FDA-AACR-SGO Workshop on Drug Development in Gynecologic Malignancies

June 14, 2018

FDA White Oak Campus | Silver Spring, MD

Workshop Cochairs:

U.S. Food and Drug Administration:

Sanjeeve Bala, MD, MPH, Clinical Team Leader Gynecologic Malignancies Group, Division of Oncology Products 1, Office of Hematology and Oncology Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Julia A. Beaver, MD, Director, Division of Oncology Products 1, Office of Hematology and Oncology Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

American Association for Cancer Research:

Deborah K. Armstrong, MD, Director, Breast and Ovarian Surveillance Service; Professor of Oncology; Professor of Gynecology & Obstetrics John Hopkins University

Gordon B. Mills, MD, PHD, Co-Director, Zayed Institute for Personalized Cancer Therapy, Department of Systems Biology 1, Division of Cancer Medicine, UT MD Anderson Cancer Center

Society of Gynecologic Oncology:

Rebecca Arend, MD, Assistant Professor of Obstetrics & Gynecology, University of Alabama at Birmingham

Robert L. Coleman, MD, FACOG, FACS, Vice Chair, Clinical Research, Department of Gynecologic Oncology and Reproductive Medicine, UT MD Anderson Cancer Center

Thomas Herzog, MD, Deputy Director & Professor of Obstetrics & Gynecology, University of Cincinnati Cancer Institute

AGENDA

INTRODUCTION

8:00 AM **Welcome**
AACR Cochair

8:05 AM **Introduction & Objectives**
Julia A. Beaver, MD, U.S. Food and Drug Administration

SESSION I: DEVELOPMENT OF IMMUNOTHERAPY IN GYNECOLOGICAL MALIGNANCIES – PART 1
SESSION COCHAIRS: SANJEEVE BALA, MD, MPH, & THOMAS HERZOG, MD

Description: To discuss the science behind why immunotherapy would work in GYN malignancies, get into the biomarker issues seen with immunotherapy.

8:10 AM **Immunotherapy Science: Approach- Biomarker Directed, Tissue-agnostic, Targeted**
Deborah K. Armstrong, MD, Johns Hopkins Kimmel Comprehensive Cancer Center

8:25 AM **Immunotherapy for Gynecologic Cancers: Rationale and Biomarkers**
Dmitriy Zamarin, MD, PhD, Memorial Sloan Kettering Cancer Center

8:40 AM **Combination Approaches**
Rebecca Arend, MD, University of Alabama at Birmingham

8:55 AM **PANEL DISCUSSION and AUDIENCE Q&A**
Moderators **Sanjeeve Bala, MD, MPH, & Thomas Herzog, MD**
Session I speakers and the following additional panelist(s):
Amreen Husain, MD, Genentech
W. Michael Korn, MD, UCSF Helen Diller Family Comprehensive Cancer Center

9:45 AM **BREAK**

SESSION II: DEVELOPMENT OF IMMUNOTHERAPY IN GYNECOLOGICAL MALIGNANCIES – PART 2
SESSION COCHAIRS: JULIA A. BEAVER, MD, & REBECCA AREND, MD

Description: To discuss innovative study design ideas to examine contribution of effect of novel immunotherapy combinations in GYN malignancies.

10:10 AM **Immunotherapy Biomarker Development and Rationale for Combinations**
Amir A. Jazaeri, MD, UT MD Anderson Cancer Center

10:25 AM **Innovations in Immuno-Oncology Combination Clinical Trial Designs**
Robert L. Coleman, MD, FACOG, FACS, UT MD Anderson Cancer Center

10:40 AM **Statistical Considerations for Combination Immuno-Oncology Trials**
William Brady, PhD, Sarah Cannon Development Innovations

10:55 AM **PANEL DISCUSSION and AUDIENCE Q&A**
Moderators **Julia A. Beaver, MD, & Rebecca Arend, MD**
Session II speakers and the following additional panelist(s):
Rajeshwari Sridhara, PhD, U.S. Food and Drug Administration
Geoffrey S. Kim, MD, AstraZeneca
Mary J. Scroggins, Patient Advocate

11:55 PM **LUNCH BREAK (ON YOUR OWN)**

SESSION III: BIOMARKER DEVELOPMENT AND PARP INHIBITORS
SESSION COCHAIRS: DEBORAH K. ARMSTRONG, MD, & ROBERT L. COLEMAN, MD, FACOG, FACS

Description: Given the recent approvals of PARPi in the BRCA unselected patients, how can we better predict who will respond to these drugs since only a small percentage of BRCA negative group will do so? How can we identify that group?

1:00 PM **FDA Perspective**
Gwynn Ison, MD, U.S Food and Drug Administration

1:15 PM **PARP Resistance Mechanisms**
Alan D'Andrea, MD, Dana-Farber Cancer Institute

1:30 PM **Rational PARP + X Agents and Design**
Anil K. Sood, MD, UT MD Anderson Cancer Center

1:45 PM	**PANEL DISCUSSION and AUDIENCE Q&A**
Moderators	**Deborah K. Armstrong, MD, & Robert L. Coleman, MD, FACOG, FACS** **Session III speakers and the following additional panelist:** **Hisani Madison, PhD, MPH,** U.S Food and Drug Administration
2:35 PM	**BREAK**

SESSION IV: DEVELOPMENT OF DRUGS FOR RARE GYNECOLOGICAL MALIGNANCIES
SESSION COCHAIR: GORDON B. MILLS, MD, PHD

Description: Development of drugs for rare GYN malignancy subset (e.g. clear cell ovarian cancer); this session will explore trouble with control arms, small sample sizes, need for more real world historic controls and single arm studies, vs. small cohorts within randomized trials.

2:50 PM	**Discussion on Different Subsets and Treatments Within Tumor Types Including Low Grade Serous, Non-epithelial Ovarian, and Small Cell** **Gordon B. Mills, MD, PhD,** UT MD Anderson Cancer Center
3:05 PM	**Approach to Drug Development for Patients with ESR1 Mutations** **Stephanie L. Gaillard, MD, PhD,** Johns Hopkins School of Medicine
3:20 PM	**Progress in Drug Development for Rare Epithelial Ovarian Cancers: The NRG Oncology (GOG) Experience** **David M. Gershenson, MD,** UT MD Anderson Cancer Center
3:35 PM	**PANEL DISCUSSION and AUDIENCE Q&A**
Moderator	**Gordon B. Mills, MD, PhD** **Session IV speakers and the following additional panelist(s):** **Amy E. McKee, MD,** U.S Food and Drug Administration **Annie E. Ellis**, Patient Advocate **Stephen Keefe, MD, MSCE**, Merck
4:25 PM	**Wrap up: Summary & Future Directions** **Robert L. Coleman, MD, FACOG, FACS**, UT MD Anderson Cancer Center
4:30 PM	**ADJOURN**

U.S. FOOD & DRUG ADMINISTRATION

American Association for Cancer Research

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Society of Gynecologic Oncology

Drug Development in Gynecologic Malignancies

June 14, 2018 | Silver Spring, MD

@FDAOncology @AACR @SGO_org

Join the conversation with #OCEGynCancers18

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Introduction & Objectives

FDA Cochair: Julia A. Beaver, MD

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SESSION I:

Development of Immunotherapy in Gynecological Malignancies – Part 1

Session Cochairs: Sanjeeve Bala, MD, MPH, and Thomas Herzog, MD

Speakers:

Dmitriy Zamarin, MD, PhD

Deborah K. Armstrong, MD

Rebecca Arend, MD

Memorial Sloan Kettering Cancer Center™

Does immunotherapy make sense in gynecologic cancers?

Dmitriy Zamarin MD PhD

Assistant Attending Physician
Gynecologic Medical Oncology Service
Immunotherapeutics Service
Memorial Sloan Kettering Cancer Center

June 14 2018

"Jenner". Giulio Monteverde, 1873

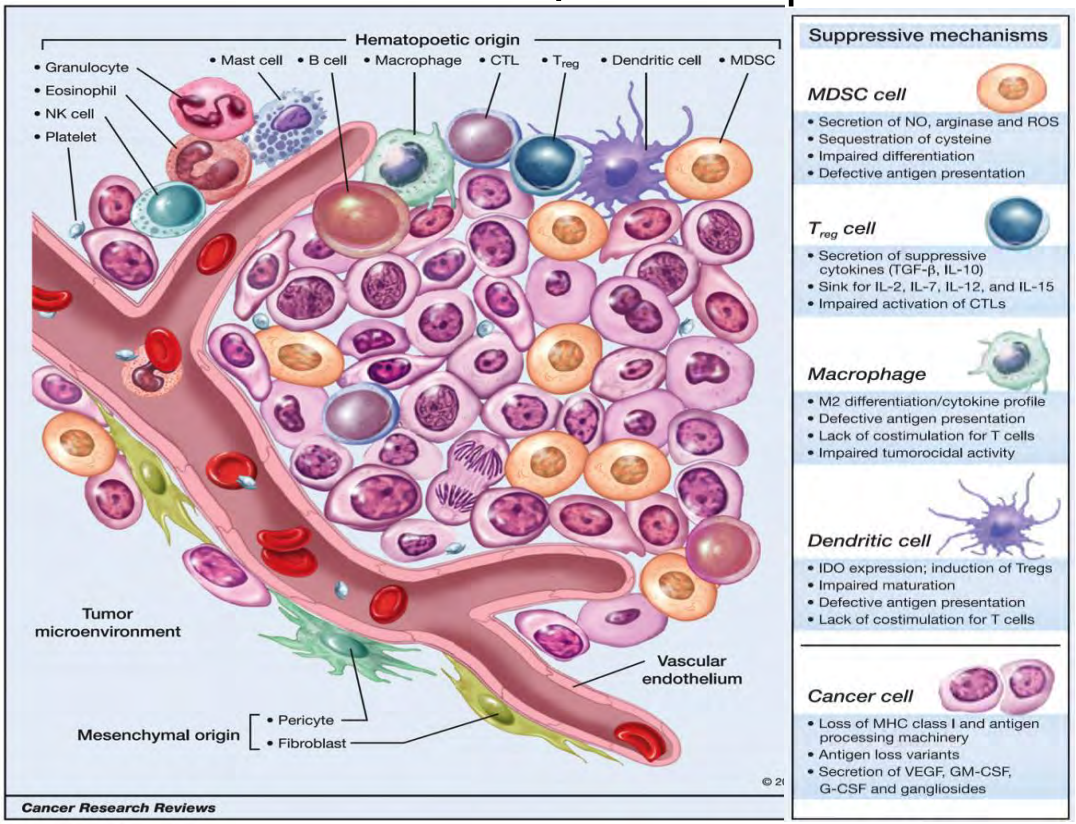
Memorial Sloan Kettering Cancer Center™

Disclosures

Merck
-Research support, consulting

Biomed Valley Discoveries
-Consulting

Established tumors are not just composed of cancer cells



Kerkar SP , Restifo NP Cancer Res 2012;72:3125-3130

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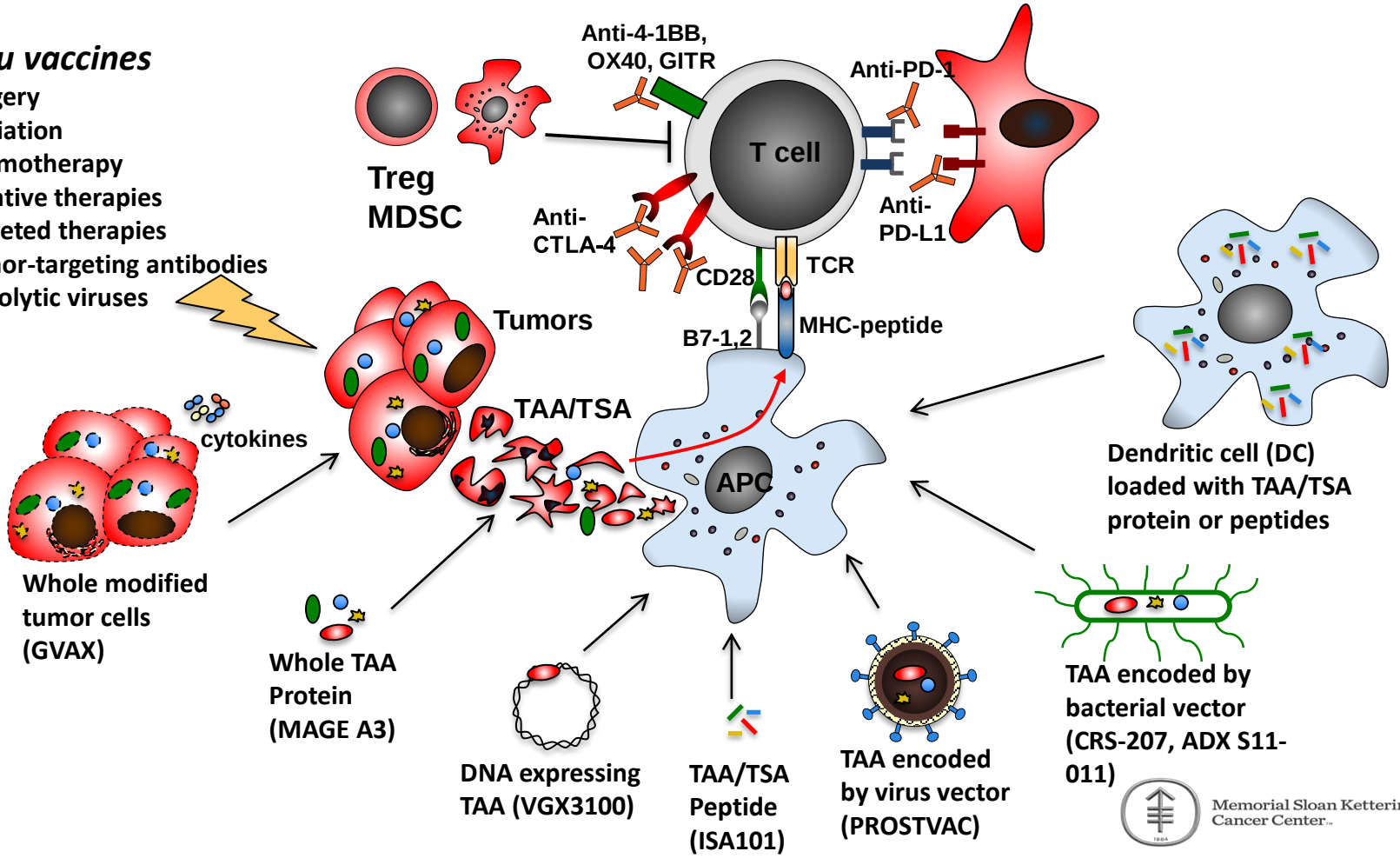
Tumor immunology and immunotherapy in 1 slide

In situ vaccines

- Surgery
- Radiation
- Chemotherapy
- Ablative therapies
- Targeted therapies
- Tumor-targeting antibodies
- Oncolytic viruses



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Biomarkers explored in immunotherapy (response/resistance)

- **Tumor microenvironment**
- TILs (high vs. low)
- immunosuppressive molecules (IDO, PD-L1) (high vs. low)
- immunosuppressive populations (Treg, MDSC) (high vs. low)
- TCR clonality (high vs. low)
- IFNg signature (high vs. low)

- **Tumor cells**
- mutational/neoantigen load (high vs. low)
- -endogenous retroviruses (high vs. low)
- -Type I IFN signaling pathways (high vs. low)

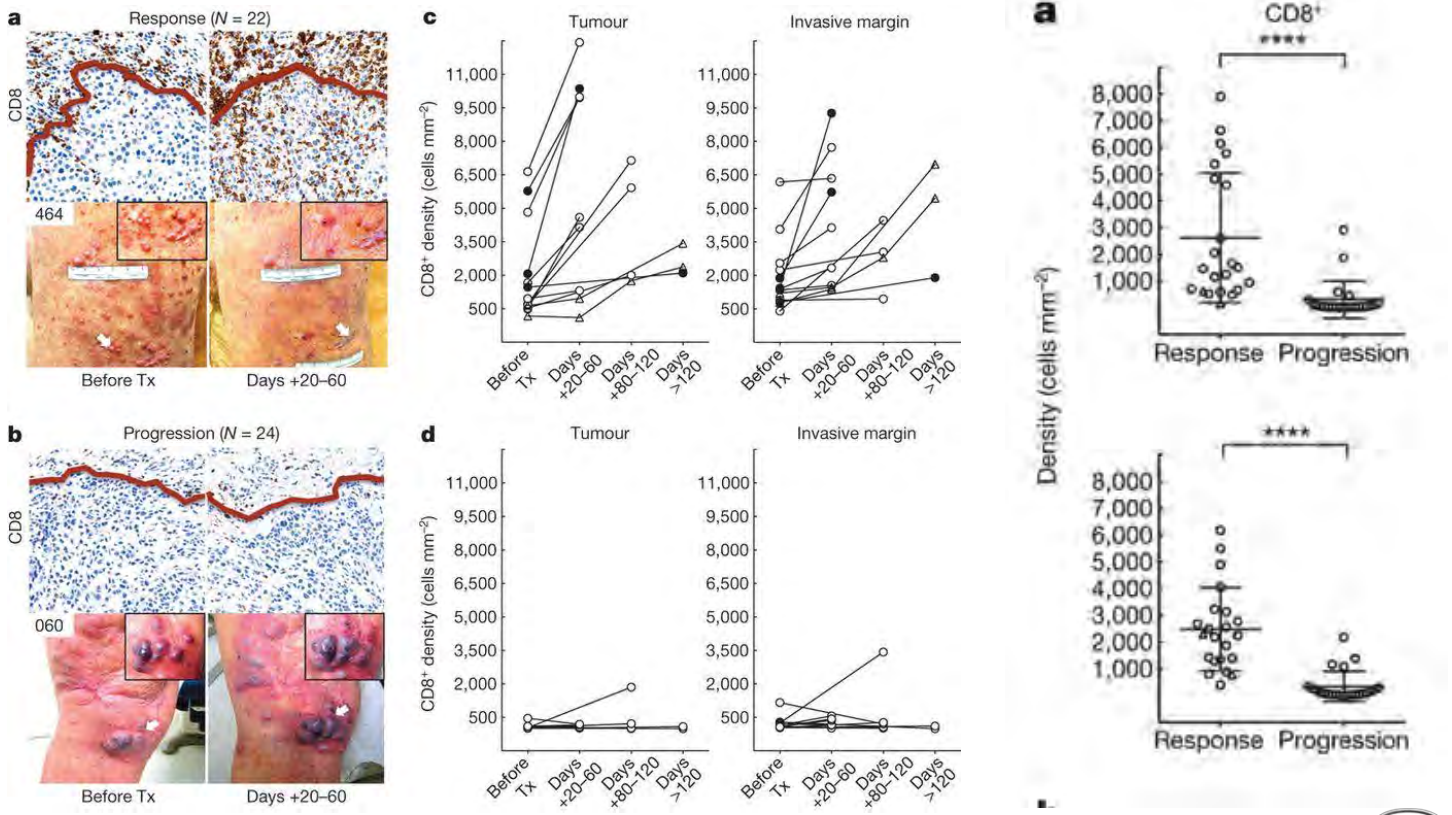
- **Blood**
- PBMC:
- Lymphocyte proliferation and activation markers (Ki-67, ICOS) (high vs. low)
- MDSC percentages (high vs. low)
- RNA/DNA:
- TCR clonality (pre and on-treatment)
- Gene expression
- Serum
- Cytokines
- serologic responses to CT antigens

- **Host**
- genetic polymorphisms in immune genes
- gut microbiome

Existing biomarkers: Rationale for immunotherapy in gynecologic cancers

- **Ovarian cancer**
  - Patients with high number of TILs at diagnosis have superior outcomes
  - Patients with immunoreactive TCGA gene expression phenotype have superior outcomes
- **Cervical cancer (and other HPV-driven cancers)**
  - Presence of foreign HPV epitopes should promote tumor immune recognition
- **Endometrial cancer**
  - Neoepitope abundance in MMR-deficient tumors promotes tumor immune recognition

Tumor microenvironment: infiltration with CD8+ lymphocytes in melanoma predicts response to PD-1 blockade



Tumeh et al., Nature 2014

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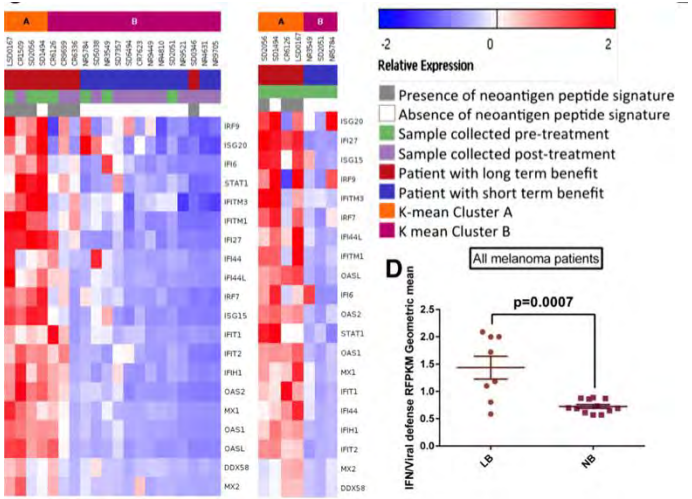
Tumor microenvironment: inflammatory gene expression signatures



Type I IFN signature is associated with clinical benefit from CTLA-4 blockade in melanoma
Chiappinelli et al., Cell 2015

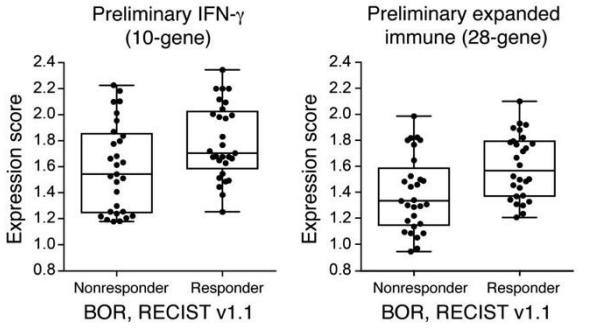


Table 2. IFN-γ and expanded immune gene signatures

IFN-γ	Expanded immune gene signature	
IDO1	*CD3D*	*IL2RG*
CXCL10	*IDO1*	*NKG7*
CXCL9	*CIITA*	*HLA-E*
HLA-DRA	*CD3E*	*CXCR6*
STAT1	*CCL5*	*LAG3*
IFNG	*GZMK*	*TAGAP*
	CD2	*CXCL10*
	HLA-DRA	*STAT1*
	CXCL13	*GZMB*

IFNγ signature in pre-treatment tumors is associated with response in different cancers
Ayers et al., JCI 2017

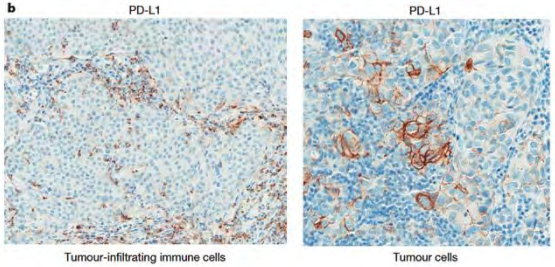
Tumor microenvironment: PD-L1 expression in tumor cells and immune cells enriches for responders, but not in all tumor types

a

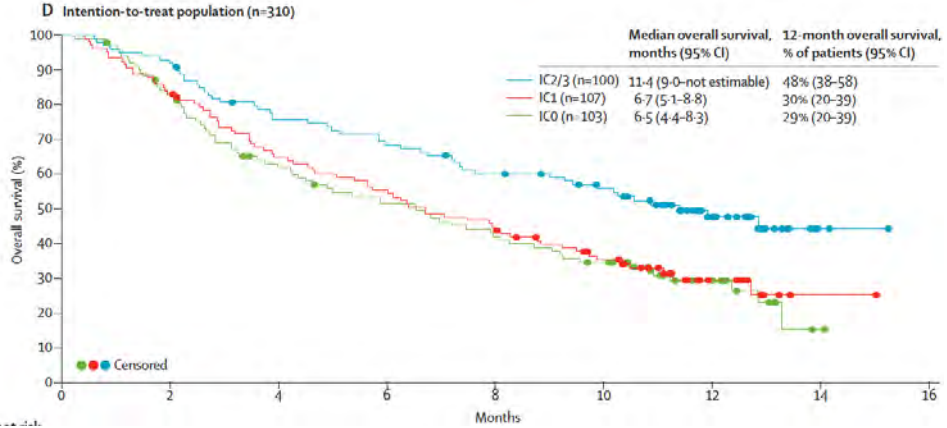
PD-L1 prevalence in UBC tumours by IHC

n = 205	PD-L1-positive tumour-infiltrating immune cells (no. of specimens (%))	PD-L1-positive tumour cells (no. of specimens (%))
IHC 3	18 (9)	14 (7)
IHC 2	37 (18)	8 (4)
IHC 1	89 (43)	37 (18)
IHC 0	61 (30)	146 (71)

b

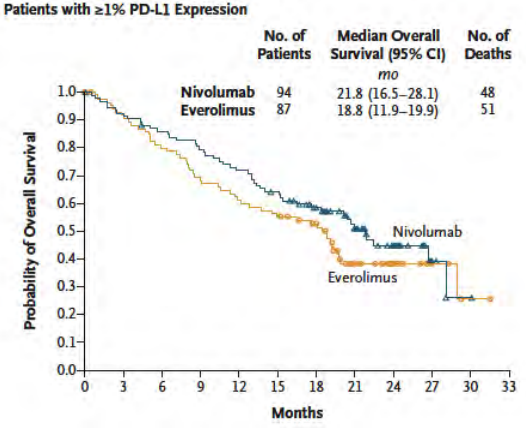


D Intention-to-treat population (n=310)

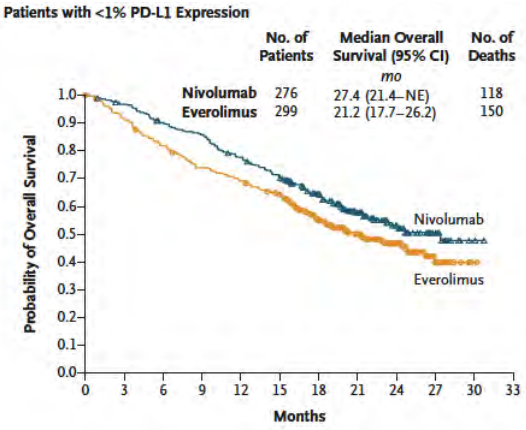


Bladder CA

A Patients with ≥1% PD-L1 Expression



B Patients with <1% PD-L1 Expression



RCC

Motzer et al. Nature 2015, Rosenberg JE, et. al, Lancet 2016

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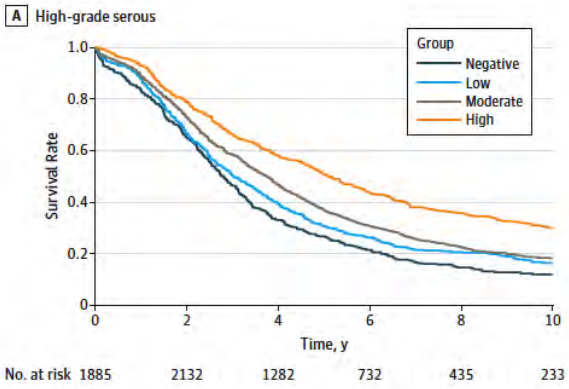
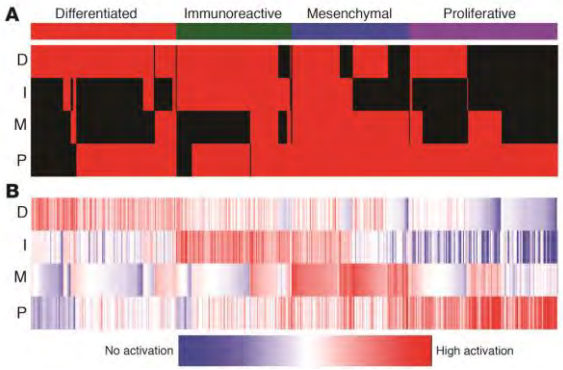
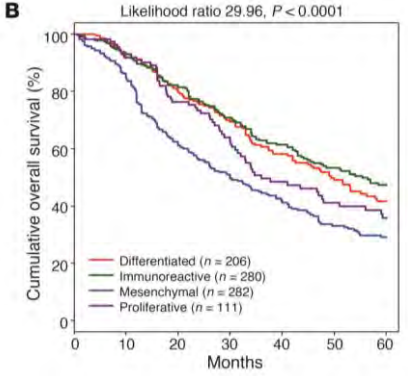
Presence of TILs and immune gene expression signatures are prognostic in ovarian cancer (hence immunotherapy makes sense)

TIL counts per HPF
Negative (17%)
Low: 1-2 (17%)
Moderate: 3-19 (44%)
High: >20 (22%)



JAMA Oncology 2017





Verhaak et al., JCI 2013

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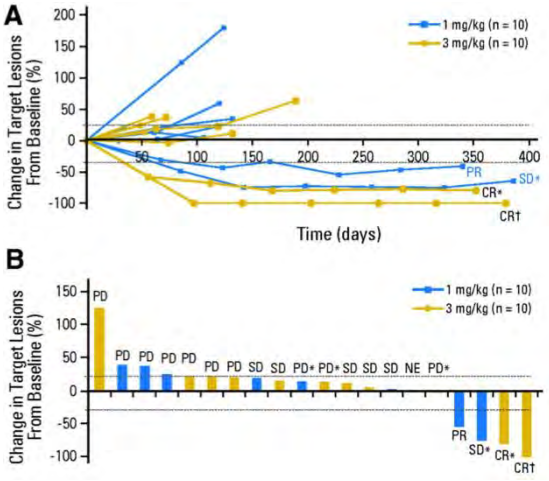
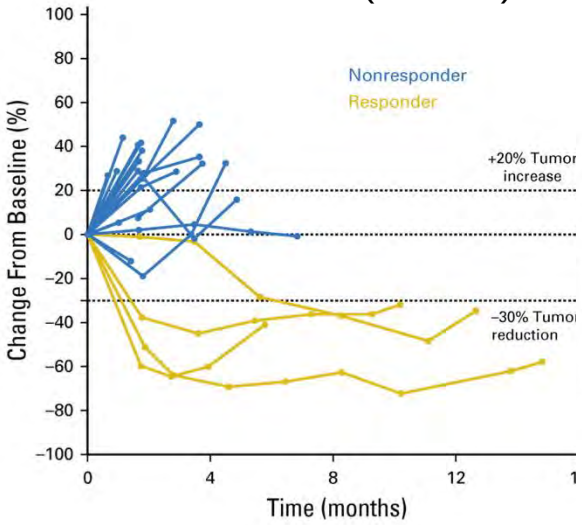
PD-1 blockade has limited activity in GYN cancers

Ovarian



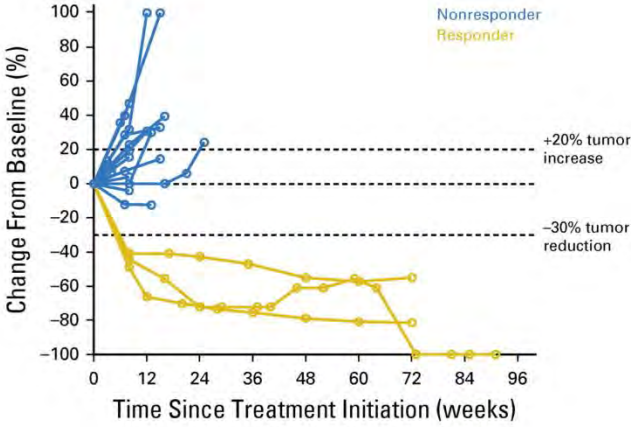
ORR 15%

Cervical (PD-L1+)



ORR 17%

Endometrial (PD-L1+)



ORR 13%

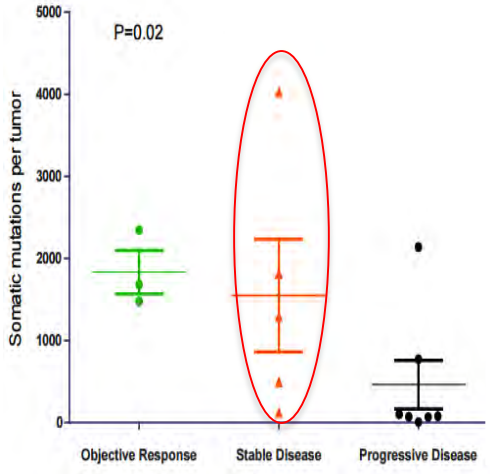
Hamanishi et al., JCO 2015, Frenel et al., JCO 2017; Ott et al., JCO 2017

1. Single-agent immunotherapies are not sufficient for most GYN patients

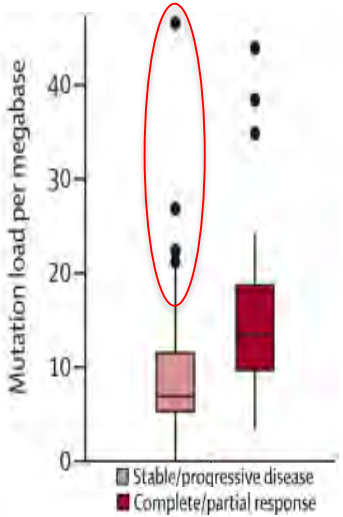
2. Existing biomarkers are not sufficient in guiding GYN patient selection for immunotherapy

Tumor cells: mutational load and neoantigens as predictors of clinical benefit

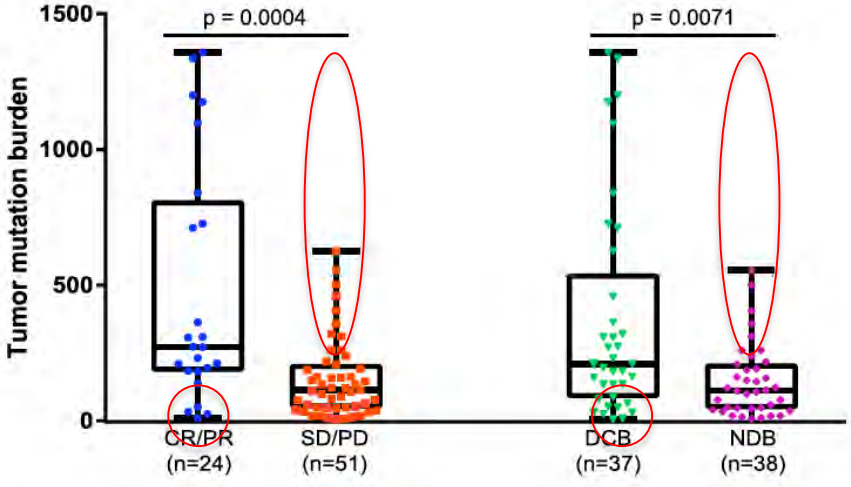
MMR-D CRC/anti-PD-1



Bladder/anti-PD-L1

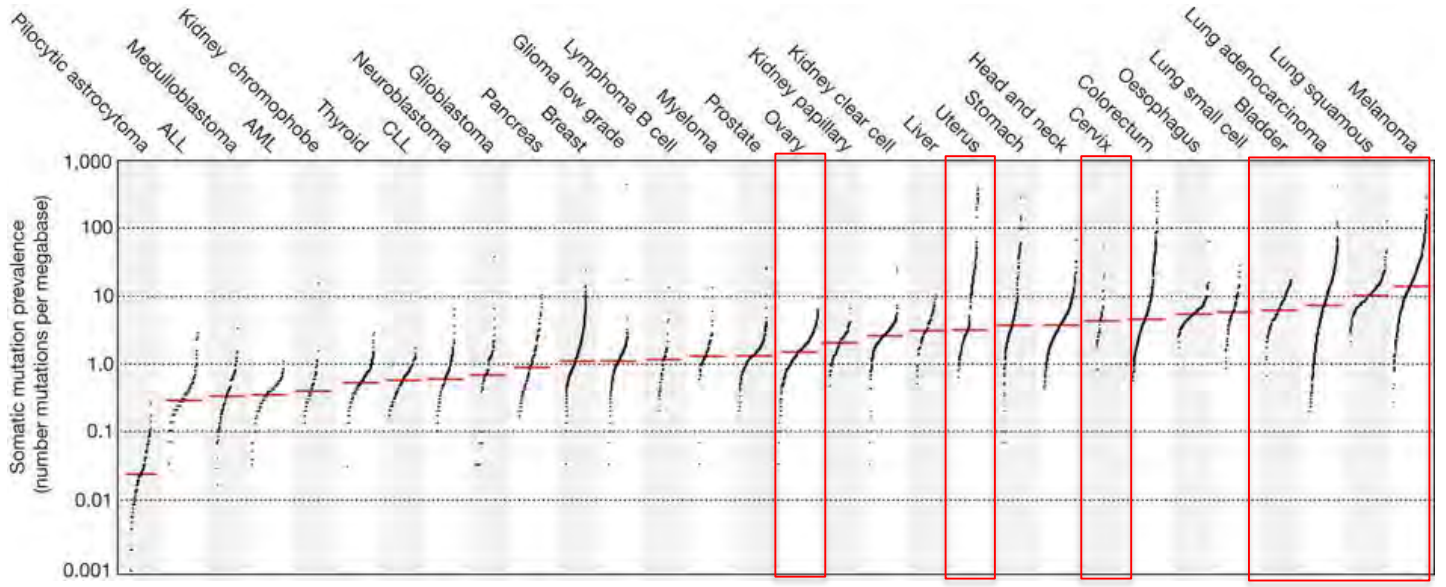


NSCLC/anti-PD-1+anti-CTLA-4



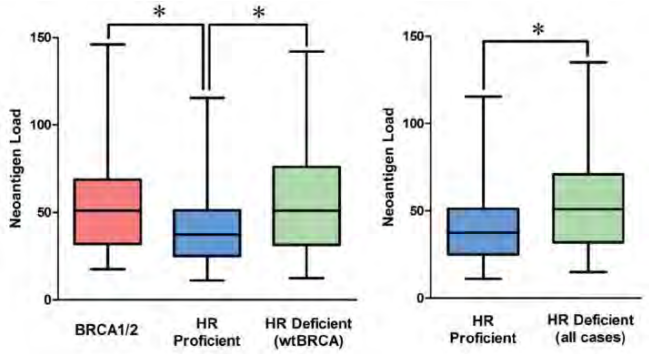
Le et al NEJM 2015, Hellmann et al Cancer Cell 2018, Rosenberg et al Lancet Oncol 2016

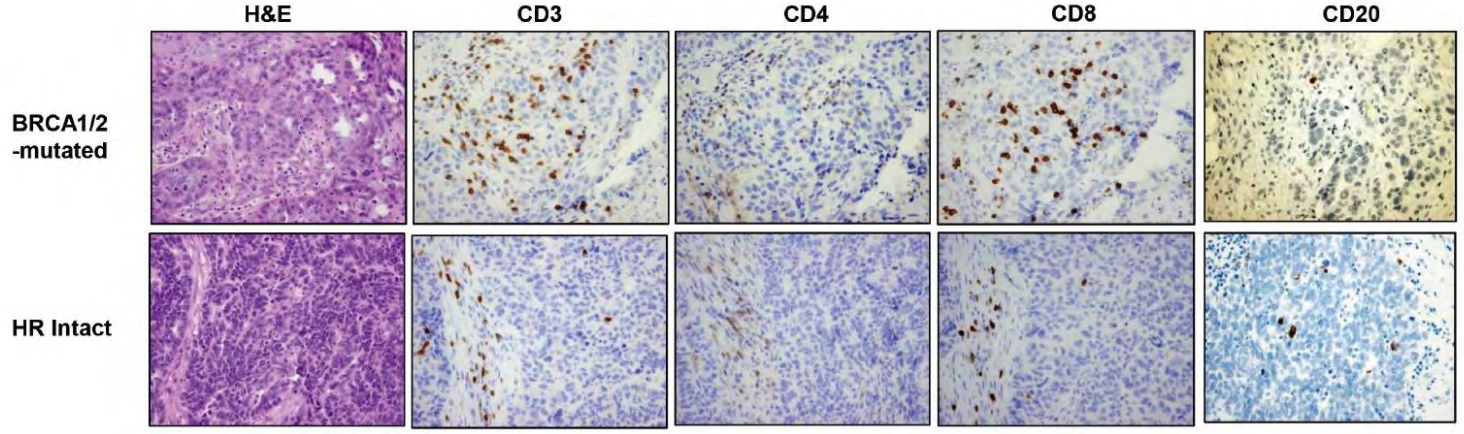
Most GYN cancers exhibit low mutational burden



Alexandrov et al., Nature 2013

BRCA mutation is associated with TIL infiltration and increased neoantigen load in HGSOC





Strickland et al, Oncotarget 2016

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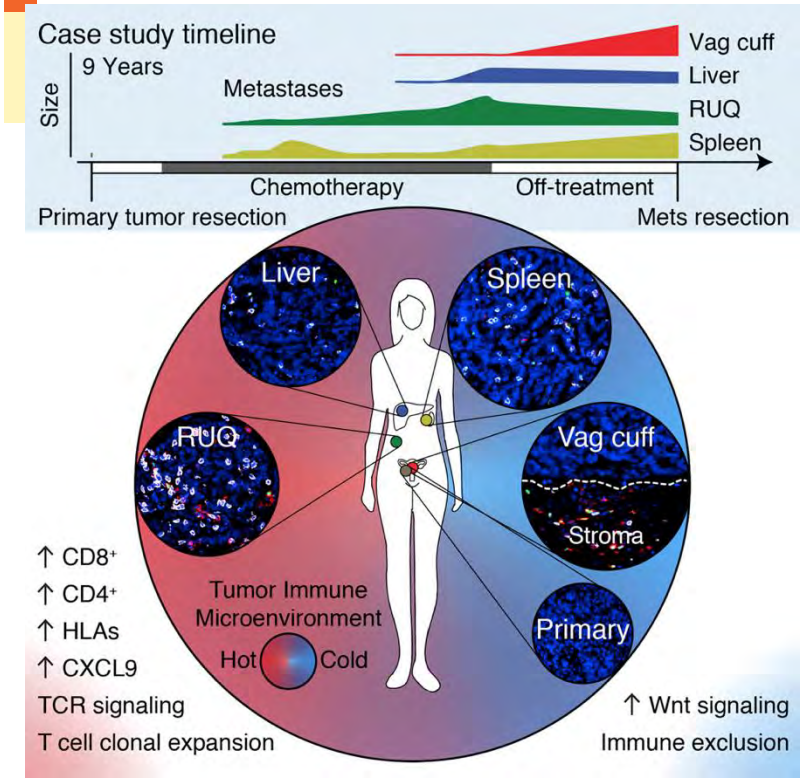
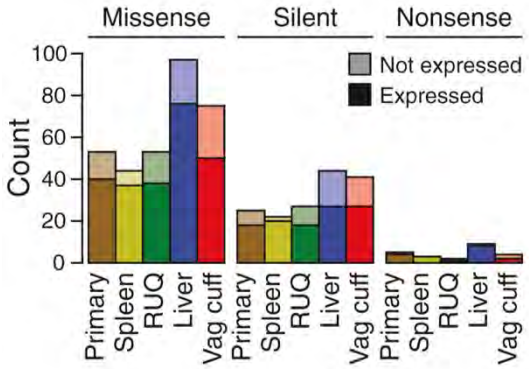
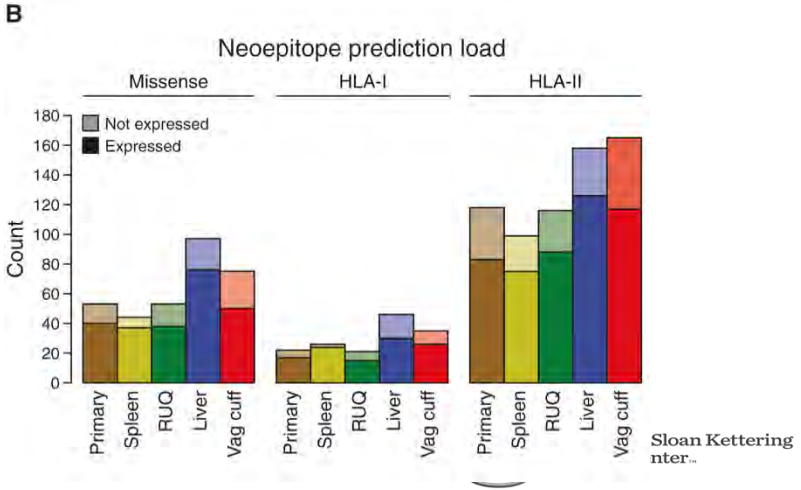
Neoepitope load does not always predict the immune phenotype and fate of ovarian tumor lesions







Jimenez-Sanchez et al., Cell 2017

The New York Times

HEALTH

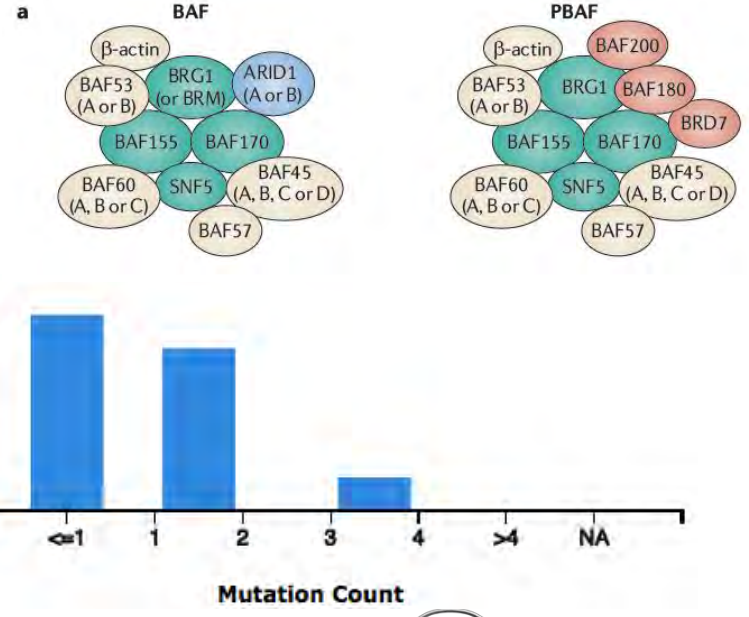
Doctors Said Immunotherapy Would Not Cure Her Cancer. They Were Wrong.

Leer en español

By GINA KOLATA FEB. 19, 2018

Oriana Sousa, 28, who lives in Marinha Grande, Portugal, had a rare, aggressive form of ovarian cancer. Traditional treatments failed, but with immunotherapy her tumors shrank so much that there is no evidence of disease. Daniel Rodrigues for The New York Times

Small cell carcinoma of the ovary hypercalcemic type (SCCOHT): a monogenic disease driven by loss of BRG1 (SMARCA4)



Jelinic et al., Nat Genetics 2014; Witkowsky et al., Nat Genetics 2014; Ramos et al., Nat Genetics 2014

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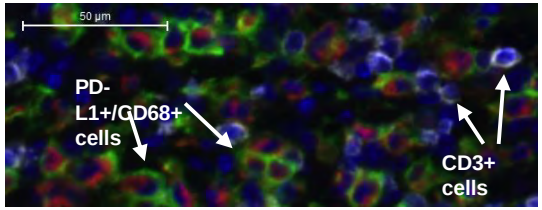
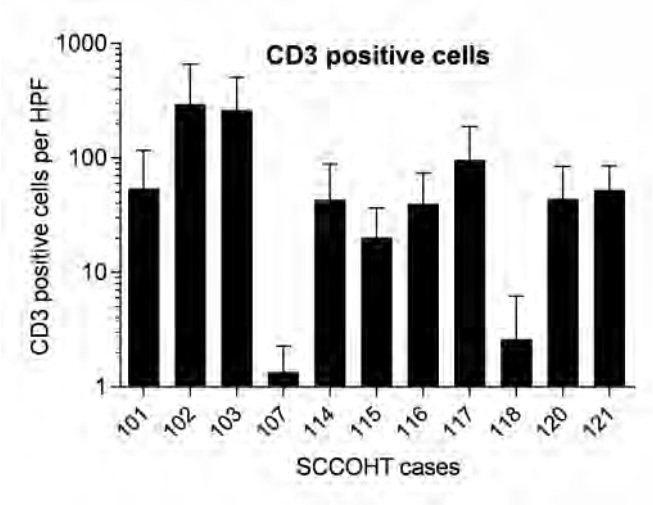
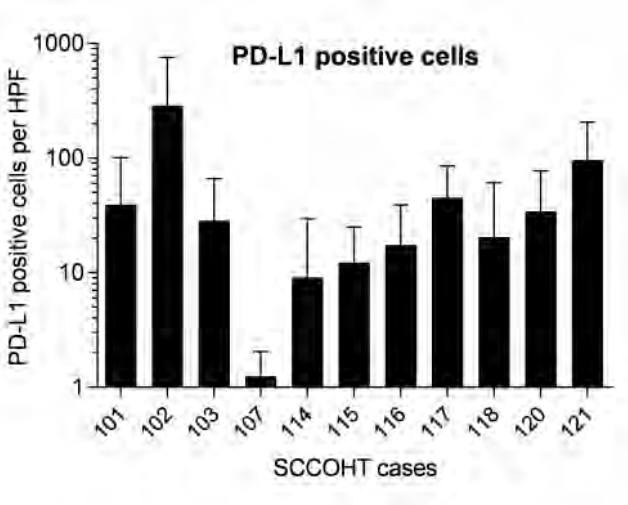
Despite low tumor mutational burden SCCOHTs exhibit immune-active tumor microenvironment.







Jelinic, Ricca, Merghoub, Levine, and Zamarin, JNCI: 2018

Memorial Sloan Kettering Cancer Center

Mutations in SWI/SNF component PBRM1 predict response to immunotherapy in kidney cancer

Science

REPORTS

Cite as: D. Miao *et al.*, *Science*
10.1126/science.aan5951 (2018).

Genomic correlates of response to immune checkpoint therapies in clear cell renal cell carcinoma

Diana Miao,[1,2] Claire A. Margolis,[1,2] Wenhua Gao,[1] Martin H. Voss,[3,4] Wei Li,[5] Dylan J. Martini,[1] Craig Norton,[1] Dominick Bossé,[1] Stephanie M. Wankowicz,[1,2] Dana Cullen,[6] Christine Horak,[6] Megan Wind-Rotolo,[6] Adam Tracy,[2] Marios Giannakis,[1,2] Frank Stephen Hodi,[1] Charles G. Drake,[7] Mark W. Ball,[8] Mohamad E. Allaf,[8] Alexandra Snyder,[3]* Matthew D. Hellmann,[3,4] Thai Ho,[9] Robert J. Motzer,[3,4] Sabina Signoretti,[1] William G. Kaelin Jr.,[1,10] Toni K. Choueiri,[1]†‡ Eliezer M. Van Allen[1,2]†‡

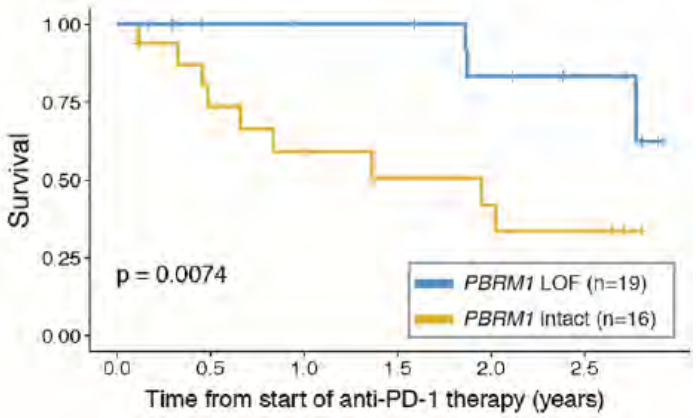
Science

RESEARCH ARTICLES

Cite as: D. Pan *et al.*, *Science*
10.1126/science.aao1710 (2018).

A major chromatin regulator determines resistance of tumor cells to T cell–mediated killing

Deng Pan,[1]* Aya Kobayashi,[1]* Peng Jiang,[2]* Lucas Ferrari de Andrade,[1] Rong En Tay,[1] Adrienne Luoma,[1] Daphne Tsoucas,[2] Xintao Qiu,[3] Klothilda Lim,[3] Prakash Rao,[3]† Henry W. Long,[3] Guo-Cheng Yuan,[2] John Doench,[4] Myles Brown,[3] Shirley Liu,[2]‡ Kai W. Wucherpfennig[1,5]‡



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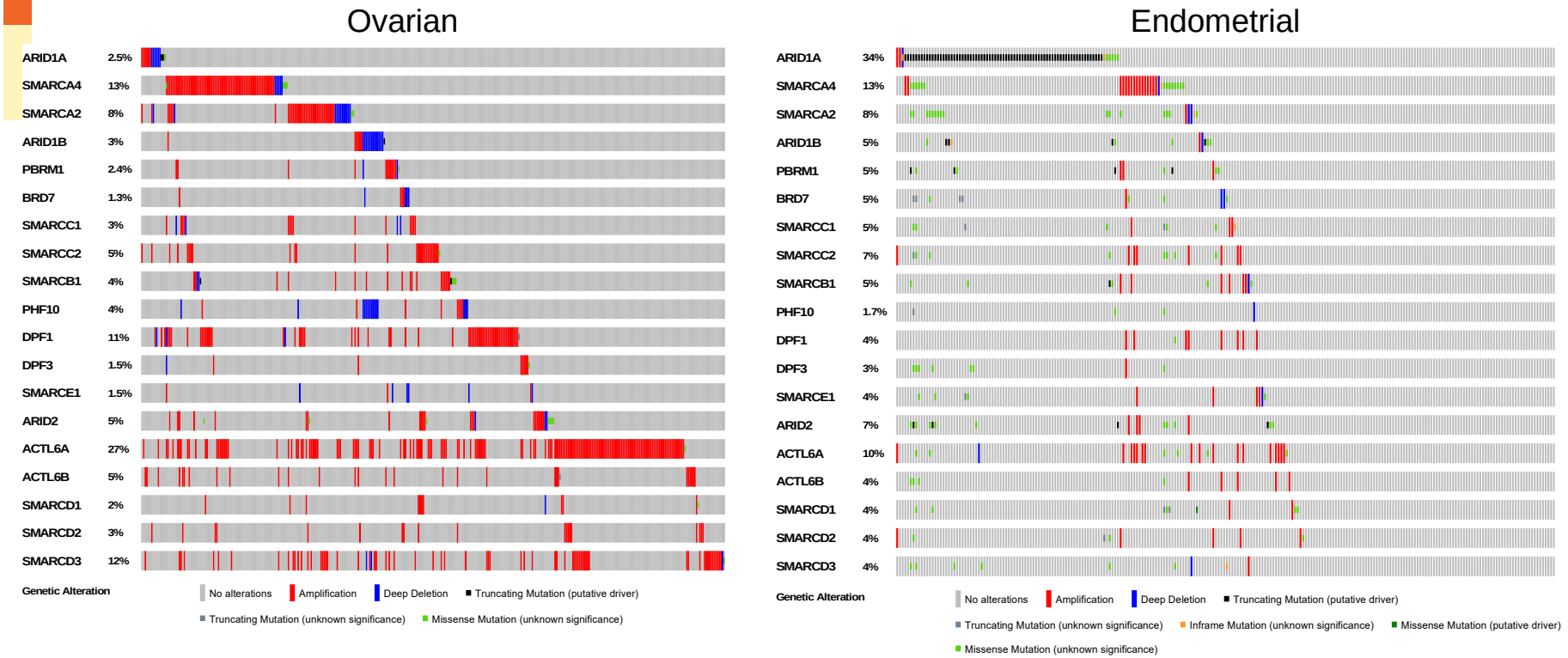
Ovarian and endometrial cancers exhibit recurrent alterations in chromatin remodeling complex components

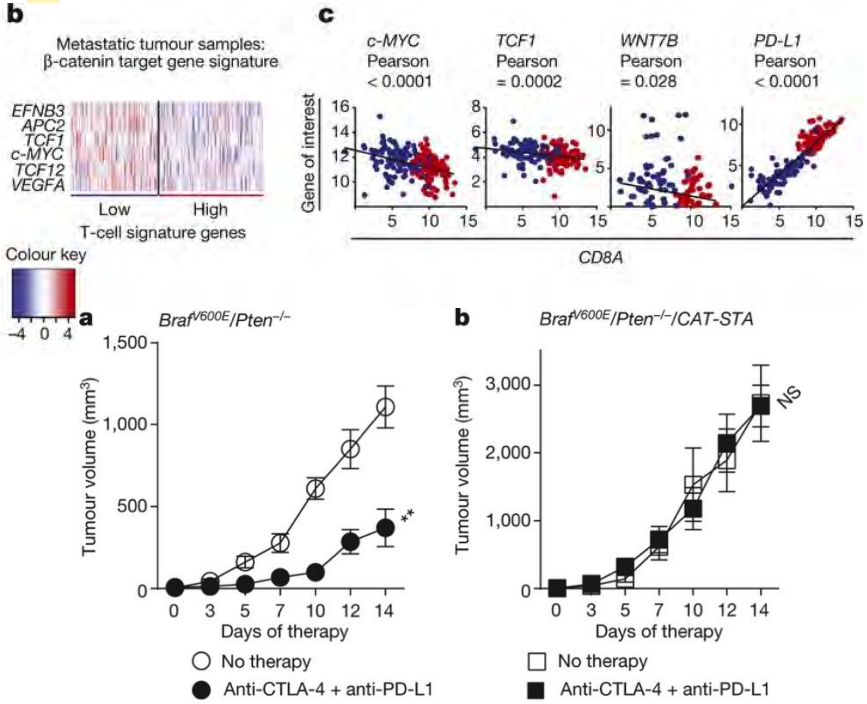


Altered in 60% of all ovarian and 62% of endometrial cancers

Memorial Sloan Kettering Cancer Center

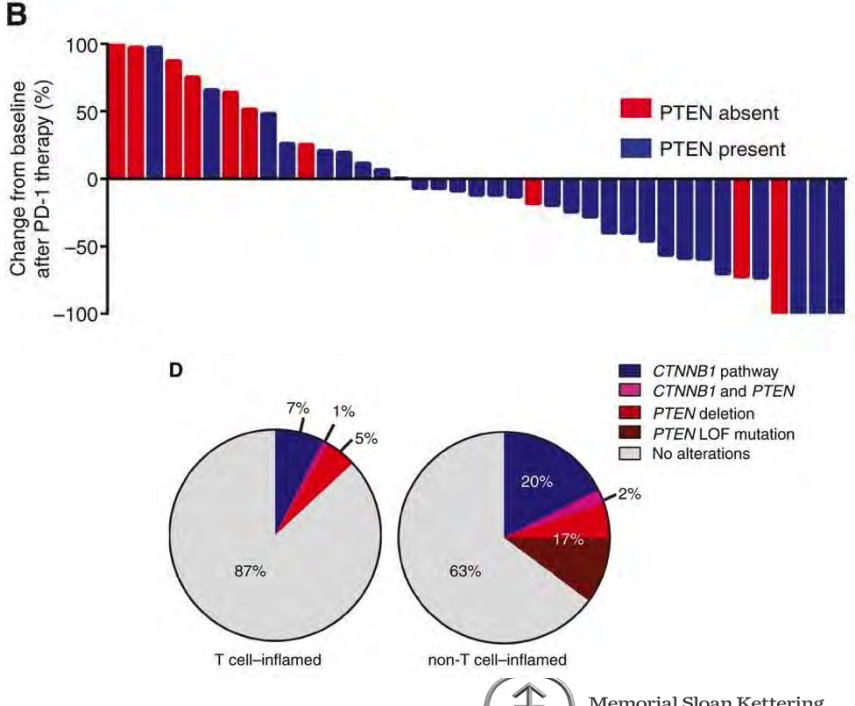
Alterations in some driver pathways can predict resistance to immunotherapy

Beta-catenin pathway in melanoma



Spranger et al., Nature 2015

PTEN pathway in melanoma



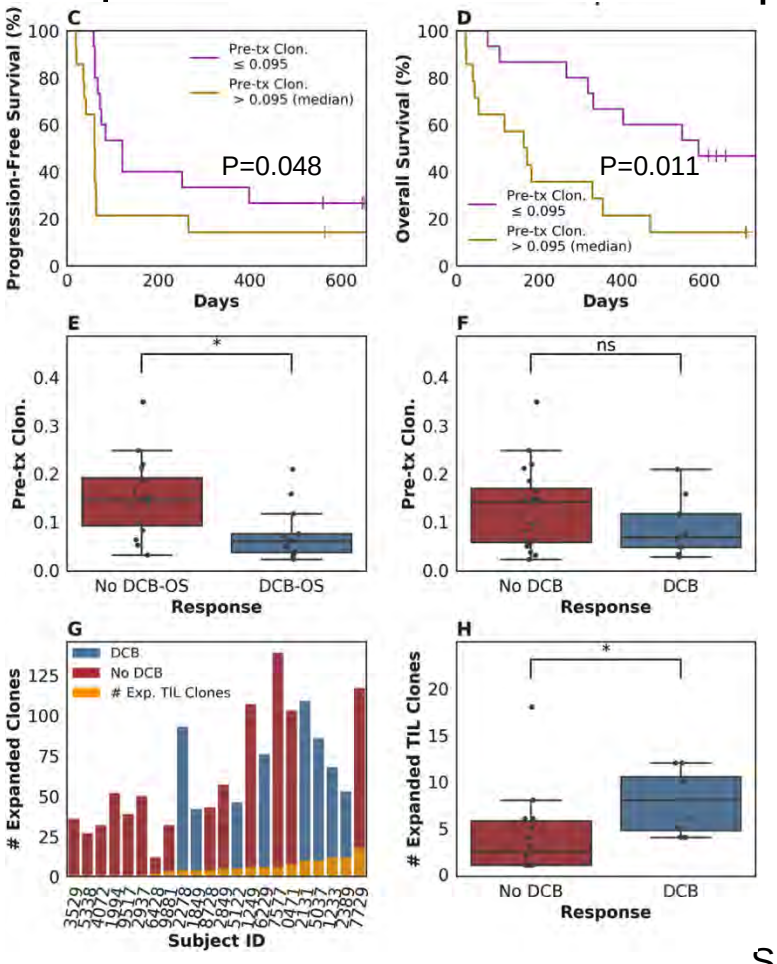
Peng, et al., Cancer Discovery 2016

Memorial Sloan Kettering Cancer Center

Changes in peripheral blood biomarkers can enrich for responders to immunotherapy

- **Absolute lymphocyte count (ALC)**
  - On treatment ALC increase is associated with survival in melanoma patients treated with ipilimumab (Ku G., et al., Cancer 2010)
- **ICOS+CD4+ lymphocytes**
  - On treatment sustained increase in ICOS+ CD4+ lymphocytes is associated with survival in melanoma patients treated with ipilimumab (Carthon, et al., CCR 2010)
- **CD8+PD-1+Ki67+ lymphocytes/tumor burden**
  - 3-6 week CD8+PD-1+Ki67+/tumor burden ratio predictive of clinical benefit (Huang A., et al., Nature, 2017)
- **Serum autoantibodies**
  - Upregulation of serum autoantibodies predicts response to CTLA-4 blockade in prostate cancer (Kwek et al, J Immunol 2012)

Peripheral blood: T cell receptor (TCR) clonality



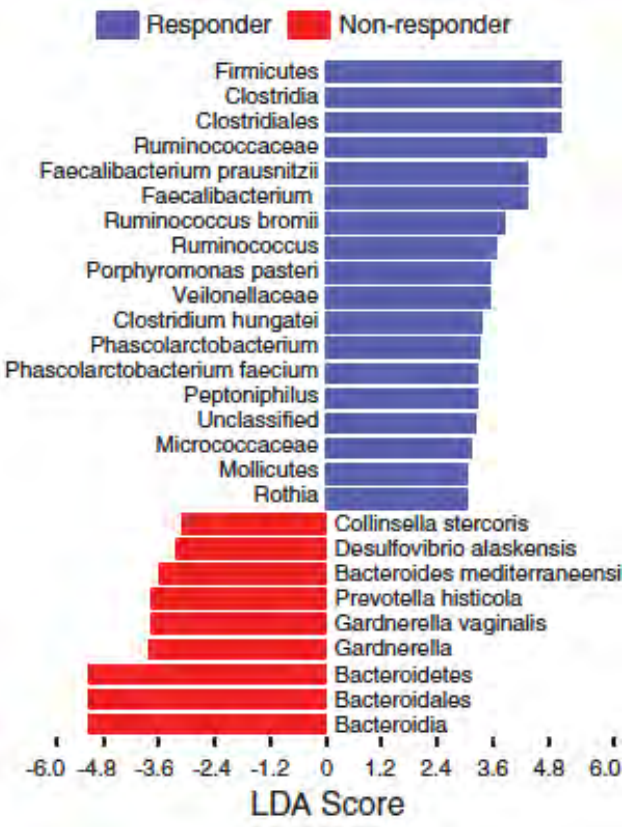
Low pre-treatment TCR clonality in blood has prognostic value.
Possibly predictive value?

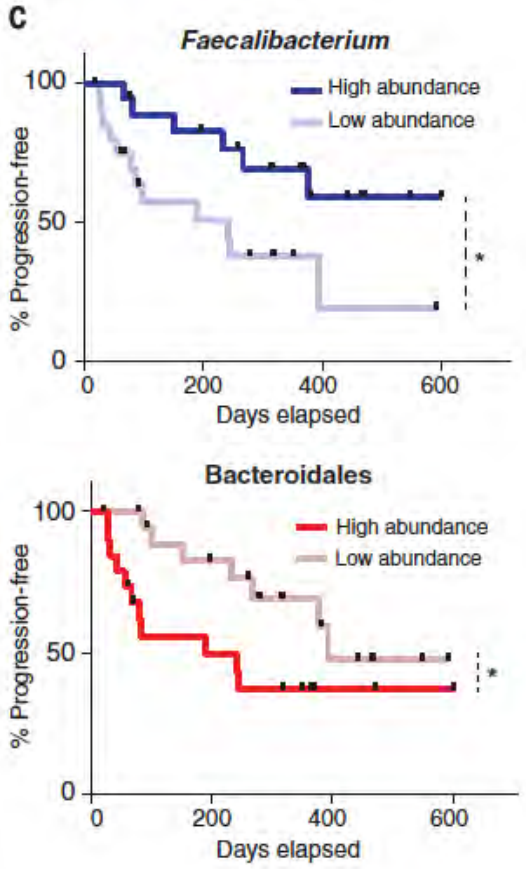
DCB is associated with increased peripheral expansion of intratumoral TCR clones

Snyder A et al. PLoS Medicine 2017

Memorial Sloan Kettering Cancer Center

Host: stool microbiota signatures





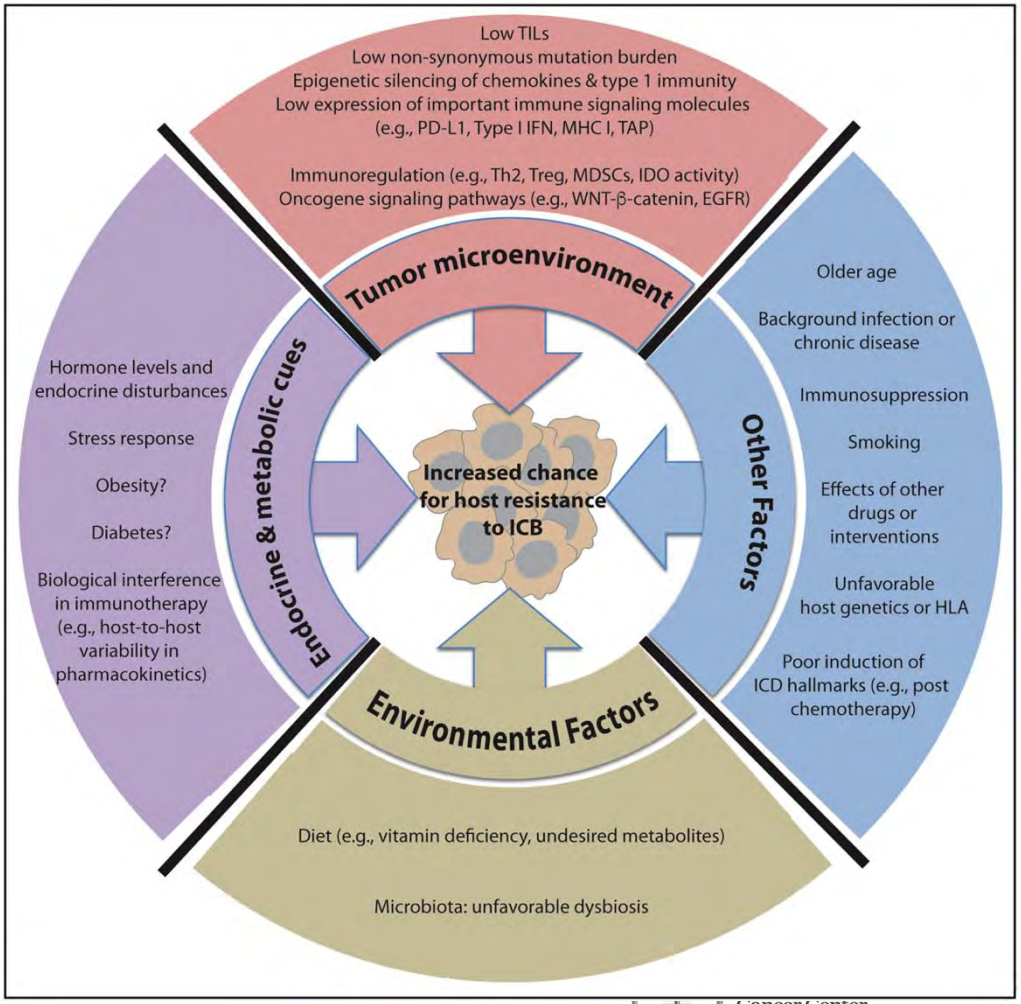
Gopalakrishnan et al., Science 2018

Memorial Sloan Kettering Cancer Center

Summary

- Immunotherapy in GYN cancers makes sense, but will likely require combinations in most patients

- There is no single biomarker: optimal patient selection will depend on integration of tumor, blood, host, and environmental factors and these should be analyzed within the context of all trials



Pitt et al., Immunity 2016

KIMMEL CANCER CENTER

Efficacy & Safety of Single Agent Immunotherapy & Immune Checkpoint Inhibitors in Gynecologic Cancer

FDA-AACR-SGO Workshop on Drug Development in Gynecologic Malignancies

Deborah K. Armstrong, M.D.

Johns Hopkins Kimmel Cancer Center

June 14, 2018

JOHNS HOPKINS MEDICINE

Disclosures: Deborah K. Armstrong, M.D.

Clinical Trial Research Funding:

Astra Zeneca	Pfizer	Genentech
Clovis	Syndax	Tesaro

Consultant/Advisory Board:

Cue Biopharma

Unlabeled/Unapproved use: I will discuss use of immune checkpoint inhibitors for currently unlabeled uses

Outline

- Endometrial Cancer
- Cervical cancer
  - Other HPV-associated gyn cancers
- Ovarian cancer

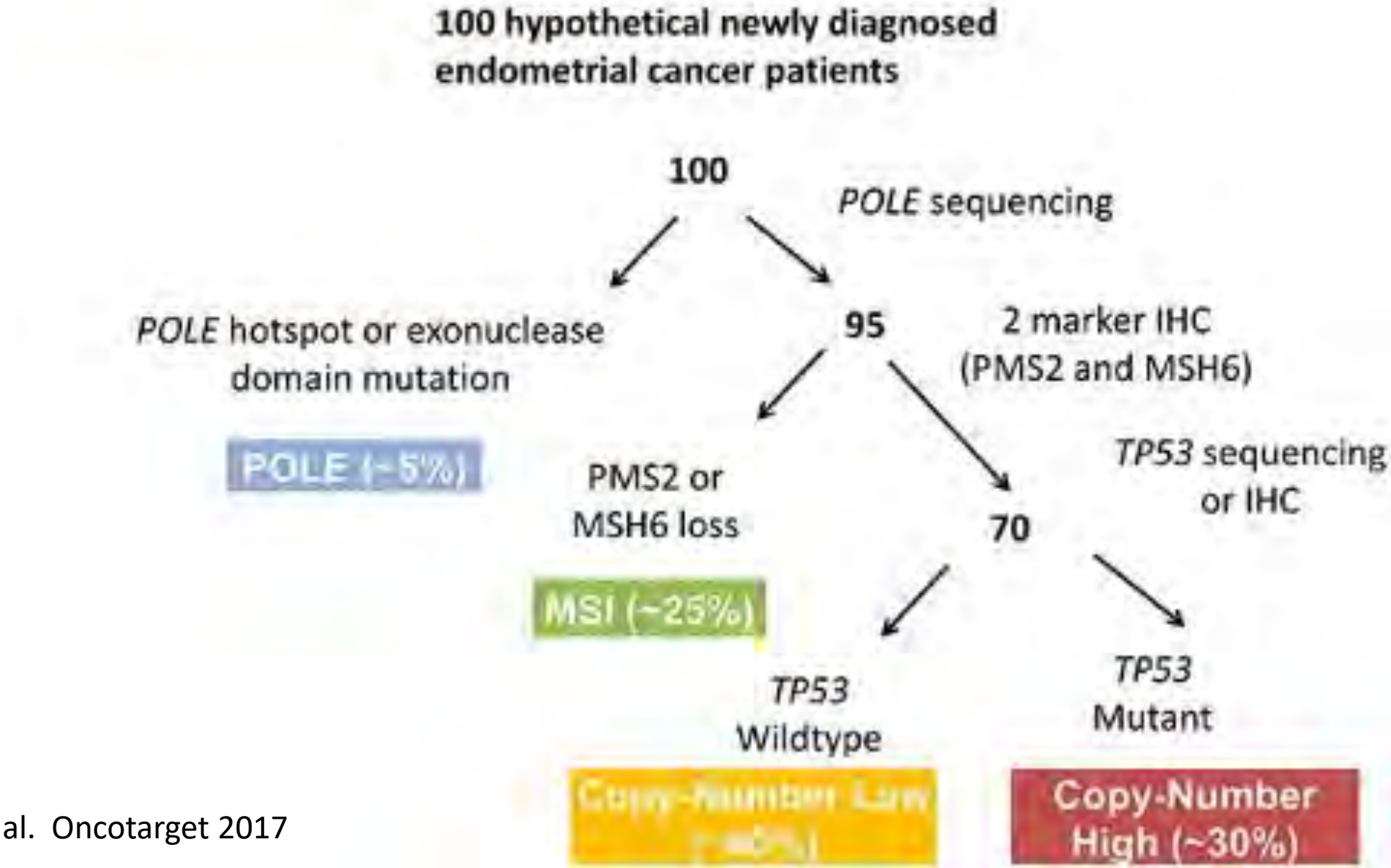
MMR Defects in Endometrial Cancer

- Loss of DNA mismatch repair is a common event in endometrial cancer
  - 22-37%, most frequent in endometrioid histology
- Most MMR defects in endometrial cancer are somatic, not inherited
  - Less than 5% overall due to germline mutations (Lynch)
  - Due to epigenetic silencing via methylation
    - Predominantly MLH1
  - Due to somatic mutations in the gene(s)
    - MSH6, MSH2, PMS2, MLH1

Sequelae of Loss of DNA Mismatch Repair

- DNA mismatches occur during normal DNA synthesis (about one in every 10^6 bases)
- DNA mismatches commonly occur in regions of repetitive nucleotide sequences called microsatellites
- A characteristic feature of loss of mismatch repair in tumors is the expansion or contraction of these microsatellite regions in the tumor compared with normal tissue
- This genetic alteration is termed microsatellite instability (MSI)
  - First defined by Papadopolous and Vogelstein in 1990's

Patients divided into TCGA subgroups



McKay H et.al. Oncotarget 2017

Endometrial Cancer (EC) – Four molecular subtypes

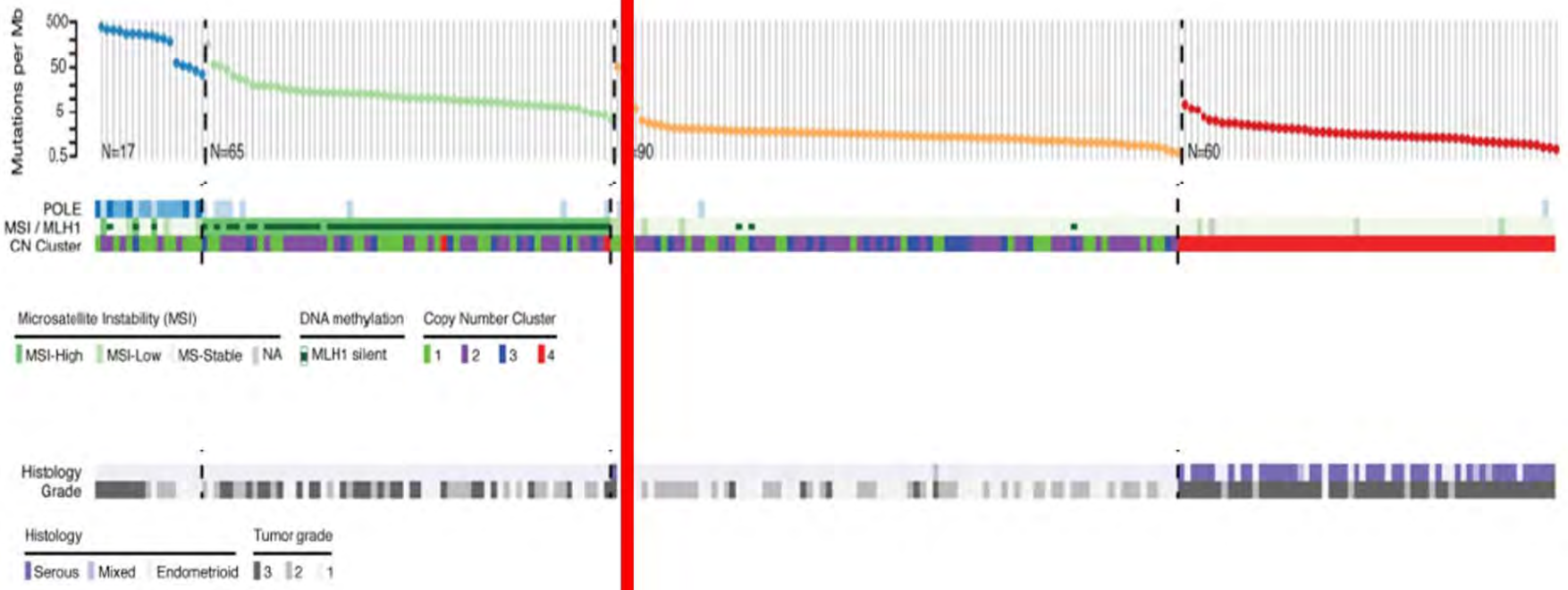
(Integrated genomic, transcriptomic and proteomic characterization)

POLE
ultra-mutated
(15x > vs MSI)

MSI
hyper-mutated
(8x > vs MSS)

Copy number low
- endometrioid -
(MSS group)

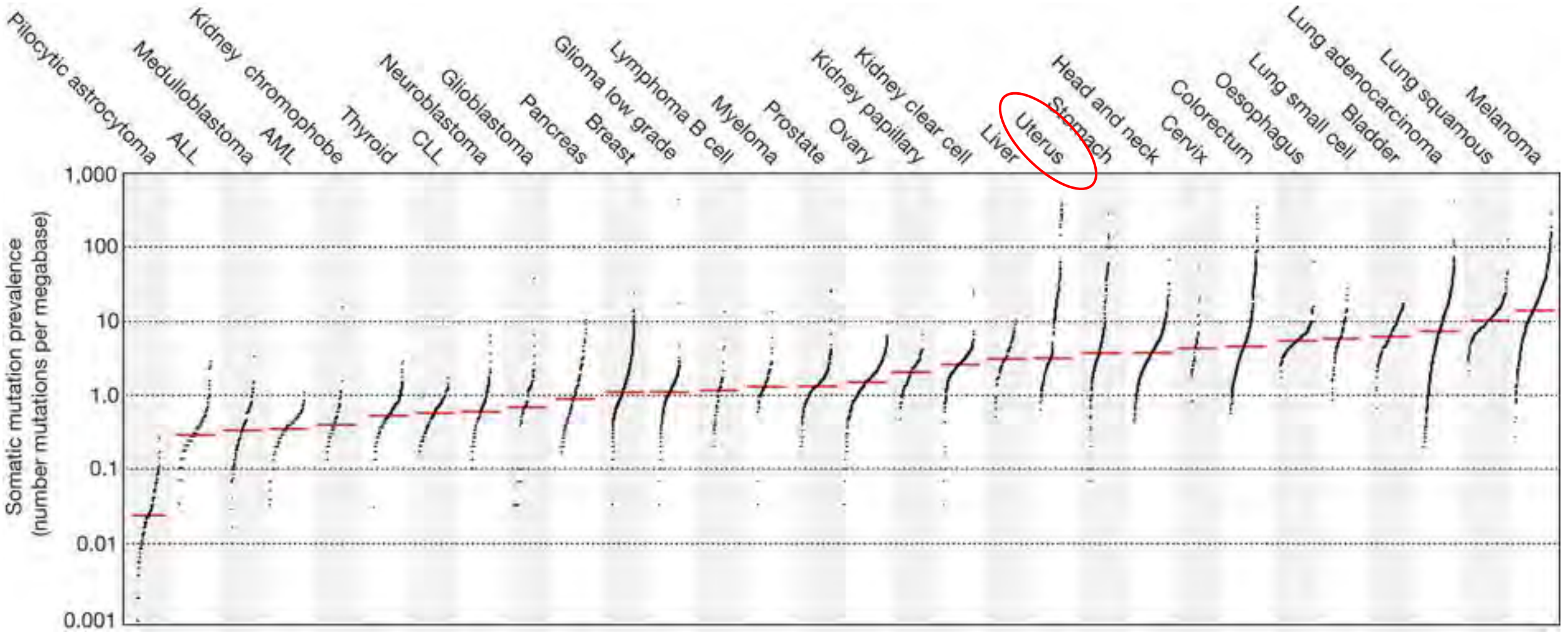
Copy number high
- serous-like -



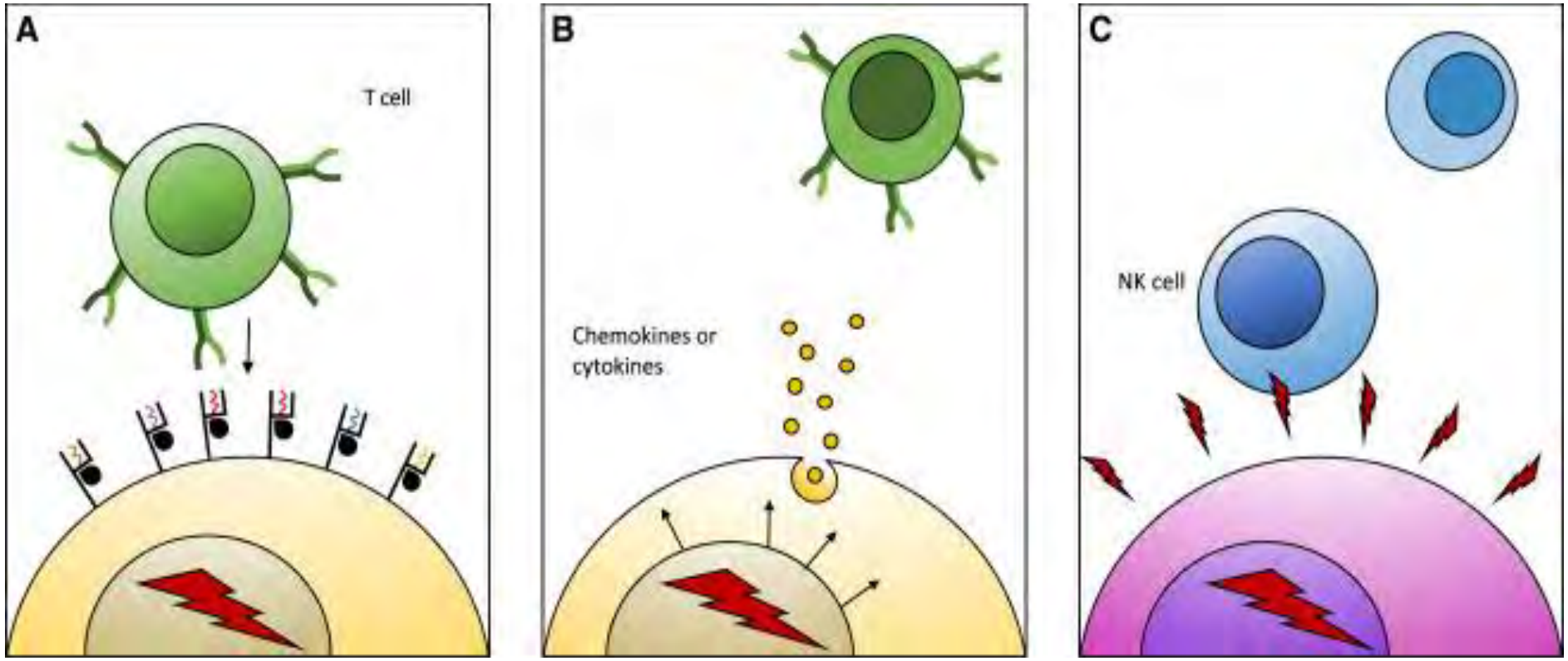
Hot tumors

Cold tumors

Kandoth et al., Nature 2013



Alexandrov et.al. Nature 2013



Potential Mechanisms of Action of Anti-PD-1 Therapy in Mismatched Repair-Deficient Tumors

(A) MMR deficiency results in a **more diverse neo-antigen repertoire**, increasing the chances of a tumor-specific T cell response.
(B) MMR deficiency is associated with the **activation of signaling pathways**, which leads to a more inflammatory tumor micro-environment.
(C) MMR deficiency leads to **cellular stress**, which, for instance, promotes T or NK cell accumulation or tumor recognition.

Sander Kelderman, et.al. Cancer Cell Volume 28, Issue 1, 2015, 11-13

Response to Anti-PD1 (Pembrolizumab) in MMR Deficient Tumors

	MMR-deficient CRC	MMR-proficient CRC	MMR-deficient non-CRC
N	13	25	10
Objective Response Rate	62%	0%	60%
Disease Control Rate	92%	16%	70%

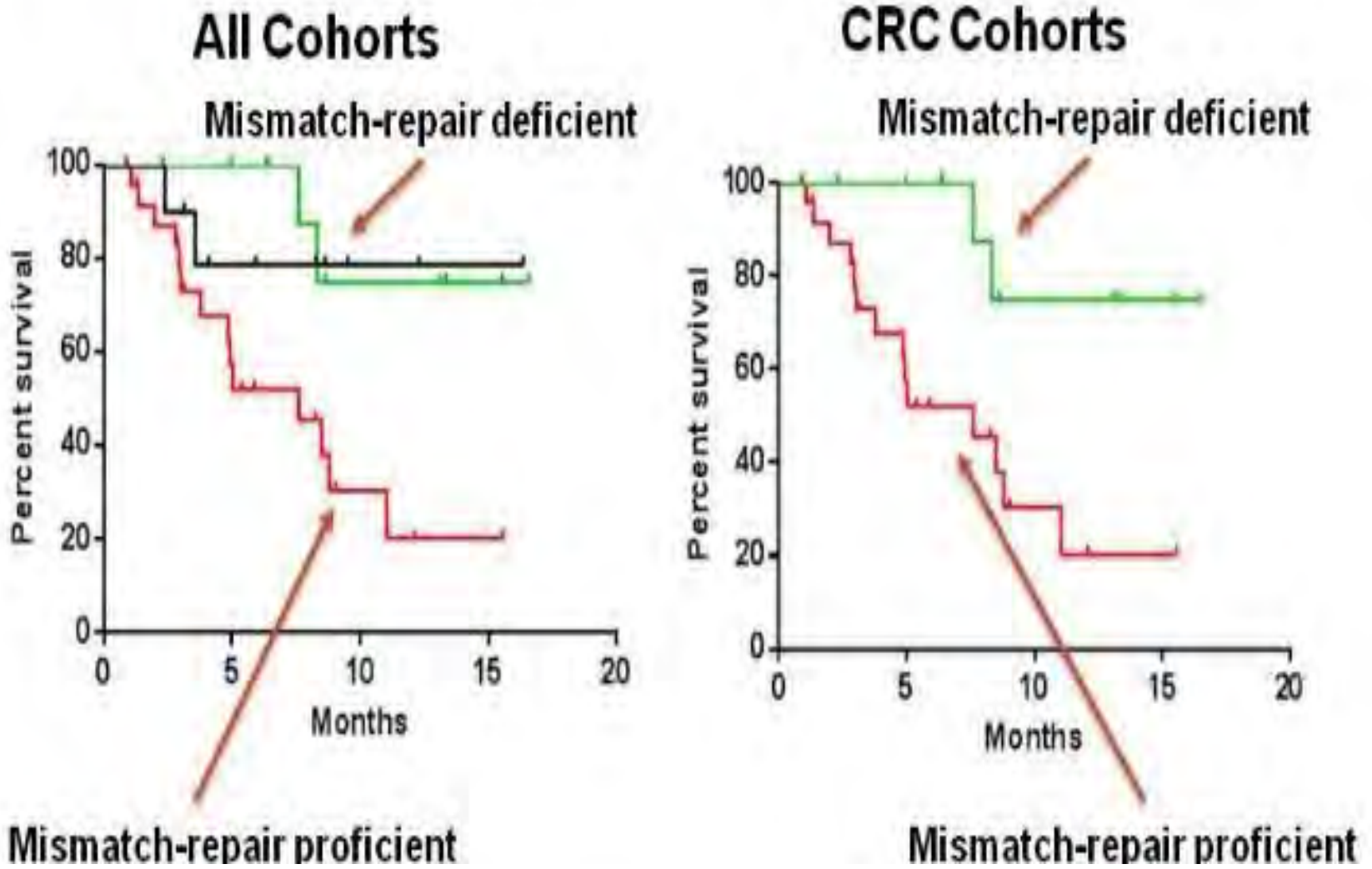
Le et al, *NEJM*, 2015

Endometrial Cancer Cohort

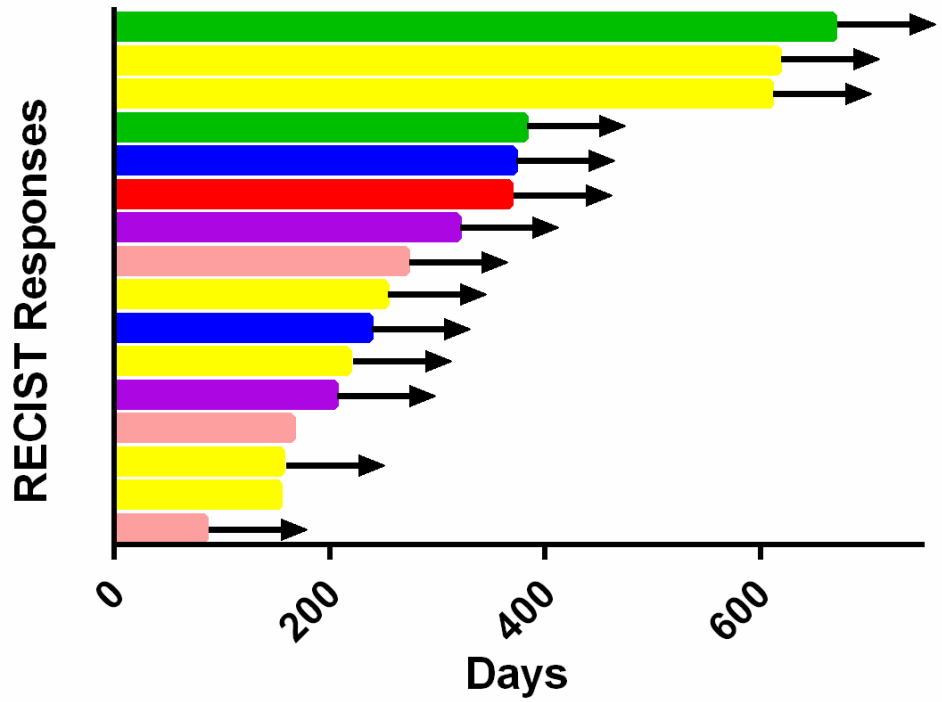
- **Nine 9 patients with MSI-high recurrent or progressive endometrioid endometrial cancer enrolled**
- **Median – 2 prior therapies**
- **Overall response rate is 56% (95% CI: 21-86%, N=5/9)**
  - **CR 1, PR 4**
  - **3 pts with prolonged SD**
- **Disease control rate, or "clinical benefit" rate (CR + PR + stable disease) is 88.9% (8/9 patients)**
- **12-month OS rate is 89%**

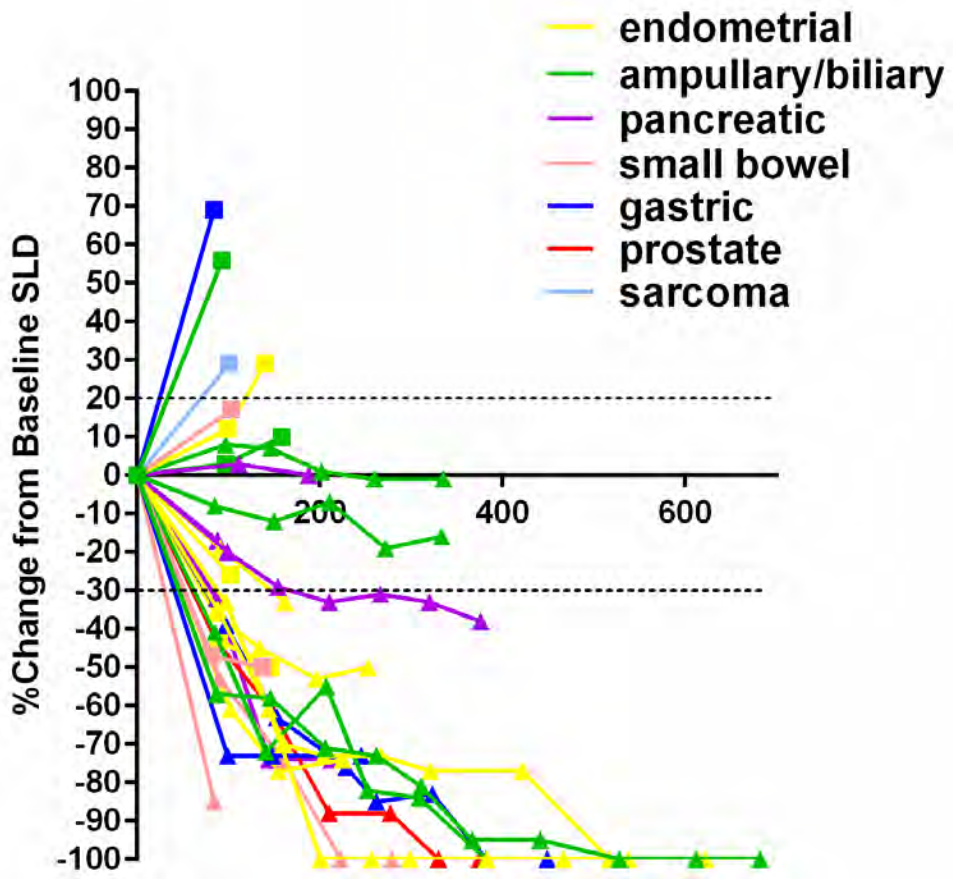
Fader, AN et.al. SGO 2016

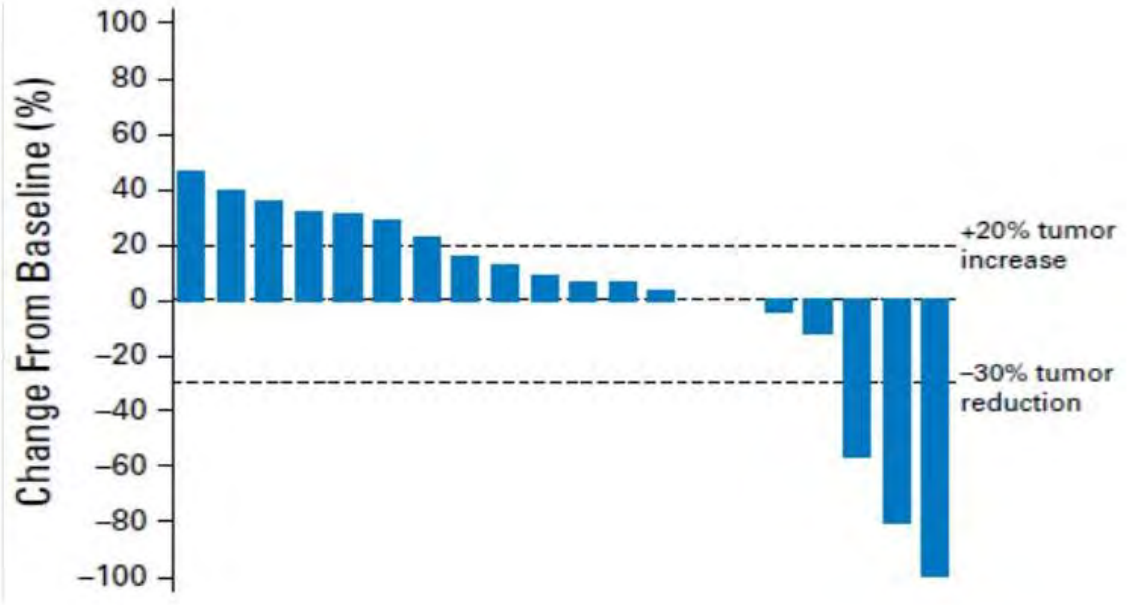
Overall Survival After Pembrolizumab



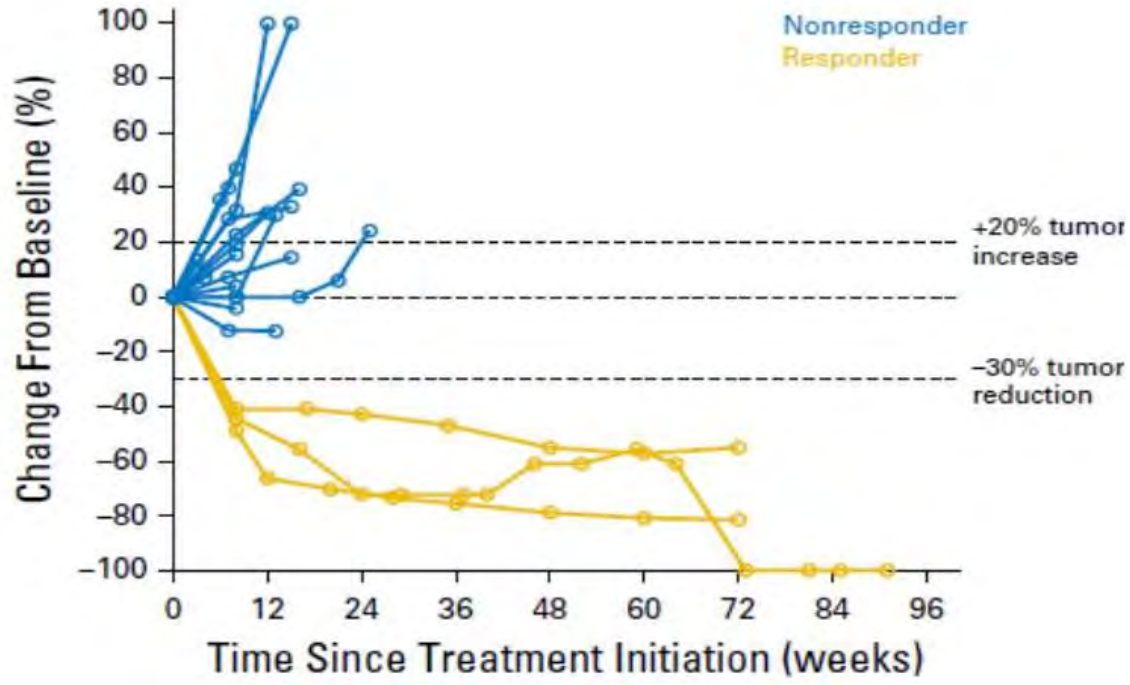
Durability of Disease Control







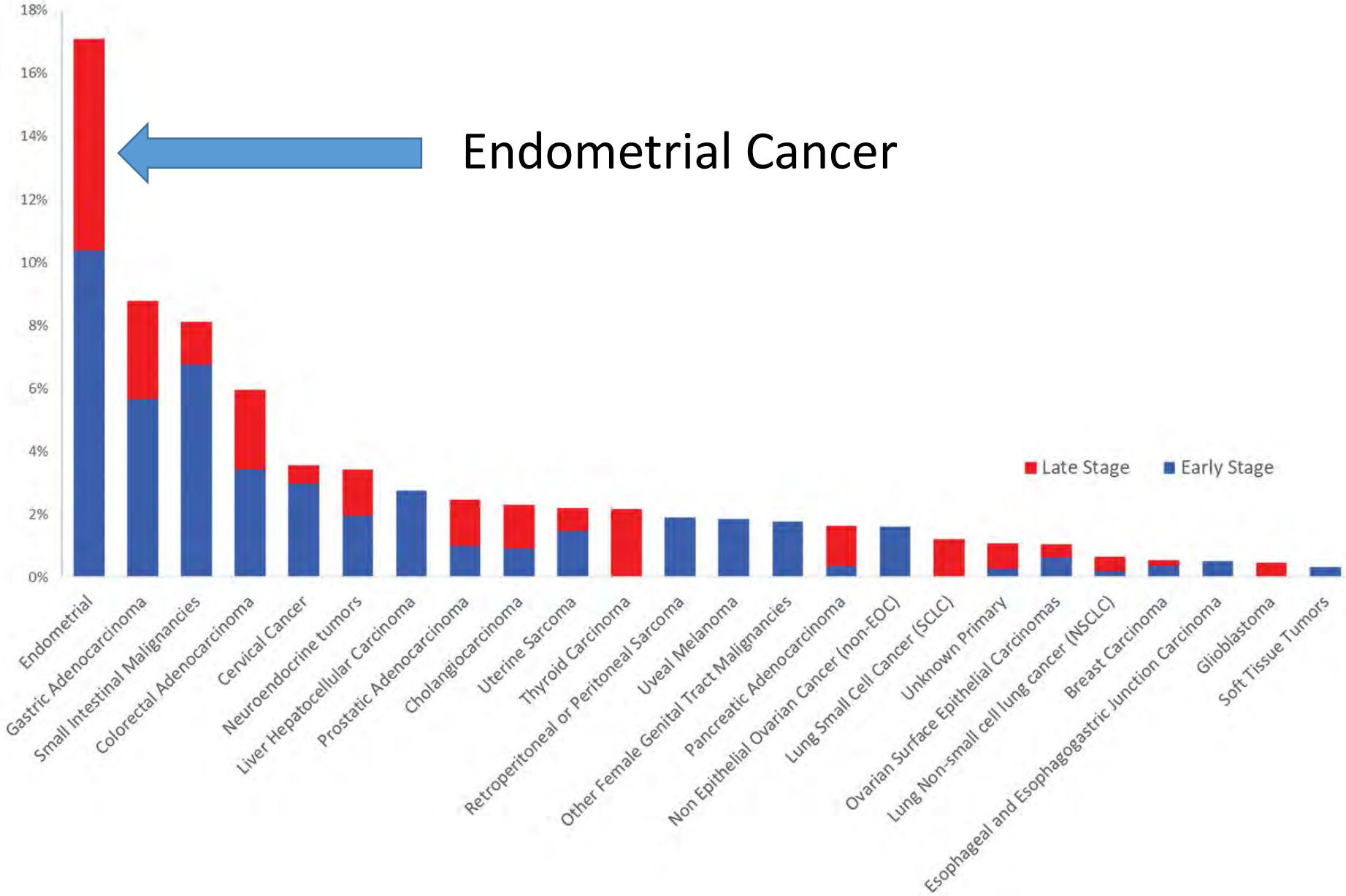
Pembrolizumab in PD-L1 Positive Endometrial Cancer KEYNOTE-028



3/24 responders (13%)
- 1 POLE mutation
- 1 MSI low
- 1 MS unknown

36/75 (48%) screened were PD-L1 positive

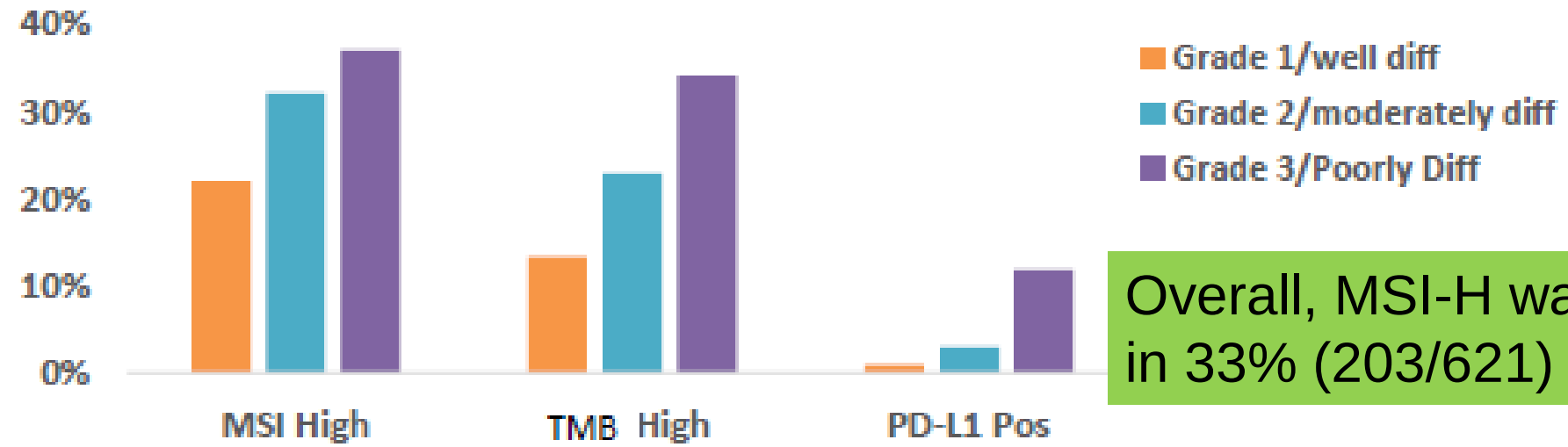
Ott et al. J Clin Oncol, 2017



Mismatch repair deficiency across 12,019 tumors. Proportion of tumors deficient in mismatch repair in each cancer subtype, expressed as a percentage. Mismatch repair deficient tumors were identified in 24 out of 32 tumor subtypes tested.

Le D, et al. Science June 8, 2017

A.



Overall, MSI-H was found in 33% (203/621) of EECs

B.

	MSI			TMB			PD-L1		
	N		%	N		%	N		%
	High	Total	High	High	Total	High	Pos	Total	Pos
Grade 1/well diff	25	113	22%	15	113	13%	1	107	1%
Grade 2/moderately diff	55	172	32%	39	171	23%	5	169	3%
Grade 3/Poorly Diff	58	156	37%	53	156	34%	18	153	12%

Figure 1. Overview of Immune Biomarker Phenotypes in EECs.

N.L. Jones et al. Immune checkpoint expression, microsatellite instability, and mutational burden: Identifying immune biomarker phenotypes in uterine cancer. Poster 84 SGO 2018

Immune Checkpoint Inhibition: Endometrial Cancer

- MSI is a biomarker for EndoCa response to anti PD-L1 therapy
  - 22-37% of endometrioid histology will have MSI-high phenotype
- PD-L1 expression alone appears to be less robust than MSI as an independent biomarker for response to pembrolizimab in EndoCa
- Need to further identify molecular characteristics that predict response to immunotherapy (POLE, POLD, MSI + PD-L1, etc)
- Multiple ongoing and pending trials of single agent ICI in MSI and MSS EndoCa
- MMR IHC or MSI testing should be done in all endometrial cancers

Rationale for Immunotherapy in Cervical Cancer

- Presence of foreign viral antigens
- Higher expression of PD-L1 in virus-associated cancers
- Upregulation of PD-1 in CIN

An Open-Label, Multicohort, Phase 1/2 Study of Nivolumab in Patients With Virus-Associated Tumors (CheckMate 358): Efficacy and Safety in Recurrent or Metastatic Cervical, Vaginal, and Vulvar Cancers

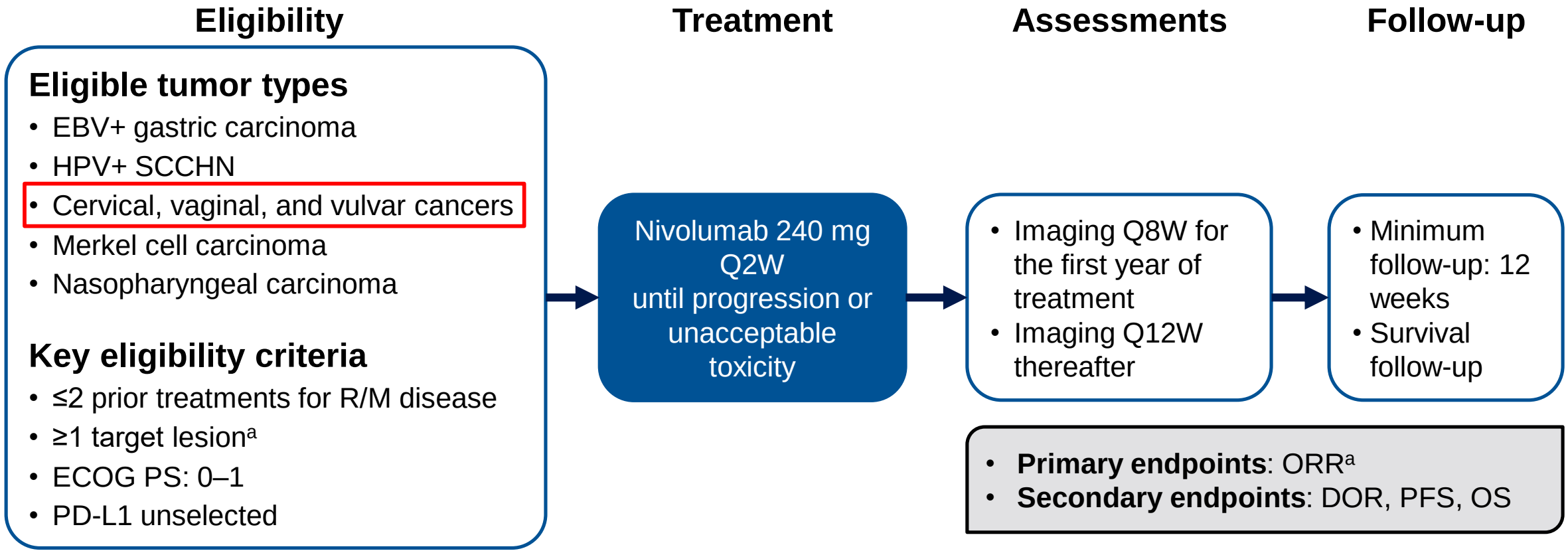
Antoine Hollebecque,[1] Tim Meyer,[2] Kathleen Nadine Moore,[3] Jean-Pascal Machiels,[4] Jacques De Grève,[5] José María López-Picazo,[6] Ana Oaknin,[7] Joseph Kerger,[8] Valentina Boni,[9] Jeff Evans,[10] Rebecca Kristeleit,[2] Shangbang Rao,[11] Ibrahima Soumaoro,[11] Alexander Cao,[11] Suzanne L. Topalian[12]

[1]Gustave Roussy Cancer Institute, Villejuif, France; [2]University College London Cancer Institute, London, UK; [3]University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; [4]Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium; [5]Vrije Universiteit Brussel, Brussels, Belgium; [6]University Clinic of Navarra, Pamplona, Spain; [7]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [8]Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium; [9]START Madrid-CIOCC Hospital Universitario HM Sanchinarro, Madrid, Spain; [10]University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow, UK; [11]Bristol-Myers Squibb, Princeton, NJ, USA; [12]The Sidney Kimmel Comprehensive Cancer Center and Bloomberg~Kimmel Institute for Cancer Immunotherapy at Johns Hopkins, Baltimore, MD, USA

PRESENTED AT: ASCO ANNUAL MEETING '17 #ASCO17

CheckMate 358 Study Design: Metastatic Monotherapy Cohort

- CheckMate 358 (NCT02488759) is an ongoing, open-label, phase 1/2, multicohort study



- Enrollment dates: October 2015 to February 2016
- Data cut-off: July 2016 (median follow-up, 31 weeks)

[a]Per investigator-assessed RECIST 1.1 criteria
DOR = duration of response; EBV = Epstein Barr Virus; OS = overall survival; QXW = every X weeks; SCCHN = squamous cell carcinoma of the head and neck

Best Overall Response

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

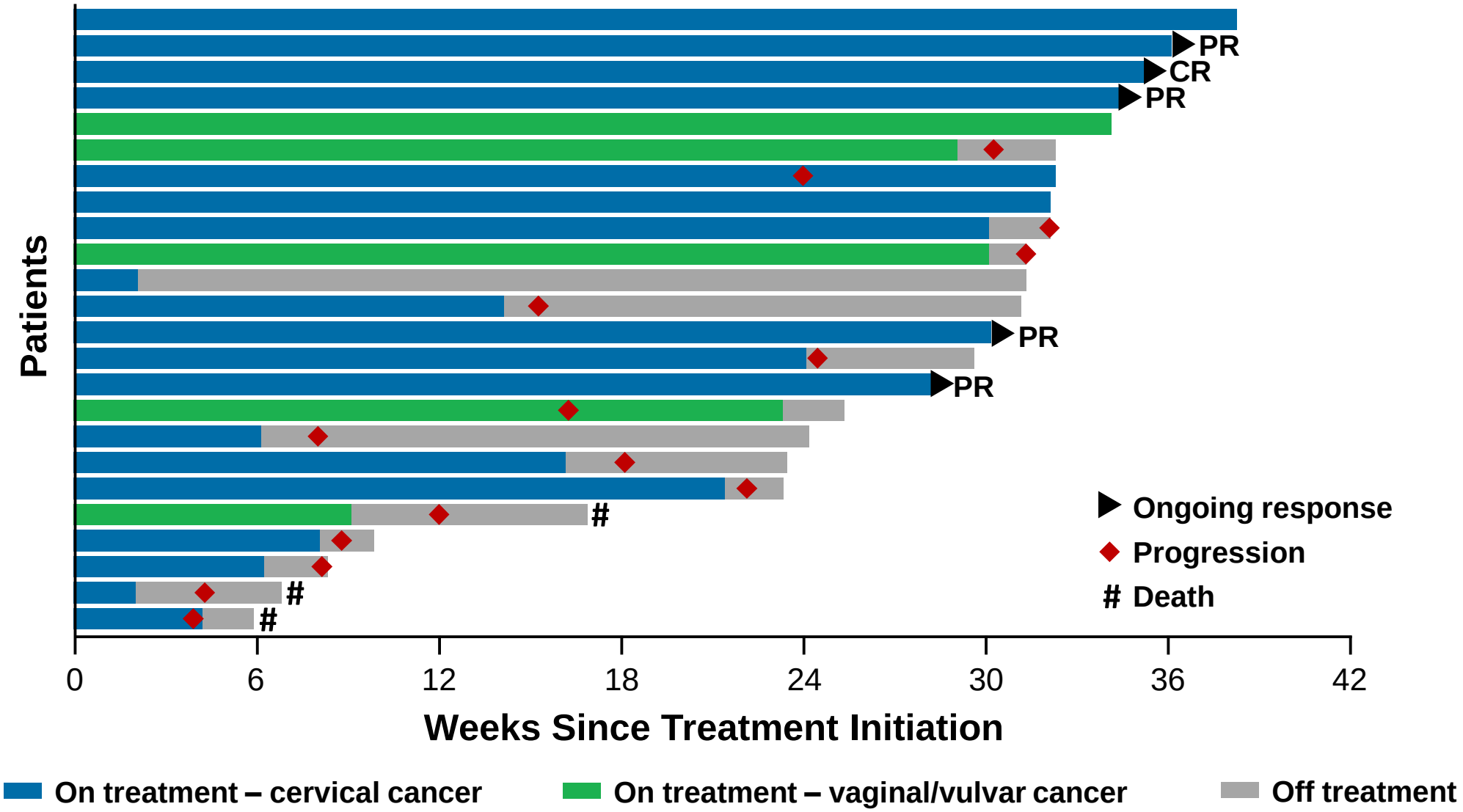
	All Patients (N = 24)	Cervical (n = 19)	Vaginal/ Vulvar (n = 5)
Best overall response, n (%)			
Complete response	1 (4.2)	1 (5.3)	0
Partial response	4 (16.7)	4 (21.1)	0
Stable disease	12 (50.0)	8 (42.1)	4 (80.0)
Progressive disease	7 (29.2)	6 (31.6)	1 (20.0)
ORR, n (%)	5 (20.8)	5 (26.3)	0
[95% CI]	[7.1, 42.2]	[9.1, 51.2]	[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

+ Ongoing response; NA = not applicable; NR = not reached

[a]All responses ongoing as of the data cut-off

Duration of Treatment

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



Best Overall Response by PD-L1 and HPV

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

	PD-L1 Expression		HPV Status[a]	
	PD-L1 ≥1% (n = 10)	PD-L1 <1% (n = 3)	Positive (n = 14)	Not reported (n = 10)
Best overall response, n (%)				
Complete response	1 (10.0)	0	0	1 (10.0)
Partial response	1 (10.0)	1 (33.3)	4 (28.6)	0
Stable disease	6 (60.0)	1 (33.3)	4 (28.6)	8 (80.0)
Progressive disease	2 (20.0)	1 (33.3)	6 (42.9)	0
ORR, n (%)	2 (20.0)	1 (33.3)	4 (28.6)	1 (10.0)
[95% CI]	[2.5, 55.6]	[0.8, 90.6]	[8.4, 58.1]	[0.25, 44.5]
Disease control rate, n (%)	8 (80.0)	2 (66.7)	8 (57.1)	9 (90.0)

[a]Per local site testing

Conclusions

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

- Nivolumab demonstrated encouraging clinical activity in patients with R/M cervical, vaginal, and vulvar cancers
  - 20.8% ORR (all 5 responses in patients with cervical cancer at time of data cut-off)
    - Responses observed across tumor PD-L1 expression
  - 70.8% disease control rate
  - Median OS was not reached; 6-month OS rate was 87.1%
- The observed safety profile was manageable and consistent with previous results seen with nivolumab monotherapy in other tumor types

Immunotherapy Trials: Cervical Cancer

	ORR n (%)	Eligibility	Med PFS	Med OS
Treatment				
Ipilimumab[1]	1/32 (3%)		2.5 M	8.5 M
Pembrolizumab (KN-28)[2]	4/24 (17%)	PD-L1+	2.0 M	11 M
Pembrolizumab (KN-158)[3]	8/47 (17%)			
Nivolumab (CM 358)[4]	5/19 (26%)			

[1]Lheureux, J Clin Oncol, Nov 2017
[2]PD-L1 pos, Frenel, J Clin Oncol, Dec 2017
[3]Unselected for PD-L1, Schellens, ASCO 2017, Abs 5514
[4]Hollebecque, ASCO 2017, Abs 5504

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journal homepage: www.elsevier.com/locate/ygyno

Lymphopenia and its association with survival in patients with locally advanced cervical cancer

Emily S. Wu [a,*,1], Titilope Oduyebo [b,1], Lauren P. Cobb [a], Diana Cholakian [a], Xiangrong Kong [b], Amanda N. Fader [a], Kimberly L. Levinson [a], Edward J. Tanner III [a], Rebecca L. Stone [a], Anna Piotrowski [c], Stuart Grossman [c], Kara Long Roche [a]

[a] Kelly Gynecologic Oncology Service, Department of Gynecology and Obstetrics, Johns Hopkins Hospital, Baltimore, MD, USA
[b] Department of Epidemiology, Johns Hopkins Hospital School of Public Health, Baltimore, MD, USA
[c] The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD, USA

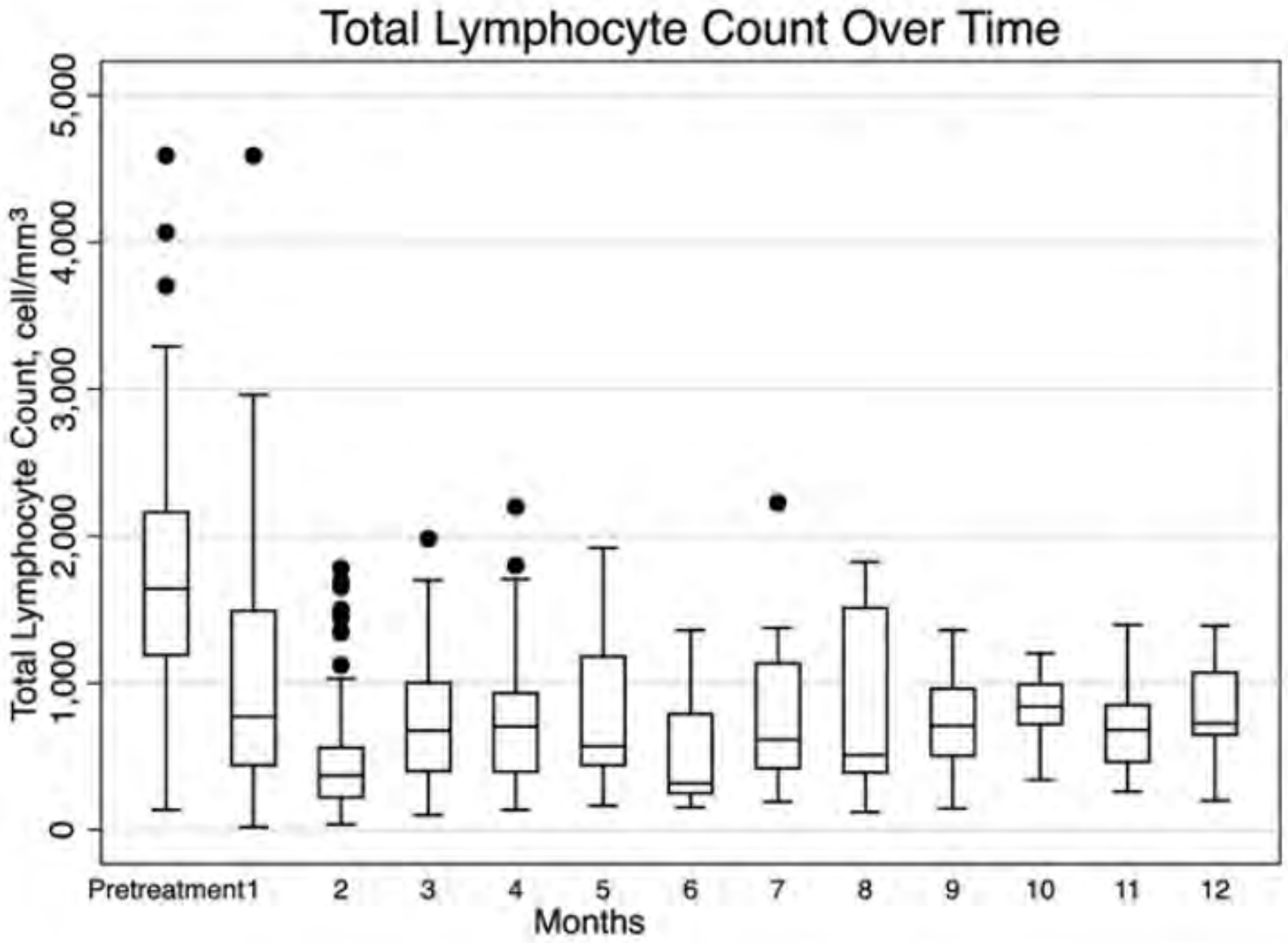


Fig. 1. Total lymphocyte count prior to treatment and in the first 12 months after initiating chemoradiation.

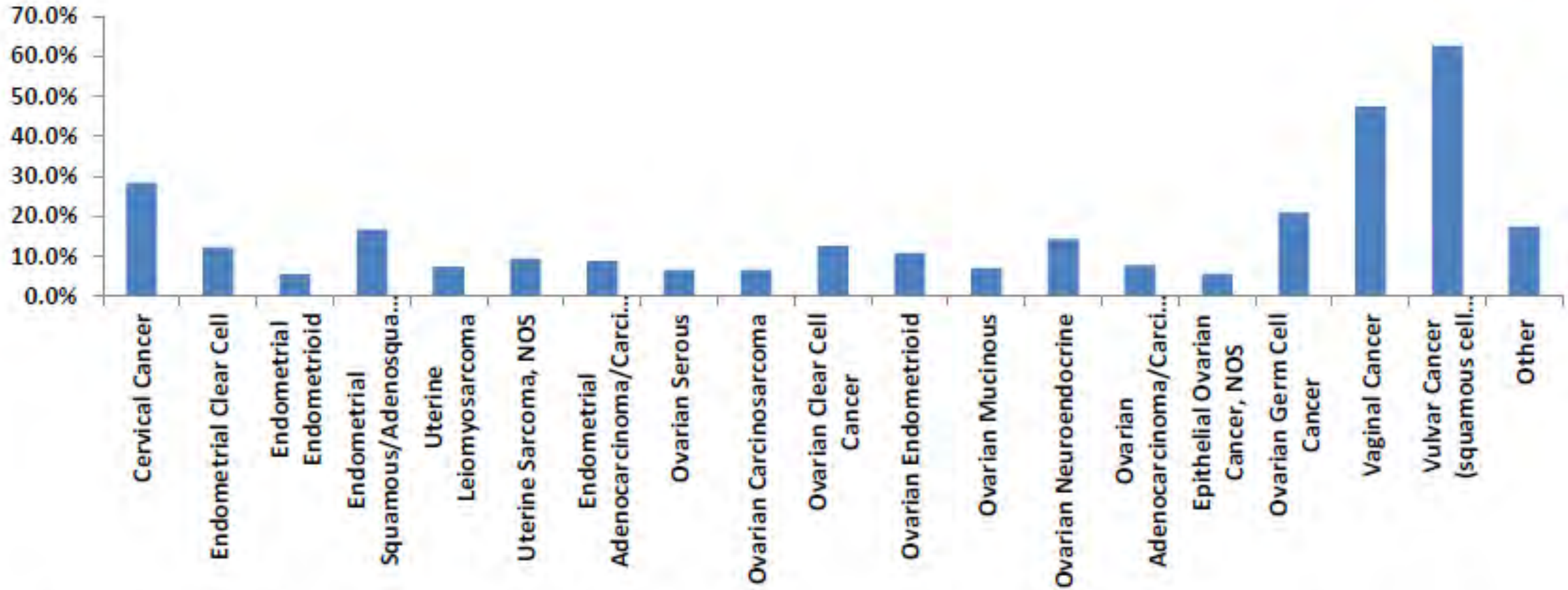


Figure 3. PDL-1 Expression via IHC in GYN Cancers. PD-L1 expression was observed in only 7% of uterine and ovarian tumors but in 28% cervical, 63% vulvar and 47% of vaginal cancers. This figure represents those tumors with >5% PDL-1 expression

I.S. Winer et al. Mutational burden, tumor PDL-1 expression, and microsatellite instability in gynecologic malignancies: Implications for immune Immune checkpoint expression, Poster 85 SGO 2018

Immune Checkpoint Inhibition: Cervical Cancer

- Single agent ICIs have variable activity in cervical cancer
  - Response rates range from 3-26%
- PD-L1 expression alone does not appear to be a robust, independent biomarker for response in cervical cancer
- Epidemiologic and therapeutic factors in cervical cancer may inhibit response to ICI
  - Lymphocyte depletion after chemoradiation may blunt ability to respond to ICI
  - T-cell exhaustion, associated with chronic viral infection, may contribute

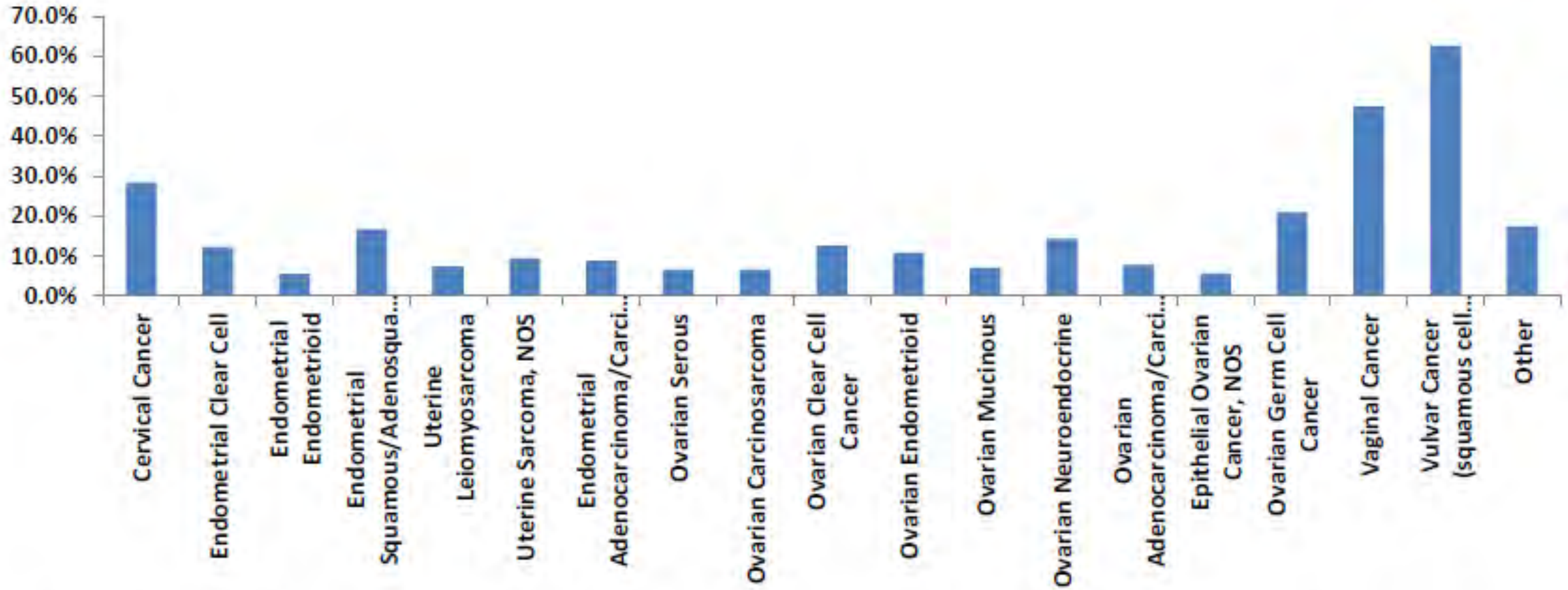
Ovarian Cancer

Immunotherapy Trials: Ovarian Cancer

	ORR n (%)	DCR*	6 M PFS
Treatment			
Anti PD-L1[1]	1/16 (6%)	3/17 (18%)	25%
Avelumab[2]	12/124 (10%)	54%	
Pembrolizumab (KN-28)[3]	3/26 (11.5%)	9/26 (35%)	
Nivolumab[4]	3/20 (15%)	9/20 (45%)	
Atezolizumab[5]	2/9 (22%)		
Pembrolizumab (KN-100)[6]	30/376 (8%)	37%	

[1]Brahmer NEJM 2012
[2]Disis ASCO 2016
[3]PD-L1-pos, Varga ASCO 2015
[4]Plat-Resistant, Hamanashi JCO 2015
[5]9/12 evaluable, Infante, ESGO 2016
[6]Matulonis ASCO 2018

***Disease control rate (CR+PR+SD)**



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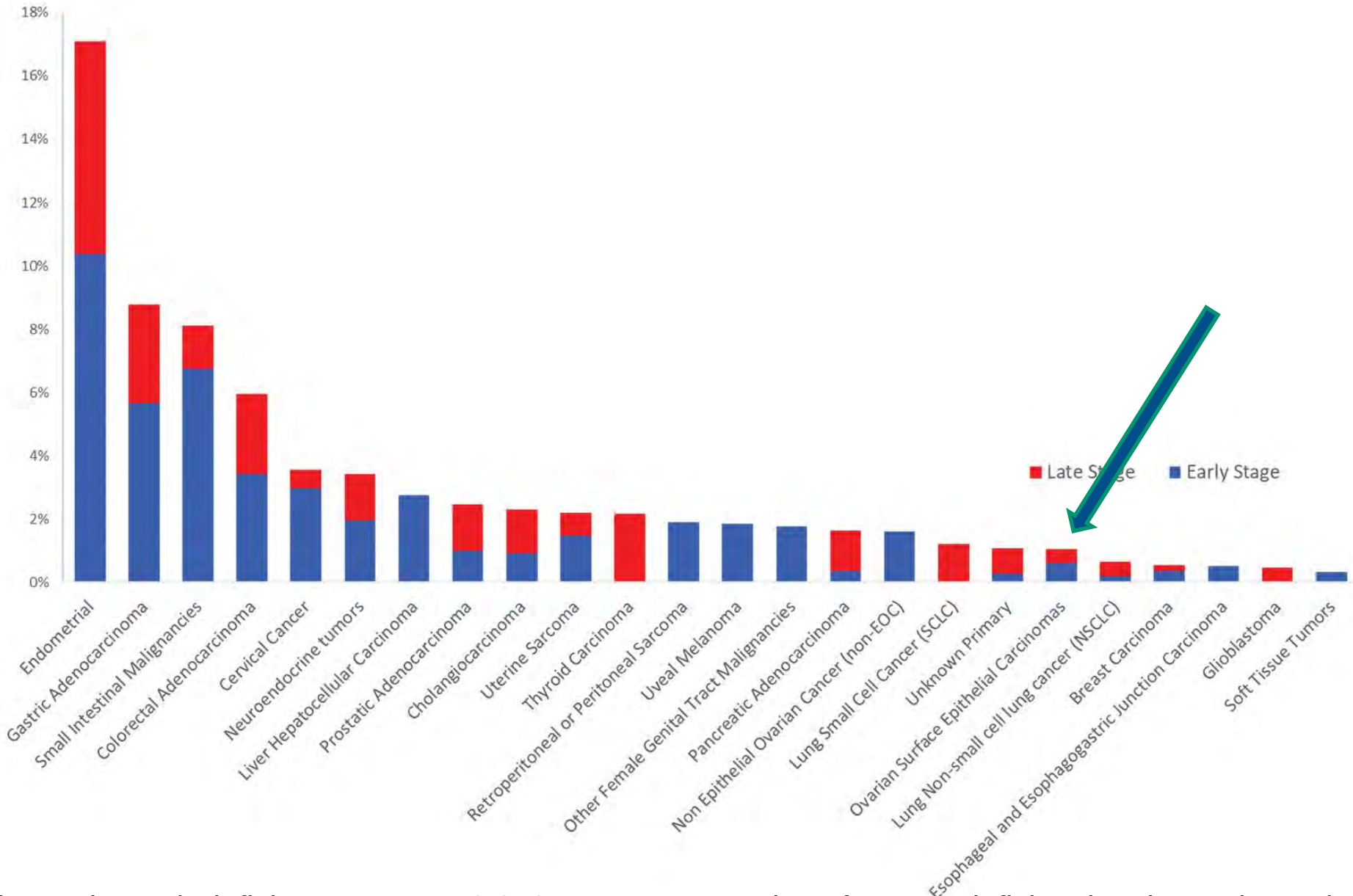
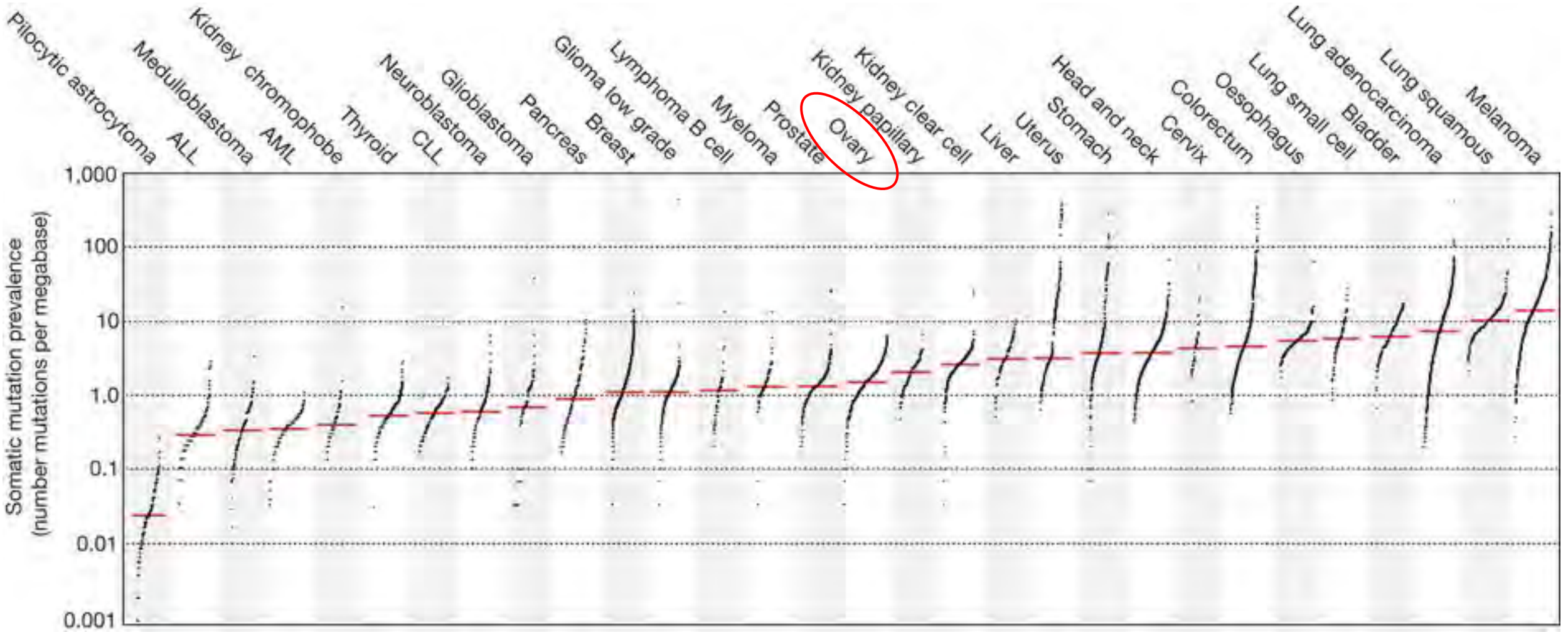


Mismatch repair deficiency across 12,019 tumors. Proportion of tumors deficient in mismatch repair in each cancer subtype, expressed as a percentage.

Le D, et.al. Science June 8, 2017



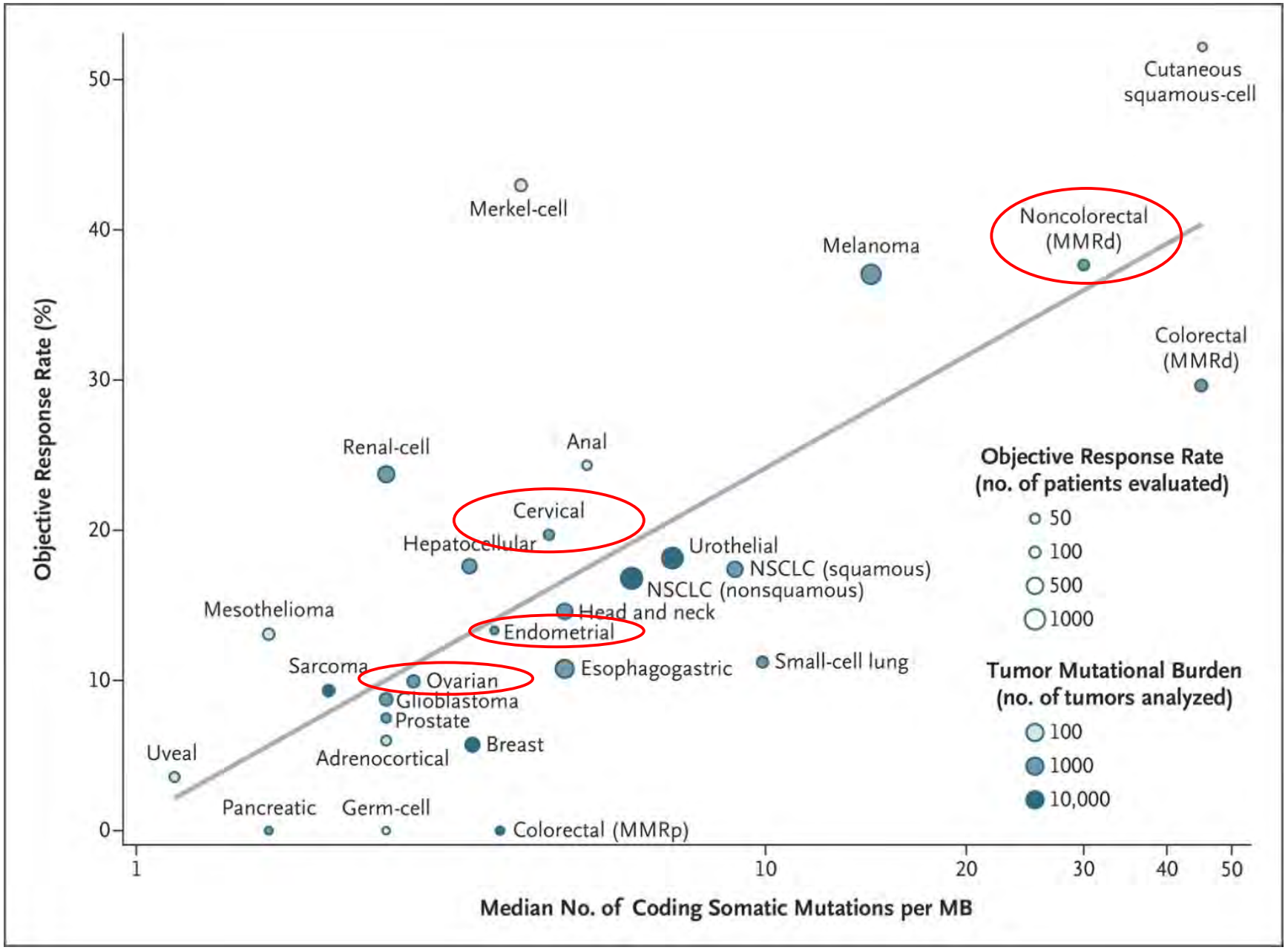
Alexandrov et.al. Nature 2013

A.

	N				%		
	TMB High	TMB Intermediate	TMB Low	Grand Total	TMB High	TMB Intermediate	TMB Low
Cervical Cancer	17	152	114	283	6.0%	53.7%	40.3%
Ovarian Cancer	59	1337	1796	3192	1.8%	41.9%	56.3%
Uterine Cancer	252	866	860	1978	12.7%	43.8%	43.5%
Vaginal Cancer	4	11	4	19	21.1%	57.9%	21.1%
Vulvar Cancer	3	22	24	49	6.1%	44.9%	49.0%
Other	2	12	10	24	8.3%	50.0%	41.7%

Tumor Mutational Burden (TMB) in GYN Cancers. TMB was studied in GYN cancers with overall levels noted in **A.** High TMB (TMB-H) was noted in 2% of ovarian cancers (9% germ cell, 6% endometrioid, 3% low grade, 7% mucinous, 4% clear cell, 3% carcinosarcoma, 1% serous).

I.S. Winer et al. Mutational burden, tumor PDL-1 expression, and microsatellite instability in gynecologic malignancies: Implications for immune Immune checkpoint expression, Poster 85 SGO 2018



Correlation between Tumor Mutational Burden and Objective Response Rate with Anti–PD-1 or Anti–PD-L1 Therapy in 27 Tumor Types. Yarchoan M, NEJM 2017

Immune Checkpoint Inhibition: Ovarian Cancer

- Low level biomarkers of Response to ICI in OvCa
  - Low level PD-L1 expression
  - Low level of MSI
  - Lowest TMB of all gyn cancers
- Effective immunotherapy with ICI will likely require combination approaches to transform tumors from cold to hot
  - With other ICI
  - With cancer vaccines
  - With adoptive cell therapy

Strategy, efficacy and safety of combination regimens using immunotherapy

Rebecca C. Arend MD

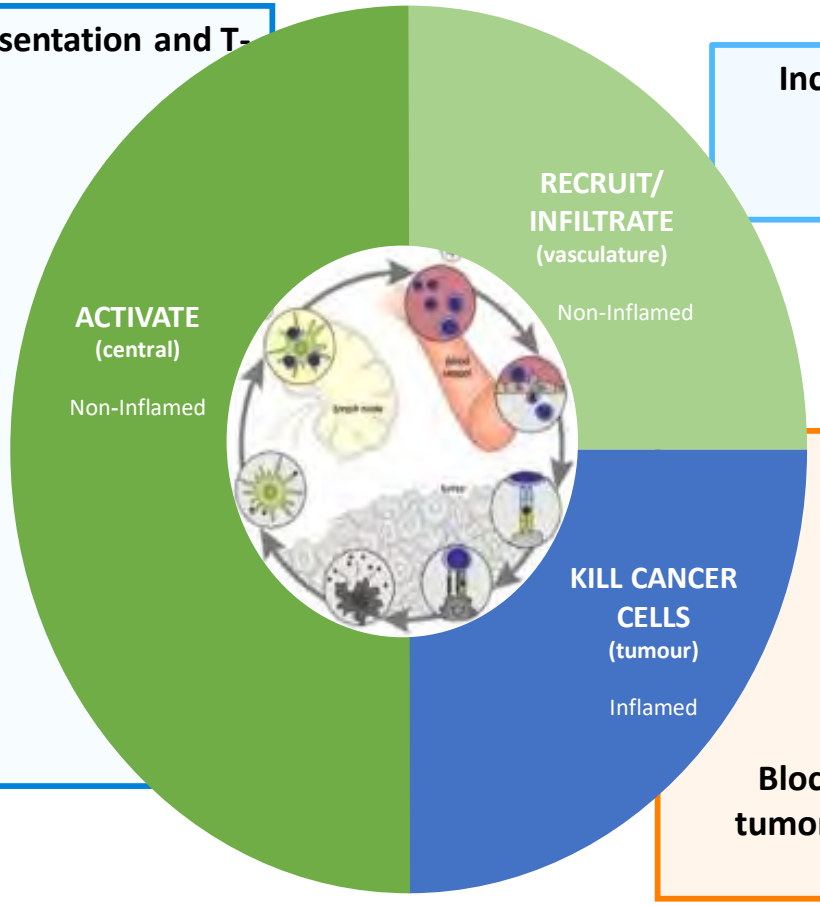
Assistant Professor

University of Alabama at Birmingham

Disclosures

- Advisory Board: Clovis, AstraZeneca, VBL, Janseen, Tesaro

Combination opportunities in cancer immunotherapy



Enhance antigen presentation and T-cell activation

EGFR inhibitors
ALK inhibitors
BRAF inhibitors
MEK inhibitors
Chemotherapy
HDAC
Radiotherapy
Anti-CD40
IFN-g
Oncolytic viruses
Neo-epitope vaccine
Anti-CEA-IL2v
Anti-FAP-IL2v
Anti-OX40
Anti-CTLA4
Anti-CD27
Anti-41BB
PARPi

Increase T-cell trafficking and infiltration into tumors

Anti-VEGF

TCBs
ImmTACs
CAR-T
BiTes
Anti-PDL1
Anti-PD1
Anti-CSF-1R
IDO inhibitors
Anti-TIGIT
Anti-TIM3
Anti-LAG3

Block immunosuppression within the tumor microenvironment and enhance tumor cell death

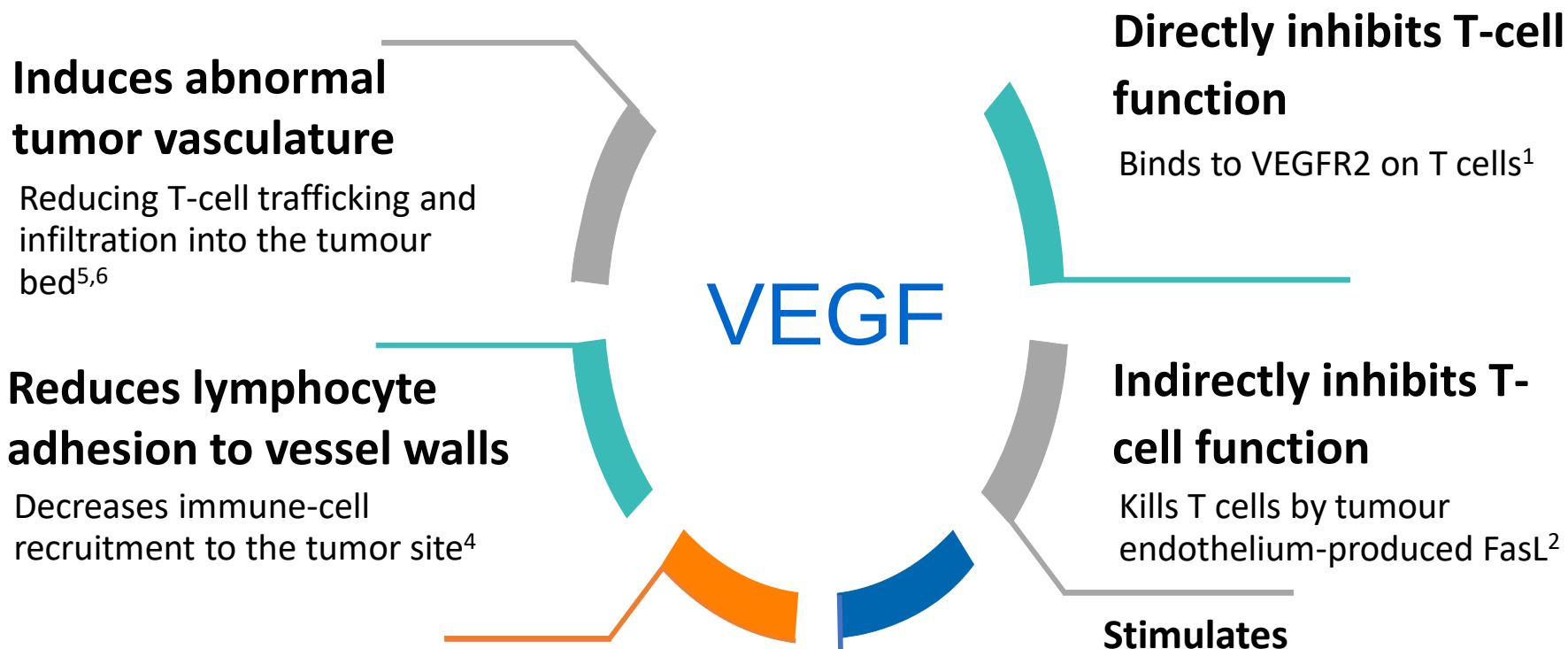
Chen & Mellman. Immunity 2013
Galluzzi, et al. Nat Rev Drug Discov 2012
Hannani, et al. Cancer J 2011; Vanneman and Dranoff. Nat Rev Cancer 2012

Novel combination strategies in development

- VEGFi + T cell modulators
- PARPi + I/O agents
  - PARP inhibition may increase immunogenicity
- I/O + chemotherapy
- I/O + I/O
- Triple Combos

I/O + VEGFi

Rationale for combining cancer immunotherapy with anti-VEGF



Induces abnormal tumor vasculature

Reducing T-cell trafficking and infiltration into the tumour bed[5,6]

Directly inhibits T-cell function

Binds to VEGFR2 on T cells[1]

Reduces lymphocyte adhesion to vessel walls

Decreases immune-cell recruitment to the tumor site[4]

Indirectly inhibits T-cell function

Kills T cells by tumour endothelium-produced FasL[2]

Inhibits dendritic cell function

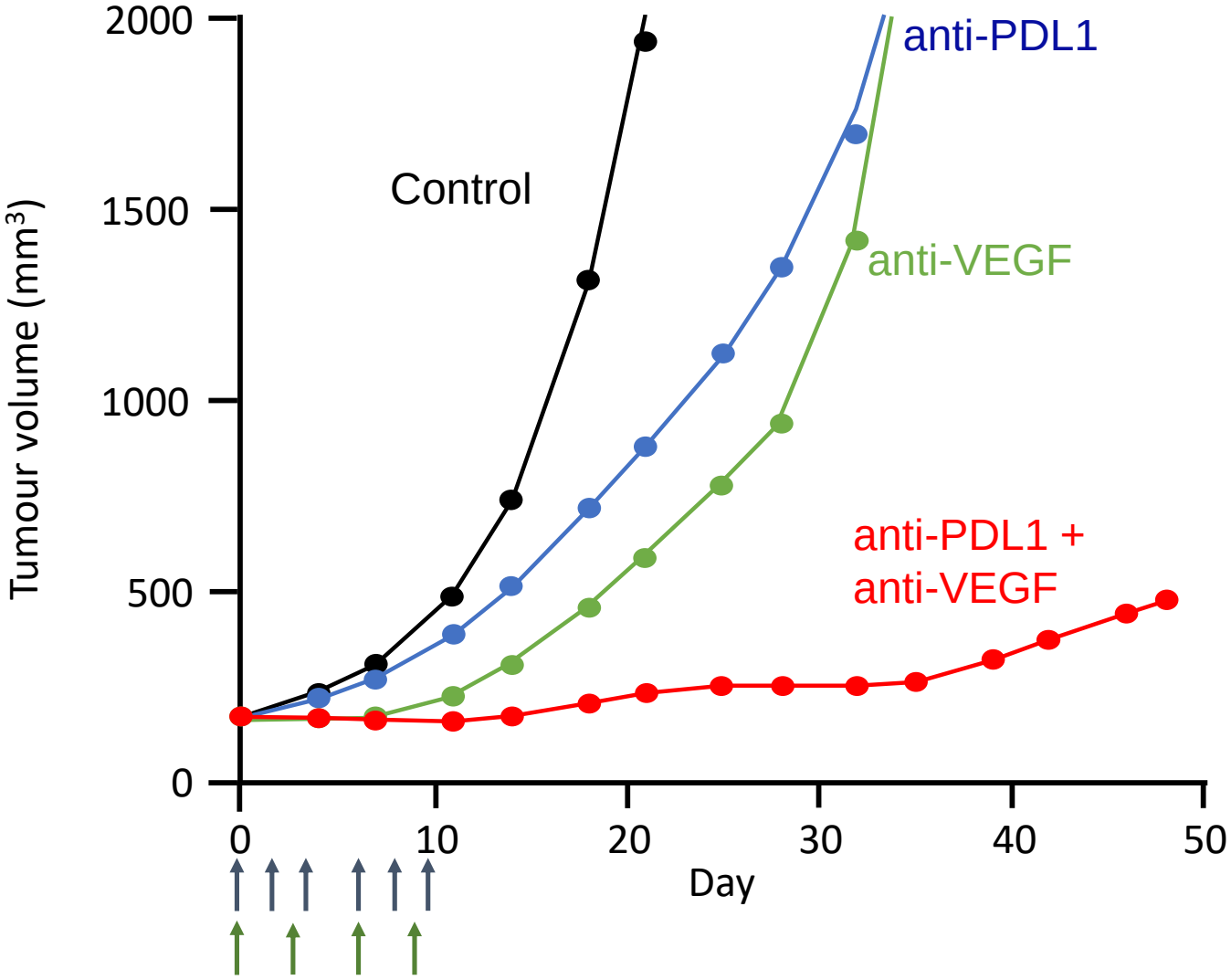
Drives them into an immature state[3]

Stimulates immunosuppressive regulatory T cells[2]

1. Gavalas et al. Br J Cancer 2012; 2. Terme et al. Cancer Res 2013
3. Coukos. Br J Cancer 2005; 4. Bouzin et al. J Immunol 2007
5. Shrimali et al. Cancer Res 2010; 6. Chen & Mellman. Immunity 2013

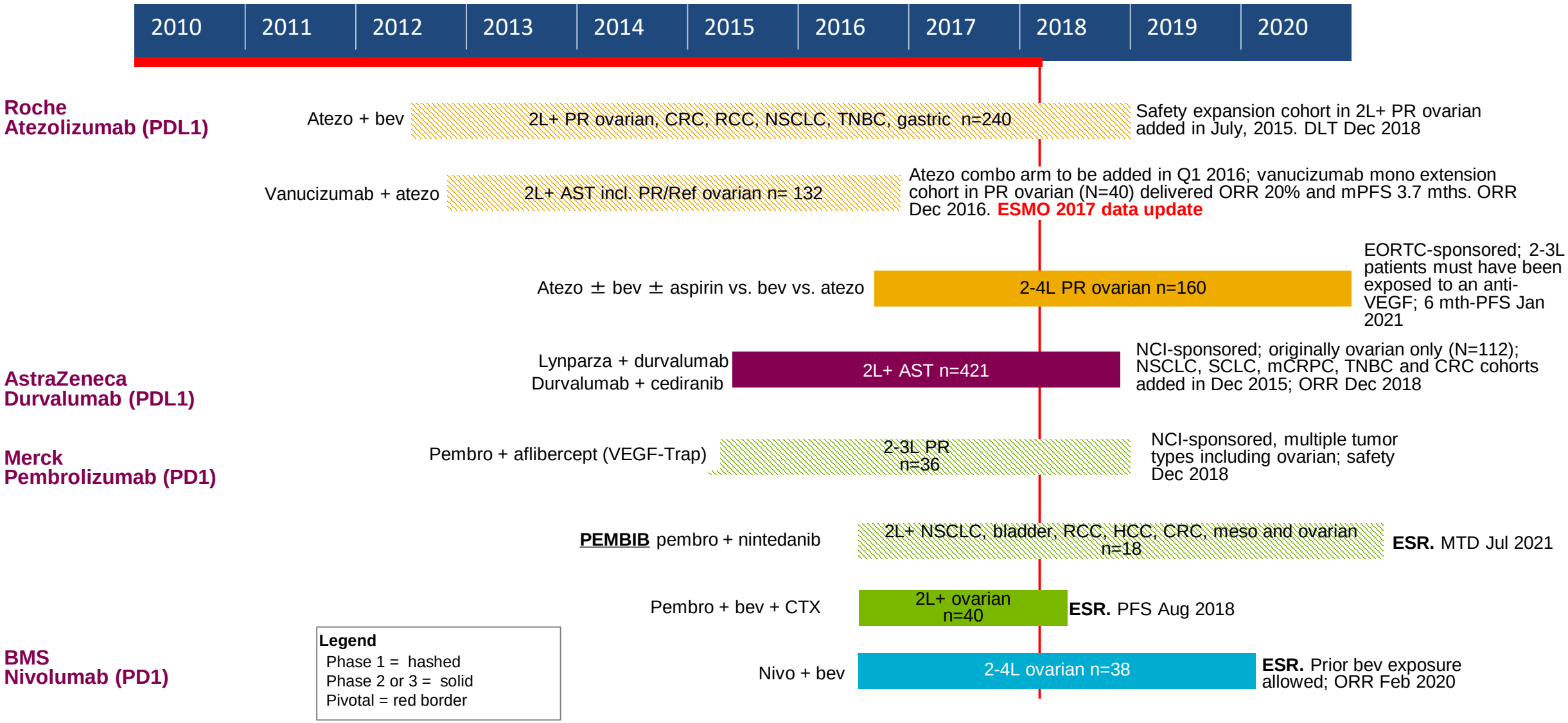
Pre-clinical data for combining anti-PD-L1 and VEGF blockade

Combined treatment with these two agents synergistically inhibited tumour growth in the Cloudman mouse tumour model



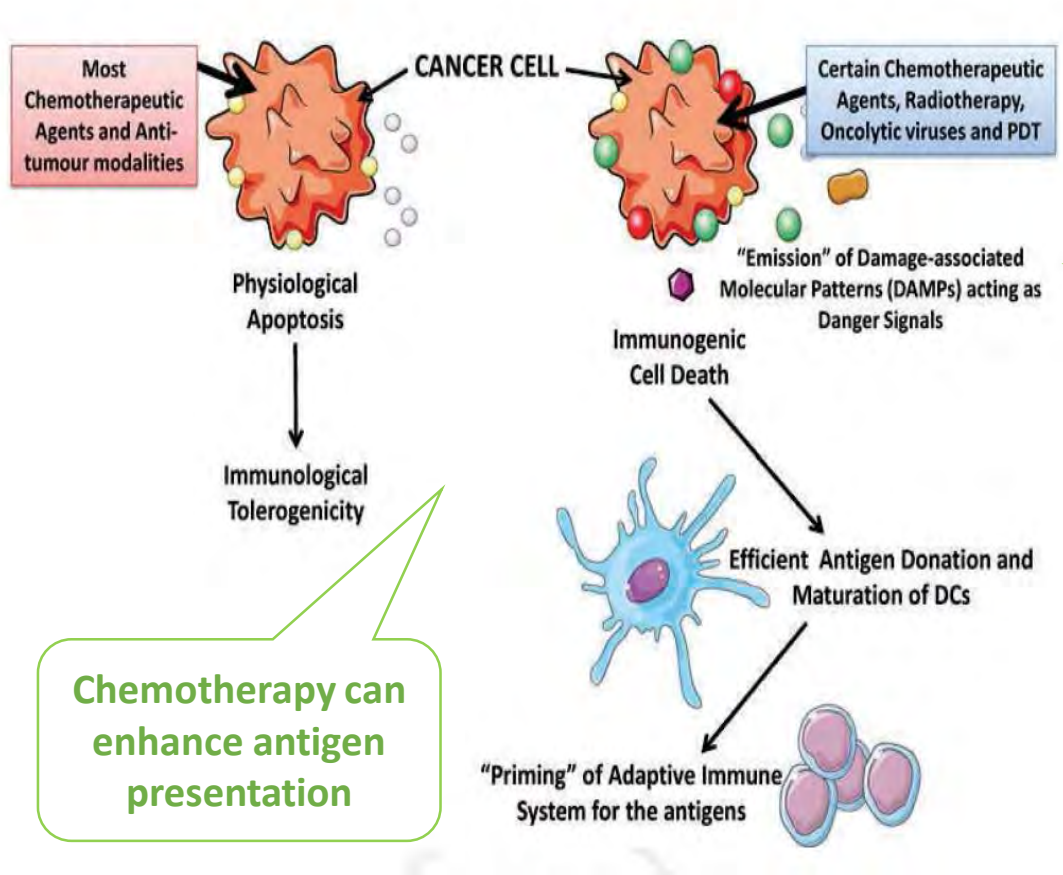
Irving. 1st Annual Expert Forum on Immuno-oncology, 2013

Immunotherapy with bevacizumab



I/O + chemo

Immunogenicity of chemotherapy



Chemotherapy can enhance immunogenicity (release of adjuvants by cells)

Chemotherapy can enhance antigen presentation

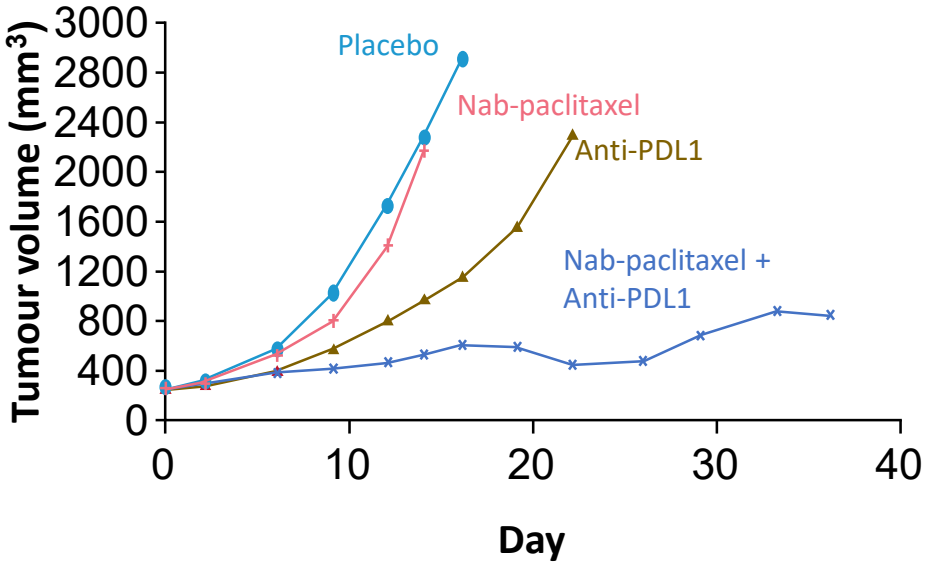
Chemotherapy can increase susceptibility to immune attack

DAMPs, danger-associated molecular patterns; DC, dendritic cell; PDT, photodynamic therapy

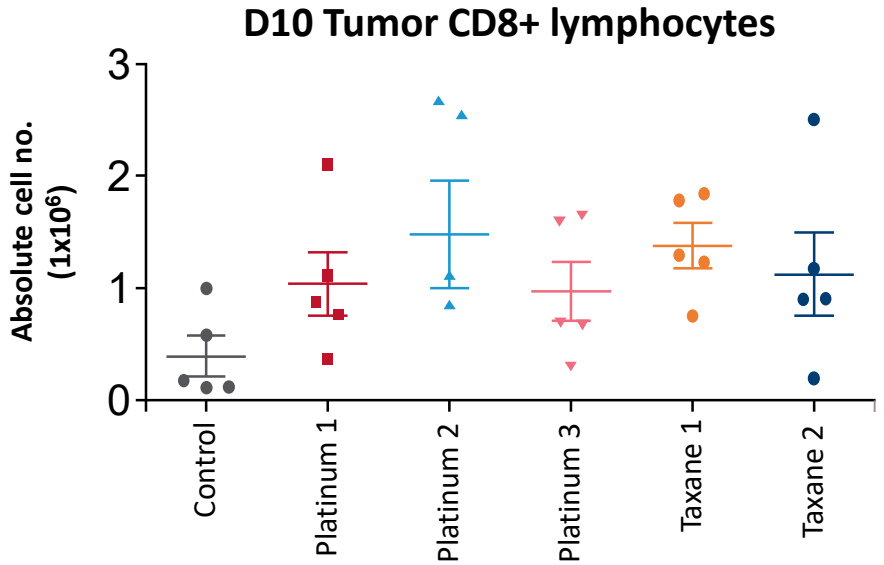
Garg et al. Biofactors 2013

Pre-clinical evidence for chemotherapy and anti-PDL1

Synergism of nab-paclitaxel plus anti-PDL1 in MC38 mouse tumour model



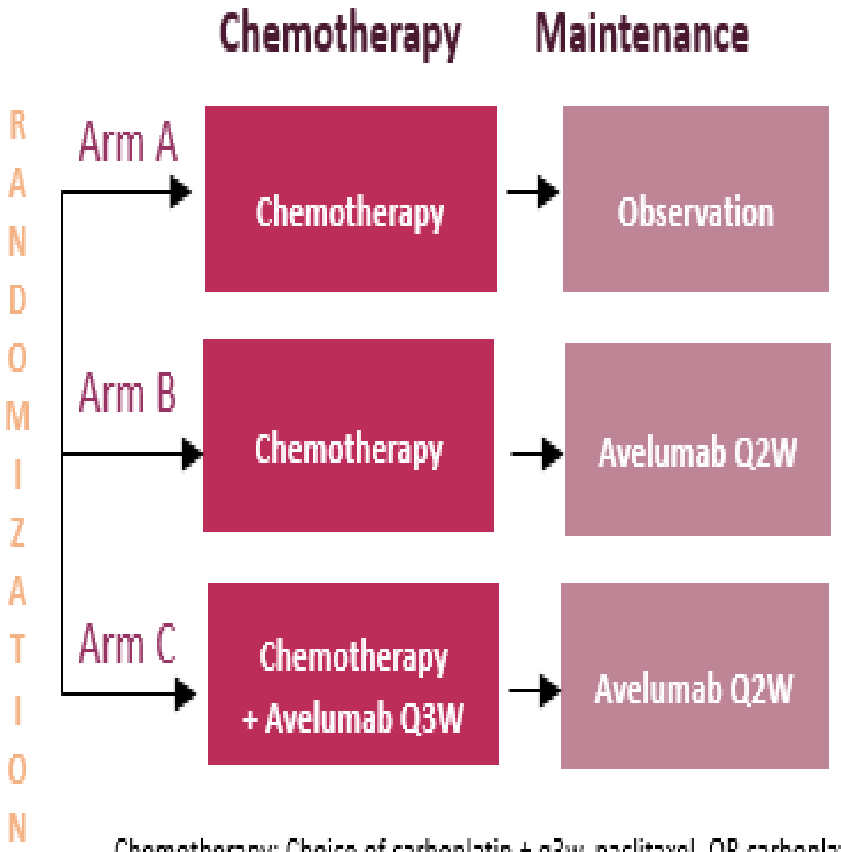
The synergism of nab-paclitaxel plus anti-PDL1 has been demonstrated in a MC38 mouse tumour model[1]



Treatment with platinum agents or taxanes increased the percentage of CD8+ tumour-infiltrating lymphocytes in immunocompetent mouse models[2]

1. Adams et al. SABCS 2015
2. Jeong Kim, Genentech; unpublished data

Javelin 100



Primary endpoint:

PFS from randomization (A vs B, A vs C)

Secondary endpoints:

Maintenance PFS, OS, ORR, duration of response, pCR, PFS2, PROs, safety, PK

Chemotherapy: Choice of carboplatin + q3w, paclitaxel, OR carboplatin + weekly paclitaxel

Maintenance avelumab up to 24 months

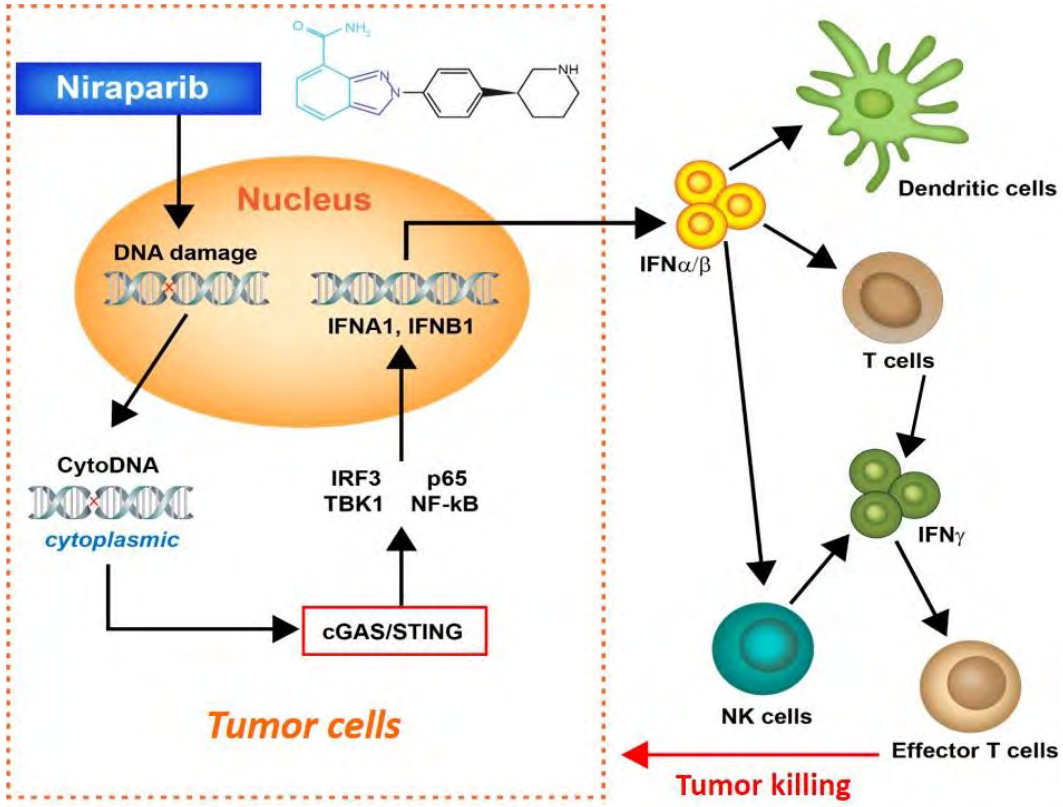
I/O + PARPi

Scientific rationale for PARPi in combination with PD-1 inhibitor

Preclinical models exhibit synergy with combination PARPi + anti-PD-1 agents regardless of BRCA mutation status or PD-L1 expression

- Unrepaired DNA damage resulting from niraparib treatment leads to the abnormal presence of DNA in the cytoplasm, which activates the stimulator of interferon gene (STING) pathway

- Activation of the STING pathway leads to increased expression and release of type 1 interferons, subsequent induction of γ-interferon, and intratumoral infiltration of effector T cells

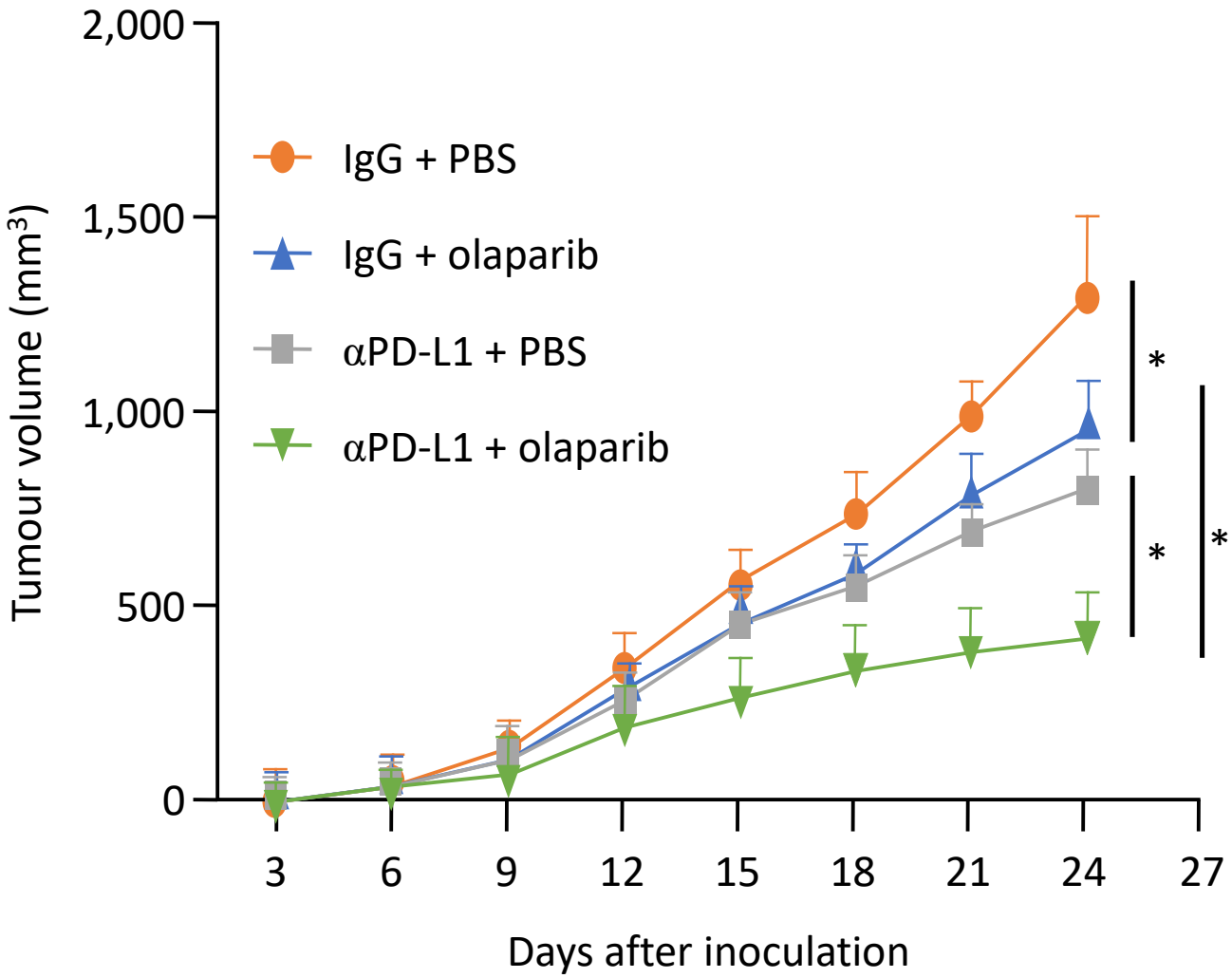


NCT02657889

Konstantinopoulos et al. SGO 2018

Pre-clinical evidence for anti-PDL1 and PARPi

Treatment with either olaparib or anti-PDL1 alone restricted tumour growth, but the combined treatment demonstrated enhanced therapeutic benefit



Jiao et al. Clin Cancer Res 2017

I/O + PARPi clinical trials

Legend
Phase 1 = hashed
Phase 2 or 3 = solid
Pivotal = red border
Potential to support registration = red dashed line

AstraZeneca Lynparza

Durvalumab + Lynparza
Durvalumab + cediranib — 2L+ AST incl. ovarian; N=421 — NCI-sponsored; originally ovarian only (N=112); NSCLC, SCLC, mCRPC, TNBC and CRC cohorts added in Dec 2015; ORR Dec 2018

Lynparza + Tremelimumab — 2L PR or PPSR ovarian; N=68 — Safety endpoint

Lynparza + Tremelimumab — 2L+ gBRCAm ovarian; N=50 — **ESR.** PR or PSR pts eligible; ORR Feb, 2018

MEDIOLA Lynparza + durvalumab — 1L+ gBRCAm ovarian; N=148 — Trial also recruiting gBRCAm HER2- BC, ATM- gastric and 2L+ SCLC; DCR, safety/tolerability Jun 2018

Durvalumab + tremelimumab + Lynparza — PSR/PRR BRCAm ovarian; N=39 — **ESR.** PRR PFS/ PSR PFS Aug 2019

DUO-O Durva + OLAP +SOC vs. Durva + SOC vs SOC (bev +CTX) — **1L tx & mtx n=927** — **Results Q4 2021**

TESARO Niraparib

Pembro + Lynparza — **1L n=TBD** — **Sponsored by MRK.; Details TBD**

TOPACIO (KN162) pembro + niraparib — TNBC, 3-5L (P1) or 3-4L (P2) PRR ovarian; N=121 — No enrichment for PDL1+ or HRD+ pts but the biomarkers will be assessed;. ORR May 2018 **ORR 25% (3% CR) in 2-6L PRR ovarian. Data update at ASCO 2018**

TSR-042 + niraparib or pac/carb vs. TSR-042 + niraparib + bev vs. TSR-042 + bev + pac/carb — AST; N=102 — Safety Sep 2018

BeiGene BGB-290

FIRST niraparib ± bev vs. niraparib +TSR042 ± bev vs. PBO ± bev — **1L mtx all-comers n=700** — **Q2 2018 start**

Niraparib + TSR042 — **2L+ PRR all-comers (TBD)** — **TSRO guides under preparation; Details: TBD**

BGB-290 + BGB-A317 (PD1) — AST; N=230 — Expansion cohort in BRCAm/HRD+ 1-4L TNBC (n~20); ORR Apr 2019 Preliminary data presented at ASCO 2017

Clovis Rucaparib

COUPLET Rucaparib + atezo — BRCAm/HRD+ PSR OC, TNBC; N=48 — Dose escalation in 2L+ ovarian & endometrial (n=6-18); FM CDx; Safety Jan 2019 RP2D is the full dose of both rucaparib and atezo, CLVS anticipates 2018 data presentation, but highlights that it is Genentech decision

Pfizer Talazoparib

ATHENA Rucaparib + nivo vs. rucaparib vs. nivo vs. PBO — **1L mtx all-comers n~1,000** — **Not yet posted; details TBD**; CLVS guides spring-2018 start. Stepdown analysis in BRCAm, then HRD+ and all-comers

Javelin Parp Medley talazoparib + avelumab — N=316; NSCLC, BC, PSR ovarian, bladder, prostate — Basket study to provide PoC data, no registration intent suggested; ORR Mar 2020

Anti-PD1 and PARPi: TOPACIO/Keynote-162

Phase I/II study dose-finding combination study of niraparib plus pembrolizumab in patients with metastatic TNBC or recurrent platinum-resistant epithelial OC

Evaluable patients*	Integrated Efficacy Analysis (combined phase 1+2) PROC Cohort N=60	
	n (%)	Still on Treatment, n
Complete response (CR)	3 (5%)	1
Partial response (PR)	12 (20%)	6
Stable disease (SD)	25 (42%)	2
Progressive disease (PD)	20 (33%)	
ORR (CR+PR)	25%	
Disease control rate (CR+PR+SD)	67%	

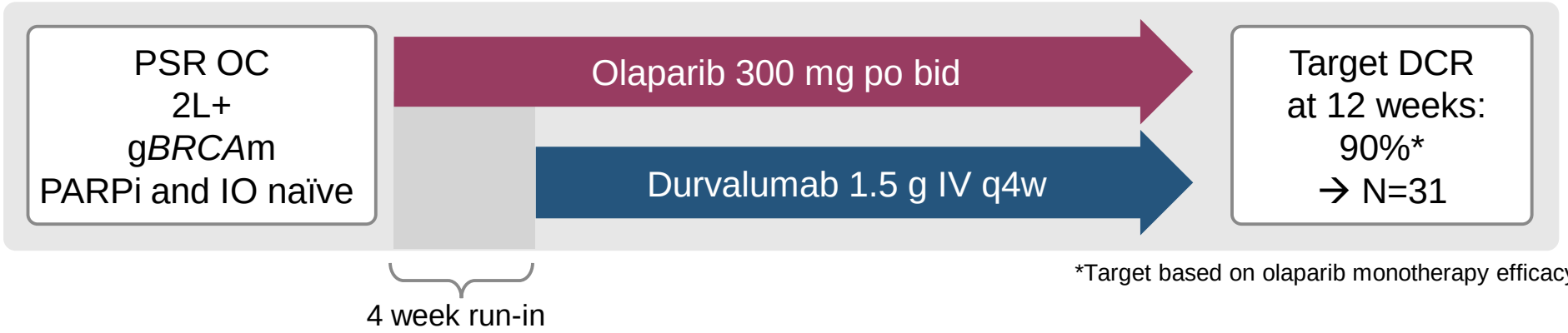
~60% (9/15) of responders (CR or PR) remain on treatment as data continue to mature; duration of response and PFS will be presented at an upcoming conference

NCT02657889
Konstantinopoulos et al. ASCO 2018

**Two patients were not evaluable for efficacy; data are immature, responses include both confirmed and unconfirmed; evaluable pts had at least one on-treatment scan; data as of April 2, 2018*

Anti-PD1 and PARPi: MEDIOLA

Initiation of therapy at the time of relapse



*Target based on olaparib monotherapy efficacy

- Primary endpoints: DCR at 12 weeks, safety
- Secondary endpoints: DCR at 28 weeks, ORR, DoR, PFS, OS, PD-L1 expression
- Exploratory endpoints: TILs

NCT02734004
Drew et al. SGO 2018

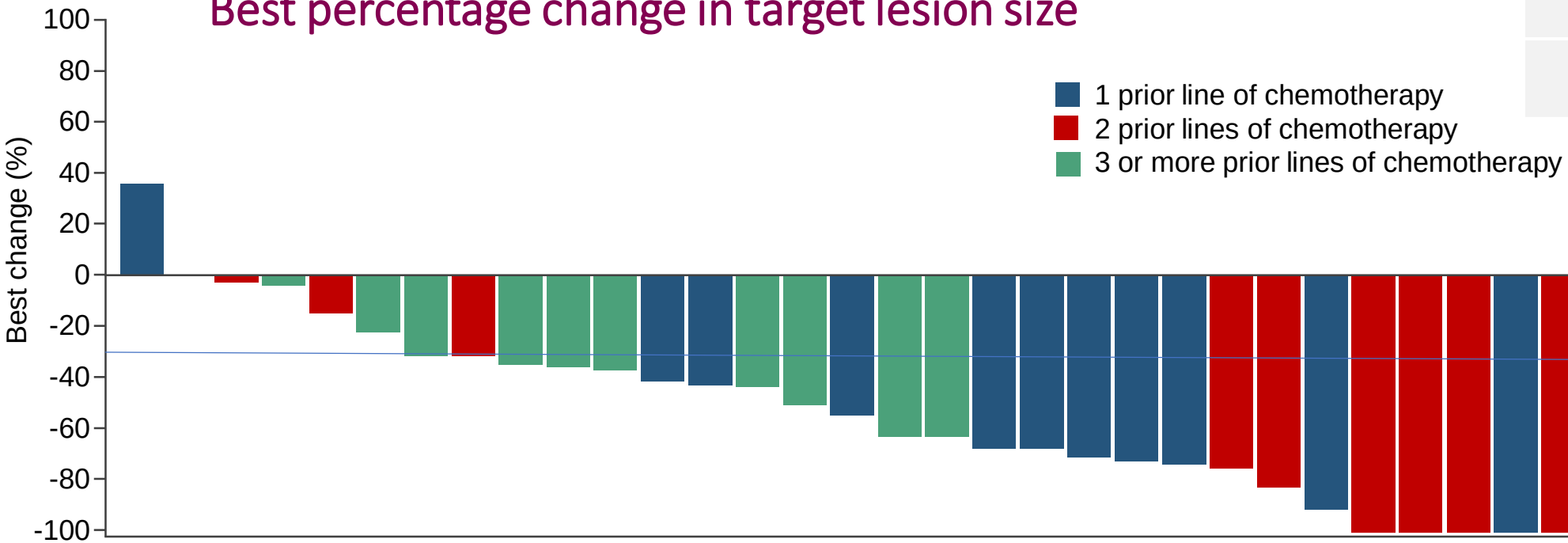
DCR, disease control rate; DoR, duration of response; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; po, oral; TILs, tumor-infiltrating lymphocytes

MEDIOLA: tumor responses

	1 prior (2L)	2 prior (3L)	3+ prior (4L)	All lines
ORR	10/13=**77%**	6/9=**67%**	7/10=**70%**	23/32=**72%**
95% CI	(46%, 95%)	(30%, 93%)	(35%, 93%)	(53%, 86%)

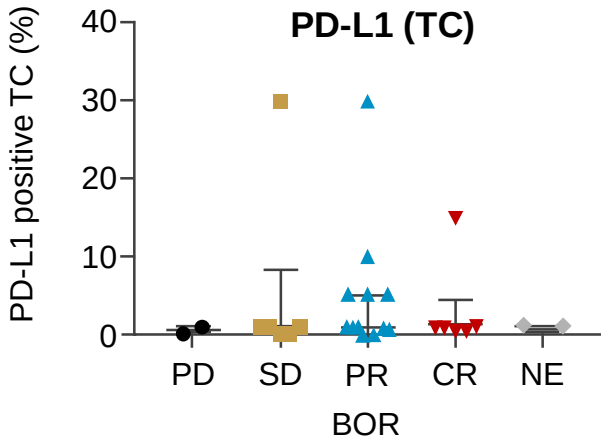
Best Response	N (%)
CR	**6 (19)**
PR	**17 (53)**
SD	3 (9)
PD	3 (9)
NE	3 (9)

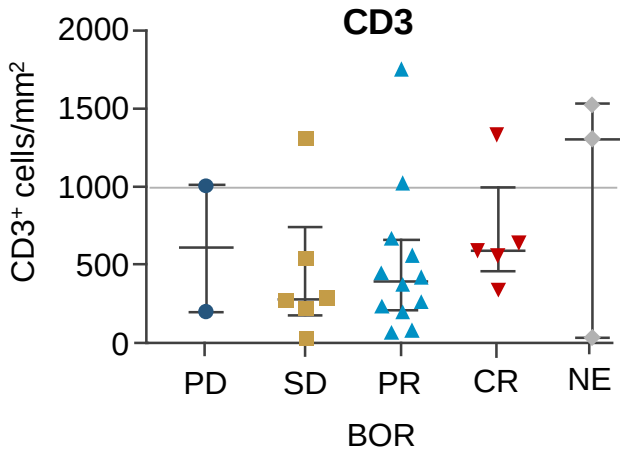
Best percentage change in target lesion size

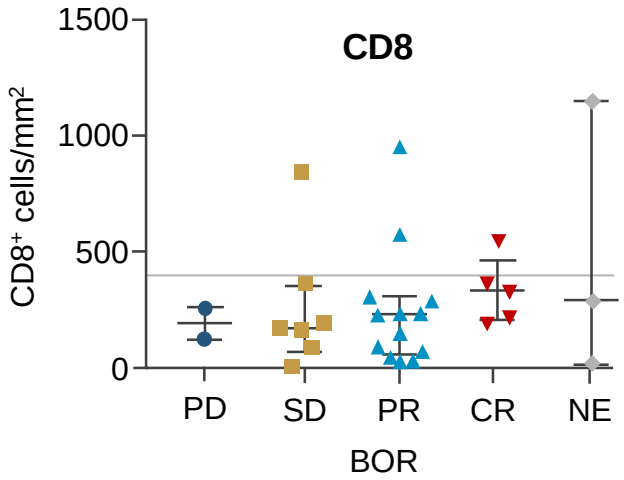


PD-L1 and TILs in archival tissue: association with clinical response

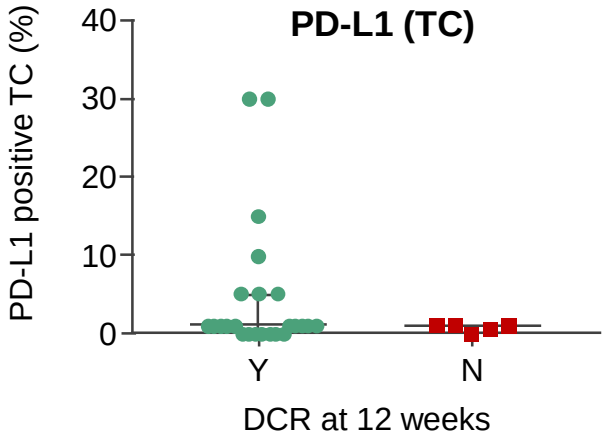
BOR







DCR

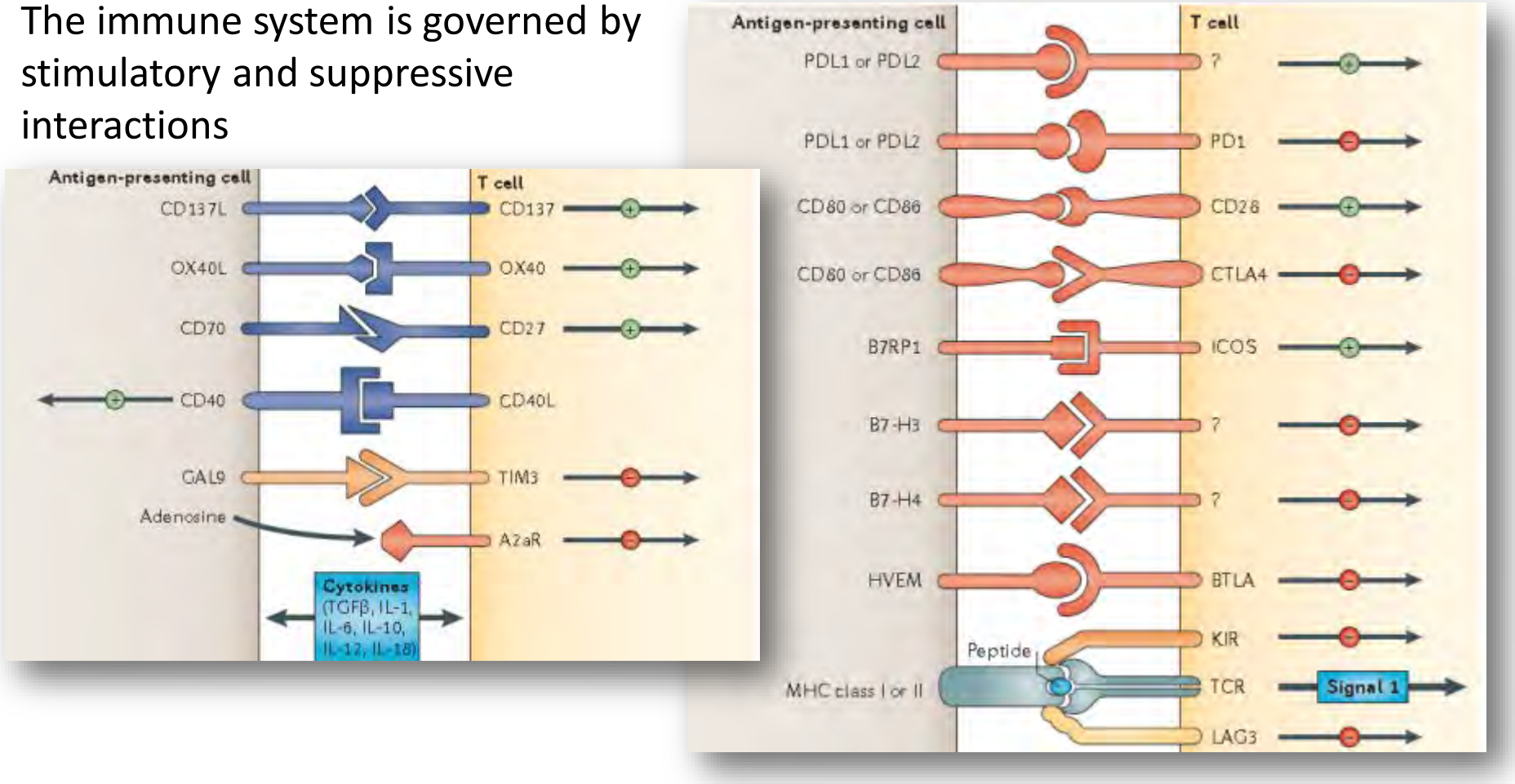


- No statistically significant associations were observed between PD-L1 TC positivity or CD3 and CD8 TILs and positive BOR
- However, a trend was observed where higher PD-L1 and increased TIL densities were observed in archival samples in patients who had SD/PR/CR – this was not seen in patients with PD
- Higher PD-L1 (TC) was observed in patients with DCR at 12 weeks

Dotted lines indicate CD3 (1000 cells/mm^2) and CD8 (400 cells/mm^2) 'hot/cold' thresholds established from unpublished data. Error bars present the median ± interquartile range.
BOR, best objective response; TC, tumor cell; TILs, tumor infiltrating lymphocytes; Y, Yes; N, No

Dual signals control immune function

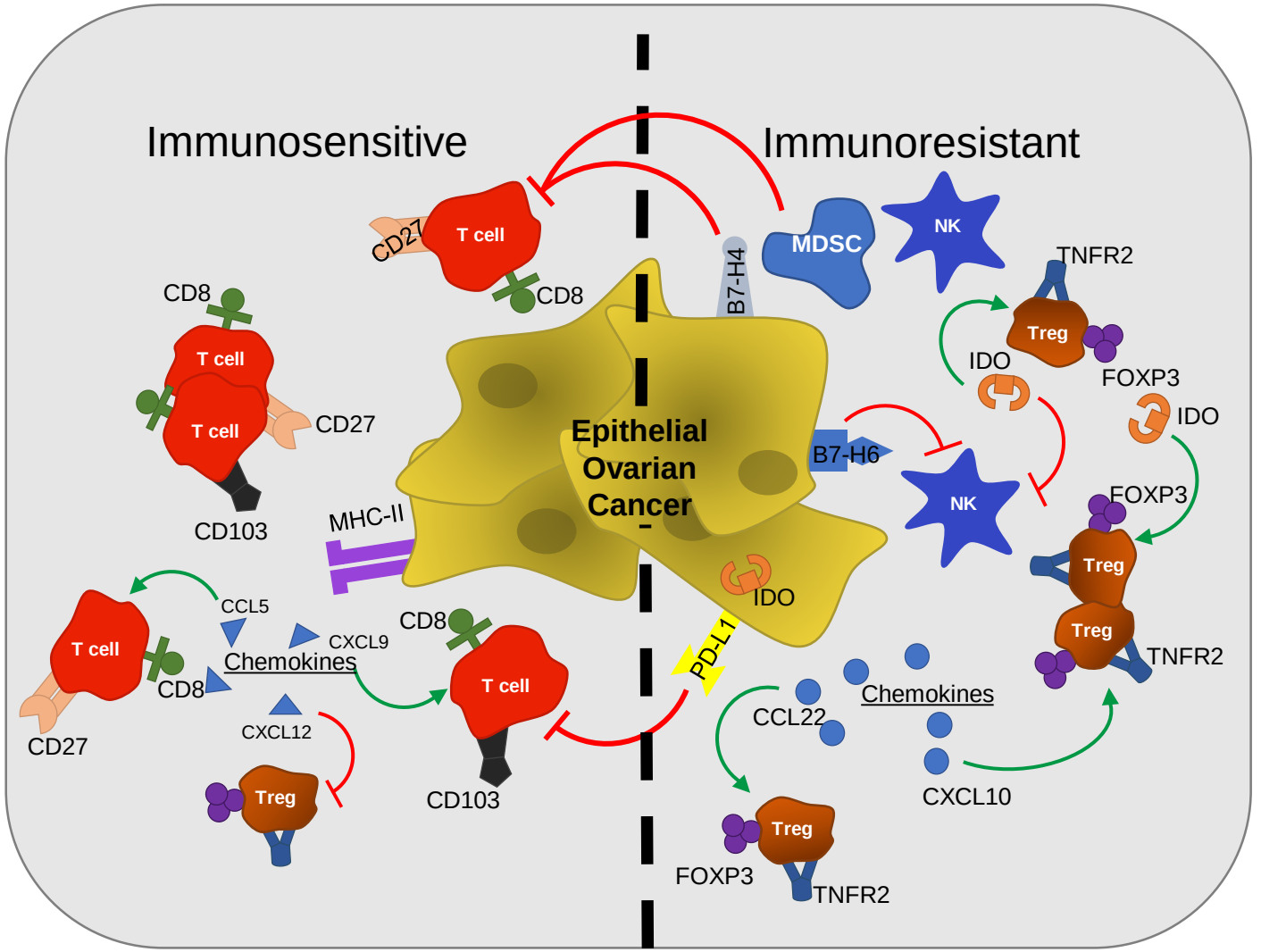
The immune system is governed by stimulatory and suppressive interactions

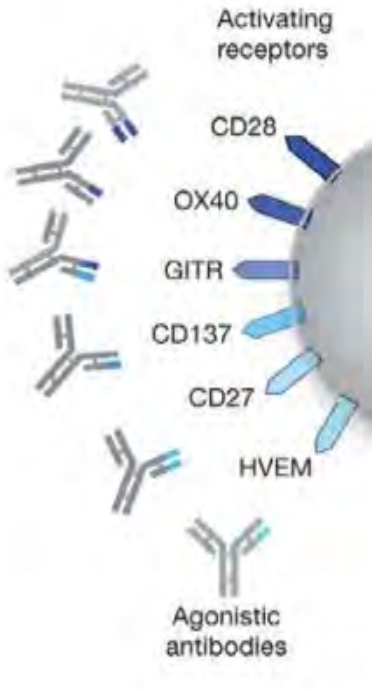


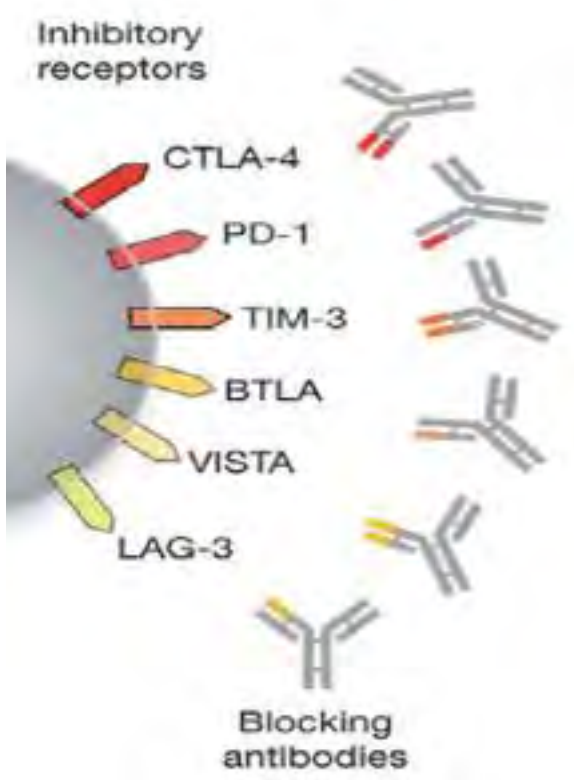
Pardoll DM. Nature Rev Cancer. 2012;12:252-264

I/O + I/O

TURN UP the GOOD and TURN DOWN the BAD







NRG GY003: nivo vs nivo/ipi

- Phase II trial in recurrent ovary CA
- Hypothesis: enhancing CD8 T cell accumulation and activity will reduce the population of T_{reg} cells and promote anti-tumor activity
- Dual blockade of PD-1 and CTLA-4:
  - ➢Tumor reactive TILs contain both
  - ➢Mice model showed that dual blockade reversed $CD8^+$ TIL dysfunction and increased multiple immunogenic markers (↑Ag specific CD8+, CD4+, cytokine release, ↓ suppressive Treg cell function, etc)

NCT#02498600

DART: Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (central and peripheral attack)

- Phase II, single arm trial with 31 histologic cohorts
- 1^{o} objective: evaluate ORR in pts with advanced rare tumors treated with nivo + ipi
- Given the impressive RR with combination nivo/ipi in melanoma (versus either as monotherapy), the combination therapy is expected to be the most efficient approach to testing immune checkpoint blockade efficacy across a variety of rare tumor types.

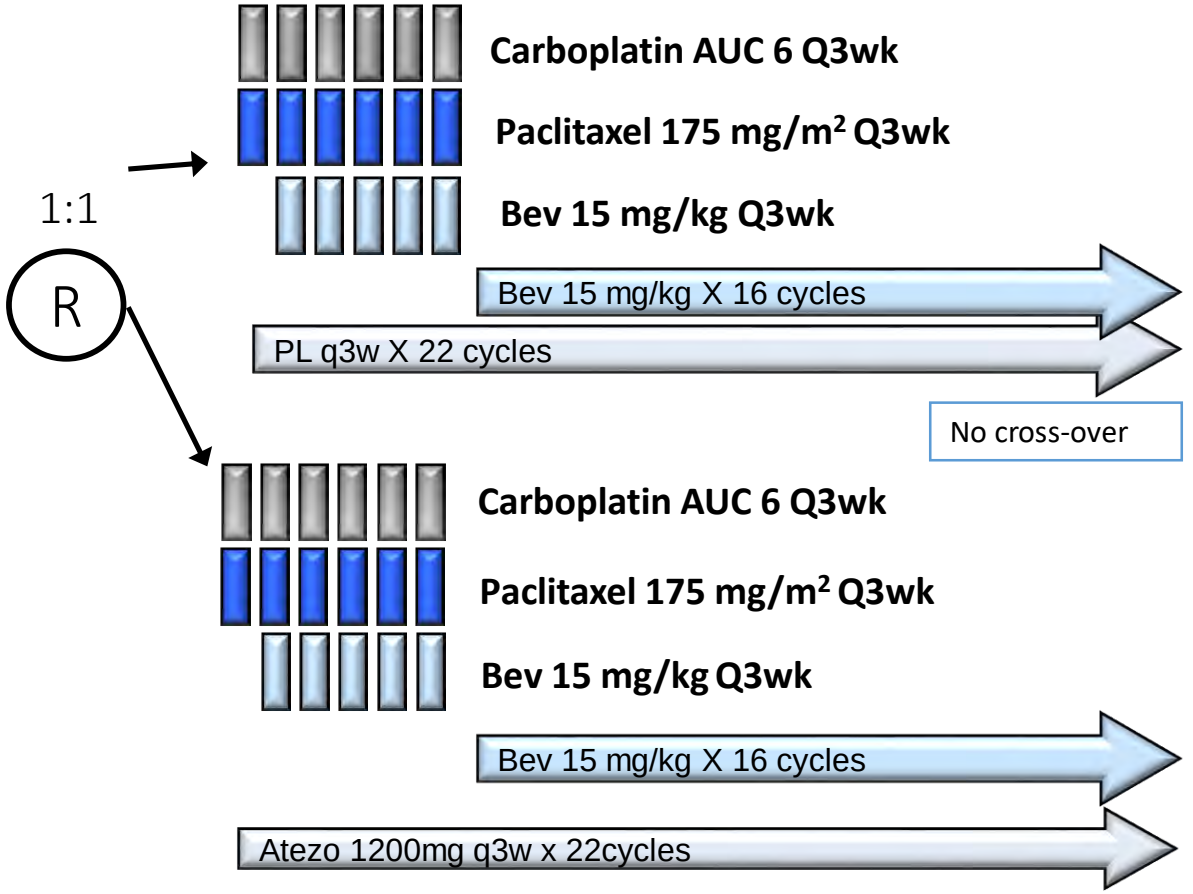
NCT#02834013

Triple Combos

Atezolizumab and bevacizumab: IMaGYN050

Double blinded, 1:1 randomized, placebo-controlled multi-center study

- Previously untreated epithelial ovarian, primary peritoneal, or fallopian tube cancer
- Stage III (sub-optimal/ optimal w/ macroscopic residual), Stage IV, or patients w/ advanced disease treated in the neo-adjuvant setting

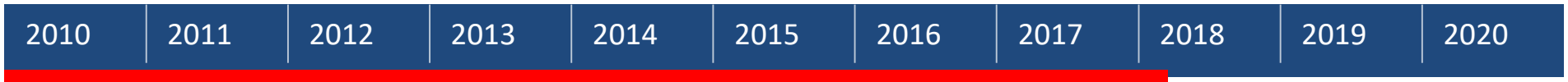


Co-Primary endpoint: PFS &OS in all comers and Dx+ (IC 1+)

NCT03038100

Other I/O combinations

Legend
Phase 1 = hashed
Phase 2 or 3 = solid
Pivotal = red border



BMS
Nivolumab (PD1)

Nivo + lirilumab **(KIR)** — Ovarian, RCC, CRC, NSCLC and mel n=650 — N=16 patients in each cohort

BMS-986016 **(LAG3)** ± nivo — AST n=1,000 — Safety Jun 2019; Ovarian cohort only in the dose escalation arm

CM032 Nivo vs nivo + ipi **(CTLA-4)** — Ovarian, TNBC, gastric, bladder pancreatic, SCLC n=1,150 — Signal finding for nivo + Ipi combo. Ovarian cohort added in Sept 2015; ORR Dec 2018

ECHO 204 Nivo + epacadostat **(IDO1)** — 2L+ ovarian, NSCLC, mel, CRC, SCCHN, NHL, HL, GBM n=485 — Incyte-sponsored; ORR/PFS Apr 2020

Nivo + varlilumab **(CD27)** — 2-6L ovarian, NSCLC, mel, CRC, SCCHN n=175 — Celldex-sponsored; ORR Apr 2019

NRG-GY003 nivo vs. Nivo + ipi **(CTLA-4)** — **2-4L PR or PPSR ovarian n=96** — NCI-sponsored; currently suspended for recruitment , 2-step design suggest pts needed for the first step have been enrolled in the first 4-weeks, ORR Dec 2020

FPA008 ± nivo **(CSF1R)** — 2L+ ovarian, NSCLC, SCLC, SCCHN, panc, RCC, Gliomas n=295 — Five Prime-sponsored; safety May 2019

Nivo + IFN-γ — 2L+ AST n=15 — **ESR.** safety Dec, 2019

Nivo + WT1 **(vaccine)** — 2L+ maintenance ovarian n=11 — **ESR.** WT1+; DLT Apr 2019

Roche
Atezolizumab (PDL1)

ABBV-428 ± nivo **(CD40)** — 2L+ AST incl. ovarian n=172 — Safety Apr 2019

Atezo + RO5509554 **(CSF1R)** — 1L+ ovarian, TNBC, gastric, bladder, sarcoma n=310 — Safety Nov 2018

Atezo + GDC-0919 **(IDO1)** — AST, n=158 — DLT Dec 2018; ovarian cohort added in Aug 2016

Atezo ±guadecitabine ± CDX-1401 vaccine **(HMA)** — 2L+ PRR ovarian, n=78 — NCI-sponsored; PFS Mar 2020

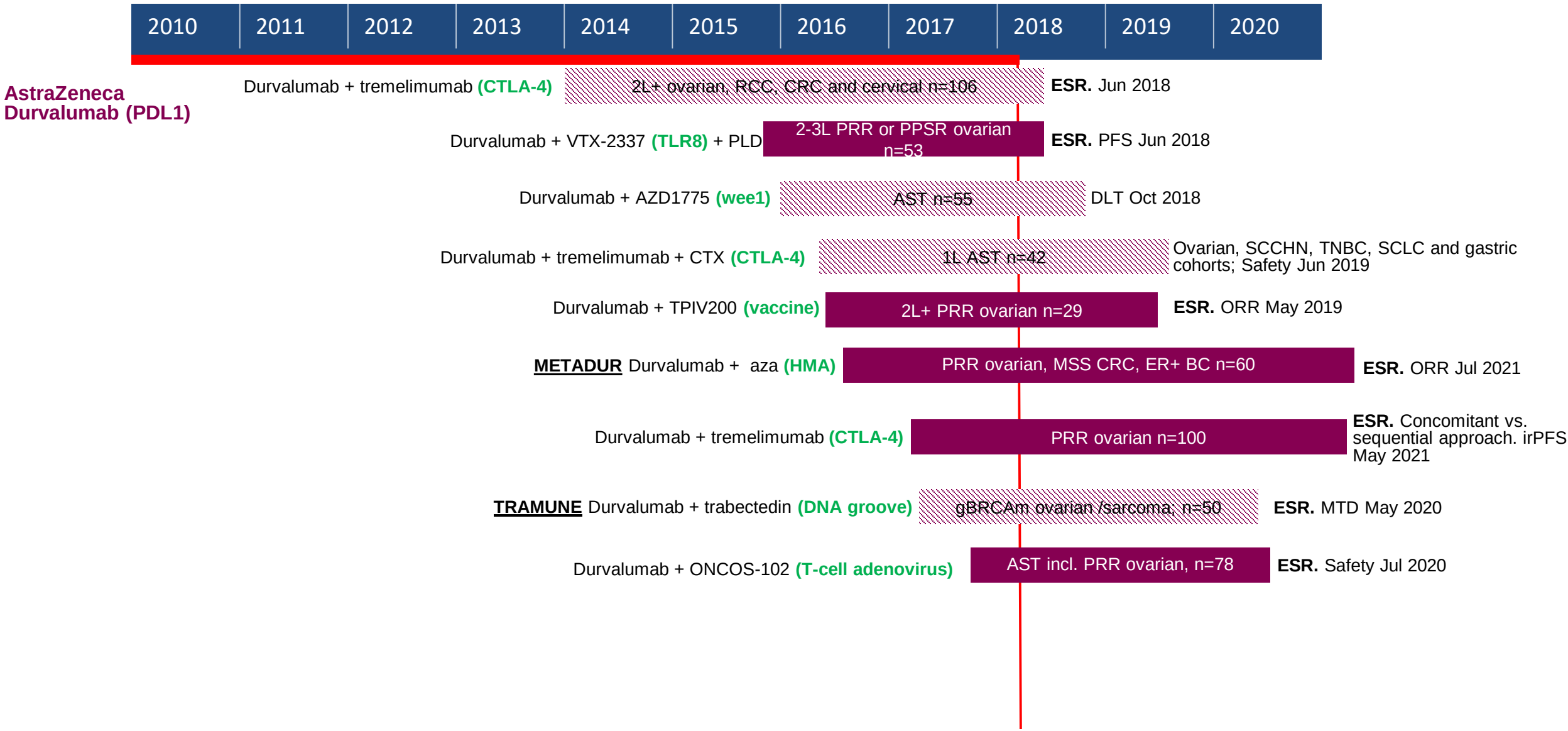
Merck Serono/Pfizer
Avelumab (PDL1)

Avelumab + defactinib **(FAK)** — 4-7L ovarian, n=98 — Verastem-sponsored; FPI announced Jan 2017; ORR Nov 2018

Avelumab + entinostat vs. avelumab **(HDAC)** — 4-7L ovarian, n=138 — Syndax-sponsored; ORR Apr 2018

Other I/O combinations

Legend
Phase 1 = hashed
Phase 2 or 3 = solid
Pivotal = red border



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American Association for Cancer Research

FINDING CURES TOGETHER℠

Society of Gynecologic Oncology

SESSION I Panel Discussion:

Development of Immunotherapy in Gynecological Malignancies – Part 1

Moderators: Sanjeeve Bala, MD, MPH, and Thomas Herzog, MD

Panelists:

Amreen Husain, MD

W. Michael Korn, MD

Dmitriy Zamarin, MD, PhD

Deborah K. Armstrong, MD

Rebecca Arend, MD

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American Association for Cancer Research

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Society of Gynecologic Oncology

SESSION II:

Development of Immunotherapy in Gynecological Malignancies – Part 2

Session Cochairs: Julia A. Beaver, MD, and Rebecca Arend, MD

Speakers:

Amir A. Jazaeri, MD

Robert L. Coleman, MD, FACOG, FACS

Rajeshwari Sridhara, PhD

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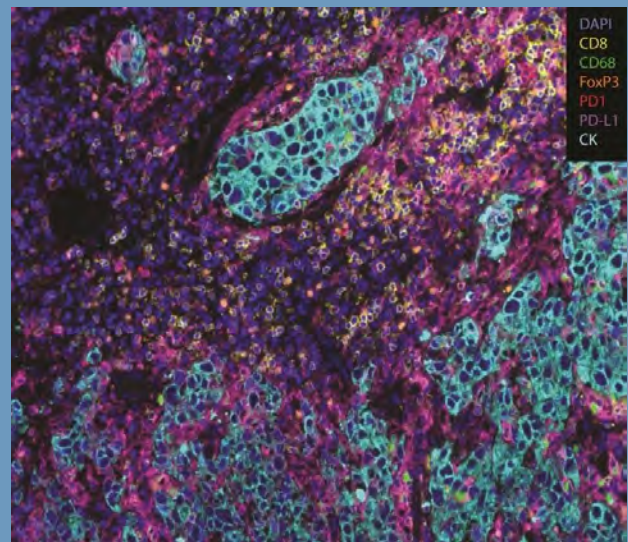
Amir Jazaeri, MD

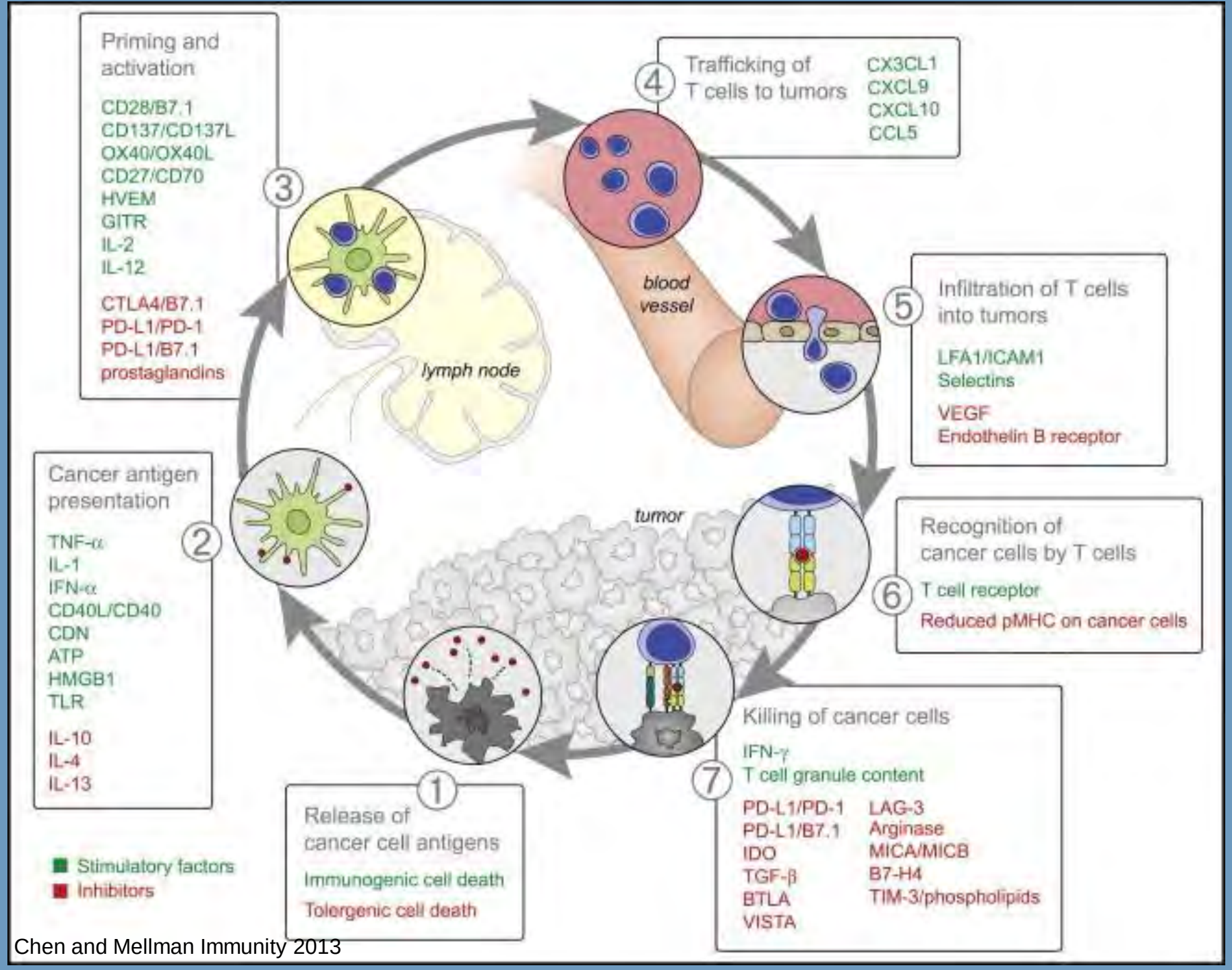
Director, Gynecologic Cancer Immunotherapy Program

MD Anderson Cancer Center, Houston TX



Disclosures

- Research Funding
  - Iovance
  - Pfizer
  - BMS
  - AZ
- Advisory Board
  - Aravive
  - Almac
- DSMB
  - Genentech-Roche

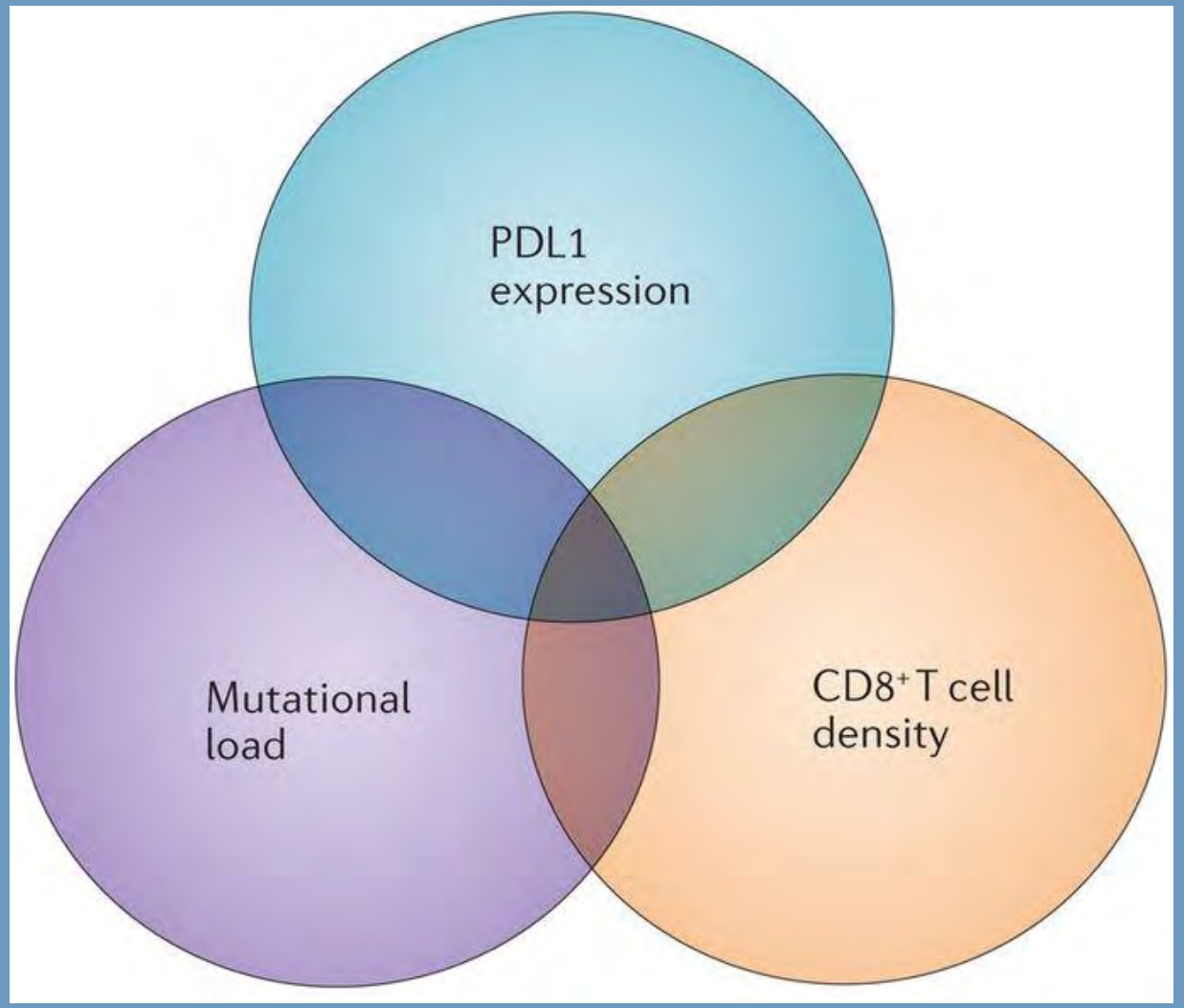


Chen and Mellman Immunity 2013

Approaches for Increasing the Efficacy of Checkpoint Inhibitors

- Increasing tumor cell death and/or DNA damage
  - Chemotherapy, radiotherapy, PARPi
- Combining with other immune-modulating drugs
  - Co-stimulatory (OX40, 4-1BB)
  - Co-inhibitory (TIM3, LAG3)
  - Vaccines, STING agonists, ACT
- Modulating the tumor micro-environment
  - Targeting components of the microenvironment (e.g. macrophages, cancer associated fibroblasts)
  - Targeting the tumor and draining lymph nodes directly
- Importance of on-treatment biopsies

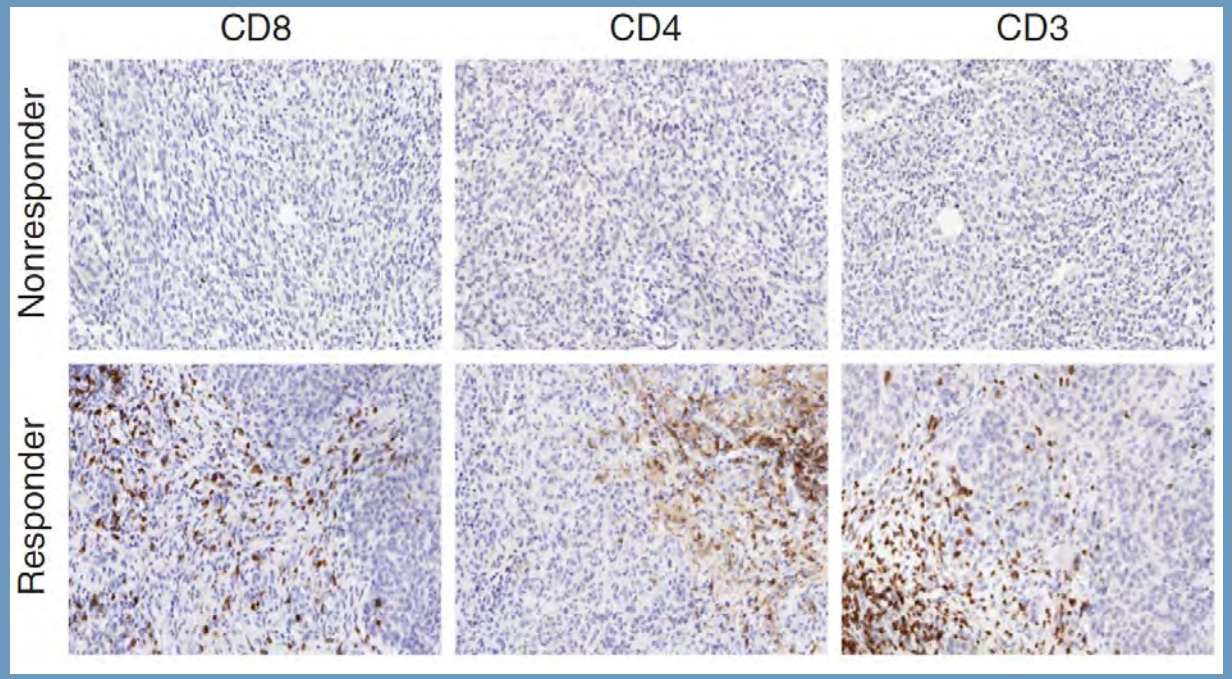
Biomarkers for Response to ICB?



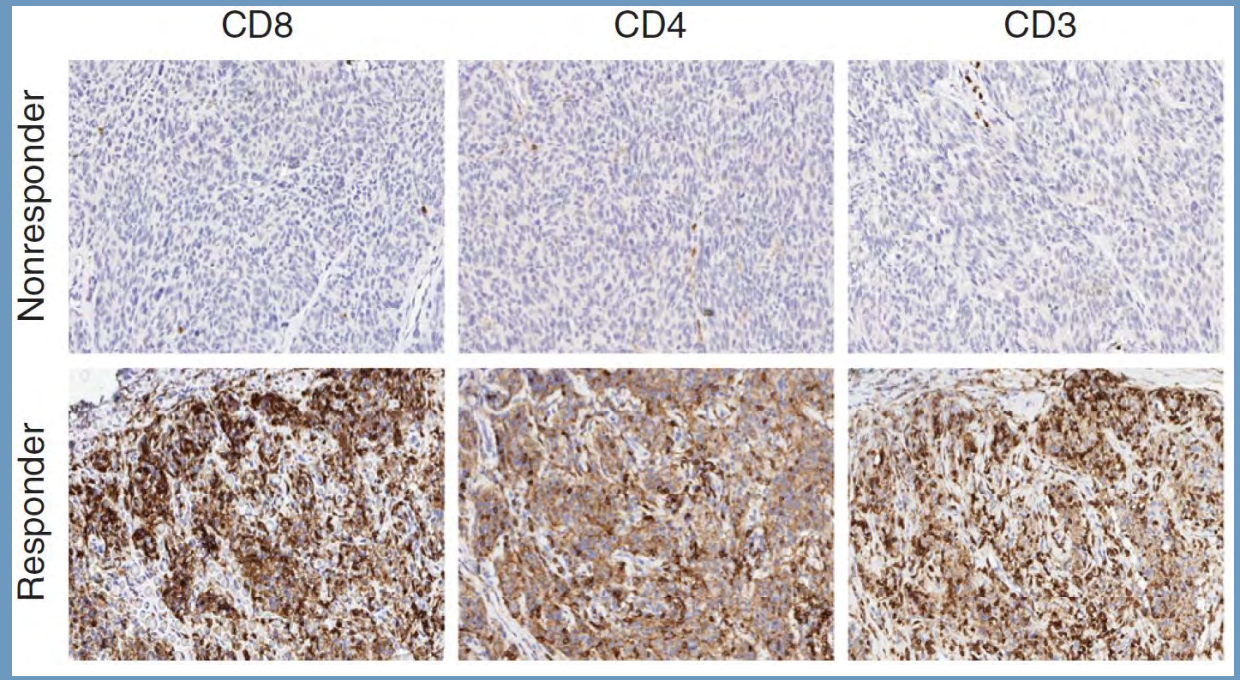
Topalian et al, *Nature Reviews Cancer*, 2016

Biomarkers: When not What?

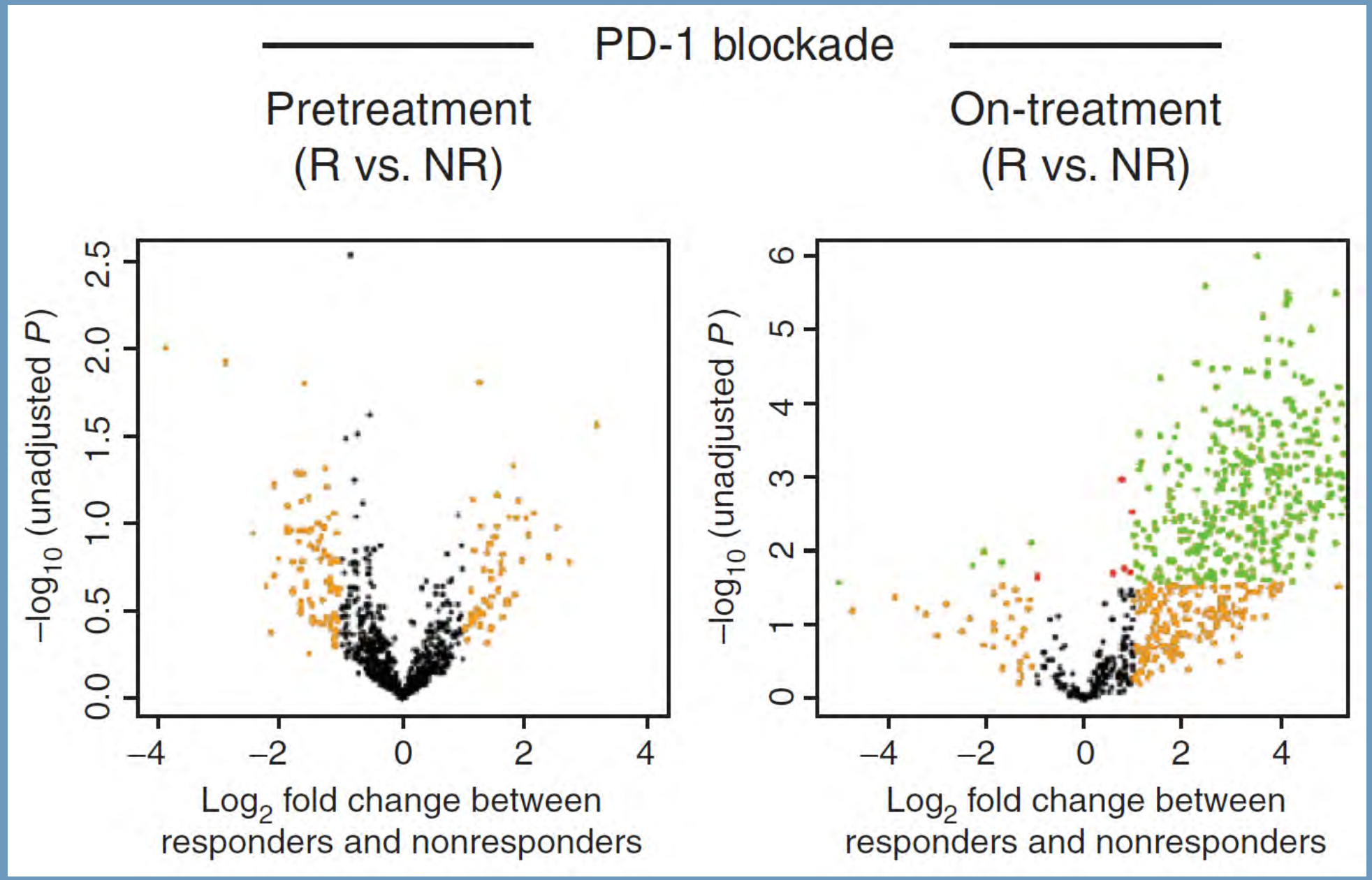
Pre-Treatment



Early On-Treatment

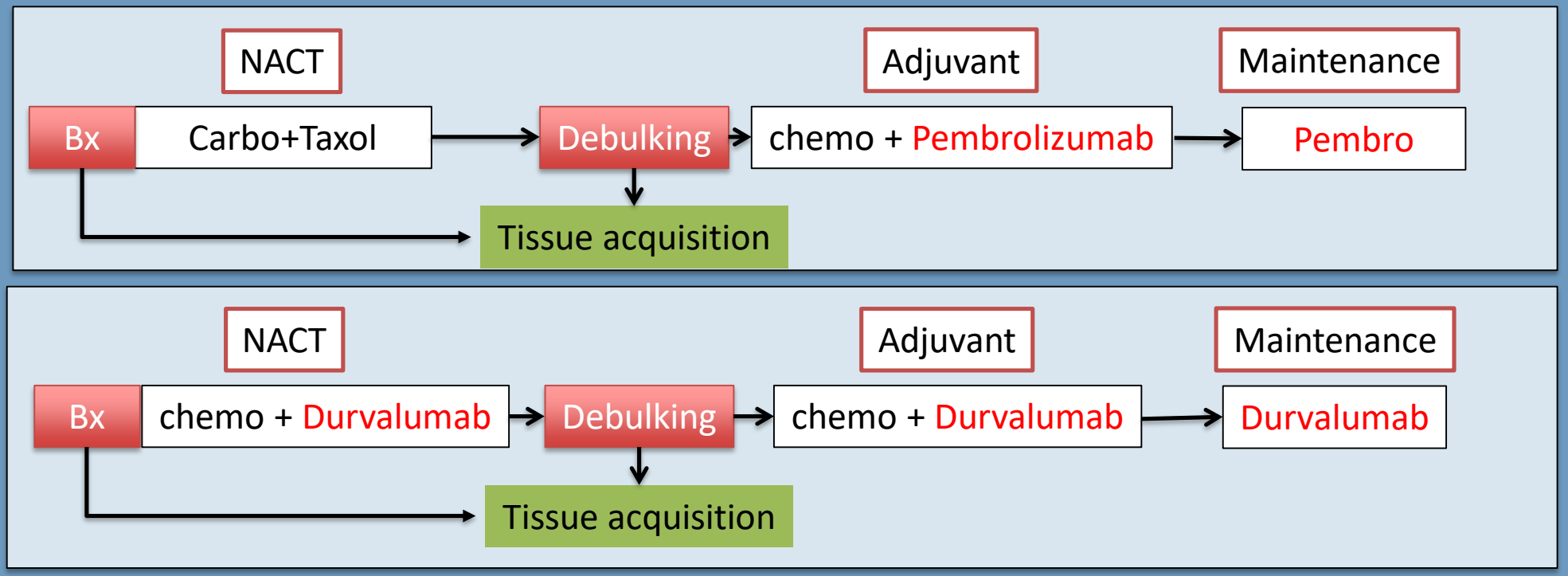


Chen..Wargo, Cancer Discovery, 2016



Chen..Wargo, Cancer Discovery, 2016

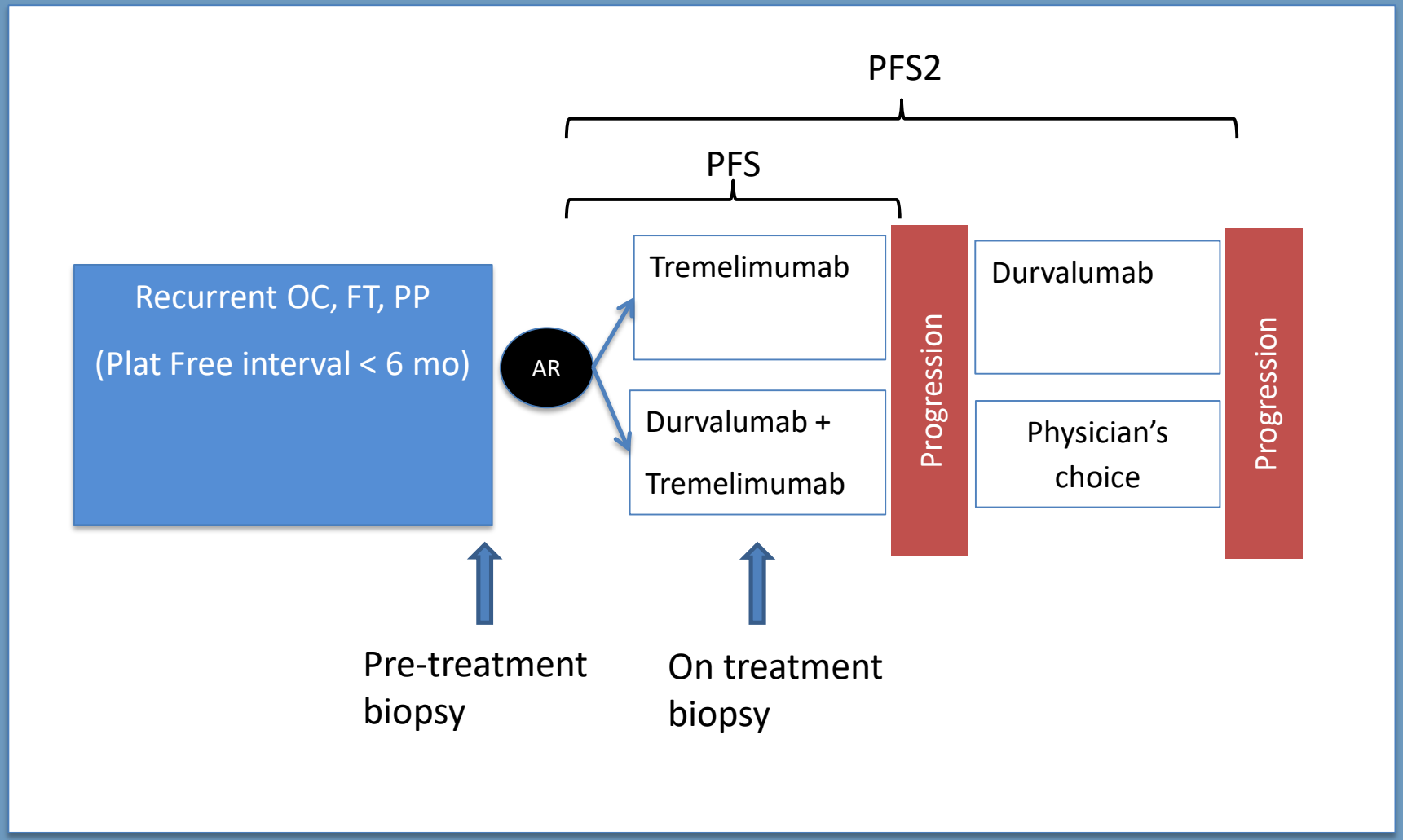
Checkpoint Inhibitors in Patients Treated with Neoadjuvant Chemotherapy



PI: Rob Coleman

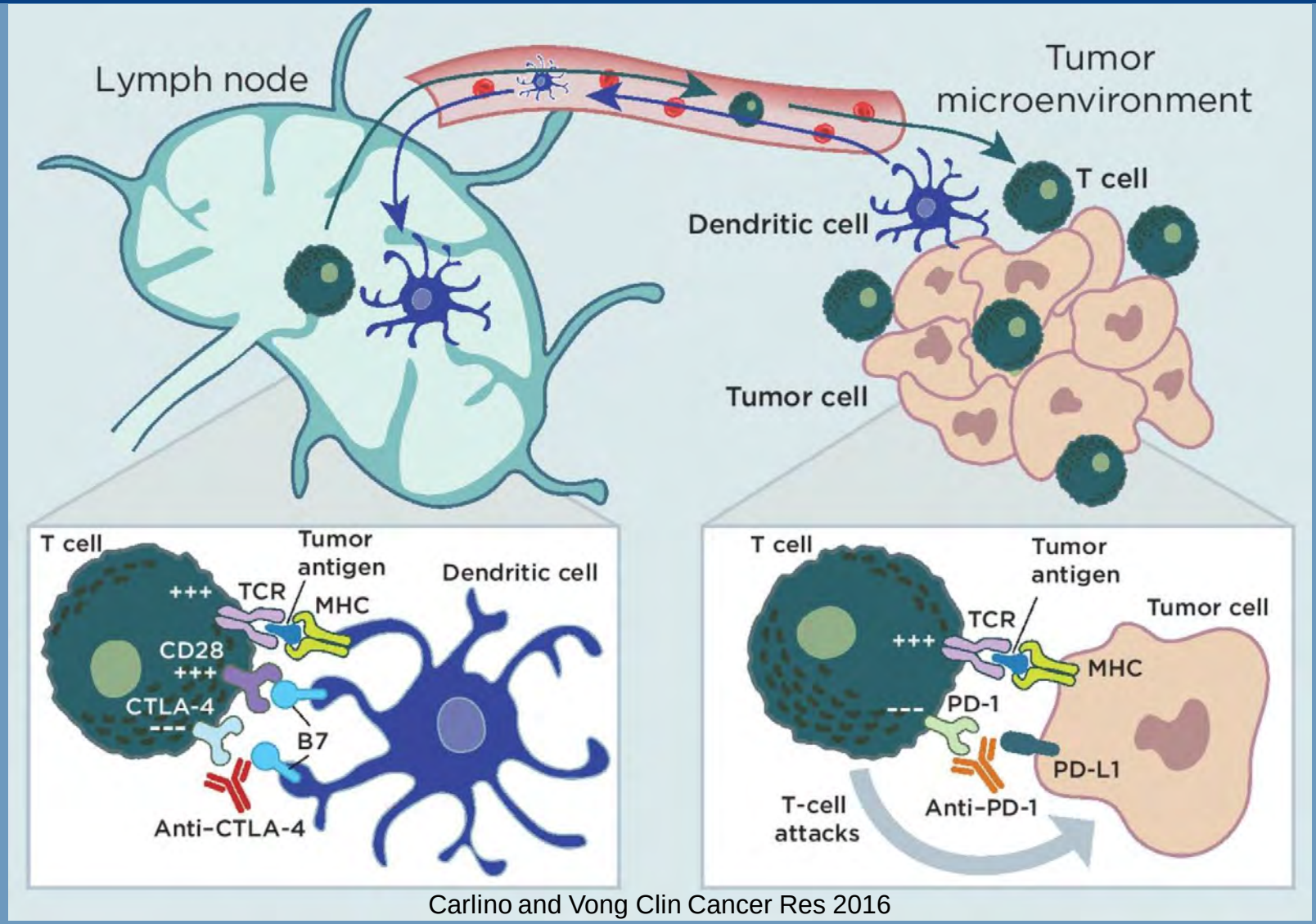
PI: Shannon Westin

Combination versus Sequential Checkpoint Inhibitors in Patients with Platinum Resistant Ovarian Cancer

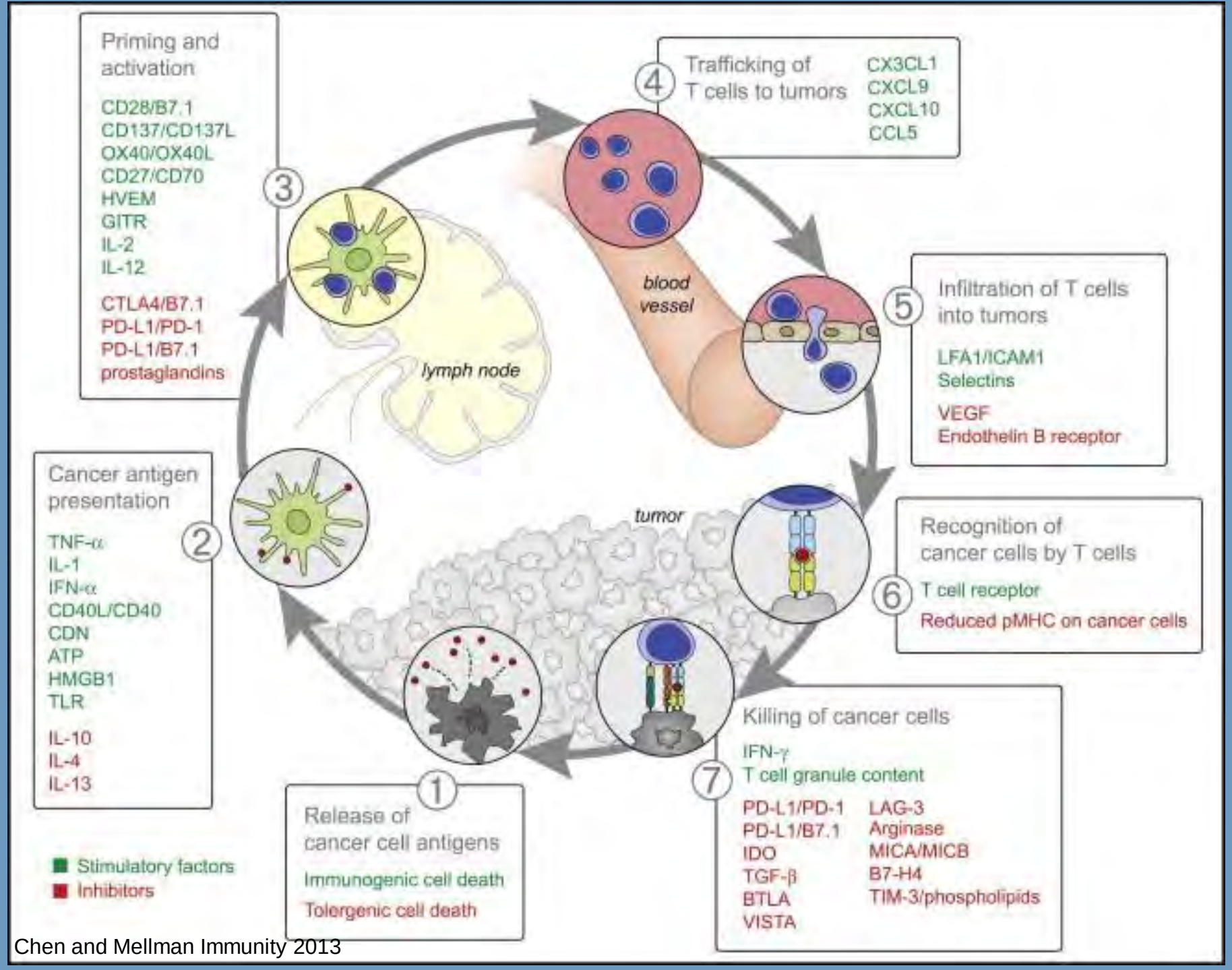


PI: Amir Jazaeri

Can Efficacy be Improved by Route of Administration?



Carlino and Vong Clin Cancer Res 2016

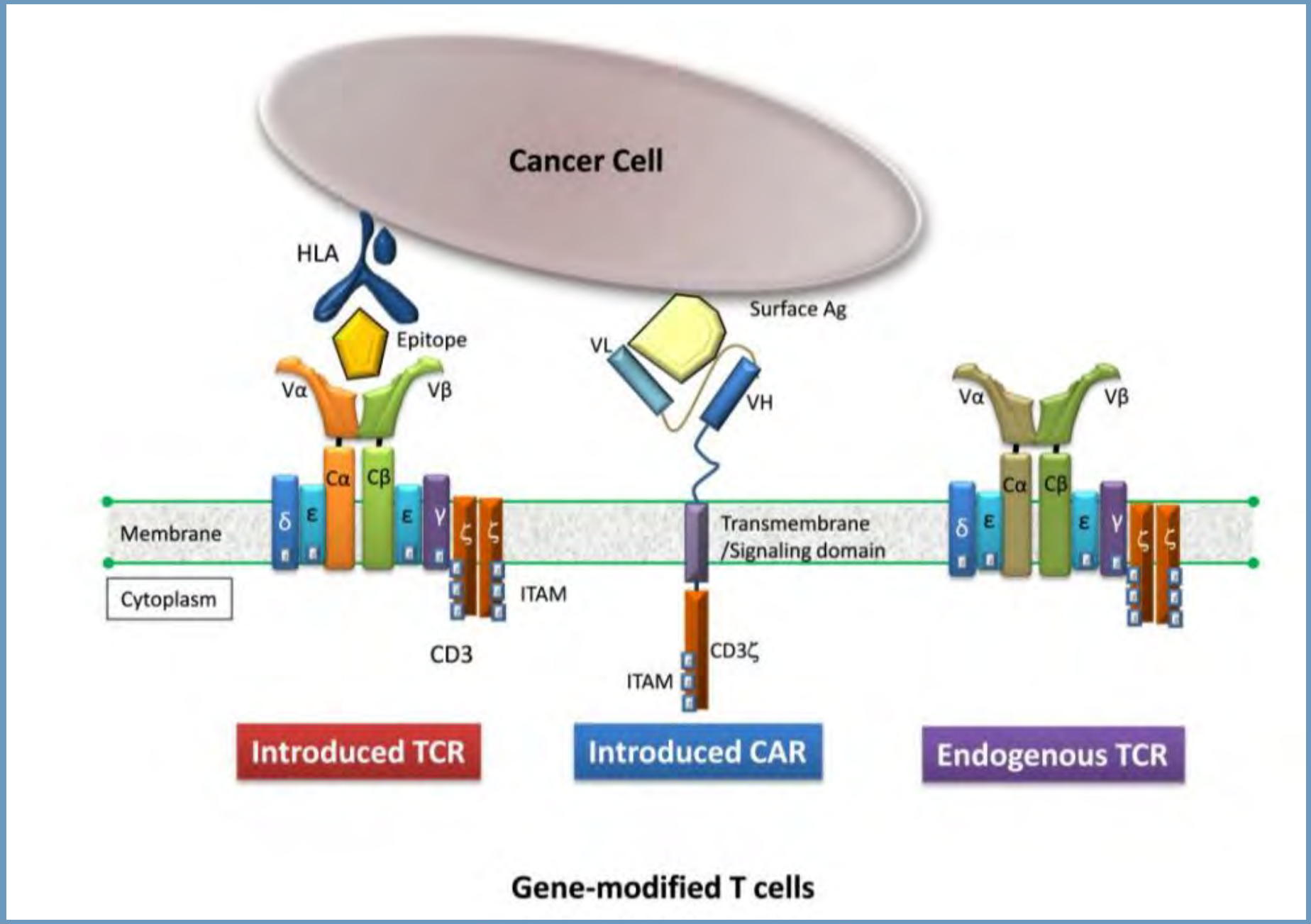


Chen and Mellman Immunity 2013

Adoptive Cell Therapies

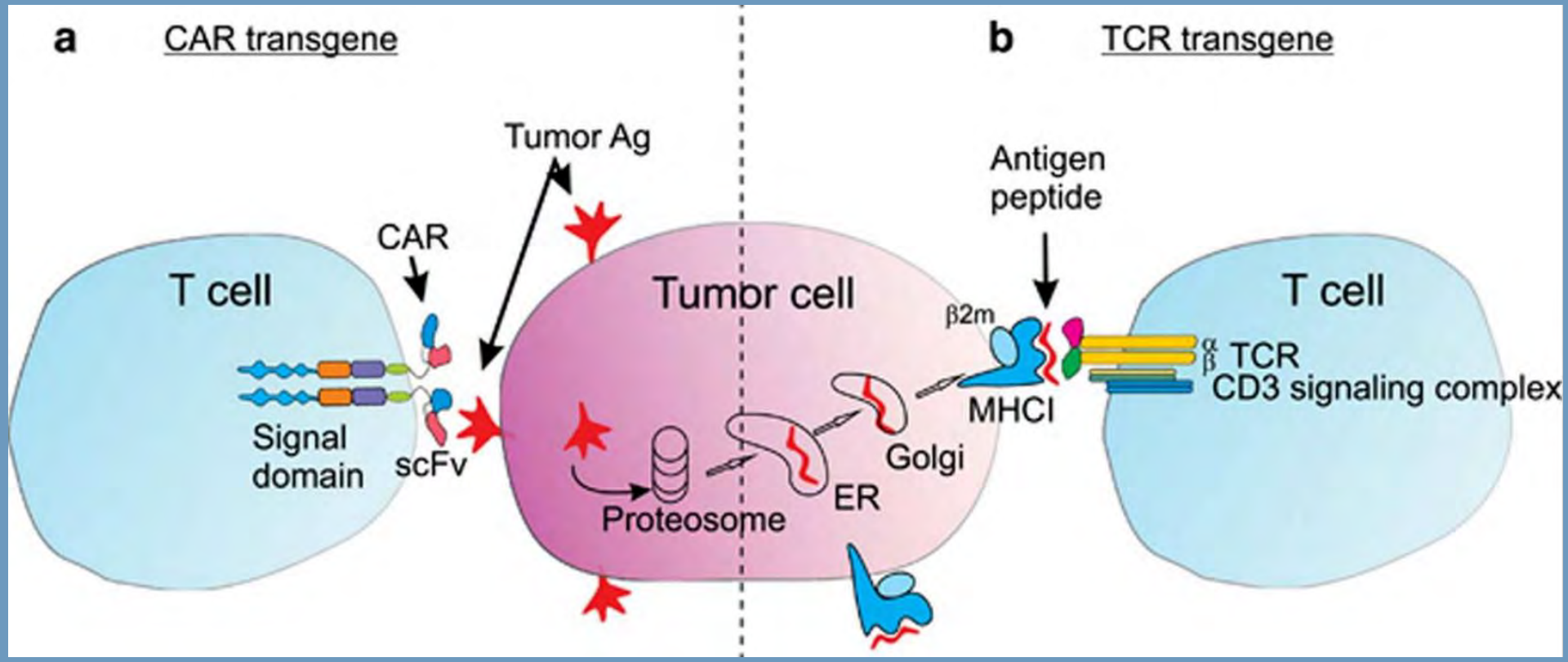
- Treatments in which T cells are collected from a patient and grown and/or modified in the laboratory
- Goal is to increases the number of T cells that are able to kill cancer cells
- T cells are given back to the patient to help the immune system fight disease.

TIL	Circulating tumor-specific T cells	Engineered Receptors (CAR/TCR)



Fujiwara Pharmaceuticals 2014

CAR vs Transgenic TCR



Kershaw et al., Clin Trans Immunology 2014

Transferred Receptor: TCR / CAR

Target Antigen/ Cancer

Antigen	CAR or TCR	Cancer
MART-1, gp100	TCR	Melanoma
HPV E6	TCR	Cervical, Anal, Vaginal
NY-ESO-1	TCR	Sarcoma, Myeloma, (Breast, Lung)
MAGE-A3	TCR	Any cancer MAGE-A3+
P53	TCR	Any cancer overexpresses p53
CD19	CAR	Lymphoma
EGFRvIII	CAR	Glioblastoma, Breast, Lung
Kappa Light Chain	CAR	CLL, B cell NHL
Her2Neu	CAR	Osteosarcoma, Breast
CD30	CAR	Lymphoma (NHL and HD)
GD2	CAR	EBV-specific CTL targeting GBM

CAR T-cell Therapy for Ovarian Cancer

Koneru et al. Journal of Translational Medicine (2015) 13:102
DOI 10.1186/s12967-015-0460-x

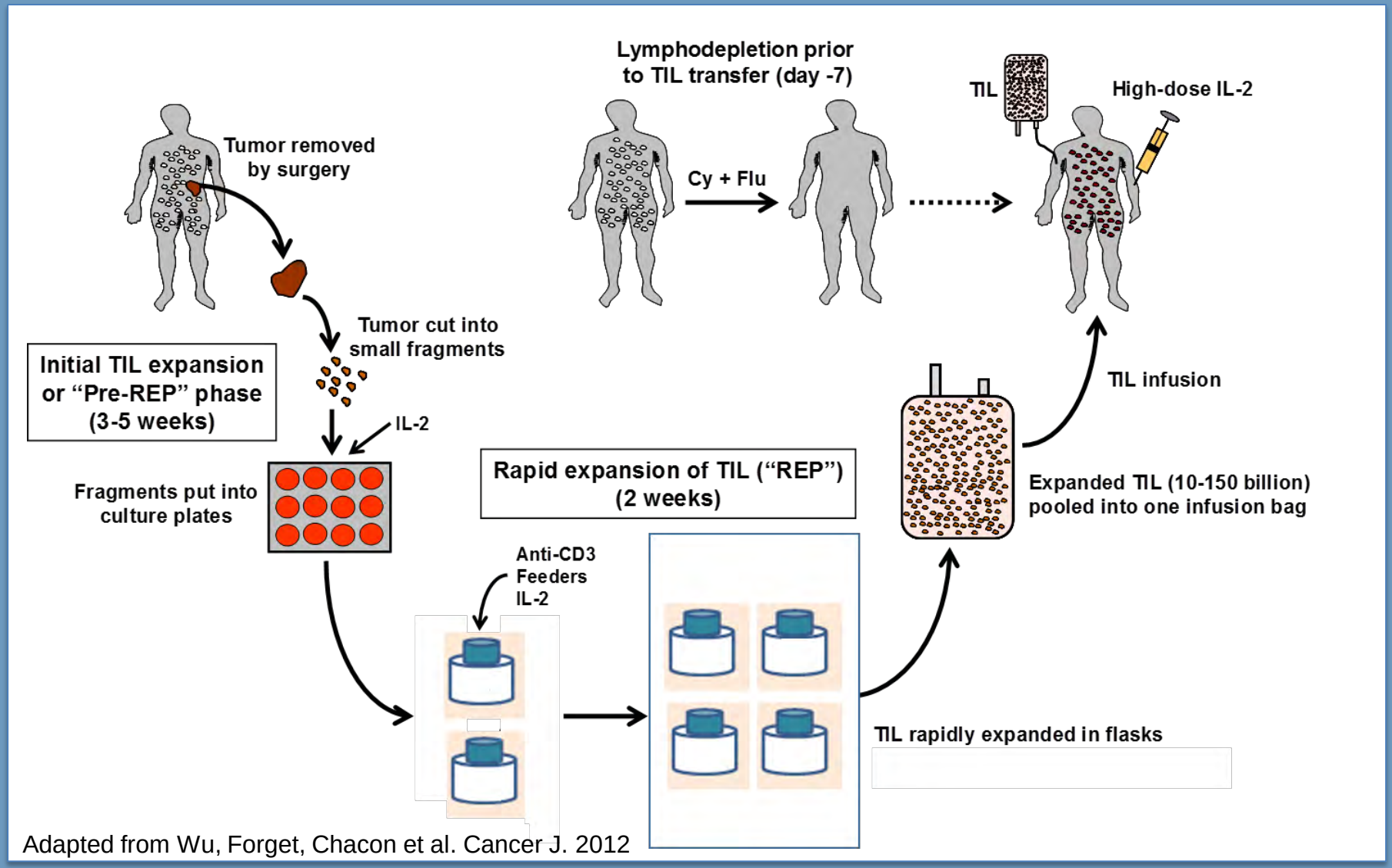
JOURNAL OF TRANSLATIONAL MEDICINE

PROTOCOL Open Access

A phase I clinical trial of adoptive T cell therapy using IL-12 secreting MUC-16^{ecto} directed chimeric antigen receptors for recurrent ovarian cancer

Mythili Koneru[1,2], Roisin O'Cearbhaill[1,2], Swati Pendharkar[1], David R Spriggs[1,2] and Renier J Brentjens[1,2*]

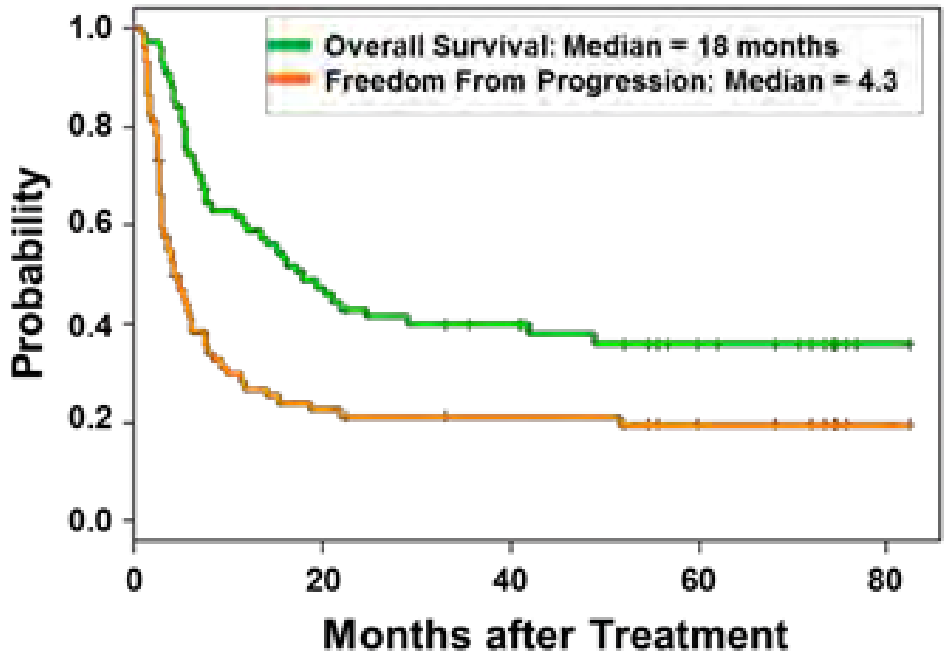
Adoptive Cell Therapy: TIL



Adapted from Wu, Forget, Chacon et al. Cancer J. 2012

TIL outcomes in melanoma

43% clinical response rate
Including 6 CR



Adapted from Wu, Forget, Chacon et al. Cancer J. 2012

TIL outcomes in Cervical Cancer

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

Stevanovic JCO 2015

TIL outcomes in melanoma

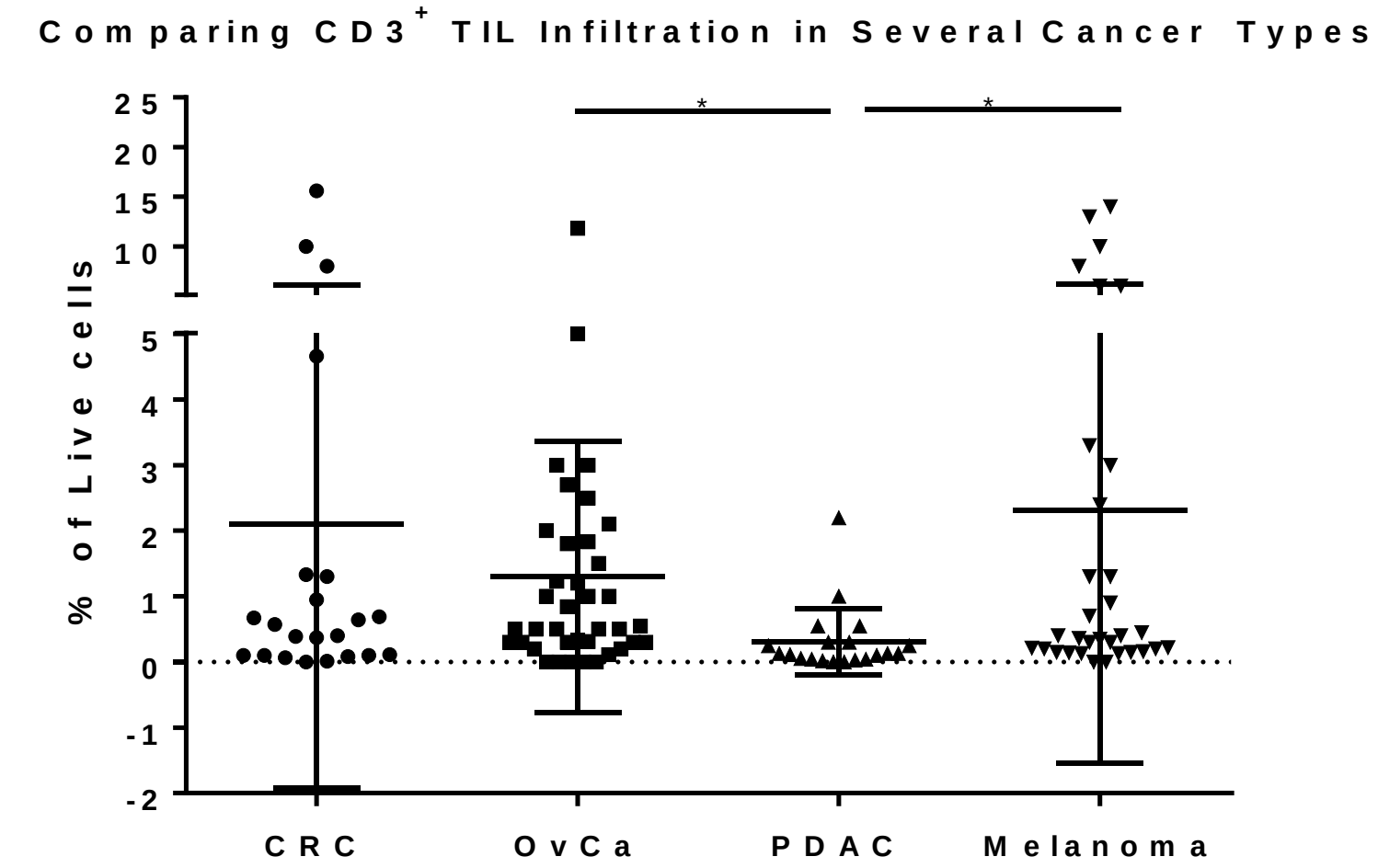
Table 1. Characteristics of Patients and Administered T Cells

Patient	Age (years)	Histology	HPV Type	Sites of Disease	Prior RT	Prior Systemic Treatment	Cells ($\times 10^9$)	Within CD3+ (%)		No. of IL-2 Doses	Response	
								CD4+	CD8+		Type	Duration or TTP (months)
1	30	ASC	18	Iliac lymph nodes, lung, lung hilum, retroperitoneum, vaginal cuff	Yes	Cisplatin	101.4	29	72	7	PD	1
2	53	SCC	18	Bone, liver, lung, lung hilum, mediastinum, pelvis	Yes	Cisplatin, carboplatin, paclitaxel, topotecan, ixabepilone dimethane sulfonate	126.0	10	94	3	PR	3
3	36	SCC	16	Iliac lymph nodes, lung hilum, mediastinum, retroperitoneum	Yes	Cisplatin, vincristine, bleomycin, gemcitabine, paclitaxel, topotecan	152.0	21	83	2	CR	22+
4	55	SCC	16	Axilla, breast, liver, omentum, pleura, soft tissue	Yes	Cisplatin, carboplatin, paclitaxel, fluorouracil, irinotecan, dovitinib, pemetrexed	80.1	23	76	7	PD	2
5	44	SCC	18	Brain, mediastinum, supraclavicular nodes	Yes	Cisplatin	90.0	66	29	5	PD	2
6	36	AC	18	Abdominal wall, liver, paracolic, pelvis, retroperitoneum	Yes	Cisplatin	74.7	61	35	8	CR	15+
7	59	AC	18	Abdominal wall, lung	Yes	Cisplatin, paclitaxel, carboplatin, bevacizumab	33.4	36	58	8	PD	1
8	31	ASC	18	Pelvis, perihepatic mass	No	Cisplatin, paclitaxel	46.1	64	29	9	PD	2
9	37	AC	18	Axilla, bone, lung, mediastinum, pelvis, retroperitoneum	Yes	Cisplatin, carboplatin, paclitaxel, ipilimumab	70.2	33	59	1	PD	1

Abbrevations: AC, adenocarcinoma; ASC, adenosquamous cell carcinoma; CR, complete response; HPV, human papillomavirus; IL-2, interleukin-2; PD, progressive disease; PR, partial response; RT, radiotherapy; SCC, squamous cell carcinoma; TTP, time to progression.

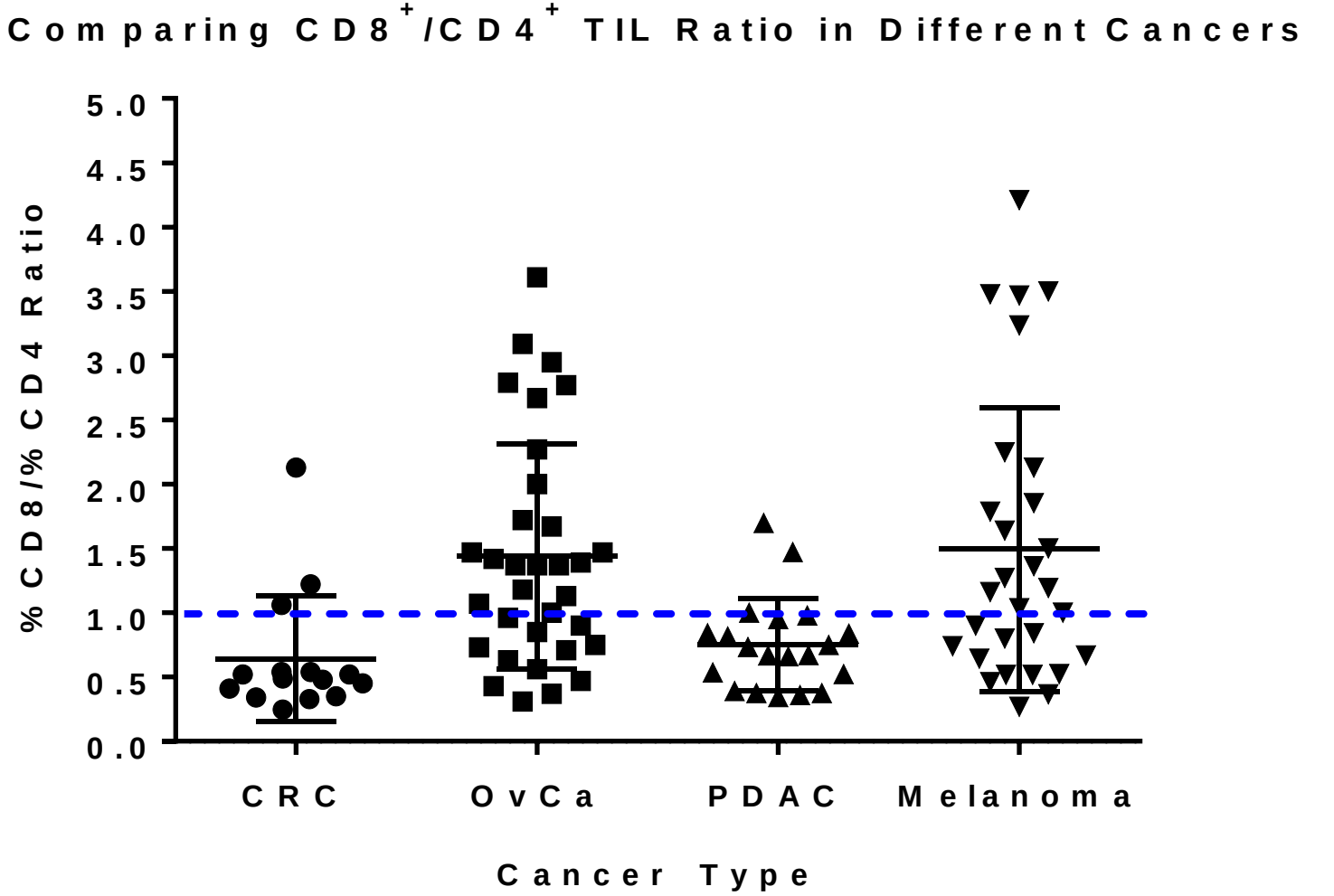
Stevanovic JCO 2015

OvCa has similar CD3+ infiltration to Melanoma



Sakellariou-Thompson et al. SITC 2016

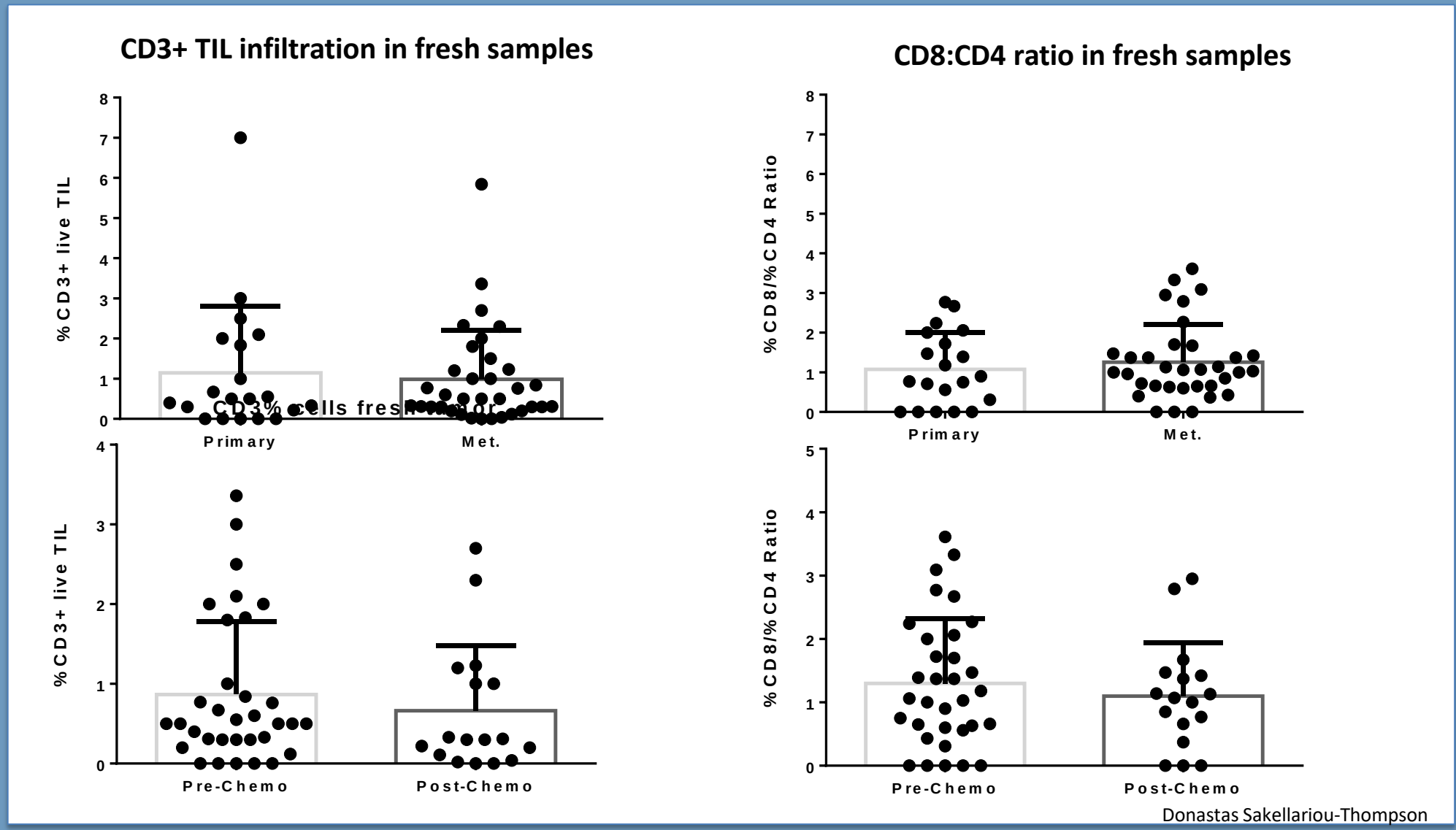
OvCa has similar CD8+ TIL infiltration to Melanoma



Sakellariou-Thompson et al. SITC 2016

Donastas Sakellariou-Thompson

T cell infiltration and CD8/CD4 ratio in primary vs metastasis or pre/post chemotherapy



Donastas Sakellariou-Thompson

Upcoming Adoptive Cell Therapy Trials at MDACC

- 2017-0505 (NCT03108495) A Phase 2, Multicenter Study to Evaluate the Efficacy and Safety Using Autologous Tumor Infiltrating Lymphocytes (LN-145) in Patients with Recurrent, Metastatic, or Persistent Cervical Carcinoma

- 2017-0672 (NCT03449108) Clinical study to assess efficacy and safety of LN-145 (Manufactured by Iovance) Across Multiple Tumor Types
  - PR ovarian cancer, bone sarcomas, and pancreatic cancer

- 2017-0671 Clinical Study to Assess Efficacy and Safety of MDA-TIL (Manufactured at MDACC) Across Multiple Tumor Types
  - PR ovarian cancer, bone sarcomas, poorly differentiated sarcomas, TBD

- 2016-0400 (NCT03318900) Phase I/Ib Study of Adoptive Cellular Therapy Using Autologous IL-21-Primed CD8+ Tumor Antigen-Specific T Cells in Combination With Utomilumab (PF-05082566) in Patients With Platinum Resistant Ovarian Cancer

nature medicine

LETTERS

https://doi.org/10.1038/s41591-018-0040-8

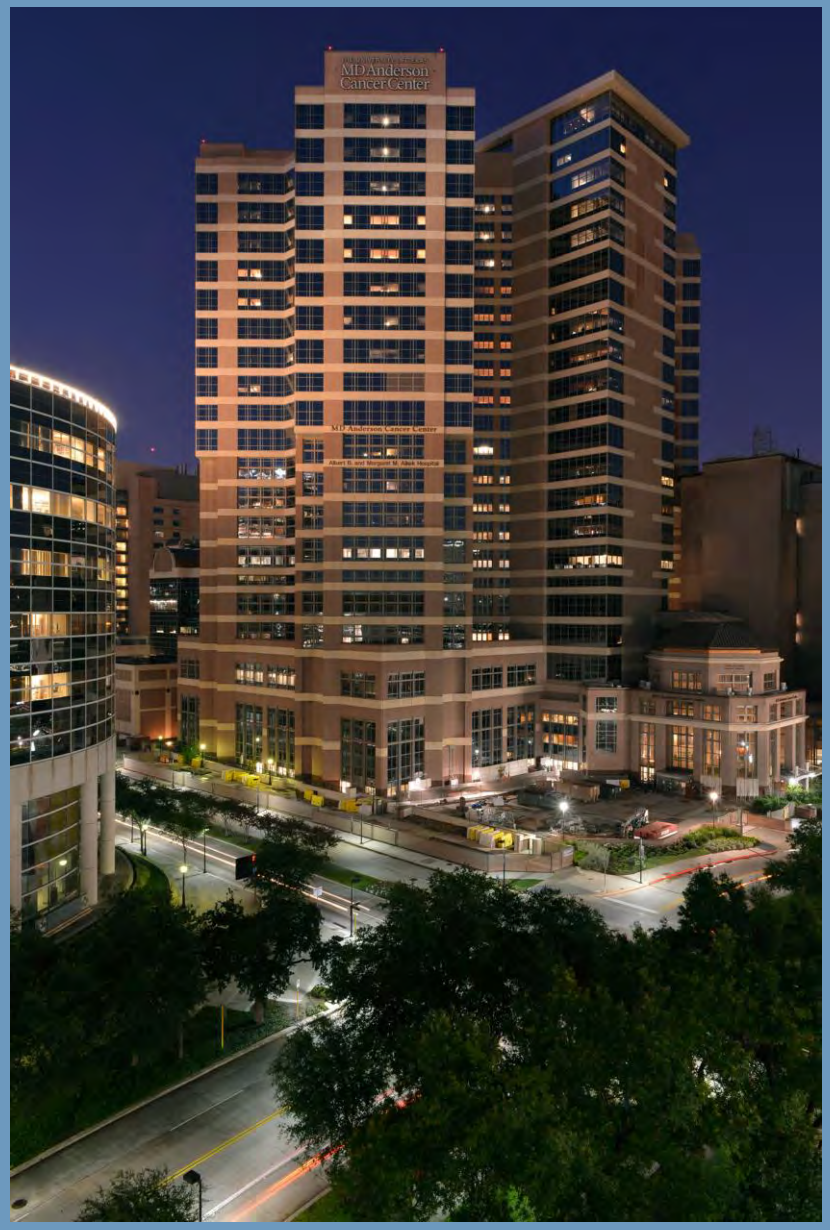
Immune recognition of somatic mutations leading to complete durable regression in metastatic breast cancer

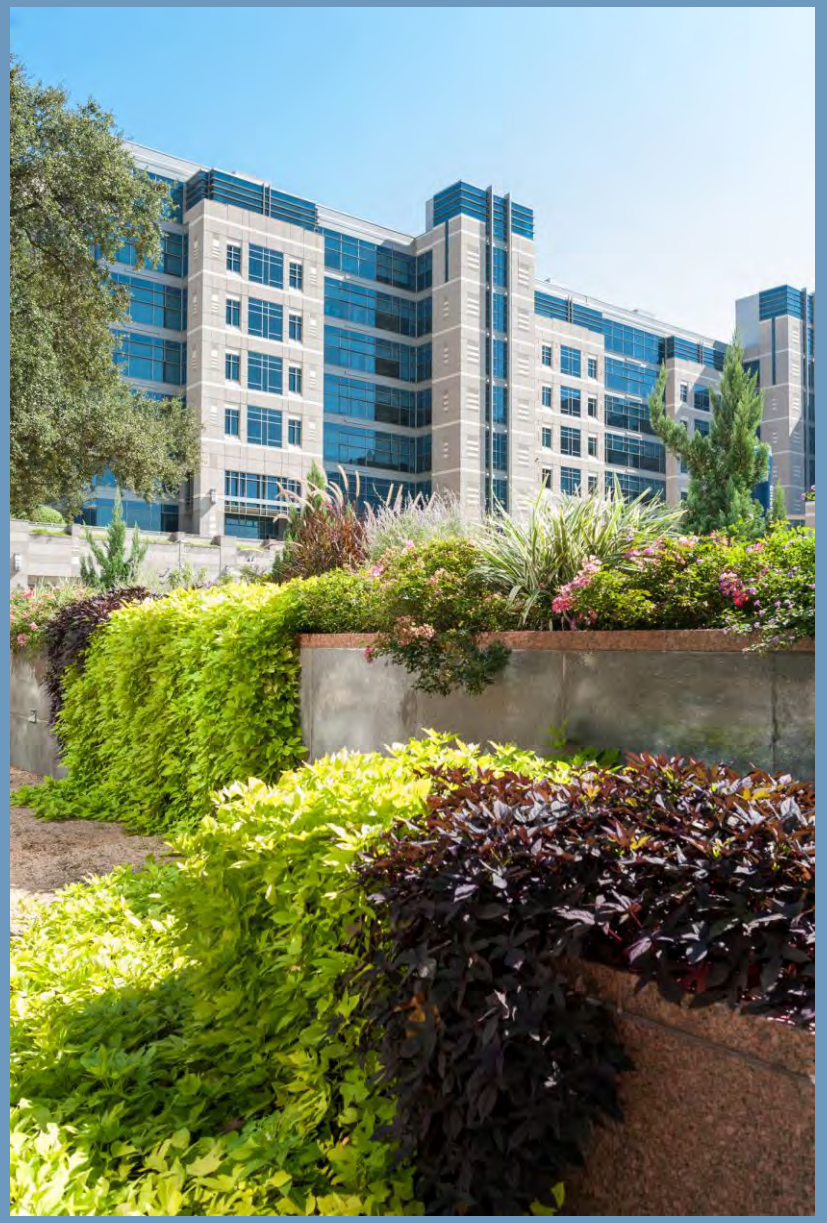
Nikolaos Zacharakis[1], Harshini Chinnasamy[1], Mary Black[1], Hui Xu[1], Yong-Chen Lu[1], Zhili Zheng[1], Anna Pasetto[1], Michelle Langhan[1], Thomas Shelton[1], Todd Prickett[1], Jared Gartner[1], Li Jia[1], Katarzyna Trebska-McGowan[2], Robert P. Somerville[1], Paul F. Robbins[1], Steven A. Rosenberg[1*], Stephanie L. Goff[1] and Steven A. Feldman[1]

Future of Immunotherapy for Gynecologic Cancers

- The goal of rational combination immuno-oncology requires understanding cancer-specific immuno-inhibitory mechanisms at work
- Significant impact will require innovative clinical trial designs and translational science (e.g. looking for dynamic changes using on-treatment biopsies).
- Partner with and industry, scientific societies, and regulatory agencies to focus on the unique win-win opportunities presented by gynecologic cancers to advance the field and improve outcomes for our patients.

Thank you





Innovations in Immune Oncology Combination Clinical Trial Designs

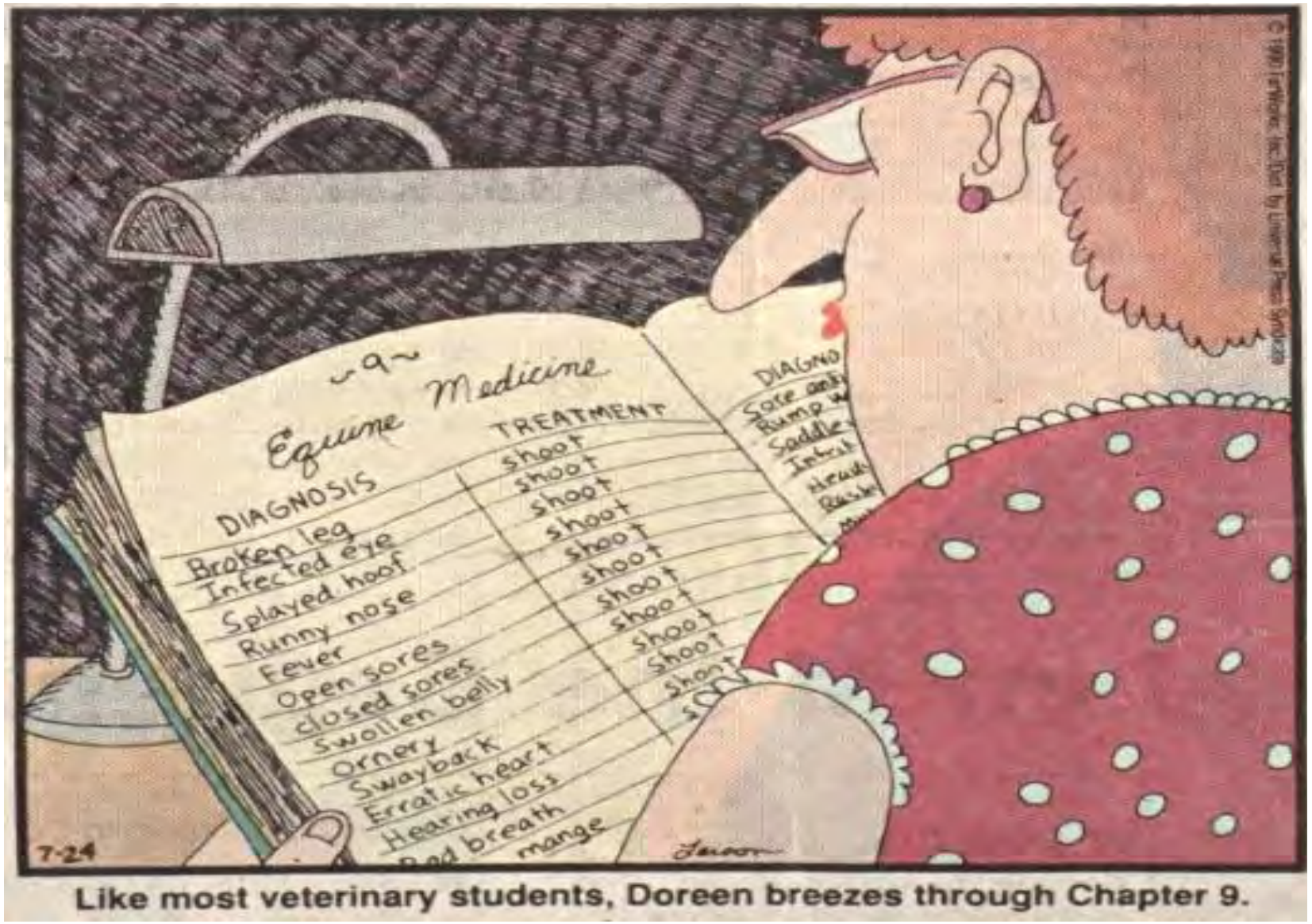
Robert L. Coleman, MD
M.D. Anderson Cancer Center
Houston, TX

Disclosures

- Research grant support from Roche/Genentech, Merck, Abbvie, Janssen, Genmab, Clovis, AstraZeneca, V-Foundation, Gateway Foundation, CPRIT

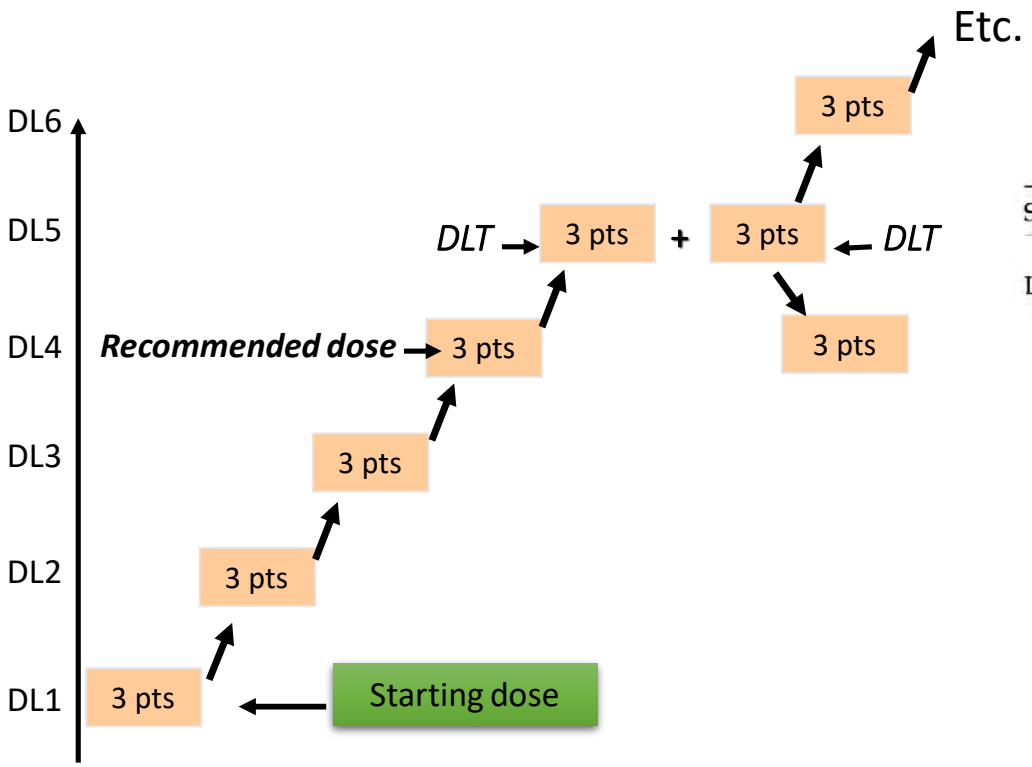
- Scientific Advisor/Steering Committee member to Roche/Genentech, Merck, Abbvie, Janssen, Genmab, Clovis, AstraZeneca, Gamamab, Immunogen, Tesaro

Clinical Studies – Traditional Options



Like most veterinary students, Doreen breezes through Chapter 9.

Phase I: ”3+3” Mantra…



Eisenhauer et al.

DRUG A dose and MTD set at 25%

Scenario		Dose	100	200	300	400	500	600	None
L2		True p_{TOX}	.01	.09	.26	.47	.64	.76	–
	BLR	% MTD	0	21	72	6	0	0	0
		#Pats	0.2	11.3	20.5	3.7	0.4	0	
	CRM	% MTD	0	16	**79**	5	0	0	0
		#Pats	0.9	10.0	21.7	3.2	0.2	0	
	3+3	% MTD	8	43	**41**	7	0	0	1
		#Pats	3.3	4.8	4.9	2.5	0.4	0	

Thall, Int J Gynecol Cancer

BLR: Bayesian logistic regression
CRM: Continuous reassessment model

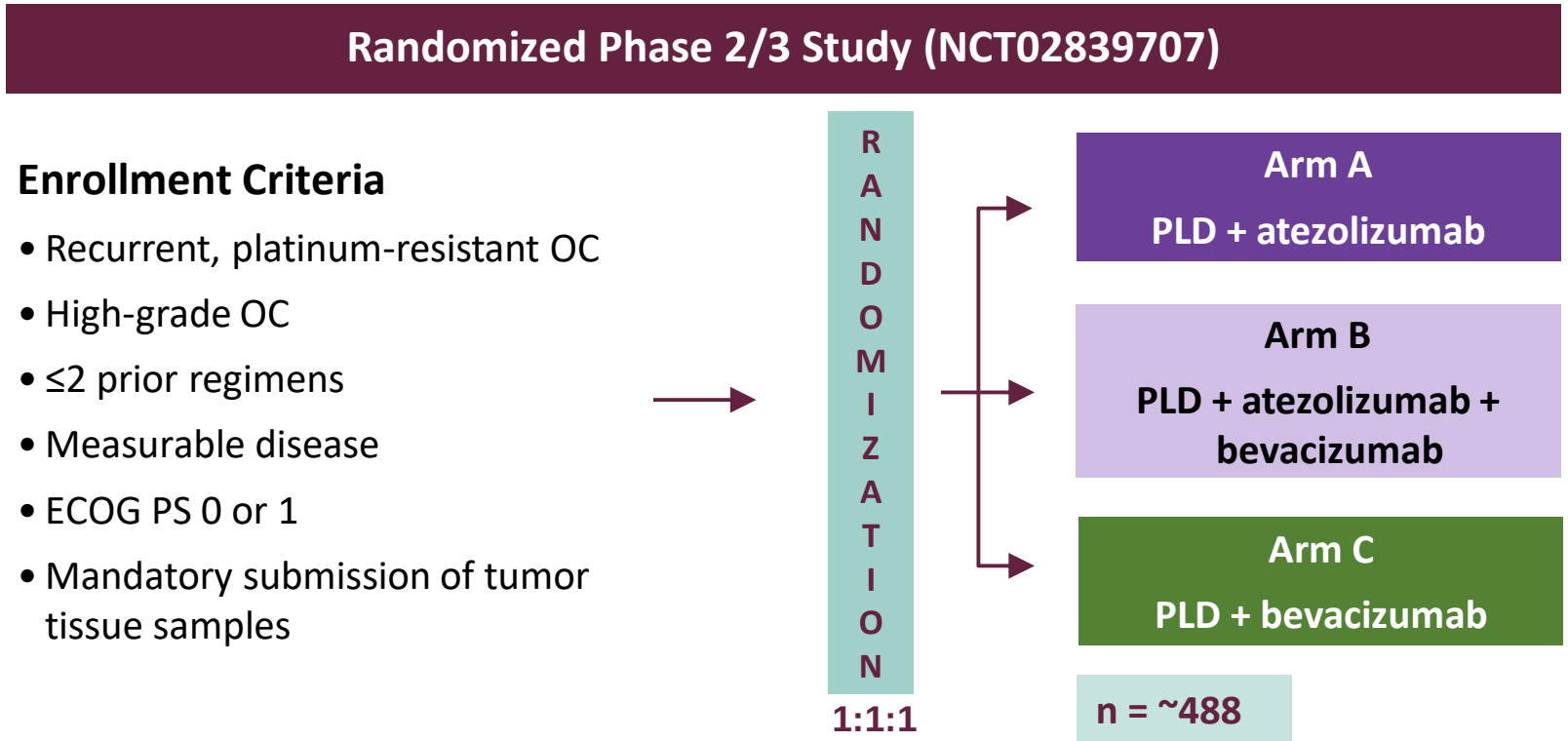
Two Agents: More Complicated (Arbitrary?)

Dose Level	Olaparib Dose	AZD2014 Dose
1	100mg BID	25mg BID continuous
2	200mg BID	25mg BID continuous
3	200mg BID	50mg BID continuous
4	300mg BID	25mg BID continuous
5	300mgBID	50mg BID continuous

Dose Level	Olaparib Dose	AZD2014 Dose
-1	100 mg BID	75 mg BID 2 days on/5 days off
1	100 mg BID	125mg BID 2 days on/5 days off
1b	100 mg BID	100mg BID 2 days on/5 days off
1c	200 mg BID	100mg BID 2 days on/5 days off
1d	300 mg BID	100mg BID 2 days on/5 days off

"Octopus" Trial; PI: Shannon Westin

NRG-GY009: PLD With Atezolizumab and/or Bevacizumab in

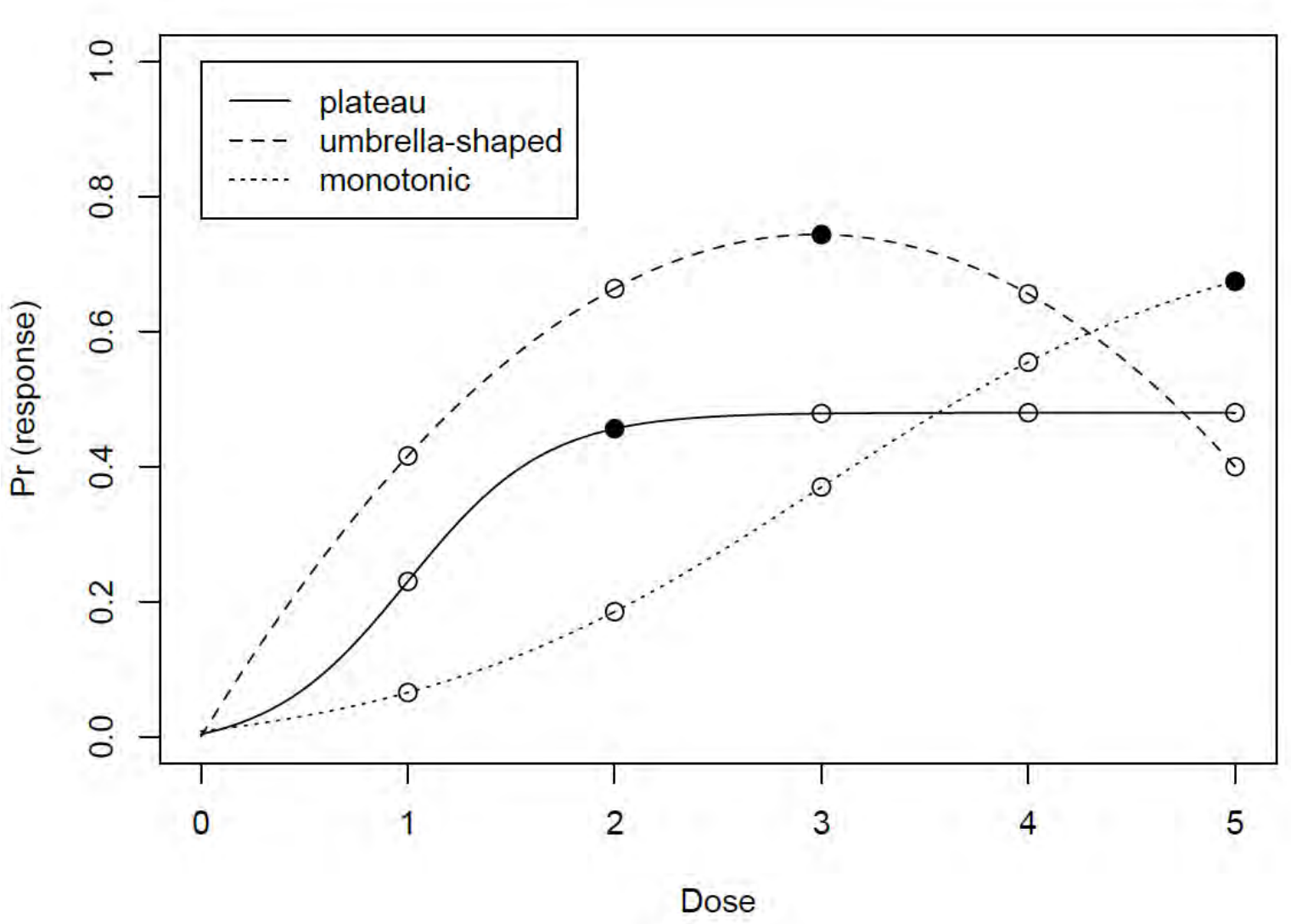


- ARM A: Patients receive PLD IV on day 1 and atezolizumab IV on days 1 and 8
- ARM B: Patients receive PLD IV on day 1, bevacizumab IV on days 1 and 8, and atezolizumab IV on days 1 and 8
- ARM C: Patients receive PLD IV on day 1 and bevacizumab IV on days 1 and 8
- In all arms, courses repeat every 28 days in the absence of disease progression or unacceptable toxicity

DLT, dose-limiting toxicity; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin.

Clinicaltrials.gov. Accessed October 11, 2016.

Non-Monotonic Dose-Efficacy Relationship



Courtesy of Y. Yuan

Challenges of Clinical Trial Design: Immunotherapy

- Dose – Response relationship may break down
  - More = or ≠ better
- Efficacy endpoints may not be immediate or may be realized in subsequent lines of therapy
  - Can objective response be used?
- Combination IO trials have difficult attribution/mitigation strategies
  - “Who dunnit?”
  - Dose reductions?
- Unclear if duration of exposure is important for efficacy

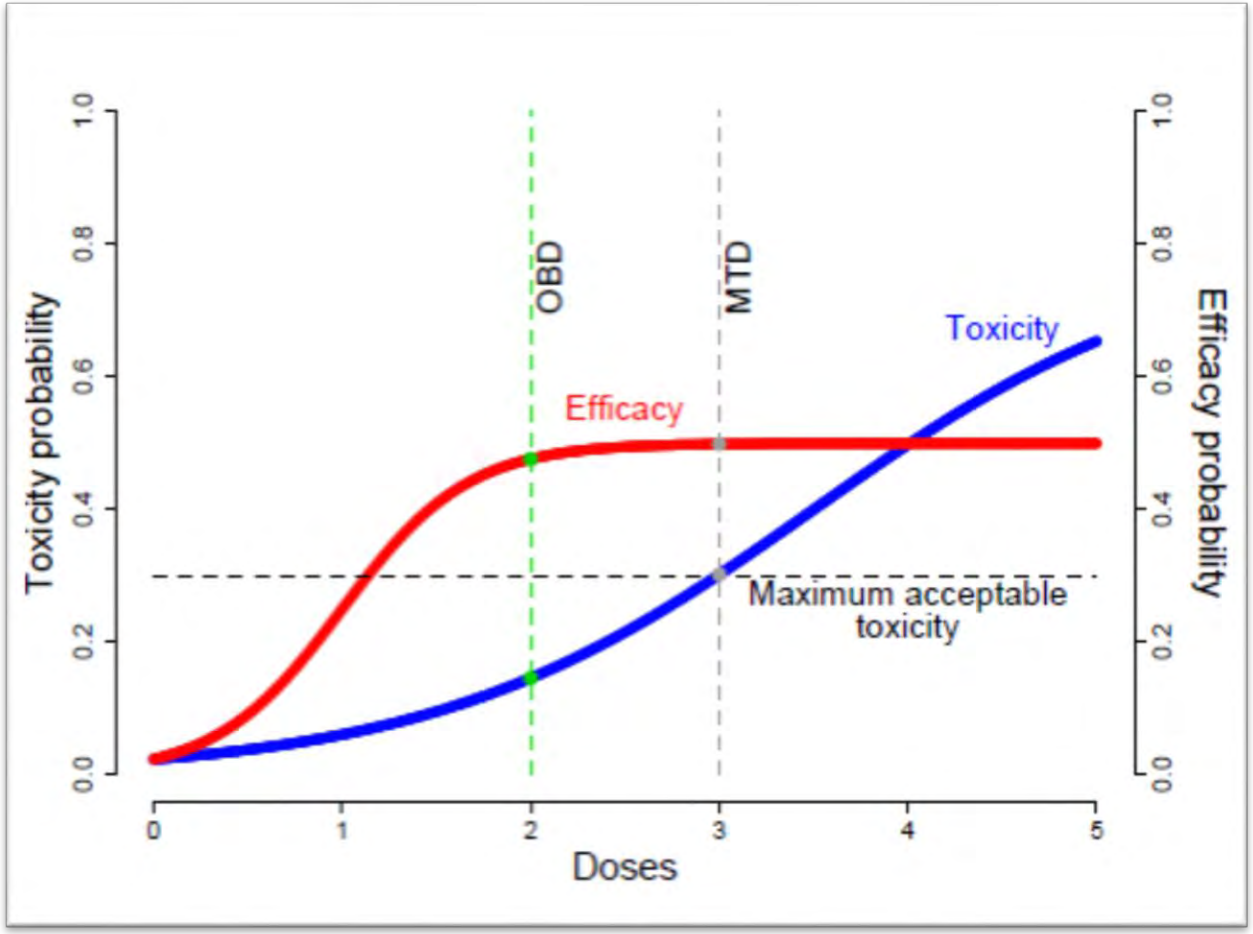
AE Management: Immunotherapy

Treatment-related Adverse Event	Grade of Event	Management/ Next Dose for *Nivolumab monotherapy (for patients who required discontinuation of ipilimumab)*	Management/Next Dose for *Combination Nivolumab plus Ipilimumab*
Neutropenia	≤ Grade 1	No change.	No change.
	Grade 2	Hold nivolumab until < Grade 2.	Hold both drugs until < Grade 2.
	Grade 3	Hold nivolumab until < Grade 2.	Hold both drugs until < Grade 2.
	Grade 4	Off protocol therapy.	If event continues >7 days, permanently discontinue ipilimumab

DART trial

Phase I-II Design Paradigm: Immunotherapy

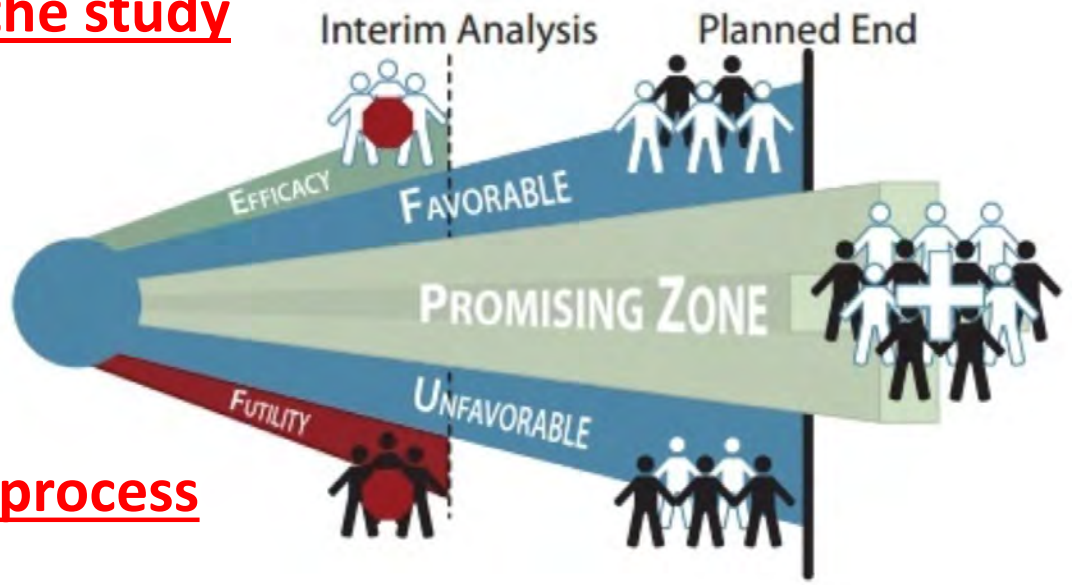
- It is imperative to consider efficacy and toxicity simultaneously, aka “phase I-II trial”.
- The primary objective of the phase I-II trial for immunotherapy is to find the optimal biological dose (OBD), rather than the maximum tolerated dose (MTD)

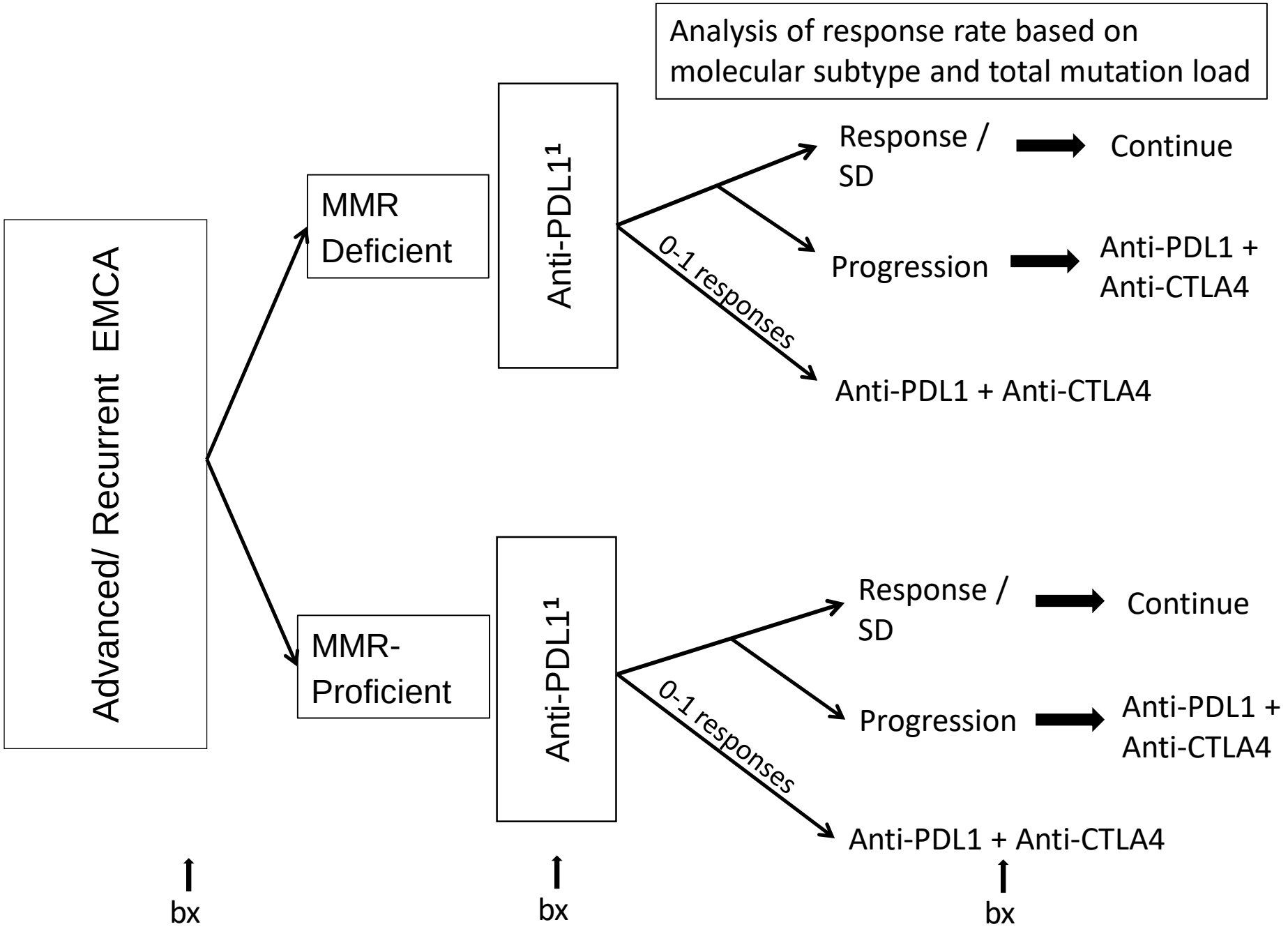


Efficacy-Driven Trial Design: Immunotherapy

Adaptation – How To Measure

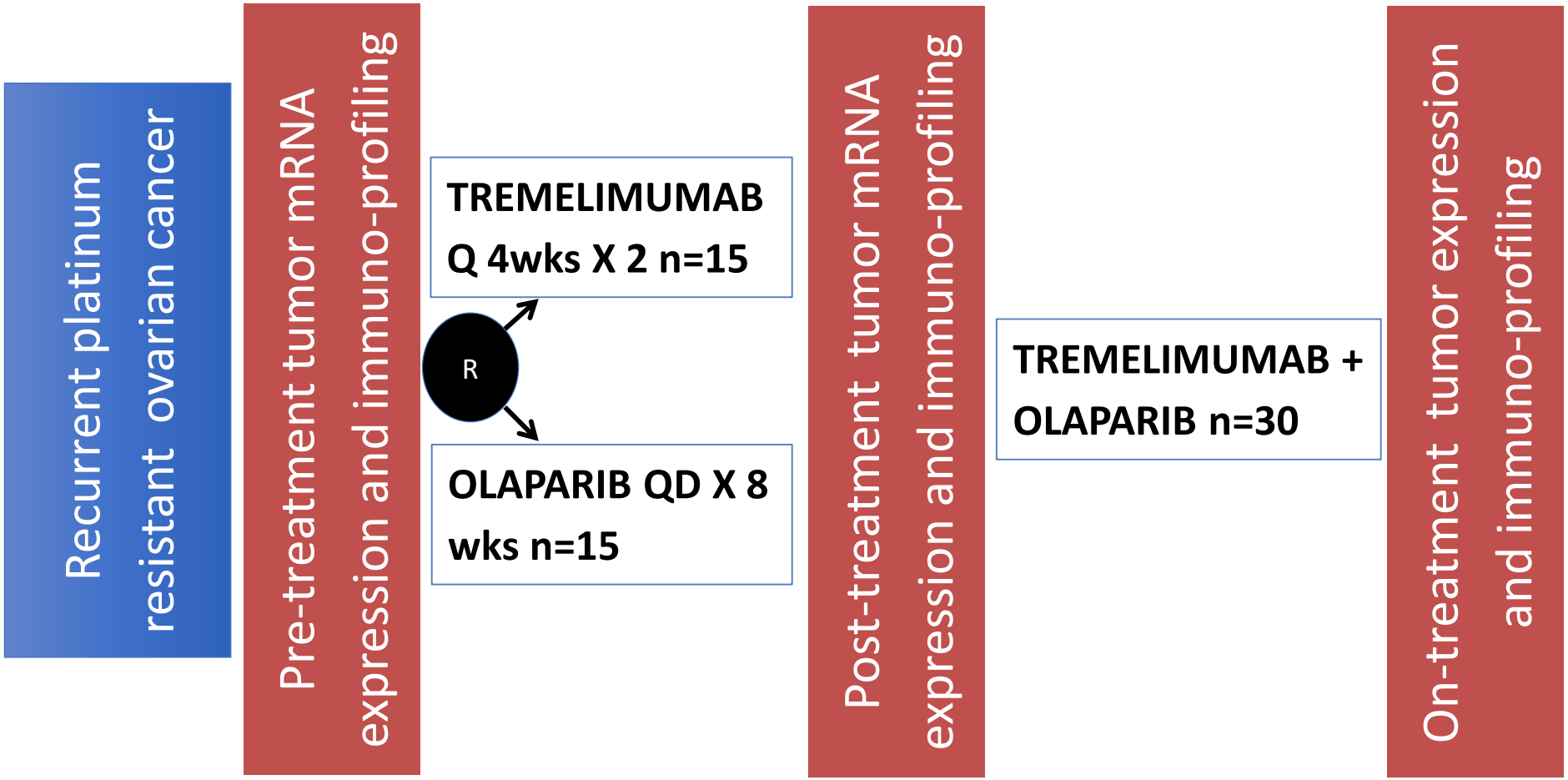
- Allows assessment of response to treatment **while the study is running**
- Can incorporate new findings from outside the trial
  - Redefine populations for study inclusion or exclusion
  - Incorporate new biomarker information
- Investigators can alter aspects of the study **while in process**
  - Add additional cohorts
  - Modify treatment schedule or dose
  - Redefine treatment for specific population needs
- This allows the trial to stay current with the latest updates



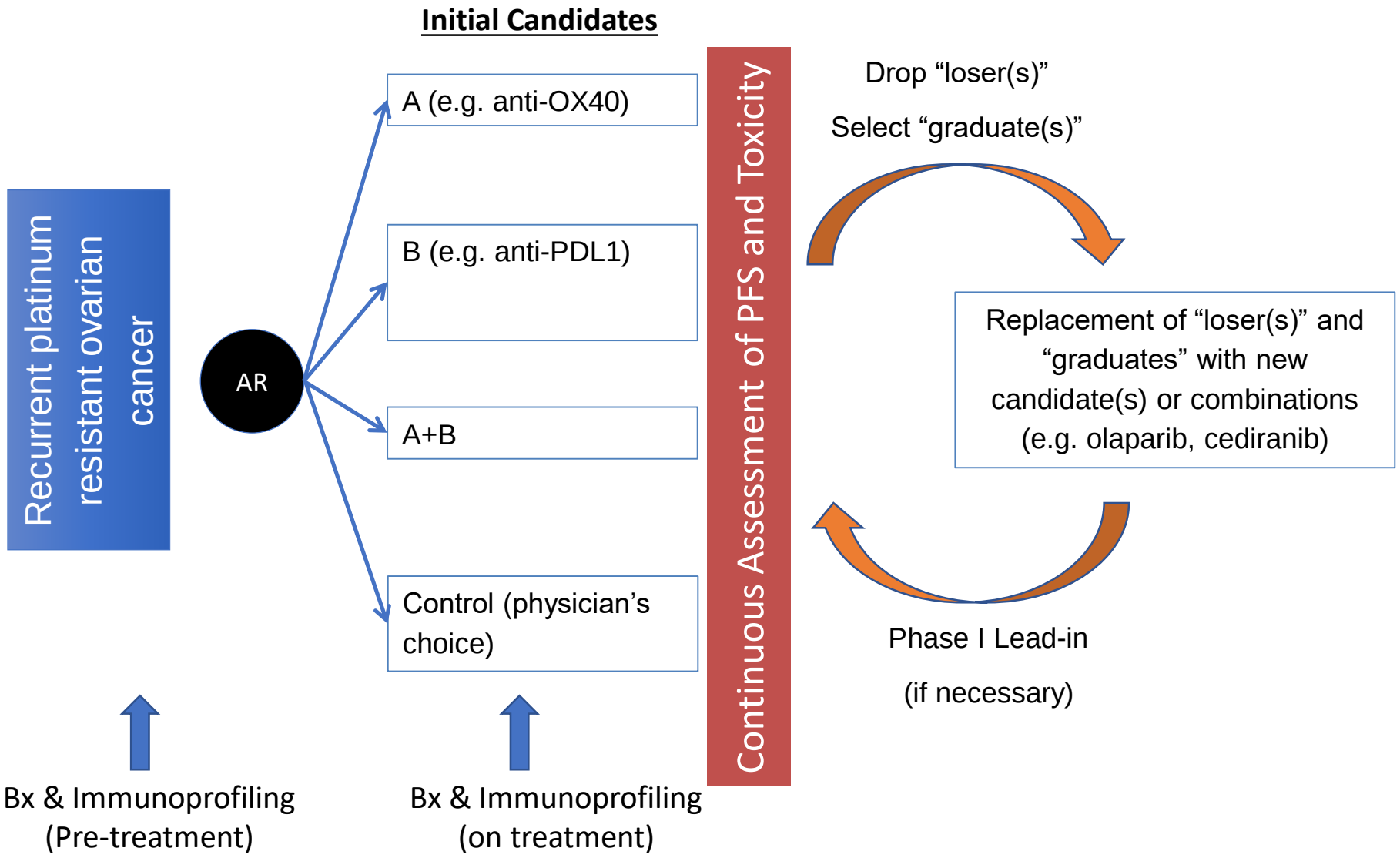


1 If zero or one responses in the first 9-10 patients, subsequent subjects will be treated with combination

Combination Biomarker + Phase II



Multi-candidate Iterative Design with Adaptive Selection (MIDAS)



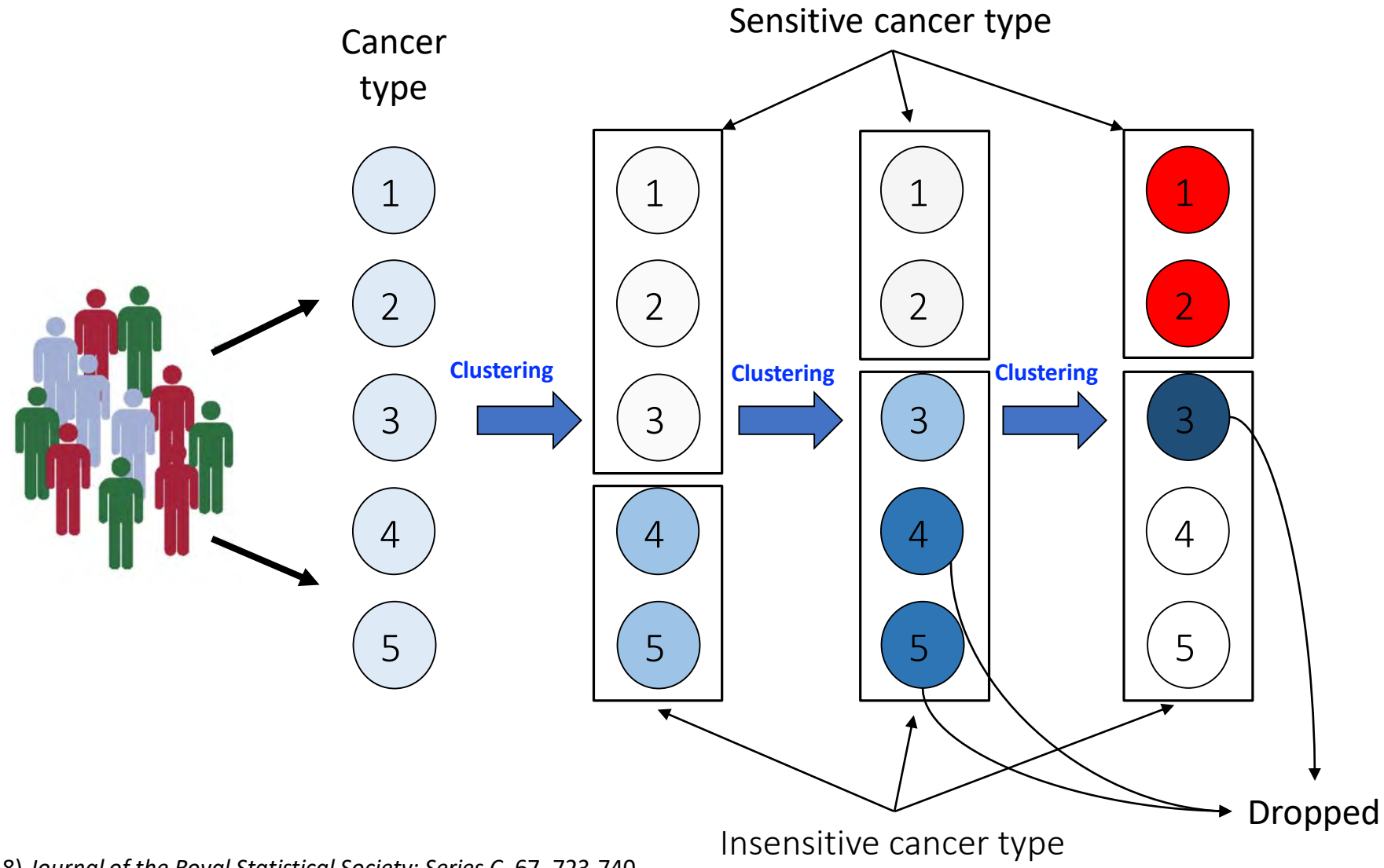
Yuan, Y., Guo, B, Munsell, M., Lu, K. and Jazaeri, A. (2016) *Stats Med*, 35, 3892-3906.

Bayesian Platform Design: MIDAS

Agent	Hazard Ratio	True toxicity rate	Entry Time (Months)	Percentage of			Number of patients
				Dropped due to toxicity	Dropped due to futility	Graduation	
				Scenario 1			
Control	1.00	0.15	0.0	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	44.5 (81.0)
1	0.83	0.03	0.0	0.0 (0.0)	69.4 (68.8)	30.6 (31.2)	19.1 (13.2)
2	0.56	0.04	0.0	0.0 (0.4)	33.8 (41.8)	66.2 (57.8)	24.3 (15.0)
3	0.42	0.03	0.0	0.0 (0.2)	13.6 (24.2)	86.4 (75.6)	25.2 (16.3)
4	1.25	0.05	9.3	0.4 (0.2)	90.9 (90.2)	8.7 (9.6)	14.3 (10.5)
5	1.67	0.04	12.7	0.1 (0.4)	97.1 (96.8)	2.8 (2.8)	12.0 (9.2)
6	2.50	0.04	16.3	0.0 (0.2)	100.0 (99.6)	0.0 (0.2)	10.7 (8.5)
7	2.50	0.03	19.5	0.2 (0.0)	99.3 (99.8)	0.5 (0.2)	11.0 (8.5)

Yuan, Y., Guo, B, Munsell, M., Lu, K. and Jazaeri, A. (2016) *Statistics in Medicine*, 35, 3892-3906.

Adaptive Basket Trial Design: BLAST

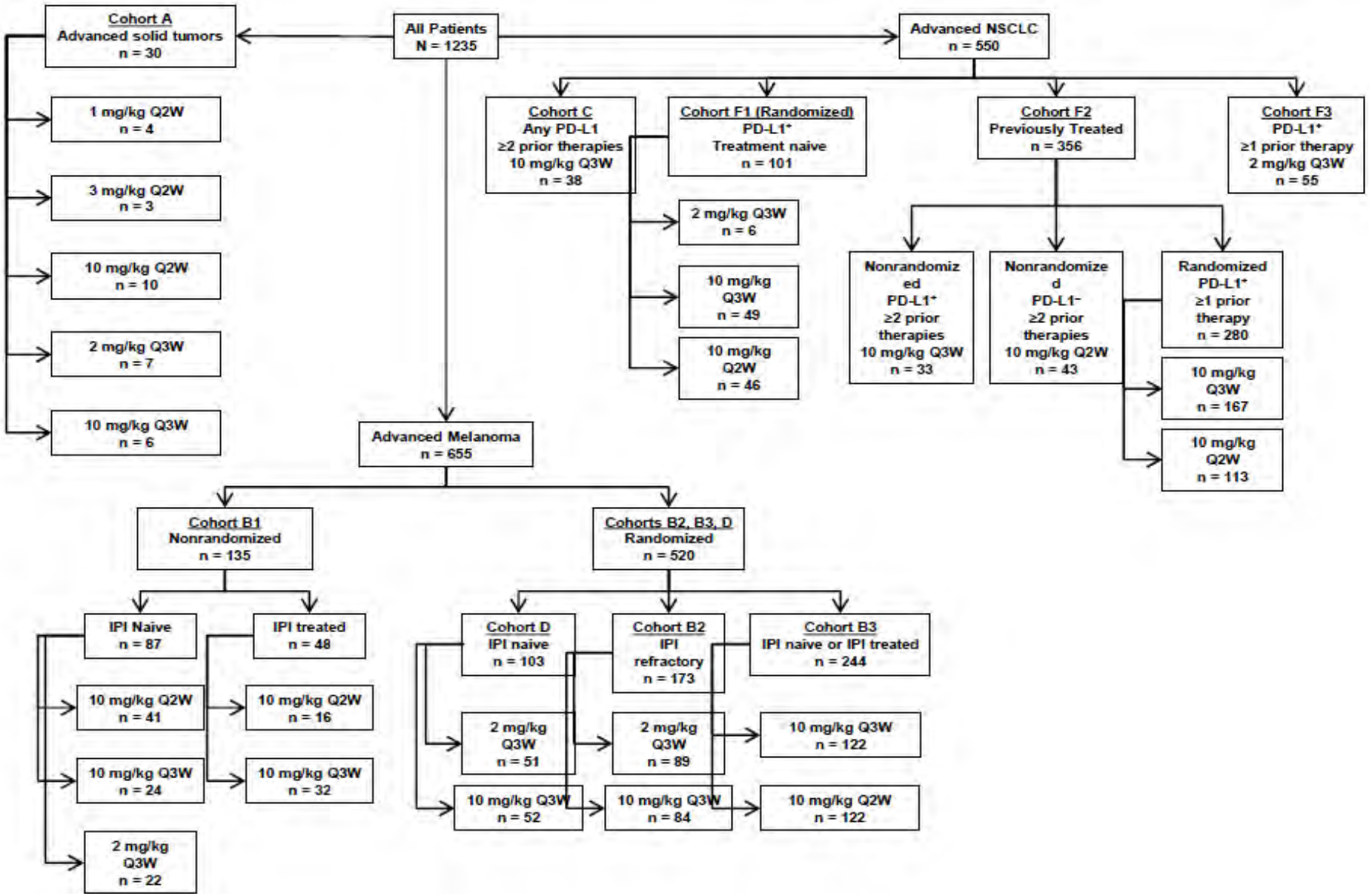


Chu, Y and Yuan, Y. (2018) *Journal of the Royal Statistical Society: Series C*, 67, 723-740.

KEYNOTE (KN-001): Pembrolizumab Trial

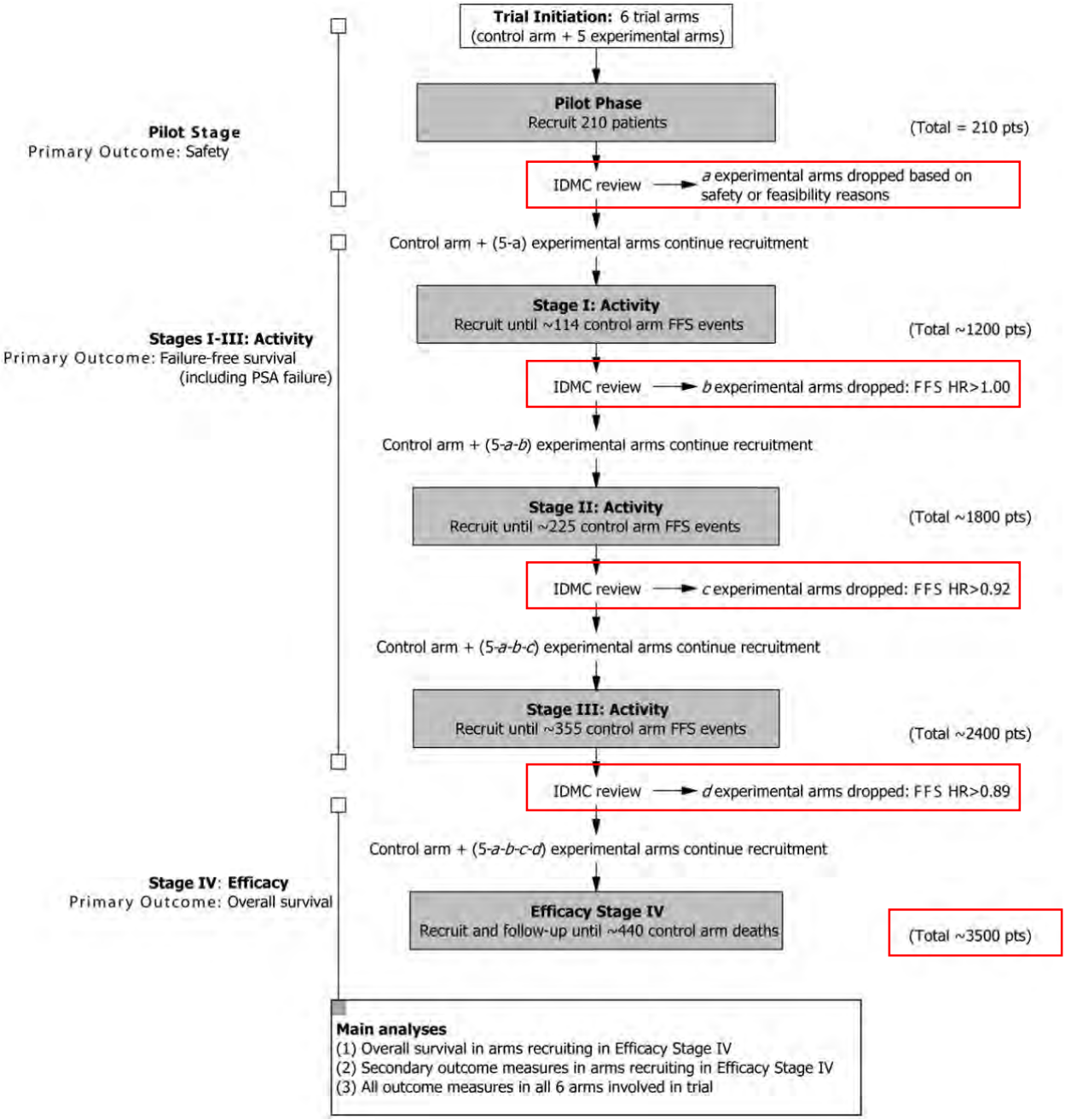
- Phase I in “advanced solid tumors” (n=40)
  - Showed high efficacy in melanoma
- Added expansion cohorts:
  - Non–small cell lung cancer
  - Testing lower doses in NSCLC and melanoma
  - To provide training and validation sets for the PD-L1 biomarker expression test
  - More disease cohorts were added as more information was collected
- Incorporated aspects of:
  - Basket trial design: different diseases
  - Umbrella trial design: biomarker variability, variable prior therapies within disease cohorts
  - Adaptive trial design: additional cohorts, different dosing
- Ultimately enrolled 1260 patients
- FDA approval (melanoma) 3.5 years after study initiation without a randomized, controlled trial
  - Other data from the study has led to approval in NSCLC, head and neck cancer, Hodgkin lymphoma, urothelial carcinoma, MSI-high cancer, and gastric cancer

KN-001: Pembrolizumab Seamless Design Study



STAMPEDE Trial: Advanced Prostate

- Outcomes:
  - Pilot: toxicity
  - Stage I: PFS (HR ≤ 0.75)
  - Stage II: PFS (HR ≤ 0.75)
  - Stage III: PFS (HR ≤ 0.75)
  - Stage IV: OS (HR ≤ 0.75)
- Overall analysis: pairwise with multiple comparisons correction ($p < 0.017$)



Take Home Messages

- Clinical trial designs based on dose to response relationships provide poor guidance for immunotherapy
- Multiagent biological trials are tricky to conduct and best leverage existing and emerging information to optimize OBD identification
- Adaptive designs are most efficient for constructing the dose-toxicity trade-offs
- Seamless designs can develop information for regulatory intent

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American Association for Cancer Research

FINDING CURES TOGETHER℠

Society of Gynecologic Oncology

SESSION II Panel Discussion:

Development of Immunotherapy in Gynecological Malignancies – Part 2

Moderators: Julia A. Beaver, MD, and Rebecca Arend, MD

Panelists:

Geoffrey S. Kim, MD

Mary J. Scroggins, MA

Amir A. Jazaeri, MD

Robert L. Coleman, MD, FACOG, FACS

Rajeshwari Sridhara, PhD

U.S. FOOD & DRUG ADMINISTRATION

American Association for Cancer Research

FINDING CURES TOGETHER℠

Society of Gynecologic Oncology

SESSION III:

Biomarker Development and PARP Inhibitors

Session Cochairs: Deborah K. Armstrong, MD, and Robert L. Coleman, MD, FACOG, FACS

Speakers:

Gwynn Ison, MD

Alan D'Andrea, MD

Gordon B. Mills, MD, PhD

U.S. FOOD & DRUG ADMINISTRATION

FDA Perspective:

Evolving Development of Parp Inhibitors

Gwynn Ison, MD

June 14, 2018

- I have no financial relationships to disclose
- I will not discuss off label or investigational use of products in my presentation

Outline

- Regulatory background/basics
  - Regulatory approvals
  - Diagnostics
- PARP overview
  - Approvals
- Next steps-
  - Combinations
  - Other gyn malignancies/ other biomarkers?

FDA approval types

- **Regular approval*** based on endpoints that demonstrate that a drug provides longer life, better life, or favorable effect on an established surrogate for longer life or better life.
  - Requires substantial evidence from adequate and well-controlled trial(s).
- **Accelerated approval (AA)** based on surrogate endpoint reasonably likely to predict clinical benefit.

*21 CFR Part 314.126

Accelerated approval

- AA regulations* allow for approval of an agent appearing to provide benefit over available therapy for serious, life-threatening diseases
- Under AA, advantage based on effect on surrogate endpoint reasonably likely to predict clinical benefit, such as response rate, or endpoint measured earlier than irreversible morbidity or mortality
- AA granted instead of regular approval because of uncertainty about ultimate patient outcome.
- Additional trial to confirm clinical benefit required and should be underway at time of AA since surrogate is not direct measure of benefit

*21 CFR, Part 314.510, 21 CFR, Part 601.41

FDA PARP approvals: Summary

	Treatment		Switch maintenance
Line of therapy	4th line	3rd line	≥ 2 prior platinum based
Agents and approval date	Olaparib (12/2014)	Rucaparib (12/2016)	Niraparib (3/2017) Olaparib (8/2017) Rucaparib (4/2018)
Population	gBRCAmut	tBRCAmut	Platinum-sensitive recurrent
Approval type	Accelerated	Accelerated	Regular
Diagnostic	Companion diagnostic	Companion diagnostic	Complementary diagnostic

Companion vs. "Complementary" diagnostic

- Companion- a medical device or test, often an *in vitro* device, provides information **essential** for safe and effective use of a drug or biologic
- Complementary*- a medical device or test that identifies a biomarker-defined subset of patients with a different therapeutic product effect, but does not restrict patients from use of a therapy based upon test result.

***THIS IS NOT AN OFFICIAL DEFINITION**

Companion vs. "Complementary": The Case of BRACAnalysis CDx

- **Olaparib 4th line**
  - **12/19/15**
- Supporting trial only studied BRCAm patients
- **Companion Dx** required; part of drug indication
  - **Example**- Used to identify ovarian cancer patients with del gBRCAm, who may be eligible for treatment with olaparib

- **Niraparib maintenance**
  - **3/27/17**
- Supporting trial enrolled BRCA and non-BRCA
- **Complementary Dx** does not restrict use of drug but may guide use
  - **Example**- Detection of gBRCA variants using the test may predict for patients who may have enhanced PFS in association with niraparib maintenance

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What next?

- Improve upon current data:
  - **PARP combinations?**: cedarinib, bevacizumab, PD-1/PD-L1 agents

Combinations

- 21 CFR 300.50-
  - Two or more drugs may be **combined** (in a single dosage form) when **each component makes a contribution to the claimed effects** and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug.

Criteria for Codevelopment

- Intended to treat serious disease or condition
- **Strong biologic rationale** for the combination
- Nonclinical model or limited clinical study
  - suggests substantial activity of the combination
  - provides greater than additive activity or more durable response
- Compelling reason for not developing agents individually
  - Rapid resistance with monotherapy (antivirals)
  - One or both agents with very limited activity as monotherapy

Codevelopment Caveats

- Intended to address 2 or more drugs not previously developed for any indication to be used in combination to treat a disease or condition
- Assess the contribution of each component in addition to the combination
- Less information about safety and effectiveness than if individual drugs were developed; how much less will depend on stage of development
- Inherent risk compared to individual development of a drug

Additional Caveats

- No fixed duration/ Δ for PFS/OS improvement
- No fixed ORR
  - Historical controls for comparison may be acceptable
- RISK:BENEFIT is key

What next?

- Improve upon current data:
  - **PARP combinations?**: cedarinib, bevacizumab, PD-1/PD-L1 agents
  - Comparing PARP inhibitors head-to-head?
  - PARP in front line ovarian cancer (SOLO1).
  - Other biomarkers (beyond BRCA and HRD) to predict response?
  - Exploratory subgroups (bulky vs. non-bulky)?
  - **PARP in other malignancies** (Other gynecologic malignancies)?

Parp in other malignancies?

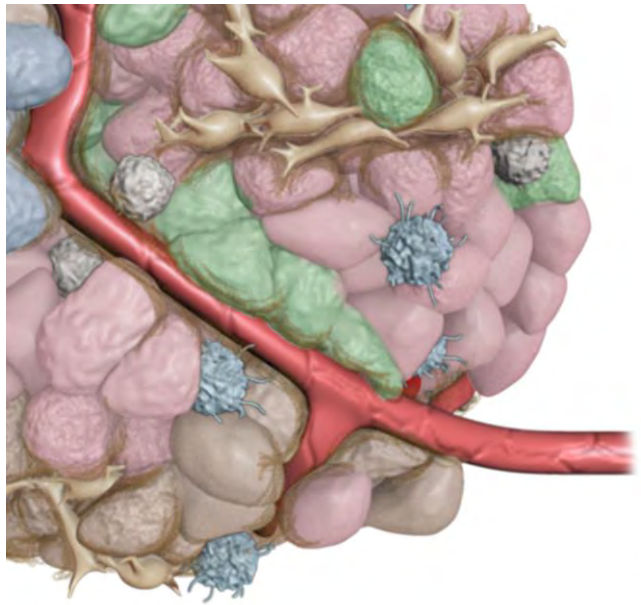
- Olaparib approved Jan 2018 for use in HER2-negative metastatic breast cancer patients with gBRCAm who had received prior chemotherapy and appropriate endocrine therapy for hormone receptor positive cancers.
- Tissue agnostic?

References

- 21 CFR, Part 314.510
- 21 CFR, Part 601.41
- FDA Guidance for Industry: Expedited Programs for Serious Conditions- Drugs and Biologics, May 2014
- FDA Guidance for Industry: Codevelopment of Two or More New Investigational Drugs for Use in Combination, June 2013

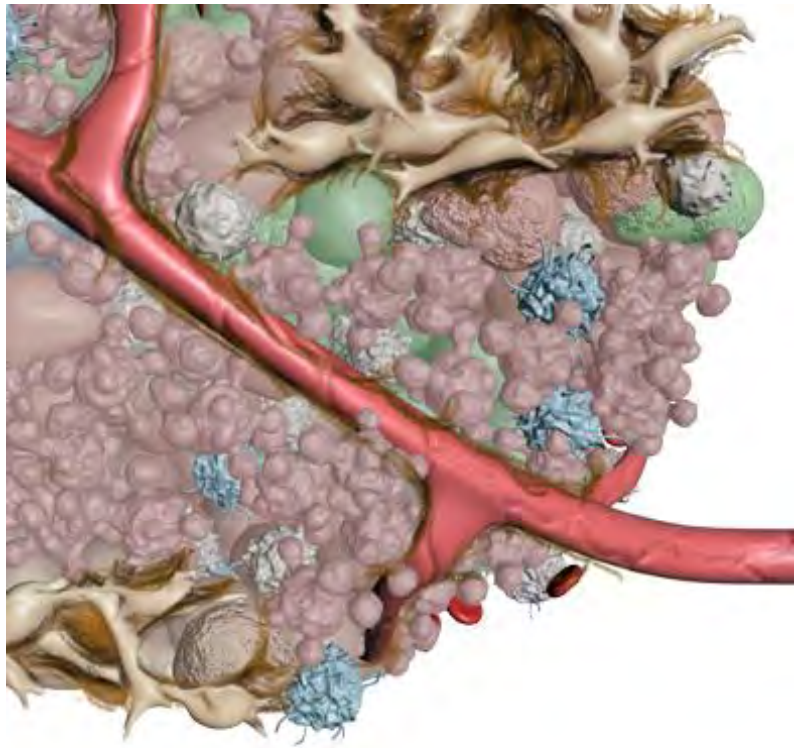
Acknowledgments

- Sanjeeve Balasubramaniam
- Julia Beaver
- Gideon Blumenthal
- Hisani Madison



Extending the utility of PARP inhibitors

Gordon Mills
Knight Cancer Institute



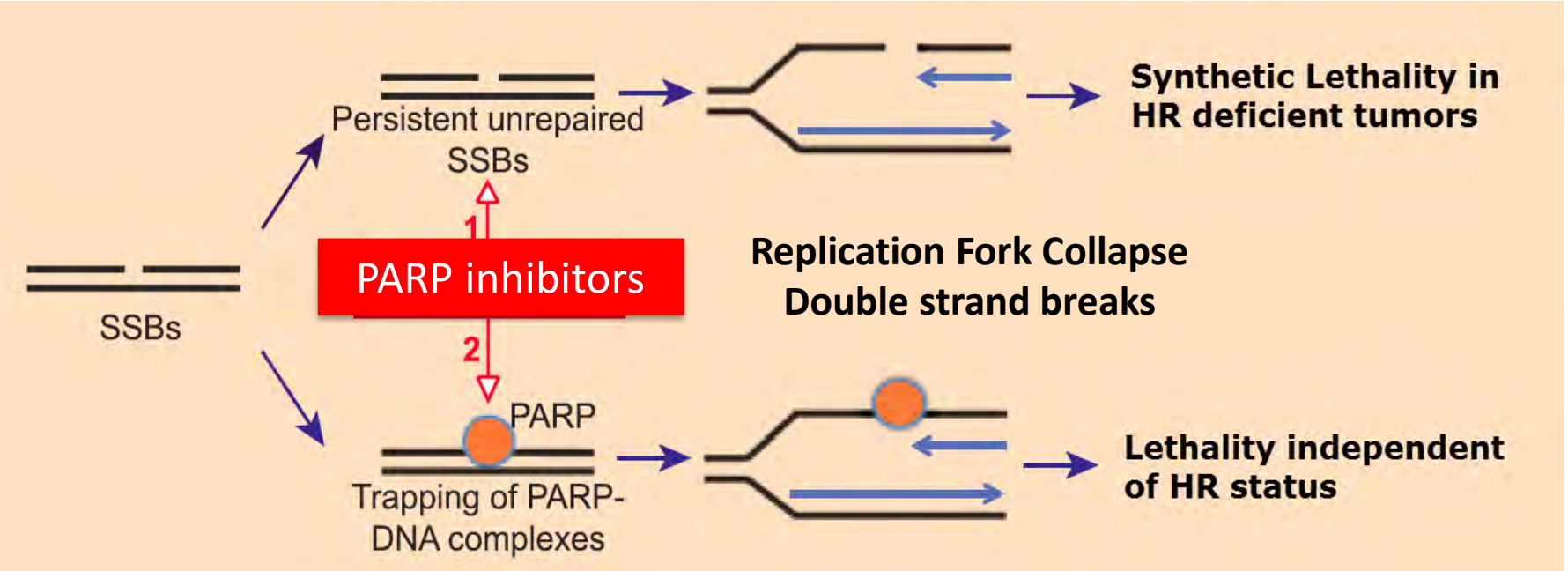
Rachel Davidowitz

POTENTIAL CONFLICT OF INTEREST DISCLOSURES

- **Financial Relationships**
  - **SAB/Consultant:** AstraZeneca, Catena Pharmaceuticals, Critical Outcome Technologies, ImmunoMET, Ionis, Medimmune, Nuevolution, Pfizer, Precision Medicine, Signalchem Lifesciences, Symphogen, Takeda/Millennium Pharmaceuticals, Tarveda,
  - **Stock/ Options/Financial:** Catena Pharmaceuticals, ImmunoMet, SignalChem, Spindle Top Ventures, Tarveda
  - **Licensed Technology** HRD assay to Myriad Genetics
  - **Sponsored Research:** Abbvie, Adelson Medical Research Foundation, AstraZeneca, Breast Cancer Research Foundation, Critical Outcomes Technology, Illumina, Ionis, Immunomet, Karus Therapeutics, Komen Research Foundation, Pfizer, Nanostring, Takeda/Millennium Pharmaceuticals, Tesaro

I will discuss off label use and/or investigational use of drugs

Dual mechanisms of action of PARPi

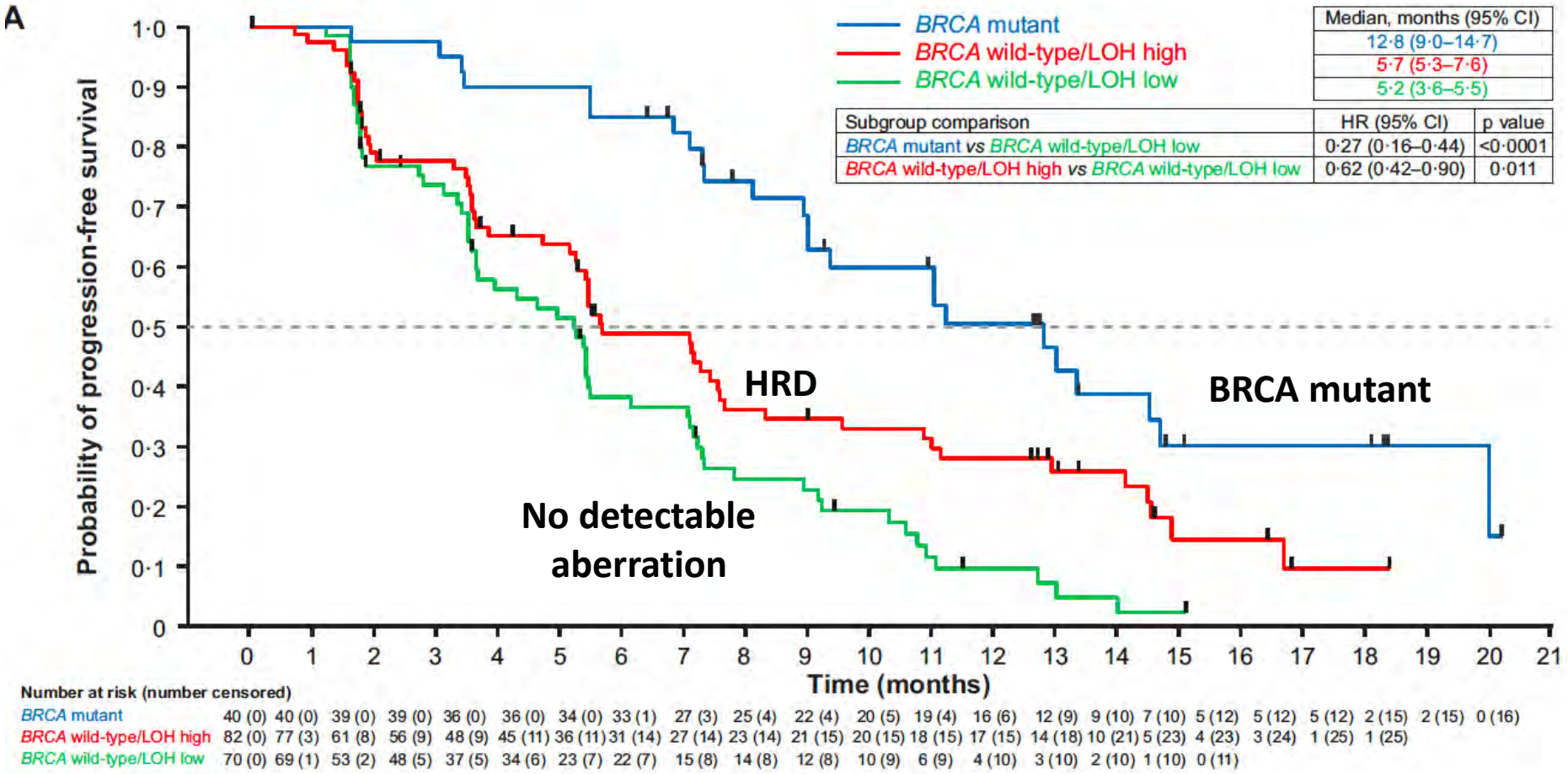


ADP ribosylation required for PARP to leave DNA

Trapped PARP creates "toxic" double strand breaks

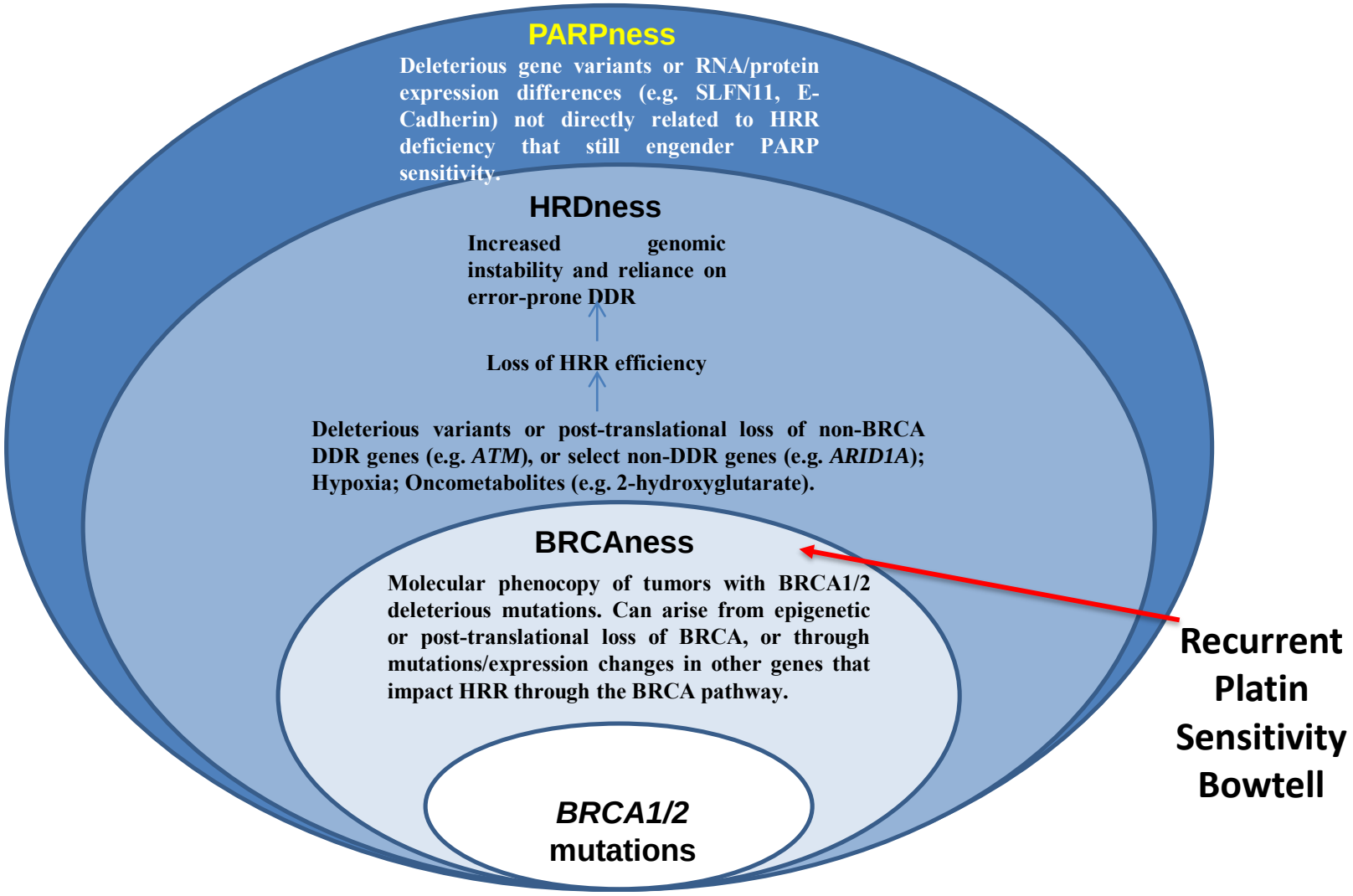
Can PARP activity be extended beyond HRD

PARP inhibitor responses are transient
Ariel 2 Rucaparib Ian McNeish Lancet:
LOH high is HRD assay performed by Foundation Med



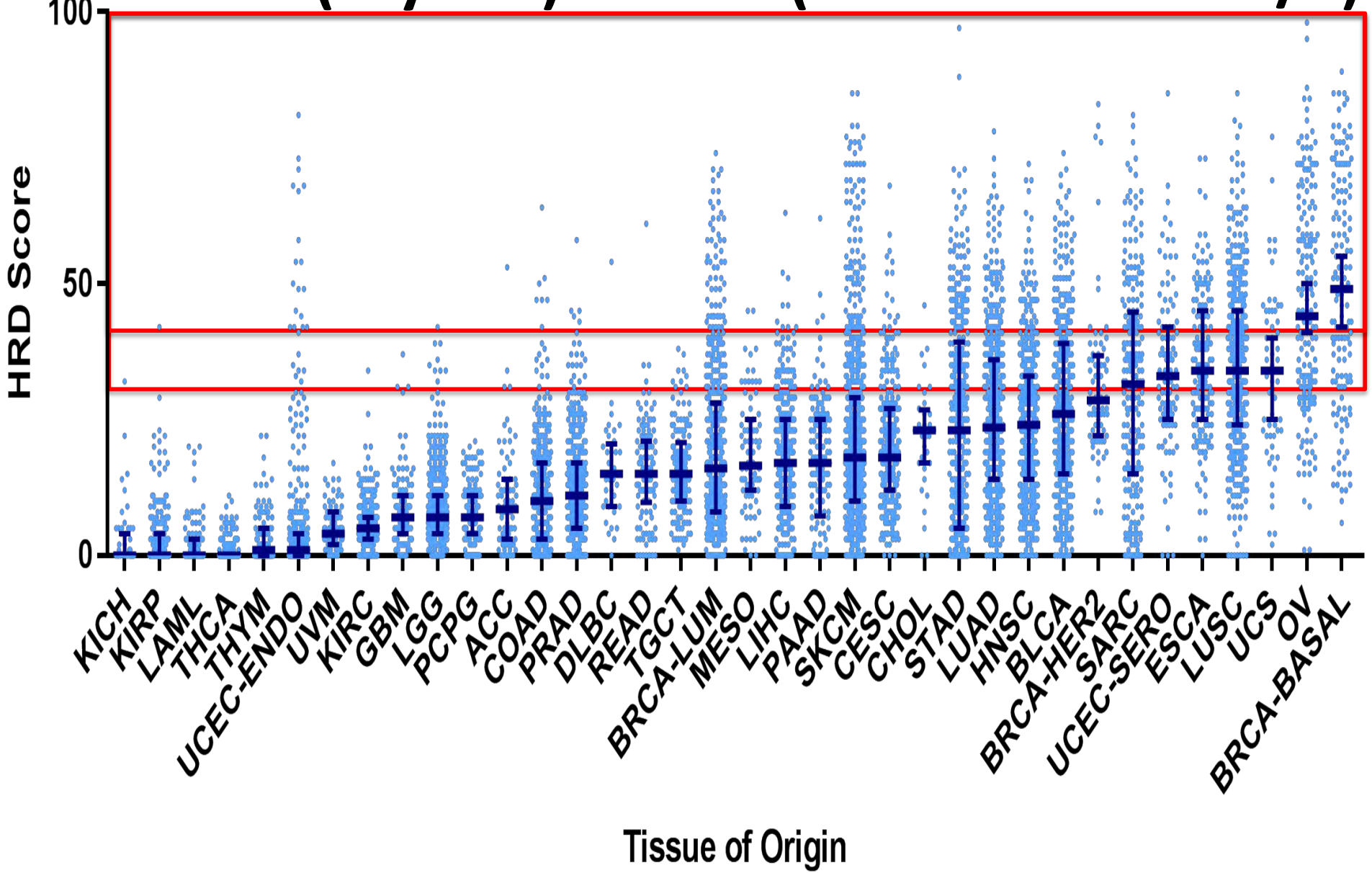
Conclusion: Germline BRCA1/2 is strongest predictor of benefit
HRD positivity identifies an additional population with significant benefit
A population of patients without HRD show modest benefit

Categorizing Predictive Biomarkers of Response for PARP inhibitors



Subpopulations of tumors are HRD

Cut off 42 (Myriad) and 31 (based on BRCA1/2)

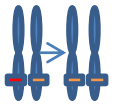


Classes of PARP inhibitor resistance

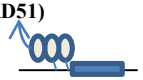
PARP Inhibitor Resistance

Restoration of HR Activity

DIRECT

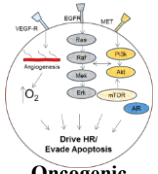


Reversion-to-WT mutations in HR genes and hypomorphic mutants (e.g. BRCA1/2, RAD51)



Promoter demethylation of HR genes

INDIRECT

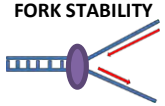


Oncogenic signaling driving HR gene activity.
53BP1 loss restoring HR activity.

Reconstitution of Rad51 foci
Healing of BRCA1/2 ,PALB2, Rad51C, Rad51D Demethylation of BRCA1/2 promoter
Upregulated hypomorphic mutant BRCA1/2 alleles
Loss of shield complex: 53BP1, RIF1, Rev7 (MAD2L2), FAM35A and C20orf196 complex

Mitigation of Replication Stress

FORK STABILITY



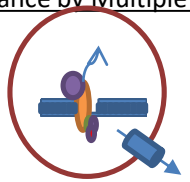
\+

CELL CYCLE CONTROL

Decreased proliferation with increased fork protections via mechanisms such as EZH2 loss , MLL3/4 loss, and/or increased dependence on ATR/CHK1.

Loss of MLL3/4 (PTIP and MUS81 effectors)
Loss of EZH2 (MRE11 nuclease effector),
Protects BRCA2 and not BRCA1
Decreased proliferation
BRCA2 and Rad51 but not BRCA1 play a role in replication fork protection

Resistance by Multiple Mechanisms



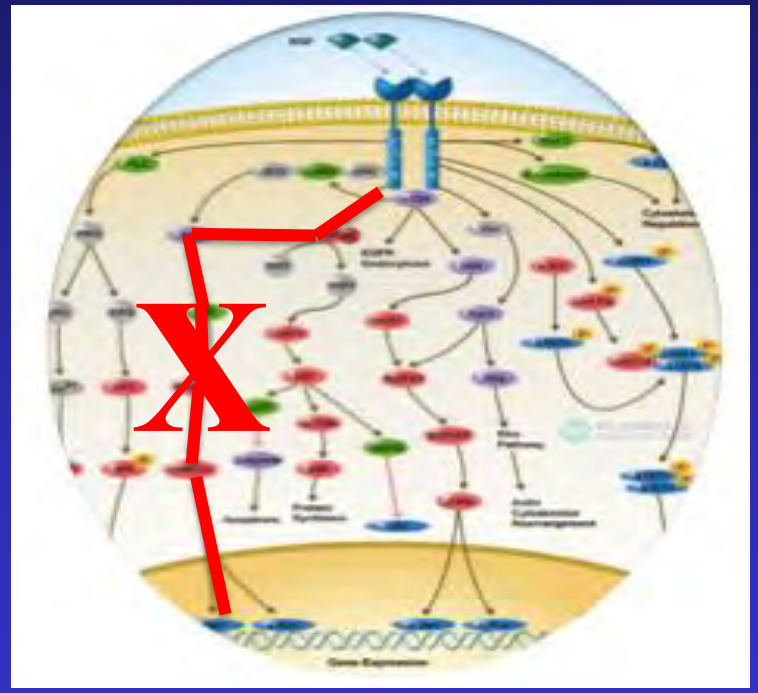
Mechanisms inherent to PARP, such as mutations in catalytic or drug binding domain.
Mechanisms that hinder PARylation and release PARP from DNA, such as PARG-mediated.
P glycoprotein /MDR/ABC drug efflux transporters.
Biomarkers of resistance of unknown mechanism include loss of SLFN11 and loss of EMT signature.

PARP loss
PARP mutations:
PARG reverses ADP ribosylation of PARP and releases PARP from DNA
P glycoprotein/MDR/ABC transporters overexpression and fusions
SLFN11 loss
EMT

Rational combinatorial therapy will be required to fulfill the promise of targeted therapy

Systems are robust to individual perturbations but are susceptible to multiple perturbations Yossi Yarden and Arthur Lander

Interdict a critical pathway mediator



Mathematical modeling indicates that by chance during phylogeny many/most molecules in cell/organism will be blocked by mutation or environmental stress

Thus response to single targeted therapy is expected to be short and transient as observed!

Rational combinatorial therapy will be required to fulfill the promise of targeted therapy

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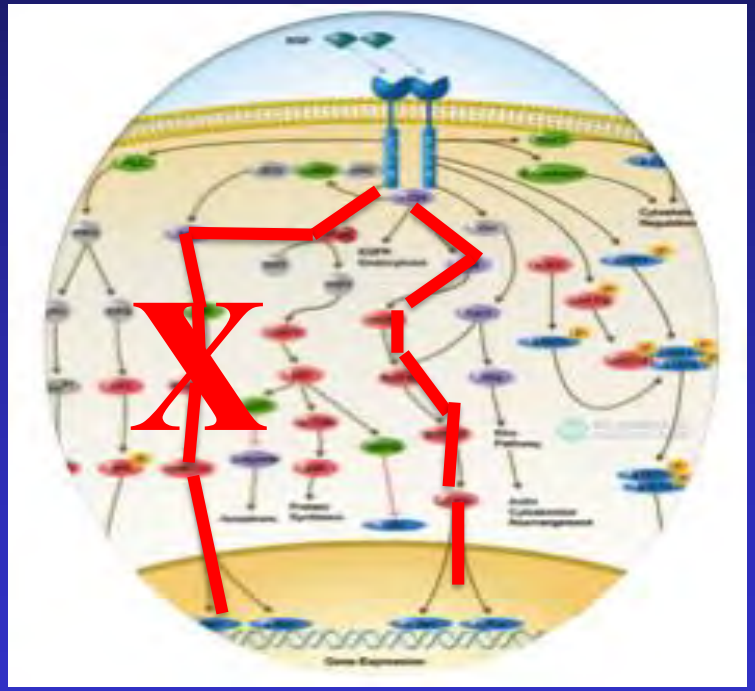
Cells adapt by using an alternative pathway

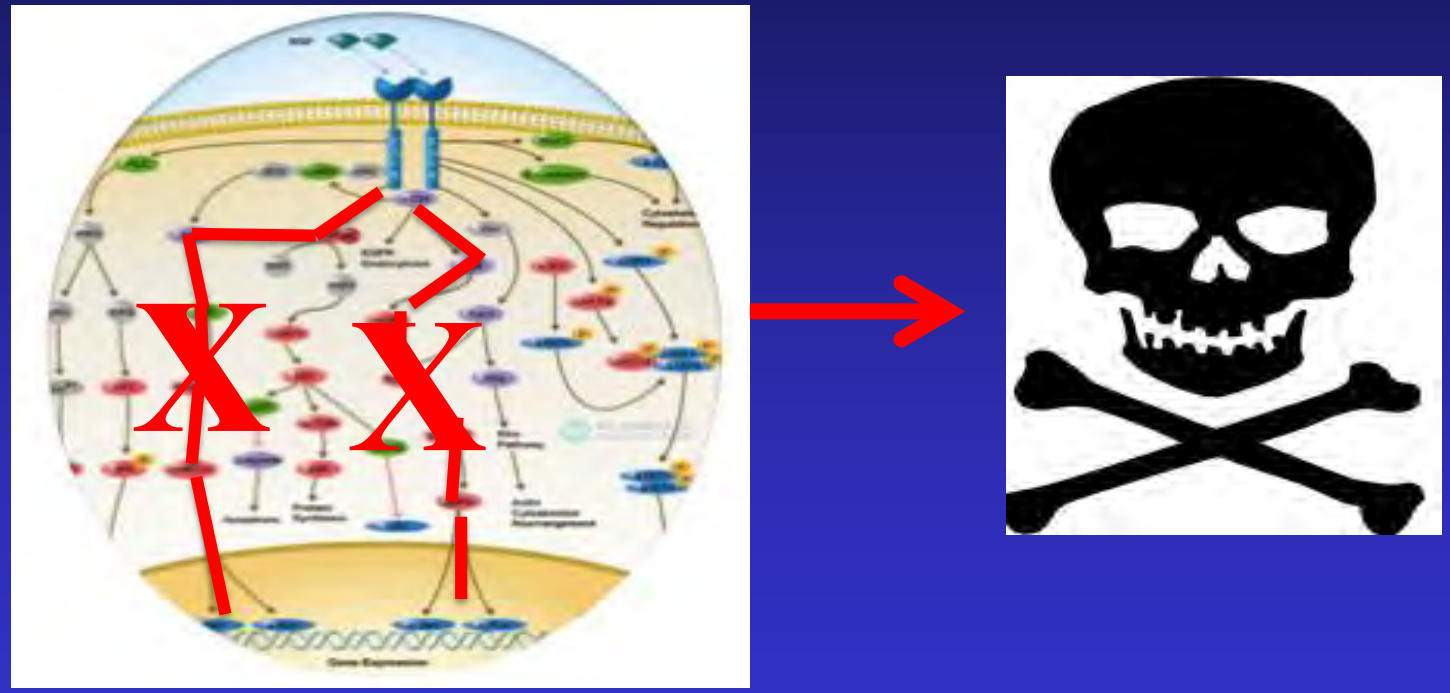


Chance that both the original target and the adaptive response will be “hit” randomly (mutation or environmental stress) is vanishingly low

Adaptation can occur at the protein level which is best assessed by post translational modification

Rational combinatorial therapy will be required to fulfill the promise of targeted therapy

Systems are robust to individual perturbations but are susceptible to multiple perturbations Yossi Yarden and Arthur Lander



Rational drug combinations will be required to convert transient responses into durable responses

A PLATFORM TO FACILITATE TARGETING ADAPTIVE RESISTANCE TO INCREASE UTILITY OF TARGETED THERAPEUTICS

Cells in 2D, 3D, in vivo, or patient tumors

↘

Add drug

Early time points: target engagement

Medium time points: adaptive responses

Late time points: genomic resistance

↘

Harvest cells for Omic analysis

DNA, RNA, protein, metabolomics

G. Gao

HUMAN PROTEOMICS ATLAS: RPPA

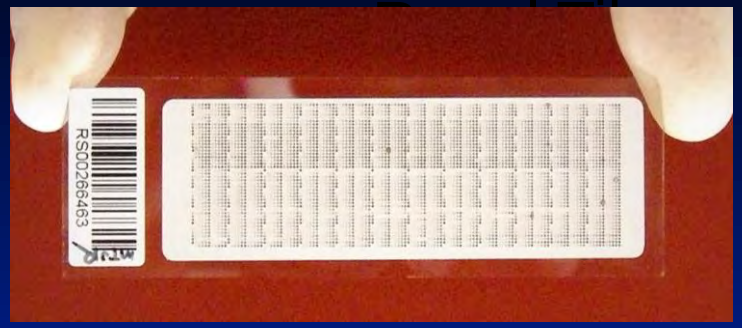
Quantitative high throughput multiplexed inexpensive ELISA

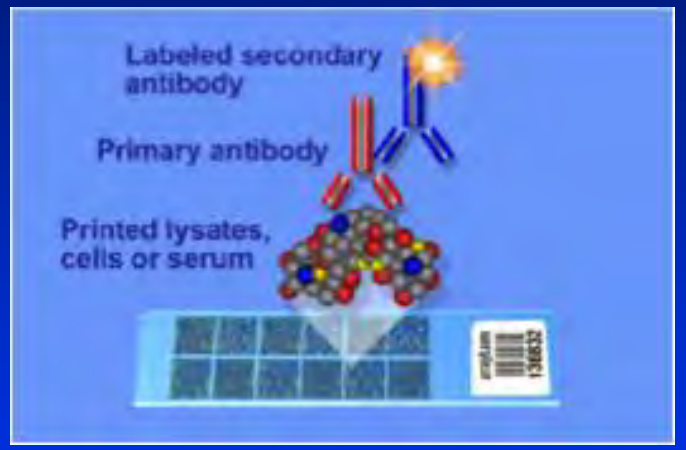
416 validated antibodies

Dot blot: less sensitive to degradation

Requires high quality validated antibodies and robotics

No Spatial orientation: combined tumor and stromal signature





Tcpaportal.org

Search Cancer Proteome Atlas

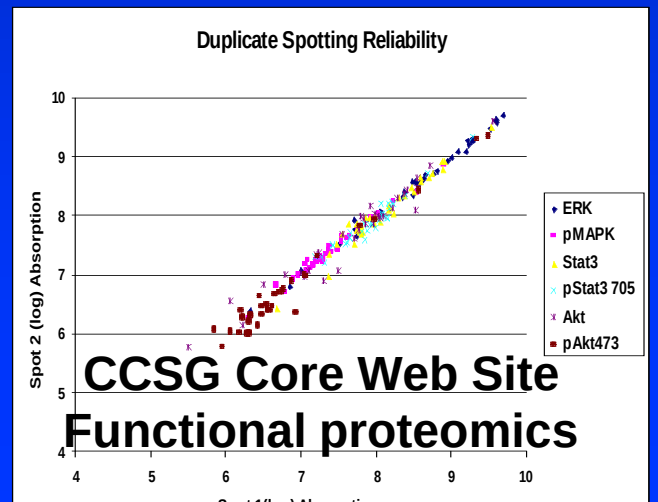
TCGA and internal patient samples (>10,000) with extensive DNA, RNA, miRNA, and clinical data

Cell lines with RNASeq and drug data

1200 cell lines

Broad Cancer Cell Line Encyclopedia

144,000 samples in total

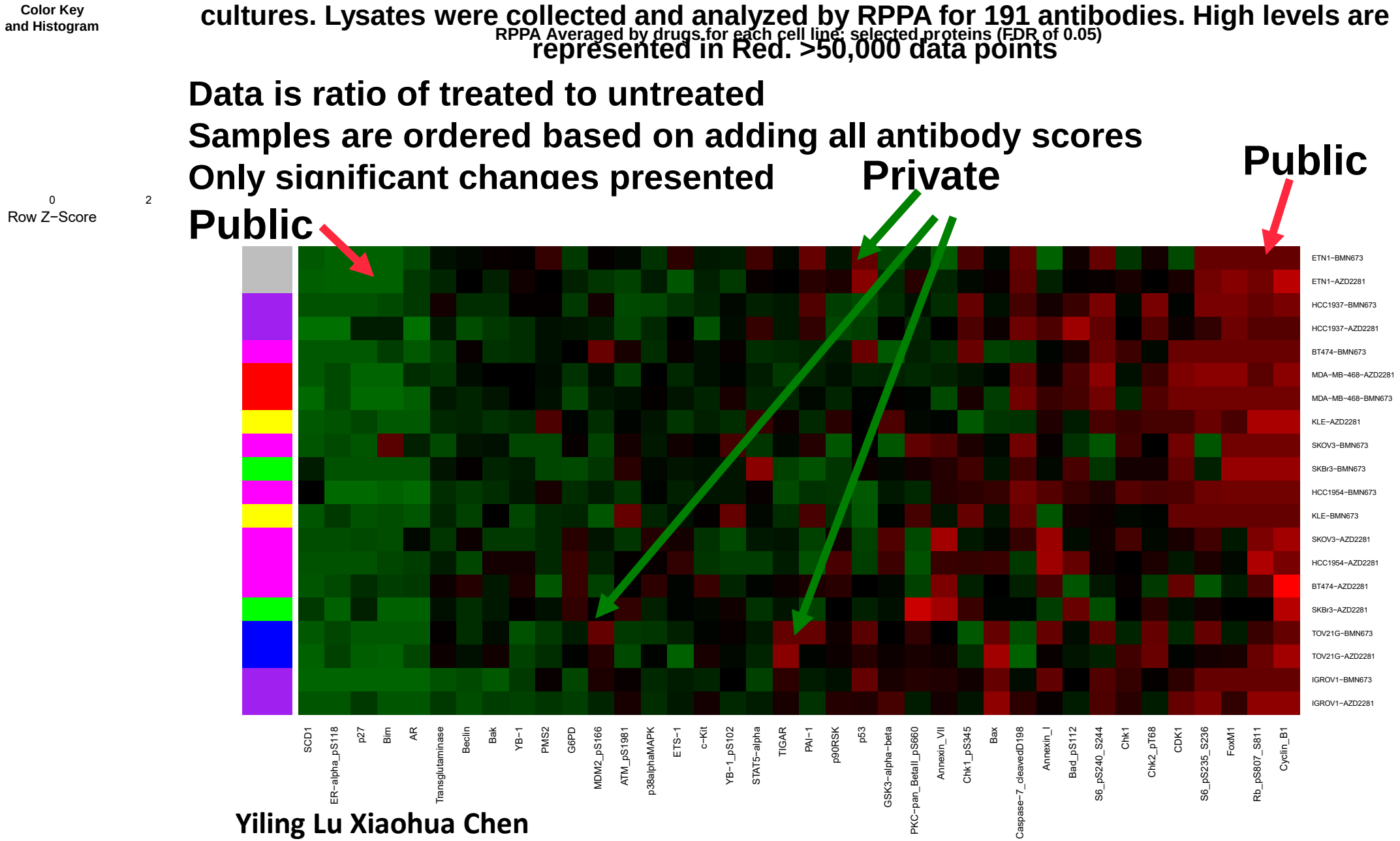


CCSG Core Web Site

Functional proteomics

Rank-Sum Analysis of AZD2281 and BMN673

5 representative cell lines were treated with 2 doses for 72 and 96 hours in 2D and 3D cultures. Lysates were collected and analyzed by RPPA for 191 antibodies. High levels are represented in Red. >50,000 data points



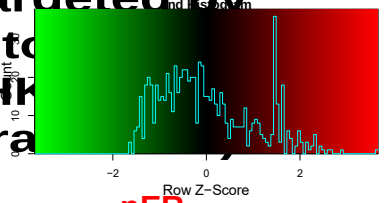
Yiling Lu Xiaohua Chen

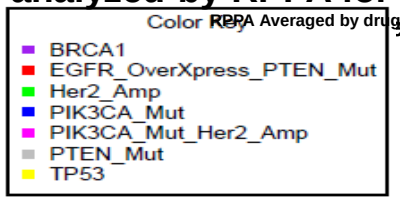
N-673 PARP inhibitors

Pathway Analysis of AZD2281 and BMN673

5 representative cell lines were treated with 2 doses for 72 and 96 hours in 2D and 3D cultures. Lysates were collected and analyzed by RPPA for 191 antibodies. High levels are represented in Red.

pRB can be targeted by
CDK4/6 inhibit
CHK1/2 by CHK
(Lilly and Astra





RPPA Averaged by drugs for each cell line, selected proteins (FDR of 0.05)

mat: 2D/3D_Cell Line_Drug_Dose (μM)_Treatment Length (days)

Yiling Lu Xiaohua Chen

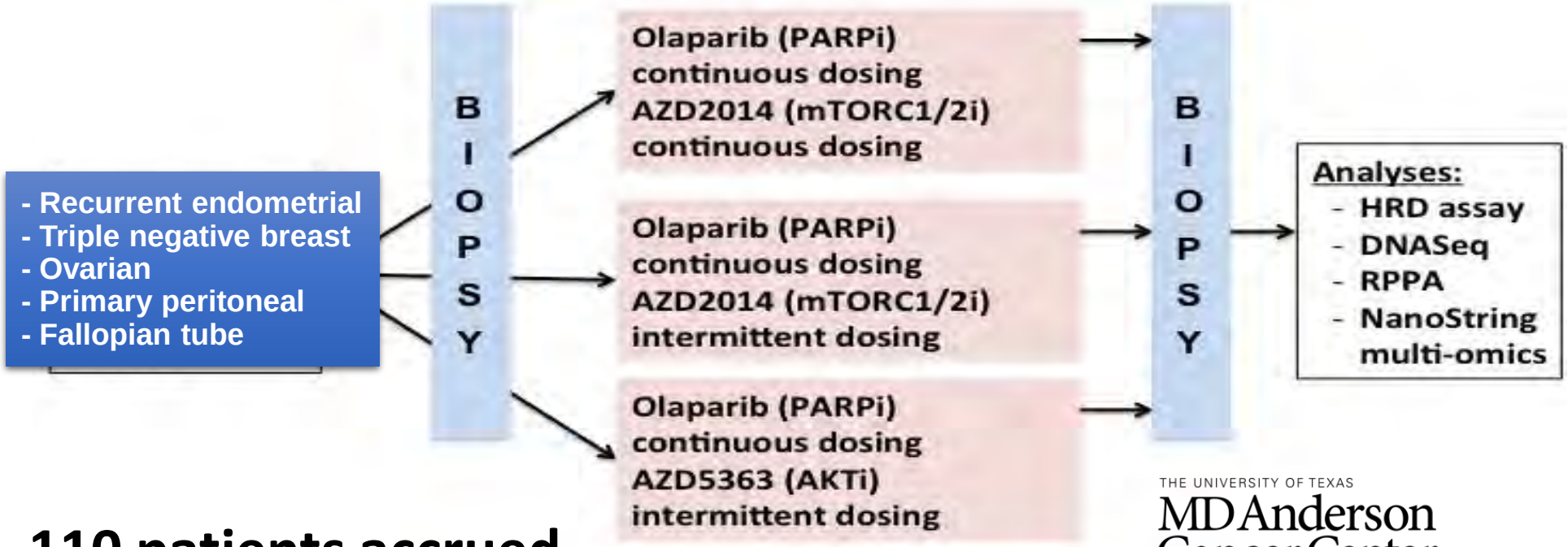
SU2C: Olaparib and BKM120: Olaparib and BYL719

30-35% RR for OC: Not dependent on BRCA1/2 status

(Lotus AND PAKT AKTi and taxol)

OCTOPUS – PARP/PI3K pathway combinations

Shannon Westin



110 patients accrued

RR ~ 30% for OC, 50% for EC for AZD536?

Prolonged responses over 2 years

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

AstraZeneca

N-673 PARP inhibitors

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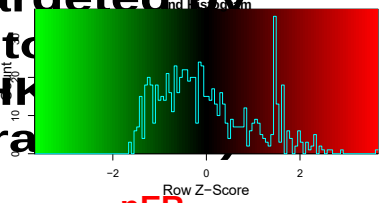
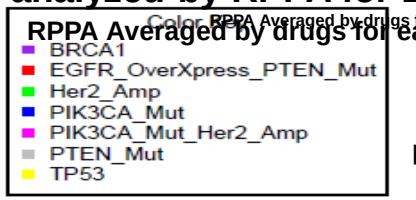




Joan Brugge

Mek

pER

Bim

p27

AR

SCD1

pATM

CDK1

FOXM1*

pRB

Cyclin B1*

pCHK1

Casp7pBAD

BAX

pS6

CHK1

pCHK2

CDK1

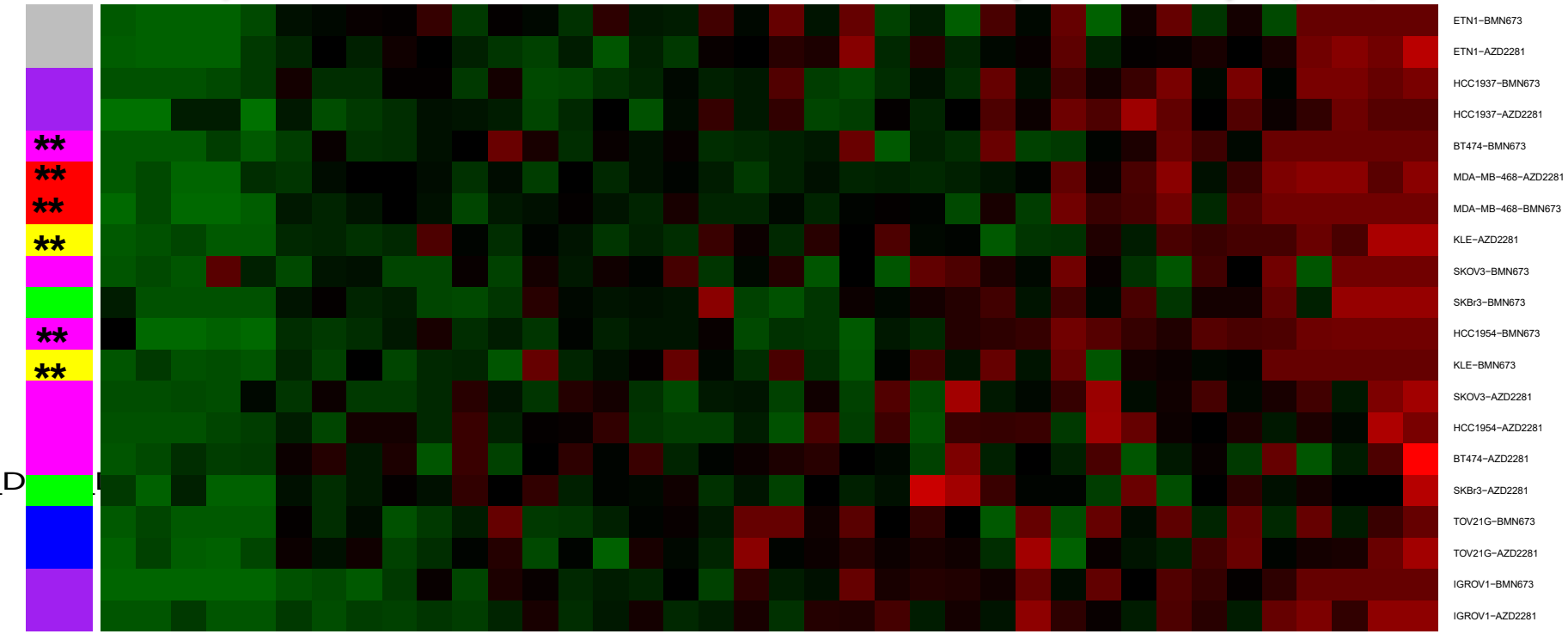
pS6

FoxM1

pRB

Cyclin B1

0 2
Row Z−Score



mat: 2D/3D_Cell Line_D

Yiling Lu Xiaohua Chen

PARP plus MEK inhibitors are synergistic in vivo

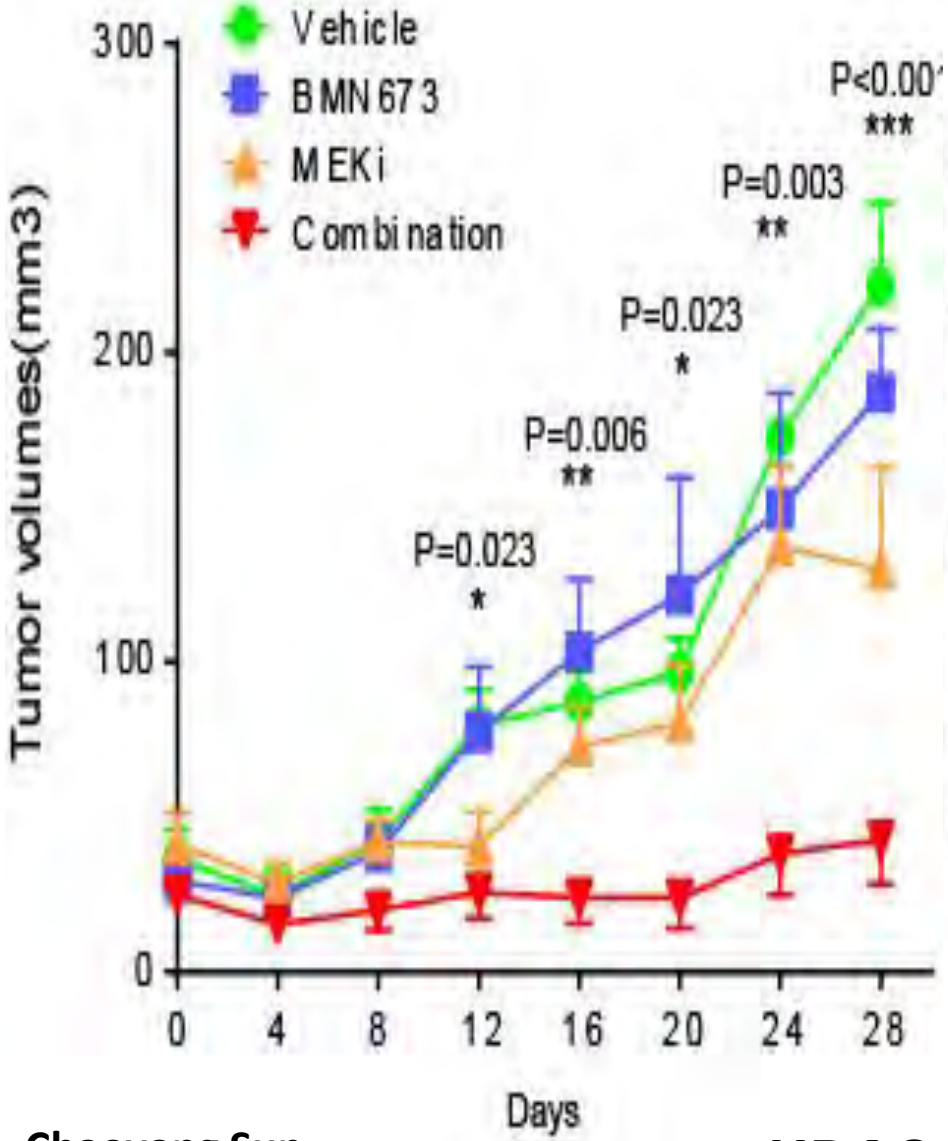
RAS pathway activation induces replication stress

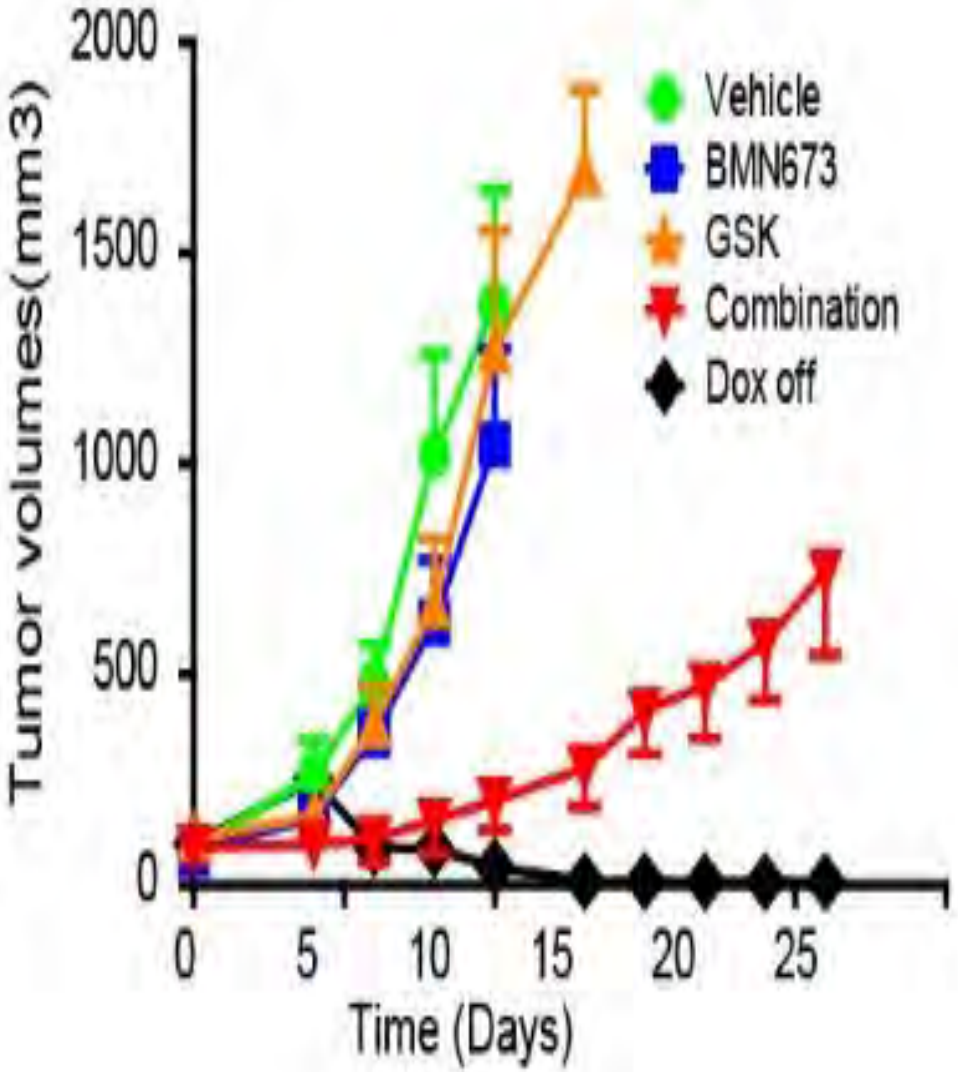
RAS pathway activation increases HR

RAS pathway activation is indicative of PARP resistance

PARP resistant cells acquire RAS mutations and increased signaling

Inhibiting MEK or ERK increases PARP activity in RAS mutant or PARP resistant cell lines





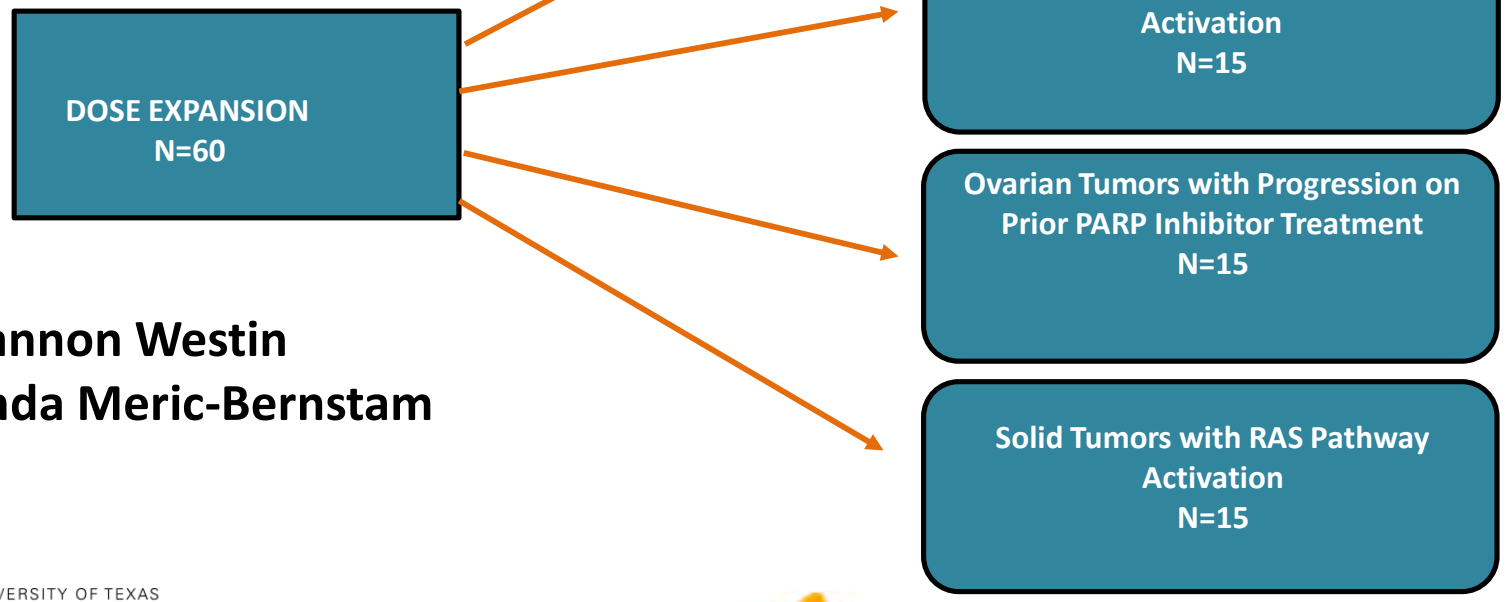
Chaoyang Sun
Dong Zhang
Yong Fang

KRAS OVCAR8

KRAS HPDE Pancreas

SOLAR study: selumetinib and olaparib in RAS activated tumors

Original observation 4/8/2015
CRC Approved, IRB 3/1/17
FDA no Objection
SIV May 30 2017
First in human Nov 2017

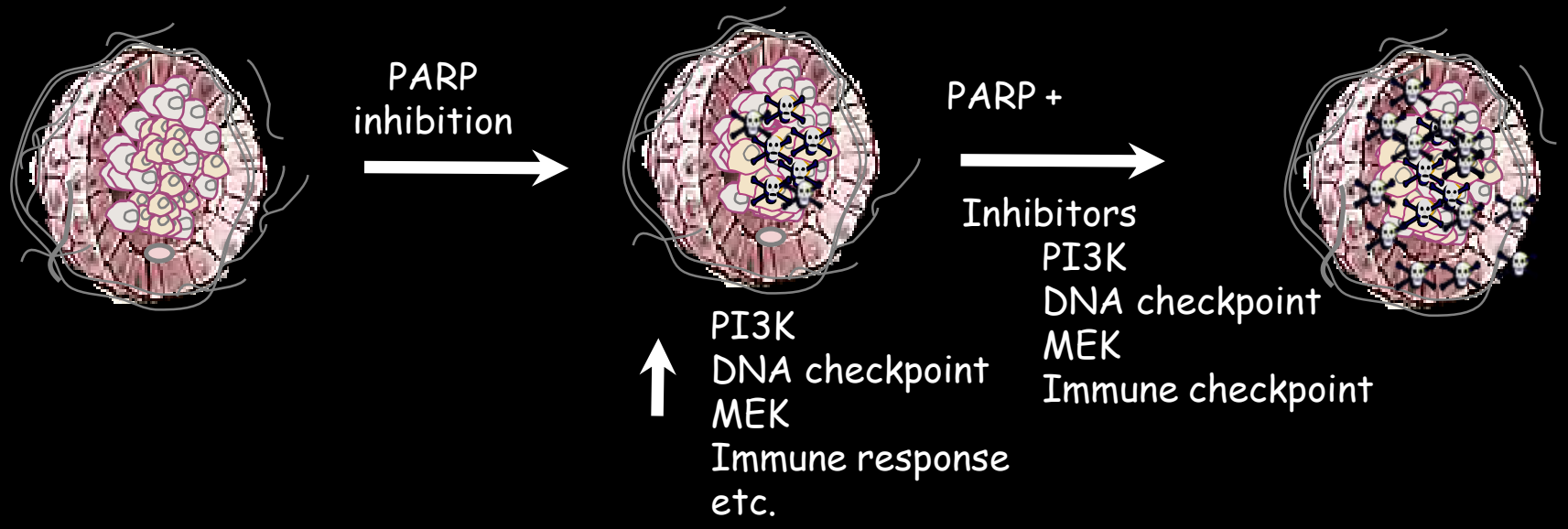


Shannon Westin
Funda Meric-Bernstam

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

AstraZeneca

Rational Strategy for Combination Therapies



Blocking critical signaling nodes "rewires" signaling pathways

Rewired networks contribute to cellular resistance to targeted therapeutics

Induced signaling events represent "vulnerabilities" that can be exploited leading to synthetic lethality

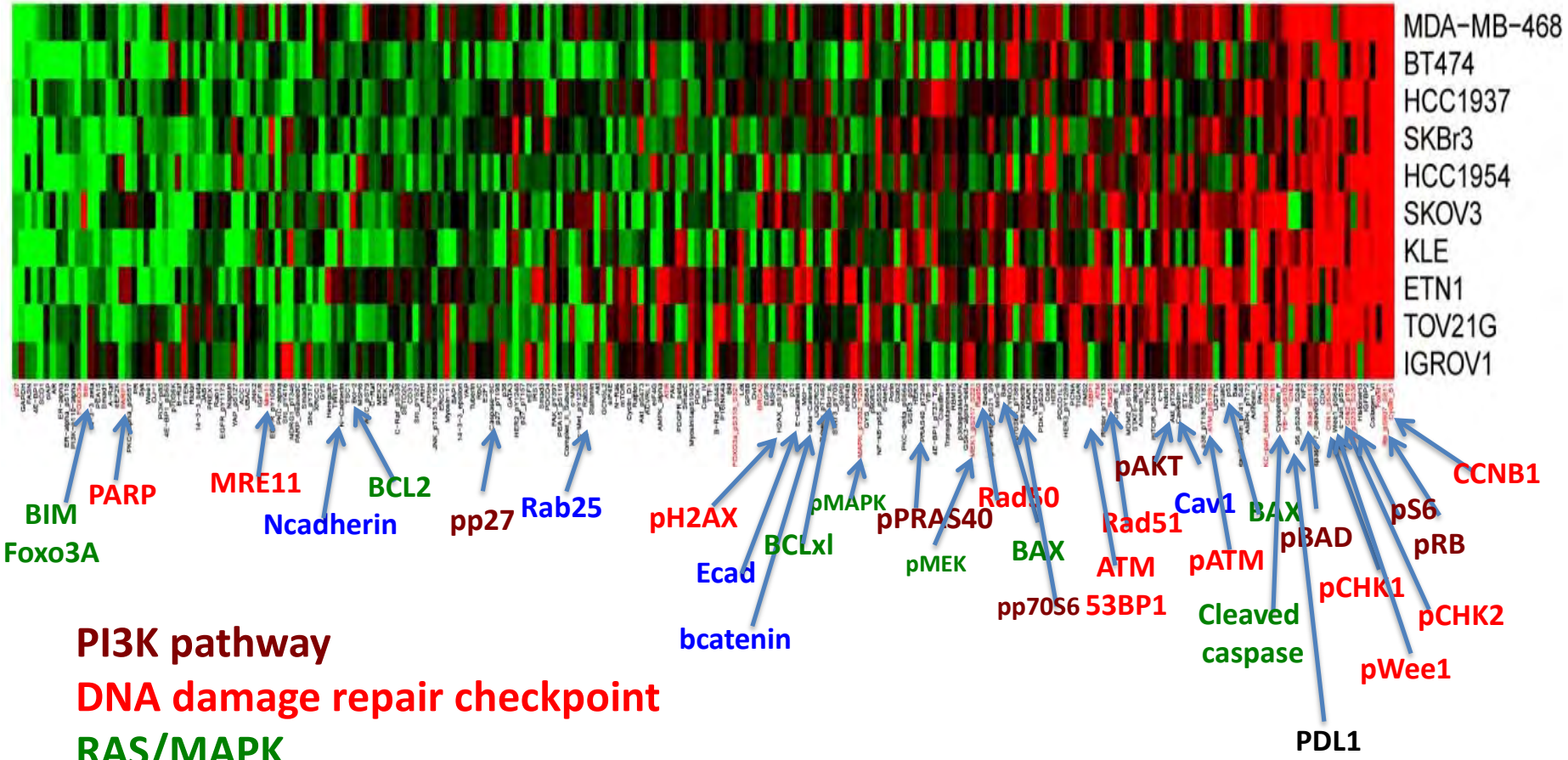
Adaptive responses can be restricted to specific tumor subpopulations

Combinatorial Adaptive Resistance Therapy
CART

Combinations with PARPi

- PI3K/AKT/mTOR inhibitors
- MEK ERK inhibitors
- DNA damage checkpoint inhibitors
- Immune checkpoint inhibitors
- BET inhibitors
- Anti-apoptotic inhibitors
- Angiogenesis inhibitors
- HSP90 inhibitors
- HDAC inhibitors
- Azacytidine
- HER2 inhibitors
- Chemotherapy/radiation to induce double strand breaks

Adaptive responses to PARP inhibitors could be used to select rational combinations



PI3K pathway

DNA damage repair checkpoint

RAS/MAPK

Apoptotic pathway

STING/Immune

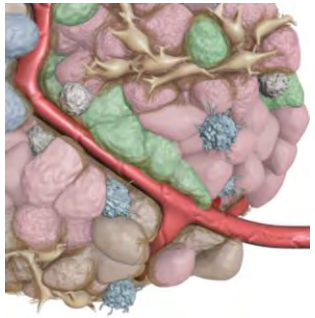
EMT

Predictor of response

Marilyne Labrie
Yiling Lu

REAL TIME SELECTION OF DRUG COMBINATIONS BASED ON ADAPTIVE RESPONSE

Resting Tumor Ecosystem

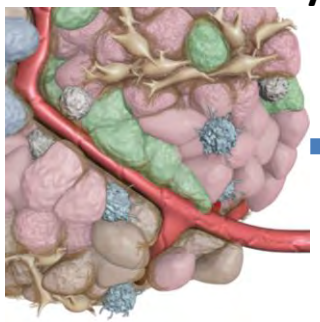


Limited systems information

Real-Time Deep Spatially Resolved Characterization of DNA, RNA, Protein from Tumor and ctDNA

REAL TIME SELECTION OF DRUG COMBINATIONS BASED ON ADAPTIVE RESPONSE

Resting Tumor Ecosystem



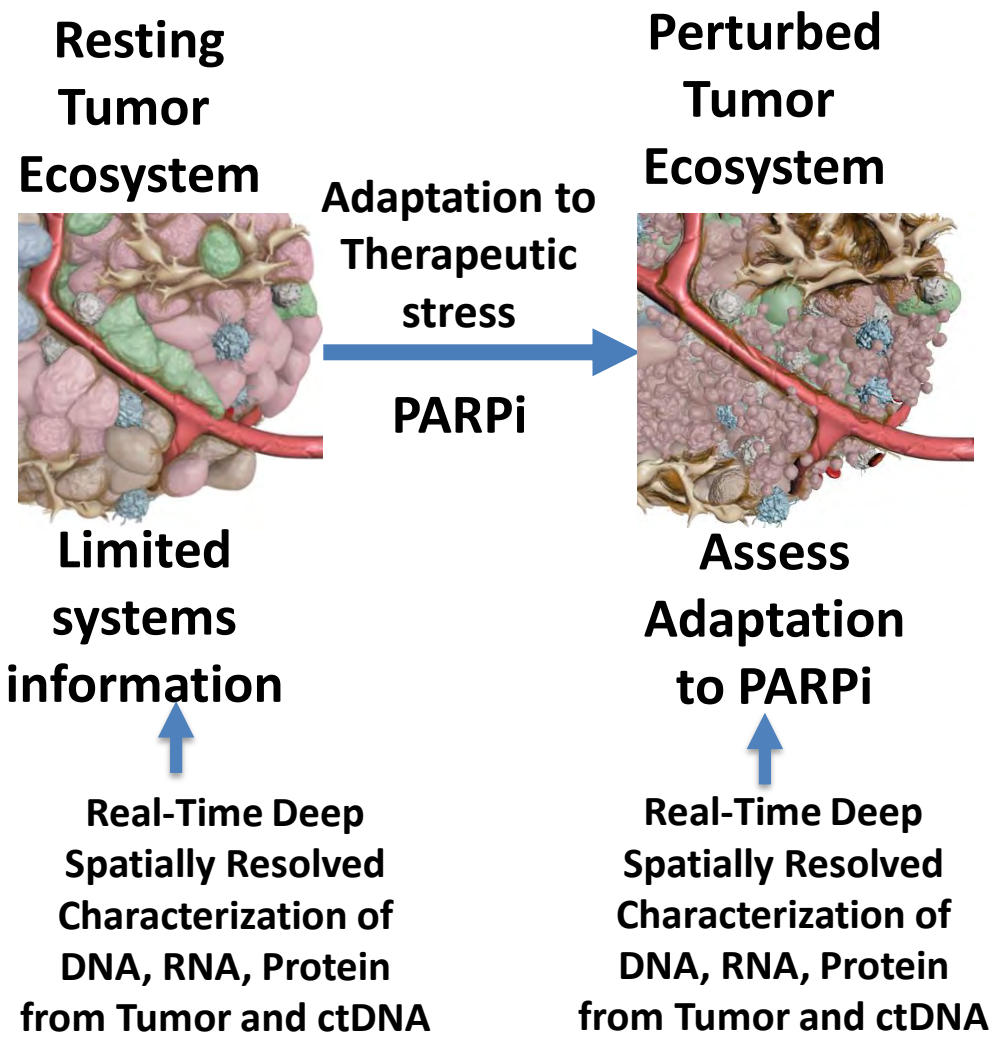
Adaptation to Therapeutic stress

PARPi

Limited systems information

Real-Time Deep Spatially Resolved Characterization of DNA, RNA, Protein from Tumor and ctDNA

REAL TIME SELECTION OF DRUG COMBINATIONS BASED ON ADAPTIVE RESPONSE



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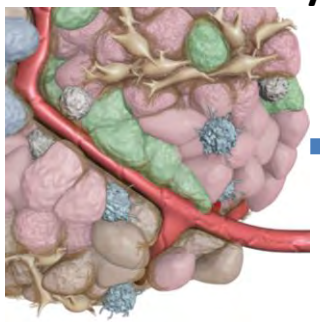
Resting Tumor Ecosystem

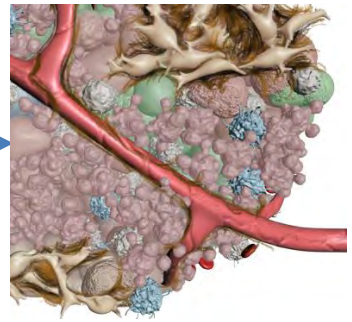


Limited systems information

Adaptation to Therapeutic stress

PARPi

Perturbed Tumor Ecosystem



Assess Adaptation to PARPi

Immune cell infiltration

Target the adaptive response PD1/PDL1

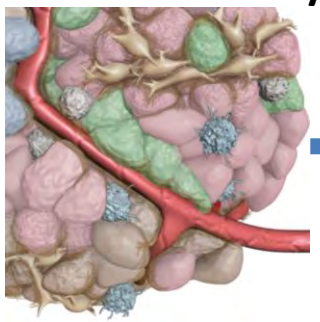
Real-Time Deep Spatially Resolved Characterization of DNA, RNA, Protein from Tumor and ctDNA

Real-Time Deep Spatially Resolved Characterization of DNA, RNA, Protein from Tumor and ctDNA

Combination selected based on tumor evolution

REAL TIME SELECTION OF DRUG COMBINATIONS BASED ON ADAPTIVE RESPONSE

Resting Tumor Ecosystem



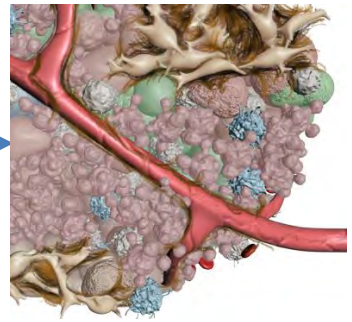
Limited systems information

Real-Time Deep Spatially Resolved Characterization of DNA, RNA, Protein from Tumor and ctDNA

Adaptation to Therapeutic stress

PARPi

Perturbed Tumor Ecosystem



Assess Adaptation to PARPi

Real-Time Deep Spatially Resolved Characterization of DNA, RNA, Protein from Tumor and ctDNA

Immune cell infiltration

PI3K pathway

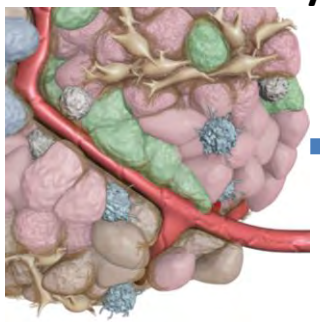
Target the adaptive response PD1/PDL1

mTOR/AKT

Combination selected based on tumor evolution

REAL TIME SELECTION OF DRUG COMBINATIONS BASED ON ADAPTIVE RESPONSE

Resting Tumor Ecosystem



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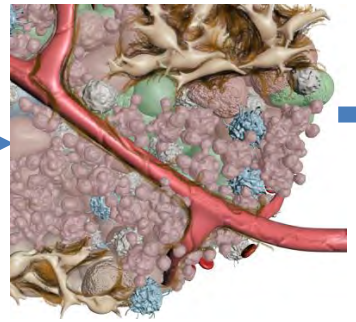
Real-Time Deep Spatially Resolved Characterization of DNA, RNA, Protein from Tumor and ctDNA

Adaptation to Therapeutic stress

PARPi

Perturbed Tumor Ecosystem



Assess Adaptation to PARPi

Real-Time Deep Spatially Resolved Characterization of DNA, RNA, Protein from Tumor and ctDNA

Immune cell infiltration

PI3K pathway

RAS/MEK pathway

Target the adaptive response

PD1/PDL1

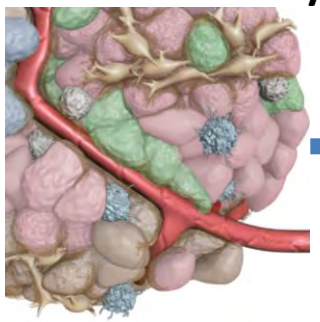
mTOR/AKT

MEK/MAPK

Combination selected based on tumor evolution

REAL TIME SELECTION OF DRUG COMBINATIONS BASED ON ADAPTIVE RESPONSE

Resting Tumor Ecosystem



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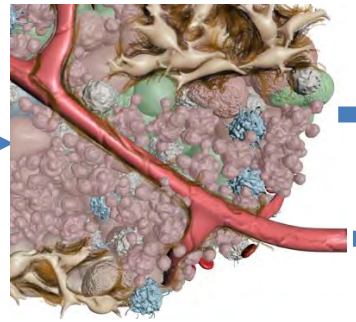
Real-Time Deep Spatially Resolved Characterization of DNA, RNA, Protein from Tumor and ctDNA

Adaptation to Therapeutic stress

PARPi

Perturbed Tumor Ecosystem



Assess Adaptation to PARPi

Real-Time Deep Spatially Resolved Characterization of DNA, RNA, Protein from Tumor and ctDNA

Immune cell infiltration → Target the adaptive response PD1/PDL1

PI3K pathway → mTOR/AKT

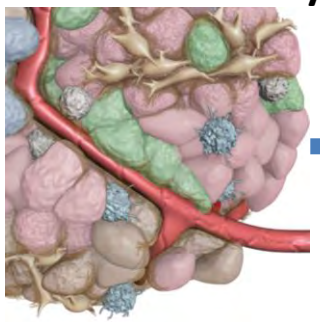
RAS/MEK pathway → MEK/MAPK

DNA damage checkpoint → Wee1/ATR

Combination selected based on tumor evolution

REAL TIME SELECTION OF DRUG COMBINATIONS BASED ON ADAPTIVE RESPONSE

Resting Tumor Ecosystem



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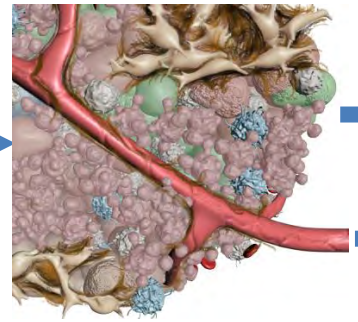
Real-Time Deep Spatially Resolved Characterization of DNA, RNA, Protein from Tumor and ctDNA

Adaptation to Therapeutic stress

PARPi

Perturbed Tumor Ecosystem



Assess Adaptation to PARPi

Real-Time Deep Spatially Resolved Characterization of DNA, RNA, Protein from Tumor and ctDNA

	Target the adaptive response
Immune cell infiltration	PD1/PDL1
PI3K pathway	mTOR/AKT
RAS/MEK pathway	MEK/MAPK
DNA damage checkpoint	Wee1/ATR
Reconstituted HR	BRD4
Apoptotic balance	BCL2/MCL1

Combination selected based on tumor evolution

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Belgium Georg Halder Sofie Claerhout

Abbvie, Adelson Medical Research Foundation, AstraZeneca, Breast Cancer Research Foundation, Critical Outcomes Technology, Illumina, Ionis, NCI, Karus Therapeutics, Komen Research Foundation, Nanostring, Takeda/Millennium Pharmaceuticals, Tesaro

U.S. FOOD & DRUG ADMINISTRATION

American Association for Cancer Research

FINDING CURES TOGETHER℠

Society of Gynecologic Oncology

SESSION III Panel Discussion:

Biomarker Development and PARP Inhibitors

Moderators: Deborah K. Armstrong, MD, and Robert L. Coleman, MD, FACOG, FACS

Panelists:

Hisani Madison, PhD, MPH

Gwynn Ison, MD

Alan D'Andrea, MD

Gordon B. Mills, MD, PhD

U.S. FOOD & DRUG ADMINISTRATION

American Association for Cancer Research

FINDING CURES TOGETHER℠

Society of Gynecologic Oncology

SESSION IV:

Development of Drugs for Rare Gynecological Malignancies

Session Cochair: Gordon B. Mills, MD, PhD

Speakers:

Anil K. Sood, MD

Stephanie L. Gaillard, MD, PhD

David M. Gershenson, MD

Emerging Opportunities in Rare Gynecologic Cancers

Anil K. Sood, M.D.
M.D. Anderson Cancer Center
Houston, TX

Disclosure

- SAB/consulting: Kiyatec, Tesaro
- Research funding: M-Trap
- Stockholder: Bio Path

Overview

- Rare cancers
- Molecular characteristics
- Therapeutic opportunities and trial development

What are rare cancers?

- NCI: <15 per 100,000 people per year
- ESMO: <6 per 100,000 people per year

Common cancers

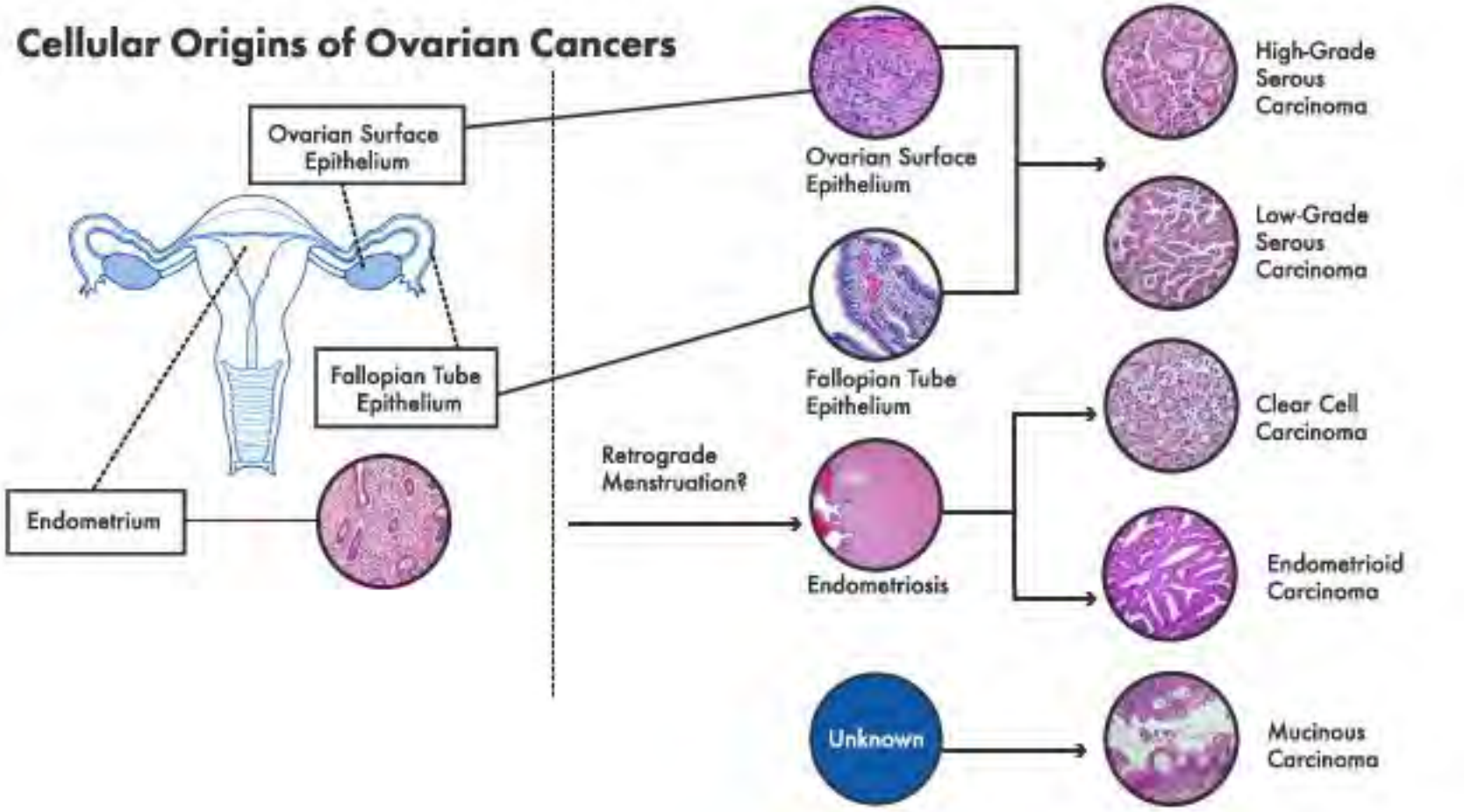
- By NCI definition, only 11 cancer types are classified as common in US adults:
  - Prostate
  - Breast
  - Lung
  - Colon
  - Uterus (endometrial)
  - Bladder
  - Melanoma
  - Rectum
  - Ovary
  - Non-Hodgkin lymphoma
  - Kidney or renal pelvis

Classification of “common cancers”

	Pathognomonic mutation	Post-genomics classification
Endometrial cancer	*POLE*	Molecularly defined subtype of common cancer
Breast cancer	*ERBB2* amplification	Molecularly defined subtype of common cancer
High-grade serous ovarian cancer	*BRCA1*, *BRCA2*	Molecularly defined subtype of common cancer
Non-small-cell lung cancers	*EML4–ALK* fusion	Molecularly defined subtype of common cancer
Prostate cancer	*TMPRSS2–ERG* fusion	Common cancer (prostate cancer)*
High-grade serous ovarian cancer	*TP53*	Common cancer (high-grade serous ovarian cancer)*

Boyd et al., Lancet Oncol, 2016

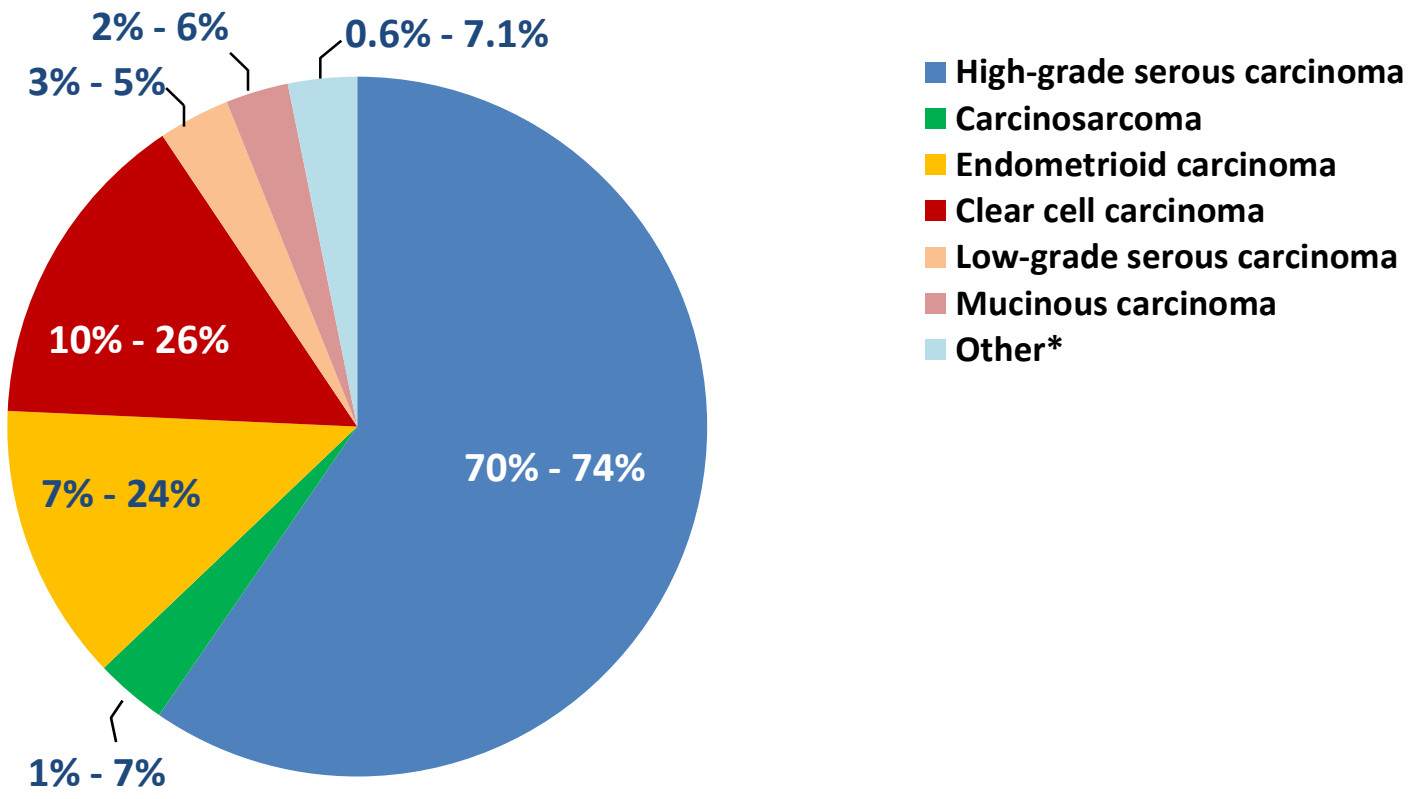
Ovarian Carcinomas – Origins



www.nas.edu/OvarianCancers

The Biology of Ovarian Cancer

Ovarian Carcinomas – Not one disease

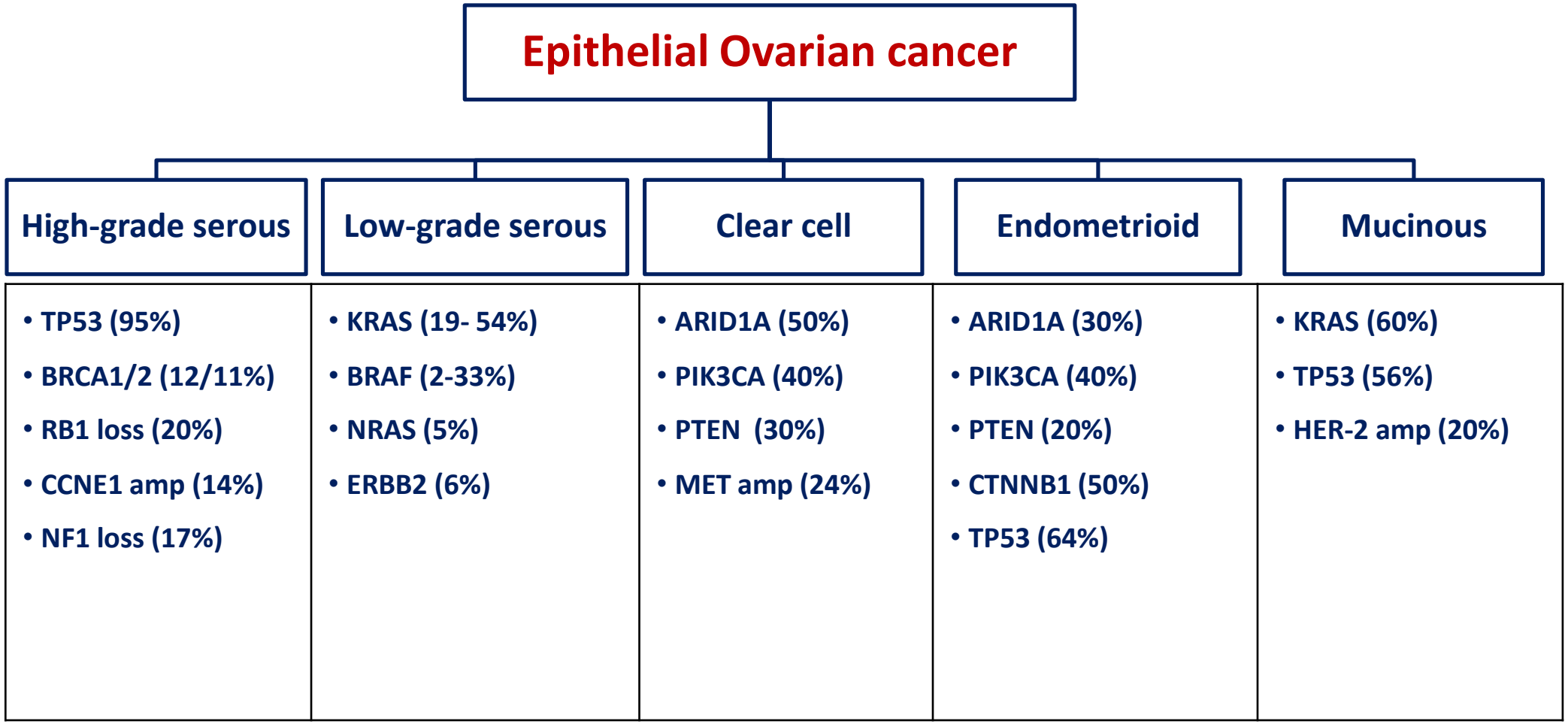


www.nas.edu/OvarianCancers

Recommendation 2

- Reach consensus on diagnostic criteria, nomenclature, and classification schemes that reflect the morphological and molecular heterogeneity of ovarian cancers
- Promote universal adoption of standardized taxonomy

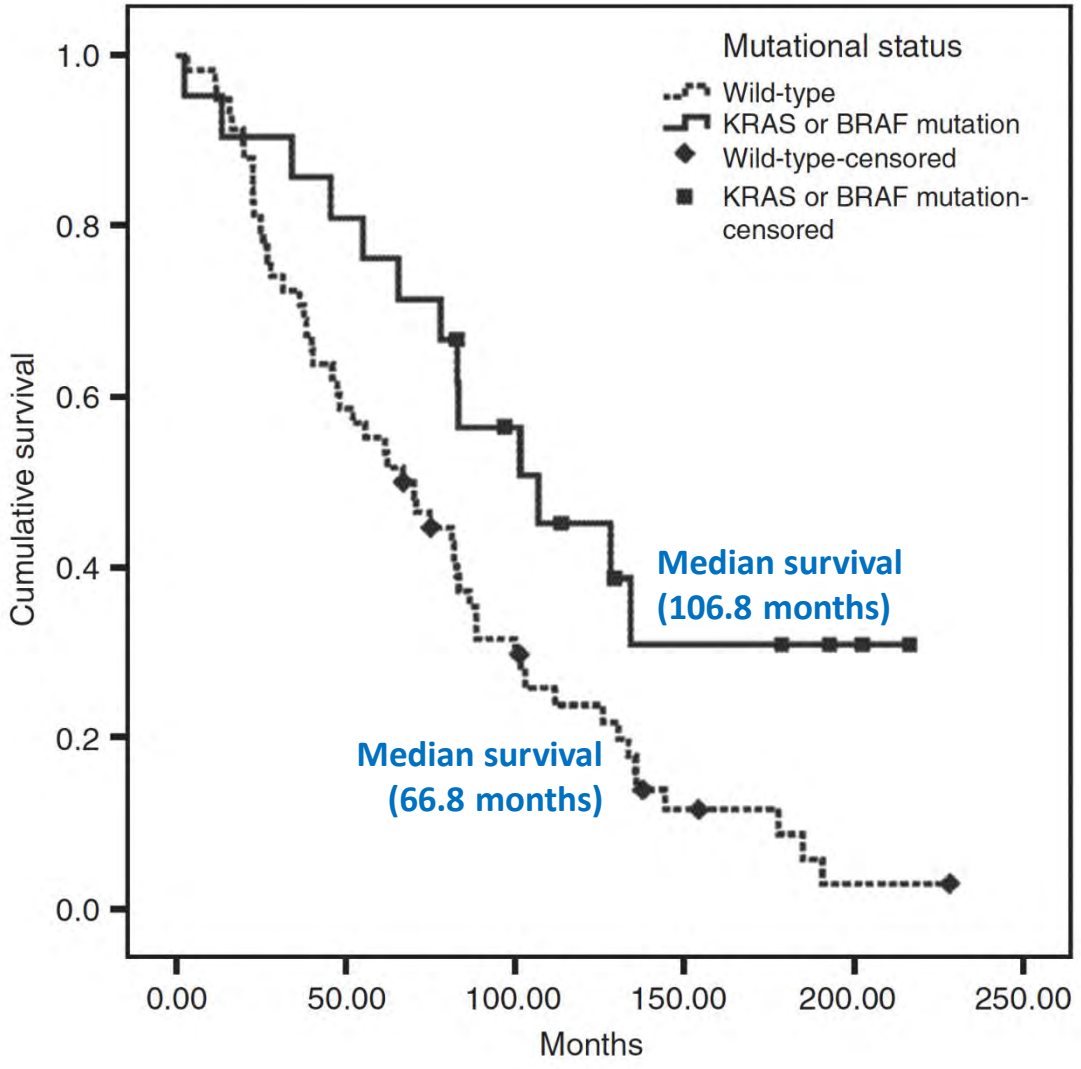
Molecular features of ovarian cancers



Mutations in major epithelial ovarian cancer subtypes

KK Wong

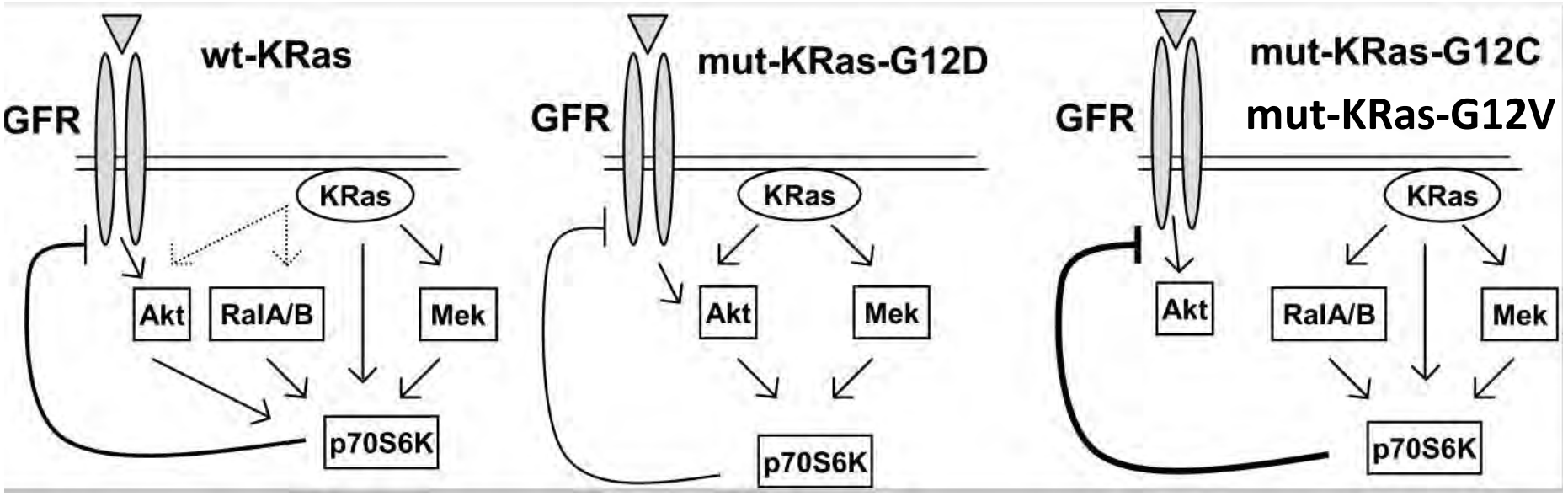
Low-grade serous carcinoma (LGSC): Impact of mutational status on survival



Median OS for women with KRAS or BRAF mutation was 106.8 months (95% CI, 50.6, 162.9) compared with 66.8 months (95% CI, 43.6, 90.0) for women whose tumors contained no KRAS or BRAF mutations (P = 0.018)

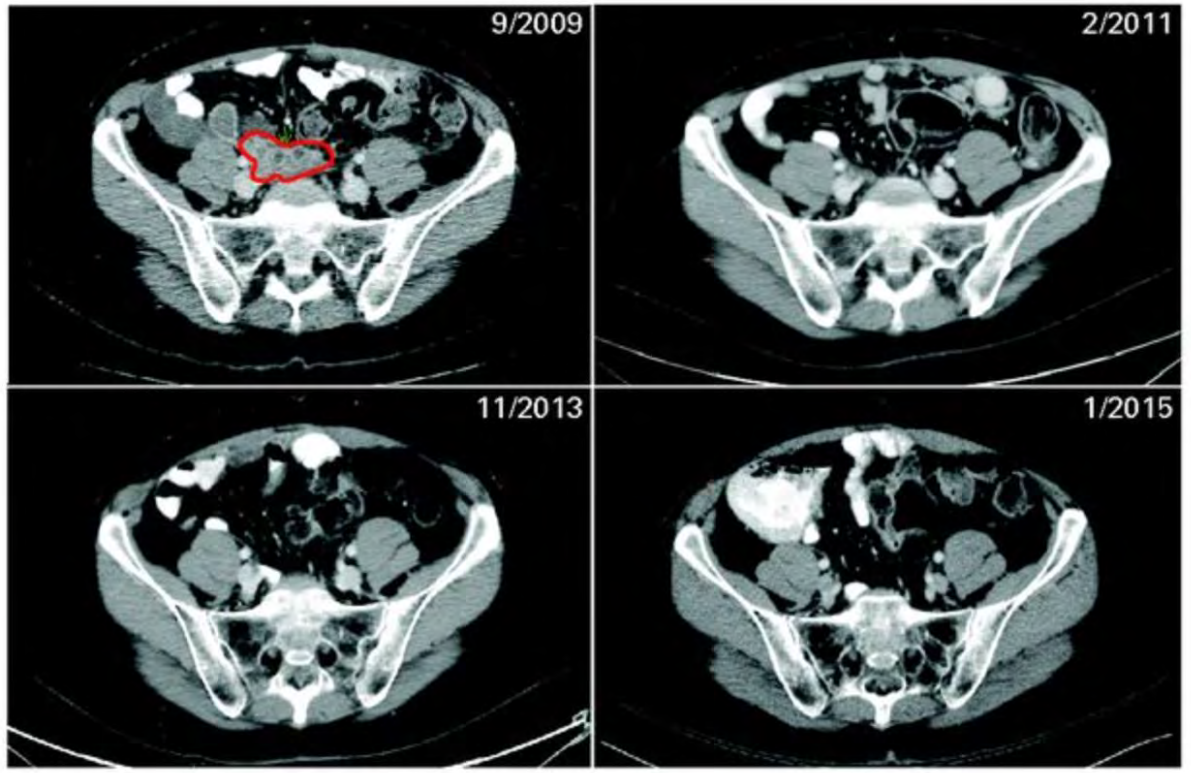
Gershenson, Sun and Wong. 2015 BJC

$KRAS^{G12D}$ and $KRAS^{G12V}$ have different cell signaling



Ihle et al., 2012. JNCI 104:228-39

An Extreme Responder with a 15–base pair deletion in *MAP2K1* gene, an activating mutation in the GOG0239 (selumetinib) study



Complete radiographic response after 17 months of therapy, which was durable at 4 and 5 years

Grisham, Gershenson et al. JCO, 2015

Ovarian clear cell adenocarcinoma (OCCC)

- A distinct histological type of cancer in the WHO-classification
- Most patients present with early stage disease (FIGO I and II)
- Incidence: 5-10% of epithelial ovarian cancers
- OCCC occurs more frequently in Japan and Taiwan (15-25%)
- More resistant to systemic chemotherapy than other types; late stage associated with poorer prognosis than other types

Molecular abnormalities in ovarian clear cell carcinoma

Gene	Overall genomic alteration frequency
PIK3CA	52.8%
ARID1A	51.2%
TP53	21.6%
ZNF217	17.6%
ERBB2	12.8%
KRAS	8%
CCNE1	7.2%
CRKL	4.8%

- N = 125 advanced/recurrent OCCCs
- FoundationOne® genomic profiling
- Genomic alterations: base pair substitutions, insertions/deletions, copy number, rearrangements

Therapeutic opportunities:

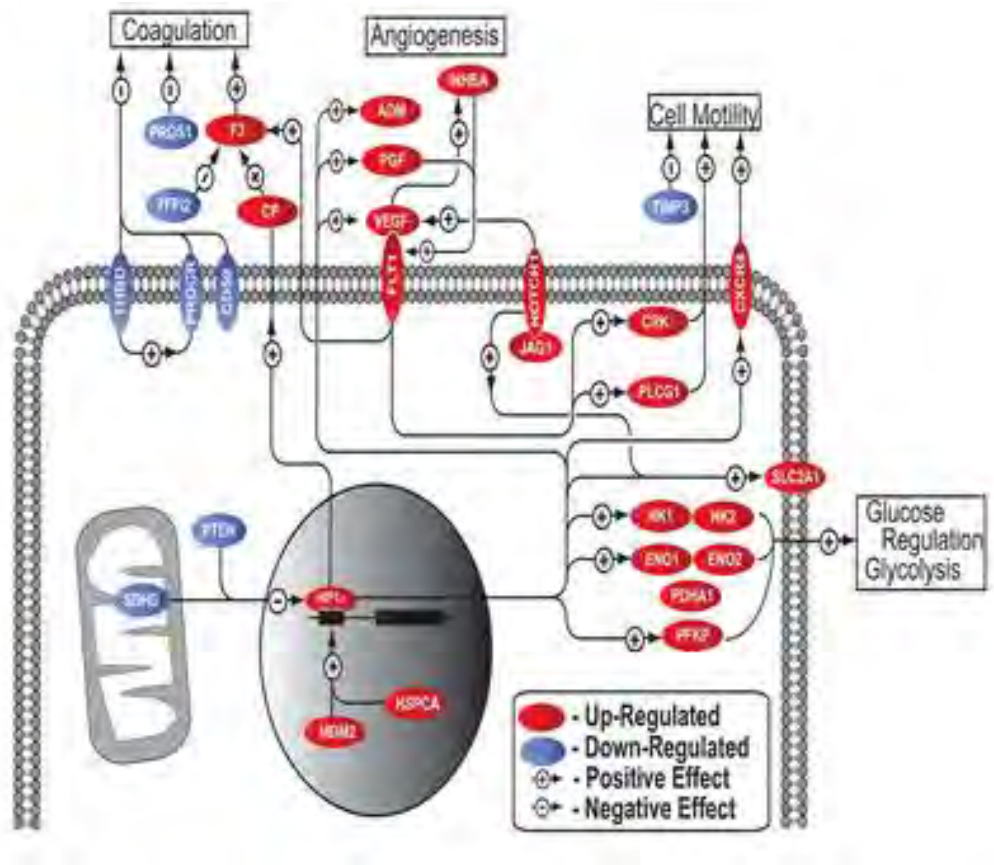
- Everolimus
- HDACi
- EZH2i
- VEGF/VEGF-R blockers
- Trastuzumab

- MMR deficiency: ~6% (check-point blockers)

Elvin et al., Gyn Onc Rep, 2017
Stewart et al., Histopathol, 2017

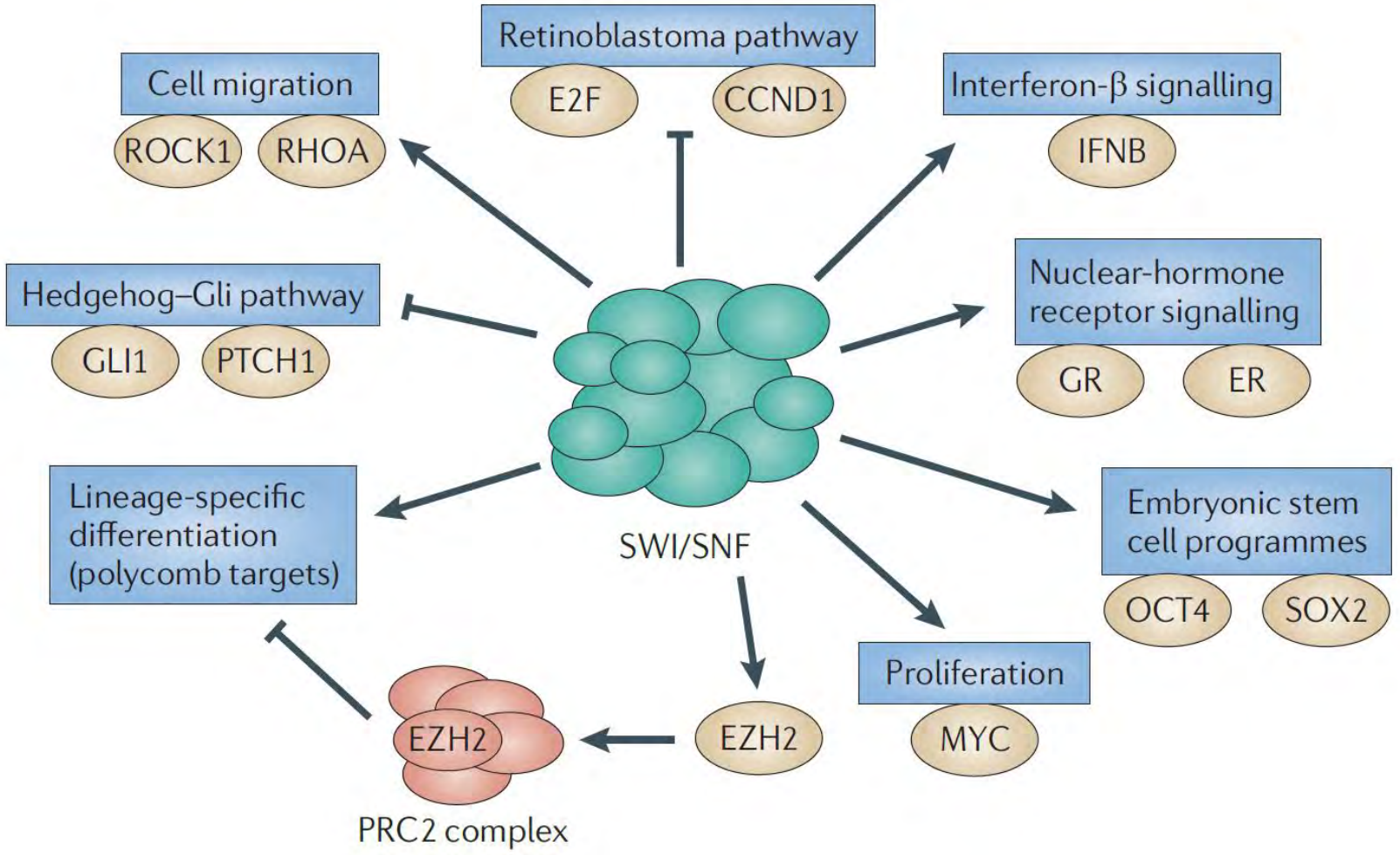
Activated pathways in ovarian clear cell carcinoma

- Microdissected clear cell cancers
- Activated pathways:
  - Angiogenesis
  - Coagulation
  - Glucose metabolism



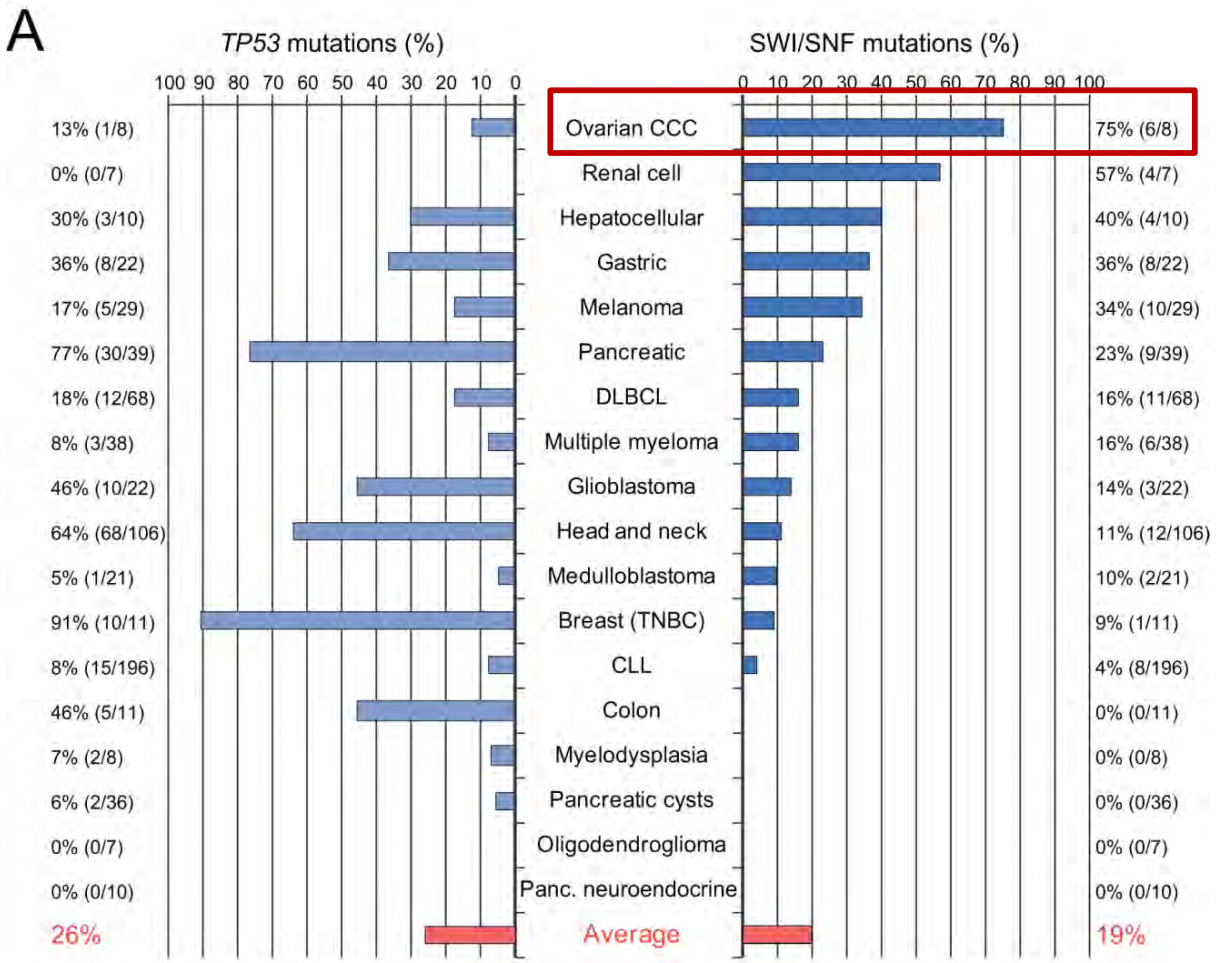
Stany et al., PLoS One, 2011

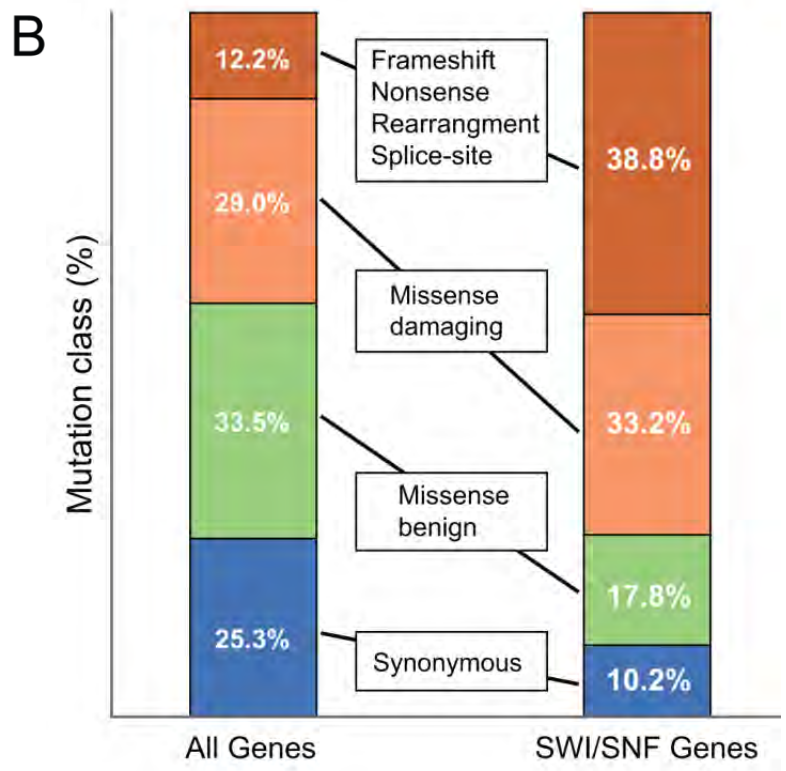
Targeted pathways implicated in the tumor suppressor activity of SWI/SNF complexes



Wilson and Roberts (2011), Nature Reviews Cancer

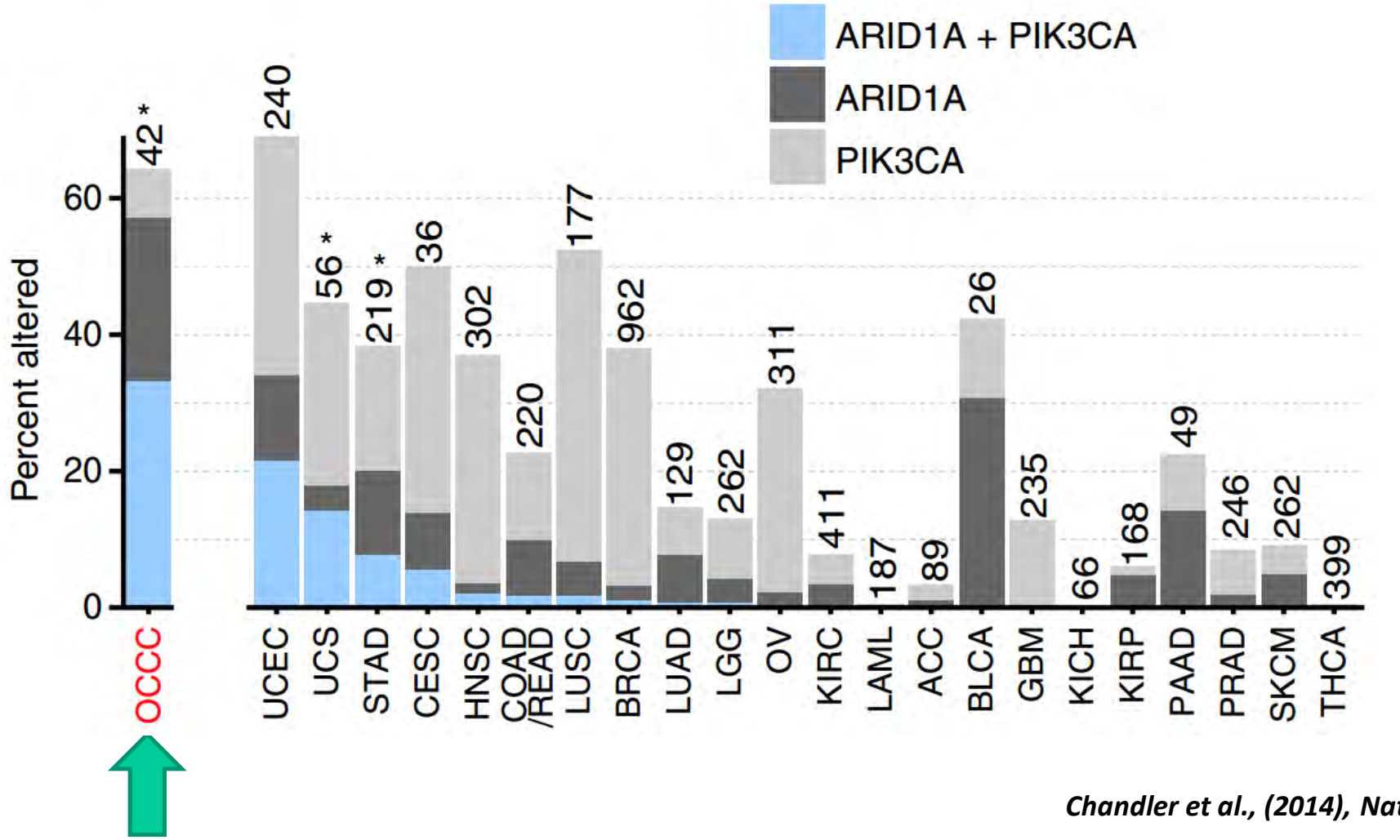
Broad spectrum of SWI/SNF mutations in human cancers





Shain and Pollack (2013), PLoS One

High frequency of co-occurring *PIK3CA* and *ARID1A* mutations in Ovarian clear cell carcinomas (OCCCs)



Chandler et al., (2014), Nature Communications

Mucinous ovarian carcinoma

Molecular features:

- Her2 amplification
- Kras mutation
- Src activation
- MSI-H
- No BRCA mutations; low rate of p53 mutations

Therapeutic opportunities:

- Ras-targeted drugs
- VEGF/VEGF-R inhibition
- Trastuzumab
- Src inhibitors
- PI3K/Akt inhibitors
- Immune therapies

Frumovitz et al., Gyn Oncol 2010
Matsuo et al., Clin Cancer Res 2011

Small cell carcinomas of the gynecologic tract

Small cell carcinoma of the ovary:

- Pulmonary type (SCCOPT)
  - Alterations in *TP53, BRCA2*
- Hypercalcemic type (SCCOHT)
  - Inactivating mutations in *SMARCA4*; loss of SMARCA2 expression

Conventional therapy:

- Chemotherapy
- Radiation

Emerging options:

- Immune therapy (PD-1/PD-L1 blockade)
- EZH2i, HDACi

Patibandla et al., Gyn Oncol 2018

Clinical trial considerations: Rare Cancers

- Create national and international networks
- Accepting greater type I and type II error
- Select trial population to minimize sample size
- Balancing scientific value and feasibility
- Incorporating Bayesian elements to quantify the resulting level of information
- N-of-1 trials; basket trials

Eur J Cancer, 2015
Lancet Oncol, 2016

Thank you!

The Challenge of Rare Subsets of Rare Cancers: A focus on *ESR1* mutations in gynecologic malignancies

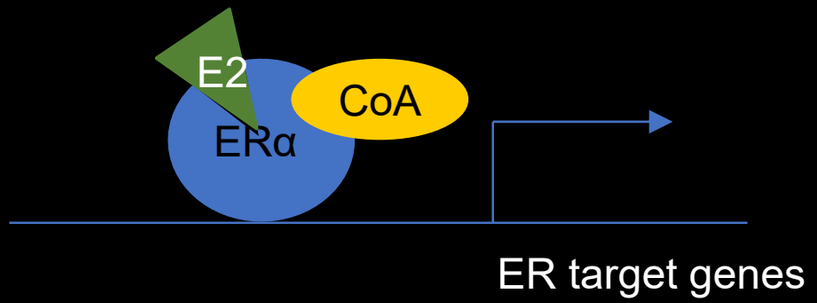
Stéphanie Gaillard, MD, PhD

Johns Hopkins Sidney Kimmel Cancer Center & Kelly Gynecologic Oncology Service

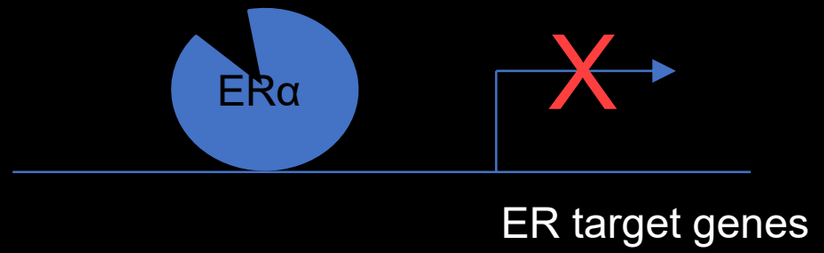
Disclosure Information
Relationships with Companies

- Consulting or Advisory Role: PharmaMar, Merck, Genentech, Tesaro
- Research Funding (to institution): PharmaMar, Merck, Genentech, Gradalis, BMS, Tetralogic, Iovance
- Patents, Royalties, and other Intellectual Property: some of the work presented has resulted in a patent filing which has been licensed by Duke University to Sermonix

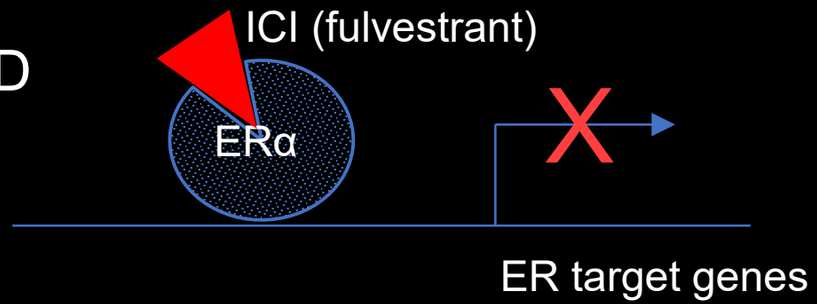
Estrogen Receptor – a ligand-dependent regulator of transcription



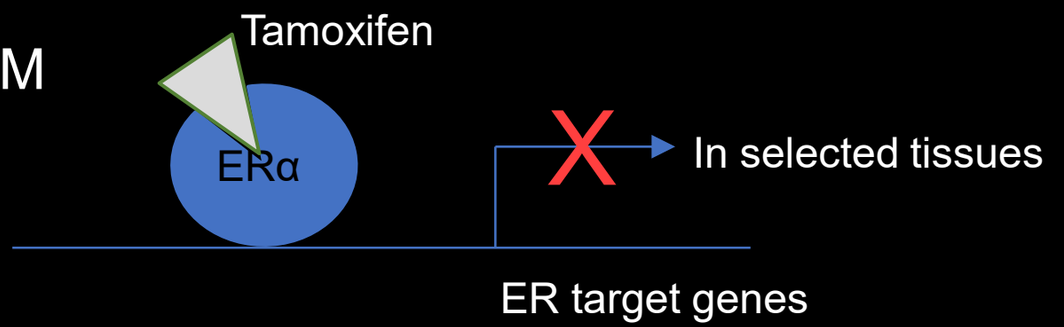
AI



SERD

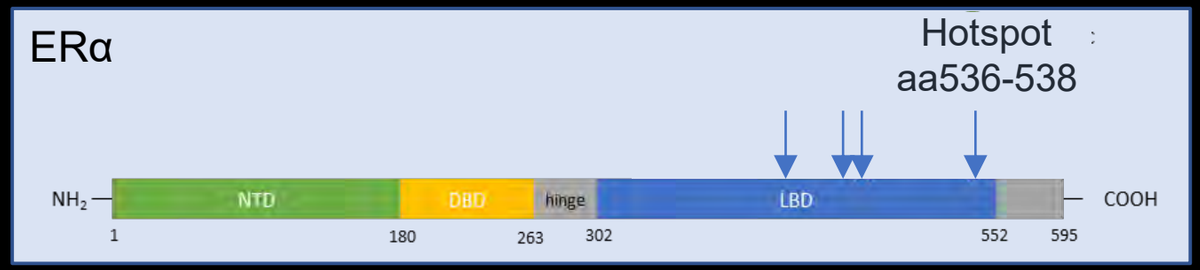


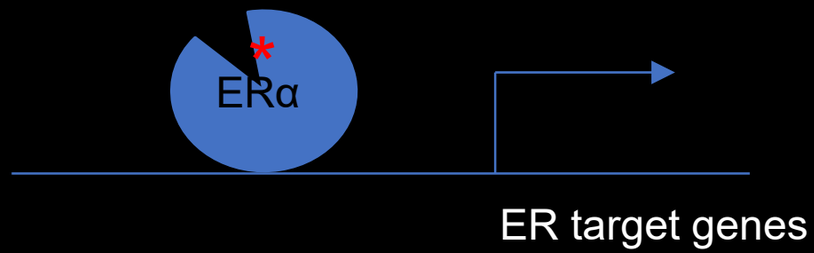
SERM

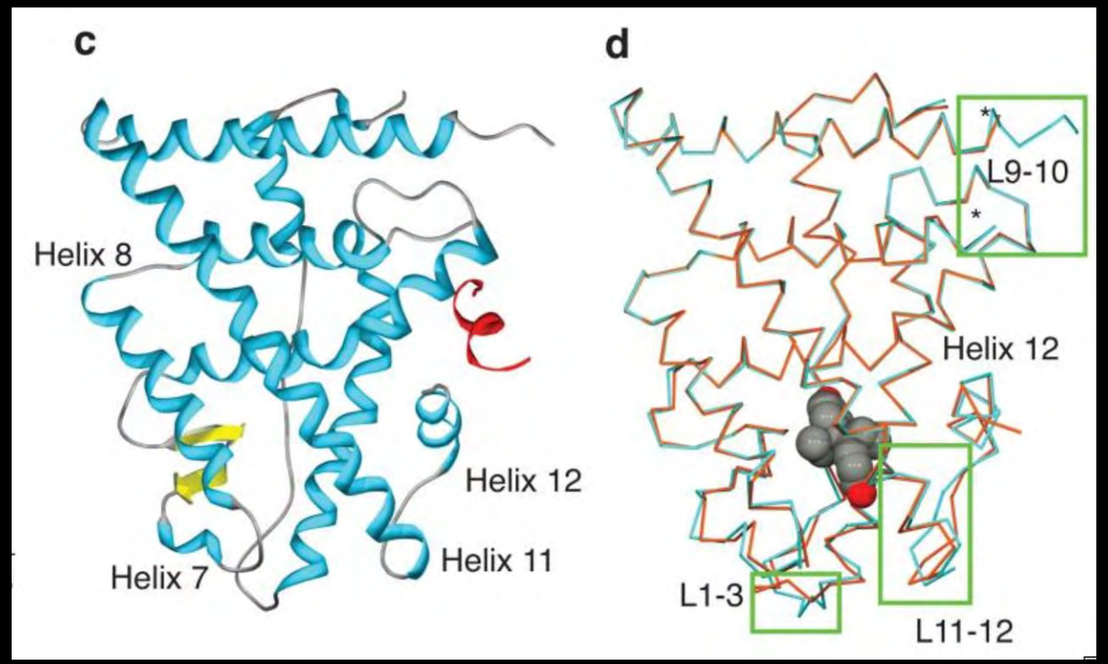


AI: Aromatase inhibitor
SERD: selective estrogen receptor disruptor
SERM: selective estrogen receptor modulator

Estrogen Receptor (*ESR1*) Activating Mutations are Associated with Resistance to Endocrine Therapy





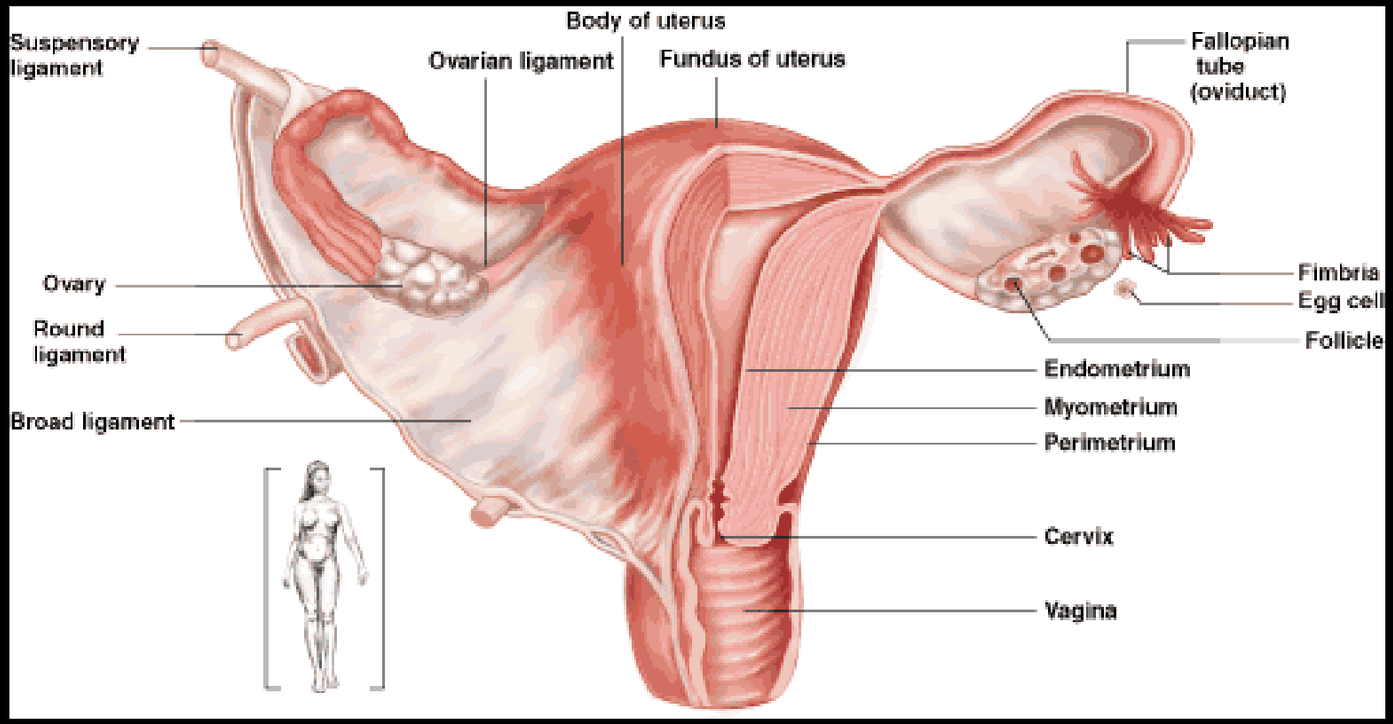


Nettles et al. Nat Chem Biol. 2008

Rare Gynecologic Cancers

OVARY

High-grade serous
Endometrioid
Low-grade serous
Clear cell
Mucinous
Carcinosarcoma
Adenosarcoma
Germ Cell Tumors
Sex Cord -Stromal Tumors (Granulosa Cell Tumors)
Small Cell Carcinoma
Carcinoid
Wolffian Tumors



UTERUS

Endometrioid
High-grade serous
Clear cell
Carcinosarcoma
Leiomyosarcoma
Low-grade endometrial stromal sarcomas
High-grade endometrial stromal sarcomas
Undifferentiated uterine sarcomas

CERVIX

Squamous cell carcinoma
Adenocarcinoma
Adenosquamous carcinoma
Small cell carcinoma

VAGINA/VULVA

Squamous cell carcinoma

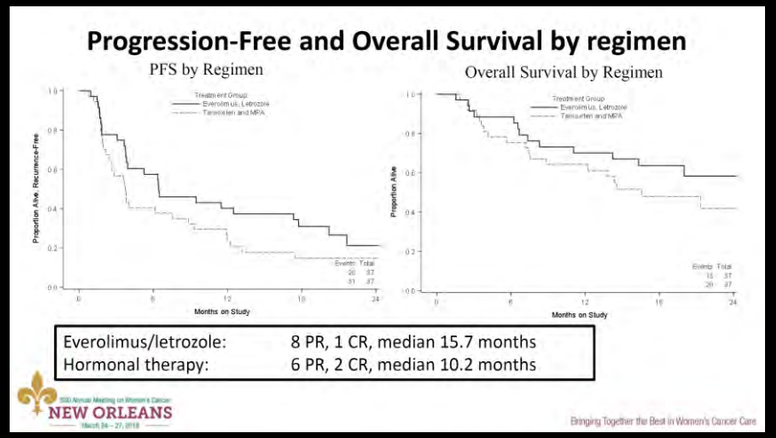
Endocrine Therapy is Associated with Modest Response

Advanced Endometrial Cancer

Table 5
Comparison of objective response rates (ORR) and median progression-free survival (PFS) outcomes with use of targeted and hormonal agents in advanced endometrial cancer.

Study	Agent	ORR (%)	PFS (months)
	Hormonal agents	21.6	2.8
	ER/+PR+	32.5	–
	ER+	26.6	–
	PR+	35.5	–
Leslie [61]	Gefitinib	3.3	1.8
Aghajanian [62]	Bevacizumab	13.2	4.5
Alvarez [63]	Bevaizumab + temsirolimus	24.5	5.6
Bender 2015 [64]	Cediranib	12.5	3.6
Castonguay [65]	Sunitinib	18	3.0
Slomovitz [66]	Everolimus + letrozole	32	3.0
Oza [67]	Erolotinib	12.5	–
Oza [68]	Temsirolimus	13.7	–

Ethier et al 2017 Gyn Onc



Slomovitz 2018 SGO Annual Mtg

Recurrent Low-Grade Serous Ovarian Cancer

9% response rate

Table 4
Summary of complete and partial responses.

Patient-regimen	Primary tumor site[a]	Regimen (no.)	Response	
			Type	Duration, months
1[b]	Peritoneum	Tamoxifen (4)	CR	117.6
2	Peritoneum	Anastrozole (2)	CR	112.2
3	Peritoneum	Letrozole (3)	CR	67.9
4	Peritoneum	Letrozole (4)	CR	52.2
5	Ovary	Letrozole (3)	CR	11.9
6[b]	Peritoneum	Letrozole (2)	CR	42.0
7	Ovary	Letrozole (2)	PR	22.0
8[c]	Peritoneum	Letrozole (4)	PR	1.63

Gershenson et al 2012 Gyn Onc

AI use in adjuvant therapy has been associated with prolonged PFS

Gershenson et al. 2017 JCO
Fader et al. 2017 Gyn Onc

Frequency of *ESR1* alterations in gynecologic malignancies

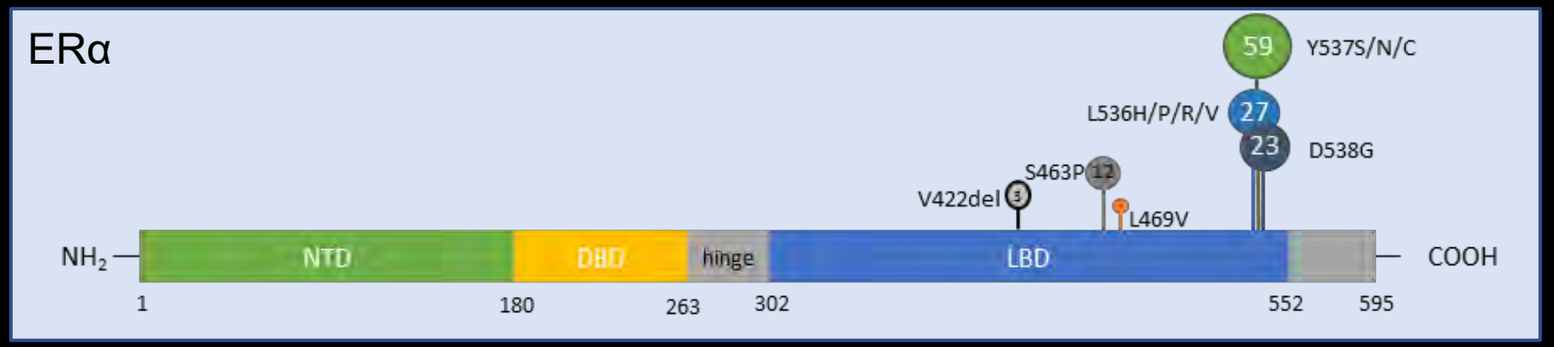
Type of alteration	Frequency N=9645	Ovary/FT N=5594	Uterus N=3101	Cervix N=720	Vulva/Vagina N=216
Total, N (%)	295 (3.1)*	120 (2.1)	160 (5.2)	9 (1.2)	6 (2.8)
Amplification	80 (0.8)	45 (0.8)	34 (1.1)	1 (0.1)	-
Deletion	1 (<0.1)	-	1 (<0.1)	-	-
Fusion	2 (<0.1)	1 (<0.1)	-	-	1 (0.5)
Rearrangements	18 (0.2)	9 (0.2)	9 (0.3)	-	-
Substitution Variants	194 (2.0)	65 (1.2)	116 (3.7)	8 (1.1)	5 (2.3)
Codon 536-538	75 (0.8)	18∞ (0.3)	56∞ (1.8)	1 (0.1)	-
Other Activating Mut	12 (0.1)	3 (<0.1)	7 (0.2)	-	2 (0.9)

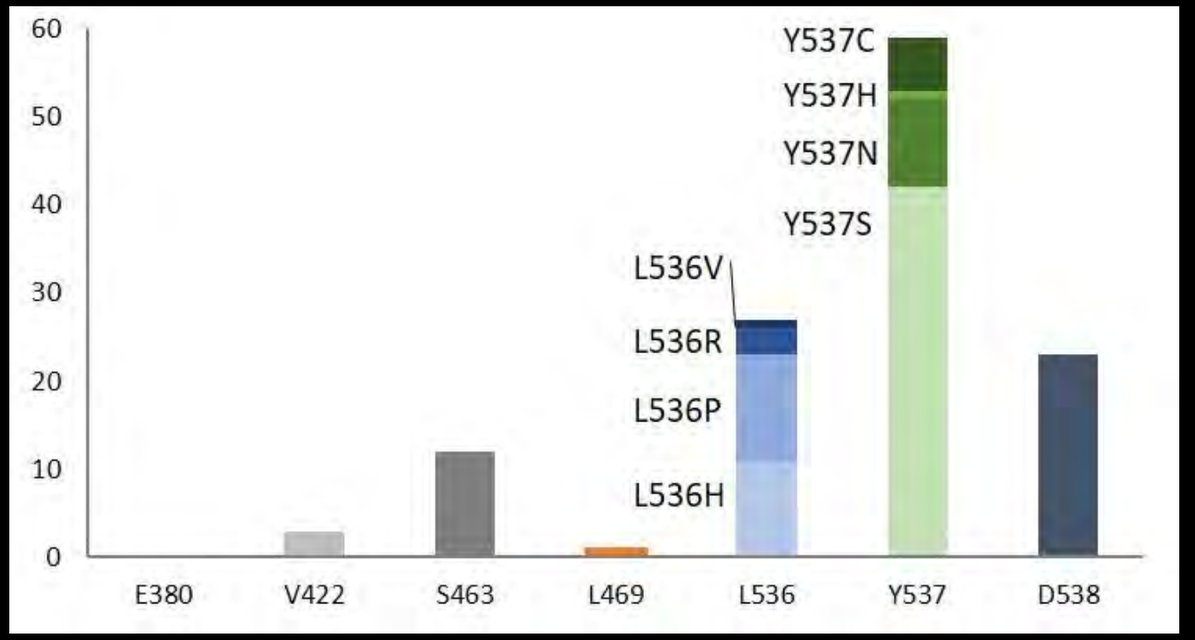
"-": none present, FT: fallopian tube, Mut: mutation *Includes 10 cases with 2 alterations each, ∞1 ovarian case & 2 uterine cases w/ 2 codon 536-538 mutations each

ESR1 mutations identified through public databases

	N in dataset	*mutESR1* N (%)	Histology	Ref
LGSOC	26	1 (3.8)	Low-grade serous	1
AACR GENIE				2
Cervix	271	1 (0.4)	Adenocarcinoma	
Ovary	1473	2 (0.1)	2 Endometrioid	
Endometrial	1076	26 (2.4)	26 Endometrioid	
Uterine Sarcoma	199	2 (1.0)	2 ESS	
TCGA				
Uterine Corpus	248	5 (2.0)	5 Endometrioid	3
Ovary		0		4
Cervix		0		5
Uterine Carcinosarcoma	22	1 (4.5)	Carcinosarcoma	6

[1]McIntyre, *Histopathology* 70, 347-358 (2017). [2]A.P.G. Consortium, *Cancer Discov* 7, 818-831 (2017). [3]N. Cancer Genome Atlas Research, *Nature* 497, 67-73 (2013). [4]N. Cancer Genome Atlas Research, *Nature* 474, 609-615 (2011). [5]Merenbakh-Lamin, *Cancer Res* 73, 6856-6864 (2013). [6]Jones, *Nature Comm* 5, 5006 (2014).


ERα
59
Y537S/N/C
L536H/P/R/V
27
23
D538G
S463P
12
V422del
3
L469V
NH2
NTD
DBD
hinge
LBD
COOH
1
180
263
302
552
595


60
50
40
30
20
10
0
Y537C
Y537H
Y537N
Y537S
L536V
L536R
L536P
L536H
E380
V422
S463
L469
L536
Y537
D538

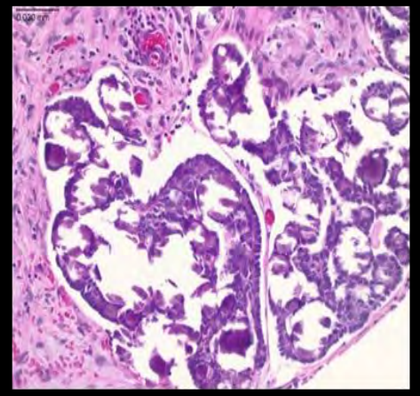
ESR1 mutations are enriched in hormone-responsive histologies

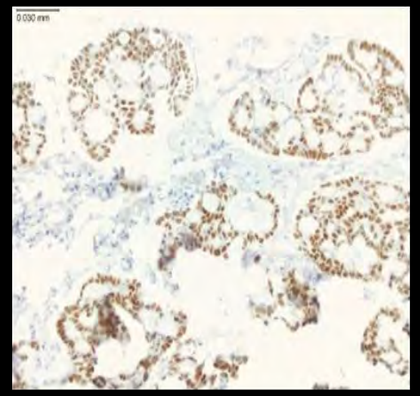
Dataset	Histology	N	*mutESR1* N (%)	p
CGP analysis				
Ovary	serous	3502	12 (0.3)	0.0004
	endometrioid	144	5 (3.5)	
Uterus	serous	446	1 (0.2)	<0.0001
	endometrioid	548	24 (4.4)	
Sarcoma	LMS	421	3 (0.7)	0.09
	ESS	103	3 (3.0)	
AACR GENIE				
Ovary	high-grade serous	687	0	0.006
	endometrioid	57	2	
Uterus	serous	203	0	0.0004
	endometrioid	518	25 (4.8)	
Sarcoma	LMS	113	0	0.018
	ESS	16	2 (12.5)	

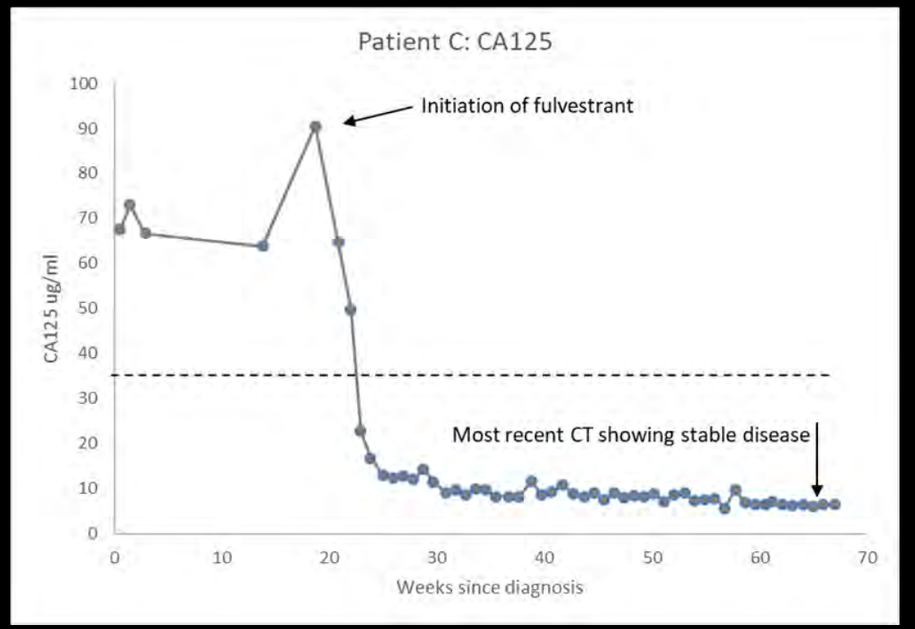
P value calculated using Fisher’s exact test

One patient's story:

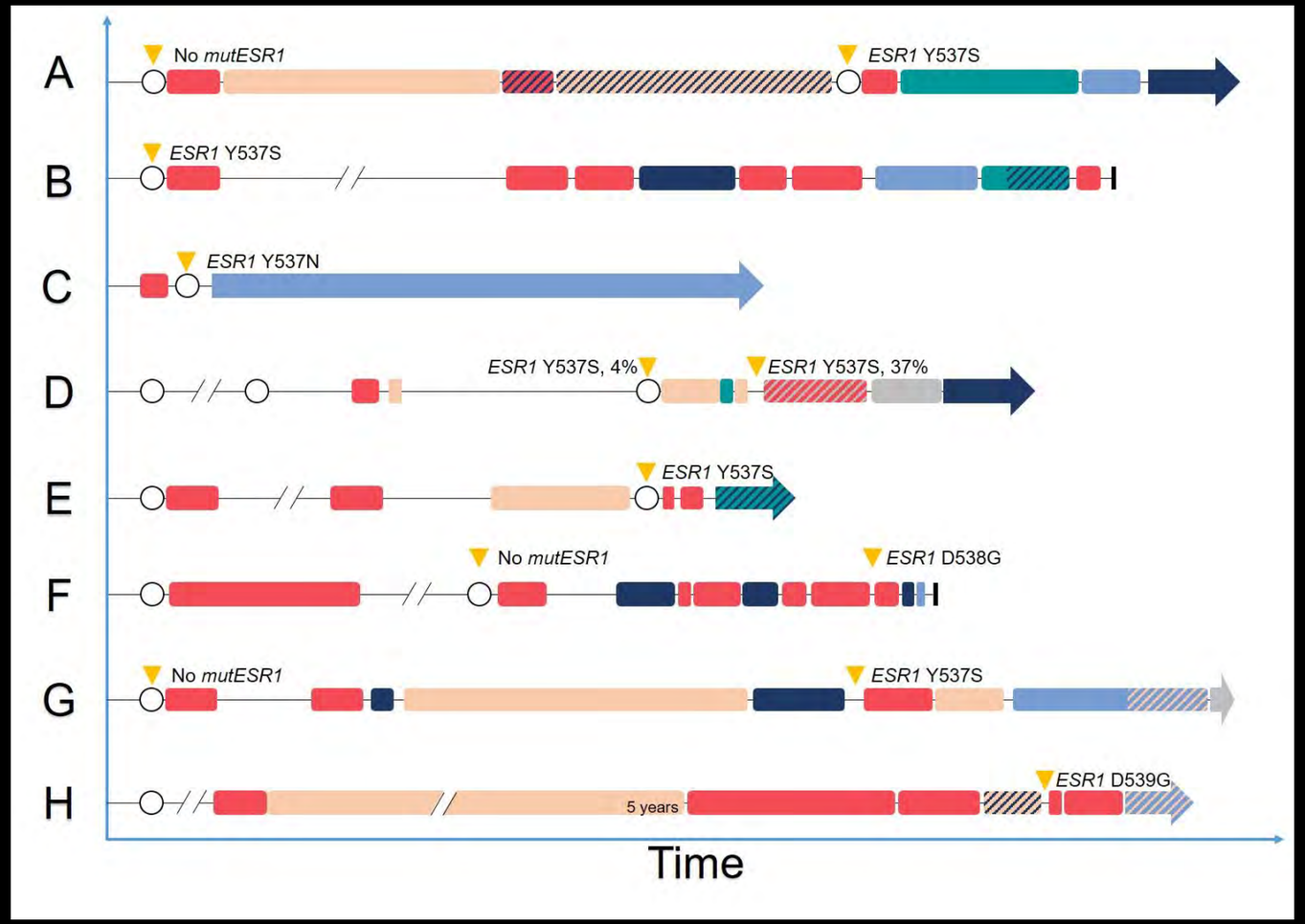
- 58F diagnosed with low-grade serous papillary carcinoma of gyn origin
  - Neoadjuvant Carboplatin/Paclitaxel
    - 3 cycles
    - CT: No change in calcified peritoneal carcinomatosis, bilateral pulmonary nodules
    - Attempted cytoreductive surgery: tumor engulfing small & large bowel, extensive adhesions

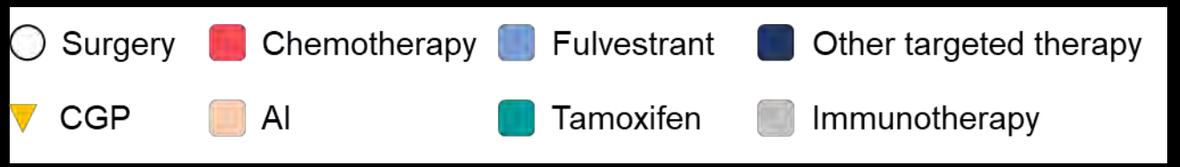






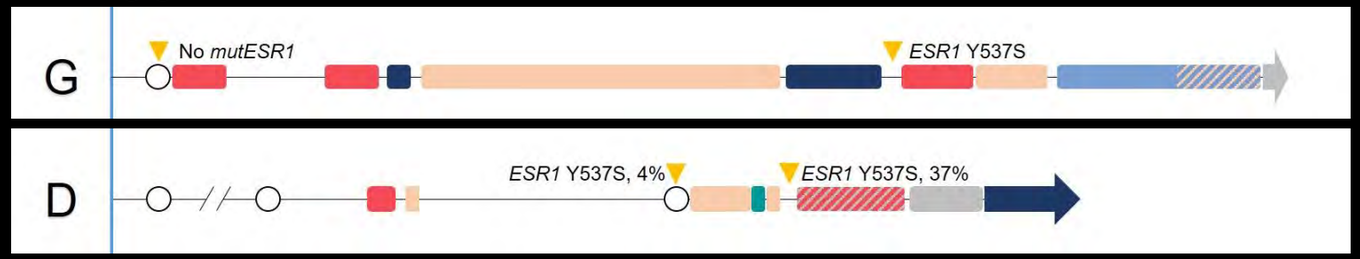
Clinical Relevance of *ESR1* mutations in Gyn Cancers

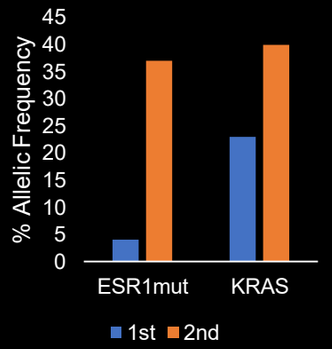




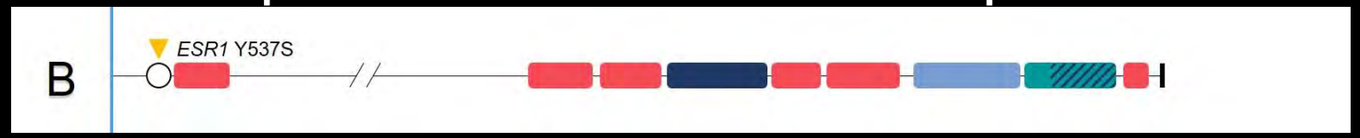
Key Points from Clinical Review

- Prior treatment with aromatase inhibitors in 5 cases
  - Suggests mutation as a mechanism of resistance





- Mutations present in absence of exposure to endocrine therapy



- *mutESR1* tumors may clinically benefit from anti-ER directed therapy

Potential Reasons for Differences in Benefit

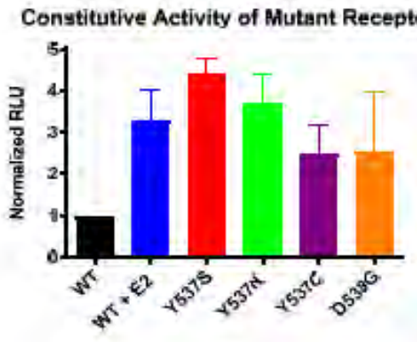
1. the use of hormone therapy in a later phase of the disease course after the cancer has had the opportunity to develop multiple adaptive/resistance mechanisms

2. the influence of co-occurring mutations

3. the specific *mutESR1* present within each tumor

Mutations Confer Partial Resistance

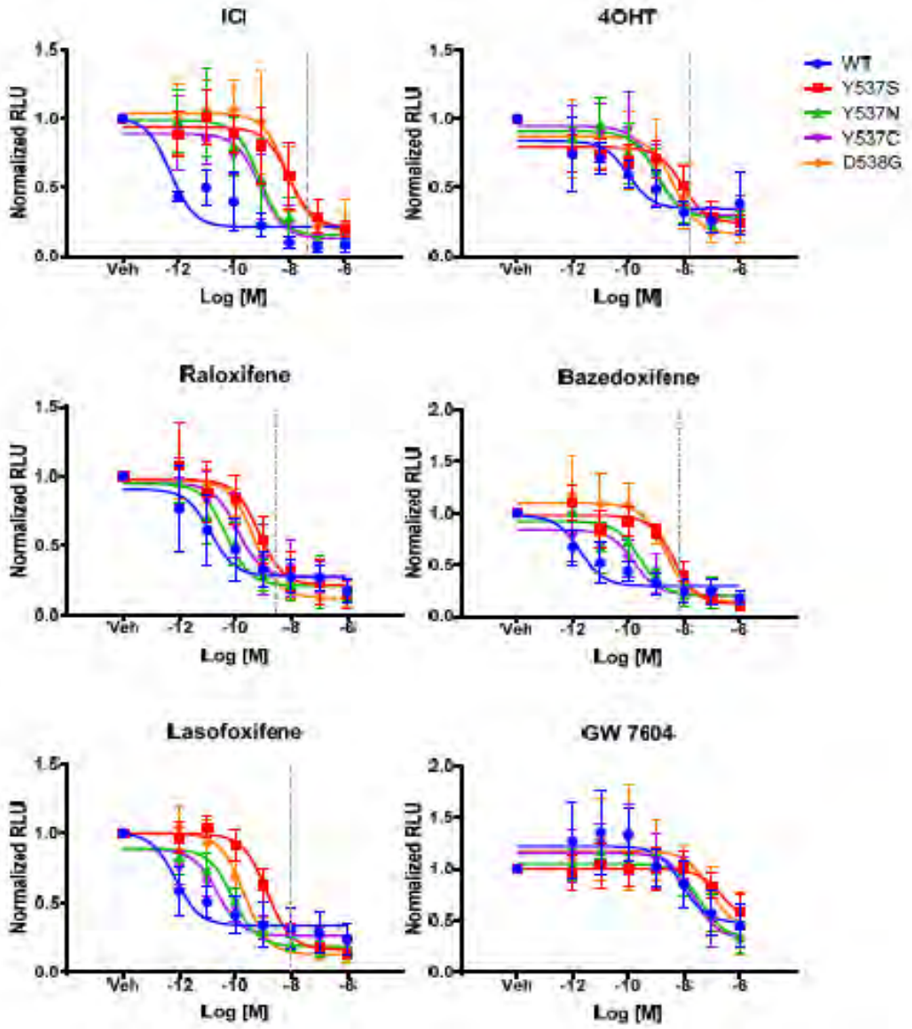
A



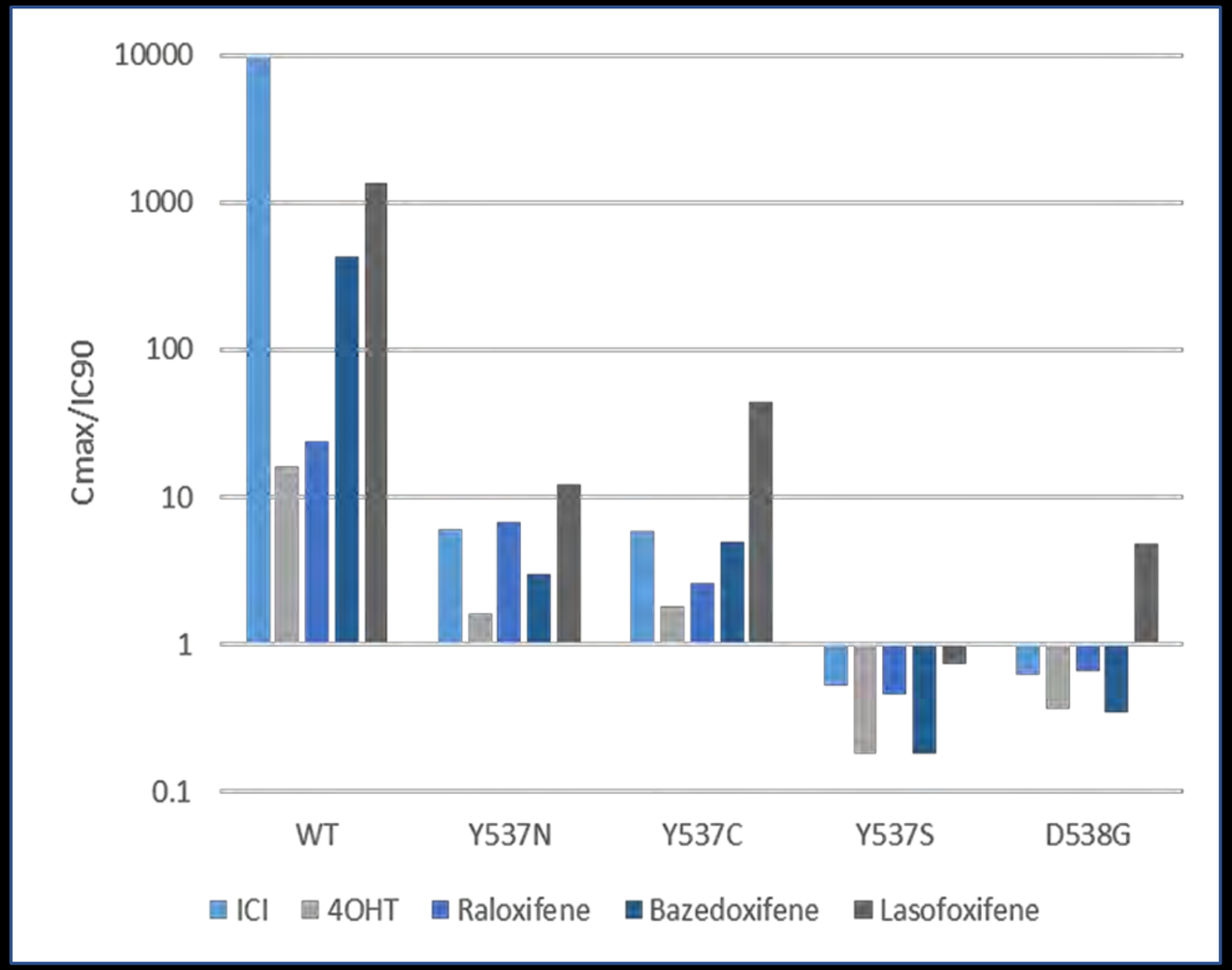
B

	ICI	4OHT	Raloxifene	Bazedoxifene	Lasofoxifene	GW 7604
			IC50 (pM)			
WT	0.53	102.7	13.27	1.867	0.7425	8576
Y537N	830.9	1050	46.98	268.1	82.75	38290
Y537C	887.8	923.1	121.3	166.1	22.69	22270
Y537S	9606	8877	696.8	4548	1351	218900
D538G	8102	4393	487.7	2301	208.5	86870
			IC90 (pM)			
WT	4.76	924	119	16.8	6.68	77200
Y537N	7480	9450	423	2410	745	345000
Y537C	7990	8310	1090	1490	204	200000
Y537S	86500	79900	6270	40900	12200	1970000
D538G	72900	39500	4390	20700	1880	782000

C



Inhibitory Blood Concentrations May Not Be Achievable for some Mutations

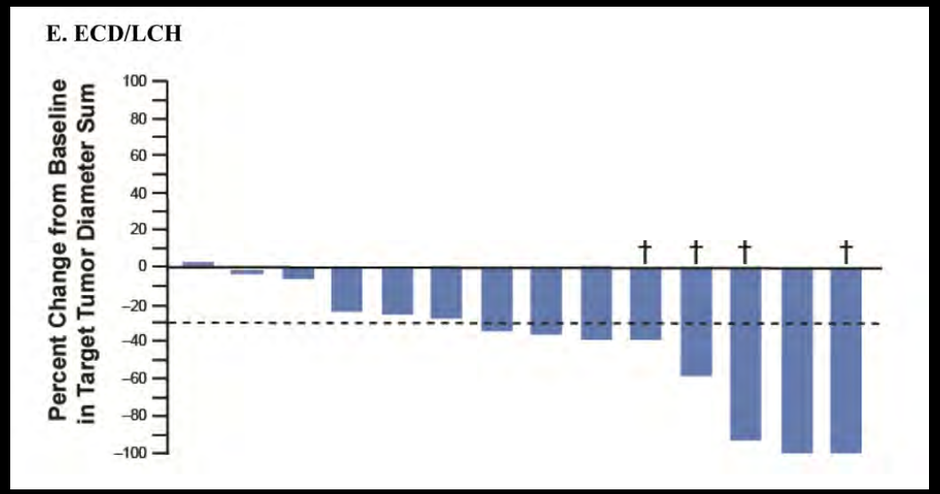


Summary

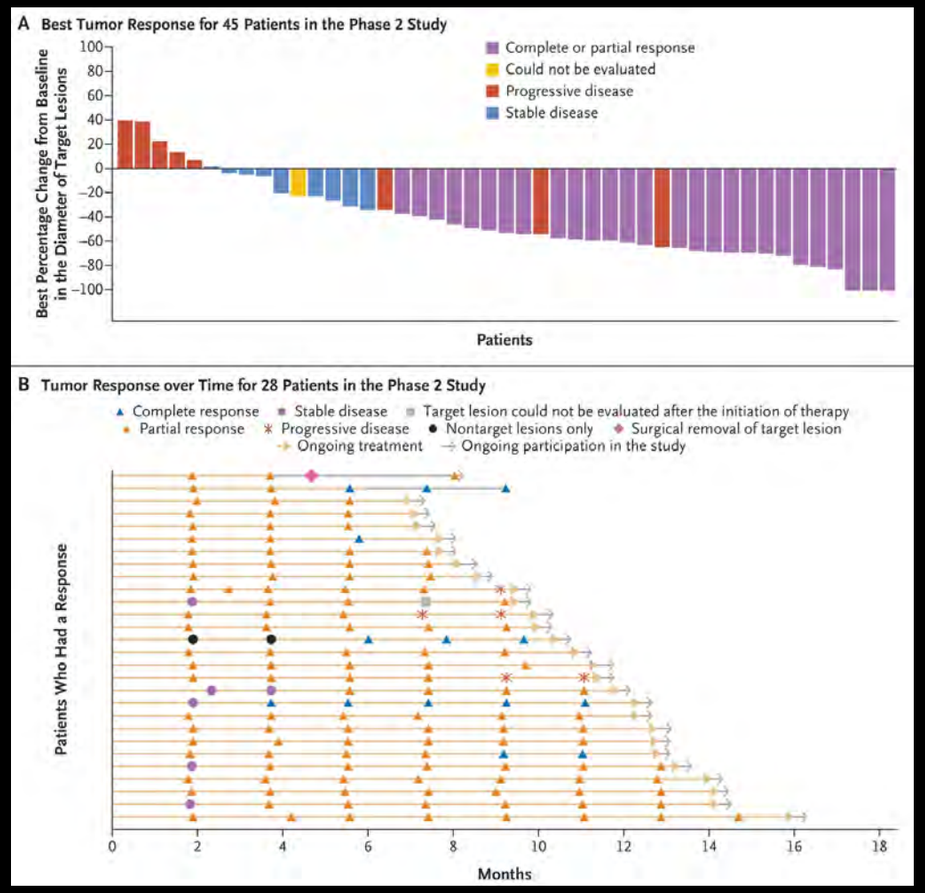
- *ESR1* mutations are rare findings in rare cancers
  - Prevalence may increase with increased use of aromatase inhibitors
  - May be present in the primary tumor
  - Hotspot sequencing may miss some cases of activating mutations
  - Heterogeneity and polyclonality
- Important Treatment implications
  - Resistance to aromatase inhibitors
  - May respond to anti-ER directed therapy (SERMs/SERDs)
  - Relative response may be affected by the mutation(s) present
- Needs
  - Determine the true prevalence and conditions under which they arise
  - Development of drugs that more effectively inhibit mutERα, esp Y537S and D538G

Clinical Trial Implications

- Challenge of recruitment given small numbers
  - Advantage of cooperative group/rare tumor committee



Hyman et al, NEJM 2015



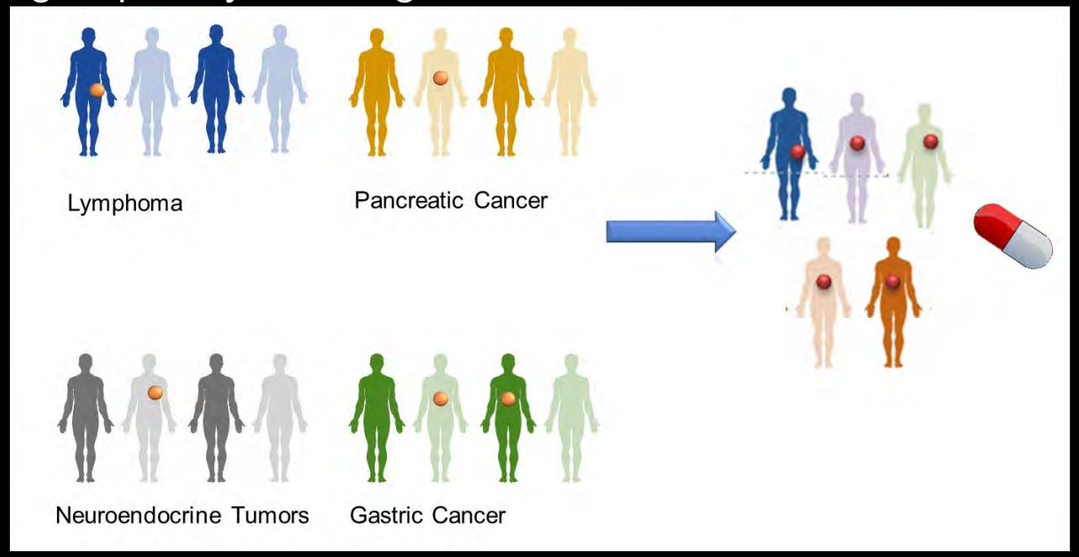
Migden, NEJM 2018

Clinical Trial Implications

- Challenge of recruitment given small numbers
  - Advantage of cooperative group/rare tumor committee
- Modern Trial Designs

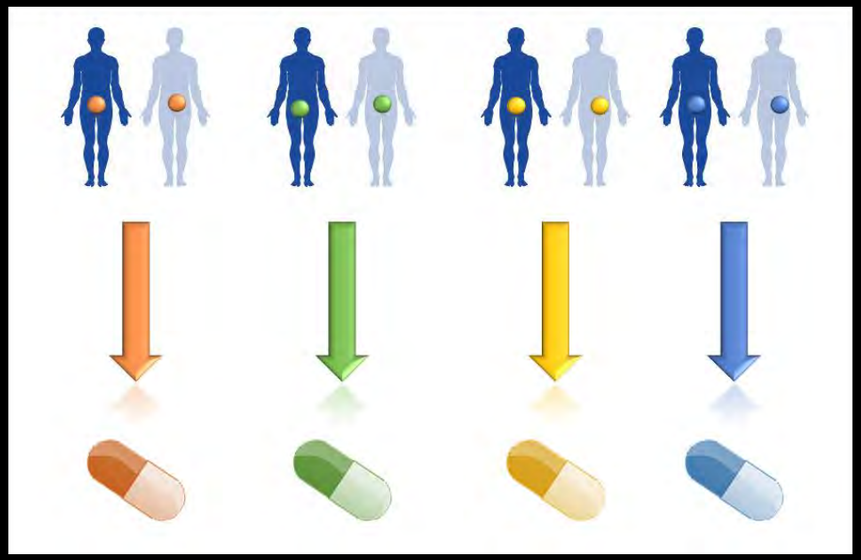
Basket Trials

Multiple tumor/histologic types are grouped by similar genomic alteration



Umbrella Trials

Single tumor type divided by individual genomic alterations



Clinical Trial Implications

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  - Hybrid designs
  - Adaptive designs

Clinical Trial Implications

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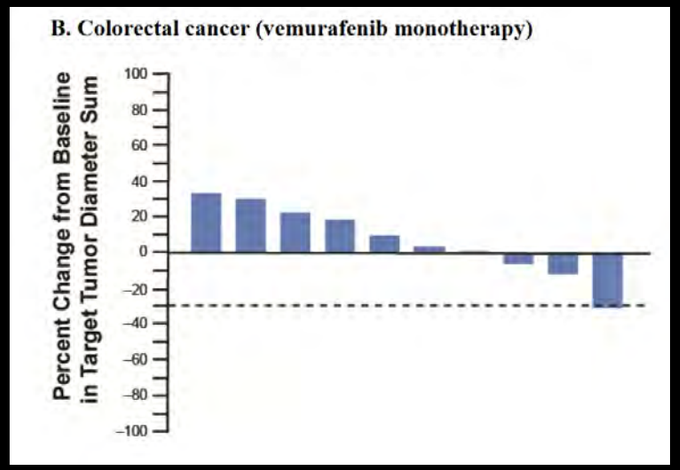
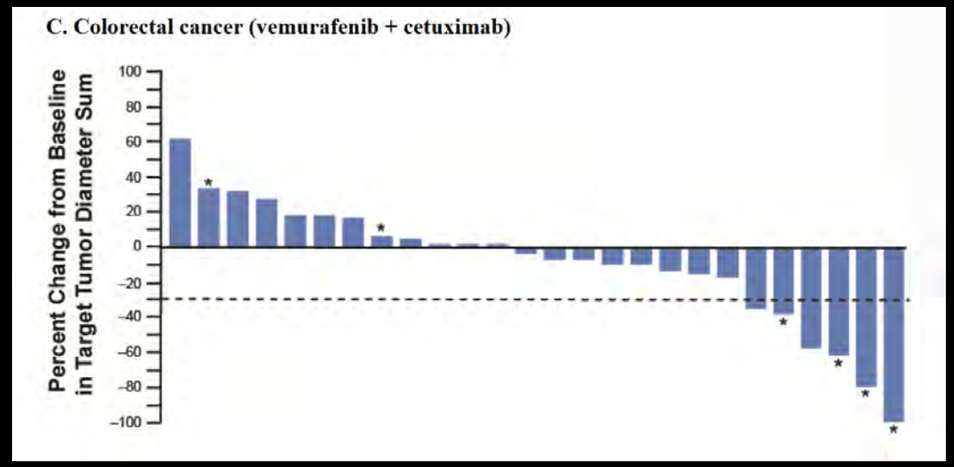
  - Adaptive designs
- Lessons from prior trials
  - Tumor context matters





Hyman, NEJM 2015

Clinical Trial Implications

- Challenge of recruitment given small numbers
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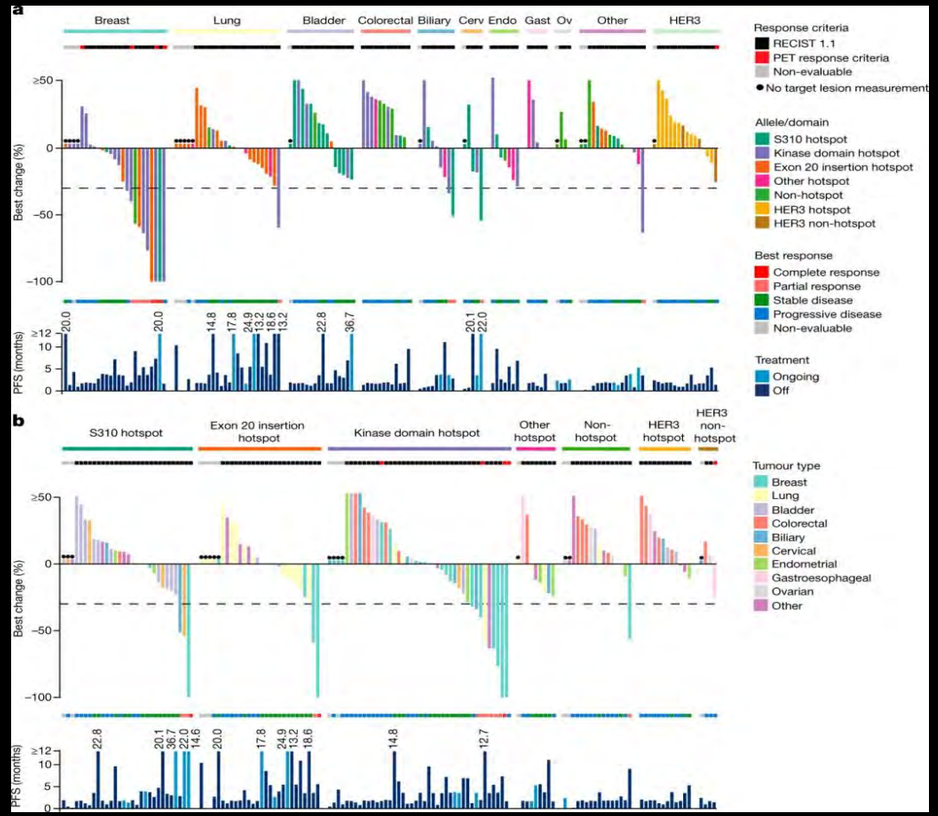
- Modern Trial Designs
  - Hybrid designs
  - Adaptive designs
- Lessons from prior trials
  - Tumor context matters
  - Not all mutations are the same



D M Hyman *et al. 2018 Nature*

Clinical Trial Implications

- Challenge of recruitment given small numbers
  - Advantage of cooperative group/rare tumor committee
- Modern Trial Designs
  - Hybrid designs
  - Adaptive designs
- Lessons from prior trials
  - Tumor context matters
  - Not all mutations are the same
- Endpoints need to be selected wisely

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Progress in Drug Development for Rare Epithelial Ovarian Cancers: The NRG Oncology Experience and Beyond

David M. Gershenson, MD
The University of Texas
MD Anderson Cancer Center

Framework

- Scope of discussion: Rare EOC
  - Clear Cell Carcinoma
  - Low-Grade Serous Carcinoma
  - Mucinous Carcinoma
- All rare ovarian cancers are not created equal
- GOG established Rare Tumor Committee in 2005
- No rare EOC trials existed prior to that time
- Essentially no prospective data for rare subtypes

Challenges and Barriers

- Small number of cases
- Long accrual times
- Few interested investigators
- Less attention by scientific community
- Funding priority has been low
- Low priority for Pharma
- Fewer patient advocates
- Lack of standard bioinformatics methods and trial designs

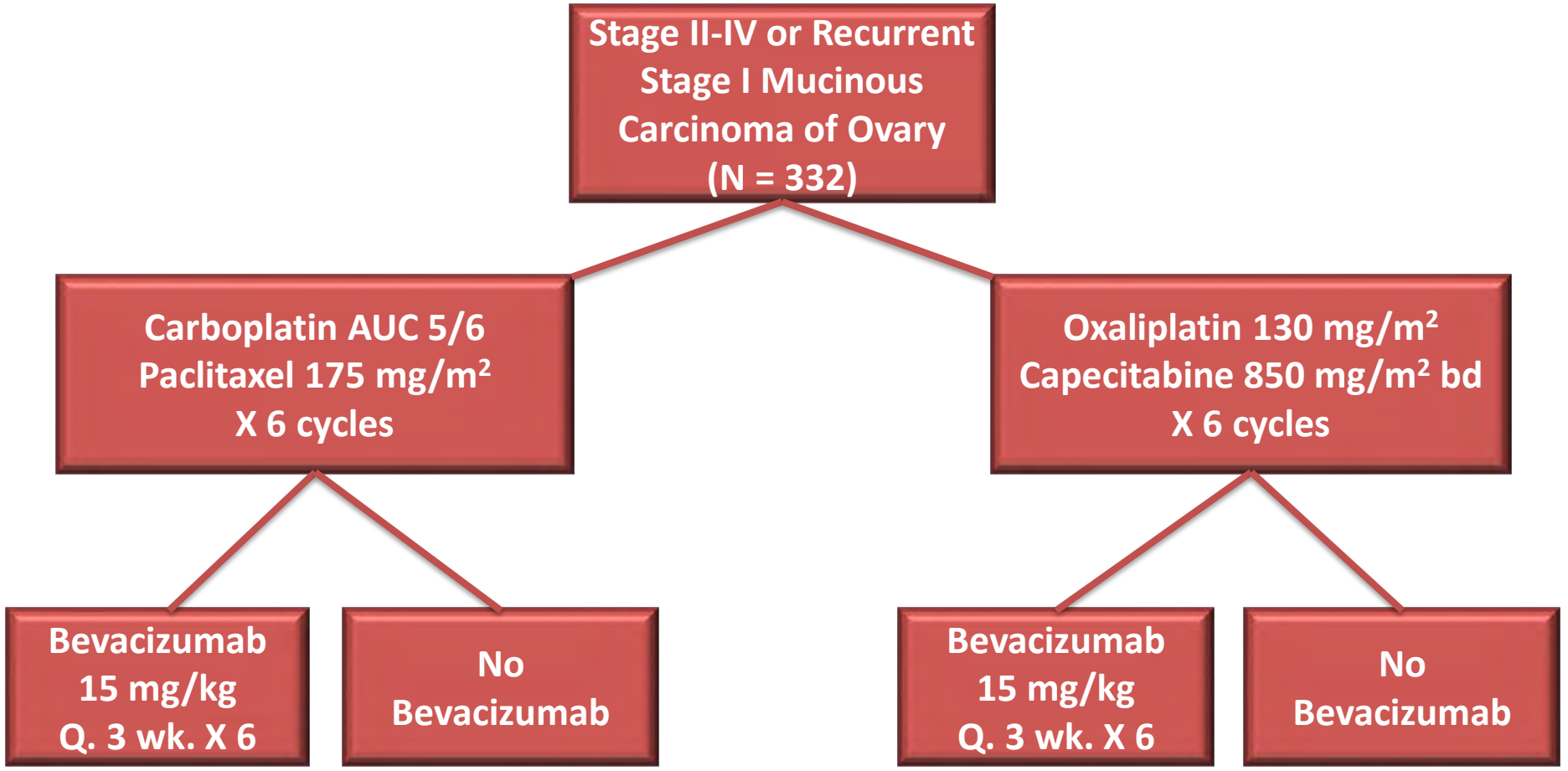
Clinical Features

Feature	Clear Cell	Low-Grade Serous	Mucinous
Incidence	5%	5%	10%
Stage Distribution			
Stages I/II	67%	10%	61%
Stages III/IV	33%	90%	39%
Biology	Aggressive	Indolent	Aggressive
Relative Chemoresistance	Yes	Yes	Yes
Outcomes in Early Stage	Similar to HGSC HR = .87	Unknown but thought to be excellent	Similar to HGSC HR = .87
Outcomes in Advanced Stage	Median OS = 21 mo Worse than HGSC HR = 2.2	Median OS = 101 mo Better than HGSC HR = ?	Median OS = 15 mo Worse than HGSC HR = 2.7

Mucinous Carcinoma:
Key Pathways & Potential Targets

- **Angiogenesis pathway**
- **HER-2/neu amplification (20%)**
- **MAPK (*KRAS* mutation, 40-50%)**

mEOC/GOG 241: A Randomized Phase III Trial of Capecitabine/Oxaliplatin vs. Paclitaxel/Carboplatin +/- Bevacizumab in Patients with Previously Untreated Mucinous Ovarian Cancer



mEOC/GOG 0241

- Target accrual = 330
- Closed early for slow accrual: Only 50 pts accrued (34 UK, 16 US)
- 40/50 cases available for central pathology review: Only 18 (45%) were diagnosed as primary mucinous ovarian cancer
- Neither of experimental regimens (Oxal/Cape vs. Pac/Carbo or Bev versus no Bev) clearly improved OS or PFS

Mucinous Carcinoma: Future Directions

- Advanced stage mucinous carcinoma is rarer than originally thought
- Path for progress: Smaller phase II trials or basket trials
- Prospective central pathology review is essential
- Potential trials:
  - Targeting KRAS mutations
  - Targeting HER-2/neu amplification
  - Immunotherapy: Pts whose tumors have high CD8+ tumor-infiltrating lymphocytes have improved survival
  - PI3K/mTOR + MEK inhibitors show synergistic anti-tumor effects preclinically
  - Oxaliplatin + dasatinib reduces cancer cell viability and promotes apoptosis in human mEOC cell lines

Clear Cell Carcinoma:
Key Pathways & Potential Targets

- ARID1A mutation 50%
- PI3K/AKT/mTOR pathway 30-40%
- Angiogenesis pathway
- PD-1 and PD-L1
- HNF-1β upregulation 100%
- IL6-HIF-1α pathway upregulation 50%
- MET amplification 20-30%
- HER-2 amplification 14%
- PPM1D amplification 10%
- Microsatellite instability (MSI) 7-18%

Clear Cell Carcinoma

Trial	Phase	Setting	No. Pts	Agent(s)	Results
JGOG3017	III	First-line	667	Irinotecan/Cisplatin vs Paclitaxel/Carboplatin	2-yr OS = 85.5% vs 87.4% (NS)
GOG 268	II	First-line	90	Paclitaxel/Carboplatin + Temsirolimus → Temsirolimus maintenance	54% with PFS > 12 mo No better than historical controls
GOG 254	II	Recurrent	35	Sunitinib	ORR = 6.7% Median PFS = 2.7 mo
NRG-GY-001	II	Recurrent	13	Cabozantinib	ORR = 0% Median PFS = 3.6 mo
Princess Margaret Cancer Centre Trial	II	Recurrent	40	ENMD-2076	ORR = 5% Median PFS = 3.7 mo

Clear Cell Carcinoma

Trial	Phase	Setting	No. Pts	Agent(s)	Results
GOG 283	II	Recurrent	35	Dasatinib	Pending analysis
NiCCC	Randomized II	Recurrent	--	Nintedanib vs SOC	Recruiting
NRG-GY-014	II (basket)	Recurrent	--	Tazemetostat	Not yet recruiting
NRG-GY-016	II	Recurrent	--	Pembrolizumab + Epacadostat	Not yet recruiting
ATARI/NCRI	II	Recurrent	--	AZD6738 +/- Olaparib	Not yet recruiting

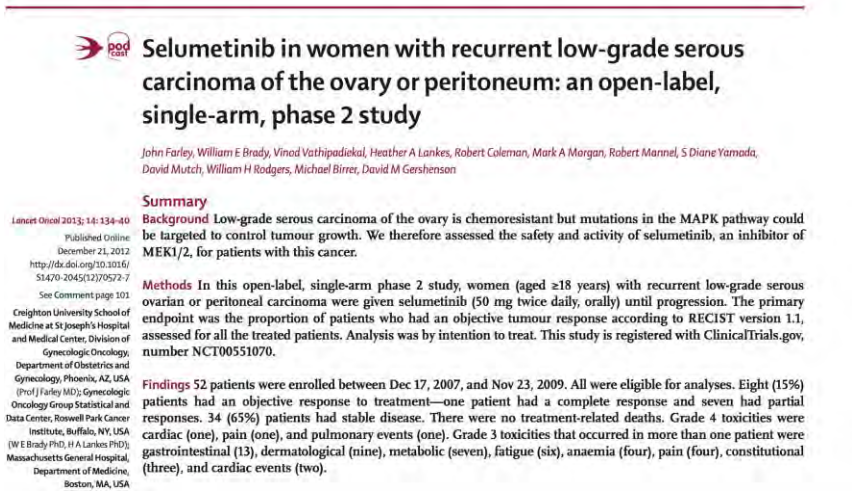
Clear Cell Carcinoma: Future Directions

- Continue to conduct phase II or basket trials
- Targets of most interest:
  - PD-1 or PD-L1
  - ARID1A mutation
  - PI3K/AKT/mTOR pathway
  - Angiogenesis pathway

Low-Grade Serous Carcinoma: Key Pathways & Potential Targets

- **MAP Kinase pathway**
  - **KRAS 20-40%**
  - **BRAF 5-10%**
  - **NRAS 15%**
- **Estrogen Receptor**
- **Angiogenesis pathway**
- **IGFR-1**

GOG 0239



Selumetinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: an open-label, single-arm, phase 2 study

John Farley, William E Brady, Vinod Vathipadiekal, Heather A Lankes, Robert Coleman, Mark A Morgan, Robert Mannel, S Diane Yamada, David Mutch, William H Rodgers, Michael Birrer, David M Gershenson

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See Comment page 101

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Summary

Background Low-grade serous carcinoma of the ovary is chemoresistant but mutations in the MAPK pathway could be targeted to control tumour growth. We therefore assessed the safety and activity of selumetinib, an inhibitor of MEK1/2, for patients with this cancer.

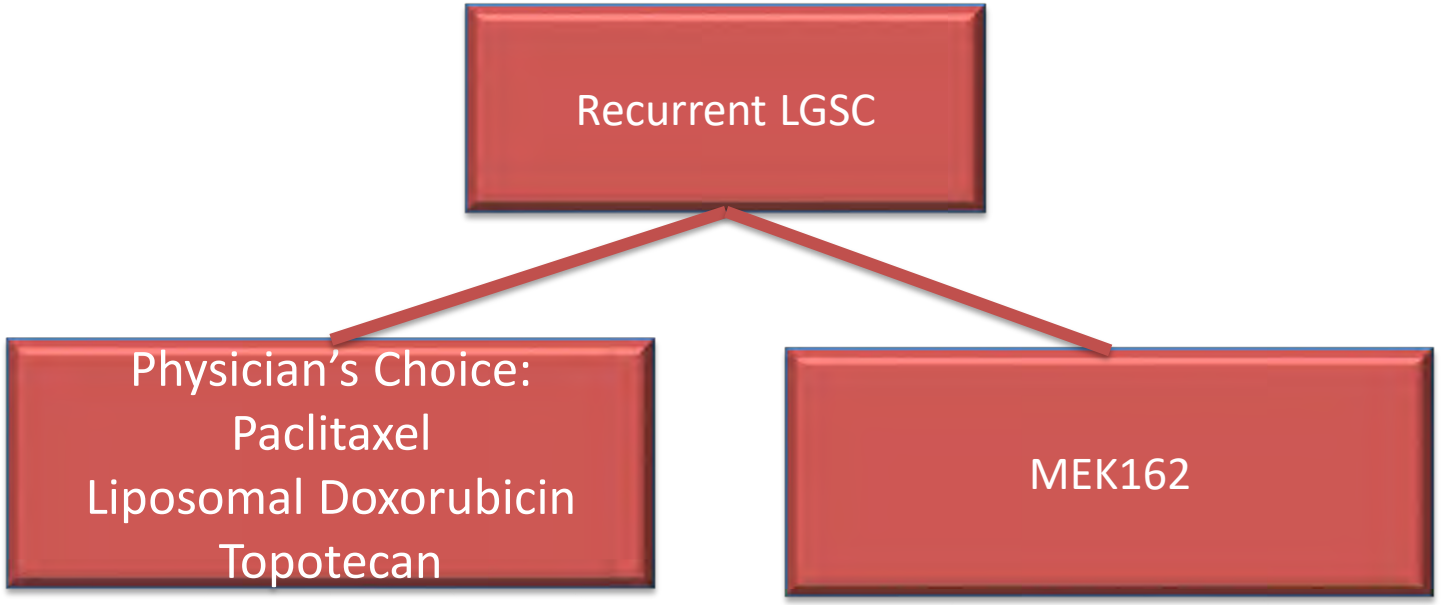
Methods In this open-label, single-arm phase 2 study, women (aged ≥18 years) with recurrent low-grade serous ovarian or peritoneal carcinoma were given selumetinib (50 mg twice daily, orally) until progression. The primary endpoint was the proportion of patients who had an objective tumour response according to RECIST version 1.1, assessed for all the treated patients. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00551070.

Findings 52 patients were enrolled between Dec 17, 2007, and Nov 23, 2009. All were eligible for analyses. Eight (15%) patients had an objective response to treatment—one patient had a complete response and seven had partial responses. 34 (65%) patients had stable disease. There were no treatment-related deaths. Grade 4 toxicities were cardiac (one), pain (one), and pulmonary events (one). Grade 3 toxicities that occurred in more than one patient were gastrointestinal (13), dermatological (nine), metabolic (seven), fatigue (six), anaemia (four), pain (four), constitutional (three), and cardiac events (two).

- **Phase II study of selumetinib (MEKi) in 52 women with recurrent LGSC**
- **ORR = 15%**
- **Clinical benefit rate = 80%**
- **No correlation of outcome with KRAS/ BRAF mutations**

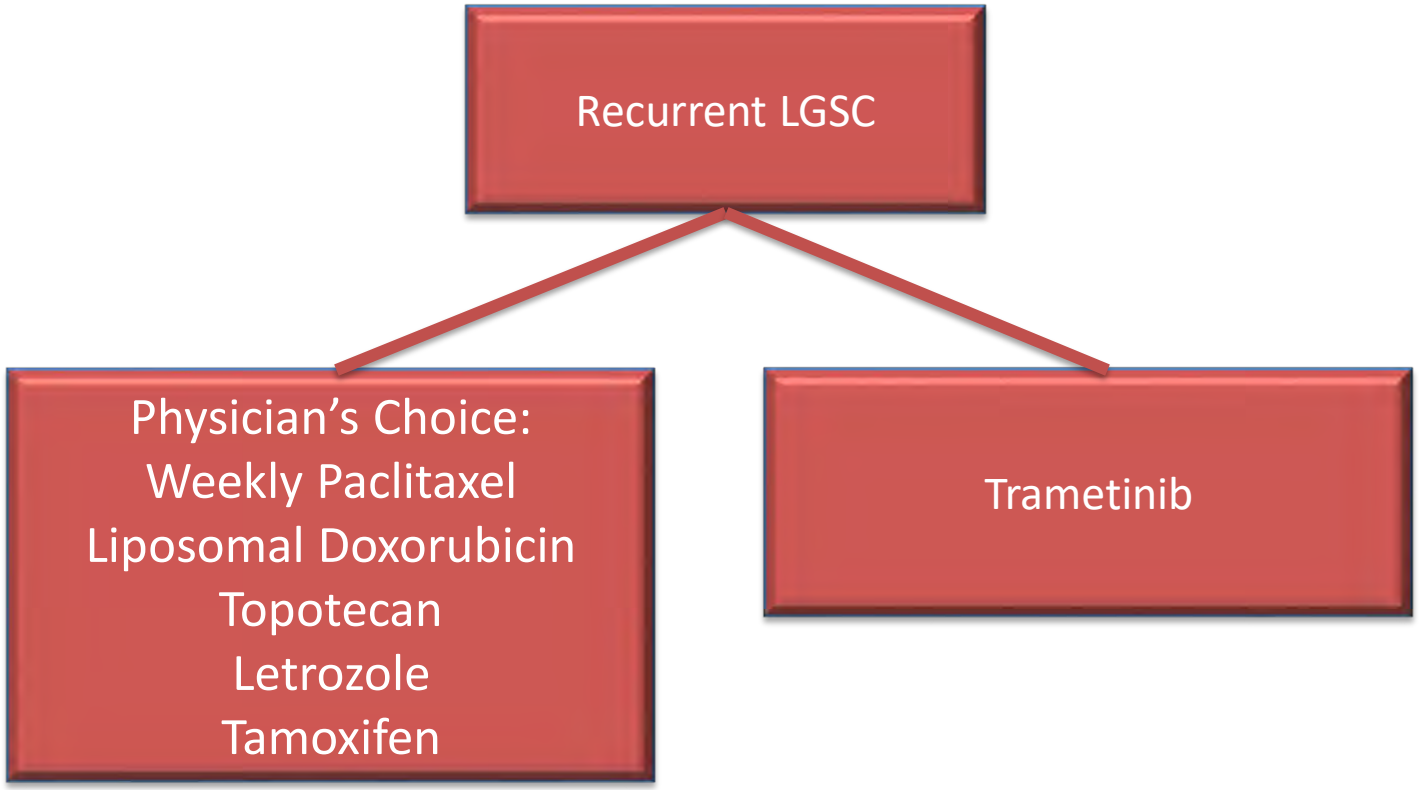
NCT01849874
MILO Trial

Randomized Phase III Trial



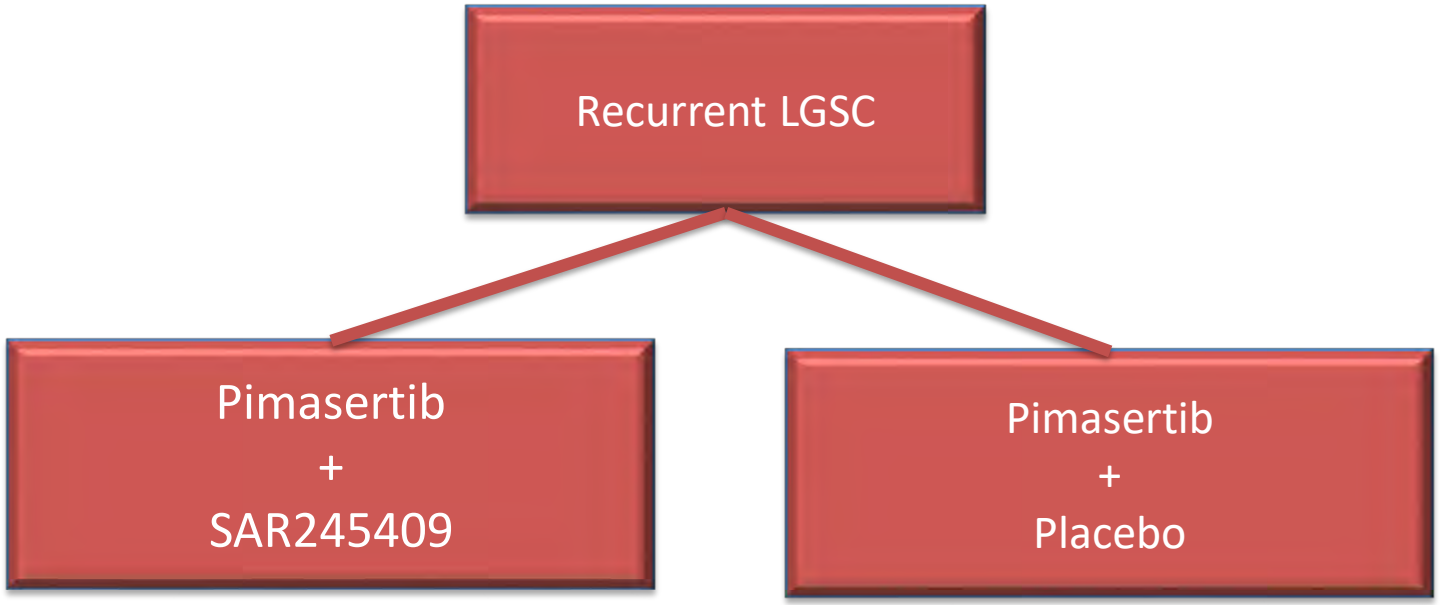
NCT02101788
GOG-0281

Randomized Phase III Trial

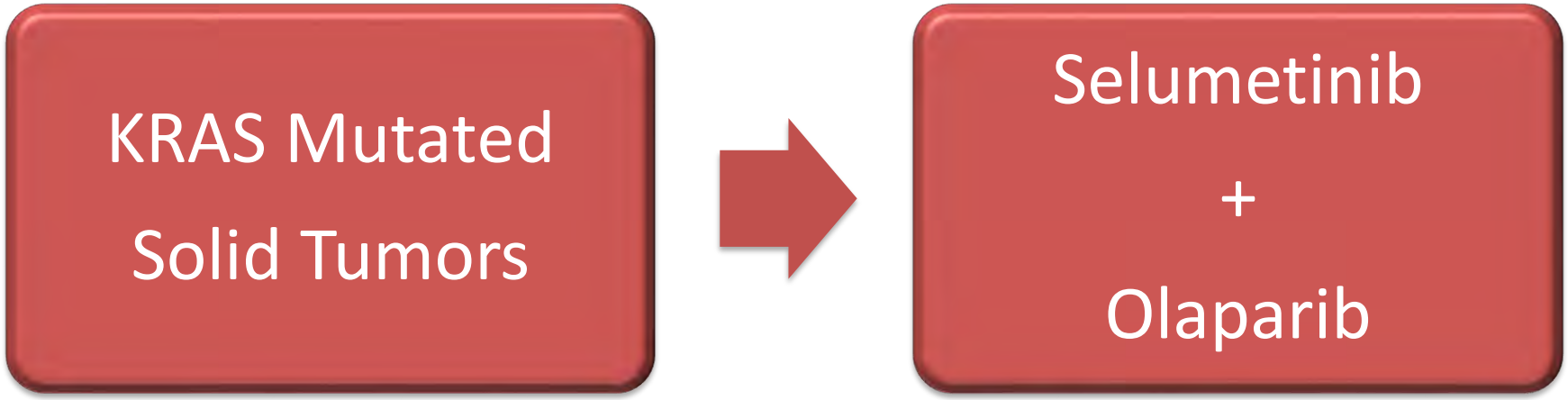


NCT01936363

Randomized Phase II Trial



Phase I Study of Selumetinib + Olaparib in Women with KRAS Mutant Tumors (SOLAR)



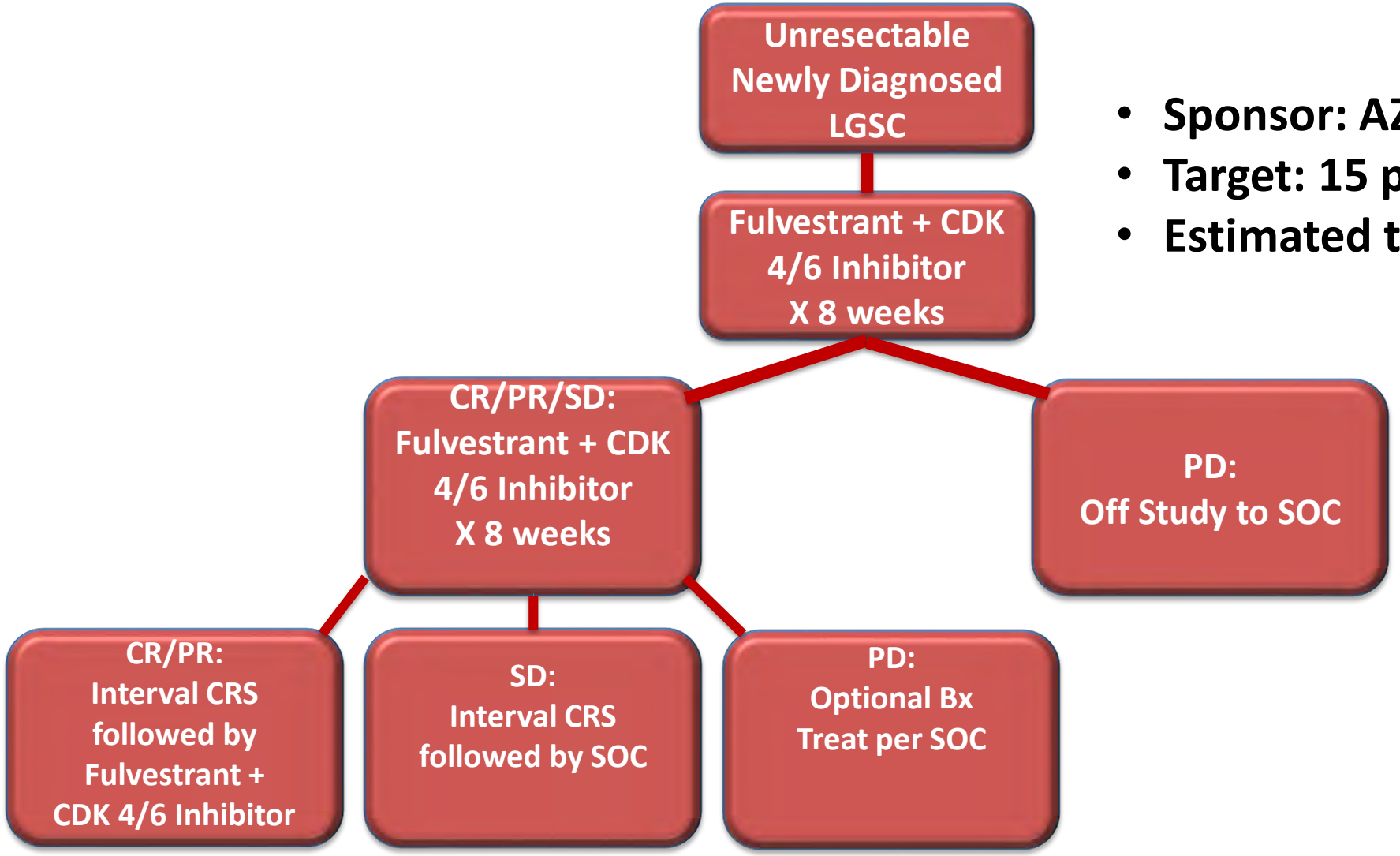
A Phase II Trial of Ribociclib + Letrozole in Women with Recurrent Low-Grade Serous Carcinoma

Recurrent
Low-Grade Serous Carcinoma

Letrozole 2.5 mg daily
+
Ribociclib 600 mg x 21d
then 7d off

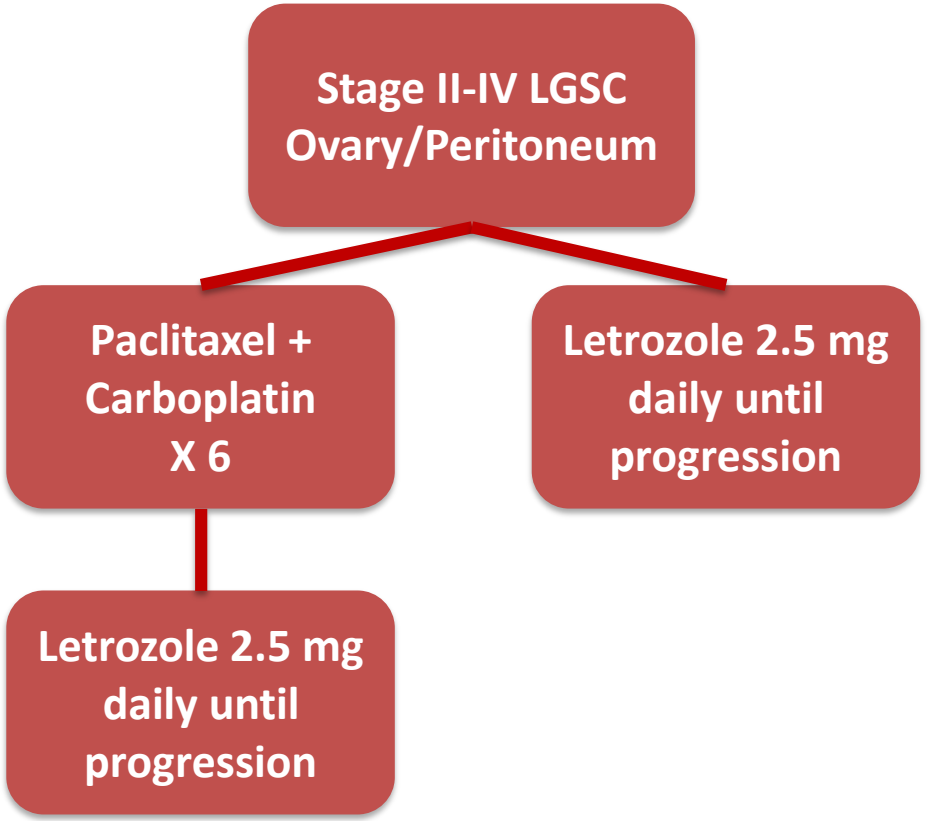
- **Sponsor: Novartis**
- **GOG Foundation Trial**
- **Target: 50 pts**
- **Estimated to activate Q3 2018**

Pilot Study of Neoadjuvant Fulvestrant + CDK 4/6 Inhibitor in Low-Grade Serous Ovarian Cancer



- **Sponsor: AZ**
- **Target: 15 pts**
- **Estimated to activate Q4 2018**

NRG-GY-019:
Randomized Phase III Trial of Paclitaxel/Carboplatin Followed by Maintenance Letrozole versus Letrozole Monotherapy in Stage II-IV Low-Grade Serous Carcinoma



- Sponsor: NCI (NRG Oncology)
- International phase III trial
- Primary Objective: PFS
- Target: 450 pts
- Estimated to activate Q2 2019

Low-Grade Serous Carcinoma: Future Directions

- Continue to study genomics of low-grade serous carcinoma
- Await findings from MEKi trials
- Conduct combination targeted aged trials
  - MEKi + PARPi
  - MEKi + Letrozole
  - MEKi + PI3Ki
  - MEKi + IGF-1R inhibitor
  - MEKi + Metformin
  - MEKi + BRAFi
- Activate trials focused on hormonal therapy

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SESSION IV Panel Discussion:

Development of Drugs for Rare Gynecological Malignancies

Moderators: Gordon B. Mills, MD, PhD

Panelists:

Amy E. McKee, MD

Annie E. Ellis

Stephen Keefe, MD, MSCE

Anil K. Sood, MD

Stephanie L. Gaillard, MD, PhD

David M. Gershenson, MD

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Summary & Future Directions

SGO Cochair: Robert L. Coleman, MD, FACOG, FACS

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Thank You

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