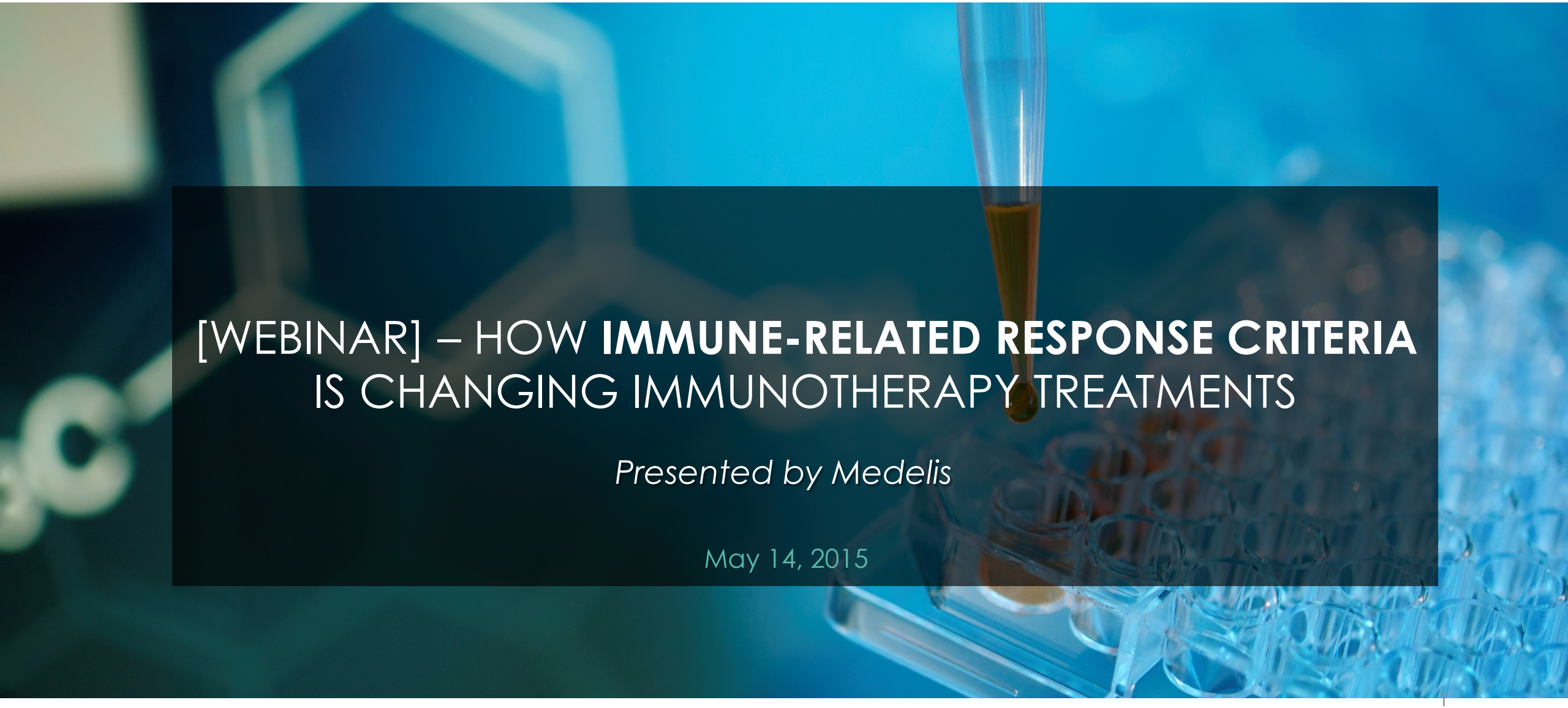
MEDELIS
Clinical answers, faster.



[WEBINAR] – HOW **IMMUNE-RELATED RESPONSE CRITERIA** IS CHANGING IMMUNOTHERAPY TREATMENTS

Presented by Medelis

May 14, 2015

Welcome! A few quick notes…

- We will handle questions via email
- Send your questions to: immunotherapy@medelis.com
- Please whitelist "@medelis.com" to avoid getting caught in your spam folder
- We promise to respond to all – please give us 1-4 days due to volume of responses

Introductions

John Grous M.D.

- Board-certified medical oncologist
- Serves as medical monitor on numerous immunotherapy trials
- Served as medical director in pharmaceutical industry for 20 years
- Study Physician at AstraZeneca on INTACT 1& 2 studies (Iressa /gefitinib) adding targeted therapy to standard chemo for front line NSCLC treatment
- Member of NDA Team which obtained accelerated FDA approval
- Consultant for Medelis serving as Vice President of Medical Affairs since 2006

David Browning

- 20+ years of drug development experience in industry and academic settings
- Directly managed over 200 studies
- Managed 15 recent immunotherapy studies in oncology
- Close working relationship with Medelis medical advisors and key opinion leaders in immunotherapy
- Oversight for all US clinical operations for Medelis

Medelis Background

- Oncology specialization
- Founded in 2003
- Phase I – Phase III in North America and Europe
- Oncology experience at all levels - from senior to all operational levels
- Often handle complex trials
- 15 immunotherapy trials over past few years
- Experienced with antibody therapies, cancer vaccines, and cytokines
- Strong working relationship with over 100 oncology investigators with immunotherapy experience

Webinar Content

Cancer Immunity Cycle

- Adaptive Immune System
- Enhancing Cancer Immunotherapy

Immune-Related Response Criteria

- Wolchok JD et al: Clin Cancer Res 2009; 15(23): 7412-20.
- irRC vs. WHO and RECIST 1.1

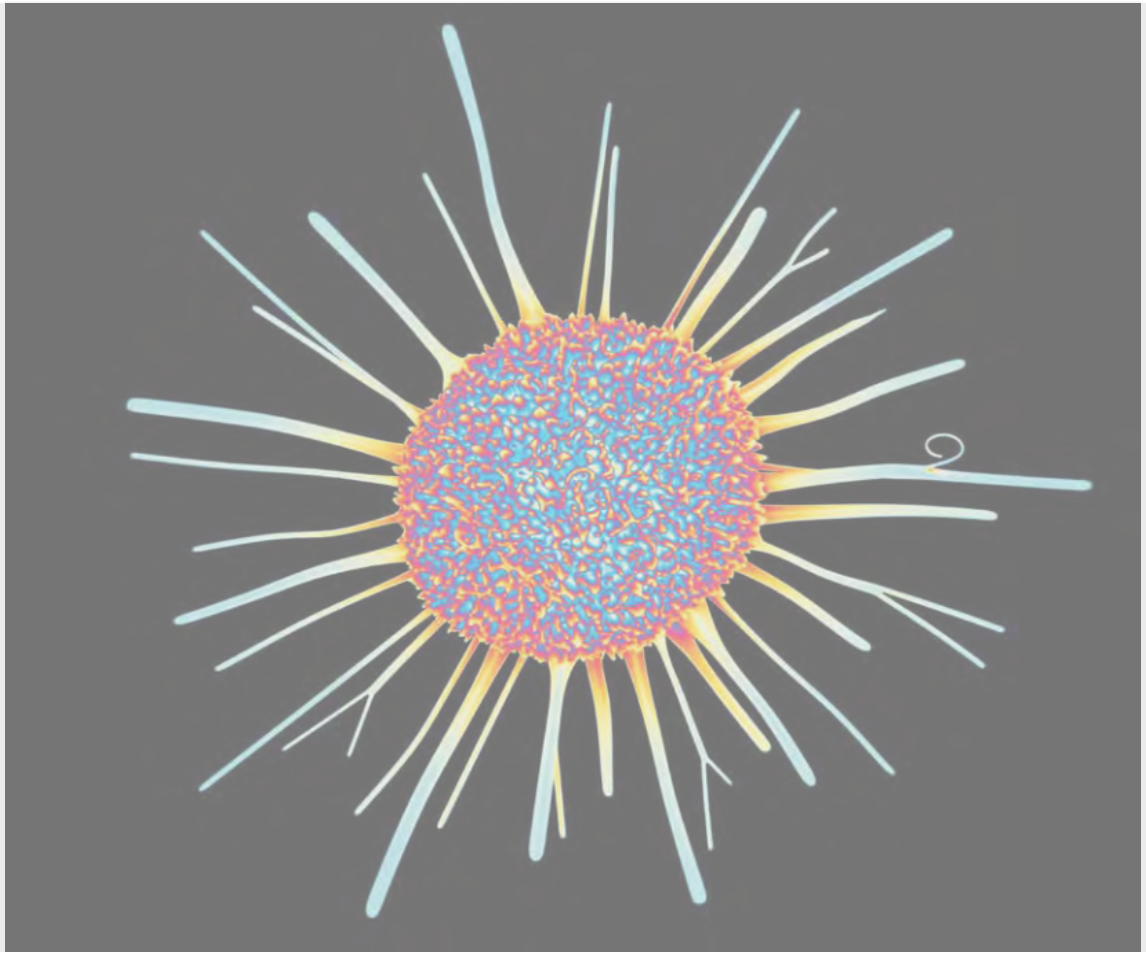
Current Status of New Immunotherapeutic Approaches in Solid Tumors

- Immune Checkpoint Inhibitors
- Combination Approaches

Cancer Immunity Cycle

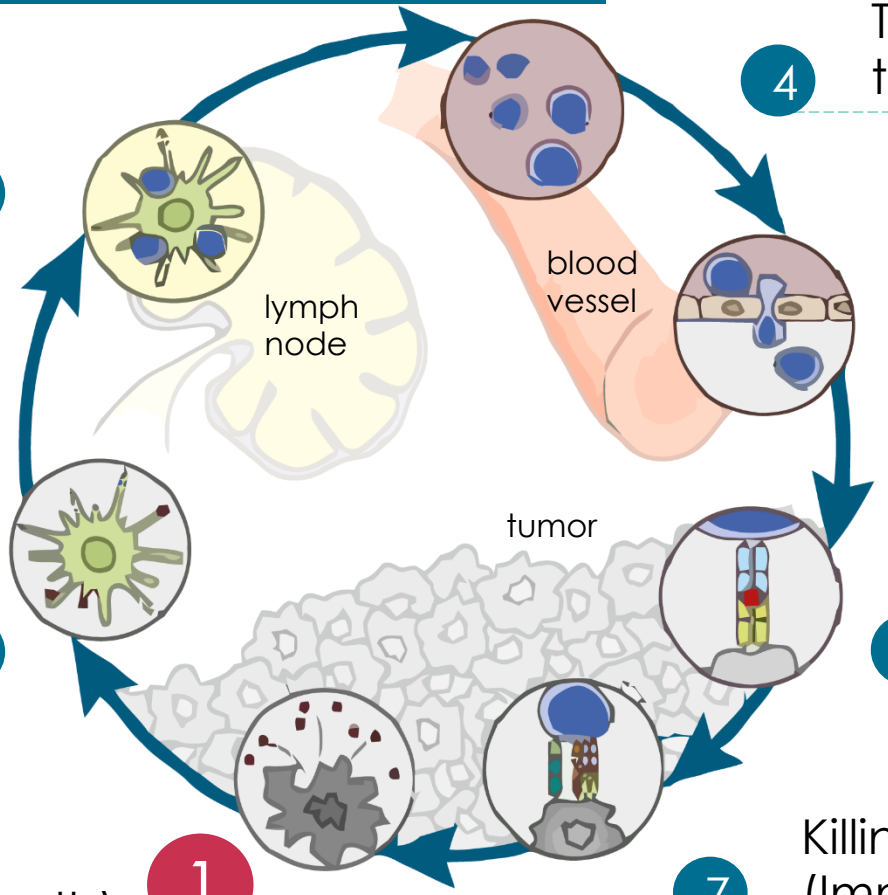
Biology Common to Neoplastic Cells

- Evading growth suppressors
- Avoiding immune destruction
- Enabling replicative immortality
- Tumor-promoting inflammation
- Activating invasion and metastasis
- Inducing angiogenesis
- Genome instability and mutation
- Resisting cell death
- Sustaining proliferative signaling
- Deregulating cellular energetics



Hanahan D, et al. *Cell*. 2011;144(5):646-674.

The Cancer-Immunity Cycle



1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells/APCs)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (Immune and cancer cells)

The generation of immunity to cancer is a cyclic process that can be self propagating, leading to an accumulation of immune-stimulatory factors that in principle should amplify and broaden T cell responses. The cycle is also characterized by inhibitory factors that lead to immune regulatory feedback mechanisms, which can halt the development or limit the immunity. This cycle can be divided into seven major steps, starting with release of antigens from the cancer cell and ending with the killing of cancer cells. Each step is described above, with the primary cell types involved and anatomic location of the activity listed. Abbreviations are as follows: APCs, antigen presenting cells: CTLs, cytotoxic T lymphocytes.: Mellman I. *Immunity* 39, July 2013; 1-10.

How Cancer Escapes Immune Recognition

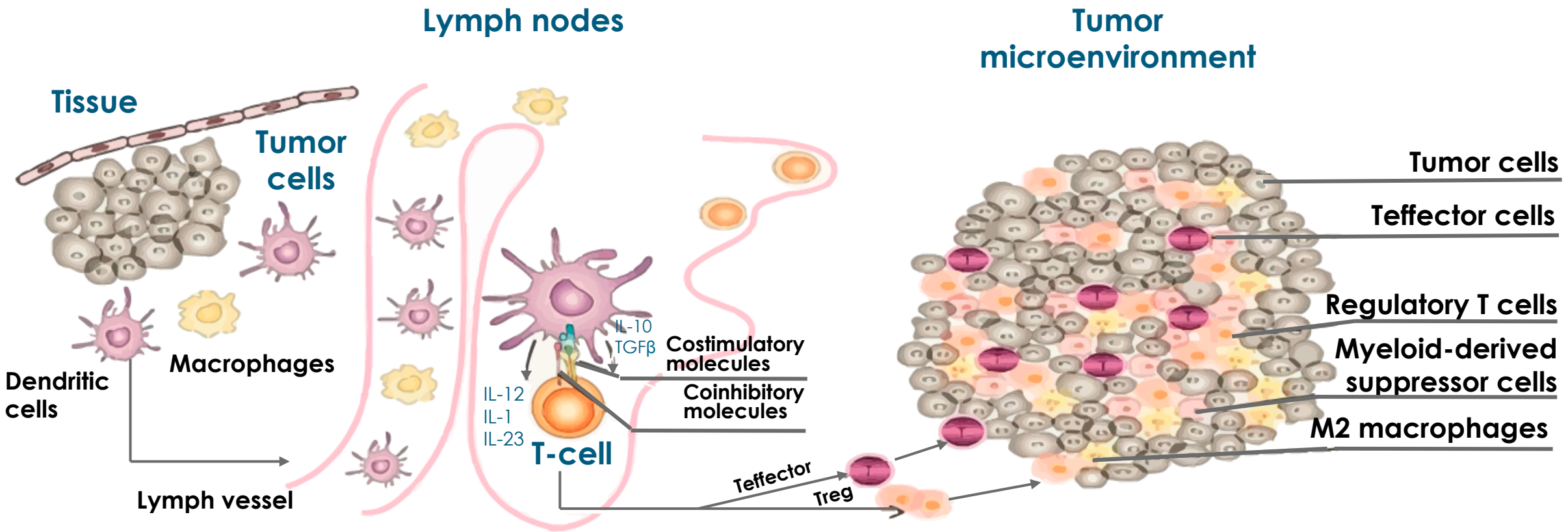
T cells require 3 signals to be fully functional killers:

Signal 1:
Antigen recognition

Signal 2:
Co-stimulation; specific receptors on the T cells must be activated appropriately

Signal 3:
Cytokine production; the cytokine environment supports T-cell proliferation/activation

How to Generate the Optimal Immune Reaction



Increase Effector T-cells

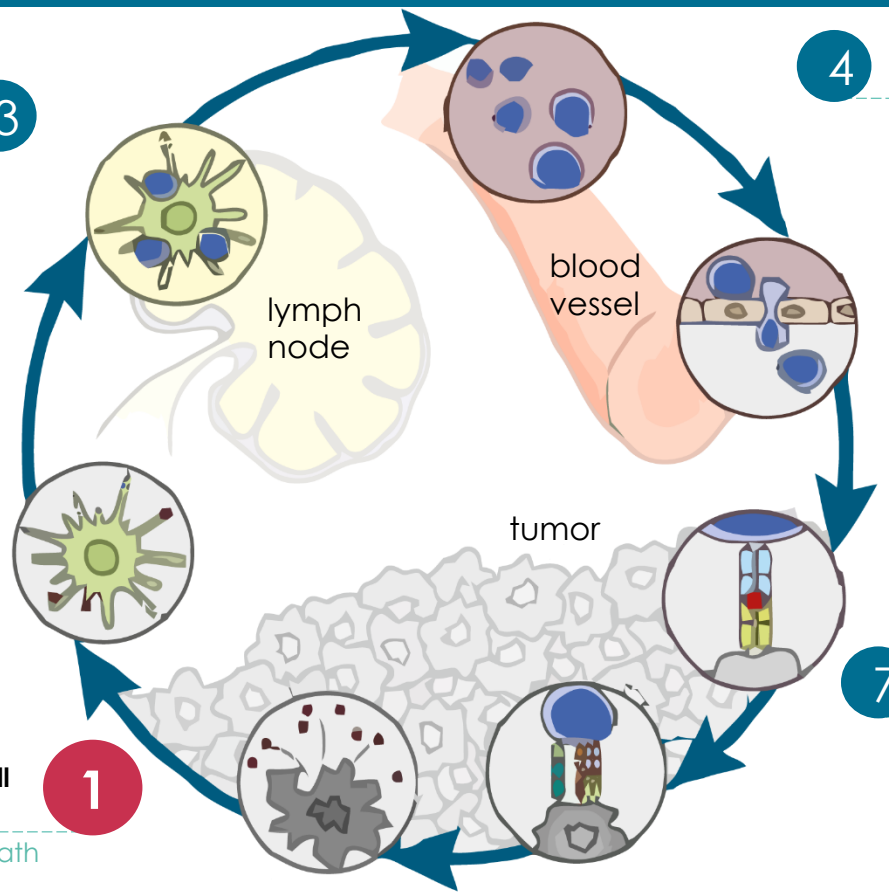
Vaccines
Adoptive T-cell therapy

Enhance Existing Immunity

Checkpoint inhibitors
Cytokine therapy (IL-15, IL-7)
Depletion Tregs
MoAB (X-IL-10, TGFβ)

→ Modulate the tumor microenvironment

Stimulatory and Inhibitory Factors in the Cancer-Immunity Cycle



1 Release of cancer cell antigens

Immunogenic cell death
Tolergenic cell death

2 Cancer antigen presentation

TNF-α
IL-1
IFN-α
CD40L/CD40
CDN
ATP
HMGB1
TLR
IL-10
IL-4
IL-13

3 Priming and activation

CD28/B7.1
CD137/CD137L
OX40/OX40L
CD27/CD70
HVEM
GITR
IL-2
IL-12
CTLA4/B7.1
PD-L1/PD-1
PD-L1/B7.1
prostaglandins

4 Trafficking of T cells to tumors

CX3CL1
CXCL9
CXCL10
CCL5

5 Infiltration of T cells into tumors

LFA1/ICAM1
Selectins
VEGF
Endothelin B receptor

6 Recognition of cancer cells by T cells

T cell receptor
Reduced pMHC on cancer cells

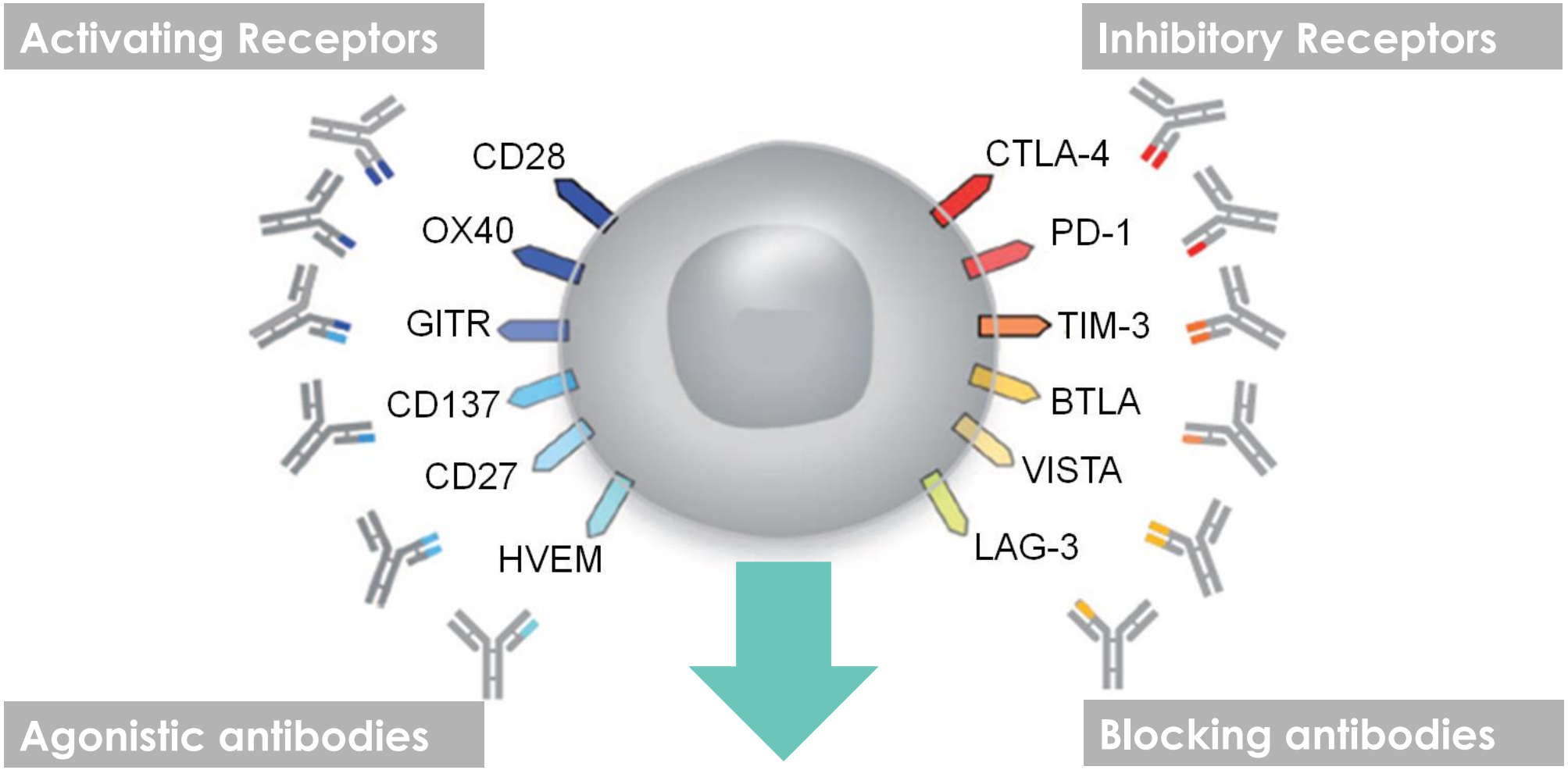
7 Killing of cancer cells

IFN-γ
T cell granule content
PD-L-1/PD-1
PD-L-1/B7.1
IDO
TGF-β
BTLA
VISTA
LAG-3
Arginase
MICA/MICB
B7-H4
TIM-3/phospholipids

Stimulatory factors
Inhibitors

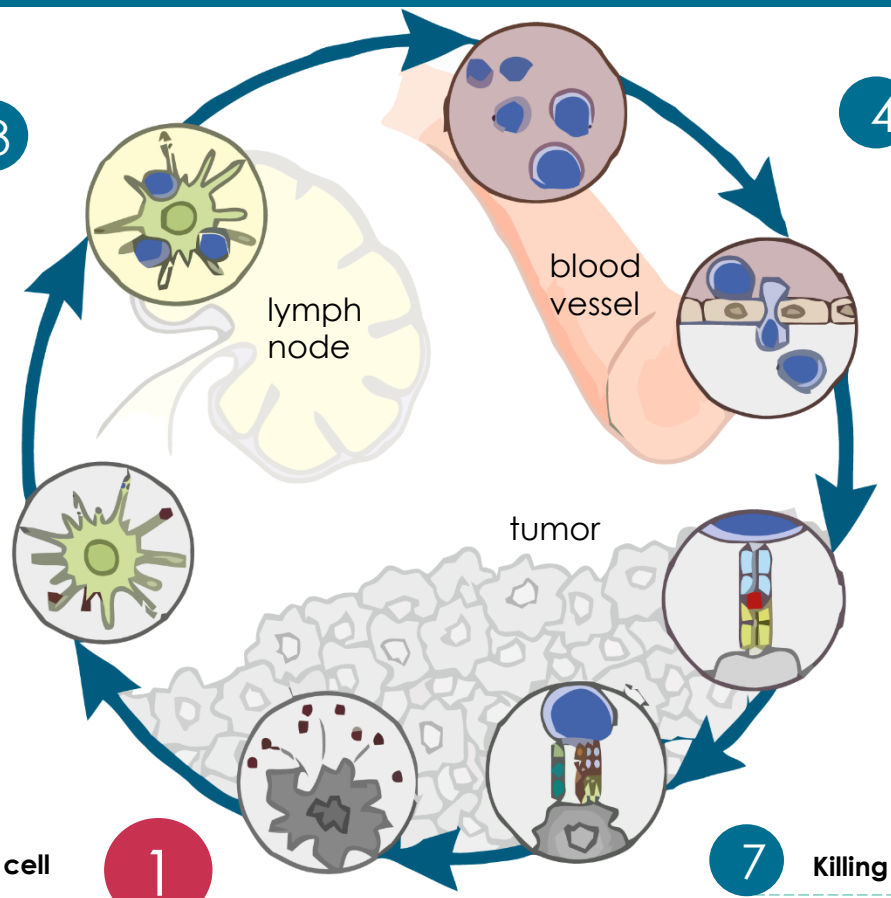
Each step of the Cancer-Immunity Cycle requires the coordination of numerous factors, both stimulatory and inhibitory in nature. Stimulatory factors shown in green promote immunity, whereas inhibitors shown in red help keep the process in check and reduce immune activity and/or prevent autoimmunity. Immune checkpoint proteins, such as CTLA4, can inhibit the development of an active immune response by acting primarily at the level of T cell development and proliferation (step3). We distinguish these from immune rheostat ("immunostat") factors, such as PD-L1, can have an inhibitory function that primarily acts to modulate active immune responses in the tumor bed (step 7). Examples of such factors and primary steps at which they can act are shown, Abbreviations are as follows: IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; CDN, cyclic dinucleotide; ATP, adenosine triphosphate; HMGB1, high-mobility group protein B1; TLR, Toll-like receptor; HVEM, herpes virus entry mediator; GITR, glucocorticoid-induced TNFR family-related gene; CTLA4, cytotoxic T-lymphocyte antigen-4; PD-L1, programmed death-ligand 1; CXCL/CCL, chemokine motif ligands; LFA1, lymphocyte function-associated antigen-1; ICAM1,intracellular adhesion molecule 1; VEGF, vascular endothelial growth factor, IDO, indoleamine2,3-dioxygenase; TGF, transforming growth factor; BTLA, B- and T-lymphocyte attenuator; VISTA, V-domain Ig suppressor of T cell activation; LAG-3 lymphocyte-activation gene 3 protein; MIC, MHC class I polypeptide-related sequence protein; TIM-3, T cell immunoglobulin domain and much domain-3. Although not illustrated, it is important to note that intratumoral T regulatory cells, macrophages, and myeloid-derived suppressor cells are key sources of many of these inhibitory factors.

Multiple Costimulatory and Inhibitory Interactions Regulate T-Cell Responses



Reproduced by permission from Macmillan Publishers Ltd.: Mellman I, et al. *Nature*. 2011; 480:480-489, ©2011[45].

Therapies That Might Affect the Cancer-Immunity Cycle



3 Priming and activation

Anti-CTLA4
Anti-CD137 (agonist)
Anti-OX40 (agonist)
Anti-CD27 (agonist)
IL-2
IL-12

4 Trafficking of T cells to tumors

5 Infiltration of T cells into tumors

Anti-VEGF

2 Cancer antigen presentation

Vaccines
IFN – α
GM-CSF
Anti-CD40(agonist)
TLR agonists

6 Recognition of cancer cells by T cells

CARs

1 Release of cancer cell antigens

Chemotherapy
Radiation therapy
Targeted therapy

7 Killing of cancer cells

Anti-PD-L1
Anti-PD-1
IDO inhibitors

The numerous factors that come into play in the Cancer-Immunity Cycle provide a wide range of potential therapeutic targets. This figure highlights examples of some of the therapies currently under preclinical or clinical evaluation. Key highlights include that vaccines can primarily promote cycle step 2, anti-CTLA4 can primarily promote cycle step 3, and anti-PD-L1 or anti-PD-1 antibodies can primarily promote cycle step 1, and inhibitors of VEGF can potentially promote T cell infiltration into tumors-cycle step 5. Abbreviations are as follows; GM-CSF, granulocyte macrophage colony-stimulating factor; CARs, chimeric antigen receptors.

Immune-Related Response Criteria

Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria

Jedd D. Wolchok, Axel Hoos, Steven O'Day, Jeffrey S. Weber, Omid Hamid, Celeste Lebbé, Michele Maio, Michael Binder, Oliver Bohnsack, Geoffrey Nichol, Rachel Humphrey, and F. Stephen Hodi

Abstract

Purpose: Immunotherapeutic agents produce antitumor effects by including cancer-specific immune responses or by modifying native immune processes. Resulting clinical response patterns extend beyond those of cytotoxic agents and can manifest after an initial increase in tumor burden or the appearance of new lesions (progressive disease). Response Evaluation Criteria in Solid Tumors or WHO criteria, designed to detect early effects of cytotoxic agents, may not provide a complete assessment of immuno-therapeutic agents. Novel criteria for the evaluation of antitumor responses with immunotherapeutic agents are required.

Experimental Design: The phase II clinical trial program with ipilimumamb, an antibody that blocks CTL antigen-4, represents the most comprehensive data set available to date for an immunotherapeutic agent. Novel immune therapy response criteria proposed, based on the shared experience from community workshops and several investigators, were evaluated using data from ipilimumab phase II clinical trials in patients with advanced melanoma.

Results: Ipilimumab monotherapy resulted in four distinct response patterns: (a) shrinkage in baseline lesions, without new lesions; (b) durable stable disease (in some patients followed by a slow, steady decline in total tumor burden); (c) response after increase in total tumor burden; and (d) response in the presence of new lesions. All patterns were associated with favorable survival.

Conclusion: Systematic criteria, designated immune-related response criteria, were defined in an attempt to capture additional response patterns observed with immune therapy in advanced melanoma beyond those described by Response Evaluation Criteria in Solid Tumors or WHO criteria. Further prospective evaluations of the immune-related response criteria, particularly their association with overall survival. are warranted. (Clin Cancer Res 2009; 15(23):7412—20)

Immune-Related Response Criteria

- Workshops in 2004 and 2005 of oncologists and immunotherapists hypothesized that conventional tumor response criteria may not adequately assess the activity of immunotherapeutic agents because early **PD** may not reflect therapeutic failure
- The appearance of measurable antitumor activity may take longer for immune therapies than for cytotoxic therapies
- Responses to immune therapies may occur after conventional **PD**
- Discontinuation of immune therapy may not be appropriate in some cases, unless **PD** is confirmed (as in confirmed responses) - **irPD**

Immune-Related Response Criteria

- Allowance for "clinically insignificant" **PD** (e.g. small new lesions in the presence of other responsive lesions) is recommended
- Durable stable disease (**SD**) may represent antitumor activity
- Workshop participants proposed a new clinical paradigm and recommended existing response criteria be refined to address these issues
- 487 advanced melanoma patients treated with ipilimumab in 3 multinational Phase II studies were studied to refine the response criteria

CTLA-4: Upregulation and Blockade

Upregulation of **CTLA-4** by tumor

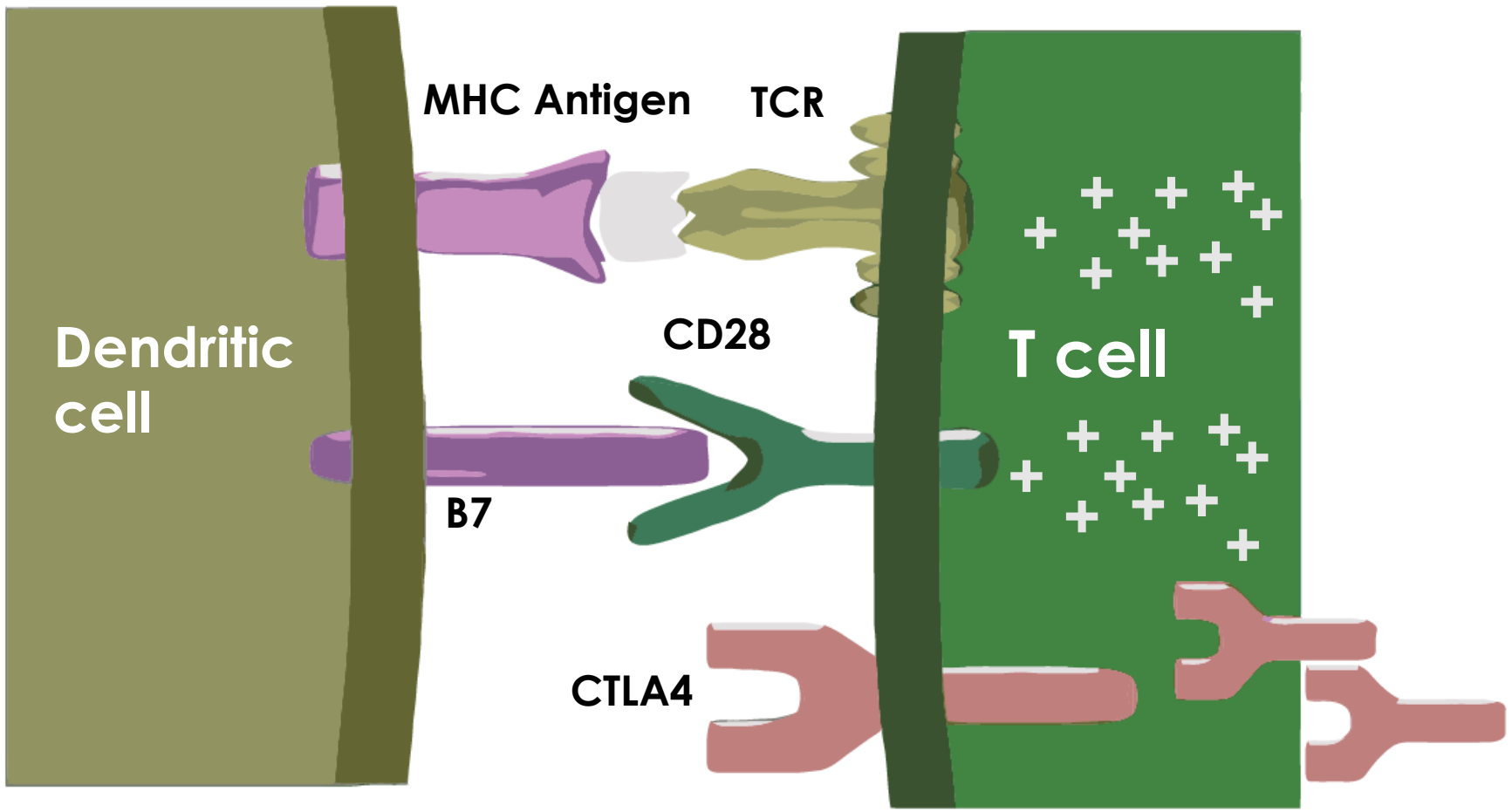
- Lung cancer can stimulate abnormally high expression of **CTLA-4** in T-cells
- Results in competition with the **CD-28** receptor/pathway that, along with binding of the T-cell receptor to the major histocompatibility complex (MHC) molecules on antigen presenting cells (**APCs**), is involved in costimulation of T-cell activation
- Inhibits T-cell response to tumor

Antibody blockade of **CTLA-4**

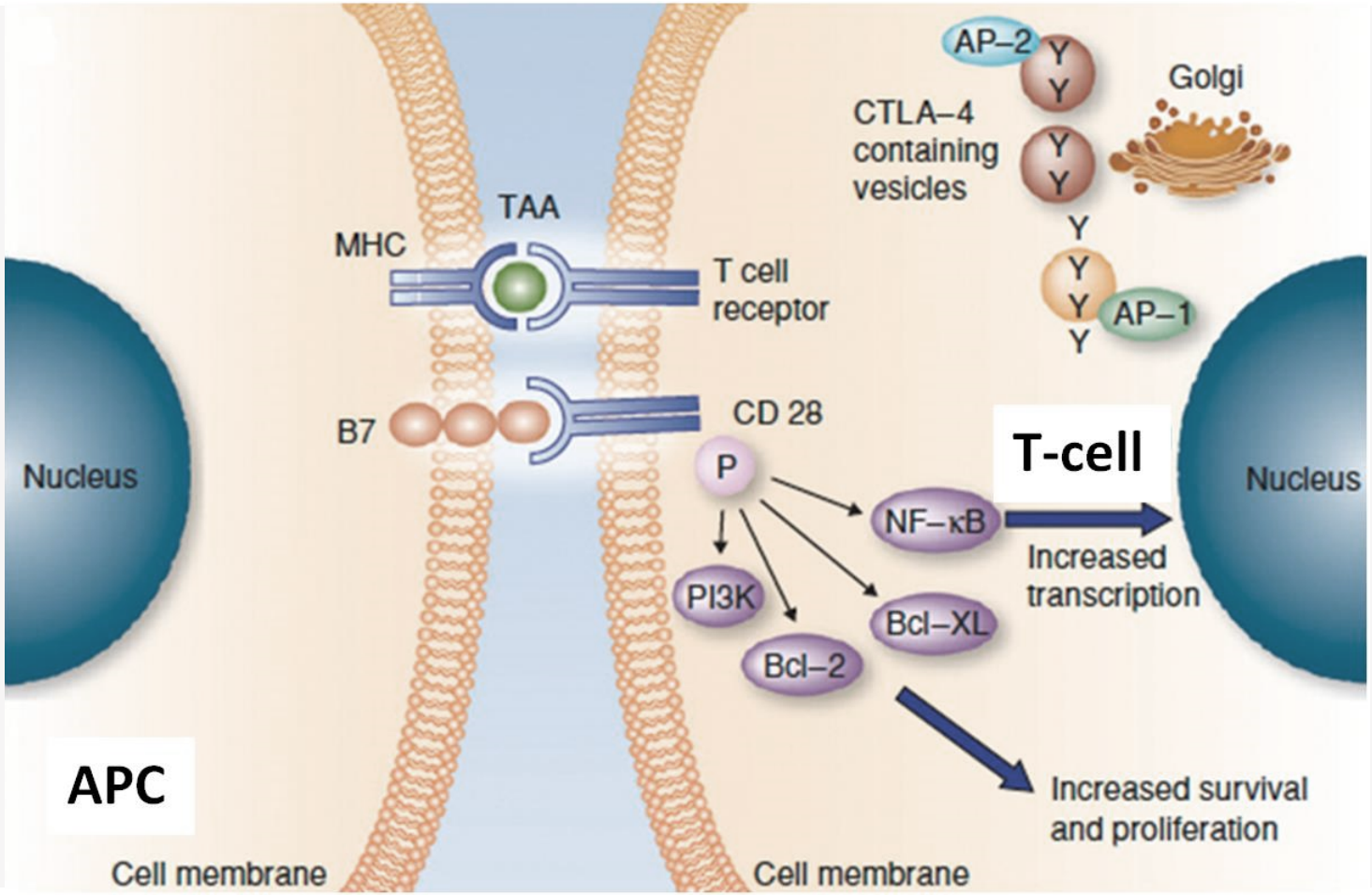
- Inhibits its associated pathway
- Allows for T-cell activation

Brahmer JR. *Semin Oncol.* 2014; 41:136-142[3]; Zielinski C, et al. *Ann Oncol.* 2013;24:1170-1179[16]; Creelan BC. *Cancer Control.* 2014; 21:80-89.[17]

CTLA4 Receptors Are Up-Regulated Following T-Cell Activation

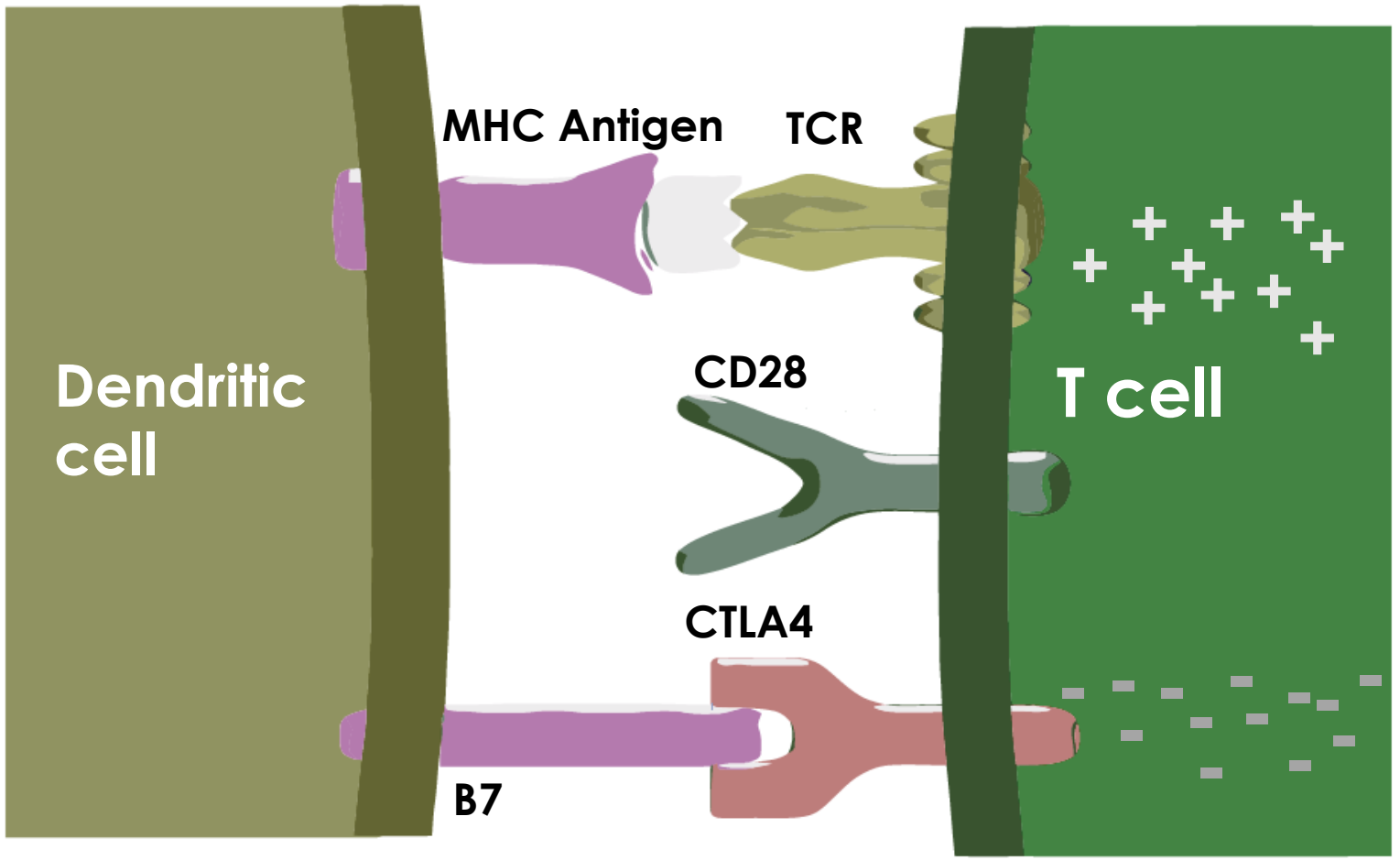


Antigen Presentation and T-Cell Priming



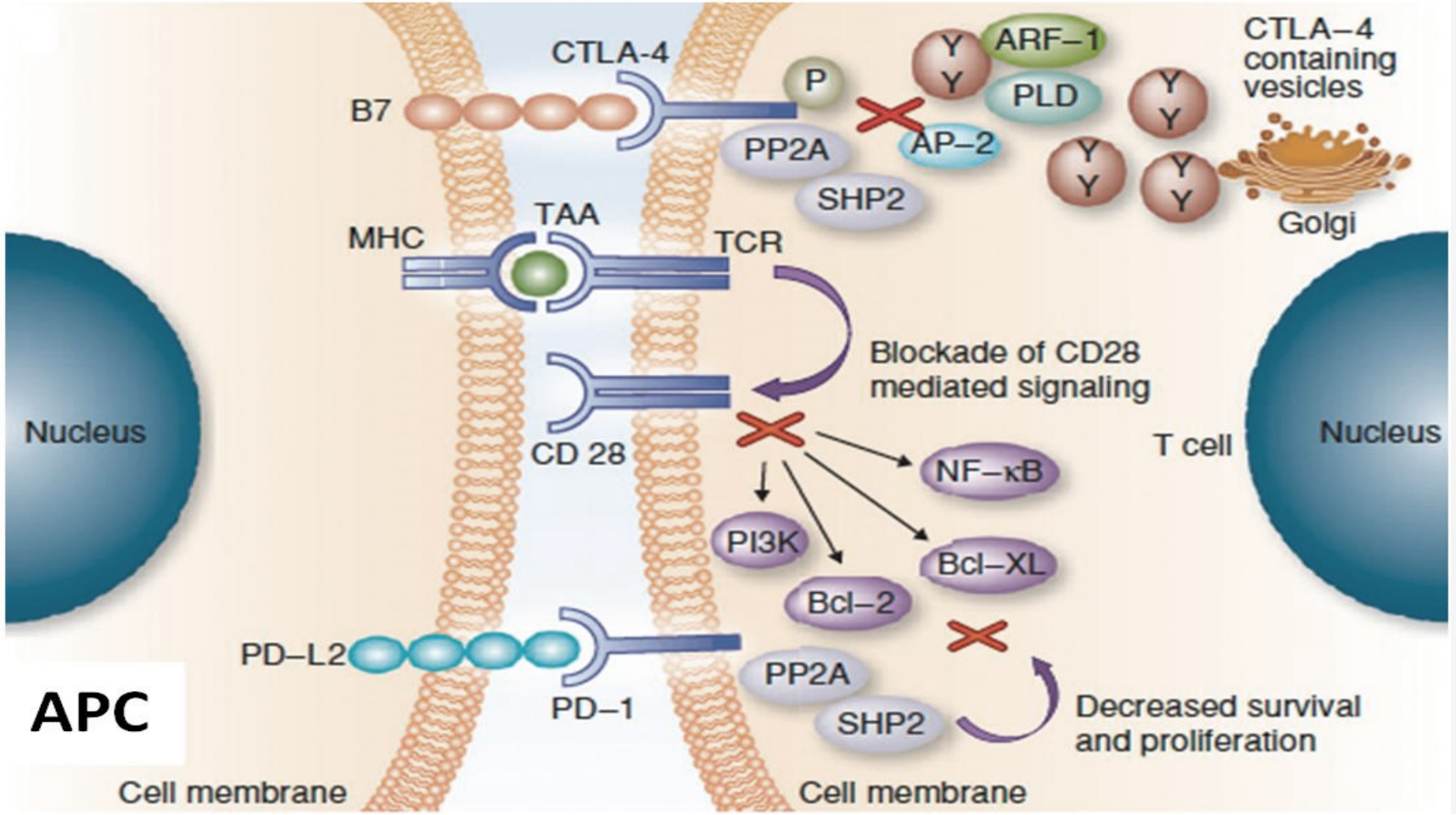
Reproduced from Salama AK, et al. Cytotoxic T-lymphocyte-associated antigen-4. Clin Cancer Res. 2011; 17: 4622-4628, with permission from AACR. [66]

CTLA4 Negatively Modulates T-Cell Activation



CTLA4 binds B7 with greater affinity than does CD28 and sends an inhibitory signal to the T cell

Immune Checkpoints Regulate the Immune System



The **PD1** pathway regulates inflammatory responses in tissues by effector T cells recognizing antigen in peripheral tissues. Activated T cells upregulate **PD1** and continue to express it in tissues. Excessive induction of **PD1** on T cells in the setting of chronic antigen exposure can induce an exhausted or anergic state in T cells.

Reproduced from Salama AK, et al. *Clin Cancer Res.* 2011; 17:4622-4628, with permission from AACR.[66]

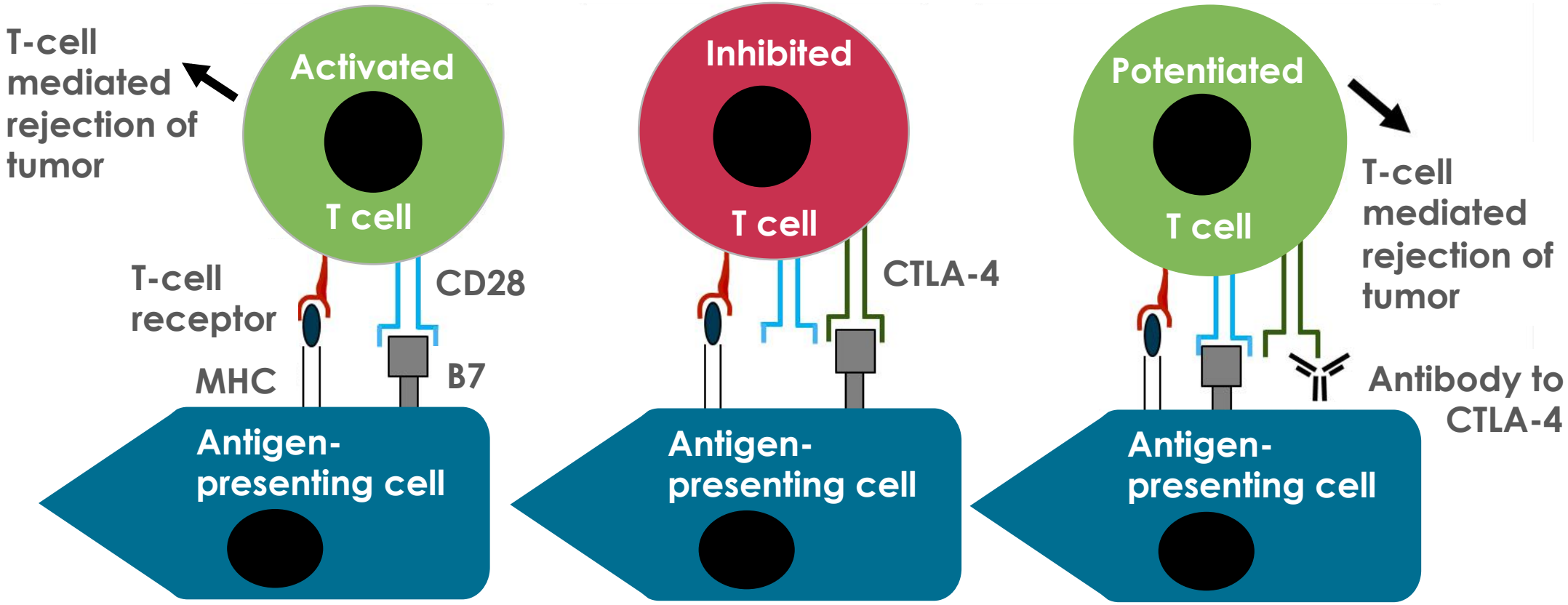
CTLA4 in the Immune Response

MEDELIS
Clinical answers, faster.

CD28-related T-cell activation

CTLA-4 blocks CD28-related T-cell activation

Antibody against CTLA-4 restores CD28-related T-cell activation



Antibodies to CTLA-4 inhibit its associated pathway, allowing for T-cell activation

Adapted from Saijo N. *Cancer Res Treat*. 2012; 44:1-10[18]

Immune-Related Response Criteria

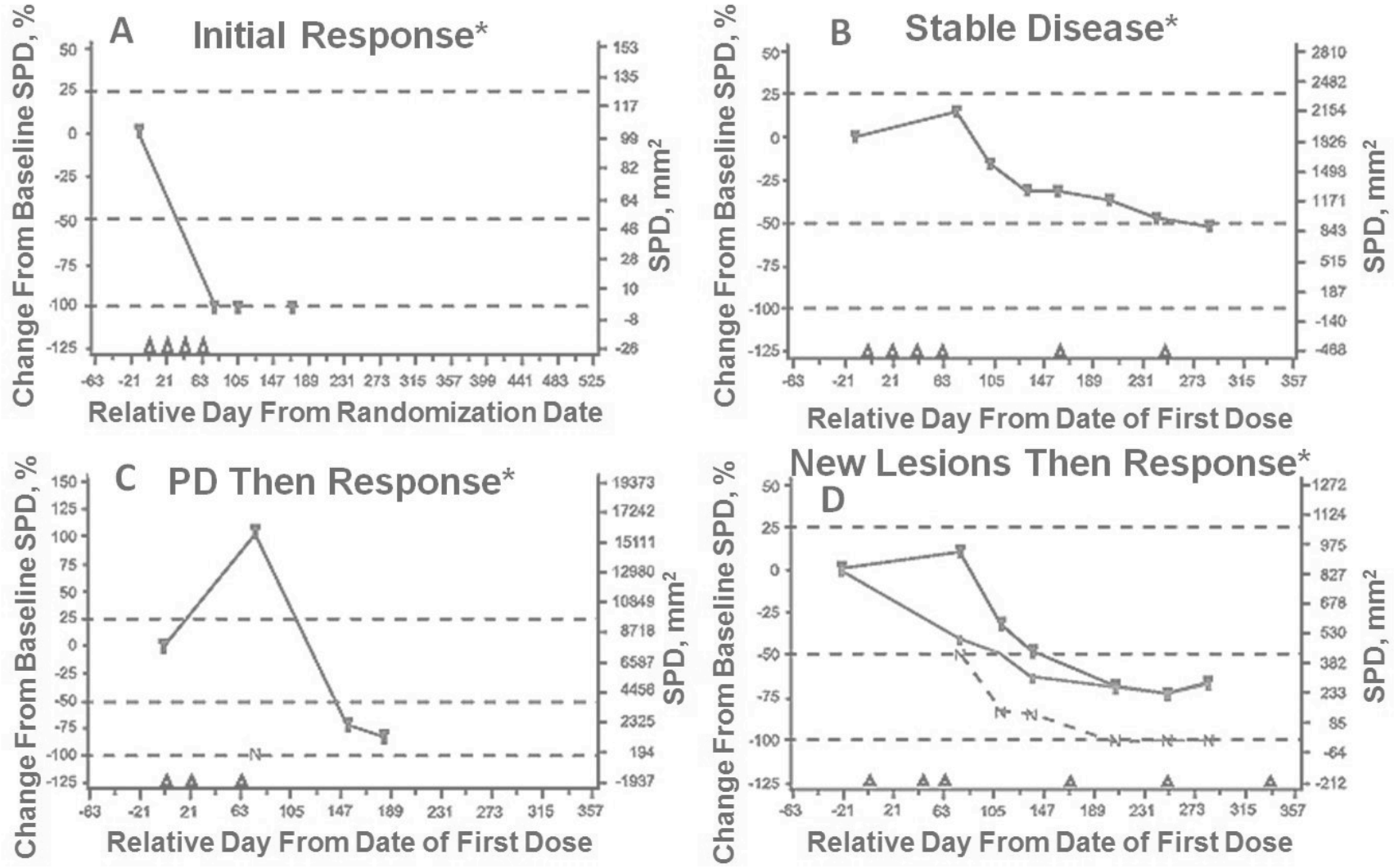
Ipilimumab monotherapy resulted in four distinct response patterns:

- Shrinkage in baseline lesions (without new lesions)
- Durable stable disease (**SD**) – in some patients followed by a slow, steady decline in total tumor burden
- Response after an increase in total tumor burden
- Response in the presence of new lesions

All patterns were associated with favorable survival

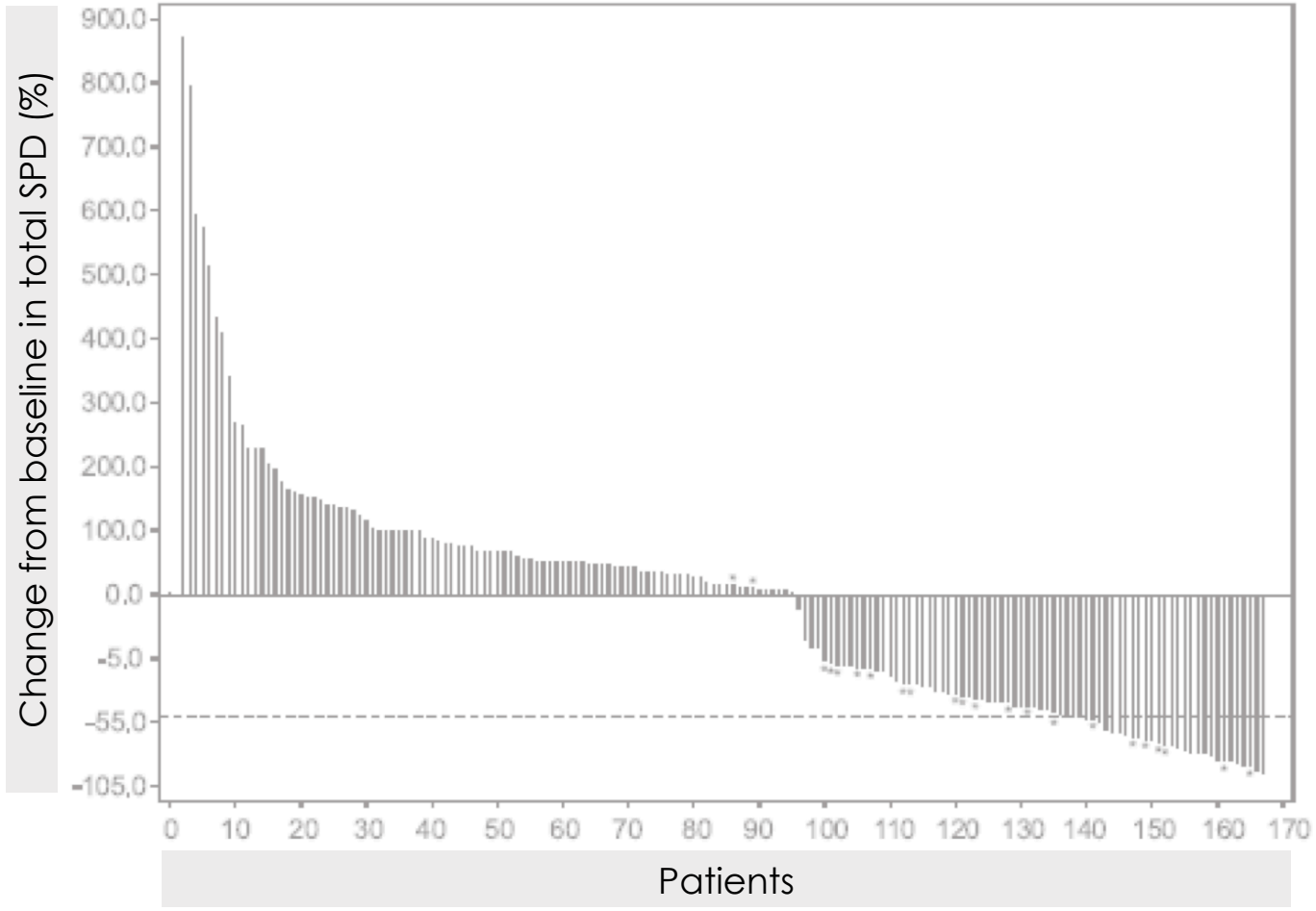
Further prospective evaluations of the **irRC** are warranted

Patterns of Response to Cancer Immunotherapy



*Patterns of response to ipilimumab observed in advanced melanoma. Reprinted from Wolchok JD, et al. Clin Cancer Res. 2009; 15 : 7420 with permission from AACR. [21]

Waterfall Plot of Maximum Percentage Reduction from Baseline in Total Tumor Burden

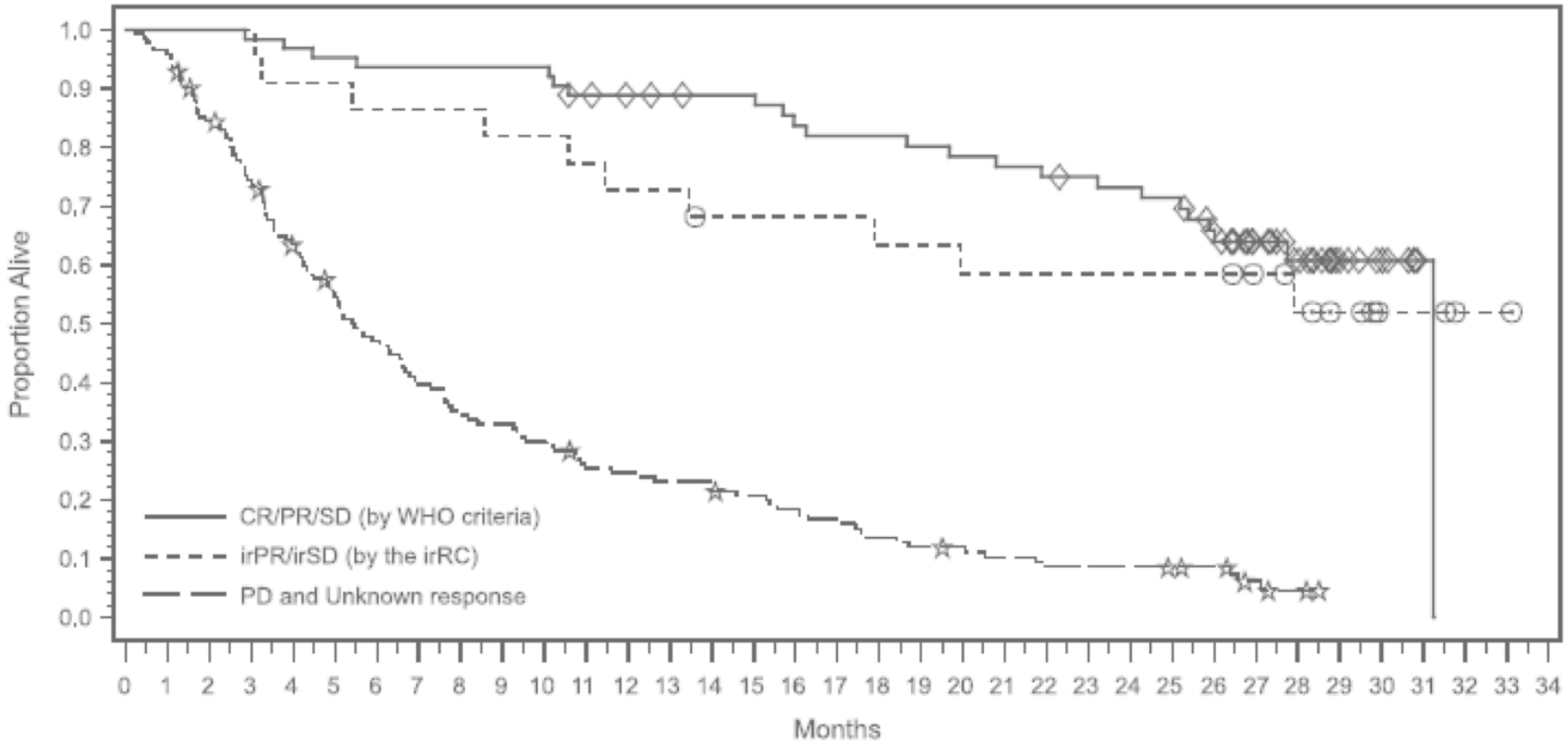


Waterfall plot of maximum percentage reduction from baseline in total tumor burden.

Included are advanced melanoma patients treated with, or randomized to, ipilimumab at 10 mg/kg in the CA184-008 and CA184-022 studies; the tumor responses of 167 evaluable patients were assessed using the irRC. Twenty-two patients were characterized as irPR (n = 5) or irSD (n = 17), who otherwise would haw been labeled "PD" by conventional WHO criteria. These patients are indicated by an asterisk.

In addition, one patient characterized as SD by WHO criteria was evaluated as irPR (patient #148)

Association of OS with Response Using WHO Criteria or irRC



Subjects at Risk

CR/PR/SD	63	63	63	62	61	60	59	59	59	59	59	55	53	52	51	51	48	47	47	46	45	44	43	42	41	40	34	24	18	10	6	1	0	0	0
irPR/irSD	22	22	22	22	20	20	19	19	19	18	18	17	16	16	14	14	14	14	13	13	12	12	12	12	12	12	12	10	8	6	3	3	1	1	0
PD/Unkown	142	136	118	102	86	73	63	53	46	44	40	33	32	30	28	26	23	21	17	15	14	12	10	10	10	9	8	4	2	0	0	0	0	0	0

Data are included for all patients treated with, or randomized to, ipilimumab at 10 mg/kg in the CA184-008 and CA184-022 studies, respectively (n = 227).

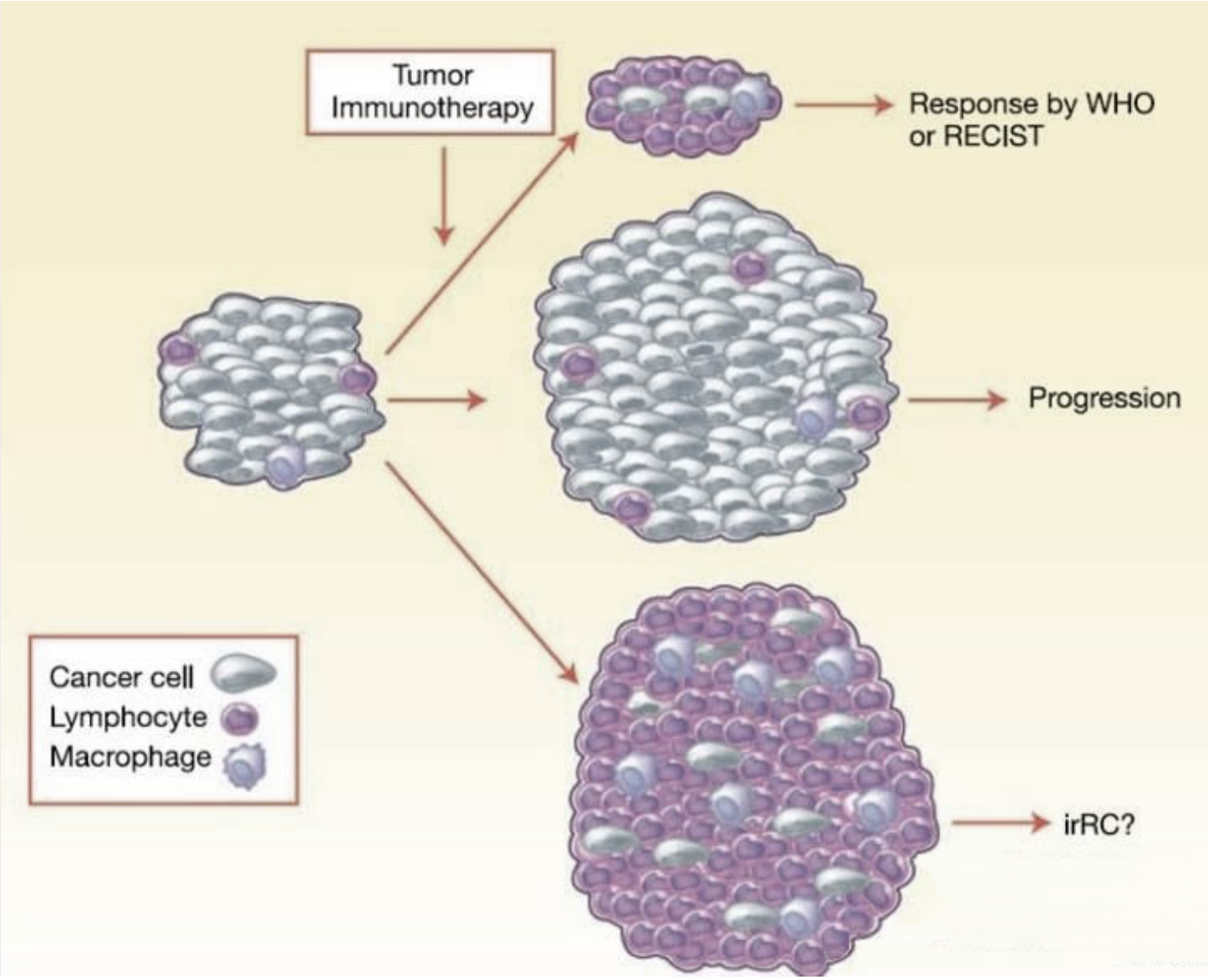
Numbers of patients by response categories were as flows: 63 with CR, PR, or SD (BOR by WHO criteria); 22 with PD (by WHO criteria) and assessment by the irRC as irPR or irSD; 142 with PD (by WHO criteria) or unknown response. Each patient is included in only one response category.

Different symbols for the respective curves indicate censored patients. Median OS in months (95% confidence intervals) corresponding to each curve CR/PR/SD, 31.2 (27.8-31.2); irPR/irSD, not reached (13.5-not reached); PD/unknown, 5.45 (4.5 – 6.77).

Metastatic cancer lesions are made up mainly of cancer cells and stromal cells, with a very limited immune and inflammatory infiltrate by lymphocytes and macrophages.

After receiving tumor immunotherapy, the size of metastatic lesions may decrease in the few patients that have and objective response, with the tumor being invaded by lymphocytes and later by macrophages; these tumor responses are well captured by the WHO and RESCIST criteria. Metastatic tumor lesions will increase in size in cases where the tumor grows progressively, leading to disease progression.

However, in some cases, the tumor lesions may become heavily infiltrated by immune and inflammatory cells resulting in an apparent increase in size of lesions, but this is due to infiltration by tumor immunotherapy-recruited cells as opposed to a progressive growth of cancer cells. In this case, the lesion would qualify as progressive disease by WHO or RECIST criteria, but as a responder following the newly proposed irRC.



Overall Response Using the irRC

The overall response according to the **irRC** is derived from time-point response assessments (based on tumor burden) as follows:

- **irCR**, complete disappearance of all lesions (whether measurable or not, and no new lesions), and confirmation by a repeat consecutive assessment no less than 4 weeks from the date first documented
- **irPR**, decrease in tumor burden ≥50% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation
- **irSD**, not meeting the criteria for irCR or **irPR**, in absence of **irPD**
- **irPD**, increase in tumor burden ≥ 25% relative to nadir (minimum recorded tumor burden) and confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented

Comparison Between WHO Criteria and the irRC

	WHO	irRC
New measurable lesions (i.e., >=5x5 mm)	Always represent PD	Incorporated into tumor burden
New nonmeasurable lesions (i.e., <5x5 mm)	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR	>=50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	>=50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD	50% decrease in SPD compared with baseline cannot be established nor 25% increase compare with nadir, in absence of new lesion or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in SPD compared with nadir and/ or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

Do We Need a Different Set of Response Assessment Criteria for Tumor Immunotherapy?

CCR Translations

Commentary on Wolchok et al., p. 7412

Antoni Ribas,[1,2,3] Bartosz Chmielowskie,[1] and John A. Glaspy[1,3]

Tumor shrinkage induced by tumor immunotherapy may be preceded by inflammatory changes. This confounds the assessment of response rates to tumor immunotherapy. In this issue of Clinical Cancer Research, Wolchok et al. attempt to address this peculiarity by proposing a new set of criteria termed immune-related response criteria. (Clin Cancer Res 2009;15(23):7116-8)

irRC Operational Considerations

Tumor Assessment
- Central reader versus local radiologist
- Understanding site's procedures for irRC interpretation
  - Who will perform the irRC assessment?
    - Oncologist versus radiologist
    - Single versus multiple observers
  - Minimize both intra-observer and inter-observer variability of interpretations by readers

Adaptation of irRC to RECIST criteria
- Sites designating a "RECIST Radiologist" for all readings

Treating patients past progressive disease
- Patient concerns
- Regulatory concerns

Current Status of New Immunotherapeutic Approaches in Solid Tumors

Combination Studies

Chemotherapy + immunotherapy

Targeted therapy + immunotherapy

Immunotherapy + immunotherapy

- Schedule
- Sequence
- Synergies
- Duration
- Maintenance
- Predictive biomarkers: PD-1, PD-L1

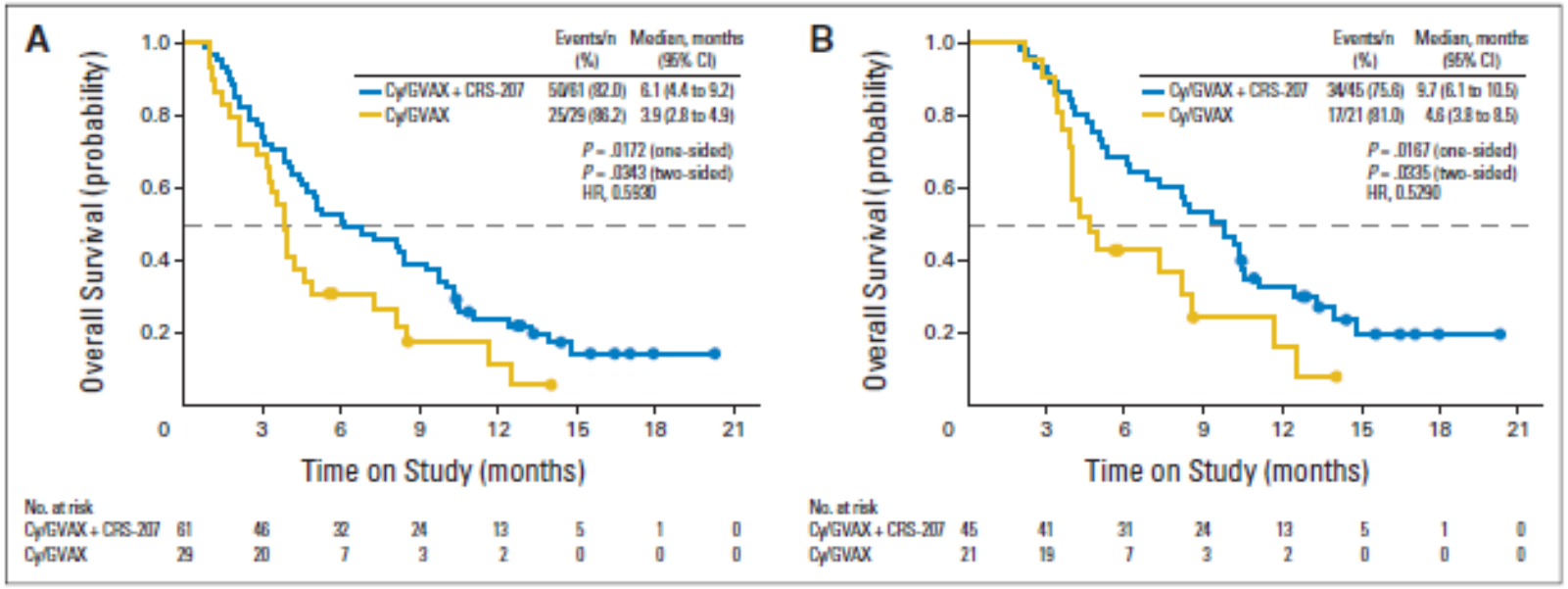
Safety and Survival With GVAX Pancreas Prime Listeria Monocytogenes - Expressing Mesothelin (CRS-207) Boost Vaccines for Metastatic Pancreatic Cancer

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Volume 33 *Number 12* *April 20, 2015*

Dung T. Le, Andrea Wang-Gillam, Vincent Picozzi, Tim F.Greten, Todd Crocenzi, Gregory Springett, Michael Morse, Herbert Zeh, Deirde Cohen, Robert L. Fine, Beth Onners, Jennifer N. Uram, Daniel A. Laheru, Eric R.Lutz, Sara Solt, Aimee Luck Murphy, Justin Skoble, Ed Lemmens, John Grous, Thomas Dubensky Jr, Dirk G. Brockstedt, and Elizabeth M.Jaffee



Kaplan-Meier estimates of overall survival (OS) according to treatment group. (A) OS for full analysis set (patients received ≥ one dose of cyclophosphamide Cy)); median OS was 6.1 months in group receiving Cy/GVAX followed by CRS-207 and 3.9 months group receiving Cy/GVAX alone. (B) OS for per-protocol analysis set (patients received ≥ three doses (≥ two doses of Cy/GVAX and one dose of CRS-207 in arm A of three doses of Cy/GVAX in arm B)); median OS was 9.7 months in group receiving Cy/GVAX followed by CRS-207 and 4.6 months in group receiving Cy/GVAX alone. Solid circles represent censored survival time for alive patients. HR, Hazard ratio.

Operational Considerations

Investigational Product Handling

- May require specialized methods for product receipt, storage, and preparation
  - NIH BioSafety Level 2 **(BSL2)** Guidelines may need to be followed for the handling of therapies utilizing microorganisms associated with human diseases
  - Cold chain management during transport and storage

Biosample collection, processing, and shipping to tumor immunology laboratories to conduct standardized immunomonitoring assays, biomarker, and correlative studies

Operational Considerations (con't)

- Site reporting and monitoring of adverse events
  - Immunotherapy safety profile **(irAEs)**
  - Combination therapies
  - Drug delivery techniques

- Site selection
  - Stricter patient eligibility
  - Collaborative efforts between departments (e.g., oncology, radiology, pathology)
  - Special equipment for product handling and biosampling

Immune Checkpoints and Their Inhibition: Key Points

CTLA-4 and **PD-1** receptors transduce signals involved in modulating the immune response

- Downregulate T-cell function

Antibody blockade of these receptors or antibodies against a ligand of the **PD-1** receptor can interfere with **CTLA-4** and **PD-1** pathways

- Allow for T-cell mediated rejection of tumor

Immune Checkpoint Blockade Approach in NSCLC

Targeting the Immune System

Cytotoxic T lymphocyte-associated antigen 4 (**CTLA-4**) and programmed cell death-1 (**PD-1**)

- Are protein receptors referred to as immune checkpoints
- Have distinct ligand specificities and biologic functions
- Provide mechanisms to control the immune system after infection AND autoimmune response
- Are critical for maintaining self-tolerance and modulating the duration and amplitude of the physiologic immune response
- Can be manipulated by cancer to allow for tumor growth that is unchecked by the immune system

Brahmer JR. *Semin Oncol.* 2014; 41:136-142[3]; Zielinski C, et al. *Ann Oncol.* 2013;24:1170-1179[16]; Creelan BC. *Cancer Control.* 2014; 21:80-89.[17]

PD-1 and PD-L1 and PD-1/PD-L1 Blockade

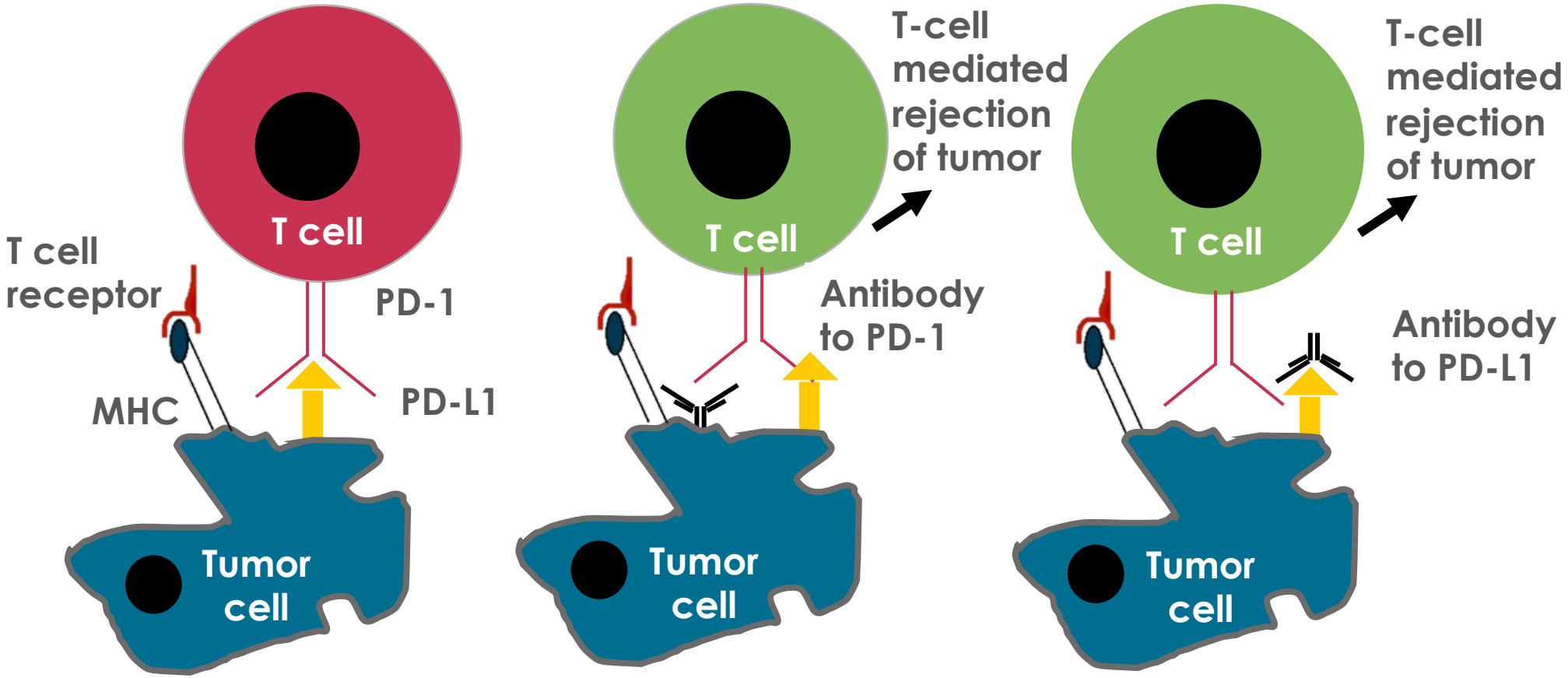
- Proteins **PD-L1** or **PD-L2** are present on **APCs** as well as tumor cells.
- These proteins are ligands for the **PD-1** receptor.
- Upregulation of **PD-L1** on tumor cells activates the **PD-1** pathway.
- **PD-1** is expressed on many cell types, including activated T cells, B cells, NK cells, and host tissues.
- The activated **PD-1** pathway downregulates T-cell effector functions.
- Antibodies to **PD-1** or **PD-L1** inhibit the **PD-1** pathway, allowing for T-cell activation and T-cell-mediated rejection of tumor.

Brahmer JR. *Semin Oncol.* 2014; 41:136-142[3]; Zielinski C, et al. *Ann Oncol.* 2013;24:1170-1179[16]; Creelan BC. *Cancer Control.* 2014; 21:80-89.[17]

PD-1/PD-L1 in the Immune Response

Binding of PD-L1 to PD-1 receptor downregulates T-cell effector functions

Antibody-mediated blockage of the binding of PD-L1 protein to PD-1 receptor restores T-cell effector functions



Antibodies to PD-1 or PD-L1 inhibit the PD-1 pathway, allowing for T-cell-mediated rejection of tumor

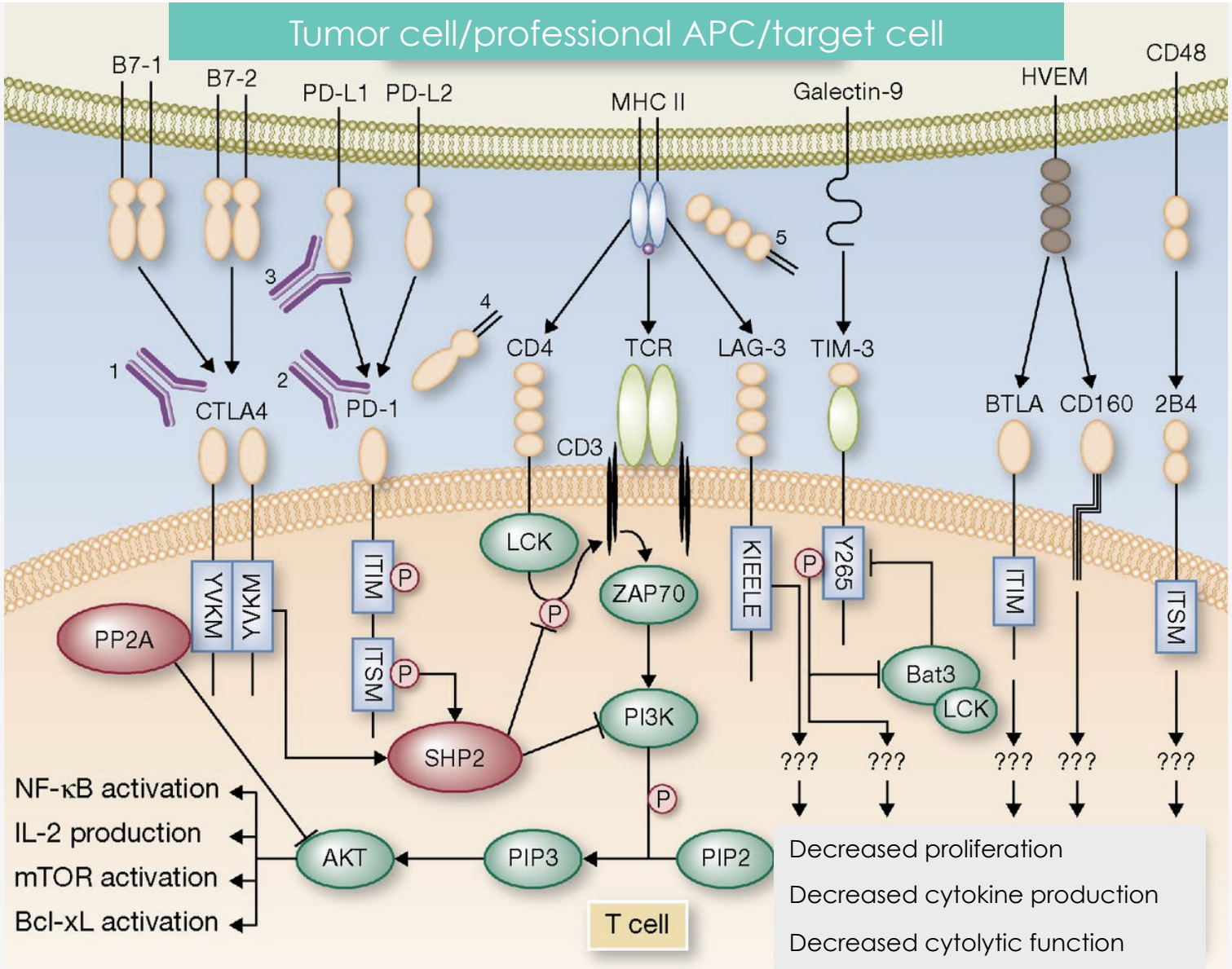
Adapted from Sznol M, et al *Clin Cancer Res.* 2013; 19:1021-1034. [19]

Antibody Blockade of Immune Checkpoints

MEDELIS
Clinical answers, faster.

Antibodies to CTLA-4	Antibodies to PD-1	Antibodies to PD-L1
Ipilimumab	Nivolumab	MPDL3280A
Tremelimumab	Pembrolizumab (MK-3475)	MEDI-4736
		BMS-936559
		MSB0010718C

Immune Checkpoints



Other Immune Checkpoint Protein Targets

Lag-3

- Lymphocyte activation gene 3
- Inhibitory receptor coexpressed with PD-1
- Also expressed on T-regulatory cells (which are important in the immune system's ability to maintain tolerance to self-antigens)
- Suppresses antigen presenting cell activation

Ox40

- Potent costimulatory receptor that augments T-cell activation by a specifically recognized antigen
- Ox40 engagement by Ligands present on dendritic cells dramatically increases the proliferation, effector function, and survival of T cells

Creelan BC. Cancer Control. 2014; 21:80-89[17]; Curti BD, et al. *Cancer Res*. 2013;73:7189-7198.[36]

Other Immune Checkpoint Protein Targets (con't)

Tim-3

- T cell immunoglobulin-3 (Tim-3) negative regulator of IFN-γ-secreting CD4(+) T helper 1 and CD8(+) T cytotoxic 1 cells
- TIM-3 acts as a negative regulator of Th1/Tc1 cell function by triggering cell death upon interaction with its ligand, galectin-9
- Tim-3 pathway may cooperate with the PD-1 pathway to promote the development of a severe dysfunctional phenotype in CD8+ T cells in cancer

Ana C. Anderson, Cancer Immunology Res; 2(5) May 2014

Other Immune Checkpoint Protein Targets (con't)

KIR

- Killer immunoglobulin receptor
- A receptor on natural killer (NK) cells that reduces their cytotoxic (killing) activity
- NK cell activity can be restored by monoclonal antibodies that bind to KIRs

Creelan BC. Cancer Control. 2014; 21:80-89[17]; Curti BD, et al. *Cancer Res*. 2013;73:7189-7198.[36]

Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma

The New England Journal of Medicine

Original Article

Michael A. Postow, M.D., Jason Chesney, M.D., Ph.D., Anna C. Pavlick, D.O., Caroline Robert, M.D., Ph.D., Kenneth Grossmann, M.D., Ph.D., David McDermott, M.D., Gerald P. Linette, M.D., Ph.D., Nicolas Meyer, M.D., Jeffrey K. Giguere, M.D., Sanjiv S. Agarwala, M.D., Montaser Shaheen, M.D., Marc S. Ernstoff, M.D., David Minor, M.D., April K. Salama, M.D., Matthew Taylor, M.D., Patrick A. Ott, M.D., Ph.D., Linda M. Rollin, Ph.D., Christine Horak, Ph.D., Paul Gagnier, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., and F. Stephen Hodi, M.D.

Results

Among patients with BRAF wild-type tumors, the rate of confirmed objective response was 61% (44 of 72 patients) in the group that received both ipilimumab and nivolumab (combination group) versus 11% (4 of 37 patients) in the group that received ipilimumab and placebo (ipilimumab-monotherapy group)(P<0.001), with complete responses reported in 16 patients (22%) in the combination group and no patients in the ipilimumab-monotherapy group. The median duration of response was not reached in either group. The median progression-free survival was not reached with the combination therapy and was 4.4 months with ipilimumab monotherapy(hazard ratio associated with combination therapy as compared with ipilimumab monotherapy for disease progression or death, 0.40; 95% confidence interval, 0.23 to 0.68; P<0.001). Similar results for response rate and progression-free survival were observed in 33 patients with BRAF mutation-positive tumors. Drug-related adverse events of grade 3 or 4 were reported in 54% of the patients who received the combination therapy as compared with 24% of the patients who received ipilimumab monotherapy. Select adverse events with potential immunologic causes were consistent with those in a phase 1 study, and most of these events resolved with immune-modulating medication.

Pembrolizumab versus Ipilimumab in Advanced Melanoma

The New England Journal of Medicine

Original Article

*Caroline Robert, M.D., Ph.D., Jacob Schachter, M.D., Georgina V. Long, M.D., Ph.D., Ana Arance, M.D., Ph.D., Jean Jacques Grob, M.D., Ph.D, Laurent Mortier, M.D., Ph.D., Adil Daud, M.D., Matteo S. Carlino, M.B., B.S., Catriona McNeil, M.D., Ph.D., Michal Lotem, M.D., James Larkin, M.D., Ph.D., Paul Lorigan, M.D., Bart Neyns, M.D., Ph.D., Christian U. Blank, M.D., Ph.D., Omid Hamid, M.D., Christine Mateus, M.D., Ronnie Shapira-Frommer, M.D., Michele Kosh, R.N., B.S.N., Honghong Zhou, Ph.D., Nageatte Ibrahim, M.D., Scot Ebbinghaus, M.D., and Antoni Ribas, M.D., Ph.D., for the KEYNOTE-006 investigators****

Background

The immune checkpoint inhibitor ipilimumab is the standard-of-care treatment patients with advanced melanoma. Pembrolizumab inhibits the programmed cell death 1 (PD-1) immune checkpoint and has antitumor activity in patients with advanced melanoma.

Methods

In this randomized, controlled, phase 3 study, we assigned 834 patients with advanced melanoma in a 1:1:1 ratio to receive pembrolizurmab (at a dose of 10 mg per kilogram of body weight) every 2 weeks or every 3 weeks or four doses of ipilimumab (at 3 mg per kilogram) every 3 weeks. Primary end points were progression-free and overerall survival.

Pembrolizumab versus Ipilimumab in Advanced Melanoma

Results

The estimated 6-month progression-free-survival rates were 47.3% for pembrolizumab every 2 weeks, 46.4% for pembrolizumab every 3 weeks, and 26.5% for ipilimumab (hazard ratio for disease progression, 0.58; P<0.001 for both pembrolizumab regimens versus ipilimumab; 95% confidence internals (CIs), 0.46 to 0.72 to 0.72 respectively). Estimated 12-month survival rates were 74.1%, 68.4%, and 58.2%, respectively (hazard ratio for death for pembrolizumab every 2 weeks, 0.63; 95% CI, 0.47 to 0.83; P=0.0005; hazard ratio for pembrolizumab every 3 weeks, 069; 95% CI, 0.52 to 0.90; P=0.0036). The response rate was improved with pembrolizumab administered every 2 weeks (33.7%) and every 3 weeks (32.9%), as compared with ipilimumab (11.9%) (P<0.001 for both comparisons). Responses were ongoing in 89.4%, 96.7%, and 87.9% of patients, respectively, after a median follow-up of 7.9 months. Efficacy was similar in the two pembrolizumab group (19.9%).

Conclusions

The anti-PD-1 antibody pembrolizumab prolonged progression-free survival and overall survival and had less high-grade toxicity than did ipilimumab in patients with advanced melanoma. (Funded by Merck Sharp & Dohme; KEYNOTE-006 ClinicalTrials.gov number, NCT01866319.)

PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma

The New England Journal of Medicine

ESTABLISHED IN 1812 *January 22, 2015* *Vol. 372 NO.4*

Stephen M. Ansell, M.D., Ph.D., Alexander M. Lesokhin, M.D., Ivan Borrello, M.D., Ahmad Halwani, M.D., Emma C. Scott, M.D., Martin Gutierrez, M.D., Stephen J. Schuster, M.D., Michael M. Millenson, M.D., Deepika Cattry, M.S., Cordon J. Freeman, Ph.D., Scott J. Rodig, M.D., Ph.D., Bjoern Chapuy, M.D., Ph.D., Azra H. Ligon, Ph.D., Lili Zhu, M.S., Joseph F. Grosso, Ph.D., Su Young Kim, M.D., Ph.D., John M. Timmerman, M.D., Margaret A. Shipp, M.D., and Philippe Armand, M.D., Ph.D.

Results

Of the 23 study patients, 78% were enrolled in the study after a relapse following autologous stem-cell transplantation and 78% after a relapse following the receipt *of* brentuximab vedotin. Drug-related *adverse* events of any grade and *of* grad' occurred in 78% and 22% of patients, respectively. An objective response was ported in 20 patients (87%), including 17% with a complete response and 70% w a partial response; the remaining 3 patients (13%) had stable disease. The rate progression-free survival at 24 weeks was 86%; 11 patients were continuing to participate in the study. Reasons for discontinuation included stem-cell transplantation (in 6 patients), disease progression fin 4 patients), and drug toxicity (in 2 patients). Analyses of pretreatment tumor specimens from 10 patients revealed copy-number gains in MU and *PDL2* and increased expression of these ligands. Reed—Sternberg cells showed nuclear positivity of phosphorylated STAT3, indicative of active JAK-STAT signaling.

Points to Remember

- Innate immunity (the first responders that do not require antigen recognition) can support and enhance the efficacy of adaptive immunity (cells that are specific to an invader).
- Therapeutic immunity can be either passive (supplying an antibody response) or active (vaccinating to create your own antibody response).
- There is strong evidence that most cancers stimulate the immune system.
- Efficacy of cancer-induced immunity is limited both by factors secreted by the tumor and stroma and by normal defense mechanisms activated to prevent autoimmunity.
- Improved understanding of tumor-immune system interactions has led to the design of therapeutic approaches that both stimulate immunity and address mechanisms of immune escape.
- There are now several promising immunologic agents that have demonstrated significant antitumor efficacy in advanced-stage clinical trials or have been approved for standard-of-care use.

Next Steps

Submit questions to: immunotherapy@medelis.com

- *(We will execute CDA if desired so we can both speak freely)*

- Look for email from us to access slides and webinar recording

- Discuss plans for your upcoming oncology trials

  - Meet at ASCO
    Connect with us via www.medelis.com or at (615) 297-6105

    Follow us via social: Twitter: @oncologycro, LinkedIn

Thank you!