Role of Immunotherapy in Gynecologic Cancers

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Vice- Dean, Mayo Clinic School of Medicine

Disclosure

- Research grant support from Novartis to Mayo Clinic for Investigator Initiated Trials

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Focus of talk

- *Checkpoint inhibitors and immune-modulators*
- Monoclonal antibodies and Immuno-conjugates
- Therapeutic vaccines
- Adoptive T-cell therapies
- Oncolytic viruses
- Adjuvant immunotherapies

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Case #1: Endometrial Cancer

- 50 year old female
- May 2015: Vaginal bleeding x 8 months. D and C: g3 endometrioid carcinoma.
- July 2015: TAH: 4.5 cm T2N2 g3 serous ca with invasion cervical stroma, 12/15mm myometrial involvement, no LVS invasion, 2 + PA LN and 5 + pelvic LNs.

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Case #1: Endometrial cancer (cont)

- Tumor cells with absent MSH2 and MSH6 by IHC.
- PE and DVT: IVC filter placed.
- August 2015: PET scan: new PA nodes and pelvic nodes and vaginal recurrence on exam.
- RT to vaginal cuff in view of bleeding.

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Case #1: Endometrial cancer (cont)

- October 2015-January 2016: Docetaxel and CBDCA for 6 cycles followed by vaginal brachytherapy.
- February 2016: Progressive disease on imaging with increasing abdominal pains, leg edema. Treated with gemcitabine and paclitaxel with response.
- August 2016: Progressed with new left SC adenopathy, worsening pain and worsening leg edema.

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Case #1: Endometrial cancer (cont...)

- September 2016: Nivolumab.

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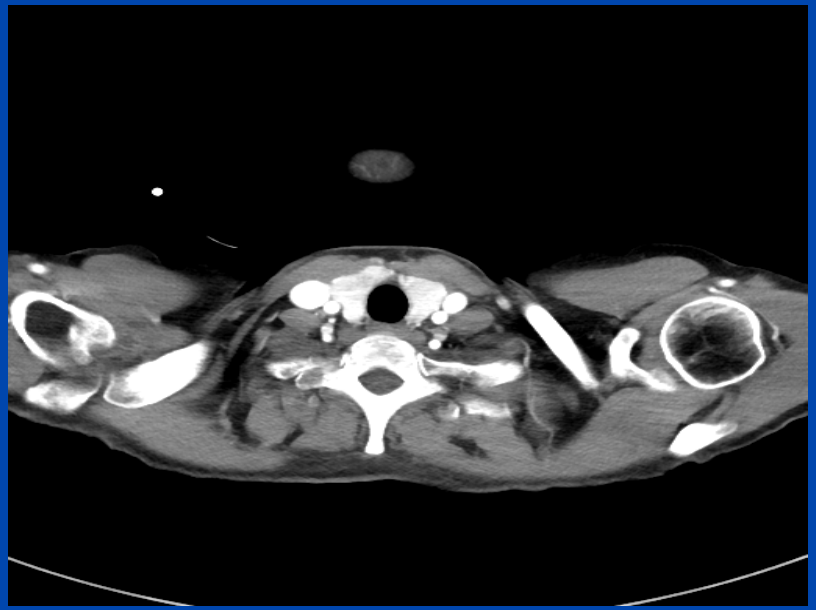
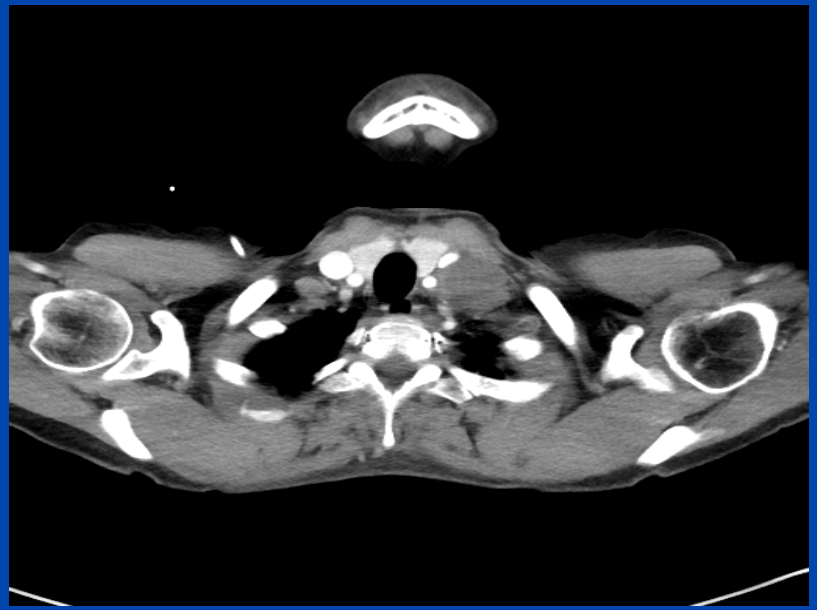
CT scans: Left SC nodes





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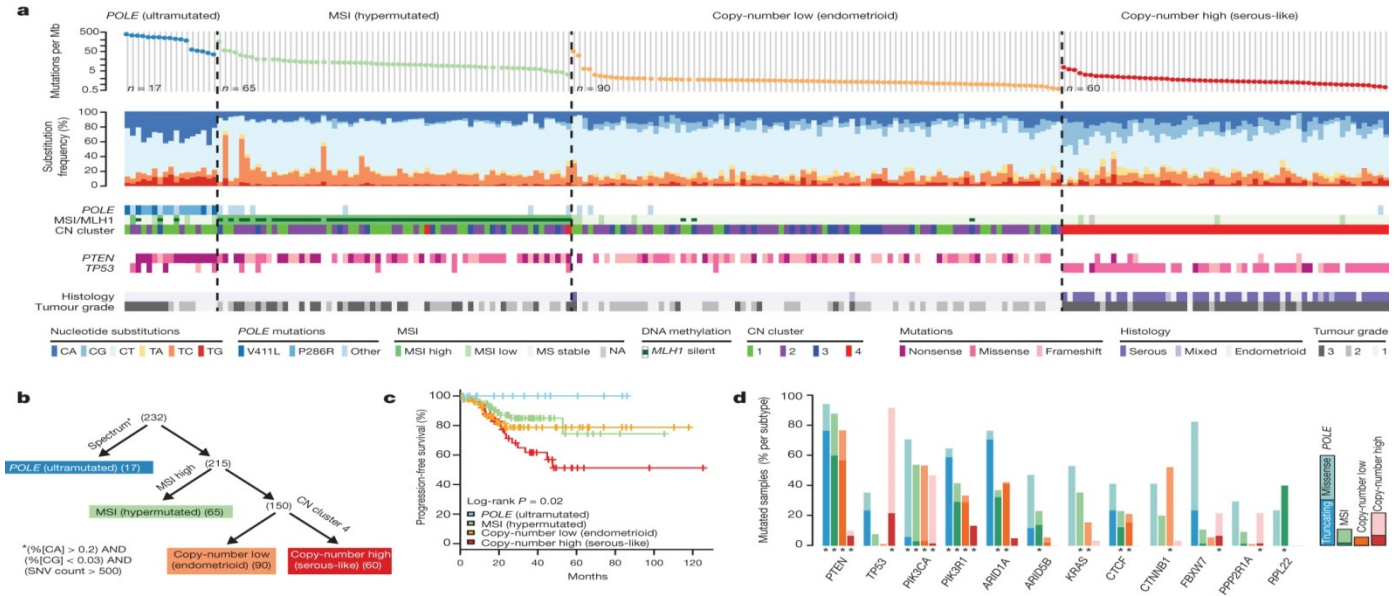
Mutation spectra across endometrial carcinomas.



G Getz *et al. Nature* **497**, 67-73 (2013) doi:10.1038/nature12113

nature

DANA-FARBER CANCER INSTITUTE

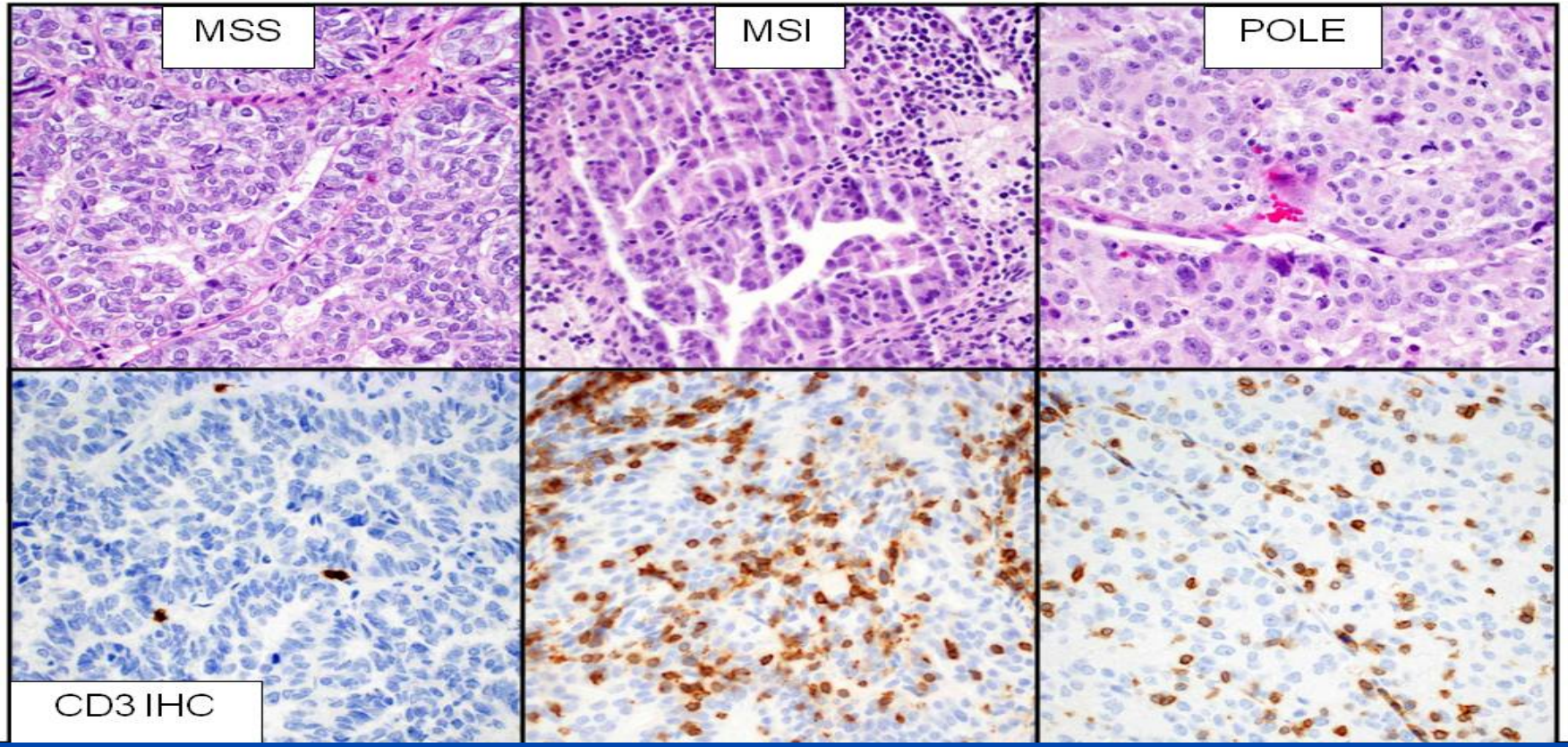
HARVARD MEDICAL SCHOOL

POLE-mutated and MSI endometrial cancers are associated with an elevated number of tumor-infiltrating and peritumoral lymphocytes and higher expression of PD-1 and PD-L1

Brooke E. Howitt[1], Lynette M. Sholl[1], Lauren L. Ritterhouse[1], Jaclyn C. Watkins[1], Scott Rodig[1], Kyle Strickland[1], Alan D. D'Andrea[2], Ursula A. Matulonis[3], Panagiotis A. Konstantinopoulos[3]

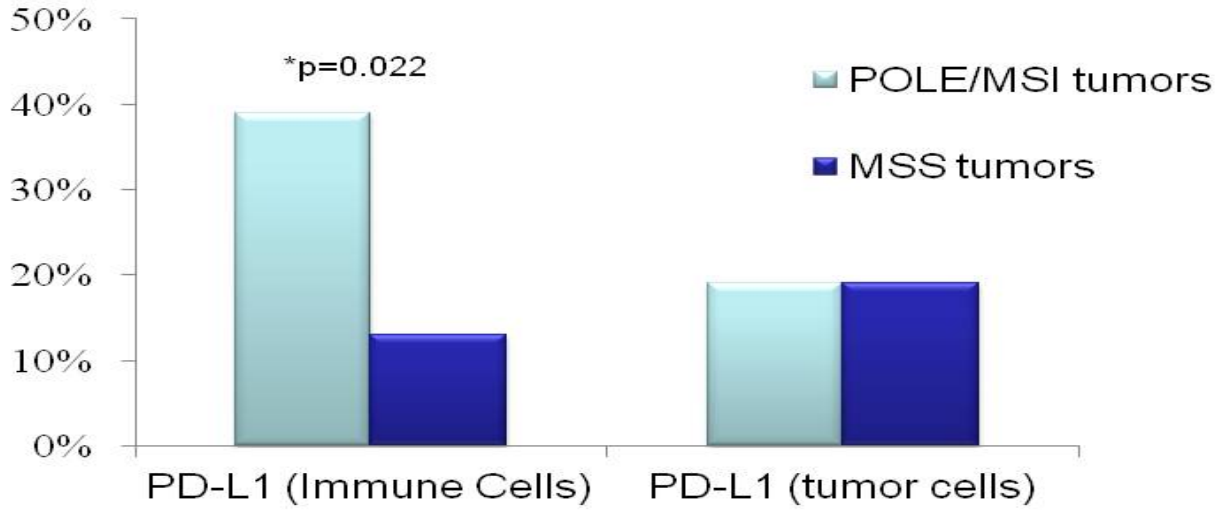
[1]Department of Pathology Brigham and Women's Hospital, Harvard Medical School
[2]Division of Genomic Stability and DNA Repair, Dana Farber Cancer Institute, Harvard Medical School
[3]Medical Gynecologic Oncology Program, Dana Farber Cancer Institute, Harvard Medical School

CD3+ Tumor Infiltrating Lymphocytes (TILs) are More Prominent in POLE/MSI Endometrial Adenocarcinomas



Presented By Brooke Howitt at 2015 ASCO Annual Meeting; JAMA Oncology 2015

PD-L1 is Expressed in Tumor-Associated Immune Cells in POLE/MSI Tumors



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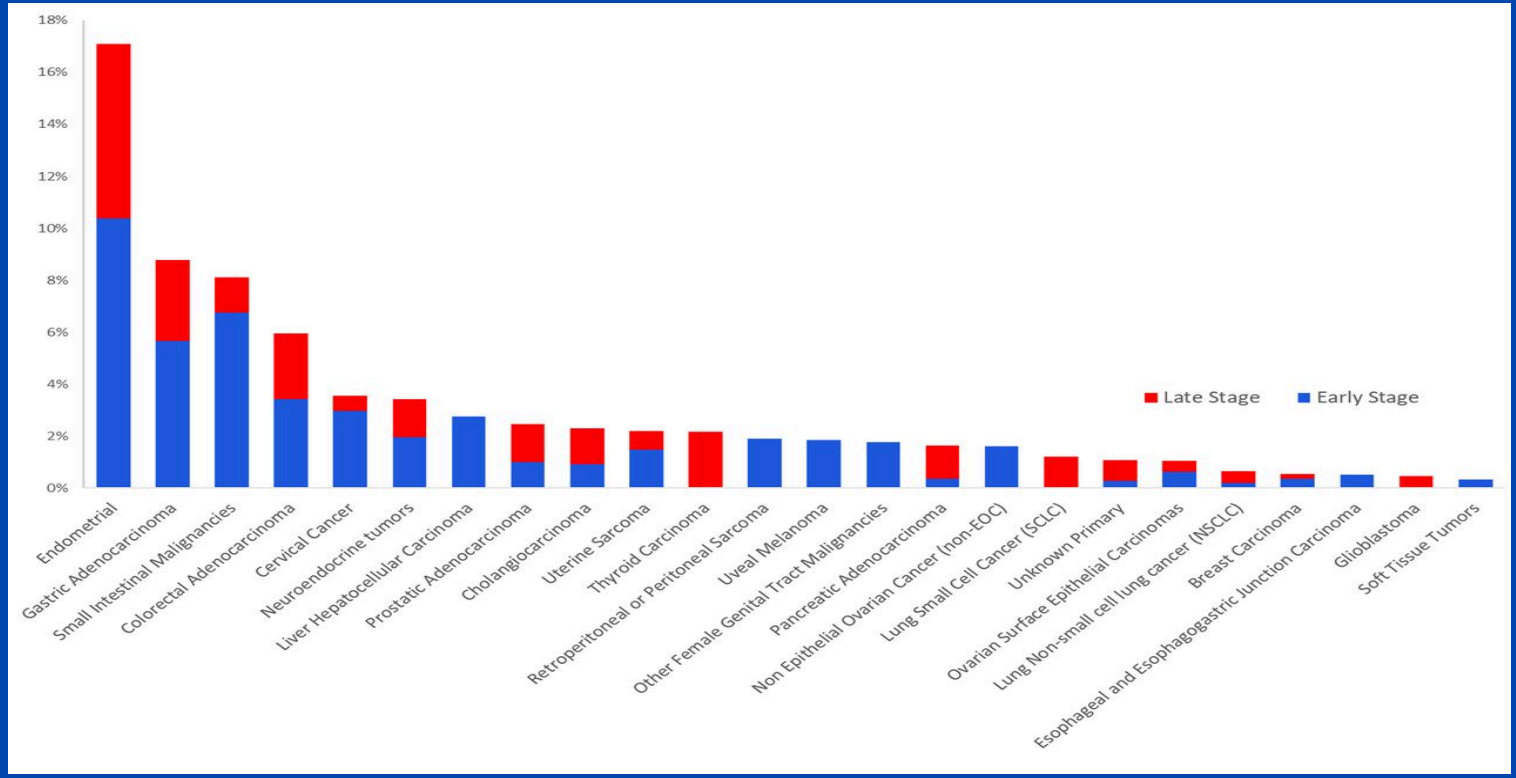
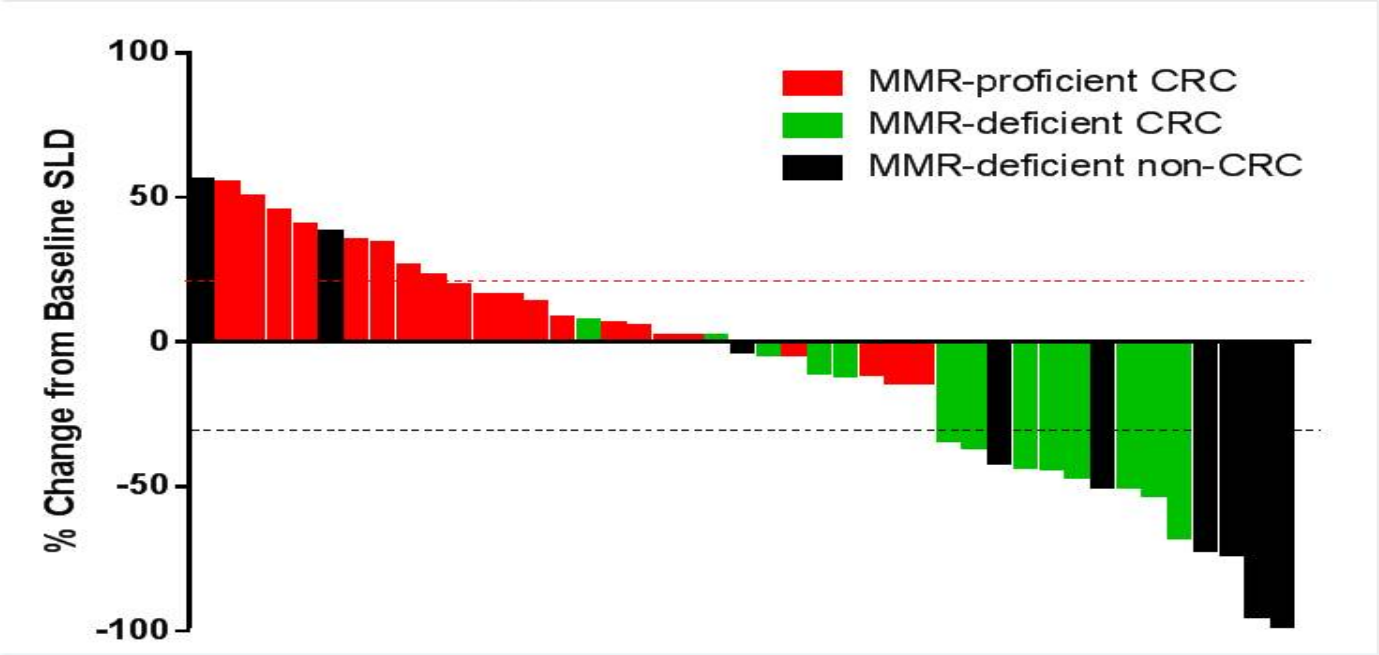
Presented By Brooke Howitt at 2015 ASCO Annual Meeting; JAMA Oncol. 2015; 1:1319–23.

Fig. 3 Mismatch repair deficiency across 12,019 tumors.

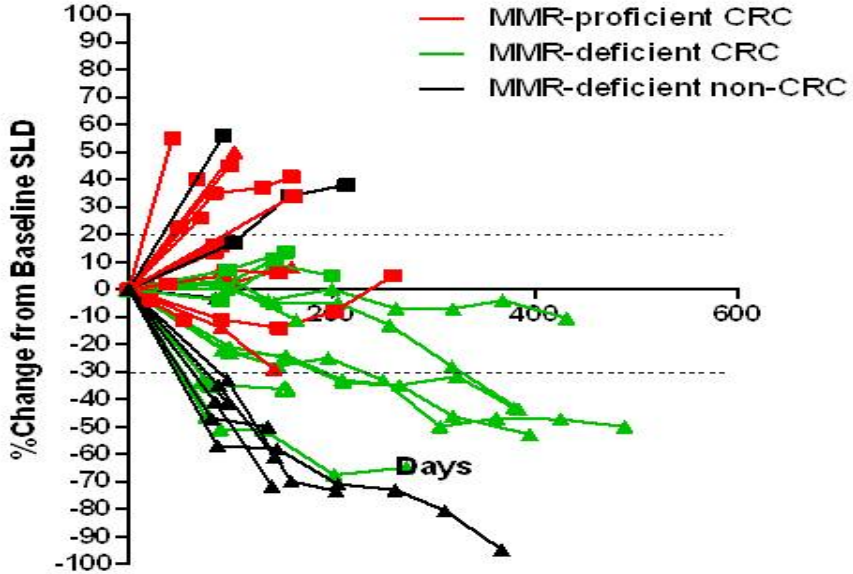


Dung T. Le et al. Science 2017;science.aan6733

Target Lesions



Duration of Disease Control



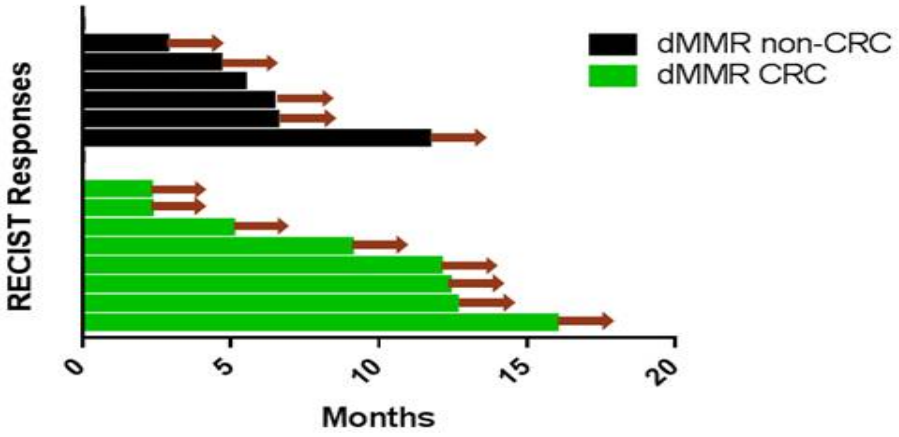
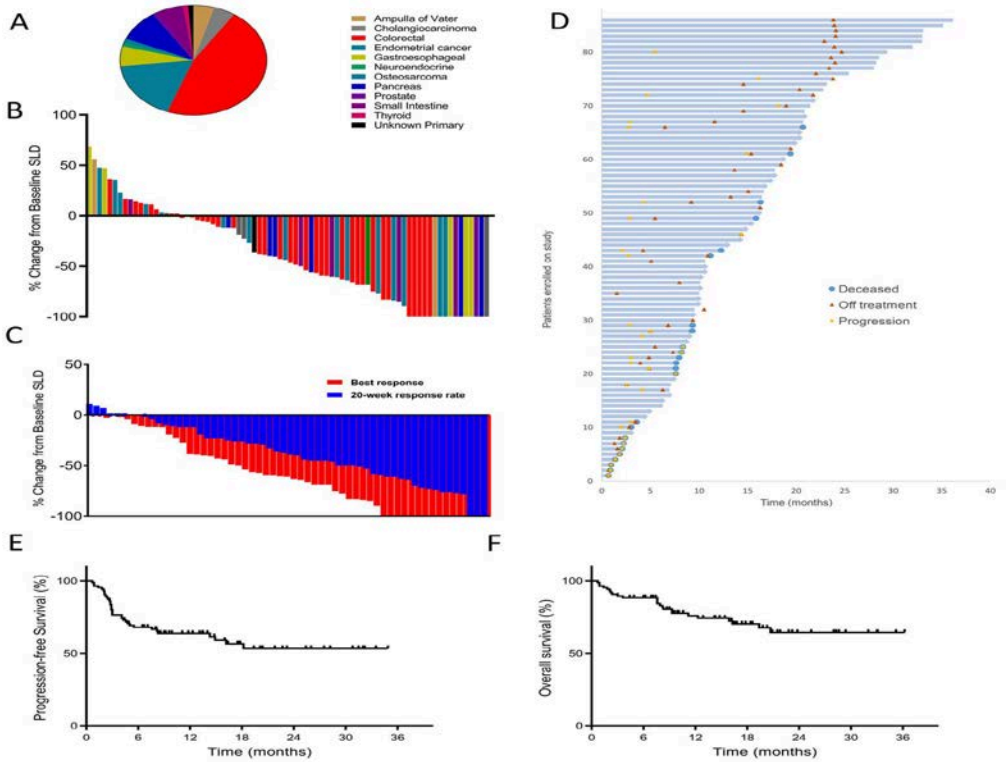


Fig. 1 Patient survival and clinical response to Pembrolizumab across 12 different tumor types with mismatch repair deficiency.



Dung T. Le et al. Science 2017;science.aan6733

Fader AN: SGO 2018 (*JCO* **2018,** 36, 2044-2051)

- HER2 amplification in 30% serous carcinomas of uterus
- Randomized Phase 2 trial: TC +/- trastuzumab
- August 2011- March 2017
- 61 patients
- Median PFS 8 months vs 12.6 months (HR 0.44, p= 0.005)
- 41 patients : primary rx: PFS 9.3 mo vs 17.9 mo (HR 0.4, p=0.013)

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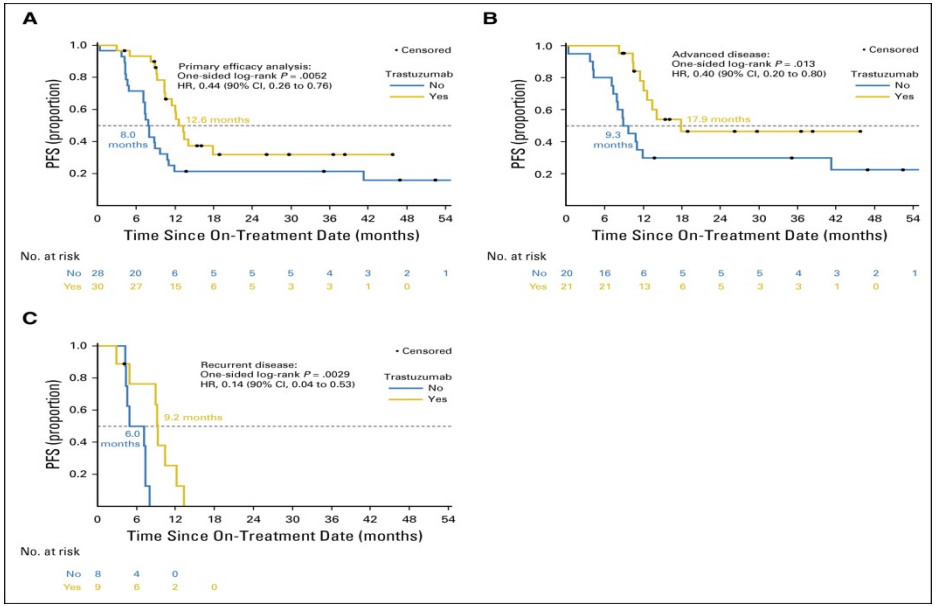


Fig 2. Progression-free survival (PFS). (A) Median progression-free survival was improved by 4.6 months in patients (n = 58) who received trastuzumab with carboplatin-paclitaxel (12.6 months) compared with those who received carboplatin-paclitaxel alone (8.0 months; P = .005; hazard ratio [HR], 0.44; 90% CI, 0.26 to 0.76). (B) The addition of trastuzumab benefitted patients (n = 41) with advanced disease in the primary treatment setting (17.9 v 9.3 months; HR, 0.40; 90% CI, 0.20 to 0.80; P = .013). (C) The addition of trastuzumab also benefitted patients (n = 17) with recurrent disease after zero, one, or two lines of prior chemotherapy (9.2 v 6.0 months; HR, 0.14; 90% CI, 0.05 to 0.54; P = .003). In total, there were 40 progression events; among those who remained alive and progression free, five were in the control arm and 13 were in the experimental arm.

Published in: Amanda N. Fader; Dana M. Roque; Eric Siegel; Natalia Buza; Pei Hui; Osama Abdelghany; Setsuko K. Chambers; Angeles Alvarez Secord; Laura Havrilesky; David M. O'Malley; Floor Backes; Nicole Nevadunsky; Babak Edraki; Dirk Pikaart; William Lowery; Karim S. ElSahwi; Paul Celano; Stefania Bellone; Masoud Azodi; Babak Litkouhi; Elena Ratner; Dan-Arin Silasi; Peter E. Schwartz; Alessandro D. Santin; *JCO* **2018,** 36, 2044-2051.
DOI: 10.1200/JCO.2017.76.5966

Intratumoral T Cells, Recurrence, and Survival in Epithelial Ovarian Cancer

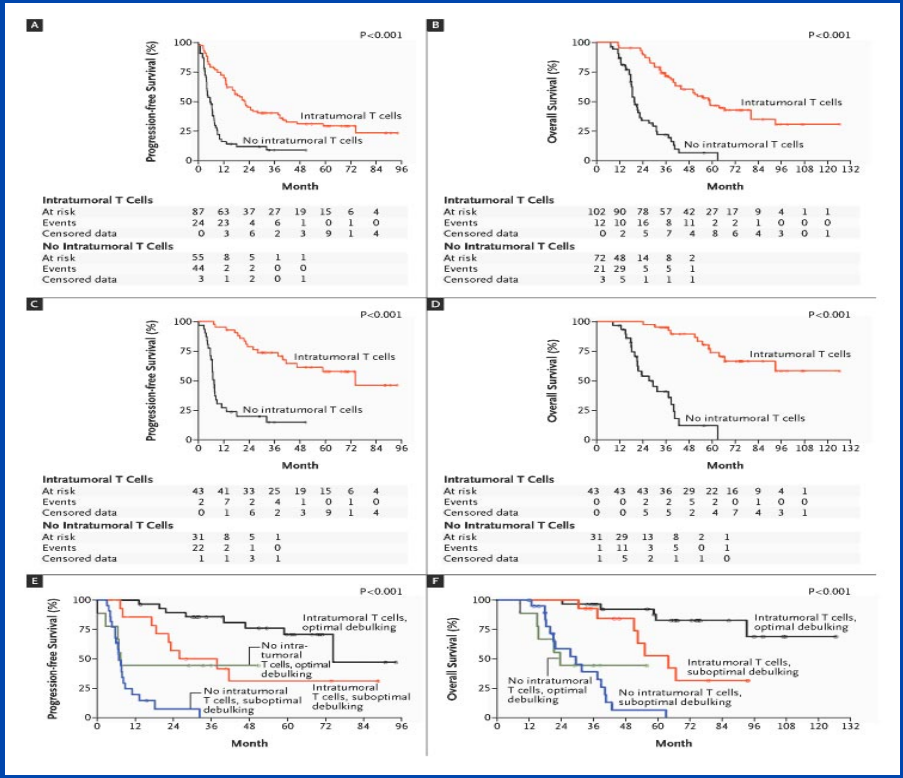
Lin Zhang, M.D., Jose R. Conejo-Garcia, M.D., Ph.D., Dionyssios Katsaros, M.D., Ph.D., Phyllis A. Gimotty, Ph.D., Marco Massobrio, M.D., Giorgia Regnani, M.D., Antonis Makrigiannakis, M.D., Ph.D., Heidi Gray, M.D., Katia Schlienger, M.D., Ph.D., Michael N. Liebman, Ph.D., Stephen C. Rubin, M.D. and George Coukos, M.D., Ph.D.

N Engl J Med
Volume 348;3:203-213
January 16, 2003

MAYO CLINIC

The NEW ENGLAND JOURNAL of MEDICINE

Survival Analyses of Patients with Ovarian Carcinoma, According to the Presence or Absence of Intratumoral T Cells



Zhang, L. et al. N Engl J Med 2003;348:203-213

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Multivariate Cox Proportional-Hazards Analysis of Progression-free and Overall Survival

Table 3. Multivariate Cox Proportional-Hazards Analysis of Progression-free and Overall Survival.

Variable	No. of Patients	Progression-free Survival	Overall Survival
		*hazard ratio (95% CI)**	
Intratumoral T cells			
Present	43	0.17 (0.08–0.36)	
Absent	31	1.00	
Residual disease			
Optimal (≤1 cm)	38	0.31 (0.15–0.67)	0.40 (0.17–0.95)
Suboptimal (>1 cm)	36	1.00	1.00
Histologic type			
Clear-cell or undifferentiated	17	1.00	1.00
Serous or mucinous or endometrioid	57	0.79 (0.35–1.75)	0.36 (0.15–0.91)
Tumor grade			
1	8	0.27 (0.04–2.17)	0.37 (0.40–3.14)
2	16	0.84 (0.40–1.80)	0.51 (0.21–1.27)
3	50	1.00	1.00
Paclitaxel therapy			
Received	42	1.16 (0.60–2.25)	1.84 (0.80–4.21)
Not received	32	1.00	1.00
Age			
<55 yr	27	1.00	1.00
≥55 yr	47	0.83 (0.42–1.65)	0.83 (0.38–1.81)

* CI denotes confidence interval.

Zhang, L. et al. N Engl J Med 2003;348:203-213

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The NEW ENGLAND JOURNAL of MEDICINE

Efficacy and safety of anti-PD-1 antibody (Nivolumab: BMS-936558, ONO-4538) in patients with platinum-resistant ovarian cancer

Junzo Hamanishi, MD, PhD
Kyoto University, Japan

Junzo Hamanishi, Masaki Mandai*, Takafumi Ikeda, Manabu Minami, Atsushi Kawaguchi, , Masashi Kanai, Yukiko Mori, Shigemi Matsumoto, Toshinori Murayama, Shunsuke Chikuma, Noriomi Matsumura, Kaoru Abiko, Tsukasa Baba, Ken Yamaguchi, Akihiko Ueda, Satoshi Morita, Masayuki Yokode, Akira Shimizu, Tasuku Honjo, Ikuo Konishi

Kyoto University, Japan , *Kinki University, Japan

Presented By Junzo Hamanishi at 2014 ASCO Annual Meeting; JCO 2015 : 33 (34): 4015

Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with previously treated, recurrent or refractory ovarian cancer: a phase Ib, open-label expansion trial

Mary Disis,[1] Manish R. Patel,[2] Shubham Pant,[3] Jeffrey R. Infante,[4] A. Craig Lockhart,[5] Karen Kelly,[6] Joseph Beck,[7] Michael Gordon,[8] Glen J. Weiss,[9] Samuel Ejadi,[10] Matthew Taylor,[11] Anja von Heydebreck,[12] Kevin Chin,[13] Jean-Marie Cuillerot,[13] James L. Gulley[14,15]

[1]Tumor Vaccine Group, University of Washington, School of Medicine, Seattle, Washington, USA; [2]Sarah Cannon Research Institute/Florida Cancer Specialists, Sarasota, Florida, USA; [3]Hematology/Oncology Section, Peggy and Charles Stephenson Oklahoma Cancer Center, Oklahoma City, Oklahoma, USA; [4]Sarah Cannon Research Institute/Tennessee Oncology, PLLC, North Nashville, Tennessee, USA; [5]Medical Oncology Section, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri, USA; [6]University of California-Davis Comprehensive Cancer Center, Sacramento, California, USA; [7]Highlands Oncology Group, Fayetteville, Arkansas, USA; [8]Pinnacle Oncology Hematology, Scottsdale, Arizona, USA; [9]Cancer Treatment Centers of America, Western Regional Medical Center, Goodyear, Arizona, USA; [10]Scottsdale Healthcare Research Institute, Scottsdale, Arizona, USA; [11]Knight Cancer Institute, Oregon Health and Science University, Portland, Oregon, USA; [12]Merck KGaA, Darmstadt, Germany; [13]EMD Serono, Billerica, Massachusetts, USA; [14]Genitourinary Malignancy Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA; [15]Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

Poster Presentation at the 51st ASCO Annual Meeting, May 29-June 2, 2015; Chicago, Illinois. Abstract No. 5509.

PRESENTED AT: ASCO Annual '15 Meeting

MAYO CLINIC

Presented By Mary Disis at 2015 ASCO Annual Meeting

Clinical activity: best overall response

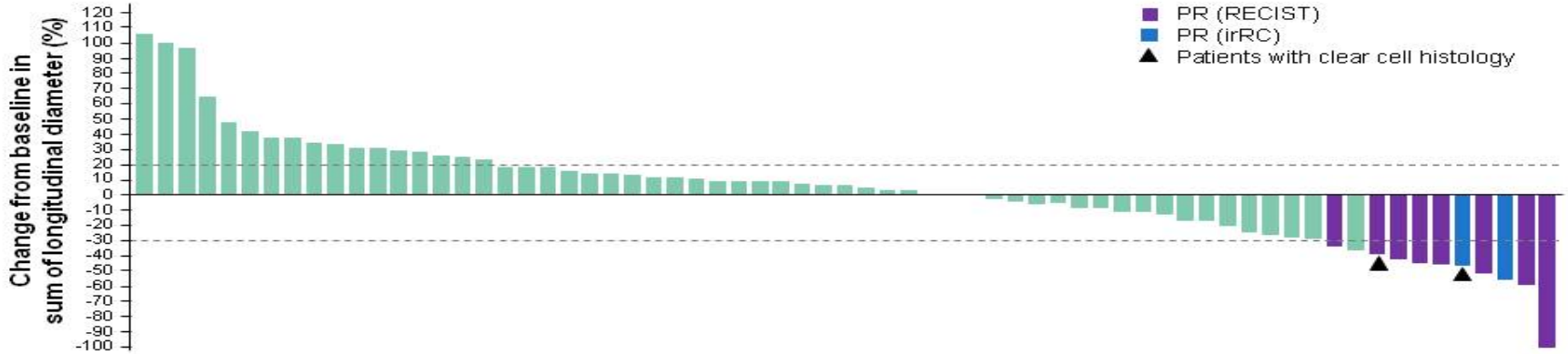
Best overall response by RECIST 1.1, unconfirmed*	Ovarian (n=75) n (%)	95% CI
Complete response (CR)	0	
Partial response (PR)	8 (10.7)	
Stable disease (SD)	33 (44.0)	
Progressive disease (PD)	26 (34.7)	
Objective response rate (ORR)	**8 (10.7)**	**4.7, 19.9**
Disease control rate (DCR)†	41 (54.7)	

Median duration of F/U: 5 months (range, 3-15 mos)

* There were 8 patients (10.7%) with "missing" and/or "not evaluable" information.
† DCR is defined as responses plus stable disease.

PRESENTED AT: ASCO Annual '15 Meeting

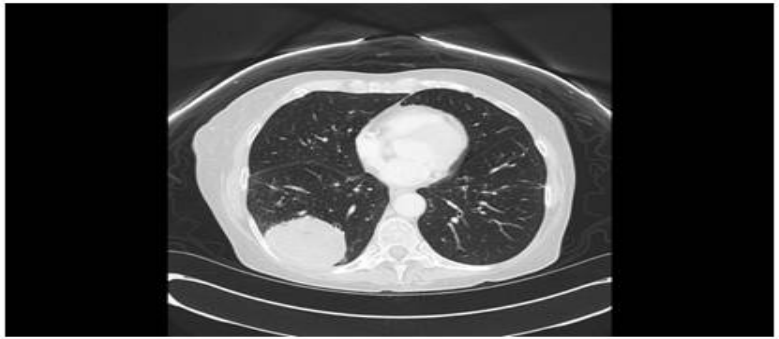
Clinical activity: best change in target lesions from baseline



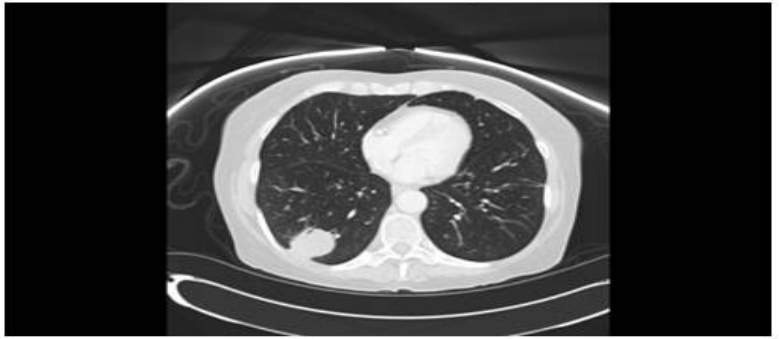
- Tumor shrinkage by ≥30% was observed in 11 patients (14.7%), including 2 of 2 patients with clear cell histology
  - 8 patients with PR by RECIST
  - 2 additional patients with PR by irRC (ongoing)

PR in metastatic clear cell

Baseline: 69 mm RLL lesion



Week 25: 41 mm (-40.6%)



- 65 years old; 6 prior lines for metastatic disease
- 4th assessment cycle, still on treatment
- Safety: well tolerated (grade 1-2 rigors; grade 1 flu-like symptoms and fatigue)
- PR by RECIST ongoing at time of analysis

Courtesy of Dr. S. Ejadi, Scotsdale, AZ

PRESENTED AT: ASCO Annual '15 Meeting

Case #2: 72 y/o Clear cell carcinoma of the ovaries

- 2010: Stage 1a clear cell carcinoma of the ovaries; TAH-BSO. 1 cycle docetaxel-CBDCA
- Aug 2015: Recurrent disease RP nodes; bx confirmed
- Sept 2015- Feb 2016: ddTC; initial PR then PROG
- March 2016: MATCH trial: FO test amplification ERBB2: pertuzumab-trastuzumab with PROG
- June 2016: Gemcitabine and CDDP with PROG
- August 2016: Nivolumab

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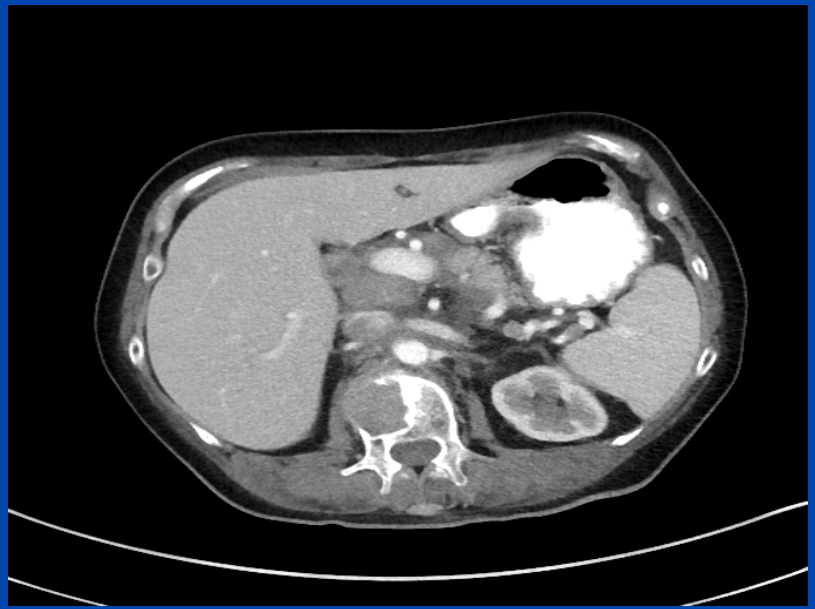
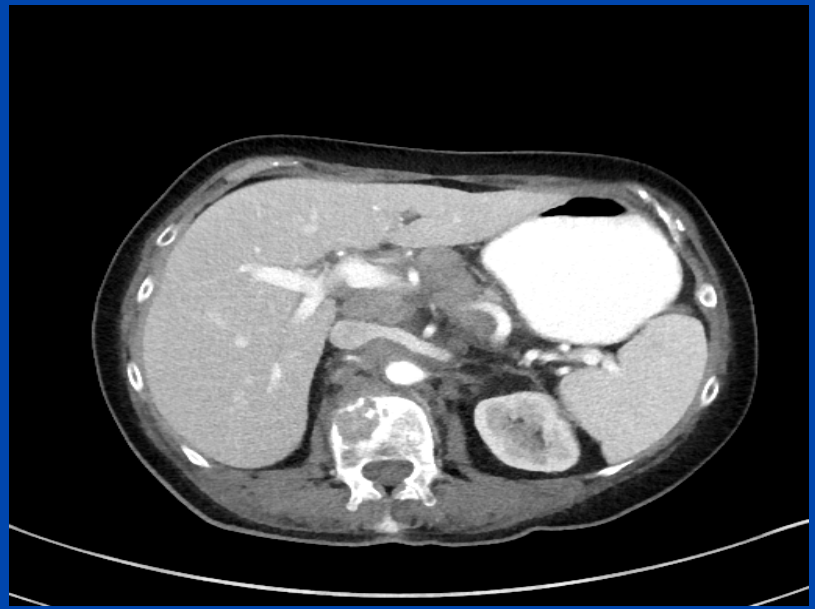
Case #2: 72 y/o female with Clear Cell Carcinoma Ovaries





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ONGOING STUDIES OVARIAN CANCER

Upfront checkpoint inhibitors plus chemotherapy (Phase 3 or Phase 2):

- Paclitaxel, carboplatin and bevacizumab +/- atezolizumab.
- Paclitaxel, carboplatin, bevacizumb +/-avelumab
- Pembrolizumab, paclitaxel and carboplatin (neo-adjuvant)

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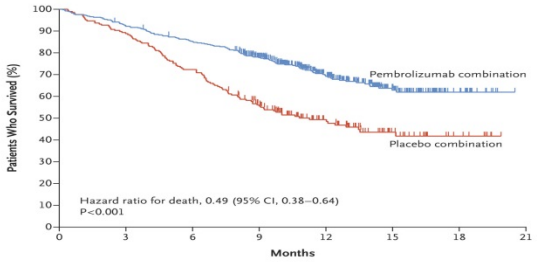
ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer

Leena Gandhi, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Shirish Gadgeel, M.B., B.S., Emilio Esteban, M.D., Enriqueta Felip, M.D., Ph.D., Flávia De Angelis, M.D., Manuel Domine, M.D., Ph.D., Philip Clingan, M.B., B.S., Maximilian J. Hochmair, Ph.D., Steven F. Powell, M.D., Susanna Y.-S. Cheng, M.D., Helge G. Bischoff, M.D., et al., for the KEYNOTE-189 Investigators*

April 16, 2018
DOI: 10.1056/NEJMoa1801005

A Overall Survival

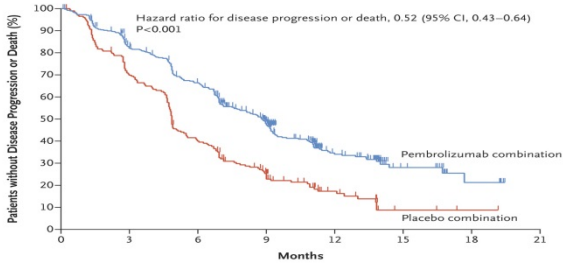


No. at Risk								
Pembrolizumab combination	410	377	347	278	163	71	18	0
Placebo combination	206	183	149	104	59	25	8	0

B Subgroup Analysis of Overall Survival

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Death (95% CI)
Overall	235/616	0.49 (0.38–0.64)
Age		
<65 yr	133/312	0.43 (0.31–0.61)
≥65 yr	102/304	0.64 (0.43–0.95)
Sex		
Male	143/363	0.70 (0.50–0.99)
Female	92/253	0.29 (0.19–0.44)
ECOG performance-status score		
0	74/266	0.44 (0.28–0.71)
1	159/346	0.53 (0.39–0.73)
Smoking status		
Current or former	211/543	0.54 (0.41–0.71)
Never	24/73	0.23 (0.10–0.54)
Brain metastases at baseline		
Yes	51/108	0.36 (0.20–0.62)
No	184/508	0.53 (0.39–0.71)
PD-L1 tumor proportion score		
<1%	84/190	0.59 (0.38–0.92)
≥1%	135/388	0.47 (0.34–0.66)
1–49%	65/186	0.55 (0.34–0.90)
≥50%	70/202	0.42 (0.26–0.68)
Platinum-based drug		
Carboplatin	176/445	0.52 (0.39–0.71)
Cisplatin	59/171	0.41 (0.24–0.69)

A Progression-free Survival



No. at Risk								
Pembrolizumab combination	410	322	256	149	60	17	5	0
Placebo combination	206	141	80	40	16	3	1	0

B Subgroup Analysis of Progression-free Survival

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Disease Progression or Death (95% CI)
Overall	410/616	0.52 (0.43–0.64)
Age		
<65 yr	224/312	0.43 (0.32–0.56)
≥65 yr	186/304	0.75 (0.55–1.02)
Sex		
Male	236/363	0.66 (0.50–0.87)
Female	174/253	0.40 (0.29–0.54)
ECOG performance-status score		
0	158/266	0.49 (0.35–0.68)
1	250/346	0.56 (0.43–0.72)
Smoking status		
Current or former	365/543	0.54 (0.43–0.66)
Never	45/73	0.43 (0.23–0.81)
Brain metastases at baseline		
Yes	81/108	0.42 (0.26–0.68)
No	329/508	0.53 (0.43–0.67)
PD-L1 tumor proportion score		
<1%	146/190	0.75 (0.53–1.05)
≥1%	238/388	0.44 (0.34–0.57)
1–49%	114/186	0.55 (0.37–0.81)
≥50%	124/202	0.36 (0.25–0.52)
Platinum-based drug		
Carboplatin	299/445	0.55 (0.44–0.70)
Cisplatin	111/171	0.44 (0.30–0.65)

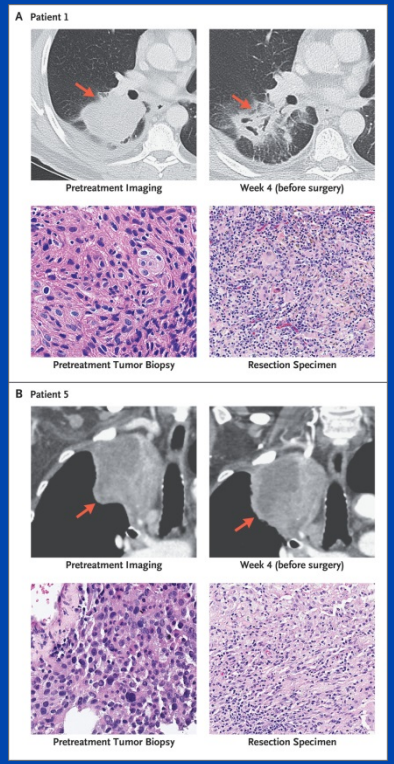
MAYO CLINIC

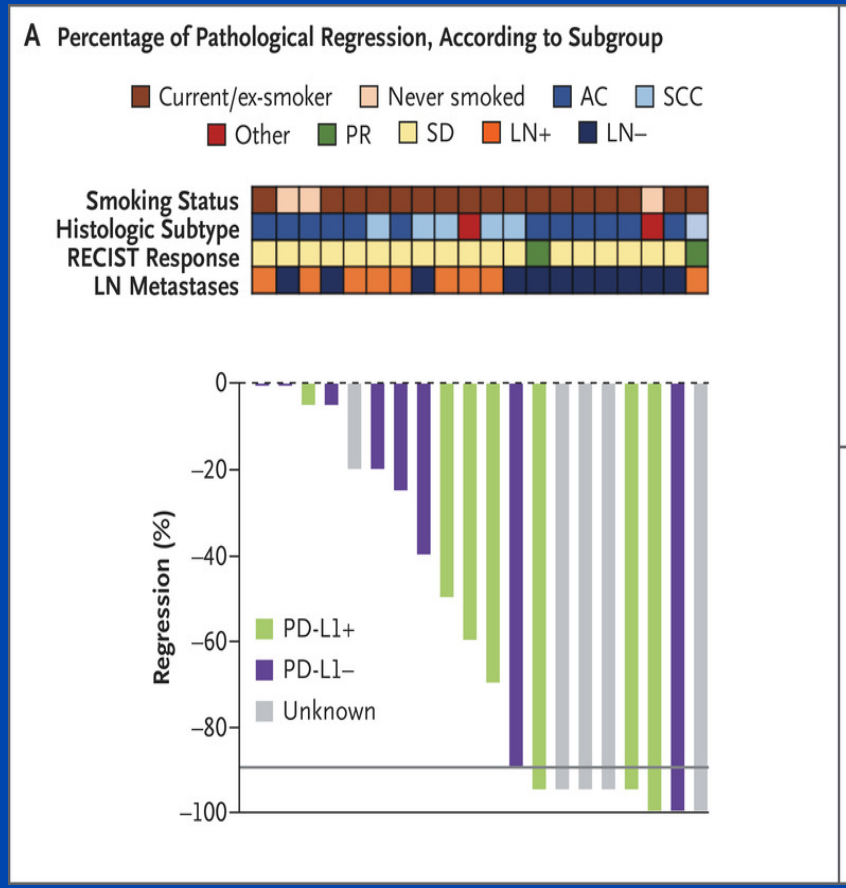
ORIGINAL ARTICLE

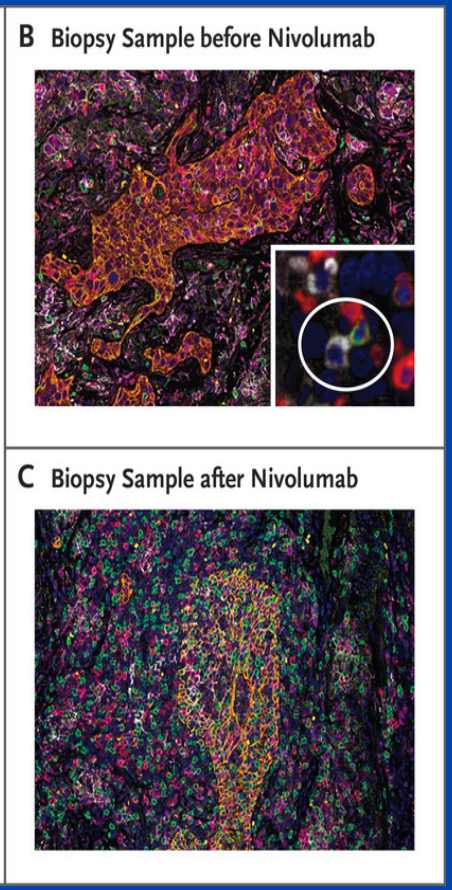
Neoadjuvant PD-1 Blockade in Resectable Lung Cancer

Patrick M. Forde, M.B., B.Ch., Jamie E. Chaft, M.D., Kellie N. Smith, Ph.D., Valsamo Anagnostou, M.D., Ph.D., Tricia R. Cottrell, M.D., Ph.D., Matthew D. Hellmann, M.D., Marianna Zahurak, M.S., Stephen C. Yang, M.D., David R. Jones, M.D., Stephen Broderick, M.D., Richard J. Battafarano, M.D., Ph.D., Moises J. Velez, M.D., et al.

April 16, 2018
DOI: 10.1056/NEJMoa1716078







Pembrolizumab plus standard neoadjuvant therapy for high-risk breast cancer: Results from the I-SPY 2 Trial

Rita Nanda, Minetta C. Liu, Douglas Yee, Angela M. DeMichele, Christina Yau, Smita M. Asare, Nola M. Hylton, Laura J. van't Veer, Jane Perlmutter, Anne M. Wallace, A. Jo Chien, Andres Forero-Torres, Erin D. Ellis, Heather S. Han, Amy S. Clark, Kathy S. Albain, Judy C. Boughey, Anthony D. Elias, **Claudine Isaacs, Kathleen Kemmer, Hope S. Rugo, Michelle Melisko, Fraser Symmans**, Donald A. Berry, Laura J. Esserman, I-SPY 2 TRIAL Investigators.

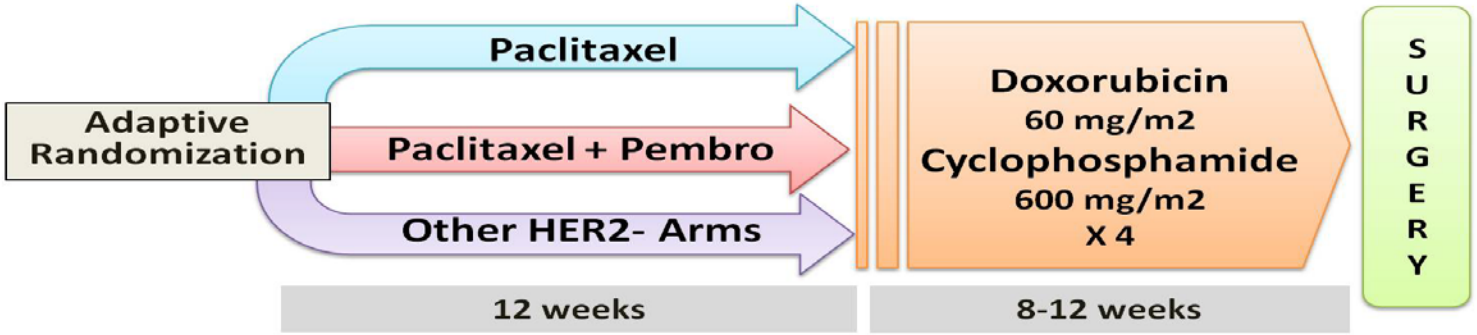
The Right Drug.
The Right Patient
The Right Time. Now.

I-SPY 2 TRIAL Eligibility

Screening

- Tumor size ≥ 2.5 cm
- Candidate for preoperative chemotherapy
- Study MRI and biopsy
- MammaPrint (MP)
- Adequate organ function, PS<2

I-SPY 2 TRIAL Schema: HER2- Signatures



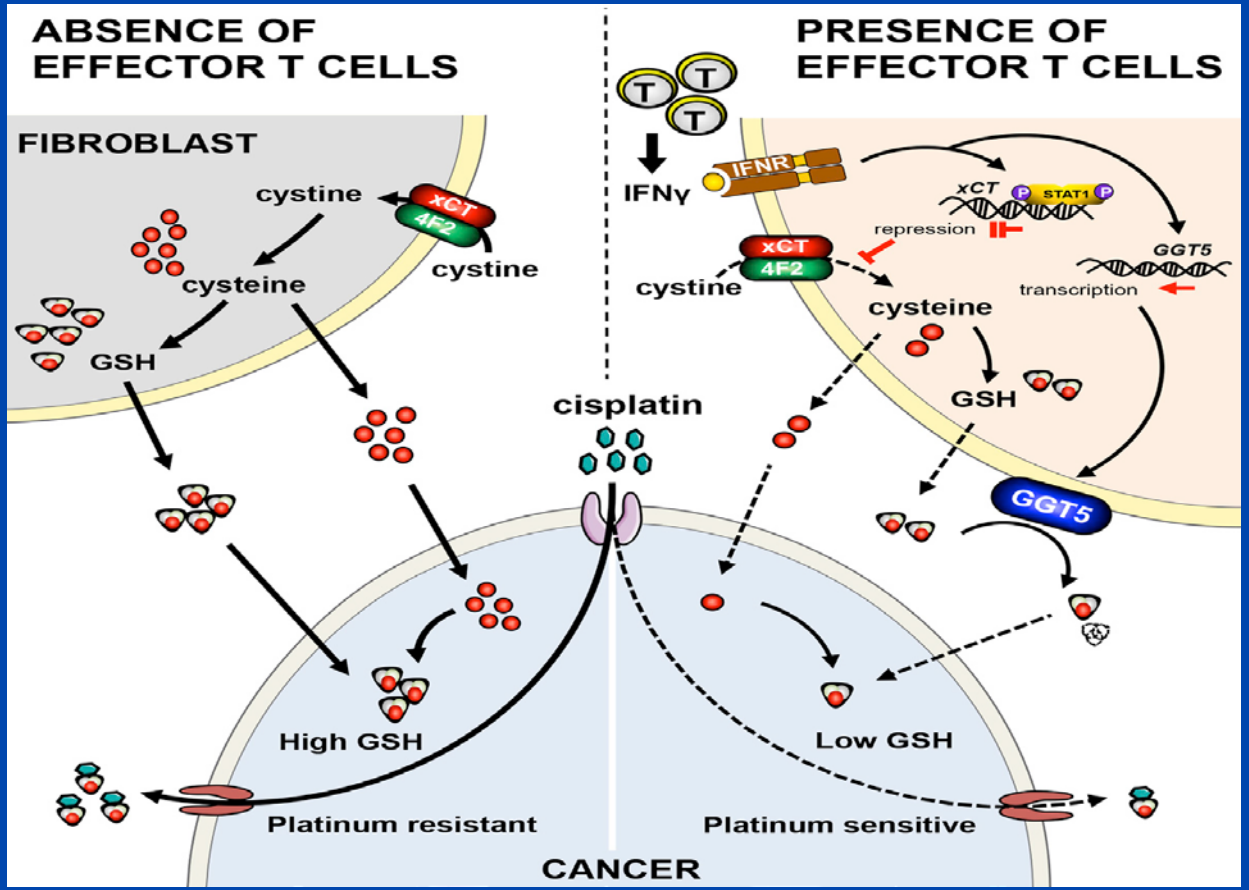
Control
Paclitaxel 80 mg/m2 every wk x 12

Experimental
Paclitaxel 80 mg/m2 every wk x 12
Pembro 200 mg every 3 wks x 4

Pembrolizumab graduated in all HER2- signatures: Both HR+/HER2- and TN

Signature	Estimated pCR rate (95% probabilty interval)		Probability pembro is superior to control	Predictive probability of success in phase 3
	Pembro	Control		
All HER2-	**0.46** (0.34 – 0.58)	**0.16** (0.06 – 0.27)	**> 99%**	**99%**
TNBC	**0.60** (0.43 – 0.78)	**0.20** (0.06 – 0.33)	**>99%**	**>99%**
HR+/HER2-	**0.34** (0.19 – 0.48)	**0.13** (0.03 – 0.24)	**>99%**	**88%**

The Bayesian model estimated pCR rates appropriately adjust to characteristics of the I-SPY 2 population.
The raw pCR rates (not shown) are higher than the model estimate of 0.604 in TNBC.



Wang et al., 2016, Cell 165, 1092–1105

OVARIAN CANCER: RELAPSED

- Avelumab +/- liposomal doxorubicin
- Liposomal doxorubicin +/- motolimod (Toll-like receptor 8 agonist)

MAYO CLINIC

OVARIAN CANCER STUDIES: Combination immunotherapies

- Durvalumab and motolimod (Toll-like receptor 8 agonist)
- Durvalumab and tremelimumab (CTLA-4 inhibitor)
- Nivolumab and INCB024360 (IDO1 inhibitor)

MAYO CLINIC

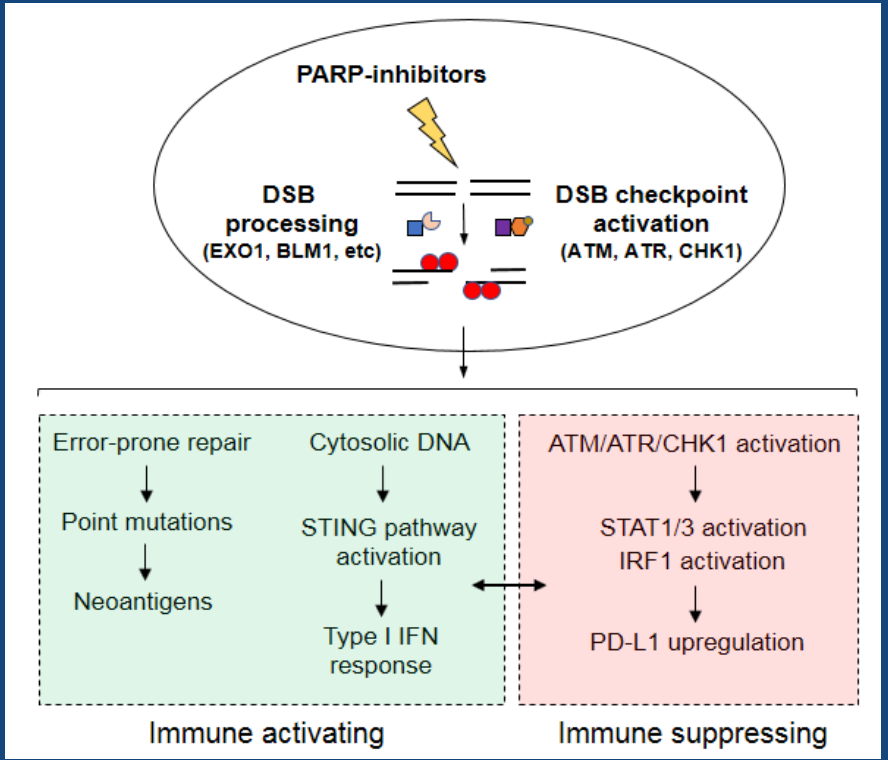
TOPACIO/Keynote-162 (NCT02657889)—A phase 1/2 study niraparib + pembrolizumab: results in platinum-resistant ovarian cancer (PROC) cohort

Panagiotis Konstantinopoulos,[1] Steven Waggoner,[2] Gregory A. Vidal,[3] Monica Mita,[4] Gini Fleming,[5] Robert Holloway,[6] Linda Van Le,[7] Jasgit Sachdev,[8] Eloise Chapman-Davis,[9] Gerardo Colon-Otero,[10] Richard Penson,[11] Ursula Matulonis,[12] Young Bae Kim,[13] Kathleen Moore,[14] Elizabeth Swisher,[15] Bruce Dezube,[16] Jing Yu Wang,[16] Nathan Buerstatte,[16] Sujata Arora,[16] Pamela Munster[17]

[1]Department of Medical Oncology, Medical Gynecologic Oncology Program, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; Center for DNA Damage and Repair, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [2]Department of Reproductive Medicine, Case Western Reserve University School of Medicine, University Hospitals of Cleveland, Cleveland, OH, USA; [3]The West Clinic, Memphis, TN, USA; [4]Cedars-Sinai Medical Center, Los Angeles, CA, USA; [5]Department of Medicine, The University of Chicago, Chicago, IL, USA; [6]Florida Hospital Gynecologic Oncology, Florida Hospital Cancer Institute and Global Robotics Institute, Orlando, FL, USA; [7]University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA; [8]Virginia G. Piper Cancer Center Clinical Trials, HonorHealth Research Institute and Translational Genomics Research Institute, Scottsdale, AZ, USA; [9]Weill Cornell Medicine, Cornell University, New York, NY, USA; [10]Mayo Clinic, Jacksonville, FL, USA; [11]Department of Medicine, Division of Hematology-Oncology, Massachusetts General Hospital, Boston, MA, USA; [12]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [13]Tufts Medical Center, Boston, MA, USA; [14]Stephenson Cancer Center, University of Oklahoma HSC; Sarah Cannon Research Institute, Nashville, TN, USA; [15]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Washington, Seattle, WA, USA; [16]TESARO, Inc., Waltham, MA, USA; [17]UCSF Medical Center at Mount Zion, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA.

Scientific Rationale for Niraparib and PD-1 Inhibitor

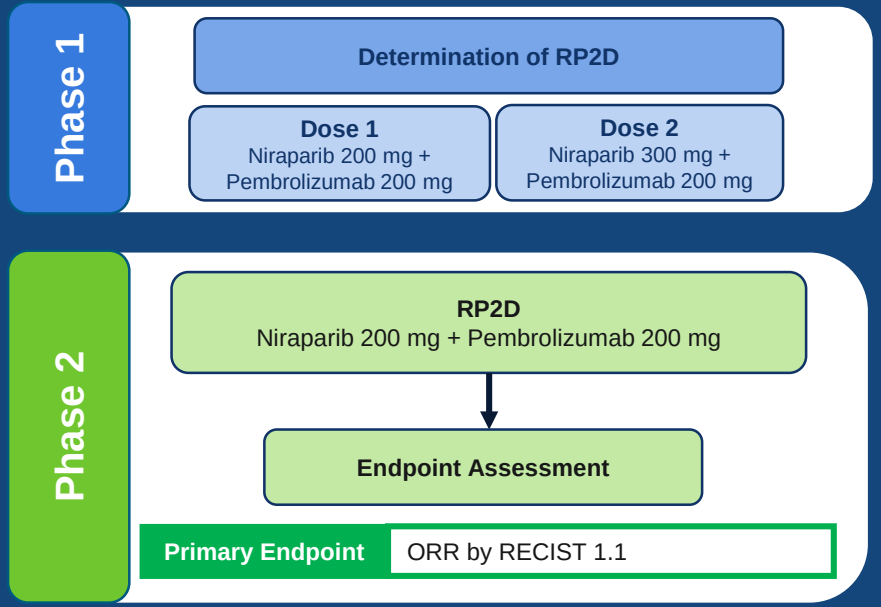
Preclinical models indicate synergy between PARPi + anti-PD-1 agents regardless of *BRCA* mutation status or PD-L1 expression



Mouw & Konstantinopoulos Brit Jour Canc 2018, Jiao et al. Clin Can Res 2017, Sato et al. Nature Commun 2017

TOPACIO Is a Phase 1/2 Study in Patients with PROC

Study Purpose: Evaluate the hypothesis that a PARPi combined with an anti-PD-1 will yield more robust efficacy than historical comparison to either drug alone in difficult-to-treat patient populations



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

TOPACIO Ovarian Cancer Patient Eligibility

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

Demographics & Baseline Characteristics

Characteristics, n (%)	Phase 1 & 2 N = 62
Age, median, years	60
ECOG performance status	
0	44 (71%)
1	18 (29%)
Prior therapies, median (range)	2 (1-5)
Previous bevacizumab therapy[1]	39 (63%)
Previous chemotherapy[2]	
Anthracycline	40 (65%)
Cyclophosphamide	5 (8%)
Gemcitabine	29 (47%)
Paclitaxel	60 (97%)
Platinum	62 (100%)
Topotecan	3 (5%)
Platinum Status	
Ineligible (PFI ≥6 months)	13 (21%)
Resistant (PFI 1 – 6 months)	31 (50%)
Refractory (PFI ≤1 month)	18 (29%)

[1]Of the 39 patients (63% of 62) who had previous bevacizumab, 7/39 (18%) were first line, 24/39 (62%) were recurrent, and 8/39 (20%) were both.
[2]Previous chemotherapy data refer to both first and subsequent lines, and include (neo)adjuvant therapy. PFI, progression-free interval.

Biomarker Status

Characteristics, n (%)	Phase 1 & 2 N = 62
t*BRCA* Status	
*BRCA*1mut	10 (16%)
*BRCA*2mut	2 (3%)
WT	48 (77%)
Unknown	2 (3%)
HRD Status	
HRDpos	24 (39%)
HRDneg	32 (52%)
Unknown	6 (10%)
PD-L1 Status	
Positive	35 (57%)
Negative	21 (34%)
Unknown	6 (10%)

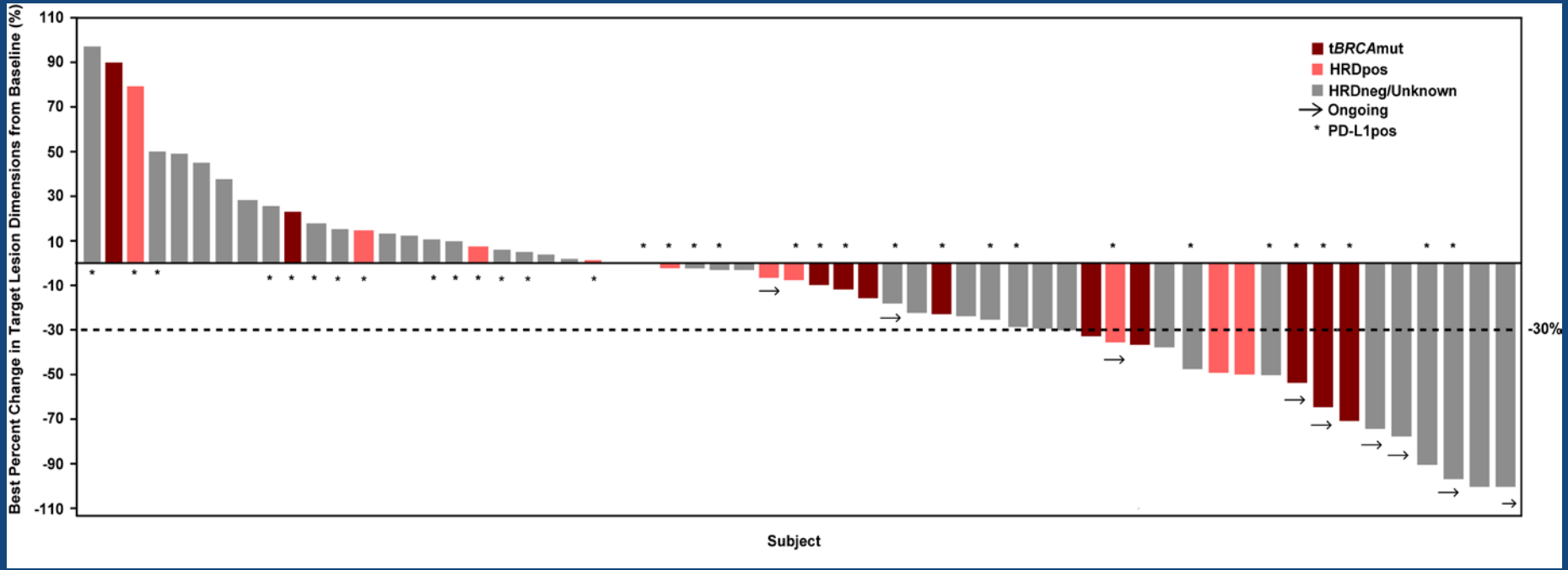
t*BRCA,* tumor *BRCA* (Myriad assay). HRD, homologous recombination deficiency.
HRD and t*BRCA* determined by Myriad assay; HRDpos includes *BRCA* mutation or HRD score ≥42; PD-L1 positive: ≥1% combined proportionality score.

TOPACIO Results of Evaluable Population

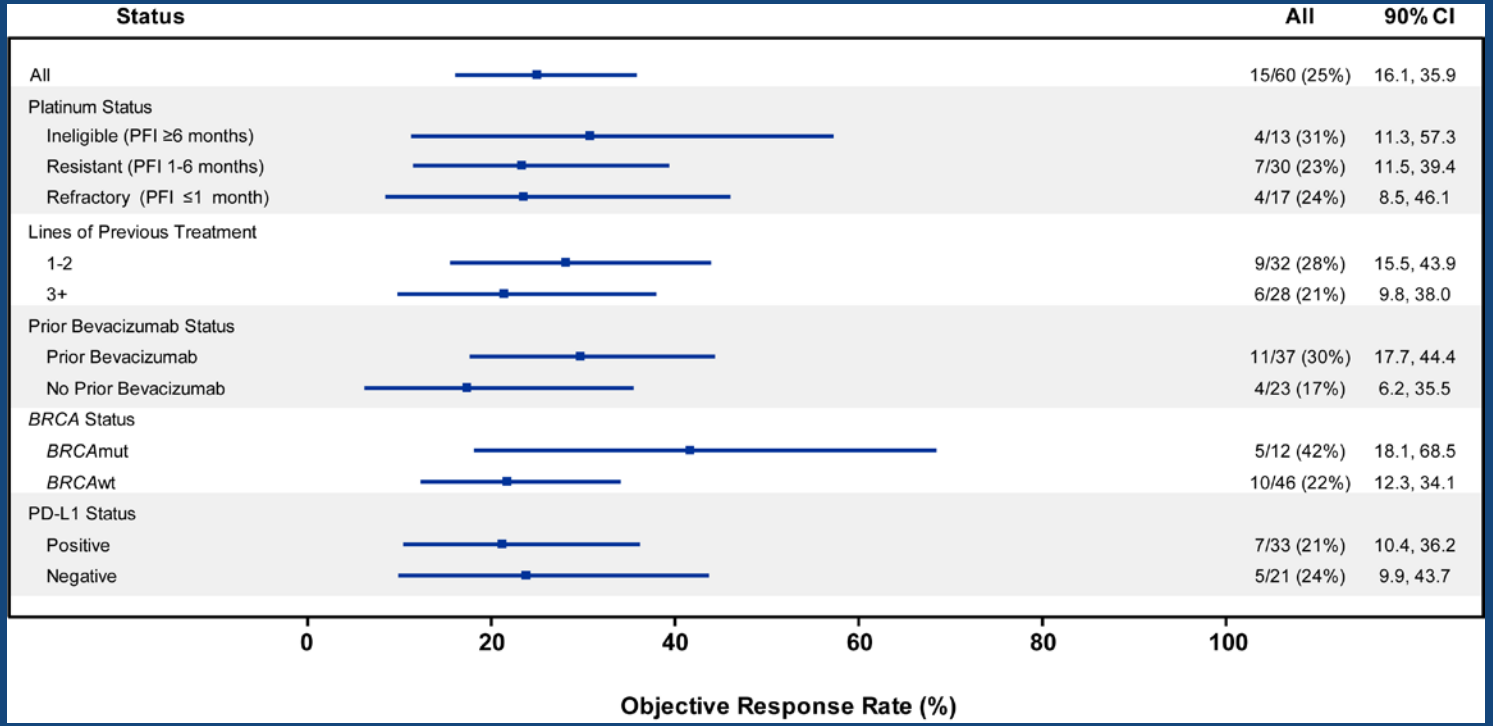
Evaluable patients*	Integrated Efficacy Analysis (combined phase 1+2) PROC Cohort N = 60 %	Still on Treatment, n
Complete response (CR)	3 (5%)	1
Partial response (PR)	12 (20%)	6
Stable disease (SD)	25 (42%)	2
Progressive disease (PD)	20 (33%)	
ORR (CR+PR)	25%	
Disease control rate (CR+PR+SD)	67%	

*Two patients were not evaluable for efficacy; evaluable patients had at least 1 on-treatment scan; responses include confirmed (11) and unconfirmed (4) responses; data as of 02 APR, 2018.

Niraparib + PD-1 Inhibitor Treatment Resulted in Clinical Activity Across a Broad Study Population



Clinical Activity of Niraparib + PD-1 Inhibitor Treatment Is Observed Across Multiple Patient Subsets



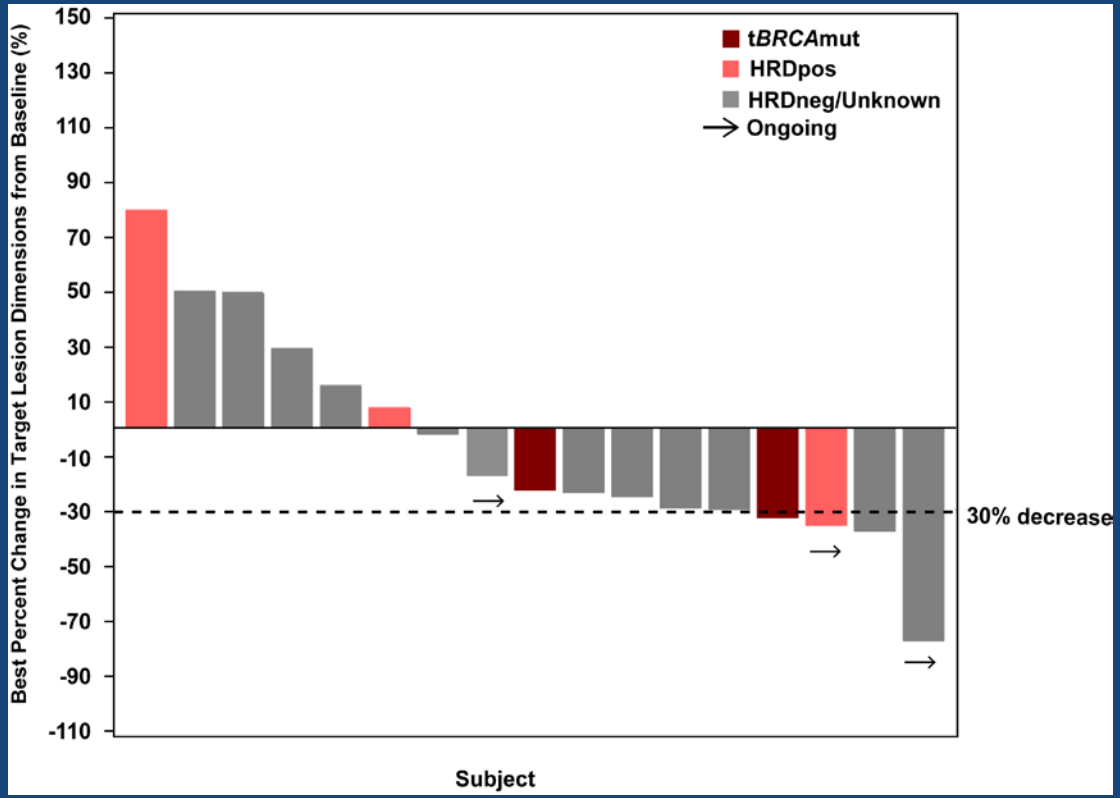
Clinical Activity Is Observed Across Biomarker Populations in Patients with Platinum-Resistant/Refractory Disease

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

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

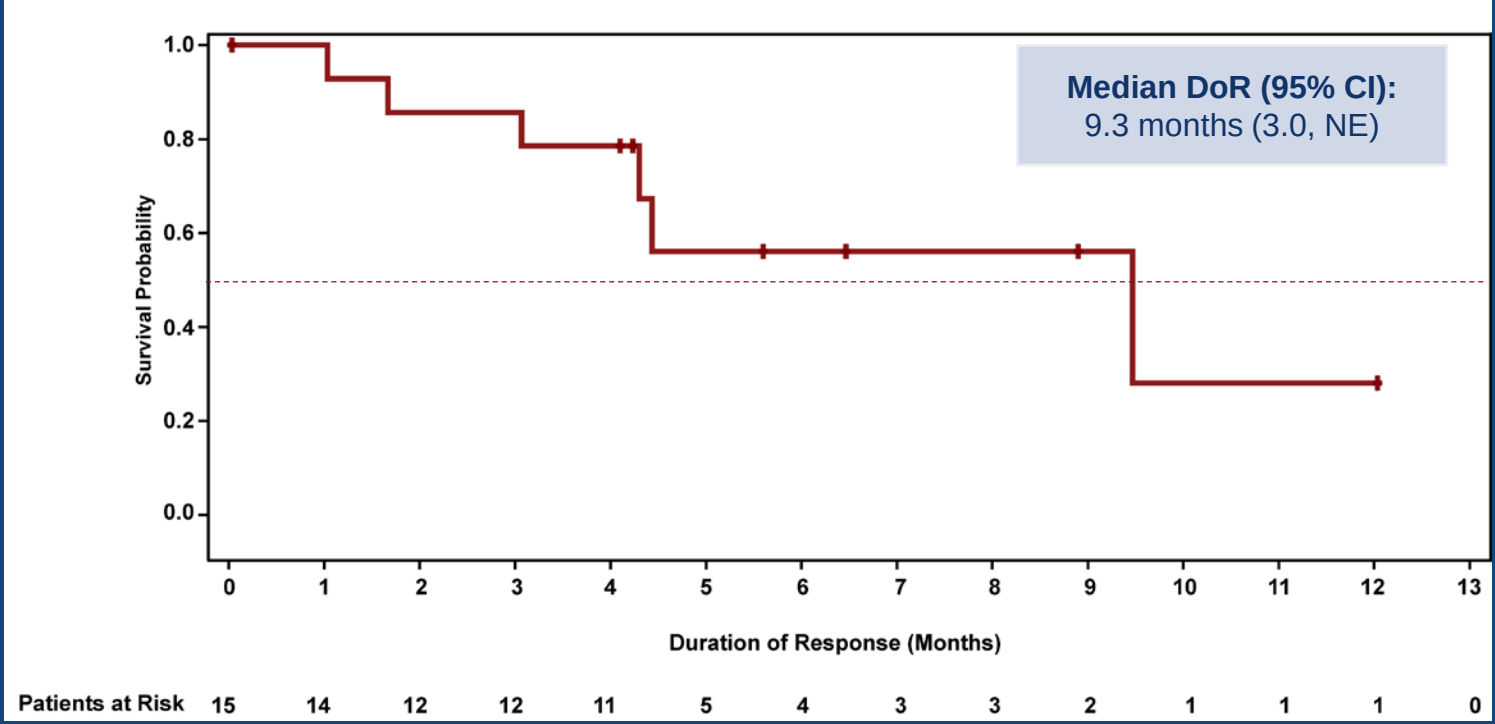
- The addition of pembrolizumab to niraparib in t*BRCA*wt and HRDneg led to ORR similar to PARPi efficacy in the t*BRCA*mut population
- HRD status does not correlate with response to this combination in platinum-resistant/-refractory disease

Response Observed in Platinum-Refractory Patients



- Evaluable platinum-refractory patients (n=17): ORR, 24%; DCR, 59%
- Biomarker-negative patients:
  - *BRCA*wt: ORR, 23%; DCR, 54%
  - HRDneg: ORR, 25%; DCR, 50%
- 2 of 4 responders still on treatment

Niraparib + PD-1 Inhibitor Treatment Produces Durable Responses Regardless of *BRCA* Status



Of 9 censored patients, 7 are ongoing; data as of 02 APR, 2018.

Ovarian cancer: Monoclonal antibodies and Immuno-conjugates

- FDA approved:

  Bevacizumab

- Under study:

  Farletuzumab

  Mirvetuximab soravtansine

  IMMU-132

  DNIB0600A

  Demcizumab

MAYO CLINIC

Ovarian cancer : Therapeutic vaccines

- ID-LV305, vaccine targeting NY-ESO-1, antigen expressed in 43%
- Vaccine targeting NY-ESO-1 plus decitabine
- P53 vaccine
- Dendritic cell vaccines

MAYO CLINIC

Ovarian cancer: Adoptive T-cell transfer

- T-cells genetically engineered to recognize NY-ESO-1
- T-cells genetically engineered to recognize MAGE-A3
- CAR-T trial targeting mesothelin.

MAYO CLINIC

Ovarian cancer: Oncolytic virus

- Randomized phase 2 Mayo trial: Modified measles virus that expresses the thyroidal sodium symporter gene (MV-NIS) in platinum resistant disease.

MAYO CLINIC

Case # 3: HPV related tumors: Cervical and vaginal cancers

- 77 y/o female with HPV related vaginal cancer
- 2014: 5 cm vaginal mass. RT and CDDP
- November 2015: Local recurrence, HPV16 positive. Rec: exenteration; declined chemotherapy.
- January 2016: Nivolumab for 12 months with regression (HPV negative).

MAYO CLINIC

Pembrolizumab in Patients with Advanced Cervical Cancer: Preliminary Results From the Phase 1b KEYNOTE-028 Study

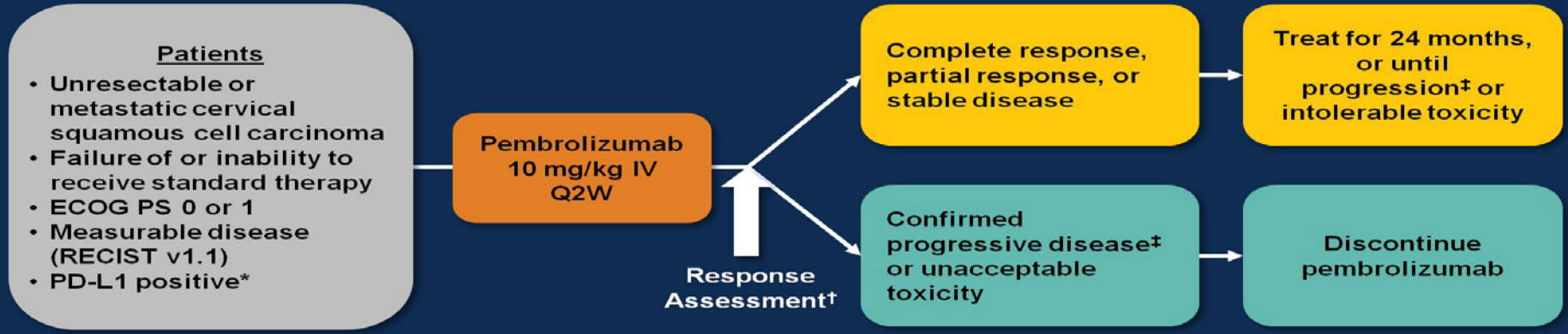
Jean-Sebastien Frenel,[1] Christophe Le Tourneau,[2] Bert O'Neil,[3] Patrick A. Ott,[4] Sarina Piha-Paul,[5] Carlos Gomez-Roca,[6] Emilie van Brummelen,[7] Hope Rugo,[8] Shari Thomas,[9] Sanatan Saraf,[9] Mei Chen,[9] Andrea Varga[10]

[1]Institut de Cancerologie de l'Ouest, Centre René Gauducheau, Saint-Herblain, France; [2]Institut Curie, Paris, France; [3]Indiana University Health University Hospital, Indianapolis, IN; [4]Dana-Farber Cancer Institute, Boston, MA; [5]The University of Texas MD Anderson Cancer Center, Houston, TX; [6]Institut Claudius Regaud, Toulouse, France; [7]The Netherlands Cancer Institute, Amsterdam, Netherlands; [8]University of California, San Francisco, San Francisco, CA; [9]Merck & Co., Inc., Kenilworth, NJ; [10]Gustave Roussy, Villejuif, France

PRESENTED AT: ASCO ANNUAL MEETING '16

Presented By Jean-Sebastien Frenel at 2016 ASCO Annual Meeting; J Clin Oncol. 2017 Dec 20;35(36):4035-4041. doi: 10.1200/JCO.2017.74.5471. Epub 2017 Nov 2.

KEYNOTE-028 (NCT02054806): Phase 1b Multicohort Study of Pembrolizumab for PD-L1–positive Advanced Solid Tumors



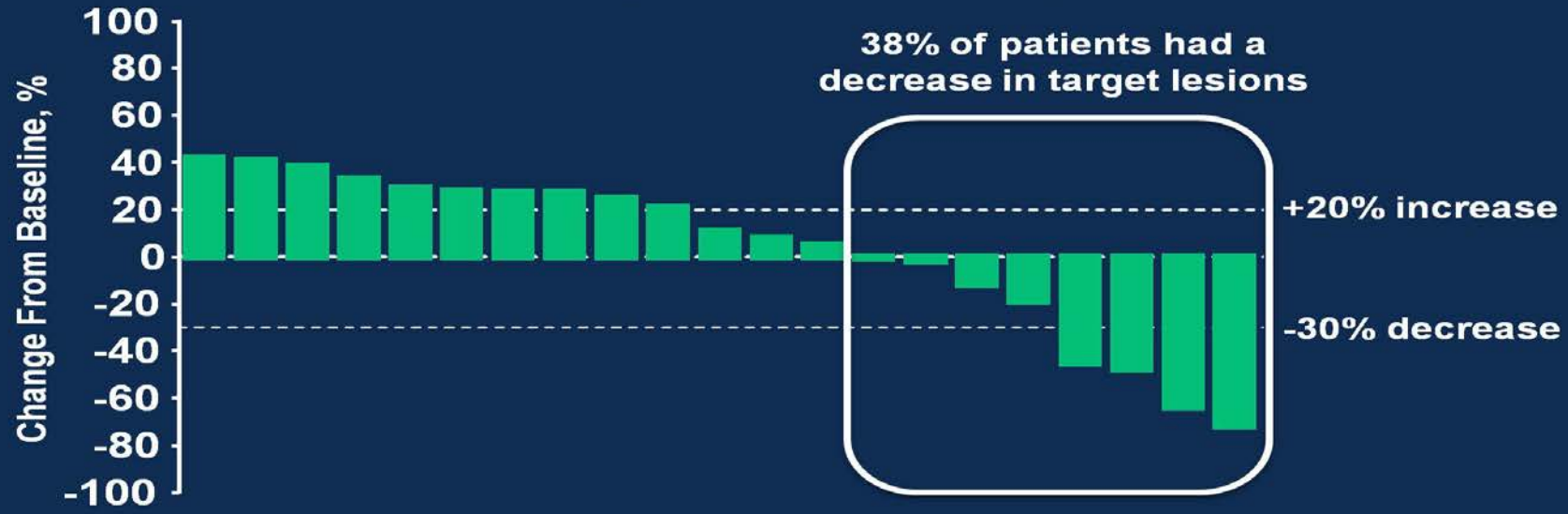
†**Response assessment:** Every 8 weeks for the first 6 months; every 12 weeks thereafter
Primary end points: ORR per RECIST v1.1 and safety
Secondary end points: PFS, OS, duration of response

*Membranous PD-L1 expression in ≥1% of tumor or stromal cells using a prototype IHC assay and 22C3 antibody (Merck). ‡Clinically stable patients were allowed to remain on pembrolizumab until progressive disease was confirmed on a second scan performed ≥4 weeks later. Patients who experienced progression after discontinuing pembrolizumab were eligible for up to 1 year of additional treatment if no other anticancer therapy was received.

ASCO ANNUAL MEETING '16

Jean-Sebastien Frenel,[1] Christophe Le Tourneau,[2] Bert O'Neil,[3] Patrick A. Ott,[4] Sarina Piha-Paul,[5] Carlos Gomez-Roca,[6] Emilie van Brummelen,[7] Hope Rugo,[8] Shari Thomas,[9] Sanatan Saraf,[9] Mei Chen,[9] Andrea Varga[10]

Best Change From Baseline in Tumor Size (RECIST v1.1, Investigator Review)



PRESENTED AT: ASCO ANNUAL MEETING '16

Data cutoff date: Feb 17, 2016.
Patients who received ≥1 dose of pembrolizumab, had a baseline scan with measurable disease per RECIST v1.1, and a post-baseline assessment are included (n = 21).

MAYO CLINIC

Presented By Jean-Sebastien Frenel at 2016 ASCO Annual Meeting

ASCO -2018

Pembrolizumab Treatment of Advanced Cervical Cancer: Updated Results from the Phase 2 KEYNOTE-158 Study

H.C. Chung[1]; J.H.M. Schellens[2]; J-P. Delord[3]; R. Perets[4]; A. Italiano[5]; R. Shapira-Frommer[6]; L. Manzuk[7]; S.A. Piha-Paul[8]; J.D. Wang[9]; S. Zeigenfuss[9]; S.K. Pruitt[9]; A. Marabelle[10]

[1]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; [2]Antoni van Leeuwenhoek Ziekenhuis, Amsterdam, The Netherlands; [3]Institut Claudius Regaud, IUCT-Oncopole, Toulouse, France; [4]Rambam Health Care Campus, Haifa, Israel; [5]Institut Bergonie, Bordeaux, France; [6]Sheba Medical Center, Ramat-Gan, Israel; [7]N.N. Blokhin NMRCO, Moscow, Russia; [8]MD Anderson Cancer Center, Houston, TX, USA; [9]Merck & Co., Inc., Kenilworth, NJ, USA; [10]Gustave Roussy, Villejuif, France

INTRODUCTION

- Pembrolizumab is a humanized, monoclonal antibody that prevents PD-1 from binding to its ligands, PD-L1 and PD-L2
- In the multicohort, phase 1b KEYNOTE-028 study, pembrolizumab monotherapy showed promising antitumor activity and manageable safety in patients with previously treated, PD-L1–positive advanced cervical cancer (N = 24)[1]
  - Objective response rate (ORR): 17% (95% confidence interval [CI], 5-37)
  - Duration of response: median 28 weeks (range, 18-52)
  - Safety: 21% incidence of grade 3-4 adverse events (AEs), no treatment-related mortality, 2 treatment-related discontinuations
- Preliminary data from the first 82 patients with previously treated, advanced cervical cancer enrolled in KEYNOTE-158[2] regardless of PD-L1 expression showed generally consistent results compared with KEYNOTE-028[1]
  - ORR: 12% (95% CI, 6-21), including 3 patients with complete response
  - All 10 responses were ongoing at the time of data cutoff
  - The safety profile was consistent with that previously observed for pembrolizumab in patients with advanced cancer
- We explored the efficacy and safety of pembrolizumab monotherapy in all 98 patients with previously treated advanced cervical cancer enrolled in the phase 2 KEYNOTE-158 study

OBJECTIVES

- Evaluate the antitumor activity, including the ORR, duration of response, progression-free survival (PFS) and overall survival (OS) of pembrolizumab monotherapy in patients with previously treated advanced cervical carcinoma
- Evaluate the safety profile of pembrolizumab monotherapy in patients with previously treated advanced cervical carcinoma

METHODS

Study Design, Patients, and Treatment

- KEYNOTE-158: ongoing, international, multicohort, open-label, phase 2 study of pembrolizumab in select advanced solid tumors that have progressed on standard-of-care therapy (ClinicalTrials.gov, NCT02628067)
- Key eligibility criteria for the cervical cancer cohort: age ≥18 years, histologically or cytologically confirmed advanced cervical cancer, progression on or intolerance to ≥1 line of standard therapy, Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1, and provision of a tumor sample for biomarker analysis (patients were enrolled regardless of biomarker expression)
- Treatment: pembrolizumab 200 mg once every 3 weeks (Q3W) for 2 years or until disease progression, intolerable toxicity, patient withdrawal, or investigator decision
  - Clinically stable patients with radiologic progression could remain on treatment until progression was confirmed on subsequent imaging assessment, or if clinically stable with approval from the Sponsor

Assessments

- Response: assessed per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) every 9 weeks for the first 12 months and every 12 weeks thereafter
- AEs and laboratory abnormalities: monitored throughout treatment and for 30 days (90 days for serious AEs) thereafter and graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0
- Tumor PD-L1 expression:
  - Assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies)
  - Scoring system: combined positive score (CPS), defined as the number of PD-L1–positive cells (tumor cells, lymphocytes, and macrophages) out of the total number of tumor cells x 100
  - Protocol-specified cutoff for positivity: CPS ≥1

Statistical Considerations

- End points
  - Primary: ORR assessed per RECIST v1.1 by independent central review
  - Secondary: duration of response and PFS assessed per RECIST v1.1 by independent central review and OS
- Analysis population for efficacy and safety: patients who received ≥1 dose of pembrolizumab
  - Patient disposition, baseline characteristics, and AEs: descriptive statistics provided
  - ORR: point estimate and binomial exact confidence intervals (CIs) provided
  - Duration of response, PFS and OS: Kaplan-Meier method
- Data cutoff date: January 15, 2018
  - Median follow-up (time from first dose to date of death or data cutoff, whichever occurred first): 10.2 months (range, 0.6 to 22.7)

RESULTS

Patients

Figure 1. Patient Disposition

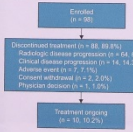


Table 1. Baseline Demographics and Disease Characteristics

Characteristic	N = 98
Age, years, median (range)	46.0 (24 to 75)
<65 years, n (%)	90 (91.8)
ECOG performance status 1, n (%)	64 (65.3)
Stage M1 disease, n (%)	92 (93.9)
PD-L1–positive tumor, n (%)	82 (83.7)
Baseline tumor size,[a] mm, median (range)	58.4 (10.2-305.1)
Prior (neo)adjuvant therapy, n (%)	21 (21.4)
No. prior therapies for recurrent/metastatic disease, n (%)	
Adjuvant/Neoadjuvant	4 (4.1)
1	30 (30.6)
2	34 (34.7)
3	16 (16.3)
≥4	14 (14.3)

[a]Sum of the longest diameters of target lesions.

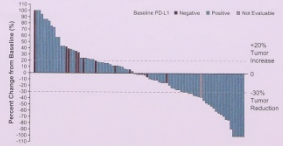
Efficacy

Table 2. Summary of Response Assessed per RECIST v1.1 by Independent Central Review

	Overall[b]	PD-L1 Positive	PD-L1 Negative
Total population	N = 98	n = 82	n = 15
ORR,[a] % (95% CI)	12.2 (6.5-20.4)	14.6 (7.8-24.2)	0 (0-21.8)
Best overall response, n (%)			
Complete response	3 (3.1)	3 (3.7)	0 (0.0)
Partial response	9 (9.2)	9 (11.0)	0 (0.0)
Stable disease	18 (18.4)	15 (18.3)	3 (20.0)
Progressive disease	55 (56.1)	44 (53.7)	10 (66.7)
Nonevaluable[c]	5 (5.1)	4 (4.9)	1 (6.7)
No assessment[d]	8 (8.2)	7 (8.5)	1 (6.7)
Patients with response	n = 12	n = 12	n = 0
Time to response, months, median (range)	2.1 (1.6 to 4.1)	2.1 (1.6 to 4.1)	—
Responders without subsequent disease progression, n (%)	6 (50.0)	6 (50.0)	—
Duration of response, months, median (range)	NR (3.7+ to 18.6+)	NR (3.7+ to 18.6+)	—

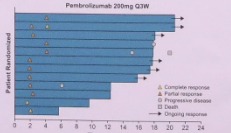
CI, confidence interval; NR, not reached.
[a]Includes 2 patients with unknown tumor PD-L1 expression level.
[b]At the time of analysis, all responses were confirmed.
[c]Patients for whom not all target lesions were captured on ≥1 postbaseline imaging assessment.
[d]Patients for whom no postbaseline tumor assessment was performed.

Figure 2. Best Percentage Change From Baseline in Target Lesion Size Assessed per RECIST v1.1 by Independent Central Review



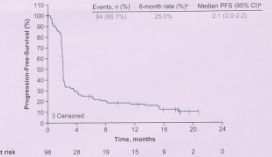
Includes patients who had ≥1 evaluable postbaseline tumor assessment (n = 86). Changes from baseline >100% were truncated at 100%.

Figure 3. Time to and Duration of Response Assessed per RECIST v1.1 by Independent Central Review



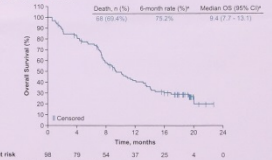
Includes patients whose best overall response was complete or partial response. The length of the bars represents the time to the last imaging assessment.

Figure 4. Progression-Free Survival Assessed per RECIST v1.1 by Independent Central Review



[a]From product-limit (Kaplan-Meier) method for censored data.

Figure 5. Overall Survival



[a]From product-limit (Kaplan-Meier) method for censored data.

Exposure and Safety

Table 3. Treatment-Related AEs of Any Grade That Occurred in ≥5 Patients or of Grade 3-4 That Occurred in ≥2 Patients

	N = 98	
	Any Grade	Grade 3-4
Any,[a] n (%)	64 (65.3)	12 (12.2)
Led to death, n (%)	0	0
Specific events, n (%)		
Hypothyroidism	10 (10.2)	0
Decreased appetite	9 (9.2)	0
Fatigue	9 (9.2)	0
Diarrhea	8 (8.2)	1 (1.0)
Aspartate aminotransferase increased	7 (7.1)	2 (2.0)
Asthenia	7 (7.1)	1 (1.0)
Pyrexia	7 (7.1)	1 (1.0)
Hyperthyroidism	7 (7.1)	0
Arthralgia	6 (6.1)	1 (1.0)
Nausea	6 (6.1)	0
Pruritus	6 (6.1)	0
Rash	6 (6.1)	0
Vomiting	6 (6.1)	0
Abdominal pain	5 (5.1)	0
Alanine aminotransferase increased	3 (3.1)	3 (3.1)

[a]Four patients (4.1%) discontinued pembrolizumab because of treatment-related AEs.

Table 4. Immune-Mediated AEs and Infusion Reactions That Occurred in ≥1 Patient[a]

	N = 98	
	Any Grade	Grade 3-4
Any, n (%)	25 (25.5)	5 (5.1)
Led to death, n (%)	0	0
Specific events, n (%)		
Hypothyroidism	11 (11.2)	0
Hyperthyroidism	9 (9.2)	0
Infusion reactions	3 (3.1)	0
Colitis	2 (2.0)	0
Hepatitis	2 (2.0)	2 (2.0)
Severe skin reactions	2 (2.0)	2 (2.0)
Adrenal insufficiency	1 (1.0)	1 (1.0)
Myositis	1 (1.0)	0
Pneumonitis	1 (1.0)	0
Uveitis	1 (1.0)	0

[a]Events were based on a list of terms specified at the time of analysis and were included regardless of attribution to study treatment or immune relatedness by the investigator. Related terms were included.

CONCLUSIONS

- Data from all 98 patients with previously treated, advanced cervical cancer enrolled in KEYNOTE-158 showed an ORR of 12.2%, including 3 patients with complete response
- For the 82 patients with PD-L1–positive tumors, the ORR was 14.6%, with no responses observed in the 15 patients with PD-L1–negative tumors
- Responses were durable, with a median duration of response that had not been reached. 6/12 responses were ongoing at the time of data cutoff
- Results were generally consistent with those previously observed in KEYNOTE-028 for pembrolizumab in patients with PD-L1–positive advanced cervical cancer[1] and with earlier data from KEYNOTE-158[2]
- The safety profile was consistent with that previously observed for pembrolizumab in patients with advanced cancer

References

1. Frenel JS et al. *J Clin Oncol* 2017;35(36):4035-4041.
2. Schellens JHM et al. *J Clin Oncol* 2017;35 15suppl):Abstr 5514.

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KEYNOTE-158

- 98 patients with recurrent metastatic cervical cancer
- PDL1 positive tumors with combined positive score of 1 or greater; 77 patients
- Median age : 45
- 65% had received 2 or more prior chemotherapies
- Median follow up of 11.7 months
- ORR: 14.3%
- 91% duration response over 6 months

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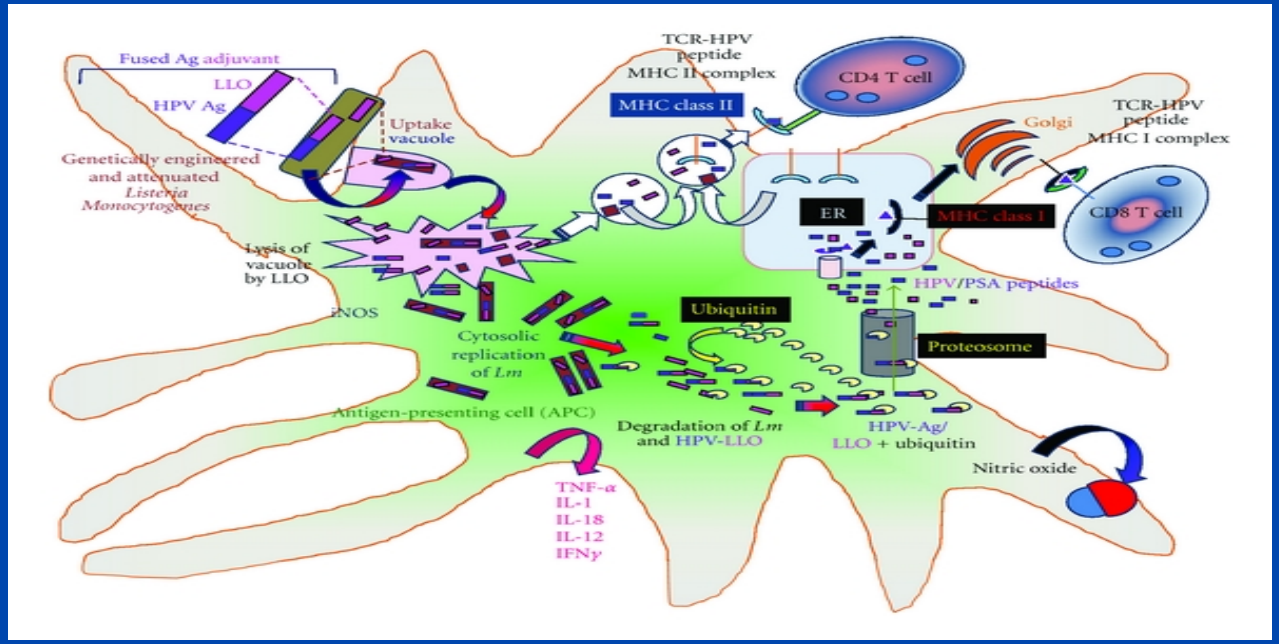
Cervical cancer – ADXS-11-001 plus MEDI



SUMMARY

Subset of patients who obtain long-lasting benefit to checkpoint inhibitor therapy:

- MMR deficient
- HPV- related cervical cancers (PDL-1 positive)
- Subsets of ovarian cancer

Combination treatments under study

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Thank you!

Come visit us in Jacksonville!

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Questions & Discussion