Gynecologic Cancer InterGroup
Cervix Cancer Research Network

IMMUNOTHERAPY IN THE TREATMENT OF CERVIX CANCER

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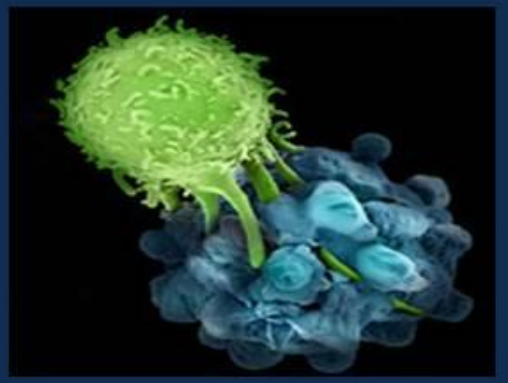
Peter MacCallum Cancer Centre, Melbourne
Australia

Cervix Cancer Education Symposium, January 2017, Mexico

Immunotherapy – The Beginning of the End for Cancer: Transforming Cancer into Chronic Disease

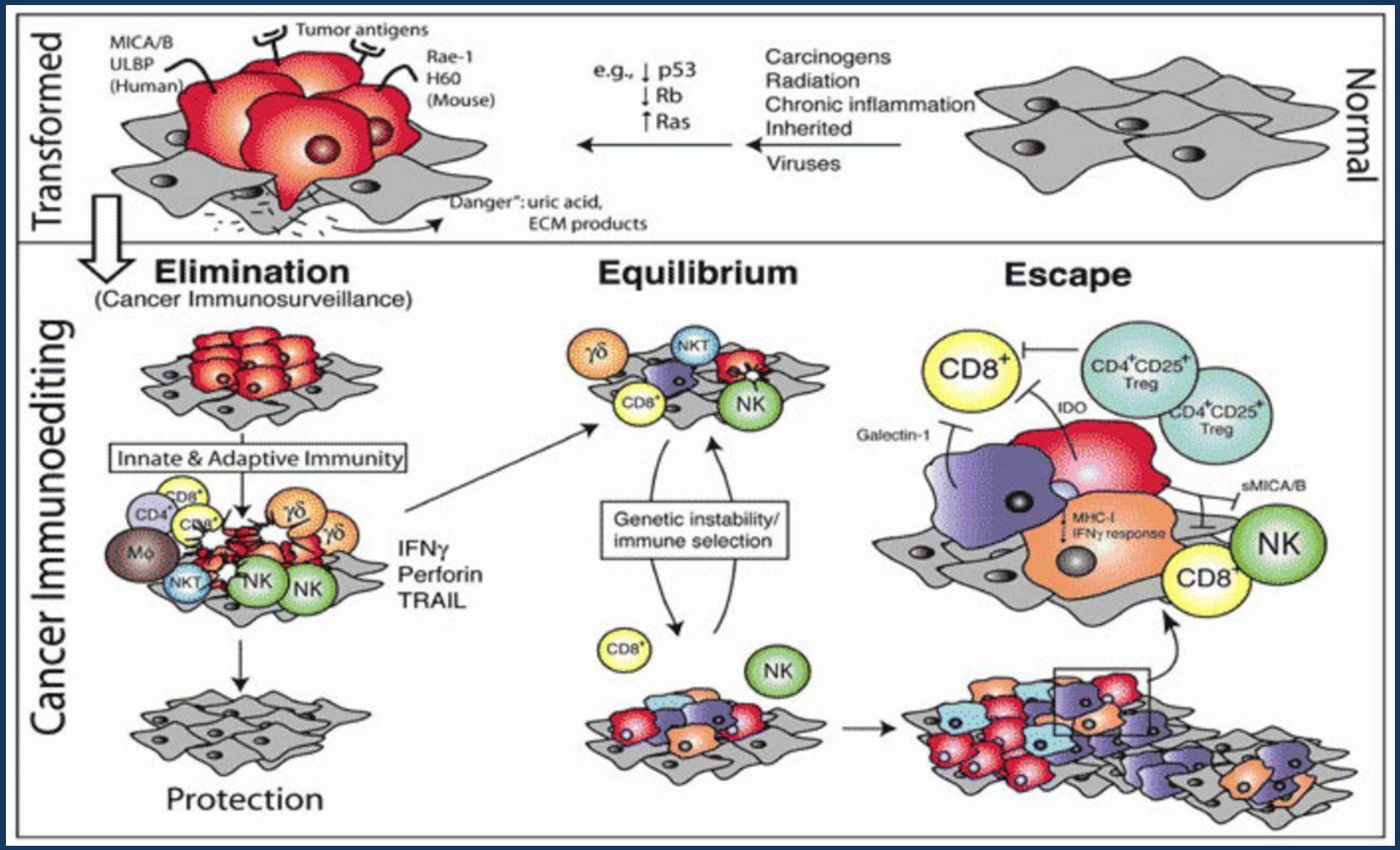
"**Immunotherapies** will likely become the treatment backbone in up to 60% of cancers over the next 10 years compared with <3% today."



Distinguishing "self" from "non-self"

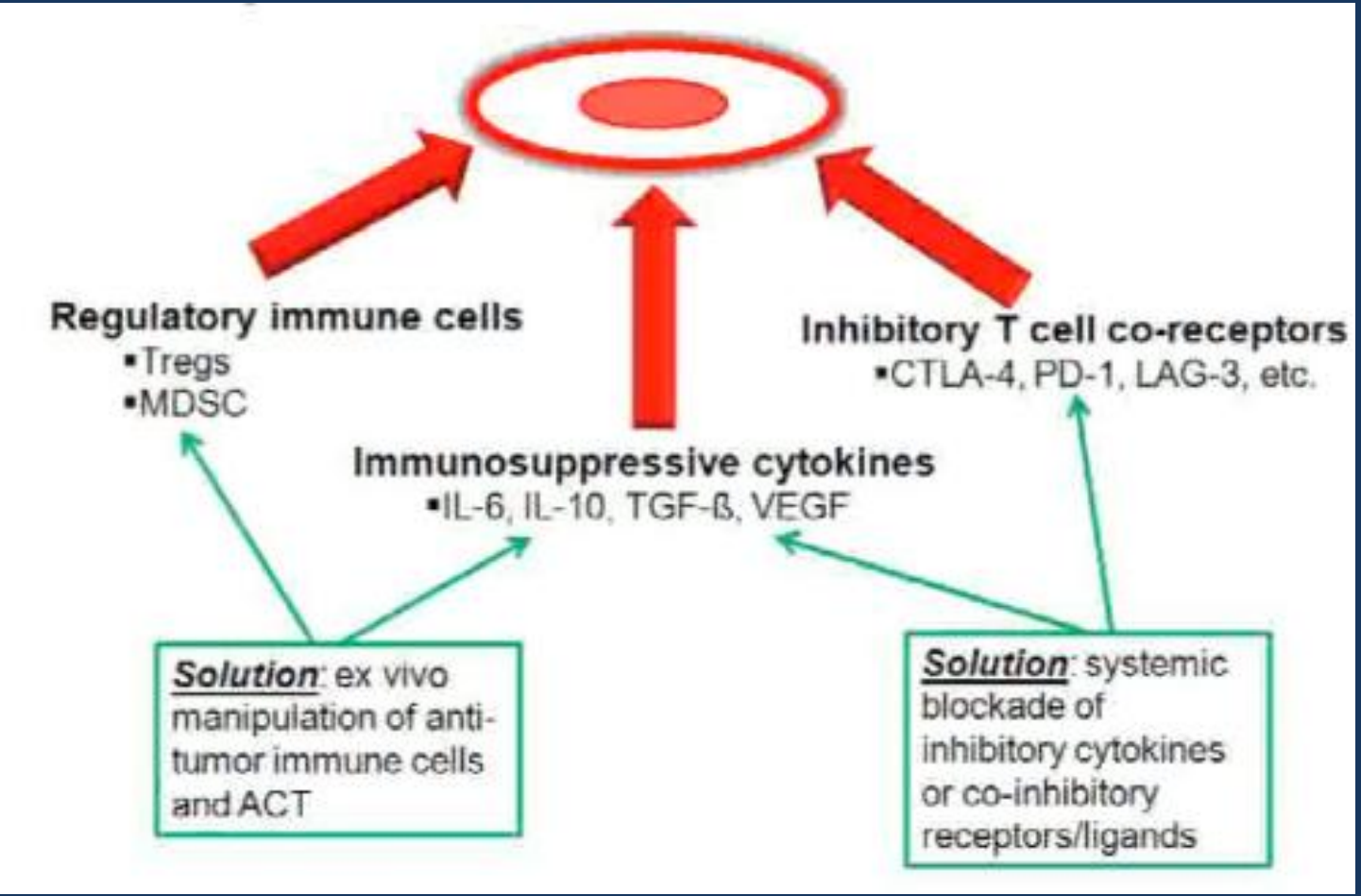
- T cells trained in the thymus as a child
- Millions of variations of T cell receptors tested
- If TCR binds to "self" then T cell retrained or eliminated
- Only 3% of T cells survive this process
- Remaining TCRs should only respond to "non-self"
- T cells roam the body waiting to recognise "non-self" antigens

Cancer and immune system



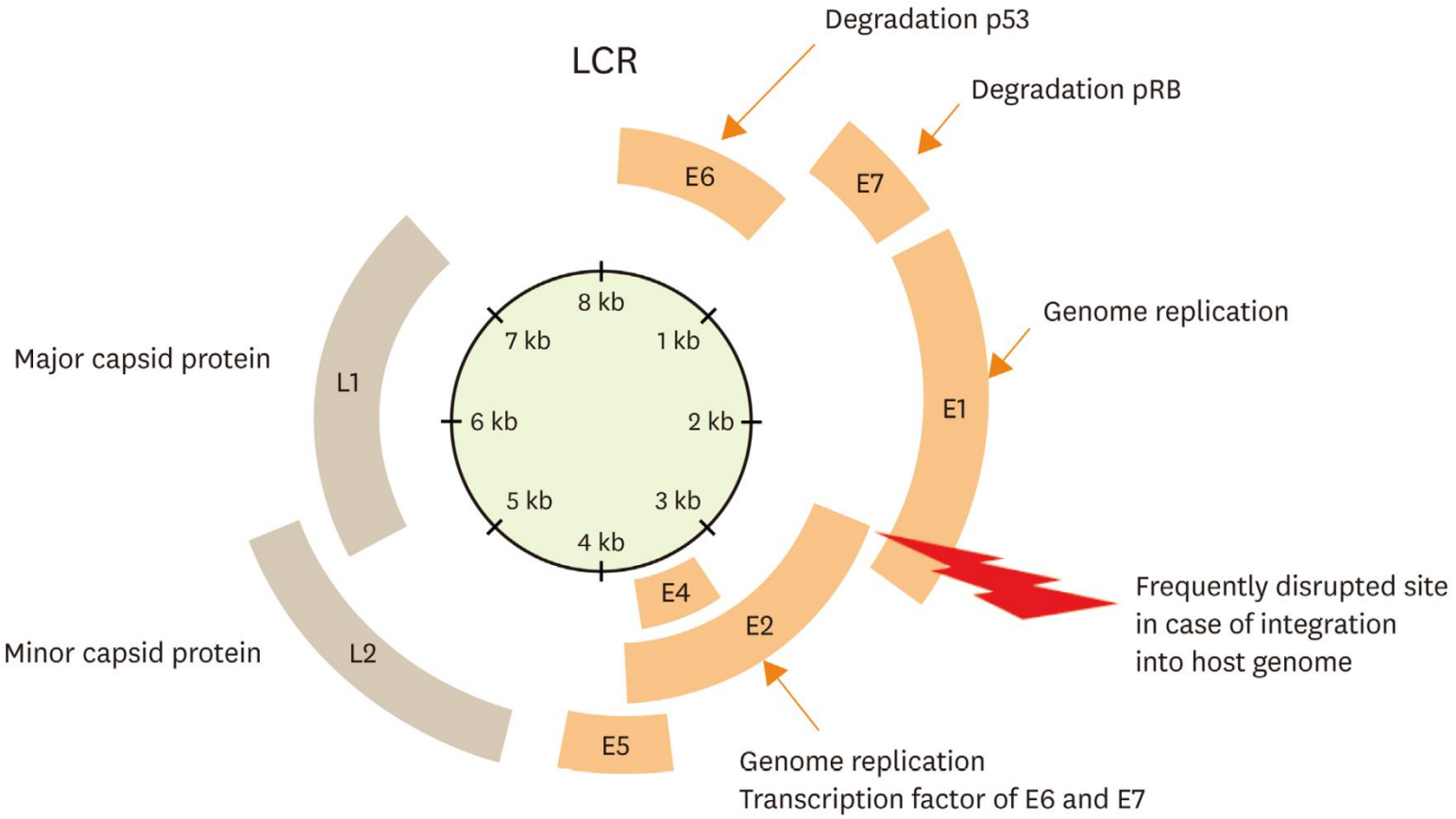
Schreiber RD, Cancer Immunol Res 2005

Immune Tolerance

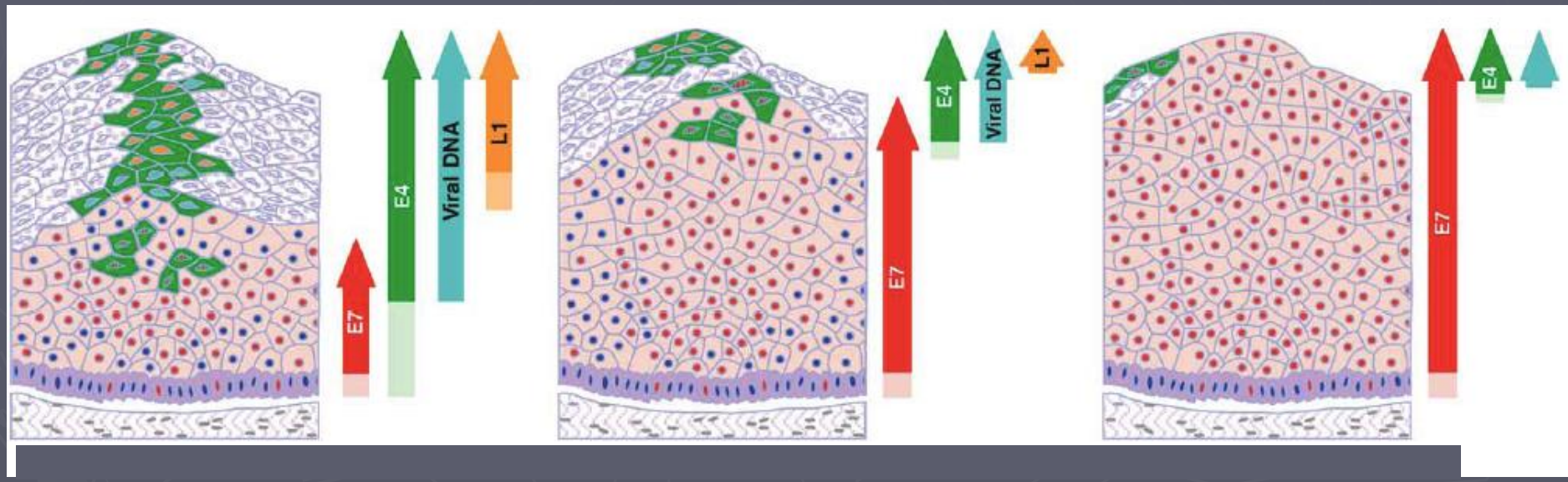


Topalian ASCO 2012

Cervix cancer as a target for immunotherapy: HPV



Progression to Cancer is Accompanied by Deregulation of Viral Gene Expression

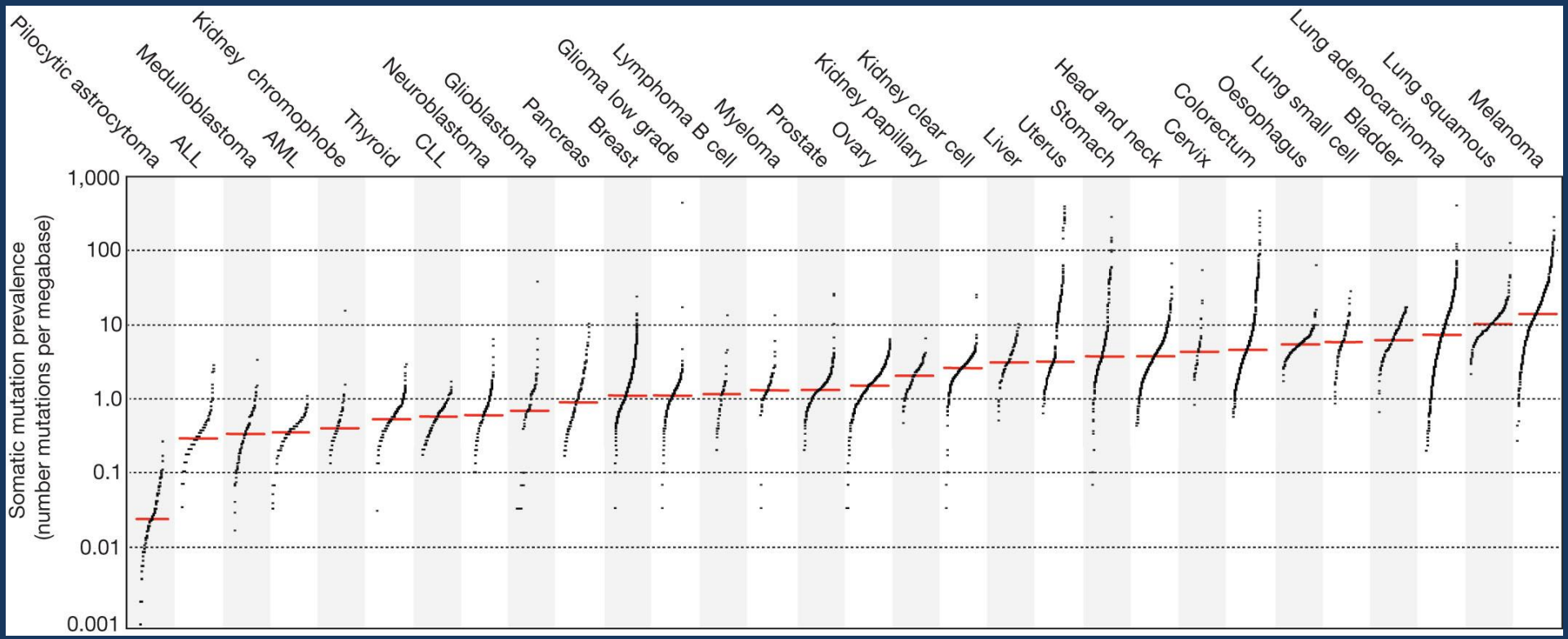


Doorbar, J Clin Virol 32:7-15, 2005

<u>Common molecular events</u>:

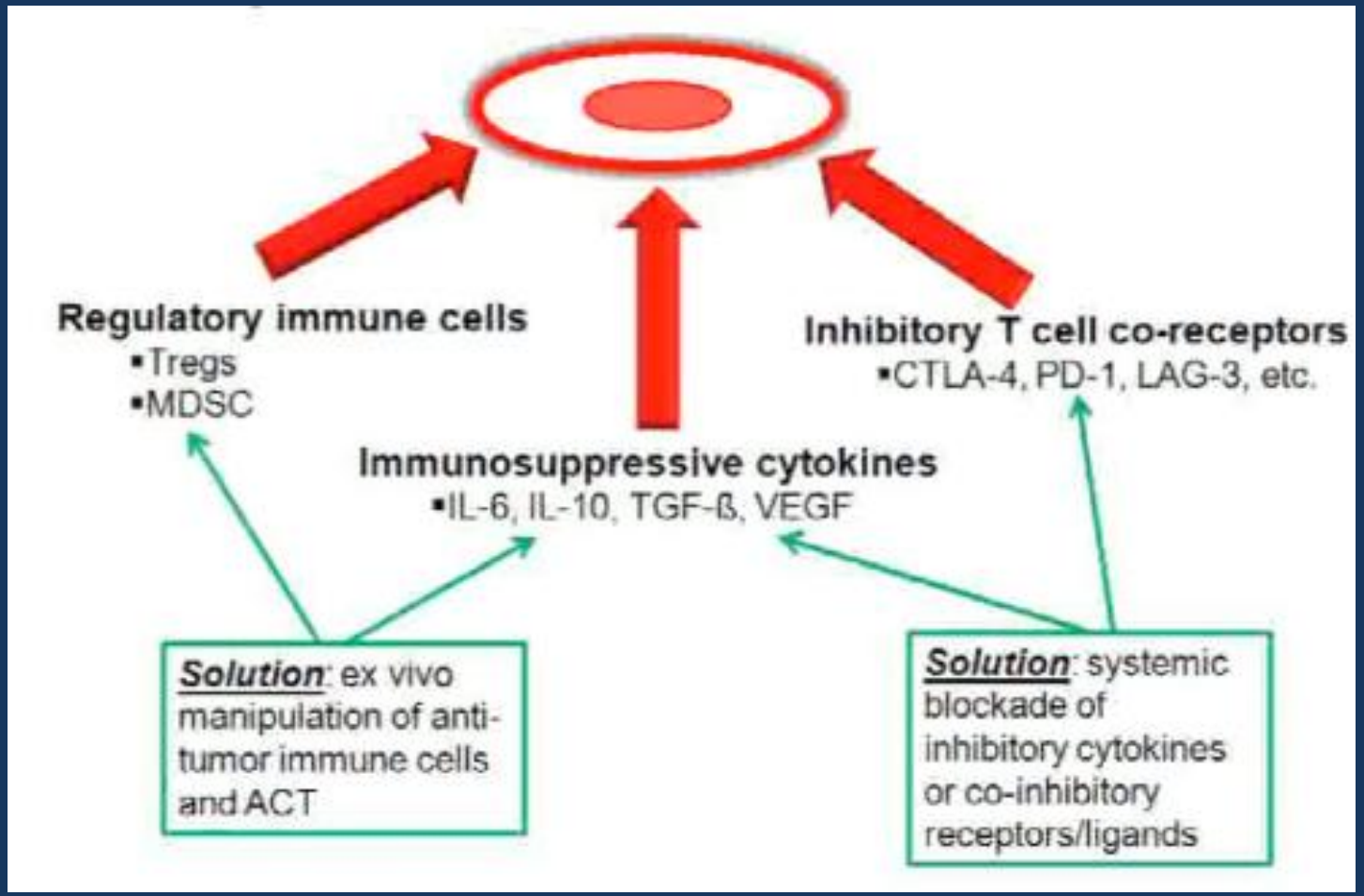
- Viral genome integration into cellular DNA
- Loss of E2 leads to increased E6/E7 expression
- Loss of L1, L2 expression. Therefore, current vaccine can't clear pre-cancerous lesions.

Mutation Burden



Alexandrov Nature 2013

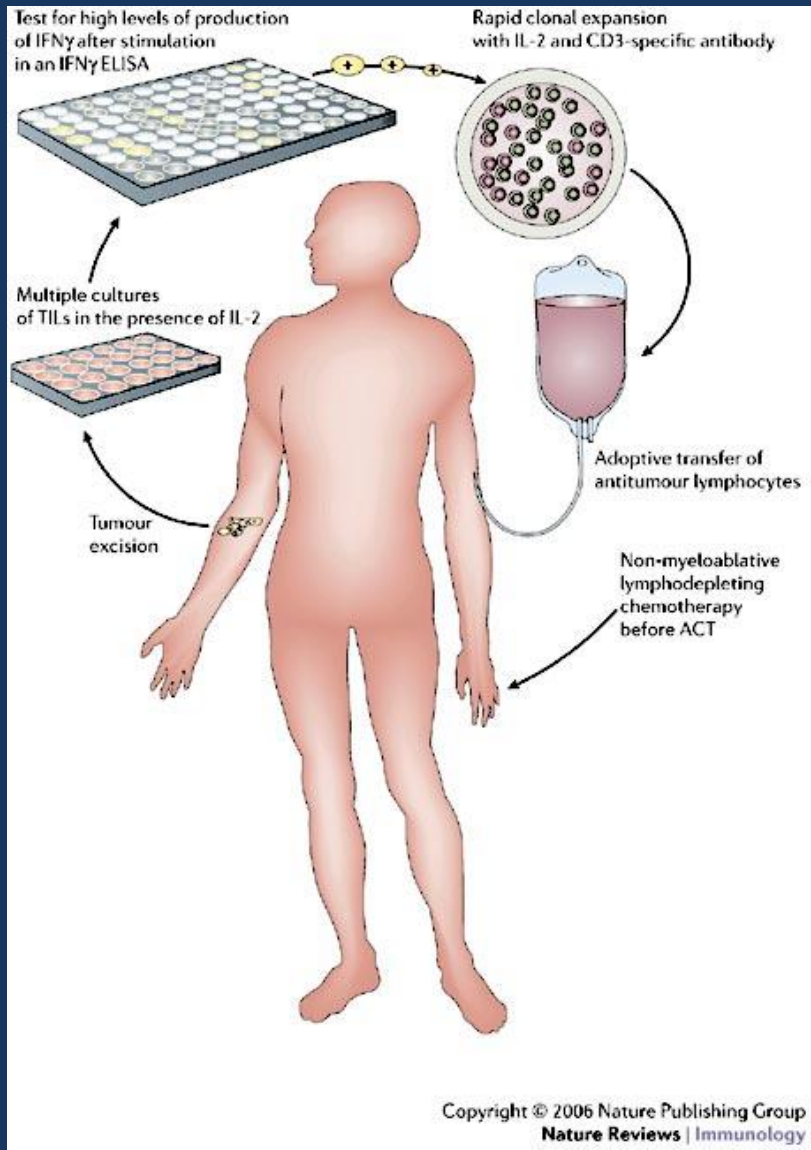
Immune Tolerance



Topalian ASCO 2012

Passive Immunotherapy

- *Adoptive Cellular Transfer (ACT)*
- Pts have T cells capable of recognizing antigens expressed by tumours (e.g. TILs)
- These cells can attack tumours ex vivo
- Pull T cells out of the tumour, activate in vitro, reinfuse to patient



Complete Regression of Metastatic Cervical Cancer After Treatment With Human Papillomavirus–Targeted Tumor-Infiltrating T Cells

Sanja Stevanović, Lindsey M. Draper, Michelle M. Langhan, Tracy E. Campbell, Mei Li Kwong, John R. Wunderlich, Mark E. Dudley, James C. Yang, Richard M. Sherry, Udai S. Kammula, Nicholas P. Restifo, Steven A. Rosenberg, and Christian S. Hinrichs

See accompanying editorial on page 1521

A B S T R A C T

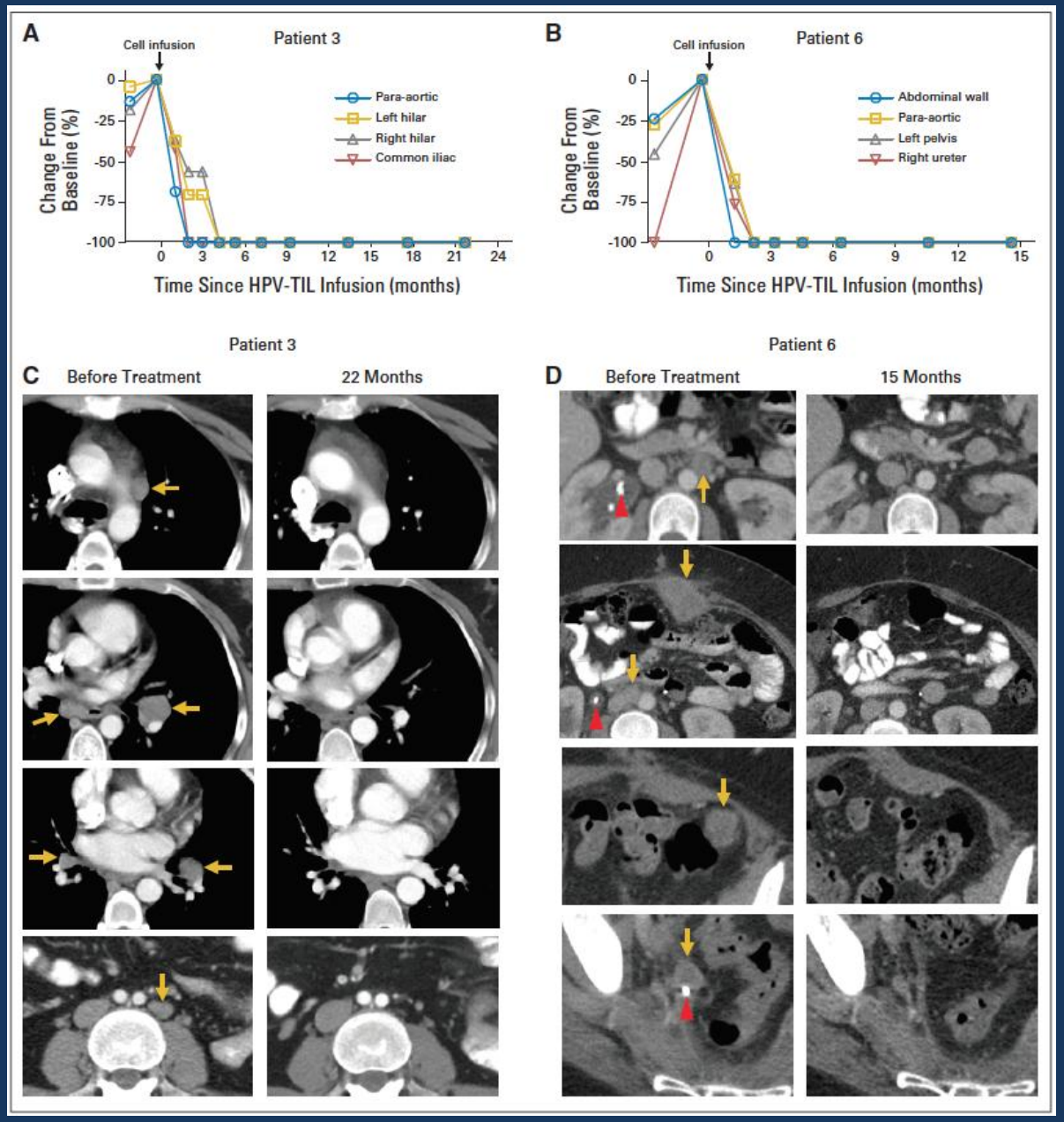
Purpose
Metastatic cervical cancer is a prototypical chemotherapy-refractory epithelial malignancy for which better treatments are needed. Adoptive T-cell therapy (ACT) is emerging as a promising cancer treatment, but its study in epithelial malignancies has been limited. This study was conducted to determine if ACT could mediate regression of metastatic cervical cancer.

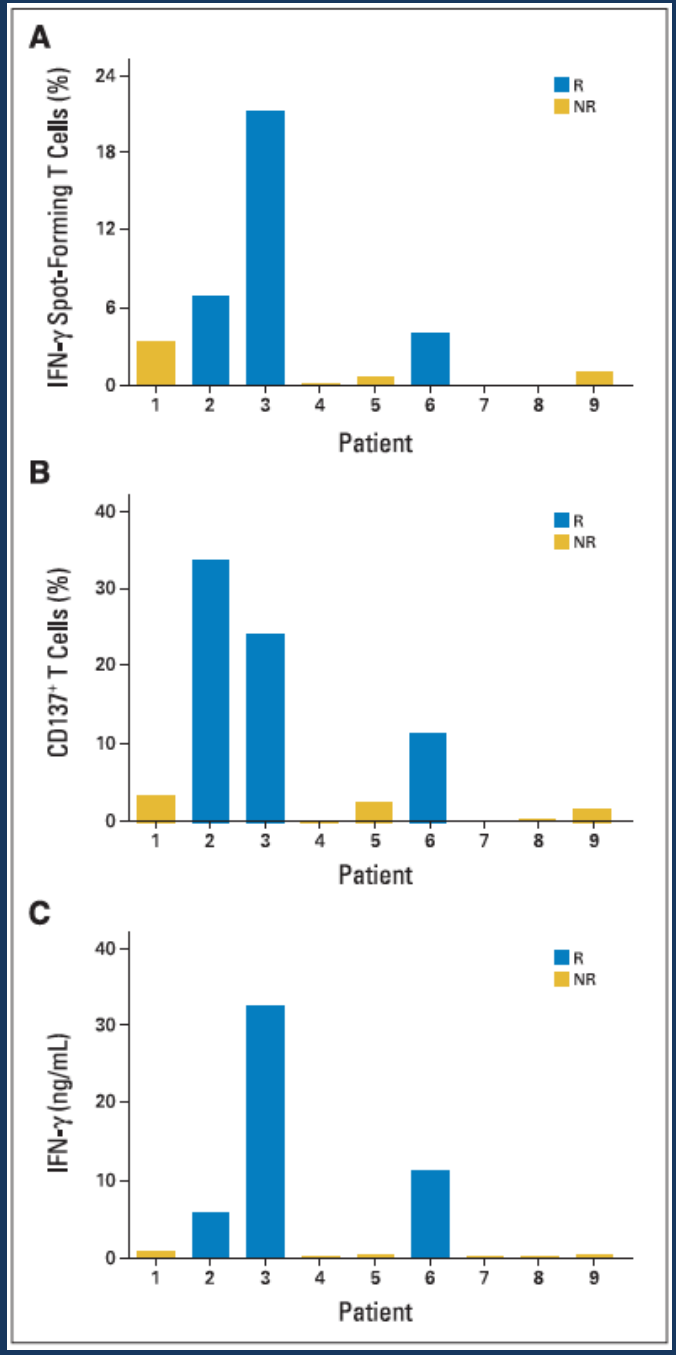
Patients and Methods
Patients enrolled onto this protocol were diagnosed with metastatic cervical cancer and had previously received platinum-based chemotherapy or chemoradiotherapy. Patients were treated with a single infusion of tumor-infiltrating T cells selected when possible for human papillomavirus (HPV) E6 and E7 reactivity (HPV-TILs). Cell infusion was preceded by lymphocyte-depleting chemotherapy and was followed by administration of aldesleukin.

Results
Three of nine patients experienced objective tumor responses (two complete responses and one partial response). The two complete responses were ongoing 22 and 15 months after treatment, respectively. One partial response was 3 months in duration. The HPV reactivity of T cells in the infusion product (as measured by interferon gamma production, enzyme-linked immunospot, and CD137 upregulation assays) correlated positively with clinical response (P = .0238 for all three assays). In addition, the frequency of HPV-reactive T cells in peripheral blood 1 month after treatment was positively associated with clinical response (P = .0238).

Conclusion
Durable, complete regression of metastatic cervical cancer can occur after a single infusion of HPV-TILs. Exploratory studies suggest a correlation between HPV reactivity of the infusion product and clinical response. Continued investigation of this therapy is warranted.

J Clin Oncol 33:1543-1550. Published by the American Society of Clinical Oncology


A
Patient 3
Cell infusion
Change From Baseline (%)
0
-25
-50
-75
-100
0 3 6 9 12 15 18 21 24
Time Since HPV-TIL Infusion (months)
Para-aortic
Left hilar
Right hilar
Common iliac
B
Patient 6
Cell infusion
Change From Baseline (%)
0
-25
-50
-75
-100
0 3 6 9 12 15
Time Since HPV-TIL Infusion (months)
Abdominal wall
Para-aortic
Left pelvis
Right ureter
Patient 3
C
Before Treatment
22 Months
Patient 6
D
Before Treatment
15 Months


A
IFN-γ Spot-Forming T Cells (%)
24
18
12
6
0
1 2 3 4 5 6 7 8 9
Patient
R
NR
B
CD137+ T Cells (%)
40
30
20
10
0
1 2 3 4 5 6 7 8 9
Patient
R
NR
C
IFN-γ (ng/mL)
40
30
20
10
0
1 2 3 4 5 6 7 8 9
Patient
R
NR

Active Immunotherapy

- Reverse immune tolerance in situ to promote recognition of endogenous tumour antigens and facilitate tumour rejection

- More generic approach but can target multiple tumour antigens

Active Immune Therapies

- Interferon α
  - Benefit in adjuvant melanoma, mRCC
- IL-2 (1998)
  - Durable CRs in a small subgroup (5-7%)
  - Toxicity +++
- Therapeutic vaccines: Disappointing in established cervix cancer
- T cell modulators (2011+)
  - Ipilimumab
  - Anti PD-1/L1
  - Many many more…..

aka "checkpoint inhibitors"

Lm Technology™ Overview:
Harnessing Unique Life Cycle of *Lm* in APCs

ADVAXIS
IMMUNOTHERAPIES™

Lm-LLO agent taken up only by phagocytic dendritic cells/APCs

▼

Lm-LLO stimulates a strong innate multipathway immune response (eg. STING) in APC

▼

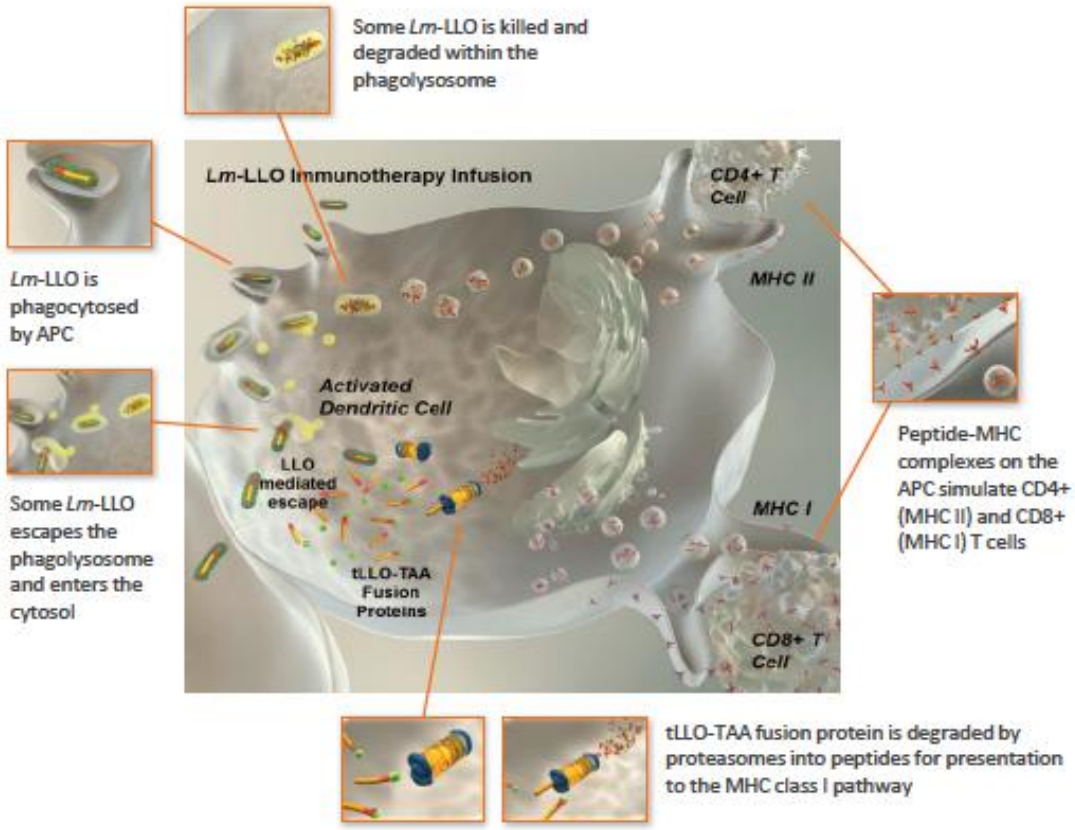
Lm-LLO expresses LLO-TAA fusion protein, which is processed by stimulated APC and activates TAA-specific T-cells

▼

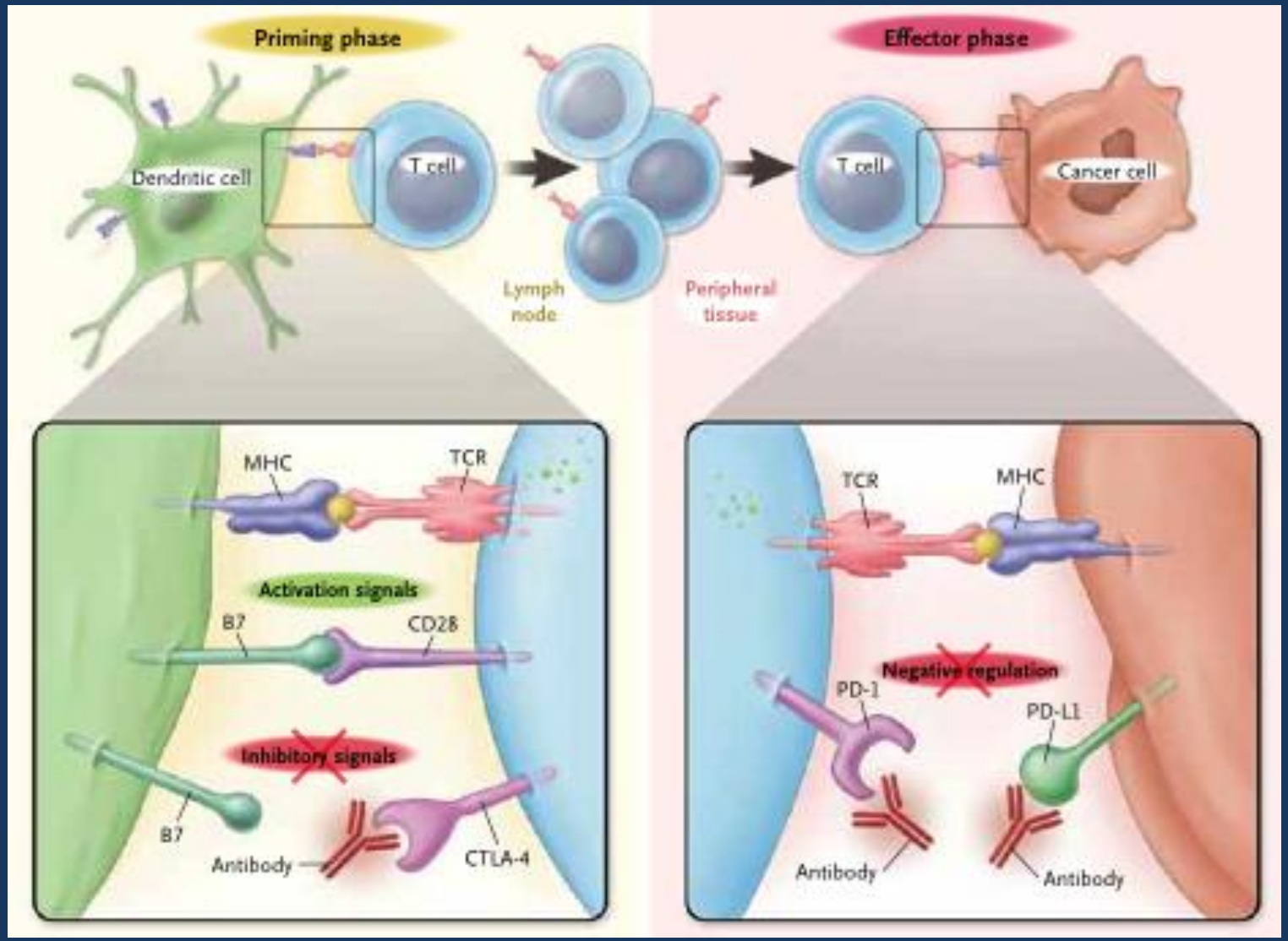
Robust T-cell response generated toward TAA, allowing tumor-specific immune response

▼

Immune activation can overcome checkpoint inhibition and negative regulators of cellular immunity

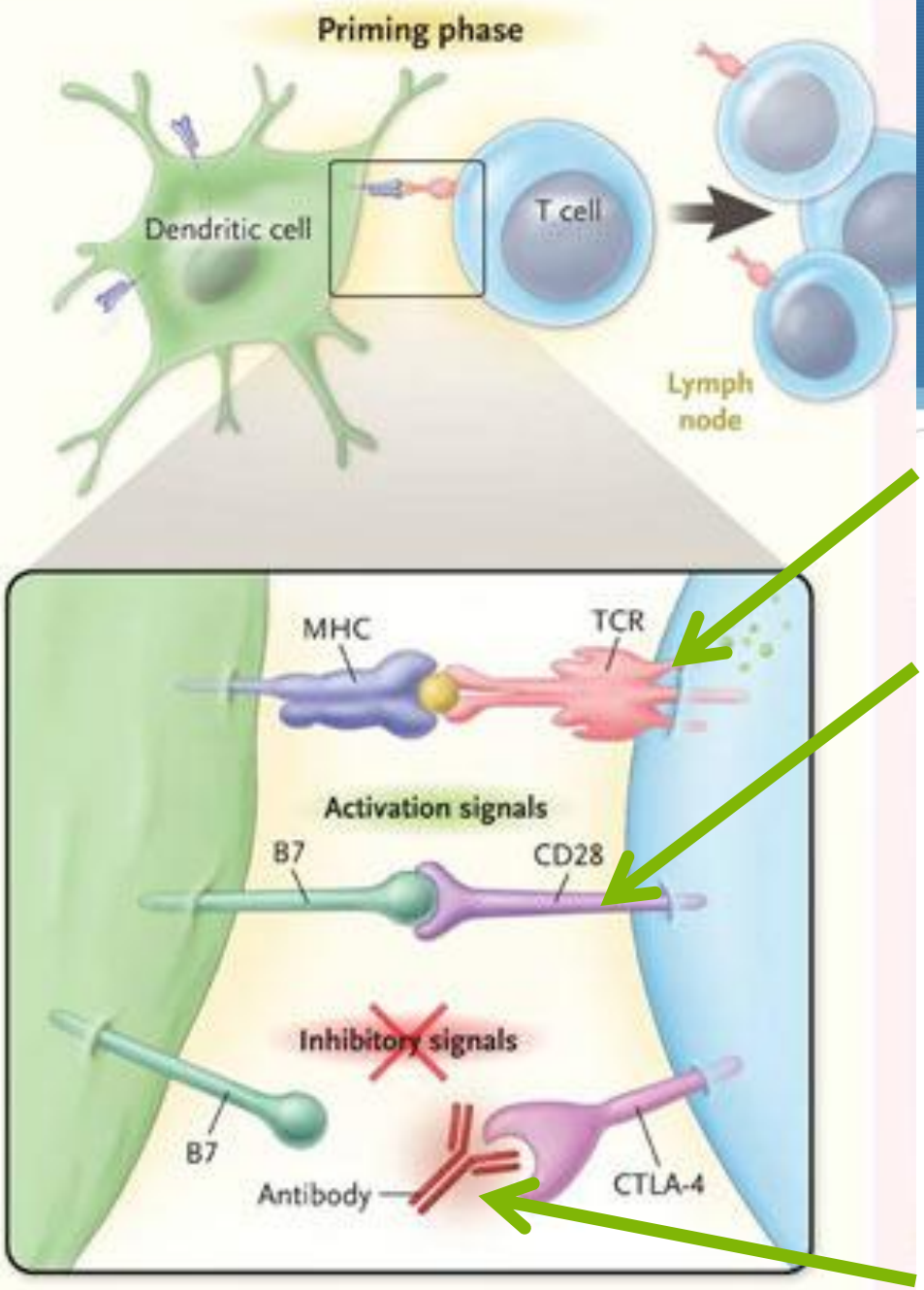


Immune checkpoints



Ribas NEJM 2012

Ipilimumab



Antigen-presenting cells present antigens to T cells

Need additional signal to activate T cell – B7 on APC binds to CD28 on T cell to provide co-stimulation.

When this happens, CTLA-4 expression by T cell is slowly induced. CTLA-4 binds better with B7 → inhibits the T cell.

CTLA-4 acts to turn off activated T cells and damp down the immune response

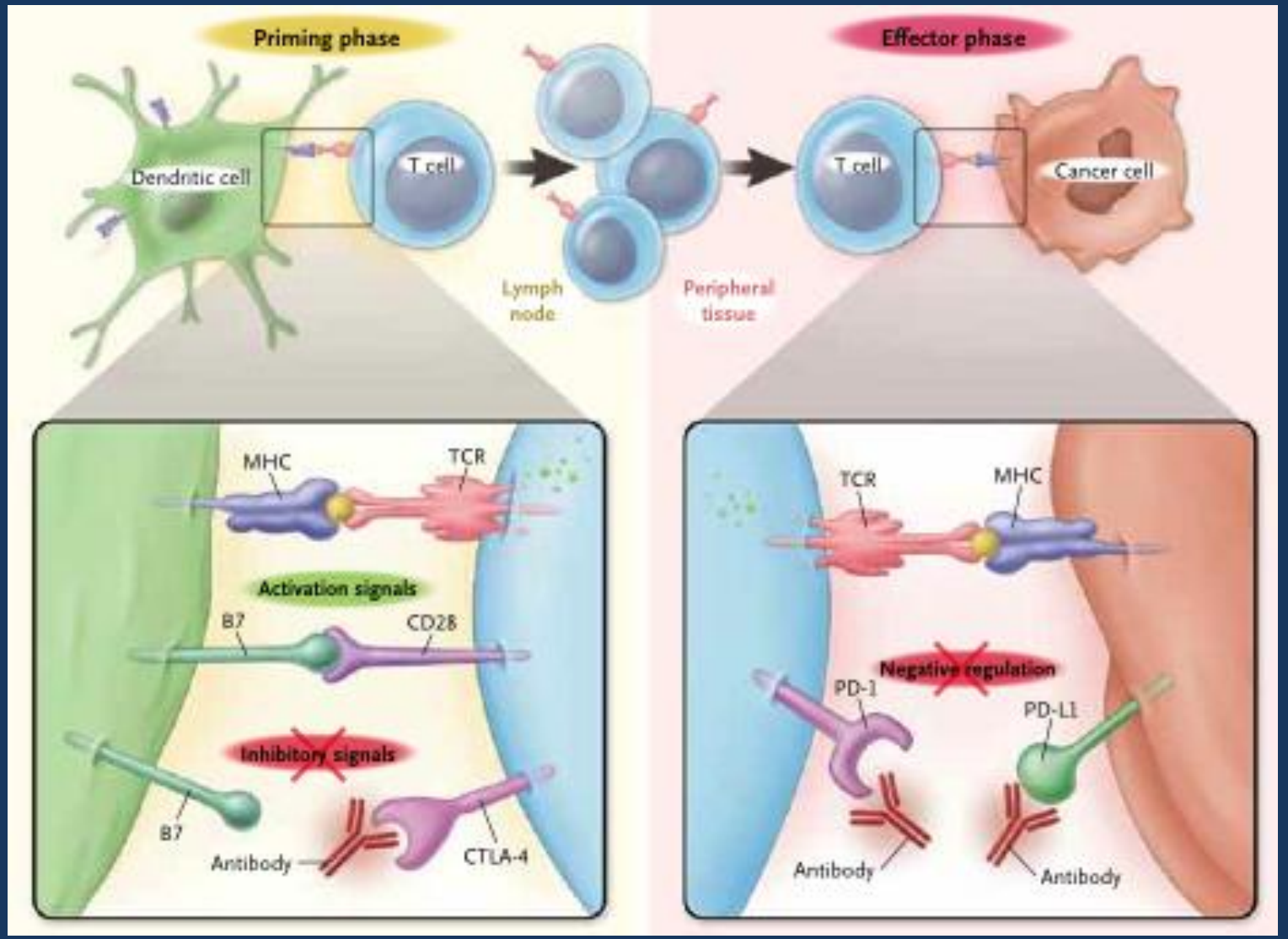
Ipilimumab blocks CTLA-4 → increased activation of T cells

Ipilimumab in cervix cancer: Phase 1/2

- 42 patients with measurable disease progression and prior platinum exposure
- 4 cycles of Ipilimumab (3-10mg/kg) every 21 days followed by 4 maintenance cycles every 12 weeks
- 35 had prior RT and 21 had 2-3 prior regimens
- "Manageable" toxicities: Grade 3 diarrhoea (x4) and grade 3 colitis (x3)
- No CRs but 3 partial responses
- Median PFS was 2.5 months

Lheureux L, ASCO annual meeting 2015

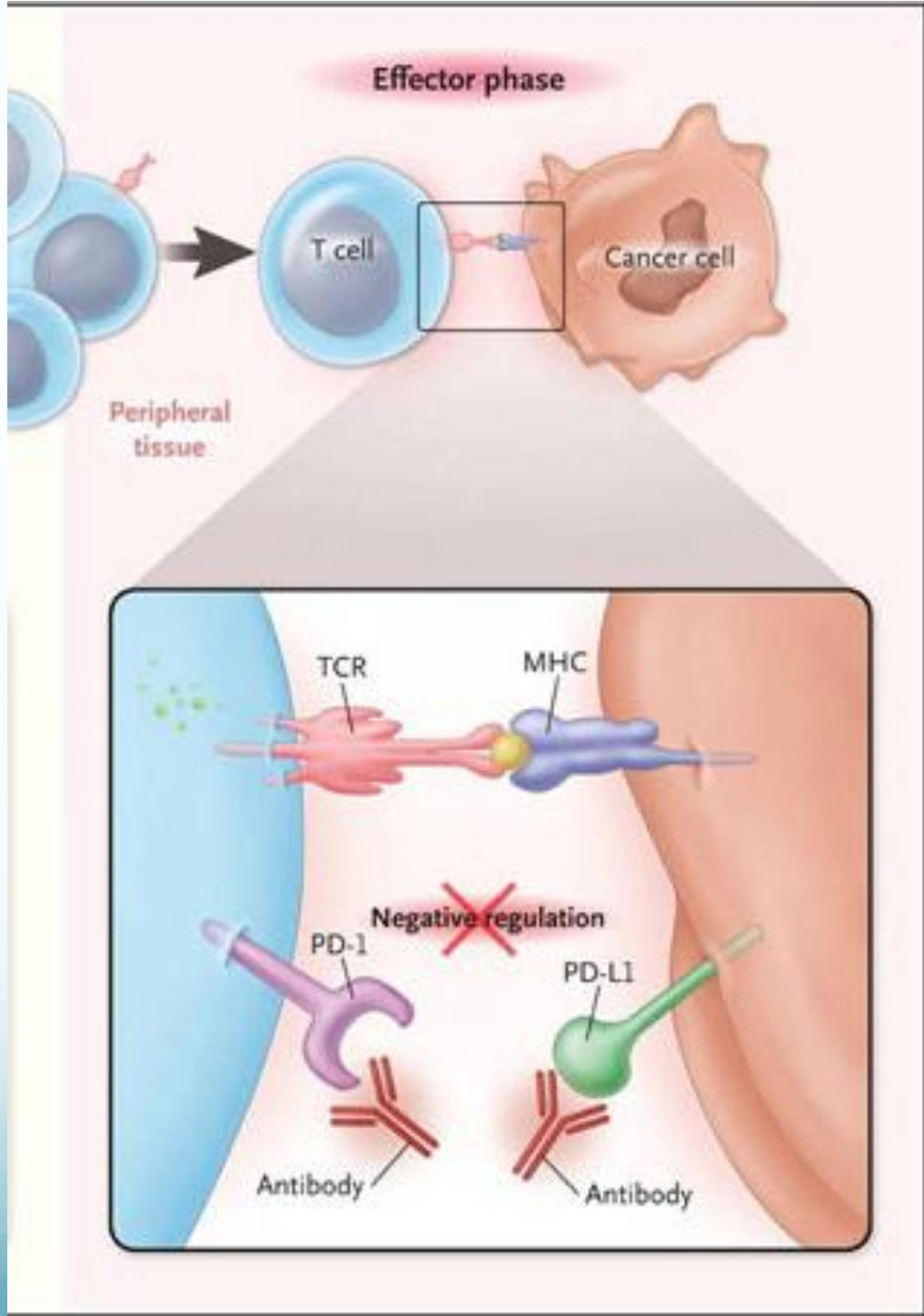
Immune checkpoints



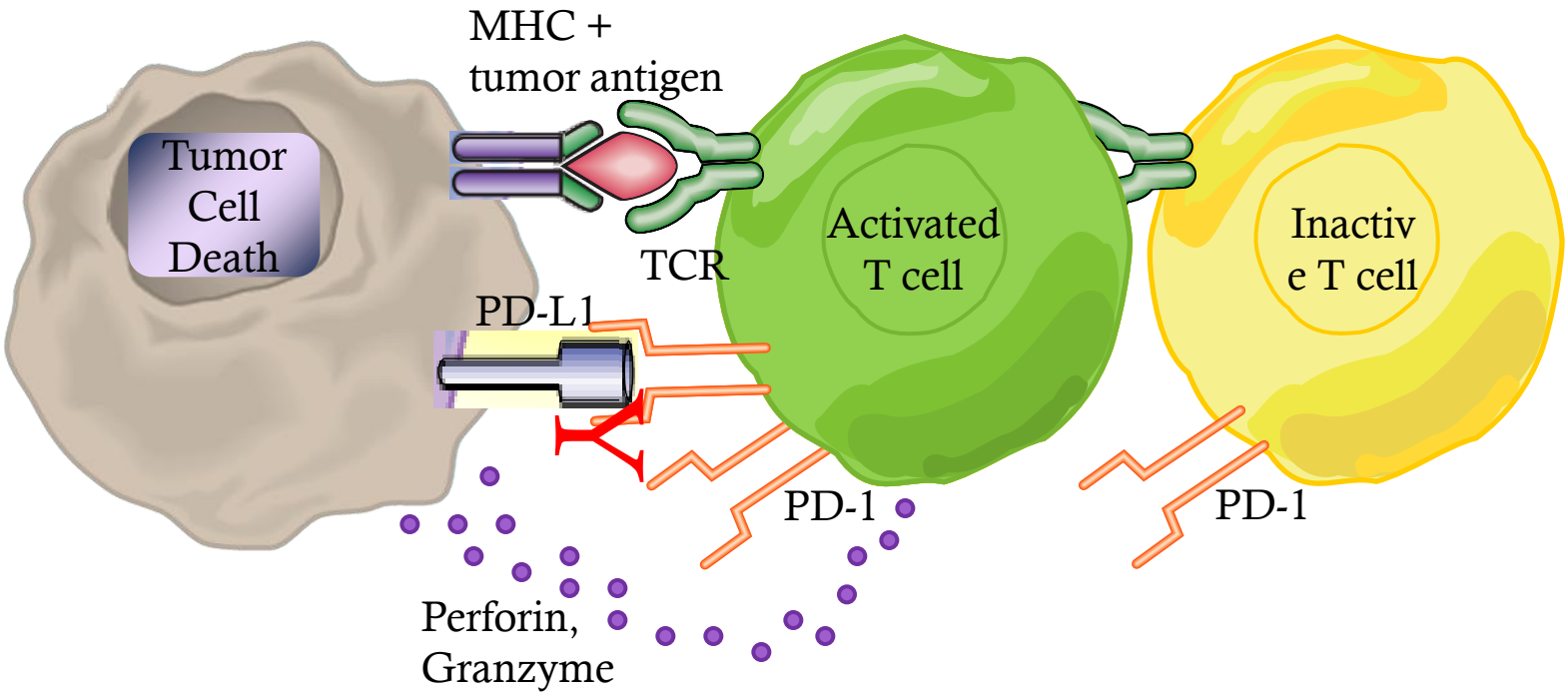
Ribas NEJM 2012

T cell silencing by the tumour

- PD-1 (programmed cell death -1) is another inhibitory receptor on the T cell surface.
- PDL-1 is its primary ligand and is frequently expressed in the tumour microenvironment (including tumour cells and tumour-infiltrating macrophages)
- When PD1 binds to PDL1, the activated T cell is switched off
- Pembrolizumab and nivolumab are PD-1 inhibitors



T cell silencing by tumour



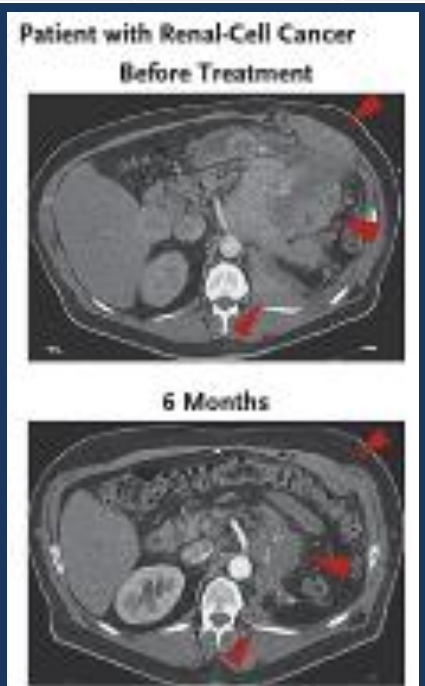
Keir ME et al, Annu Rev Immunol 2008; Pardoll DM, Nat Rev Cancer 2012

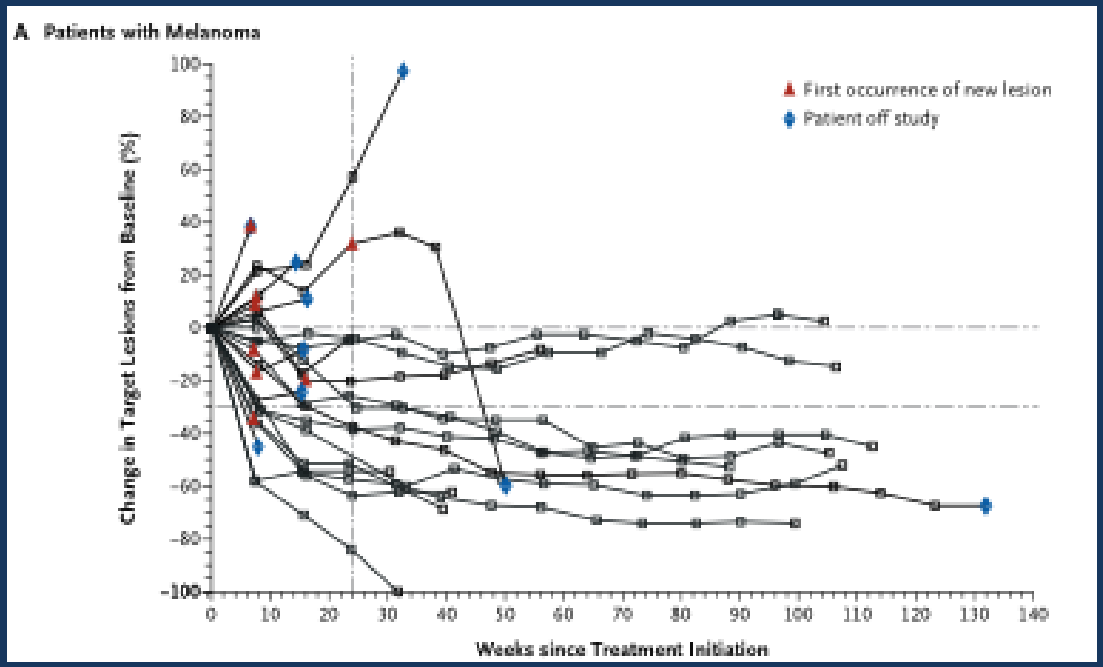
Toplalian NEJM 2012

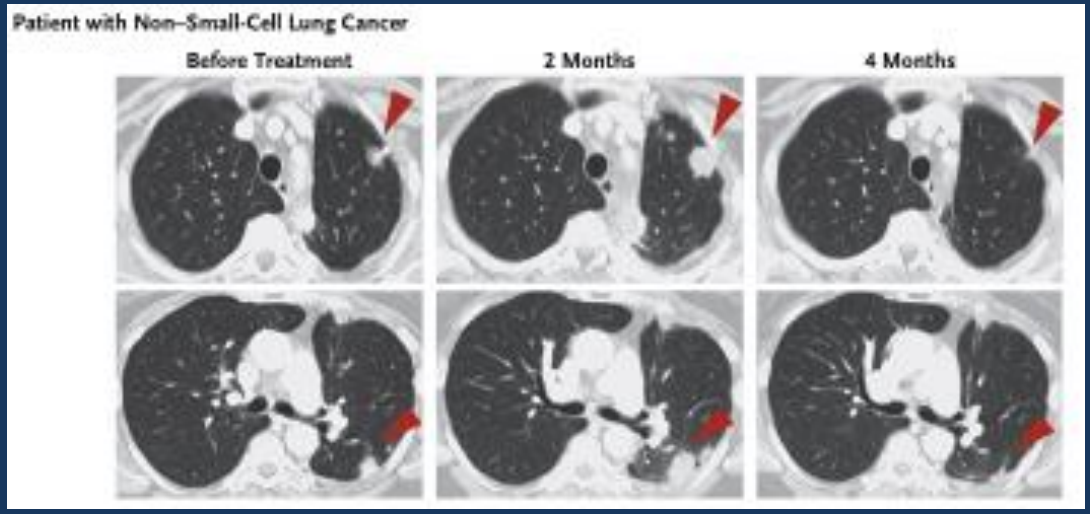
Nivolumab Phase 1

N=296

Cancer	N.	RR
melanoma	94	41%
NSCLC	76	18%
RCC	33	27%
CRPC	17	0
CRC	19	0







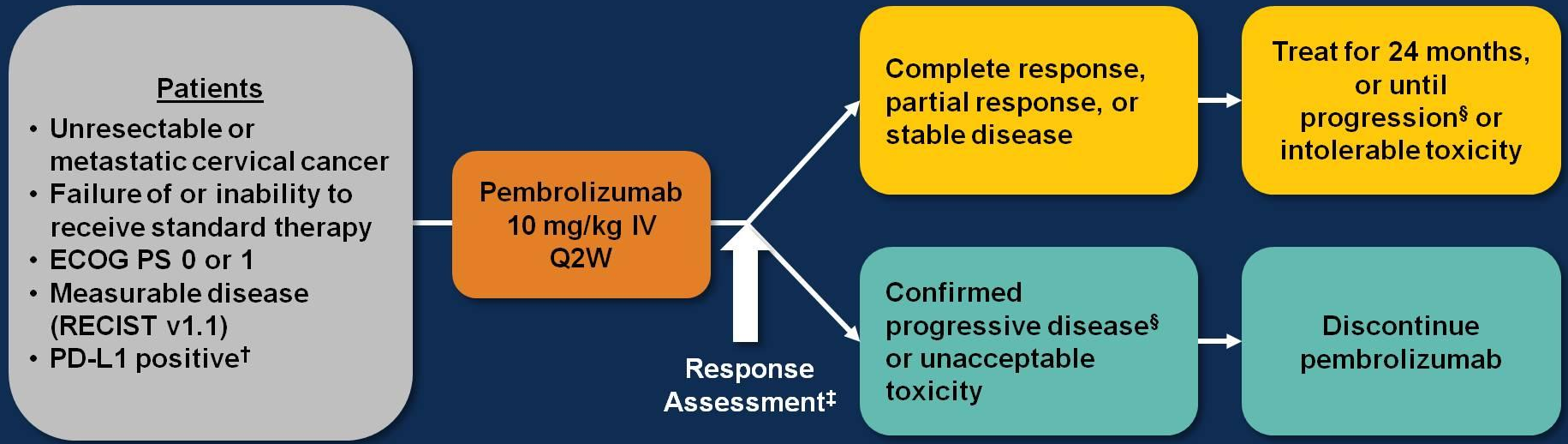
Defining Response: RECIST v1.1 vs irRC

Category	RECIST v1.1[1]	irRC[2] (immune-related response criteria)
Measurement of tumor burden	• Unidimensional	• Bidimensional
Complete response (CR)	• Disappearance of all target and non-target lesions • Nodes must regress to <10 mm short axis • No new lesions • Confirmation required	
Partial response (PR)	• ≥30% decrease in tumor burden compared with baseline • Confirmation required	• ≥50% decrease in tumor burden compared with baseline[a] • Confirmation required
Progressive disease (PD)	• ≥20% + 5 mm absolute increase in tumor burden compared with nadir • Appearance of new lesions or progression of non target	• ≥25% increase in tumor burden compared with baseline, nadir, or "reset" baseline[a] • New lesions added to tumor burden • Confirmation required
Stable disease (SD)	• Neither PR nor PD	

[a]If an increase in tumor burden is observed at the first scheduled assessment, baseline is reset to the value observed at the first assessment.

1. Eisenhauer EA et al. *Eur J Cancer*. 2009;45(2):228-247.
2. Wolchok JD et al. *Clin Cancer Res*. 2009;15(23):7412-7420.

KEYNOTE-028 (NCT02054806): Phase 1b Multicohort Study of Pembrolizumab for PD-L1–positive Advanced Solid Tumors



‡**Response assessment:** Every 8 weeks for the first 6 months; every 12 weeks thereafter

Primary end points: ORR per RECIST v1.1 and safety

Secondary end points: PFS, OS, duration of response

†Membranous PD-L1 expression in ≥1% of tumor or stromal cells using a prototype immunohistochemistry assay and 22C3 antibody (Merck). §Clinically stable patients were allowed to remain on pembrolizumab until progressive disease was confirmed on a second scan performed ≥4 weeks later. Patients who experienced progression after discontinuing pembrolizumab were eligible for up to 1 year of additional treatment if no other anticancer therapy was received.

Baseline Characteristics

Characteristic, n (%)	N = 24
Median age, years (range)	41 (26–62)
Race, n (%)	
White	15 (63)
Asian	1 (4)
Not specified	8 (33)
ECOG performance status of 1, n (%)	18 (75)
Histology, n (%)	
Squamous cell carcinoma	23 (96)
Adenocarcinoma	1 (4)
Metastatic stage, n (%)	
MX	1 (4)
M0	6 (25)
M1	15 (63)
Unknown	2 (8)

Characteristic, n (%)	N = 24
Prior radiotherapy	23 (96)
Prior lines of therapy for advanced disease	
1	9 (38)
2	6 (25)
≥3	9 (38)
Prior platinum	23 (96)
Prior bevacizumab	10 (42)

Data cutoff date: Feb 17, 2016.

Treatment-Related Adverse Events

Any Grade Occurring in ≥2 Patients	N = 24 n (%)
Any	18 (75)
Pyrexia	4 (17)
Rash	3 (13)
Fatigue	2 (8)
Asthenia	2 (8)
Constipation	2 (8)
Diarrhea	2 (8)
Dry mouth	2 (8)
Anemia	2 (8)
Proteinuria	2 (8)
Dry skin	2 (8)
Pruritus	2 (8)

Grade 3 Occurring in ≥1 Patient	N = 24 n (%)
Any	5 (21)
Rash	2 (8)
Neutropenia	1 (4)
Colitis	1 (4)
Guillain-Barre syndrome	1 (4)
Proteinuria	1 (4)

- Median follow-up duration: 43 weeks (range, 6–92)
- No grade 4 treatment-related AEs
- No treatment-related mortality
- 2 treatment-related discontinuations: grade 3 colitis; grade 3 Guillain-Barre syndrome

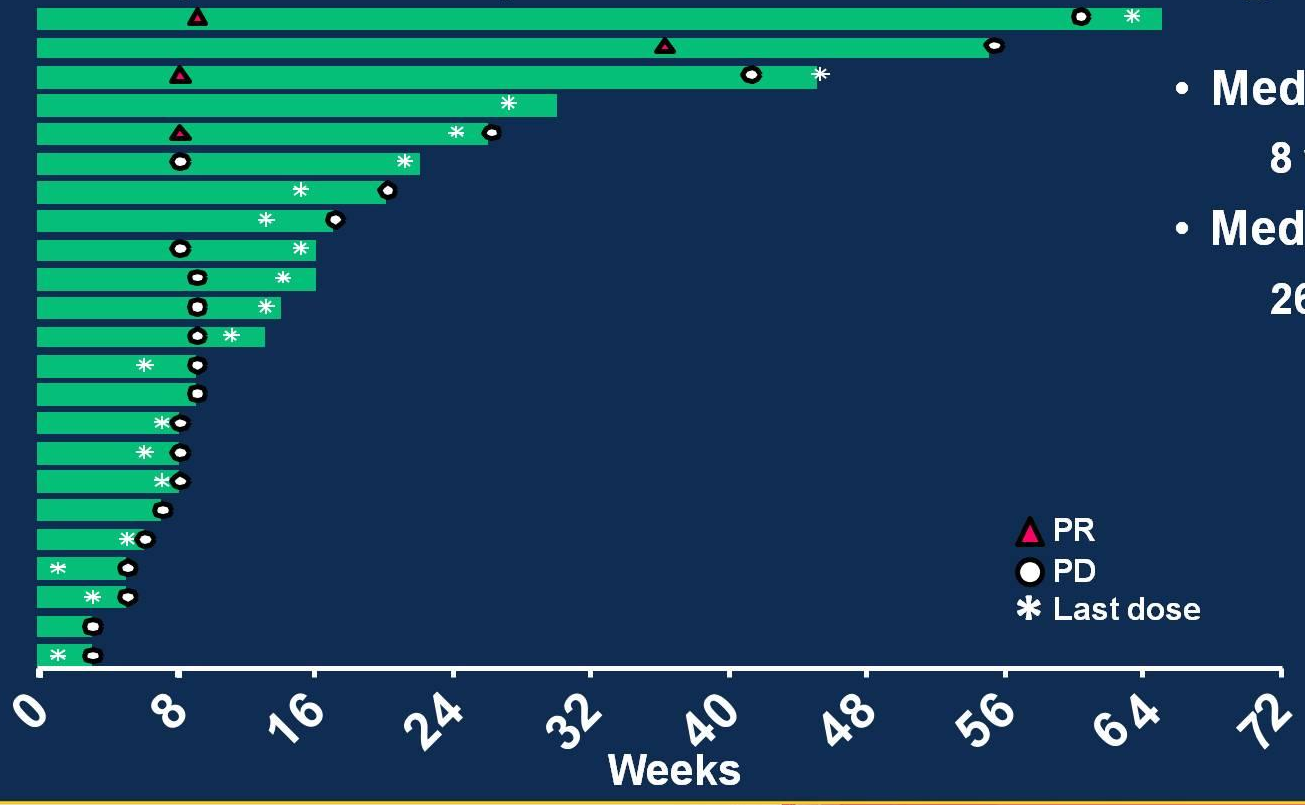
Data cutoff date: Feb 17, 2016.
Includes patients who received ≥1 dose of pembrolizumab.

Antitumor Activity (RECIST v1.1, Investigator Review)

	N = 24		
	n	%	95% CI
ORR†	**4**	**17**	**5–37**
Partial response	4	17	5–37
Stable disease	3	13	3–32
Progressive disease	16	67	45–84
No assessment‡	1	4	<1–21

Data cutoff date: Feb 17, 2016. Only confirmed responses are included. Patients who received ≥1 dose of pembrolizumab and had a baseline scan with measurable disease per RECIST v1.1 are included.
†There were no complete responses. ‡Patient did not have a postbaseline response evaluation.

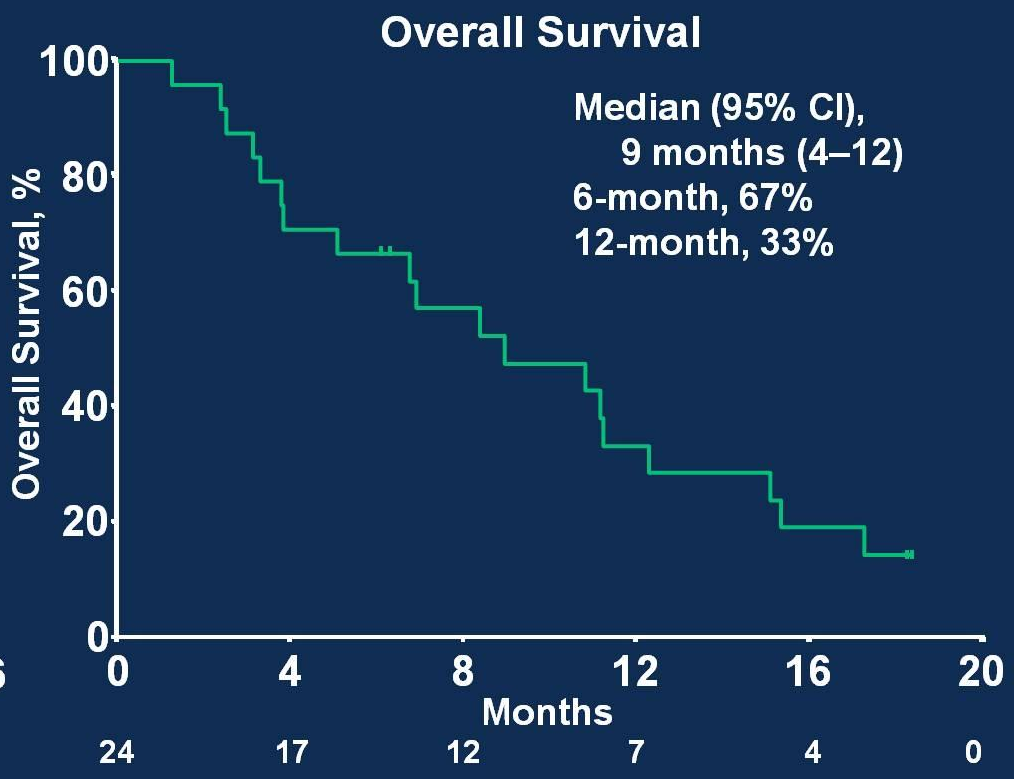
Treatment Exposure and Duration of Response in Responders (RECIST v1.1, Investigator Review)



- **Median time to response:**
  8 weeks (range, 8–36)
- **Median response duration†:**
  26 weeks (range, 18–52)

Data cutoff date: Feb 17, 2016. Only confirmed responses are included. Patients who received ≥1 dose of pembrolizumab, had a baseline scan with measurable disease per RECIST v1.1, and a post-baseline assessment are included (n = 23). The length of each bar represents time to the last tumor assessment. †Computed from Kaplan-Meier method for censored data.

Progression-Free Survival† and Overall Survival



PRESENTED AT: ASCO ANNUAL MEETING '16

Data cutoff date: Feb 17, 2016.
Patients who received ≥1 dose of pembrolizumab and had a baseline scan with measurable disease per RECIST v1.1 are included. †RECIST v1.1 by investigator review.

How best to select patients?

Merck's Pembrolizumab Demonstrates Superior Progression-Free and Overall Survival Compared to Chemotherapy as First-Line Treatment in Patients with Advanced Non-Small Cell Lung Cancer

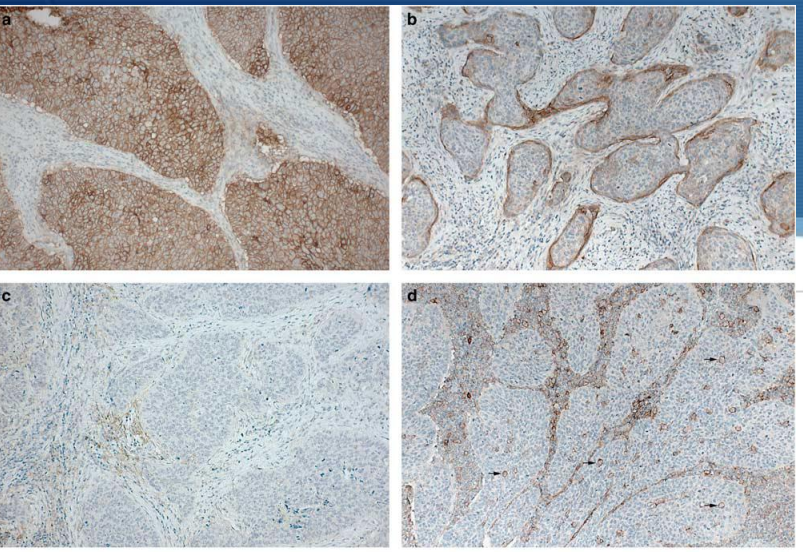
KEYNOTE-024 Studied Patients Whose Tumors Expressed High Levels of PD-L1

KIRKLAND, QC., June 16, 2016 – Merck (NYSE: MRK), known as MSD outside Canada and the United States, today announced that the KEYNOTE-024 trial investigating the use of pembrolizumab, in patients with previously untreated advanced non-small cell lung cancer (NSCLC) whose tumors expressed high levels of PD-L1 (tumor proportion score of 50 percent or more), met its primary endpoint. In this trial, pembrolizumab was superior compared to chemotherapy for both the primary endpoint of progression-free survival (PFS), and the secondary endpoint of overall survival (OS). Based on these results, an independent Data Monitoring Committee (DMC) has recommended that the trial be stopped, and that patients receiving chemotherapy in KEYNOTE-024 be offered the opportunity to receive pembrolizumab.

Whereas Nivolumab trial that didn't select for PDL-1 was negative!

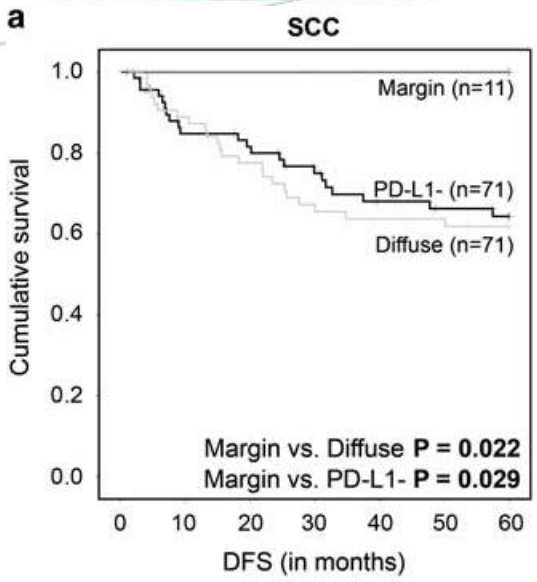
PD-L1 expression and cervix cancer

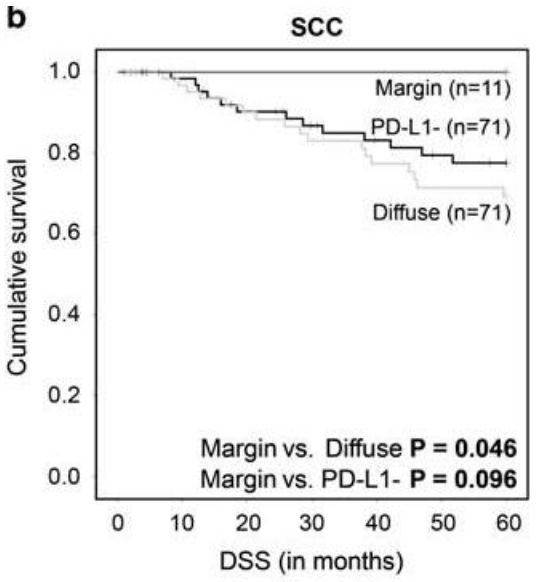
- Little published!
- Marijne Heeren et al, Modern Pathology 2016
- 156 SCC and 49 adenocarcinoma plus 31 primary and paired metastatic tumour samples
- 54% of SCC and 14% of adenocarcinoma were >5% PDL1 positive
- No significant difference between primary and metastatic samples but some became positive
- Different staining patterns had different associations with survival times: diffuse, marginal, positive tumor infiltrating macrophages

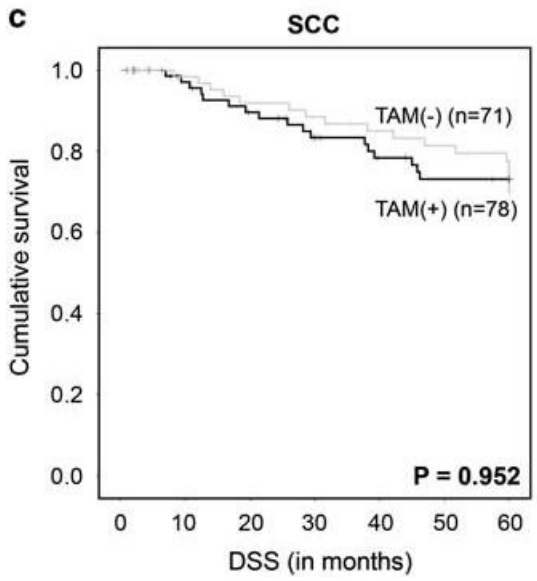


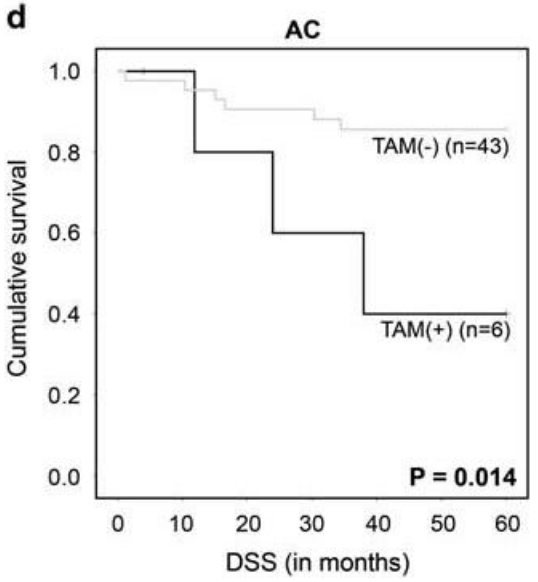
Diffuse staining bad in SCC but marginal staining good

Positive TAMs bad in adeno





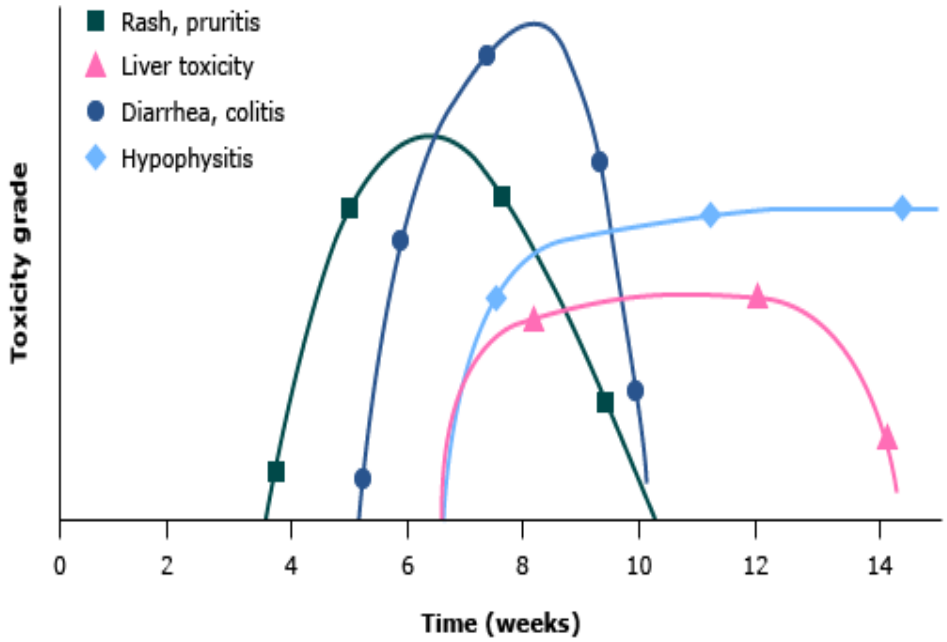


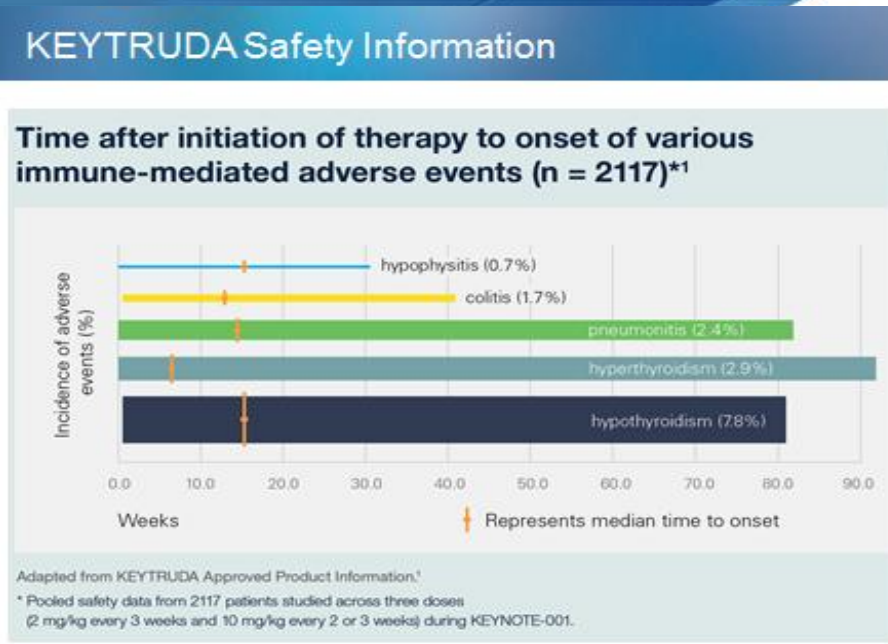


Side effects of checkpoint inhibitors

- Ipilimumab causes a more general activation of the immune system → higher rate of side effects
  - 20-30% pts will have severe side effects
- PD-1 inhibitors more specific to the tumour microenvironment → better tolerated
  - 10-15% will have severe side effects
- Spectrum of side effects similar
- Autoimmune and inflammatory in nature
  - Treatment is early recognition and steroids (generally)

Timing of side effects





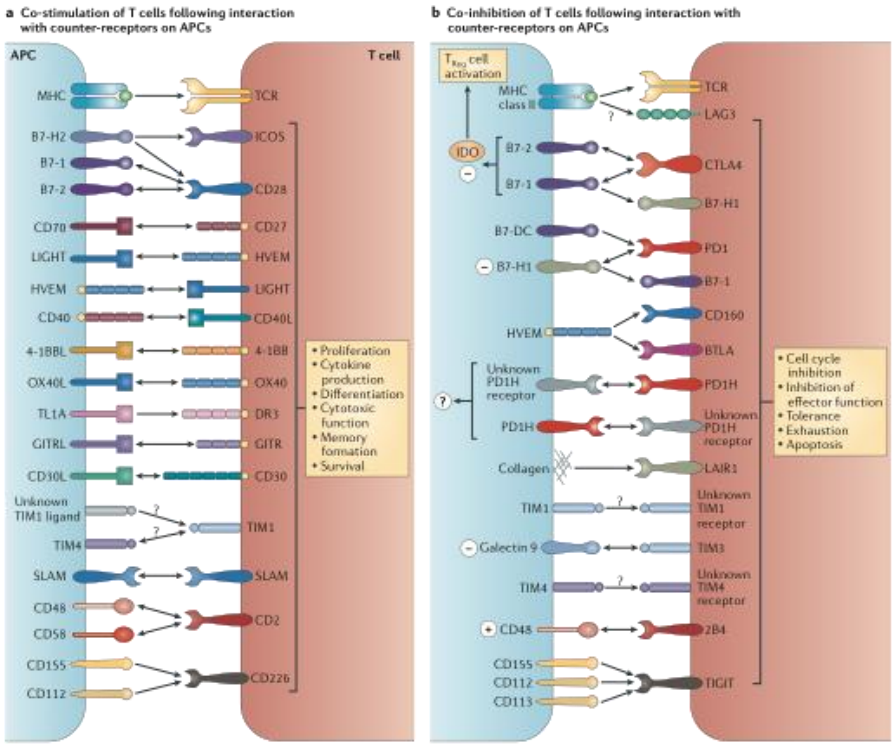
Weber JCO 2012 30:2691

Any autoimmune problem…

- Autoimmune disease can affect any system
- Broad spectrum of potential side effects
- Still learning
- Autoimmune hepatitis, pneumonitis, type 1 diabetes, arthritis, uveitis, nephritis, Guillain-Barre, aseptic meningitis, red cell aplasia, neutropenia, thrombocytopenia, acquired haemophilia A.
- Other side effects – fatigue, nausea, reduced appetite, fever

Improving on the efficacy of single-agent PD-1

- Combinations with other checkpoint inhibitors
- Cmbinations with therapeutic vaccines
- Combinations with radiotherapy
- Combinations with cytotoxics
- Working out who to treat!
- Working out when to treat



Combined immunotherapy and radiation for treatment of mucosal melanomas of the lower genital tract☆

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ABSTRACT

Objective: To report our experience using ipilimumab, a monoclonal antibody targeting CTLA-4, combined with radiation therapy in women diagnosed with mucosal melanoma of the lower genital tract.
Methods: We retrospectively identified all patients who received ipilimumab with concurrent radiation treatment of mucosal melanoma of the lower genital tract at Memorial Sloan Kettering Cancer Center from 2012 to 2015. Various clinicopathologic data and treatment response were abstracted and analyzed.
Results: Four patients were identified. Median age was 61.5 years (range 44–68); 3 were diagnosed with vaginal melanoma, 1 with cervical melanoma. All would have required extensive surgical procedures to remove entirety of disease. Median size of lesions was 4.7 cm (range, 3.3–5.3); all were Ballantyne stage I. Median number of doses of upfront ipilimumab was 4 (range, 3–4). Two patients suffered CTCAE grade 3 adverse events (colitis, rash). All received external beam radiation: 3 to 3000 cGy, 1 to 6020 cGy. Post-radiation surgical resection was performed in 3 patients (75%); 1 (33%) of 3 patients achieved complete pathologic response. Complete local radiographic response was observed in all patients after completion of initial therapy and surgery. Two developed recurrence at 9 and 10 months post-diagnosis (mediastinum, lung); 2 remain disease-free at 20 and 38 months.
Conclusions: Mucosal melanoma of the lower genital tract is rare, and data-driven treatment strategies limited. Immunotherapy has demonstrated durable efficacy in the treatment of cutaneous melanomas. Our small case series shows a favorable response to combined ipilimumab and radiation therapy. Larger studies are needed to validate these promising results.

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Rank	Status	Study
1	Recruiting	Combination of Cryosurgey and NK Immunotherapy for Recurrent Cervical Cancer **Condition:** Recurrent Cervical Cancer **Interventions:** Device: Cryosurgery; Biological: NK immunotherapy
2	Recruiting	Study of the Therapeutic Vaccine (ISA101/ISA101b) to Treat Advanced or Recurrent Cervical Cancer **Condition:** Cervical Cancer **Intervention:** Drug: ISA101/ISA101b
3	Recruiting	Pembrolizumab and Chemoradiation Treatment for Advanced Cervical Cancer **Condition:** Cervical Cancer **Interventions:** Drug: Pembrolizumab; Radiation: Brachytherapy; Drug: Cisplatin
4	Recruiting	CAR T Cell Receptor Immunotherapy Targeting Mesothelin for Patients With Metastatic Cancer **Conditions:** Cervical Cancer; Pancreatic Cancer; Ovarian Cancer; Mesothelioma; Lung Cancer **Interventions:** Drug: Fludarabine; Biological: Anti-mesothelin CAR; Drug: Cycolphosphamide; Drug: Aldesleukin
5	Recruiting	E7 TCR T Cells With or Without PD-1 Blockade for Human Papillomavirus-Associated Cancers **Conditions:** Cervical Cancer; Vaginal Cancer; Anal Cancer; Penile Cancer; Oropharyngeal Cancer **Interventions:** Biological: E7 TCR cells; Drug: pembrolizumab; Drug: aldesleukin; Drug: fludarabine; Drug: cyclophosphamide
6	Recruiting	Study Of OX40 Agonist PF-04518600 Alone And In Combination With 4-1BB Agonist PF-05082566 **Condition:** Neoplasms **Interventions:** Drug: PF-04518600; Drug: PF-04518600 plus PF-05082566