Gynecologic Cancer InterGroup
Cervix Cancer Research Network

THE ROLE OF TARGETED THERAPY AND IMMUNOTHERAPY IN THE TREATMENT OF ADVANCED CERVIX CANCER

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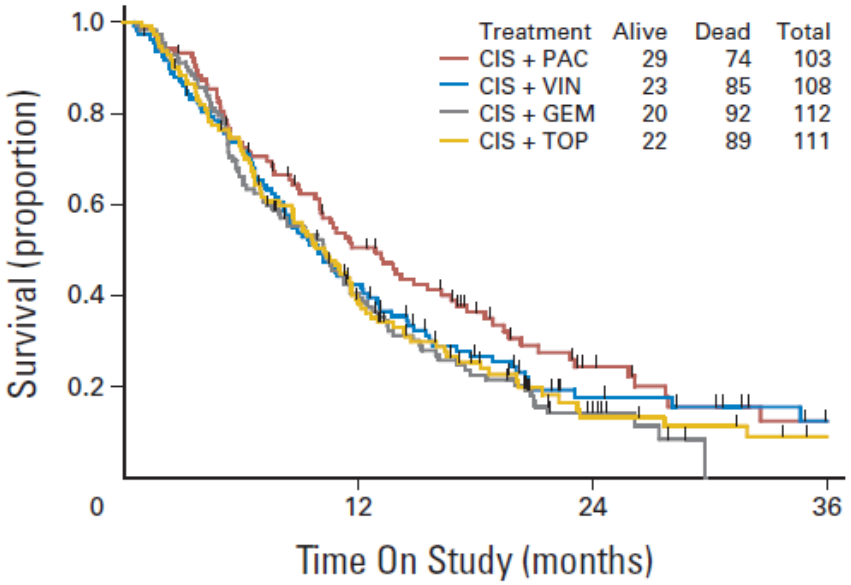
Cervix Cancer Education Symposium, January 2019, South Africa

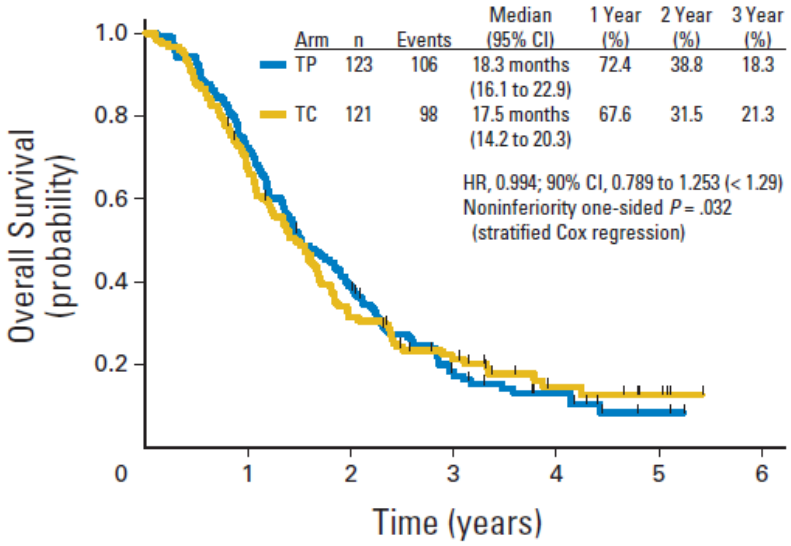
Cervix ca – Advanced disease

- Consider symptoms and prognostic factors
  - ECOG, previous RT, disease free interval
- Palliative RT if appropriate
  - Potentially can be used as salvage therapy in localised recurrence
- Palliative benefit of chemotherapy not well studied
- Response rates between 15-30%
- Multi-disciplinary supportive care is needed!

Cervix cancer – Chemo in advanced disease

- GOG-204: 4 x Cisplatin doublets in recurrent/metastatic cervix cancer
- No significant difference in all 4 regiments
- Established Cisplatin/Paclitaxel as standard of care
  - Median OS 12.9months, RR 25-30%
- JGOG0505 – Carbo/Taxol non-inferior to Cis/Taxol





Monk et al, JCO 2009; Kitagawa et al, JCO 2015

Predictive factors for PFS and OS in women treated with Cisplatin combinations

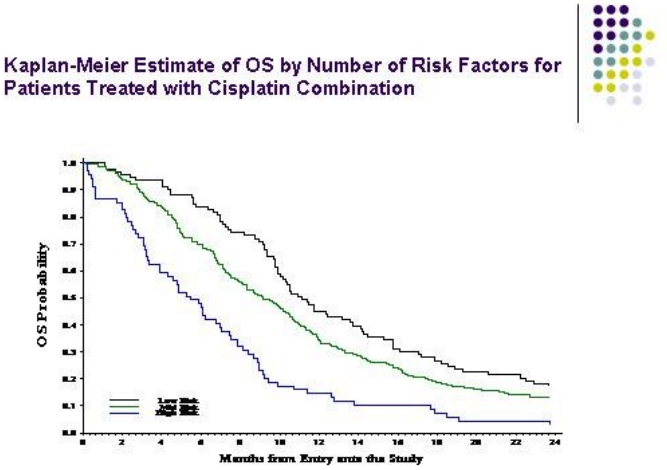
- African-American
- ECOG > 0
- Pelvic disease
- Prior radiosensitizer
- Recurrence < 1 yr

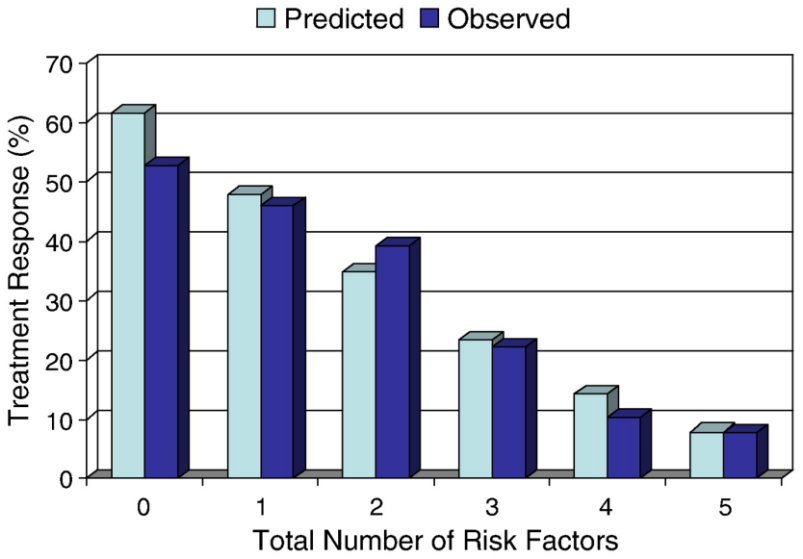
If 4-5 factors:

RR 13%

PFS 2.8

OS 5.5 months





Targeted therapies in cervical cancer

- Multiple pathways studied
- Generally disappointing apart from targeting angiogenesis
  - Bevacizumab : approved for 1st line therapy of advanced disease

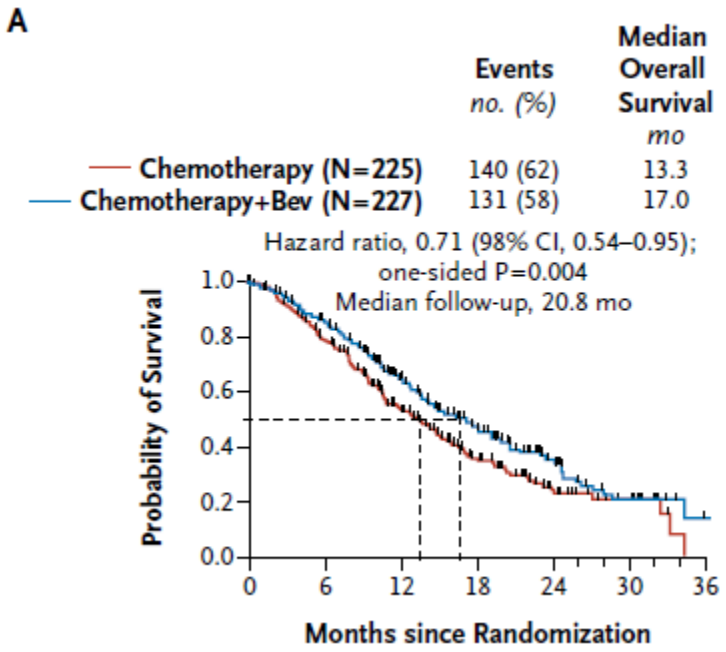
Table 1. Molecular pathways targeted in cervical cancer

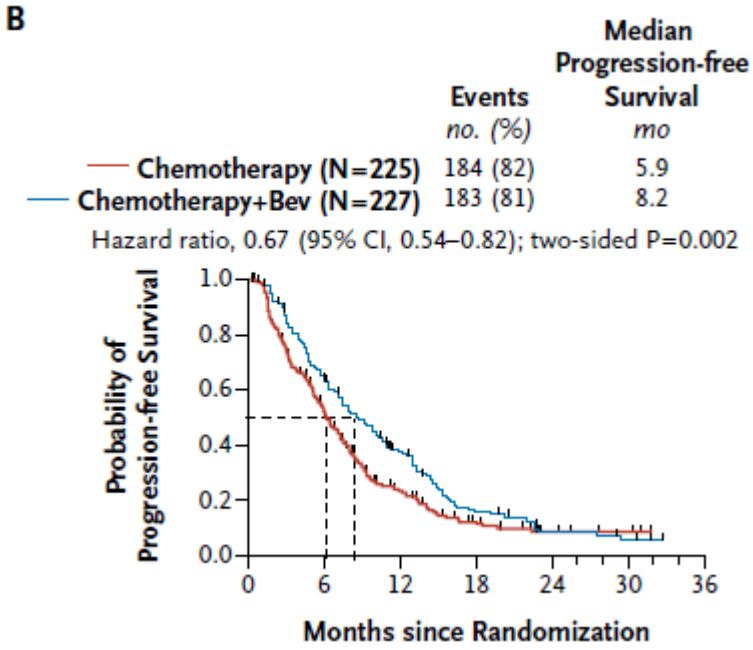
Pathway	Therapeutic agent
EGFR	Cetuximab, matuzumab, gefitinib, erolotinib
Her2	Lopatanib
Folic acid	Pemetrexed
HDAC	Valproic acid
mTOR	Temsirolimus
Wee1	PD0166285 MK1775
Notch	NCT01158404*
HSP 90	Geldanamycin
PARP	Olaparib, veliparib

New hope of using immunotherapy to target cervical cancer

Cervix cancer - Bevacizumab

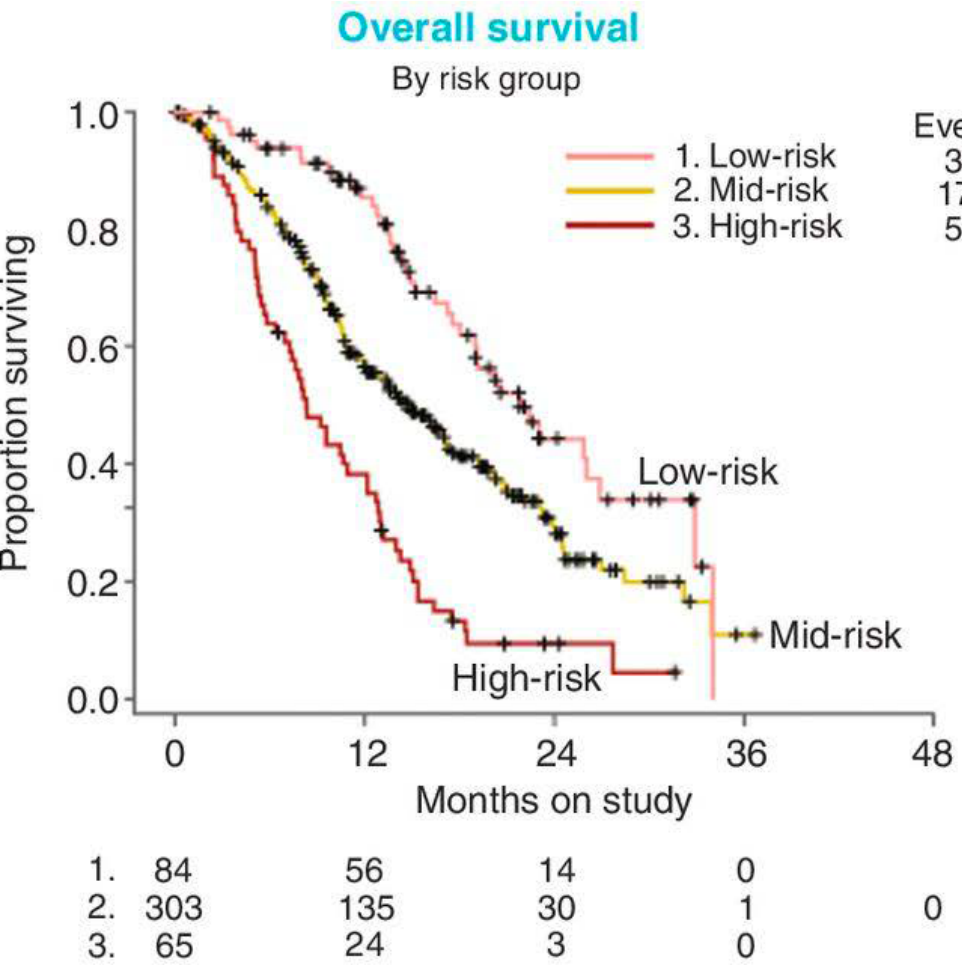
- GOG-240
  - Role of non-platinum doublet (Topotecan-Paclitaxel)
  - Role of adding Bevacizumab
- Improved PFS & OS with addition of Bevacizumab
- RR 48% vs 36% but risk of fistula up to 15%





Tewari et al, NEJM 2014

MOORE criteria using Bevacizumab



	Median OS (mo)	Median PFS (mo)	RR (%)
Low-risk	21.8	9.2	57.1
Mid-risk	14.7	6.9	43.2
High-risk	8.2	4.7	18.5
P (likelihood ratio)	<0.0001	0.0050	<0.0001

Addition of Bevacizumab (OS)

Low-risk: 21.8 vs 22.9 months HR 0.96

Mid-risk: 12.1 vs 17.9 months HR 0.67

High risk: 6.3 vs 12.1 months HR 0.54

Immunotherapy basics: 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 & Immune System

- Oncogenic viruses
  - HPV and cervical, H&N, anal
  - EBV and gastric cancer
- Immunosuppression and cancer
  - HIV and Kaposi sarcoma plus others
  - Organ transplants and lymphoma, skin cancers

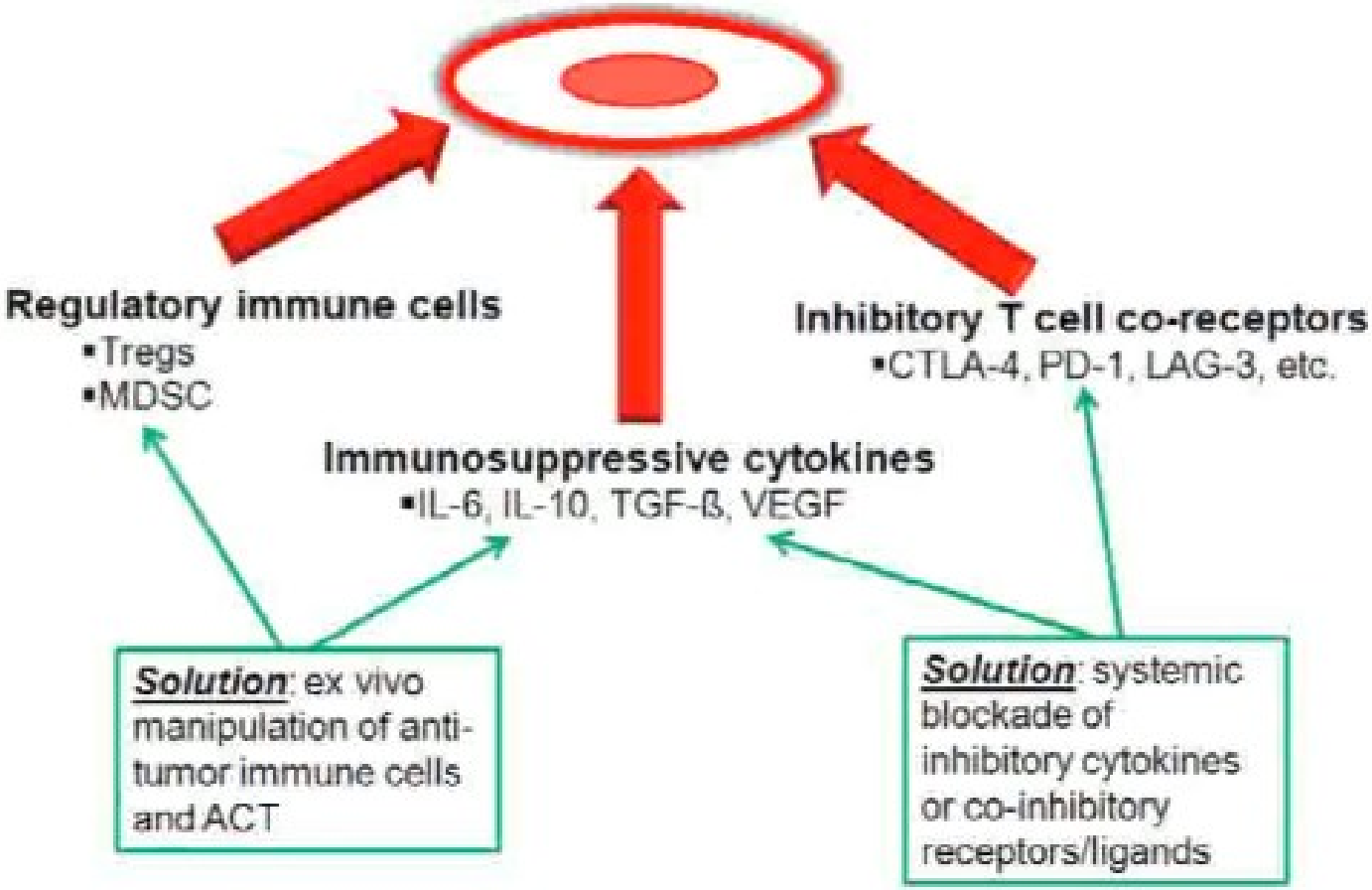
Immune System and Cancer

- 20th century "immune surveillance"
  - Tumour antigens treated as foreign antigens
  - Natural response of immune system is to survey the body for tumours and eliminate them

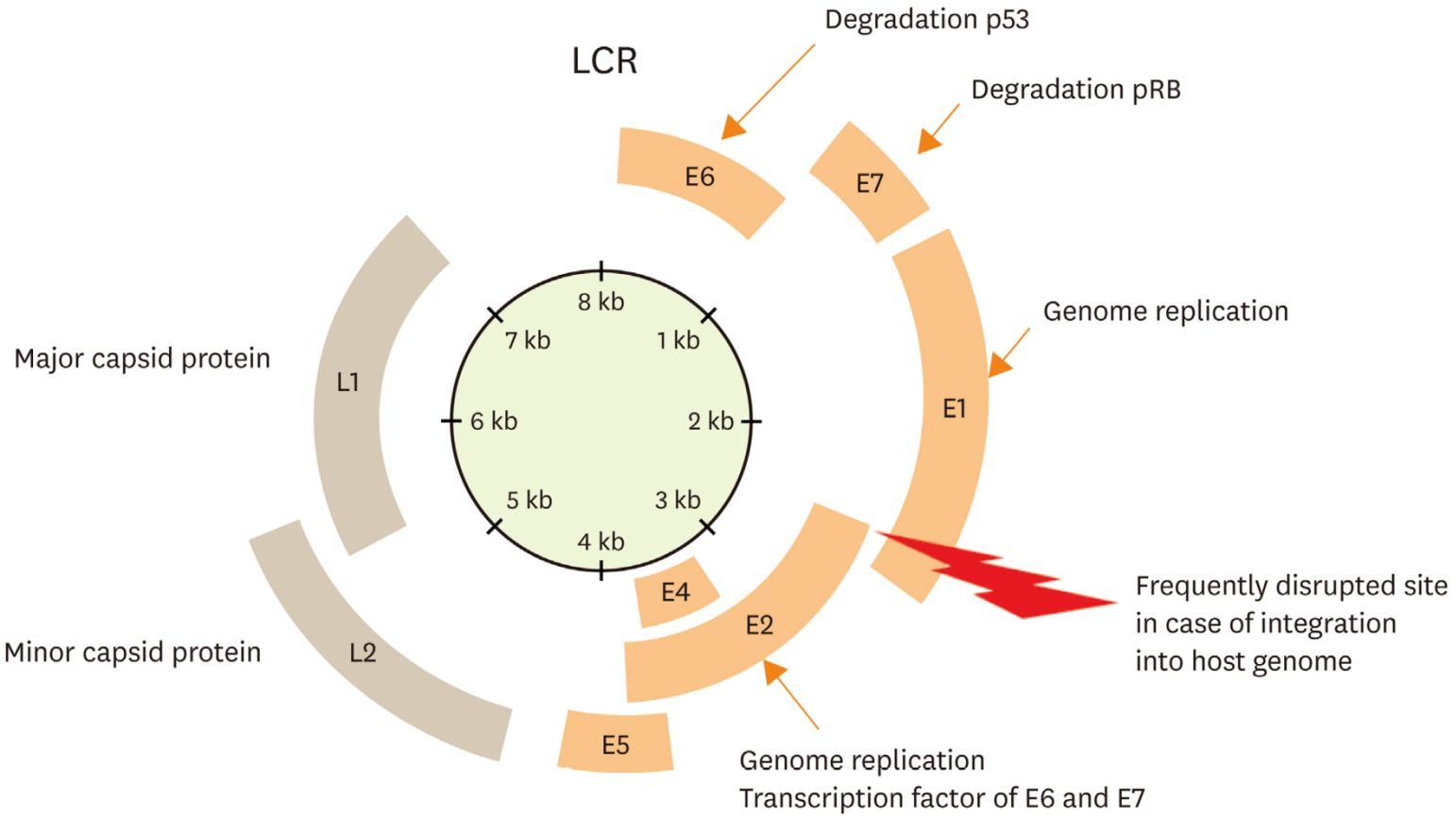
- 21st century "immune tolerance"
  - Tumour antigens treated as self antigens
  - Natural response of immune system to tumour antigens is tolerance

Goal is to ***overcome tolerance***

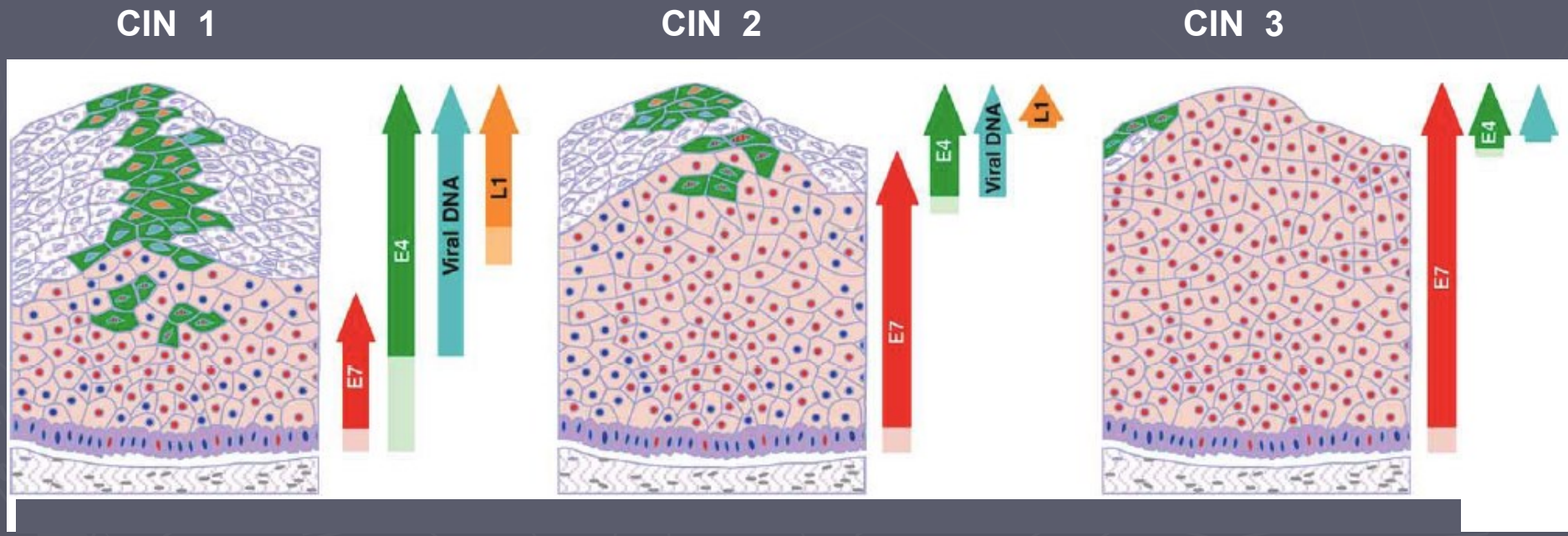
Roads leading to immune Tolerance



Cervix cancer as a target for immunotherapy: HPV



Progression to Cancer is Accompanied by Deregulation of Viral Gene Expression

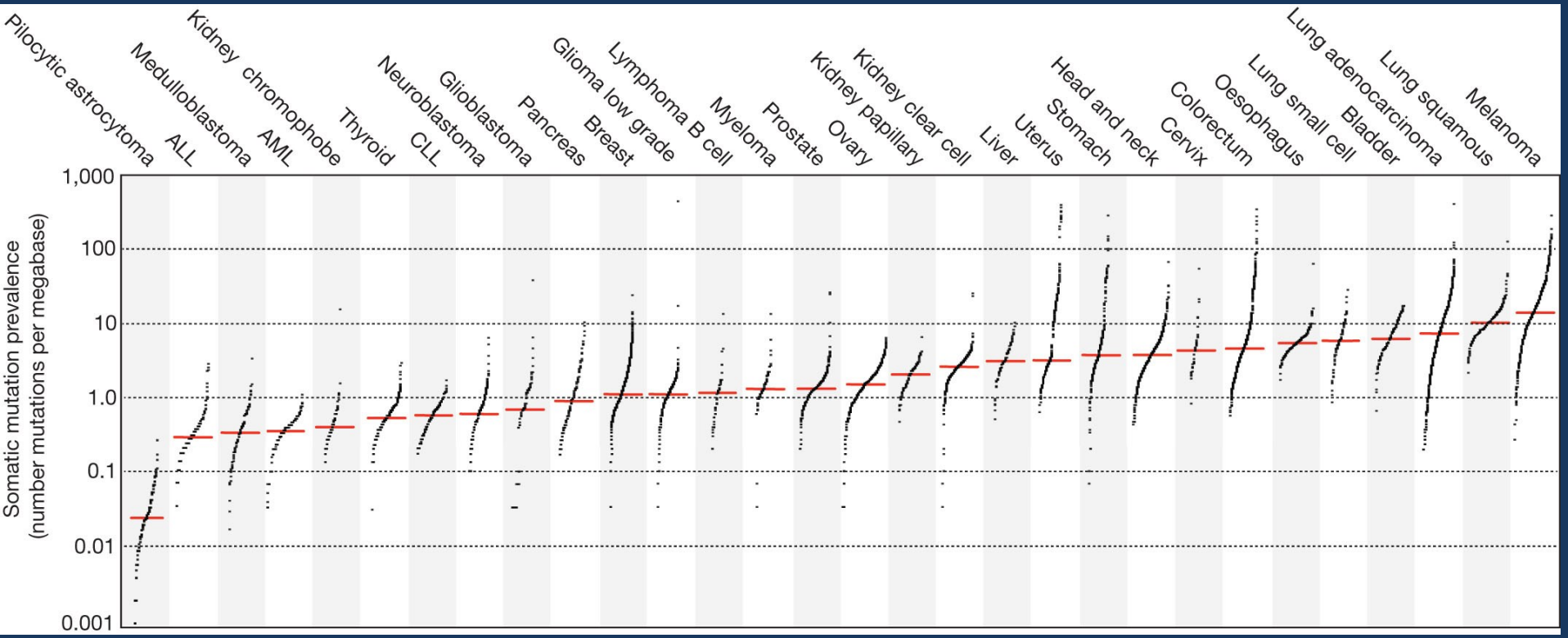


Doorbar, J Clin Virol 32:7-15, 2005

<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

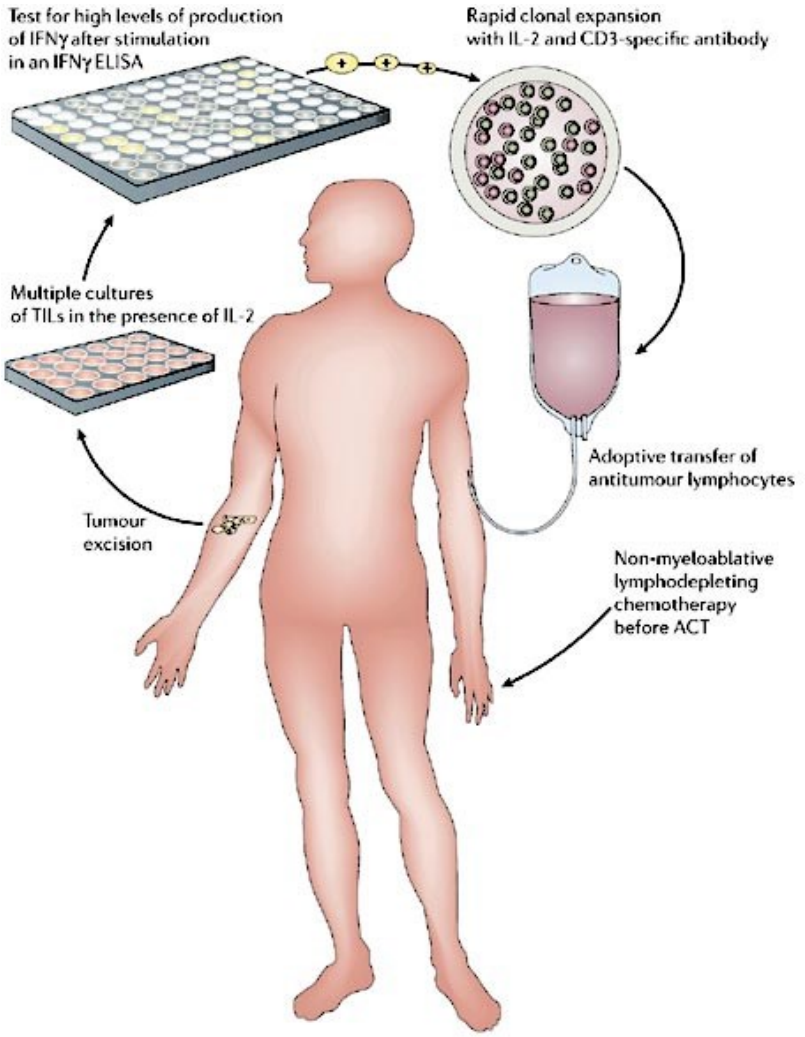


Cervix Cancer: Mutation burden intermediate but potentially still responsive to immunotherapy because of HPV (viral antigen)

Alexandrov Nature 2013

Passive Immunotherapy

- *Adoptive Cellular Transfer (ACT)*
- Pts have T cells capable of recognizing antigens expressed by tumours (e.g. Tumour Infiltrating Lymphocytes)
- 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

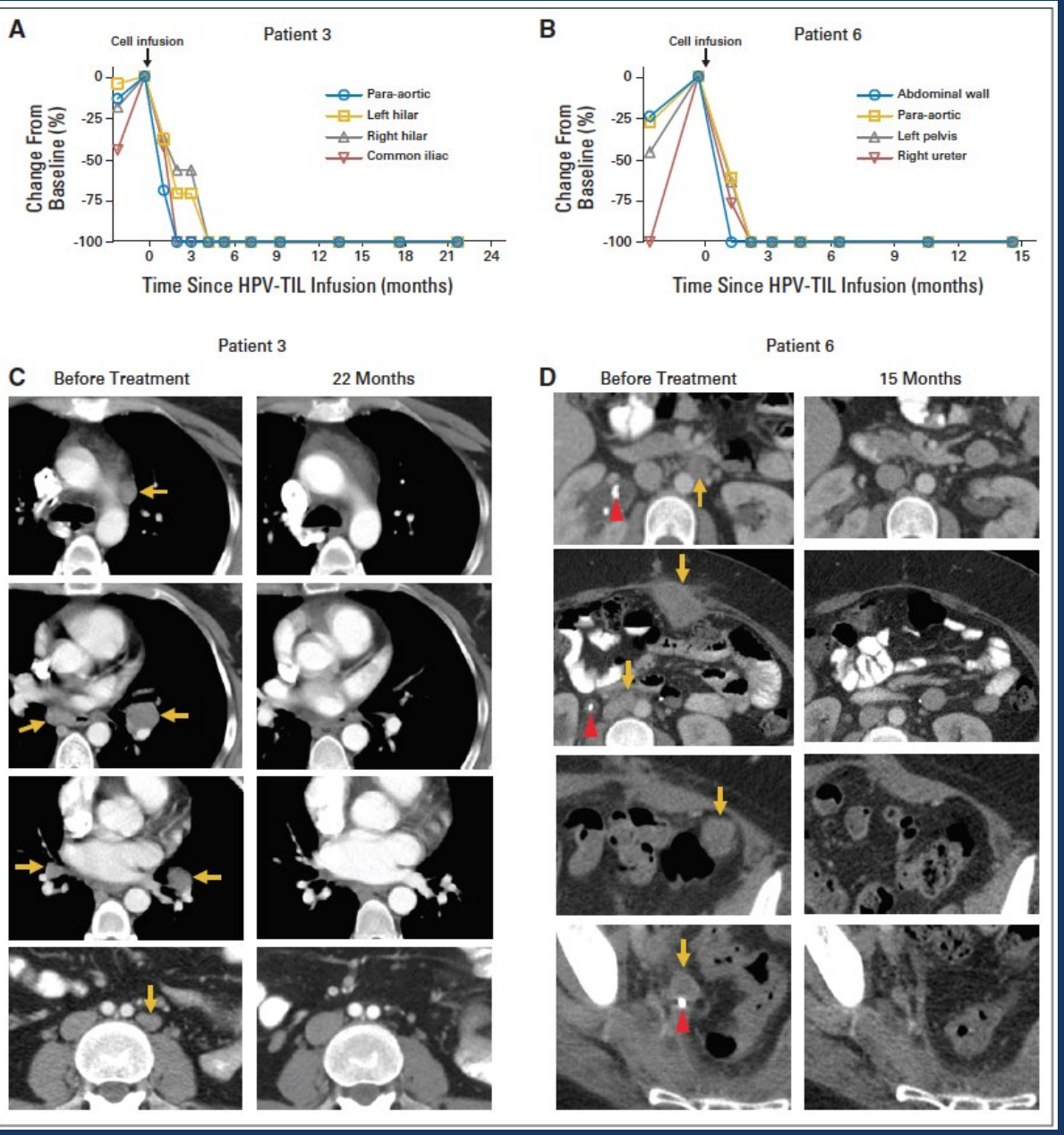
Purpose
Metastatic cervical cancer is a prototypical chemotherapy-refractory epithelial malignancy for which better treatments are needed. Adoptive T-cell therapy (ACT) is emerging as a promising cancer treatment, but its study in epithelial malignancies has been limited. This study was conducted to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

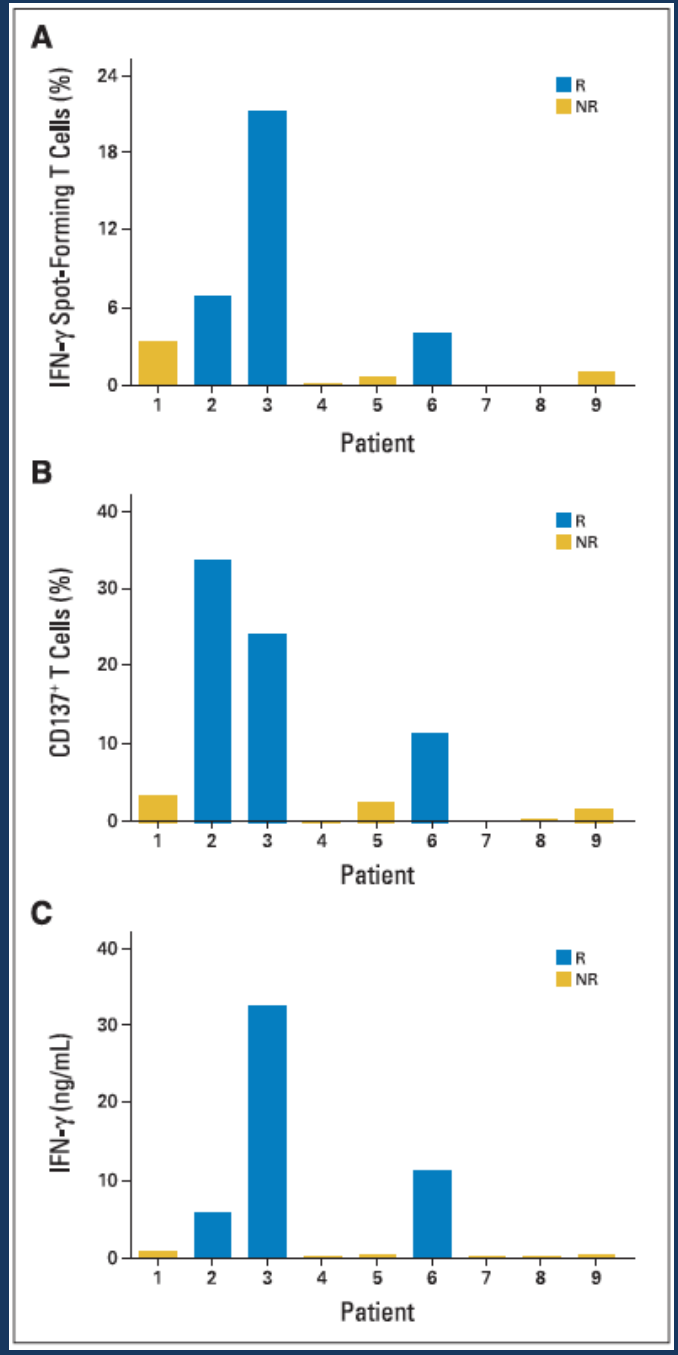
Patients and Methods
Patients enrolled onto this protocol were diagnosed with metastatic cervical cancer and had previously received platinum-based chemotherapy or chemoradiotherapy. Patients were treated with a single infusion of tumor-infiltrating T cells selected when possible for human papillomavirus (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

1. Therapeutic vaccines: ongoing active research in cervix cancer
2. T cell modulators (2011+)
   - Ipilimumab
   - Anti PD-1/L1
   - Many many more…..

AXAL: a live, attenuated, nonpathogenic, bioengineered *Lm*-LLO immunotherapy for treatment of HPV-associated cancers

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

▼

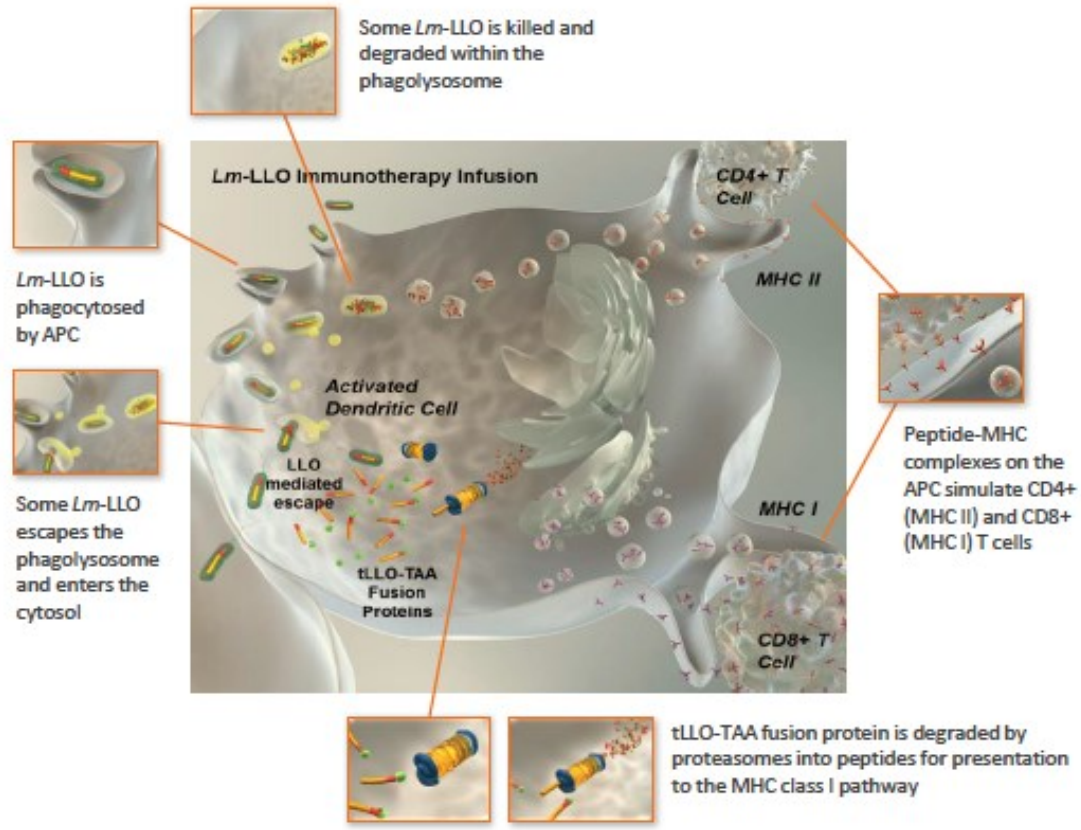
Lm-LLO expresses LLO-TAA fusion protein, which is processed by stimulated APC and activates TAA-specific T-cells

▼

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

▼

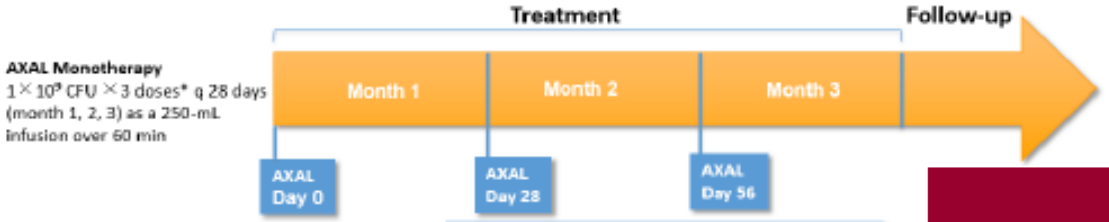
Immune activation can overcome checkpoint inhibition and negative regulators of cellular immunity



PHASE 2 trial

GOG/NRG-0265: Study design and eligibility

- N = ~63†; Simon two-stage design
- ≥18 years
- Persistent/recurrent metastatic (PRmCC) squamous/non-squamous cervical cancer
- ≥1 prior line of systemic-dose therapy for PRmCC, *excluding that received as a component of primary curative treatment*
- Prior bevacizumab allowed, but not required
- GOG PS 0/1
- Measurable disease ≥1 target lesion (RECIST 1.1)



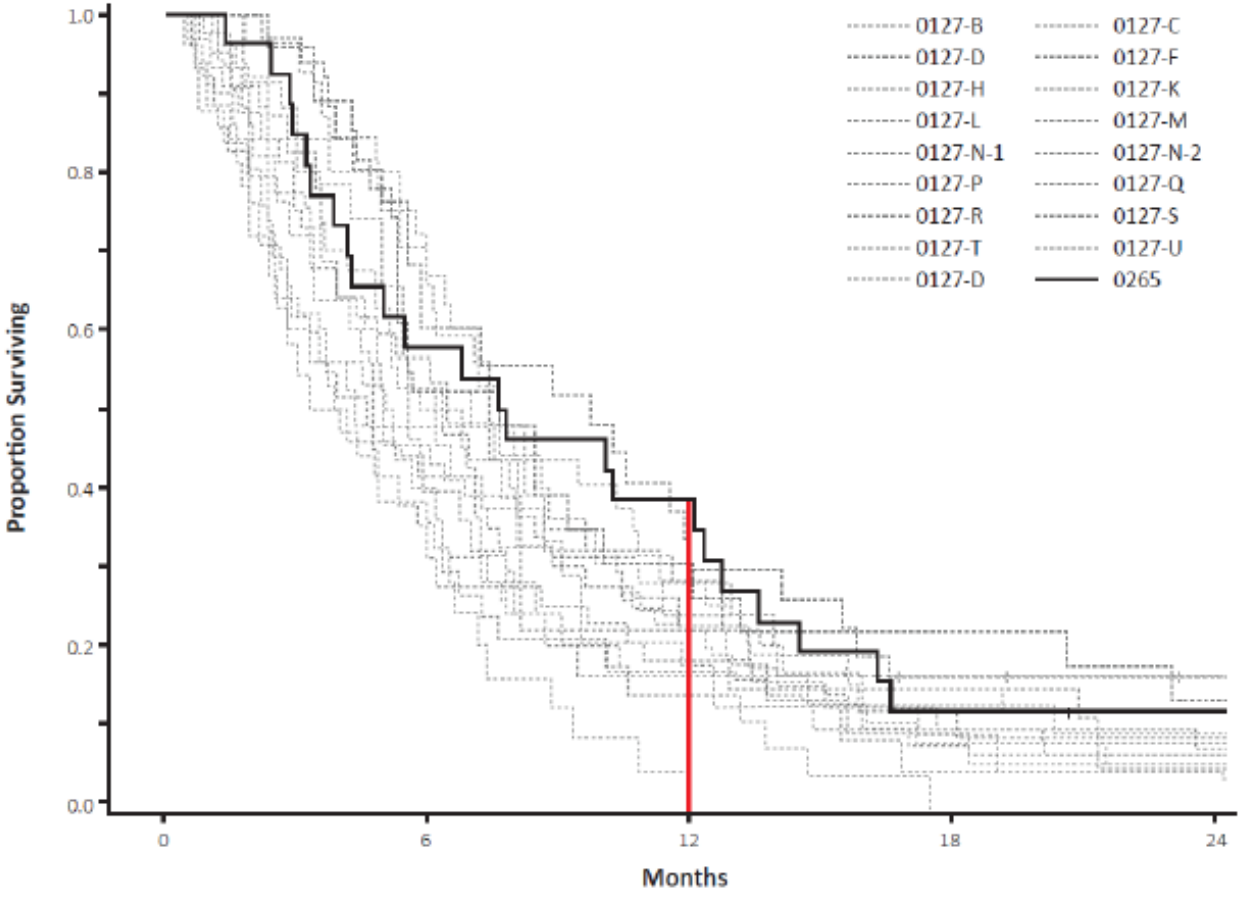
Co-primary Endpoints:
- 12-month survival rate
- Tolerability/safety of AXAL

Secondary Endpoints:
- PFS
- OS
- ORR

	Stage 1 (N = 26)	Stage 2 (N = 24)
Tumor best response, n (%)		
CR	0 (0)	1 (4)
SD	7 (27)	8 (33)
PD	10 (38)	11 (46)
NE	6 (23)	4 (17)

†N = total 54 enrolled, as a result of clinical hold interruption during Stage 2.
*Stage 2 amended to allow continuous (>3) dosing of AXAL.
AXAL, axalimogene filolisbac; CFU, colony-forming units; GOG PS, Gynecologic Oncology Group performance status; HPV, human papillomavirus; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRmCC, persistent/recurrent metastatic cervical cancer; RECIST, Response Evaluation Criteria In Solid Tumors.

GOG/NRG-0265: Survival in the Context of Historical GOG PRmCC Clinical Trials

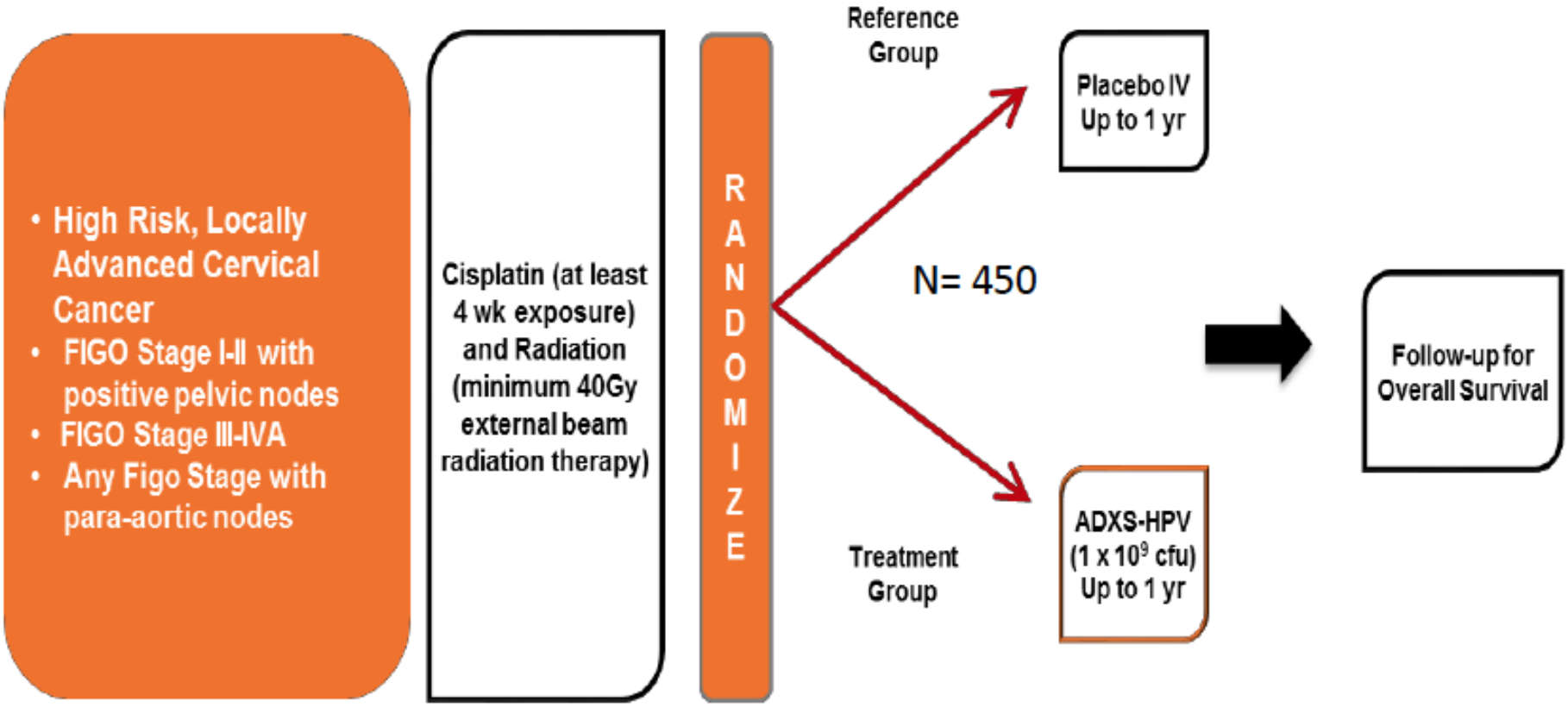


1. Tewari KS, Monk BJ. *Curr Oncol Rep*. 2005;7(6):419-434; 2 Muggia F, et al. *Gynecol Oncol*. 2004;92(2):639-643; 3. Plaxe SC, et al. *Cancer Chemother Pharmacol*. 2002;50(2):151-154; 4. Armstrong DK, et al. *Invest New Drugs*. 2003;21(4):453-457; 5. Fracasso PM, et al. *Gynecol Oncol*. 2003;90(1):177-180; 6. Brewer CA, et al. *Gynecol Oncol*. 2006;100(2):385-388; 7. Rose P, et al. *Gynecol Oncol*. 2006;102(2):210-213; 8.Garcia AA, et al. *Am J Clin Oncol*. 2007;30(4):428-431; 9. Miller DS, et al. *Gynecol Oncol*. 2008;110(1):65-70; 10. Fiorica JV, et al. *Gynecol Oncol*. 2009;115(2):285-289; 11. Monk BJ, et al. *J Clin Oncol*. 2009;27(7):1069-1074; 12. Schilder RJ, et al. *Int J Gynecol Cancer*. 2009;19(5):929-933; 13. National Cancer Institute. Vaccine therapy in treating patients with persistent or recurrent cervical cancer. http://www.cancer.gov/about-cancer/treatment/clinical-trials/search/view?cdrid=691288. Accessed May 25, 2016; 14. Gynecologic Oncology Group/NRG Oncology. Data on file, 2016.

NRG ONCOLOGY™

AIM2CERV/GOG 3009

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

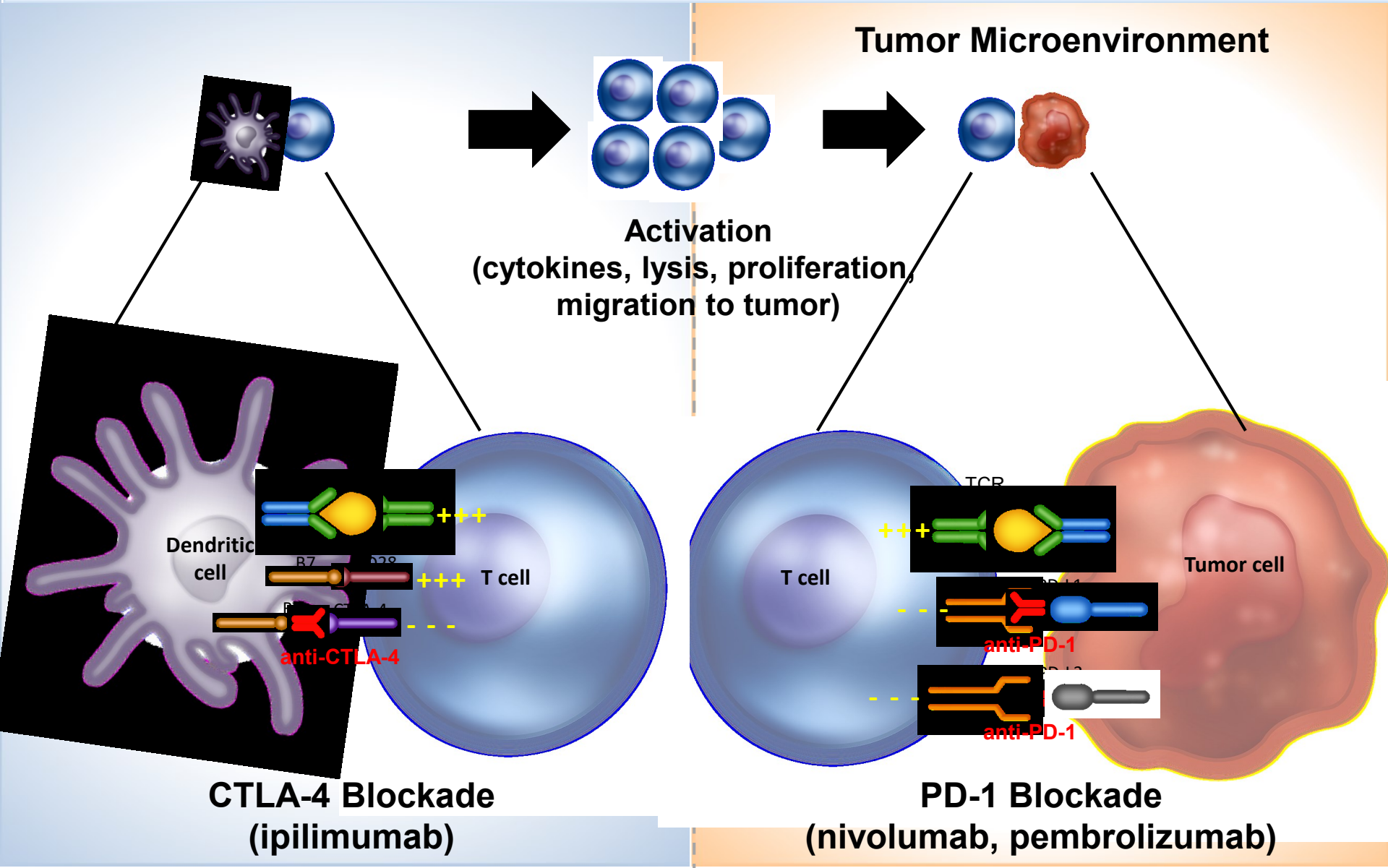


Baseline tumor imaging must be performed within 28 days prior to the first study treatment infusion

Randomization 1:2 Reference and Treatment Groups

Primary Objective is Progression Free Survival

T-cell immune checkpoints

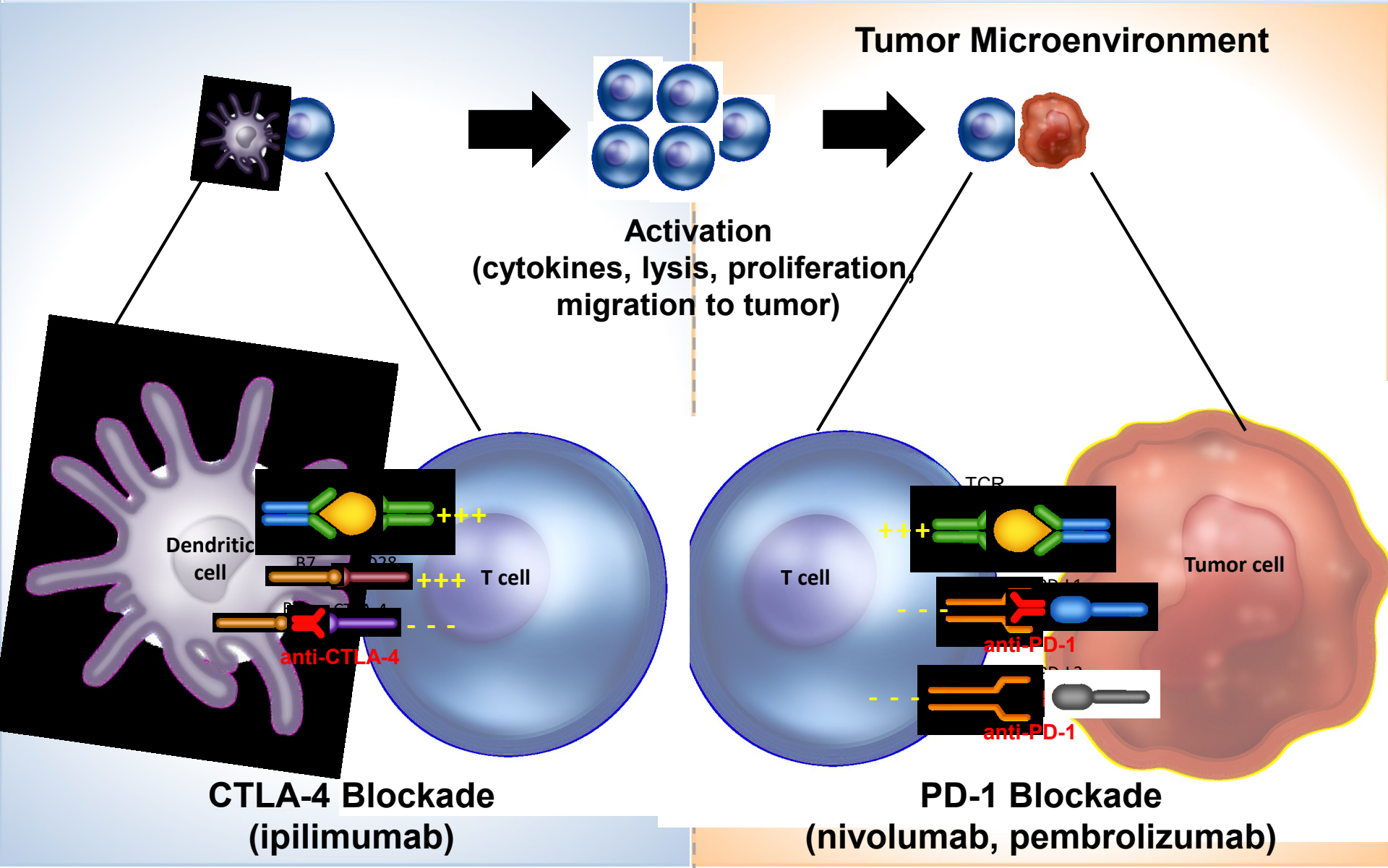


Ipilimumab in cervix cancer: Phase 1/2

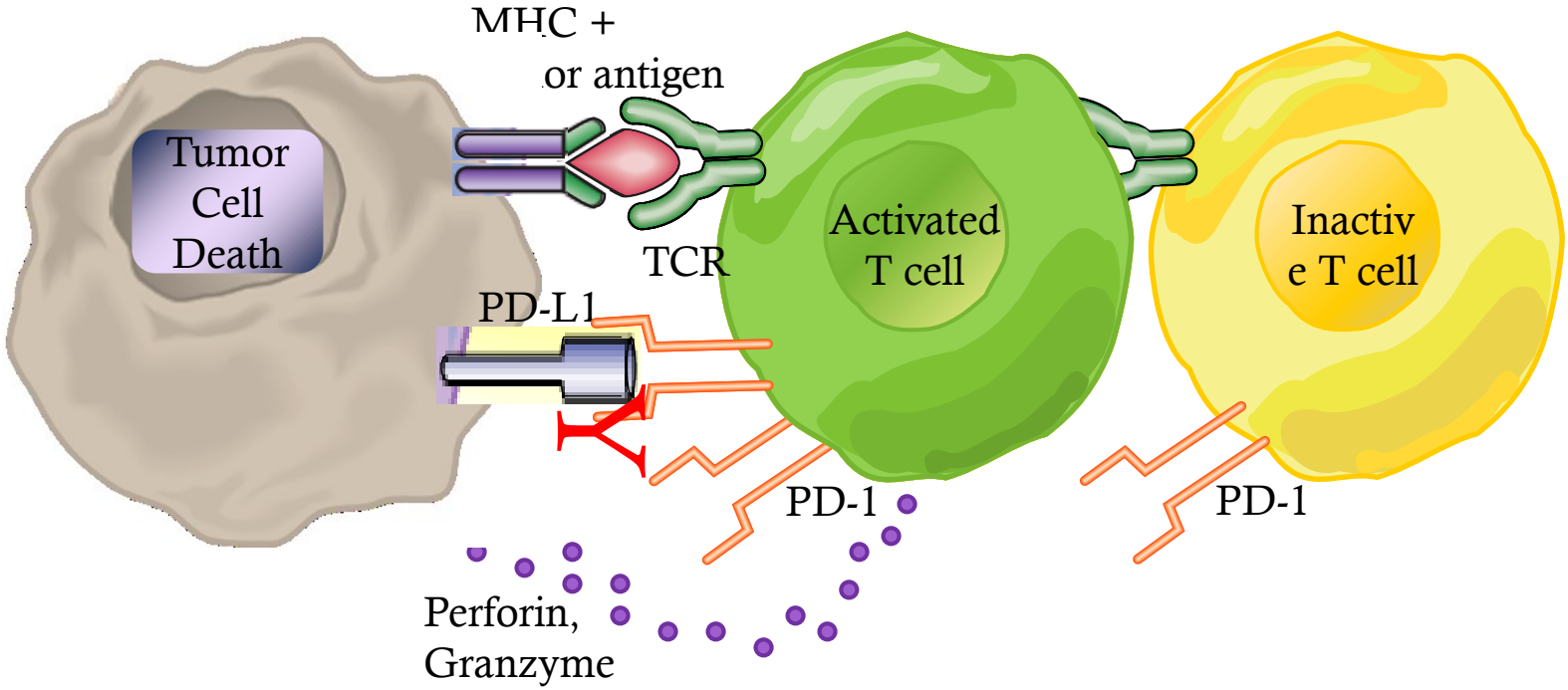
- 42 patients with measurable disease progression and prior platinum exposure
- 4 cycles if Ipilimumab (3-10mg/kg) every 21 days followed by 4 maintenance cycles every 12 weeks
- 35 had prior RT and 21 had 2-3 prior regimens
- "Manageable" toxicities: Grade 3 diarrhoea (x4) and grade 3 colitis (x3)
-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

Lheureux L, ASCO annual meeting 2015

T-cell immune checkpoints

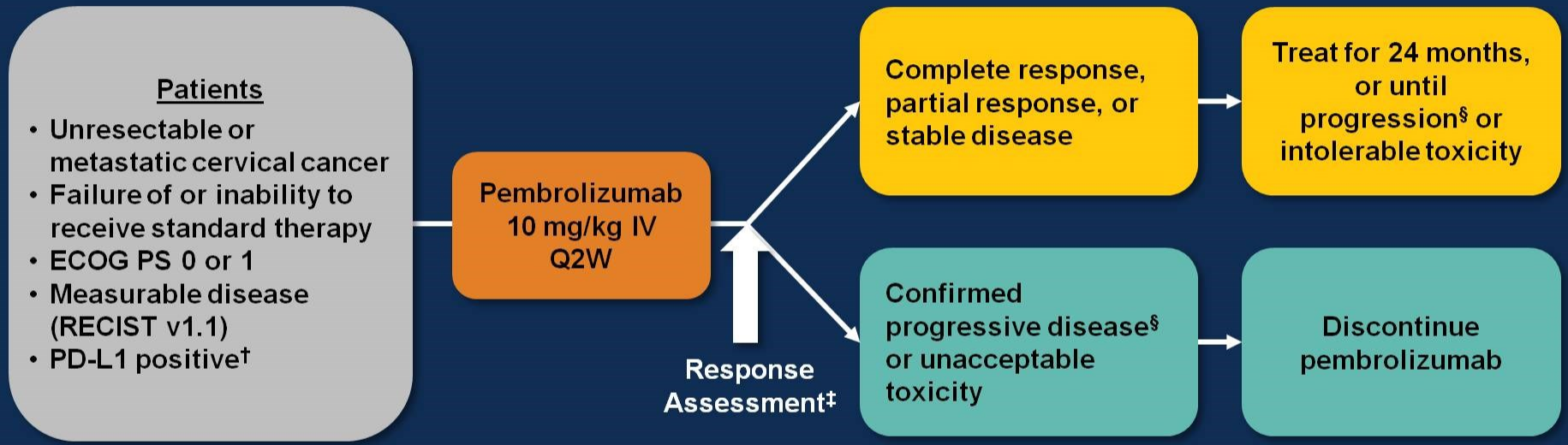


T cell silencing by tumour



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

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

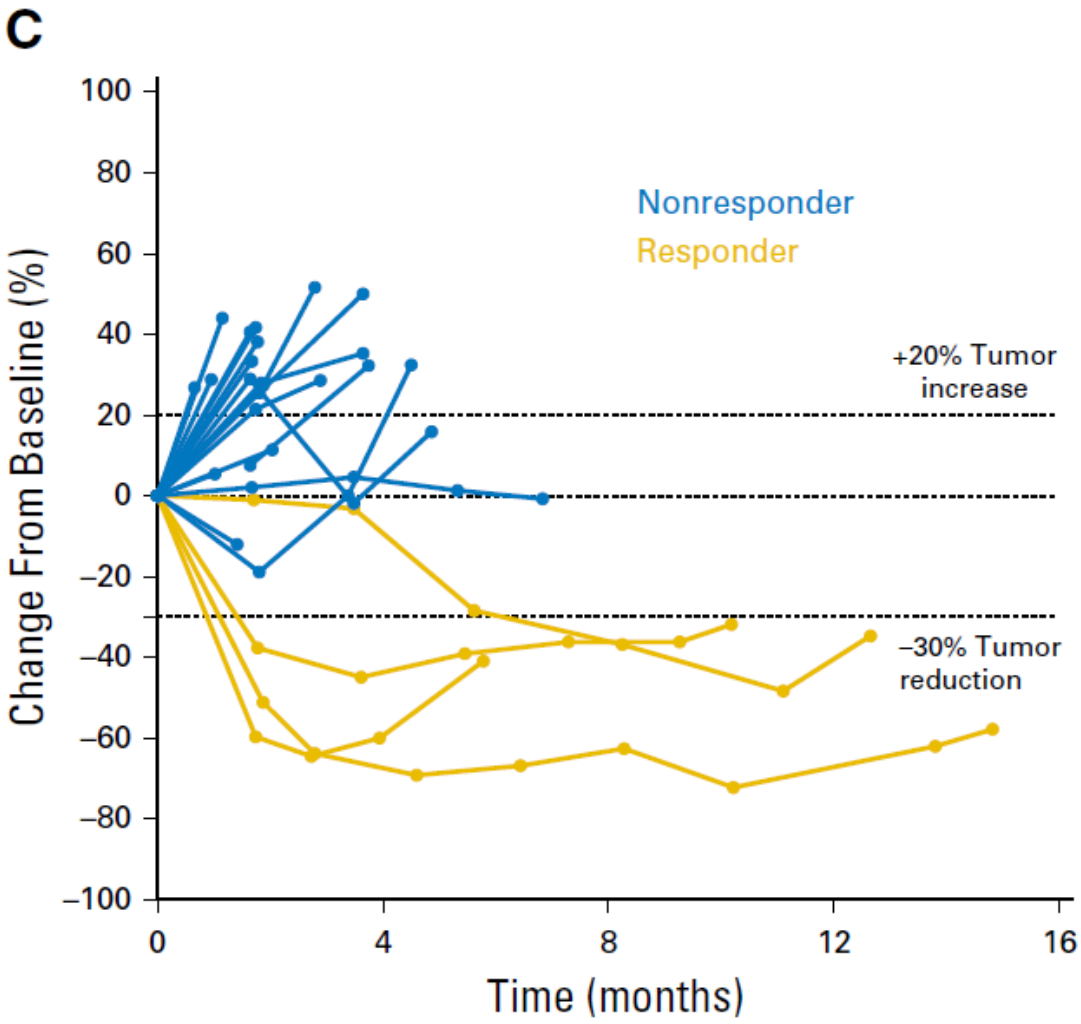
Secondary end points: PFS, OS, duration of response

†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.

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.



FDA approval June 2018

77 pts from Keynote158
- median age 45
- all ECOG 0-1
- overall response rate = 14.3%
- complete responses = 2.6%

- no responses in PDL-1 neg
- median response duration NR but at least 6 months in 91%

Presented By Jean-Sebastien Frenel at 2016 ASCO Annual Meeting, Published JCO Dec 2017

GOG 316 (R2810-ONC-1676)

NCT03257267

- Recurrent, persistent, and/or metastatic cervical cancer
- Progressed within 6 months of the last dose of platinum

RANDOMIZE

→ REGN2810 350 mg Q3W, for up to 96 weeks

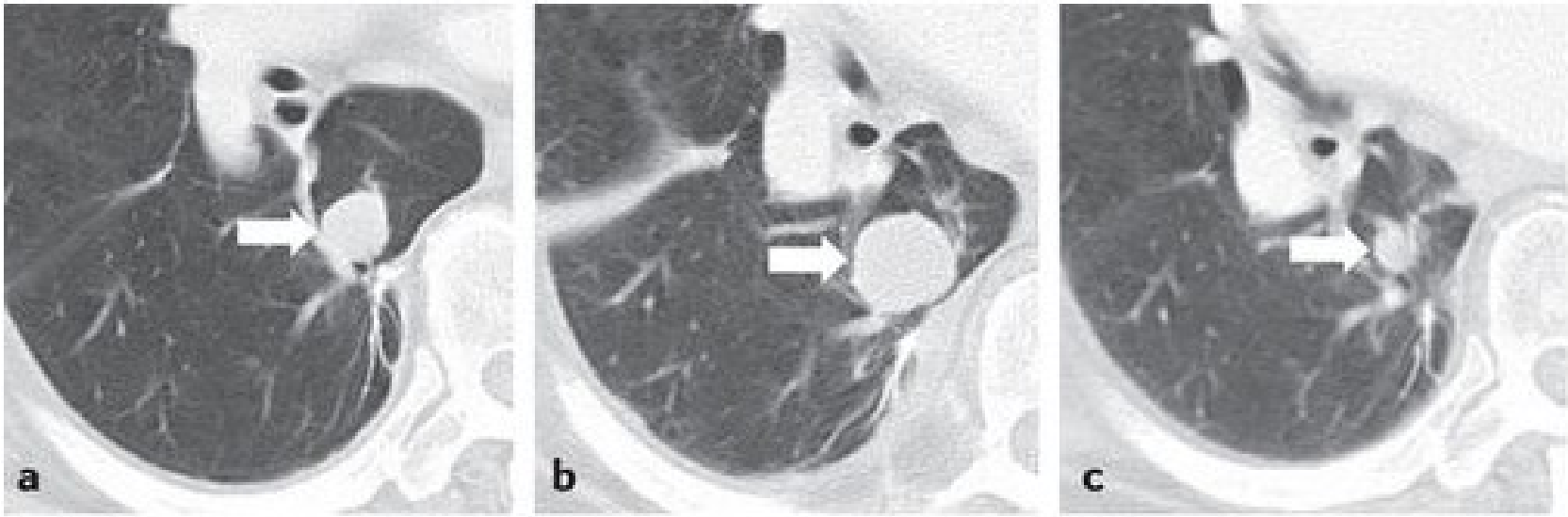
→ Physicians choice chemotherapy

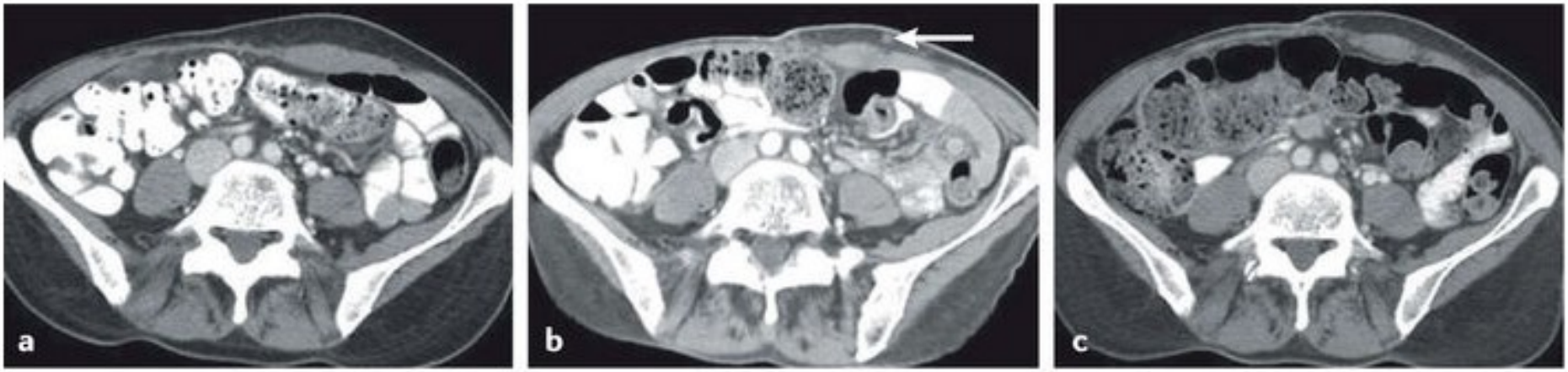
Pemetrexed 500 mg/m2 Q3W
Topotecan 1 mg/m2 daily for 5 days, Q21 days
Irinotecan 100 mg/m2 days 1, 8, 15, & 22, followed by 2 weeks rest (6-week cycle)
Vinorelbine 30 mg/m2 days 1 & 8, Q21 days
Gemcitabine 1000 mg/m2 on days 1 & 8, Q21 days

PI = Krishnansu S. Tewari, MD
N = 436
Primary Endpoint = OS

REGN2810, a fully human monoclonal antibody against programmed death-1 (PD-1)

Cancer Immunotherapy| Pseudoprogression





Described in 10 – 15% of melanoma patients
Much less common in other tumour types: 1- 3%

Nicshino et al. Nature Reviews Clinical Oncology 2017

Cancer Immunotherapy| Immunotoxicity

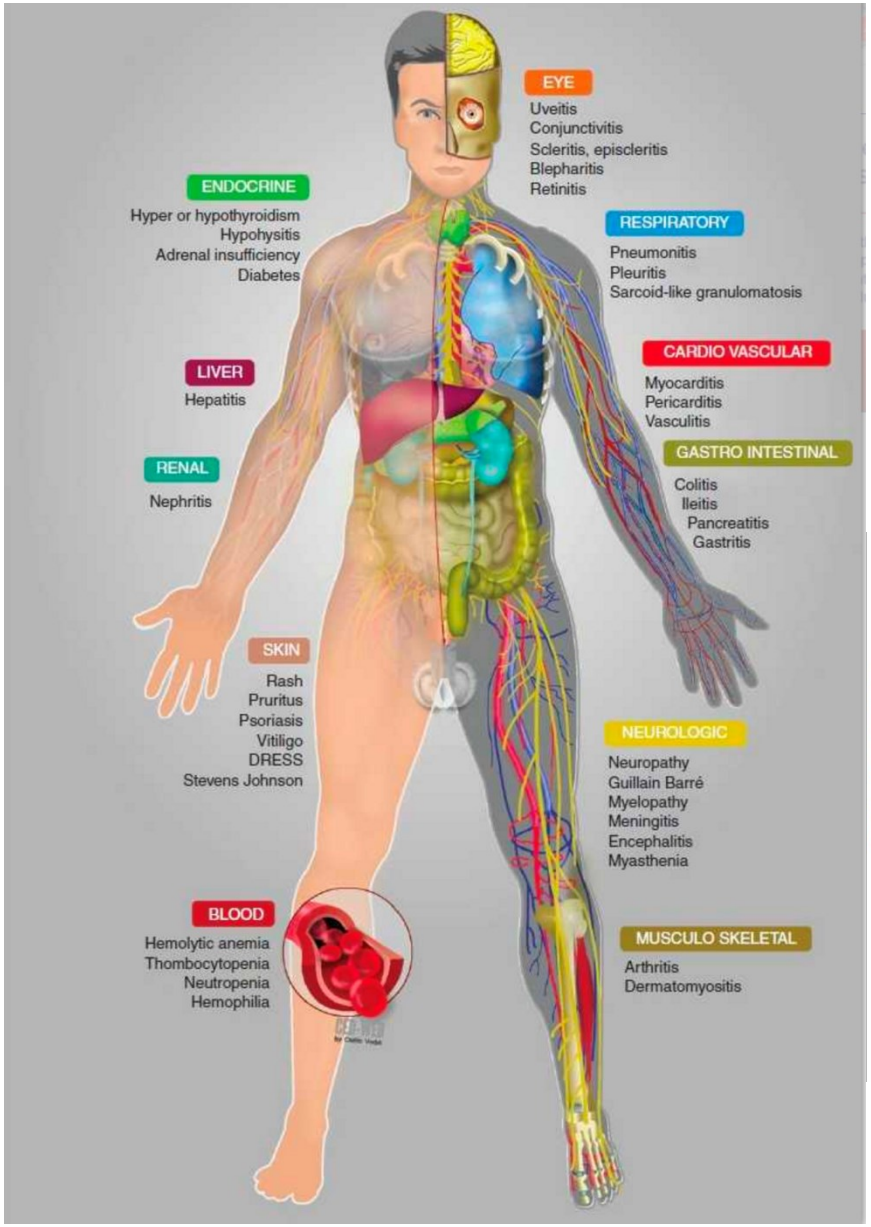
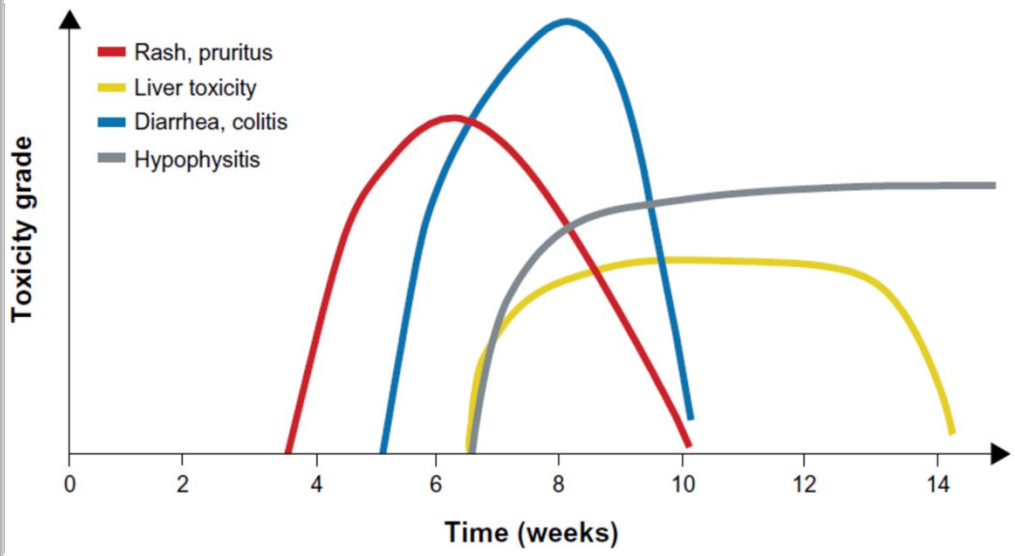


Table 1 Incidence of Immune-Related Adverse Events Associated With Ipilimumab and Pembrolizumab

	Ipilimumab (n = 1,498)[8] (%)		Pembrolizumab (n = 411)[39] (%)	
Toxicity	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
GI (eg, enterocolitis)	33	9.1	1	< 1
Pneumonitis	< 1	< 1	2.9	< 1
Hepatitis	1.6	1.1	< 1	< 1
Dermatologic	45	2.6	11–30	0
Hypophysitis	2.7	2.1	< 1	< 1
Thyroiditis	1.8	< 1	9.5	< 1
Nephritis	< 1	< 1	< 1	< 1



Champiat et al. Annals of Oncology 201
Tepley et al. Oncology 2014
Weber et al. JCO 2015

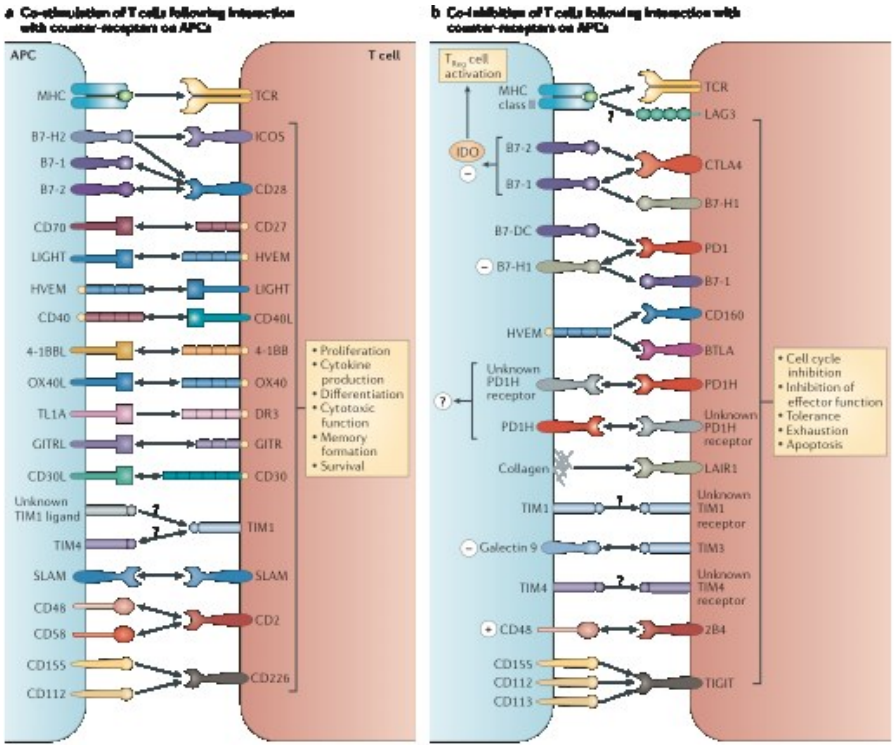
Cancer Immunotherapy| Immunotoxicity

- **Unless there is a good alternative diagnosis for inflammation, symptoms should be considered autoimmune in nature and treated as such.**
- Most irAE are reversible provided vigilant monitoring and early treatment
  - *excludes most endocrinopathies which are rarely reversible
- Detailed treatment guidelines for management of irAE exist

  eg. **Management of Immune-related adverse events in patients treated with immune checkpoint inhibitor therapy (ASCO Clinical Practice Guideline, JCO Feb 2018)**

Improving on the efficacy of single-agent PD-1

- Combinations with other checkpoint inhibitors
- Combinations 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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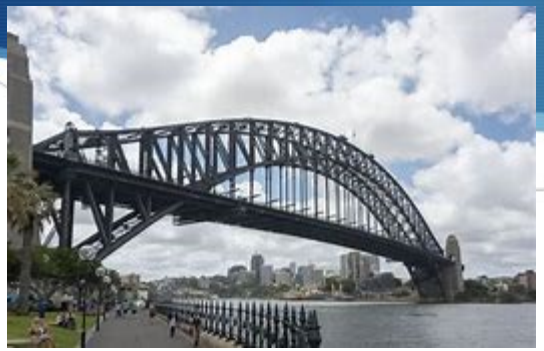
ABSTRACT

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.

Immunotherapy changing lives



Climbing the Sydney Harbour Bridge