Immunotherapies in Gynecologic Malignancies

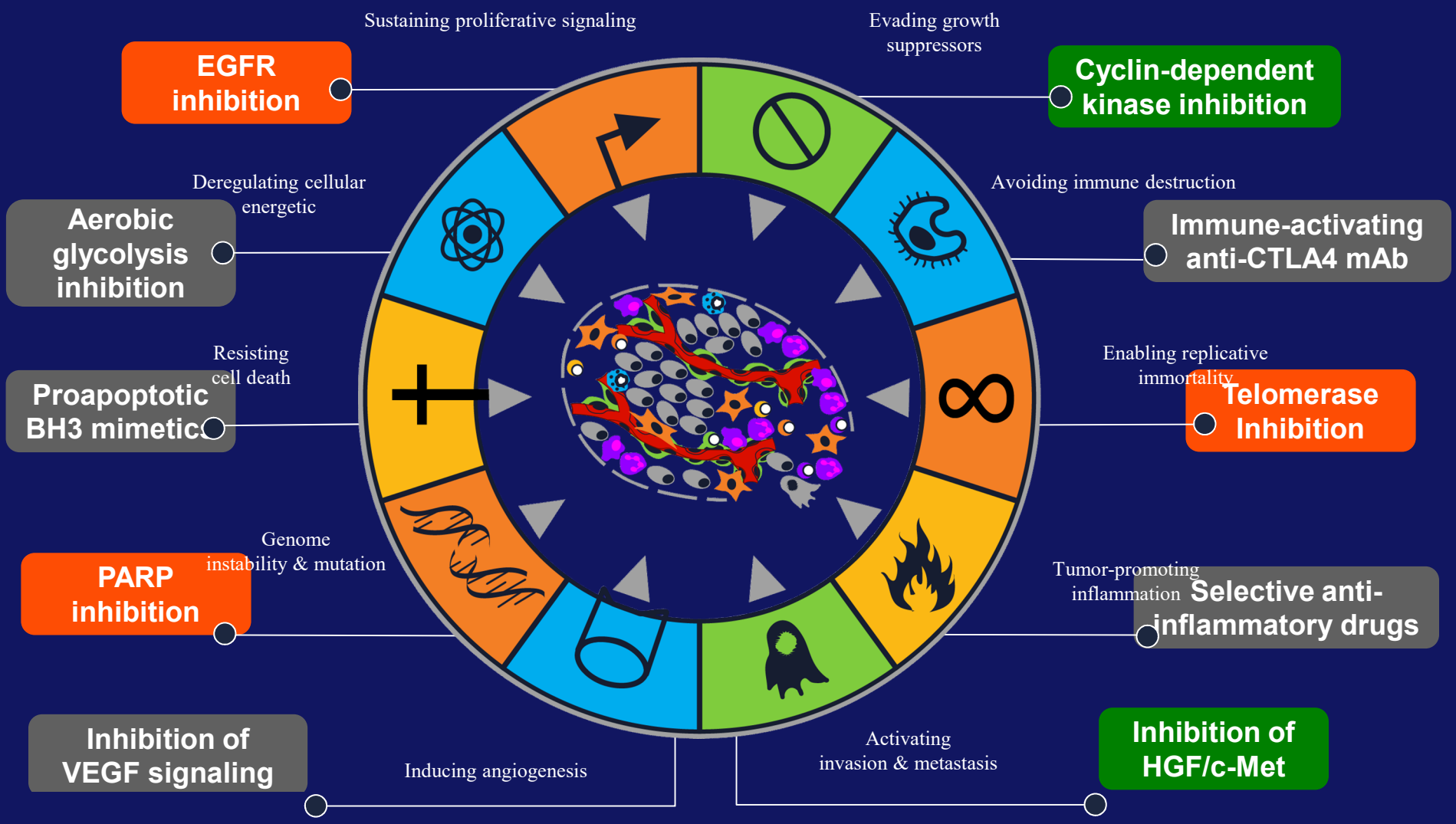
Thomas J. Herzog, MD
Paul & Carolyn Flory Professor
Deputy Director, UC Cancer Institute
Vice Chair Quality & Safety, Dept Ob/Gyn
University of Cincinnati

Disclosures

Scientific Advisory Board:

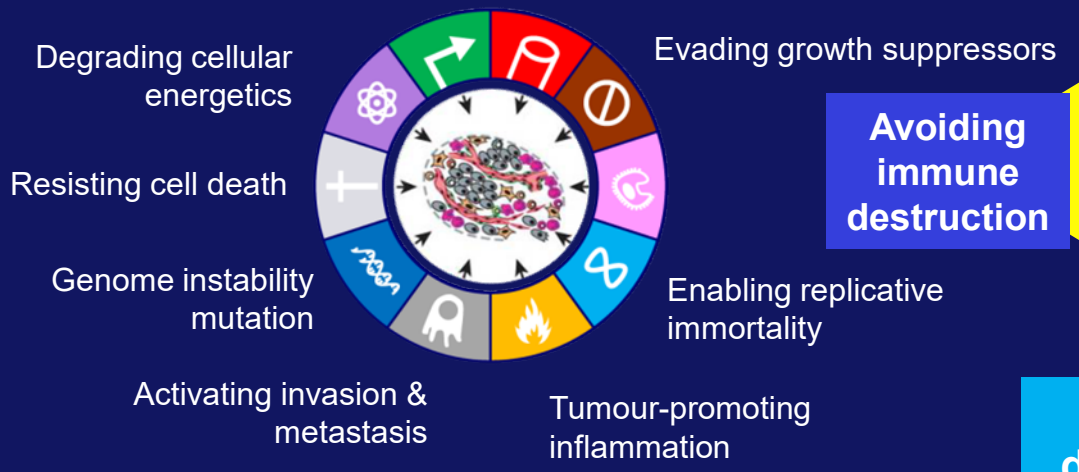
AZ, Caris, Clovis, Genentech, J & J, Tesaro

Strategies Targeting Hallmarks of Cancer



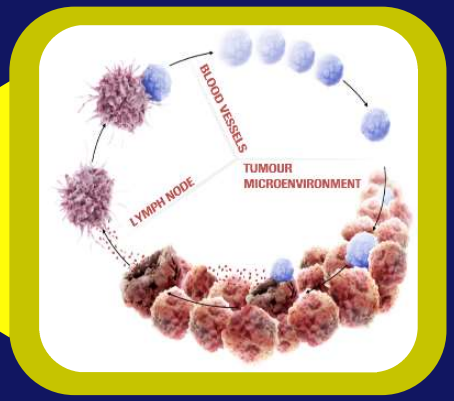
Hanahan and Weinberg. Cell. 2011;144(5):646-74.

Avoiding immune destruction is a hallmark of cancer



Avoiding immune destruction

Cancer-immunity cycle

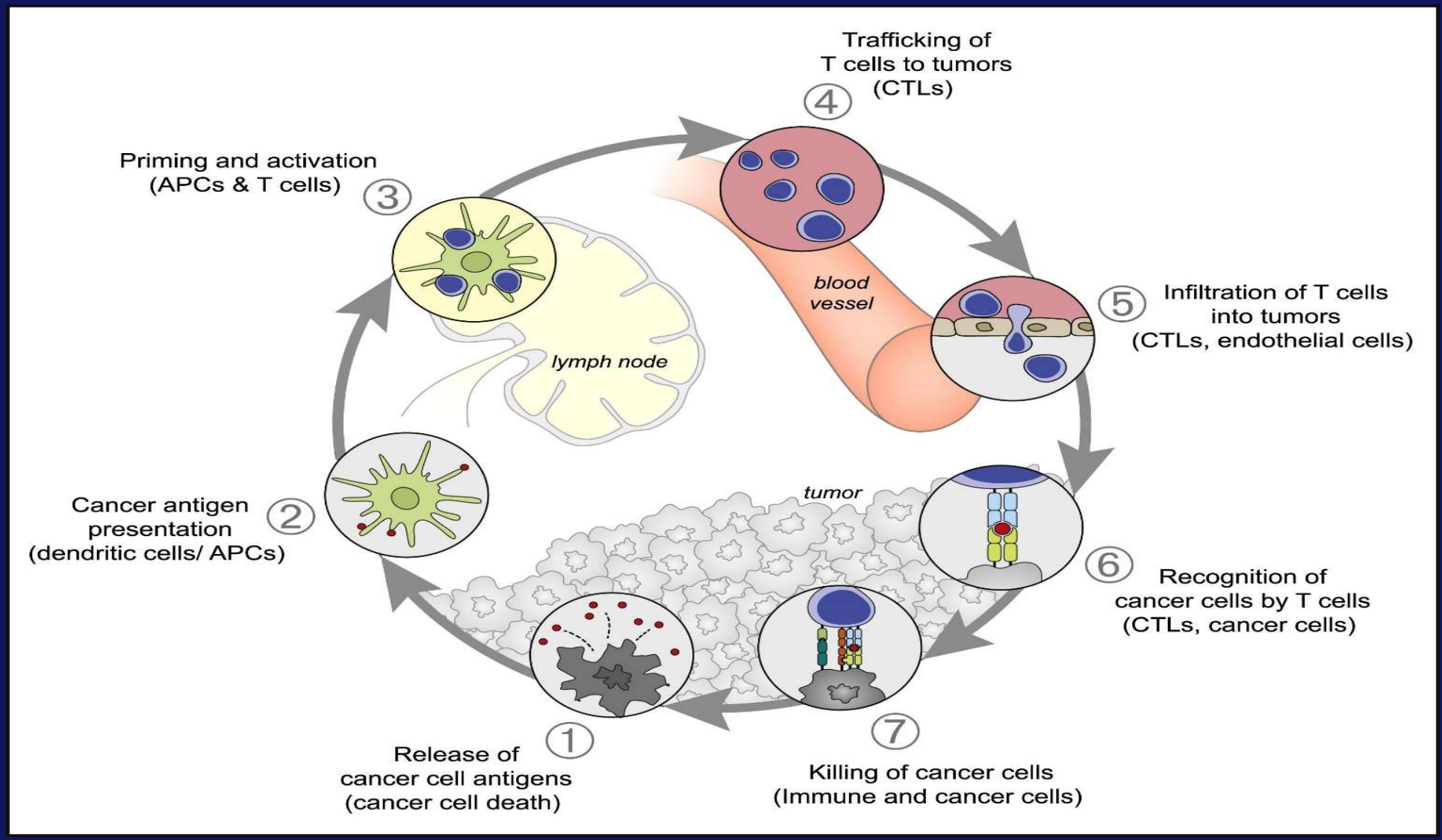


The cancer-immunity cycle describes the process by which the immune system recognises, targets and kills cancer cells

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

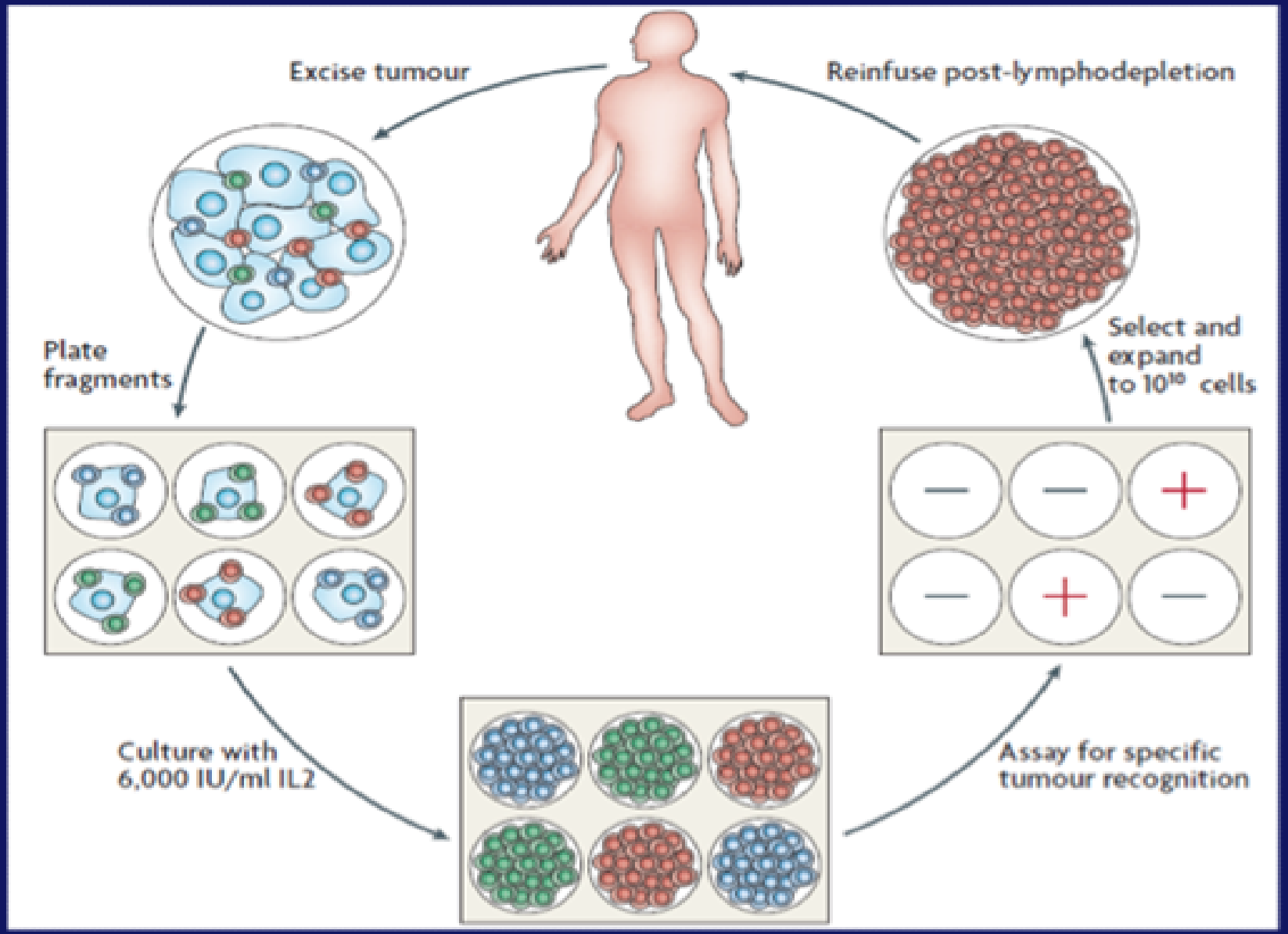
1. Hanahan & Weinberg. Cell 2011; 2. Chen & Mellman. Immunity 2013

Cancer-Immunity Cycle

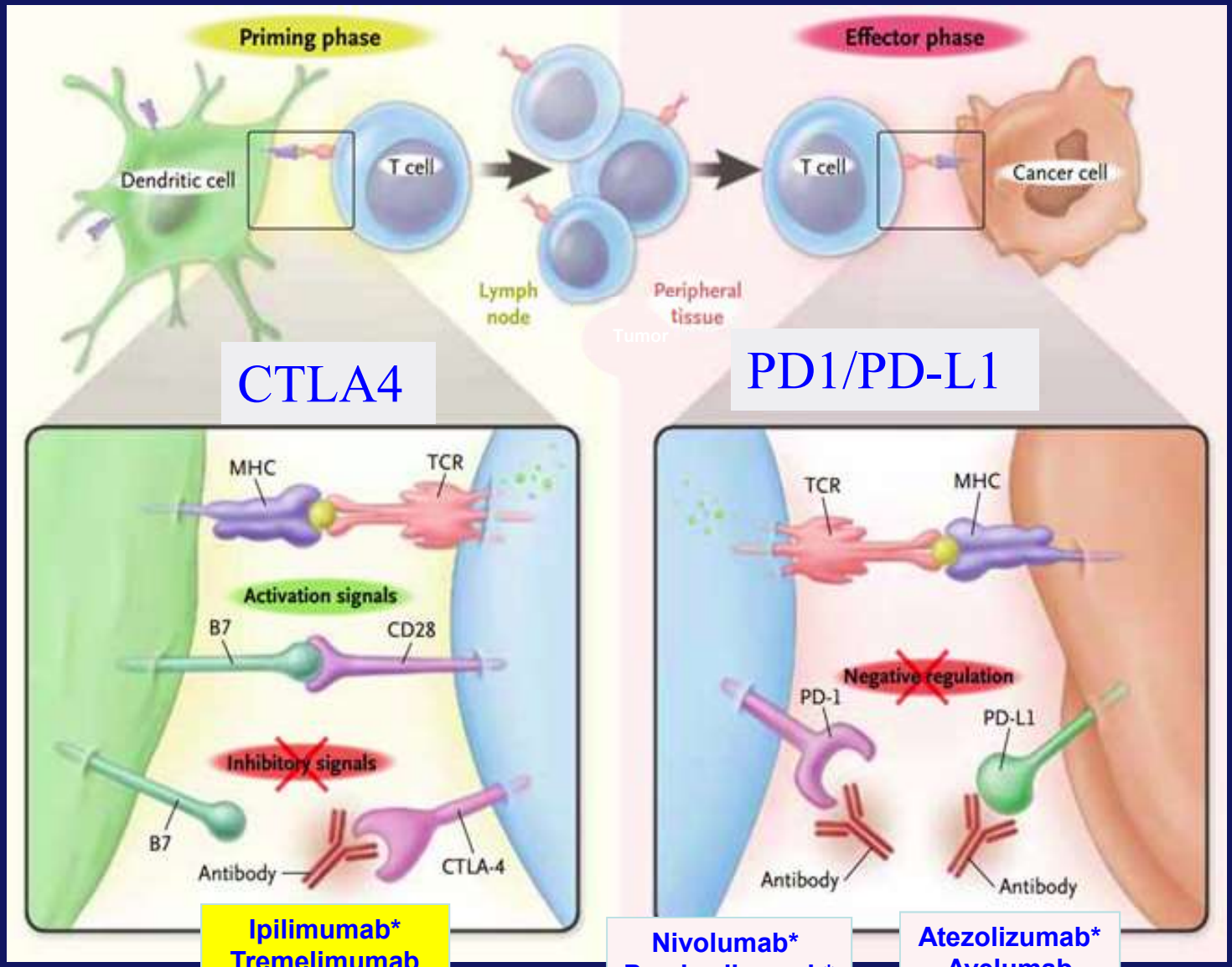


Immunity 2013 39, 1-10DOI: (10.1016/j.immuni.2013.07.012)

Ex vivo TIL Expansion



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



Ipilimumab*
Tremelimumab

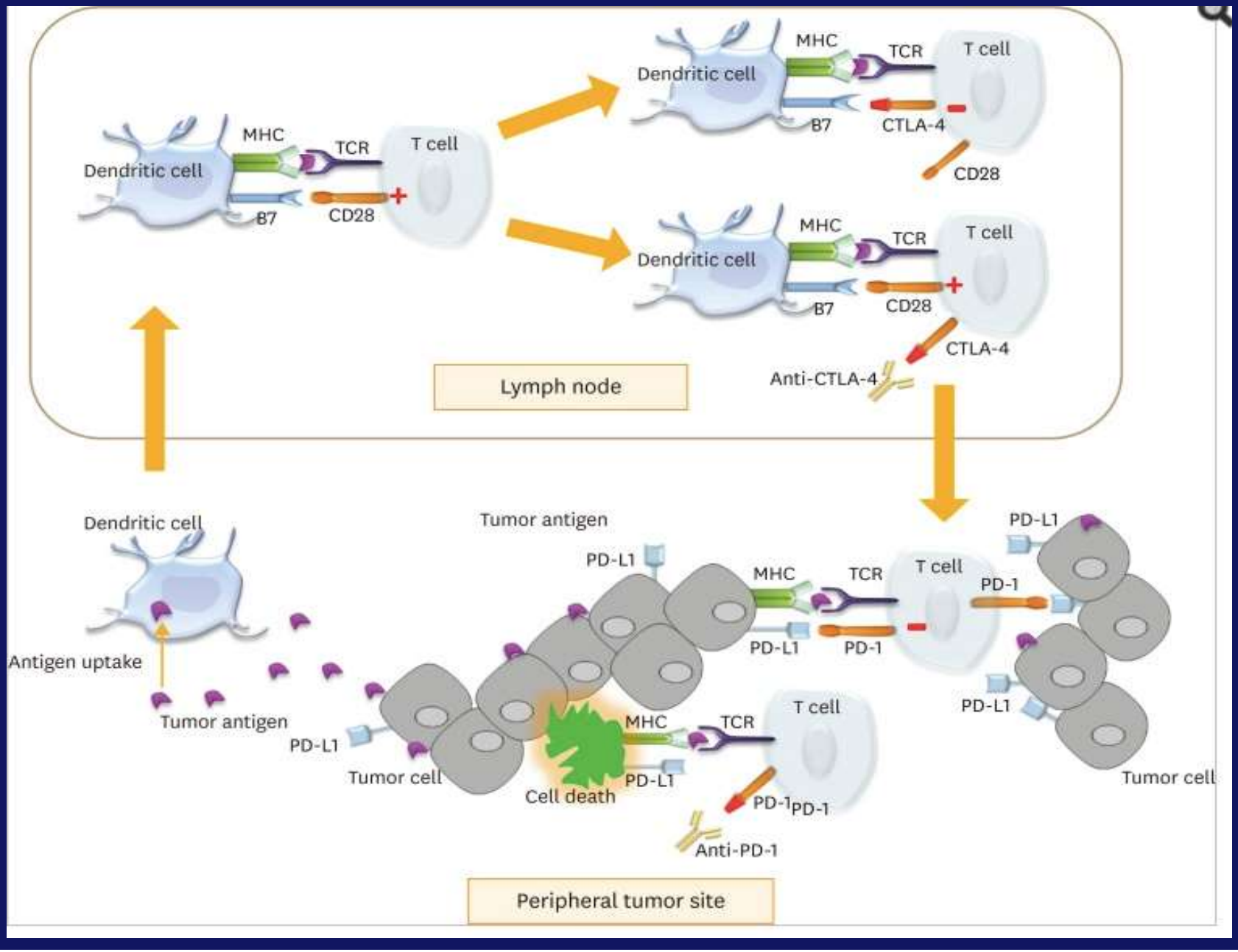
Nivolumab*
Pembrolizumab*

Atezolizumab*
Avelumab
Durvalumab

* FDA-approved

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

Checkpoint Inhibition



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)

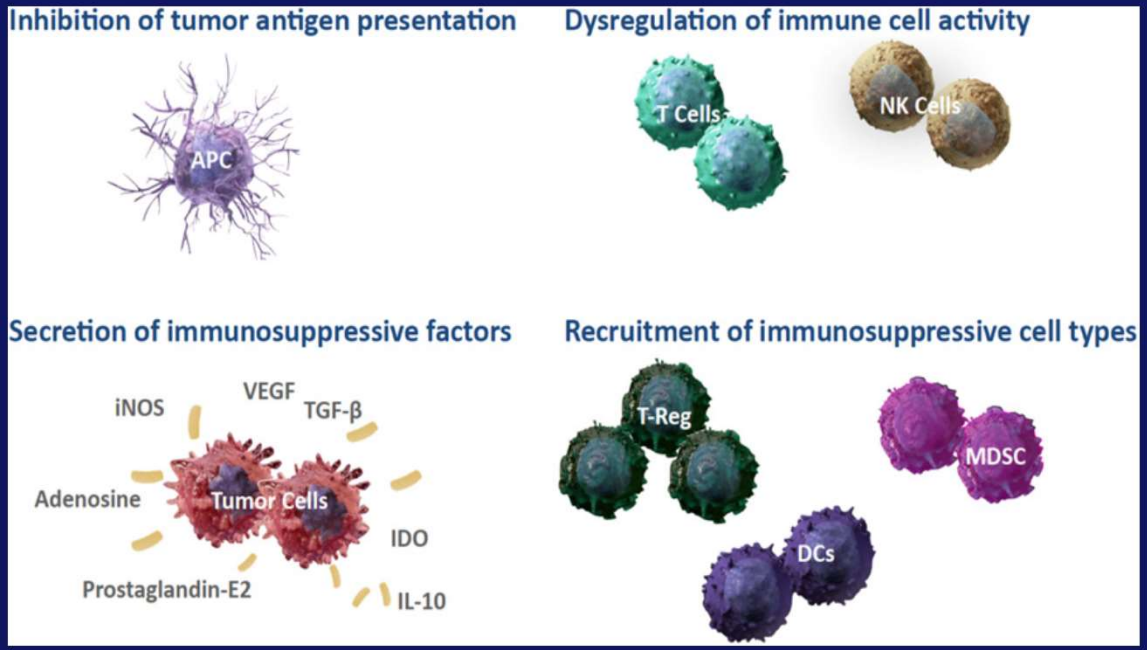
1. Hodi FS et al. *Proc Natl Acad Sci USA*. 2008;105:3005-3010. **2.** Hamanishi J et al. *J Clin Oncol*. 2015;33:4015-4022. **3.** Varga A et al. Presented at ASCO 2015. Abstract 5510. **4.** Disis ML et al. Presented at ASCO 2016. Abstract 5533 **5.** Romano E et al. *Proc Natl Acad Sci U S A*. 2015;112(19):6140-6145. **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.

Harnessing the Immune System for Therapeutic Benefit

Predictors of Response to Checkpoint Inhibition

1. PD-L1 expression
2. Amount of TIL's tumor-infiltrating lymphocytes (inflamed tumor)
3. Mutational burden (neoantigens)
4. Other unknown

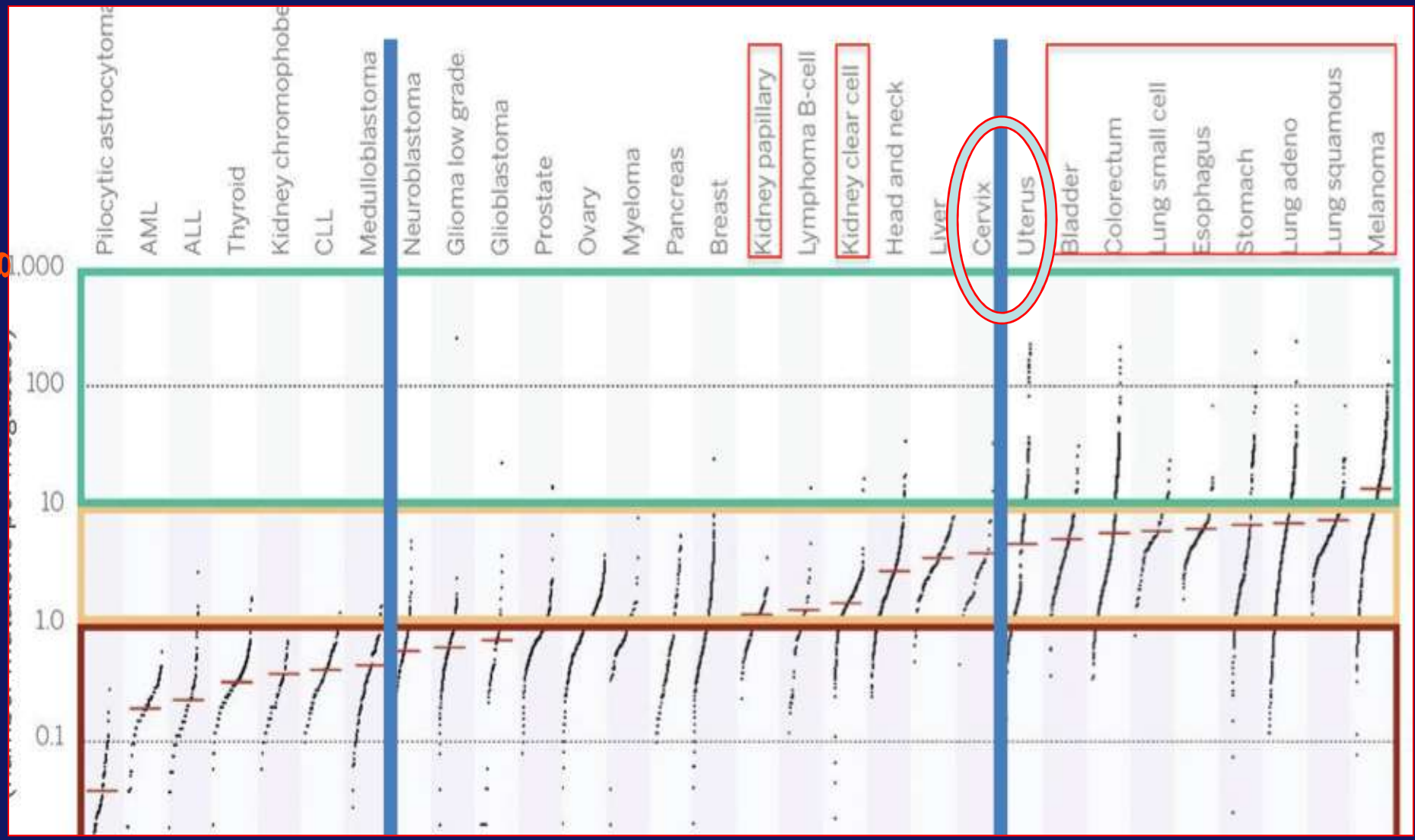
Mechanisms exploited by tumors to evade & suppress immune system



Pennock GK, et al. *Oncologist*. 2015;20(7):812-22.

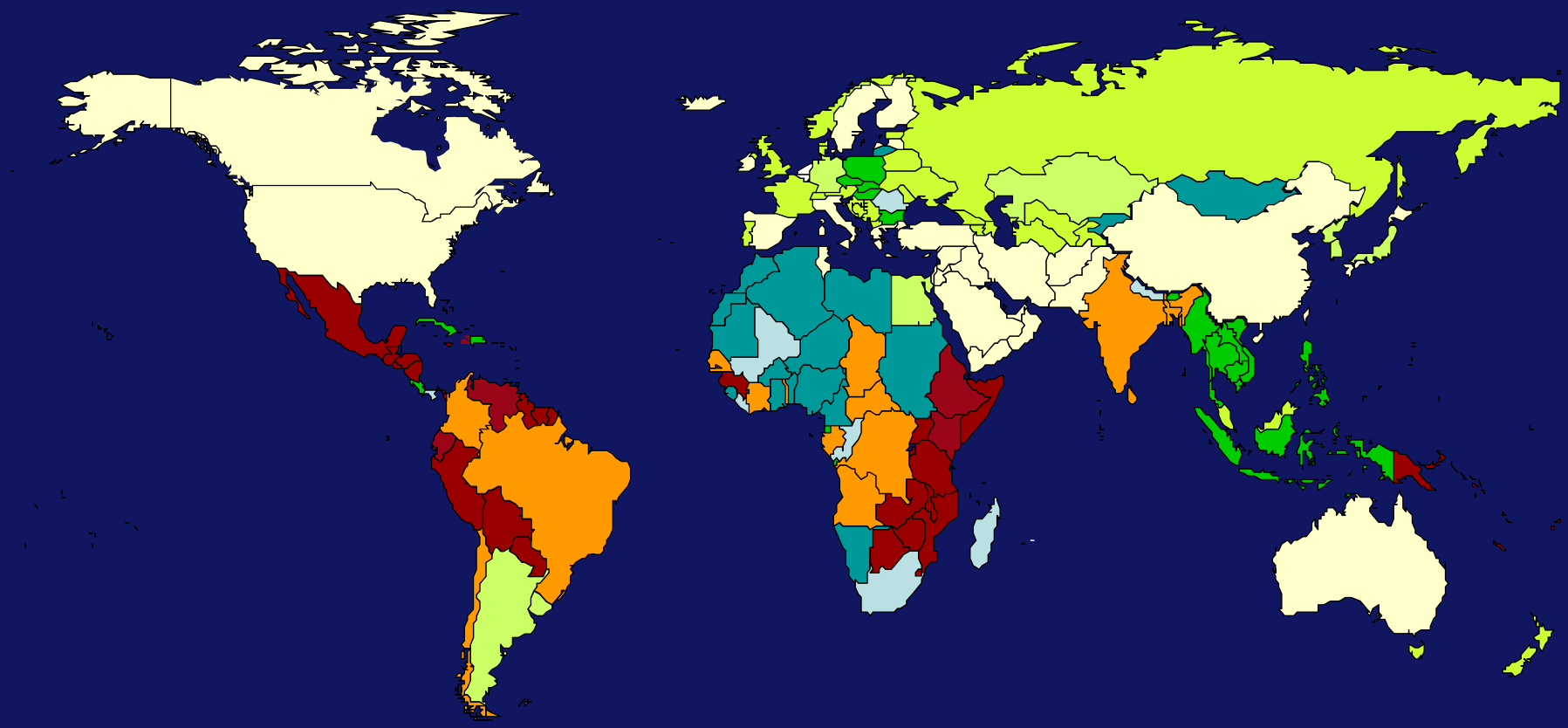
DC, dendritic cell; IDO, indoleamine 2,3-dioxygenase; iNOS, inducible nitric oxide synthase; MDSC, myeloid-derived suppressor cell; NK, natural killer

Frequency of Somatic Mutations Across Tumor Types



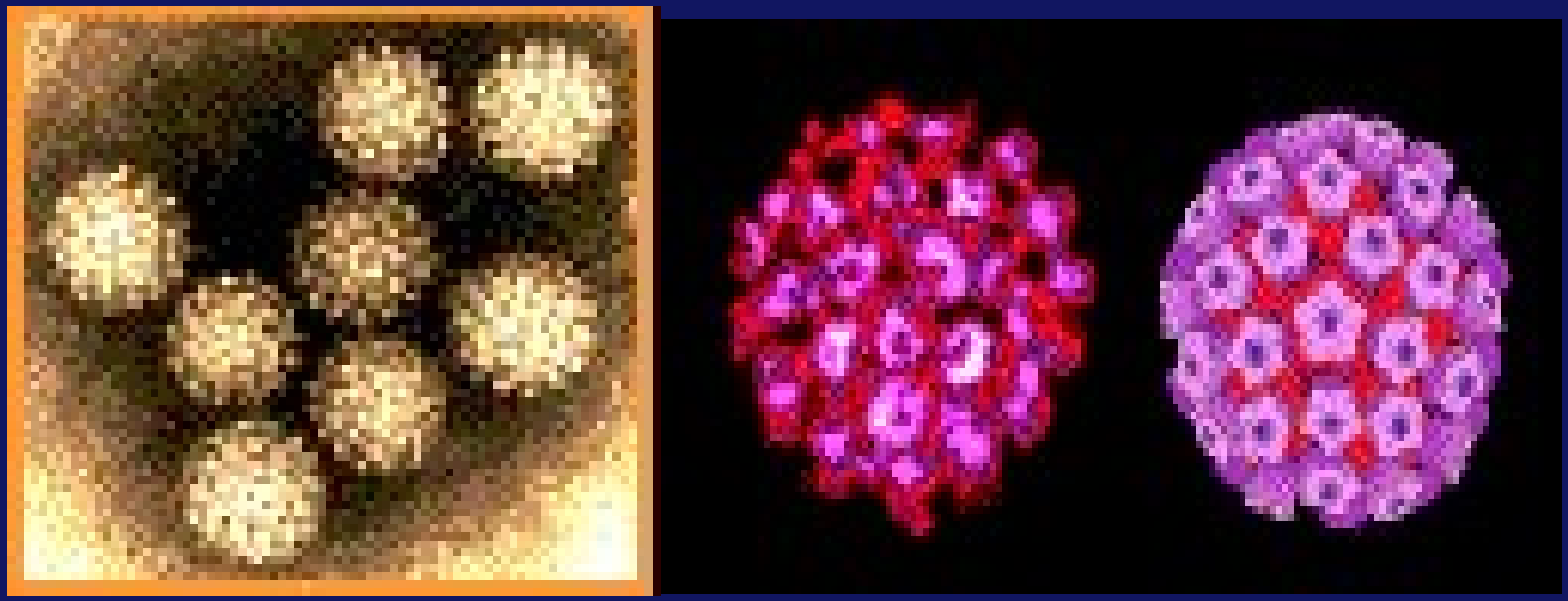
Schumacher TN and Schreiber RD, *Science*, 2015

Estimates of the Worldwide Incidence of Cervical Cancer



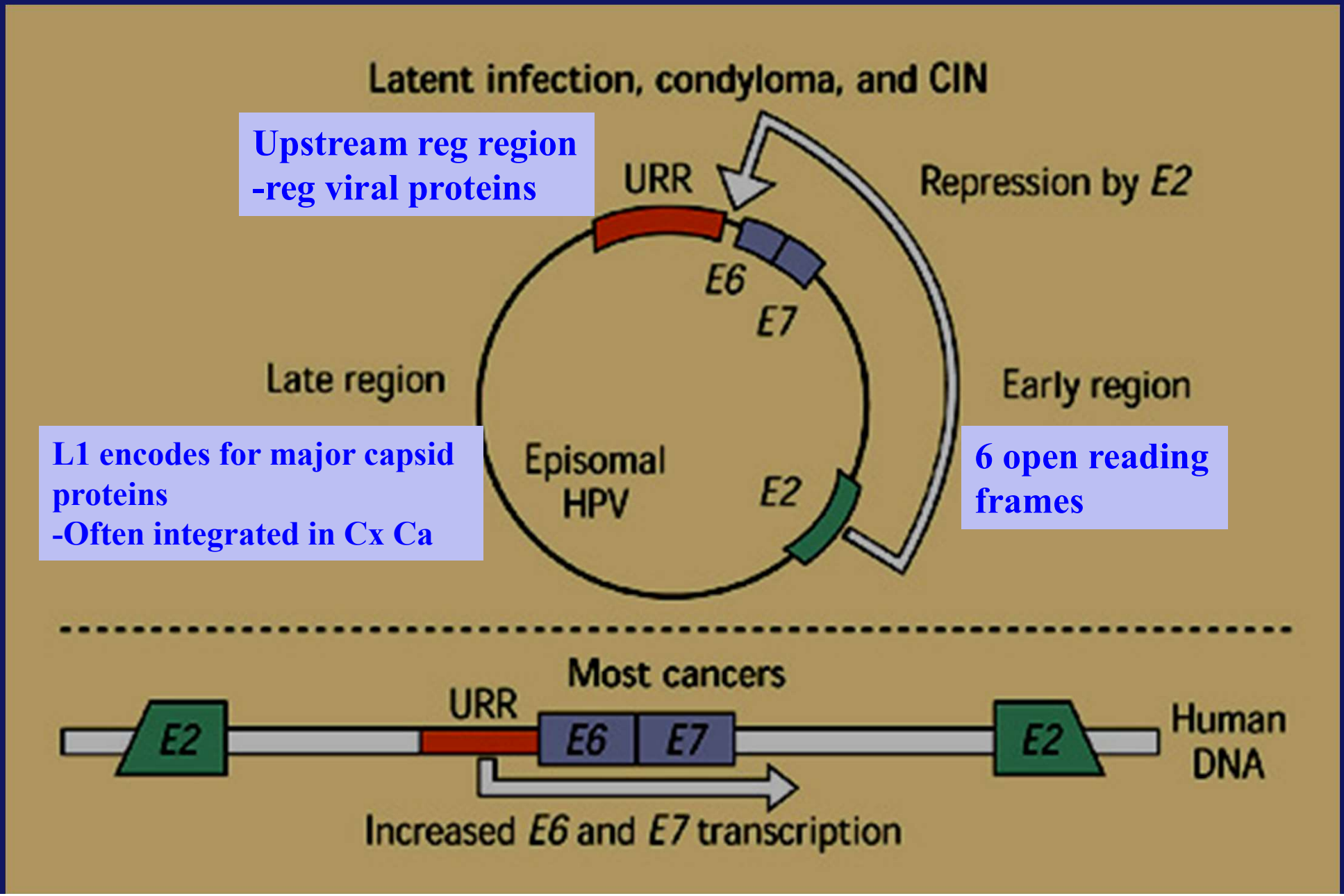
Source : GLOBOCAN 2014; IARC

Human Papillomavirus



Non enveloped Icosahedral DNA Virus

HPV Genome & Carcinogenesis

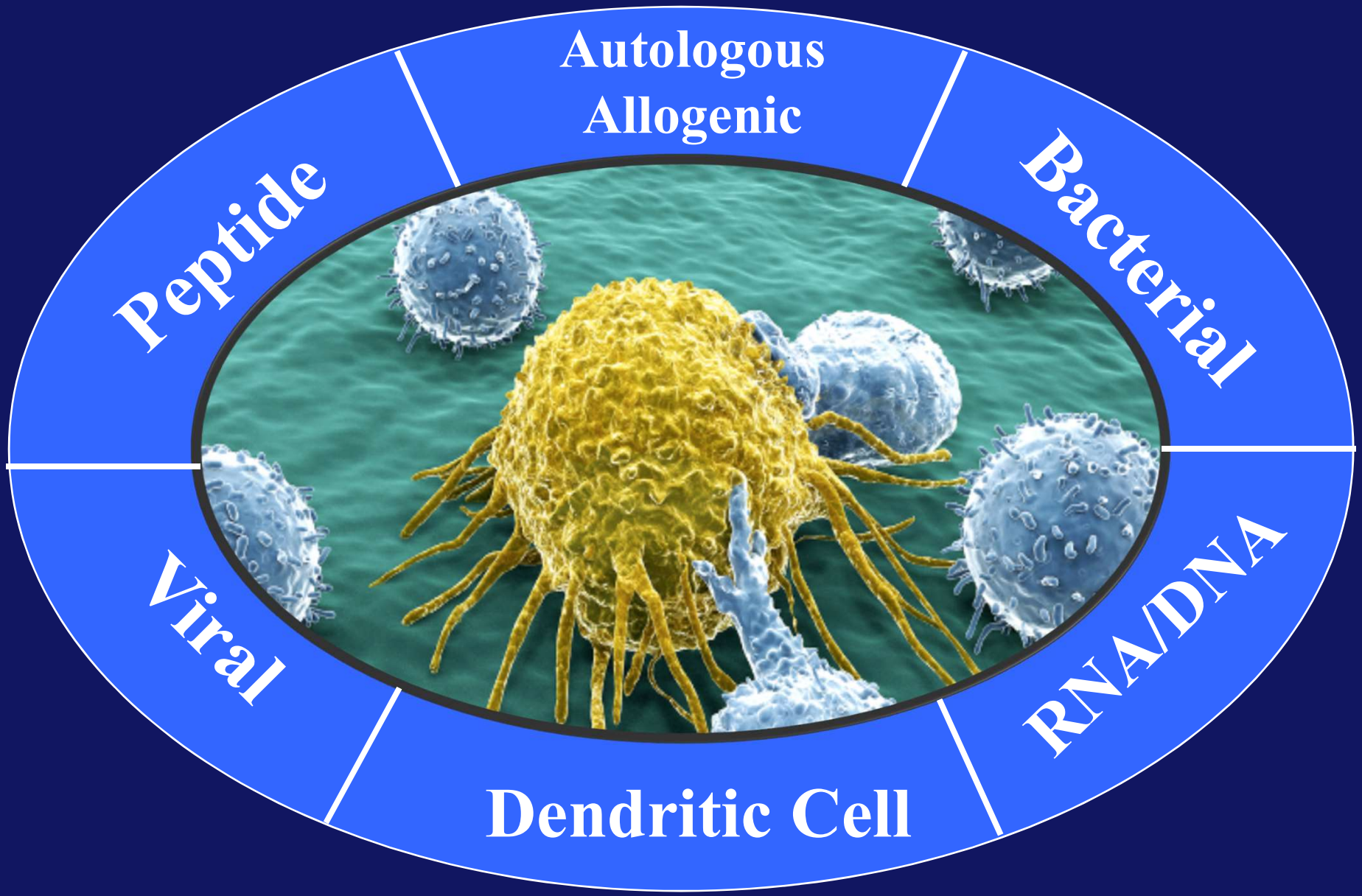


Categories of HPV Vaccines

- ***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*

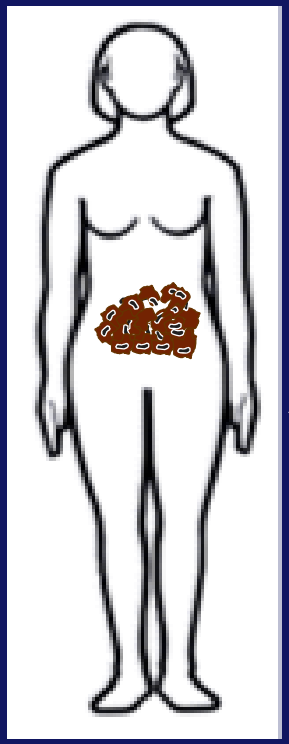
Vaccine Approaches



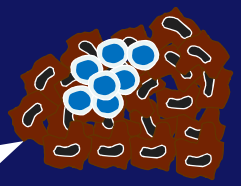
Select HPV Vaccines

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

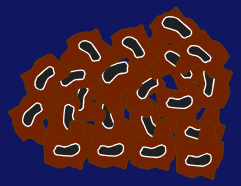


TIL^{+}



+ Checkpoint blockade

TIL^{-}

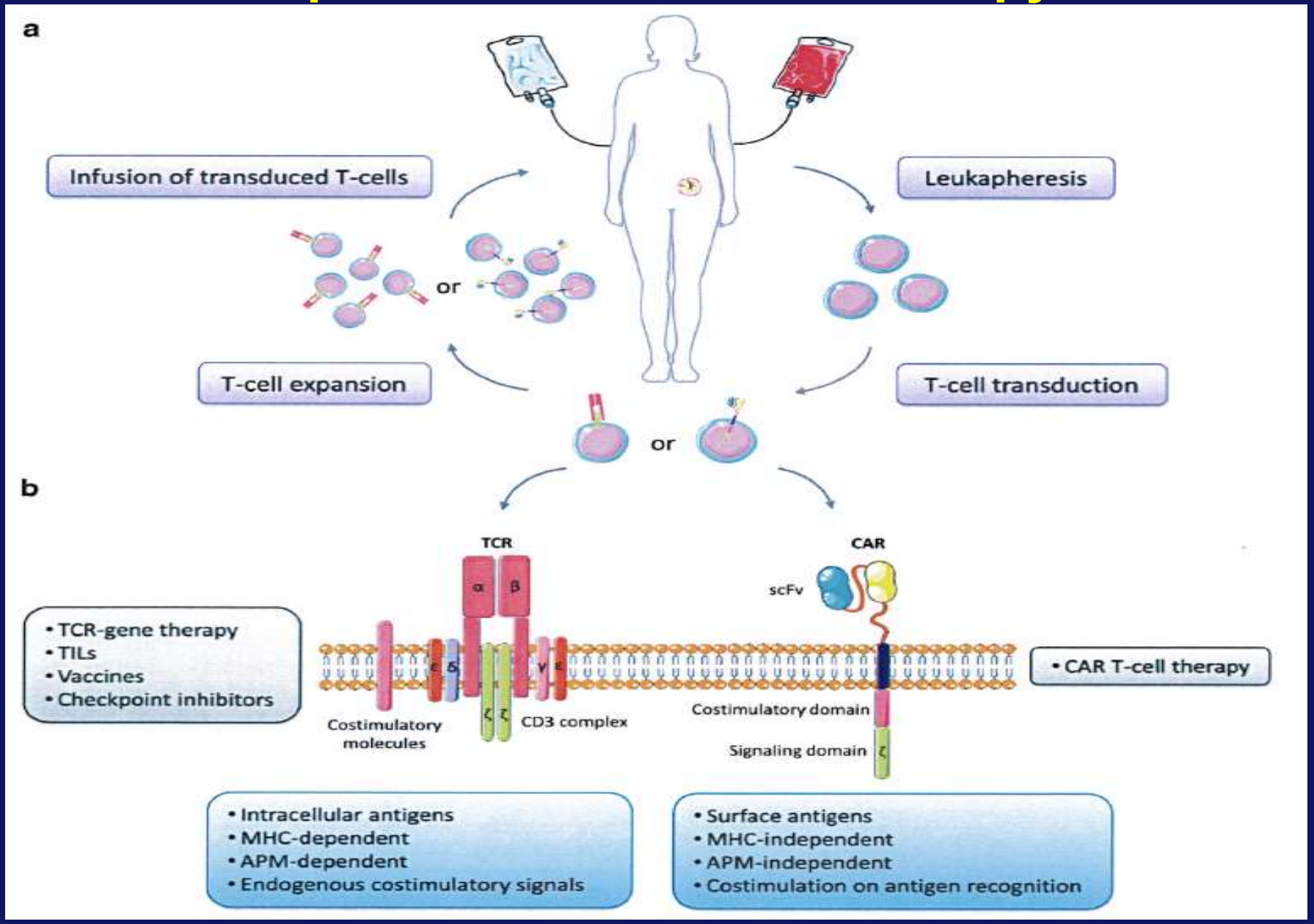


+ Immune-activating cytokines
+ TLR agonists
+ oncolytic viruses

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

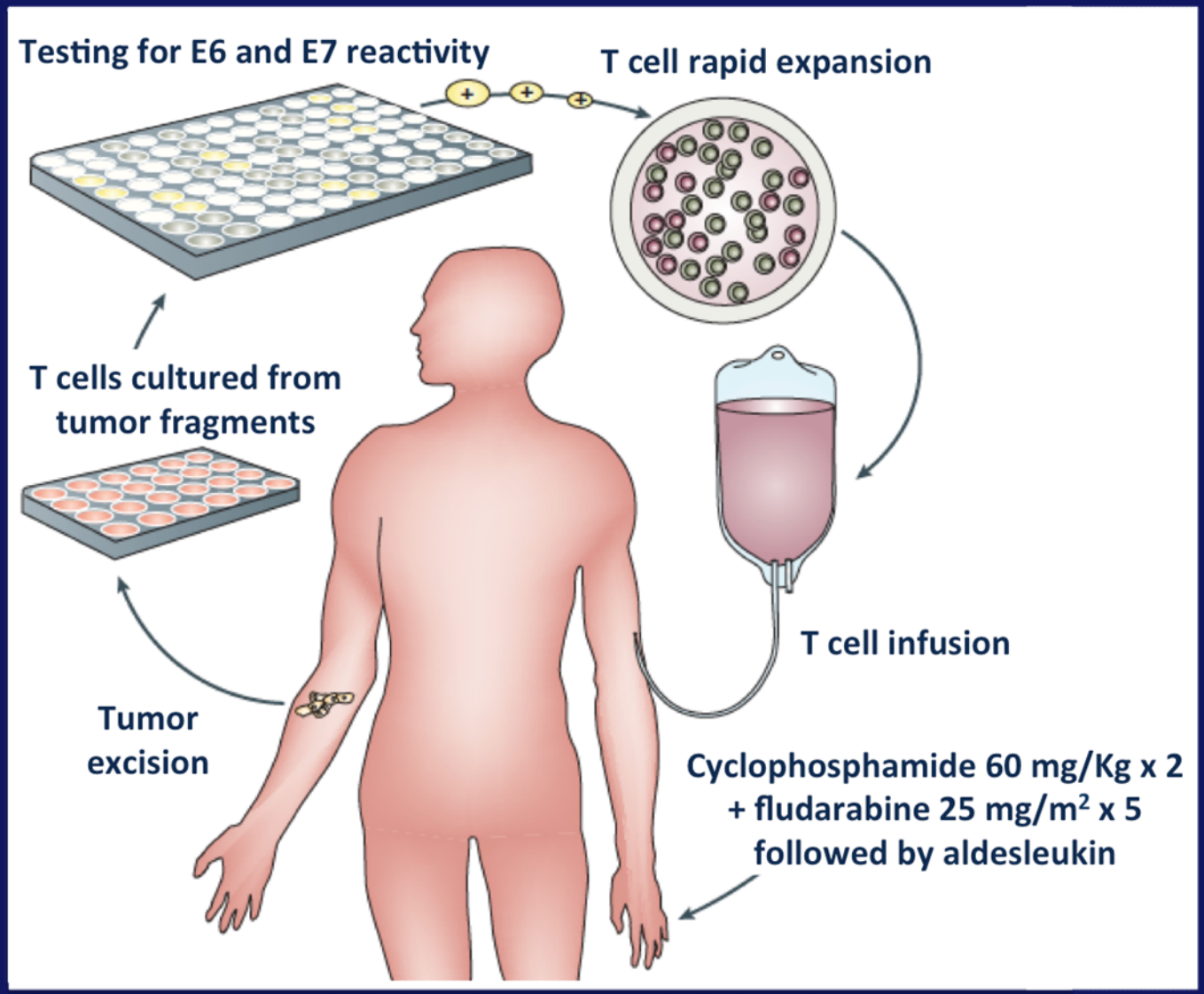
Ribas *et al*, Cancer Discov 2015

Adoptive T-cell Transfer Therapy



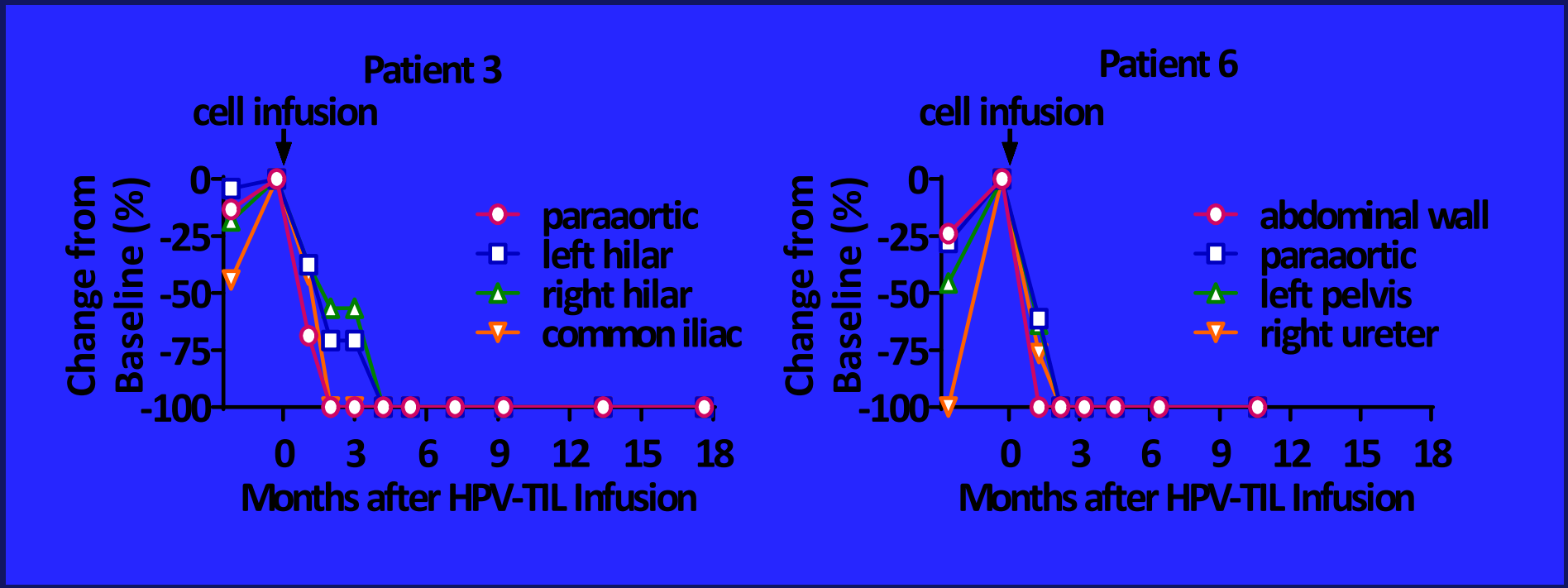
Rodriguez-Garcia A et al Gyn Onc 2017

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

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

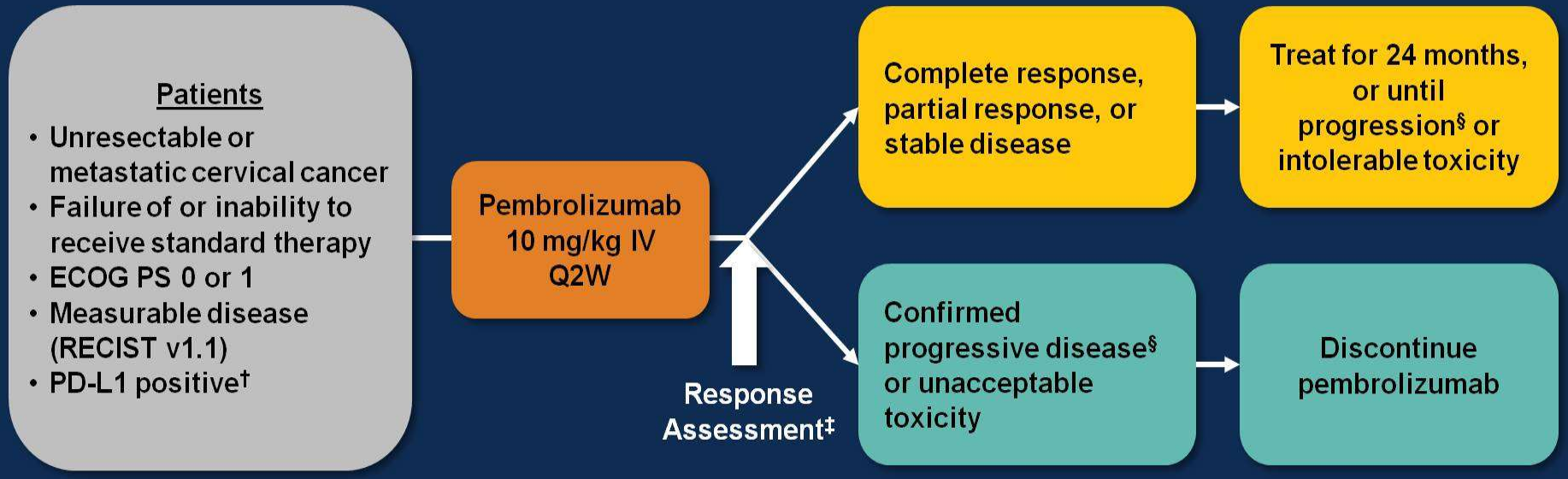
- 10 mg/kg every 21 days for four cycles; followed by four cycles of maintenance therapy (same dose) every 12 weeks
- 42 patients, median age of 49 years (23-78)
  - 29 squamous, 13 adenocarcinoma
  - 35 had prior radiation completed
  - 21 had received 2/3 prior regimens
- 34 evaluable patients: 2 PR (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.

PRESENTED AT: ASCO ANNUAL MEETING '16

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

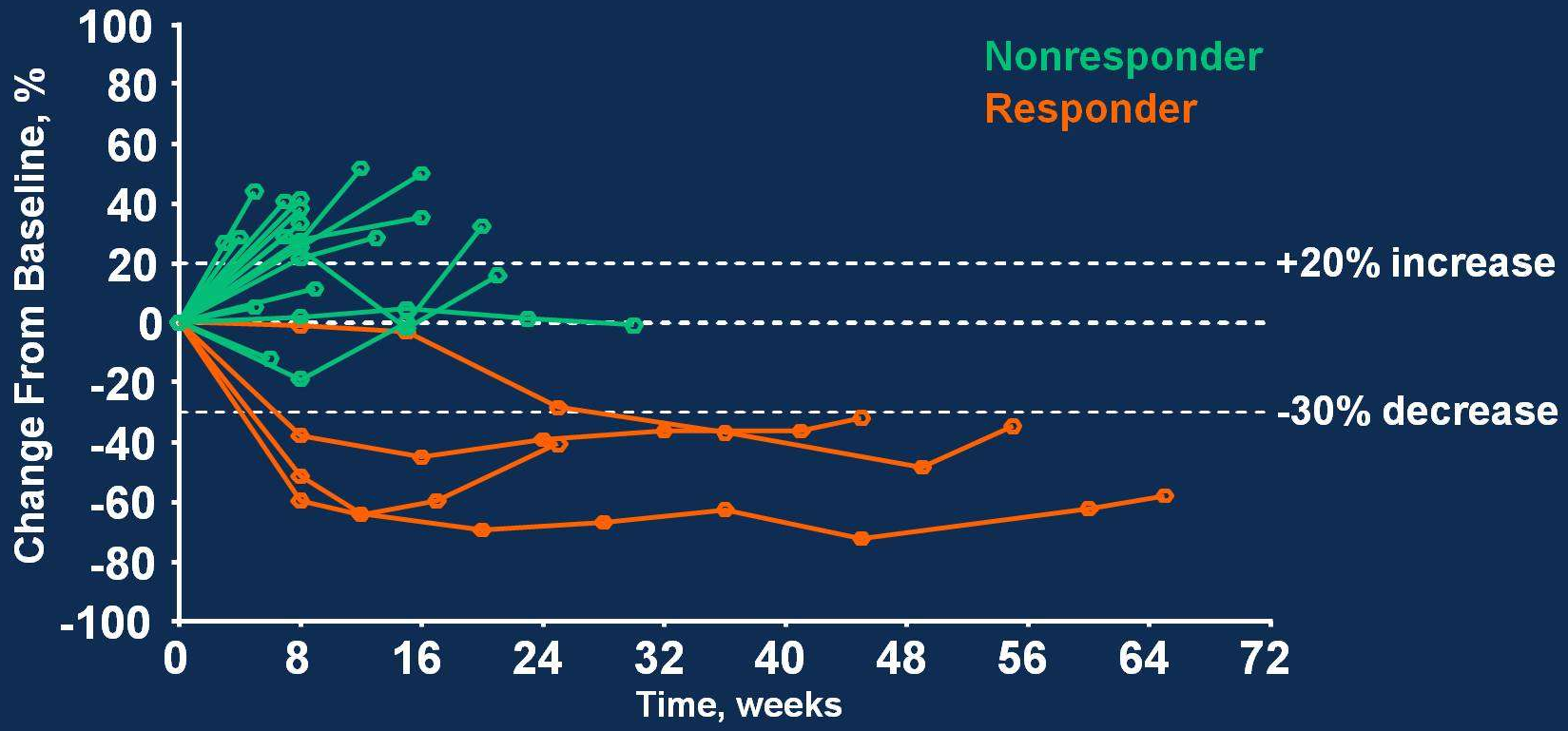
Antitumor Activity (RECIST v1.1, Investigator Review)

	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)



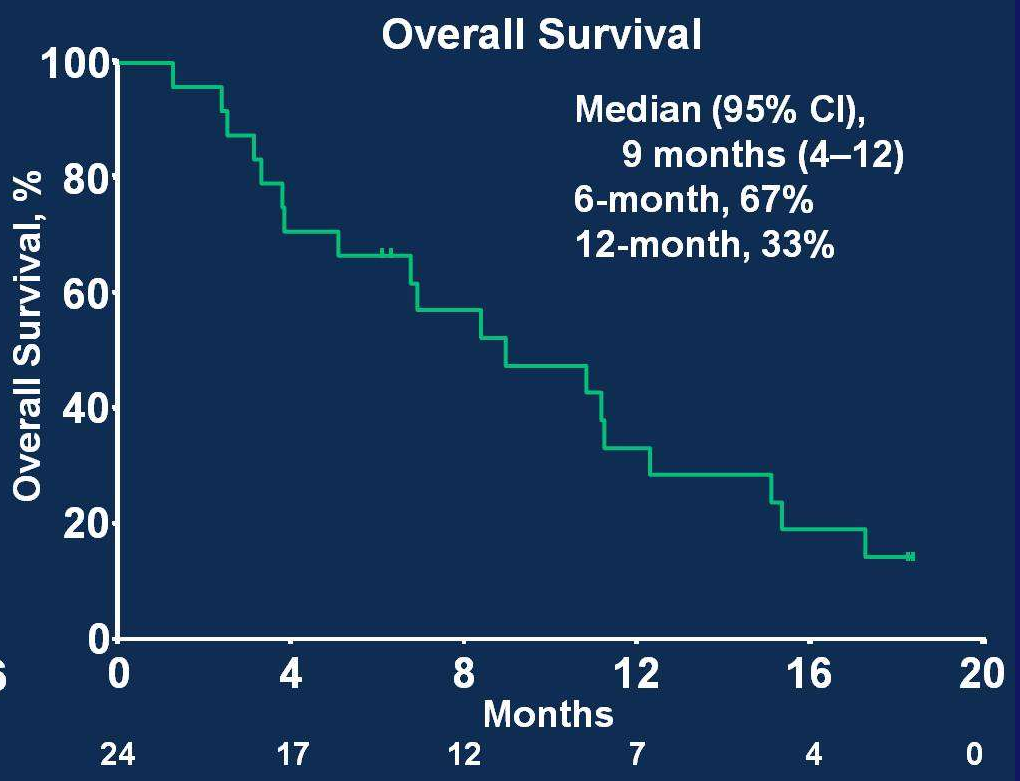
PRESENTED AT: ASCO ANNUAL MEETING '16

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.

Presented By Jean-Sebastien Frenel at 2016 ASCO Annual Meeting

Pembrolizumab in Adv Cervical Cancer: Ph Ib

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.

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 q 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

Checkpoint Inhibitor Data in Cervical & Vulvar Cancer From ASCO 2017

udy	Agent	Demographics	ORR	PFS
eckMate 358 llebecque, et al. stract 5504	Nivolumab	N = 24 19/24 cervix 71% <2 therapies	20.8% (all pts) 26.3% (cervical) 27% 0 priors 17.6% 1+ priors 0 (vaginal/vulva)	5.5 months (medi
ynote 158 hellens et al. stract 5514	Pembrolizumab	N = 47	12% In the 15 pts with >27 weeks follow-up ORR was 27%	Not reported

TRAEs are common: 71% in CheckMate
Grade 3-4 12.5% in CheckMate

Hollebecque A, et al. *J Clin Oncol*. 2017;35(suppl): Abstract 5504. Schellens JH, et al. *J Clin Oncol*. 2017;35(suppl): Abstract 5514.

KEYNOTE-158 (NCT02628067)

Multicenter, nonrandomized, open-label, multicohort trial

- **Pembrolizumab 200 mg every 3 weeks until toxicity or progression**
- **Assessment q 9 weeks for the first 12 months, and then every 12 weeks**
  - **Primary endpoint ORR according to RECIST 1.1 as assessed by blinded independent central review, and duration of response**
- **Among the 98 patients in Cohort E, 77 (79%) had tumors that expressed PD-L1 with a CPS ≥1 and received at least one line of chemotherapy in the metastatic setting**
  - **The baseline characteristics of these 77 patients**
    - **Median age was 45 years (range: 27 years to 75 years)**
    - **81% were White, 14% Asian, 3% Black**
    - **ECOG PS was 0 (32%) or 1 (68%); 92% had squamous cell carcinoma, 6% adenocarcinoma, and 1% adenosquamous histology**
    - **35% had one and 65% had two or more prior lines of therapy in the recurrent or metastatic setting**

Pembrolizumab [prescribing information]. Whitehouse Station,NJ:Merck & Co., Inc.;2018.

KEYNOTE-158 Cervical Cancer

' patients

- Median follow-up time of 11.7 months

ajor efficacy outcomes

- ORR according to RECIST 1.1 as assessed by blinded independent central review
- Response duration

RR was 14.3% (95% CI: 7.4 – 24.1)

- 2.6% complete responses
- 11.7% partial responses

stimated median response duration (n = 11)

- Not reached (range 4.1, 18.6+ months)
- 91% had a response duration of greater than or equal to 6 months

o responses were observed in 17 other patients whose tumors did not express PD-L

Pembrolizumab [prescribing information]. Whitehouse Station,NJ:Merck & Co., Inc.;2018.

Pembrolizumab Approved by FDA June 12, 2018

KEYNOTE-826

- **Untreated persistent, recurrent, or metastatic cervical**
- **Measurable disease per RECIST 1.1**
- **Available archival tumor tissue**
- **Performance status of 0 to1**
- **Adequate organ function**

Every 3 week pembrolizumab 200 mg PLUS investigator choice of chemotherapy*

R

Every 3 week placebo PLUS investigator choice of chemotherapy*

Stratification:
- Metastatic at diagnosis (yes vs no)
- Bevacizumab use (yes vs no)
- PD-L1 status (CPS<1 vs CPS 1 to <10 vs CPS ≥10)

*Ptx 175 mg/m2 PLUS cisplatin 50 mg/m2 WITH or WITHOUT bev 15 mg/kg OR Ptx 175 mg/m2 PLUS carboplatin AUC 5, WITH or WITHOUT bev 15 mg/kg

N = 600
60 Sites as of 6/ 2018

endpoints: 1) Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) as assessed by blinded indepen
view (BICR), or, 2) overall survival (OS); Secondary endpoints: ORR, DOR, PFS, AEs, PROs

ational Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT03635567. Accessed 24 January 2018.

Adv Recurrent Cx Ca:BEATcc Trial

Primary st IVB, persistent or recurrent carcinoma of the cervix

Meas disease by RECIST v1.1

ECOG-PS: 0-1

No previous systemic chemotherapy for advanced or recurrent disease

N = 404 pts

R: 1:1

Control Arm

Cisplatin + Ptx + Bev (GOG#240) until disease progression, unacceptable toxicity, death or withdrawal of consent

Experimental Arm

Cisplatin + Ptx + Bev + atezolizumab until disease progression, unacceptable toxicity, death or withdrawal of consent

Safety run-i
12 pts after
of treatr

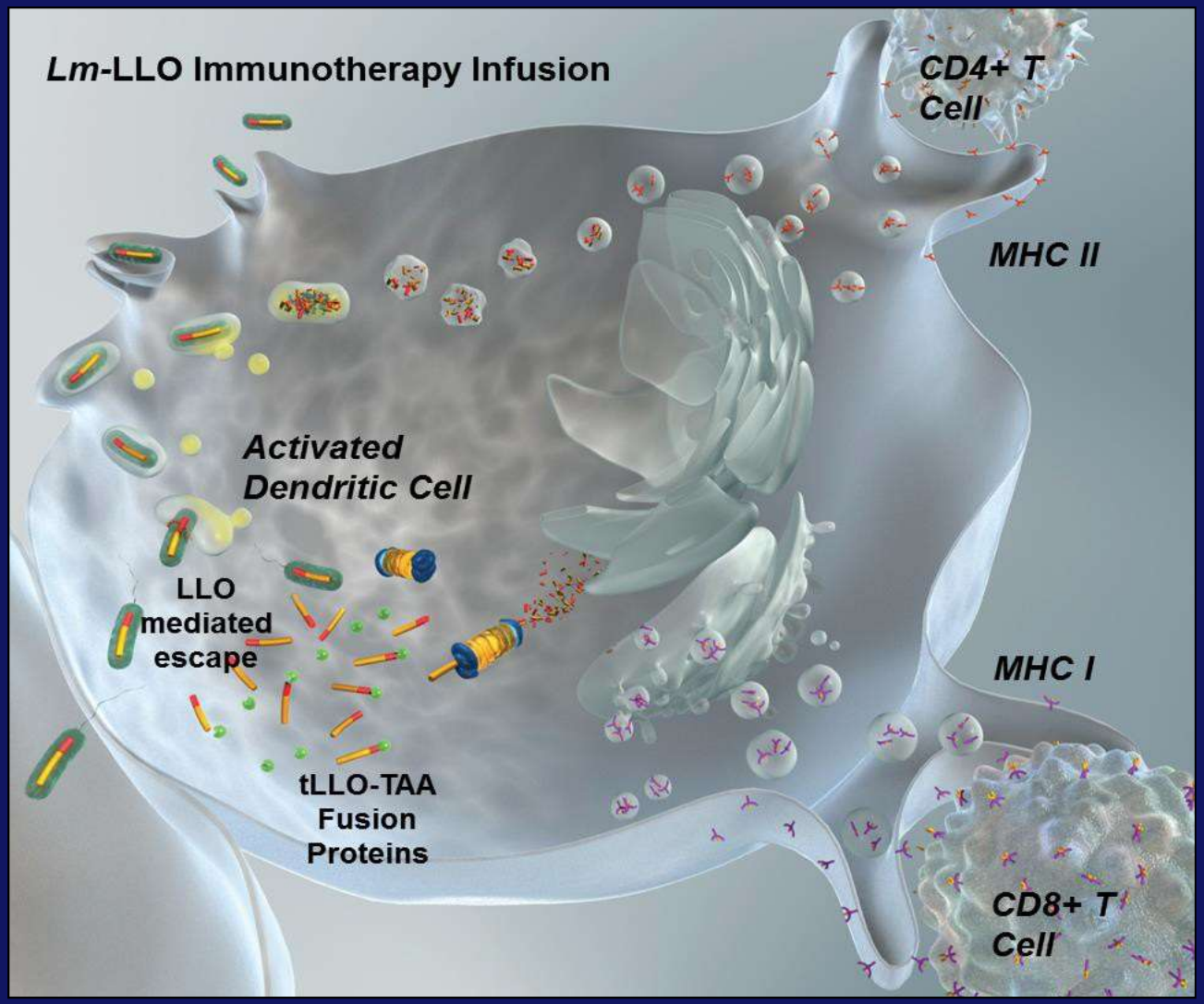
nary Endpoints:
rall survival (OS)
ondary Endpoints:
S
RR
OR
fety
R-QOL

Stratification Factors:
- Prior concurrent cisplatin-RDT
- Histology: SCC vs ADK (including adenosquamous)
- Chemotherapy backbone: Cisplatin vs carboplatin

tumor specimen is mandatory at study entry. Archival Bx or, in its absence, tumor biops
obtained within 3 mos of randomization from a non-irradiated lesion.

National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT03556839. Accessed 24 January 2018.

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

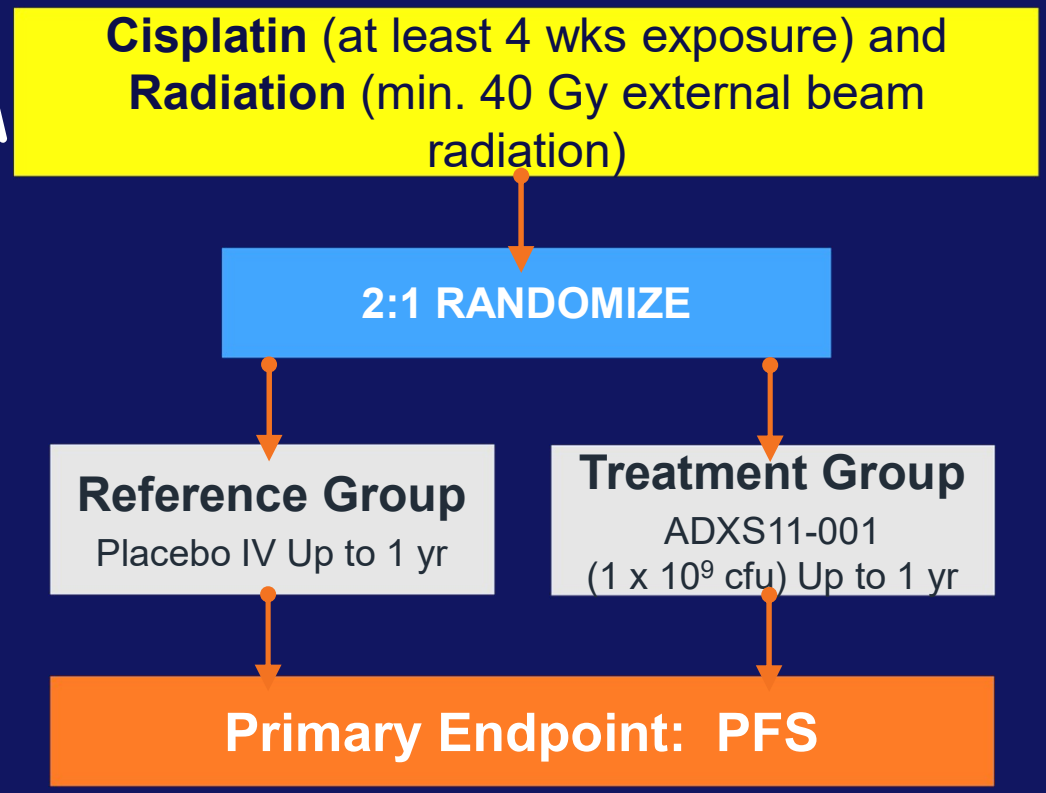
MHS, major histocompatibility complex

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

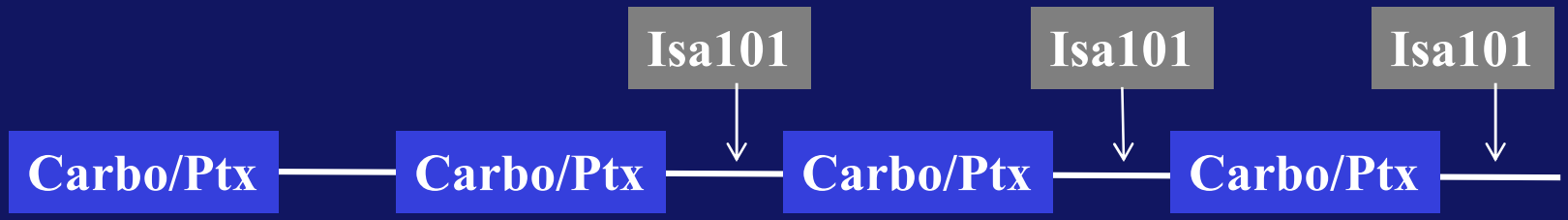
High risk, locally advanced cervical cancer

- **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 35
	2	1b	2	1/2
tion	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 tu including recurre metastatic cx, vagina cancers
s, n	42[a]	24	77[d]	24
ent	Ipilimumab	Pembrolizumab	Pembrolizumab	Nivolumab
%	8.8[c]	12.5[c]	14.3	ITT: 20.8[c] Cervical cancer pts
%	32.3	25.0	—	70.8
	—	19.3 wk	NR (range: 4.1–18.6+ mo)	NR
	mPFS: 2.5 mo	6-mo PFS: 13.0%	—	mPFS: 5.5 m
	—	6-mo OS: 66.7%	—	NR
	Manageable toxicities	≥Gr 3 TRAEs: 20.8%	Serious AEs: 39%	Gr 3/4 TRAEs: 1
-up	—	48.9 wk	11.7 mo	31 wk

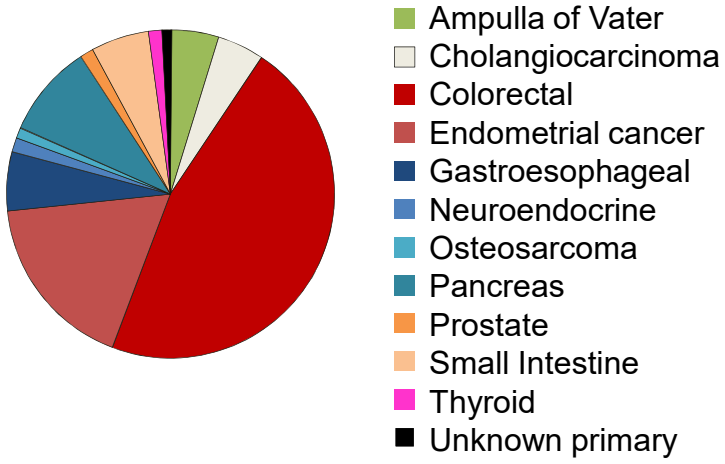
able for efficacy. [b] trial led to the approval of pembrolizumab for treatment of patients with cervical cancer. [c] Primary endpoint.
= 98 pts, but pembrolizumab label includes data for response in 77 patients whose tumors expressed PD-L1.

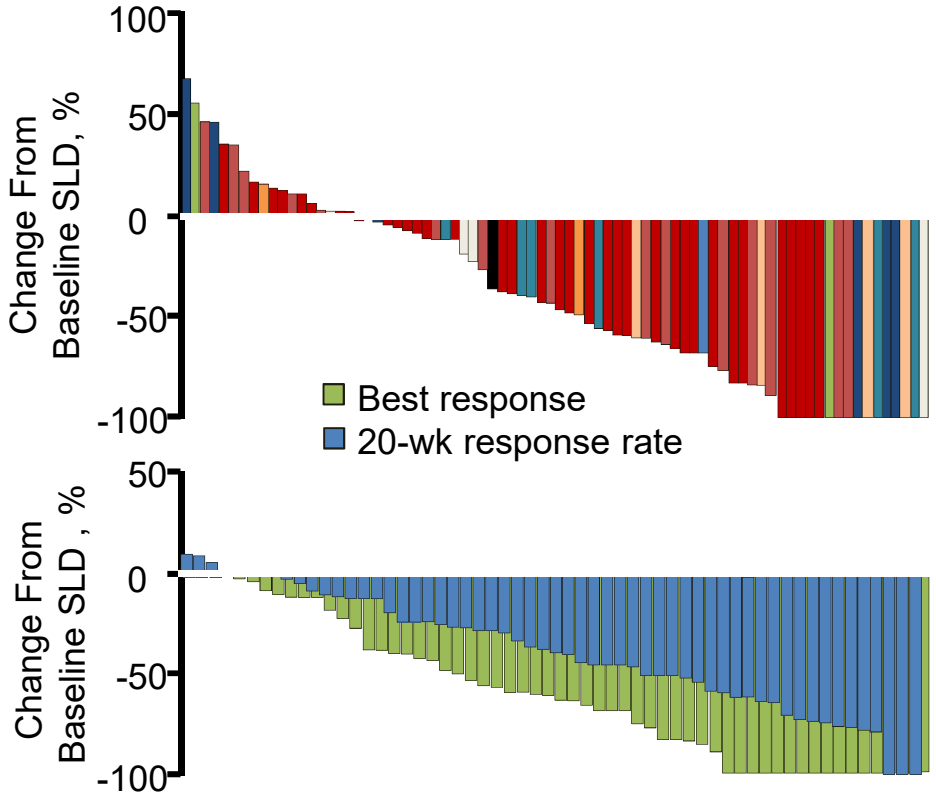
bined positive score; DCR, disease control rate; ITT, intent to treat; mDOR, median duration of response;; NR, not reached; ORR, overall response rate;; PD-L1, programmed death ligand 1;; TRAE, treatment-related advers

ux 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.** Ho
sented at ASCO Annual Meeting, 2017. Abstract 5504.

Pembrolizumab Response in MMRD Tumors (N = 86)

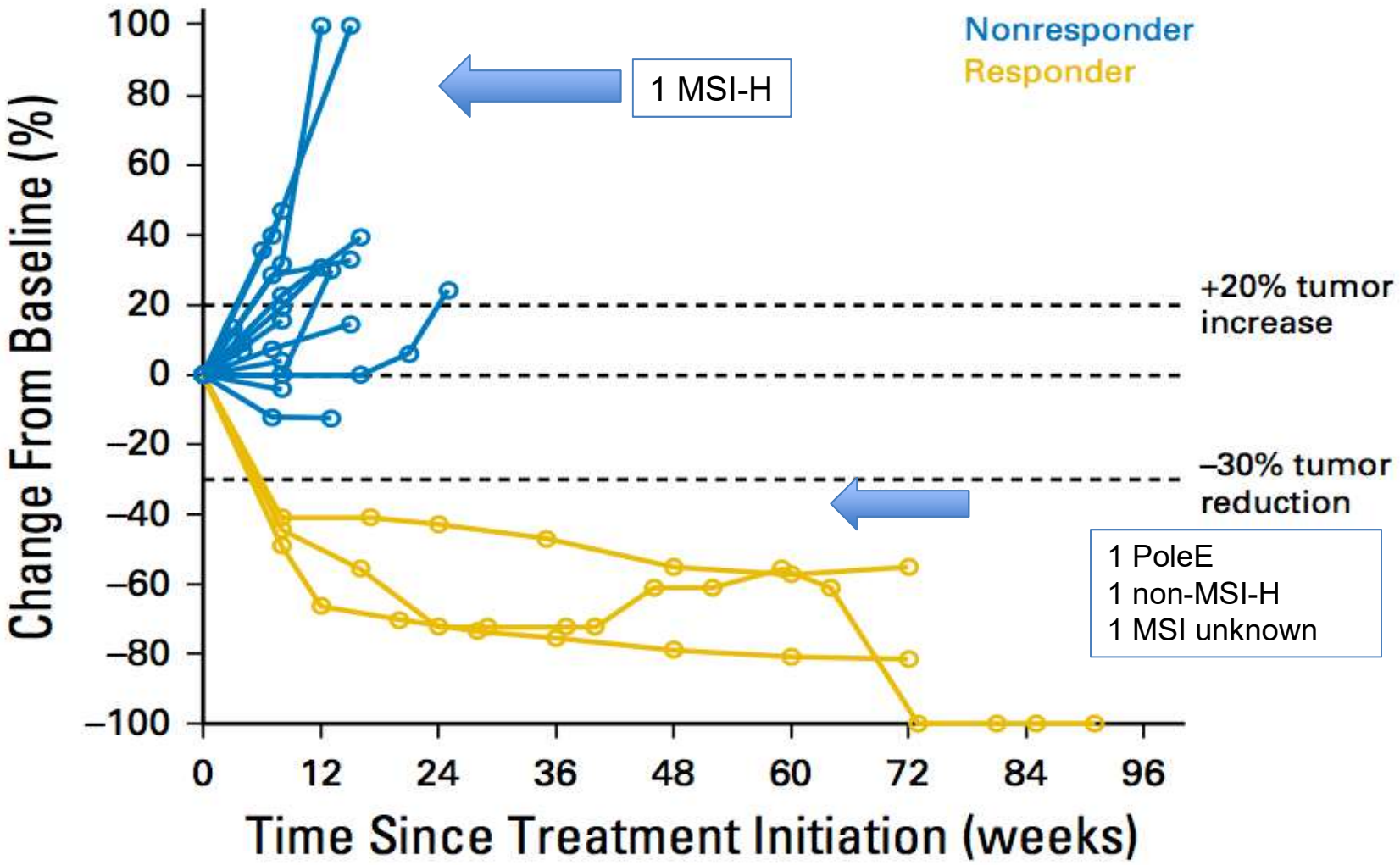
Radiographic responses across 12 tumor types at 20 wks





Le DT, et al. *Science*. 2017;357(6349):409-413.

KEYNOTE-028 (Endometrial Cancer Cohort)



Ott PA, et al. *J Clin Oncol*. 2017;35(22):2535-2541.

Study Design in MSI-H Trials

cacy of pembrolizumab was evaluated in patients with MSI-H or dMMR, solid tumors enrolled in 1 of 5 uncontrolled, oper ticohort, multicenter, single-arm trials.

ents with active autoimmune disease or a medical condition that required immunosuppression were ineligible in these 5

KEYNOTE Study	Design and Patient Population[a]	Patients (N)	MSI-H/dMMR Testing
KEYNOTE-016 NCT01876511	• Prospective, investigator-initiated • 6 sites • CRC and other tumors	28 CRC 30 non-CRC	Local PCR or IHC
KEYNOTE-164 NCT02460198	• Prospective international multicenter • CRC	61	Local PCR or IHC
KEYNOTE-012 NCT01848834	• Retrospectively identified patients with PD-L1–positive gastric, bladder, or TNBC	6	Central PCR
KEYNOTE-028 NCT02054806	• Retrospectively identified patients with PD-L1–positive esophageal, biliary, breast, endometrial, or CRC	5	Central PCR
KEYNOTE-158 NCT02628067	• Prospective international multicenter enrollment of patients with MSI-H/dMMR non-CRC • Retrospectively identified patients who were enrolled in specific rare-tumor non-CRC cohorts	19	Local PCR or IHC (central PCR for patients in rare-tumor non-CRC cohorts)
Total		**149**	

Pembrolizumab Approved by FDA with May 23, 2017

CRC, colorectal cancer; dMMR, mismatch repair deficient; IHC, immunohistochemistry; MSI-H, microsatellite instability-high; PCR, polymerase chain reaction; PD-L,= programmed death ligand 1; TNBC, triple-negative breast cancer.

Patient Demographics and Baseline Characteristics

	All MSI-H/dMMR Cancers N=149
Median age, years	55
Age ≥65 years, %	36
Male, %	56
White, %	77
Asian, %	19
Black, %	2
ECOG PS 0, %	36
ECOG PS 1, %	64
Metastatic disease, %	98
Locally advanced, unresectable disease, %	2
Cancer type and prior therapy	
CRC, n	90
Non-CRC,[a] n	59
Median no. prior therapies[b]	2
≥2 prior lines of therapy, % Metastatic CRC Non-CRC solid tumors	 84 53

[a]Other cancers were
- Endometrial
- Biliary
- Gastric/GE junction
- Pancreatic
- Small intestinal
- Breast
- Prostate
- Bladder
- Esophageal
- Sarcoma
- Thyroid
- Retroperitoneal adenocarcinoma
- Small cell lung
- Renal cell

[b]For metastatic or unresectable disease.
CRC = colorectal cancer; dMMR = mismatch repair deficient; ECOG PS = Eastern Cooperative Oncology Group performance status; GE = gastroesophageal; MSI-H = microsatellite instability-high.

Data on file. Merck, Inc.

Efficacy Results for Patients With Previously Treated Advanced MSI-H/dMMR Cancers

d Point	All MSI-H/dMMR Cancers n=149
jective response rate	
ORR (95% CI)	39.6% (31.7, 47.9)
Complete response rate	7.4%
Partial response rate	32.2%
sponse duration	
Median in months (range)	Not reached (1.6+, 22.7+)
% with duration ≥6 months	78%

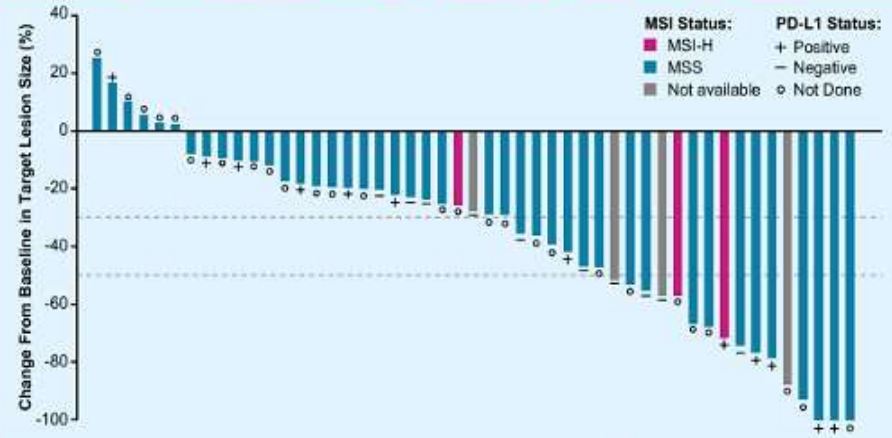
Pembrolizumab Approved by FDA with on May 23, 2017

Data on file. Merck, Inc.

CI = confidence interval; dMMR = mismatch repair deficient; MSI-H = microsatellite instability-high; ORR = objective response rate.

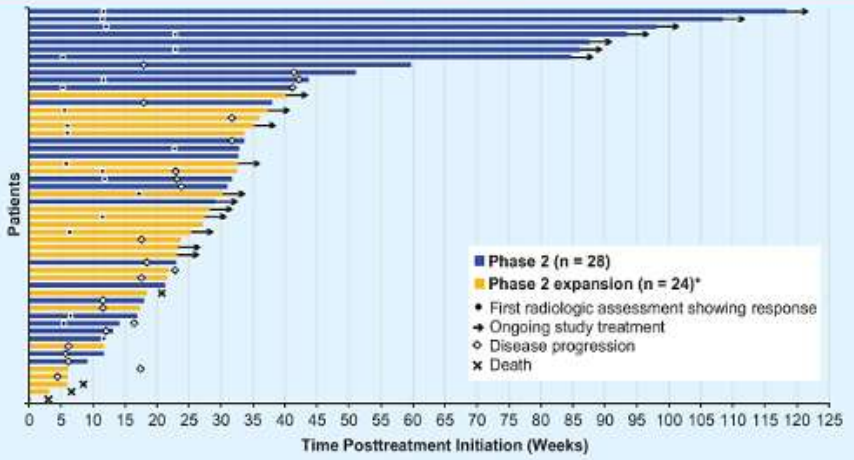
Adding Lenvatinib to Pembrolizumab to Improve Efficacy in MMRp Tumors (KEYNOTE-146)

Figure 3. Mean Maximum Percentage Change From Baseline in Sum of the Diameters of Target Lesions by MSI or PD-L1 Status



MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSS, microsatellite stable; PD-L1, programmed death receptor-1 ligand.

Figure 2. Duration of Treatment and Timeline of Significant Events for Individual Patients



*All phase 2 expansion patients were enrolled after March 2017 and therefore have shorter follow-ups.

Parameter	Lenvatinib + Pembrolizumab (n = 53)	
	Investigator Review	Independent Radiology Review
ORR[Week 24]*, n (%) 95% CI	21 (39.6) 26.5–54.0	24 (45.3) 31.6–59.6
Overall ORR, n (%) 95% CI	21 (39.6) 26.5–54.0	25 (47.2) 33.3–61.4

Makker V, et al. *J Clin Oncol.* 2018;36(15_suppl): Abstract 5596.

Breakthrough designation granted by FDA Aug 6, 2018

KEYNOTE-775

vanced, recurrent or metastatic
lometrial
gressive disease 1-2 prior
tinum regimens
asurable disease per
CIST 1.1
ilable archival tumor tissue
formance status of 0 to 1
equate organ function

N = 770
175 Sites as of Jan 12, 2018

R

1:1

Pembrolizumab 200 mg IV q 3 weeks + lenvatinib 20 mg PO qd during each 21-d cycle for up to 35 cycles.

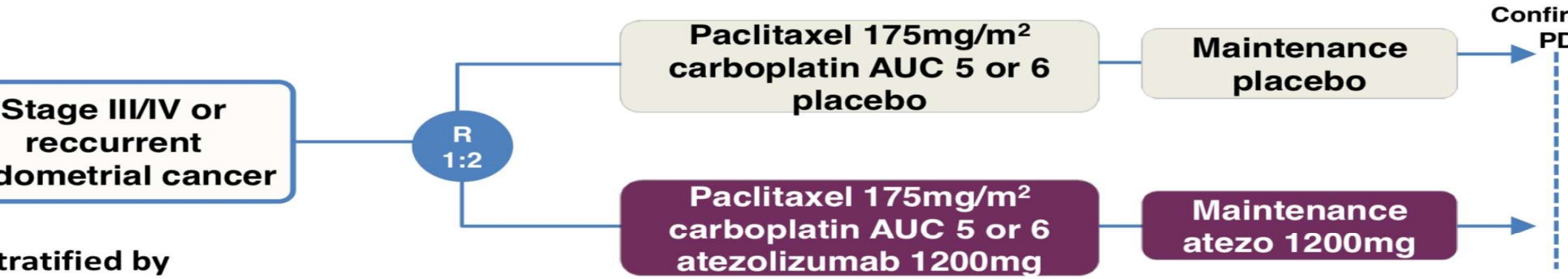
EITHER: Doxorubicin 60 mg/m^2 IV q 3 wks (max cum dose of 500 mg/m^2) OR Ptx 80 mg/m^2 administered by IV on a 28-day cycle: 3 weeks on weekly paclitaxel & 1 week off.

Stratification:
1. MMR status (pMMR or dMMR)
2. ECOG performance status (0 or 1)
3. Geographic region (Region 1 [Western Europe, North America, Australia] or Region 2 [rest of world])
4. Prior history of pelvic radiation (yes or no)

Primary endpoints: 1) Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) as assess
by blinded independent central review (BICR), or, 2) Overall Survival (OS).
Secondary endpoints: ORR, DOR, TTF, AEs, PK, PROs

National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT03517449. Accessed 24 January 2019.

Combinatorial IO Approach: Chemotherapy + Atezolizumab (AtTEnd/MaNGO)



tratified by
Prior RT
Recurrent disease
MSI

Atezolizumab\Placebo will be administered:
as I.V. infusion **every 21 days** until **progression confirmed at least weeks after the first evidence of progression according to RECIST 1.1.**

Primary Endpoint: OS and PFS

Secondary Endpoints: PFS in MSI, PFS2, RR, QoL, safety

Translational Endpoints: PD1, PDL1, TILs, blood based biomarkers

Study Duration: accrual 2 years; **Follow-up**: 2 years

National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT03603184. Accessed 24 January 2019.

Combinatorial IO Approach: Chemo + Pembrolizumab NRG GY018

ENDOMETRIAL CANCER (known MMR IHC status)

Measurable Stage III; Measurable Stage IVA; Measurable OR Nonmeasurable Stage IVB; Measurable OR Nonmeasurable Recurrent

N = 810
pMMR 590
dMMR 220

STRATIFICATION

Mismatch repair deficient (dMMR) (yes/no)
Performance status (0 vs 1)
Prior chemotherapy (yes/no)

RANDOMIZATION

Arm 1

Combination Phase:
Placebo IV Day 1
Paclitaxel 175 mg/m^2 IV over 3 hours Day 1
Carboplatin AUC 5 IV Day 1
x 6 cycles
Maintenance Phase:
Placebo IV Day 1
x up to 29 cycles

One cycle = 3 weeks

n number of placebocycles (combination phase + maintenance phase)

Arm 2

Combination Phase:
Pembrolizumab 200 mg IV Day 1
Paclitaxel 175mg/m^2 IV over 3 hours Day 1
Carboplatin AUC 5 IV Day 1
x 6 cycles
Maintenance Phase:
Pembrolizumab 200 mg IV Day 1
x up to 29 cycles

One cycle = 3 weeks

Maximum number of pembrolizumab cycles (combination phase + maintenar phase) = 35

PI and Personal Communication Ramez Eskander

HTE5 Does this text go in the boxes?
Heather Tomlinson, ELS, 1/23/2019

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

	Fader et al.[1]	KEYNOTE-028[2]	NCT01375842[3]	NCT02501096[4]	GARNET[5]	Pooled M
	2	1b	1a	1b/2	1/2	1 and
on	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 trea H/dMMR
n	9	24	15	54	35	14
t	Pembrolizumab	Pembrolizumab	Atezolizumab	Pembrolizumab + lenvatinib	TSR-042	Pembroliz
	56[a]	13.0[a]	13	36.7	52[a]	36[a]
	89	26.0	27	—	64	—
	—	—	—	NR	NR	Rang 4.2+–17.3
	—	1.8 mo	1.7 mo	10.1 mo	—	—
	NR	NR	9.6 mo	—	—	—
	No AEs >Gr 3	≥Gr 3 TRAEs: 16.7%	Any TRAE: 47%	≥Gr 3 TRAEs: 59%	≥Gr 3 TRAEs: 11.4%	Per lab
ollow-	9.1 mo	76.2 wk	Min: 11.2 mo	4.0 mo	—	—

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

se 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; llite instability high; NR, not reached;
rall response rate; TRAE, treatment-related adverse event.

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 5596. **5.** Oaknin A, et al. Presented at ESMO, 2018. Abstract 935PD. **6.** Pembrolizumab package insert. Merck & Co, Inc; December 2018.

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

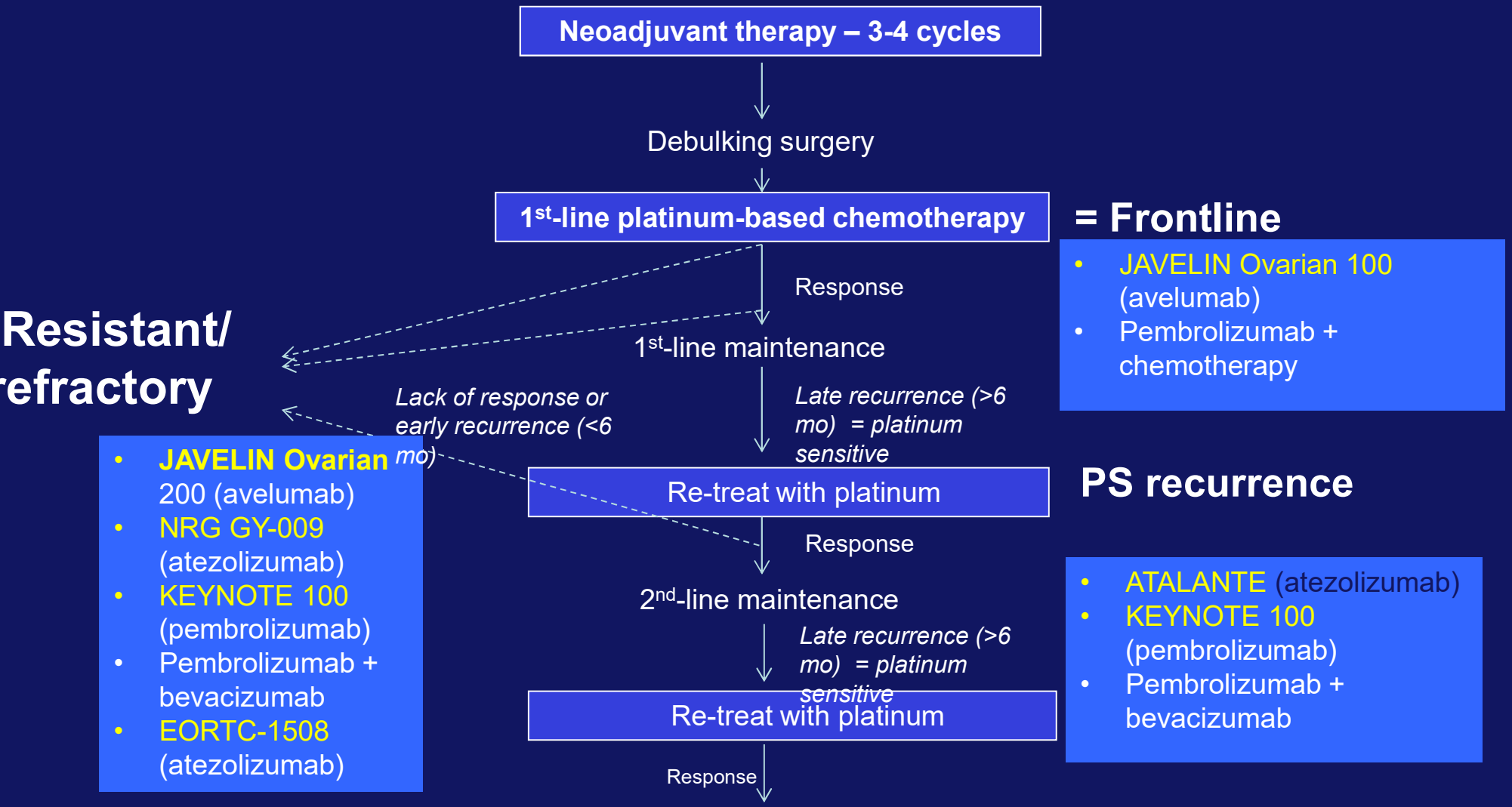
Ovarian Immune Checkpoint Inhibitors

	Ipilimumab[1]	Nivolumab[2]	Pembrolizumab[3]	Avelumab[4]
	9	20	26	124
ulation	Metastatic ovarian carcinoma	Platinum-resistant, post-taxane	Failure or inability to receive standard Tx; PD-L1+	Recurrent post-platinum
pies	NR	≥4: 55%	≥4: 80.8%	≥3: 65.3% (not including adjuv
evalence	NR	80% (IC 2/3)	100% (≥1% TC)	77% (≥1% TC)
low-up	NR	11 months	NR	12.4 months
	22%	95%	69.2%	66.1%
3+	NR	40%	3.8%	6.5%
CI)	NR	15% (3.2-37.9)	11.5% (2.4-30.2)	9.7% (5.1-16.3
CI)	NR	45% (23-69)	34.6% (17-56)	54% (45-63)
	NR	3.5 months	NR	2.6 months
	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



PS, platinum sensitive.

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

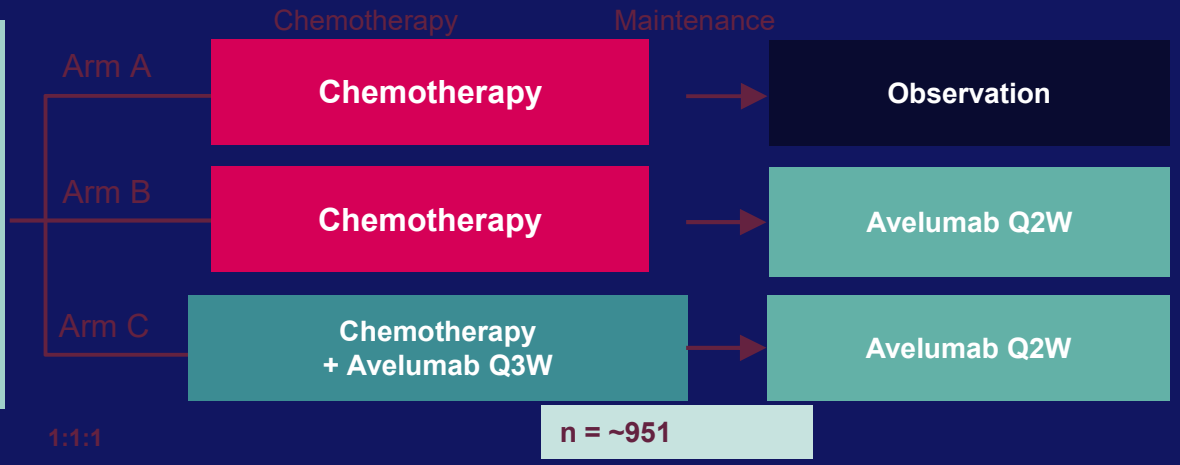
JAVELIN Ovarian 100
Avelumab Platinum Combo + Maintenance (Frontline)

Randomized Phase 3 Study (NCT02718417)

Enrollment Criteria

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

RANDOMIZATION



Primary Endpoint: PFS

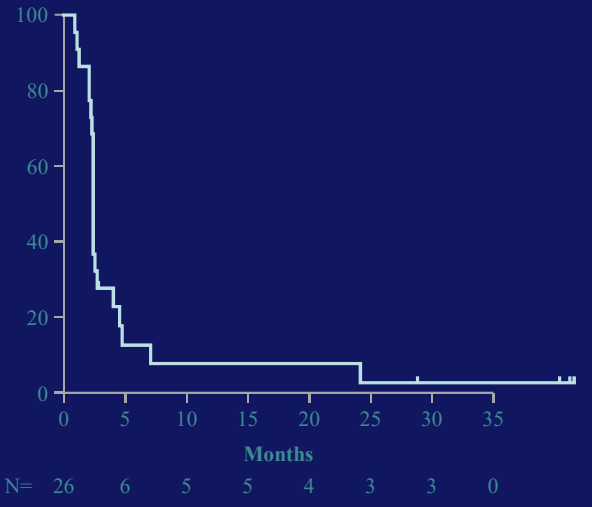
Secondary Endp Maintenance PFS, OS, ORR, duration of response, pCR, PROs, safety, PK

- 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

Checkpoint Inhib. Monotherapy in Ovarian Ca

	Hamanishi[1]	JAVELIN Solid Tumor[2]	KEYNOTE-028[3]	KEYNOTE-100[4]
	2	1b	1b	2
	PROC (80% PD-L1 high)	PROC (77% PD-L1+)	PD-L1+ PROC	Advanced OC with recurrence after 1L Pt
	20	124	26	376
	Nivolumab	Avelumab	Pembrolizumab	Pembrolizumab
	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]
	45	54.0	38.4	All comers: 37.2
	—	—	NR	All comers: 8.2 mo
	3.5 mo	11.3 wk	1.9 mo	Cohort A: 2.1 mo[a] Cohort B: 2.1 mo[b]
	20.0 mo	10.8 mo	13.8 mo	Cohort A: NR[a] Cohort B: 17.6 mo[b]
	Gr 3/4 TRAEs: 40%	Gr 3/4 TRAEs: 6.4%	Gr 3 AE: 1 pt	Gr 3/4 TRAEs: 19.7%
	11.0 mo	12.4 mo	15.4 mo	16.9 mo

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



N is small, but there appears to be pati have durable PFS with checkpoint in therapy

nes of therapy; PFI/TFI 3 to 12 months. [b] 4 to 6 prior lines of therapy; PFI/TFI ≥3 months. mDOR, median duration of response; mPFS, median progression-free survival; NR, not reached; nse 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 ent-related adverse event.

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

Ovarian Cancer Checkpoint Inhibitor Trials: Combination

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

e control rate; mDOR, median duration of response; mPFS, median progression-free survival; Not estimable;
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-emerge
treatment-related adverse event.

opoulous 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.
al. Presented at IGCS, 2018.

Ongoing Checkpoint Inhibitors Trials in Ovarian Cancer

Phase I/II

merous Phase 1 & 2 trials are estigating checkpoint inhibitors ne or in combination with other rapies[1]

ombinations being evaluated clude CPIs in combination with emotherapy, PARPi, IO therapies, Kls, 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

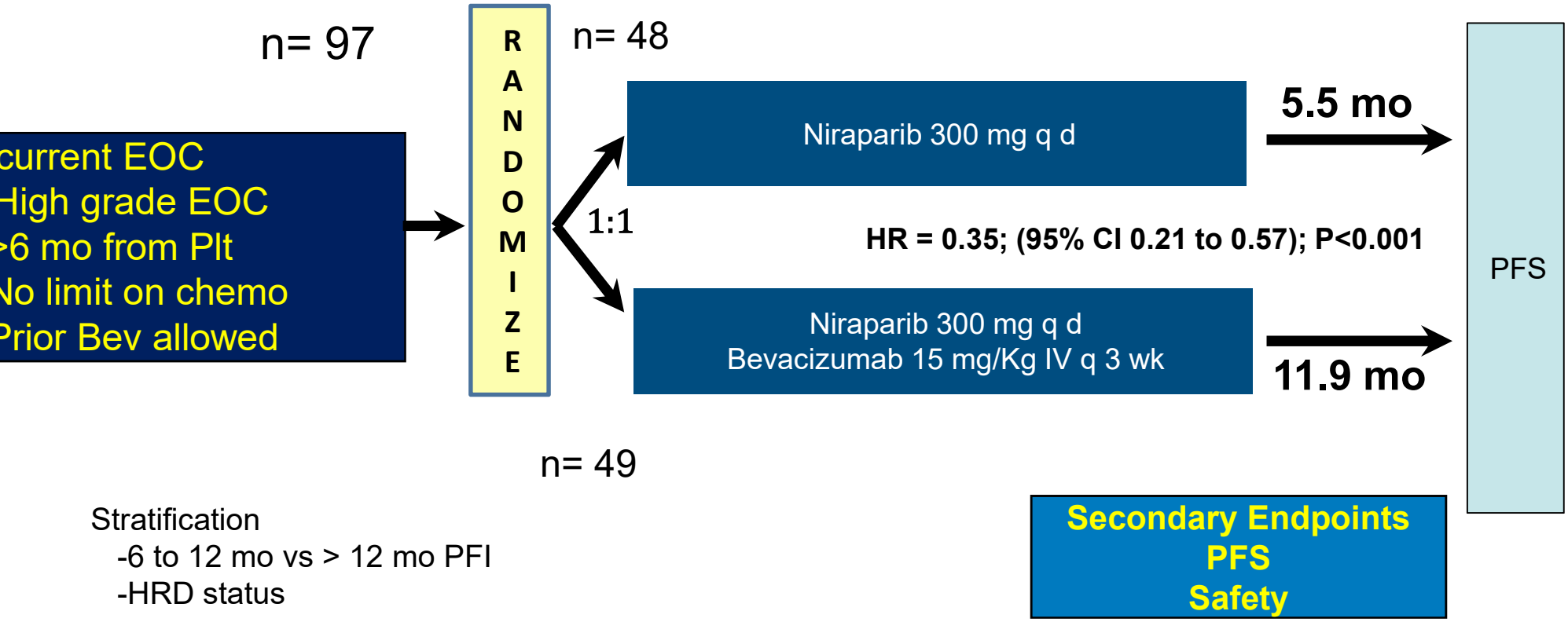
- NCT03598270 (ANITA): atezolizumab + niraparib + chemotherapy
- NCT03602859 (FIRST): TSR-042 + chemotherapy + niraparib
- NCT03740165 (ENGOT-ov43/KEYLYNK-001): pembrolizumab + chemoth + olaparib

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 2 & 2019.

point inhibitor; IO, immuno-oncology; L, line; PARP, poly ADP ribose polymerase; PARPi, poly ADP ribose polymerase inhibitor; PLD, pegylated liposoma
n; TKI, tyrosine kinase inhibitor.

o T, et al. *Clin Ther.* 2018;40(3):372-88. 2. Clinicaltrials.gov. NCT03642132, NCT03522246, NCT03737643, NCT03353831, NCT02891824, NCT02839707, 100, NCT03598270, NCT03602859, NCT03740165. Accessed Jan 18, 2019.

nbination of niraparib & bevacizumab vs. niraparib alone as treatme urrent Platinum-sensitive Ov Ca: Randomized chemotherapy-free st NSGO-AVANOVA2/ENGOT-OV24



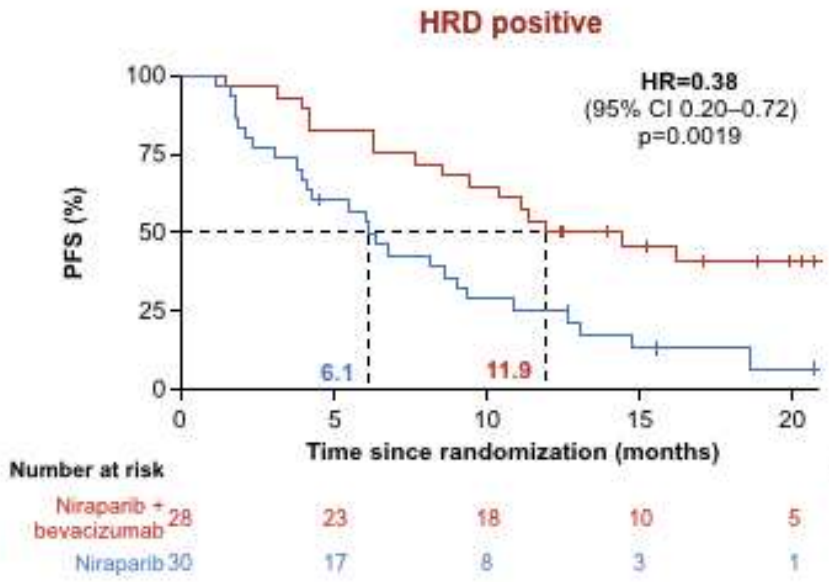
Stratification
-6 to 12 mo vs > 12 mo PFI
-HRD status

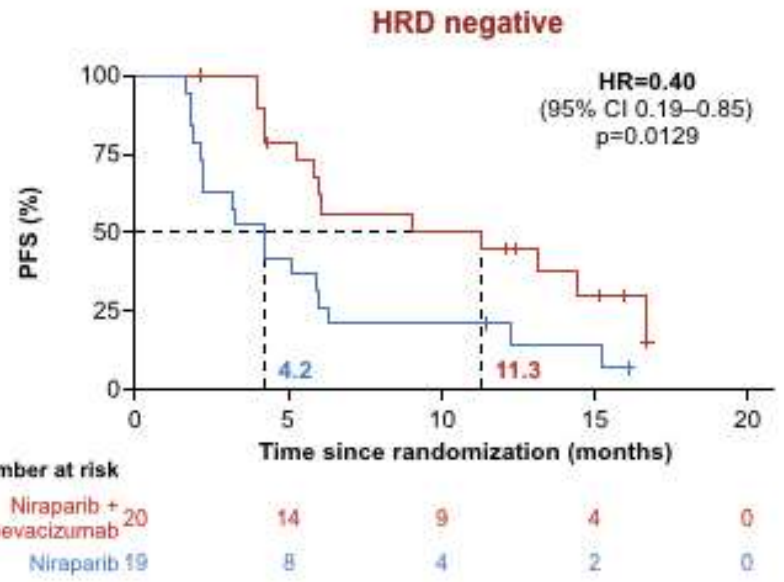
Secondary Endpoints
PFS
Safety

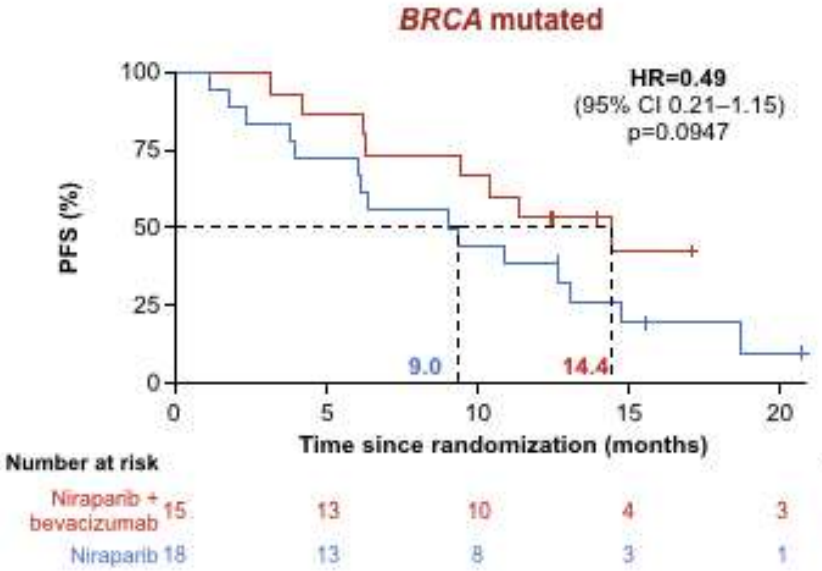
Mirza MR, J Clin Oncol 37, 2019 (suppl; abstr 5505)

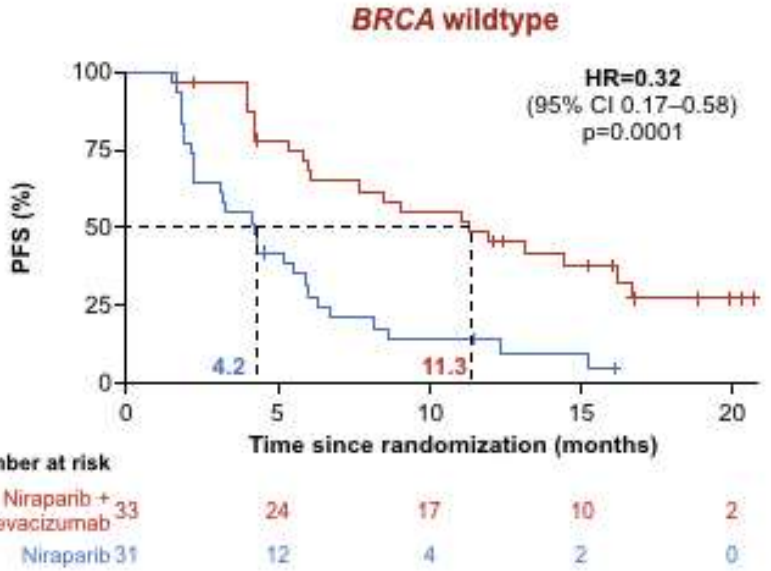
NCT02354131

AVANOVA


HRD positive
HR=0.38
(95% CI 0.20–0.72)
p=0.0019
PFS (%)
100
75
50
25
0
6.1
11.9
0
5
10
15
20
Time since randomization (months)
Number at risk
Niraparib + bevacizumab 28 23 18 10 5
Niraparib 30 17 8 3 1


HRD negative
HR=0.40
(95% CI 0.19–0.85)
p=0.0129
PFS (%)
100
75
50
25
0
4.2
11.3
0
5
10
15
20
Time since randomization (months)
Number at risk
Niraparib + bevacizumab 20 14 9 4 0
Niraparib 19 8 4 2 0


BRCA mutated
HR=0.49
(95% CI 0.21–1.15)
p=0.0947
PFS (%)
100
75
50
25
0
9.0
14.4
0
5
10
15
20
Time since randomization (months)
Number at risk
Niraparib + bevacizumab 15 13 10 4 3
Niraparib 18 13 8 3 1


BRCA wildtype
HR=0.32
(95% CI 0.17–0.58)
p=0.0001
PFS (%)
100
75
50
25
0
4.2
11.3
0
5
10
15
20
Time since randomization (months)
Number at risk
Niraparib + bevacizumab 33 24 17 10 2
Niraparib 31 12 4 2 0

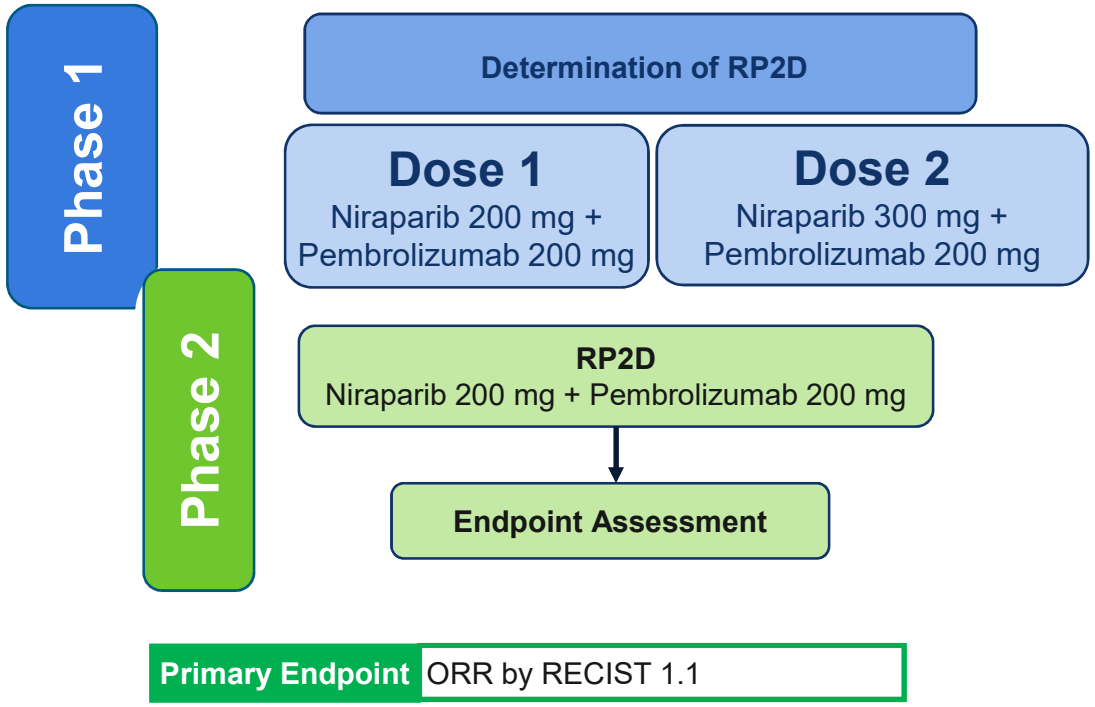
mbination of niraparib & bevacizumab vs. niraparib alone as treatm recurrent platinum-sensitive ovarian cancer: Randomized contro chemotherapy-free study—NSGO-AVANOVA2/ENGOT-OV24

- No difference in treatment-emergent grade 3-4 adverse events except
  - Hypertension (26.5% vs. 0%)
  - Neutropenia (12% vs. 2%)
- Patient-reported outcomes measured using EORTC QLQ C30 and OV28 were similar for both treatment arms

Mirza MR, J Clin Oncol 37, 2019 (suppl; abstr

TOPACIO: Ph 1/2 in Patients with PROC

Study Purpose: Evaluate the hypothesis that PARPi with an anti-PD-1 will increas
efficacy vs. either drug alone in difficult-to-treat patient populations

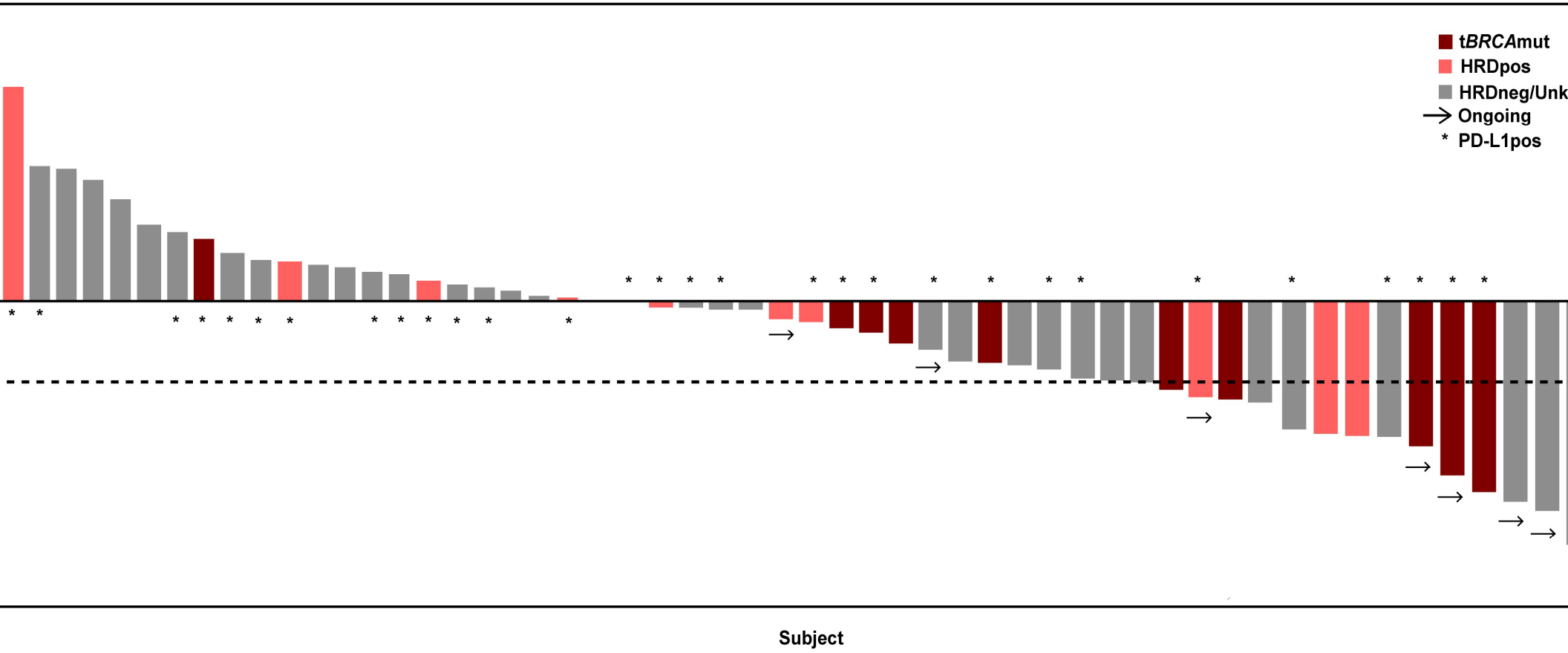


PROC, platinum-resistant/refractory ovarian cancer
ORR, objective response rate
RP2D, recommended phase 2 dose

TOPACIO Ovarian Cancer Eligibility

- Response lasting ≥6 months to 1st-line
- Considered plat-resistant by investigato
  - Patients with plat-sensitive dz who were not eligible for further platinum (platinum ineligible) were allowed
- Secondary platinum-refractory disease allowed
- ≤5 prior lines of treatment

liraparib + PD-1 Inhibitor Treatment Resulted in linical Activity Across a Broad Study Populatio



nical Activity Is Observed Across Biomarker Populations Patients with Platinum-Resistant/Refractory Disease

esponse	**All (%)**	t*BRCA*mut (%)	**HRDpos* (%)**	t*BRCA*wt (%)	**HRDneg (%)**
ORR	**11/47 (23%)**	**2/8 (25%)**	**4/16 (25%)**	**9/37 (24%)**	**7/26 (27%**
DCR	30/47 (64%)	5/8 (63%)	11/16 (69%)	24/37 (65%)	15/26 (58%

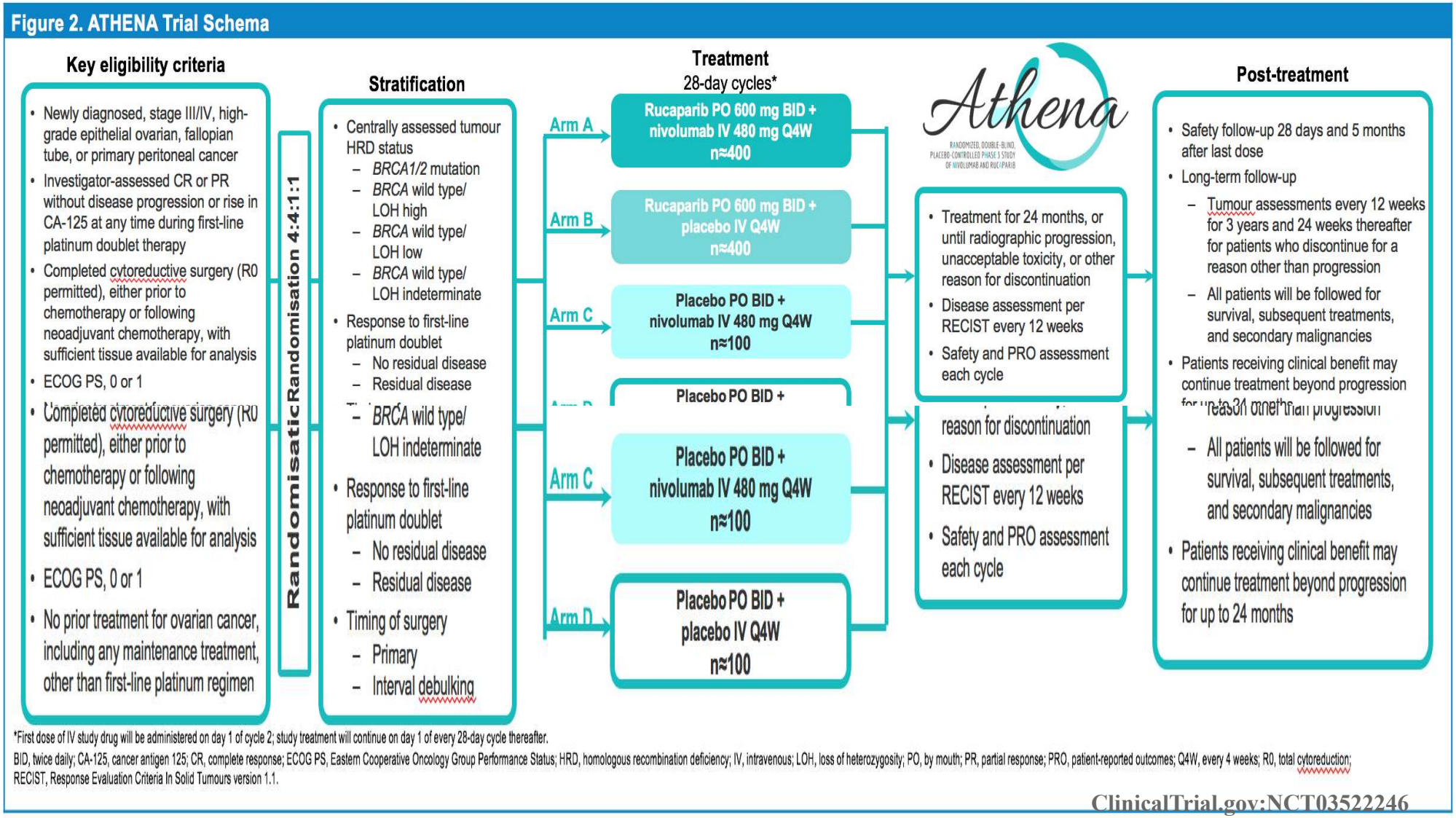
*HRDpos includes *BRCA* mutation or HRD score ≥42 per Myriad assay.
Patients with inconclusive biomarker results were not included in the biomarker subpopulations.
Responses include confirmed and unconfirmed responses.

The addition of pembrolizumab to niraparib in t*BRCA*wt and HRDneg led to ORR similar to PARPi efficacy the t*BRCA*mut population

HRD status does not correlate with response to this combination in platinum-resistant/ -refractory disease

Panagiotis Konstantinopoulos ASCO 2018

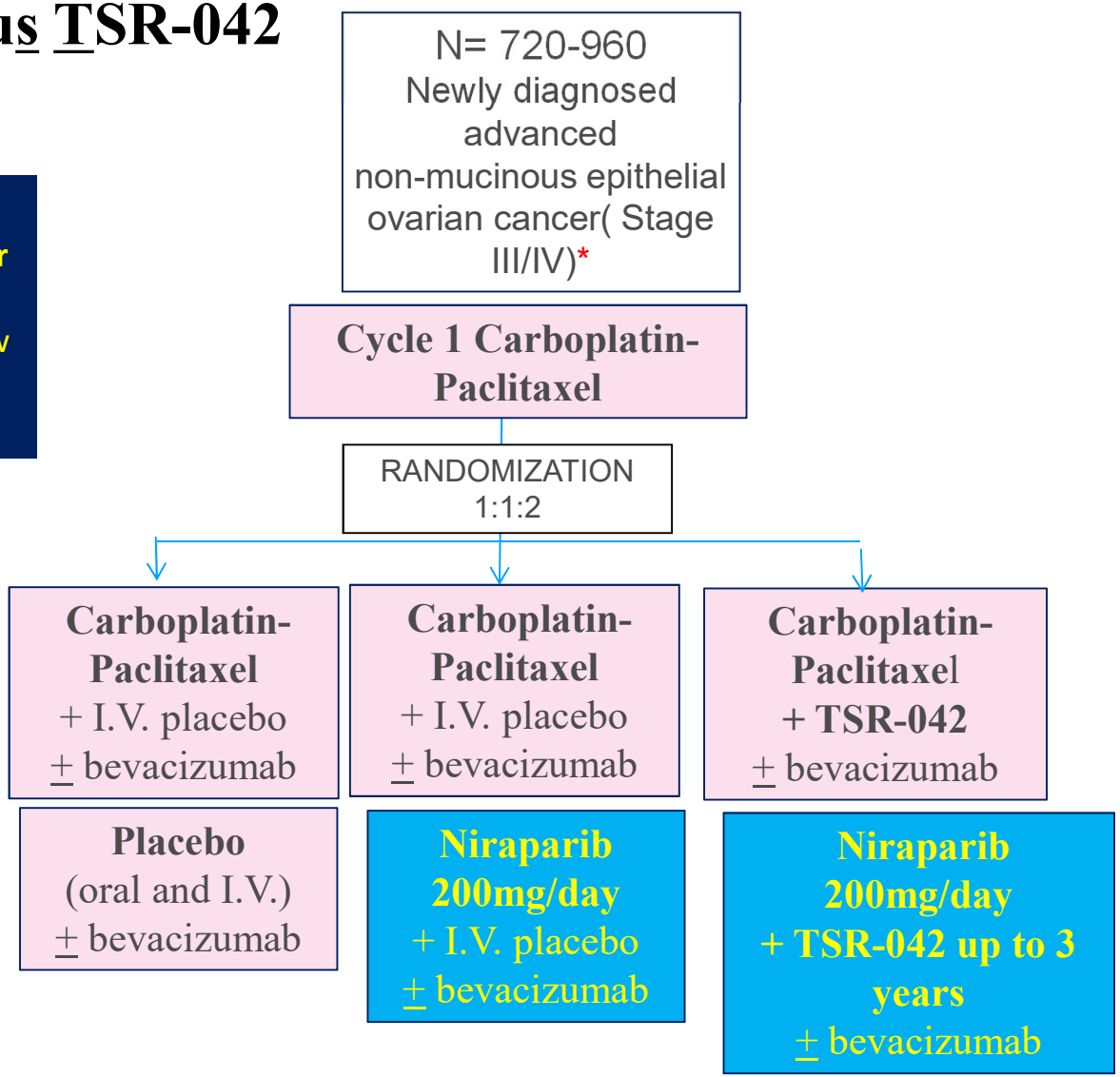
ATHENA (GOG-3020/ENGOT-ov45): Ph 3 study of Rucaparib + nivolumab as maintenance treatment following front-line platinum-based chemotherapy for advanced epithelial ovarian cancer



FIRST Trial: First-line ovarian cancer treatment with Niraparib plus TSR-042

Primary objective:
PFS by Investigator assessment per RECIST v1.1. PFS based upon blinded independent central review committee (BICR) will be a sensitivity analysis.

Secondary endpoints:
OS
ORR/DOR/DCR
Safety and tolerability of all treatments
Patient-reported outcomes (PROs)
Time to first subsequent therapy (TFST)
Time to second subsequent therap (TSST)
PFS2

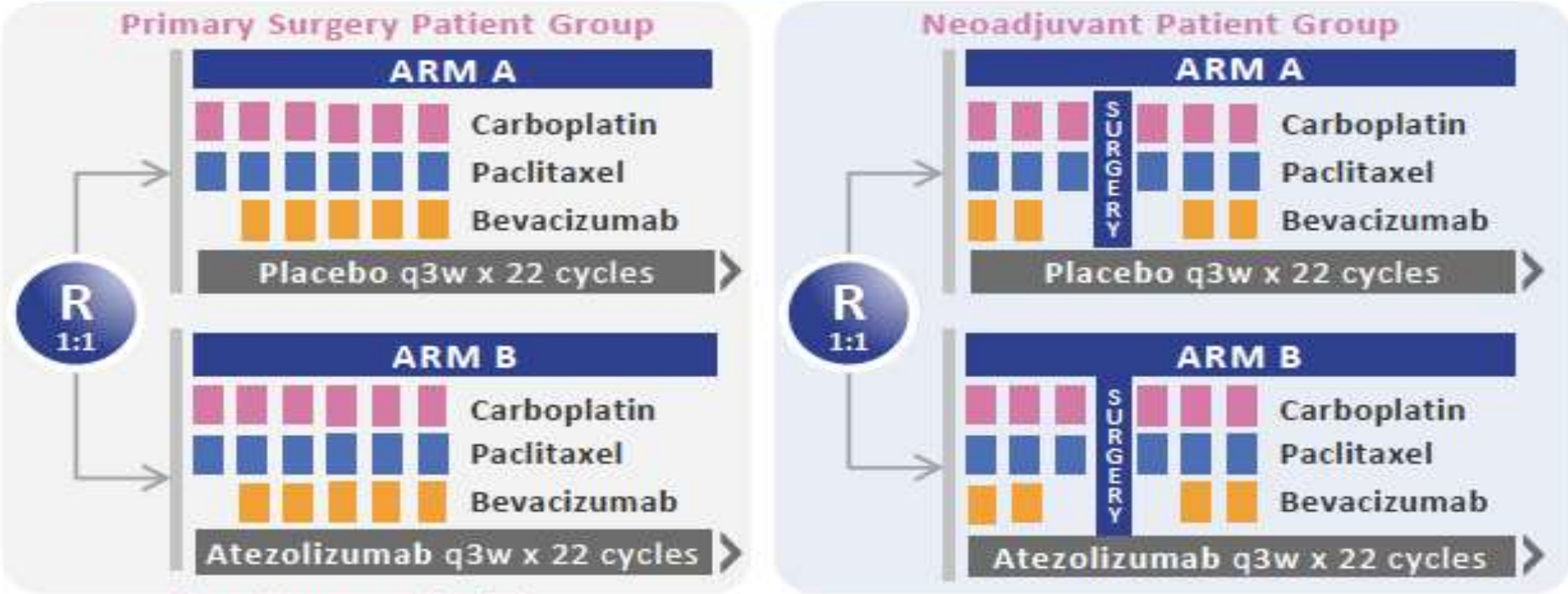


*Not eligible: complete surgical resection at primary debulking surgery **and low risk of relapse.**

-ClinicalTrials.gov Identifier: NCT03602859

IMAGYN050: Bevacizumab & Atezolizumab in combination with chemotherapy

Study Design



Co-primary endpoint

- PFS and OS

Select Secondary endpoints

- Duration of response
- Patient-reported abdominal symptoms related to ovarian cancer and health-related quality of life

The First-Line Ovarian Cancer Space is a Crowded Landscape!

st include active agent in combination with carboplatin-paclitaxel

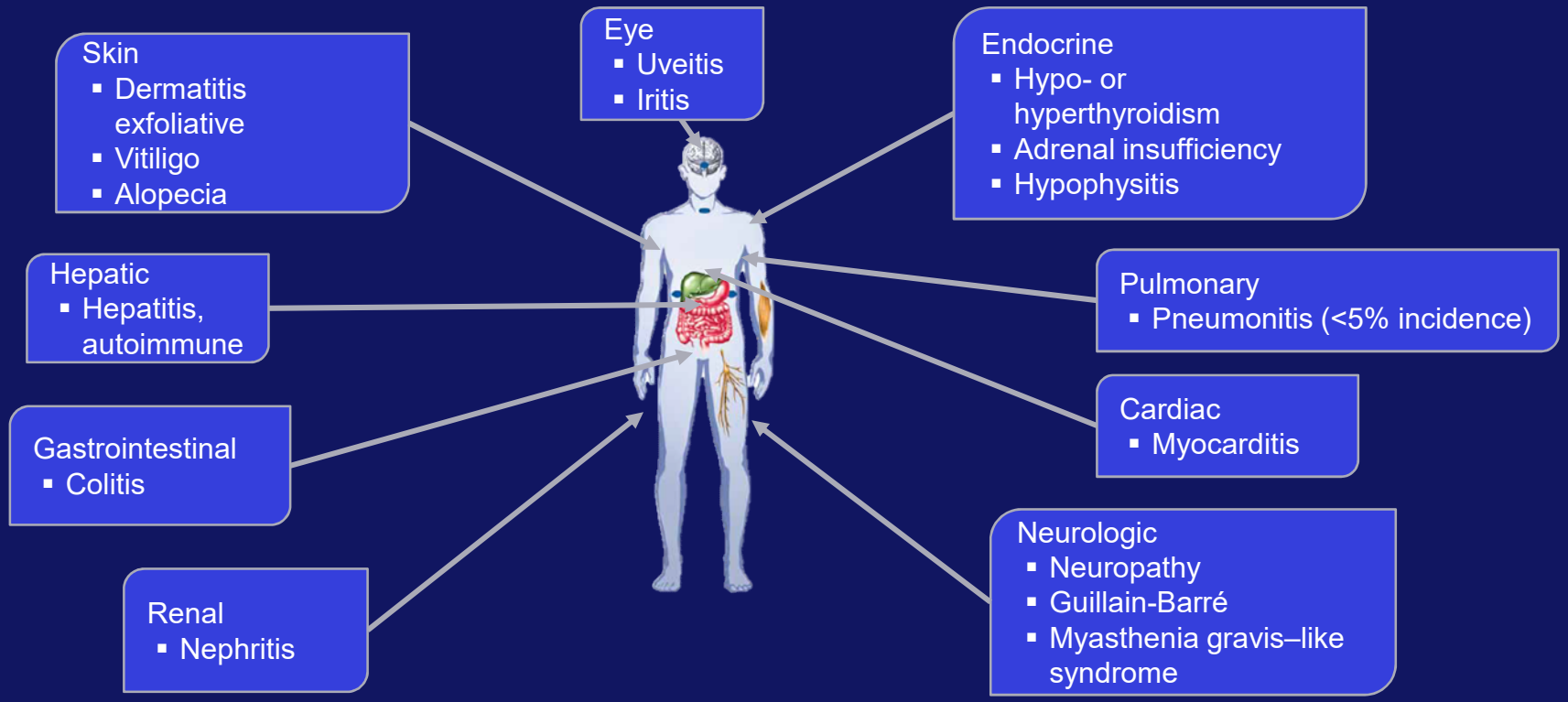
HENA is switch maintenance only IOi study

ree virtually identical studies (FIRST, ENGOT-ov43, ENGOT-ov46/DUO-O)

hers incorporate active agents in both treatment and as maintenance (continuous or swit

ne Treatment ntenance	First Line Switch Maintenance	First Line Treatment/Maintenance with IO	First Line Treatment/Maintenanc IO and PARPi
GOG 218	PAOLA-1	~~Javelin Ovarian 100~~	
~~in Ovarian 100~~	PRIMA	~~Javelin Ovarian 100 PARP~~	~~Javelin Ovarian 100 PA~~
~~Ovarian 100 PARP~~	ATHENA	ImaGyn50 3015	
/ELIA 3005		FIRST	FIRST
aGyn50 3015		ENGOT-ov43	ENGOT-ov43
FIRST		ENGOT-ov46/DUO-O	ENGOT-ov46/DUO-
NGOT-ov43		ATHENA	ATHENA
T-ov46/DUO-O			

Immune-Related Adverse Events Can Affect Any Organ System



Vigilance…as may result in serious immune-related AEs

Conclusions

- mmuno-oncology: exciting, emerging & extremely compl
- NextGen technologies & systems biology will dynamically ofile vulnerabilities
- Checkpoint blockade may unleash diverse antitumor T ce -activities.
- MSI High is Universal target
- Multiple I/O trials in Gyn Cancers- combos appear most omising


Thank You!