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Updates on immunotherapy of gynecologic cancers: opportunities and challenges

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Disclosures

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Dmitriy Zamarin: none

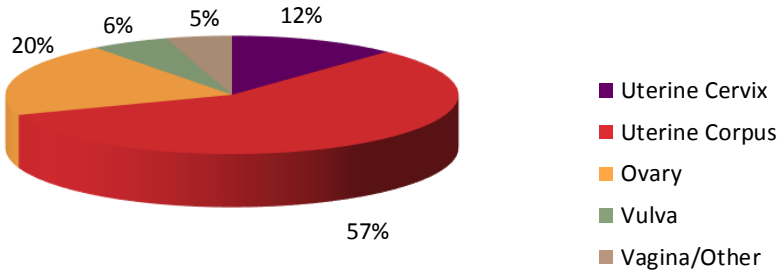
Unrelated to this presentation:

Merck
-Research support, consulting

Biomed Valley Discoveries, Synlogic Therapeutics, Hookipa Biotech, Psioxus Therapeutics, Tesaro
-Consulting

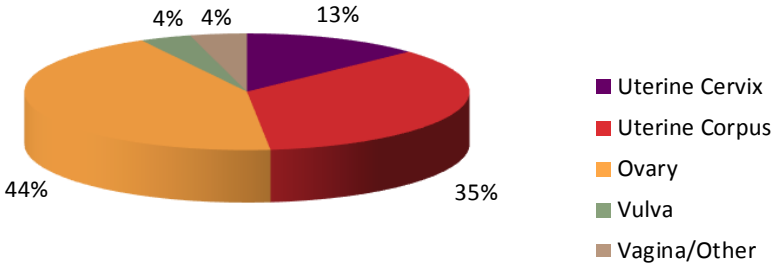
Gynecologic Cancer – Estimated incidence and deaths in 2018

Incidence



Vagina and other	**5,170**
Vulva	**6,190**
Uterine Cervix	**13,240**
Ovary	**22,240**
Uterine Corpus	**63,230**

Deaths



Vulva	**1,200**
Vagina and other	**1,330**
Uterine Cervix	**4,170**
Uterine Corpus	**11,350**
Ovary	**14,070**

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Cervical Cancer

PD-1 blockade in advanced cervical cancer

Keynote-158: pembrolizumab (led to 6/2018 FDA approval)

- 98 patients
- >1% PD-L1+ (in 83% of patients)
- ORR: 13.3%, DCR 30.6%
- ORR in PD-L1+: 16%
- ORR in PD-L1-: 0%
- mPFS/mOS: 2.1/9.4 months

Chung et al., ASCO 2018

Checkmate 358: nivolumab

- 24 patients (19 cervical, 5 vulvar/vaginal

Cervical:

- ORR: 5(26.3%), SD: 8(42%)

Vulvar/Vaginal

- ORR: 0%, SD: 4 (80%)

Hollebeque et al., ASCO 2017

Advanced cervical cancer, selected upcoming/ongoing phase III studies

Upfront:

- Keynote 826: carboplatin/cisplatin+paclitaxel +/- bevacizumab +/- pembrolizumab

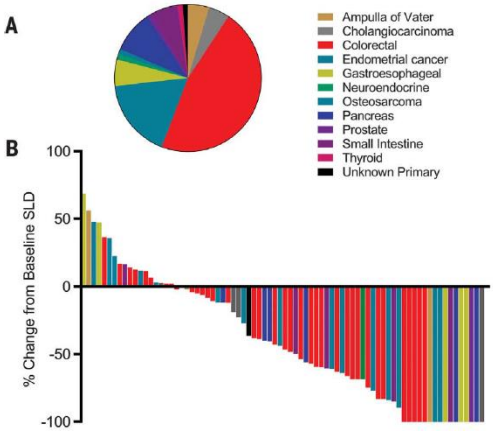
Second line and later:

- GOG3016: cemiplimab vs. physician's choice chemotherapy

Endometrial Cancer

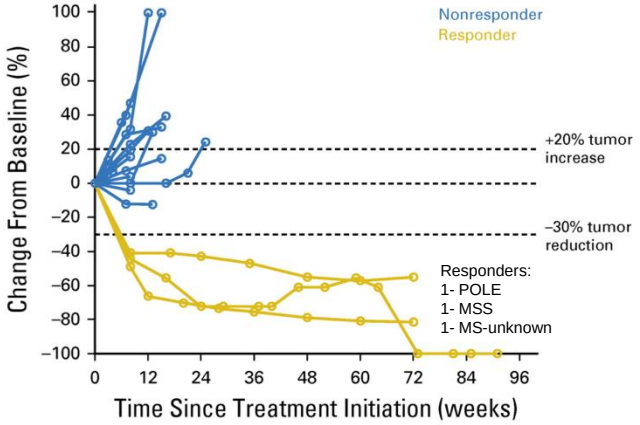
Response to single-agent PD-1 blockade in endometrial cancer

MSI



Endometrial cohort (n=15)
CR: 3 (20)
PR: 5 (33)
SD: 3 (20)

Non-MSI Endometrial (PD-L1+)



ORR 13%

Le D. et al., Science 2017; Ott et al., JCO 2017

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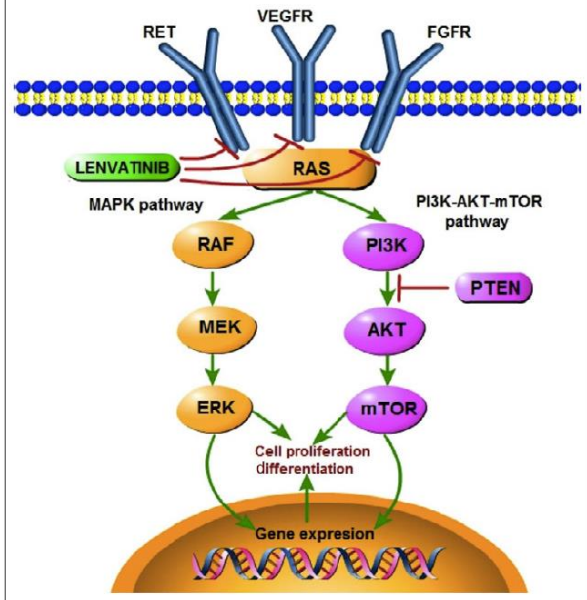
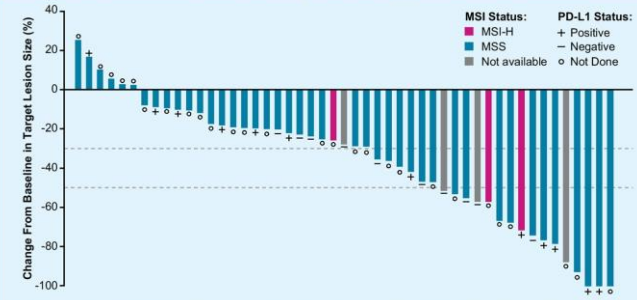
Pembrolizumab and lenvatinib in patients with advanced endometrial cancer

Figure Kinase signaling cascade involved in development of thyroid carcinomas and representing the two main pathways, MAPK and PI3K-AKT-mTOR.



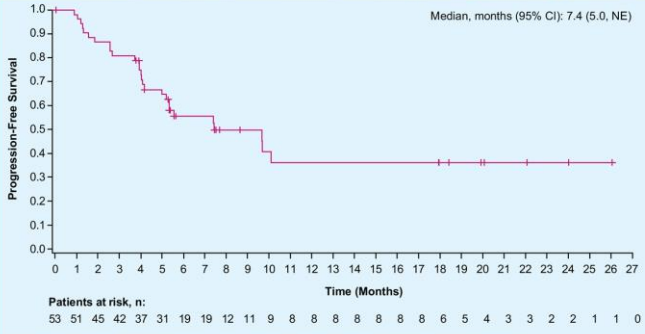
Reprinted with permission from Stjepanovic N, Capdevila J. Multikinase inhibitors in the treatment of thyroid cancer: specific role of lenvatinib. *Biologics: Targets and Therapy*. 2014;8:129-139. ©2014. Permission conveyed through Copyright Clearance Center, Inc.

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



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

Figure 4. Kaplan-Meier Plot of PFS as Assessed by Investigator Using irRECIST



CI, confidence interval; irRECIST, immune-related Response Evaluation Criteria In Solid Tumors; NE, not estimable; PFS, progression-free survival.

Combination was granted breakthrough designation by the FDA in 8/2018

Makker et al., ASCO 2018

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Advanced endometrial cancer, selected upcoming/ongoing phase III studies

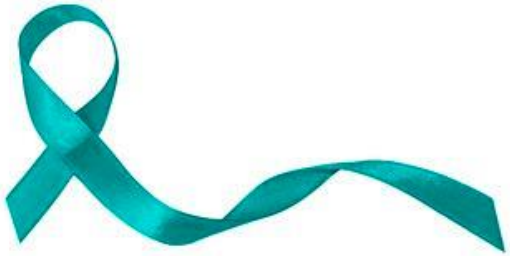
Upfront (advanced/metastatic disease):

- NRG-GY018: carboplatin+paclitaxel +/- pembrolizumab (with maintenance)
- AtTEnd: carboplatin+paclitaxel +/- atezolizumab (with maintenance)

Second line:

- Keynote 775: lenvatinib+pembrolizumab vs. physician's choice chemotherapy

Ovarian Cancer



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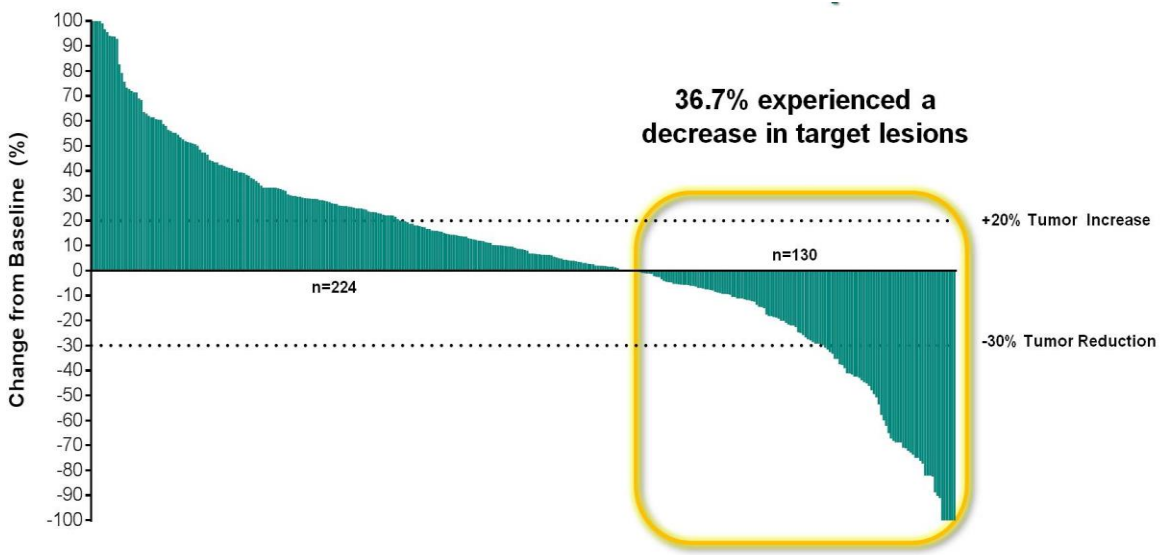
PD-1 blockade as a single agent has limited activity in ovarian cancer

Pembrolizumab: Keynote 100

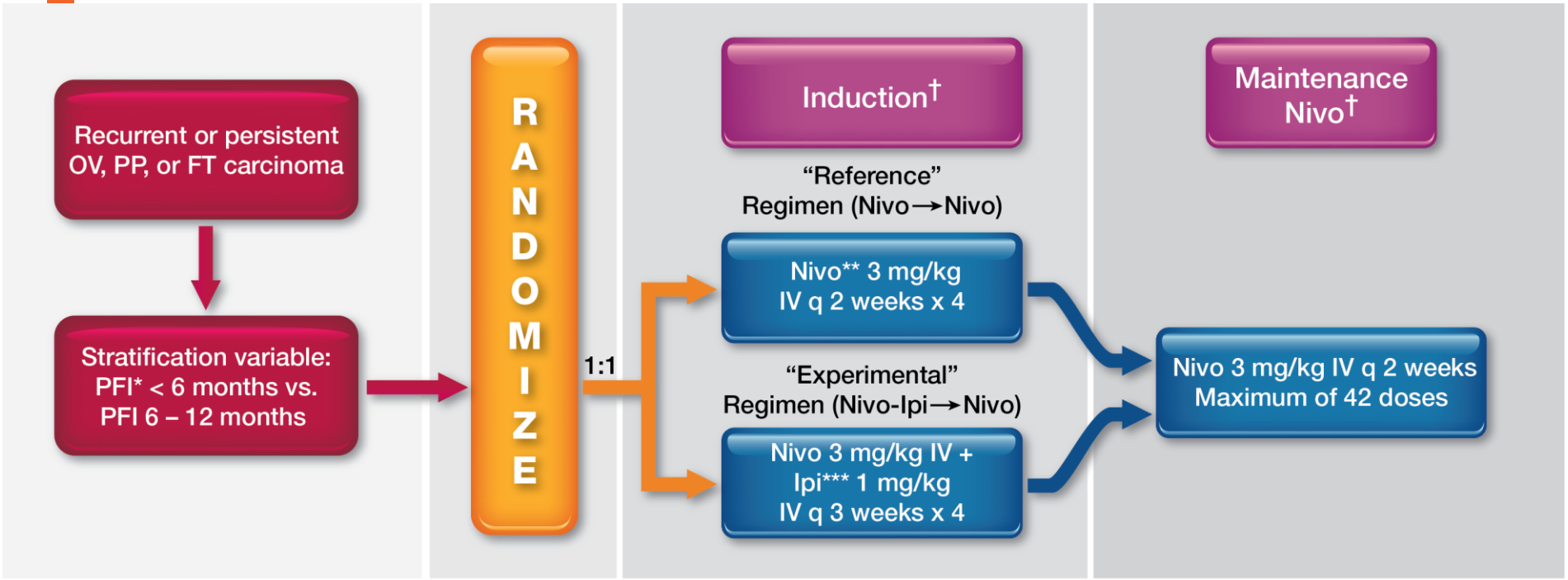


Values higher than or equal to 100 are set to 100. RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1. BICR, Blinded Independent Central Review.
All Subjects as Treated Population. Database cut-off date: April 26, 2018.

ORR 9%

Matulonis et al., ASCO 2018

NRG GY003: Phase II Randomized Trial of Nivolumab with or without Ipilimumab in Patients with Recurrent Ovarian Cancer



* Platinum-Free Interval
** Nivolumab
*** Ipilimumab
† Protocol-directed therapy until progression or unacceptable toxicity

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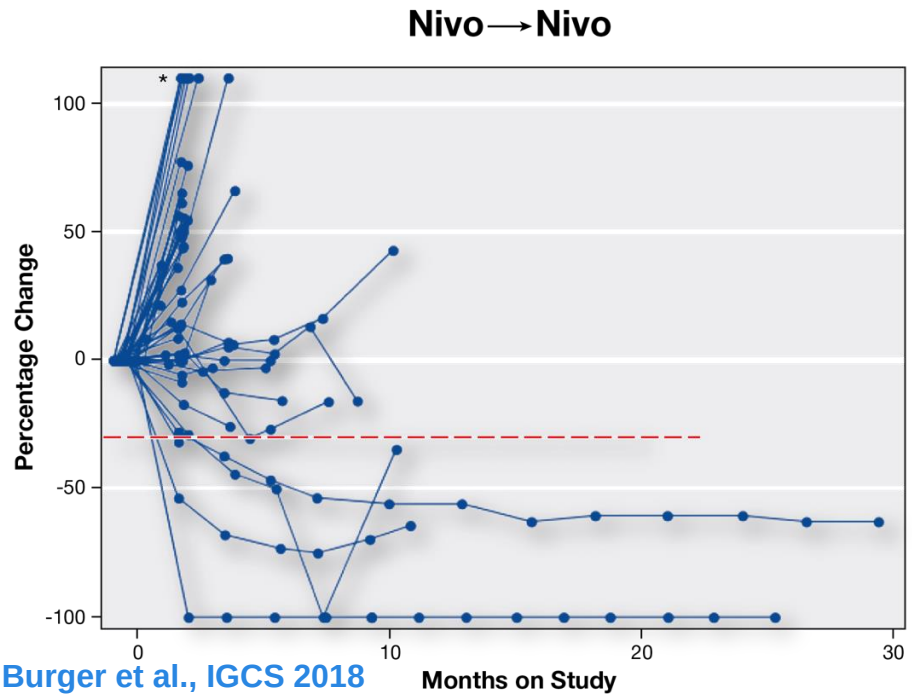
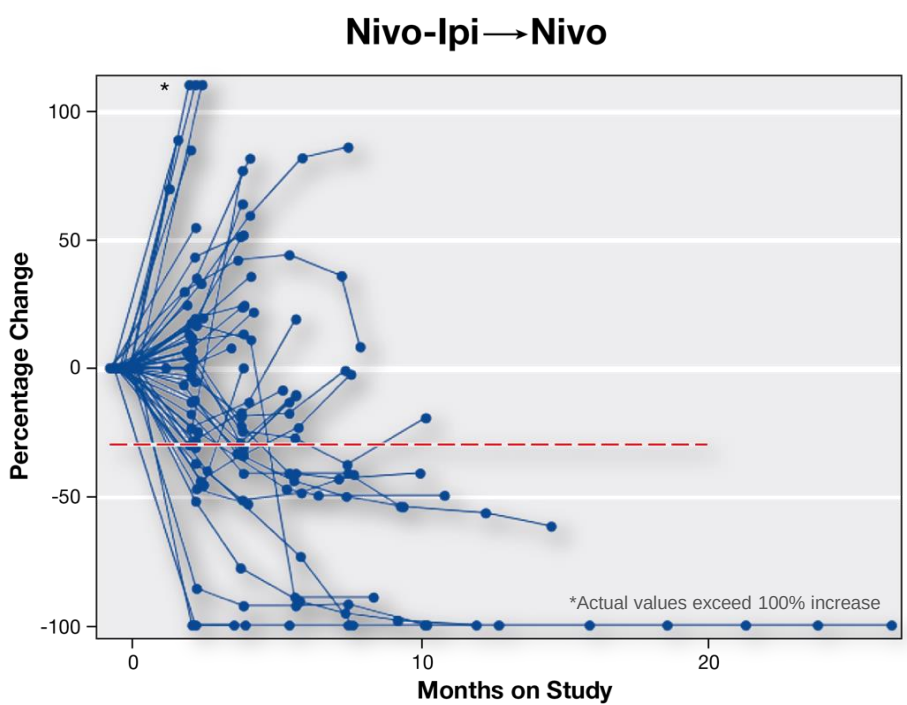
NRG GY003: RECIST Sum

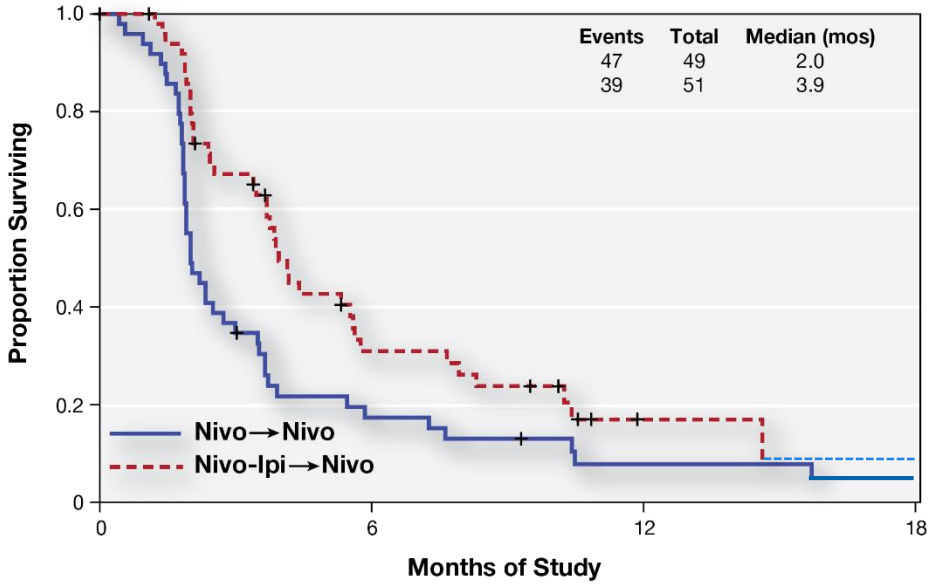
ORR Within 6 months**	Nivo→Nivo N (%)	Nivo-Ipi→Nivo N (%)	p-value
	6 (12.2)	16 (31.4)	0.034





Burger et al., IGCS 2018

NRG GY003: PFS by Treatment Group



Nivo→Nivo	49	8	3	2
Nivo-Ipi→Nivo	51	13	2	1

		Nivo→Nivo (n=49)	Nivo-Ipi→Nivo (n=51)
Patients with event, n (%)		47 (95.9)	39 (76.5)
Median PFS, months		**2.0**	**3.9**
Stratified by PFI	HR (95% CI)	Reference	0.528 (0.339–0.821)
	Two-sided p-value (log-rank)		0.0041

Burger et al., IGCS 2018

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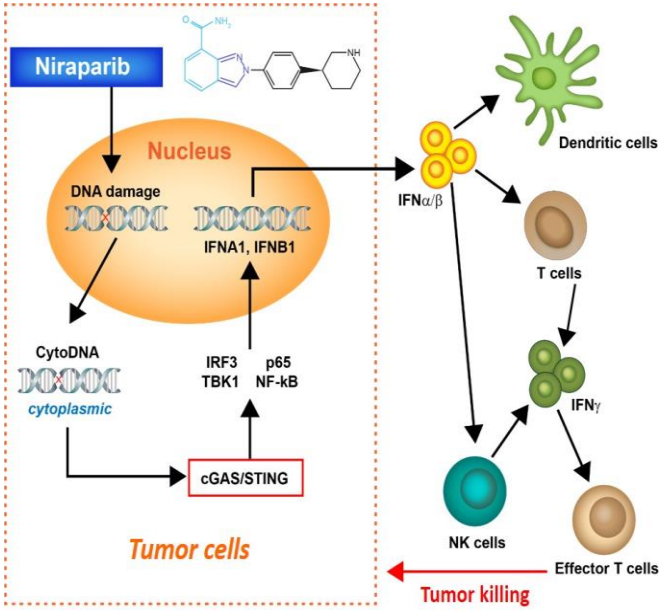
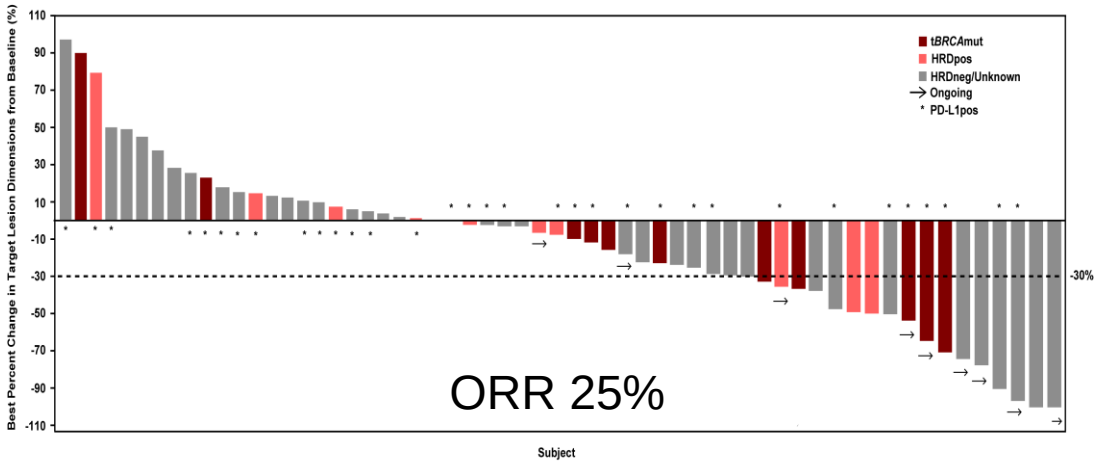
TOPACIO: Niraparib (PARPi) + pembrolizumab in platinum-resistant HGSOC





Sato et al., Nat Commun 2017; Konstantinopoulos et al, ASCO 2018.

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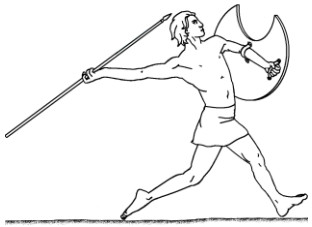
Ongoing/upcoming checkpoint inhibitor phase III trials in upfront management of ovarian cancer:

Javelin Ovarian 100
CP
CP -> Avelumab
CP + Avelumab -> Avelumab



IMaGYN50/GOG 3015/ENGOT-ov39

CP + BEV -> BEV

CP + BEV + Atezo -> BEV + Atezo

GOG 3025/DUO-O

CP + BEV -> BEV

CP + BEV + Durva -> BEV + Durva

CP + BEV + Durva -> BEV + Durva +olaparib

First Trial/ENGOT-OV44

CP +/- BEV -> +/-BEV

CP +/- BEV -> +/- BEV + Niraparib

CP +/- BEV + TSR042 -> +/- BEV + Niraparib + TSR042

ATHENA - Maintenance

Rucaparib

Rucaparib + Nivolumab

Predictors of response/resistance to immunotherapy in gynecologic cancers

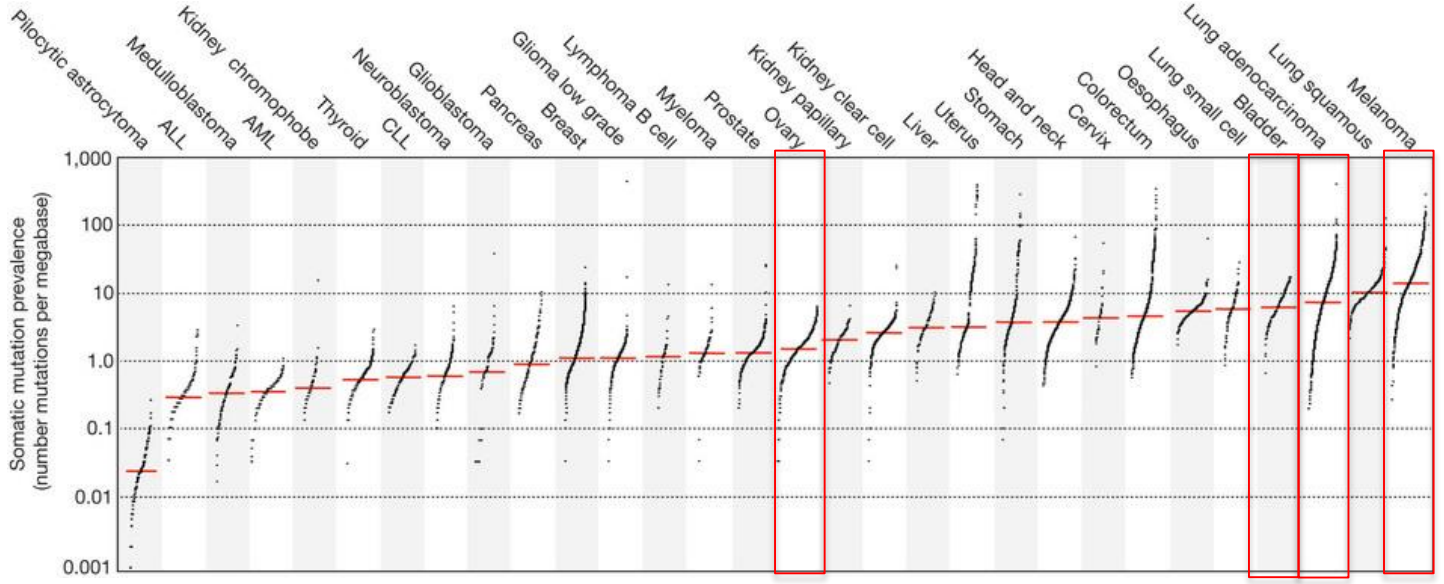
Tumor microenvironment: PD-L1 expression does not enrich for DCR in ovarian cancer.

	Cohort B N = 91			Cohorts A + B N = 376		
	CPS <1 n = 34	CPS ≥1 n = 50	CPS ≥10 n = 22	CPS <1 n = 141	CPS ≥1 n = 197	CPS ≥10 n = 82
ORR % (95% CI)	**8.8 (1.9 - 23.7)**	**10.0 (3.3 - 21.8)**	**18.2 (5.2 - 40.3)**	**5.0 (2.0 - 10.0)**	**10.2 (6.3 - 15.2)**	**17.1 (9.7 - 27.0)**
DCR % (95% CI)	38.2 (22.2 - 56.4)	38.0 (24.7 - 52.8)	45.5 (24.4 - 67.8)	32.6 (25.0 - 41.0)	38.1 (31.3 - 45.2)	41.5 (30.7 - 52.9)
Best overall response						
Complete response n (%)	0 (0.0)	2 (4.0)	2 (9.1)	0 (0.0)	7 (3.6)	7 (8.5)
Partial response n (%)	3 (8.8)	3 (6.0)	2 (9.1)	7 (5.0)	13 (6.6)	7 (8.5)
Stable disease n (%)	10 (29.4)	14 (28.0)	6 (27.3)	39 (27.7)	55 (27.9)	20 (24.4)
Progressive disease n (%)	18 (52.9)	29 (58.0)	12 (54.5)	87 (61.7)	113 (57.4)	44 (53.7)

Pembrolizumab, Ovarian CA

Matulonis et al., ASCO 2018

Ovarian cancers exhibit low mutational burden



Alexandrov et al., Nature 2013

The New York Times

HEALTH

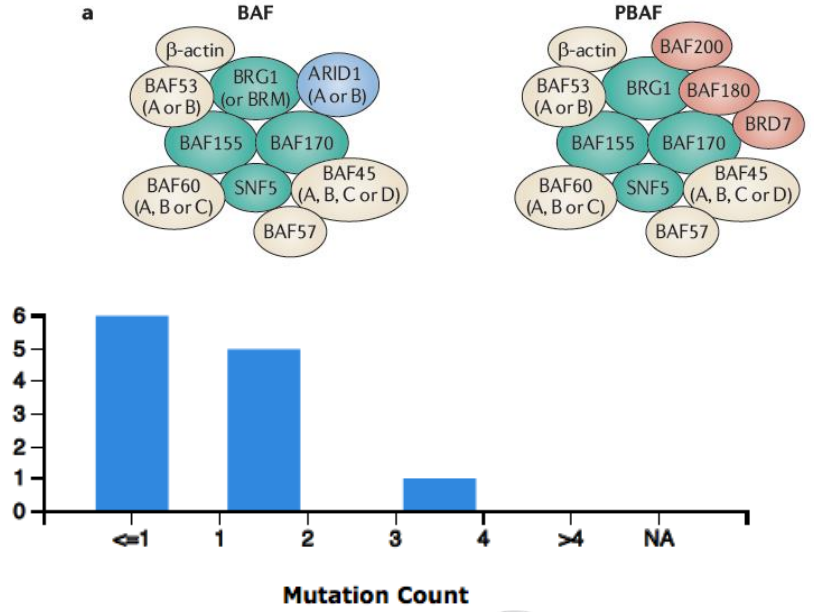
Doctors Said Immunotherapy Would Not Cure Her Cancer. They Were Wrong.

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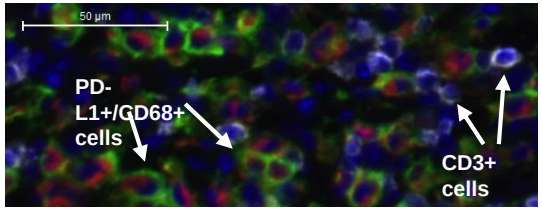
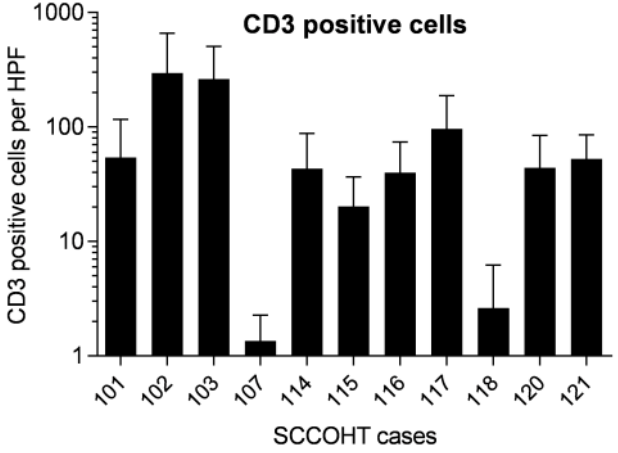
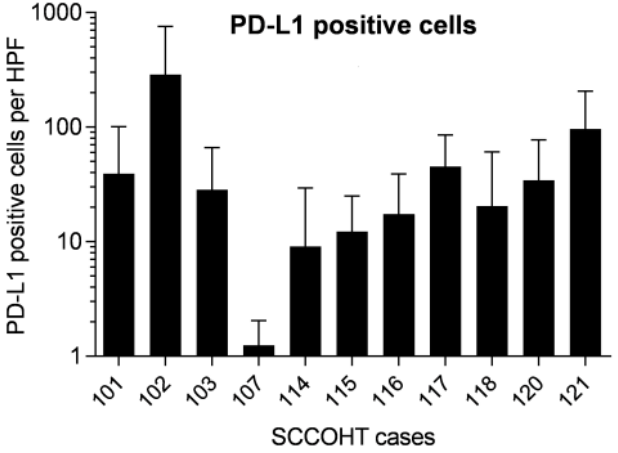
Despite low tumor mutational burden SCCOHTs exhibit immune-active tumor microenvironment.







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

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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]†‡

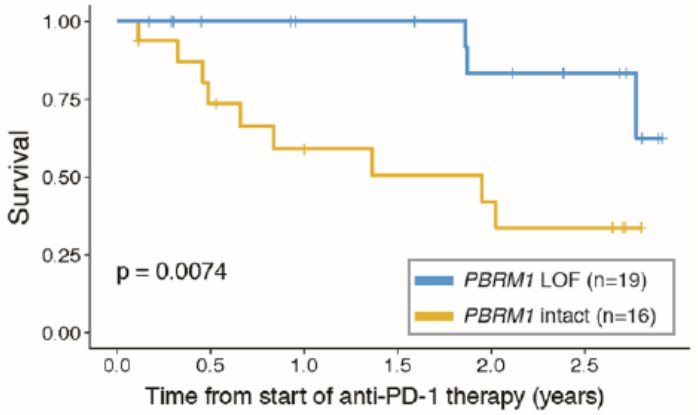
Science

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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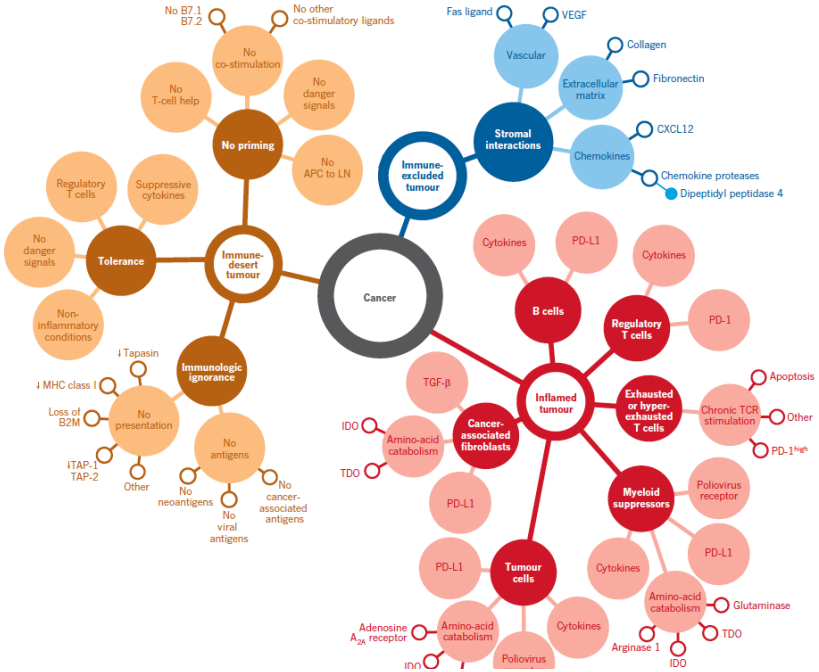
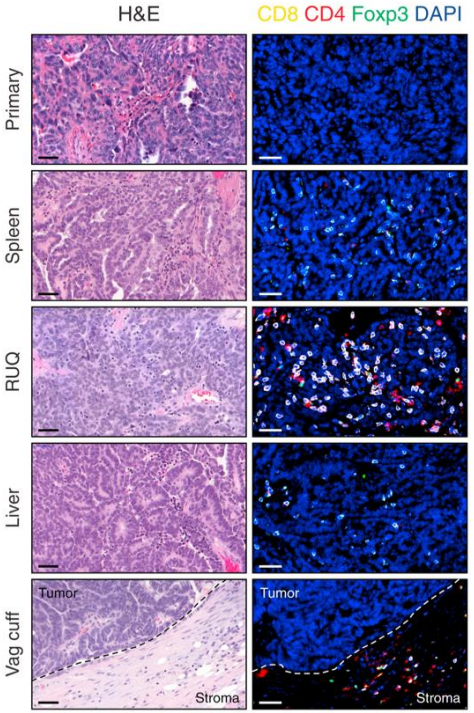
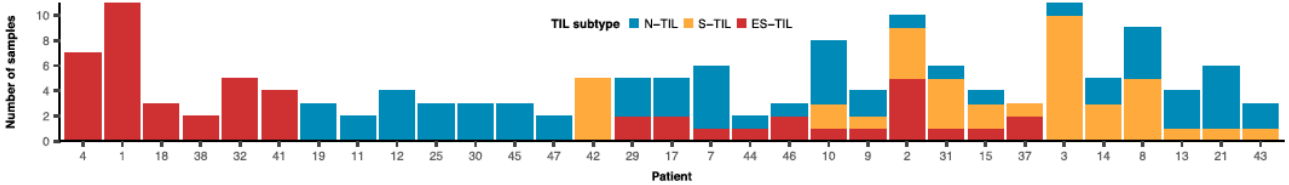
Intra and inter-tumor heterogeneity may influence response to immunotherapy in ovarian cancer







Chen and Mellman, Nature 2017; Jimenez-Sanchez et al., Cell 2017; Zhang A.… Shah S, Cell 2018

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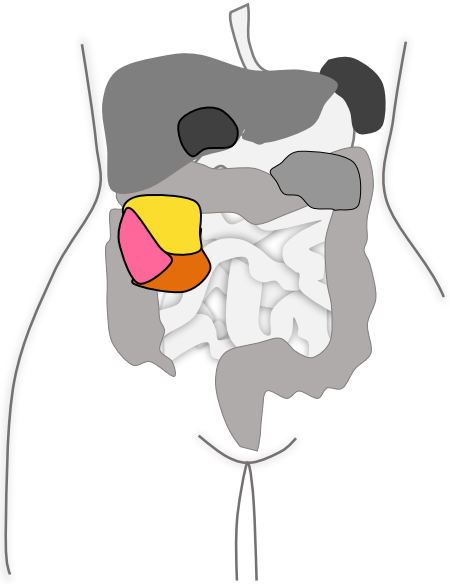
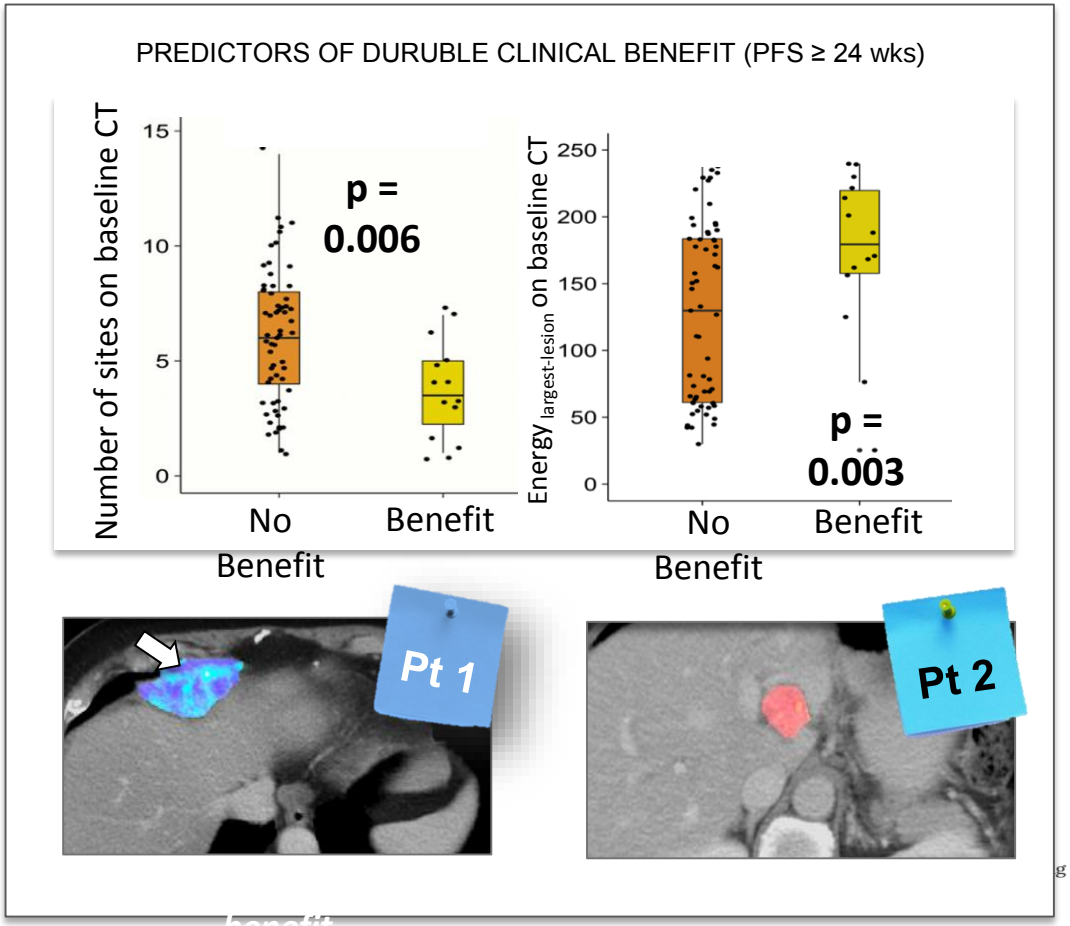
Texture Heterogeneity + Basic Measures From Baseline CT Predict Durable Clinical Benefit

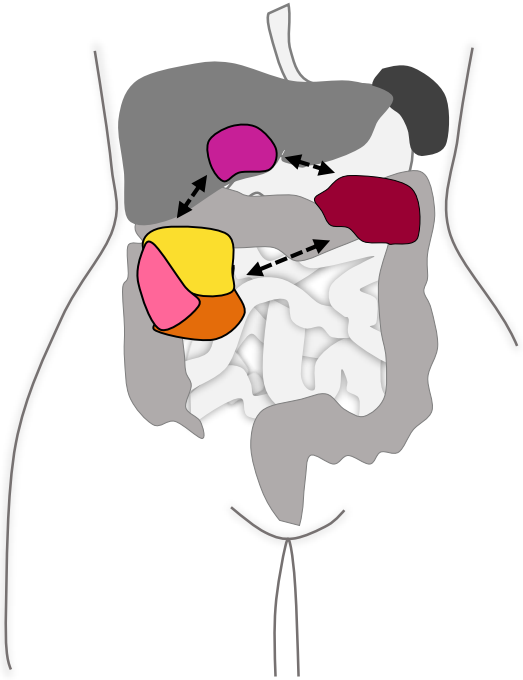


N=75

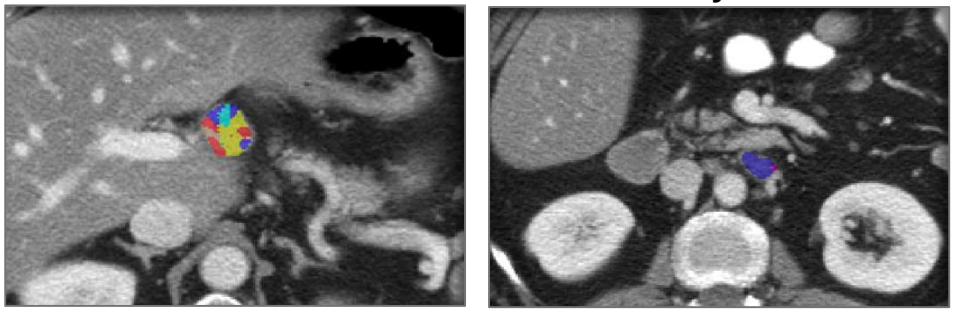
- Number of disease sites
- Intratumor heterogeneity
- Intertumor heterogeneity



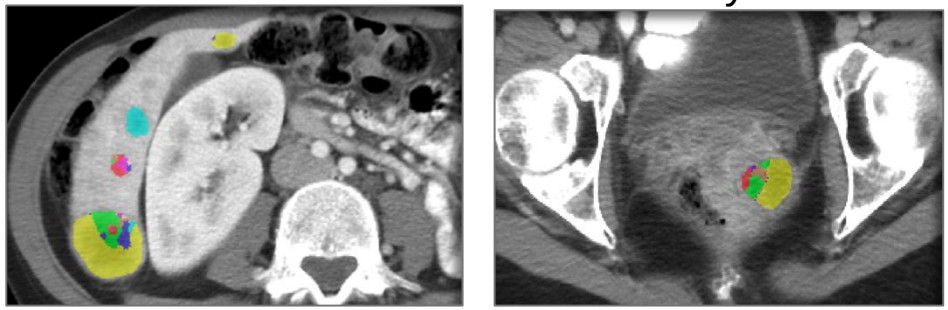
Higher Inter-Tumor Heterogeneity On Baseline CT is associated with Quicker Time to Off-Treatment



Baseline CT cluster-site-dissimilarity 1,648
time to off-treatment 569 days

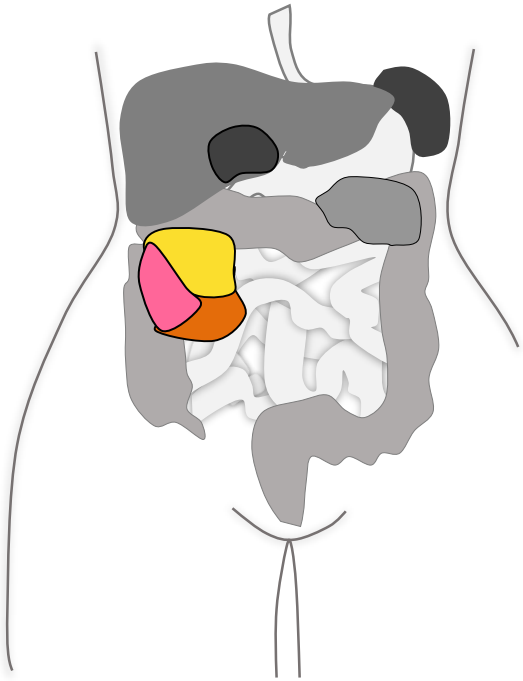


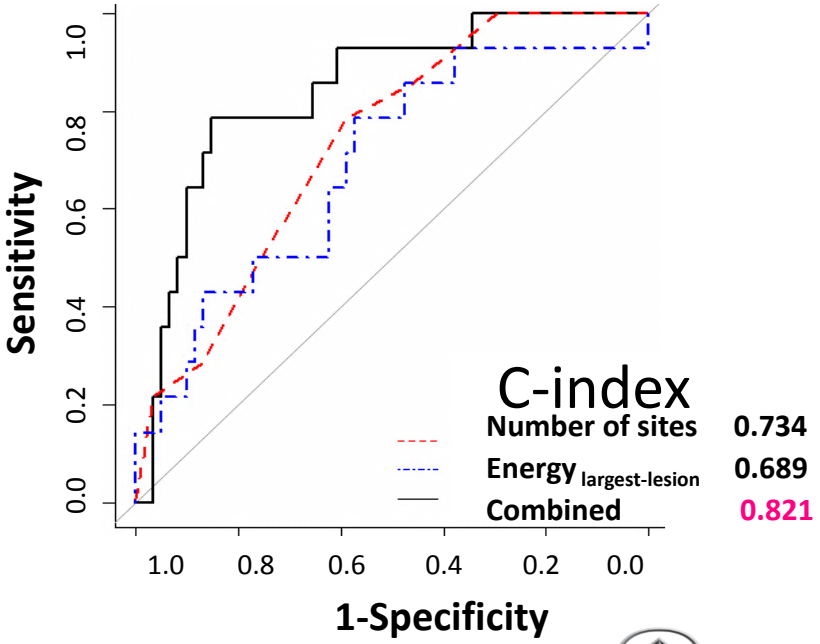
Baseline CT cluster-site-dissimilarity 568,399
time to off-treatment 42 days



Kettering

Combined *Texture Heterogeneity + Basic Measures* From Baseline CT Predicts Durable Clinical Benefit With Higher Accuracy





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Take Home Messages

- Immune checkpoint blockade is promising in some GYN cancer patients, but we have a long way to go
- Combination therapies will be a key to success and may include other immunotherapies, targeted therapy, or chemotherapy
- Biomarkers predictive of response in other cancer types may be of limited value in GYN cancers
- High intra- and inter-tumor heterogeneity may negatively influence the outcomes of immunotherapy in GYN cancers

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- Harini Veeraraghavan

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New York University
- Douglas Levine

University of Pennsylvania
- Robert Burger
- Dan Powell

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Gynecologic Cancer Awareness • Research • Education

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Damon Runyon Cancer Research Foundation

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