Tumor growth inhibition was associated with increased numbers of CD11b(+) and CD11c(+) myeloid cells in the tumor draining lymph nodes, greater infiltration of CD8(+) effector T and natural killer (NK) cells, and a more sustained presence of neutrophils at the tumor site. Depletion of T or NK cells or neutrophils reduced efficacy, confirming their contribution to an effective therapeutic response. We further extended this conclusion through results from IFNγ-deficient mice. In summary, our findings offered a proof-of-concept for a combinatorial approach to enhance the antitumor efficacy of an OV, suggesting a strategy to improve their use as an immunotherapeutic treatment for cancer.







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Preclinical Combinatorial Studies:

Costimulation + Checkpoint Inhibition + Oncolytic Virus

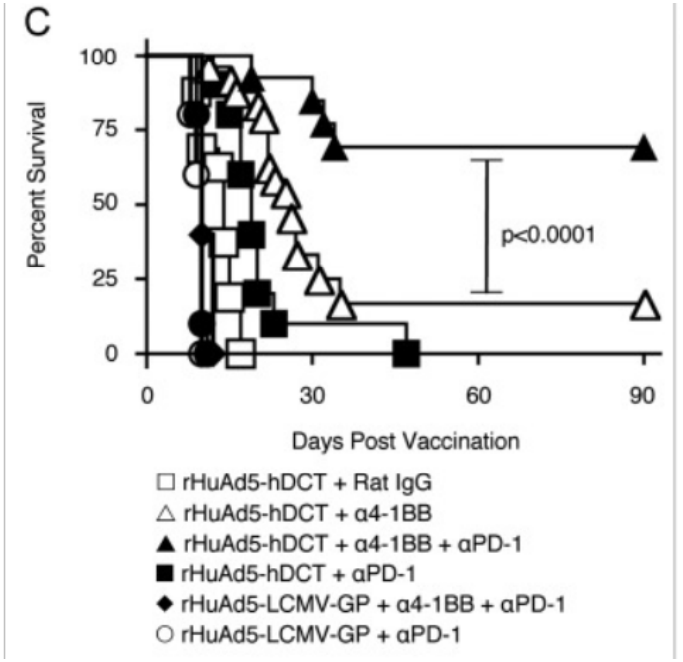
Combined vaccination and immunostimulatory antibodies provides durable cure of murine melanoma and induces transcriptional changes associated with positive outcome in human melanoma patients

A.J. Robert McGray, Dannie Bernard, Robin Hallett, Ryan Kelly, Mayank Jha, Caitlin Gregory, Jennifer D. Bassett, John A. Hassell, Guillaume Pare, Yonghong Wan and Jonathan L. Bramson*

Department of Pathology and Molecular Medicine; McMaster University; Hamilton, ON Canada

Keywords: T lymphocyte, vaccine, immune suppression, 4-1BB, PD-1, gene profiling

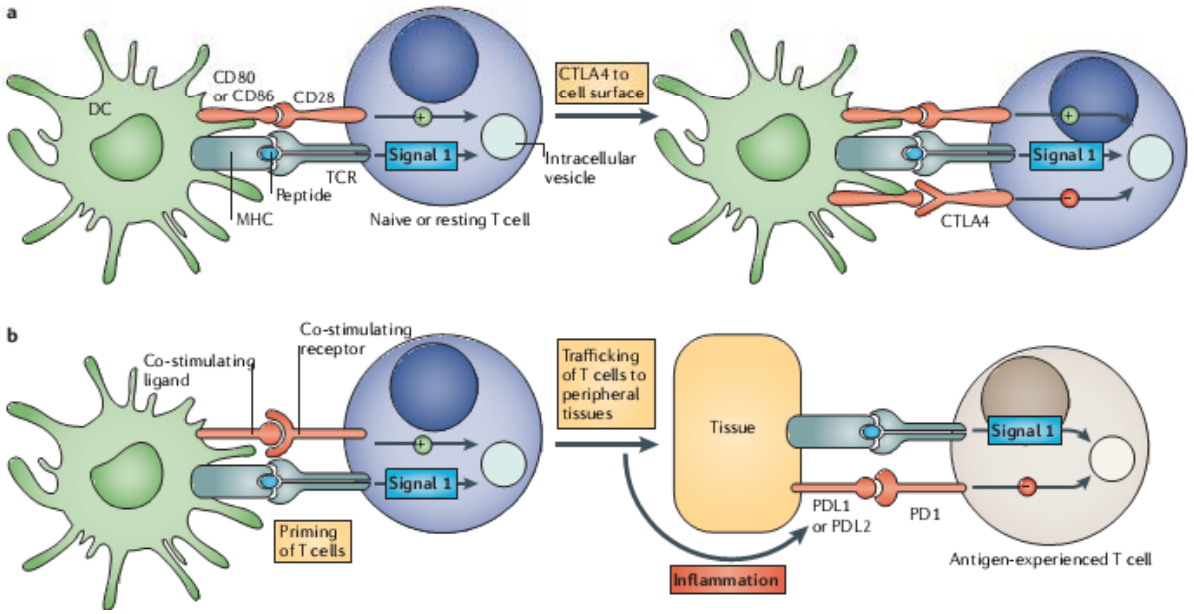
We have developed a recombinant adenovirus vaccine encoding dopachrome tautomerase (rHuAd5-hDCT) that produces robust DCT-specific immunity, but only provides modest suppression of murine melanoma. In the current study, an agonist antibody against 4-1BB was shown to enhance rHuAd5-hDCT efficacy and evoke tumor regression, but most tumors ultimately relapsed. The vaccine triggered upregulation of the immune inhibitory PD-1 signaling pathway and PD-1 blockade dramatically enhanced the rHuAd5-hDCT + anti-4-1BB strategy, resulting in complete regression of growing tumors in > 70% of recipients. The impact of the combined anti-4-1BB/anti-PD-1 treatment did not manifest as a dramatic enhancement in either the magnitude or functionality of DCT-specific tumor infiltrating lymphocytes relative to either treatment alone. Rather, a synergistic enhancement in intratumoral cytokine expression was observed, suggesting that the benefit of the combined therapy was a local event within the tumor. Global transcriptional analysis revealed immunological changes within the tumor following the curative vaccination, which extended beyond the T cell compartment. We identified an immune signature of 85 genes associated with clearance of murine melanoma that correlated with improved survival outcome in two independent cohorts of human melanoma patients. Our data reinforce the concept that successful vaccination must overcome local hurdles in the tumor microenvironment that are not manifest within the periphery. Further, tumor rejection following vaccination involves more than simply T cells. Finally, the association of our immune signature with positive survival outcome in human melanoma patients suggests that similar vaccination strategies may be promising for melanoma treatment.



OncoImmunology 1:4, 419–431; July 2012

Some Data Do Suggest Targeting PD-1 Could Be Better (Safer) Than CTLA4

- B7-H1/PD-L1, unlike B7-1/-2, is selectively upregulated by many human cancers. Although CTLA-4 regulates de novo immune responses, the PD-1pathway exerts its major influence on ongoing (effector) immune responses. This is supported by the preclinical data, especially the distinct phenotypes of PD-1 genetic knockout mice, which develop delayed-onset organ-specific inflammation, as opposed to the uncontrolled global T-cell proliferation seen in CTLA-4 knockout mice.
- Therefore, CTLA4 functions as a signal dampener to maintain a consistent level of T cell activation in the face of widely varying concentrations and affinities of ligand for the TCR. On the other hand, the major role of the programmed cell death protein 1 pathway is not at the initial T cell activation stage but rather to regulate inflammatory responses in tissues by effector T cells recognizing antigen in peripheral tissues.



Nat Rev Cancer. 2012 Mar 22;12(4):252-64

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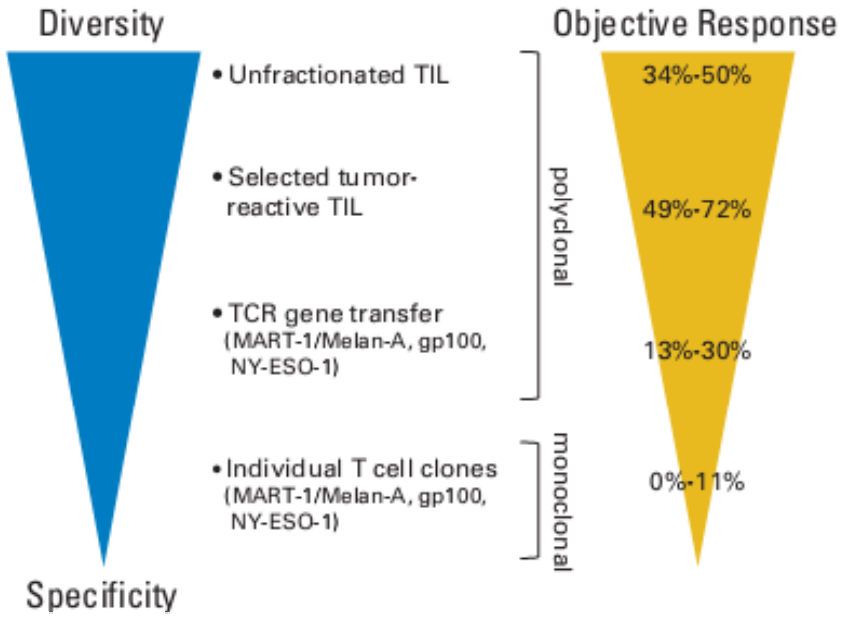
Final Thoughts

Combination Immunotherapy – The Good, The Bad & The Ugly

Strengths	***Weaknesses***
▪ Dialing in/out of specificity (single tumor type versus multiple, depending on approach) ▪ Synergy with many other modalities (as we will discuss) ▪ Immune response as surrogate of drug activity	▪ Preclinical models of synergy may be difficult, especially with human co-stimulatory or checkpoint targets ▪ Dosing, dosages, timing: no good industrialized way to test all the possible combinations of approaches, sequencing and schedules ▪ Regulatory challenges, while improving, still exist for combinations ▪ Safety limitations ▪ Company-Company collaboration challenges
Opportunities	***Threats***
▪ Various biomarkers of immune response are becoming correlated with outcomes - predictive ▪ Depending on approach (e.g., checkpoint inhibitors, multi-antigen vaccines), it might be harder for tumors to escape an optimized immunotherapy than some key drivers of tumor growth and spread ▪ Utility across multiple cancers, depending on antigen(s) ▪ "Epitope spreading"/"cross-priming" may broaden activity	▪ Other anticancer approaches and combinations might prove more tractable to standard drug development and commercialization models

Where Do We Go From Here?

- How to balance complexity and activity, logistics and cost, efficacy and safety?
- What will be the most effective immunotherapy combinations, at what dose, and in which sequence?



;*J Clin Oncol* 29:4828-4836, Dec 2011

Association between immunologic diversity of transferred T cells and improved clinical outcomes from adoptive cell transfer (ACT) in patients with metastatic melanoma. Autologous unfractionated tumor-infiltrating lymphocytes (TILs) infused in conjunction with systemic interleukin 2 yielded objective responses in 34% to 50% of patients. Biomarker studies correlating clinical responses with in vitro TIL properties of tumor-specific cytolysis and cytokine secretion led to development of more complex culture methods to deliberately select tumor-reactive subcultures for therapy. Combined with more intense chemoradiotherapy preconditioning regimens, objective clinical response rates of 49% to 72% were achieved with selected TILs. In contrast, lower response rates were observed in ACT studies using T-cell receptor (TCR) –transduced T cells (mixtures of CD4and CD8cells) or monoclonal CD4or CD8T-cell cultures specific for single melanoma antigen (MART-1/Melan-A, gp100, NY-ESO-1). Outgrowth of antigen-loss tumor variants in these patients, reflect-ing successful antigen targeting, also indicated capacity of rapidly adaptable tumor cells to evade narrowly focused therapies. Although these summarized results are gleaned from nonrandomized ACT studies, there seems to be association between immunologic diversity of infused cells and likelihood of clinical activity.

Cancer Immunotherapy: Legit at Last?

Immunotherapy Comes Of Age At ASCO 2012

June 18, 2012 |

Until just recently, immunotherapy (or stimulation of the immune system to treat disease) was regarded as an ill-conceived approach in cancer drug development. Many scientists and investors did not consider immunotherapy treatment to be a legitimate area of cancer research. The skepticism was not totally unfounded as there had been years of failures, such as those from CancerVax, IDM, and Cell Genesys to name a few. However, the immunotherapy sector learned from previous mistakes and is now beginning to prevail. In April 2010, the FDA approved the first cancer immunotherapy, Dendreon's (DNDN) Provenge for prostate cancer. It then approved Bristol-Myers Squibb's (BMY) Yervoy for melanoma in March of the following year. Immunotherapy has emerged as a validated approach in the treatment of cancer, resulting in significant survival benefits with a superior safety profile to chemotherapy and radiation treatment. At the American Society of Clinical Oncology (ASCO) conference in early June, there were over 300 abstracts relating to immunotherapy. The technology's advancement is evident by its growth from that of less than 125 abstracts in 2009. This article highlights some of advancements in cancer immunotherapy that were presented at ASCO 2012.

According to Semantelli, a market research firm that tracks social media in the drug world, Bristol-Myers Squibb generated the third largest amount of buzz at ASCO this year with its cancer immunotherapy, BMS-936558. The anti-PD-1 antibody was shown to significantly reduce tumors in certain patients with melanoma, kidney, and lung cancers. Nine patients suffered from serious side effects, with three deaths resulting from lung inflammation. However, the safety profile did appear to be milder than that of Yervoy, which has already obtained marketing approval. What attracted so much attention was that previous treatment with conventional therapies was unsuccessful in these patients, so this was a difficult to treat patient set. BMS-936558 belongs to the same class of immunomodulators as Yervoy. Both antibodies target proteins (PD-1 and CTLA-4, respectively) that are found on and regulate the activity of cytotoxic T-lymphocytes, a type of immune cell that can kill foreign cells in the body. Cytotoxic T-cells are like blood hounds that can hunt down and kill tumors. Cancer cells have been shown to escape the body's immune system by suppressing the activity of cytotoxic T-cells via these two proteins. While BMS-936558 is relatively early in development, investment analysts are already forecasting peak sales of $2 billion for the drug.

FierceBiotech
THE BIOTECH INDUSTRY'S DAILY MONITOR

BIO 2012: Immunotherapies make a comeback at Big Pharma

June 25, 2012 | By John Carroll

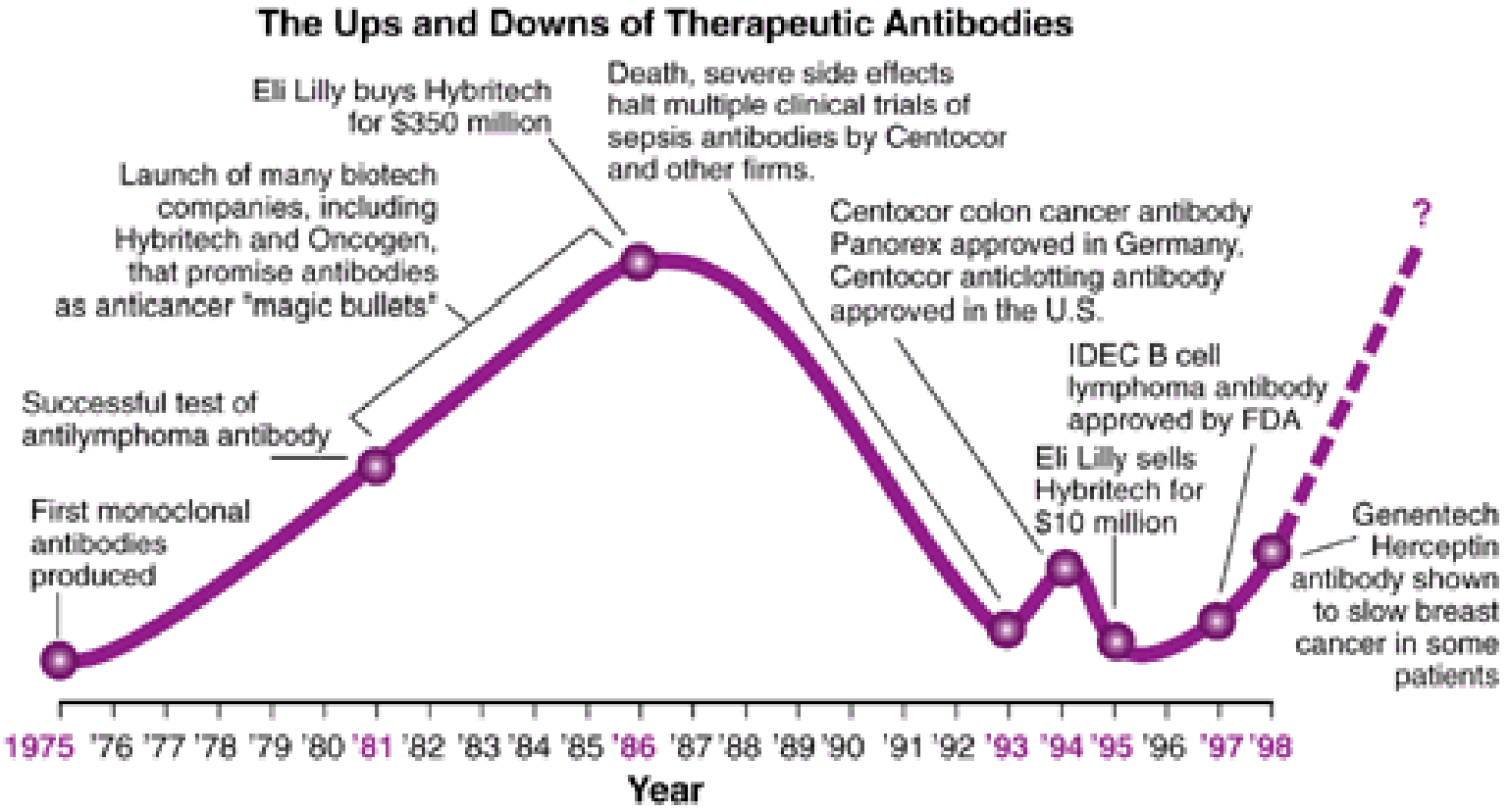
BIO 2012 International Convention Slideshow
Launch slideshow >>

The annual BIO meeting is typically short on news. But it's a great place to pick up on the latest trends in drug development. With that in mind, I wanted to flag a few interesting remarks gleaned from last week's confab in Boston.

It's now clear that some prominent Big Pharma companies have gained a healthy appetite for immunotherapies. Developers have blown hot and cold on immunotherapies in recent years. At first viewed as a hot new field, they often failed to measure up as solo therapies for cancer. But now the sparkle is back in the eyes of the licensing groups.

"It reminds me of monoclonal antibodies," says Joe McCracken, the global head of business development at Roche ($RHHBY). Antibodies, he explains, went through the classic ups and downs usually associated with a long and winding development path for a new technology. Like a lot of new therapeutic arenas, interest peaked early, then slumped and eventually swelled back up. And immunotherapies are going through the same metamorphosis.

Pharma – Early Adopters and Late Entrants: Just Like Monoclonal Antibodies



Antibodies Stage a Comeback in Cancer Treatment"
Science, Volume 280, Number 5367 Issue of 22 May 1998, pp. 1196 - 1197

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- Joel Sandler, PhD, Consultant, Defined Health
- Jedd Wolchuk, Memorial Sloan-Kettering Cancer Center
- Neil Berinstein, Sunnybrook Research Institute

Defined Health is pleased to present…

March 5 – 6, 2013 | **Conrad New York**
www.cancerprogressbyDH.com

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www.therapeuticinsight.com

Defined Health will also be participating in the following industry events:

ICAAC | September 9 - 12, 2012 | San Francisco
BioPharm America™ 2012 | September 19 - 21, 2012 | Boston
LES 2012 Annual Meeting | October 14 - 17, 2012 | Toronto
IDSA | October 17 - 21, 2012 | San Diego
US Japan Health Sciences Dialogue 2012 | November 27 - 28, 2012 | Philadelphia
ASH | December 8-11, 2012 | Atlanta

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24th ANNUAL CANCER PROGRESS CONFERENCE

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THERAPEUTIC INSIGHT

Topics include:

- Translational Oncology
- Cancer Metabolism
- Diagnosis with Next Generation Sequencing
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- Epigenetics
- Growing a Cancer-Focused Biotech
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- Next Generation Biologics

2013 Keynote Speakers:

- Giulio Draetta, PhD, MD, MD Anderson Cancer Center
- Sir Michael Rawlins, MD, NICE

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- Robert Cohen, Genentech
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