Criteria to move single agents into clinical trials: Anti-PD-1

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DISCLOSURES
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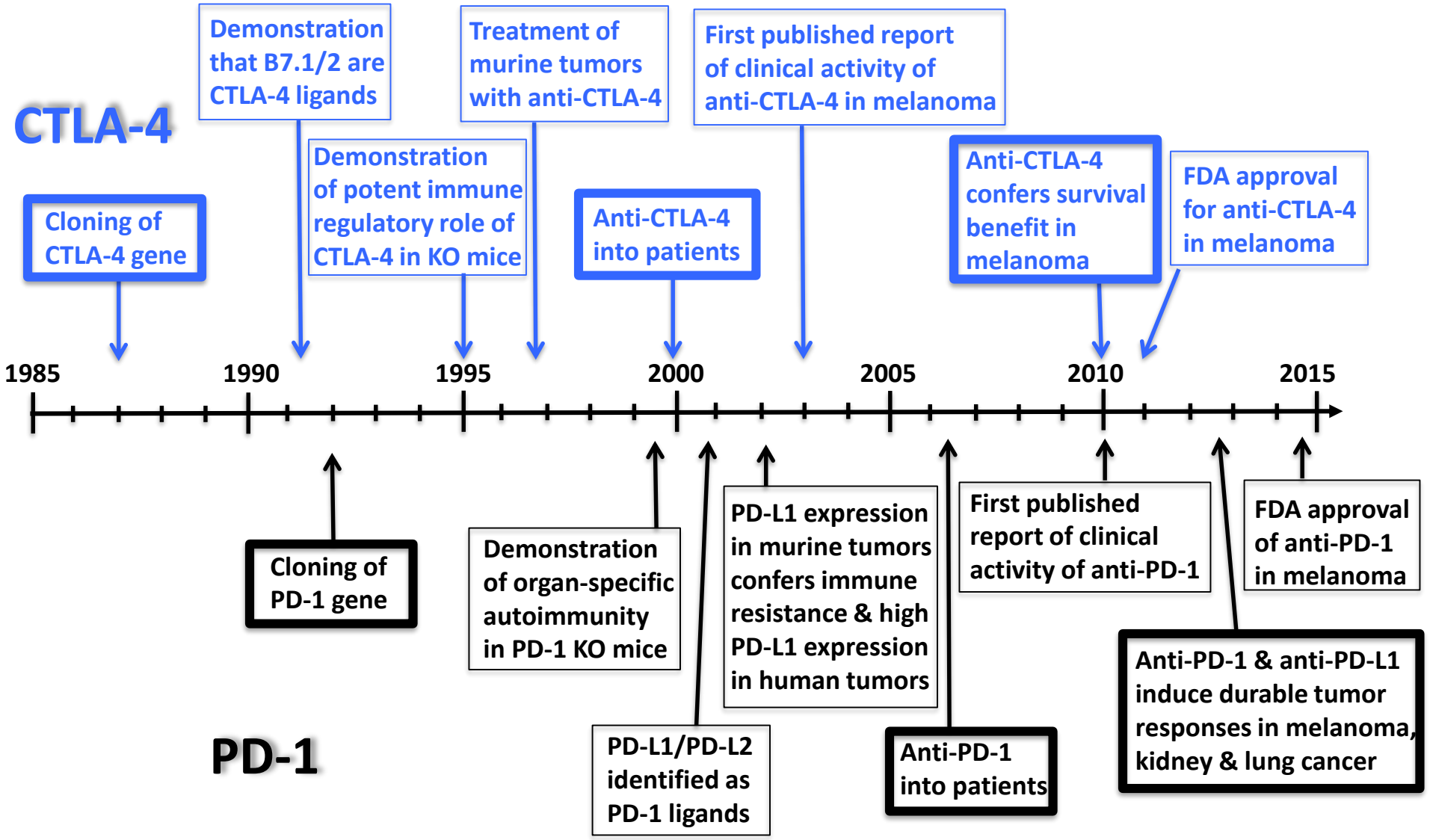
-- and –

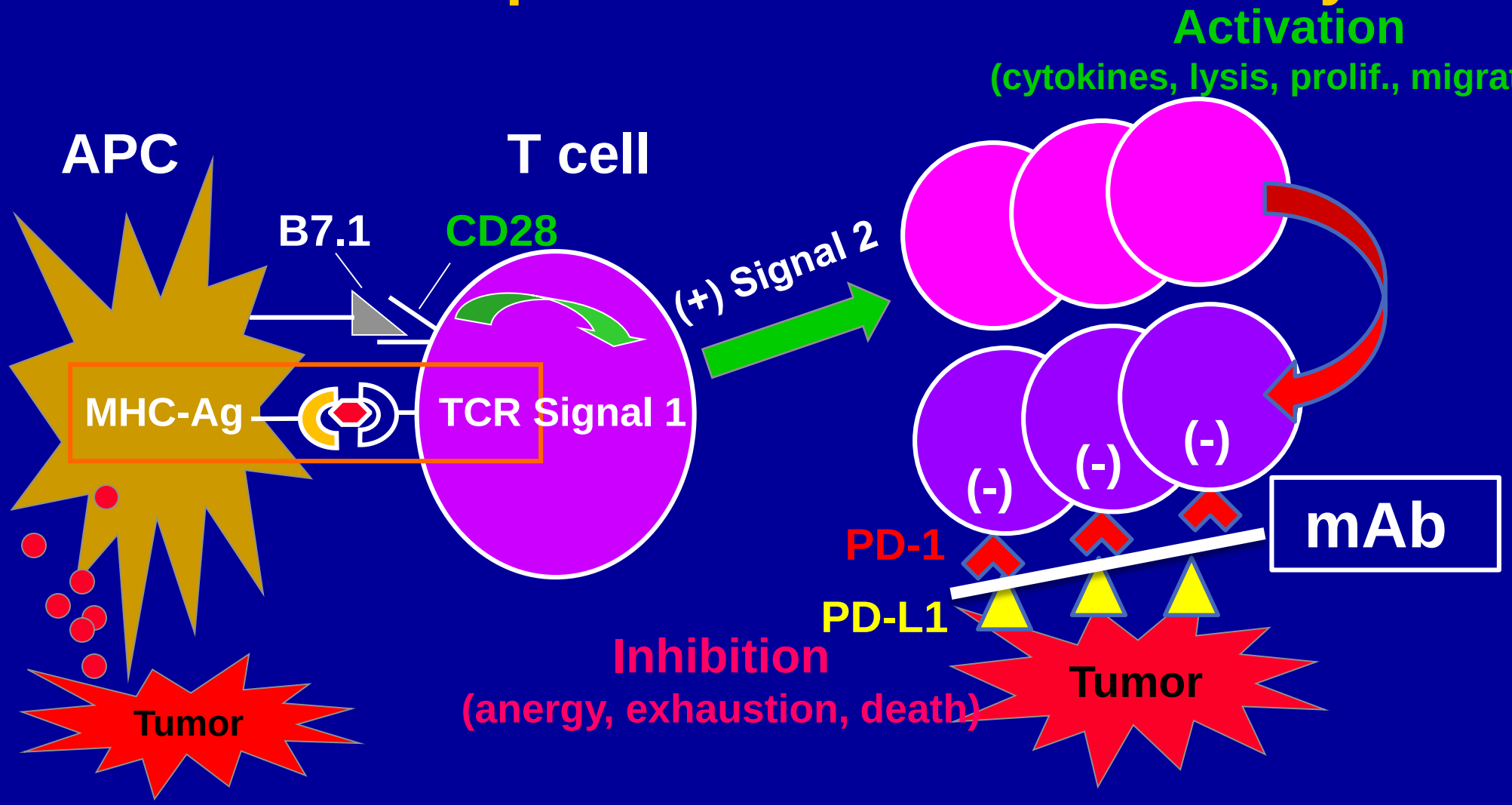
I will discuss investigational uses for anti-PD-(L)1 drugs in my presentation.

Single-agent anti-PD-1 and anti-CTLA-4: breakthrough or evolution?



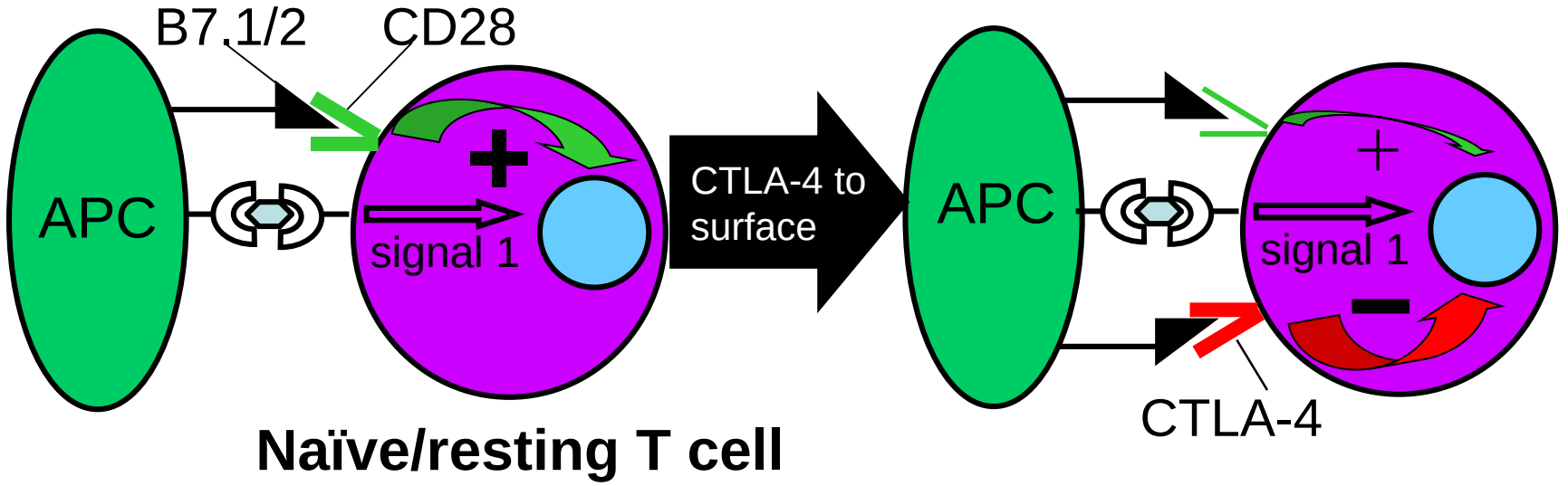
Adapted from Pardoll , Nature Immunol 2012

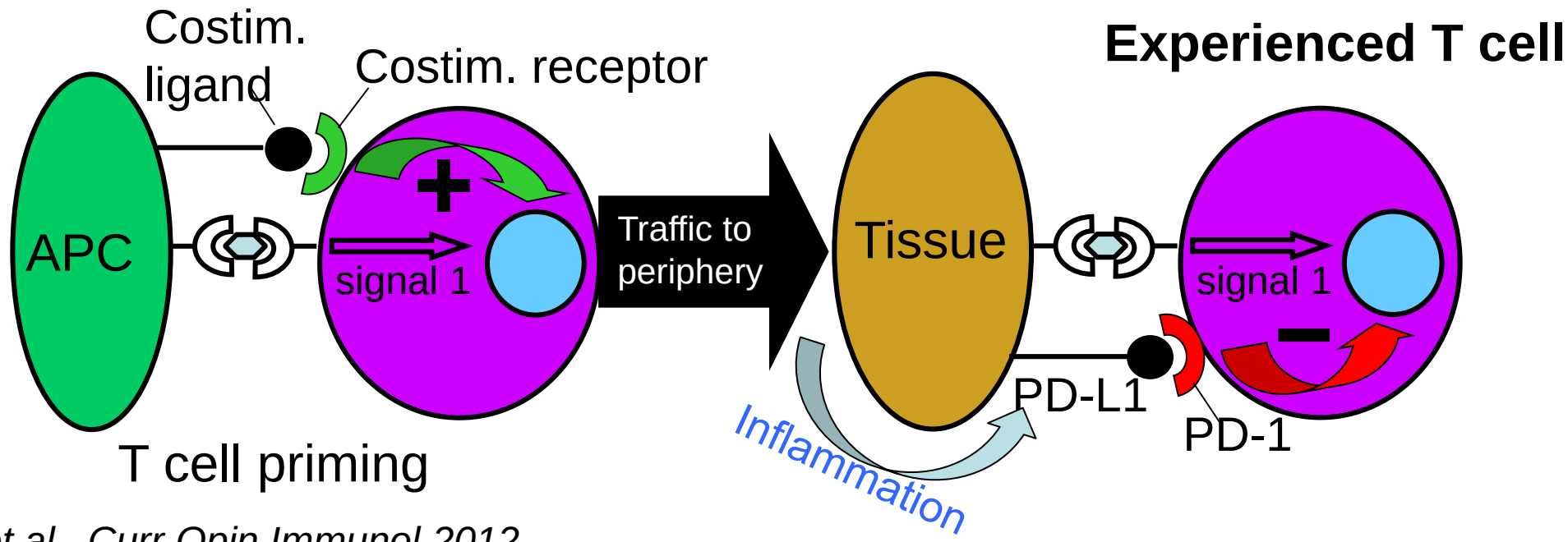
Mechanism of action: the PD-1/PD-L1 pathway is a dominant checkpoint in antitumor immunity



Keir et al, Annu Rev Immunol 2008; Pardoll, Nat Rev Cancer 2012

PD-1 vs CTLA-4: Distinct immune checkpoints





Topalian et al., Curr Opin Immunol 2012

Selective expression of the PD-L1 (B7-H1) ligand by human cancers

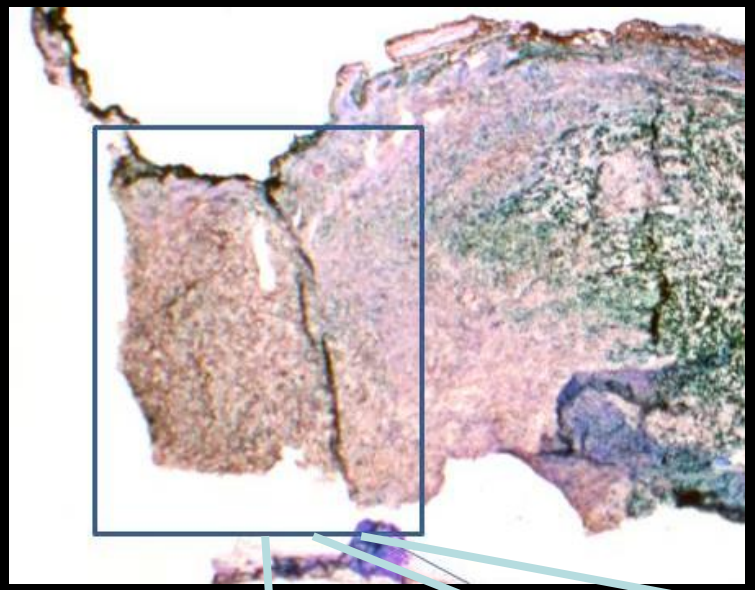
- PD-L1 is a member of the B7 family.
- Expression normally limited to hematopoetic cells, but inducible in heart, lung, kidney, spleen, and endothelial cells in response to IFN-γ.
- Expressed on syncytiotrophoblasts and extravillous cytotrophoblasts continuous with maternal blood and tissue.
- Expressed by human tumors arising from various tissues, including a very high proportion of lung cancers and melanomas.

(*Dong, Chen et al. Nat Med 2002)*

Table 1 Expression of B7-H1 in human cancer tissues

Diagnosis	Specimen numbers, positive/total (%)	Cases with staining intensity[a] –	+	++	+++
Lung cancer	20/21 (95)	1	9	10	1
Adenocarcinoma	10/10	0	5	5	0
Squamous cell carcinoma	8/8	0	2	5	1
Large cell carcinoma	1/2	1	1	0	0
Neuroendocrine carcinoma	1/1	0	1	0	0
Ovarian cancer	20/23 (87)	3	8	11	1
Adenocarcinoma	19/22	3	7	11	1
Carcinosarcoma	1/1	0	1	0	0
Melanoma	22/22 (100)	0	5	12	5
Skin	13/13	0	4	6	3
Lymph node metastasis	5/5	0	0	4	1
Brain metastasis	1/1	0	0	1	0
Axilla metastasis	2/2	0	1	0	1
Breast metastasis	1/1	0	0	1	0
Colon adenocarcinoma	10/19 (53)	9	6	2	2

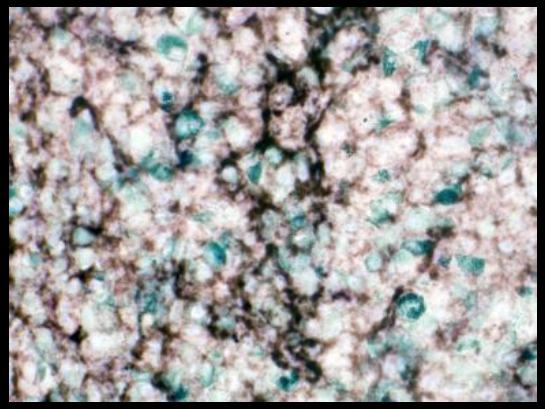
[a], Intensity of staining by monoclonal antibody against B7-H1: –, negative; +, focal expression in 10–40% of cancer tissues; ++, focal expression in 40–80% of cancer tissues; +++, diffuse expression in >80% of cancer tissues.



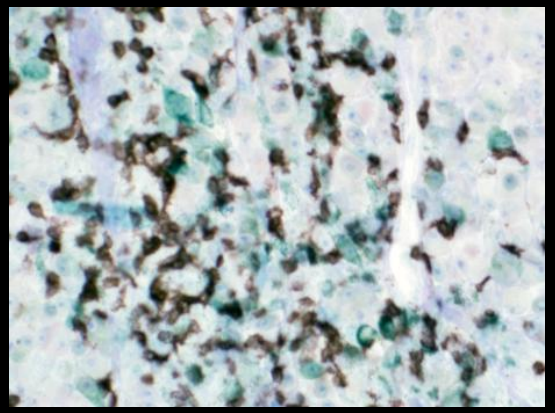
PD-1 pathway expression in human cancers:
PD-1+ T cells and
PD-L1+ tumor & immune cells

(shown: primary ocular melanoma)

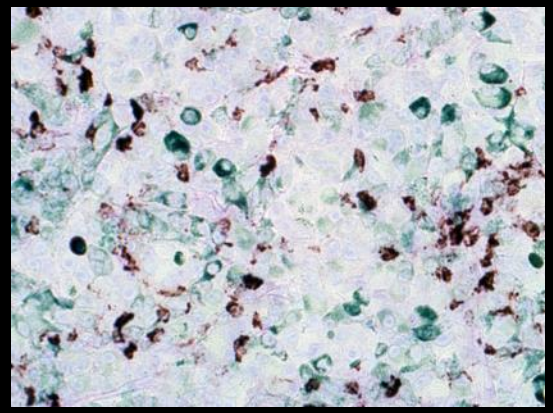
PD-L1



CD3

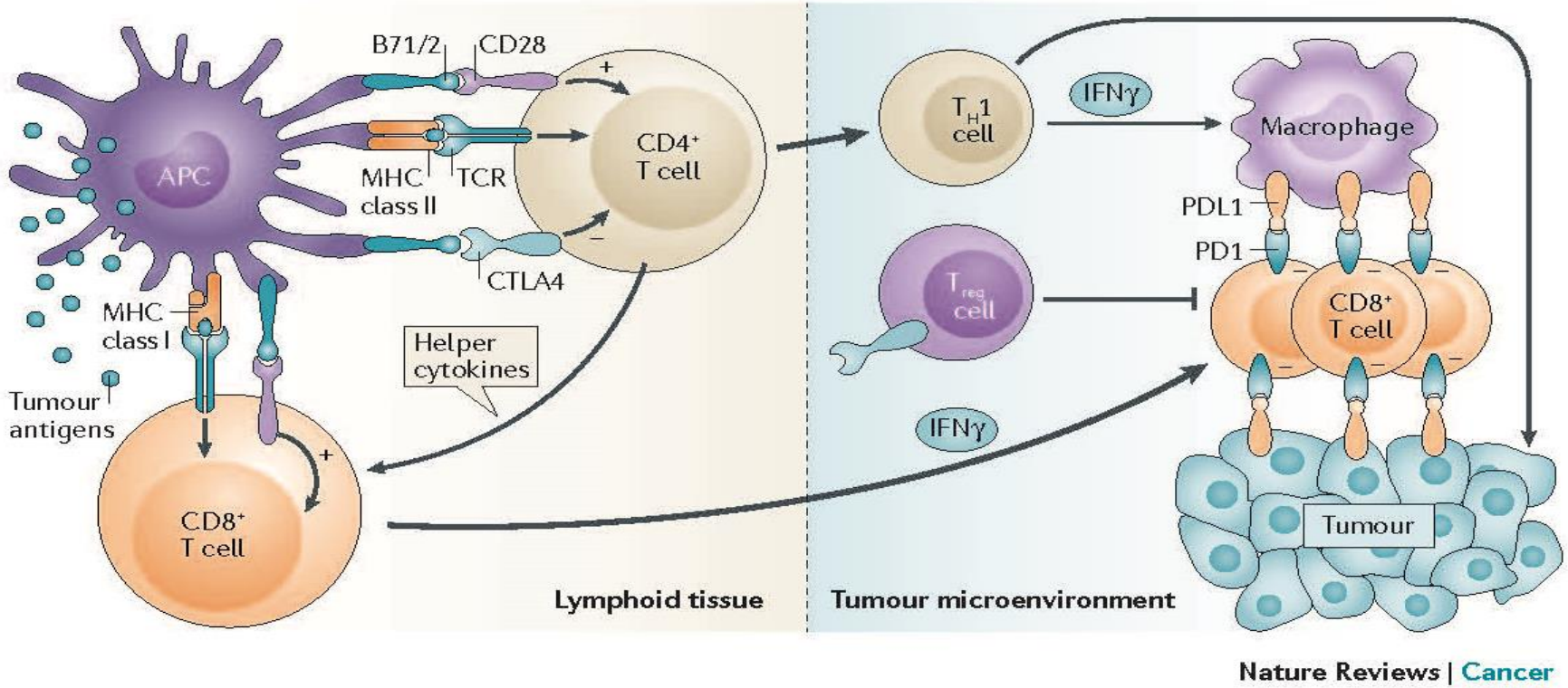


PD-1



J. Taube, Johns Hopkins University

Addressing treatment response and resistance: mechanism-driven biomarkers for immune checkpoint blockade

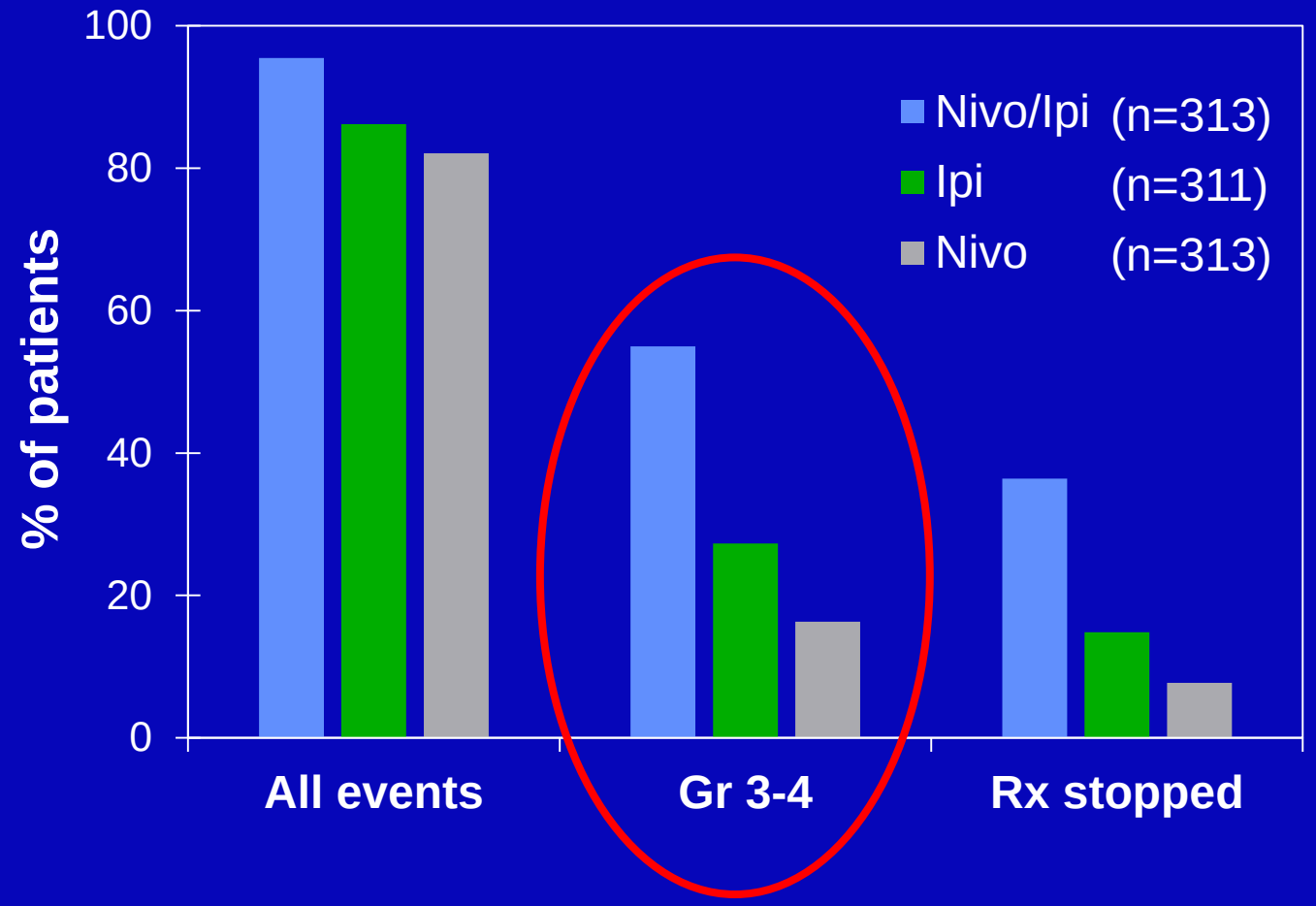


Topalian et al., 2016

Current FDA-approved biomarkers for anti-PD-1 therapy:

- PD-L1 immunohistochemistry (expression by tumor and/or immune cells)
- dMMR/MSI-high (extremely high mutation/neoantigen burden)
- TMB high (≥ 10 muts/Mb)

Distinct safety profiles for anti-PD-1 vs anti-CTLA-4 were predicted by murine KO models: results in melanoma from the CM-067 randomized trial



% of patients with AE (any grade)

Event	N + I	Ipi	Nivo
Diarrhea	44	33	19
Fatigue	35	28	34
Pruritis	33	35	19
Rash	40	33	26
ALT increased	18	4	4
AST increased	15	4	4
Hypothryroidism	15	4	9

Larkin et al., NEJM 2015

Anti-PD-(L)1: A foundational "common denominator" for cancer therapy *(Topalian et al., Cancer Cell 2015)*

FDA APPROVALS IN 21 TYPES OF ADVANCED CANCER:

- Melanoma (~24-45% of patients responding)
- Lung cancer (10-30%)
- Kidney cancer (12-29%)
- Bladder cancer (15-30%)
- Head and neck cancer (20-25%)
- Hodgkin lymphoma (65-87%)
- Merkel cell carcinoma (32-64%)
- Hepatocellular (liver) carcinoma (~15%)
- Gastric cancer (13-25%)
- Cervical cancer (14-20%)
- Primary mediastinal large B-cell lymphoma (45%)
- Small-cell lung cancer (with chemo, 60%)
- Cutaneous squamous cell carcinoma (34-47%)
- Triple negative breast cancer (with chemo, 53%)
- Esophageal cancer (~20%)
- Endometrial cancer (with kinase inhibitor, 38%)
- Mesothelioma (with ipilimumab, 40%)
- Basal cell carcinoma (20-30%)
- Biliary tract cancers (with chemo, 27%)
- MSI-hi cancers (~50%)
- TMB-hi cancers (~30%)

IN TESTING:

Ovarian cancer, nasopharyngeal Ca, adrenocortical Ca, sarcomas, anaplastic thyroid Ca,.....

SUCCESS:

- **Nobel Prize in Medicine** awarded to Drs. Allison and Honjo in 2018.
- Two anti-PD-1 drugs, pembrolizumab (Keytruda) and nivolumab (Opdivo), were among the **top 10** best-selling drugs **of any kind** in 2020.