IMMUNOTHERAPY IN THE TREATMENT OF CERVIX CANCER

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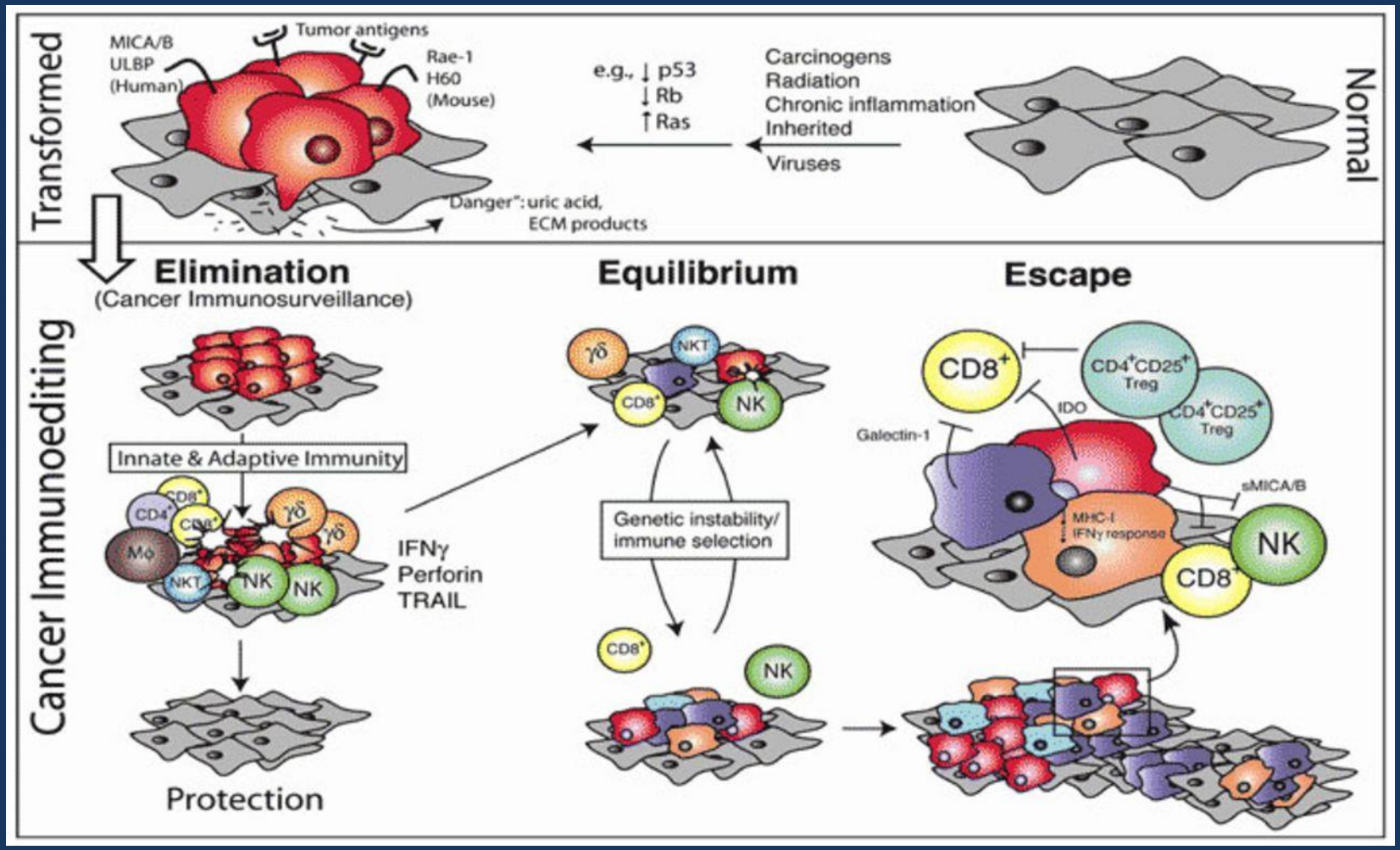
Distinguishing "self" from "non-self"

- 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

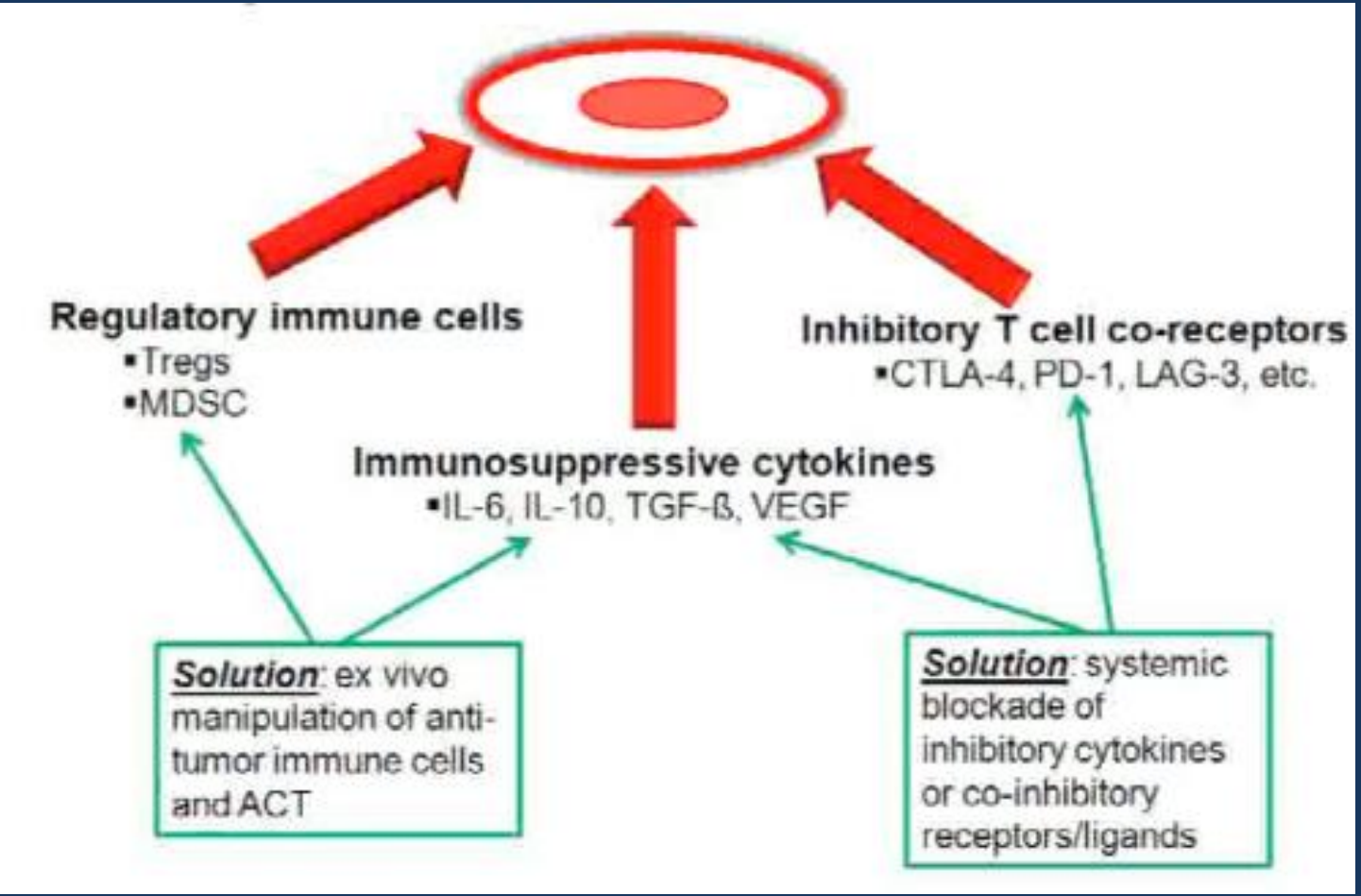
Immune System and Cancer

- 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

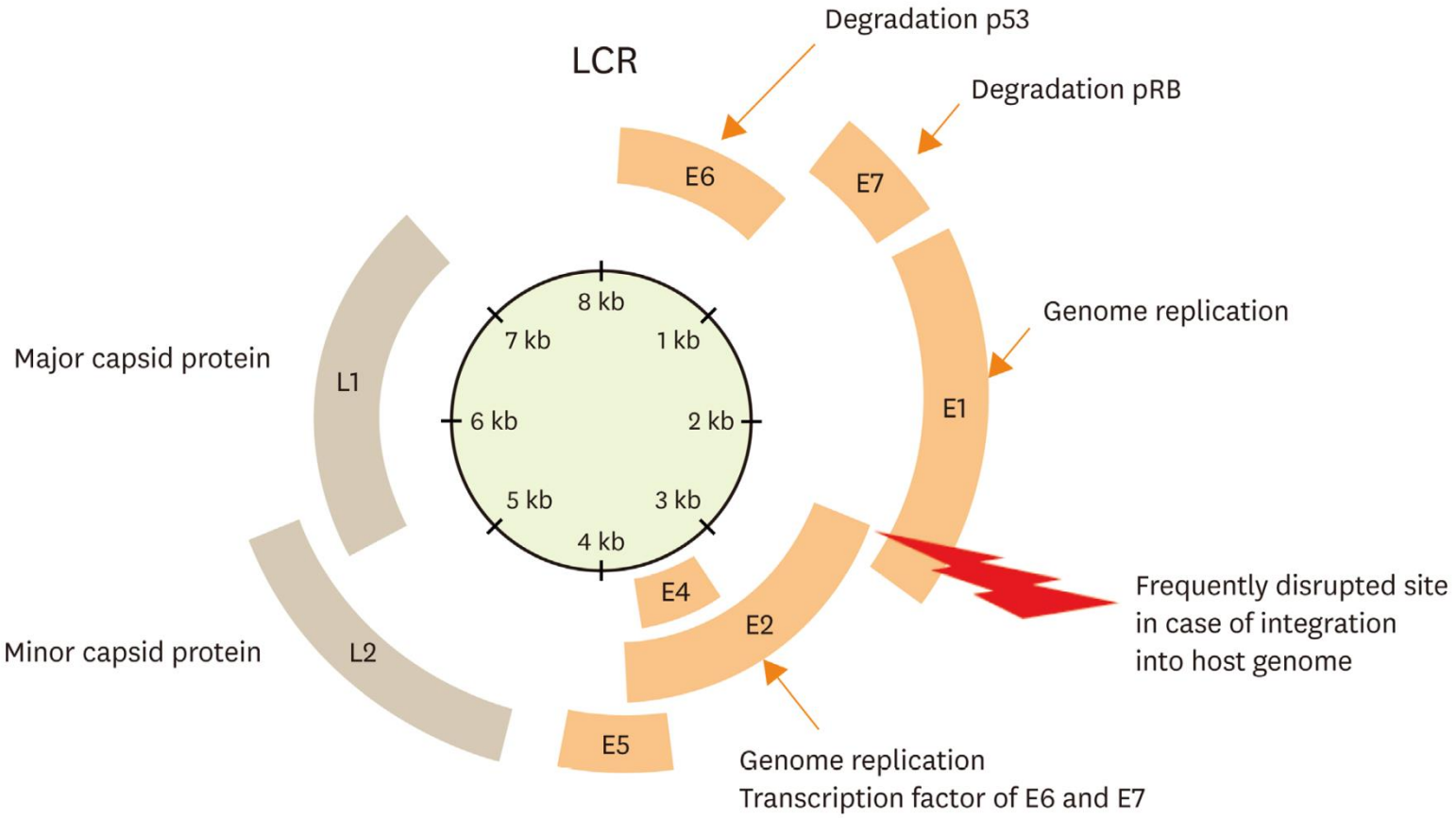
Goal is to ***overcome tolerance***

Immune Tolerance

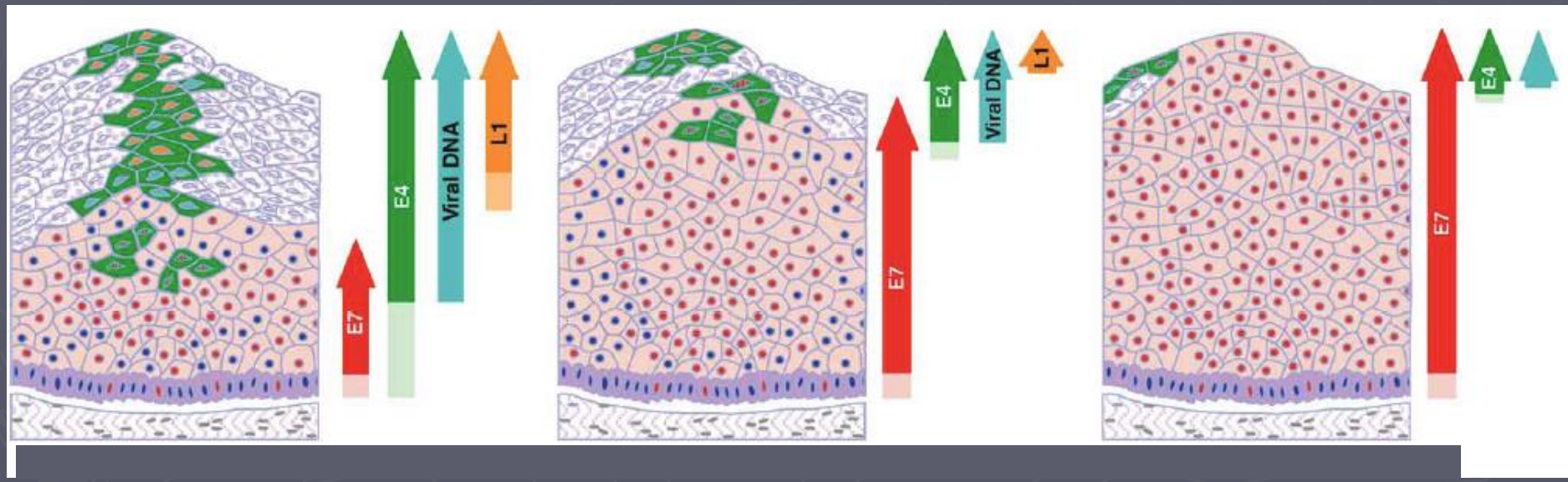


Topalian ASCO 2012

Cervix cancer as a target for immunotherapy: HPV



Progression to Cancer is Accompanied by Deregulation of Viral Gene Expression

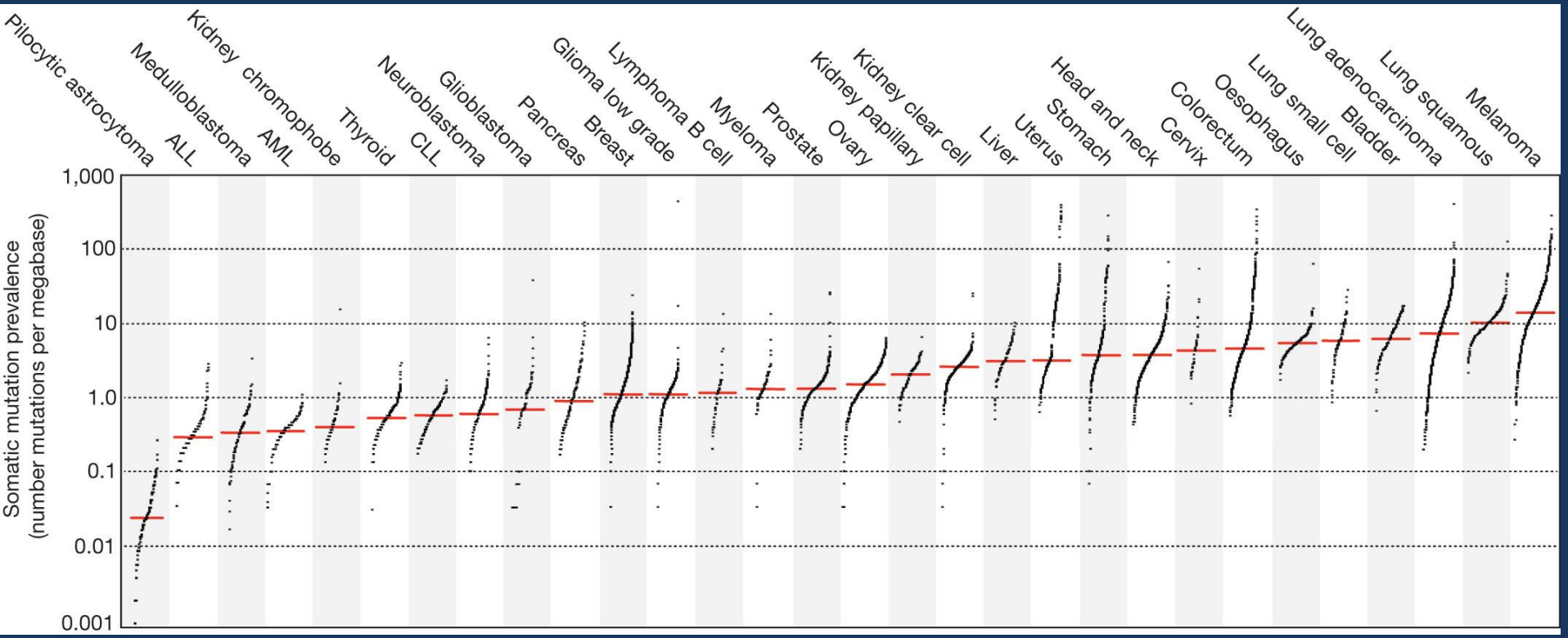


Doorbar, J Clin Virol 32:7-15, 2005

<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.

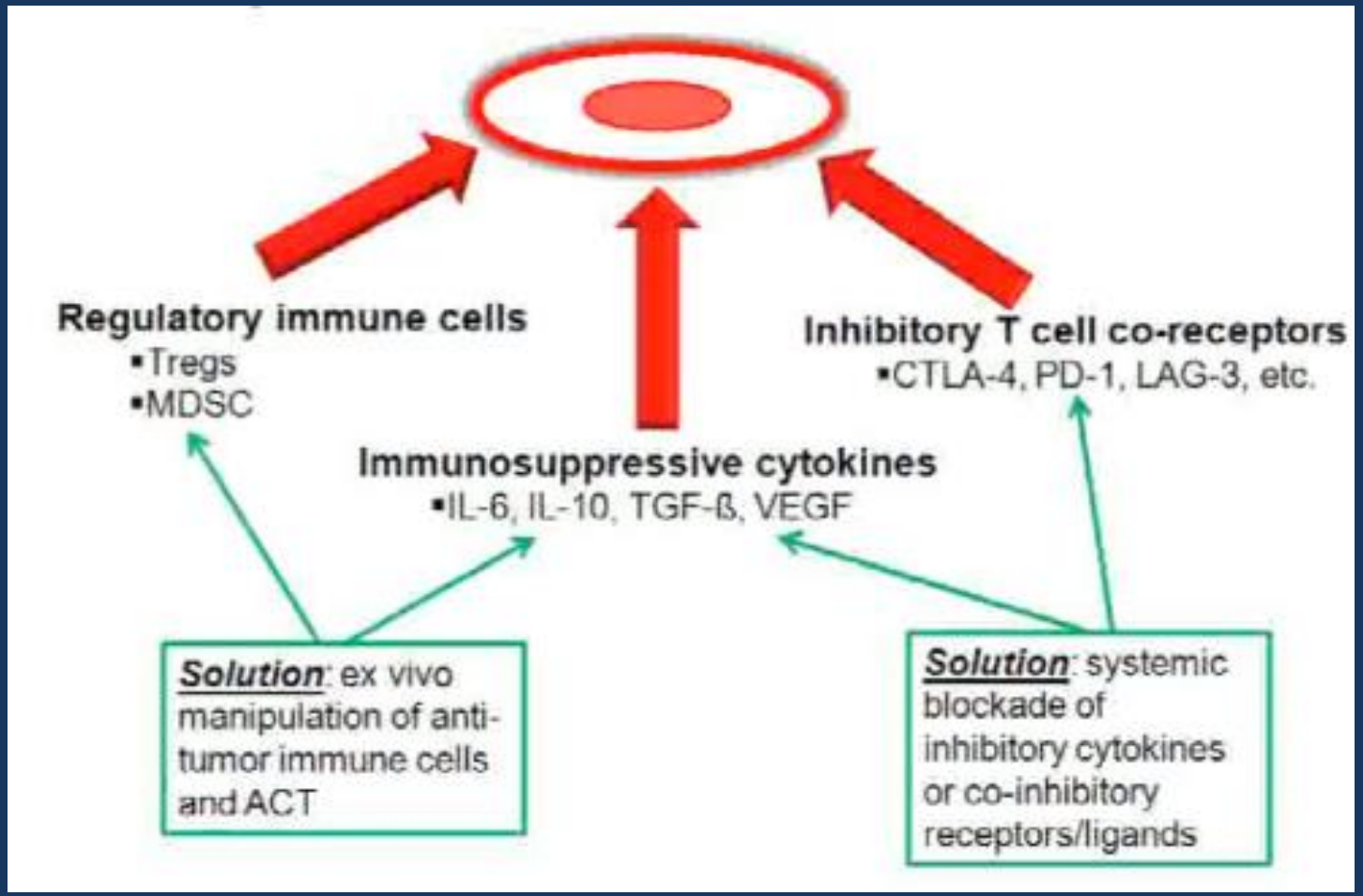
Mutation Burden



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

Alexandrov Nature 2013

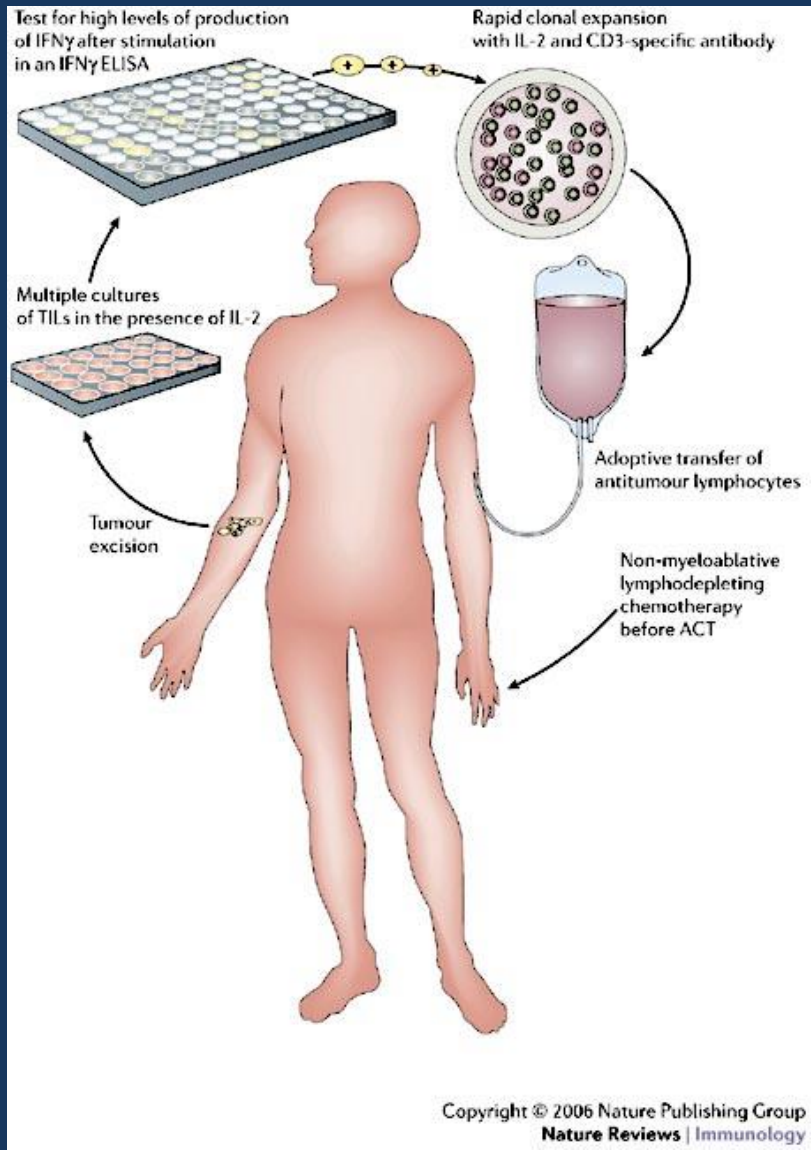
Immune Tolerance



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

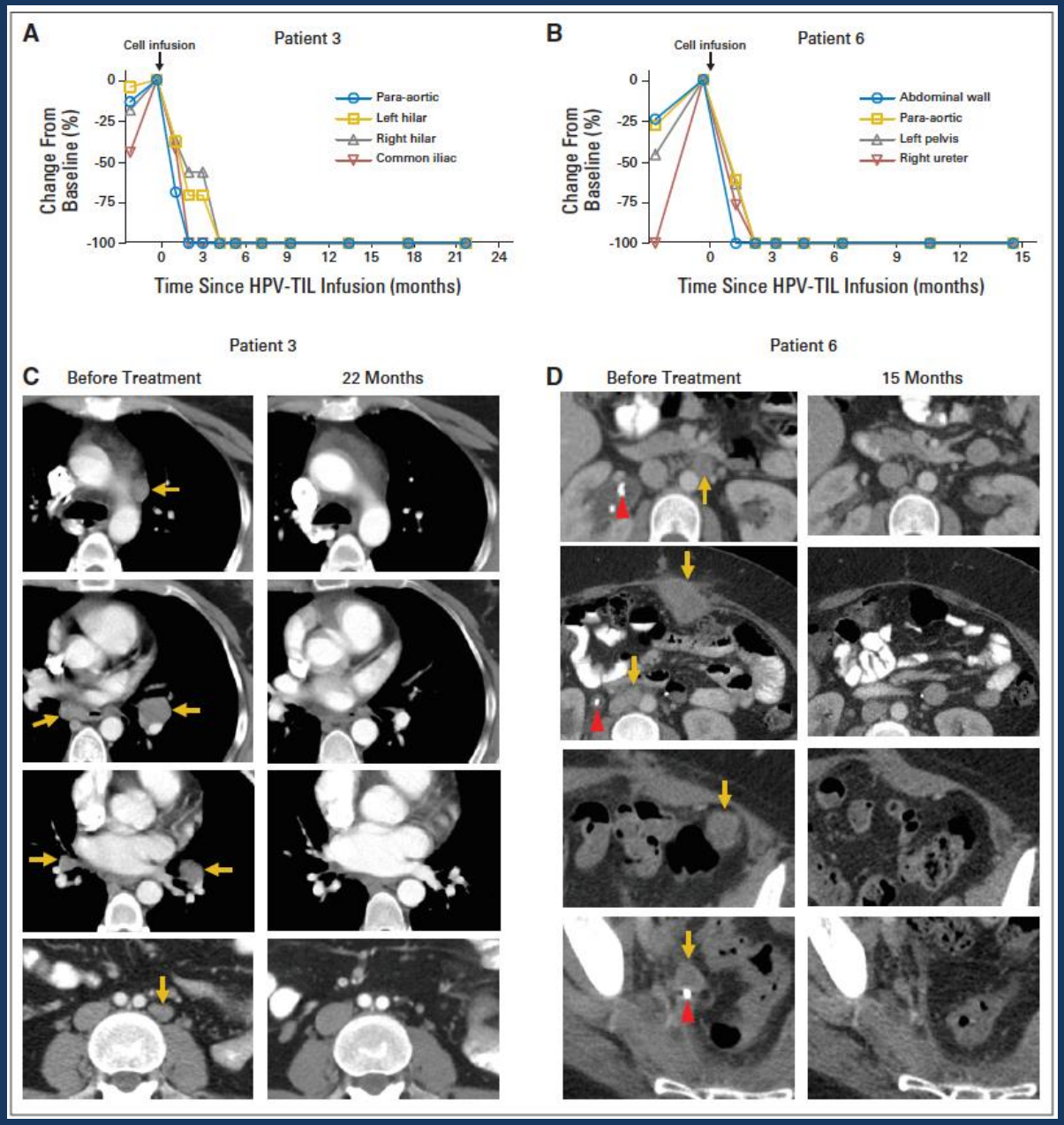
Purpose
Metastatic cervical cancer is a prototypical chemotherapy-refractory epithelial malignancy for which better treatments are needed. Adoptive T-cell therapy (ACT) is emerging as a promising cancer treatment, but its study in epithelial malignancies has been limited. This study was conducted to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

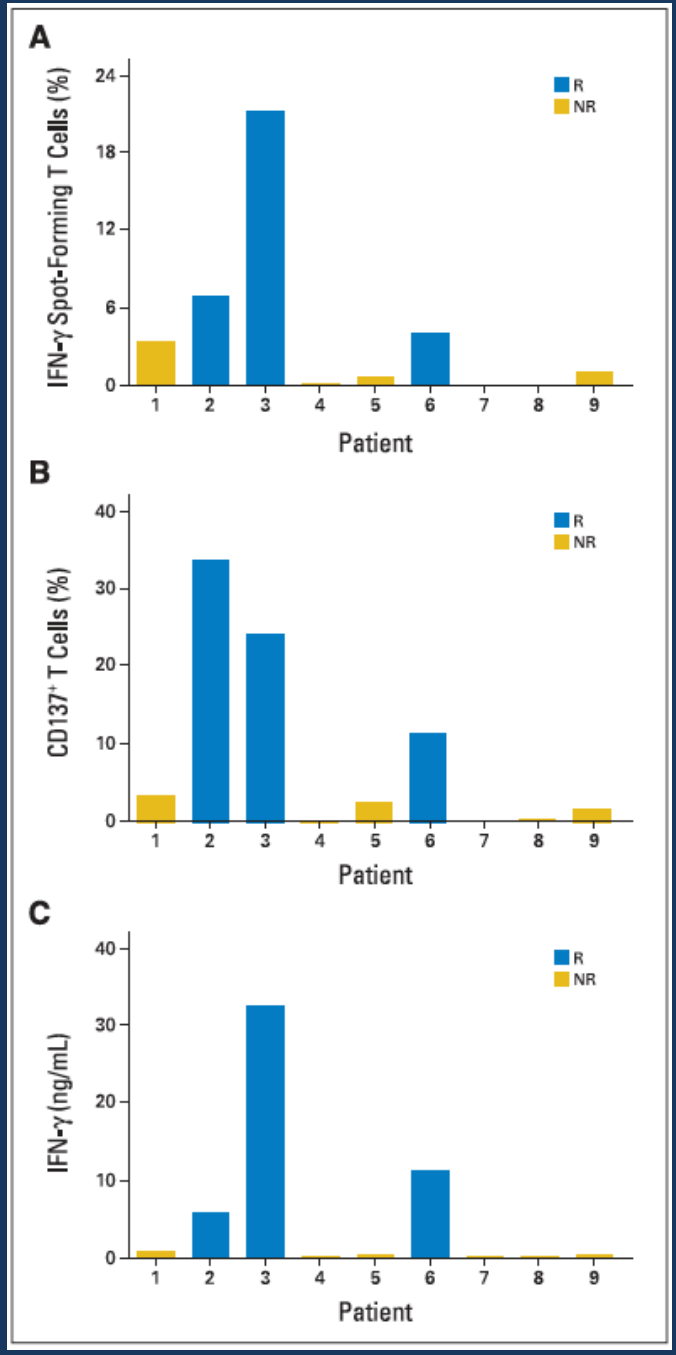
Patients and Methods
Patients enrolled onto this protocol were diagnosed with metastatic cervical cancer and had previously received platinum-based chemotherapy or chemoradiotherapy. Patients were treated with a single infusion of tumor-infiltrating T cells selected when possible for human papillomavirus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

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

▼

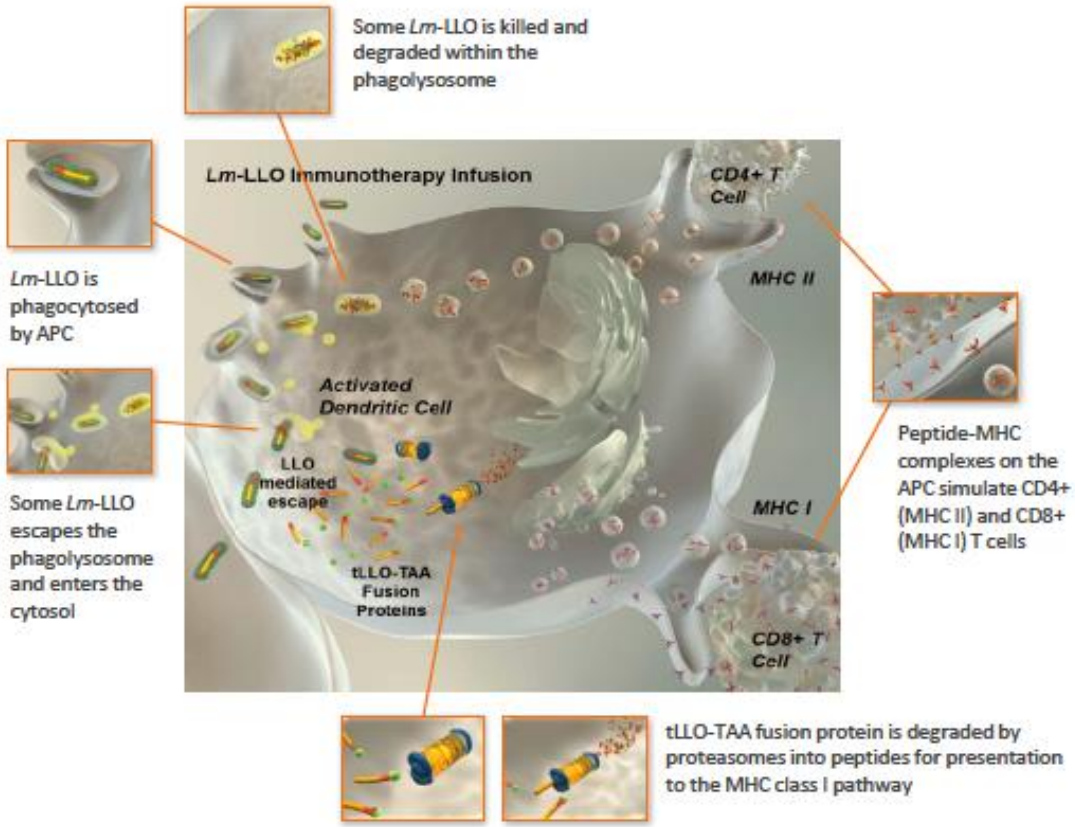
Lm-LLO expresses LLO-TAA fusion protein, which is processed by stimulated APC and activates TAA-specific T-cells

▼

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

▼

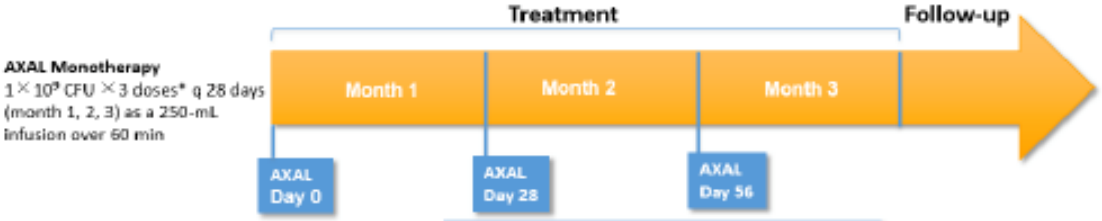
Immune activation can overcome checkpoint inhibition and negative regulators of cellular immunity



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)

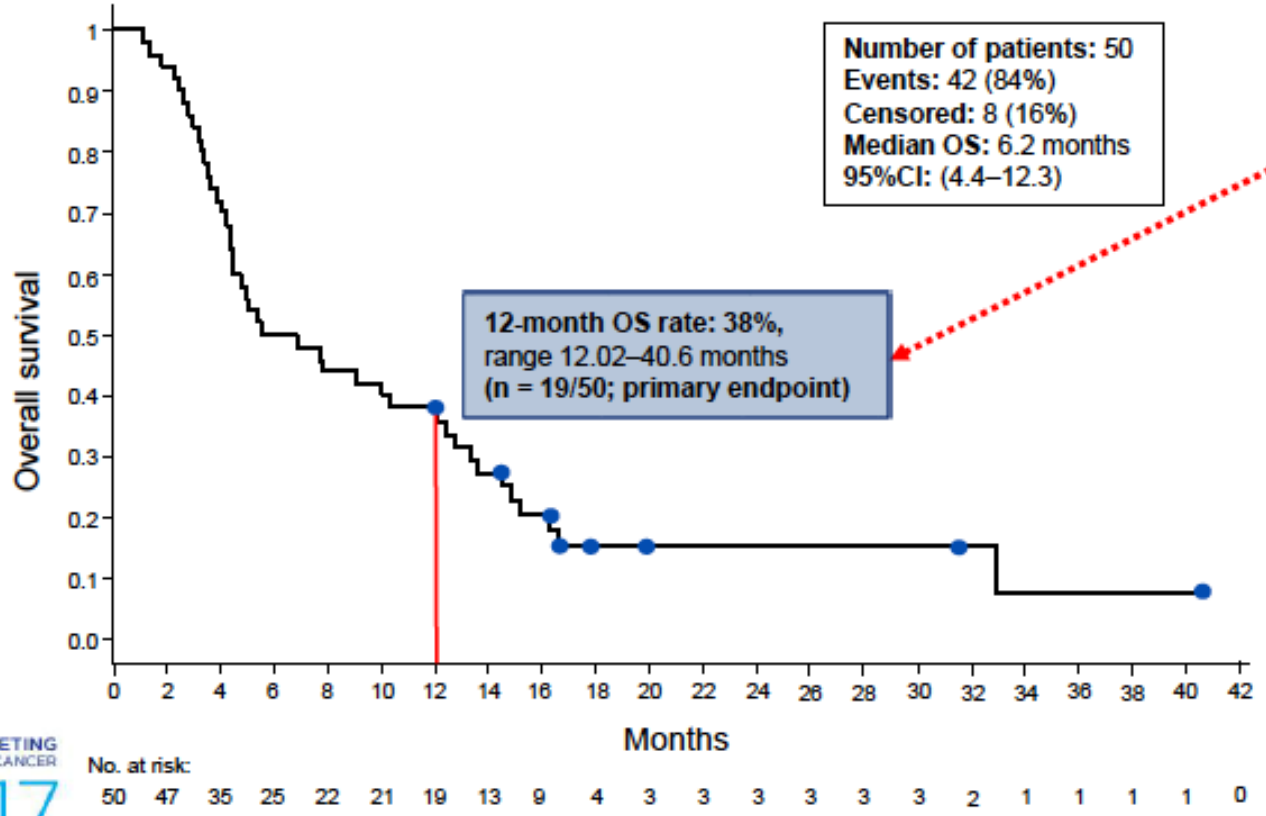


Co-primary Endpoints:
- 12-month survival rate
- Tolerability/safety of AXAL

Secondary Endpoints:
- PFS
- OS
- ORR

†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.

12-month and median overall survival



- Represents a 52% improvement vs logistic model-predicted milestone survival rate of 24.5%
- The probability of this survival advantage being detected by chance vs a true treatment effect was 0.02
- 8 patients remain alive as of January 31, 2017

CI, confidence interval; OS, overall survival.

AIM2CERV/GOG 3009

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

- High Risk, Locally Advanced Cervical Cancer
- FIGO Stage I-II with positive pelvic nodes
- FIGO Stage III-IVA
- Any Figo Stage with para-aortic nodes

Cisplatin (at least 4 wk exposure) and Radiation (minimum 40Gy external beam radiation therapy)

RANDOMIZE

N= 450

Reference Group

Placebo IV Up to 1 yr

Treatment Group

ADXS-HPV (1×10^9 cfu) Up to 1 yr

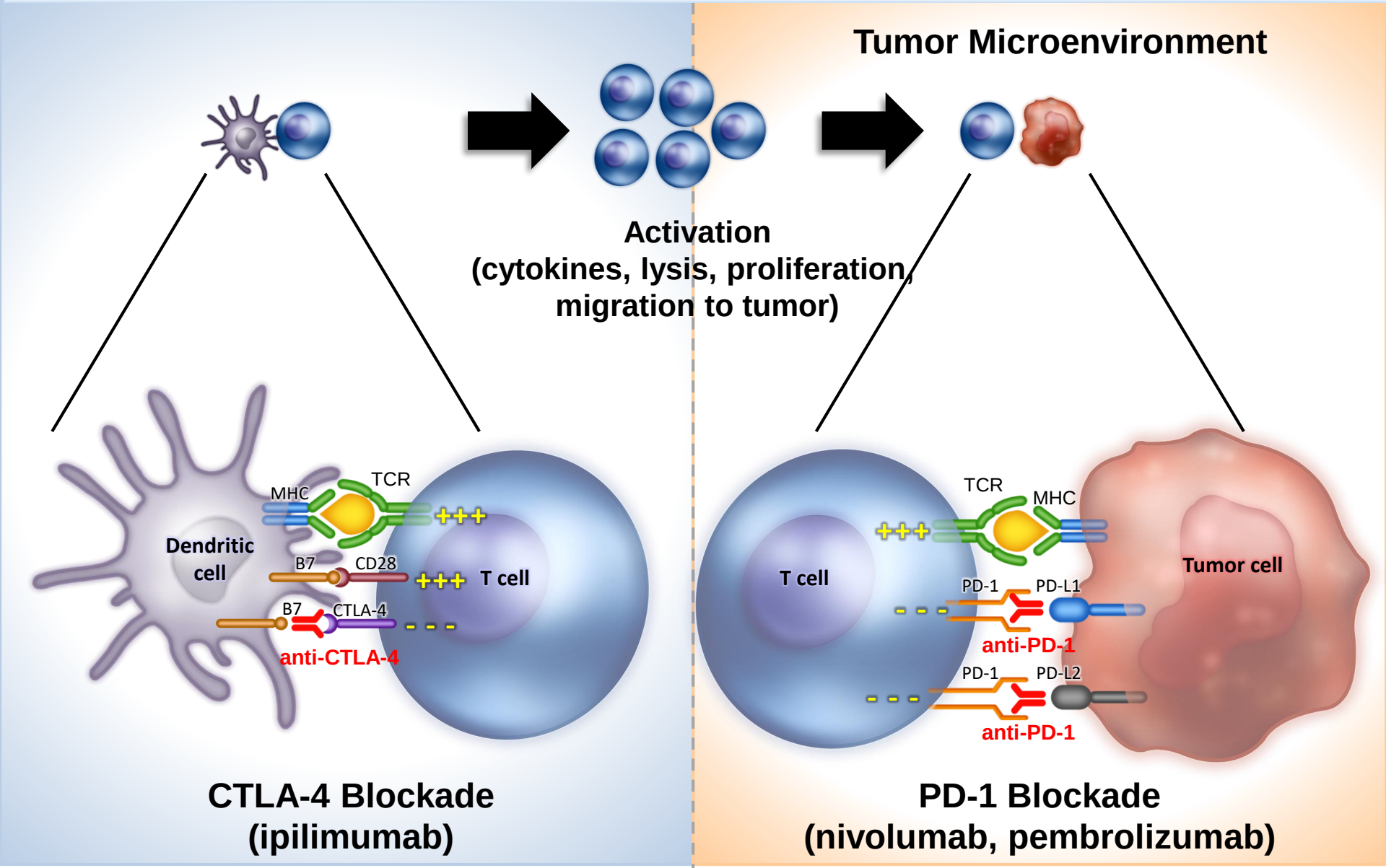
Follow-up for Overall Survival

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

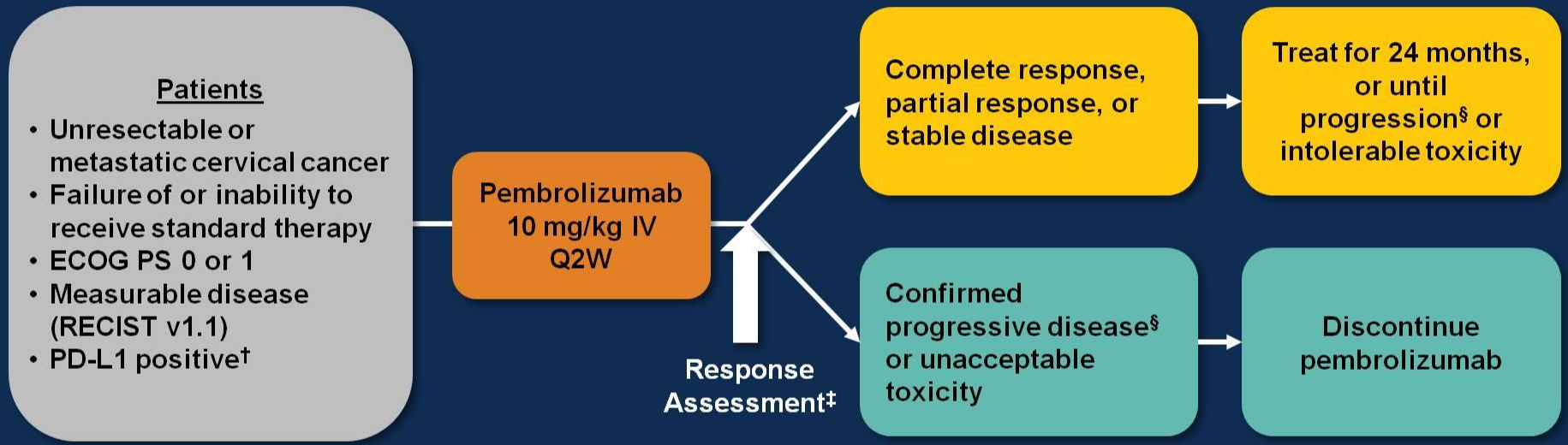


Ipilimumab in cervix cancer: Phase 1/2

- 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

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)

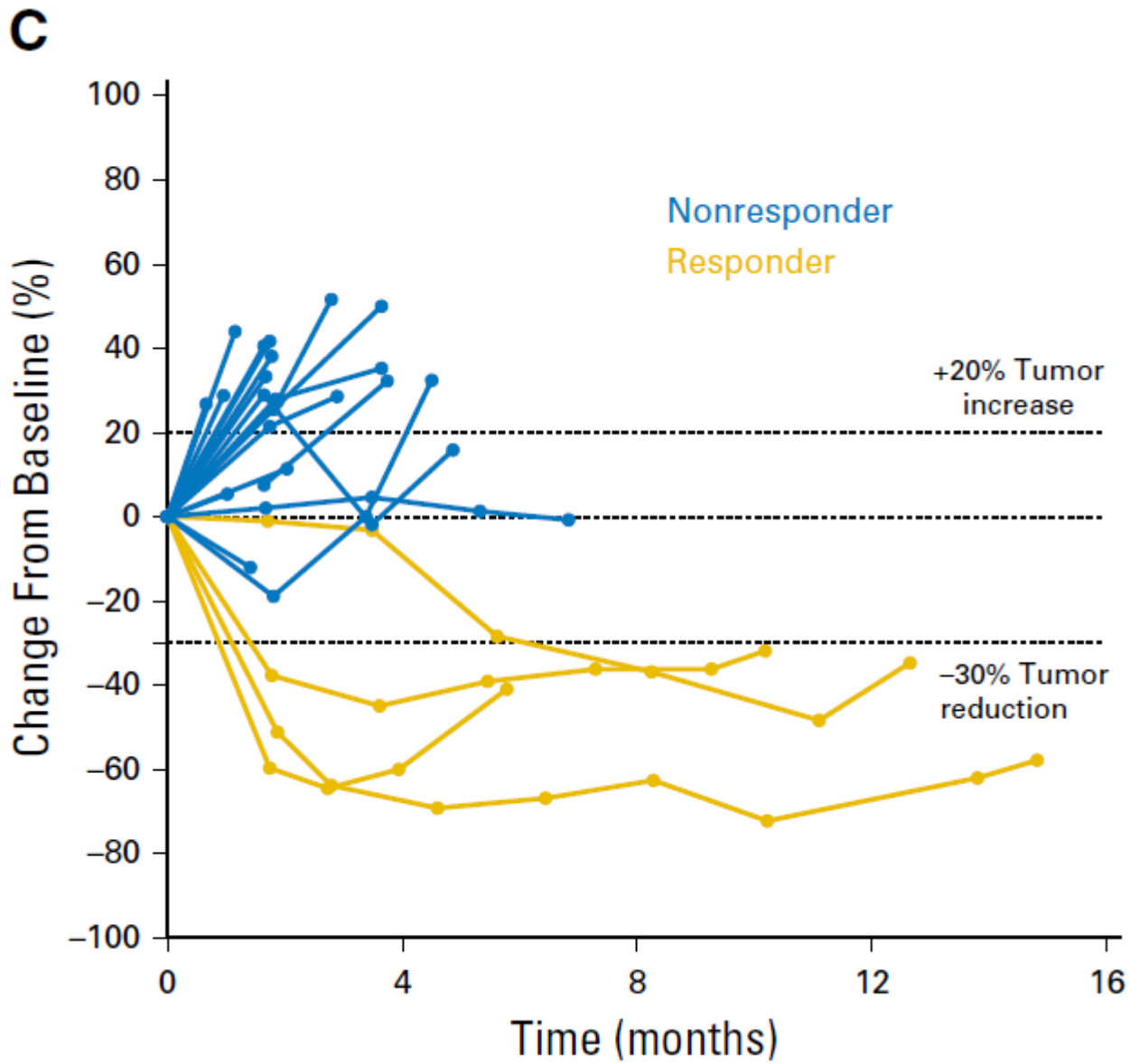
Characteristic, n (%)	N = 24
Prior radiotherapy	23 (96)
Prior lines of therapy for advanced disease	
1	9 (38)
2	6 (25)
≥3	9 (38)
Prior platinum	23 (96)
Prior bevacizumab	10 (42)

Data cutoff date: Feb 17, 2016.

Antitumor Activity (RECIST v1.1, Investigator Review)

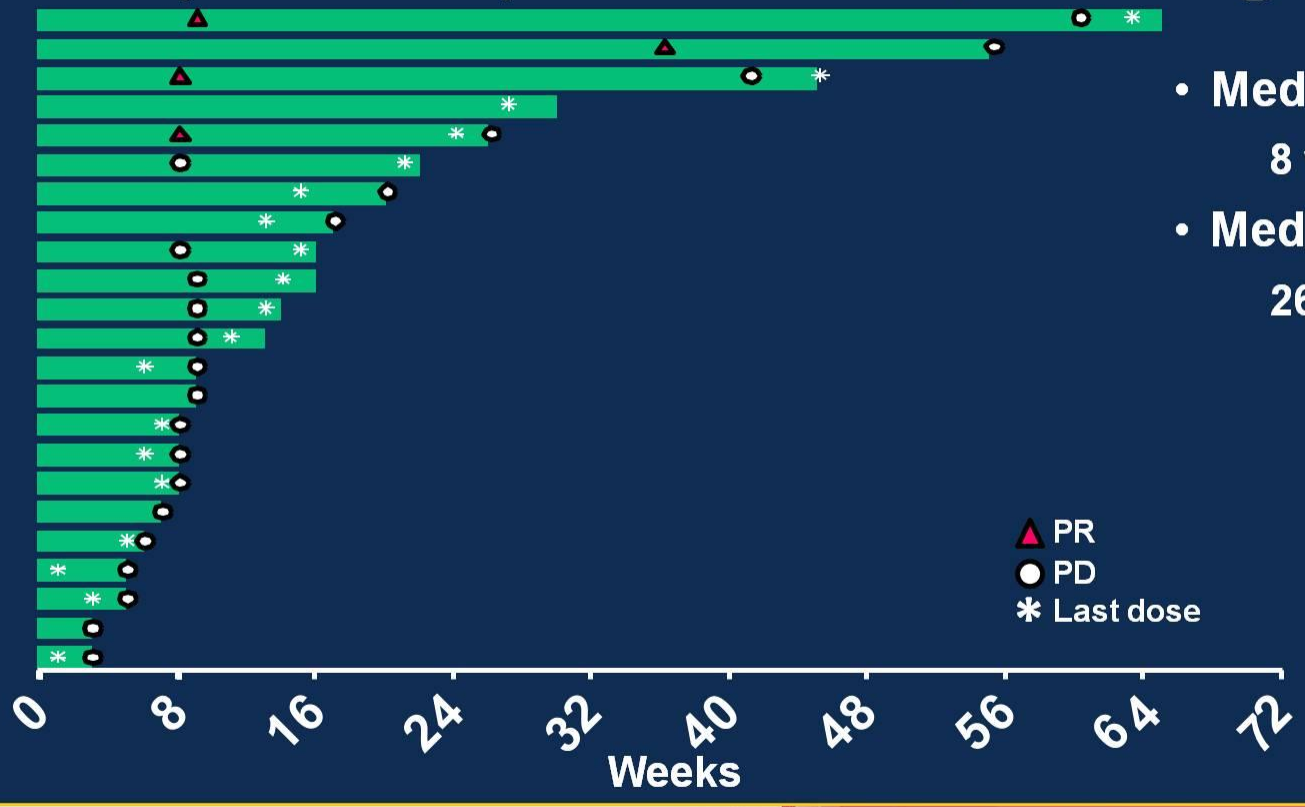
	N = 24		
	n	%	95% CI
ORR†	**4**	**17**	**5–37**
Partial response	4	17	5–37
Stable disease	3	13	3–32
Progressive disease	16	67	45–84
No assessment‡	1	4	<1–21

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.



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

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.

Toxicities as expected with no new safety signals

Presented By Jean-Sebastien Frenel at 2016 ASCO Annual Meeting

Best Overall Response

CheckMate 358: Nivolumab Monotherapy in R/M Cervical, Vaginal, and Vulvar Cancers

	All patients (N = 24)	Cervical (n = 19)	Vaginal/ Vulvar (n = 5)
Best overall response, n (%)			
Complete response	1 (4.2)	1 (5.3)	0
Partial response	4 (16.7)	4 (21.1)	0
Stable disease	12 (50.0)	8 (42.1)	4 (80.0)
Progressive disease	7 (29.2)	6 (31.6)	1 (20.0)
ORR, n (%) [95% CI]	5 (20.8) [7.1, 42.2]	5 (26.3) [9.1, 51.2]	0 [0.0, 52.2]
Disease control rate, n (%)	17 (70.8)	13 (68.4)	4 (80.0)
Duration of response, median (range), months	NR[a] (0.0–5.8+)	NR[a] (0.0–5.8+)	NA

[a]All responses ongoing as of the data cutoff
+ Ongoing response; CI = confidence interval; NA = not applicable; NR = not reached

PD-L1 unselected patients

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

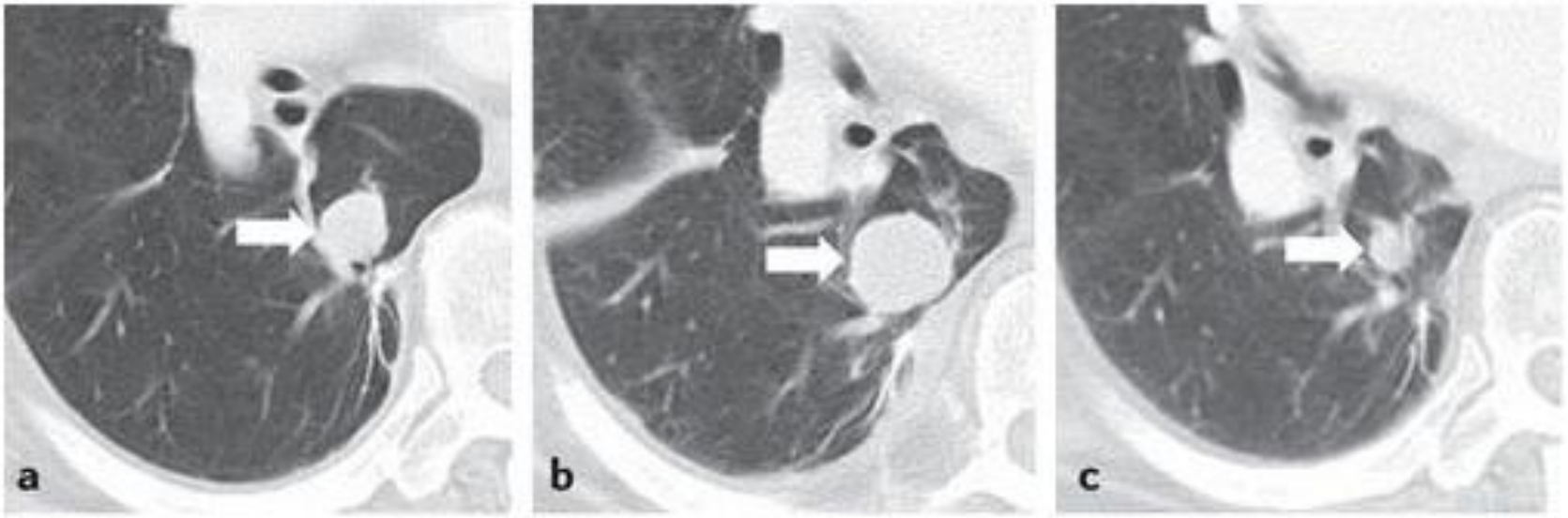
REGN2810, a fully human monoclonal antibody against programmed death-1 (PD-1)

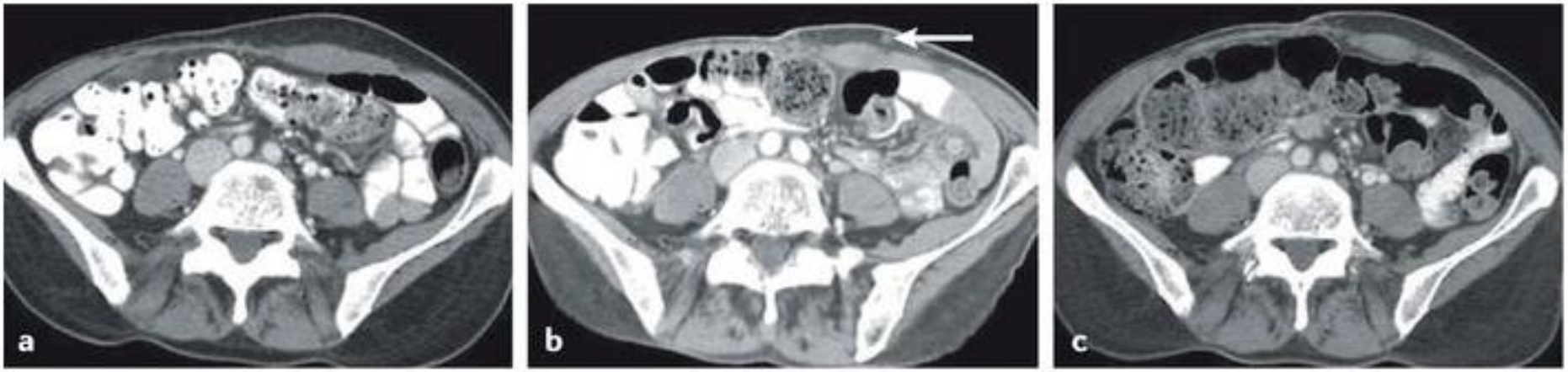
Cancer Immunotherapy| Immune Related Response Criteria

irRECIST (Immune-related Response Evaluation Criteria in Solid Tumours)	
Bidimensional measurement of tumour burden, with up to 15 index lesions	
Immune-related Complete Response	All lesions gone
Immune-related Partial Response	A decrease in tumour burden of 50%. Can have progression of some lesions or the appearance of new lesions as long as the TOTAL tumour burden meets the response criterion
Immune-related Stable Disease	Not meeting above criteria OR progressive disease
Immune-related Progressive Disease	An increase in tumour burden of 25% of more relative to the nadir Must be confirmed 4/52 later

Hodi et al. JCO 2016

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

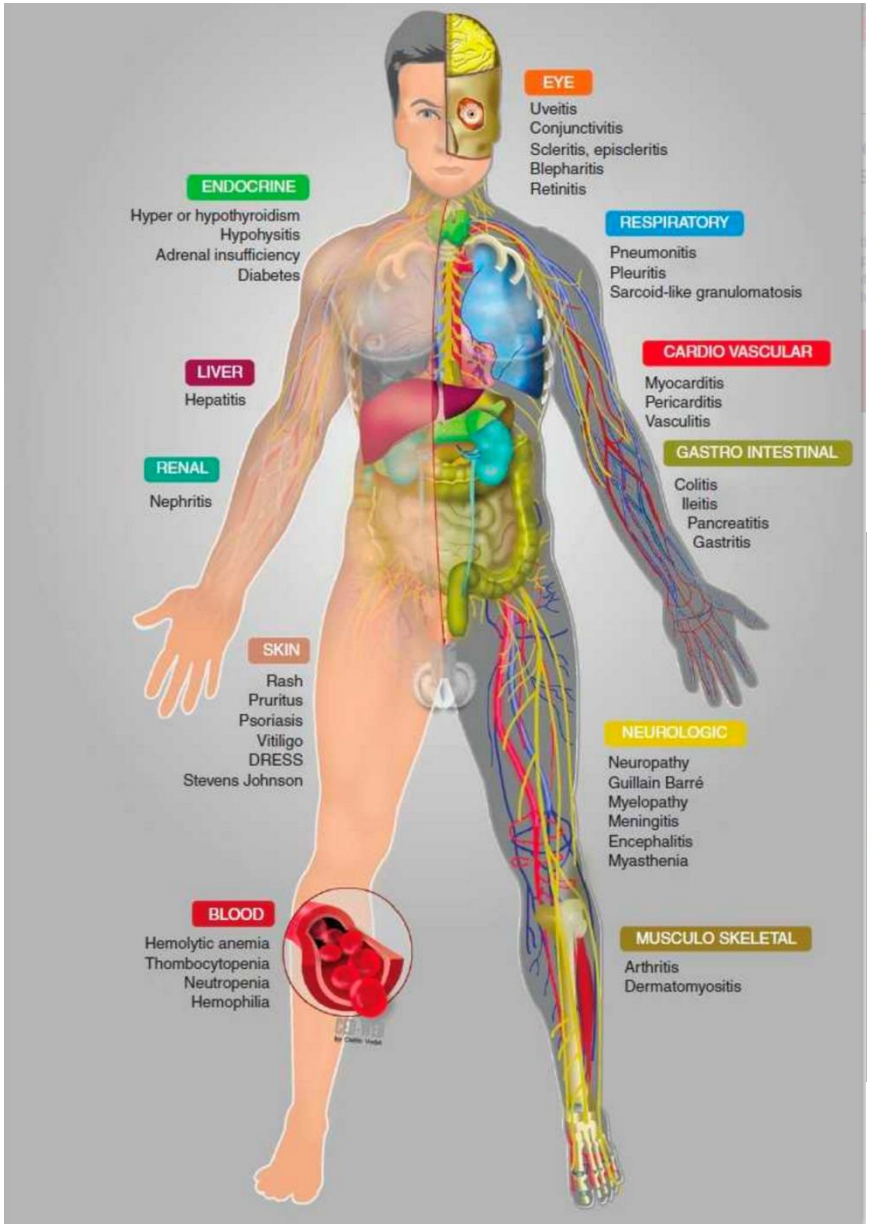
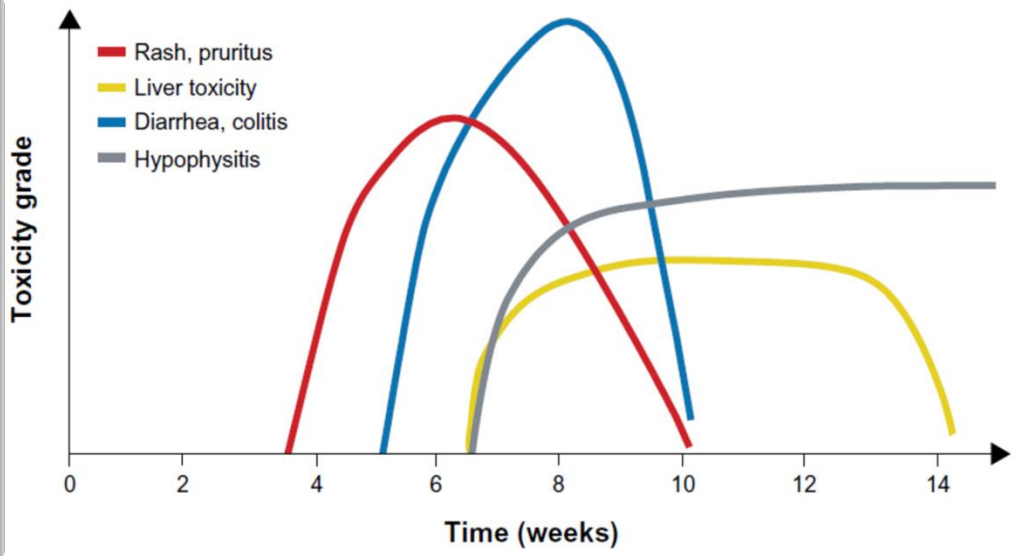


Table 1 Incidence of Immune-Related Adverse Events Associated With Ipilimumab and Pembrolizumab

	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)**

Choosing Candidate Biomarkers

- Candidate biomarkers include markers of a preexisting antitumor immune infiltrate that is observed in certain developing tumors
- Response to immunotherapy has been linked to an “inflamed” TME
  - Expression of PD-L1 and indoleamine, IFNγ production, M1 macrophages, and a robust T-cell infiltrate and fewer immunosuppressive cells such as M2 macrophages and myeloid-derived suppressor cells
- Gene signatures associated with T-cell–inflamed tumors have also predicted response
- Presence of tumor-infiltrating lymphocytes (TIL) in the TME is mechanistically a logical biomarker for T cell-based therapies

Mehnert *et al. CCR Focus.* 2017[7]

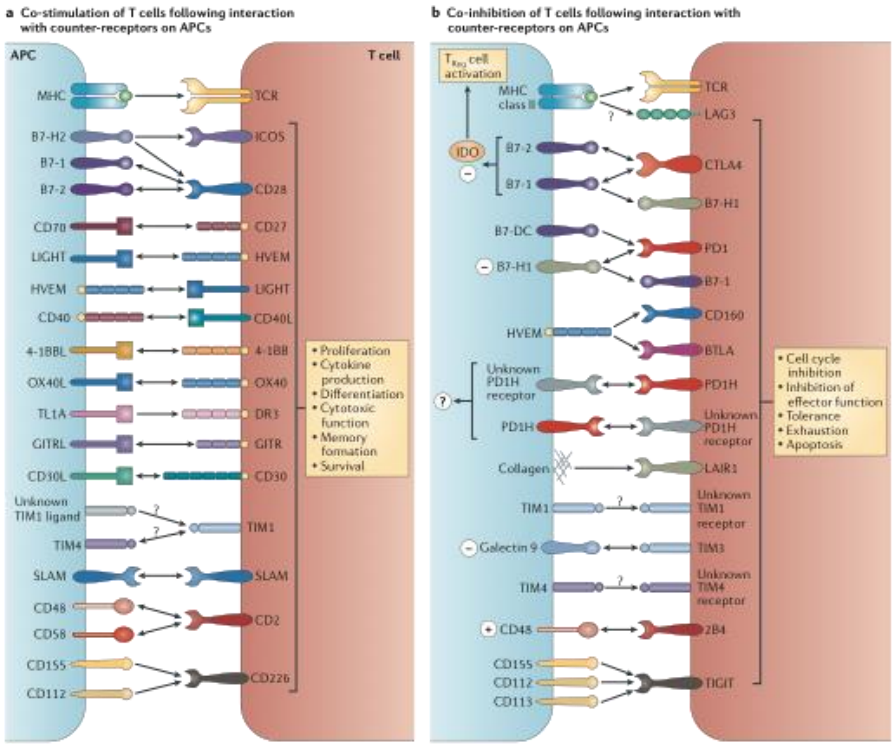
STILL A WORK IN PROGRESS! – PDL-1 staining probably not the answer

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

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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Radiation therapy

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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1		Unknown †	**Immunotherapy** of Recurrent **Cervical Cancers** Using Dendritic Cells (DCs)	• **Cervical Cancer**	• Biological: HPV16 E7 peptide-pulsed autologous DCs	• National Taiwan University Hospital Taipei, Taiwan
2		Recruiting	Combination of Cryosurgey and NK **Immunotherapy** for Recurrent **Cervical Cancer**	• Recurrent **Cervical Cancer**	• Device: Cryosurgery • Biological: NK **immunotherapy**	• Fuda cancer institute of Fuda cancer hospital Guangzhou, Guangdong, China
3		Completed	SGN-00101 **Immunotherapy** in Treating Patients With Grade III Cervical Intraepithelial **Neoplasia**	• **Cervical Cancer** • Precancerous Condition	• Biological: HspE7	• Albert Einstein Cancer Center at Albert Einstein College of Medicine Bronx, New York, United States • New York Weill Cornell Cancer Center at Cornell University New York, New York, United States
4		Completed	Advanced **Cervical Cancer** Trial in India	• **Cervical Cancer**	• Drug: Interferon, Retinoic Acid and radiation • Drug: Cisplatin and radiation	• Chittaranjan National Cancer Institute Kolkata, India
5		Unknown †	Panitumumab, Cisplatin, and Pelvic Radiation Therapy in Treating Patients With Stage IB, Stage II, or Stage III **Cervical Cancer**	• **Cervical Cancer**	• Biological: panitumumab • Drug: cisplatin • Radiation: brachytherapy • Radiation: external beam radiation therapy	• Innsbruck Universitaetsklinik Innsbruck, Austria

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