Ovarian Cancer: Contemporary Management & Clinical Trial Endpoint Considerations

Thomas J. Herzog, MD
Paul & Carolyn Flory Professor
Deputy Director, UC Cancer Institute
Vice Chair Quality & Safety, Dept Ob/Gyn
University of Cincinnati

Disclosures

Scientific Advisory Board:

AZ, Caris, Clovis, Genentech, J & J, Tesaro

Strategies Targeting Hallmarks of Cancer

Sustaining proliferative signaling

EGFR inhibition

Evading growth suppressors

Cyclin-dependent kinase inhibition

Deregulating cellular energetic

Aerobic glycolysis inhibition

Avoiding immune destruction

Immune-activating anti-CTLA4 mAb

Resisting cell death

Proapoptotic BH3 mimetics

Enabling replicative immortality

Telomerase Inhibition

Genome instability & mutation

PARP inhibition

Tumor-promoting inflammation

Selective anti-inflammatory drugs

Inhibition of VEGF signaling

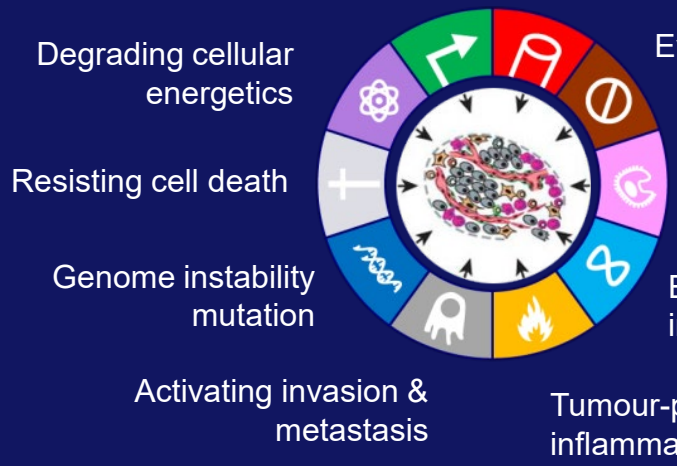
Inducing angiogenesis

Activating invasion & metastasis

Inhibition of HGF/c-Met

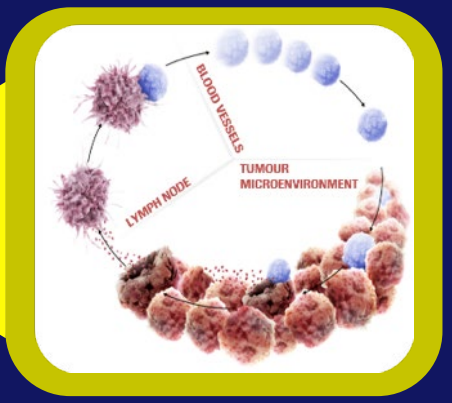
Hanahan and Weinberg. Cell. 2011;144(5):646-74.

Avoiding immune destruction is a hallmark of cancer



Avoiding immune destruction

Cancer-immunity cycle

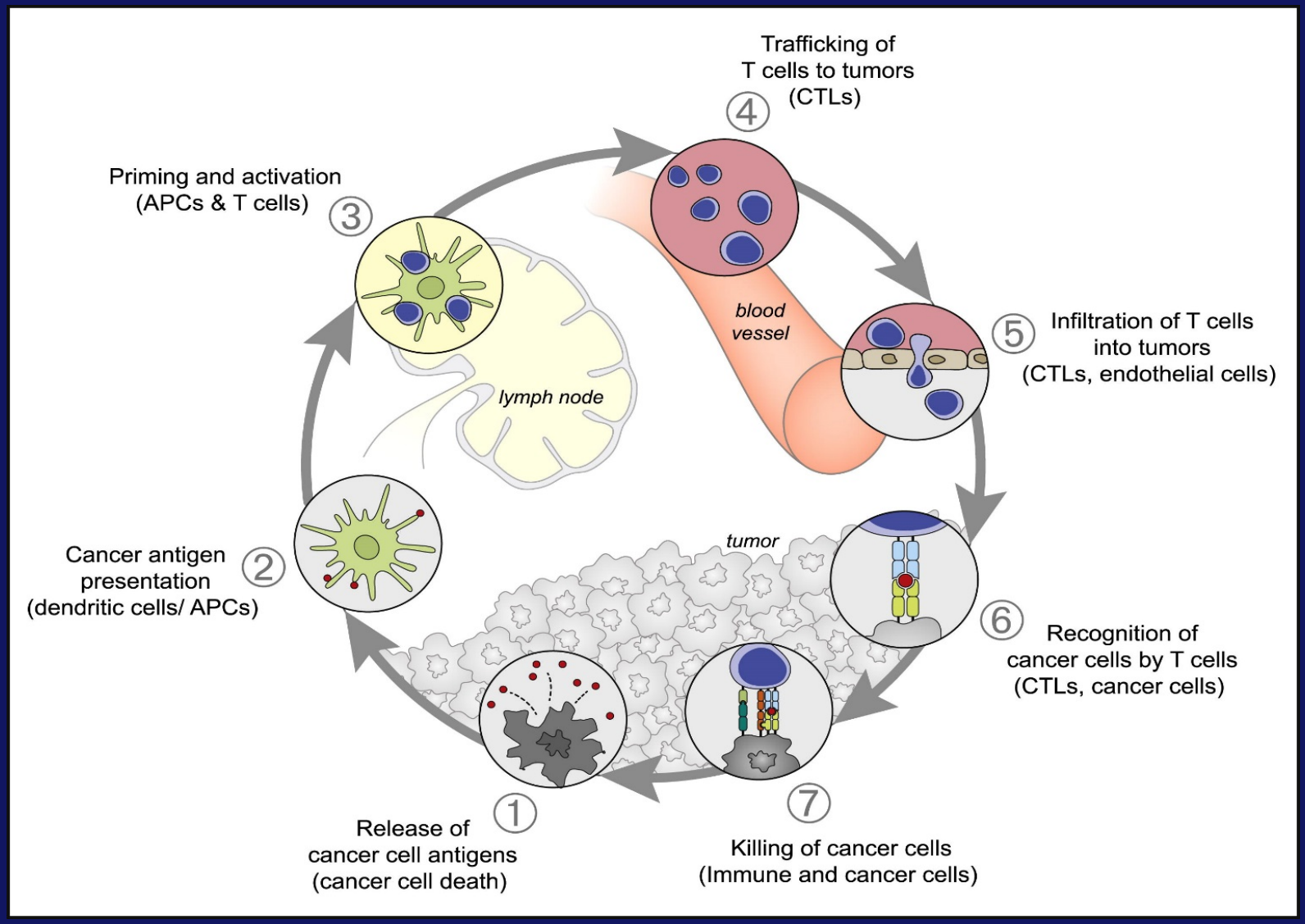


The cancer-immunity cycle describes the process by which the immune system recognises, targets and kills cancer cells

Tumors can inhibit the anti-tumour immune response by disrupting the balance of the cancer-immunity cycle via immune checkpoints[1,2]

1. Hanahan & Weinberg. Cell 2011; 2. Chen & Mellman. Immunity 2013

Cancer-Immunity Cycle



Immunity 2013 39, 1-10DOI: (10.1016/j.immuni.2013.07.012)

Key studies Establishing Immune Response in OC

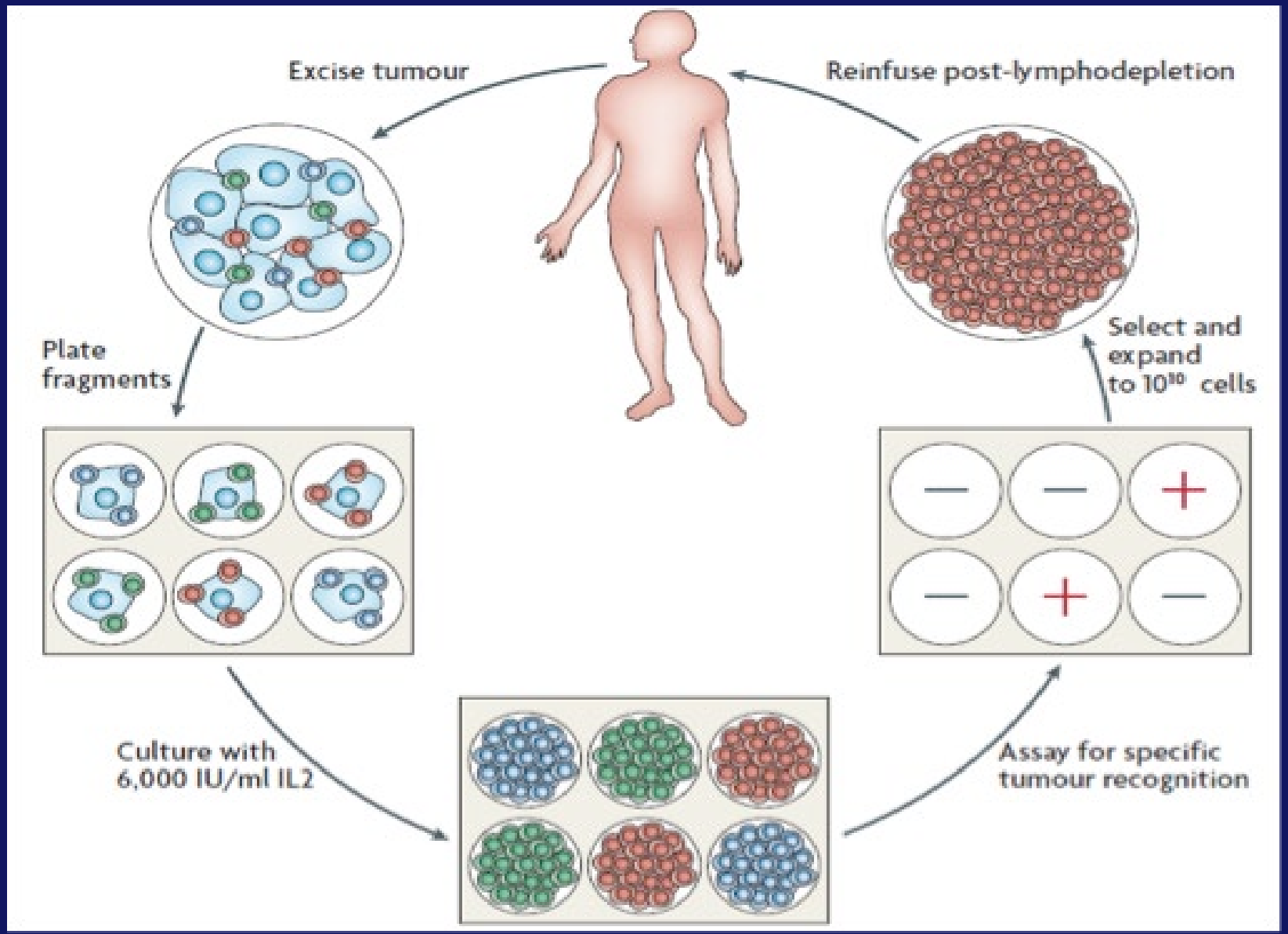
Reference	Number of patients	Immune cell type	Outcomes	Findings
Zhang et al.	186	CD3+ TILs	PFS, OS	Presence of TILs positively correlates with PFS, OS
Mariya et al.	122	CD3+, CD4+, CD8+ TILs	OS	CD8+ TIL presence correlates with platinum response
The Cancer Genome Atlas Group	489	Exome, mRNA, miRNA sequencing, somatic copy number analysis	NA	Immunoreactive subset of ovarian cancers identified by mRNA expression of chemokines and receptors
Curiel et al.	70	CD4+CD25+FOXP3+ Treg cells in ascites and tumor slices	OS	Tumor recruitment of immunosuppressive Tregs predicts decreased OS
Sato et al.	117	CD8+ TILs, CD4+TILs, CD4+ CD25+ FOXP3+ Tregs	OS	High CD8 TIL to Treg ratio associated with improved OS
Hamanishi et al.	70	Tumor cells expressing PD-L1, CD8+ TILs	OS	PD-L1 expression on tumors predicts decreased OS, and CD8 TILs are associated with improved OS

Turner et al. *Gynecologic Oncology,* 2016

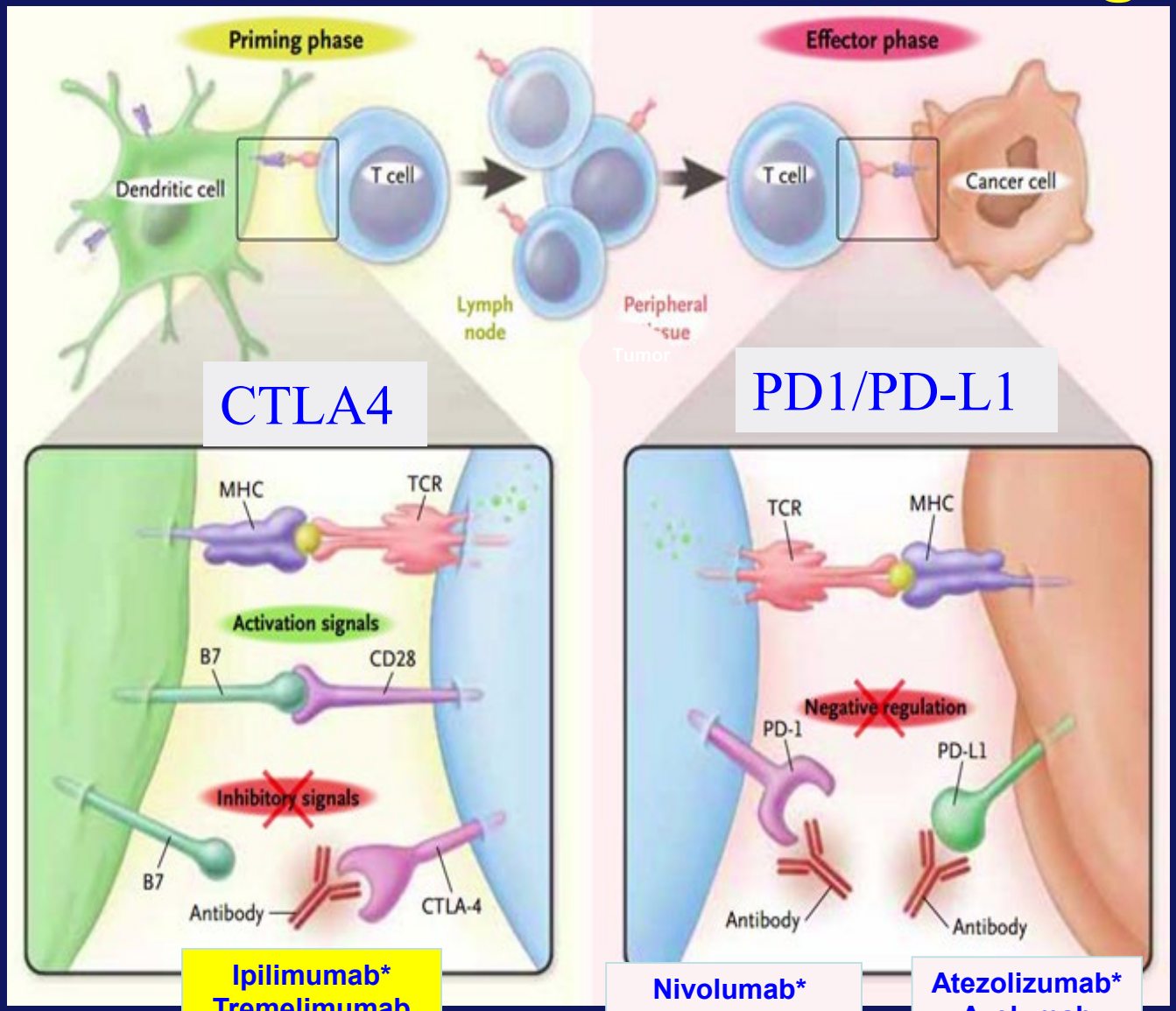
Antibody-drug Conjugates

- **IMGN-853** (anti-folate receptor): being tested in ovarian cancer and endometrial cancer
- **DMUC4064A** (anti-MUC16): ovarian cancer
- **DNIB0600A** (anti-NaPi2b): ovarian cancer
- **PF-06647263** (anti-EFNA4): ovarian cancer
- **BAY 94-9343** (anti-mesothelin): ovarian cancer

Ex vivo TIL Expansion



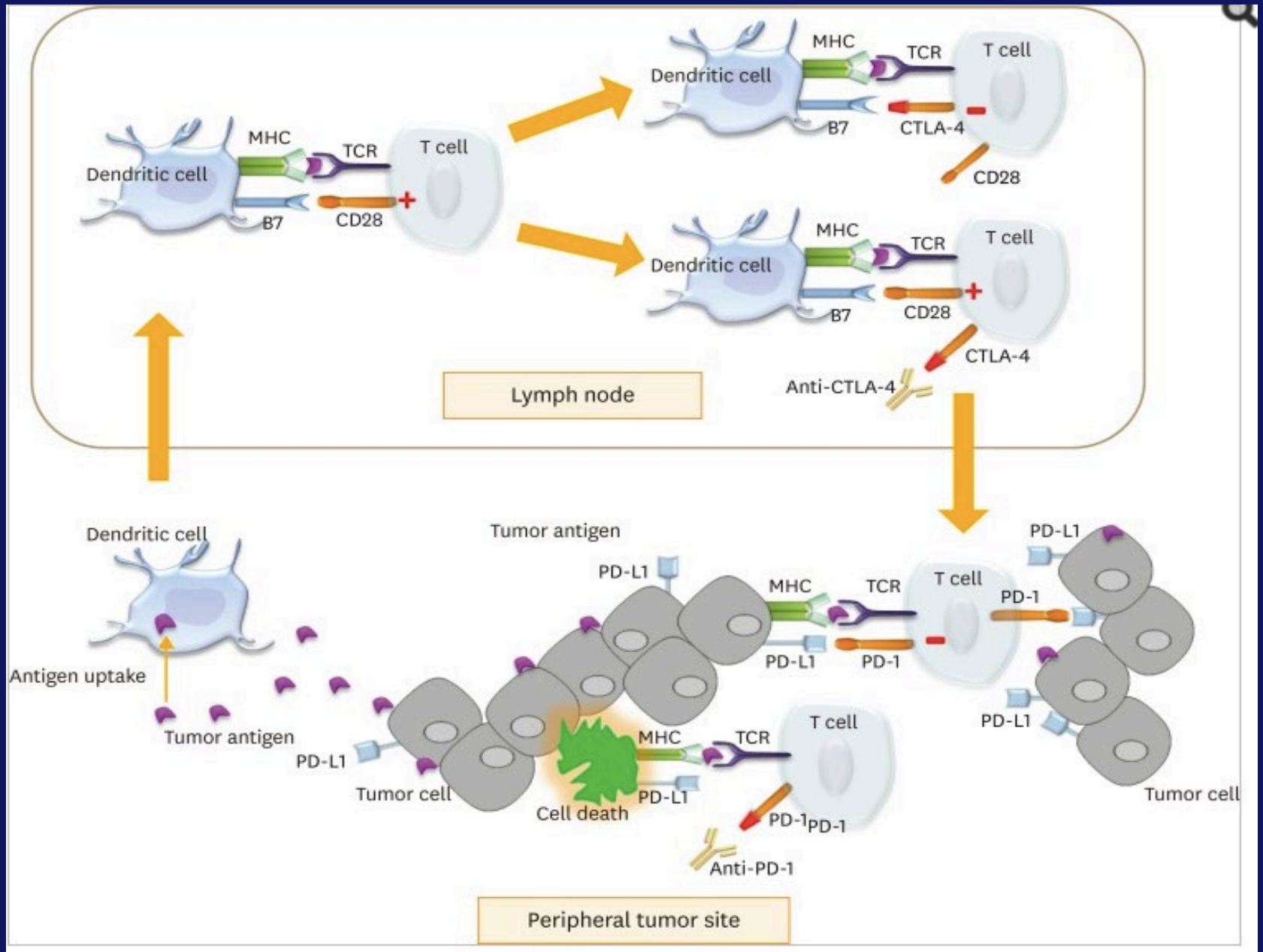
Blockade of PD-1/PD-L1 or CTLA-4 Signaling



* FDA-approved

Adapted from Ribas A. *N Engl J Med*. 2012;366(26):2517-2519.

Checkpoint Inhibition



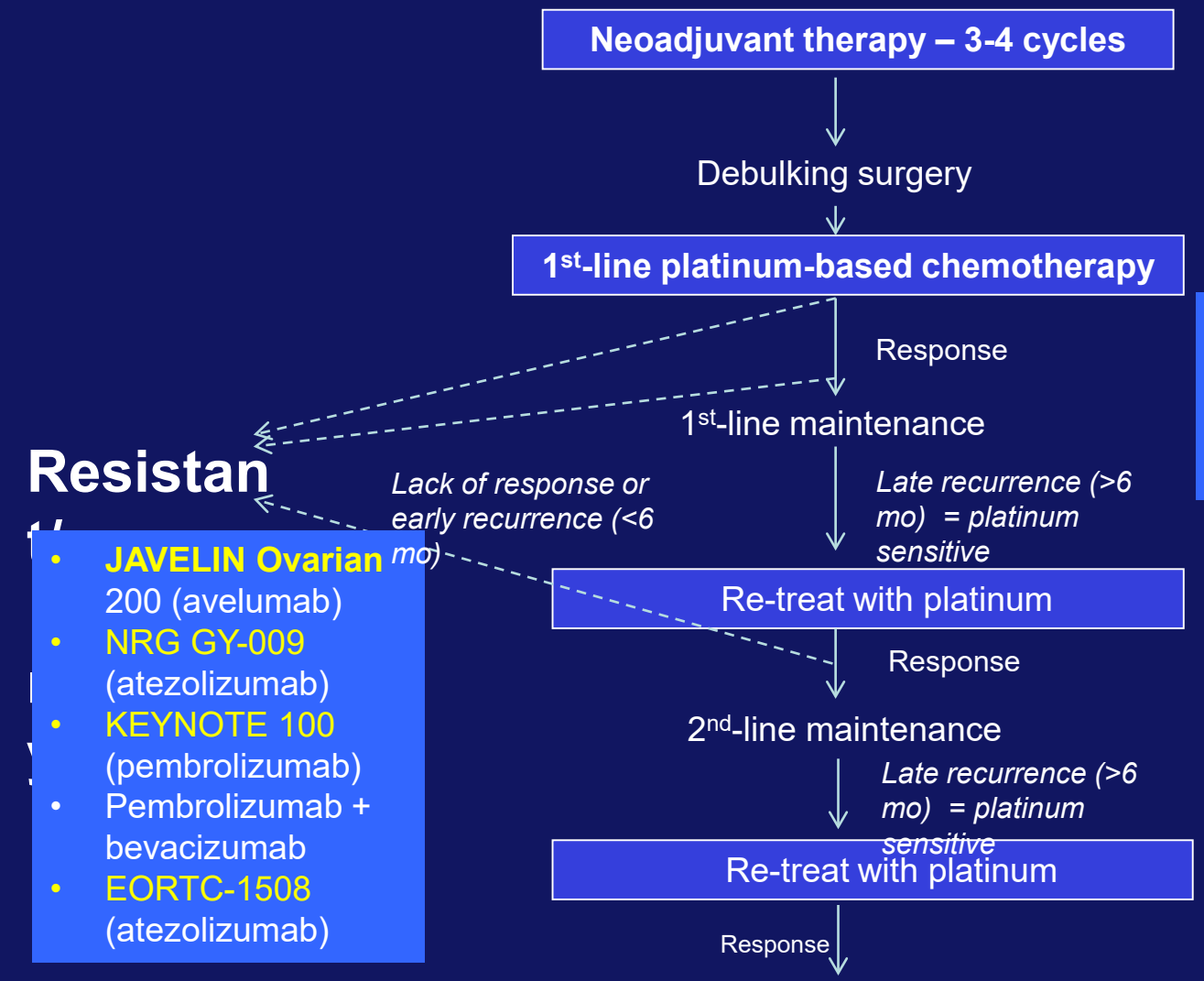
Ovarian Immune Checkpoint Inhibitors

	Ipilimumab[1]	Nivolumab[2]	Pembrolizumab[3]	Avelumab[4]
N	9	20	26	124
Patient population	Metastatic ovarian carcinoma	Platinum-resistant, post-taxane	Failure or inability to receive standard Tx; PD-L1+	Recurrent post-platinum
Prior therapies	NR	≥4: 55%	≥4: 80.8%	≥3: 65.3% (not including adjuvant)
PD-L1+ prevalence	NR	80% (IC 2/3)	100% (≥1% TC)	77% (≥1% TC)
Median follow-up	NR	11 months	NR	12.4 months
TRAE, any	22%	95%	69.2%	66.1%
TRAE, Gr 3+	NR	40%	3.8%	6.5%
ORR (95% CI)	NR	15% (3.2-37.9)	11.5% (2.4-30.2)	9.7% (5.1-16.3)
DCR (95% CI)	NR	45% (23-69)	34.6% (17-56)	54% (45-63)
mPFS	NR	3.5 months	NR	2.6 months
mOS	NR	20 months	NR	10.8 months

DCR, disease control rate; NR, not reached; TC, tumor cell; TRAE, treatment-related adverse event.

1. Hodi FS et al. *Proc Natl Acad Sci U S A*. 2008;105:3005-3010. 2. Hamanishi J et al. *J Clin Oncol*. 2015;33:4015-4022. Abstract 5510. 3. Varga A et al. Presented at ASCO 2015. 4. Disis ML et al. Presented at ASCO 2016. Abstract 5533.

Potential Impact of Immuno-Oncology Agents on Ovarian Cancer Treatment Paradigm



Resistan

- **JAVELIN Ovarian** 200 (avelumab)
- NRG GY-009 (atezolizumab)
- KEYNOTE 100 (pembrolizumab)
- Pembrolizumab + bevacizumab
- EORTC-1508 (atezolizumab)

= Frontline

- JAVELIN Ovarian 100 (avelumab)
- Pembrolizumab + chemotherapy

PS recurrence

- ATALANTE (atezolizumab)
- KEYNOTE 100 (pembrolizumab)
- Pembrolizumab + bevacizumab

PS, platinum sensitive.

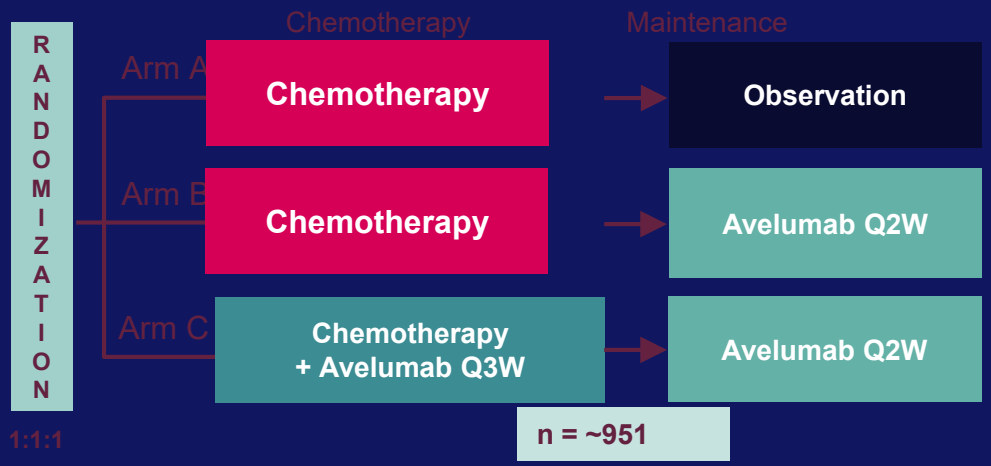
1. NCCN guidelines. Version 1.2016. 2. Clinicaltrials.gov. Accessed October 11, 2016. 3.

JAVELIN Ovarian 100
Avelumab Platinum Combo + Maintenance (Frontline)

Randomized Phase 3 Study (NCT02718417)

Enrollment Criteria

- Previously untreated
- Stage III-IV
- Prior debulking surgery or plan for neoadjuvant chemotherapy
- ECOG PS 0 or 1
- Mandatory archival tissue



Primary Endpoint: PFS

Secondary Endpoints: Maintenance PFS, OS, ORR, duration of response, pCR, PROs, safety, PK

- Patients with SD or better will be allowed to continue to maintenance
- Chemotherapy: Choice of Q3W carboplatin-paclitaxel OR carboplatin + weekly paclitaxel
- Maintenance avelumab up to 2 years

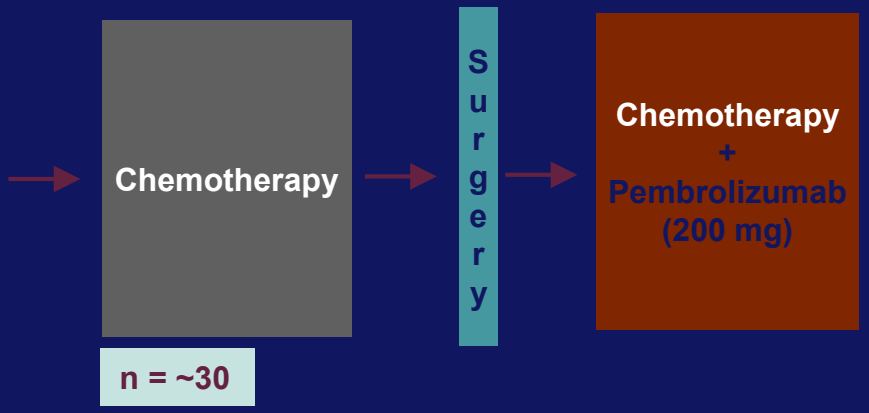
Clinicaltrials.gov. Accessed October 11, 2016.

Pembrolizumab in Combination With Chemotherapy in Frontline Ovarian Cancer

Phase 2 Study (NCT02520154)

Enrollment Criteria

- High-grade ovarian cancer
- No prior treatment
- Disposition to neoadjuvant chemotherapy
- Peripheral neuropathy Grade 0 or 1
- Measurable disease
- ECOG PS 0 or 1
- Mandatory archival tissue or new tissue sample



Primary Endpoint: PFS [illegible]

- Participants receive carboplatin IV on day 1 and paclitaxel 80 mg/m^2 IV on days 1, 8, and 15 every 21 days for 3 cycles of therapy
- After observation, participants without evidence of progression will undergo interval cytoreductive surgery
- After surgery, participants will restart chemotherapy as previously prescribed, with the addition of pembrolizumab 200 mg IV on day 1 every 21 days for 3 cycles
- Pembrolizumab maintenance therapy (200 mg IV every 21 days) will be given for a total of 20 cycles or until progression

Clinicaltrials.gov. Accessed October 11, 2016.

Pembrolizumab, Bevacizumab, and Cyclophosphamide in Recurrent Ovarian Cancer

Phase 2 Study (NCT02853318)

Enrollment Criteria

- Recurrent ovarian cancer
- Measurable disease
- ECOG PS 0 or 1
- Mandatory submission of tumor tissue samples

Pembrolizumab + Bevacizumab + Cyclophosphamide

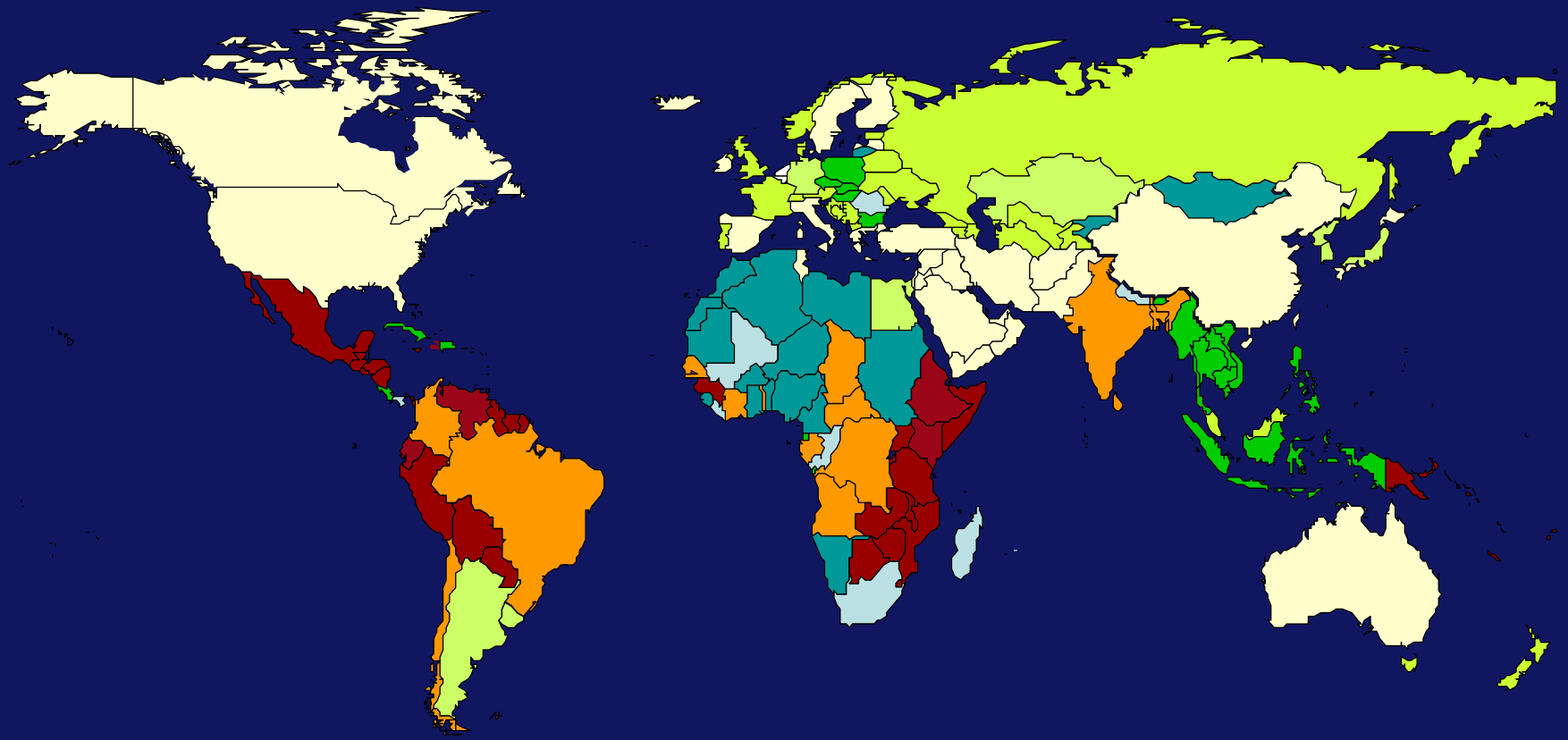
Chemotherapeutic agents

n = ~40

Primary Endpoint:	[illegible]
Secondary Endpoints:	OS, antitumor immune response, objective tumor response

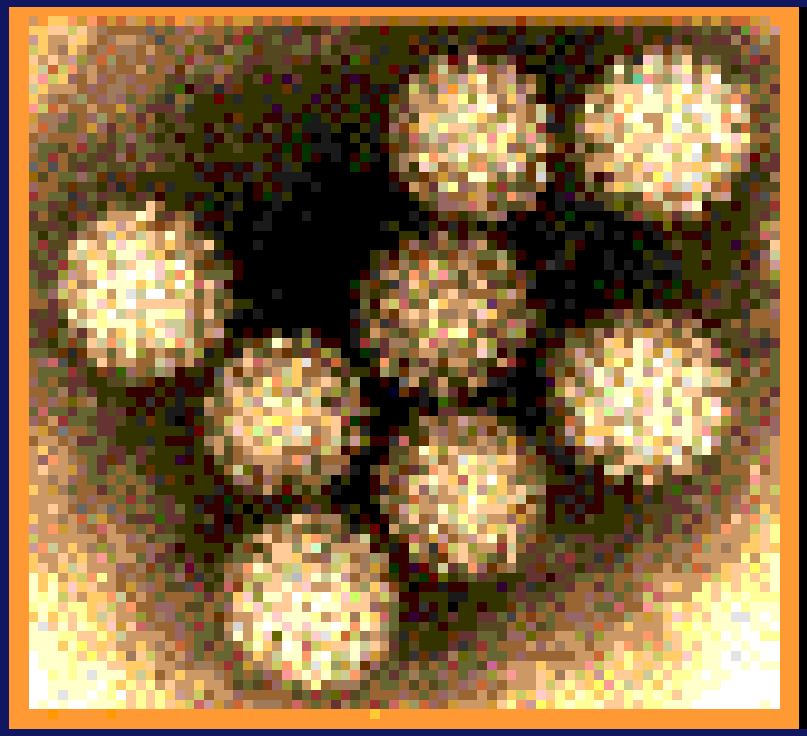
- Patients receive pembrolizumab IV and bevacizumab IV on day 1 and cyclophosphamide PO QD on days 1-21
- Treatment repeats every 3 weeks for up to 17 courses in the absence of disease progression or unacceptable toxicity

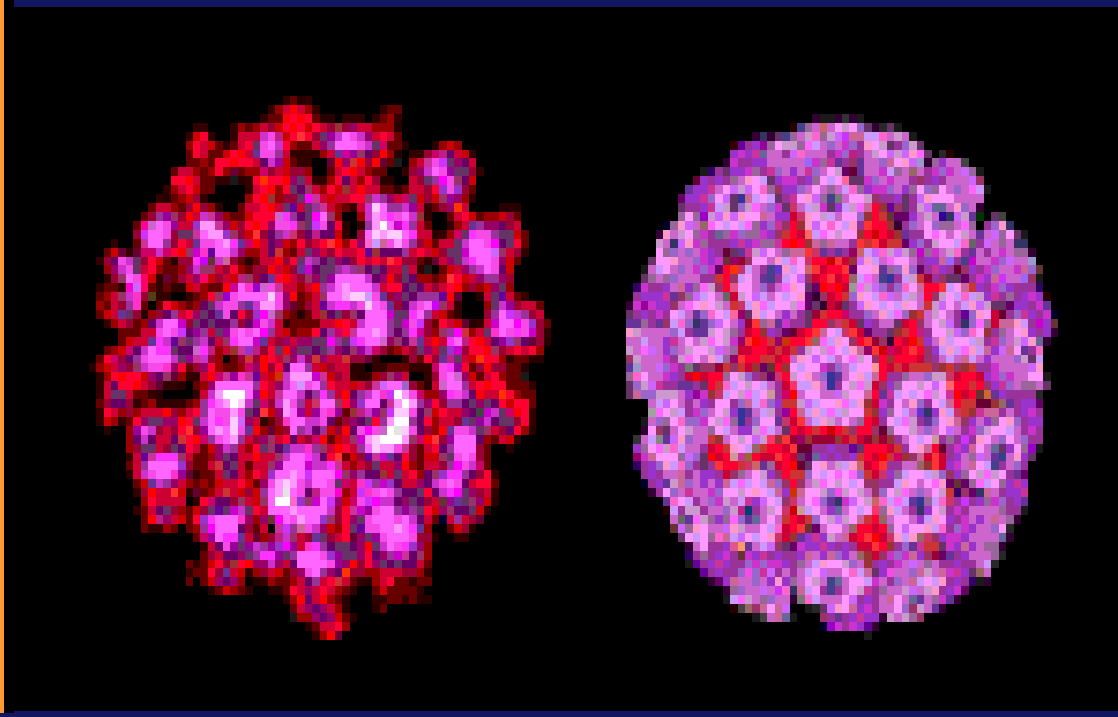
Estimates of the Worldwide Incidence of Cervical Cancer



Source : GLOBOCAN 2014; IARC

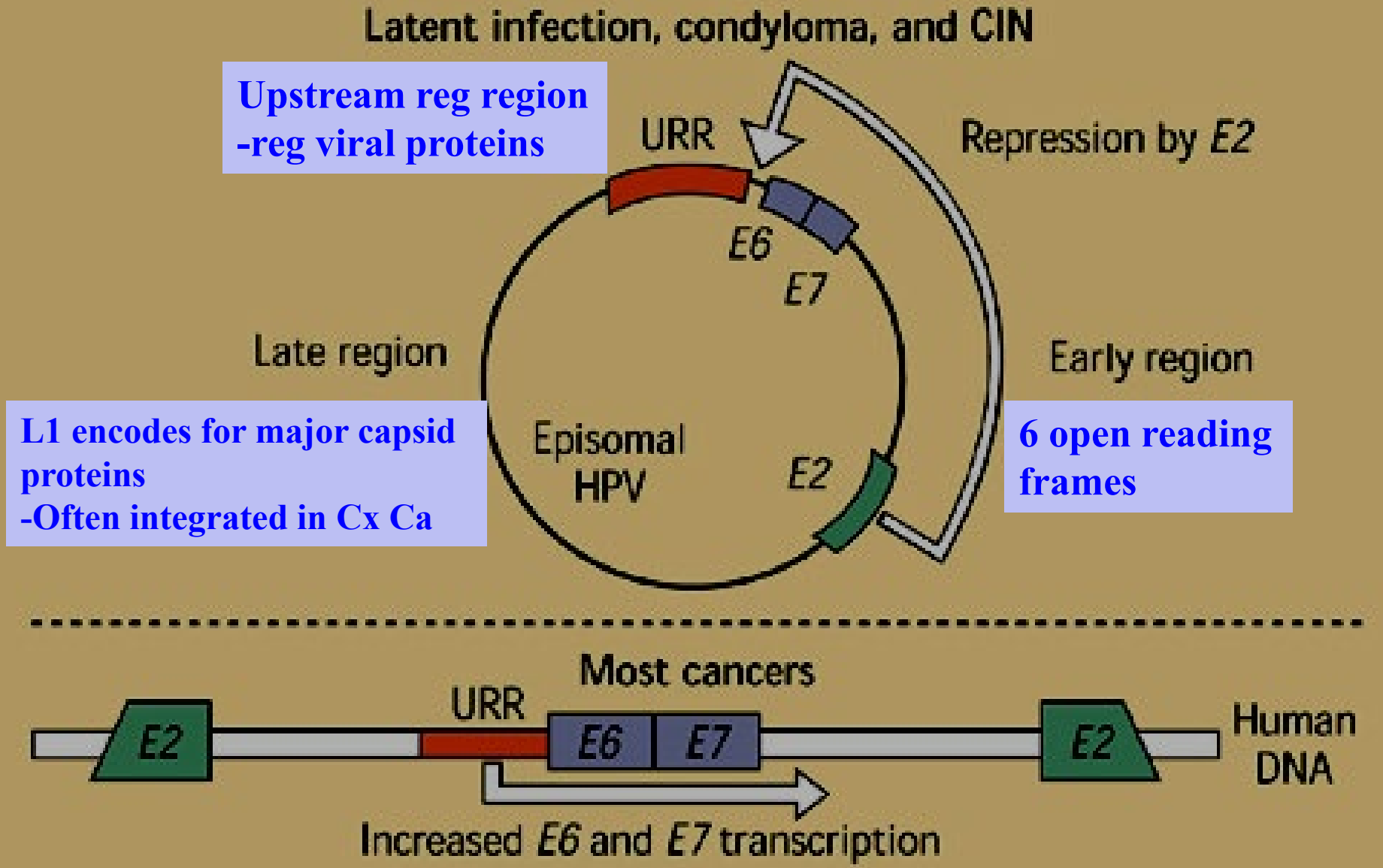
Human Papillomavirus





Non enveloped Icosahedral DNA Virus

HPV Genome & Carcinogenesis

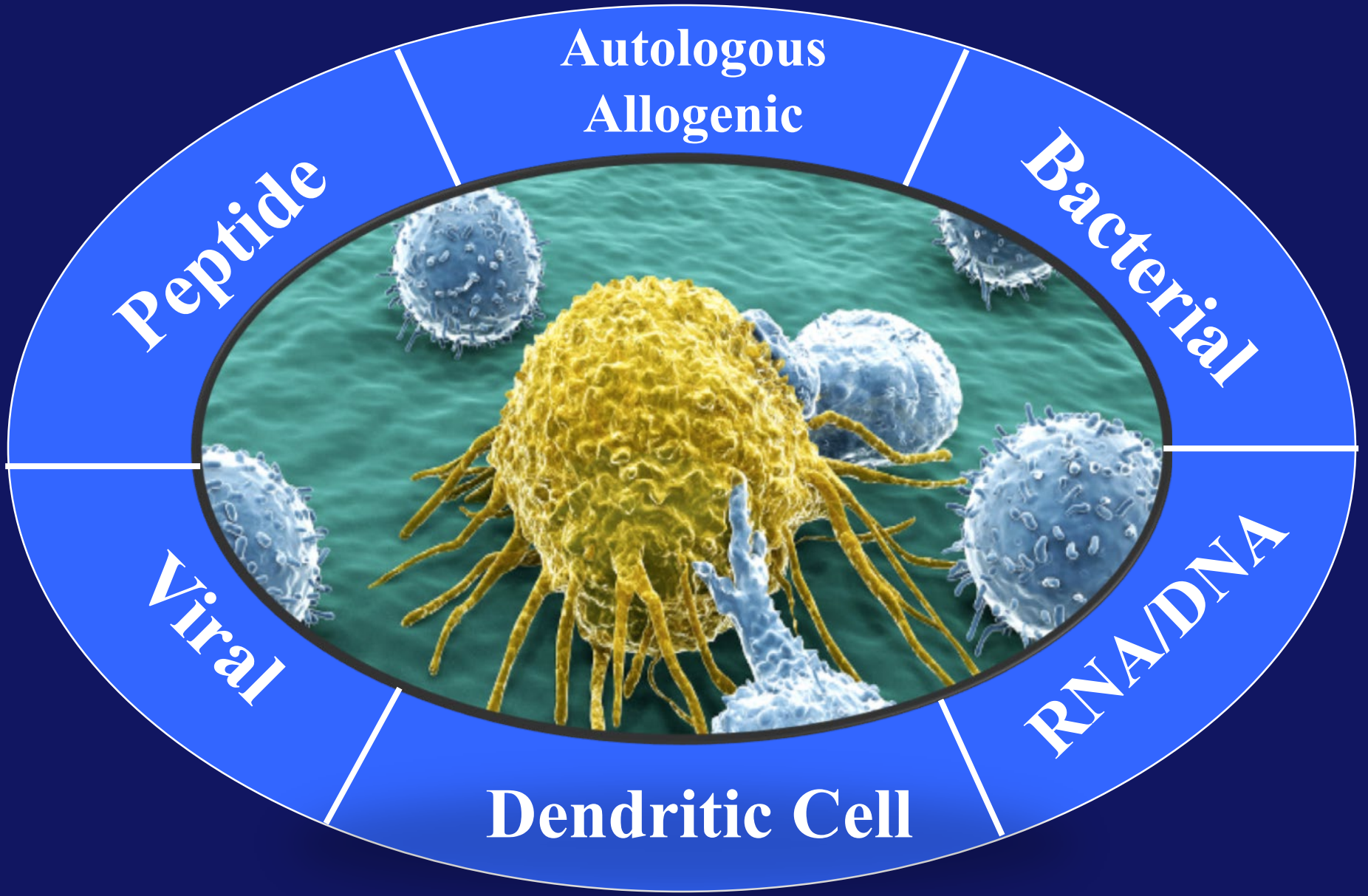


Categories of HPV Vaccines

- ***Prophylactic***
  - Induce neutralizing antibodies to the L1 capsid protein
  - Protect against transmission and acquisition of HPV infection
- ***Therapeutic***
  - Induce immunity to the E6/ E7 and other antigens expressed in HPV-infected epithelial cells
  - Induce Type 1 T-cell responses

Kadish and Einstein, *Curr Opin Oncol 2005*

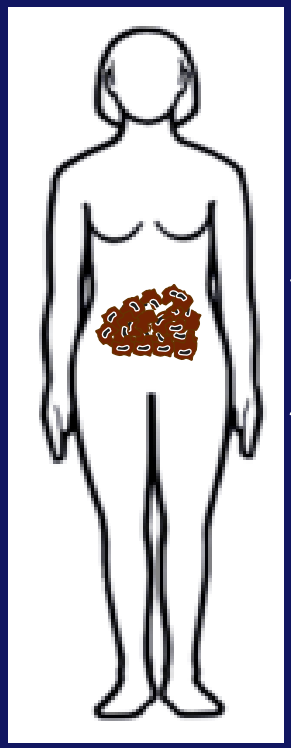
Vaccine Approaches



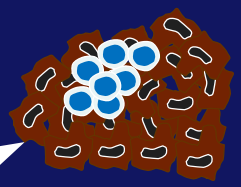
Select HPV Vaccines

Company/Institution	Antigen	Type	HPV
Zycos/MGI/Eisai	E6, E7	Microparticle delivered DNA	16, 18
Stressgen	E7	Fusion Protein: mycobacterial heat shock protein/E7 (Hsp E7)	16
Johns Hopkins	E7	pNGVLa-Sig/E7(detox)/HSP70	16
Transgene/Roche	E6,E7, IL2	Live rVaccinia virus (TA-HPV)	16
Xenova/Cantab	E6,E7	Live rVaccinia virus (TA-HPV)	16, 18
Xenova/Cantab	L2/E6/E7	Fusion Protein (TA-CIN)	16
Cantab	L2/E7	Fusion Protein (TA-GW)	6
CSL	E6/E7	Fusion Protein (CerVax 16)	16
Cytel	E7	Peptide	16
Medigene	L1, E7	Chimeric VLPs	16
University of Leiden	E7	Peptide	16
Inovio	E6, E7	DNA Vaccine-Electroporation	16, 18
Aduro	E7	Listeria monocytogenes	16
Advaxis	E7	Listeria monocytogenes	16

Tailoring selection of immunotherapy based on detecting adaptive immune resistance

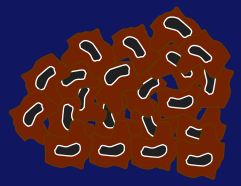


TIL^{+}



+ Checkpoint blockade

TIL^{-}

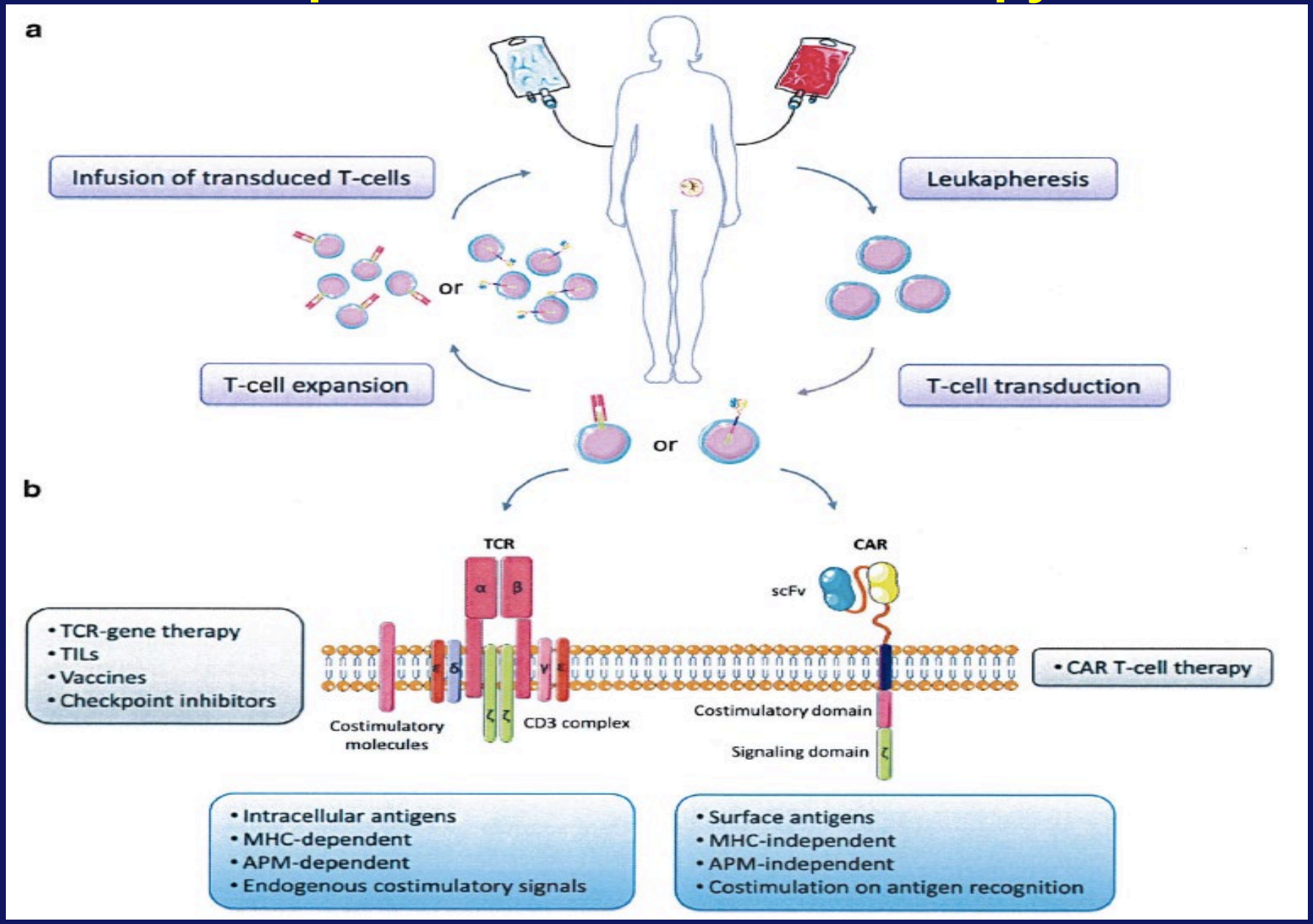


+ Immune-activating cytokines
+ TLR agonists
+ oncolytic viruses

+ Vaccines
+ TCR-engineered ACT
+ CAR-engineered ACT

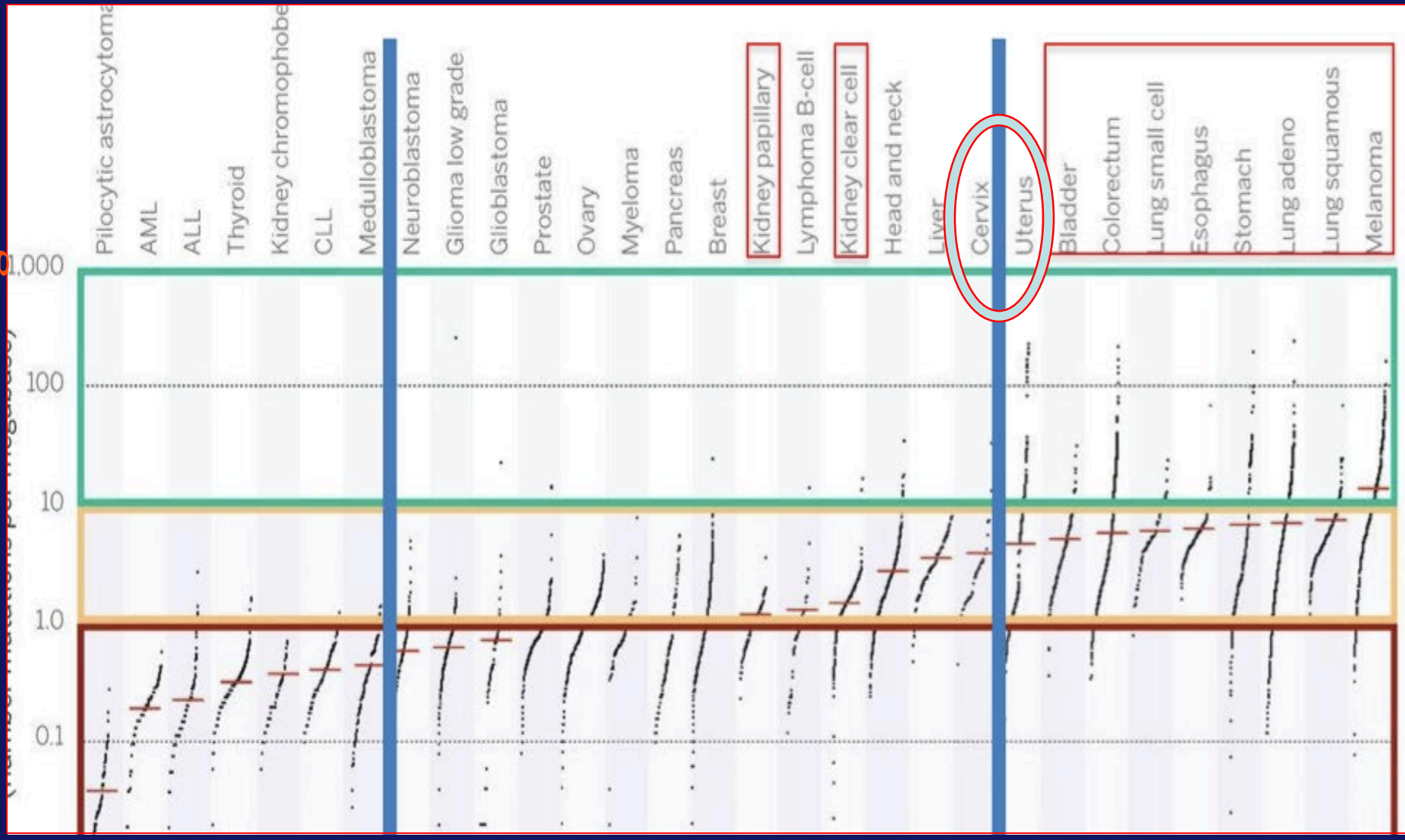
Ribas *et al*, Cancer Discov 2015

Adoptive T-cell Transfer Therapy



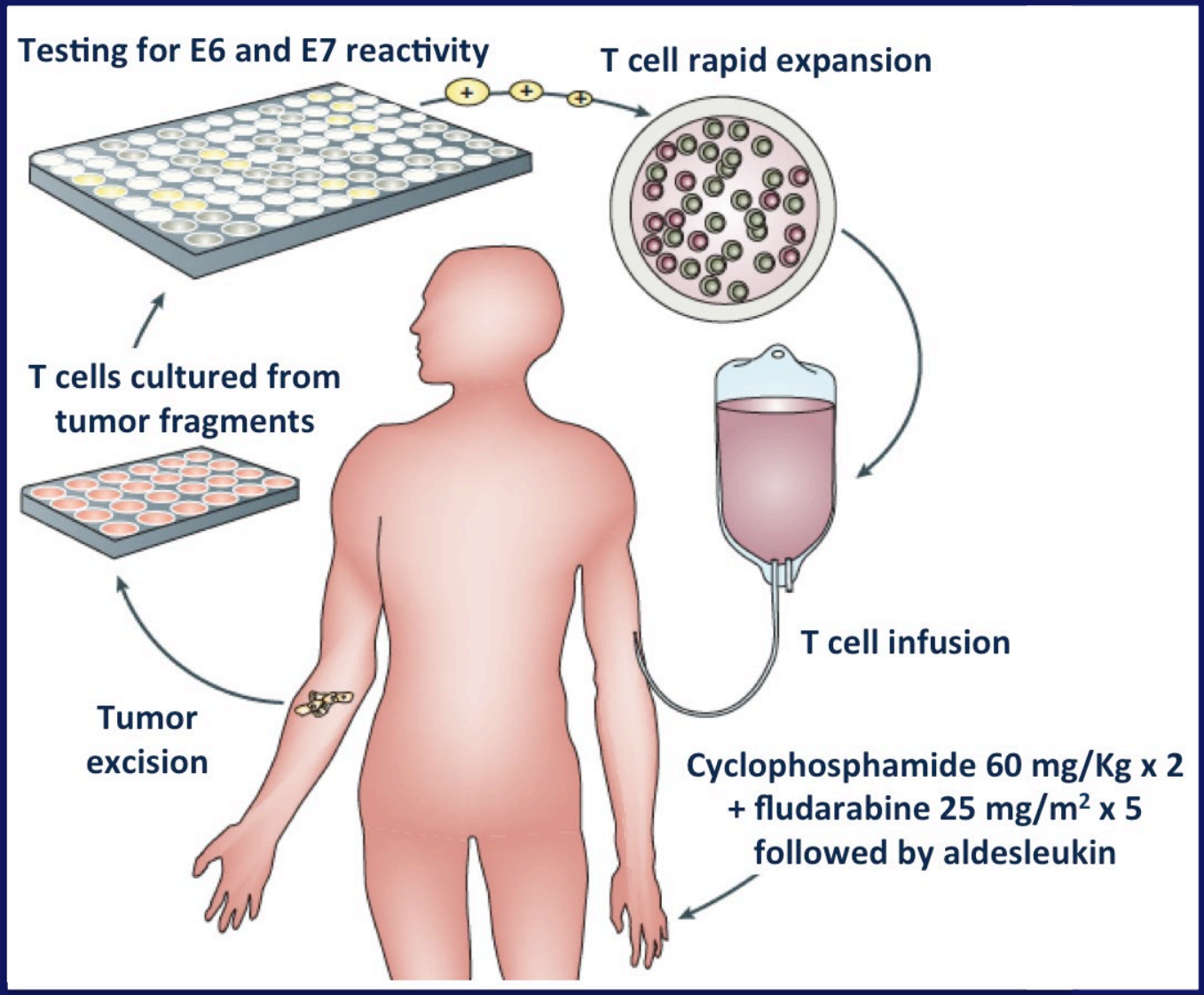
Rodriguez-Garcia A et al Gyn Onc 2017

Frequency of Somatic Mutations Across Tumor Types



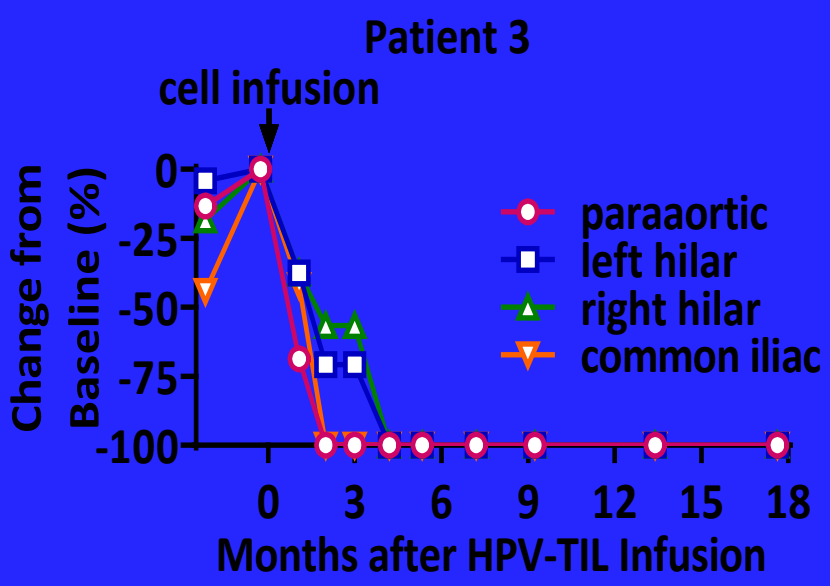
Schumacher TN and Schreiber RD, *Science*, 2015

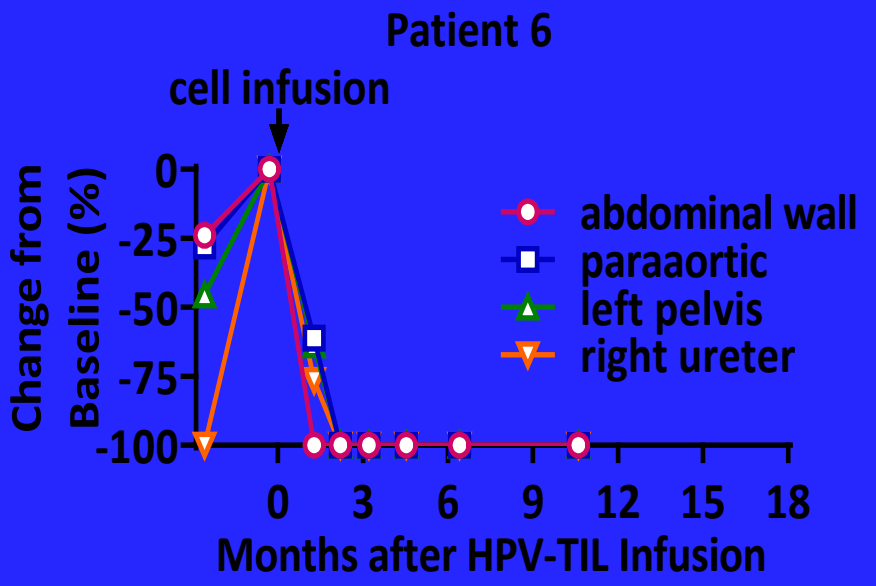
Adoptive T Cell Therapy: Schema for HPV-Targeted Tumor-Infiltrating Lymphocytes (HPV-TIL)



Hinrichs CS, et al. *J Clin Oncol*. 2014;32(5s): Abstract LBA3008.

Prolonged Tumor Regression Following Single Infusion of Autologous Tumor-Targeted T Cells





Stevanovic S, et al. LBA3008 (ASCO 2014)
Stevanovic S, et al. *J Clin Oncol.* 2015;33(14):1543
Stevanovic S, et al. Science 356; 200- 205, 2017

Immune Checkpoint Inhibitors Overview

	Ipilimumab[1]	Nivolumab[2]	Pembrolizumab[3]	Avelumab[4]	Atezolizumab
Isotype	IgG1	IgG4	IgG4	IgG1	IgG1
Targets	CTLA-4	PD-1	PD-1	PD-L1	PD-L1
ADCC	Yes[5]	No[6]	No/Minimal[7]	Yes[8]	Yes[8]
Approved indications (Date)	Melanoma (2011) Adv Renal with Nivo (2018)	Melanoma (2014), RCC (2015), NSCLC (2015) Hodgkin's (2016), Melanoma +nodes/mets (2017) RCC with Ipi (2018)	Melanoma (2014), NSCLC (2015) H & N (2016) GU (2017) Any MSI-H (2017) Gastric GE jnct (2017) Cx PDL-1 (2018) Hepato (2018) Merkeel (2018)	Merkel cell Pend (2016)	Bladder (2016) NSCL (2016) Lung (2018)

1. Hodi FS et al. *Proc Natl Acad Sci USA*. 2008;105:3005-3010. **2.** Hamanishi J et al. *J Clin Oncol*. 2015;33:4015-4022. **3.** Varga A et al. Presented at ASCO 2015. Abstract 5510. **4.** Disis ML et al. Presented at ASCO 2016. Abstract 5533 **5.** Romano E et al. *Proc Natl Acad Sci U S A*. 2015;112(19):6140-6145. **6.** Wang C, Thidium KB, Han M, et al. *Cancer Immunol Res*. 2014;2(9):846-856. **7.** Homet Moreno B, Ribas A, et al. *Br J Cancer*. 2015;112(9):1421-1427. **8.** Boyerinas B et al. *Cancer Immunol Res*. 2015;3:1148-1157.

A Phase I/II Study of Ipilimumab in Metastatic or Recurrent Cervical Carcinoma

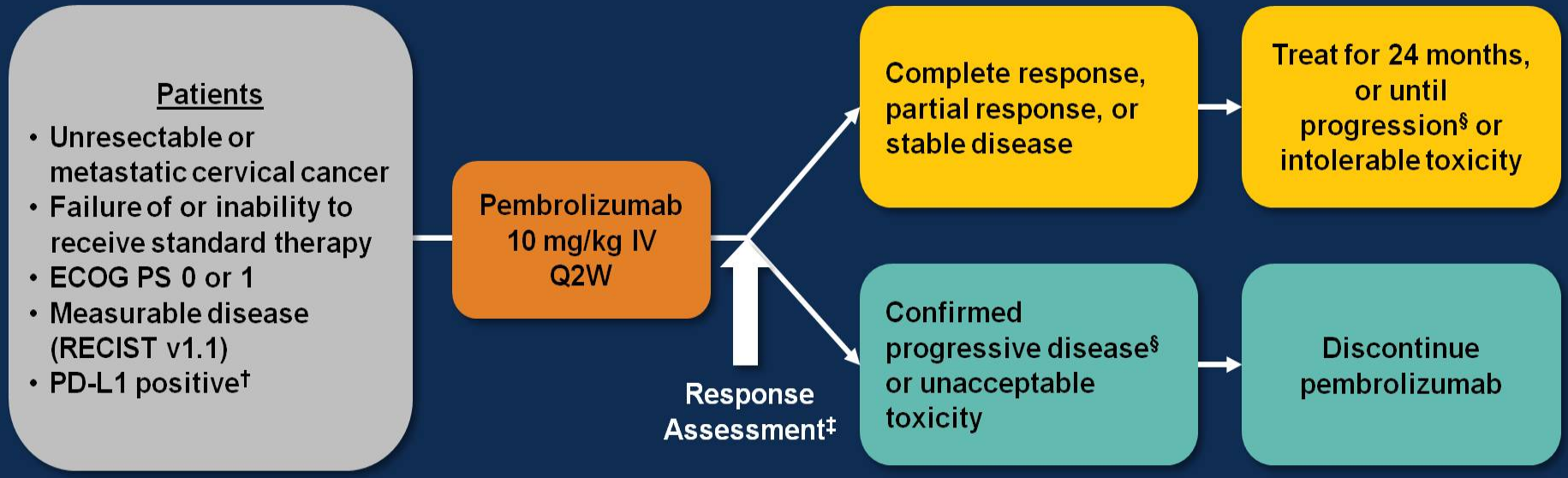
- 10 mg/kg every 21 days for four cycles; followed by four cycles of maintenance therapy (same dose) every 12 weeks
- 42 patients, median age of 49 years (23-78)
  - 29 squamous, 13 adenocarcinoma
  - 35 had prior radiation completed
  - 21 had received 2/3 prior regimens
- 34 evaluable patients: 2 PR (6%) , 9 SD and 23 PD
- Median PFS was 2.5 months (95% CI: 2.3-3.2)
- Grade 3 toxicities included diarrhea (4 patients) and colitis (3 patients)
- Did not meet the objective of 4 responders

Lheureux S, et al. *J Clin Oncol.* 2015;33(suppl): Abstract 3061.

ClinicalTrials.gov Identifier: NCT01693783

Pembrolizumab in Adv Cervical Cancer: Ph Ib

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.

Pembrolizumab in Adv Cervical Cancer: Ph Ib

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.

Pembrolizumab in Adv Cervical Cancer: Ph Ib

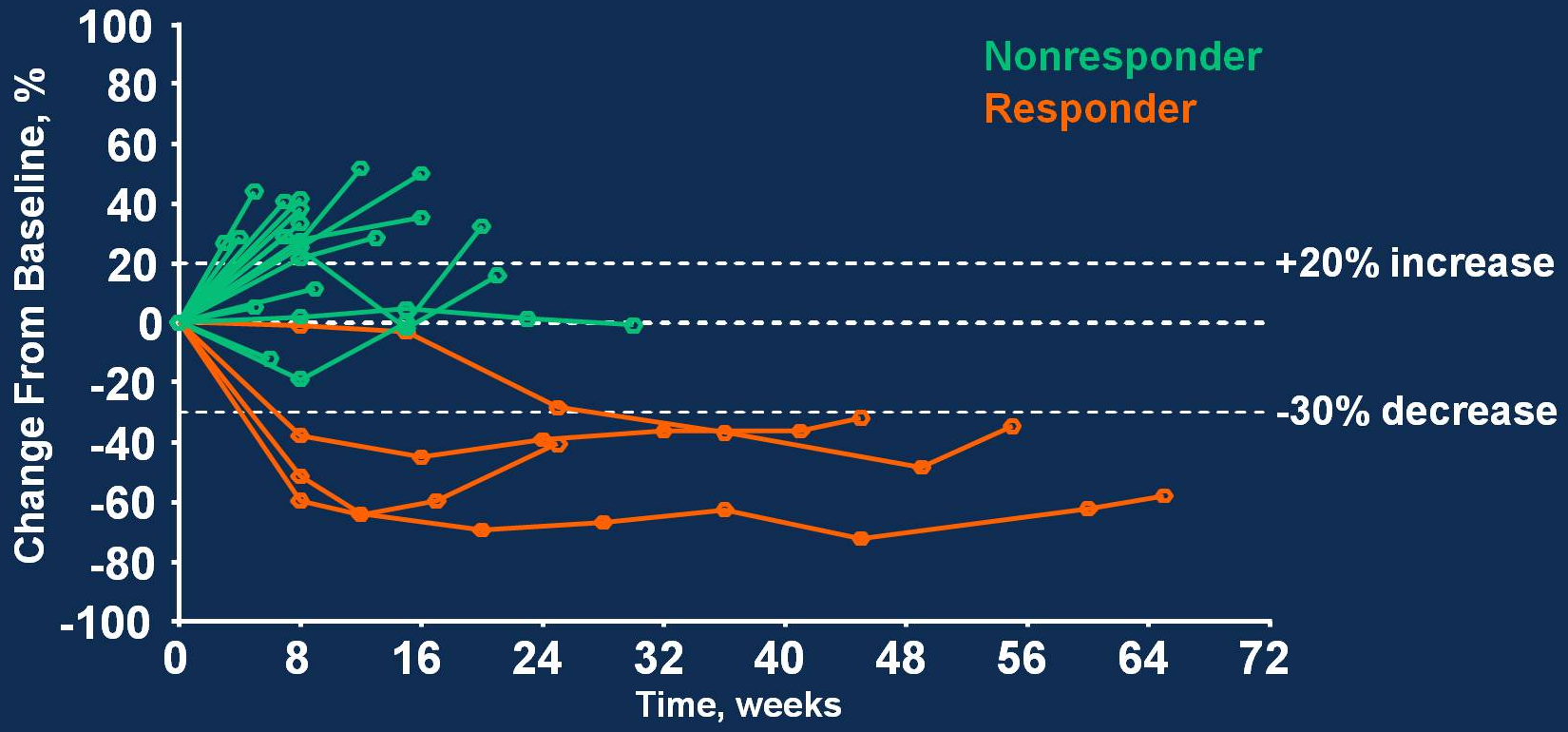
Antitumor Activity (RECIST v1.1, Investigator Review)

	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.

Pembrolizumab in Adv Cervical Cancer: Ph Ib

Longitudinal Change From Baseline in Tumor Size (RECIST v1.1, Investigator Review)

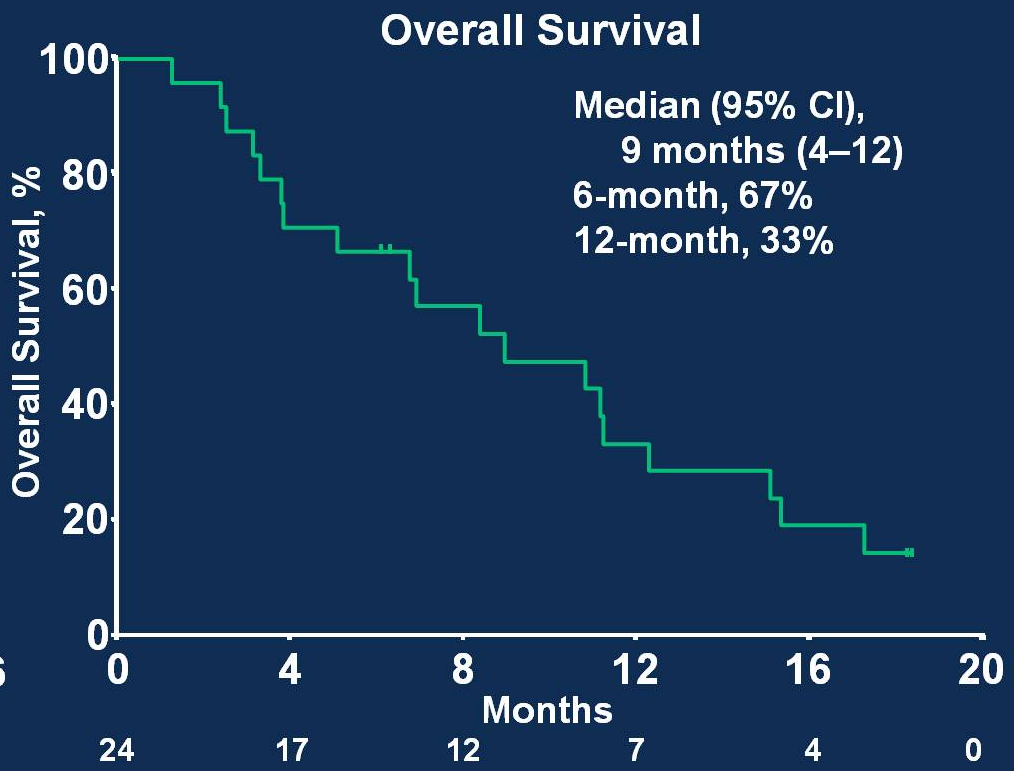


PRESENTED AT: ASCO ANNUAL MEETING '16

Data cutoff date: Feb 17, 2016. 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 = 20). One patient was excluded due to 2 scans for the same assessment out of window.

Pembrolizumab in Adv Cervical Cancer: Ph Ib

Progression-Free Survival† and Overall Survival



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.

Presented By Jean-Sebastien Frenel at 2016 ASCO Annual Meeting

NRG GY002

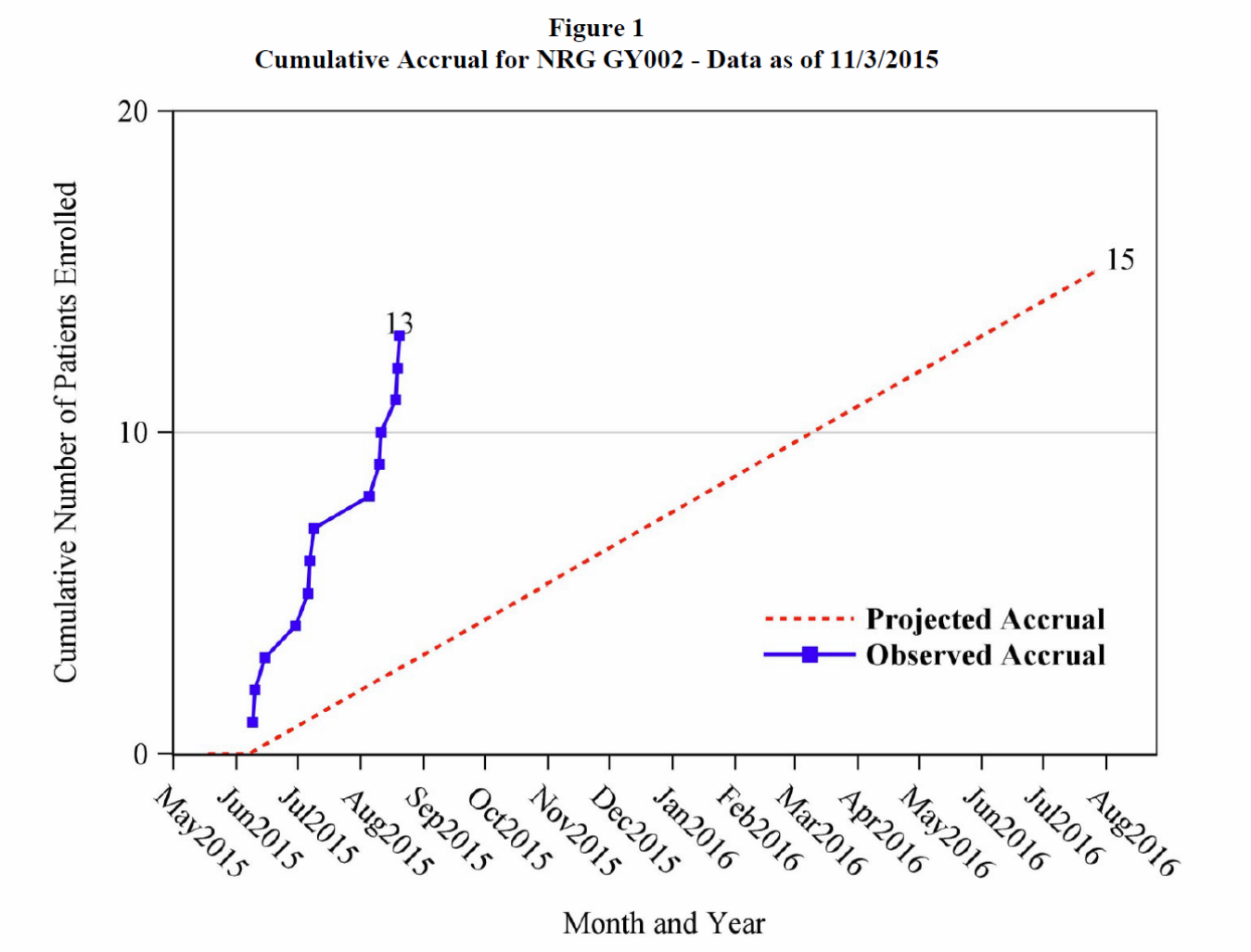
Nivolumab in Persistent, Recurrent, or Metastatic Cervical Cancer

- Measurable disease
- only 1 prior systemic regimen for management of persistent, recurrent or metastatic disease
- Nivolumab 3 mg/kg IV every 2 weeks
- 2 stage design
  - First stage: n = 12
  - Second stage (if warranted): n = 13
  - Activated May 18, 2015
  - Temporarily Closed August 2015 after first stage
    - 1 response needed to move to second stage
  - Closed June 2016

PI: Alessandro Santin ClinicalTrials.gov Identifier: NCT02257528

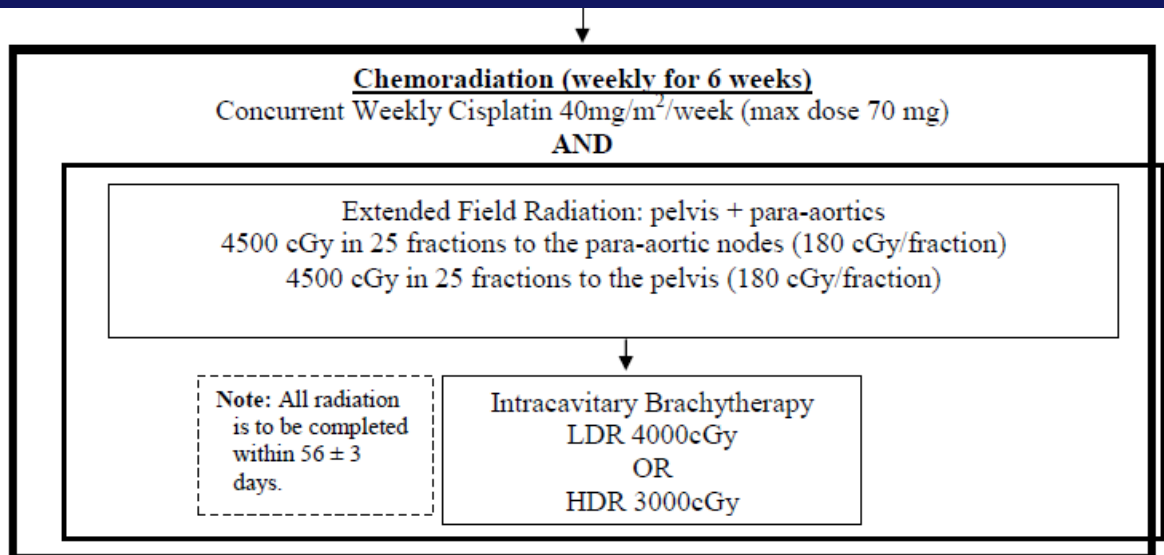
NRG GY002

Nivolumab in Persistent, Recurrent, or Metastatic Cervical Cancer



PI: Alessandro Santin ClinicalTrials.gov Identifier: NCT02257528

Ph I GOG (NRG) 9929: Schema



Adjuvant Immunotherapy

Ipilimumab will be given ~2 weeks following completion of all chemoradiation and be given every 3 weeks x 4 doses total. Patients may commence ipilimumab up to 6 weeks following completion of all chemoradiation to allow resolution of chemoradiation associated acute toxicities

Dose Escalation Schema

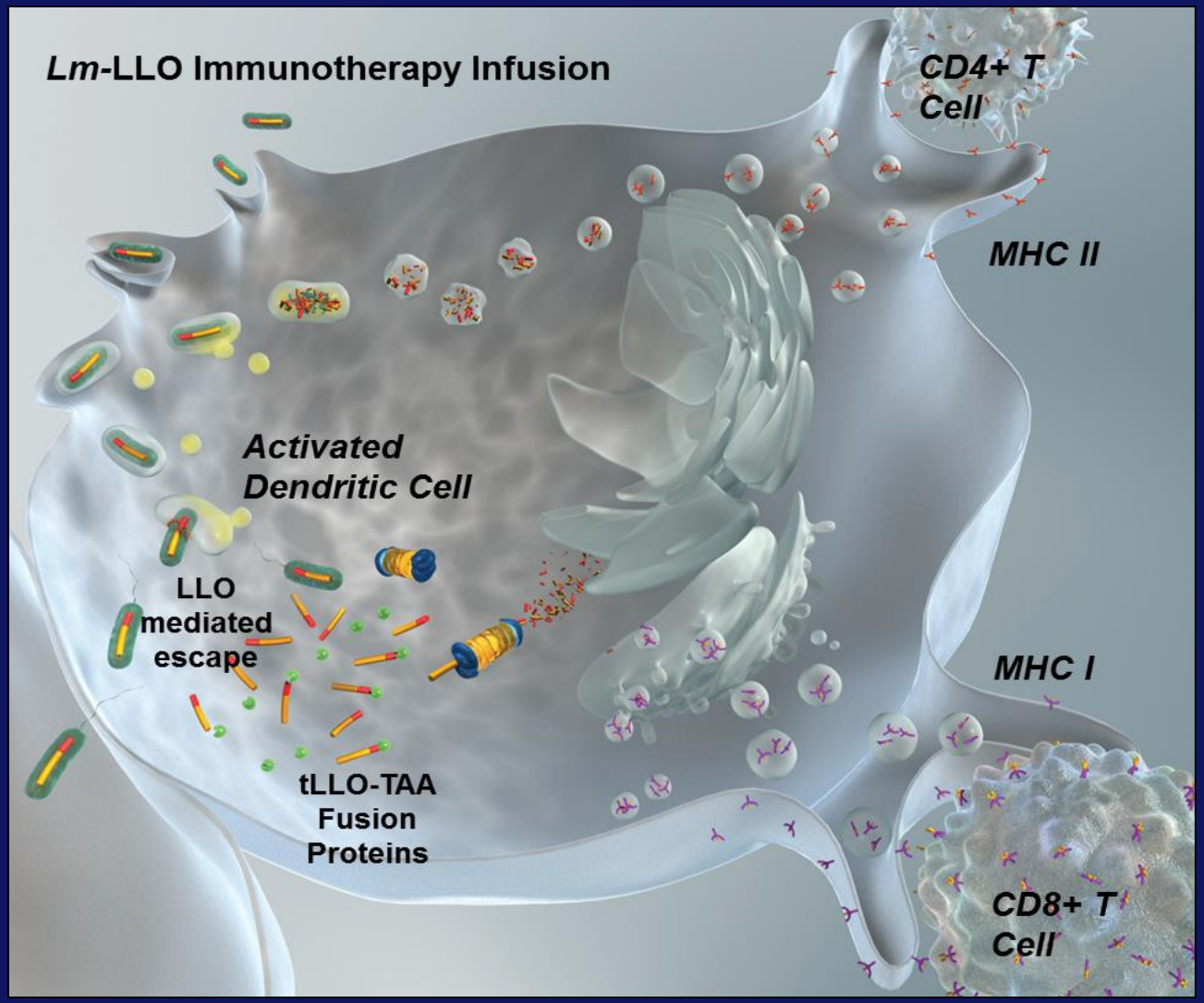
Dose Level	Ipilimumab	Rx Schedule
1 (Starting Dose)	3 mg/kg	q3 weeks x 4*
2	10 mg/kg	q3 weeks x 4*
1a§	6 mg/kg	q3 weeks x 4*

‡Once the MTD is estimated, the expansion cohort will start.

§ Dose level 1a will be used if 10 mg/kg is found to exceed the MTD.

ClinicalTrials.gov Identifier:
NCT01711515

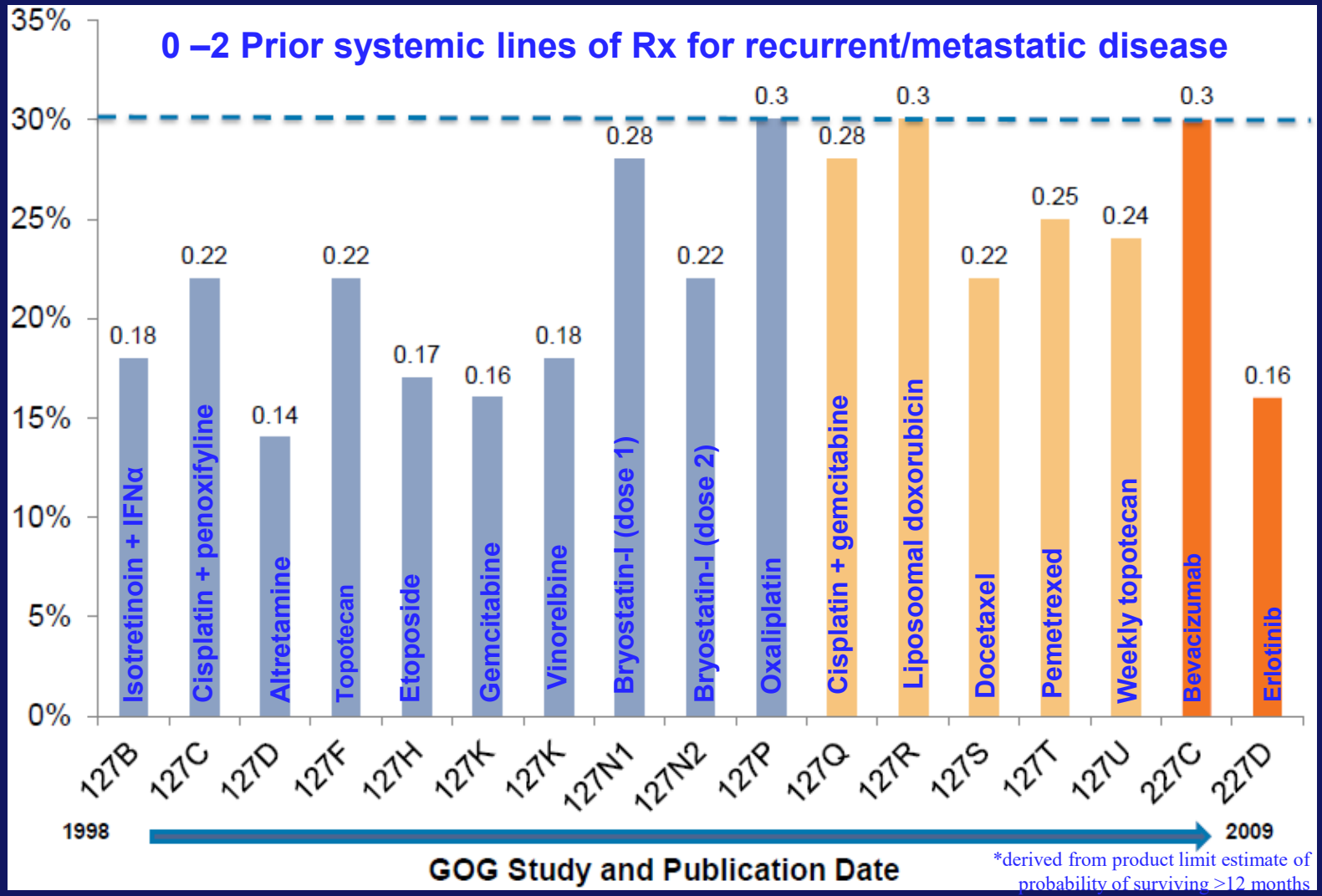
Lm Technology™: Harnessing Unique Life Cycle of *Lm* in APCs



- *Lm*-LLO & HPV E7 antigen presented & taken up by dendritic cells (antigen presenting cells or APCs)
- Dendritic cells activated & generate immune response through both the MHC I & II pathways
- Robust T-cell response generated towards antigen secreted by *Lm*-LLO & redirected to tumors expressing the same HPV E7 antigen
- "Perceived" acute listeriosis causes immune response
- Over-rides checkpoint inhibitors & negative regulators of cellular immunity

MHS, major histocompatibility complex

12-month Survival Rates in Pre-treated PRmCC

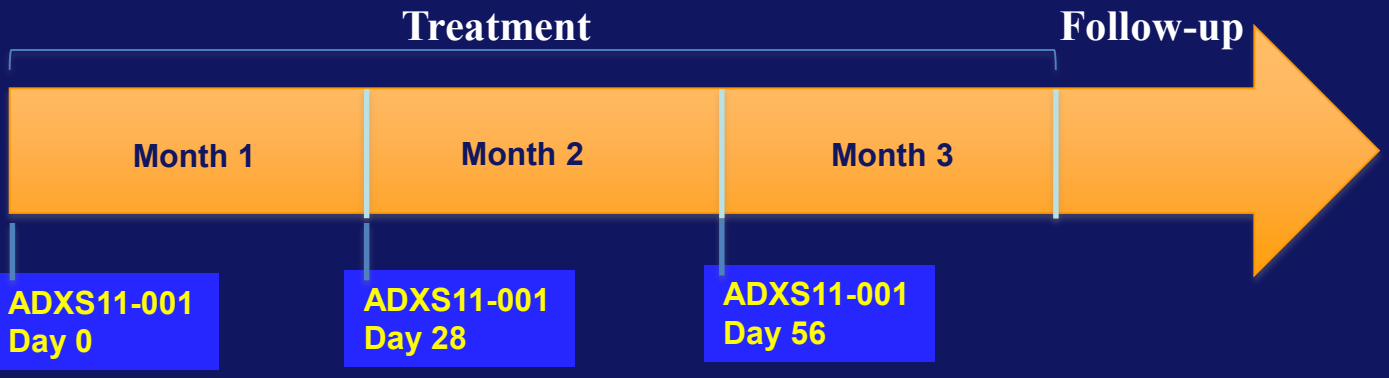


1. Tewari KS & Monk BJ. Curr Oncol Rep. 2005;7(6):419-34; 2 Muggia F, et al. *Gynecol Oncol*. 2004;92(2):639-43; 3. Plaxe SC, et al. Cancer Chemother Pharmacol. 2002;50(2):151-4; 4. Armstrong DK, et al. Invest New Drugs. 2003;21(4):453-7; 5. Fracasso PM, et al. *Gynecol Oncol*. 2003;90(1):177-80; 6. Brewer CA, et al. *Gynecol Oncol*. 2006;100(2):385-8; 7. Rose P, et al. *Gynecol Oncol*. 2006;102(2):210-3; 8.Garcia AA, et al. Am J Clin Oncol. 2007;30(4):428-31; 9. Miller DS, et al. *Gynecol Oncol*. 2008;110(1):65-70; 10. Fiorica JV, et al. *Gynecol Oncol*. 2009;115(2):285-9; 11. Monk BJ, et al. .J Clin Oncol. 2009;27(7):1069-74; 12. Schilder RJ, et al. Int J Gynecol Cancer. 2009;19(5):929-33; 13. GOG-0265 Protocol NCI Version: 04/22/15, Re.

GOG/NRG 0265 Study Design & Eligibility

- N = ~67 Simon 2 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)

ADXS11-001 Monotherapy
1x10^9 cfu x 3 doses q 28 days (month 1, 2, 3) as an 80 ml infusion over 15 min

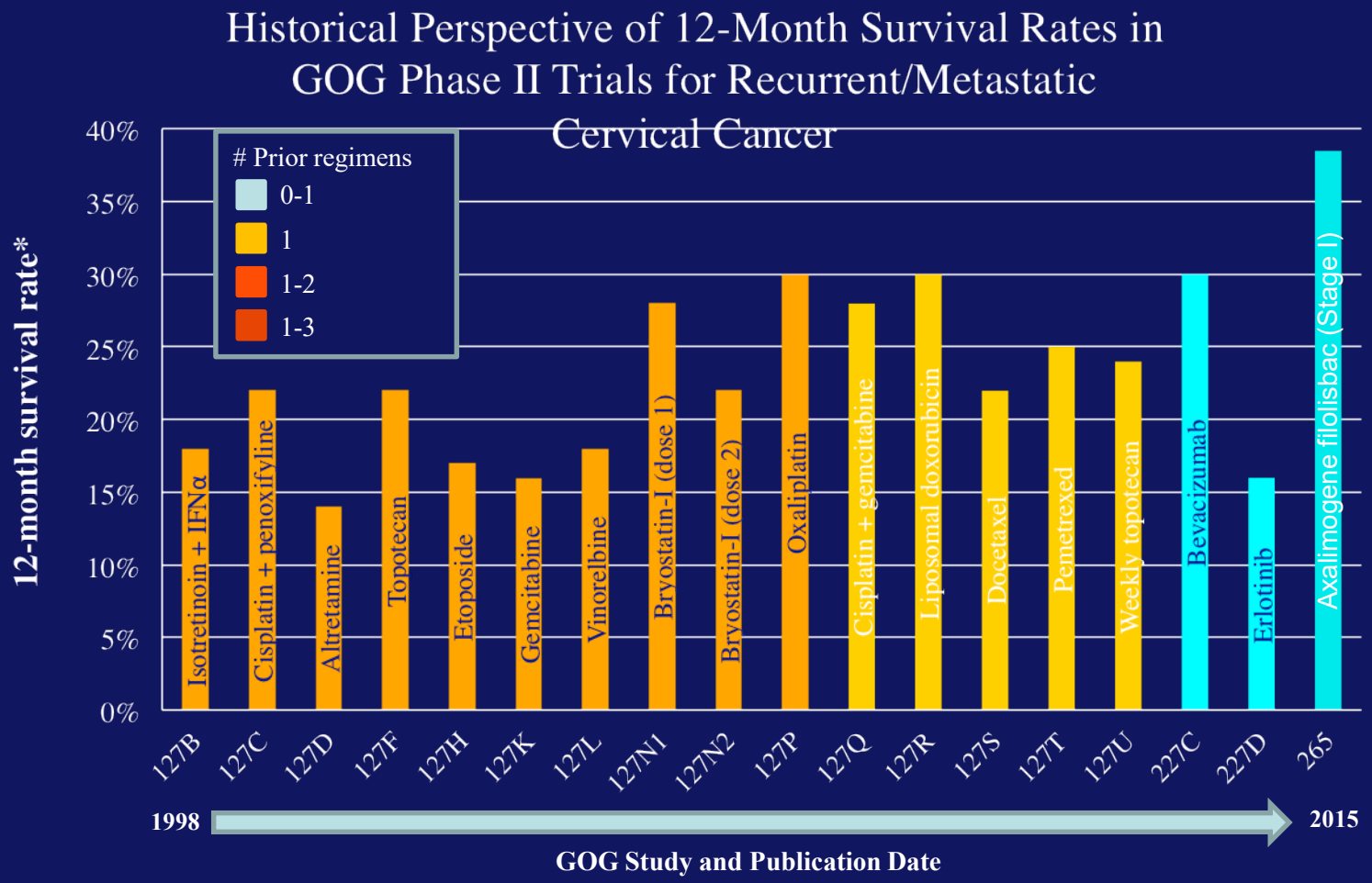


Co-Primary Endpoints:
- 12-month survival rate
- Tolerability/safety of ADXS11-001

Secondary Endpoints:
- Progression-free survival (PFS)
- Overall survival (OS)
- Objective response rate (ORR)

https://www.clinicaltrials.gov/ct2/show/NCT01266460

NRG 0265- 12 mos. Overall Survival vs. Historical Cohorts



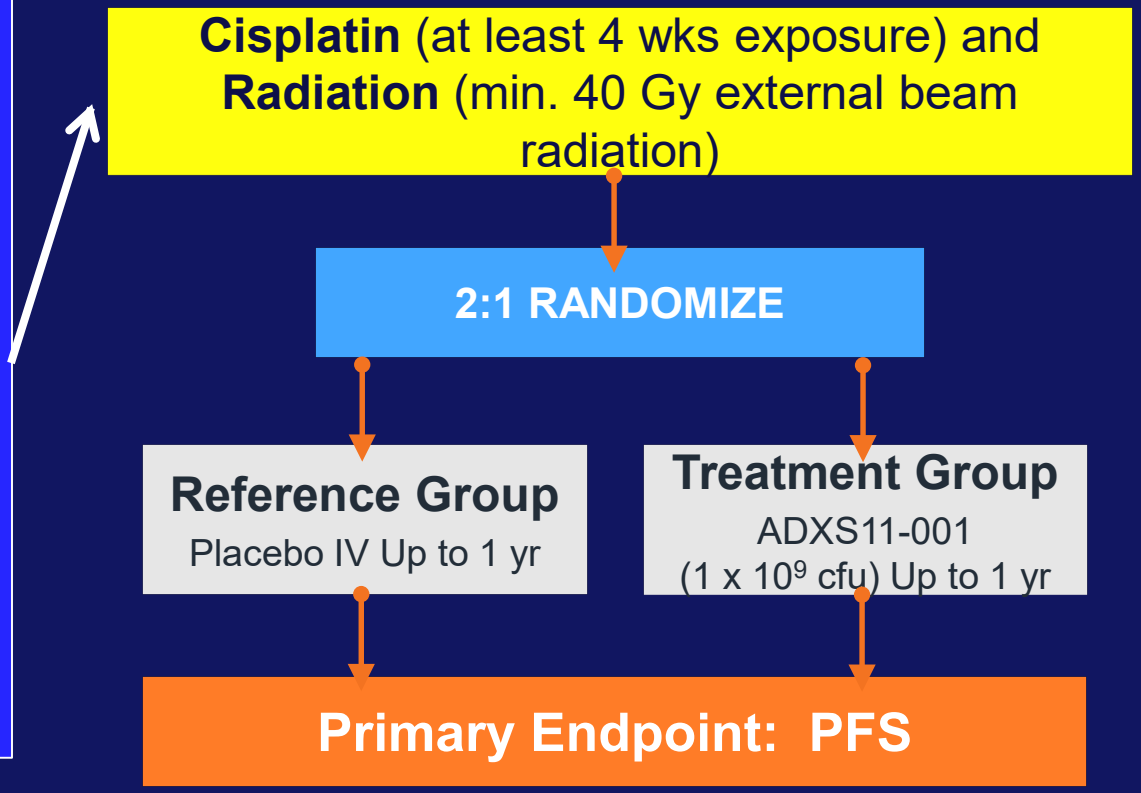
Tewari KS, Monk BJ. *Semin Oncol.* 2009;36(2):170-180.

Axalimogene Filolisbac (ADXS-HPV): Phase 3 AIM2CERV Study Schema

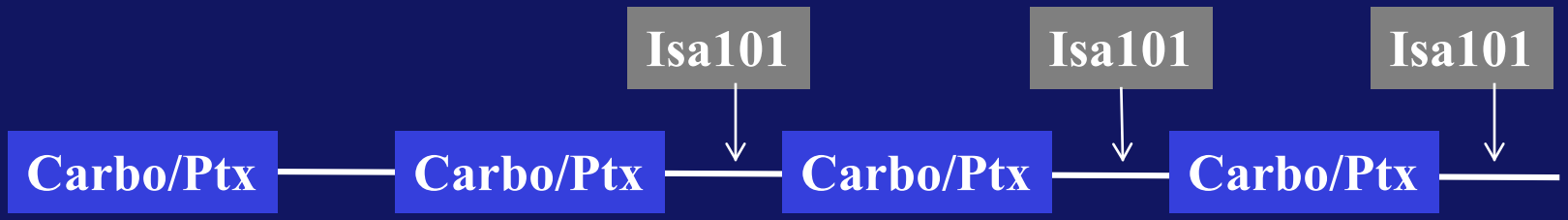
High risk, locally advanced cervical cancer

- **FIGO stage I-II with positive pelvic nodes**
- **FIGO stage III-IV**
- **Any FIGO stage with para-aortic nodes**

- **N = 450**



Ph I/II CervISA:



- Advanced Cervical Cancer
- ISA101 vaccine = 13 overlapping HPV16 (E6 & 7) synthetic long peptides
- N = 60 pts 4 dose levels of vaccine; strong association btw HPV-specific T-cell response measured via ELISpot
- Med OS not reached for 2 highest doses

Melief CJ et al ASCO –SITC 2017

Cervical Cancers & Checkpoint Blockade

	Lheureux et al.[1]	KEYNOTE-028[2]	KEYNOTE-158[3] (Cohort E)[b]	Checkmate 358[4]
Phase	2	1b	2	1/2
Population	Metastatic or recurrent cervical cancer with progression after prior platinum chemotherapy	PD-L1+ advanced cervical squamous cell cancers after failure of prior systemic therapy	Advanced cervical cancer with progression on or intolerance to ≥1 line of prior therapy, PD-L1+ (CPS ≥1)	HPV-associated tumors, including recurrent or metastatic cx, vaginal, vulvar cancers
Patients, n	42[a]	24	77[d]	24
Treatment	Ipilimumab	Pembrolizumab	Pembrolizumab	Nivolumab
ORR, %	8.8[c]	12.5[c]	14.3	ITT: 20.8[c] Cervical cancer pts: 26.3%
DCR, %	32.3	25.0	—	70.8
mDOR	—	19.3 wk	NR (range: 4.1–18.6+ mo)	NR
PFS	mPFS: 2.5 mo	6-mo PFS: 13.0%	—	mPFS: 5.5 mo
OS	—	6-mo OS: 66.7%	—	NR
Safety	Manageable toxicities	≥Gr 3 TRAEs: 20.8%	Serious AEs: 39%	Gr 3/4 TRAEs: 12.5%
Follow-up	—	48.9 wk	11.7 mo	31 wk

[a] 34 evaluable for efficacy. [b] trial led to the approval of pembrolizumab for treatment of patients with cervical cancer. [c] Primary endpoint.
[d] Cohort E = 98 pts, but pembrolizumab label includes data for response in 77 patients whose tumors expressed PD-L1.

CPS, combined positive score; DCR, disease control rate; ITT, intent to treat; mDOR, median duration of response;; NR, not reached; ORR, overall response rate;; PD-L1, programmed death ligand 1;; TRAE, treatment-related adverse event.

1. Lheureux S, et al. Presented at ASCO Annual Meeting, 2015. Abstract 3061. **2.** Frenel JS, et al. Presented at ASCO Annual Meeting, 2016. Abstract 5515. **3.** Pembrolizumab package insert. Merck & Co, Inc; December 2018. **4.** Hollebecque A, et al. Presented at ASCO Annual Meeting, 2017. Abstract 5504.

Em Ca IO Trials

Durvalumab, Vigil (bi-shRNAfurin & GMCSF Aug. Autologous Tumor Cell Immunotherapy)	Locally advanced or metastatic EM, uterine, breast, ovarian, FT, primary peritoneal, cervical	NCT02725489	Recruiting
Durvalumab; Durvalumab, Tremelimumab	Persistent or recurrent endometrial carcinoma (endometrioid, serous, undifferentiated, dedifferentiated, clear cell, mixed, other adenocarcinoma) or carcinosarc	NCT03015129	Recruiting
Pembrolizumab	Persistent or recurrent EM CA (endometrioid, serous, clear cell, undifferentiated, mixed, other adenocarcinoma) or CS that is hypermutated (MMR gene defect) or ultra-mutated (POLE mutation) on NGS	NCT02899793	Recruiting
Avelumab	Persistent or recurrent EM CA that are either 1) POLE mutated or MMR loss or 2) microsatellite stable on IHC	NCT02912572	Recruiting
Nivolumab; Nivolumab, Cabozantinib	Advanced, recurrent, or metastatic endometrial carcinoma or carcinosarcoma with MSI/MMR results available	NCT03367741	Not yet recruiting
Atezolizumab, Carboplatin, Cyclophosphamide	Advanced gynecologic cancer (endometrial, cervical, ovarian) or advanced breast cancer	NCT02914470	Active, not recruiting
Pembrolizumab, IMGN853	Advanced endometrial, epithelial ovarian, primary peritoneal, or fallopian tube cancer with folate receptor alpha positive tumor expression	NCT02606305	Recruiting
Nivolumab, Ipilimumab	Advanced or metastatic endometrial cancer (grade 3 endometrioid, serous, clear cell, or mixed high grade) or bone/soft tissue sarcoma; all must have MMR expression loss on IHC	NCT02982486	Not yet recruiting
Pembrolizumab, Carboplatin, Taxol	Advanced or recurrent endometrial carcinoma	NCT02549209	Recruiting
Durvalumab, Radiation Therapy; Durvalumab, Tremelimumab, Radiation Therapy	Advanced or recurrent endometrial, ovarian, fallopian tube, primary peritoneal, cervical, vaginal, or vulvar cancer	NCT03277482	Not yet recruiting

Em Ca IO Trials

Nivolumab	Metastatic or recurrent EM CA, carcinosarcoma, LMS, undiff. sarcoma, high grade endometrial stroma sarcoma, or ovarian/fallopian tube carcinosarcoma that are MSI-high, MMR-deficient, or hypermutated	NCT03241745	Recruiting
Vesicular stomatitis virus-human interferon beta-sodium iodide symporter (VSV-hIFNbeta-NIS)	Stage IV or recurrent EM CA (endometrioid, serous, undiff., clear cell, mixed, or other adenocarcinoma)	NCT03120624	Suspended (per study design)
Pembrolizumab, Immune Modul Cocktail (Vitamin D, Lansoprazole Teva, Cyclophosphamide, Aspirin), Radiation Therapy, Curcumin	Persistent or recurrent endometrial carcinoma, cervical carcinoma, or uterine sarcoma	NCT03192059	Recruiting
Spartalizumab, MCS110 (Anti-M-CSF Monoclonal Antibody)	Advanced EM CA, melanoma, pancreatic, or triple negative breast cancer	NCT02807844	Recruiting

Checkpoint Inhibitors in EM CA: Increased Activity with MSI-H

	Fader et al.[1]	KEYNOTE-028[2]	NCT01375842[3]	NCT02501096[4]	GARNET[5]	Pooled MSI-H[6]
Phase	2	1b	1a	1b/2	1/2	1 and 2
Population	Previously treated dMMR-recurrent or persistent EC	Previously treated locally advanced or metastatic PD-L1+ EC	Recurrent EC	Advanced EC	Previously treated recurrent/advanced MSI-H EC	Previously treated MSI-H/dMMR EC[b]
Patients, n	9	24	15	54	35	14
Treatment	Pembrolizumab	Pembrolizumab	Atezolizumab	Pembrolizumab + lenvatinib	TSR-042	Pembrolizumab
ORR, %	56[a]	13.0[a]	13	36.7	52[a]	36[a]
DCR, %	89	26.0	27	—	64	—
DOR	—	—	—	NR	NR	Range: 4.2+–17.3+ mo[a]
mPFS	—	1.8 mo	1.7 mo	10.1 mo	—	—
mOS	NR	NR	9.6 mo	—	—	—
Safety summary	No AEs >Gr 3	≥Gr 3 TRAEs: 16.7%	Any TRAE: 47%	≥Gr 3 TRAEs: 59%	≥Gr 3 TRAEs: 11.4%	Per label
Median follow-up	9.1 mo	76.2 wk	Min: 11.2 mo	4.0 mo	—	—

[a] Primary endpoint. [b] Data pooled across 5 trials; these data led to approval of pembrolizumab for advanced or unresectable MSI-H/dMMR tumors.

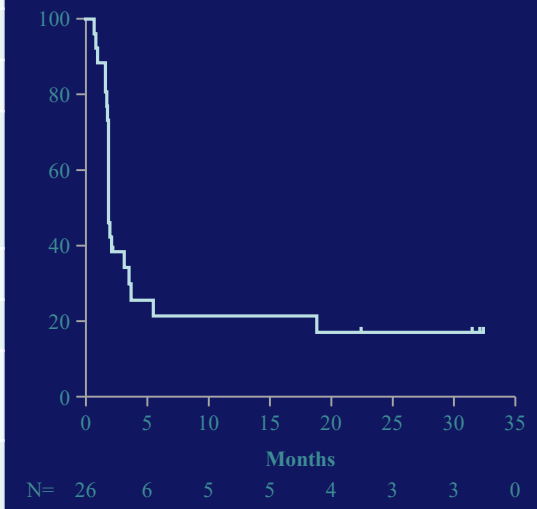
AE, adverse event; DCR, disease control rate; dMMR, deficient mismatch repair; DOR, duration of response; EC, endometrial cancer; Gr, grade; Min, minimum; mOS, median overall survival; mPFS, median progression-free survival; MSI-H, microsatellite instability high; NR, not reached; ORR, overall response rate; TRAE, treatment-related adverse event.

1. Fader AN, et al. Presented at SGO, 2016. **2.** Ott PA, et al. *J Clin Oncol*. 2017;35(22):2535-41. **3.** Fleming GF, et al. Presented at ASCO Annual Meeting, 2017. Abstract 5585. **4.** Makker V, et al. Presented at ASCO Annual Meeting, 2018. Abstract 5596. **5.** Oaknin A, et al. Presented at ESMO, 2018. Abstract 935PD. **6.** Pembrolizumab package insert. Merck & Co, Inc; December 2018.

Checkpoint Inhib. Monotherapy in Ovarian Ca

	Hamanishi[1]	JAVELIN Solid Tumor[2]	KEYNOTE-028[3]	KEYNOTE-100[4]
Phase	2	1b	1b	2
Population	PROC (80% PD-L1 high)	PROC (77% PD-L1+)	PD-L1+ PROC	Advanced OC with recurrence after 1L Pt
Patients, n	20	124	26	376
Treatment	Nivolumab	Avelumab	Pembrolizumab	Pembrolizumab
ORR, %	15 PD-L1 high: 12.5	9.7 PD-L1+: 12.3	11.5	All comers: 8.0 Cohort A: 7.4[a] Cohort B: 9.9[b]
DCR, %	45	54.0	38.4	All comers: 37.2
mDOR	—	—	NR	All comers: 8.2 mo
mPFS	3.5 mo	11.3 wk	1.9 mo	Cohort A: 2.1 mo[a] Cohort B: 2.1 mo[b]
OS	20.0 mo	10.8 mo	13.8 mo	Cohort A: NR[a] Cohort B: 17.6 mo[b]
Safety summary	Gr 3/4 TRAEs: 40%	Gr 3/4 TRAEs: 6.4%	Gr 3 AE: 1 pt	Gr 3/4 TRAEs: 19.7%
Follow-up	11.0 mo	12.4 mo	15.4 mo	16.9 mo

PFS Observed With Pembrolizumab Treatment in KEYNOTE-028[3]



N is small, but there appears to be a population of patients who have durable PFS with checkpoint inhibitor therapy

[a] 1 to 3 prior lines of therapy; PFI/TFI 3 to 12 months. [b] 4 to 6 prior lines of therapy; PFI/TFI ≥3 months.

DCR, disease control rate; Gr, grade; mDOR, median duration of response; mPFS, median progression-free survival; NR, not reached; ORR, overall response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFI, platinum-free interval; PFS, progression-free survival; PROC, platinum resistant ovarian cancer; TFI, treatment-free interval; TRAE, treatment-related adverse event.

1. Hamanishi J, et al. *J Clin Oncol*. 2015;33(34):4015-22. **2.** Disis ML, et al. Presented at ASCO Annual Meeting, 2016. Abstract 5533.
3. Varga A, et al. *Gynecol Oncol*. 2019;243-50. **4.** Matulonis UA, et al. Presented at ASCO Annual Meeting, 2018. Abstract 5511.

Ovarian Cancer Checkpoint Inhibitor Trials: Combinations

	TOPACIO / KEYNOTE-162[1]	NCT02484404[2]	NCT02431559[3]	NRG-GY003[4]
Phase	1/2	1/2	1/2	2
Population	PROC cohort	Persistent/recurrent OC	Recurrent PROC	Persistent/recurrent OC
Patients, n	62 (60 eval)	35	40	100
Treatment	Pembrolizumab + niraparib	Durvalumab + olaparib	Durvalumab + PLD	Nivolumab + ipilimumab
ORR, %	25 PD-L1+: 21	14 (not sufficient for further study)	15.0	31.4
DCR, %	67	37	60.0	—
mDOR	9.3 mo	—	125.5 days	—
mPFS	—	5 mo	5.5 mo	—
OS	—	—	NE	—
Safety summary	Anemia (21%), thrombo (9%),	Gr 3 TRAEs: 19 pts Grade 4 TRAEs: 0	≥ Gr 3 TRAEs: 48%	≥ Gr 3 TEAEs: 67%

DCR, disease control rate; mDOR, median duration of response; mPFS, median progression-free survival; Not estimable; OC, ovarian cancer; ORR, overall response rate; OS, overall survival; PD-L1, programmed death ligand 1; PLD, pegylated liposomal doxorubicin; PROC, platinum resistant ovarian cancer; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

1. Konstantinopoulous P, et al. Presented at ASCO Annual Meeting, 2018. Abstract 106. **2.** Lee JM, et al. Presented at ESMO, 2018. Abstract 936PD. **3.** O'Cearbhaill RE, et al. Presented at ESMO, 2018. Abstract. 945P. **4.** Burger R, et al. Presented at IGCS, 2018.

Ongoing Checkpoint Inhibitors Trials in Ovarian Cancer

Phase I/II

Numerous Phase 1 and 2 trials are investigating checkpoint inhibitors alone or in combination with other therapies[1]

- Combinations being evaluated include CPIs in combination with chemotherapy, PARPi, IO therapies, TKIs, anti-angiogenics

Phase III

Checkpoint Inhibitor + PARPi

- NCT03642132 (Javelin Ovarian PARP 100): avelumab + talazoparib
- NCT03522246 (ATHENA): rucaparib + nivolumab

Checkpoint Inhibitor + Anti-angiogenic + Chemotherapy

- NCT03737643 (DUO-O): durvalumab + bevacizumab + chemotherapy
- NCT03353831 (AGO-OVAR 2.29) atezolizumab + bevacizumab + chemotherapy
- NCT02891824 (ATALANTE): atezolizumab + bevacizumab + chemotherapy
- NCT02839707 (NRG-GY009): atezolizumab + PLD ± bevacizumab*
- NCT03038100 (IMagyn050/GOG 3015/ENGOT-ov39): atezolizumab + chemotherapy + bevacizumab

Checkpoint Inhibitor + PARPi + Chemotherapy

- NCT03598270 (ANITA): atezolizumab + niraparib + chemotherapy
- NCT03602859 (FIRST): TSR-042 + chemotherapy + niraparib
- NCT03740165 (ENGOT-ov43/KEYLYNK-001): pembrolizumab + chemotherapy + olaparib

JAVELIN Ovarian 100 (NCT02718417) & **JAVELIN Ovarian 200** (NCT02580058) trials of avelumab in treatment of 1L or 2L ovarian ca- terminated after failing to meet primary endpoints in 2019 & 2018.

CPI, checkpoint inhibitor; IO, immuno-oncology; L, line; PARP, poly ADP ribose polymerase; PARPi, poly ADP ribose polymerase inhibitor; PLD, pegylated liposomal doxorubicin; TKI, tyrosine kinase inhibitor.

1. Castellano T, et al. *Clin Ther.* 2018;40(3):372-88. 2. Clinicaltrials.gov. NCT03642132, NCT03522246, NCT03737643, NCT03353831, NCT02891824, NCT02839707, NCT03038100, NCT03598270, NCT03602859, NCT03740165. Accessed Jan 18, 2019.

Conclusions

- Immuno-oncology: exciting, emerging & extremely complex
- NextGen technologies & systems biology will dynamically profile vulnerabilities
- PD-1 blockade may unleash diverse antitumor T cell re-activities.
- MSI High is Universal target
- Multiple I/O trials in Gyn Cancers- combos appear promisng