Immuno-Oncology, The New Era of Cancer Treatment

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Disclosures

Dr. Ted Lee is an employee of Bristol-Myers Squibb Co.

New Therapies are Needed to Improve the Survival of Patients With Advanced Disease

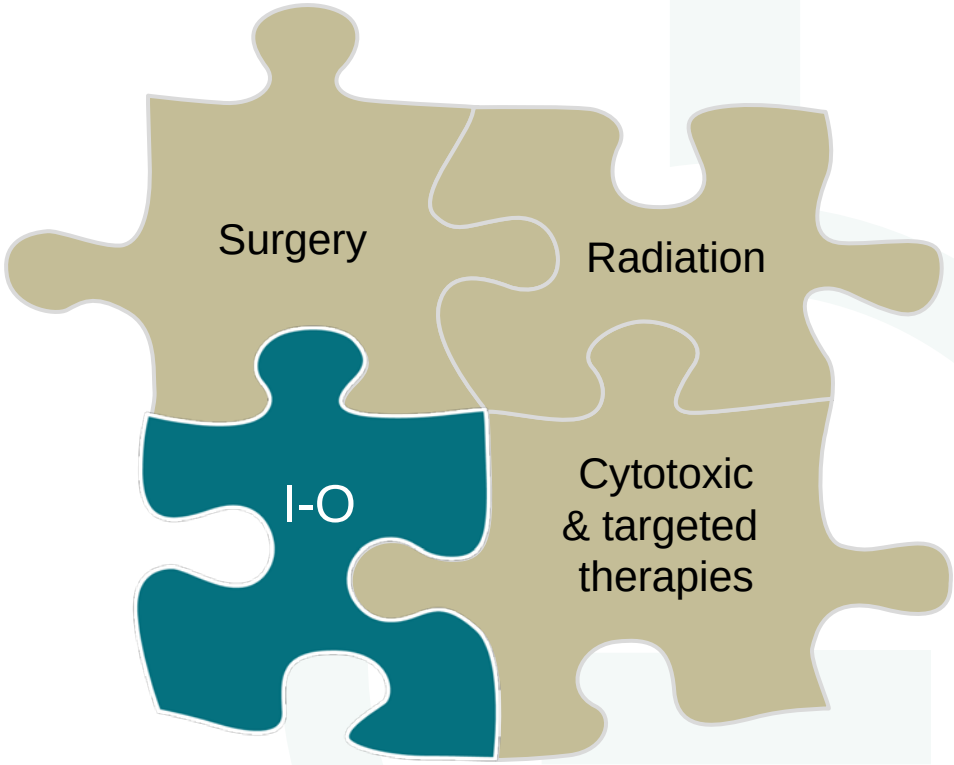
- 5-year survival rates are poor for many patients with advanced cancer[a]

Tumor Type	5-Year Survival Rate	
	Overall	Advanced Disease
Prostate	99.2%	27.9%
Melanoma	91.3%	16.0%
Breast	89.2%	24.3%
Kidney/renal pelvis	71.8%	12.3%
Colorectal	64.9%	12.5%
Ovarian	44.2%	27.3%
Stomach	27.7%	3.9%
Lung	16.6%	3.9%
Pancreatic	6.0%	2.0%

[a]Based on patients diagnosed in the United States between 2003 and 2009. Surveillance, Epidemiology and End Results (SEER) Program. http://seer.cancer.gov.

Immuno-Oncology

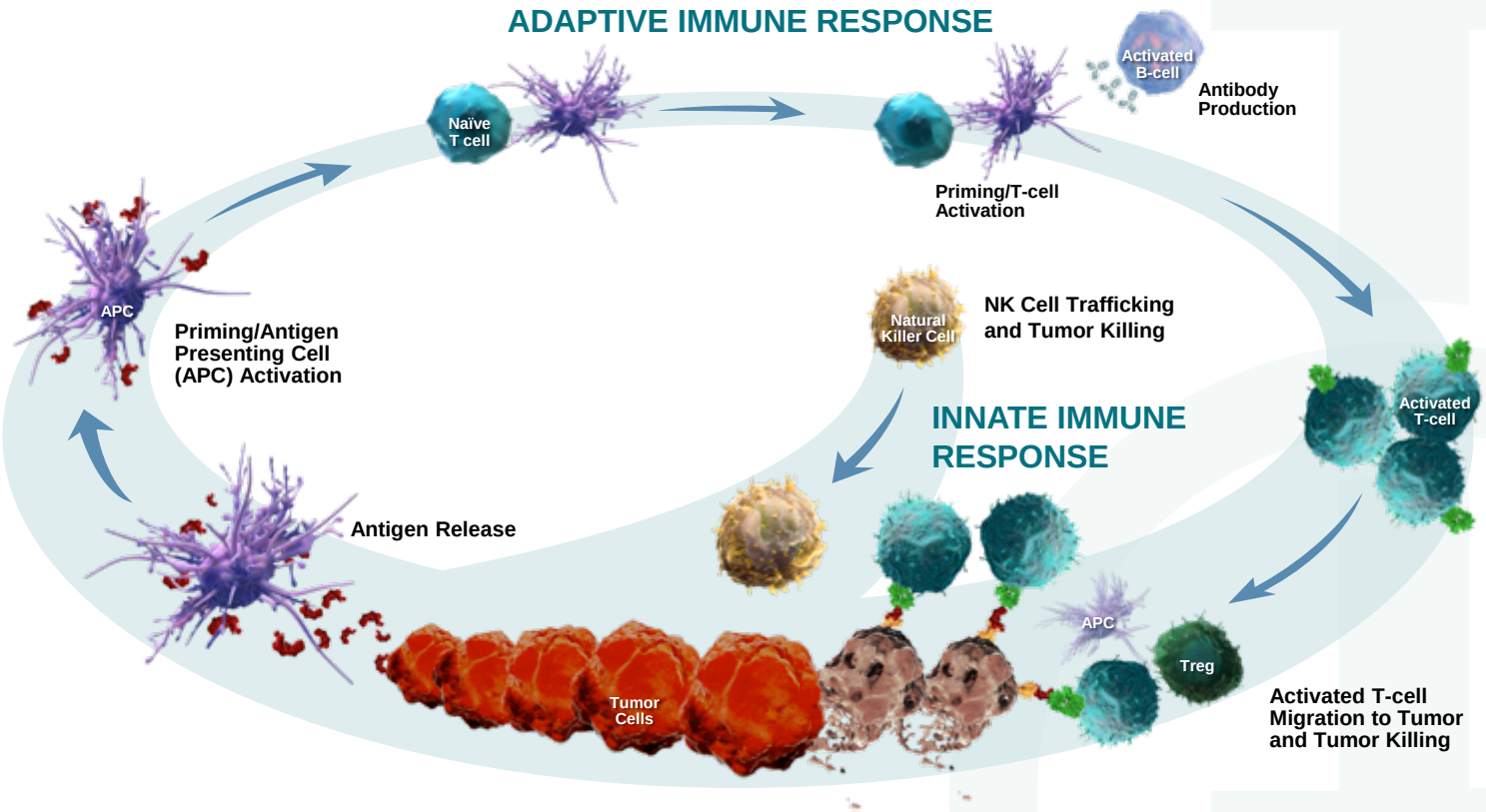
- I-O treatments are different from other treatment modalities
- Rather than directly targeting the tumor, I-O agents use the natural capability of the patient's own immune system to fight cancer



I-O=immuno-oncology.

DeVita VT, Rosenberg SA. *N Engl J Med*. 2012;366:2207–2214; Borghaei H, et al. *Eur J Pharmacol*. 2009;625:41–54.

The adaptive and innate immune system



	Innate immune response[1]	Adaptive immune response[1]
Response	Rapid response within hours that is identical upon repeat infection “first line of defense”	Slower response that happens within days and requires innate immune system to induce More rapid upon repeat infection
Specificity	Limited, fixed	Highly diverse; improves during course of response

1. Dranoff G. *Nat Rev Cancer*. 2004;4:11–22.

Immunoediting: The role of the immune system in cancer development and progression

Elimination
Cancer immunosurveillance

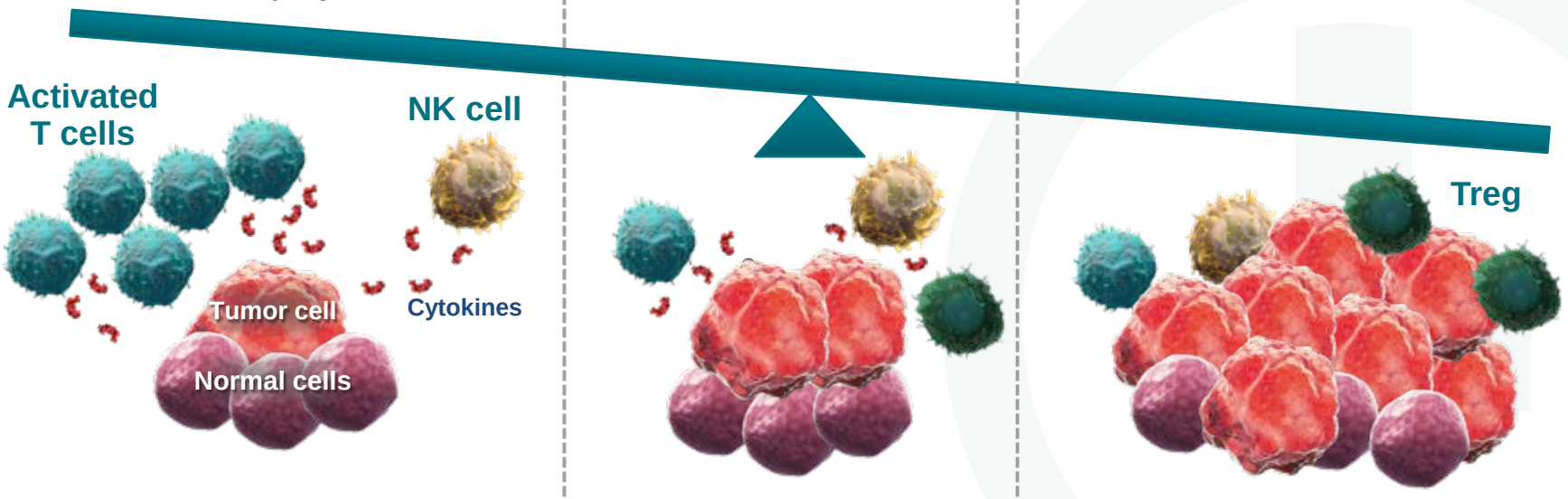
- Effective antigen processing/presentation
- Effective activation and function of effector cells
  - eg, T-cell activation without co-inhibitory signals

Equilibrium
Cancer dormancy

- Genetic instability
- Tumor heterogeneity
- Immune selection

Escape
Cancer progression

- Tumors may avoid elimination by the immune system through outgrowth tumor cells that can suppress, disrupt, or “escape” the immune system



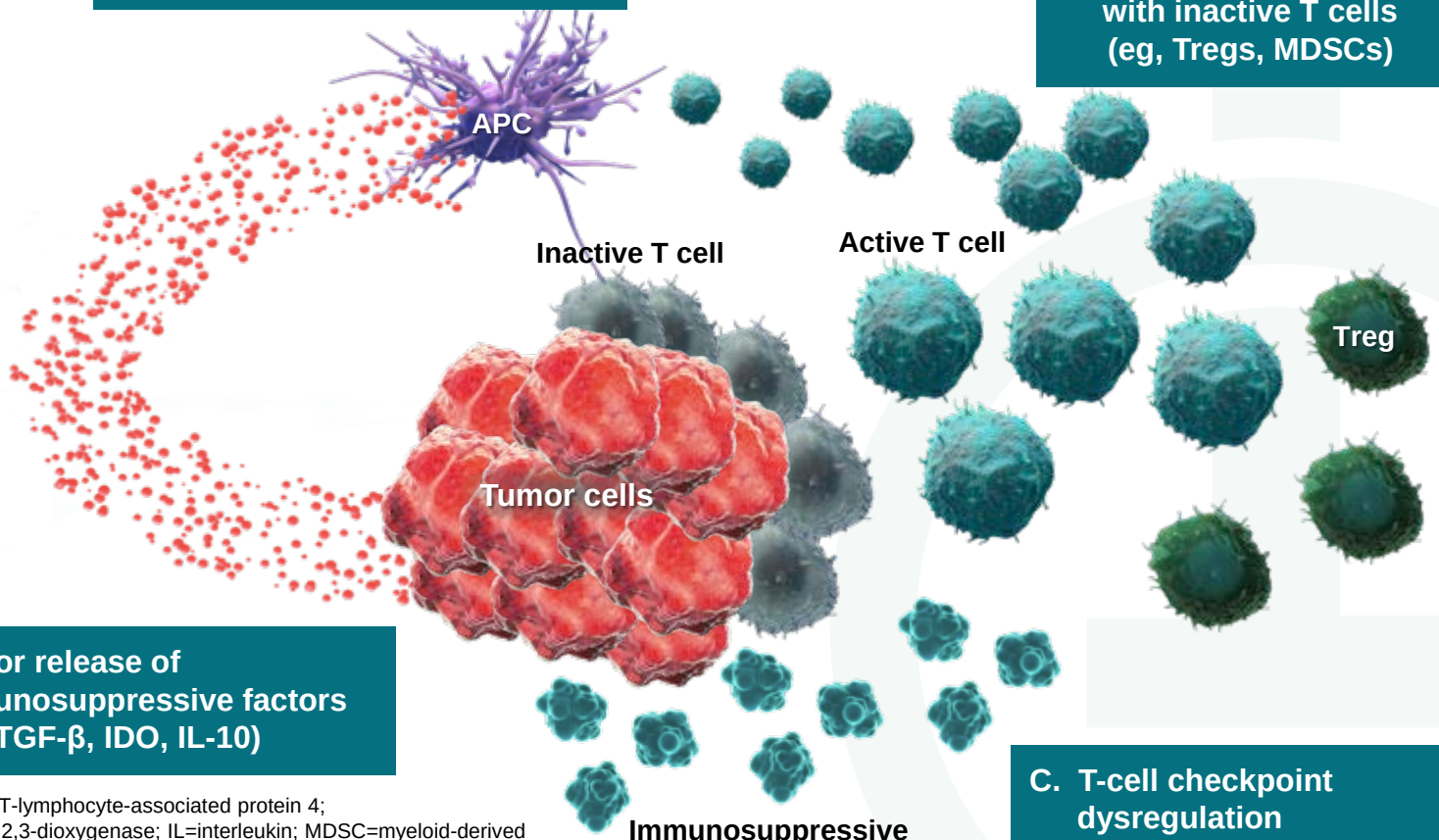
NK=natural killer.

Vesely MD, et al. *Ann Rev Immunol*. 2011;29:235–271.

Tumors use complex, overlapping mechanisms to evade and suppress the immune system

A. Ineffective presentation of tumor antigens (eg, downregulation of MHC I)

B. Recruitment of immunosuppressive cells with inactive T cells (eg, Tregs, MDSCs)



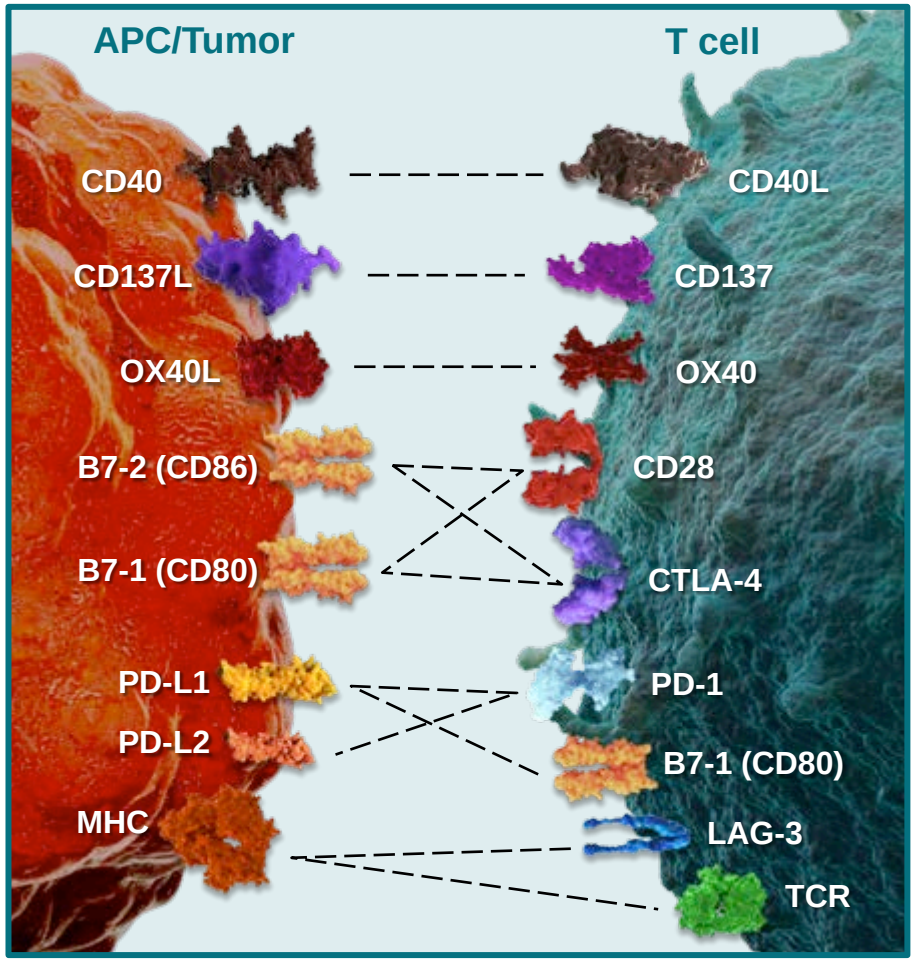
D. Tumor release of immunosuppressive factors (eg, TGF-β, IDO, IL-10)

C. T-cell checkpoint dysregulation (eg, PD-1, CTLA-4)

CTLA-4=cytotoxic T-lymphocyte-associated protein 4; IDO= indoleamine 2,3-dioxygenase; IL=interleukin; MDSC=myeloid-derived suppressor cell; MHC=major histocompatibility complex; TGF-β=transforming growth factor beta.

Vesely MD et al. *Ann Rev Immunol*. 2011;29:235–271.

T-cell checkpoint and co-stimulatory pathways



Activation
Activation
Activation
Activation

Inhibition
Inhibition
Inhibition
Inhibition

These pathways can be **activated** via I-O agents to counteract tumor-mediated inhibition

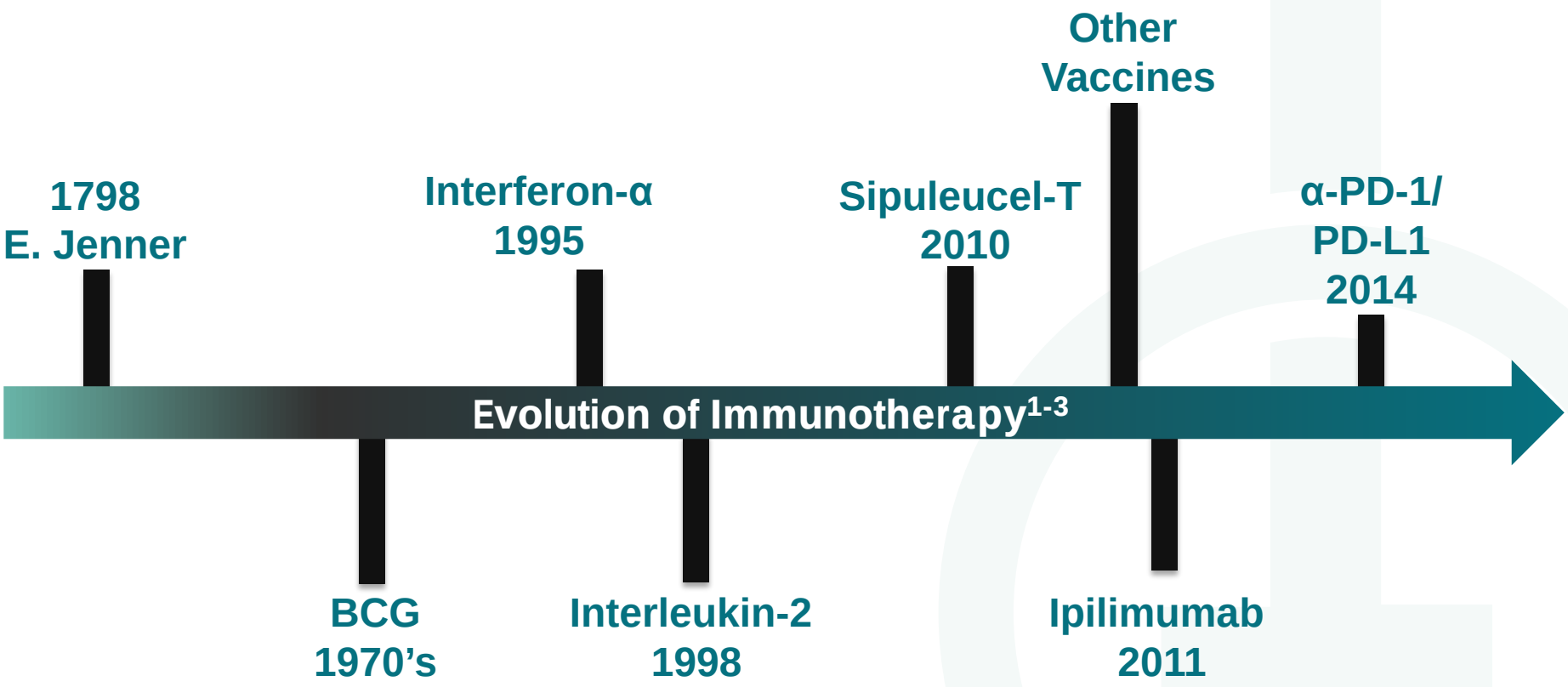
These pathways can be **blocked** via I-O agents to counteract tumor-mediated inhibition

Adapted from Pardoll DM 2012.

LAG-3=lymphocyte activation gene-3; TCR=T-cell receptor.

Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

Evolution of Immunotherapy

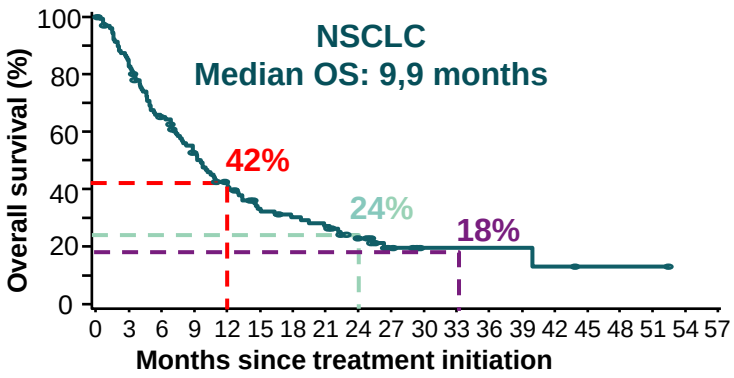


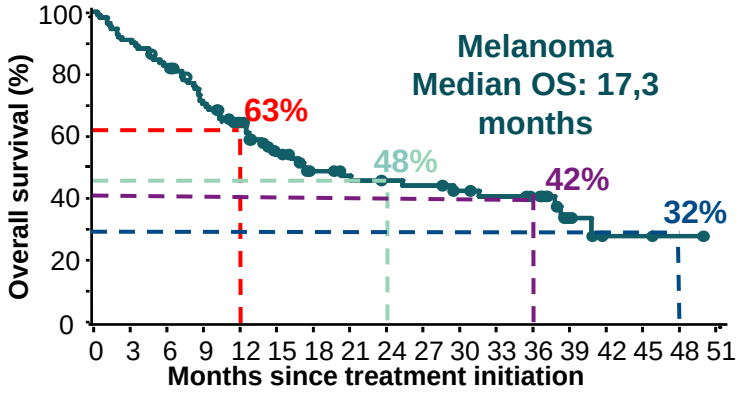
BCG, Bacillus Calmette-Guerin; PD-1, programmed death-1; PD-L1, programmed deathligand-1.

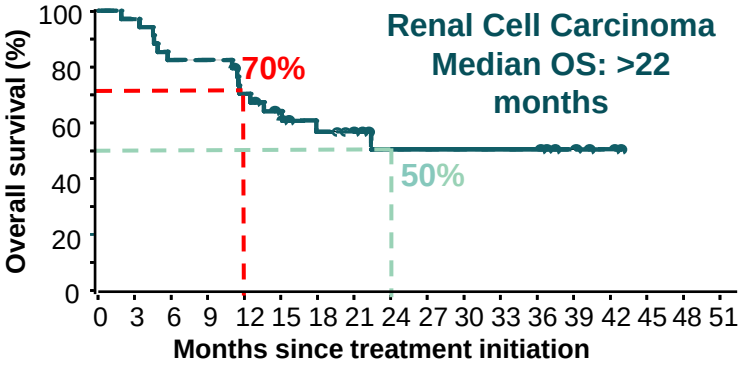
1. Lesterhuis WJ et al. Nat Rev Drug Discov. 2011;10(8):591-600. 2. FDA.gov. 3. http://www.ema.europa.eu/ema.

Immuno-oncology:
A cross-indication mechanism of action

- Clinical activity of nivolumab (anti PD-1) in advanced solid tumors (phase I)



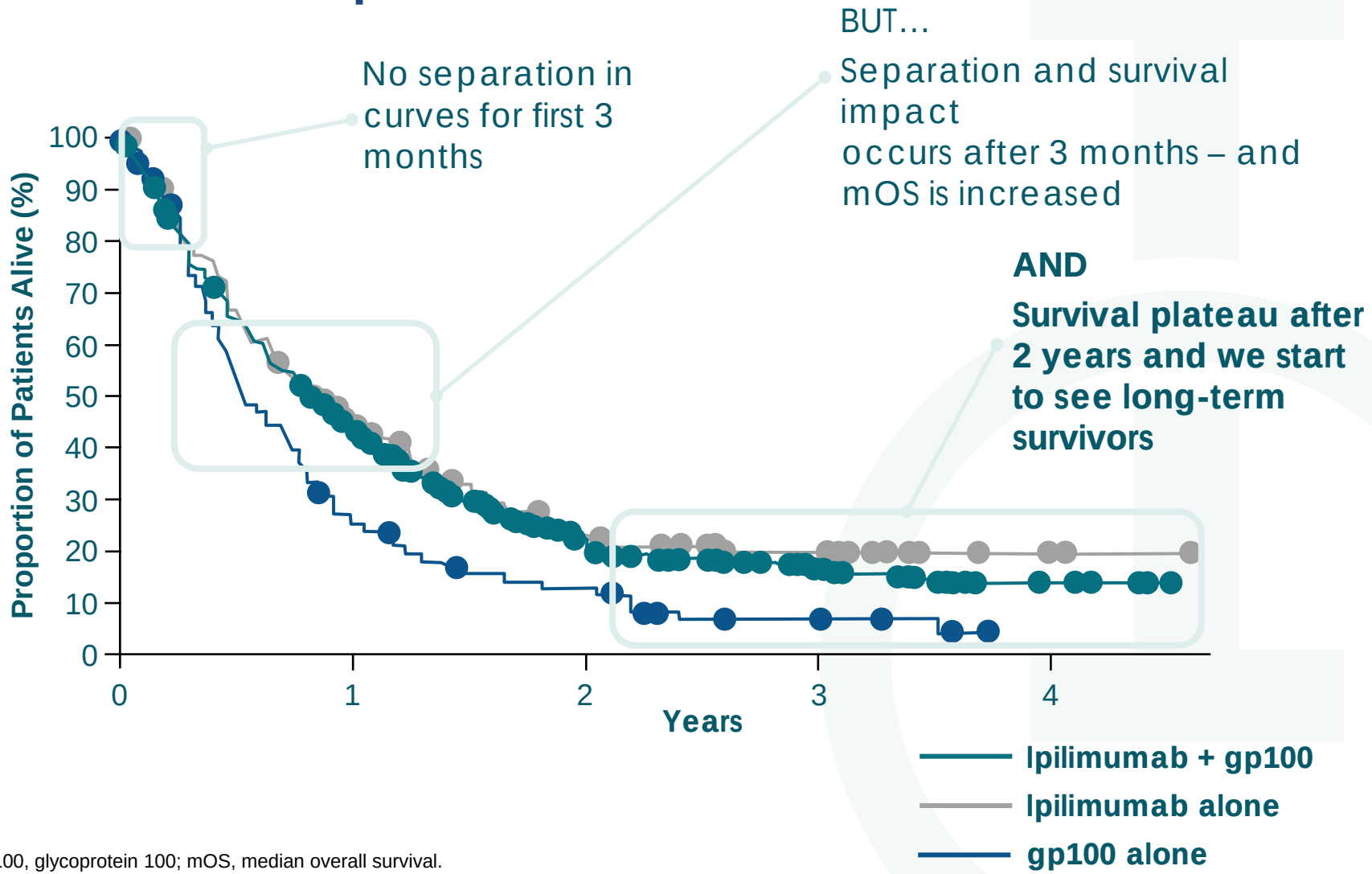




	% Survival			
(95% CI); Pts at risk	1 Year	2 Years	3 Years	4 Years
NSCLC	42 (33, 50)	24 (17, 33)	18 (11, 25)	
Mel	63	48	42	32
RCC	70 (55, 86)	50 (31, 70)		

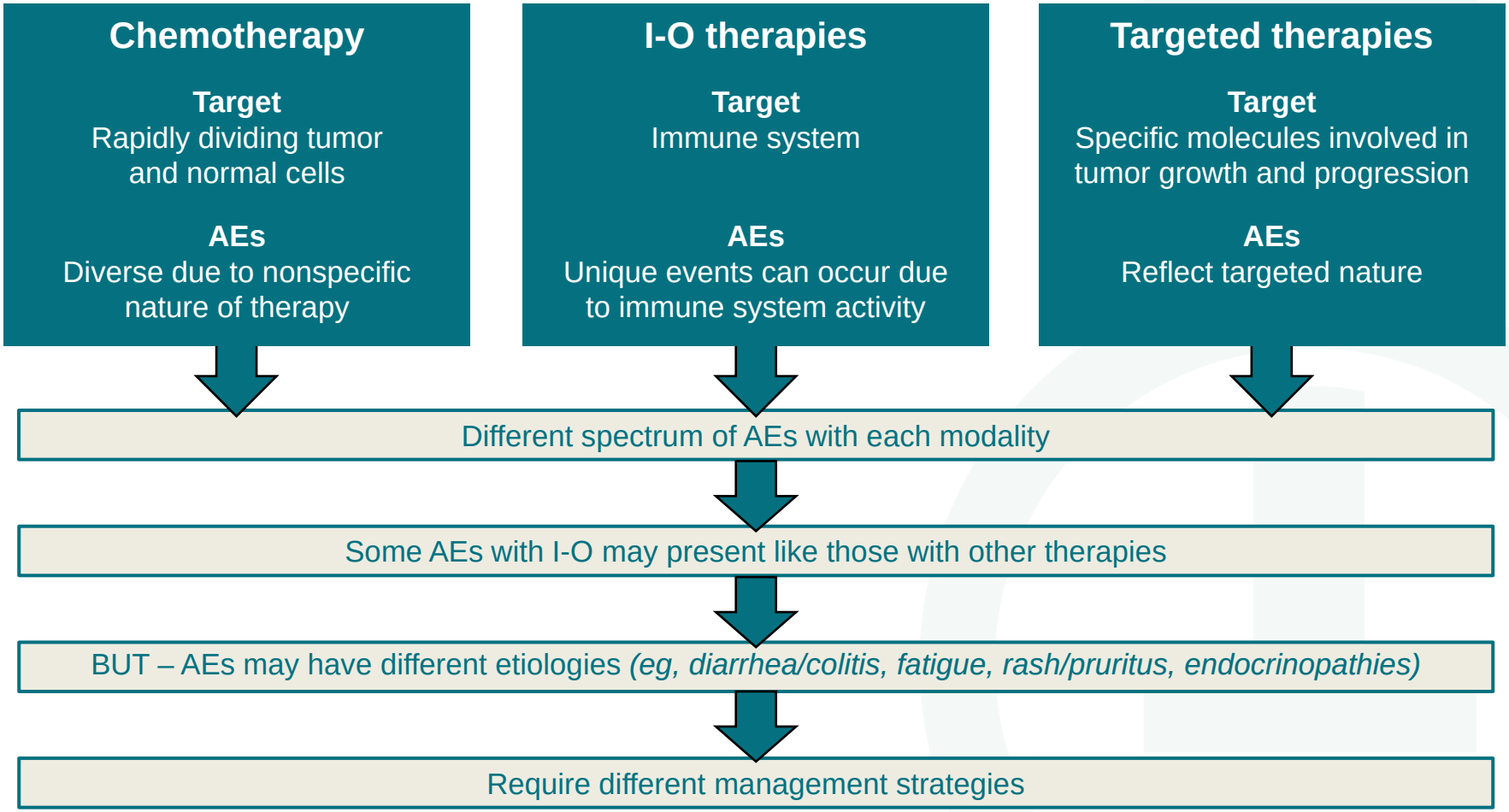
Adapted from Topalian SL, et al. Oral presentation at ASCO 2013: J Clin Oncol 2013;31(15 suppl): abstract 3002 Hodi et al, Poster presentation at ECC 2013:abstract 880. Brahmer et al, presented at WCLC 2013; Robert et al, SMR Nov 2013; Hodi et al. SMR 2014; Gettinger et al. CMSTO 2014

Immuno-oncology:
Immune checkpoint inhibitors in Melanoma



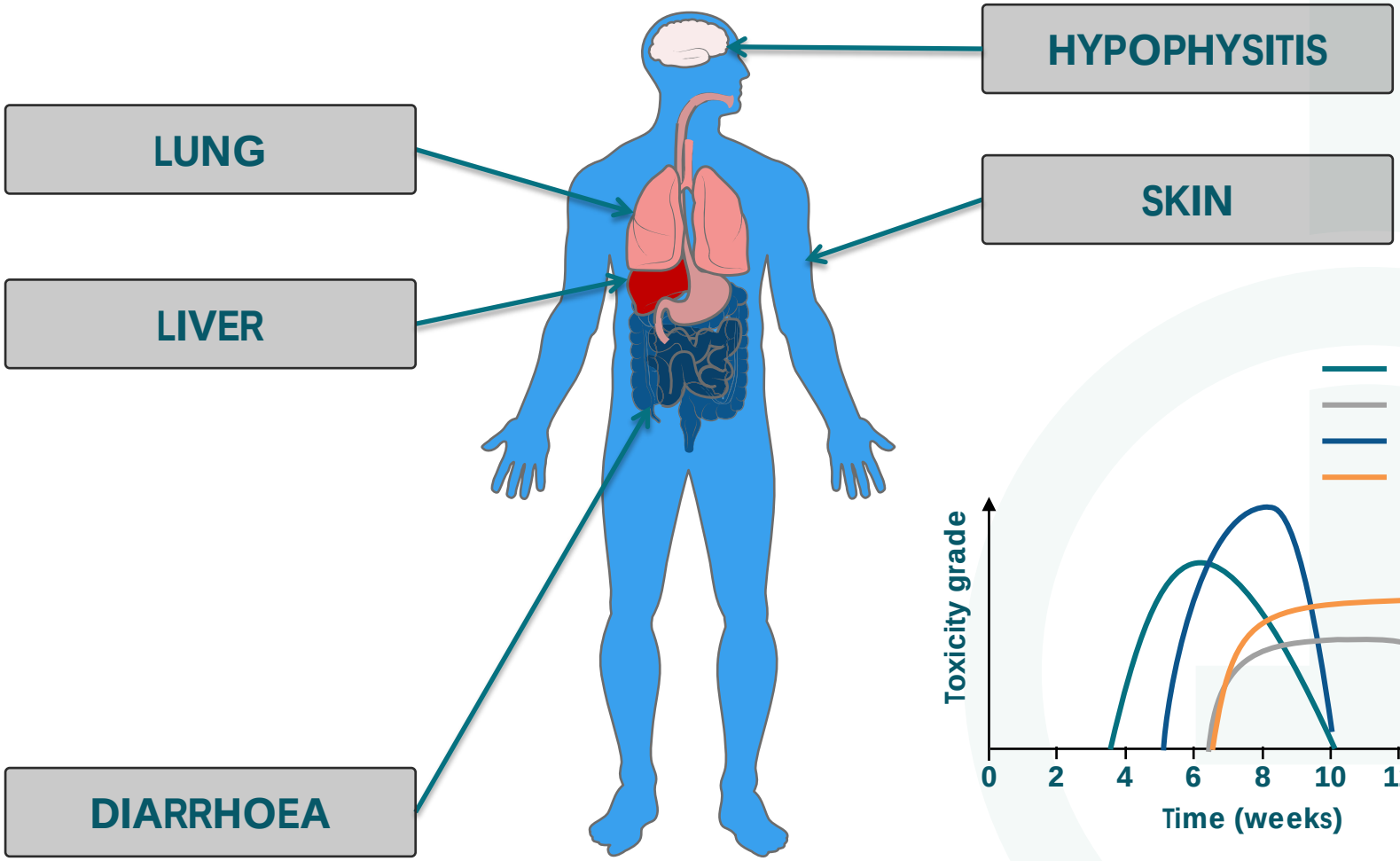
gp100, glycoprotein 100; mOS, median overall survival.
Hodi FS et al. *N Engl J Med*. 2010;363:711-723.

Tolerability of I-O therapies



American Cancer Society. Treatment types. http://www.cancer.org/. Topalian SL, et al. *N Engl J Med.* 2012;366:2443–2454 and oral presentation at ASCO 2013, Abstract 3002. Hamid O, et al. *N Engl J Med.* 2013;369:134–144. Dendreon. PROVENGE® Prescribing Information updated June 2011. Bristol-Myers Squibb. YERVOY (ipilimumab) REMS and Prescribing Information. http://www.yervoy.com. Accessed July, 2015. Bristol-Myers Squibb. OPDIVO (nivolumab) Prescribing Information.

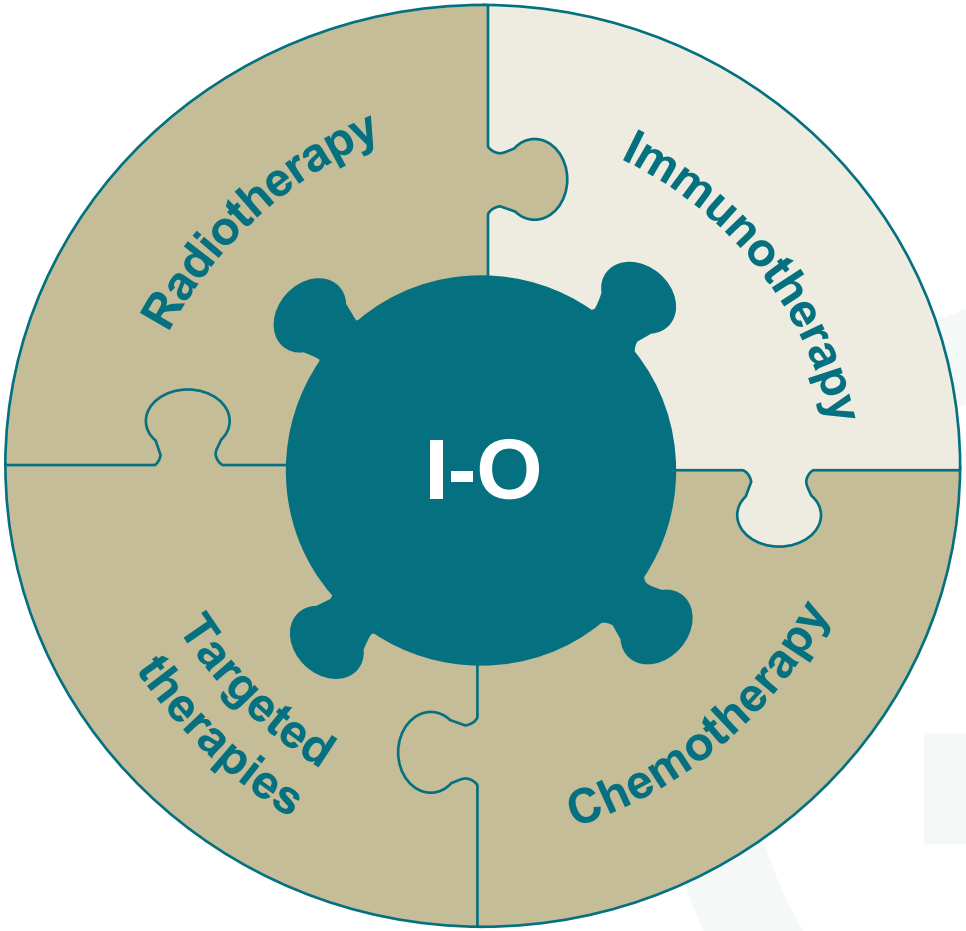
Immune-related Adverse Events



PD-L1, programmed death ligand-1.

1. Amos SM et al. *Blood*. 2011;118(3):499–509. 2. Weber JS et al. *J Clin Oncol*. 2012;30(21):2691-2697.

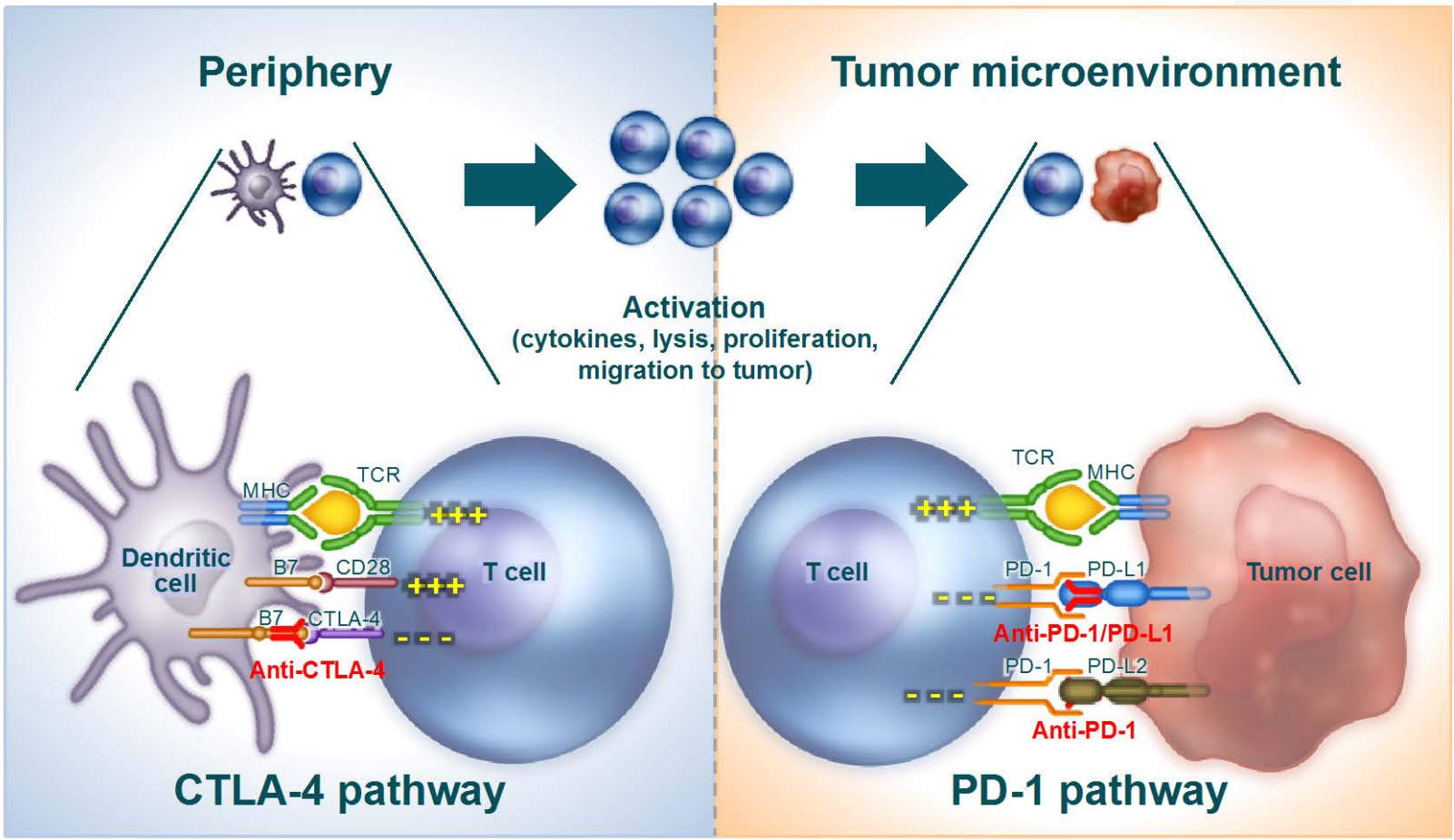
I-O agents have a unique mechanism of action, offering the opportunity for combination with other agents



Drake C. *Ann Oncol.* 2012;23(suppl 8):viii41–viii46; Hannani D, et al. *Cancer J.* 2011;17:351–358; Ménard C, et al. *Cancer Immunol Immunother.* 2008;57:1579–1587; Ribas A, et al. *Curr Opin Immunol.* 2013;25:291–296.

Immune checkpoint inhibitors: Potential as part of a combination regimen

- Data suggest certain combinations may overcome the limitations of monotherapy[1,2]



1. Sharma P, et al. *Science*. 2015;348:56–66. 2. Wolchock J, et al. *J Clin Oncol.* 2013;31(15 suppl):abstract 9012.

Examples of ongoing combination studies with I-O therapies in NSCLC

	Chemotherapy	Radiotherapy (RT)	Targeted	Immunotherapy
Nivolumab (anti-PD-1)	+ gemcitabine/cisplatin or carboplatin/paclitaxel (NCT01454102)	NR	+ bevacizumab maintenance or erlotinib (NCT01454102) + EGF816 or INC280 (NCT02323126) + ceritinib (NCT02393625)	+ ipilimumab (NCT02477826/ NCT01454102) + GM.CD40L vaccine (NCT02466568)
Pembrolizumab (anti-PD-1)	+ carboplatin/paclitaxel (±bevacizumab) or + paclitaxel/pemetrexed (NCT02039674) + entinostat (NCT02437136) + carboplatin/nab-paclitaxel (NCT02382406) + gemcitabine (NCT02422381)	+ hypofractionated stereotactic RT (NCT02444741) + stereotactic body RT (NCT02492568)	+ erlotinib or gefitinib (NCT02039674) + crizotinib (NCT02511184) + necitumumab (NCT02451930) + ACP-196 (NCT02448303) + afatinib (NCT02364609)	+ ipilimumab (NCT02039674) + INCB024360 (NCT02178722)
Durvalumab (anti-PD-L1)	NR	NR	+ AZD9291 (NCT02454933) + gefitinib (NCT02088112)	+ tremelimumab (NCT02000947)
Atezolizumab (anti-PD-L1)	+ carboplatin/paclitaxel or nab-paclitaxel (NCT02367794/NCT02367781) + carboplatin/paclitaxel (±bevacizumab) (NCT02366143) + gemcitabine/cisplatin or carboplatin (NCT02409355) + cisplatin or carboplatin/ pemetrexed (NCT02409342)	+ stereotactic ablative RT (NCT02400814) + hypofractionated image-guided RT(NCT02463994)	+ erlotinib (NCT02013219)	+ INCB02436 (NCT02298153) + CDX-1401(NCT02495636)
Ipilimumab (anti-CTLA-4)	+ carboplatin/paclitaxel (NCT02279732)	+ ionizing RT (NCT02221739)	+ erlotinib or crizotinib (NCT01998126)	+ nivolumab (NCT02477826/ NCT01454102) + pembrolizumab (NCT02039674)
Tremelimumab (anti-CTLA-4)	NR	NR	+ gefitinib (NCT02040064)	+ durvalumab (NCT02000947)

NR=no studies reported. www.clinicaltrials.gov. Accessed August 2015.

Selected immunotherapies under evaluation for different tumor types

NHL, AML, CLL, lymphoma
- Vaccines
- PD-1 pathway targeting agents
- CD40 agents
- Anti-4-1BB agents
- Anti KIR agents

NSCLC/SCLC
- Vaccines
- PD-1 pathway targeting agents
- CTLA-4 pathway targeting agents

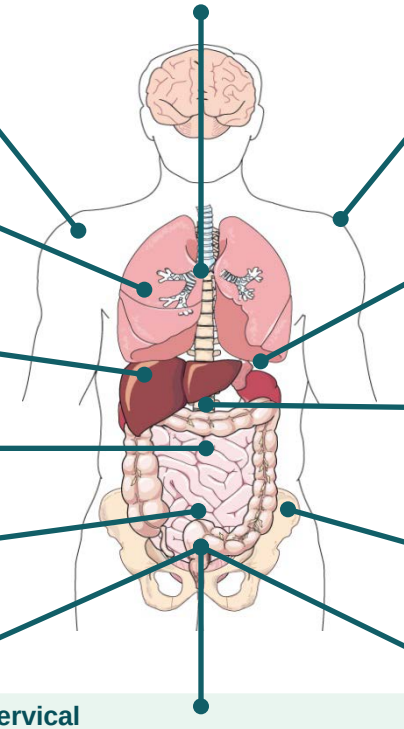
HCC
- CTLA-4 pathway targeting agents

GIST
- CTLA-4 pathway targeting agents

CRC
- CTLA-4 pathway targeting agents

PC/CRPC
- Vaccines
- CTLA-4 pathway targeting agents
- PD-1 pathway targeting agents

Breast
- CTLA-4 pathway targeting agents
- LAG-3 protein targeting



Cervical
- CTLA-4 pathway targeting agents

Melanoma
- Vaccines
- CTLA-4 pathway targeting agents
- PD-1 pathway targeting agents
- LAG-3 protein targeting agents
- GITR targeting agents
- CD40 agents

RCC
- Vaccines
- CTLA-4 pathway targeting agents
- PD-1 pathway targeting agents
- LAG-3 protein targeting agents

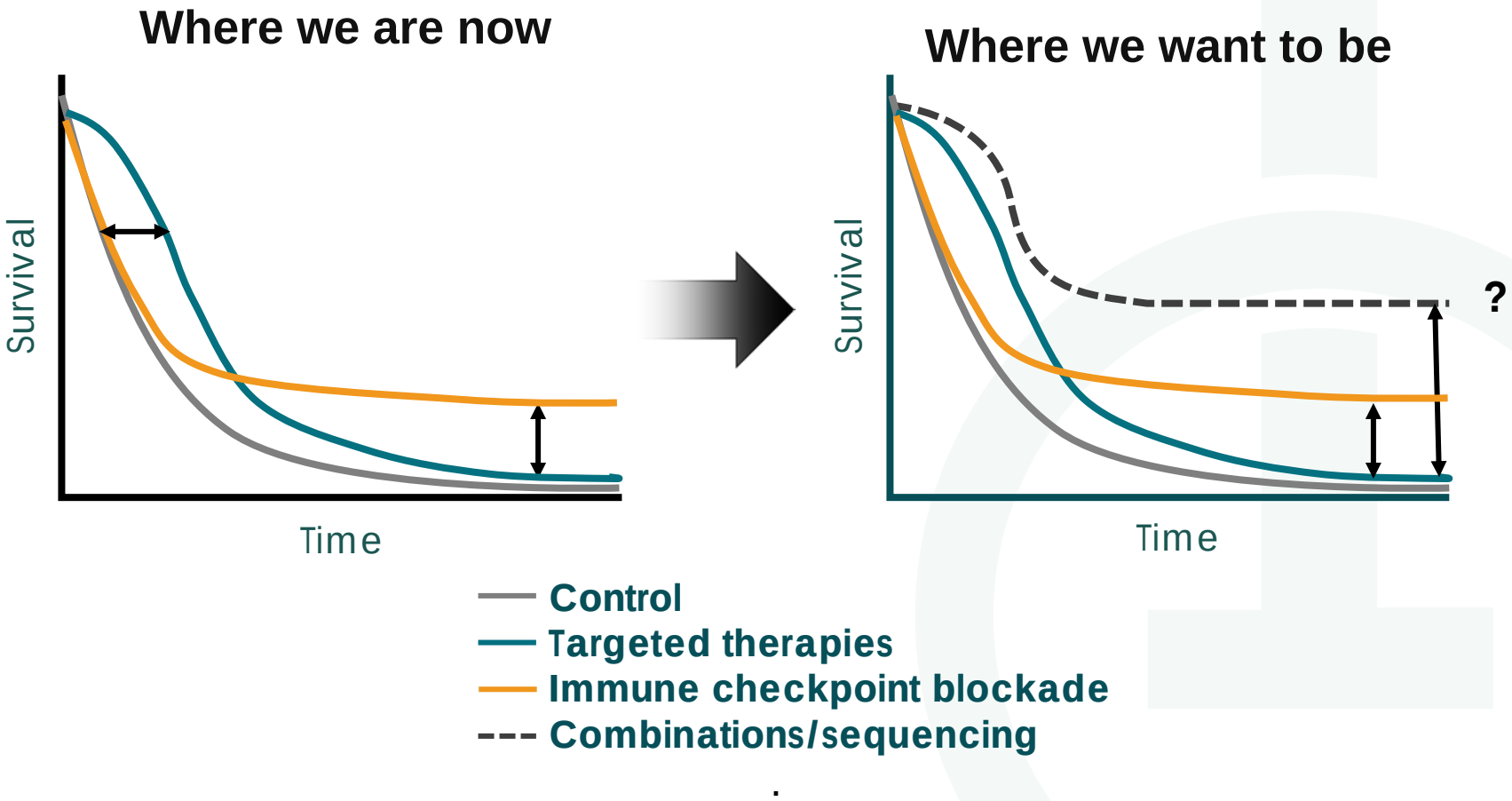
Pancreatic
- Vaccines
- CTLA-4 pathway targeting agents
- PD-1 pathway targeting agents
- CD40 agents

Hematologic
- CTLA-4 pathway targeting agents
- Targeting CD27

Ovarian
- Vaccines
- CTLA-4 pathway targeting agents

www.clinicaltrials.gov, Stand March 2014
Representation not complete

Hypothetical Effect of Targeting Distinct and Potentially Complementary Immune Evasion Pathways: Advanced Melanoma



1. Adapted from Ribas A, presented at WCM, 2013; 2. Ribas A, et al. *Clin Cancer Res.* 2012;18:336–341; 3. Drake CG. *Ann Oncol*. 2012;23(suppl 8):viii41–viii46.

The Future of Immune Modulation