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

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

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JOHNS HOPKINS MEDICINE

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Astra Zeneca	Pfizer	Genentech
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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

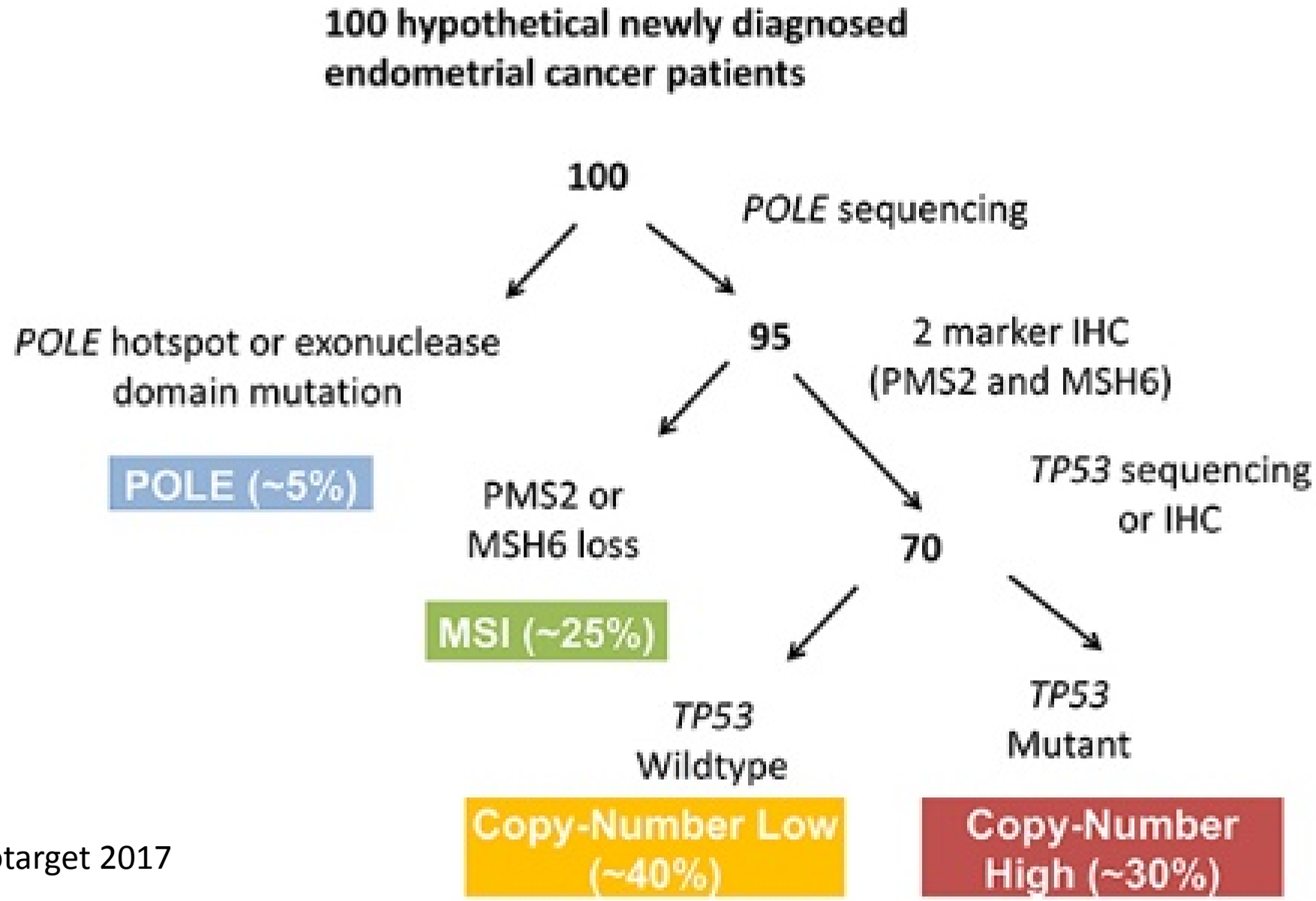
MMR Defects in Endometrial Cancer

- 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

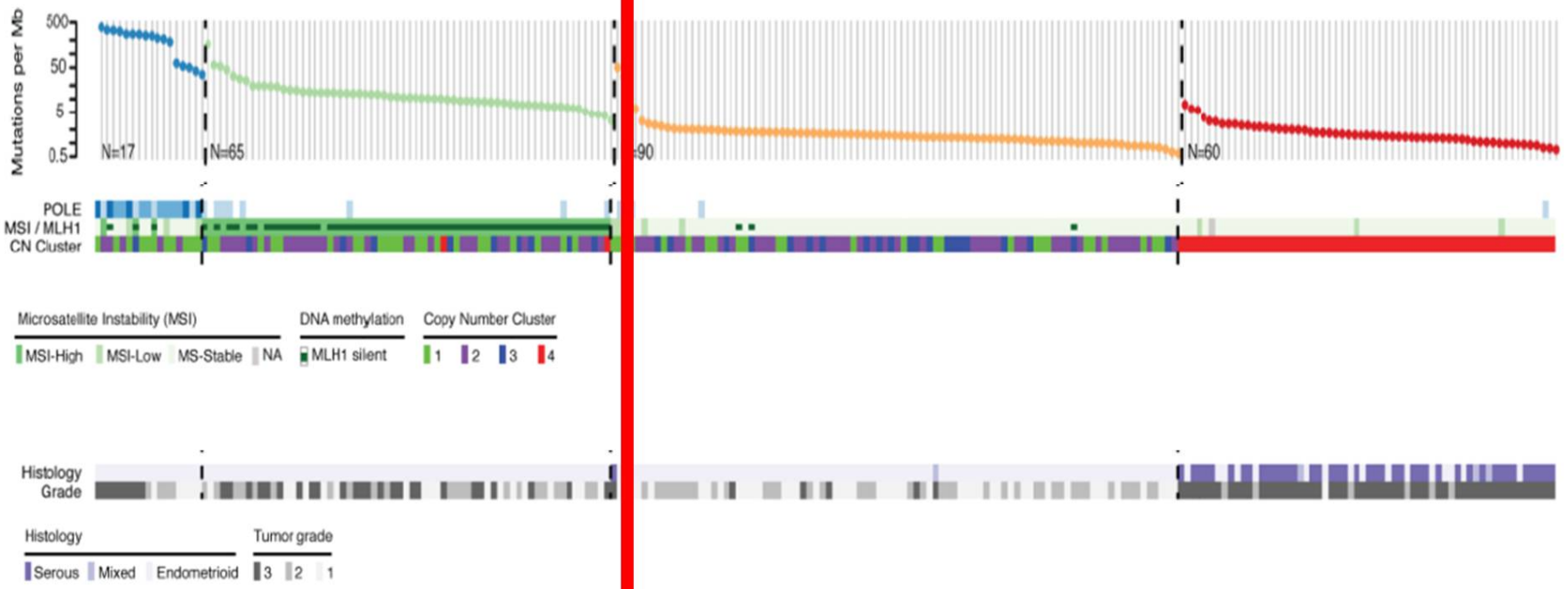
(Integrated genomic, transcriptomic and proteomic characterization)

POLE
ultra-mutated
(15x > vs MSI)

MSI
hyper-mutated
(8x > vs MSS)

Copy number low
- endometrioid -
(MSS group)

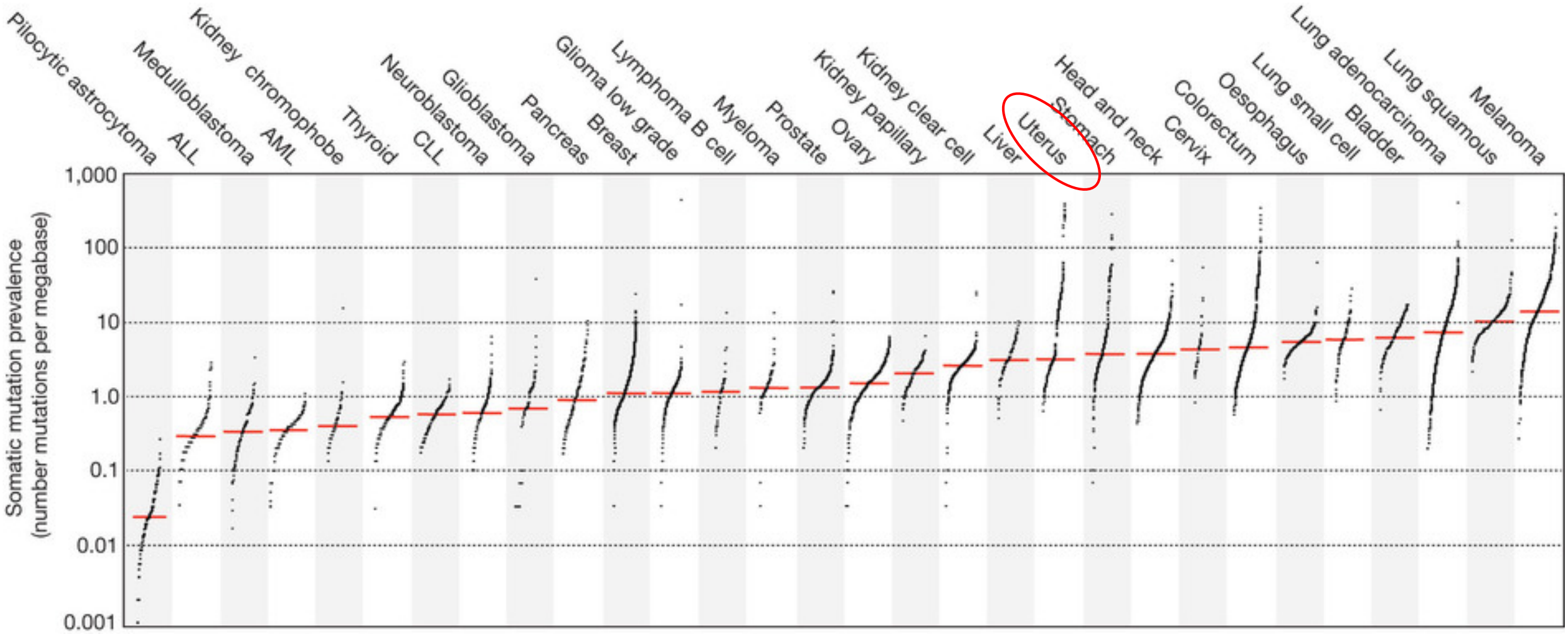
Copy number high
- serous-like -



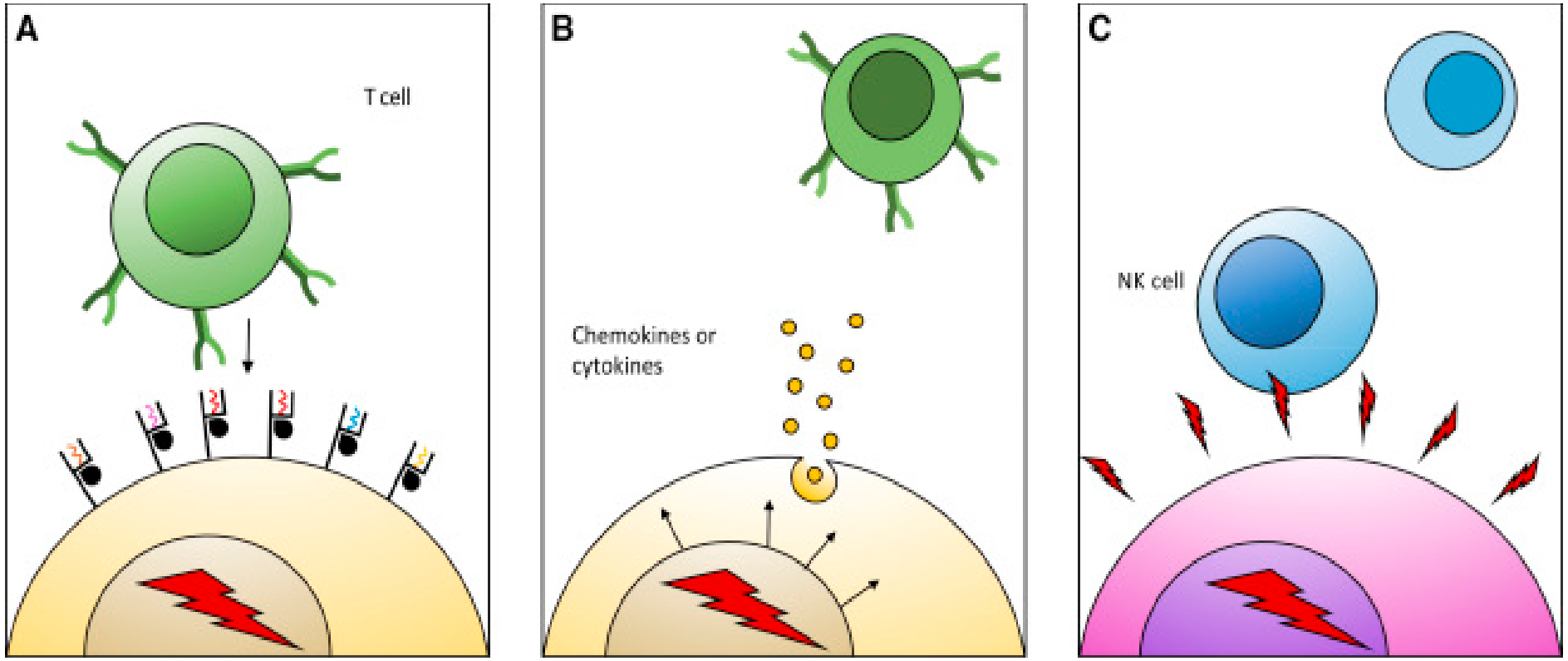
Hot tumors

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%

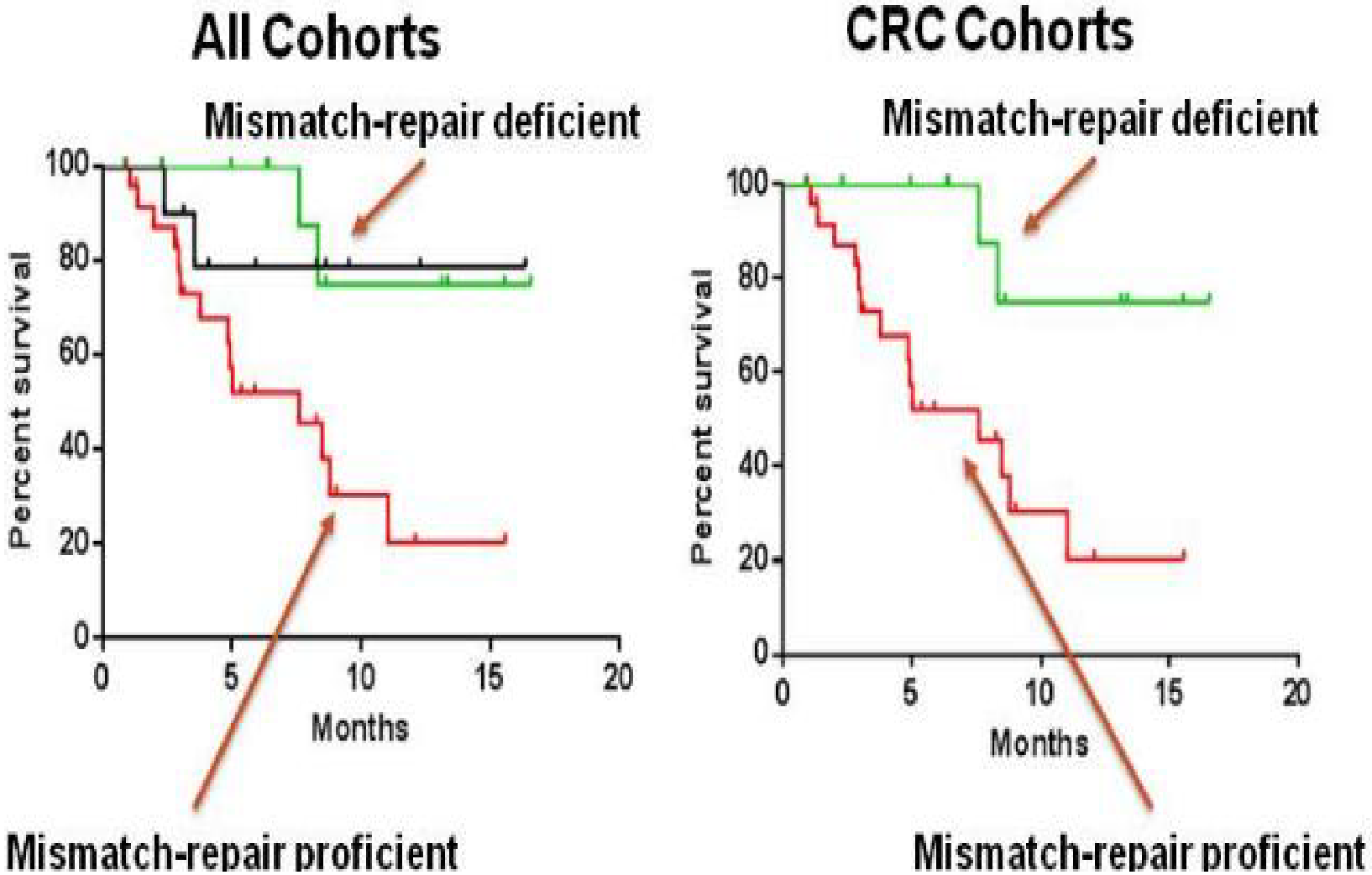
Le et al, *NEJM*, 2015

Endometrial Cancer Cohort

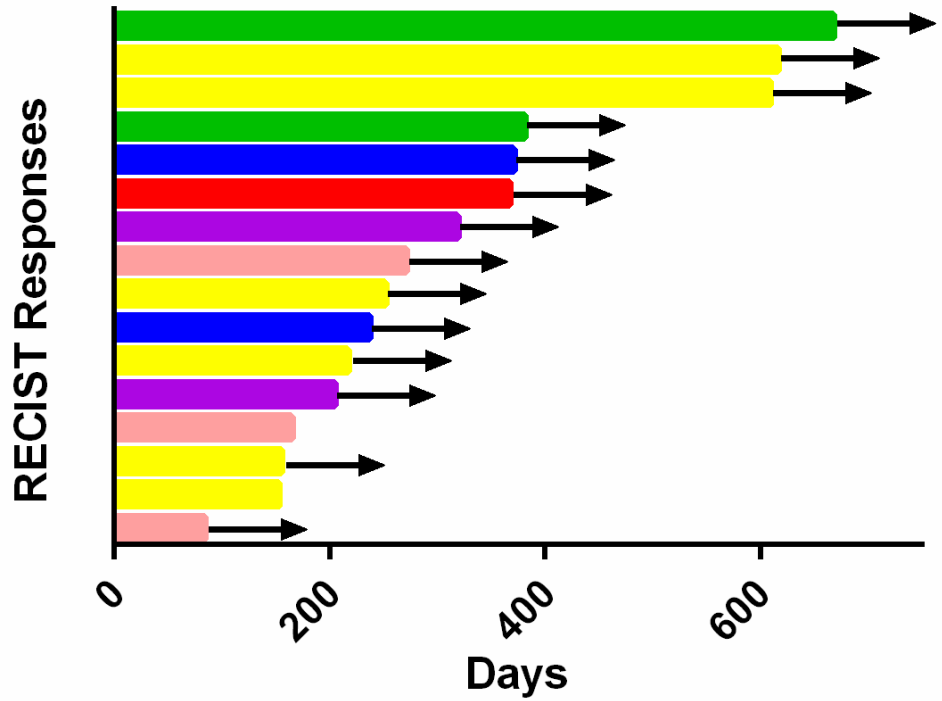
- **Nine 9 patients with MSI-high recurrent or progressive endometrioid endometrial cancer enrolled**
- **Median – 2 prior therapies**
- **Overall response rate is 56% (95% CI: 21-86%, N=5/9)**
  - **CR 1, PR 4**
  - **3 pts with prolonged SD**
- **Disease control rate, or "clinical benefit" rate (CR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

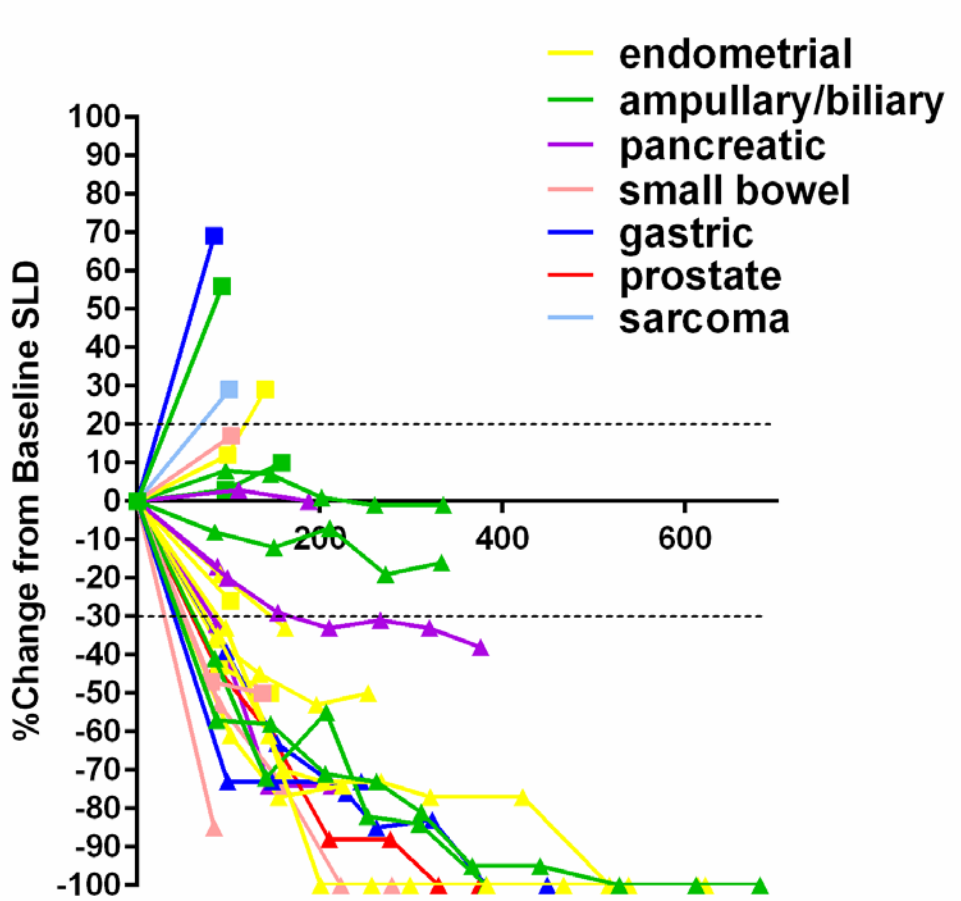
Fader, AN et.al. SGO 2016

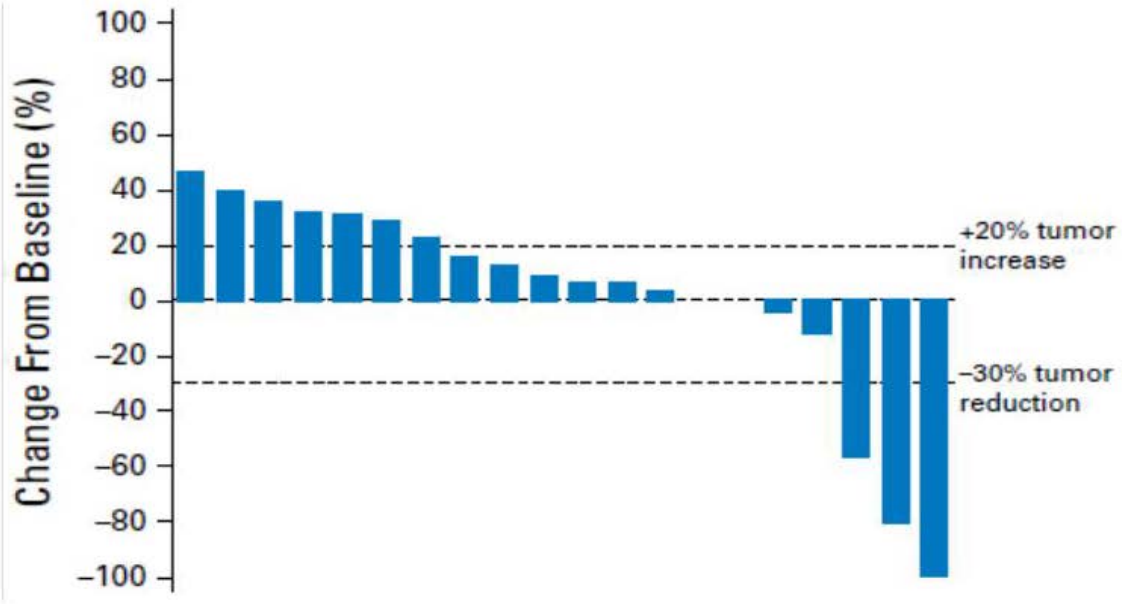
Overall Survival After Pembrolizumab



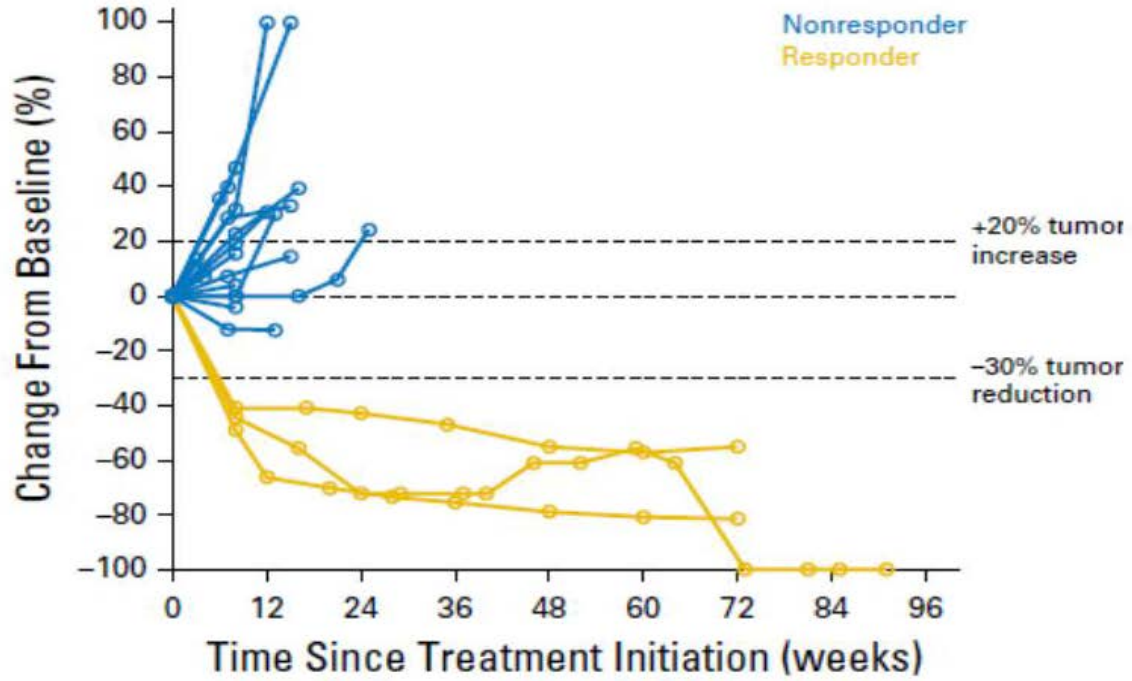
Durability of Disease Control







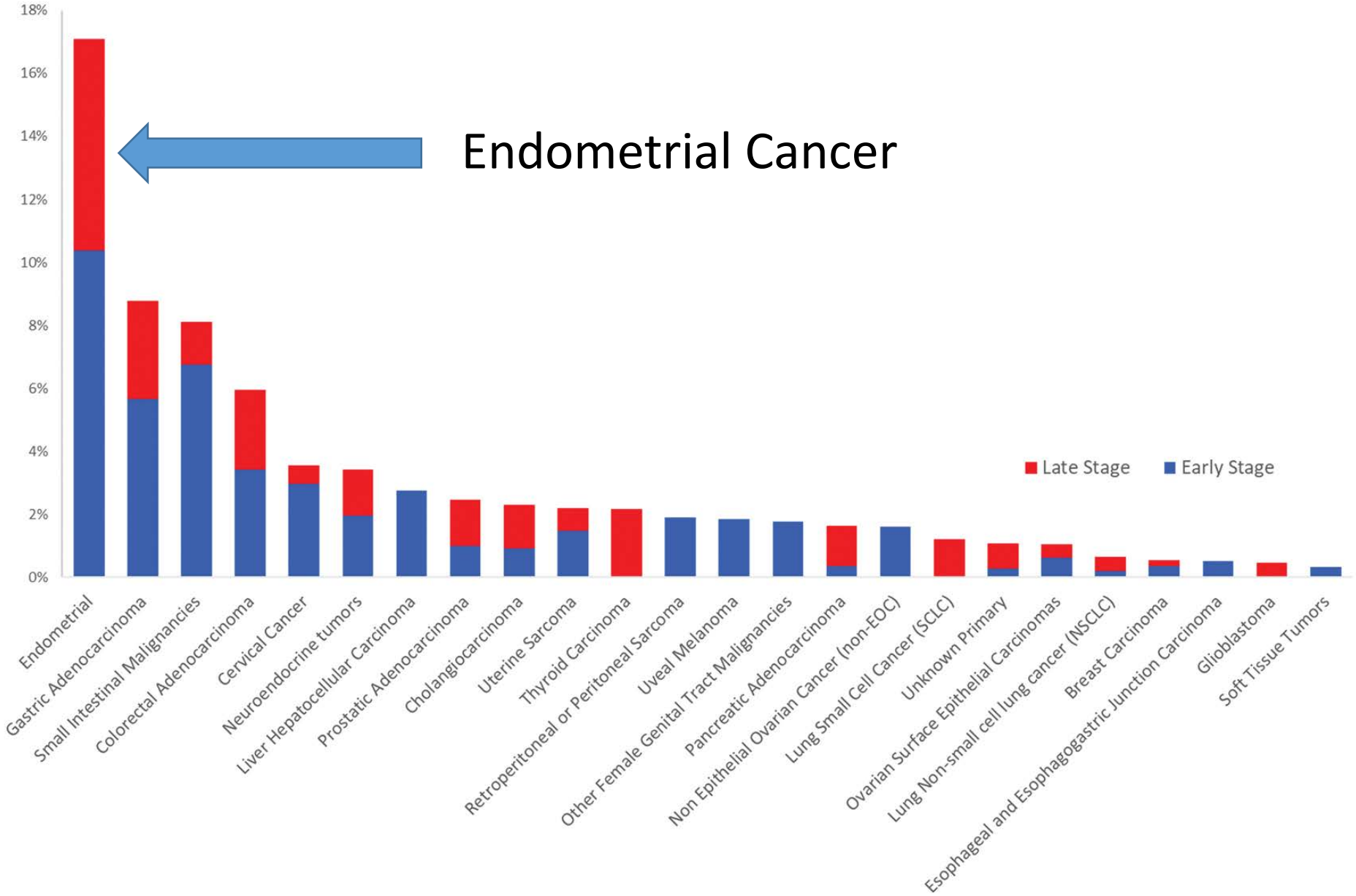
Pembrolizumab in PD-L1 Positive Endometrial Cancer KEYNOTE-028



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

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

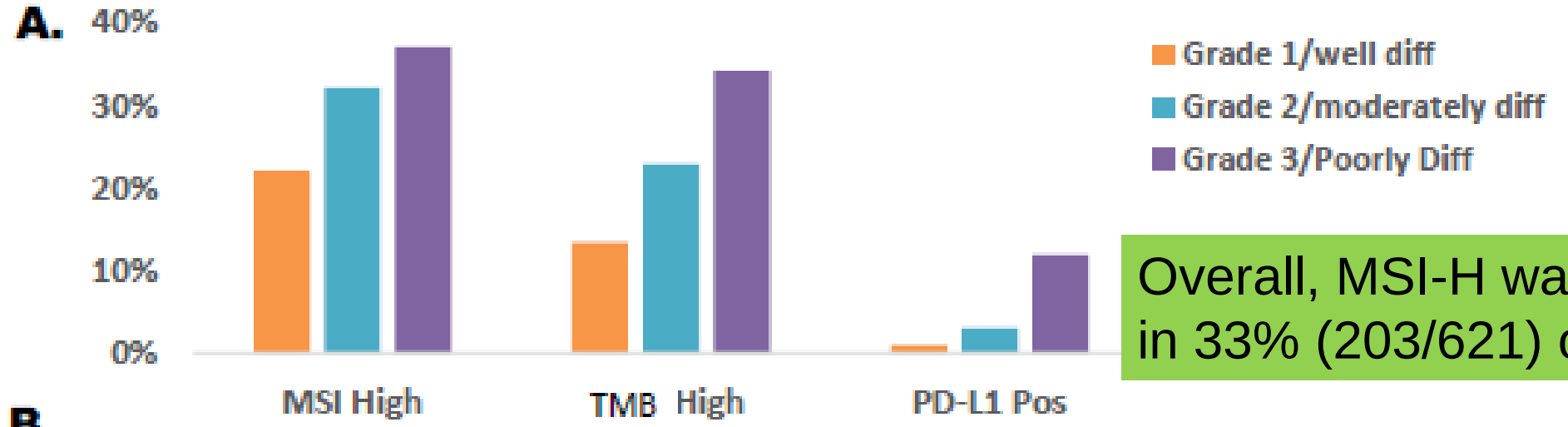
Ott et al. J Clin Oncol, 2017



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

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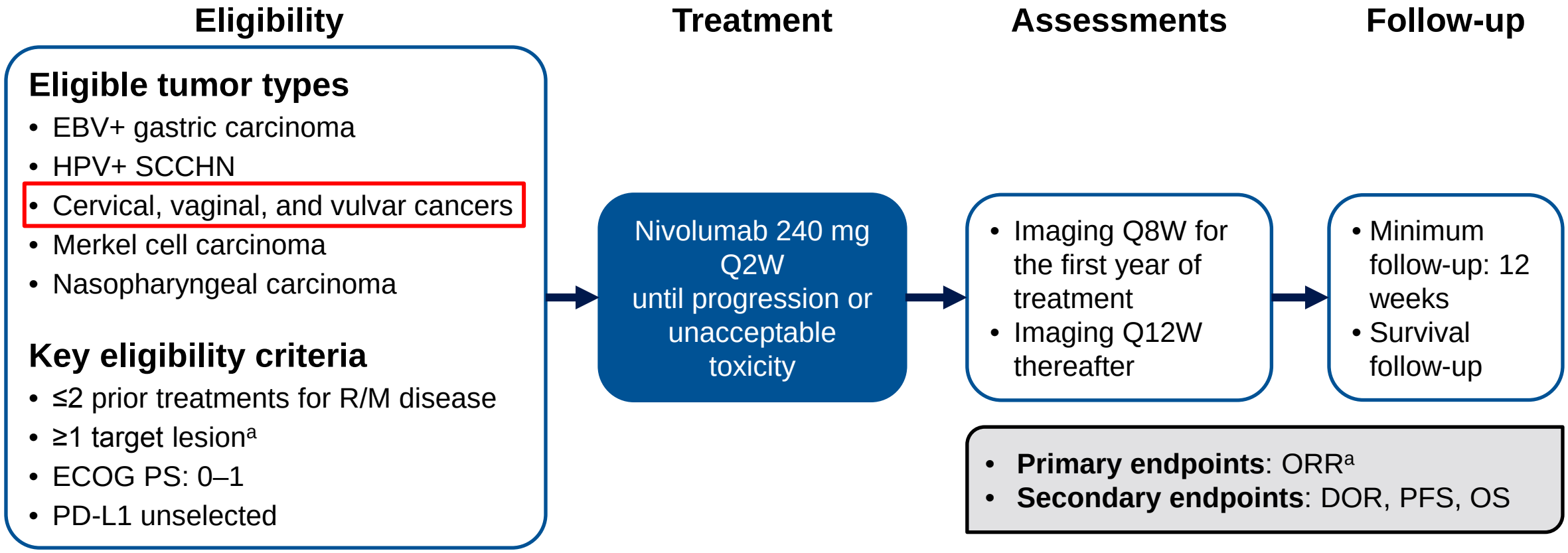
[1]Gustave Roussy Cancer Institute, Villejuif, France; [2]University College London Cancer Institute, London, UK; [3]University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; [4]Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium; [5]Vrije Universiteit 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

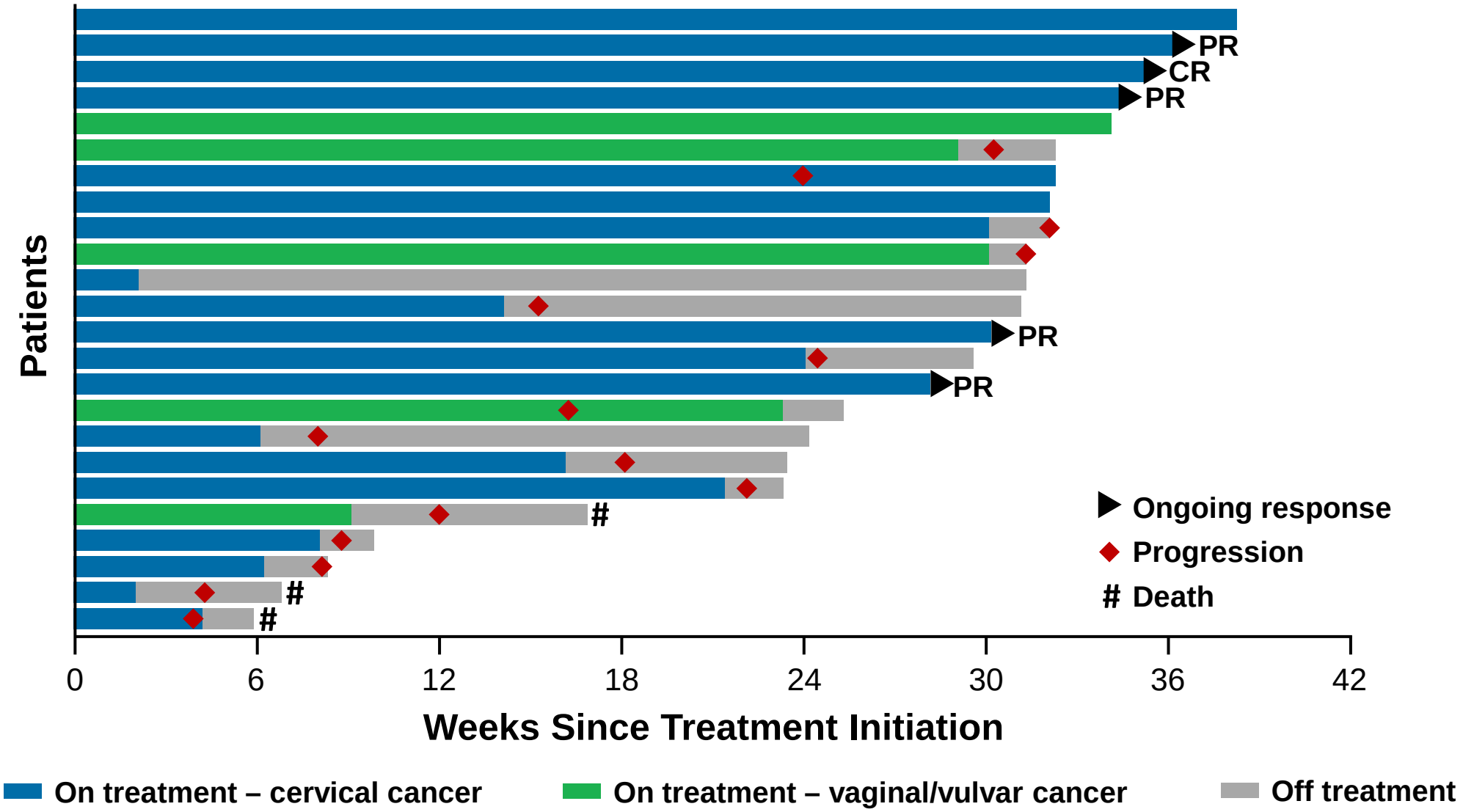
	All Patients (N = 24)	Cervical (n = 19)	Vaginal/ Vulvar (n = 5)
Best overall response, n (%)			
Complete response	1 (4.2)	1 (5.3)	0
Partial response	4 (16.7)	4 (21.1)	0
Stable disease	12 (50.0)	8 (42.1)	4 (80.0)
Progressive disease	7 (29.2)	6 (31.6)	1 (20.0)
ORR, n (%)	5 (20.8)	5 (26.3)	0
[95% CI]	[7.1,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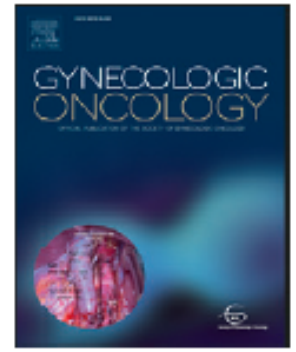


Lymphopenia and its association with survival in patients with locally advanced cervical cancer

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

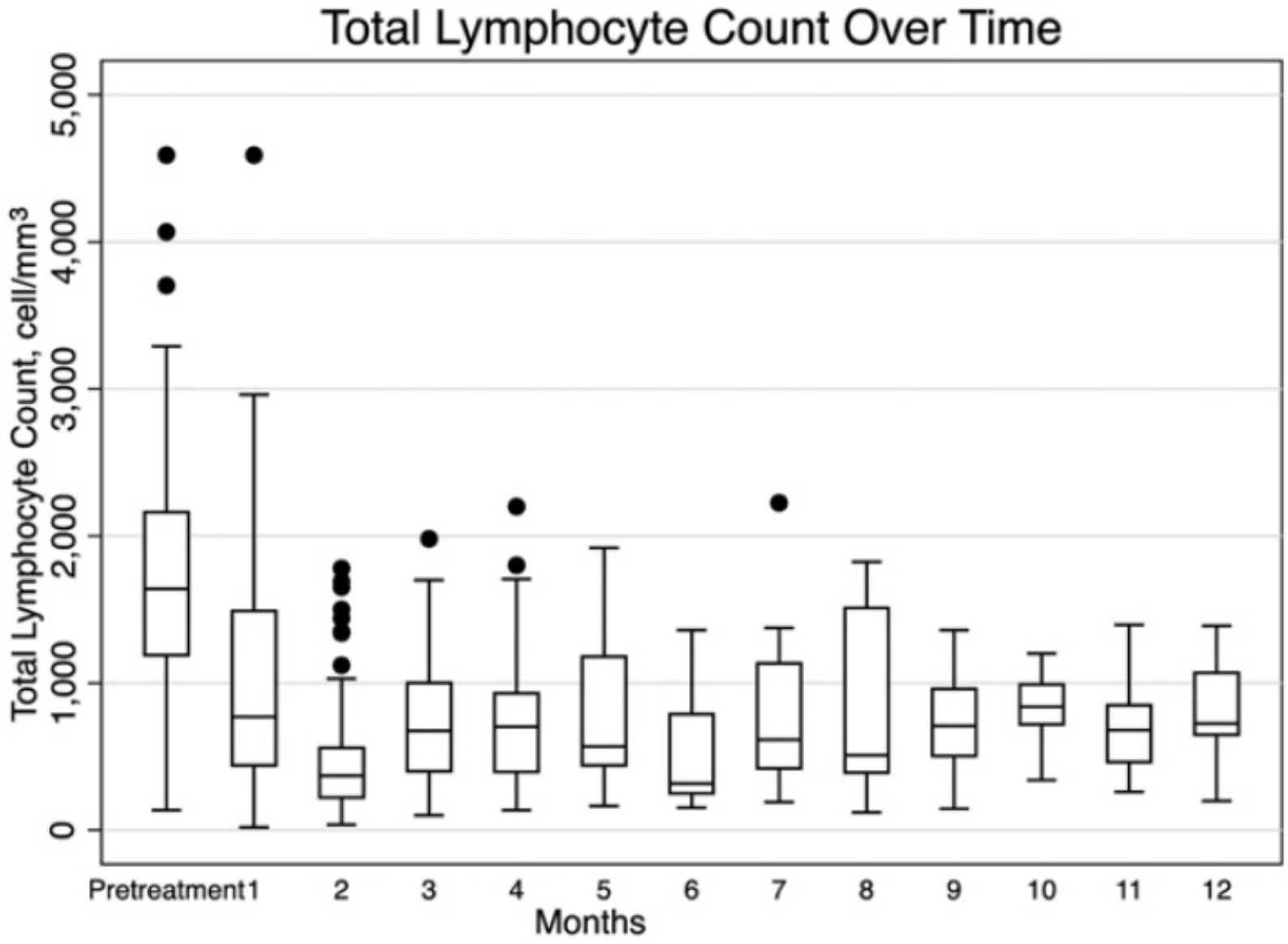


Fig. 1. Total lymphocyte count prior to treatment and in the first 12 months after initiating chemoradiation.

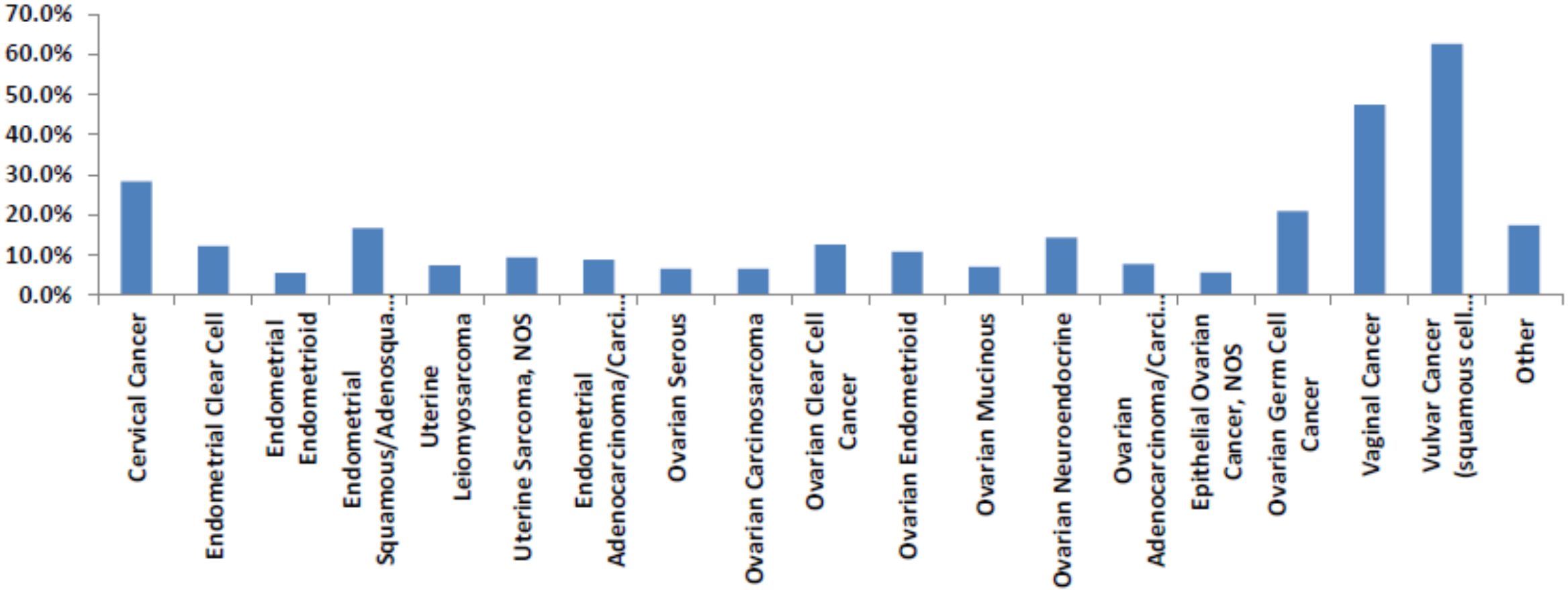


Figure 3. PDL-1 Expression via IHC in GYN Cancers. PD-L1 expression was observed in only 7% of uterine and ovarian tumors but in 28% cervical, 63% vulvar and 47% of vaginal cancers. This figure represents those tumors with >5% PDL-1 expression

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

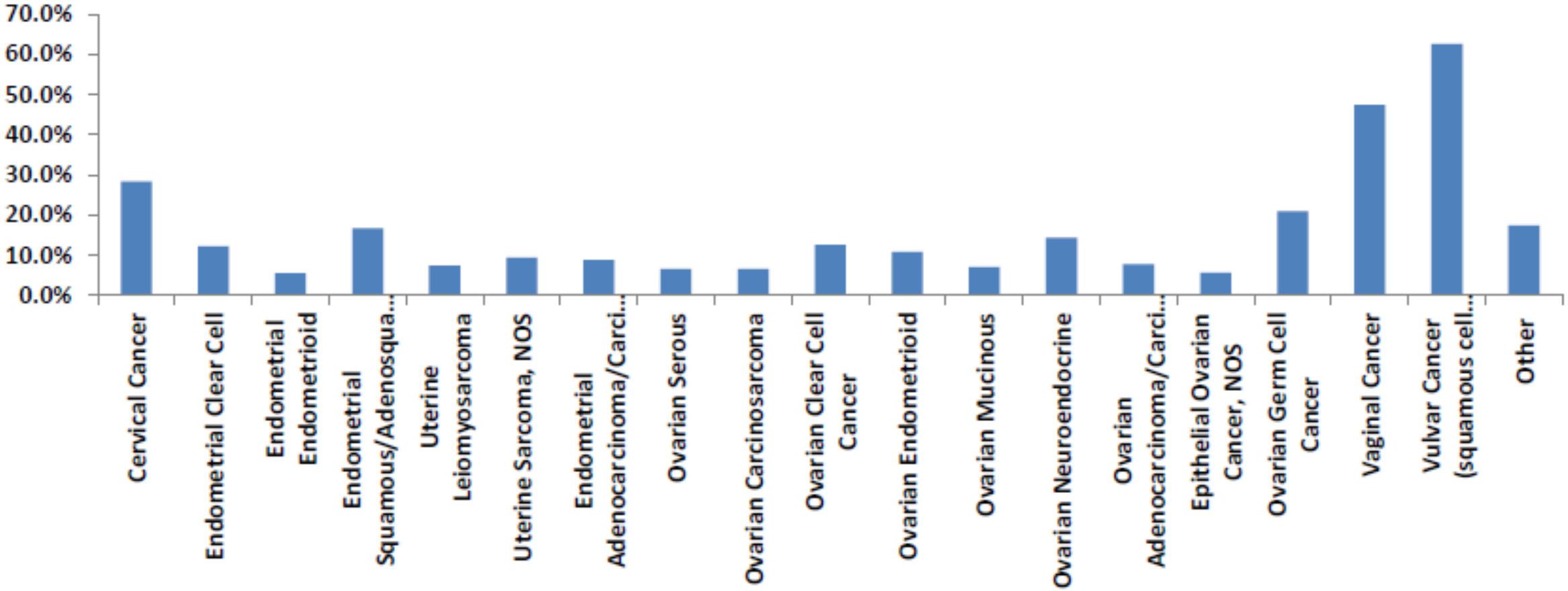
Ovarian Cancer

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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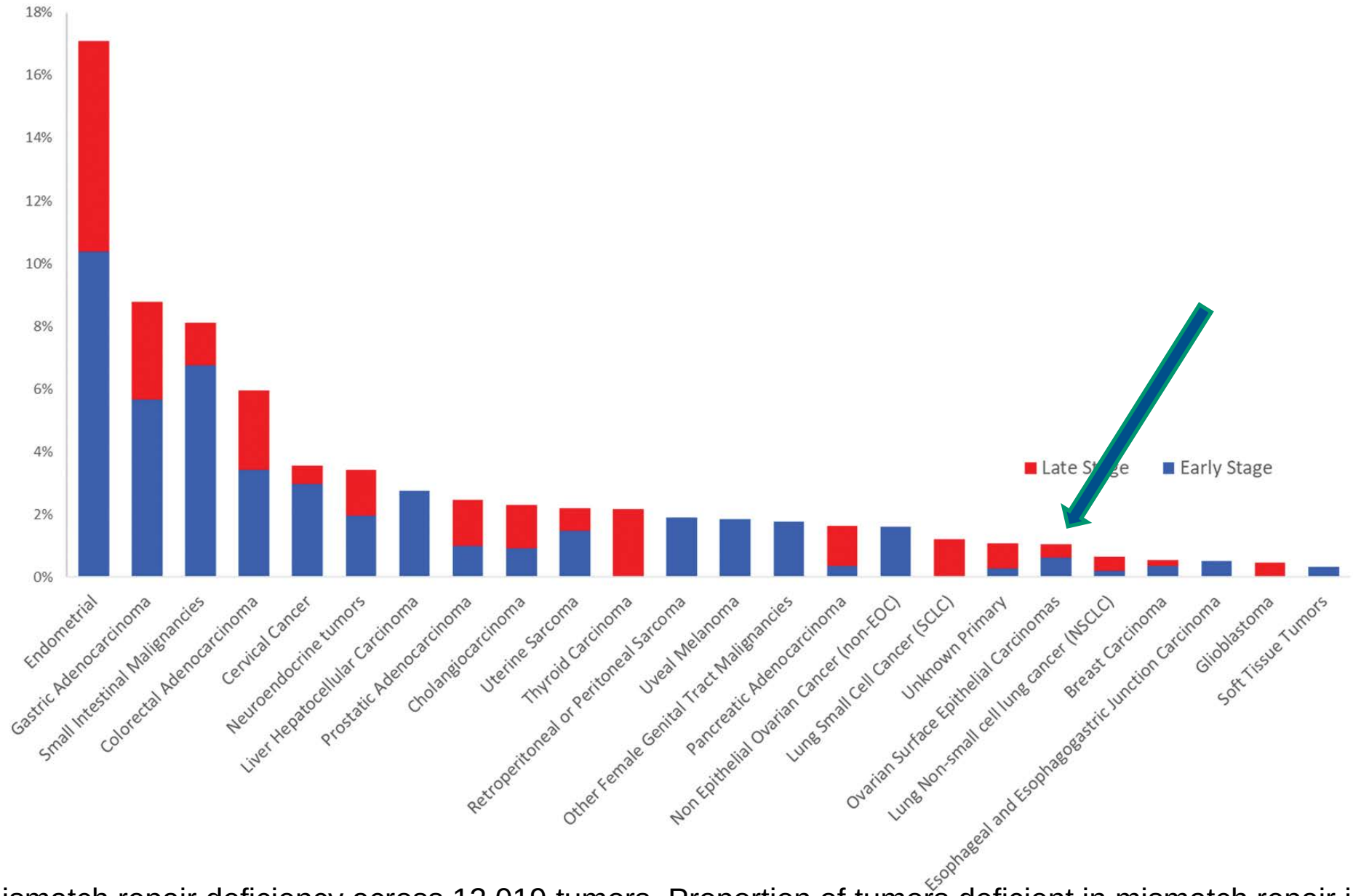

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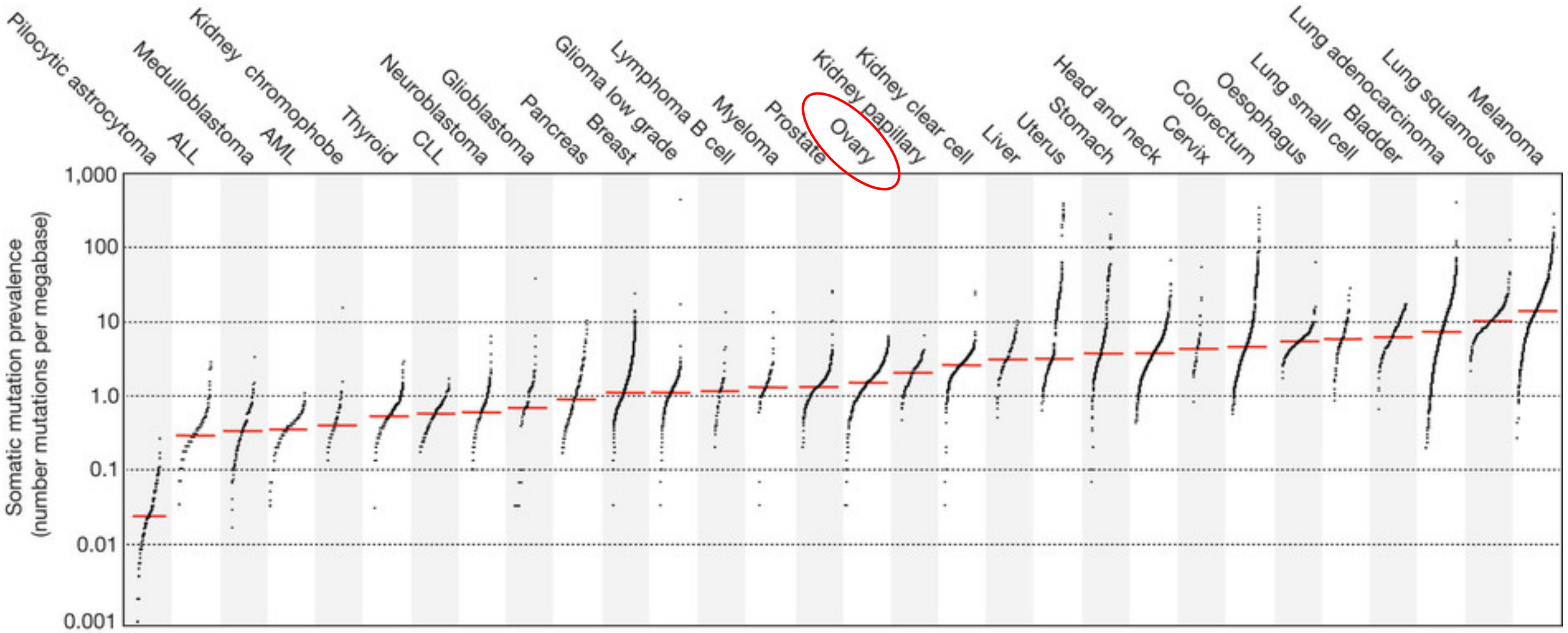
Le D, et.al. Science June 8, 2017



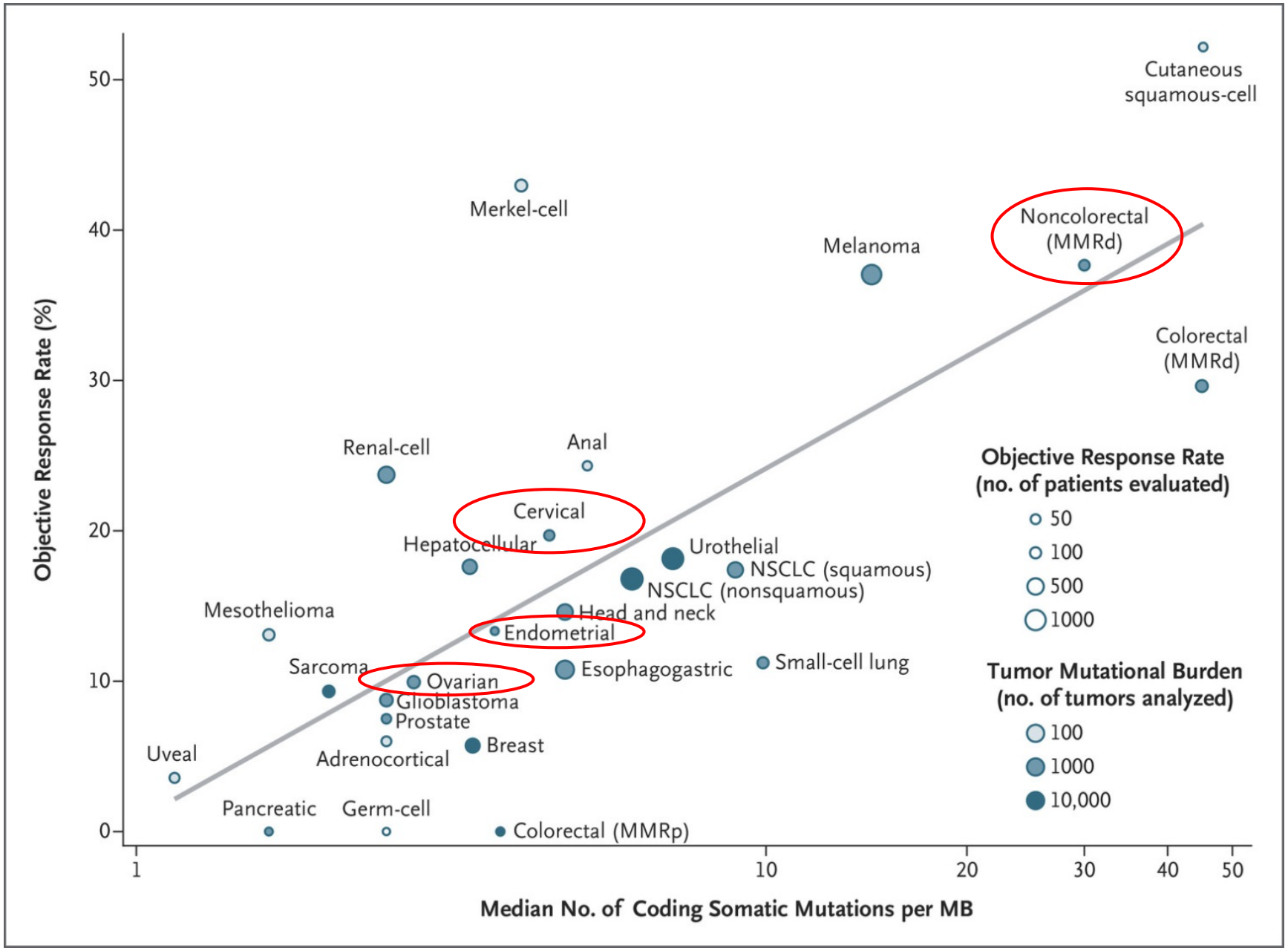
Alexandrov et.al. Nature 2013

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