Mereo BioPharma

Virtual R&D Day

May 13th 2021

Mereo BioPharma Group plc

NASDAQ: MREO

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Mereo Biopharma Virtual R&D Day - Agenda

- Welcome, introductions and Agenda - ***Denise Scots-Knight, PhD, CEO Mereo Biopharma***
- Etigilimab : TIGIT as a target/MOA - ***John Lewicki, PhD, CSO Mereo Biopharma***
- Biomarker strategy - ***Ann Kapoun, PhD, SVP Translational R&D Mereo Biopharma***
- Etigilimab and the ACTIVATE study - ***Suba Krishnan, MD, SVP Clinical Development Mereo Biopharma***
- MD Anderson and the Focus Fund/Mereo Collaboration - ***Denise Scots-Knight, PhD, CEO Mereo Biopharma***
- Clear Cell Ovarian Cancer - ***Shannon Westin, MD MPH, Associate Professor of Gynecologic Oncology and Reproductive Medicine, MD Anderson***
- Cervical Cancer - ***Kathleen Moore, MD, MS, Director, Oklahoma TSET Phase 1 Program, Associate Professor, Section of Gynecologic Oncology***
- Sarcoma - **Priscilla** ***Merriam , MD, Clinical Director, Sarcoma Center, Dana-Farber Cancer Institute***

Q&A

Today's Speakers

Shannon Westin, MD, MPH
Associate Professor of Gynecologic Oncology and Reproductive Medicine, MD Anderson

Kathleen Moore, MD, MS,
Director, Oklahoma TSET Phase 1 Program, Associate Professor, Section of Gynecologic Oncology

Priscilla Merriam, MD,
Clinical Director, Sarcoma Center, Dana-Farber Cancer Institute

Dr. Denise Scots-Knight
Chief Executive Officer

Dr. John Lewicki
Chief Scientific Officer

Dr. Ann Kapoun
Senior Vice President
Translational R&D

Dr. Suba Krishnan
Senior Vice President
of Clinical Development

Mereo Biopharma : Late Stage Diversified Clinical Pipeline

Core Programs

Product Candidate / Indication	Phase 1a	Phase 1b	Phase 2	Phase 3	Next Milestones
Etigilimab Solid tumors					Phase 1b/2
Alvelestat Alpha-1 antitrypsin deficiency COVID-19					Phase 2 AATD Phase 1b/2 COVID
Setrusumab Osteogenesis imperfecta					Adult extension study ultragenyx pharmaceutical

With partnering opportunities on non-core programs

Product Candidate / Indication	Phase 1	Phase 2	Phase 3	Financing Milestones
Acumapimod Acute exacerbations of COPD				Separate funding
Leflutrozole HH Infertility				Partner
Navicixizumab Ovarian Cancer				OncXerna ~ $300M milestones + royalties

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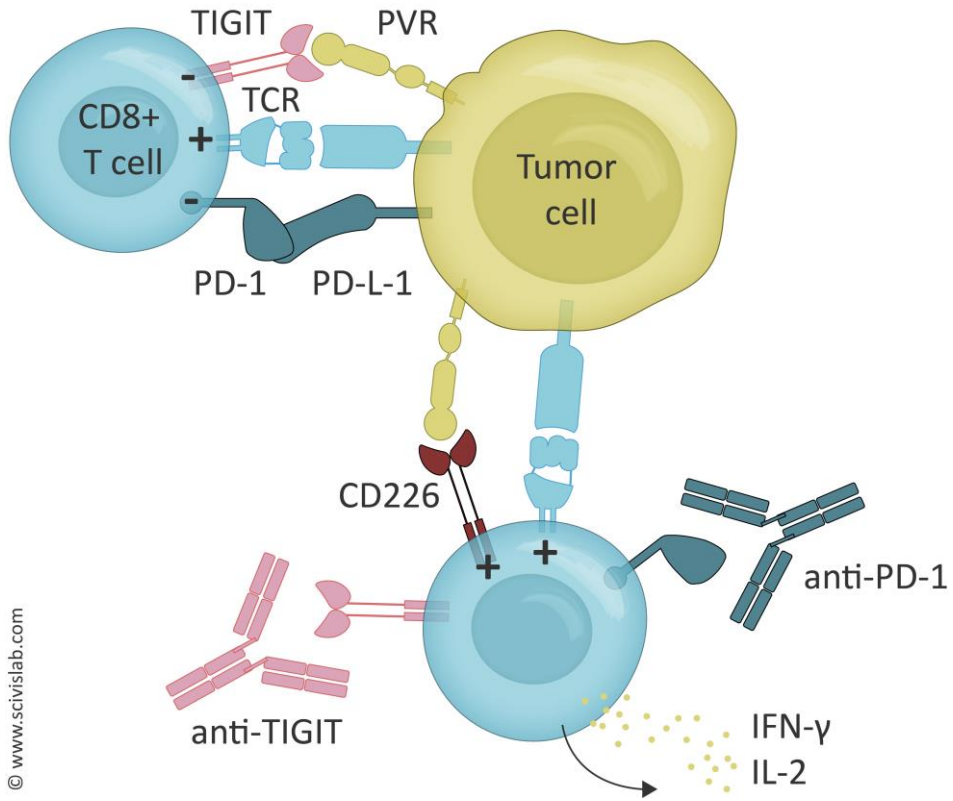
Etigilimab

TIGIT is a negative regulator of T cell responses



T cell Immunoreceptor with Ig and ITIM domains (TIGIT)

Negative regulator of T cell response:

- Competes with CD226 for PVR, disrupts CD226 activation, and directly inhibits T cells

Expressed on CD4, CD8 and NK cells and is elevated upon activation; co-expressed with PD1 on T memory stem cells

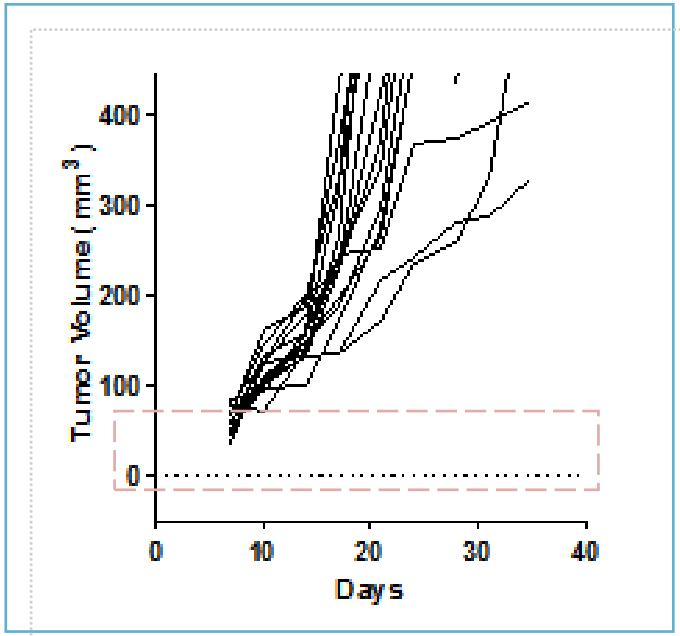
Highly expressed on regulatory T cells (Tregs), exhausted T-cells

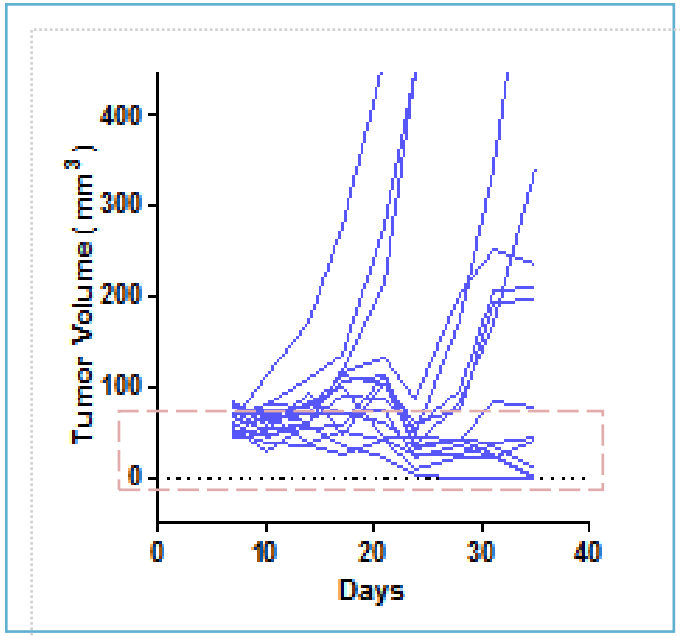
Human tumors co-express high levels of TIGIT and PD1

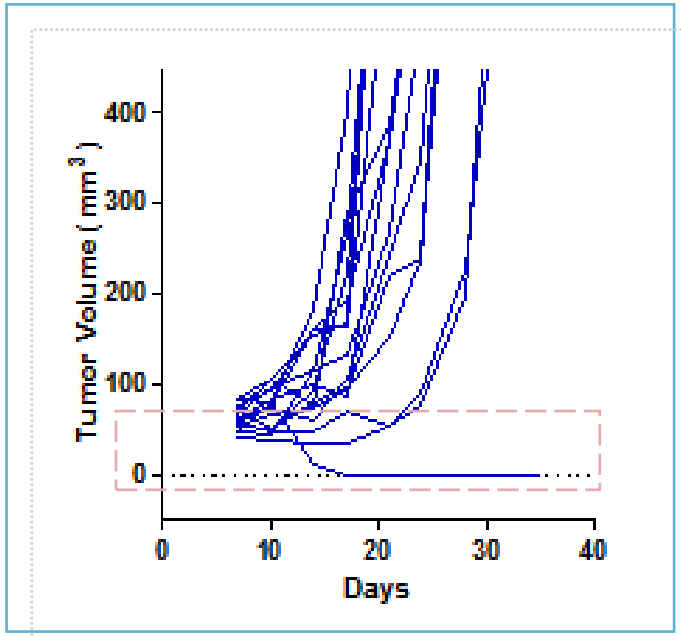
Co-blockade of anti-TIGIT and anti-PD1 elicits anti-tumor activity preclinically and clinically (Johnson et al. 2014, Cancer Cell; Rodriguez-Abreu et al. 2020, ASCO)

Etigilimab is an IgG1 anti-TIGIT antibody with inhibitory and ADCC characteristics

Control Ab	Effector function competent	Effector function silent







Mereo's Anti-TIGIT has key differentiating features

- Anti-TIGIT antibody designed to elicit anti-tumor activity via:
  - Activation of NK and T-cell subpopulations
  - Reduction of T-regulatory cells
  - Increased CD8/Treg ratio

- Demonstrated key mechanisms of anti-TIGIT in a dose dependent manner in preclinical models and in patients treated with etigilimab

Phase 1 Clinical Findings

- Seven subjects (30%, n=23) had stable disease as their best response in single-agent Phase 1a
  - Majority of patients are heavily pretreated and have tumor types typically non-responsive to anti-PD1 agents
  - Clinical benefit observed at doses as low as 3 mg/kg with modest tumor shrinkage in some patients including ovarian and endometrial cancers
  - Several patients showing durability, on study >200 days
- One partial response (ovarian) and 1 stable disease (gastric) evident in initial Phase 1b nivolumab combination (n=8 evaluable, n=7 with tumor assessments)

Safety and Biomarkers

- No DLTs were observed; etigilimab generally well tolerated
- Etigilimab elicited adverse events consistent with immune system activation
- Biomarkers confirm target engagement
  - Dose dependent decreases in T regulatory cells and other biomarkers

Mereo's etigilimab has key differentiating features

High affinity IgG1 antibody

- IgG1 backbone activates antibody-dependent cellular cytotoxicity (ADCC). Preclinical data suggest advantages of this backbone over competitor ADCC-null anti-TIGIT mAbs

Phase 1a and Phase 1b dose escalation and safety data available

- Early clinical signals observed: 30% SD in Phase 1a; 1PR in Phase1b.
- Majority of patients are heavily pre-treated including patients with prior checkpoint inhibitors, some in non-IO responsive tumor types. Durability of over 200 days in some patients

Advanced Biomarker capabilities in place

- Target engagement of etigilimab demonstrated in Phase 1a patients
- Identified tumors with high expression of TIGIT/PVR based on survey of large cohorts of tumors tissues
- Biomarker methods established to evaluate and enable future patient stratification and selection, e.g. IHC for PVR, TIGIT, PVRL2, FOXP3, CD226 and multiple panels for >15 immune related tumor parameters

ACTIVATE TRIAL

Differentiated Phase 1b/2 Trial Design

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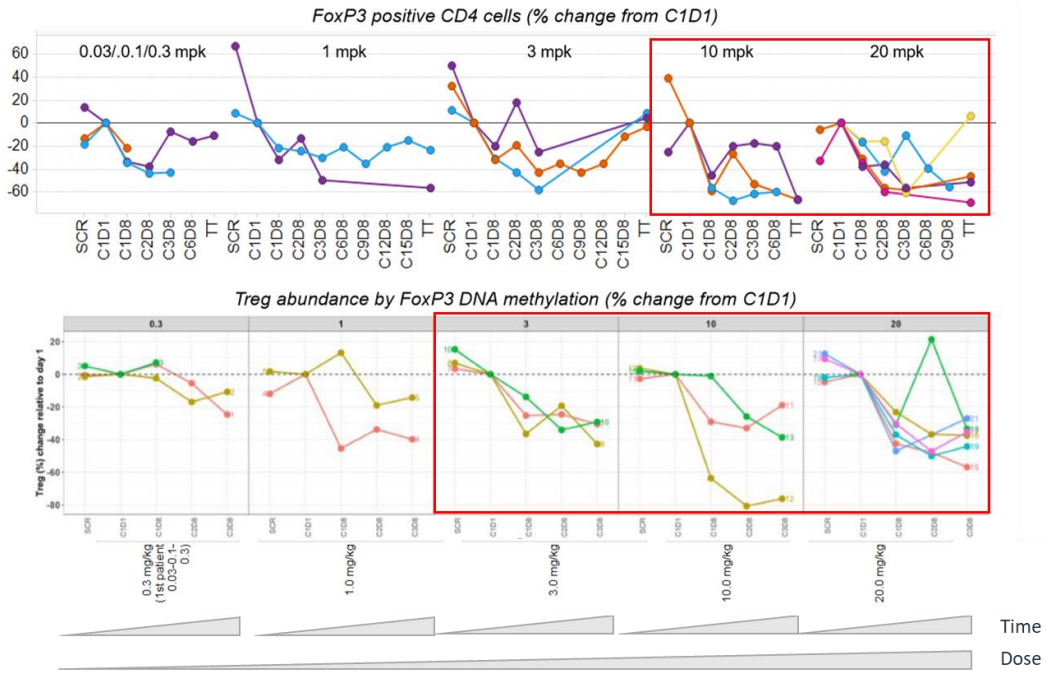
BIOMARKER STRATEGY

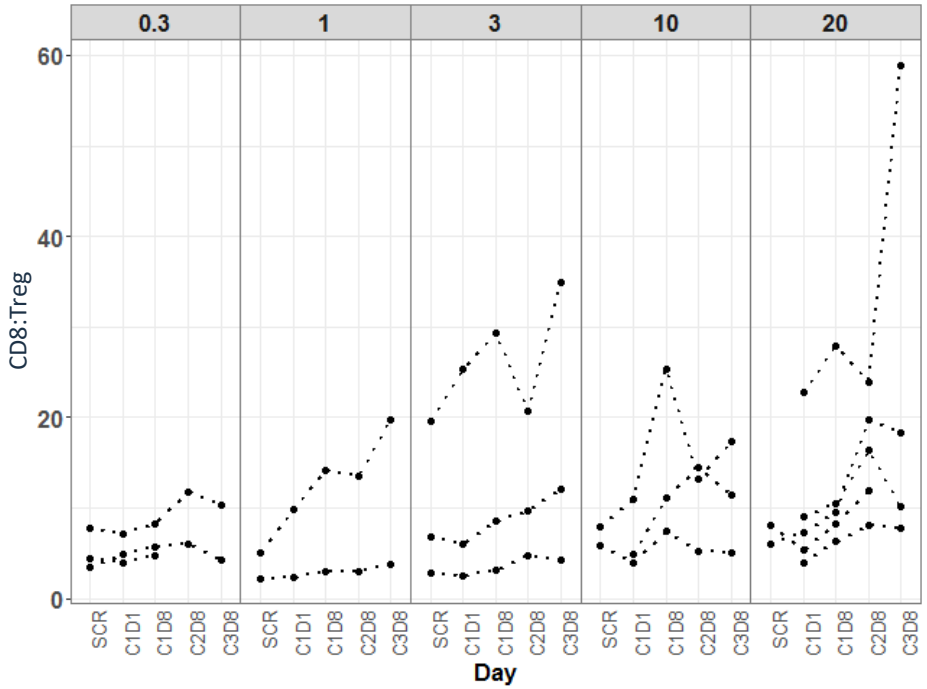
Demonstration of Target Engagement in Phase 1a Patients

Etigilimab decreases Tregs and increases CD8/Treg ratio

Etigilimab decreased the number of Treg Cells in circulation



Etigilimab increases CD8/Treg ratio



Flow data shown, increase in CD8/Treg ration also observed by DNA methylation

No change in circulating CD8 or CD4 T-cell frequency

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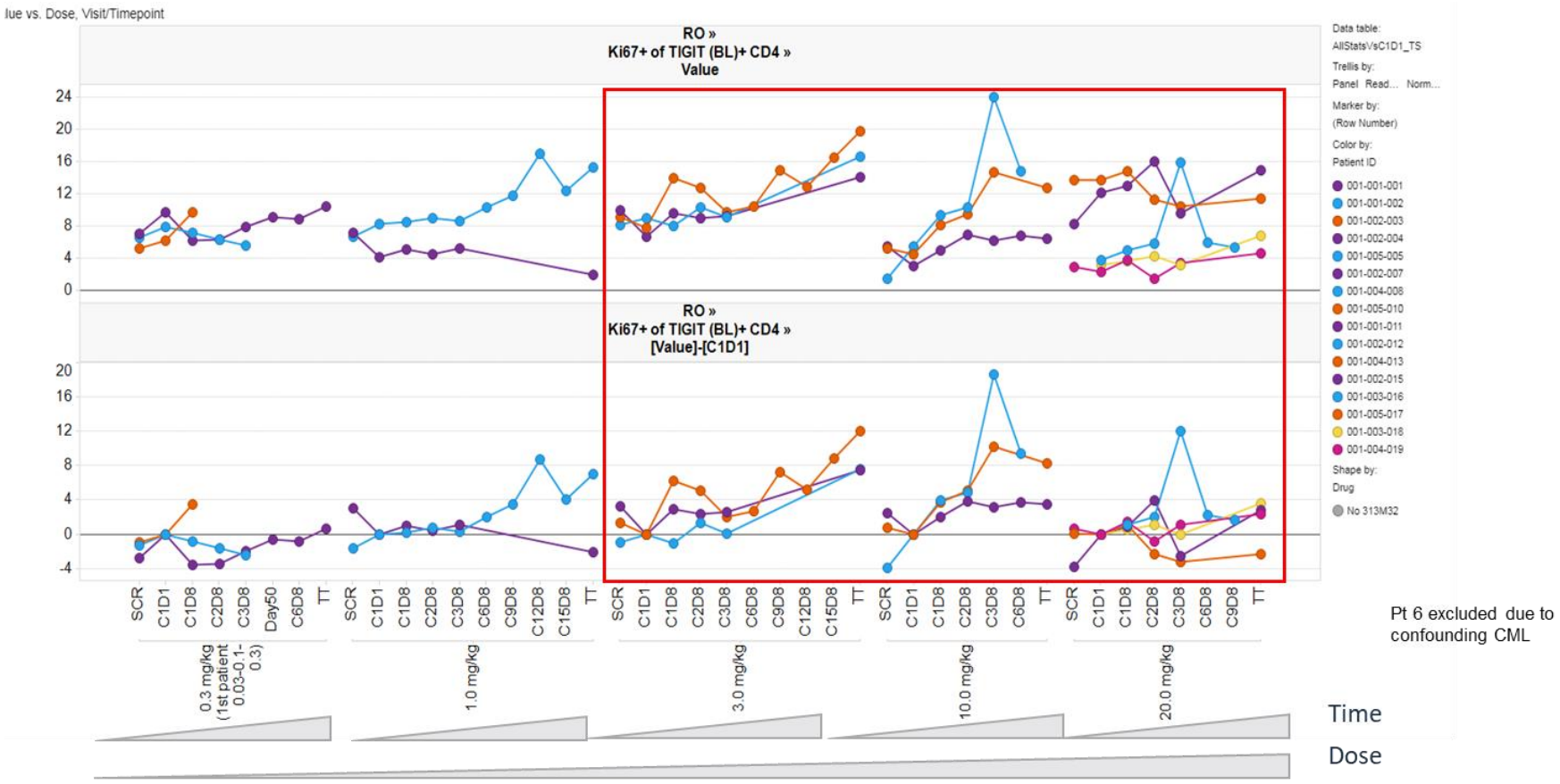
Sharma et al, Huang et al

Demonstration of Target Engagement in Phase 1a Patients

Etigilimab increases activation and proliferation of effector T cells and NK cells

Etigilimab increased markers of cell proliferation in T and NK cells



Pt 6 excluded due to confounding CML

Increases in Ki67+ observed in CD4 T cells as well as NK & Treg

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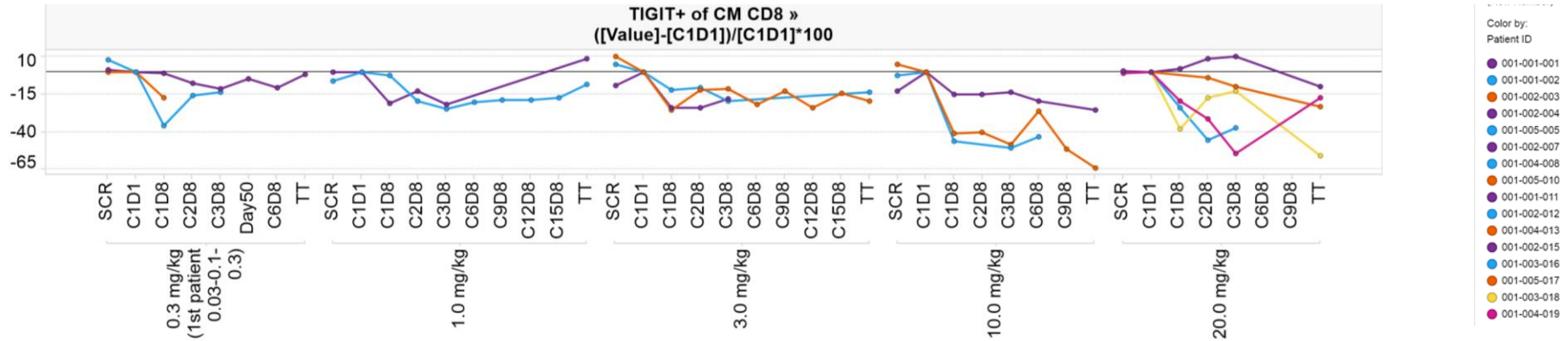
Sharma et al, Huang et al

Etigilimab Reduces Cells Destined for Exhausted T-cell lineage in Phase 1a Patients

Etigilimab reduces progenitor CD8 cells thought to be committed to exhausted-like fate



- Exhausted and functional memory T cells arise from separate populations of stem-like progenitor committed to distinct fates
- Two distinct subsets of CCR7+ progenitors distinguished by PD1 and TIGIT expression

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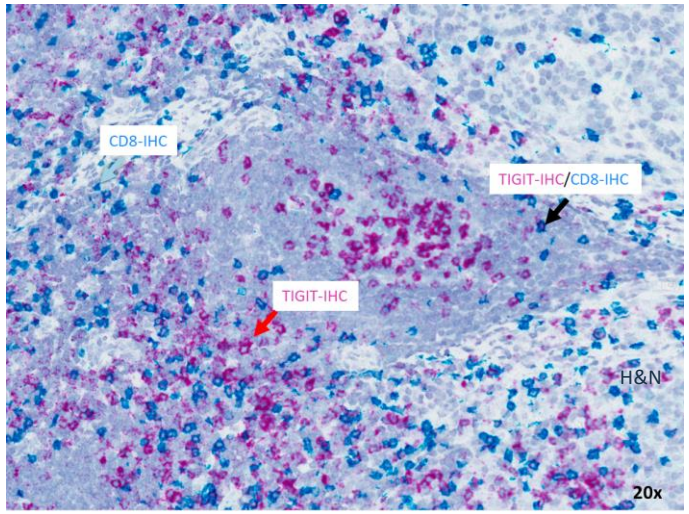
Galletti et al., Nature Immunology, 2020: Two subsets of stem-like CD8+ memory T cell progenitors with distinct fate commitments in humans

Biomarker capabilities in place

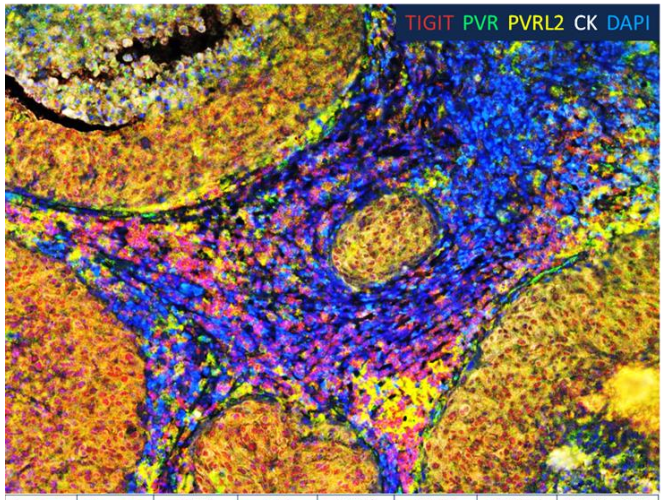
Example TIGIT & PVR Immunohistochemistry

- TIGIT biomarker single & multiplex IHC/IF assays developed with image analysis
- These assays were used to survey large cohorts of tumor tissues for indication selection
- Robust multiplex IHC assays and staining for PVR, TIGIT, and ~15 immune related tumor parameters including TIGIT, PVR, PVRL2, CD226, CD4, CD8, FOXP3, PD1, PDL1
- TIGIT and PVR assays developed and establishing as CLIA-validated to enable prospective pt selection at central lab

TIGIT/CD8

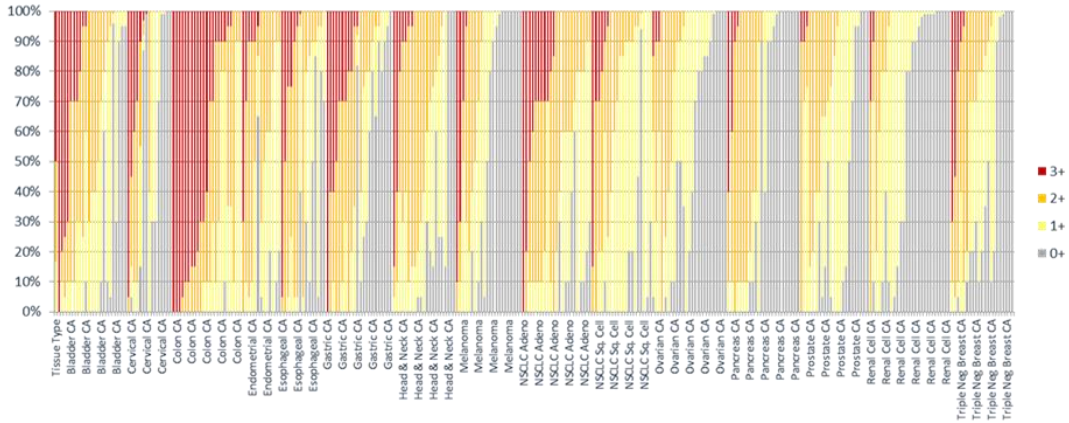


TIGIT/PVR/PRVL2



Specimen ID	Tumor type	% TIGIT	% PVR	% PVRL2	TIGIT:PVR	TIGIT:PVRL2	TIGIT:PVR or PVRL2
CR-9-1264-2	Head &Neck	30%	10%	8%	824	756	1216

PVR



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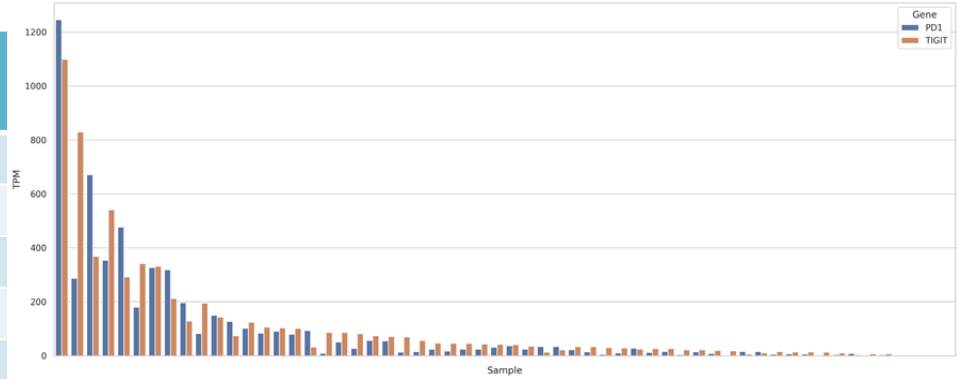
Example Rare Tumors Analysis

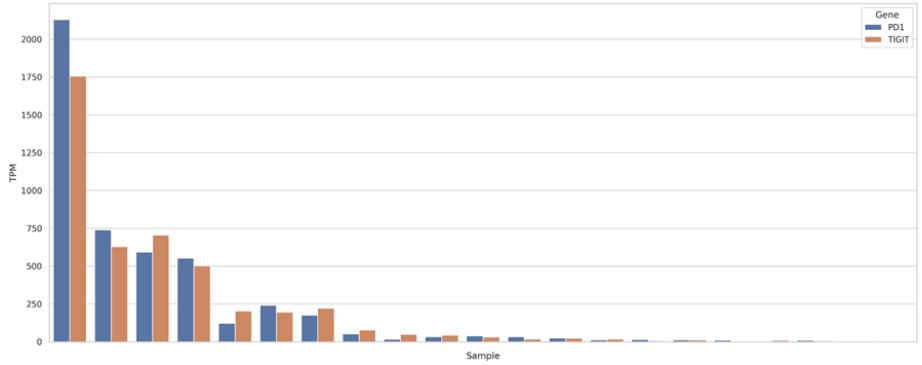
Sarcoma subtypes with high correlation of TIGIT and PD1 expression

	Correlation	Median TIGIT Expression	Median PD1 Expression	Num. Samples
All	0.88	22.50	19.88	263
Dedifferentiated liposarcoma	0.88	38.09	23.75	58
Undifferentiated Pleomorphic Sarcoma (UPS)	0.99	37.28	32.72	21
Leiomyosarcoma (LMS)	0.93	15.73	10.98	104
Myxofibrosarcoma	0.87	51.91	28.59	25
Pleomorphic 'MFH'/ Undifferentiated pleomorphic sarcoma	0.98	35.38	25.49	29
Synovial Sarcoma - Biphasic	1.0	1.02	121.15	2
Synovial Sarcoma - Monophasic	-0.29	0.46	115.05	6
Sarcoma; synovial; poorly differentiated	1.0	3.65	53.03	2
Giant cell 'MFH' / Undifferentiated pleomorphic sarcoma with giant cells	N/A	9.05	20.82	1
Malignant Peripheral Nerve Sheath Tumors (MPNST)	0.95	20.24	18.50	9
Desmoid Tumor	1.0	7.96	6.54	2

Dedifferentiated liposarcoma



Undifferentiated Pleomorphic Sarcoma (UPS)



TCGA data

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Immune Classification of Sarcoma Subtypes

Tumors assigned to distinct sarcoma immune classes (SIC)

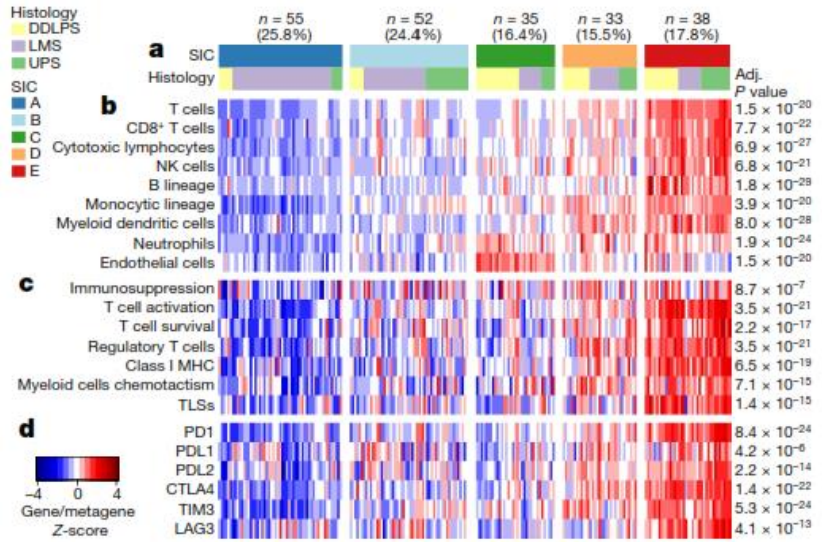
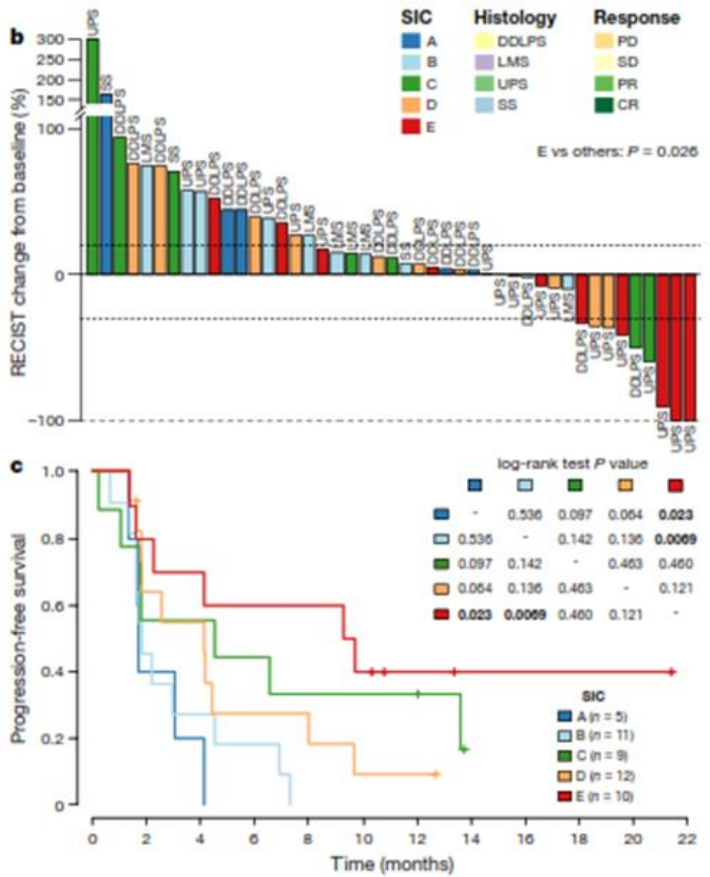


Fig. 1 | The SICs exhibit strongly different TMEs. This figure refers to the TCGA SARC cohort ($n = 213$). **a**, Composition of the TCGA SARC cohort by SIC, and histology. **b**, Composition of the TME by SIC as defined by the MCP-counter *Z*-scores. NK cells, natural killer cells. **c**, Expression of gene signatures related to the functional orientation of the immune TME by SIC. **d**, Expression of genes related to immune checkpoints by SIC. Adjusted *P* values are obtained from Benjamini–Hochberg correction of two-sided Kruskal–Wallis tests *P* values.

Petitprez et al 2020 Nature

SIC E group - improved survival and high response rate to PD1 blockade with Pembro



B cells strongest prognostic factor even in context of high or low CD8 T cells

Biomarker Capabilities Established

- Biomarkers key component of indication selection for Phase1a/b basket trial
- Demonstrated key mechanisms of anti-TIGIT in preclinical models and in patients treated with etigilimab
- Dose dependent biomarker changes observed
  - Activation of NK and T-cell subpopulations
  - Reduction of T-regulatory cells
  - Increased CD8/Treg ratio
  - Reduction of CD8 T cells destined for exhausted T-cell lineage
- Potential future patient selection in cohort(s) based on biomarker (PDL1, PVR, TIGIT)
  - CLIA IHC assays to be run in central lab

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THE ACTIVATE STUDY

ACTIVATE Phase 1b/2 Study

ACTIVATE: A Phase 1b/2 Open-Label Study of the Efficacy and Safety of Etigilimab (MPH313) Administered in Combination with Nivolumab to Subjects with Locally Advanced or Metastatic Solid Tumors

- Overview of study design
- Key elements of differentiation strategy
- Study status update

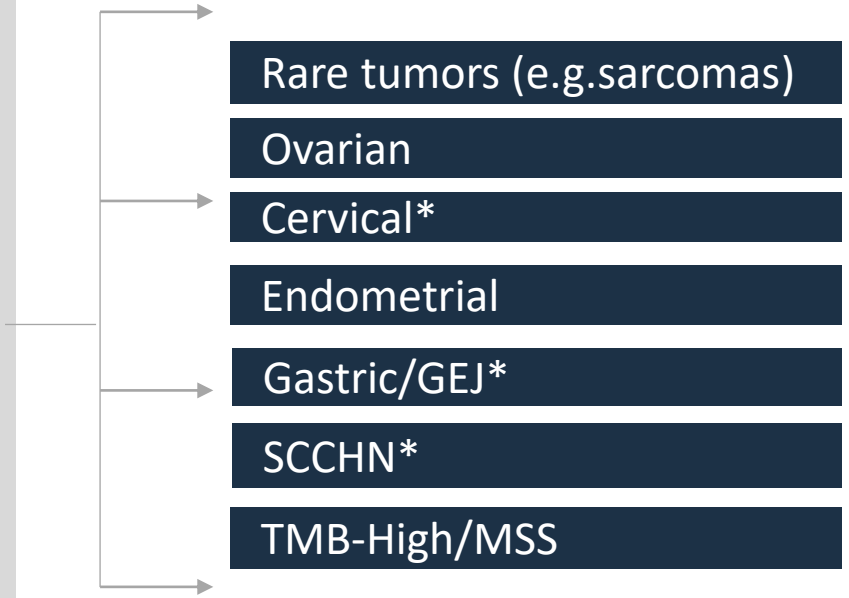
ACTIVATE Phase 1b/2 Study Design: Etigilimab plus Nivolumab in Advanced/Metastatic solid Tumors

Primary endpoint
- Overall Response Rate

Secondary
- Safety and Tolerability
- PK/PD
- Duration of response

Exploratory
- Biomarker
- PFS
- OS

Flat dosing Q2W



***PDL1+**

Simon two-stage design allowing for dynamic decision making and flexible design
N= ~ 125 subjects

Study Design: Decision Making

- Statistical rigor provided by Simon 2-step design:
  - *Stage 1 futility monitoring for progression to Stage 2*
  - *Clinically meaningful benchmark for Go/No-go beyond Stage 2*

- Open label design allows for dynamic decision making
- Totality of safety and efficacy data will be considered including durability
- Each cohort to be managed uniquely

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Differentiated Clinical Strategy

Key Elements of Etigilimab Phase 1b/2: Differentiated Clinical Development

- Focus on **Checkpoint-naïve** populations
- Prioritize TIGIT expressing tumors by:
  - **(i) Low monotherapy checkpoint inhibitor activity**
  - **(ii) Rare cancers**
  - **(iii) High unmet need**

Gyn-onc indications	***ORR with Anti-PD-1 Monotherapy***
Cervical	KN158 **14%** (KN158)
Ovarian	KN100 **8.1%** (</=2 prior lines); **9.9%** (3-5 prior lines)
Rare Cancers	***ORR with Anti-PD-1 Monotherapy***
Sarcoma (Select histological subtypes)	**0-20%** [Sarc028]
Others	***0-5%***

Key Elements of Etigilimab Phase 1b/2 Clinical Biomarker Strategy

Multi-Pronged Biomarker Approaches

Prospective *selection,* ***established*** *biomarker* *PD-L1*	*Cervical, gastric, SCCHN as per indication on label*
Prospective *selection,* ***emerging*** *biomarker*	*TMB-H/MSS tumors*
Retrospective *evaluation by* ***potential novel biomarkers*** *PVR/TIGIT expression*	*All enrolled subjects*

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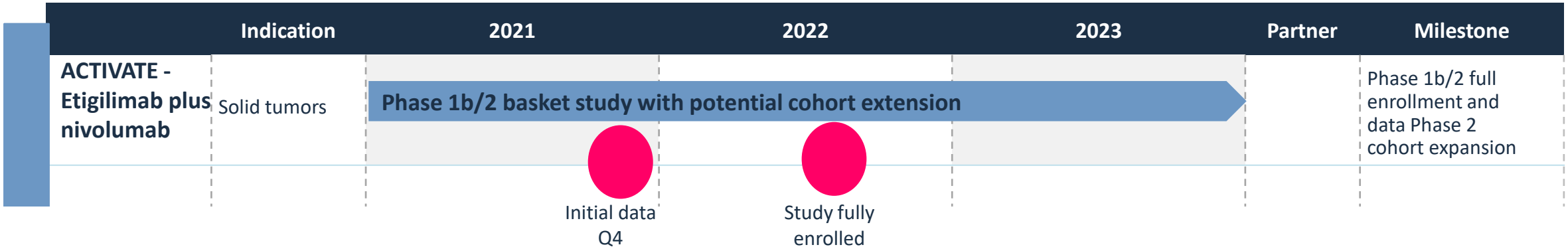
ACTIVATE Study: Status Update

ACTIVATE Study Status



- ACTIVATE study well under way
- Q4 early data from initial cohorts
- Study fully enrolled by mid-2022
- Robust engagement of site PI's as well as “Champion” PI's by indication

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MD ANDERSON & CANCER FOCUS FUND COLLABORATION

Etigilimab – Cancer Focus Fund & MD Anderson Collaboration

- Cancer Focus Fund, LP
  - Unique investment fund established in collaboration with The University of Texas MD Anderson Cancer Center.
  - Provides investment support to advance promising cancer therapies, clinical trial expertise and infrastructure of MD Anderson
  - Collaboration represents the first investment from the Cancer Focus Fund

- Funding provided for :
  - Investigator sponsored clinical study in Phase 1/2 for etigilimab in combination with nivolumab in clear cell ovarian cancer
  - Support for CMC and pharmaco-viglence expenses

- Terms
  - $1.5 million in equity
  - Milestones for licensing (capped) and FDA/EMA approval that includes ovarian clear cell carcinoma

Etigilimab - Cancer Focus Fund & MD Anderson Collaboration

- Rationale :
  - Study runs in parallel to Mereo's ACTIVATE study that has an ovarian cancer cell arm (which excludes clear cell)
  - Clear cell represents ~10% of ovarian carcinomas in US/EU
  - Ovarian cancer generally has poor treatment outcomes but data on clear cell subtype with anti-PD1 therapy promising albeit limited data set
  - Rare tumor type - Dr Shannon Westin, at MD Anderson is one of the primary referral centers for clear cell ovarian patients
  - MD Anderson also key study site for ACTIVATE study

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CLEAR CELL OVARIAN CANCER

Mereo Research and Development Day:
Opportunties for Etigilimab in Ovarian Cancer

Shannon N. Westin, MD, MPH

Associate Professor
Director, Early Drug Development and Phase 1 Trials

Department of Gynecologic Oncology and Reproductive Medicine

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Disclosure Information

- Research Support: AstraZeneca, ArQule, Clovis Oncology, Novartis, Roche/Genentech, Cotinga Pharmaceuticals, GSK/Tesaro, Bayer, Bio-Path, Mereo

- Consultant: Agenus, AstraZeneca, Clovis Oncology, Roche/Genentech, Novartis, Circulogene, Pfizer, GSK/Tesaro, Merck, Eisai, Zentalis

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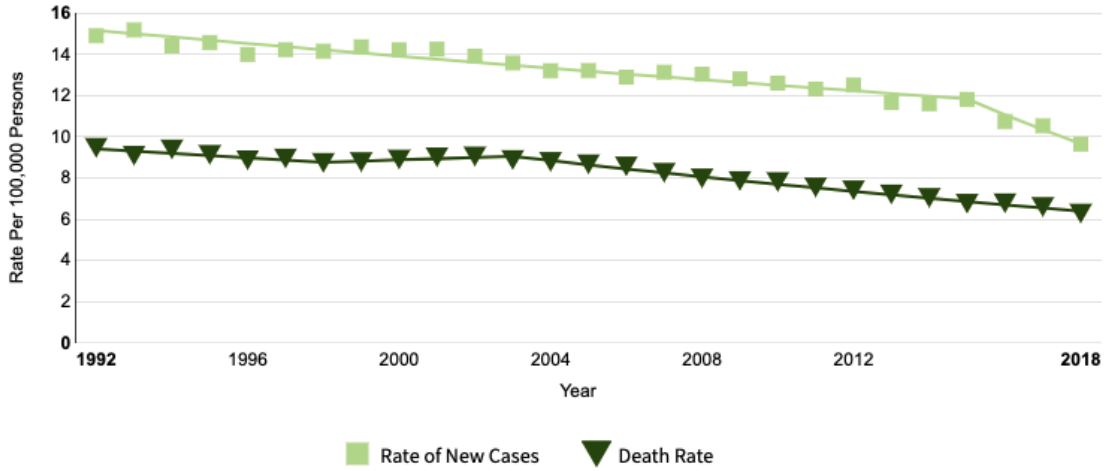
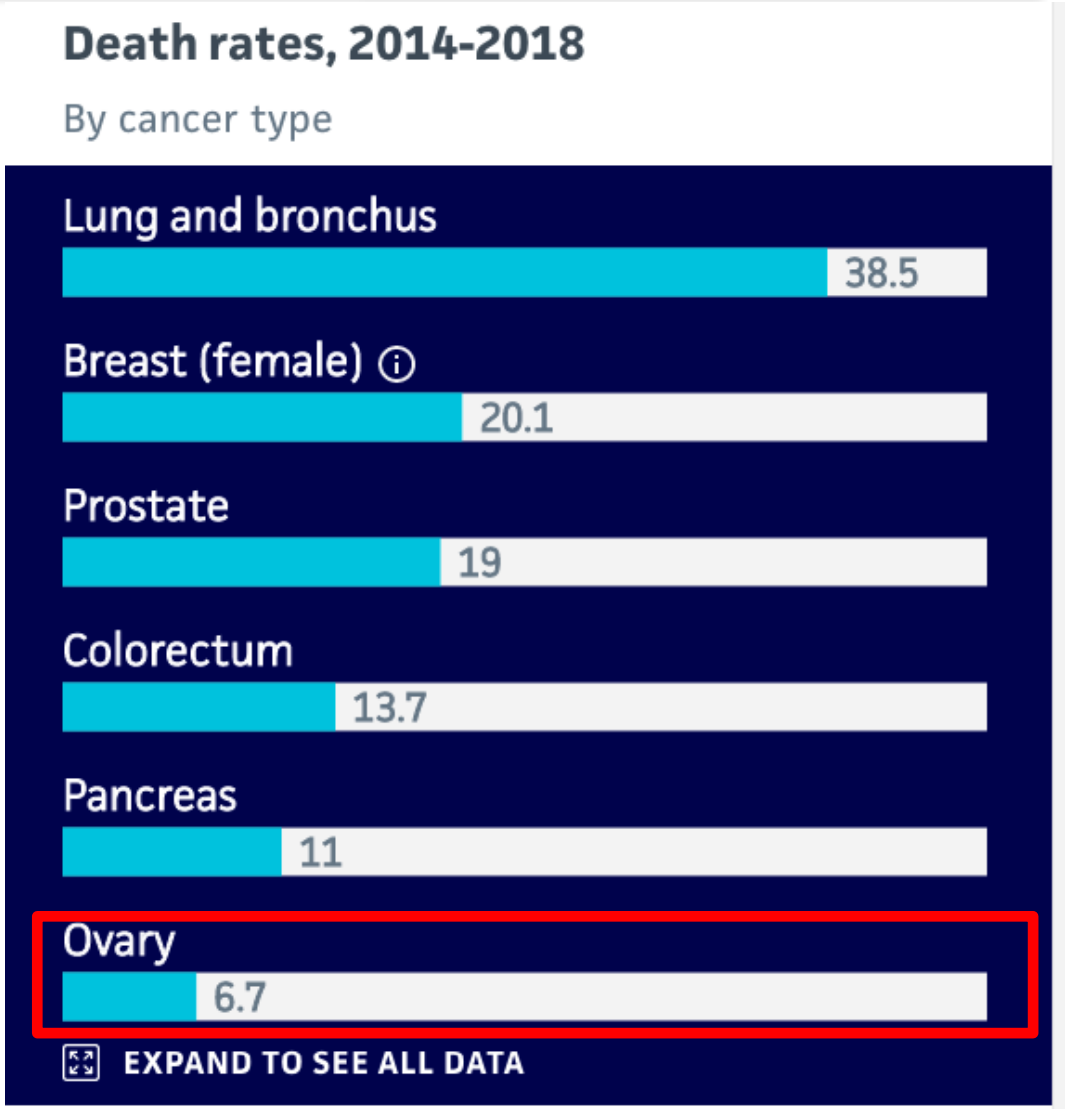
Ovarian Cancer Basics

Estimated New Cases in 2021	21,410
% of All New Cancer Cases	1.1%

Estimated Deaths in 2021	13,770
% of All Cancer Deaths	2.3%

5-Year Relative Survival
49.1%
2011–2017





- **Worldwide: 300,000**
- **Risk 1/75**

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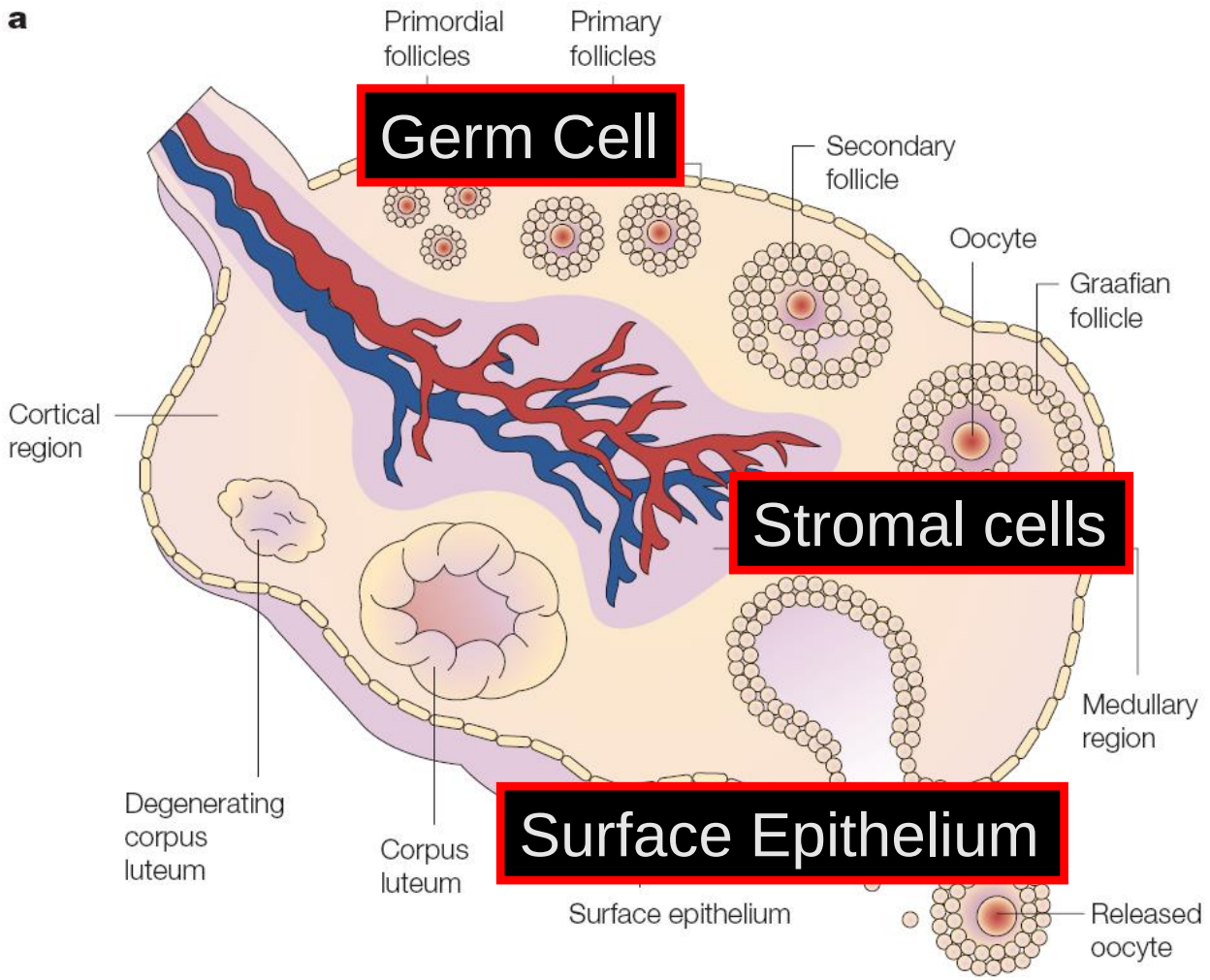
Where does ovarian cancer originate?



Naora *et al*., 2005

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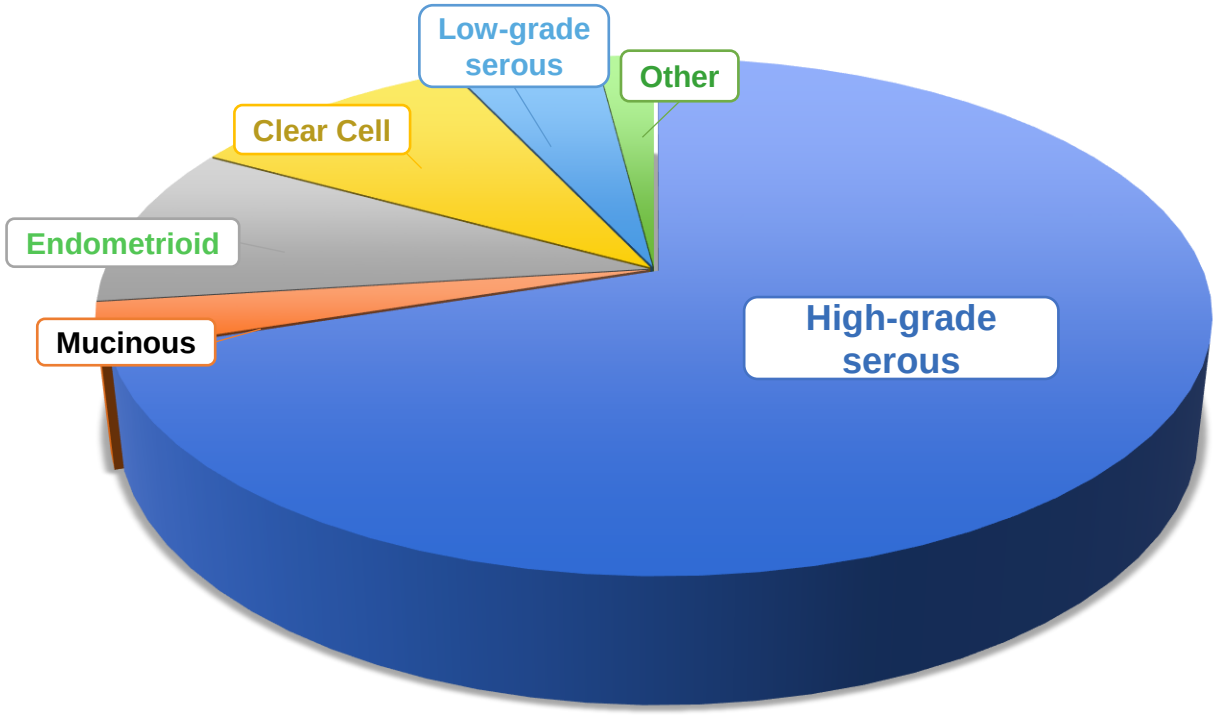
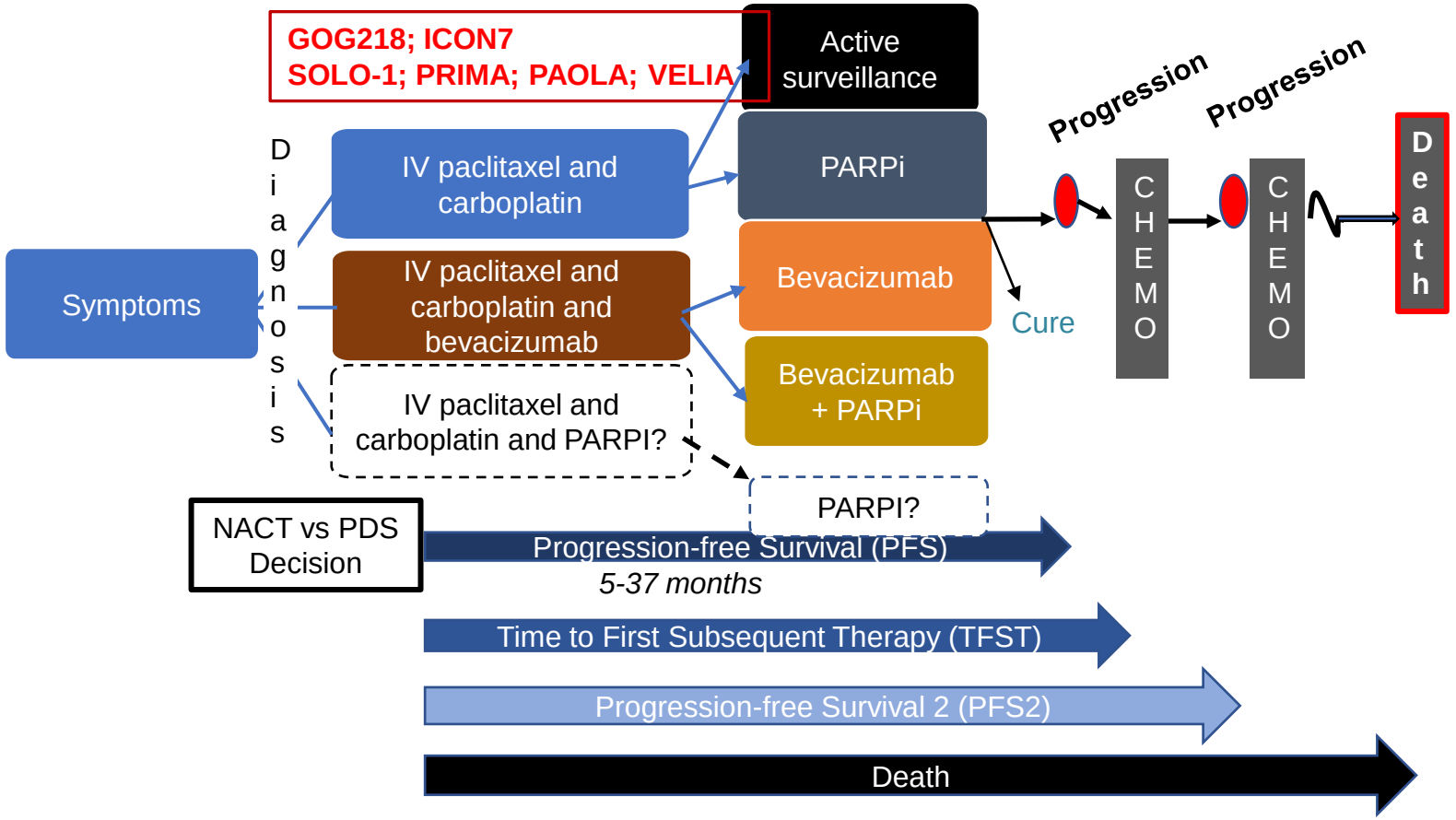
Epithelial Ovarian Cancer: Histologies

90% of ovarian cancers are malignant epithelial tumors



Prat and FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstet. 2014

2020 Treatment Paradigm: Frontline Therapy for Ovarian Cancer



Courtesy of Angeles Alvarez Secord, MD

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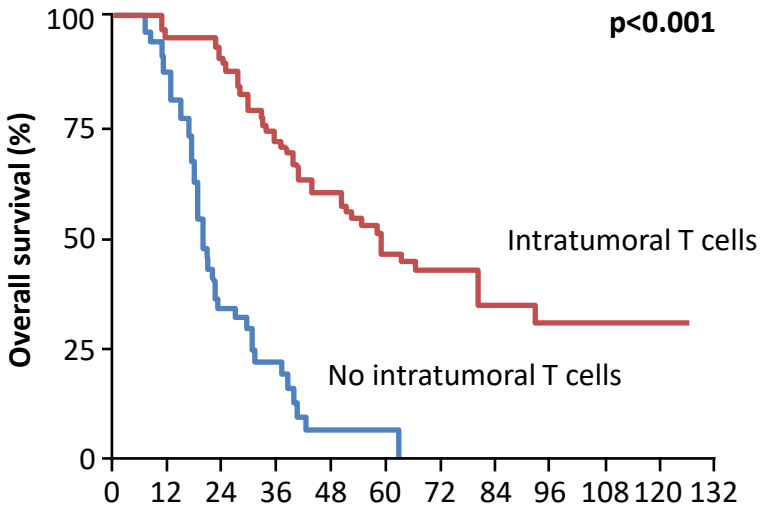
Presence of TILs is associated with better clinical outcomes in OC

OC is immunogenic

- TILs found at diagnosis in ~55% of patients
- Spontaneous anti-tumour response reported in some patients in clinical practice

TILs* are associated with longer OS



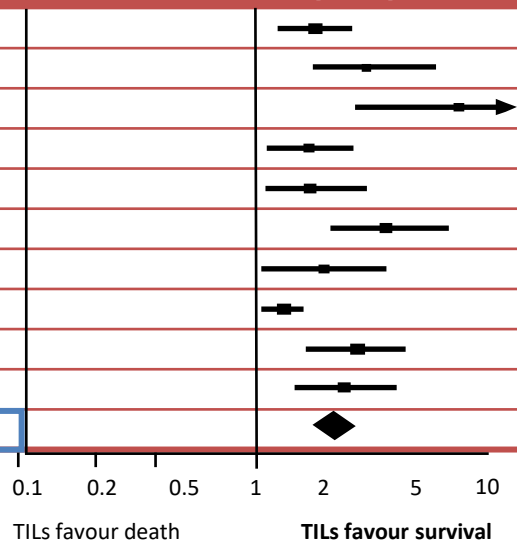
- *T cells measured in samples taken after debulking surgery (advanced OC)
- OC, ovarian cancer; OS, overall survival; TILs: tumour-infiltrating lymphocytes

- **Turner et al. Gynecol Oncol 2016; Coukos et al. Ann Oncol 2016 Mandai et al. Int J Clin Oncol 2016; Zhang et al. N Engl J Med 2003 Schlienger et al. Clin Cancer Res 2003**

The correlation between TILs and survival is supported by multiple clinical studies in OC

Independent of tumour grade, stage or histologic subtype[1]

Study or Subgroup	Log [HR]	SE	Weight (%)	HR [95% CI]
Zhang (2003)	0.61	0.18	12.5	1.84 [1.29–2.62]
Sato (2005)	1.11	0.307	8.8	3.03 [1.66–5.54]
Hamanishi (2007)	2.031	0.518	4.8	7.62 [2.76–21.04]
Callahan (2008)	0.548	0.222	11.2	1.73 [1.12–2.67]
Han (2008)	0.563	0.258	10.1	1.76 [1.06–2.91]
Tomsova (2008)	1.308	0.296	9.1	3.70 [2.07–6.61]
Adams (2009)	0.694	0.315	8.6	2.00 [1.08–3.71]
Clarke (2009)	0.282	0.106	14.5	1.33 [1.08–1.63]
Leffers (2009)	1.02	0.251	10.3	2.77 [1.70–4.54]
Stumpf (2009)	0.895	0.258	10.1	2.45 [1.48–4.06]
Total (95% CI)			**100.0**	**2.24 [1.71–2.92]**



Test for overall effect: p<0.00001

CI, confidence interval; HR, hazard ratio; OC, ovarian cancer; SE, standard error; TILs, tumour-infiltrating lymphocytes

Hwang et al. Gynecol Oncol 2012

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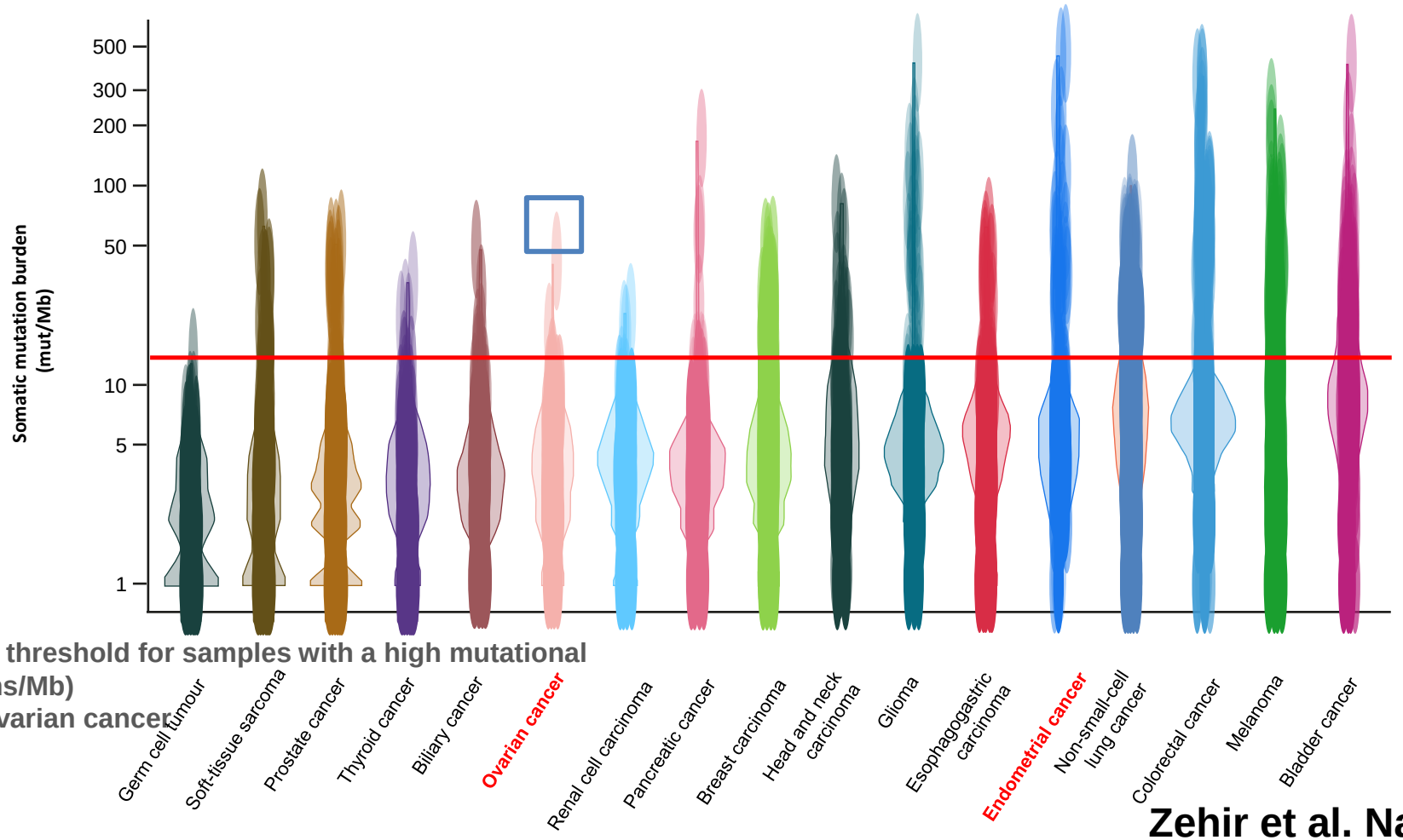
Mutational Load Matters



- Red line indicates the threshold for samples with a high mutational burden (13.8 mutations/Mb)
- Mb, megabase; OC, ovarian cancer

Zehir et al. Nat Med 2017

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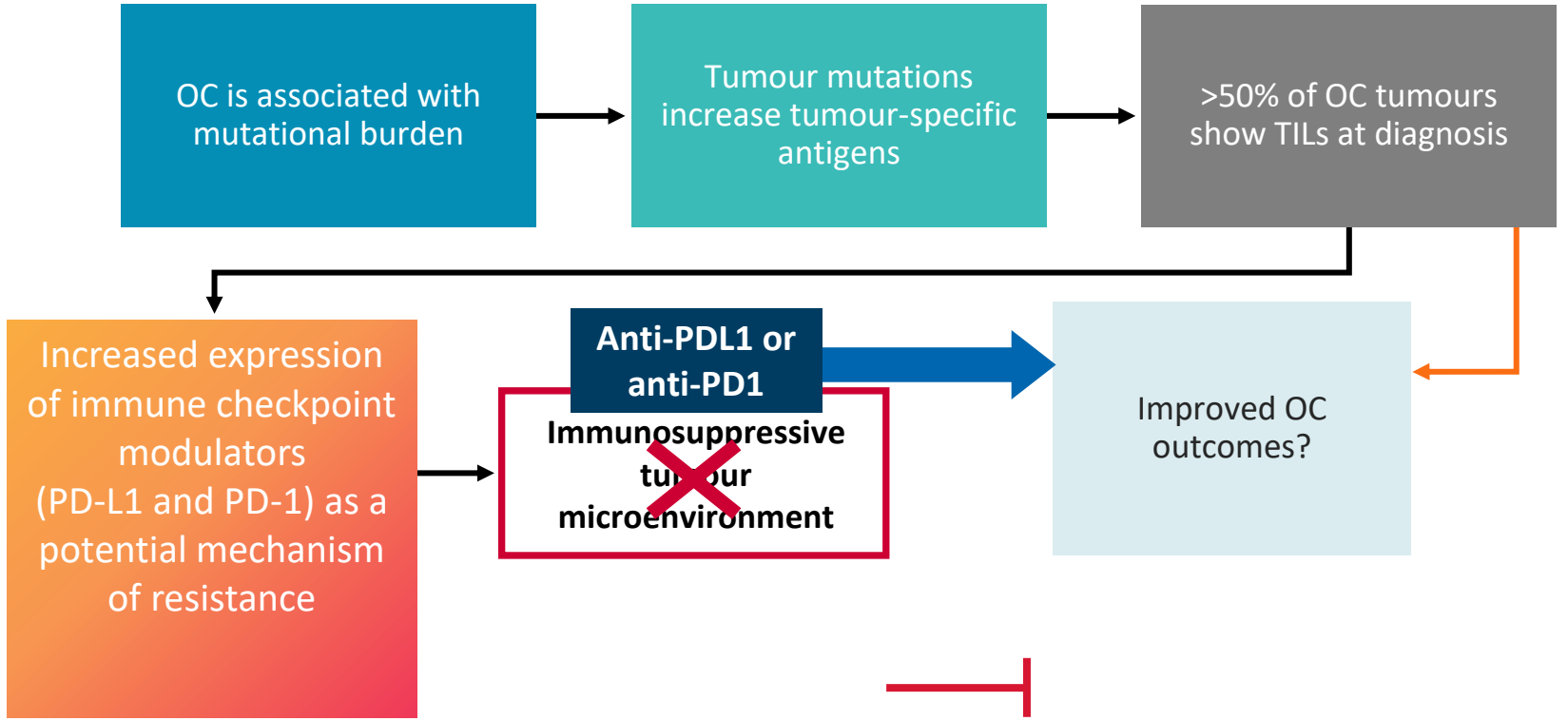
Rationale for targeting PD-L1 in OC



Lawrence et al. Nature 2013; Imielinski et al. Cell 2012; Chen et al. Clin Cancer Res 2012; Seghal et al. Cancer Res 2008; Rooij et al. J Clin Oncol 2013; Strickland et al. ASCO 2015; Zhang et al. N Eng J Med 2003; Hamanishi et al. PNAS 2007; Abiko et al. Clin Cancer Res 2013

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Anti-PDL1/PD1 have minimal activity as a single agent in OC

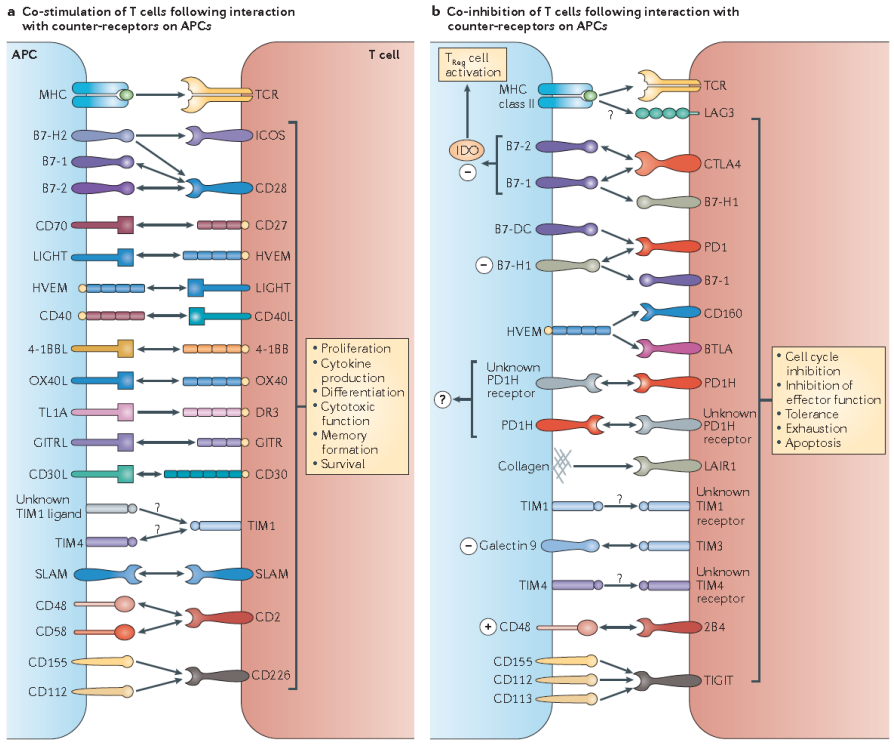
Therapeutic agent	Phase and trial name	N	Setting	ORR, n/N (%)
Atezolizumab	Ia (PCD4989g)[1]	12	PR ROC	2/8 (25)
Avelumab	Ib (JAVELIN solid tumour)[2]	75	ROC	8/75 (11)
Nivolumab	II (UMIN000005714)[3]	20	PR ROC	3/20 (15)
Pembrolizumab	Ib (KEYNOTE-028)[4]	26	ROC	3/26 (12)

PD-L1/PD-1 inhibitors demonstrate encouraging but modest activity in EOC, suggesting an opportunity for combinations

1. Infante et al. ESMO 2016 (abs 871P); 2. Disis et al. J Clin Oncol 2015 (abs 5509) 3. Hamanishi et al. J Clin Oncol 2015 (abs 5570); 4. Varga et al. J Clin Oncol 2015 (abs 5510)

Immunotherapy Combinations

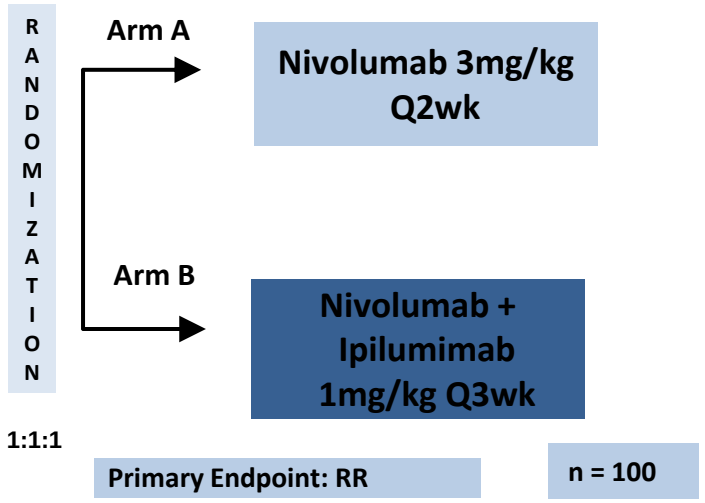
- **Differential expression of checkpoints on immune cells**
- **Differential downstream signaling that follows receptor activation**
- **Opportunity for combination with checkpoint agonists**



Chen and Flies Nature Rev Immunology 2013, Rotte *Annals Oncol* 2018

Nivolumab and Ipilumimab in recurrent ovarian cancer

NRG GY003: Randomized phase II of nivolumab with or without ipilumimab for recurrent ovarian cancer (NCT 02498600)



Response Rate
- Arm A: 12.2% (6/49)
- Arm B: 31.4% (16/51)

Progression Free Survival
- HR 0.528 (95% CI 0.339 – 0.821)

Grade > 3 Adverse Events
- Arm A: 55% (27/49)
- Arm B: 67% (34/51)

Zamarin JCO 2020

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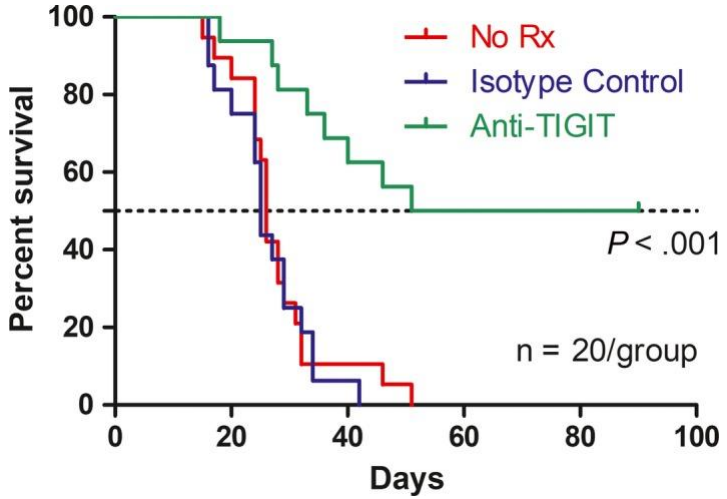
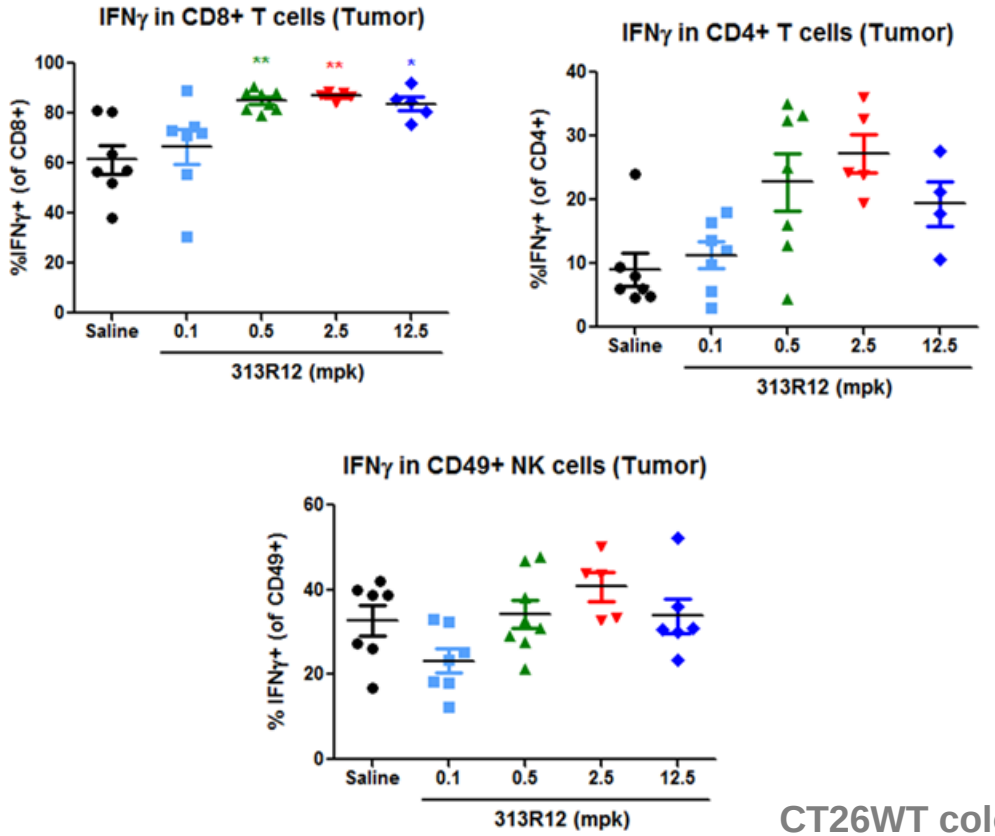
Preclinical evidence supports a role for TIGIT inhibition

Anti-TIGIT treatment significantly improved the survival rates of ovarian cancer mice induced by ID8 cells[1]



Anti-TIGIT Promotes Activation of CD8⁺ and CD4⁺ T Cells and NK Cells in the Tumor Microenvironment



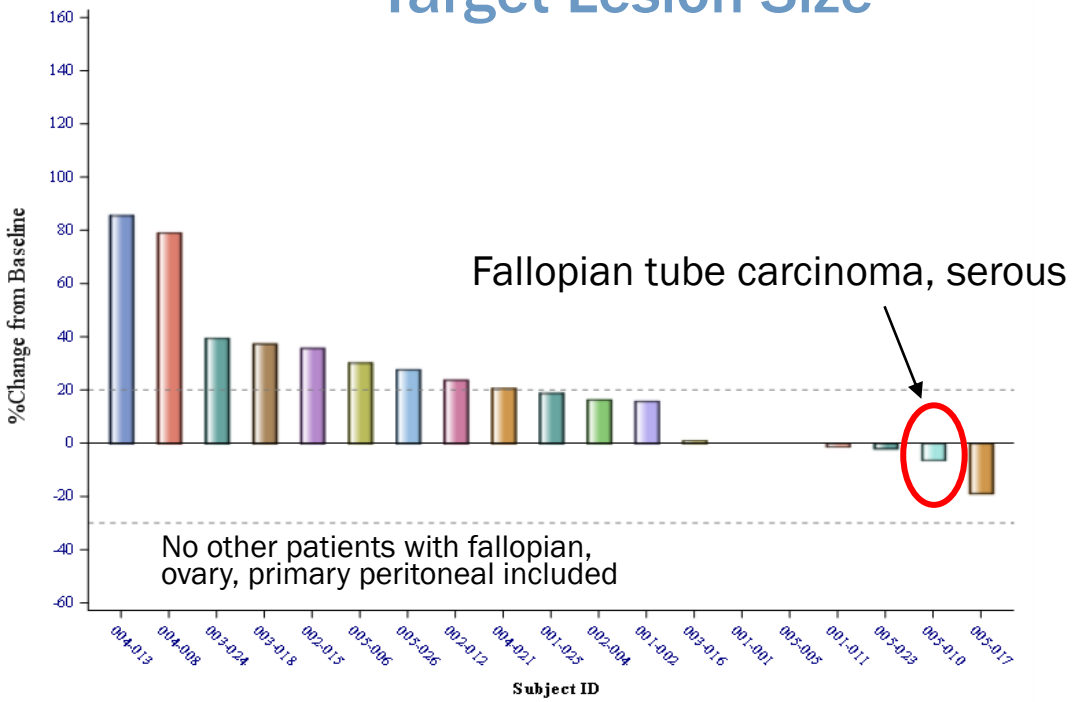
CD155 and PD-L1 exhibit contrasting expression patterns and TIL associations in ovarian cancer, suggesting non-redundant immunosuppressive mechanisms[2]

CT26WT colon line, *Mereo; Argast et. al. 2018, AACR*

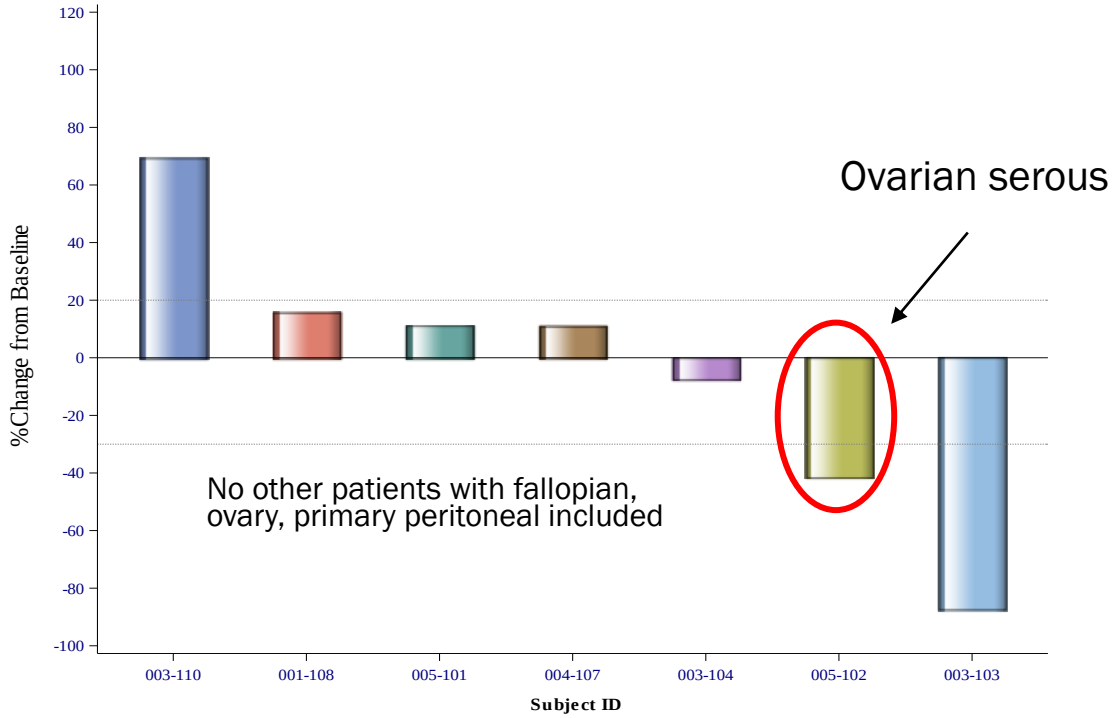
1. Chen et al. Cancer Med 2020 May;9(10):3584-3591, 2. Smazynski et al. 2020 Jul;158(1):167-177

Early clinical evidence demonstrates potential for use in ovarian cancer

Phase 1a: Best % Reduction in Target Lesion Size



Phase 1b: Best % Reduction in Target Lesion Size



Plan for High Grade Serous

Addition of arm to ongoing “A Phase 1b/2 Open-Label Study of the Efficacy and Safety of Etigilimab (MPH313) Administered in Combination with Nivolumab to Subjects with Locally Advanced or Metastatic Solid Tumors”

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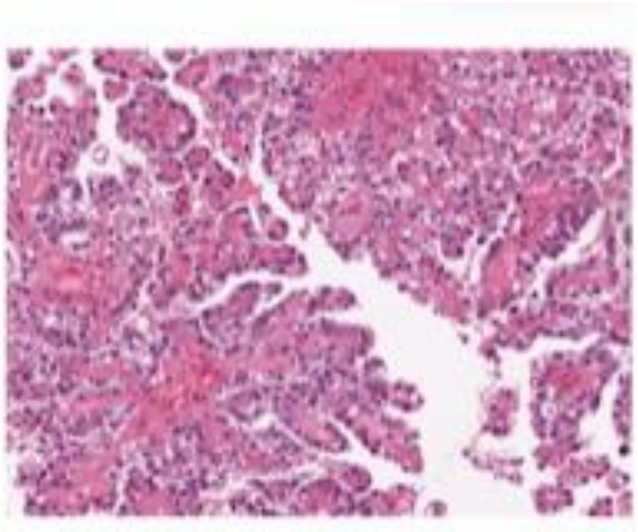
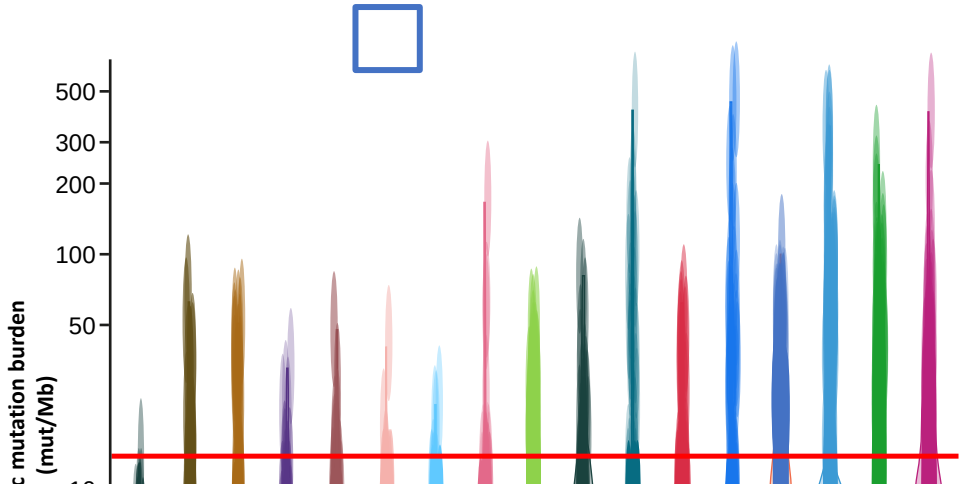
Novel opportunity: Clear Cell Ovarian Cancer

- Younger age
- 10% of all EOC
- 67% Stage 1
- Chemoresistance
- Molecular aberrations
  - *PIK3CA* mutations
  - *ARID1A* mutations
- High mutation load





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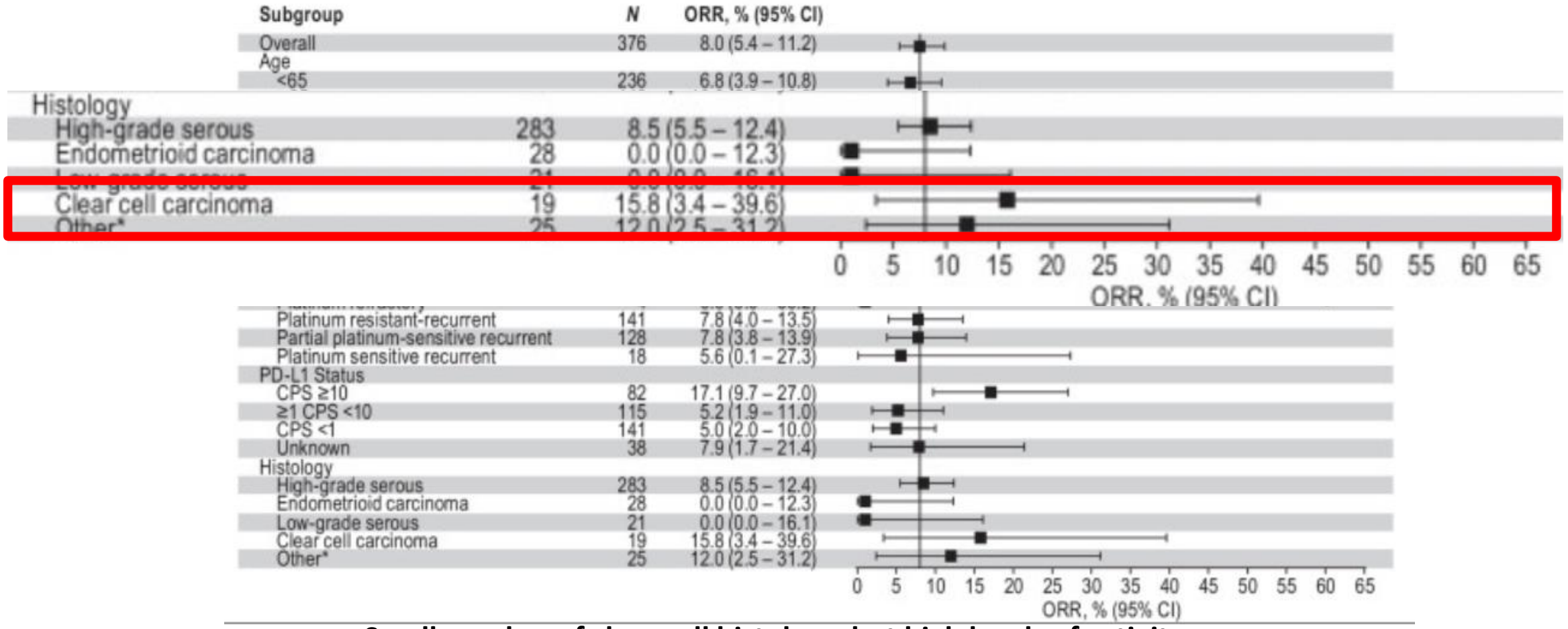
Interesting signal in clear cell ovarian cancer



Small number of clear cell histology, but high levels of activity

1. Infante et al. ESMO 2016 (abs 871P); 2. Disis et al. JAMA Oncology 2019;
3. Hamanishi et al. JCO 2015; 4. Varga et al. J Clin Oncol 2015 (abs 5510), Matulonis Annal Oncol 2019

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Potential for combination success in clear cell ovarian cancer

RANDOM

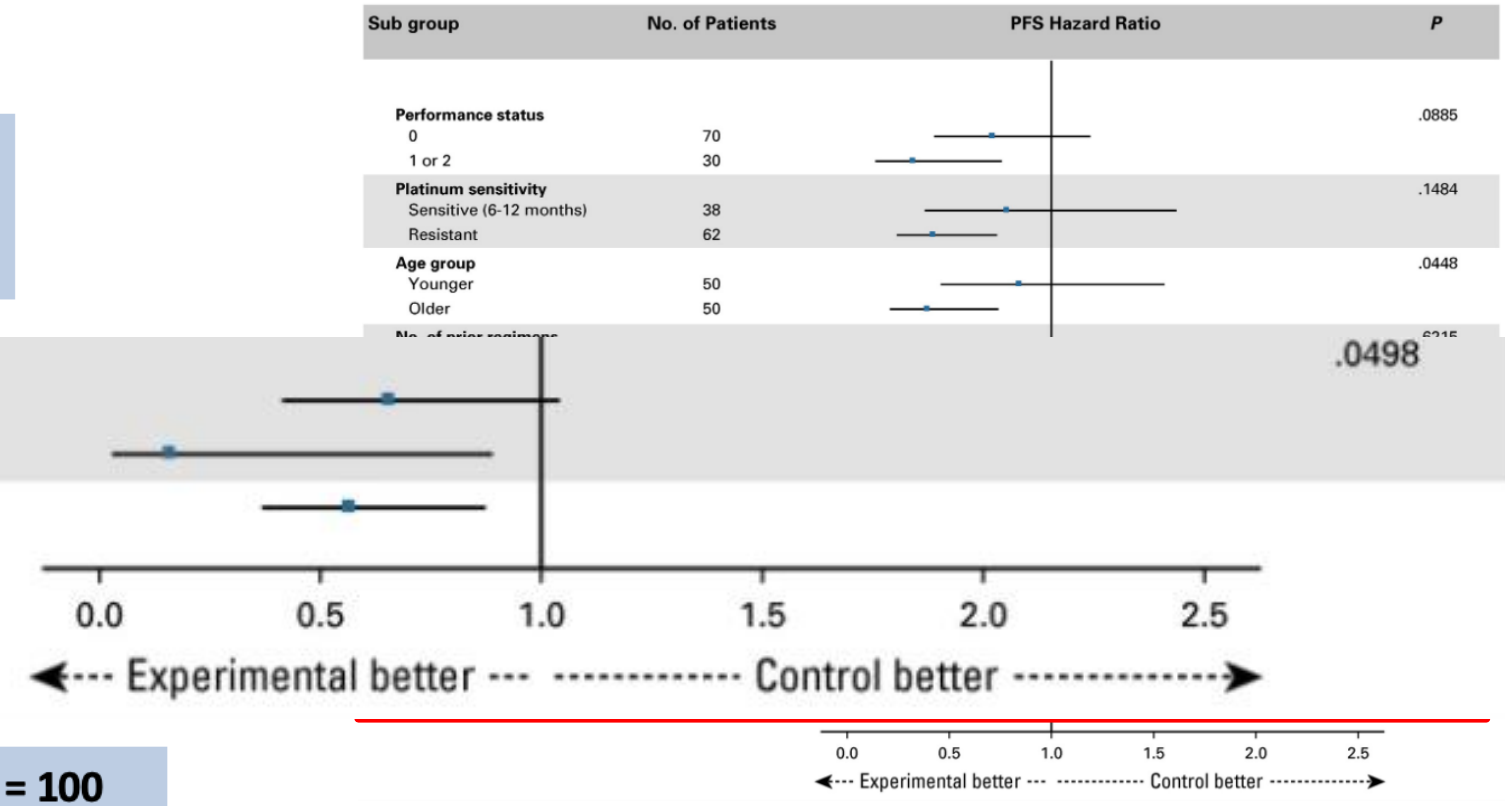
Arm A → **Nivolumab 3mg/kg Q2wk**

Clear cell histology	
Other cell types	88
Clear cell	12
Overall	100

1:1:1

Primary Endpoint: RR

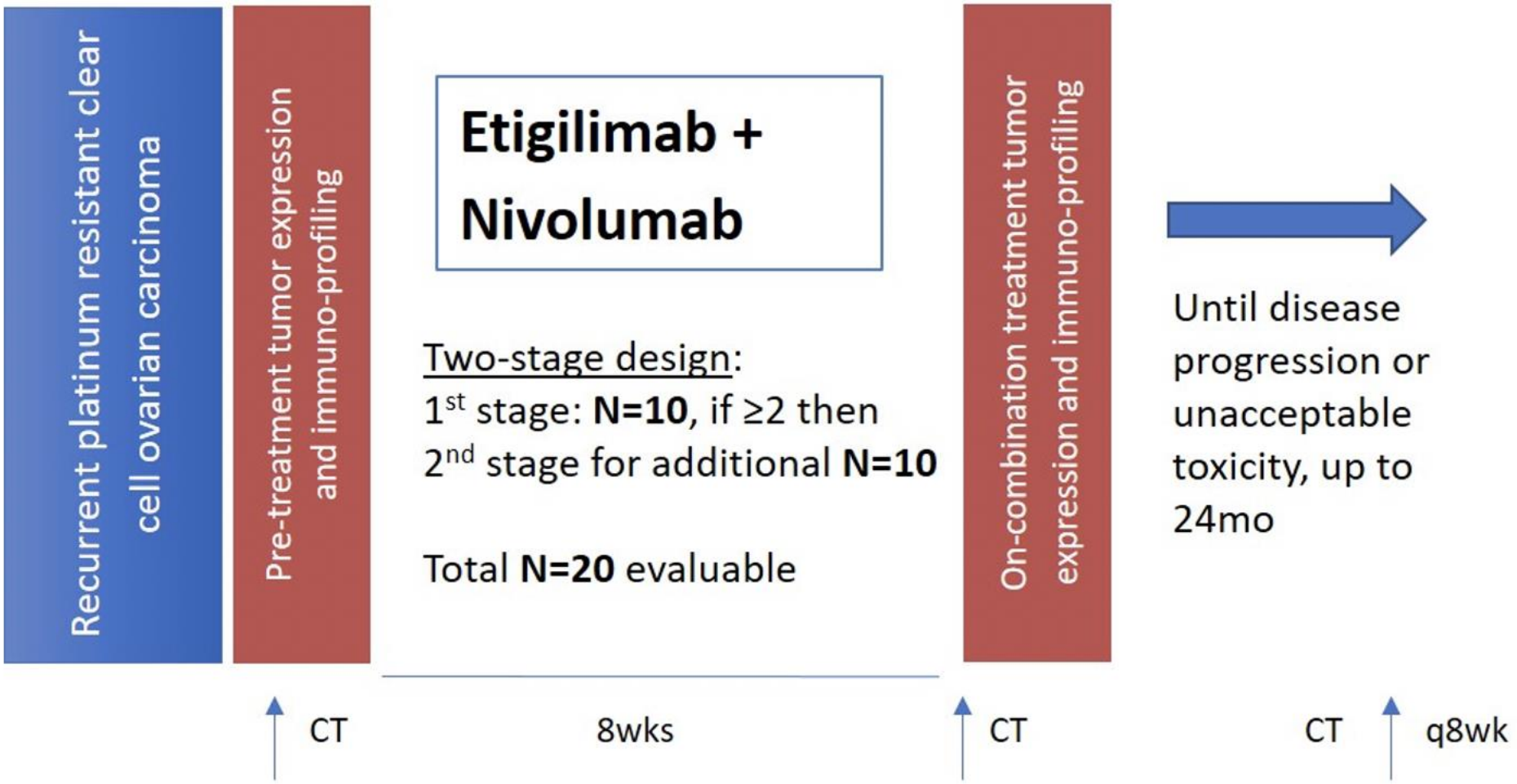
n = 100



Association with clear cell histology and benefit from experimental arm/combination therapy

Plan for Clear Cell

EON: A Single-arm Phase II study of Etigilimab (OMP-313M32) in Combination with Checkpoint Inhibition (Nivolumab) in Patients with Platinum-resistant, Recurrent Epithelial Ovarian Cancer



Two Stage Phase 1/2 BOP2 Design

- Stopping boundaries for efficacy and toxicity
- Continuous monitoring of toxicity

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Objectives

Primary

- To estimate the objective response rate of the combination of etigilimab and PD-1/PD-L1 inhibitor in patients with clear cell ovarian cancer.

- To evaluate the toxicity of the combination of etigilimab and PD-1/PD-L1 inhibitor in patients with clear cell ovarian cancer.

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Objectives

Secondary

- To determine PFS of the combination of etigilimab and PD-1/PD-L1 inhibitor in patients with platinum resistant clear cell ovarian cancer

- To estimate the disease control rate of the combination of etigilimab and PD-1/PD-L1 inhibitor in patients with platinum resistant clear cell ovarian cancer

- To investigate molecular and immunological changes associated with the combination of TIGIT and PD-1/PD-L1 inhibition; specifically to describe changes in T cell populations (including but not limited to CD3, CD8, CD4, FOXP3) and cell proliferation, as well as report changes in the proportion of macrophage phenotypes M1 and M2 (with phenotypic markers potentially including arginase1, CD11b, PDL-1, and CD206)

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Key Inclusion Criteria

- Patients with platinum refractory* and platinum resistant** high grade clear cell ovarian, fallopian tube or peritoneal carcinoma
  * Platinum refractory: progression during platinum-containing therapy or within 4 weeks of last dose
  ** Platinum resistant: relapse-free interval 1-6 months of a platinum-containing therapy
- Prior Therapy: Unlimited prior therapies are allowed, prior checkpoint inhibition is allowed
- Measurable disease
- ECOG PS 0-2

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Conclusions

- There are critical opportunities to improve outcomes in ovarian cancer
  - Improving activity of checkpoint inhibition in high grade serous
  - Potential registration pathway for clear cell subtype
  - Transition to upfront therapy if activity in the recurrent setting
- Translational studies in the current trial
  - Guide future development
  - Identify mechanism of response and resistance

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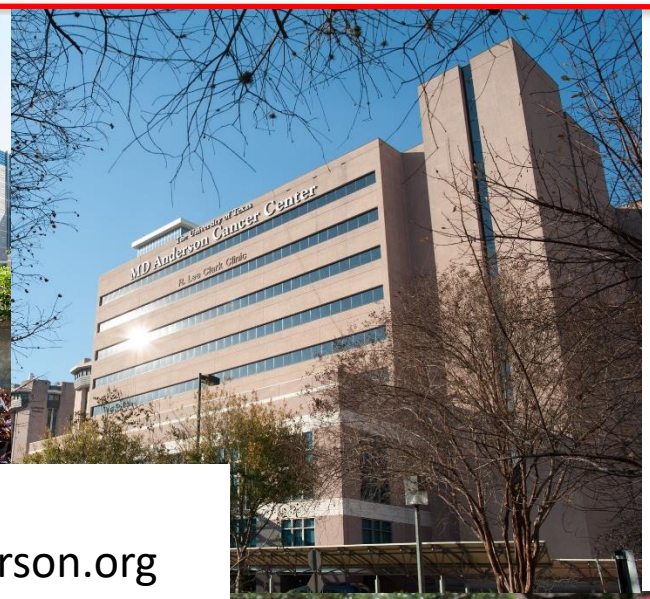
Thank you



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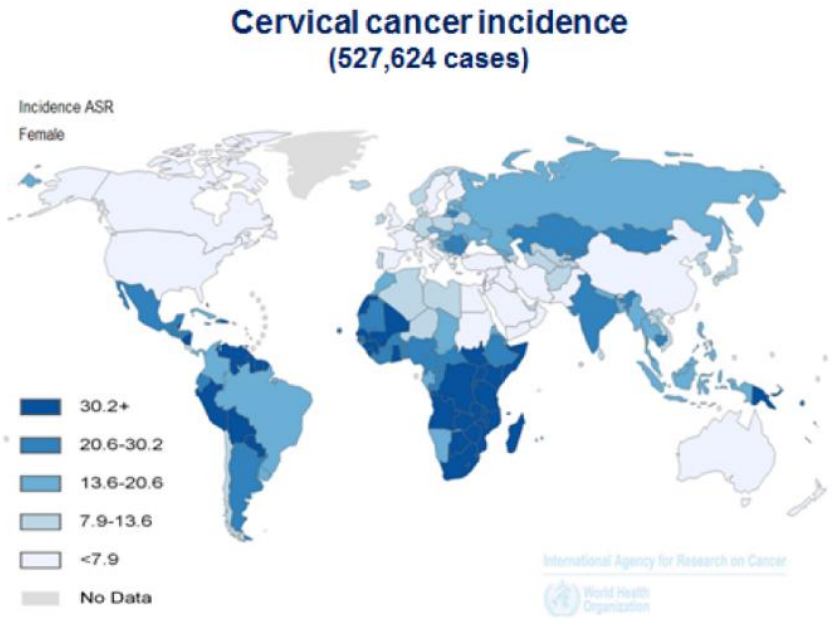
Mereo BioPharma

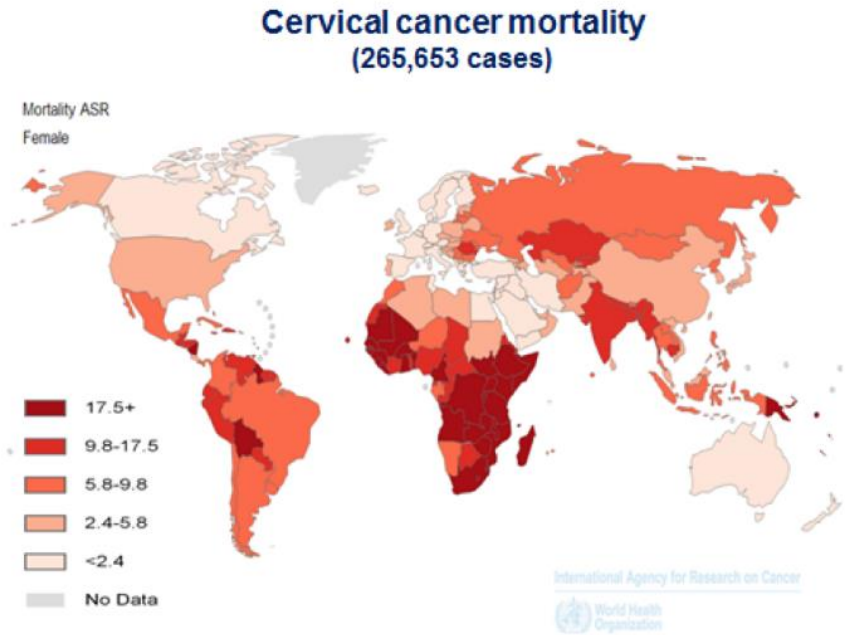
CERVICAL CANCER

MANAGEMENT OF ADVANCED CERVICAL CANCER

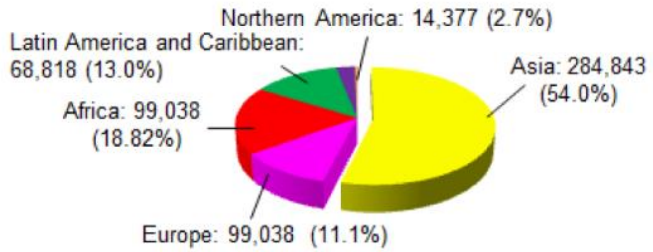
Kathleen N. Moore, MD
Associate Director, Clinical Research
Director, TSET Phase I Drug Development Unit
Stephenson Cancer Center at the University of Oklahoma
Director, Gynecologic Fellowship
Division of Gynecologic Oncology

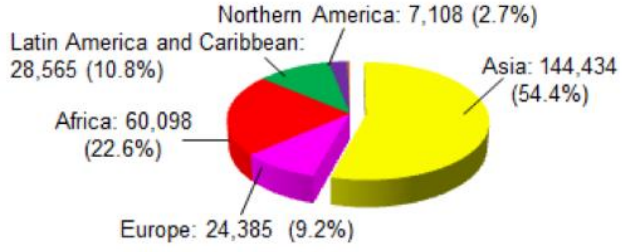
Cervical Cancer in an International Health Concern





Mortality: Incidence ratio: 50%





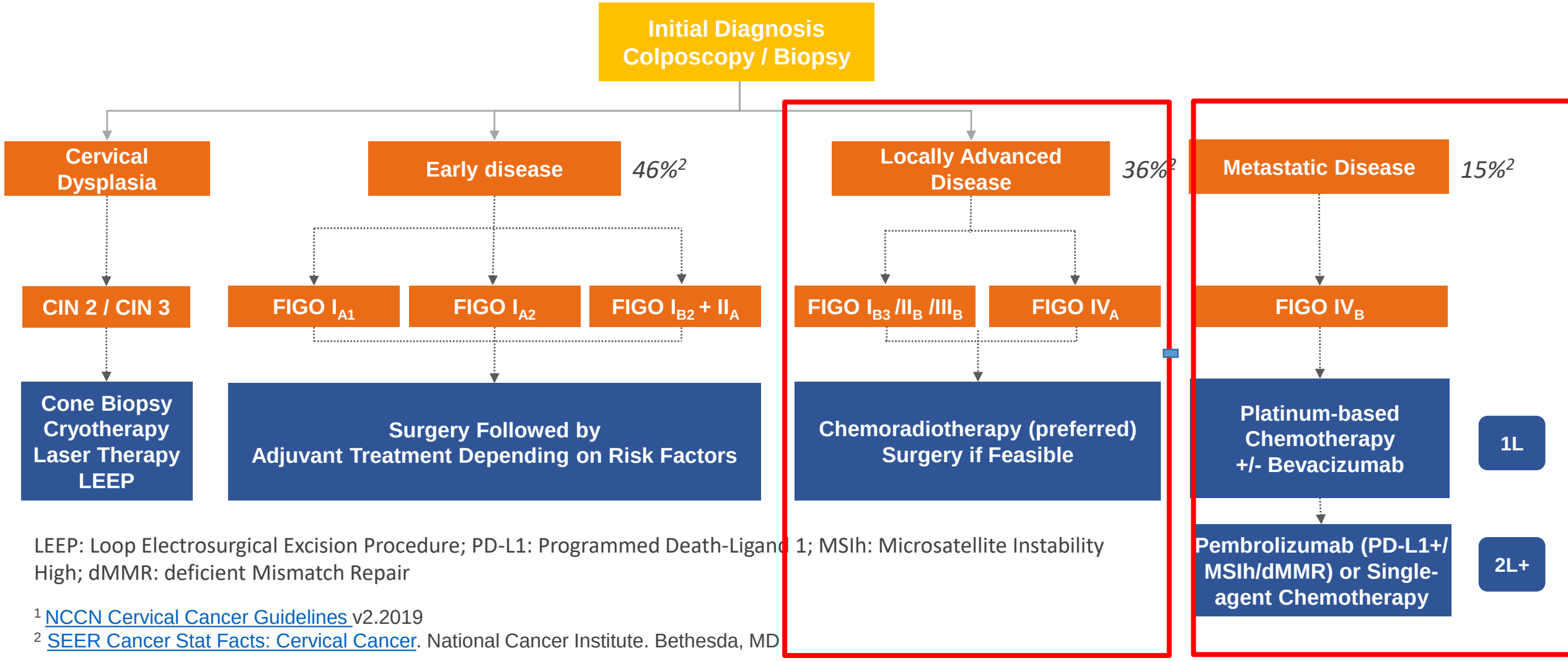
Jung HS et al. J Clin Med. 2015. 4(5): 1126

An Estimated 13,800 Cases of Invasive Cervical Cancer in the US in 2020

- ✓ **Death rate in 2016 (2.2 per 100,000) was less than half that in 1975 (5.6 per 100,000)**
- ✓ **From 2007 to 2016, the death rate decreased by about 1% per year in women > 50 years of age and older, but was stable in < 50**

1. SEER Stat Fact Sheets: Cervix Uteri Cancer. http://seer.cancer.gov/statfacts/html/cervix.html. 2. American Cancer Society. *Cancer Facts & Figures 2020*. Atlanta, GA: American Cancer Society; 2019.

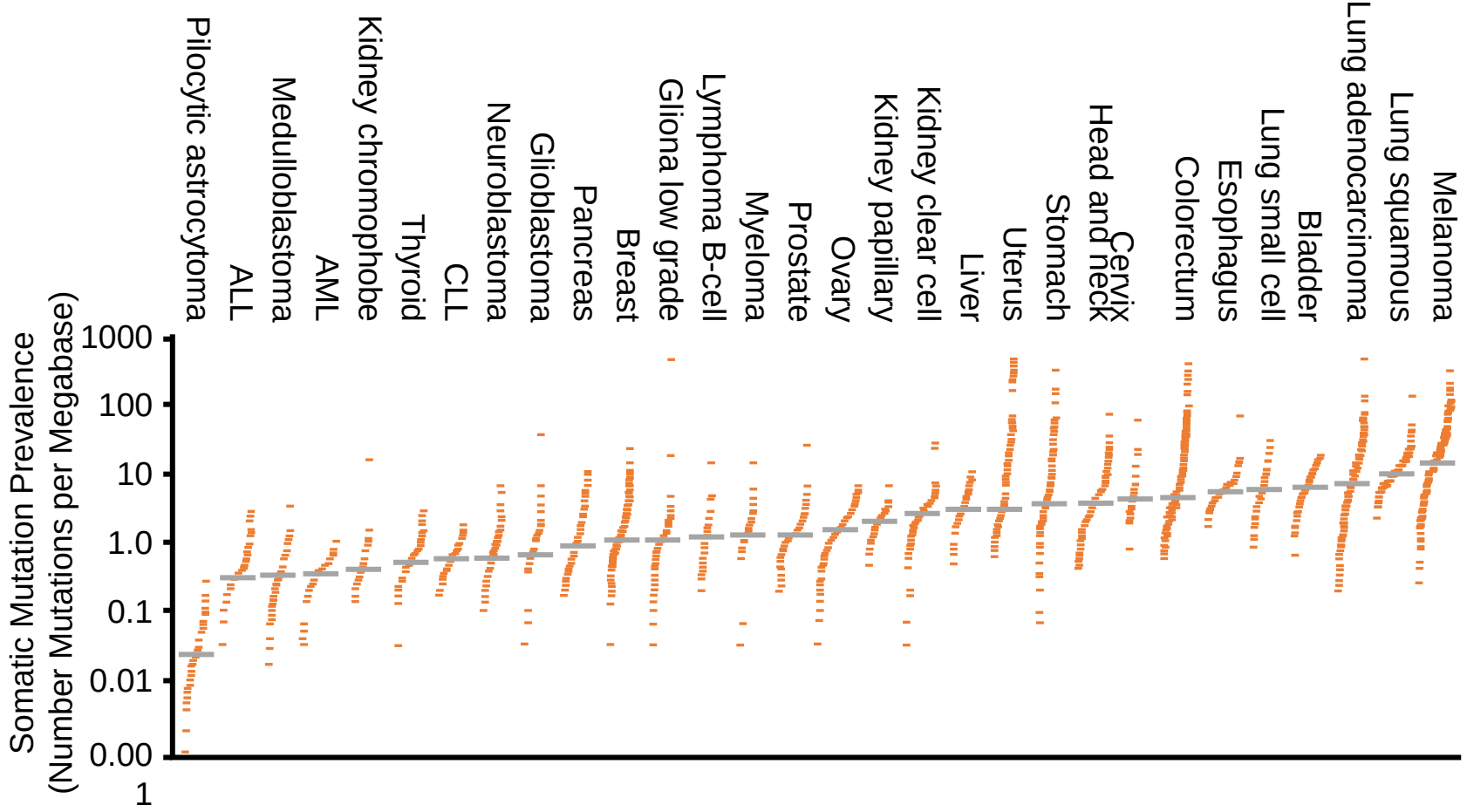
Cervical Cancer: Summary of Treatment



LEEP: Loop Electrosurgical Excision Procedure; PD-L1: Programmed Death-Ligand 1; MSIh: Microsatellite Instability High; dMMR: deficient Mismatch Repair

[1] NCCN Cervical Cancer Guidelines v2.2019
[2] SEER Cancer Stat Facts: Cervical Cancer. National Cancer Institute. Bethesda, MD

Mutational Burden Compared With Other Tumors



Alexandrov LB, et al. *Nature*. 2013;500(7463):415-421.

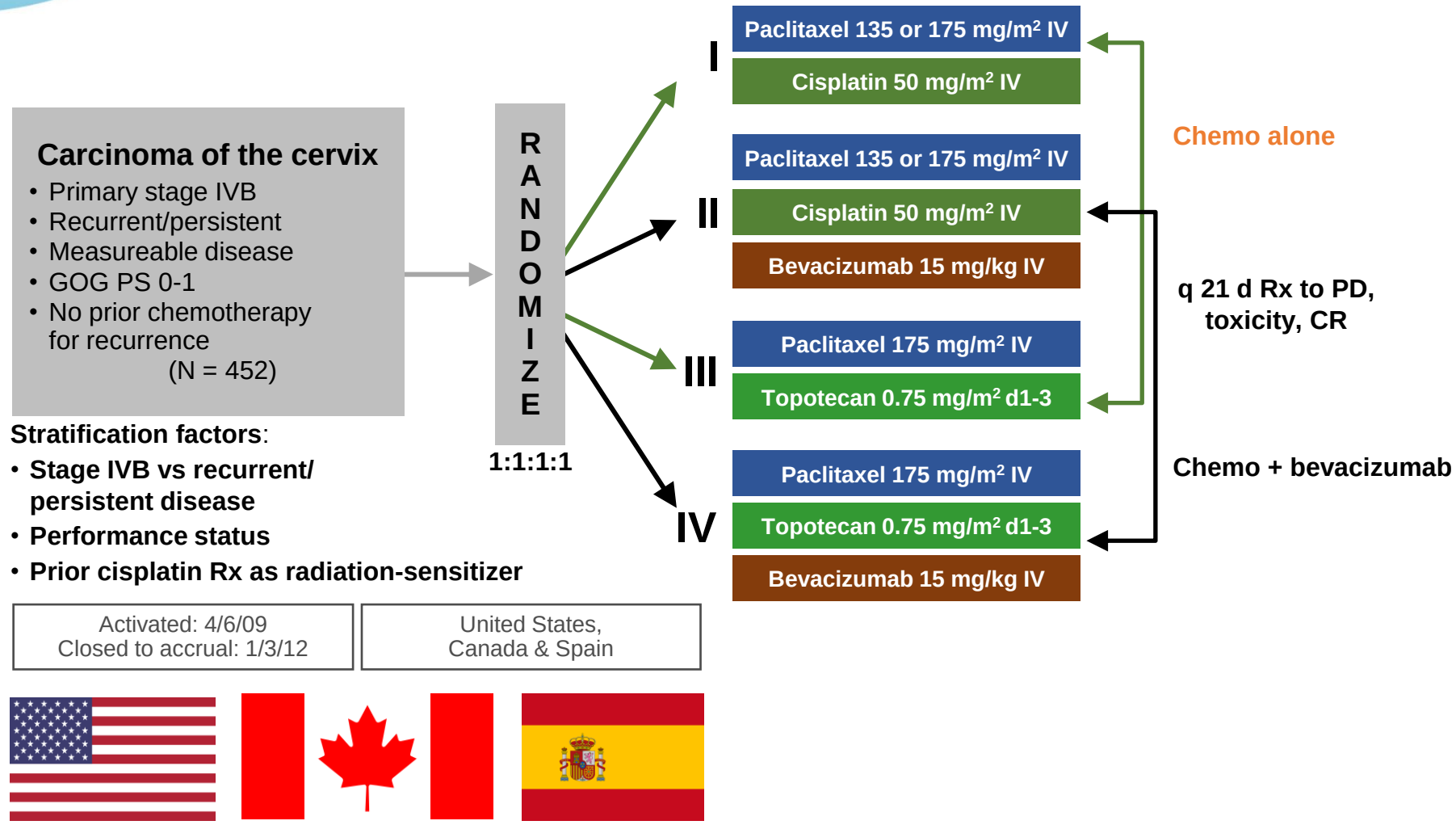
Evolution of 1L metastatic Cervical Cancer Treatment

Design	N	ORR (%)	PFS (months)	P-value	OS (months)	P-value	Reference
Bev + PC or TP vs. PC or TP	227 225	48 36	8.2 5.9	0.0002	17.0 13.3	0.0004	GOG 240 Study Tewari et al., NEJM.2014
PC vs. Carbo/Pacli	121 123	-- --	6.9 6.21	0.053	18.3 17.5	0.032	JCOG 0505 Study Kitagawa et al., JCO.2012
PC VC GC TC	103 108 112 111	29.1 25.9 22.3 23.4	5.82 3.98 4.7 4.57	 0.06 0.04 0.19	12.87 9.99 10.28 10.25	 0.71 0.90 0.89	GOG 204 Study Monk et al., JCO.2009
PC Cisplatin	130 134	36 19	4.8 2.8	0.001	9.7 8.8	NS	GOG 169 Study Moore et al., JCO.2004
TC Cisplatin	147 146	27 13	4.6 2.9	0.014	9.4 6.5	0.021	GOG 179 Study Long et al., JCO.2005

Addition of bevacizumab significantly increased rates of grade 3 or higher gastrointestinal or genitourinary fistula (6% vs. 0%, P=0.002), in addition to thromboembolic events (8% vs. 1%, P=0.001)

GC: gemcitabine/cisplatin; NS: not stated; PC: paclitaxel/cisplatin; TC:Topotecan/cisplatin; VC: vinorelbine/cisplatin

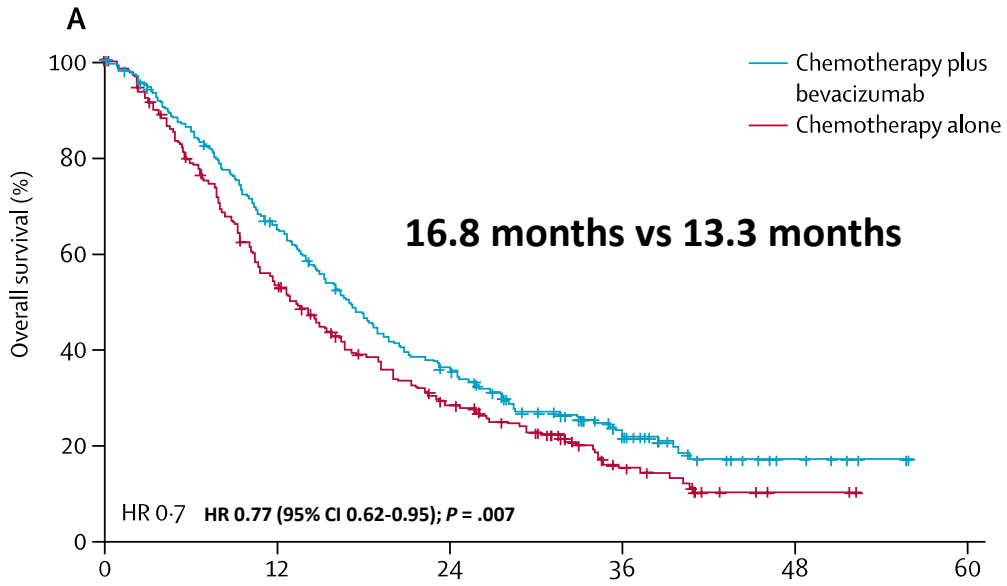
GOG 240



National Institutes of Health. http://clinicaltrials.gov/ct2/show/NCT00803062. Accessed 15 January 2018.

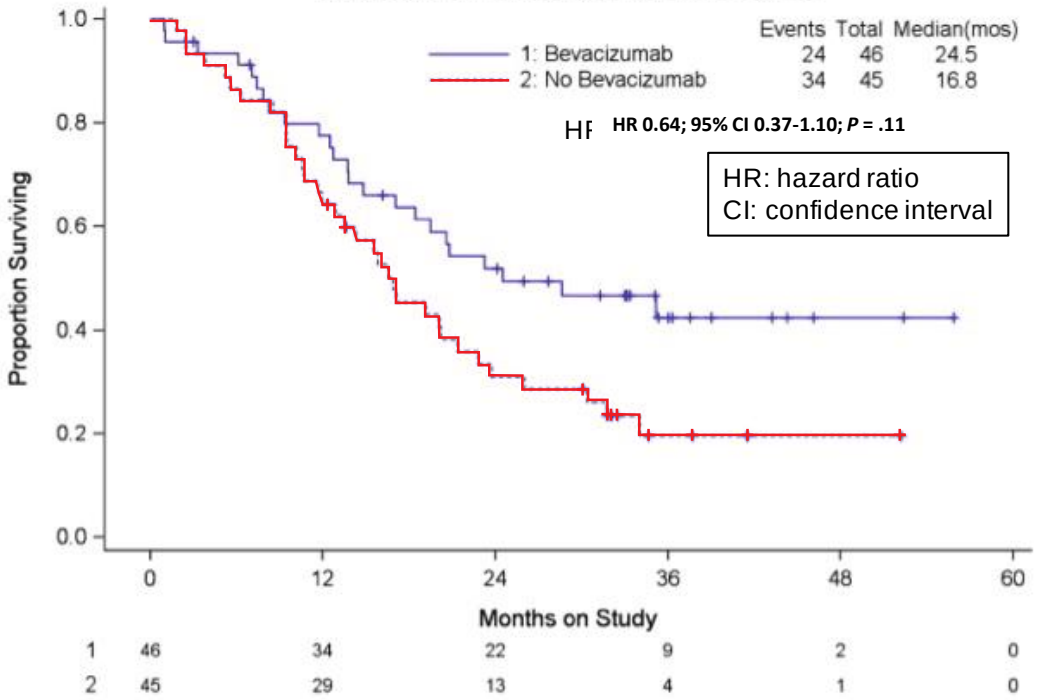
GOG 240 : Mature OS

ITT



Number at risk (number censored)						
Chemotherapy plus bevacizumab	227 (0)	142 (9)	75 (12)	30 (31)	6 (51)	0 (57)
Chemotherapy alone	225 (0)	114 (9)	54 (18)	17 (35)	2 (45)	0 (47)

Not Previously Irradiated



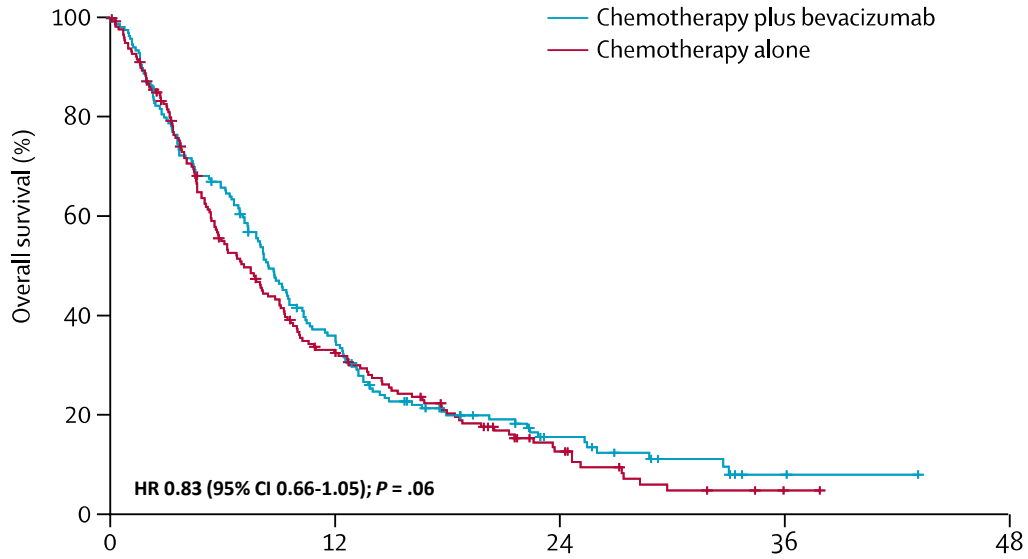
ITT, intent to treat

Tewari KS, et al. *Lancet*. 2017;390(10103):1654-1663.

GOG 240 Mature Post-Progression OS

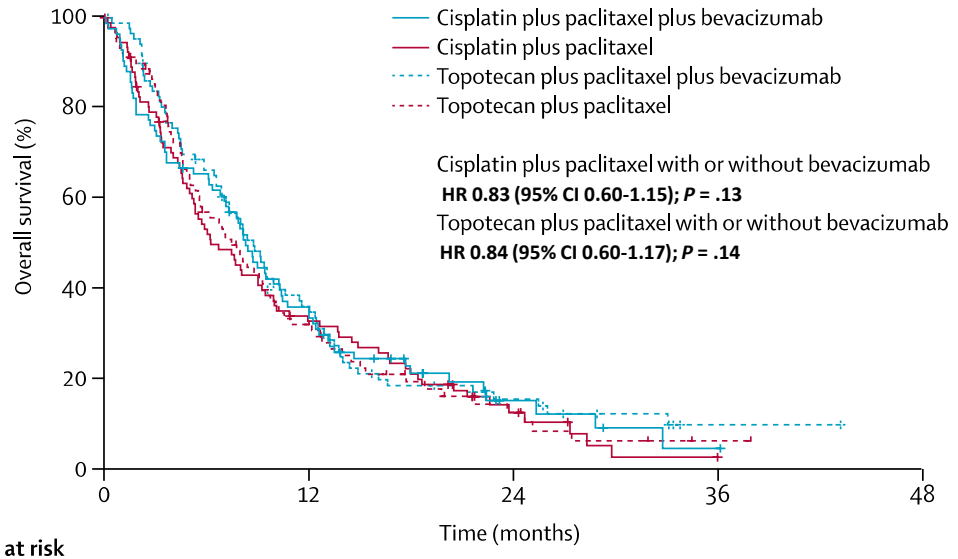
Varies between 6.2 months to 8.7 months

ITT



Number at risk (number censored)					
Chemotherapy plus bevacizumab	172 (0)	56 (7)	15 (20)	2 (27)	0 (29)
Chemotherapy alone	181 (0)	52 (12)	14 (21)	1 (27)	0 (28)

All 4 Arms



Number at risk (number censored)					
Cisplatin plus paclitaxel	92 (0)	28 (4)	7 (9)	0 (12)	0 (12)
Cisplatin plus paclitaxel plus bevacizumab	85 (0)	27 (3)	5 (13)	1 (14)	0 (15)
Topotecan plus paclitaxel	89 (0)	24 (8)	7 (12)	1 (15)	0 (16)
Topotecan plus paclitaxel plus bevacizumab	87 (0)	29 (4)	10 (7)	1 (13)	0 (14)

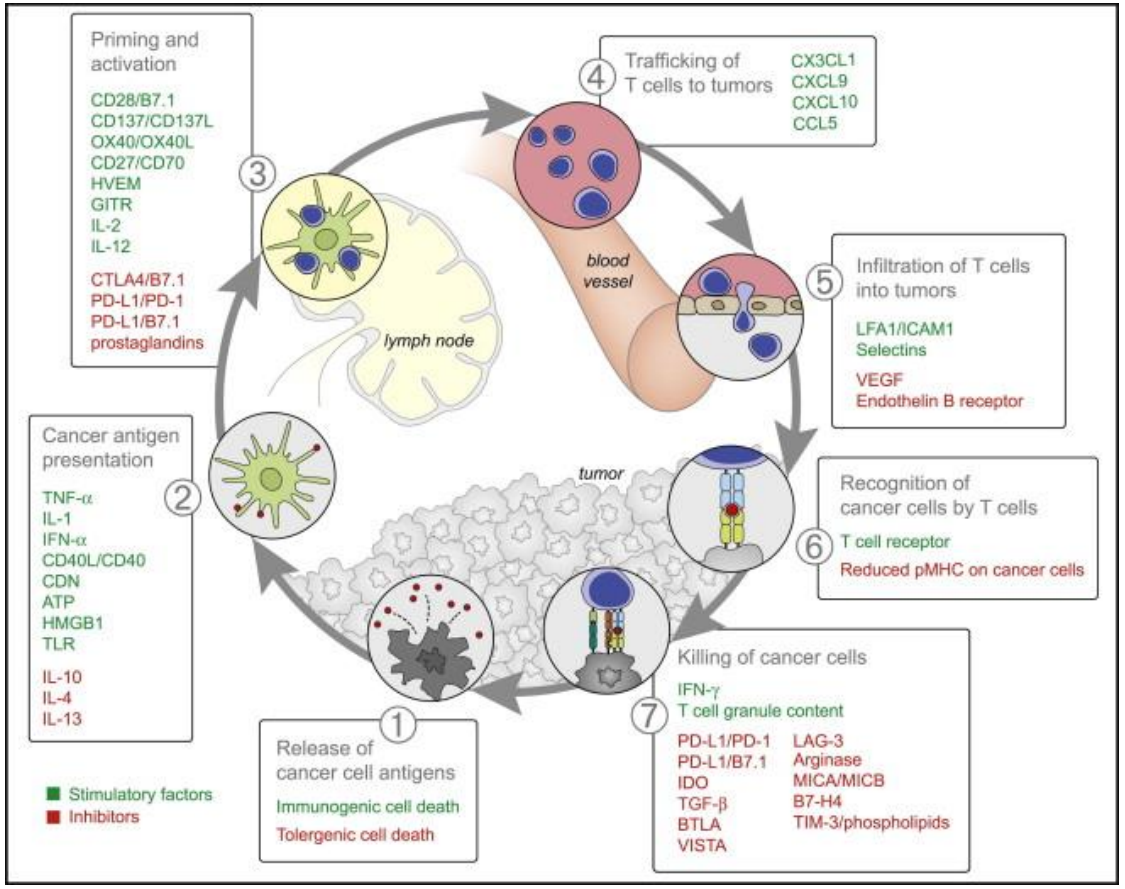
Tewari KS, et al. *Lancet*. 2017;390(10103):1654-1663.

Regimen for 2L+ Metastatic Cervical Cancer

Design	N	ORR (%)	PFS (months)	OS (months)
Topotecan	45	12.5	2.1	6.6
Vinorelbine	44	13.7	NS	NS
Pemetrexed	**29**	**15**	**3.1**	**7.4**
Pemetrexed	**43**	**13.9**	**2.3**	**8.05**
Docetaxel	**27**	**8.7**	**3.8**	**7.0**
Gemcitabine	22	4.5	2.1	6.5
Bevacizumab	46	10.9	3.4	7.29
Pembrolizumab	**77**	**14.3**	**--**	**--**

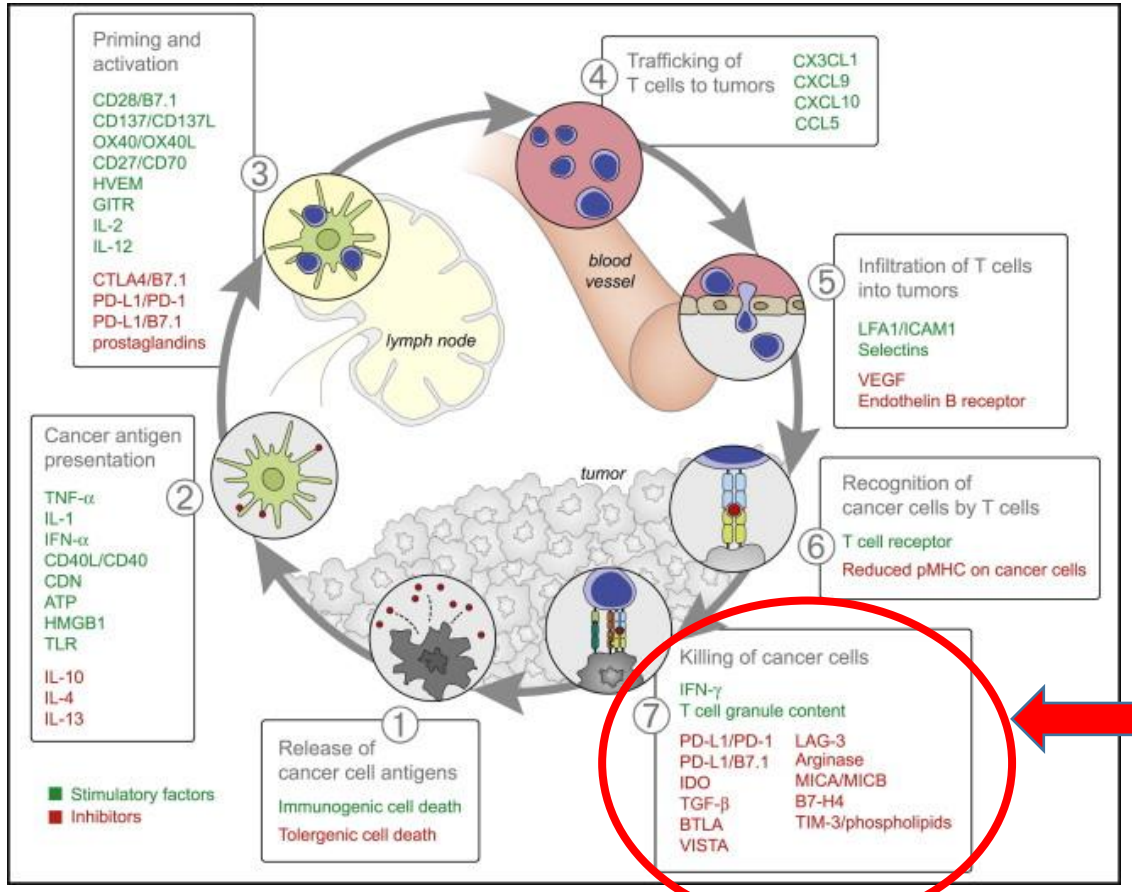
[1] Yu et al., Am J Hematol Oncol 2015;11:27-31

The Cancer Immunity Cycle



Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity. 2013 Jul 25;39(1):1-10

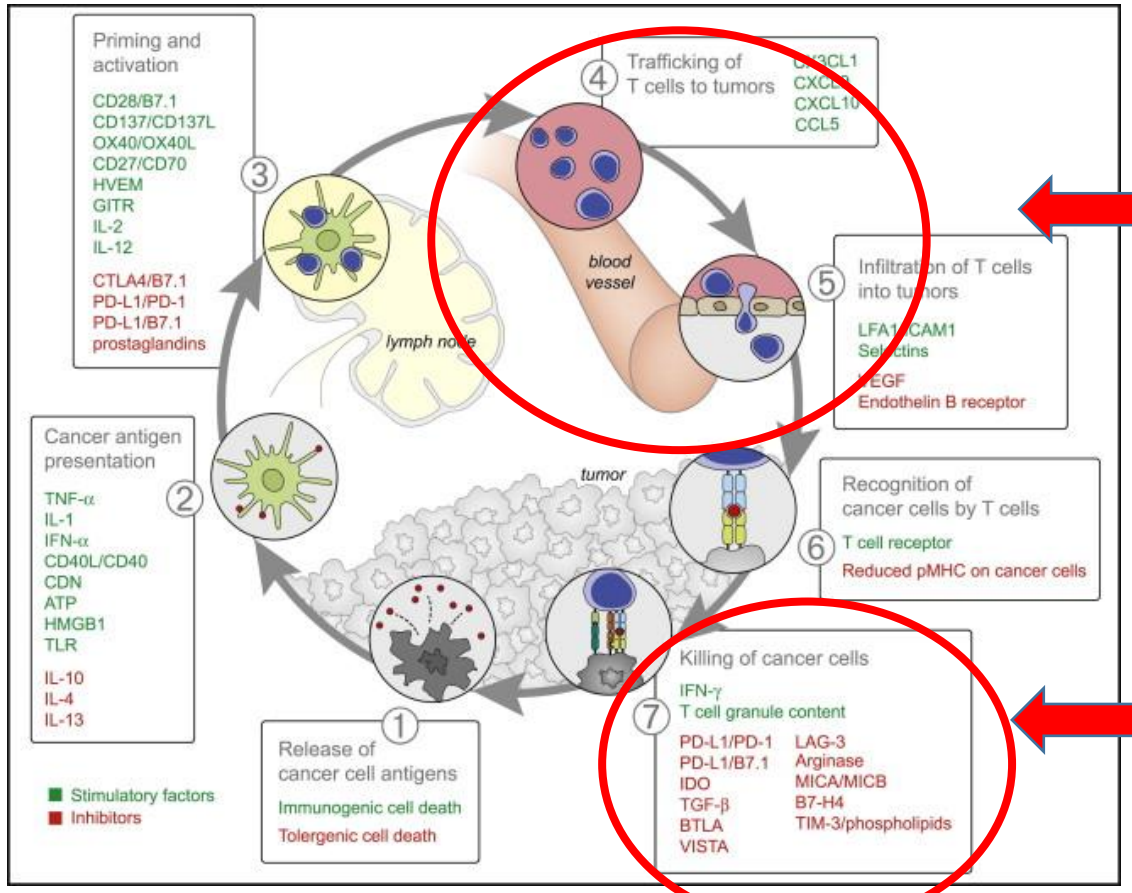
The Cancer Immunity Cycle



Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity. 2013 Jul 25;39(1):1-10

Immune Check Point Inhibition
PD-1, PDL-1 Blockade
TIGIT is emerging

The Cancer Immunity Cycle



Adoptive Cell Therapy
TIL, CAR, TCR

Immune Check Point Inhibition
PD-1, PDL-1 Blockade

Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity. 2013 Jul 25;39(1):1-10

KEYNOTE-158 (NCT02628067): Phase II basket study, single-agent pembrolizumab, cervical cancer cohort

- Advanced cervical squamous cell carcinoma with progression on/intolerance to ≥1 prior line of standard therapy
- ECOG PS 0/1

84% PD-L1-positive; 77/98 (79%) had CPS ≥1
65% ≥2 prior therapies for recurrent/metastatic CC)

Primary endpoint: IRC-assessed ORR (RECIST v1.1)

Secondary endpoints: DoR, IRC-assessed PFS, OS, safety

FDA approval: recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumours express PD-L1 (CPS ≥1) as determined by an FDA-approved test

Response	All patients (n=98)	PD-L1 positive (n=82)	PD-L1-negative (n=15)
ORR (95% CI)	12.2%	14.6% (8–24)	0% (0–22)
CR	3%	4%	0%
PR	9%	11%	0%
SD	18%	18%	20%

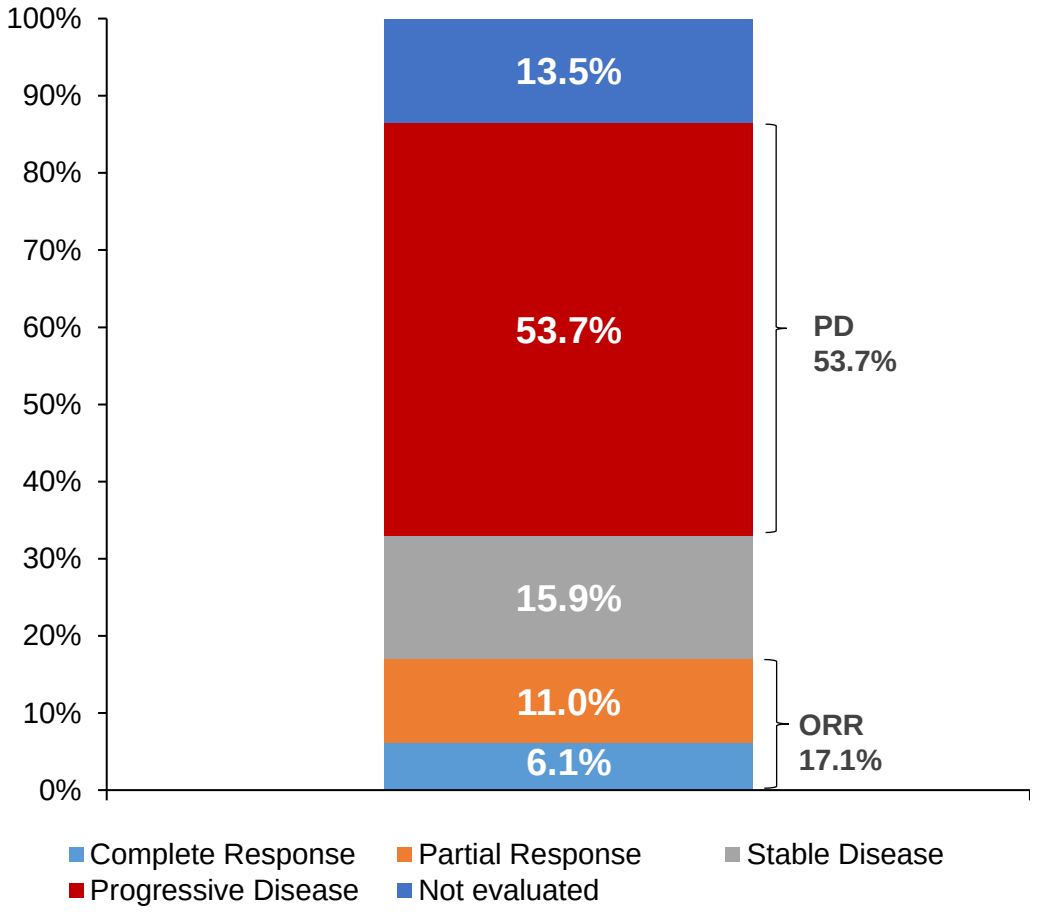
- Median time to response: 2.1 months (range 1.6–4.1)
- Median DoR: not reached (range 3.7+–18.6+)
- 6/12 responses ongoing at data cut-off

Pembrolizumab 200 mg q3w for 2 years or until PD, intolerable toxicity, patient withdrawal or investigator decision

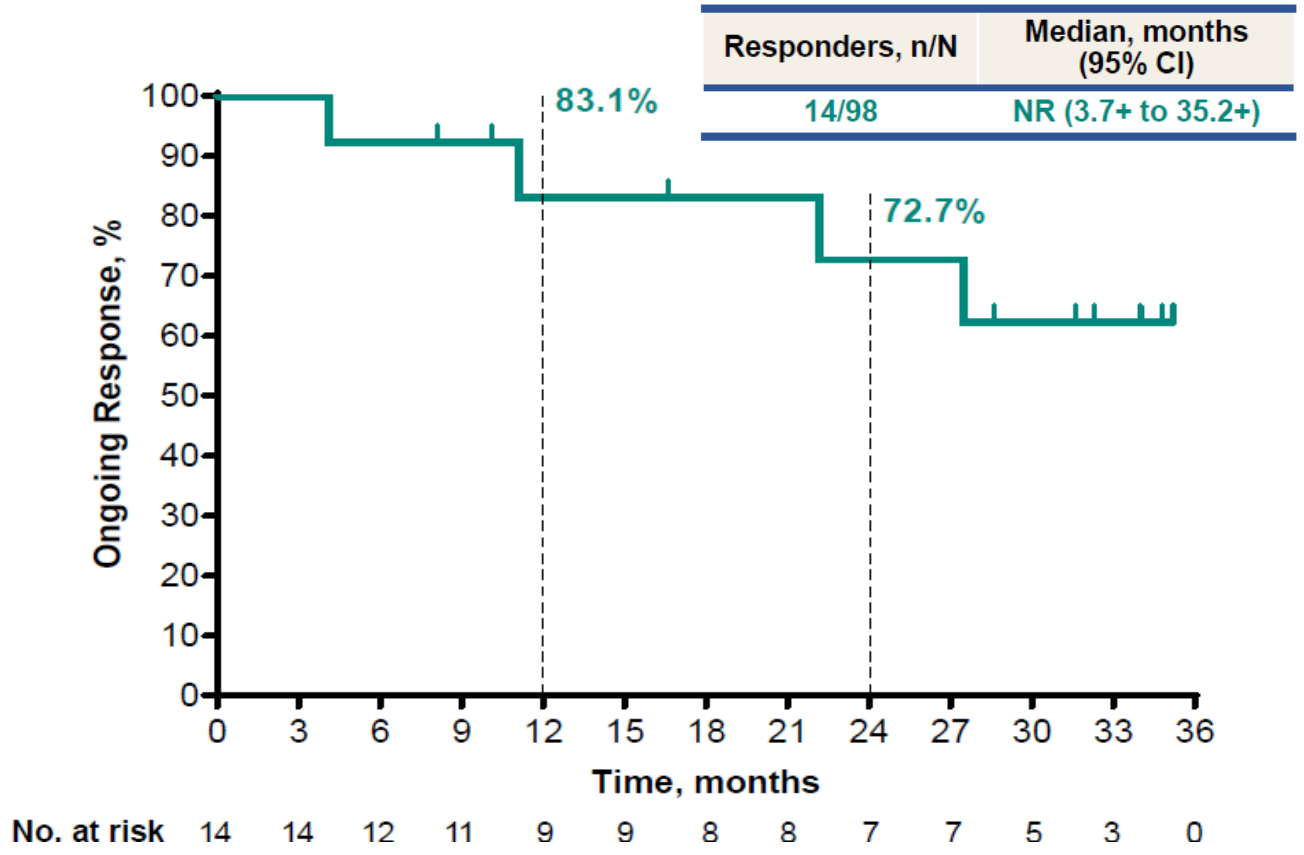
Published in: Hyun Cheol Chung; Willeke Ros; Jean-Pierre Delord; Ruth Perets; Antoine Italiano; Ronnie Shapira-Frommer; Lyudmila Manzuk; Sarina A. Piha-Paul; Lei Xu; Susan Zeigenfuss; Scott K. Pruitt; Alexandra Leary; *Journal of Clinical Oncology* Ahead of Print
DOI: 10.1200/JCO.18.01265

Keynote-158: SGO 2021 Update

ORR 17.1% (PDL1+ patients; n=82)



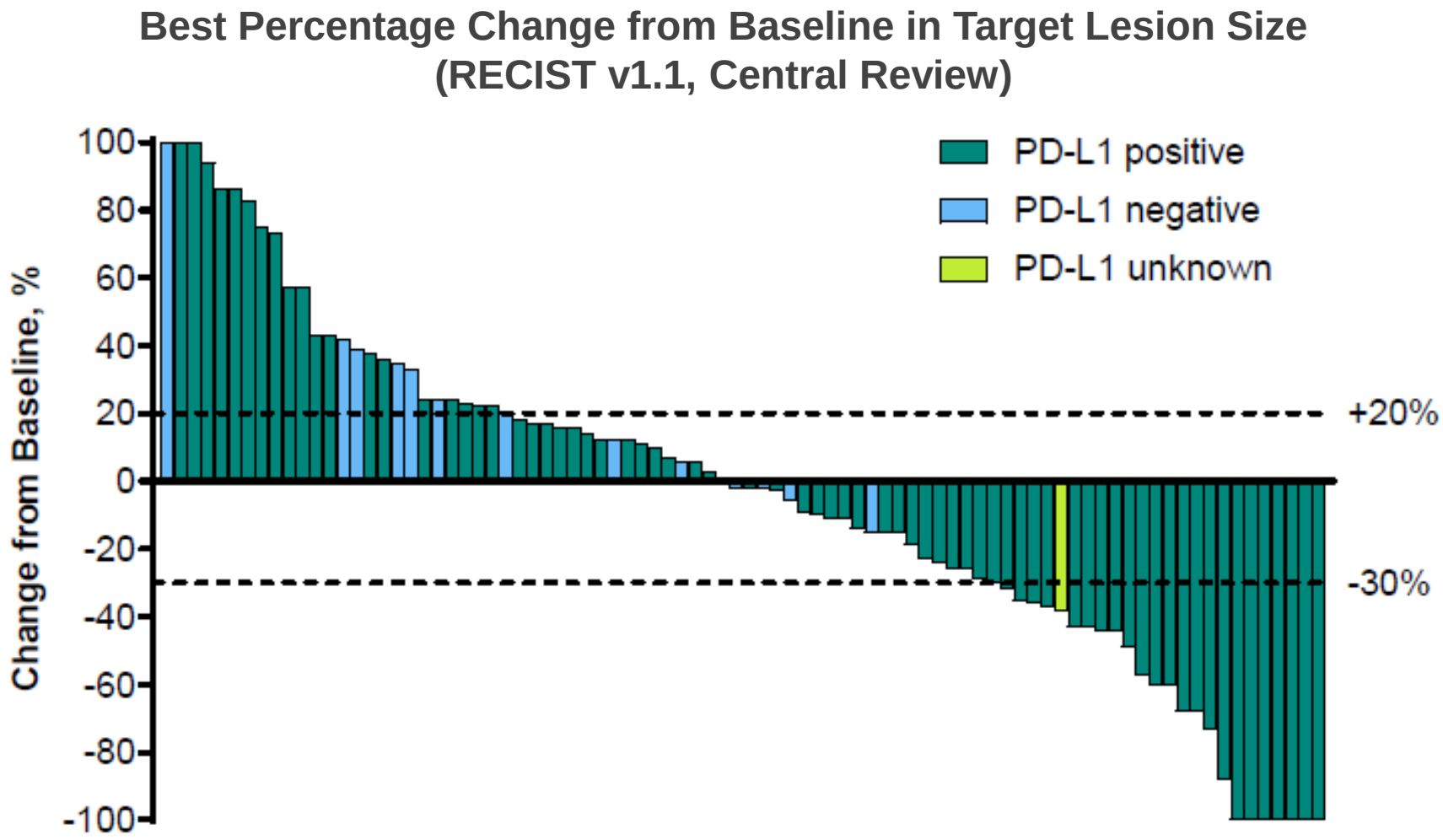
Median DOR not reached (all patients; N=98)



DOR, duration of response; SGO, Society of Gynecologic Oncology. Data cutoff date: June 27, 2019.

1. Chung, HC, et al, Presented at SGO 2021.

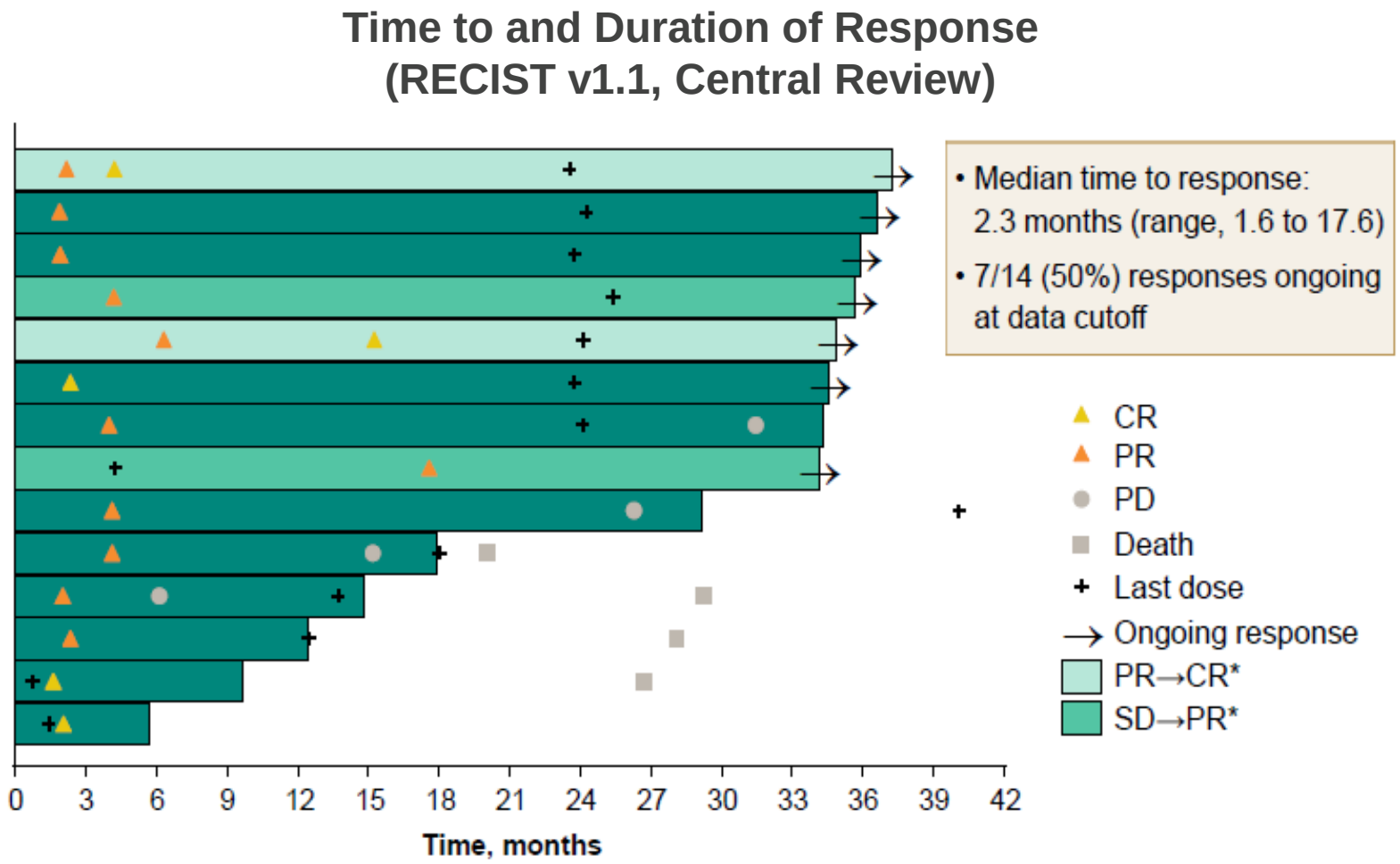
Keynote-158: SGO 2021 Update (cont)



Includes patients with ≥1 evaluable pose-baseline tumor assessment (n=86). Data cutoff date: June 27, 2019.

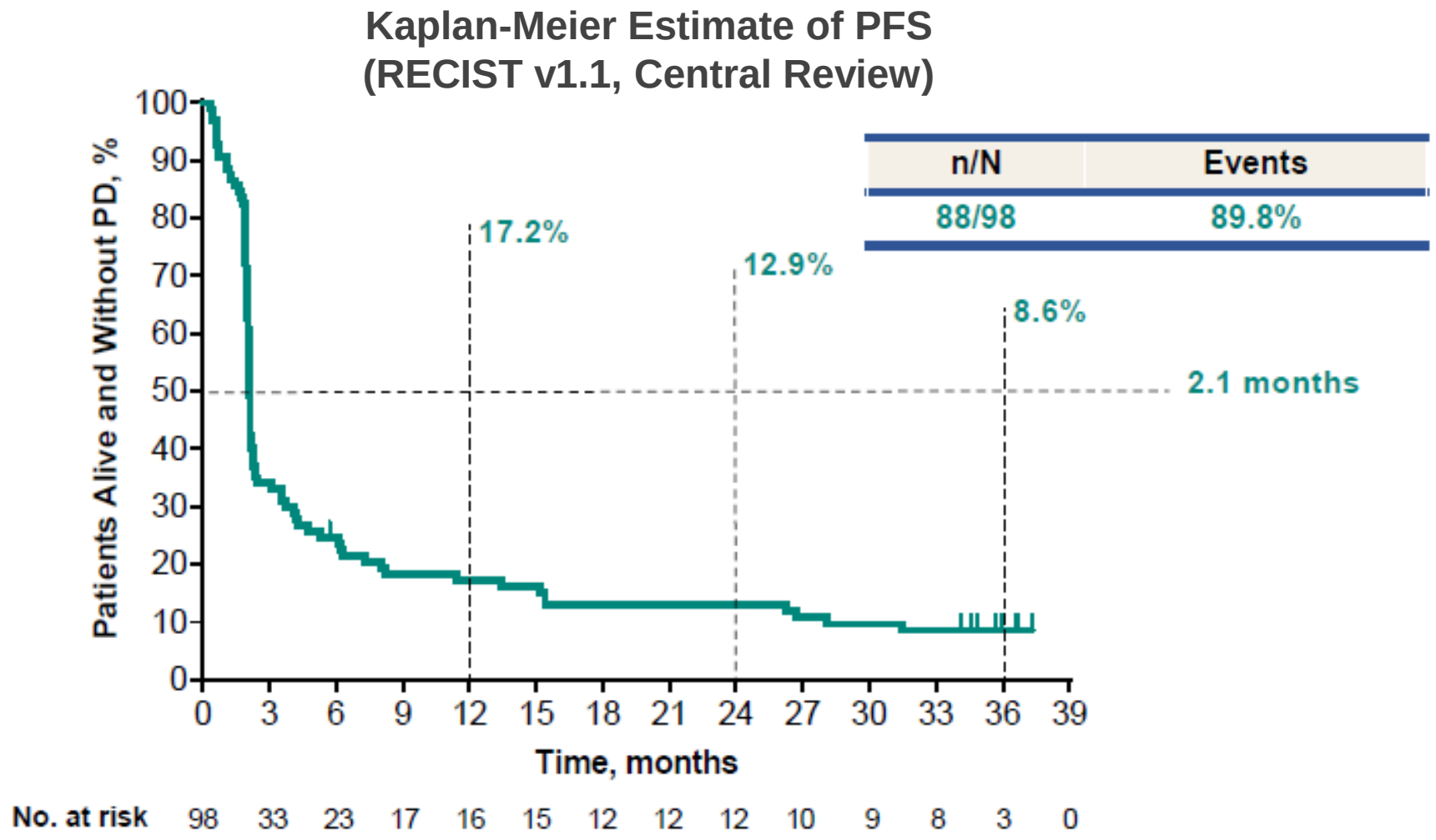
1. Chung, HC, et al, Presented at SGO 2021.

Keynote-158: SGO 2021 Update (cont)



CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
Includes patients with best overall response of complete or partial response (n=14). The length of the bars represents the time to the last imaging assessment.
*Updated since prior report (data cutoff date: January 15, 2018). Data cutoff date: June 27, 2019.
1. Chung, HC, et al, Presented at SGO 2021.

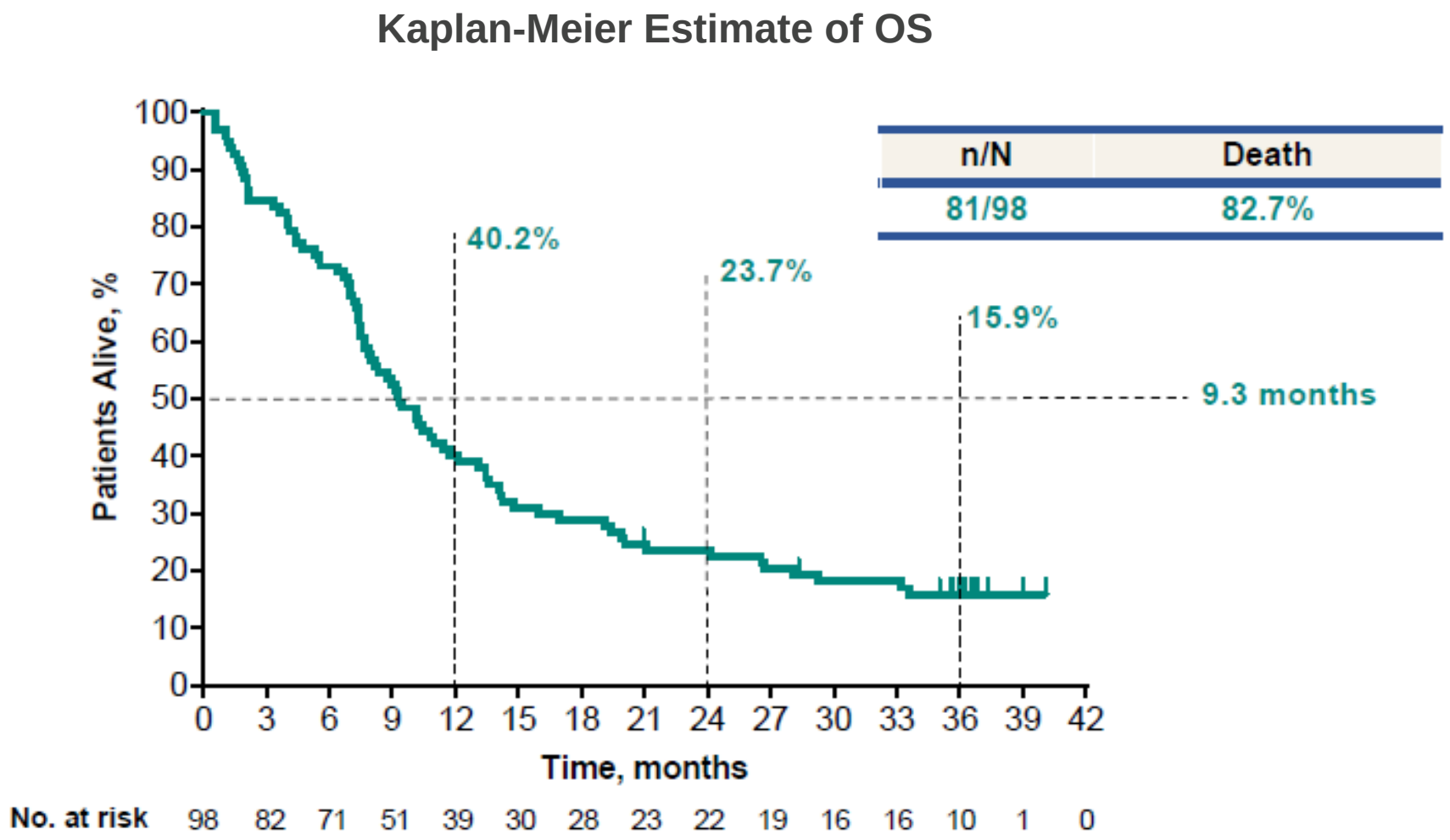
Keynote-158: SGO 2021 Update (cont)



PFS, progression-free survival. Data cutoff date: June 27, 2019.

1. Chung, HC, et al, Presented at SGO 2021.

Keynote-158: SGO 2021 Update (cont)



OS, overall survival. Data cutoff date: June 27, 2019.

1. Chung, HC, et al, Presented at SGO 2021.

Randomized Phase III Trial of Cemiplimab Versus Investigator's Choice of Chemotherapy in Cervical Cancer: "EMPOWER- CERVICAL 1" (GOG 3016)

Metastatic cervical cancer resistant to platinum-based chemotherapy, ≥ Second-Line (N = 436) ECOG PS 0 or 1

Primary Endpoint is OS

Investigators' choice

Options:

- **Antifolate**: Pemetrexed
- **Nucleoside analogue**: Gemcitabine
- **Topisomerase 1 inhibitor**: Topotecan or Irinotecan
- **Vinca Alkaloid**: Vinorelbine

Cemiplimab

Cemiplimab 350 mg IV every 3 weeks

Statistical Considerations for Study Design	
Power	90%
Median Survival	7 months
Hazard Ratio	0.7
Timing of Final Analysis (Ha)	30.5 months

All treatment regimens are for up to 96 weeks, with option for retreatment

PI Tewari KS
Dec 11, 2018:

National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT03257267. Accessed 16 January 2018.

Libtayo (cemiplimab): Top-Line Results from the Phase 3 EMPOWER Cervical-01 Study

Study design

- Largest P3 randomized controlled trial in advanced CC
- Recurrent or metastatic cervical cancer following progression on platinum-based chemotherapy
- Women with either squamous cell carcinoma or adenocarcinoma
- Any PD-L1 status
- Randomized to cemiplimab monotherapy (350 mg q3w) or investigator's choice of commonly used chemotherapy*

	Cemiplimab	Chemotherapy
Total population (N)	304	304
mOS	12 months	8.5 months
	HR: 0.69 (95% CI: 0.56-0.84); *P*<0.001	
Squamous cell carcinoma (N)	239	238
mOS	11.1 months	8.8 months
	HR: 0.73 (95% CI: 0.58-0.91); *P*=0.003	
Adenocarcinoma (N)	65	66
mOS	13.3 months	7.0 months
	HR: 0.56 (95% CI: 0.36-0.85); *P*<0.005, not adjusted for multiplicity	

On March 15, 2021, the EMPOWER Cervical-01 trial was stopped early for positive result on OS

- **Overall population: cemiplimab reduced the risk of death by 31% compared to chemotherapy**
  - Squamous cell carcinoma: 27% reduced risk of death
  - Adenocarcinoma: 44% reduced risk of death

*Pemetrexed, vinorelbine, topotecan, irinotecan or gemcitabine.

Sanofi [press release]. https://www.sanofi.com/en/media-room/press-releases/2021/2021-03-15-07-00-00-2192446. March 15, 2012. Accessed March 24, 2021.

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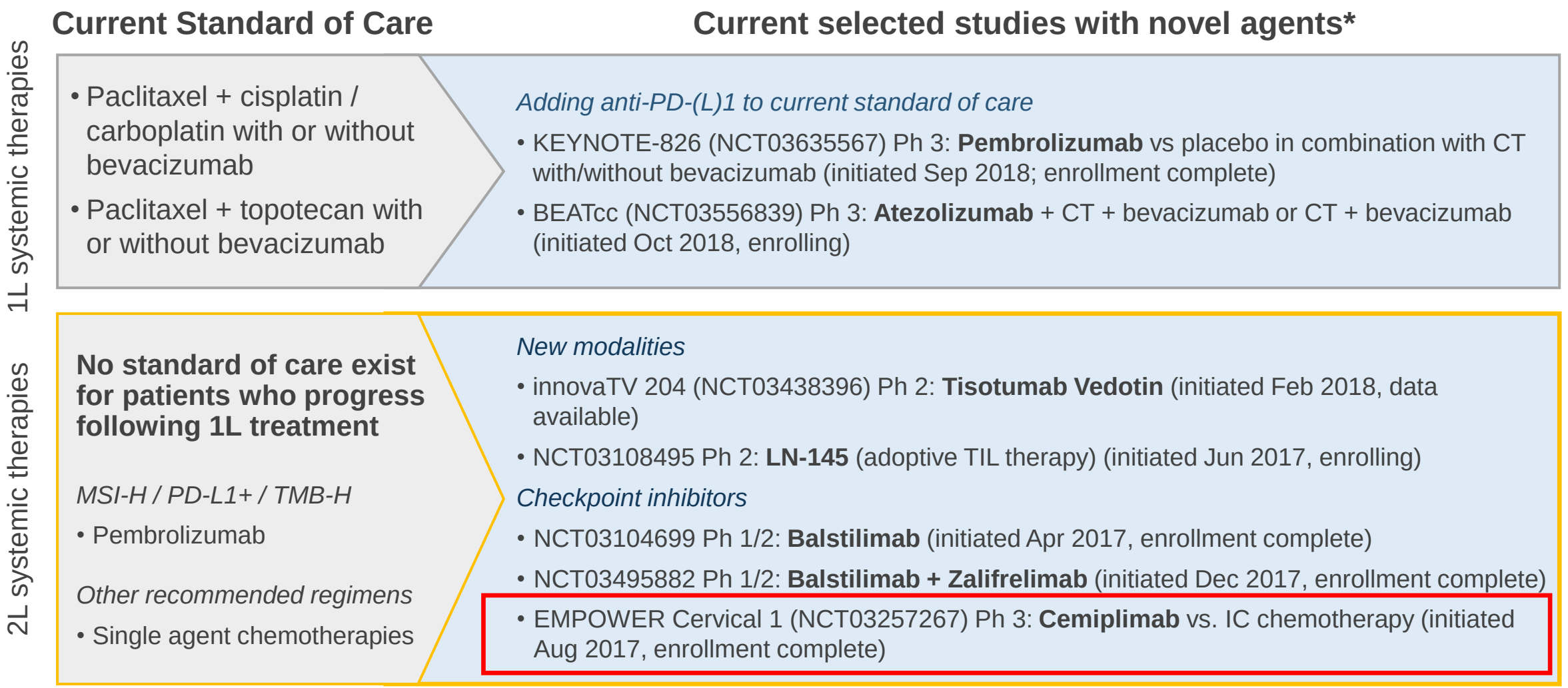
Checkpoint Inhibitors in Cervical Cancer

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

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

Evolving r/mCC Treatment Landscape



1L, first-line; 2L, second-line; CT, paclitaxel + cisplatin or carboplatin; r/mCC, recurrent and/or metastatic cervical cancer.
* Current studies with known registrational intent

KEYNOTE-826

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

R

1:1

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

Every 3 week placebo PLUS investigator choice of chemotherapy*

N = 600
57 Sites as of Jan 12, 2018

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

All treatments are administered until disease progression or toxicity, for up to 35 cycles (up to approximately 2 years)

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

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

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

BEATcc: Study Design

- Primary stage IVB, persistent or recurrent carcinoma of the cervix
- Measurable disease by RECIST v1.1
- ECOG-PS: 0-1
- No previous systemic chemotherapy for advanced or recurrent disease
- N = 404 pts

Control Arm

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

Experimental Arm

Cisplatin + paclitaxel + bevacizumab + atezolizumab until disease progression, unacceptable toxicity, death or withdrawal of consent

Safety run-in cohort: 12 pts after 2 cycles of treatment

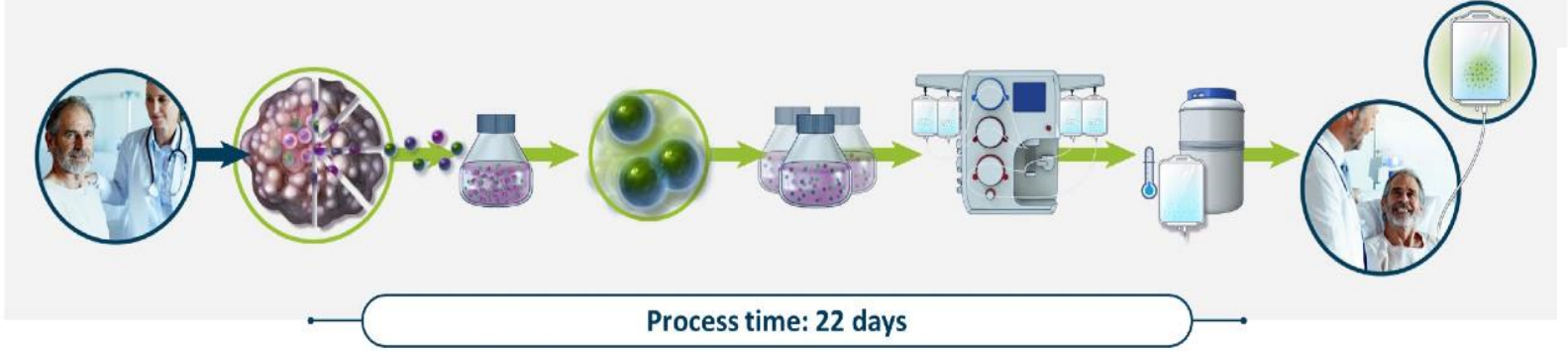
Primary Endpoints:
Overall survival (OS)
Secondary Endpoints:
- PFS
- ORR
- DOR
- Safety
- HR-QOL

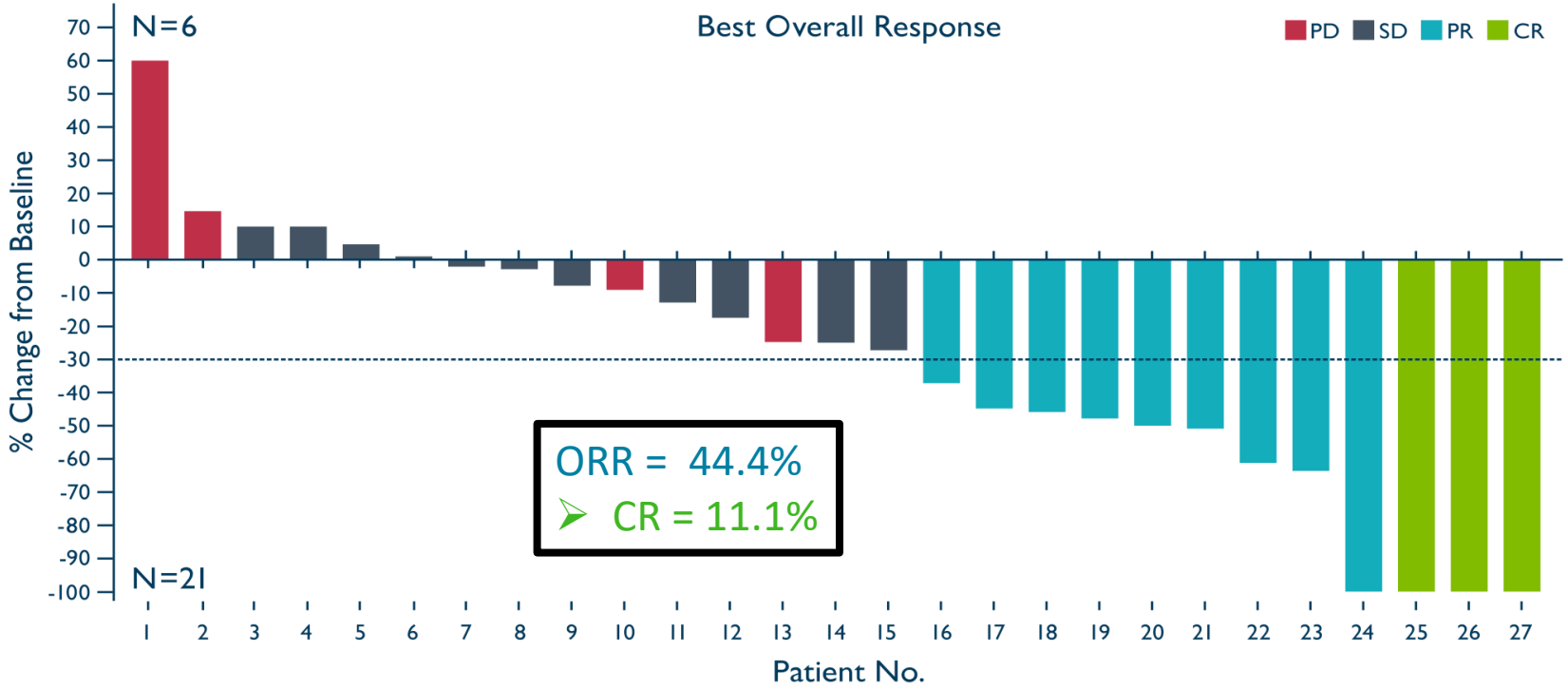
Stratification Factors:
- Prior concurrent cisplatin-RDT
- Histology: SCC vs ADK (including adenosquamous)
- Chemotherapy backbone: Cisplatin vs carboplatin

A tumor specimen is mandatory at study entry. This may be an archival biopsy or, in its absence, a tumor biopsy obtained within 3 months of randomization from a non-irradiated lesion.

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

Autologous TILs (LN-145) 2L+
FDA Breakthrough Designation





- 78% of patients had a reduction in tumor burden
- Median follow up is 7.4 months
- Mean number of TIL cells infused: 28 x 10^9
- Median number of IL-2 doses administered was 6.0

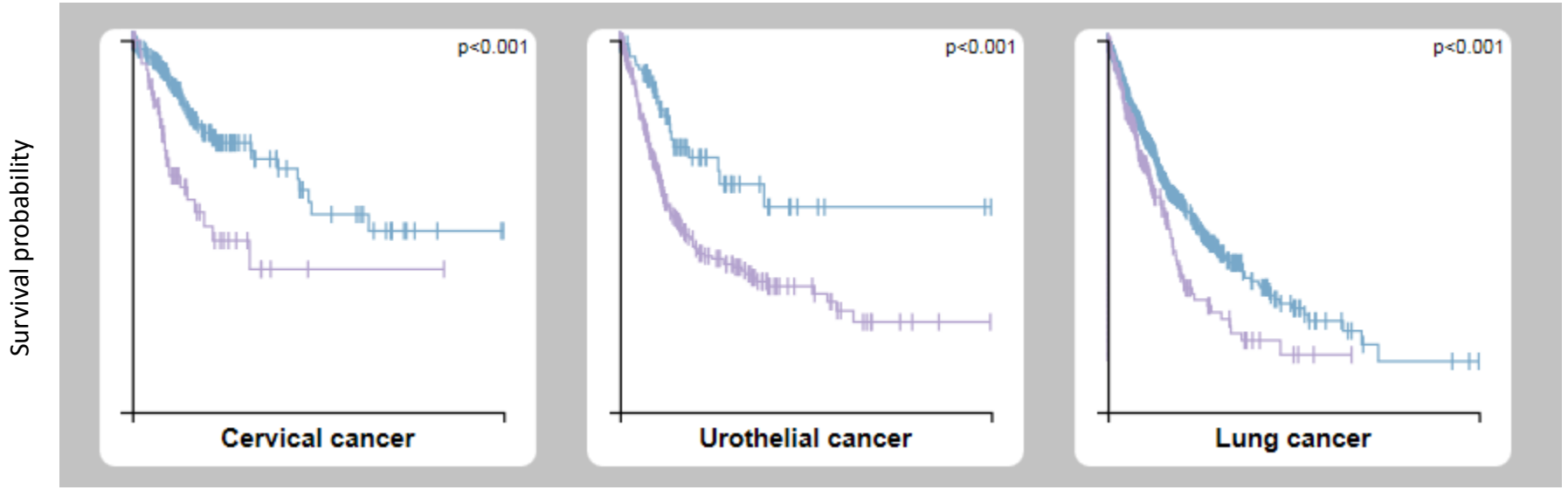
NCT03108495; Jazaeri AA et al. *J Clin Onc*. 2019;37(15)2538.

Prevalence of TIGIT in TCGA Tumors

Code	Tumor	>3rd Quartile (100.3)	Total Samples	Freq	Rank
DLBC	Lymphoid Neoplasm Diffuse Large B-cell Lymphoma	46	48	95.83%	1
TGCT	Testicular Germ Cell Tumors	88	150	58.67%	2
LUAD	Lung adenocarcinoma	267	515	51.84%	3
HNSC	Head and Neck squamous cell carcinoma	235	520	45.19%	4
SKCM	Skin Cutaneous Melanoma	206	470	43.83%	5
LUSC	Lung squamous cell carcinoma	214	502	42.63%	6
CESC	Cervical squamous cell carcinoma and endocervical adenocarcinoma	127	305	41.64%	7
KIRC	Kidney renal clear cell carcinoma	181	533	33.96%	8
STAD	Stomach adenocarcinoma	132	415	31.81%	9
BRCA	Breast invasive carcinoma	344	1097	31.36%	10
PAAD	Pancreatic adenocarcinoma	51	178	28.65%	11
BLCA	Bladder Urothelial Carcinoma	109	408	26.72%	12
MESO	Mesothelioma	20	87	22.99%	13
SARC	Sarcoma	56	259	21.62%	14
UCEC	Uterine Corpus Endometrial Carcinoma	114	545	20.92%	15
THYM	Thymoma	24	120	20.00%	16
CHOL	Cholangiocarcinoma	7	36	19.44%	17
ESCA	Esophageal carcinoma	33	184	17.93%	18
THCA	Thyroid carcinoma	86	505	17.03%	19
LIHC	Liver hepatocellular carcinoma	57	371	15.36%	20
COAD	Colon adenocarcinoma	65	460	14.13%	21
READ	Rectum adenocarcinoma	16	166	9.64%	22
LAML	Acute Myeloid Leukemia	16	173	9.25%	23
UVM	Uveal Melanoma	6	80	7.50%	24
OV	Ovarian serous cystadenocarcinoma	20	305	6.56%	25
UCS	Uterine Carcinosarcoma	3	57	5.26%	26
PRAD	Prostate adenocarcinoma	26	497	5.23%	27
KIRP	Kidney renal papillary cell carcinoma	13	290	4.48%	28
ACC	Adrenocortical carcinoma	2	79	2.53%	29
LGG	Brain Lower Grade Glioma	4	516	0.78%	30
GBM	Glioblastoma multiforme	1	161	0.62%	31
KICH	Kidney Chromophobe	0	66	0.00%	32
PCPG	Pheochromocytoma and Paraganglioma	0	179	0.00%	32

The quartile RSEM value of TIGIT gene is ~100

High PVR expression associated with poor clinical outcome



TCGA
Blue=low PVR
Purple=high PVR

Mereo Biopharma, unpublished

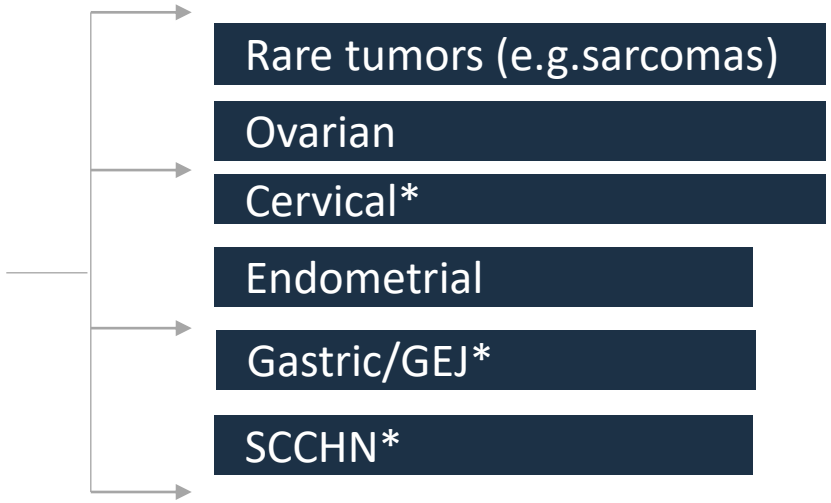
ACTIVATE Phase 1b/2 Study Design: Etigilimab plus Nivolumab in Advanced/Metastatic solid Tumors

Primary endpoint
- Overall Response Rate

Secondary
- Safety and Tolerability
- PK/PD
- Duration of response

Exploratory
- Biomarker
- PFS
- OS

Flat dosing Q2W



Simon two-stage design allowing for dynamic decision making and flexible design
N= ~ 125 subjects

Key Phase 2/3 Trials in Cervical Cancer

1. Phase 3: CALLA (Durvalumab with chemotherapy and radiation)*
2. Phase 3: KN-826 (Pembrolizumab added to chemotherapy +/- bevacizumab in 1-L)*
3. Phase 3: EMPOWER- CERVICAL 1 (Cemiplimab vs chemotherapy in 2-L)*
4. Phase 2: innovaTV 204 (tisotumab vedotin in 2-L)
5. Phase 2: (LN-145 in 2-L)*
6. Phase 2: SKYSCRAPER-04 (Tiragolumab Plus Atezolizumab in 2-L)*

* Results Pending

Summary and Conclusions

- **Weekly cisplatin plus radiotherapy (CCRT) global standard in locally advanced primary disease**
- **Platinum + paclitaxel +/- bevacizumab for metastatic disease**
- **Immunotherapy is the new frontier!**
  - **Checkpoint inhibitors (PD-1, PDL-1, TIGIT)**
  - **Accelerated approval of pembrolizumab in second-line metastatic disease (June 2018) in the USA**
    - **TIL and ADC exciting opportunities**
  - **Randomized trials ongoing and necessary for EU and global regulatory approval in both in first-line and second-line metastatic disease**
  - **Greatest opportunity is adding IO to front-line CCRT**

Mereo BioPharma

SARCOMA

Immunotherapy in Sarcoma

Priscilla Merriam, MD
Clinical Director
Sarcoma Center
Dana-Farber Cancer Institute
Boston, MA

May 13, 2021

Disclosures

None

Sarcoma Overview

- <1% of cancers in adults
- Cancer that arises from mesenchymal cells (connective tissue precursors)
- More than 50 kinds of sarcomas of soft tissue and bone (80% STS)
  - 50% of large high-grade sarcomas develop metastasis
  - Median overall survival < 2 yrs for metastatic disease
  - First-line for metastatic disease usually chemo
  - **No approved immunotherapy specifically for sarcoma**

Liposarcoma	20%
Leiomyosarcoma	14%
Undifferentiated pleomorphic sarcoma	14%
Gastrointestinal stromal tumor	9%

Brennan et al. *Ann Surg* 2014

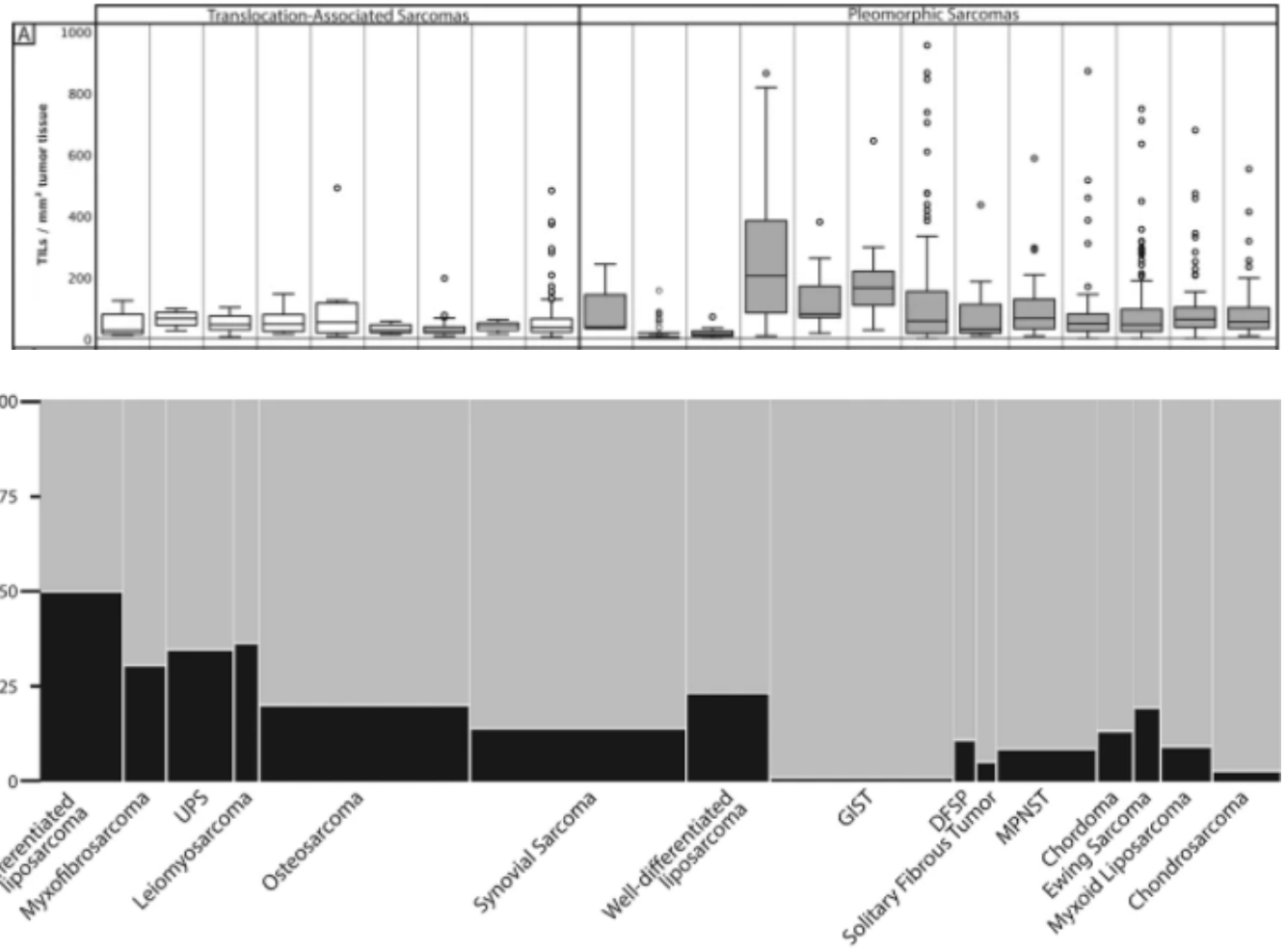
Sarcoma: Current Standard of Care

Chemotherapy	Overall Response Rate (CR+PR)	Progression Free Survival (months)
Doxorubicin	18%	6.8
Ifosfamide	21%	2.2
Gemcitabine + Docetaxel	20%	5.4
Trabectedin	10%	4.2
Pazopanib	6%	4.6
Eribulin	4%	2.6

Tap et al. *ASCO Annual Meeting* 2019
Antman et al. *J Clin Oncol* 1989
Lorigan et al. *J Clin Oncol* 2007
Seddon et al. *Lancet Oncol* 2017
Demetri et al. *J Clin Oncol* 2015
van der Graaf et al. *Lancet* 2012
Schoffski et al. *Lancet* 2016

Sarcoma: Many subtypes, variable immunogenicity

- Tumor mutational burden in translocation associated sarcomas lower than non-translocation associated sarcoma
- Variability in tumor infiltrating lymphocytes by histology
- PD-1 and PD-L1 expression low overall 10% and 22% respectively
- There may be higher expression of emerging immune checkpoint targets



Dancsok et al. *Modern Pathology* 2019

Sarcoma Immunology: Sarcoma Immune Classes

- Tumor mutations burden low overall
- Immune classification based on tumor environment (B cells) may better represent immune status
- Immune class status may be associated with overall survival

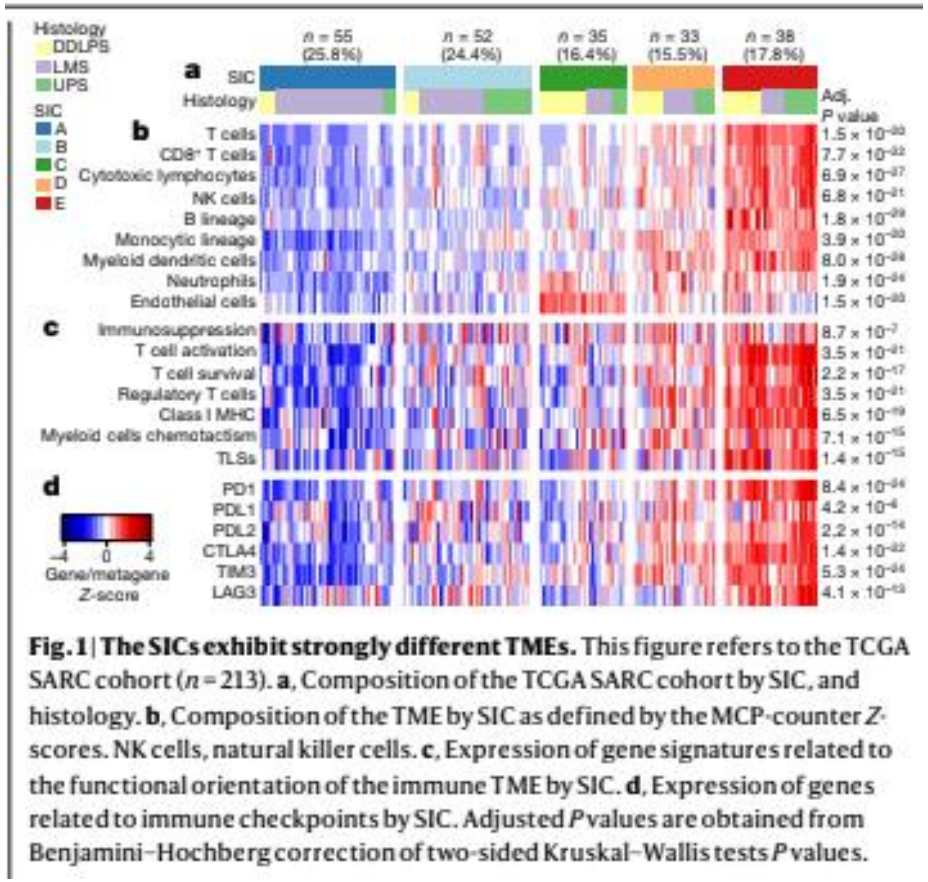
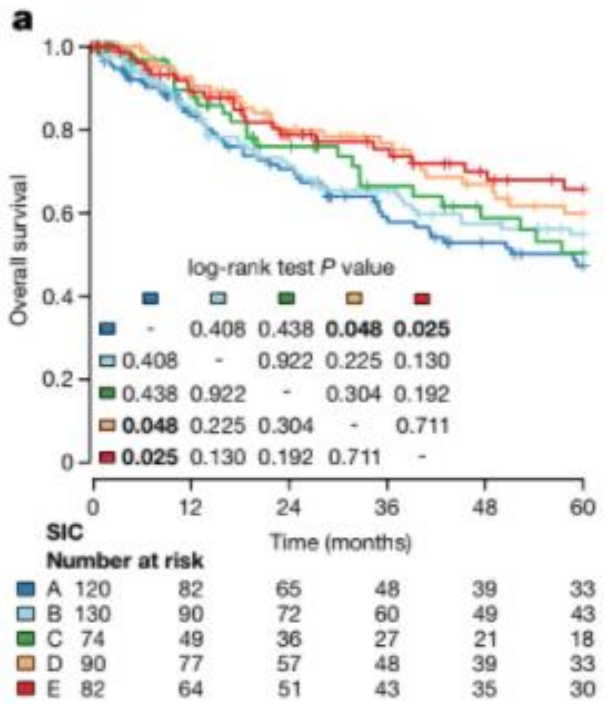


Fig. 1 | The SICs exhibit strongly different TMEs. This figure refers to the TCGA SARC cohort ($n = 213$). **a**, Composition of the TCGA SARC cohort by SIC, and histology. **b**, Composition of the TME by SIC as defined by the MCP-counter Z-scores. NK cells, natural killer cells. **c**, Expression of gene signatures related to the functional orientation of the immune TME by SIC. **d**, Expression of genes related to immune checkpoints by SIC. Adjusted P values are obtained from Benjamini–Hochberg correction of two-sided Kruskal–Wallis tests P values.



Petitprez et al. *Nature* 2020

Multicenter phase II study of pembrolizumab in advanced soft tissue and bone sarcomas (SARC028)

- Pembrolizumab 200 mg IV every 3 weeks
- Primary objective: ORR
- Over 50% in both cohorts previously treated

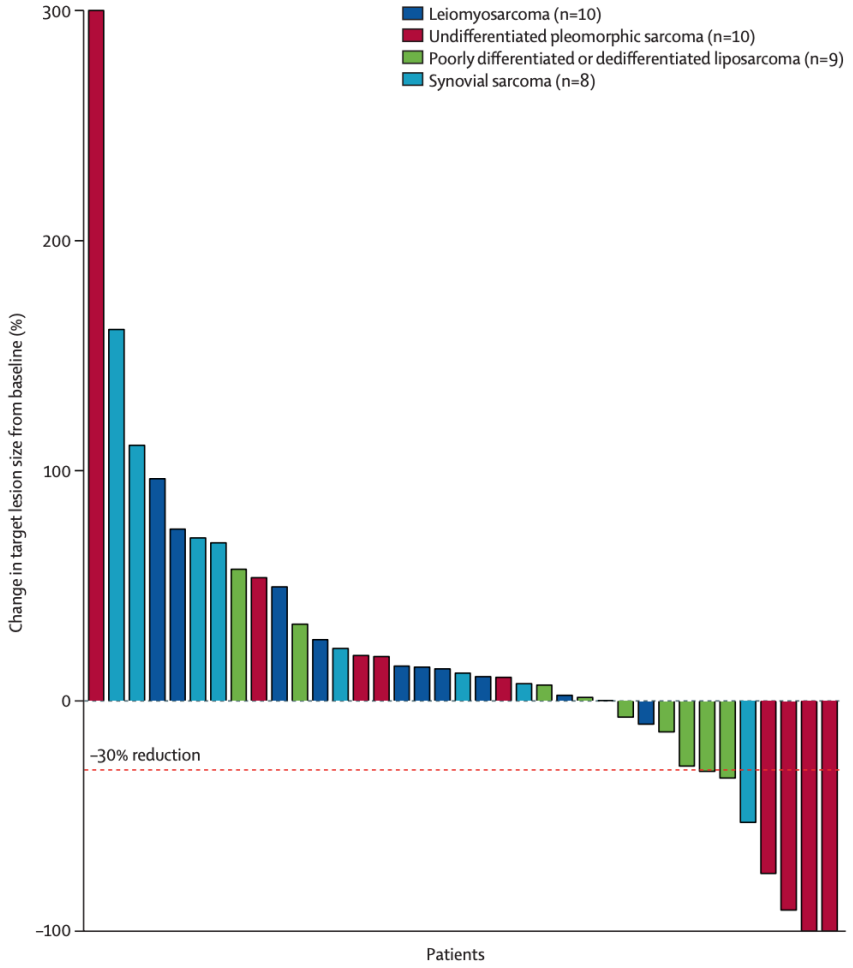
Soft Tissue Sarcoma (n=40)	Number
Leiomyosarcoma	10
Undifferentiated pleomorphic sarcoma (UPS)	10
Liposarcoma	10
Synovial sarcoma	10
Bone Sarcomas (n=40)	**Number**
Chondrosarcoma	5
Ewing's sarcoma	13
Osteosarcoma	22

Tawbi et al. *Lancet Oncol* 2017

Multicenter phase II study of pembrolizumab in advanced soft tissue and bone sarcomas (SARC028)

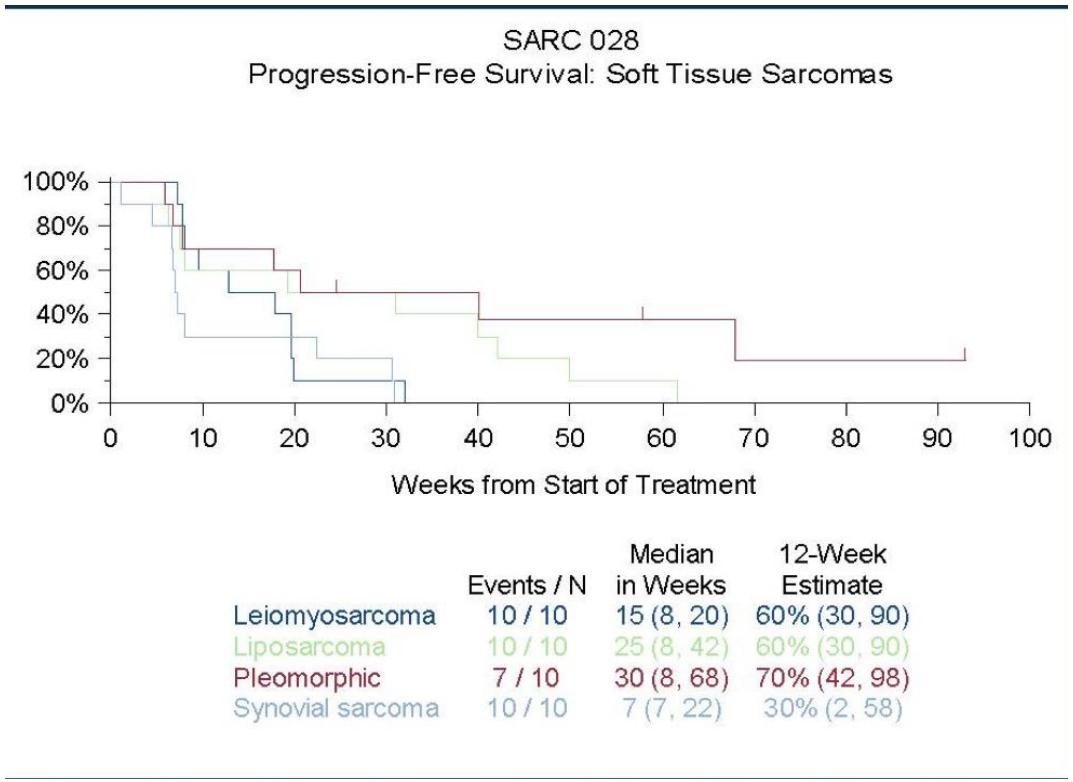
- UPS ORR 40%
- Liposarcoma with ORR 20% and SD

Cohort	CR	PR	ORR
Leiomyosarcoma (n=10)	0	0	0% (0/10)
UPS (n=10)	1	3	40% (4/10)
Liposarcoma (n=10)	0	2	20% (2/10)
Synovial sarcoma (n=10)	0	1	10% (1/10)
Chondrosarcoma (n=5)	0	1	20% (1/5)
Ewing's sarcoma (n=13)	0	0	0% (0/13)
Osteosarcoma (n=22)	0	1	5% (1/22)



Tawbi et al. *Lancet Oncol* 2017

Multicenter phase II study of pembrolizumab in advanced soft tissue and bone sarcomas (SARC028)

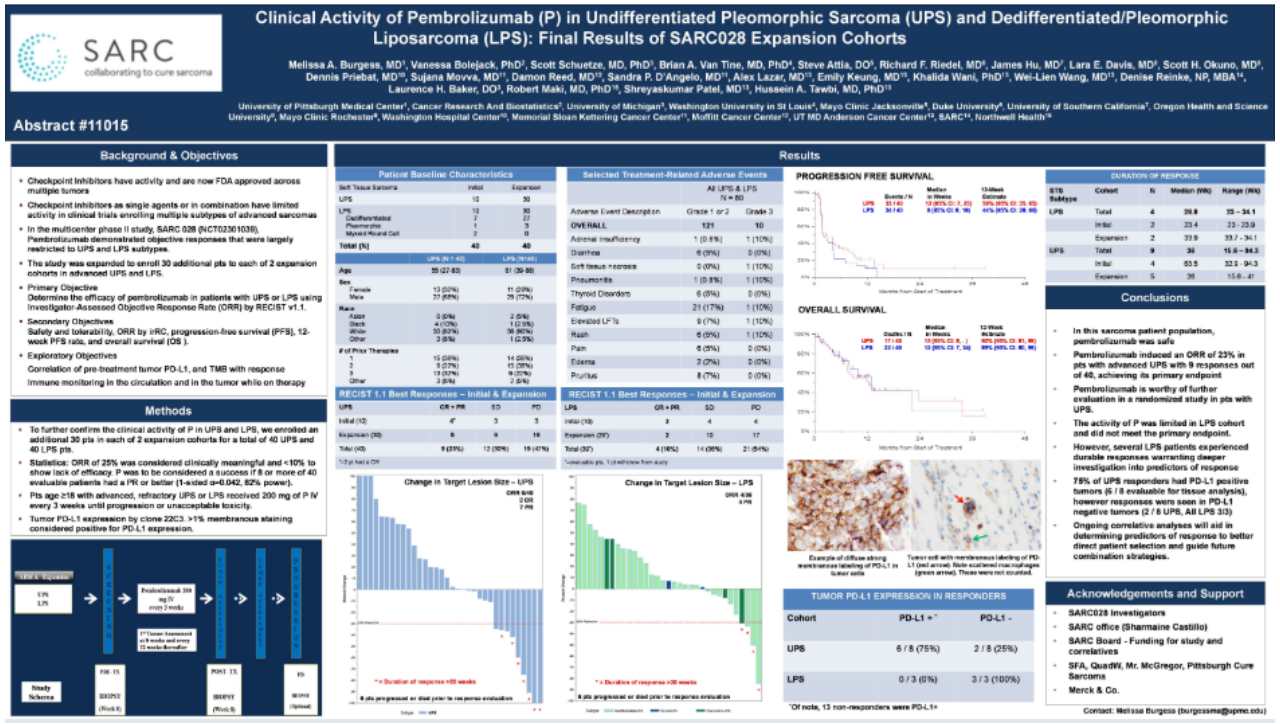


Median PFS in soft tissue (STS) cohort: 18 wks (~4 mo)

Tawbi et al. *Lancet Oncol* 2017
Burgess et al. *ASCO Annual Meeting* 2017

Pembrolizumab in Undifferentiated Pleomorphic Sarcoma (UPS) and Dedifferentiated/Pleomorphic Liposarcoma (LPS): SARC028 Expansion Cohorts

- Enrolled 30 additional pts to UPS cohort and 30 to LPS cohorts
- Primary objective: ORR in UPS and LPS

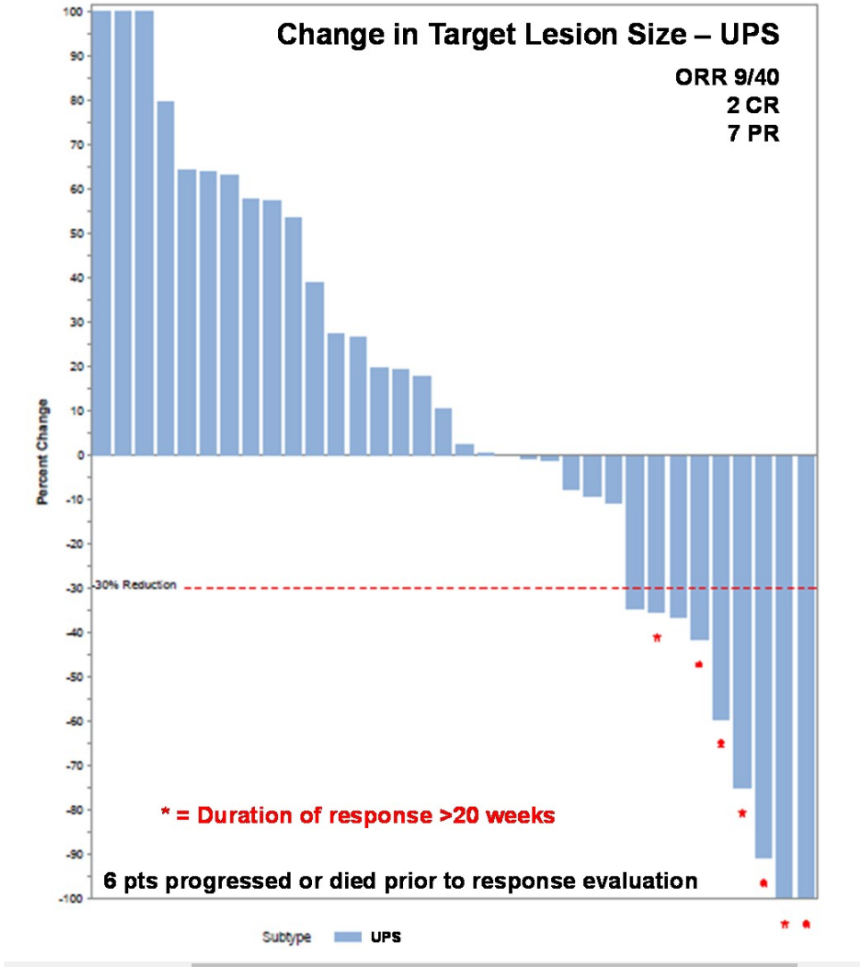


Burgess et al. *ASCO Annual Meeting* 2019 (Abstract 11015)

Final Results of SARC028 Expansion Cohorts: UPS

RECIST 1.1 Best Responses – Initial & Expansion			
UPS	**CR + PR**	SD	PD
Initial (10)	**4***	3	3
Expansion (30)	**5**	9	16
Total (40)	**9 (23%)**	12 (30%)	19 (47%)
*=2 pt had a CR			

- 23% ORR (9/40)

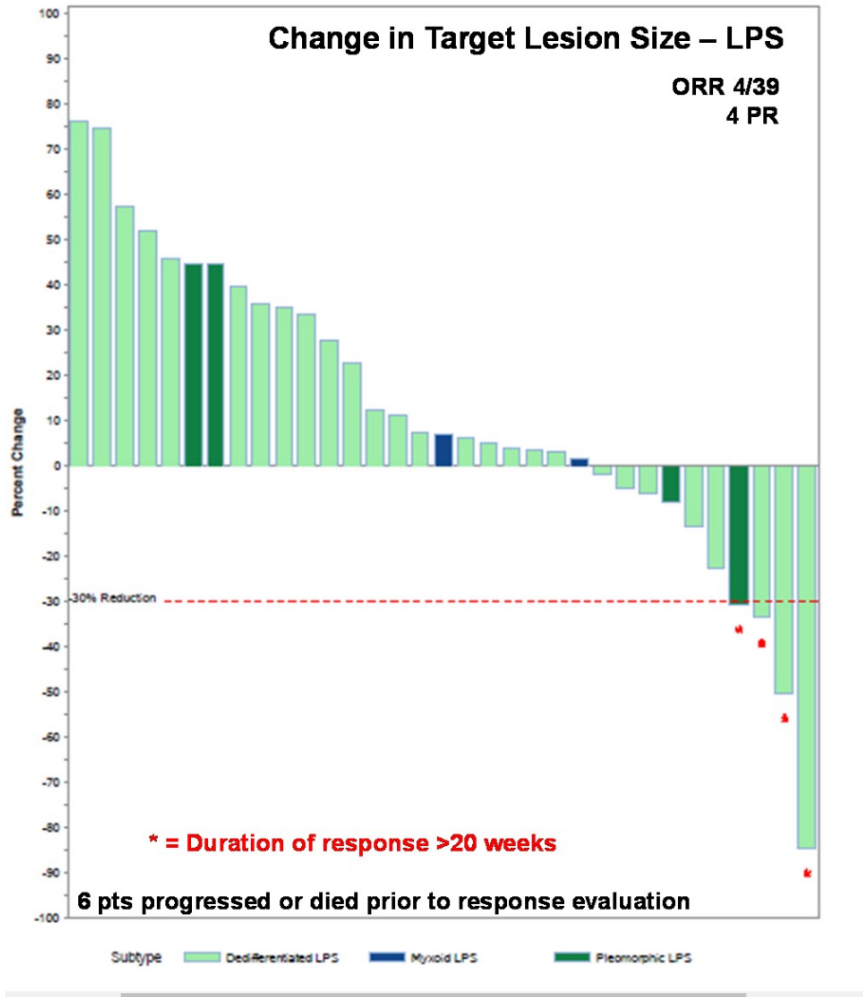


Burgess et al. *ASCO Annual Meeting* 2019

Final Results of SARC028 Expansion Cohorts: Liposarcoma

RECIST 1.1 Best Responses – Initial & Expansion			
LPS	**CR + PR**	SD	PD
Initial (10)	**2**	4	4
Expansion (29*)	**2**	10	17
Total (39*)	**4 (10%)**	14 (36%)	21 (54%)
*=evaluable pts, 1 pt withdrew from study			

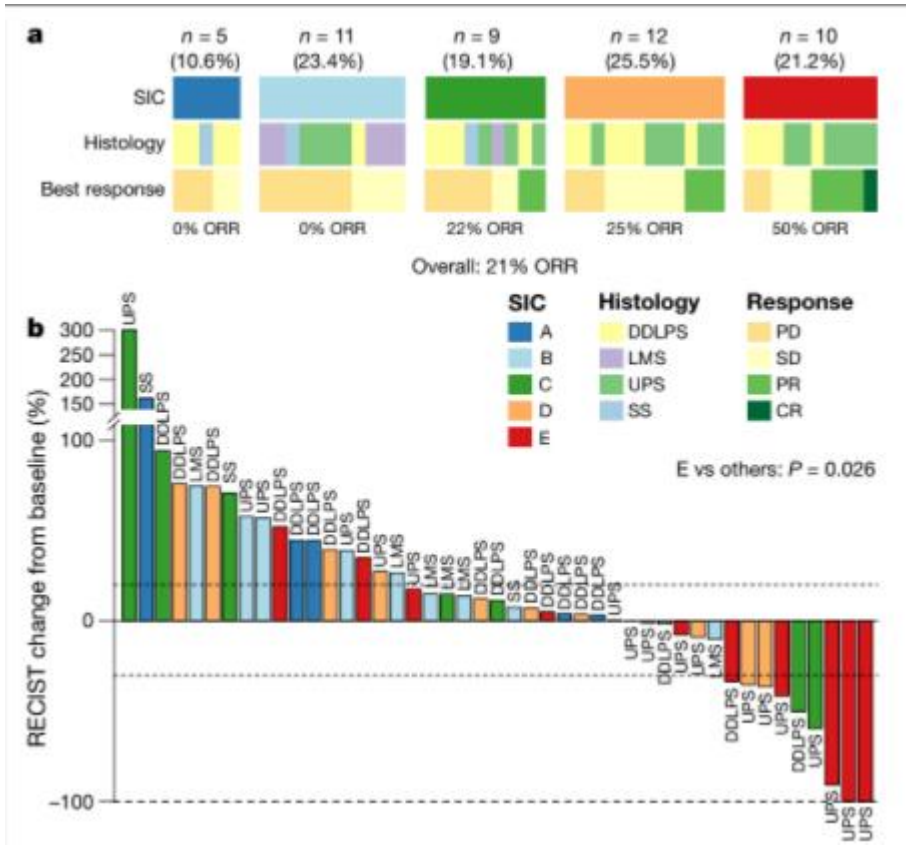
- 10% ORR (4/40)
- Not meet endpoint
- Histology matters



Burgess et al. *ASCO Annual Meeting* 2019

Sarcoma Immunology: Sarcoma Immune Classes

- Evaluated 47 pre-treatment biopsies from patients in SARC028 and expansion cohort
- Responses in SARC028 clustered mainly in SIC E (immune high class) responses to PD-1 inhibition in SIC class E
- No responses seen in SIC A or B



Petitprez et al. *Nature* 2020

Nivolumab with or without ipilimumab for metastatic sarcoma (Alliance A091401)

- Diversity in histologies
- Randomized to nivolumab 3 mg/kg q2w or nivolumab 3 mg/kg + ipilimumab 1 mg/kg q3 weeks x 4 then nivolumab 3 mg/kg q2w
- Primary objective: confirmed RR

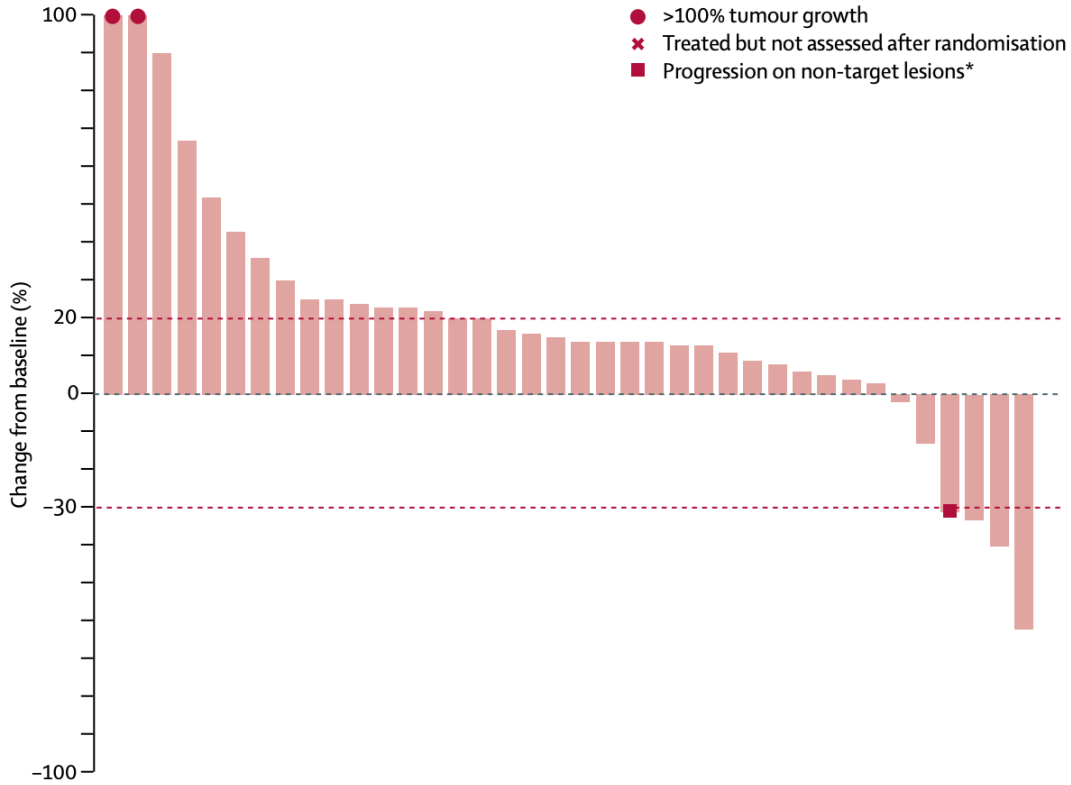
D'Angelo et al. *Lancet Oncol* 2018

Histology	Nivolumab n=43 (%)	Nivolumab + Ipilimumab n=42 (%)
Angiosarcoma	0	3 (7)
Bone *	5 (12)	4 (10)
Leiomyosarcoma	15 (35)	14 (33)
Liposarcoma (well/dediff)	3 (7)	2 (5)
Sarcoma, NOS	2 (5)	1 (2)
Spindle cell sarcoma	5 (12)	6 (14)
Synovial sarcoma	2 (5)	2 (5)
UPS/MFH	5 (12)	6 (14)
Other *	6 (14)	4 (10)
Bone: Chondrosarcoma, osteosarcoma, Ewing's sarcoma		
Other: Alveolar soft part sarcoma, epithelioid sarcoma, solitary fibrous tumor, MPNST, PEComa, myxofibrosarcoma		

Nivolumab with or without ipilimumab for metastatic sarcoma (Alliance A091401): Monotherapy

- 38 evaluable pts
- Confirmed PR in alveolar soft part sarcoma (1) and non-uterine leiomyosarcoma (1)
- 1 with sarcoma NOS had an unconfirmed PR
- mPFS 1.7 months and mOS 10.7 months
- Low RR with PD-1 monotherapy due to unselected population?

Nivolumab Monotherapy

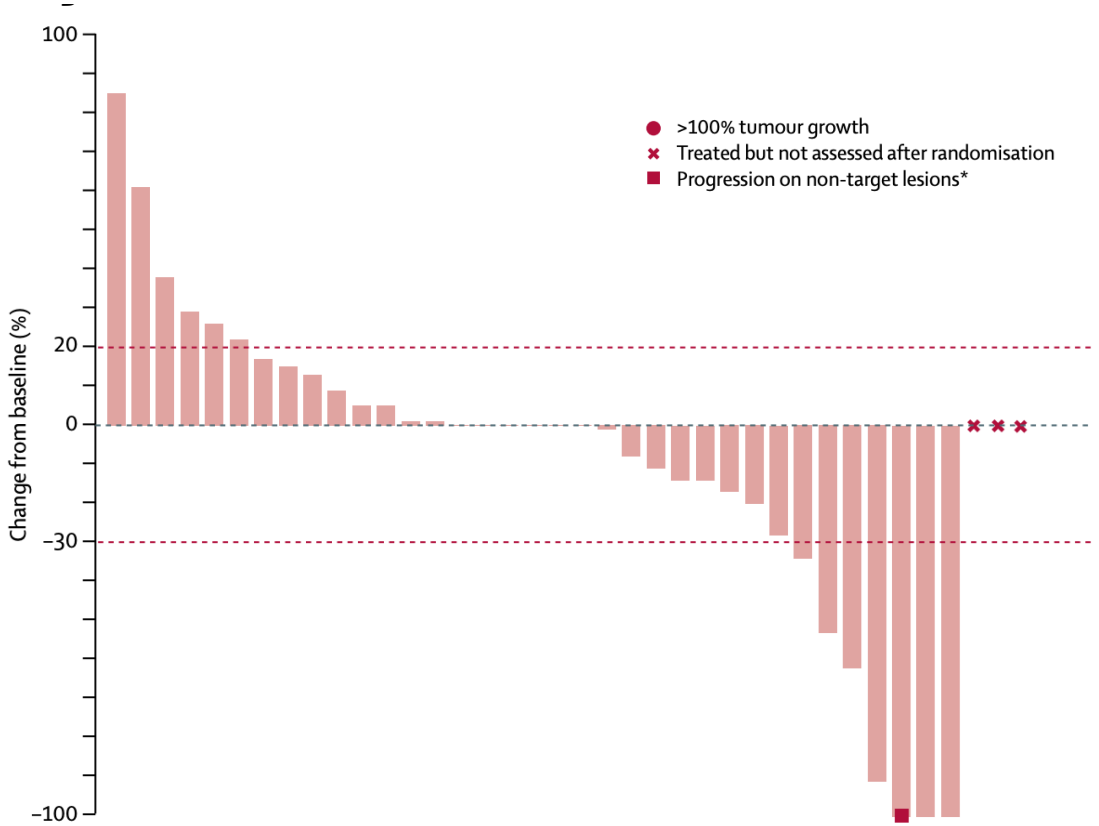


D'Angelo et al. *Lancet Oncol* 2018

Nivolumab with or without ipilimumab for metastatic sarcoma (Alliance A091401): Nivolumab + ipilimumab

- 6/38 evaluable confirmed PR or CR (ORR 16%)
  - ➢ CR in uterine leiomyosarcoma (1), myxofibrosarcoma (1)
  - ➢ PR non-uterine leiomyosarcoma (1), UPS (2), angiosarcoma (1)
- mPFS 4.1 months, mOS 14.3 months

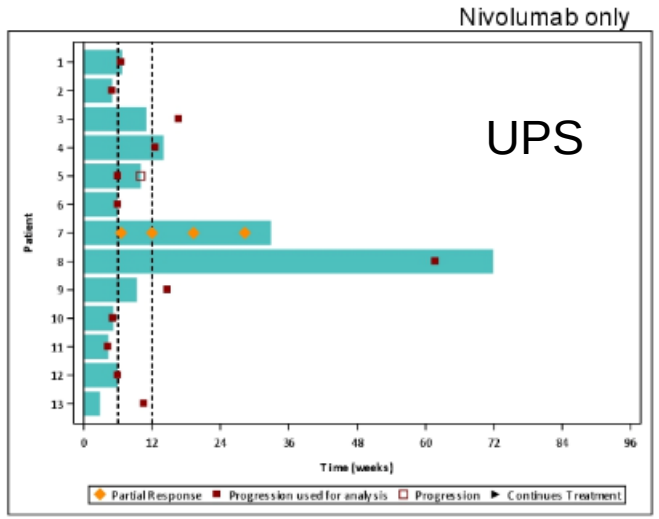
Nivolumab + Ipilimumab

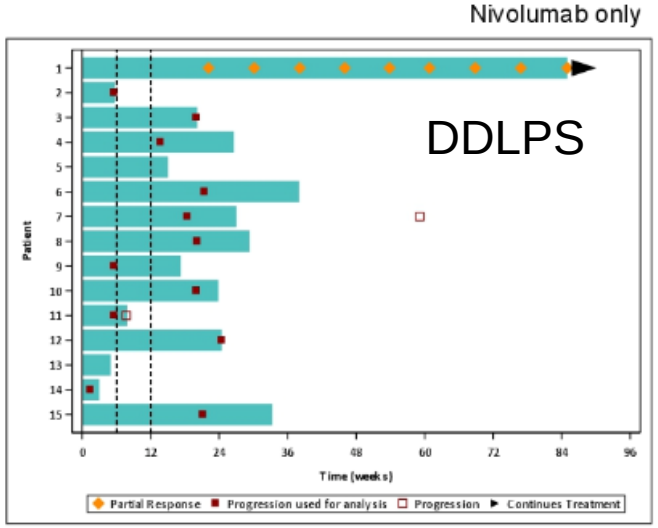


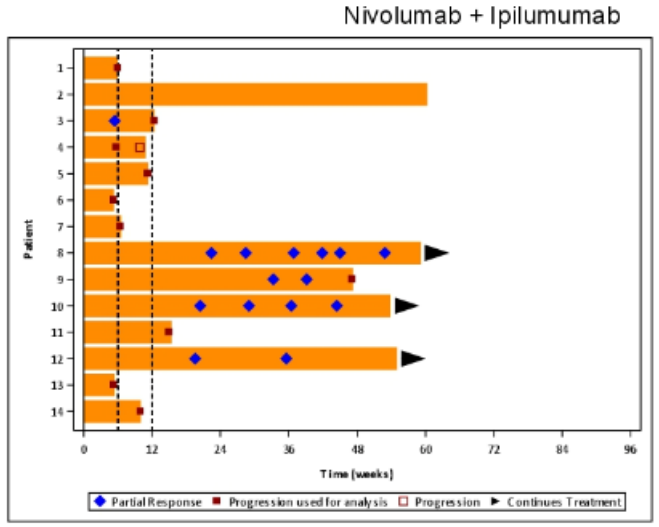
D'Angelo et al. *ASCO Annual Meeting* 2017
D'Angelo et al. *Lancet Oncol* 2018

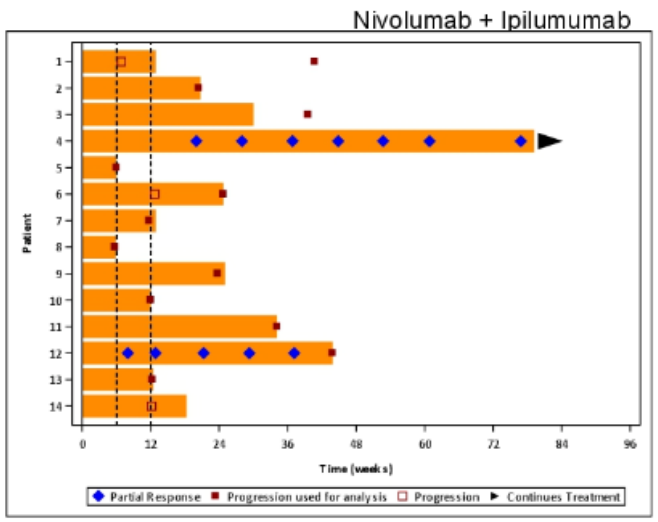
Nivolumab with or without ipilimumab for metastatic sarcoma (Alliance A091401): Expansion Cohorts

- Expansion cohorts included dedifferentiated liposarcoma and undifferentiated pleomorphic sarcoma subtypes
- Pretreated patients, randomized to nivolumab or nivolumab + ipilimumab
- Primary endpoint met for nivolumab + ipilimumab but not nivolumab alone









Chen et al. *ASCO Annual Meeting* 2020 (Abstract 11511)

Conclusions

- Standard of care chemotherapy options are lacking with low response rates, transient benefits, and undesirable side effects
- Rates of expression of PD-1 and PD-L1 low, other potential targets may have higher expression in sarcomas
- Single-agent PD-1 and PD-L1 inhibitors with some encouraging early results but responses still limited and not yet significantly better than chemotherapy
- Combination immunotherapy approaches may be needed

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Q&A

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Thank You

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NASDAQ: MREO, AIM: MPH

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