Targeted Agents and Chemotherapy in Gynecologic Malignancies in 2018

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Disclosures

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

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GOALS

- Review potentially practice changing new data presented in Society of Gynecologic Oncology meeting (SGO) in March 2018, AACR April 2018 and new publications 2017-18.
- Incorporate that data into the standard care of gynecologic cancers.

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Gynecologic cancers 2018

- Ovarian cancer
- 22,240 new cases
- 14,070 deaths
- Endometrial cancer
- 63, 230 new cases
- 11,350 deaths
- Cervical, vaginal, vulvar cancers
- 24,800 new cases
- 6,700 deaths

Total Gyn cancers

110,000 new cases

32,000 deaths

Siegel: Ca 68 (1): 7-10, 2018

MAYO CLINIC

Siegel: Ca 68 (1): 7-10, 2018

Estimated New Cases

Males				Females		
Prostate	164,690	19%		Breast	266,120	30%
Lung & bronchus	121,680	14%		Lung & bronchus	112,350	13%
Colon & rectum	75,610	9%		Colon & rectum	64,640	7%
Urinary bladder	62,380	7%		Uterine corpus	63,230	7%
Melanoma of the skin	55,150	6%		Thyroid	40,900	5%
Kidney & renal pelvis	42,680	5%		Melanoma of the skin	36,120	4%
Non-Hodgkin lymphoma	41,730	5%		Non-Hodgkin lymphoma	32,950	4%
Oral cavity & pharynx	37,160	4%		Pancreas	26,240	3%
Leukemia	35,030	4%		Leukemia	25,270	3%
Liver & intrahepatic bile duct	30,610	4%		Kidney & renal pelvis	22,660	3%
All Sites	**856,370**	**100%**		**All Sites**	**878,980**	**100%**

Estimated Deaths

Males				Females		
Lung & bronchus	83,550	26%		Lung & bronchus	70,500	25%
Prostate	29,430	9%		Breast	40,920	14%
Colon & rectum	27,390	8%		Colon & rectum	23,240	8%
Pancreas	23,020	7%		Pancreas	21,310	7%
Liver & intrahepatic bile duct	20,540	6%		Ovary	14,070	5%
Leukemia	14,270	4%		Uterine corpus	11,350	4%
Esophagus	12,850	4%		Leukemia	10,100	4%
Urinary bladder	12,520	4%		Liver & intrahepatic bile duct	9,660	3%
Non-Hodgkin lymphoma	11,510	4%		Non-Hodgkin lymphoma	8,400	3%
Kidney & renal pelvis	10,010	3%		Brain & other nervous system	7,340	3%
All Sites	**323,630**	**100%**		**All Sites**	**286,010**	**100%**

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Gynecologic cancers 2018

- Ovarian cancer
- 22,240 new cases
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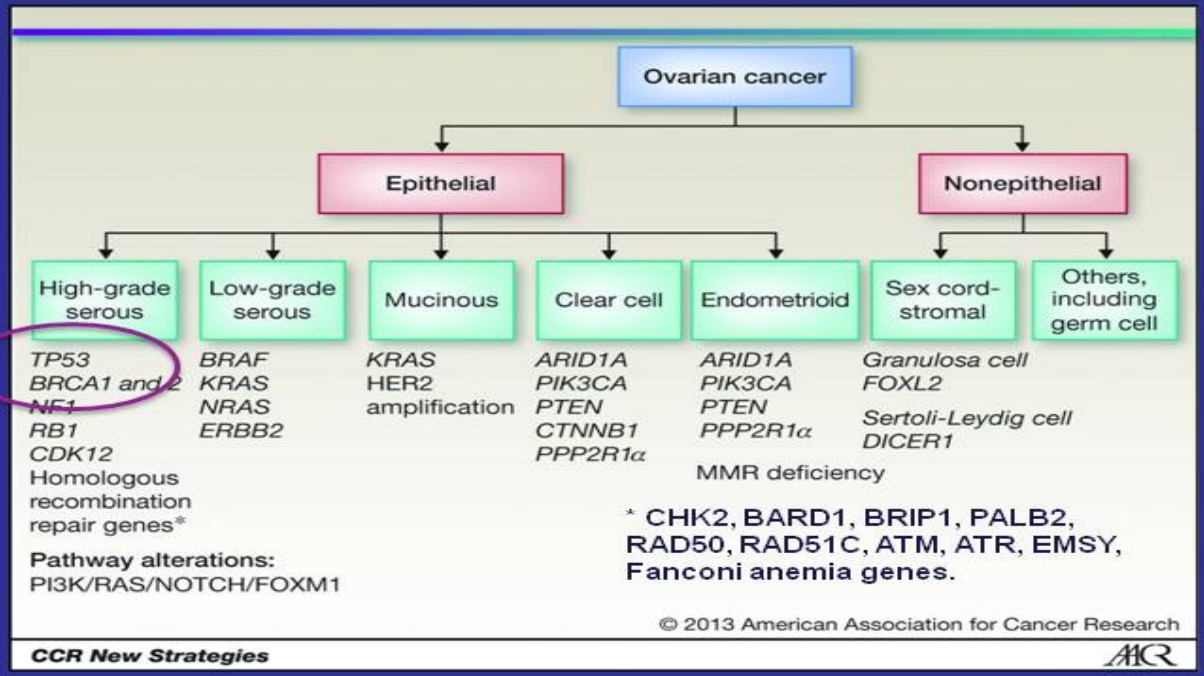
MAYO CLINIC

Targets in Ovarian Cancer: Mutations and Molecular Aberrations

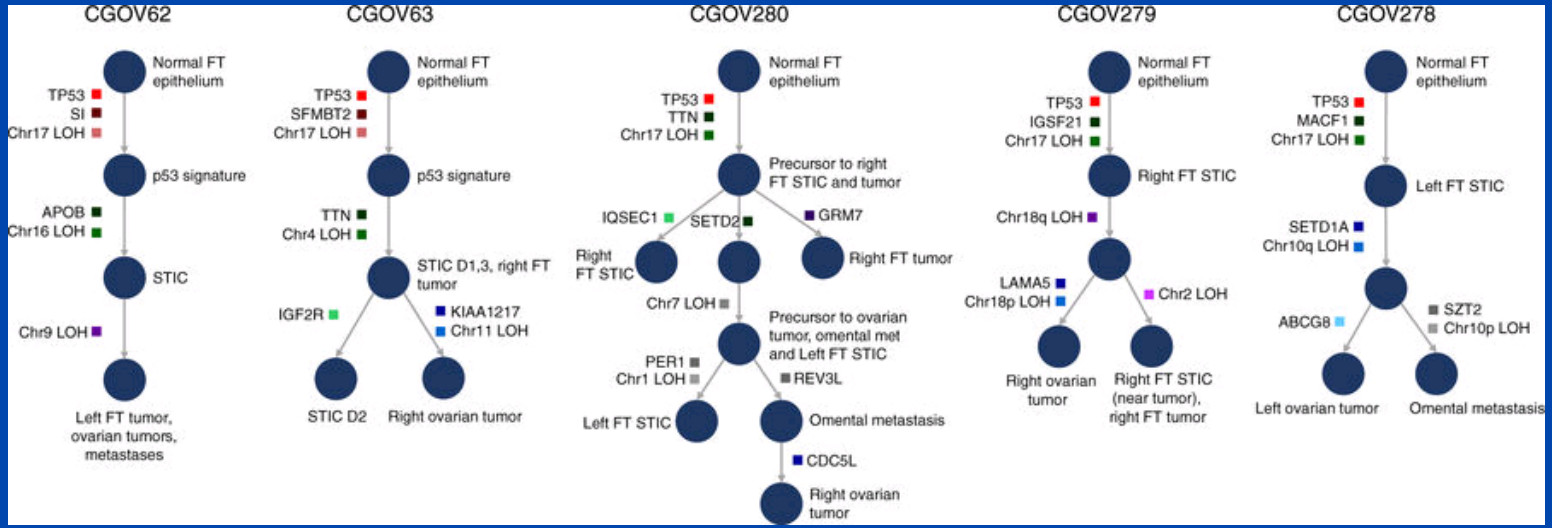


Banerjee S, and Kaye S B Clin Cancer Res 19: 2013

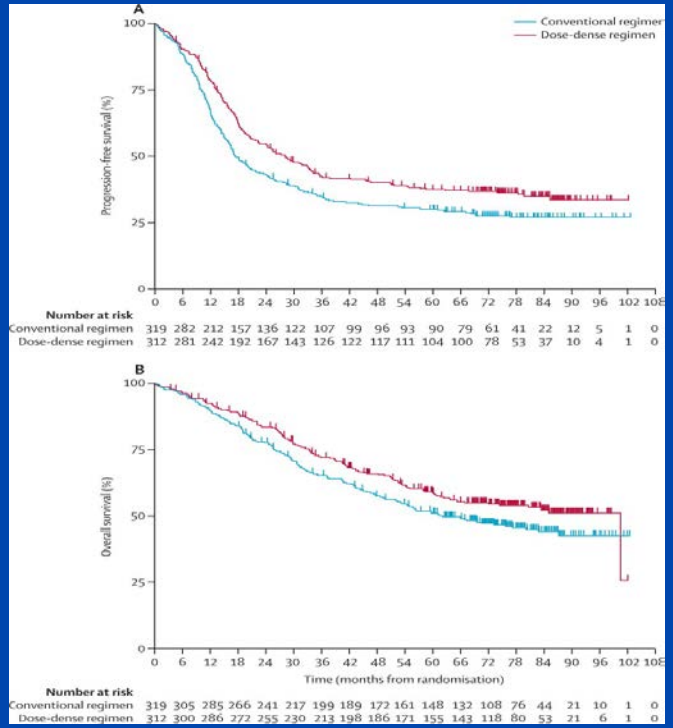
PRESENTED AT: ASCO Annual '13 Meeting

Presented By Paul Sabbatini, MD at 2013 ASCO Annual Meeting

Labidi-Galy et al: Nature Comm 2017; 8: 1093.



Katsumata et al: Lancet Oncology 2013



Ovarian cancer: High grade serous carcinomas

- Neo-adjuvant chemotherapy vs upfront debulking surgery followed by adjuvant chemotherapy
- IP chemotherapy vs dose dense chemotherapy vs weekly chemotherapy vs every 3 weeks IV chemotherapy
- HIPEC during interim debulking surgery (NEJM 2017)

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Chemotherapy or upfront surgery for newly diagnosed advanced ovarian cancer

Results from the MRC CHORUS trial

S Kehoe, JM Hook, M Nankivell, GC Jayson, HC Kitchener, T Lopes, D Luesley, TJ Perren, S Bannoo, M Mascarenhas, S Dobbs, S Essapen, J Twigg, J Herod, WG McCluggage, M Parmar, AM Swart on behalf of the CHORUS trial collaborators and NCRI Gynaecological Cancer Studies Group

Presented at the 2013 ASCO Annual Meeting. Presented data is the property of the author.

Deaths within 28 days of surgery

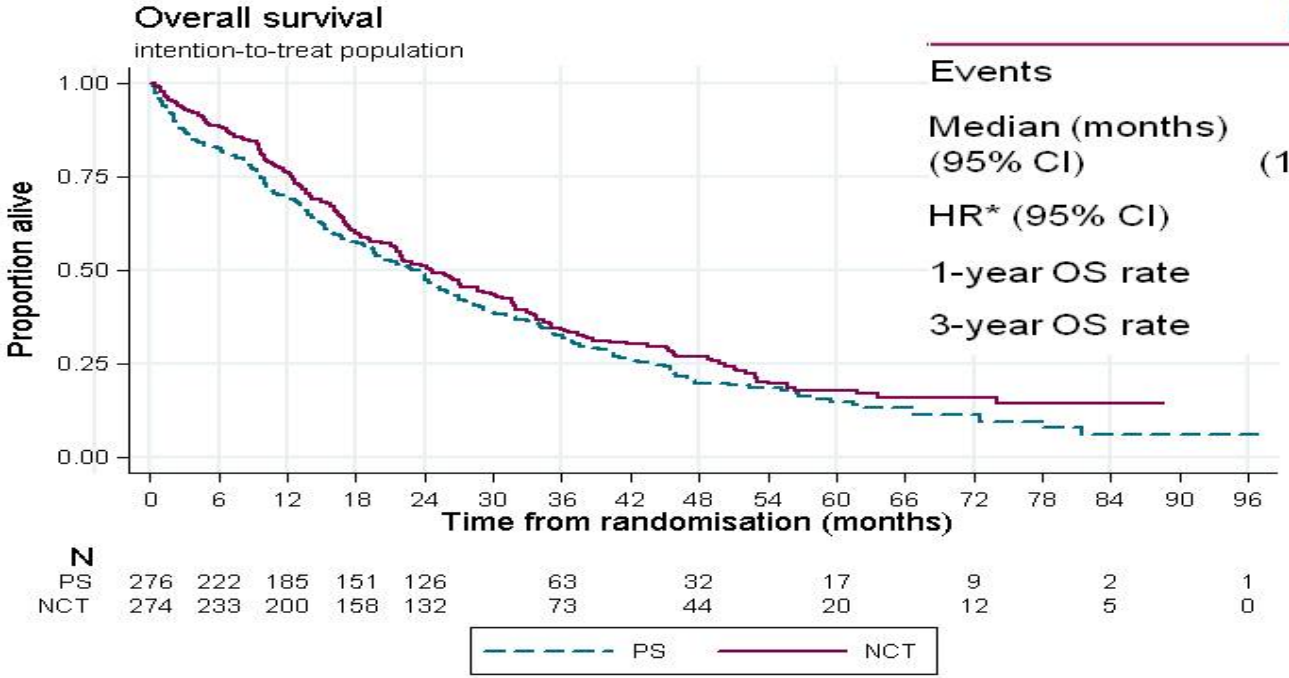
MRC Clinical Trials Unit

	PS	NACT
Surgery	14 (5.6%)	1 (0.5%)

- Review of deaths within 28 days of surgery
  - PS
    - Disease progression = 4
    - Pulmonary embolism = 2; infection = 3; problems with fluid balance or renal failure = 2; hemorrhage = 1; intra-operative problems = 1
    - *Still under review = 1*
  - NACT
    - Pulmonary embolism = 1

MRC | Medical Research Council

Overall survival



	PS (N=276)	NACT (N=274)
Events	211	199
Median (months) (95% CI)	22.8 (19.1, 26.0)	24.5 (21.3, 29.1)
HR* (95% CI)	0.87 (0.71, 1.05)	
1-year OS rate	70%	76%
3-year OS rate	32%	34%

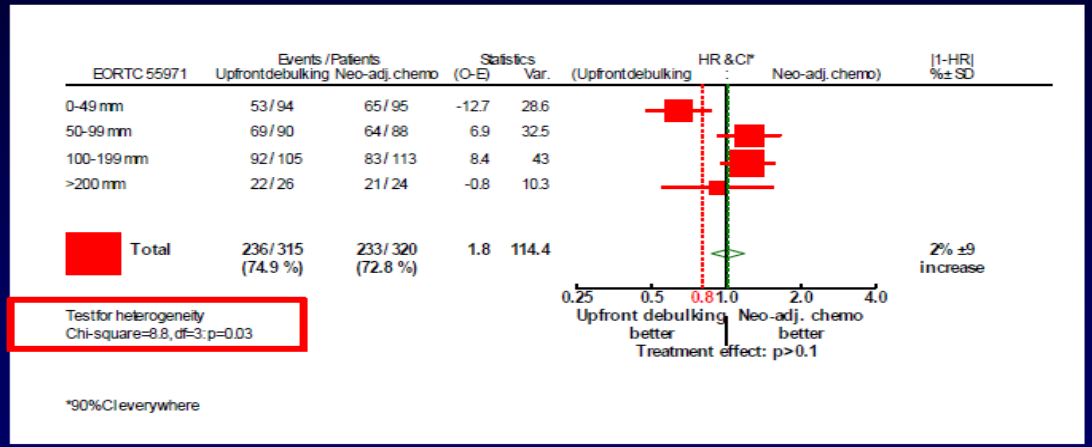
* HR adjusted for baseline stratification factors.

MRC | Medical Research Council

Presented By Sean Kehoe, MD at 2013 ASCO Annual Meeting; Lancet May 20, 2015

Vergote- SGO 2016

EORTC: NACT + IDS vs PDS: PP1
Overall Survival: Largest Metastatic Tumor Size



- **<5 cm: HR, 0.64; 95% CI: 0.45-0.93**

Vergote I, et al. *N Engl J Med.* 2010;363(10):943-953.

Ovarian cancer: High grade serous carcinomas

- Neo-adjuvant chemotherapy vs upfront debulking surgery followed by adjuvant chemotherapy
- IP chemotherapy vs dose dense chemotherapy vs weekly chemotherapy vs every 3 weeks IV chemotherapy
- HIPEC during interim debulking surgery (NEJM 2017)

MAYO CLINIC

- IP therapy remains important as predictor of survival at 10 years
- HR=0.77

J Clin Oncol. 2015 May 1;33(13):1460-6

Long-Term Survival Advantage and Prognostic Factors Associated With Intraperitoneal Chemotherapy Treatment in Advanced Ovarian Cancer: A Gynecologic Oncology Group Study

Devansu Tewari, James J. Java, Ritu Salani, Deborah K. Armstrong, Maurie Markman, Thomas Herzog, Bradley J. Monk, and John K. Chan

Purpose
To determine long-term survival and associated prognostic factors after intraperitoneal (IP) chemotherapy in patients with advanced ovarian cancer.

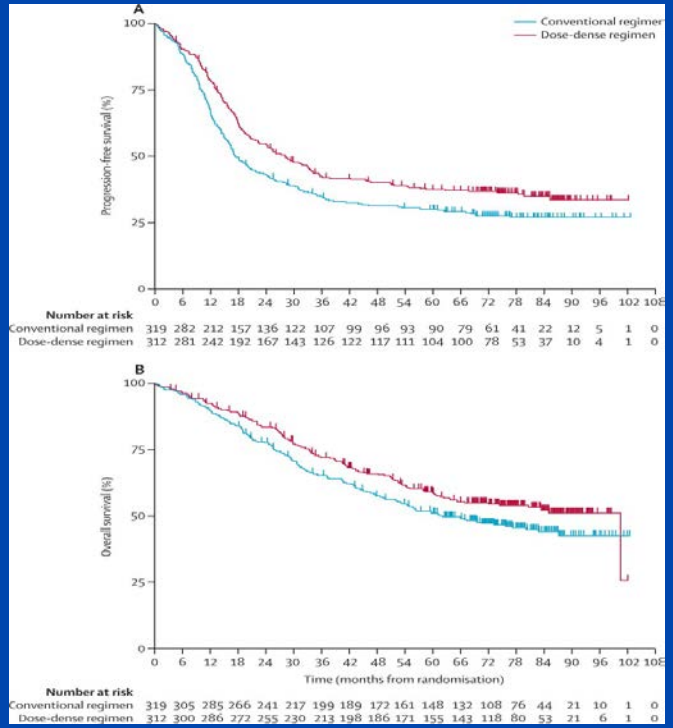
Patients and Methods
Data from Gynecologic Oncology Group protocols 114 and 172 were retrospectively analyzed. Cox proportional hazards regression models were used for statistical analyses.

Results
In 876 patients, median follow-up was 10.7 years. Median survival with IP therapy was 61.8 months (95% CI, 55.5 to 69.5), compared with 51.4 months (95% CI, 46.0 to 58.2) for intravenous therapy. IP therapy was associated with a 23% decreased risk of death (adjusted hazard ratio [AHR], 0.77; 95% CI, 0.65 to 0.90; $P = .002$). IP therapy improved survival of those with gross residual (≤ 1 cm) disease (AHR, 0.75; 95% CI, 0.62 to 0.92; $P = .006$). Risk of death decreased by 12% for each cycle of IP chemotherapy completed (AHR, 0.88; 95% CI, 0.83 to 0.94; $P < .001$). Factors associated with poorer survival included: clear/mucinous versus serous histology (AHR, 2.79; 95% CI, 1.83 to 4.24; $P < .001$), gross residual versus no visible disease (AHR, 1.89; 95% CI, 1.48 to 2.43; $P < .001$), and fewer versus more cycles of IP chemotherapy (AHR, 0.88; 95% CI, 0.83 to 0.94; $P < .001$). Younger patients were more likely to complete the IP regimen, with a 5% decrease in probability of completion with each year of age (odds ratio, 0.95; 95% CI, 0.93 to 0.96; $P < .001$).

Conclusion
The advantage of IP over intravenous chemotherapy extends beyond 10 years. IP therapy enhanced survival of those with gross residual disease. Survival improved with increasing number of IP cycles.

PRESENTED AT: ASCO Annual '15 Meeting

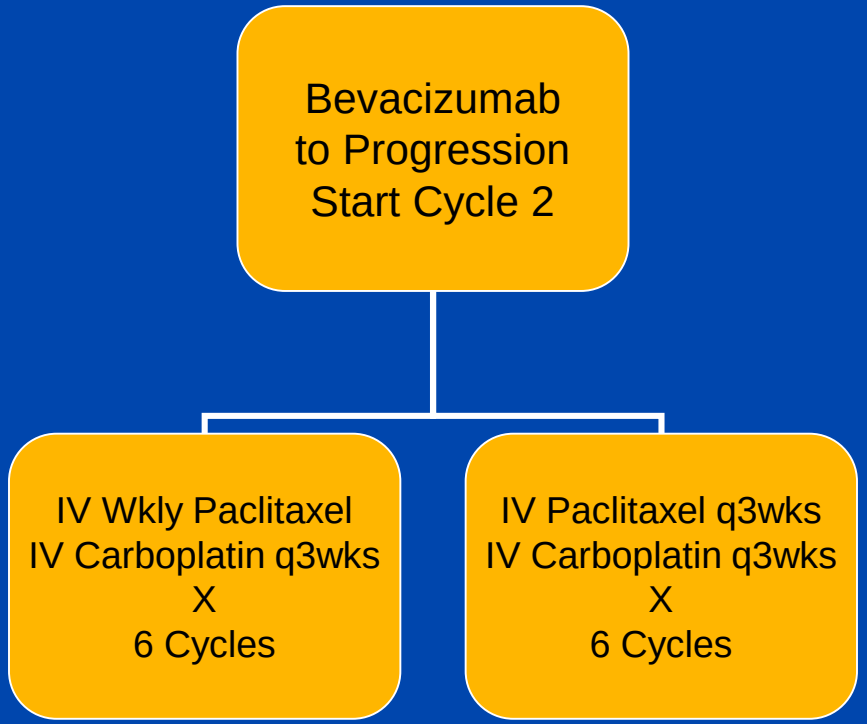
Katsumata et al: Lancet Oncology 2013



- *Weekly vs. Every-3-Week Paclitaxel and Carboplatin for Ovarian Cancer*
- J.K. Chan, M.F. Brady, R.T. Penson, H. Huang, M.J. Birrer, J.L. Walker, P.A. DiSilvestro, S.C. Rubin, L.P. Martin, S.A. Davidson, W.K. Huh, D.M. O'Malley, M.P. Boente, H. Michael, and B.J. MonkN Engl J Med 2016;374:738-48.
- DOI: 10.1056/NEJMoa1505067

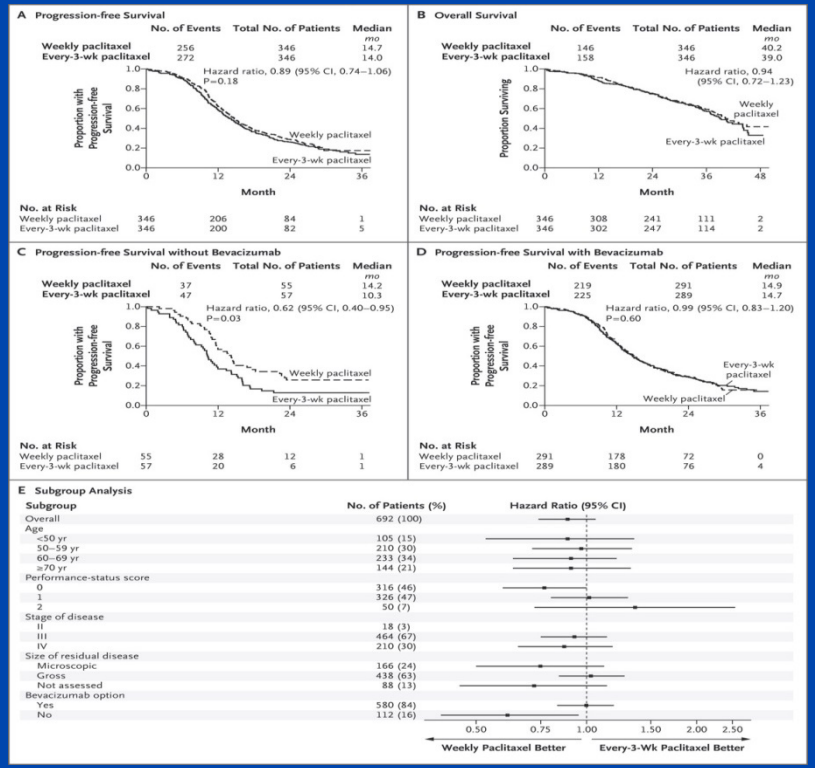
Ovarian Cancer First-Line Treatment Trials: Where Are We Now? (cont.)

- GOG 262: Randomized phase III trial for suboptimally cytoreduced patients
  - Neoadjuvant
  - Targeted/novel therapeutics
  - QOL
  - 692 patients



US NIH, 2011c.

Primary and Subgroup Analyses of Progression-free Survival, According to Treatment Group.

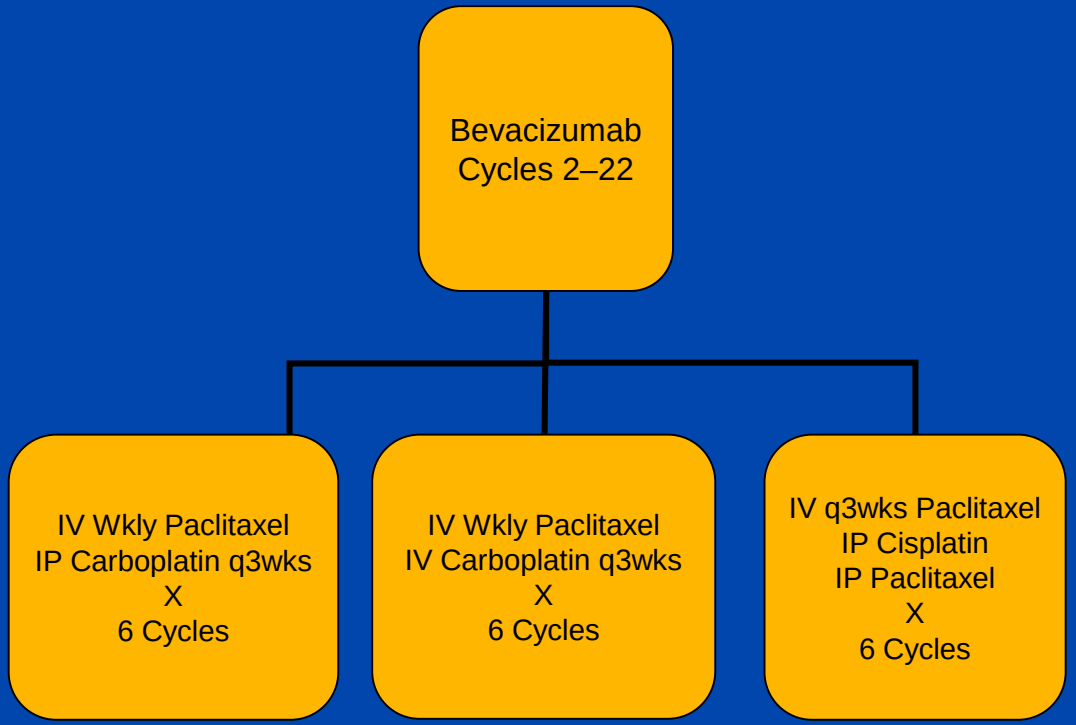


Chan JK et al. N Engl J Med 2016;374:738-748.

The NEW ENGLAND JOURNAL of MEDICINE

Ovarian Cancer First-Line Treatment Trials: Where Are We Now? (cont.)

- GOG 252: Randomized phase III trial for optimally cytoreduced patients
  - IP vs. IV
  - Targeted/novel therapeutics
  - QOL
  - Maintenance
  - 1,500 pts



IV = intravenous.

US NIH. 2011b


ANNUAL MEETING ON WOMEN'S CANCER
SAN DIEGO
MARCH 19–22, 2016

Progression Free Survival Optimal Stage II-III (10% stage II)

Arm	N	Events	Median PFS	HR [95% CI]	Logrank	Logrank
IV Carbo	461	303	26.8 months	Reference arm	P-value	Chi square
IP Carbo	464	300	28.7 months	0.947 [0.808-1.11]	0.416	0.661
IP Cisp	456	307	27.8 months	1.01 [0.858-1.18]	0.727	0.122

- Estimated hazard ratios, and logrank tests are adjusted for stage of disease and size of residual disease micro vs < 1cm
- CT required every 6 months for surveillance (not required in GOG 114/172)

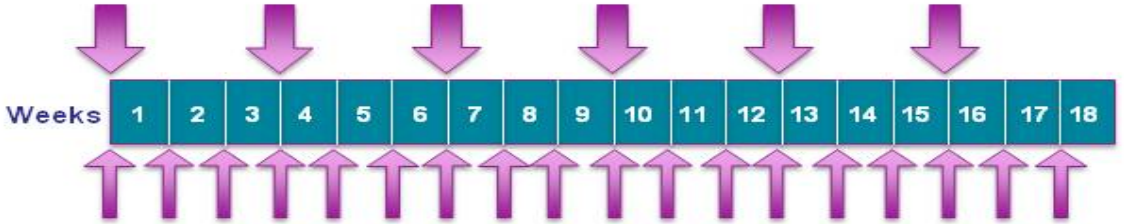
Study design

Random

1:1

Control arm

Carboplatin AUC 6, d1 q21
Paclitaxel 175 mg/m², d1 q21
Treatment repeated for 6 cycles



Experimental arm

Carboplatin AUC 2, d1, 8, 15 q21
Paclitaxel 60 mg/m², d1, 8, 15 q21
Treatment repeated for 6 cycles

Strata:
- Center
- PS (0, 1, 2)
- Residual disease after surgery (absent, ≤1 cm, >1 cm, no surgery)

ClinicalTrials.gov NCT00660842

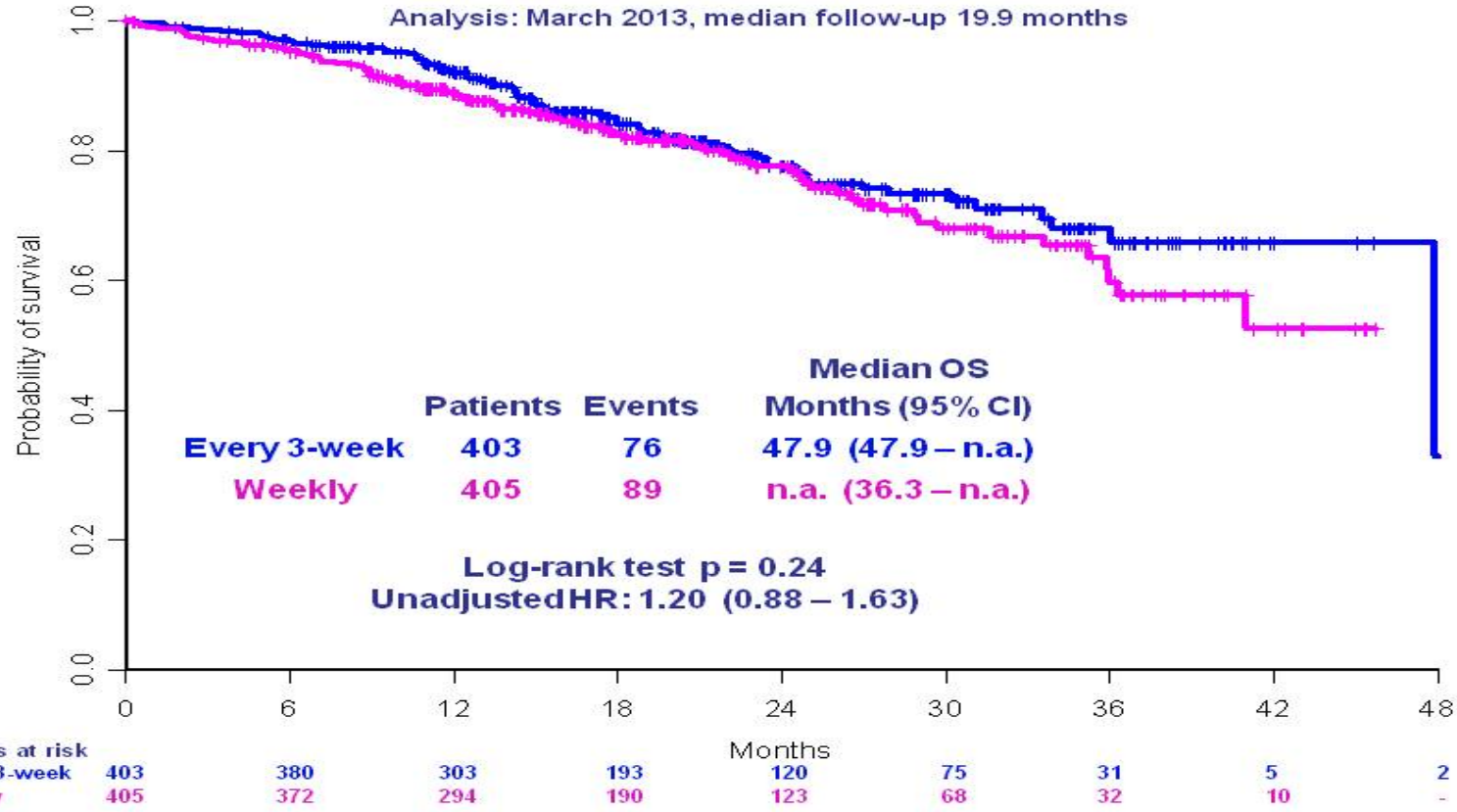
Presented by: S.Pignata

PRESENTED AT: ASCO Annual '13 Meeting

Pignata, MD, PhD 2013 ASCO Annual Meeting; Lancet Oncology 2014

Overall survival

Analysis: March 2013, median follow-up 19.9 months



	Patients	Events	Median OS Months (95% CI)
Every 3-week	403	76	47.9 (47.9 – n.a.)
Weekly	405	89	n.a. (36.3 – n.a.)

Log-rank test p = 0.24
Unadjusted HR: 1.20 (0.88 – 1.63)

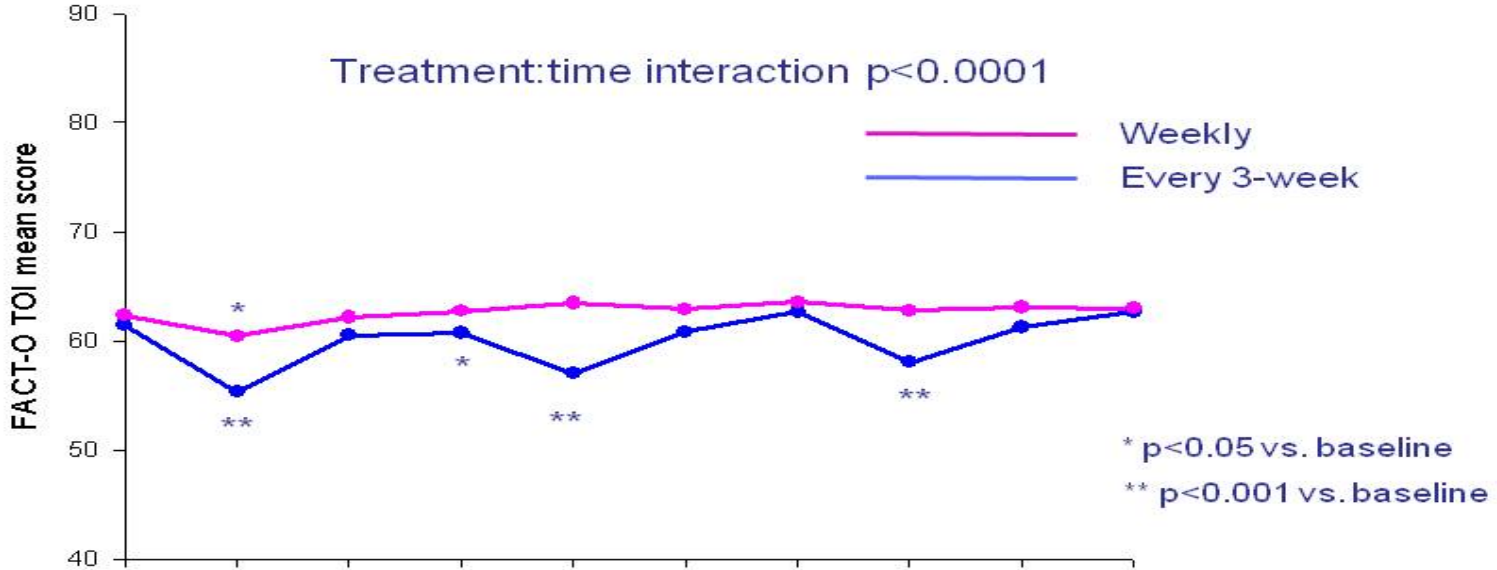
Patients at risk									
Every 3-week	403	380	303	193	120	75	31	5	2
Weekly	405	372	294	190	123	68	32	10	-

Presented by: S.Pignata

PRESENTED AT: ASCO Annual '13 Meeting

Pignata, MD, PhD 2013 ASCO Annual Meeting; Lancet Oncology 2014

QoL: FACT-O TOI, first 9 weeks



Week	0	1	2	3	4	5	6	7	8	9
Pts (weekly)	308	266	254	237	239	238	218	212	223	177
Pts (q3w)	301	229	208	250	209	195	221	193	177	169

In all scales, higher values represent better outcome.
All tests are adjusted by performance status, stage, residual disease after surgery, age category, and size of the institution

Presented by: S.Pignata

PRESENTED AT: ASCO Annual '13 Meeting

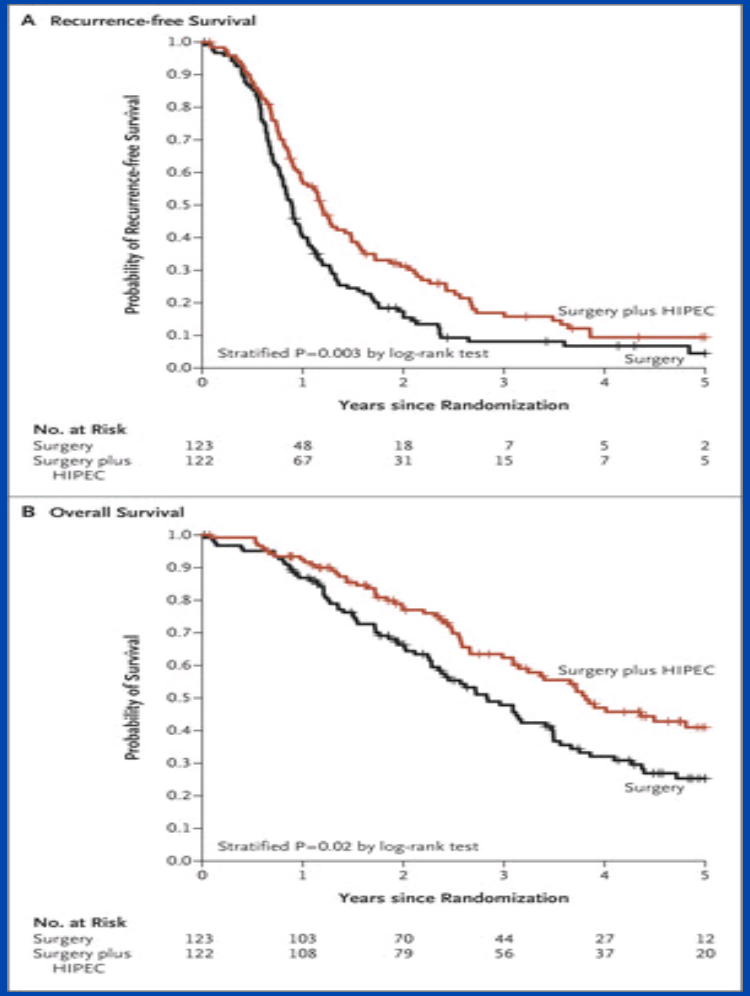
Pignata, MD, PhD 2013 ASCO Annual Meeting; Lancet Oncology2014

ORIGINAL ARTICLE

Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer

Willemien J. van Driel, M.D., Ph.D., Simone N. Koole, M.D., Karolina Sikorska, Ph.D., Jules H. Schagen van Leeuwen, M.D., Ph.D., Henk W.R. Schreuder, M.D., Ph.D., Ralph H.M. Hermans, M.D., Ph.D., Ignace H.J.T. de Hingh, M.D., Ph.D., Jacobus van der Velden, M.D., Ph.D., Henriëtte J. Arts, M.D., Ph.D., Leon F.A.G. Massuger, M.D., Ph.D., Arend G.J. Aalbers, M.D., Victor J. Verwaal, M.D., Ph.D., et al.

January 18, 2018
N Engl J Med 2018; 378:230-240
DOI: 10.1056/NEJMoa1708618
Chinese Translation 中文翻译



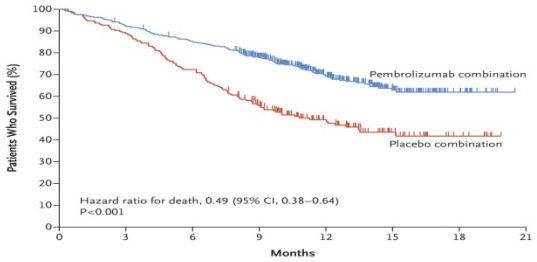
ORIGINAL ARTICLE

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

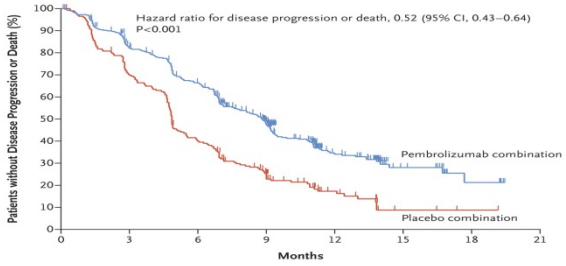


No. at Risk								
Pembrolizumab combination	410	377	347	278	163	71	18	0
Placebo combination	206	183	149	104	59	25	8	0

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)

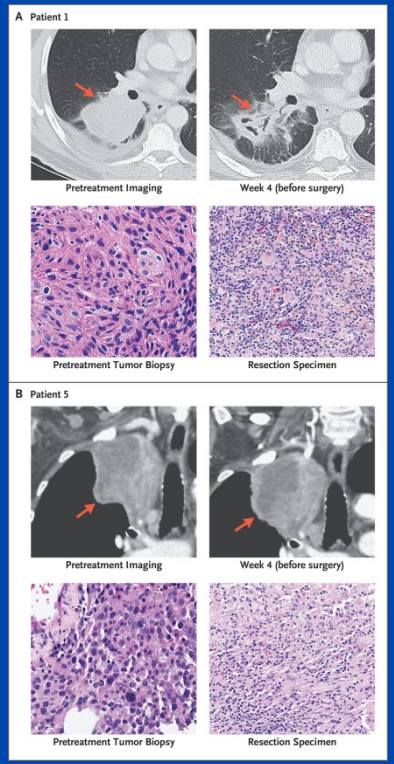
MAYO CLINIC

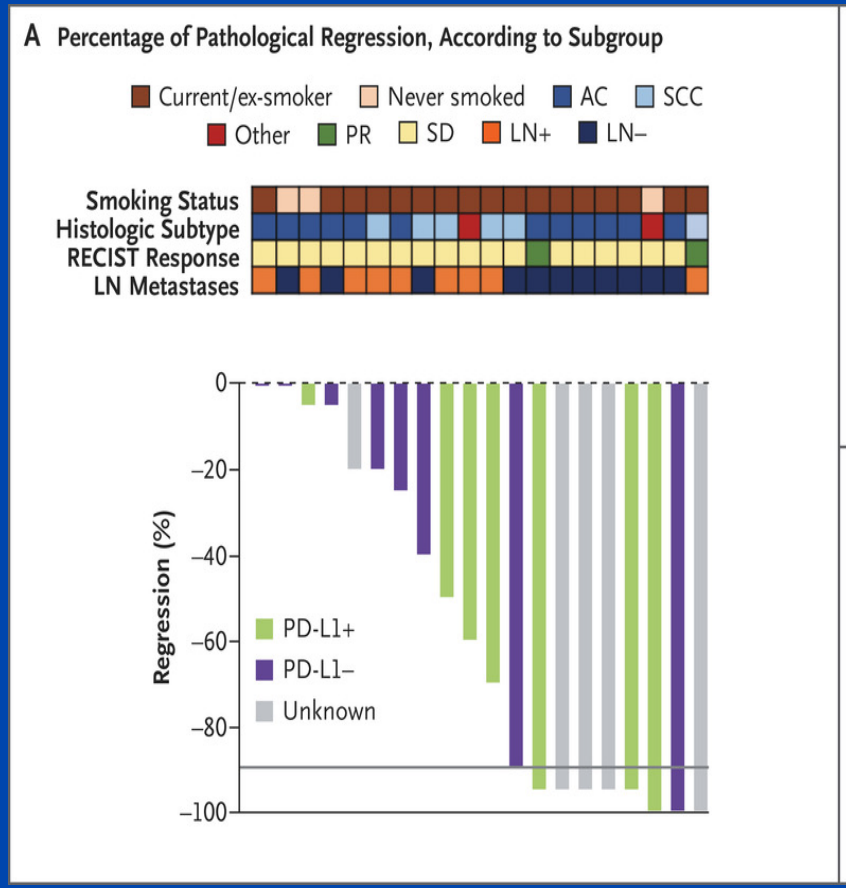
ORIGINAL ARTICLE

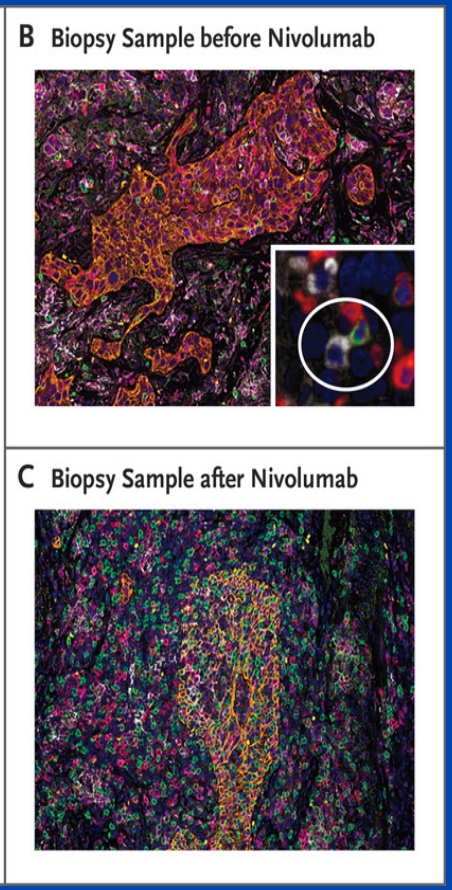
Neoadjuvant PD-1 Blockade in Resectable Lung Cancer

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.

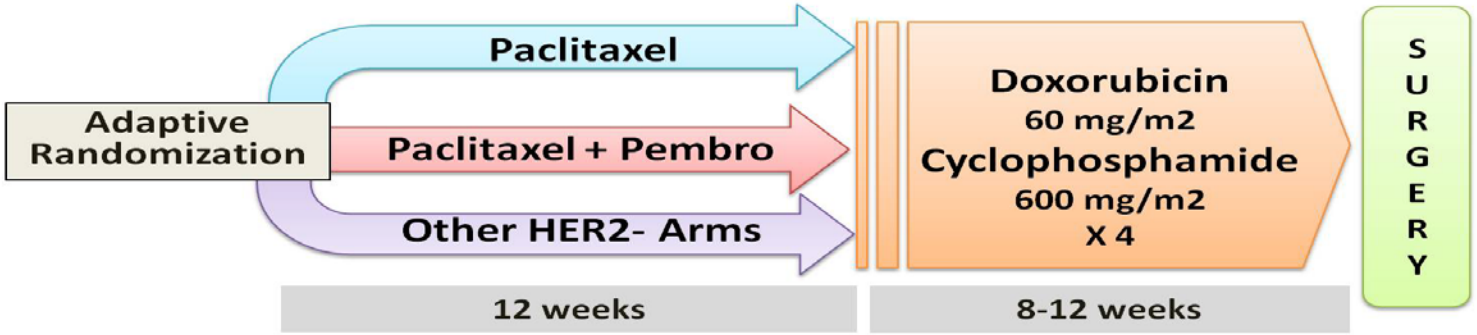
The Right Drug.
The Right Patient
The Right Time. Now.

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



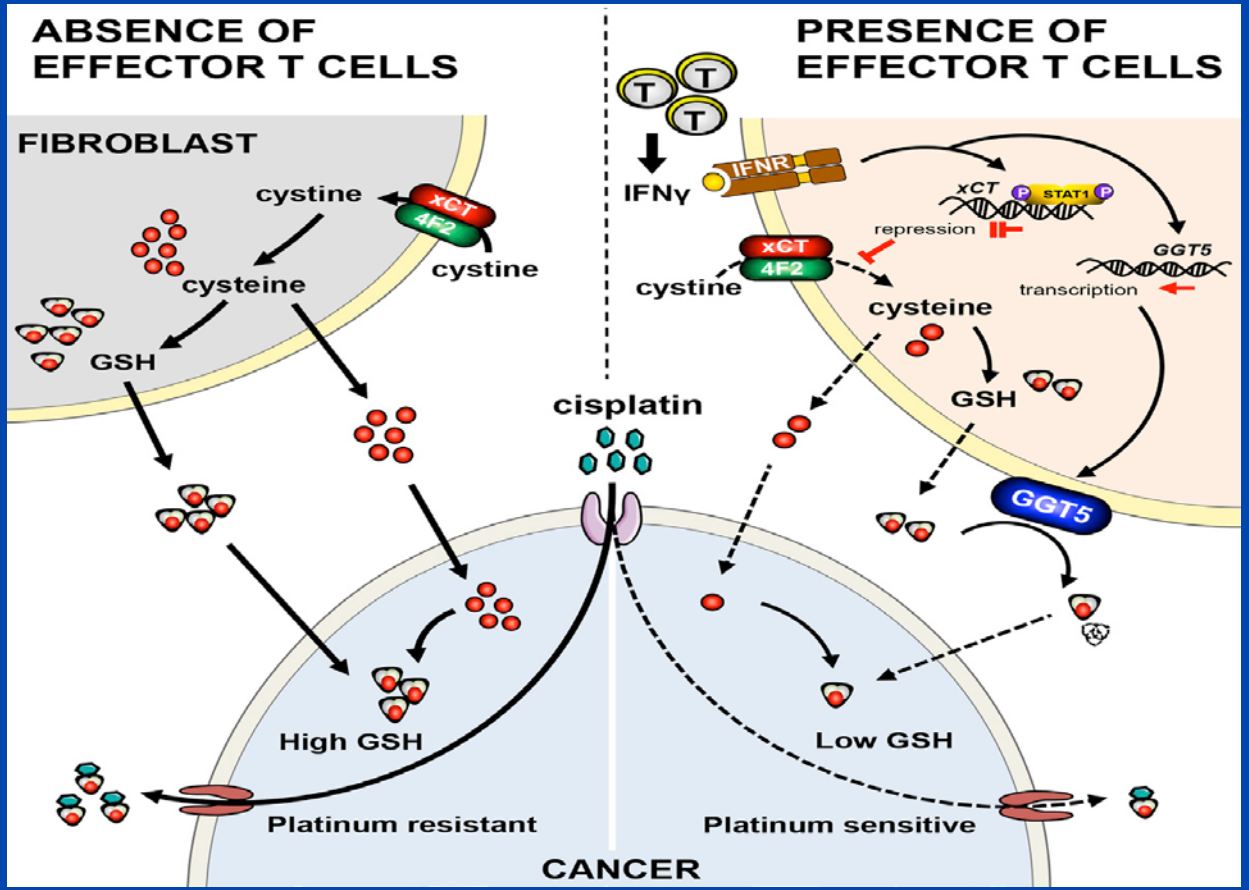
Control
Paclitaxel 80 mg/m2 every wk x 12

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

BRCA mutated and HRD Ovarian Cancers: Future

- Upfront maintenance PARP inhibitors
- Maintenance rucaparib or niraparib or olaparib following relapse
- Evaluation of PARP inhibitors and checkpoint inhibitors

MAYO CLINIC

RELAPSED OVARIAN CANCER (70% of all cases)

- Don’t forget about debulking surgery
- Angiogenesis inhibitors: bevacizumab
- PARP inhibitors: olaparib, rucaparib, niraparib
- PARP inhibitors plus anti-angiogenesis: olaparib and cediranib
- Monoclonal antibodies and immuno-conjugates
- Immunotherapy (checkpoint inhibitors)
- PARP inhibitors and checkpoint inhibitors
- Cyclin kinase 1,2 inhibitors

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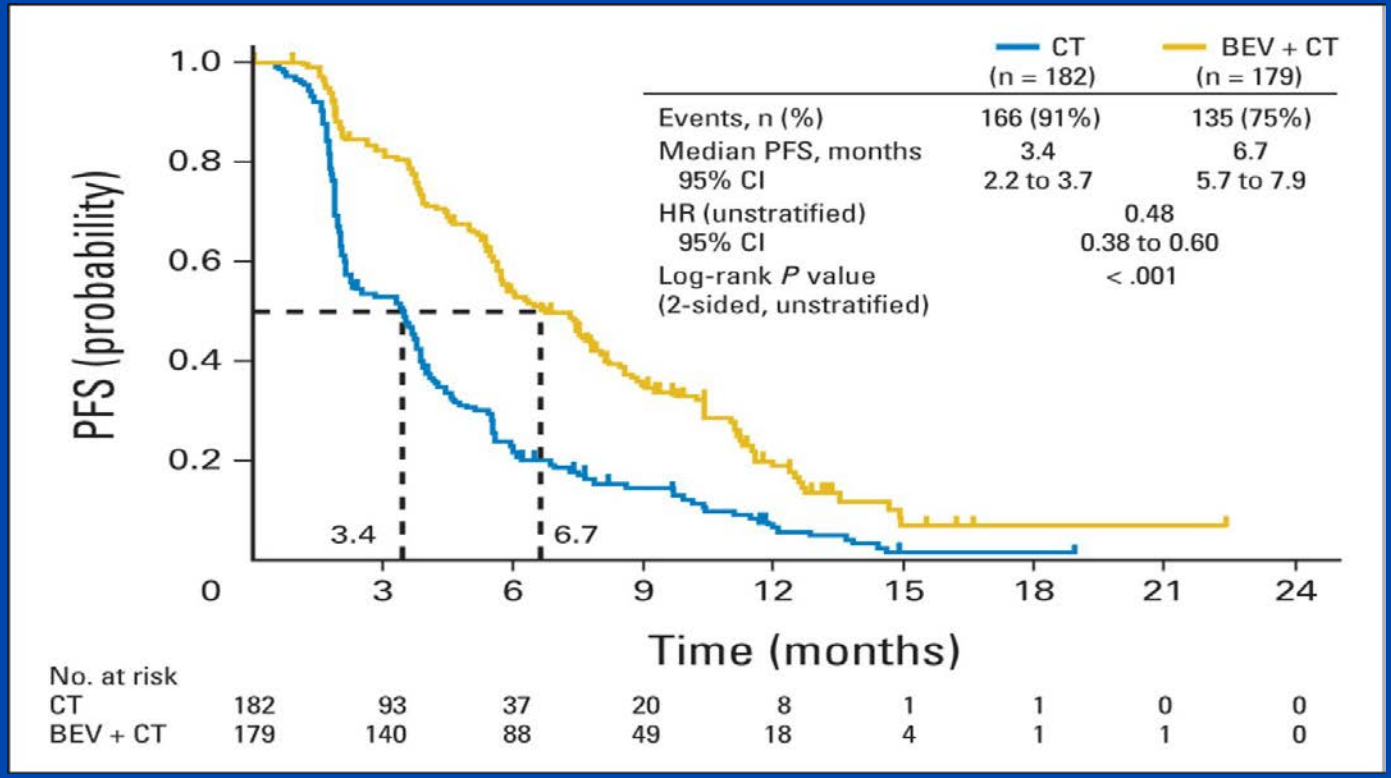
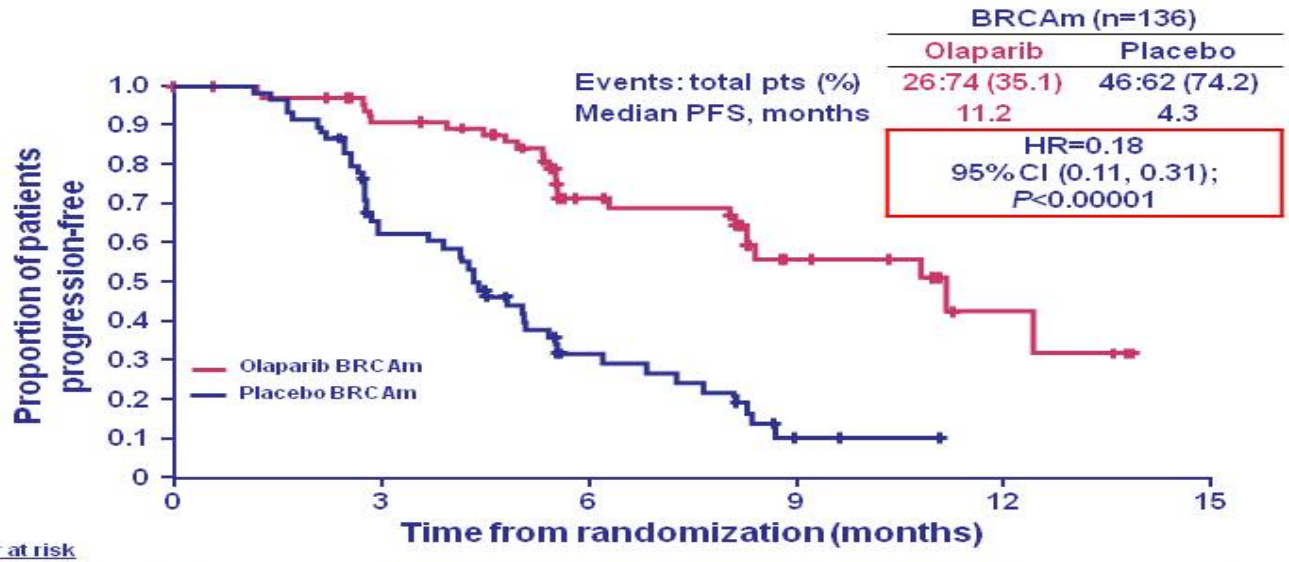
Progression-free survival (PFS).



Eric Pujade-Lauraine et al. JCO 2014;32:1302-1308

PFS by BRCAm status



Number at risk

Olaparib BRCAm	74	59	33	14	4	0
Placebo BRCAm	62	35	13	2	0	0

- 82% reduction in risk of disease progression or death with olaparib

Presented by: Jonathan Ledermann

PRESENTED AT: ASCO Annual '13 Meeting

Presented By Jonathan A. Ledermann, BSc MD FRCP at 2013 ASCO Annual Meeting; Lancet Oncology July 2014

Results of ARIEL2: A phase 2 trial to prospectively identify ovarian cancer patients likely to respond to rucaparib using tumor genetic analysis

Iain McNeish,[1] Amit Oza,[2] Robert L. Coleman,[3] Clare Scott,[4] Gottfried Konecny,[5] Anna Tinker,[6] David M. O'Malley,[7] James Brenton,[8] Rebecca Kristeleit,[9] Katherine Bell-McGuinn,[10] Ana Oaknin,[11] Alexandra Leary,[12] Kevin K. Lin,[13] Mitch Raponi,[13] Heidi Giordano,[13] Sandra Goble,[13] Lindsey Rolfe,[13] Roman Yelensky,[14] Andrew Allen,[13] and Elizabeth Swisher[15]

[1]Institute of Cancer Sciences, University of Glasgow, [2]Princess Margaret Cancer Centre, [3]The University of Texas MD Anderson Cancer Center, [4]Royal Melbourne Hospital, [5]University of California, [6]British Columbia Cancer Agency, [7]The Ohio State University, [8]Cancer Research UK Cambridge Institute, [9]University College London, [10]Memorial Sloan-Kettering Cancer Center, [11]Vall d'Hebron University Hospital, [12]Institut Gustave Roussy, [13]Clovis Oncology Inc., [14]Foundation Medicine Inc., [15]University of Washington School of Medicine

PRESENTED AT: ASCO Annual '15 Meeting

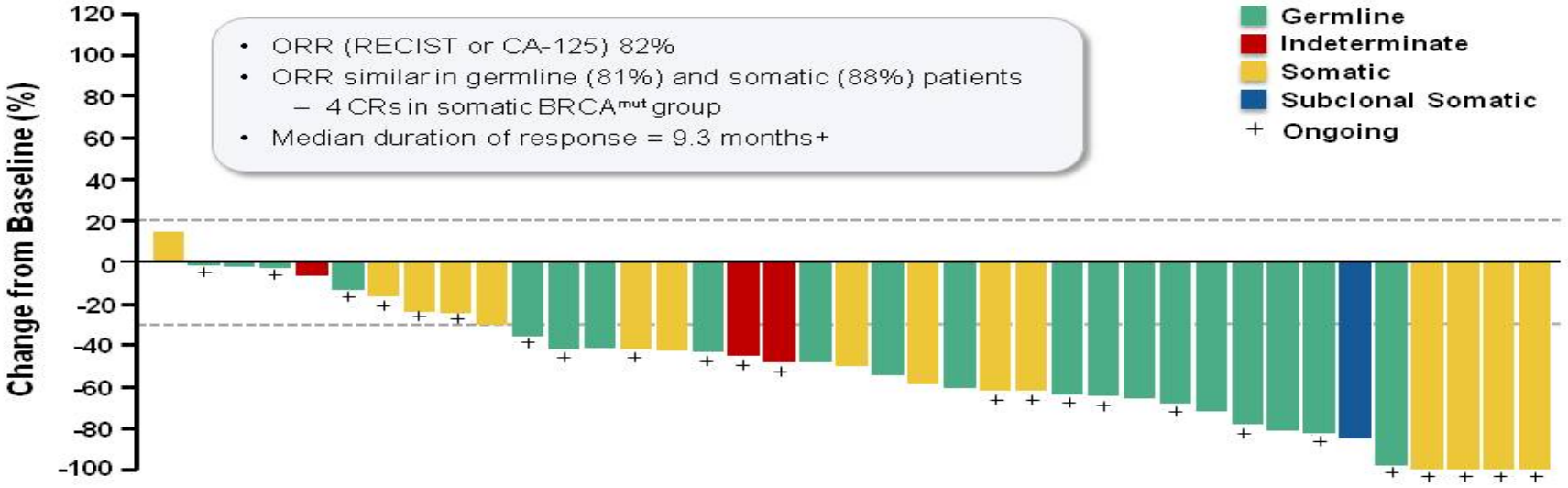
In BRCA^{wt} tumors, the BRCA-like subgroup derives enhanced benefit from rucaparib

	HRD Subgroup	Median PFS, mo (90% CI)	Overall Response Rate, % (N)	
			RECIST	RECIST + CA-125
	BRCA^{mut}	9.4 (7.3, NR)	69 (27/39)	82 (32/39)
BRCA^{wt}	BRCA-like	7.1 (3.7, 10.8)	30 (22/74)	45 (33/74)
BRCA^{wt}	Biomarker Negative	3.7 (3.5, 5.5)	13 (8/62)	21 (13/62)

NR=not reached.

PRESENTED AT: ASCO Annual '15 Meeting

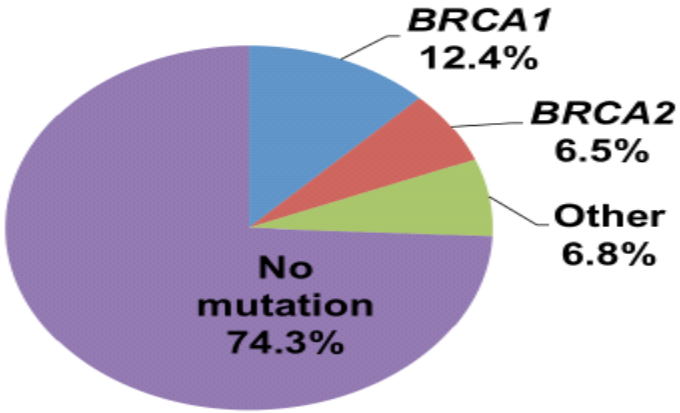
Response rate striking in BRCA^{mut} tumors



PRESENTED AT: ASCO Annual '15 Meeting

Proportion of OC patients with mutations in homologous recombination genes

Gene	N	
BRCA1	148	
BRCA2	78	
Other	81	
Total	**307**	**(25.7%)**



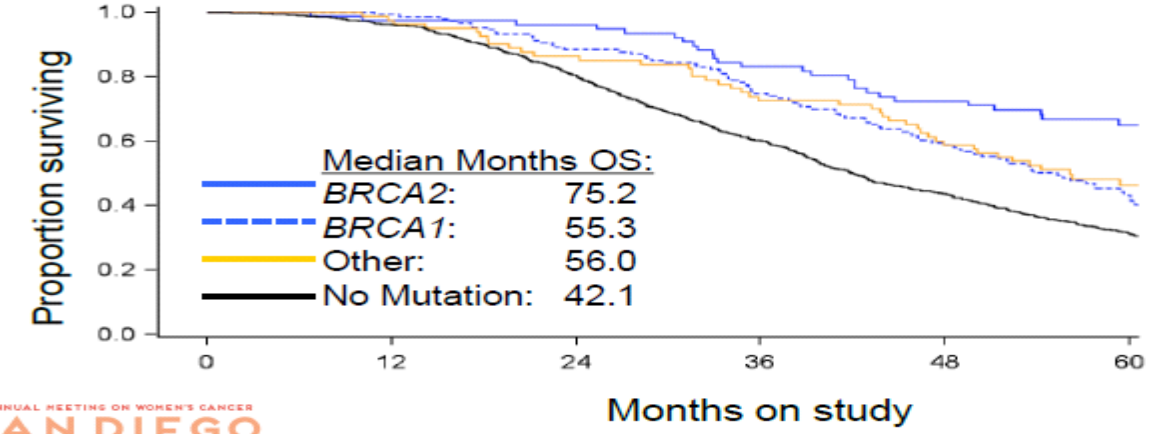
N = 1195

ANNUAL MEETING ON WOMEN'S CANCER
SAN DIEGO
MARCH 19–22, 2016

Bringing Together the Best in Women's Cancer Care

MAYO CLINIC

Overall survival by mutation status



Estimated relative hazards of death by mutation category

Mutation Category	Hazard Ratio (95% CI)	P-Value
BRCA2	0.36 (0.25 – 0.53)	<0.0001
BRCA1	0.74 (0.59 – 0.94)	0.01
Other HR	0.67 (0.49 – 0.90)	0.007

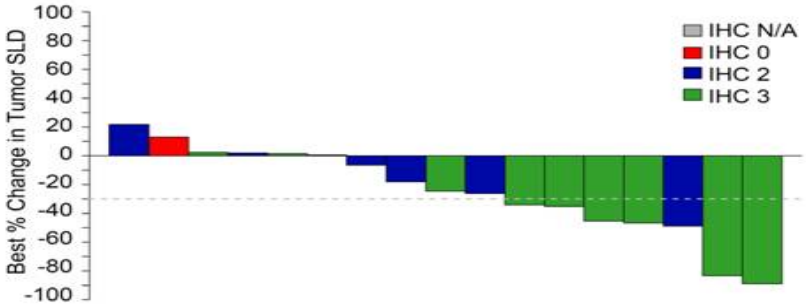
- Reference group is those with no mutation
- Hazard ratios are adjusted for study treatment, stage of disease, size of residual disease, initial performance status

Selected Antibody Drug Conjugates in Development – Solid Tumors

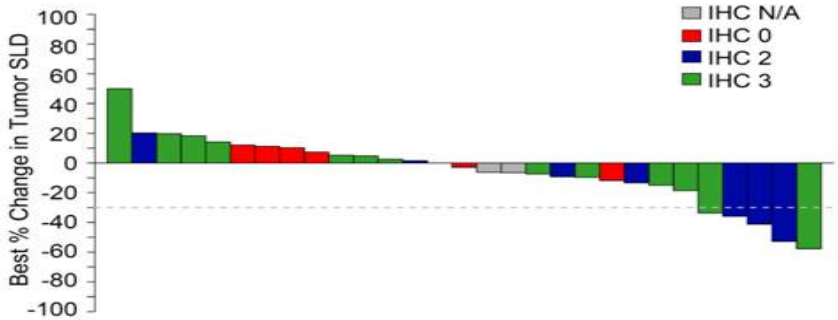
Drug	Company	Biomarker	Tumor	Phase of Development
PSMA-ADC	Progenics	PSMA	Prostate	II
ABT-414	AbbVie	EGFR	GBM, NSCLC	I, II
IMGN901 (Lorvotuzumab mertansine)	Immunogen	CD56	SCLC, MM, Ovarian, MCC	I, II
CDX-011 (glembatumumab vedotin)	Celldex	Glycoprotein NMB (GNMB)	Breast, Melanoma	I, II
IMGN853	Immunogen	Folate receptor α	Ovarian, NSCLC	I
SGN-75 (vorsetuzumab mafodotin)	Seattle Genetics	CD70	RCC	I
DMUC5754A	Roche/Genentech	MUC16	Ovarian	I
BAY 94-9343	Bayer	Mesothelin	Mesothelioma, Ovarian, Gastric, Pancreatic, Lung	I
Anti-NaPi2b-vc-E	Roche/Genentech	NaPi2b	Lung, Ovarian	I
SC16LD6.5	StemCentRx	SCLC surface protein	SCLC	I
IMMU-132	Immunomedics	TACSTD2 (TROP2/EGP1)	Solid tumor	I
Labetuzumab-SN-38	Immunomedics	CEA (CD66e)	CRC	I
RG-7636	Genentech	Endothelin receptor ETB	Melanoma	I
RG-7450	Genentech	STEAP1	Prostate	I
AGS-5ME	Agensys	SLC44A4 (AGS-5)	Pancreatic, Stomach	I
AGS-22M6E	Agensys	Nectin 4	Solid tumor	I
AGS-16M8F	Agensys	AGS-16	RCC	I
MLN-0264	Millennium	Guanylyl cyclase C	GI	I
SAR-566658	Sanofi	Mucin 1	Solid tumor	I
AMG-172	Amgen	CD70	RCC	I
AMG-595	Amgen	EGFRvIII	Glioma	I

Response to Treatment and Maximum Declines in Measureable Disease by IHC Score

Ovarian



Lung



Response Assessment at RP2D (2.4 mg/kg)	Ovarian IHC 0	Ovarian IHC 2/3+	Lung IHC 0	Lung IHC 2/3+
Confirmed RECIST Response Rate	**0%** *(0/1)*	***41%*** *(7/17)*	**0%** *(0/5)*	**10%** *(2/21)*
Clinical Benefit Rate (cPR or SD ≥ 3 months)	**0%** *(0/1)*	***53%*** *(9/17)*	**20%** *(1/5)*	**48%** *(10/21)*

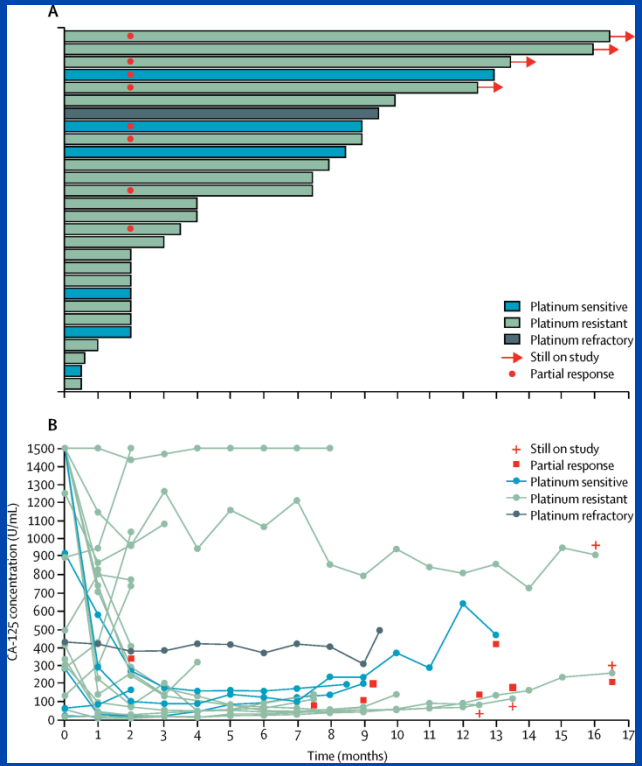
None of the patients with tissue unevaluable for NaPi2b staining demonstrated response to treatment

Banerjee et al: Lifastizumab (Anti-NaPi2b vedotin-MMAE) vs liposomal doxorubicin (Abstract 5569, ASCO 2016)

- 95 patients, randomized phase 2
- PFS: 5.3 mo vs 3.1 mo
- RR: 34% vs 15%

MAYO CLINIC

Prexasertib: CK1,2 Tyrosine Kinase Inhibitor
Lee J-M et al: Lancet Oncology 19 (2): 207-15, 2018

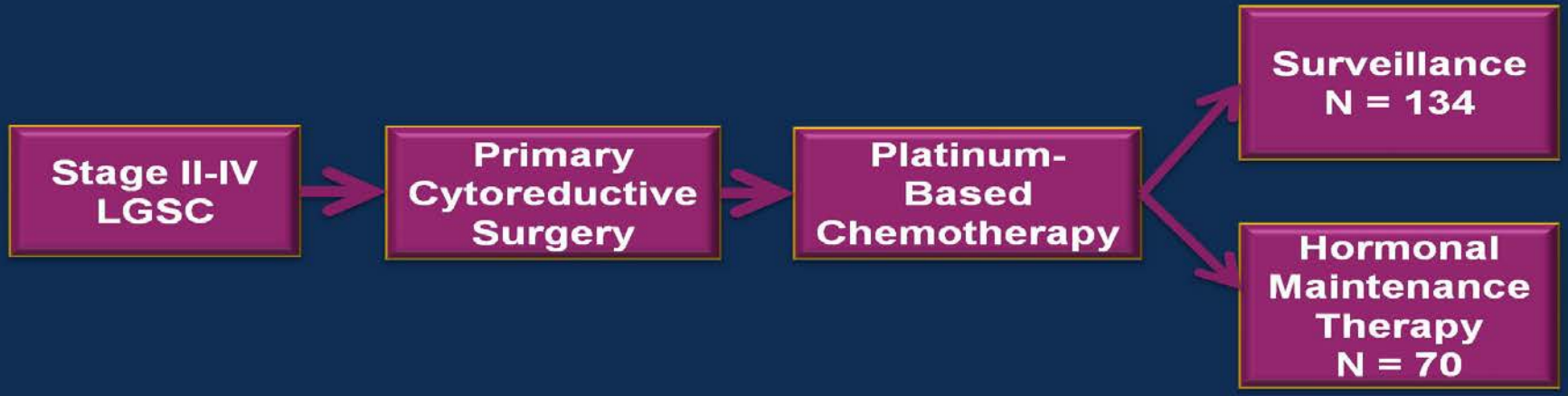


Hormonal Maintenance Therapy for Women with Low-Grade Serous Carcinoma of the Ovary or Peritoneum

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

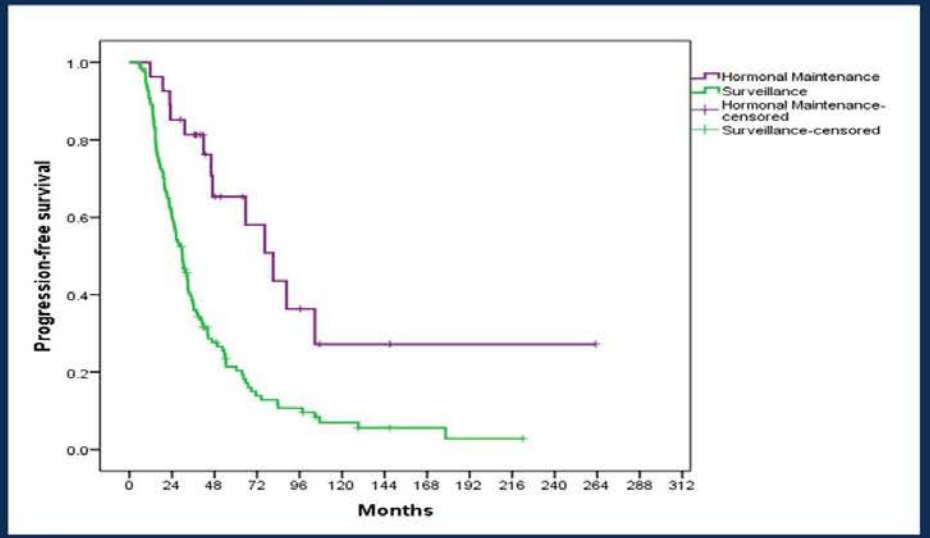
PRESENTED AT: ASCO ANNUAL MEETING '16

Results: Schema



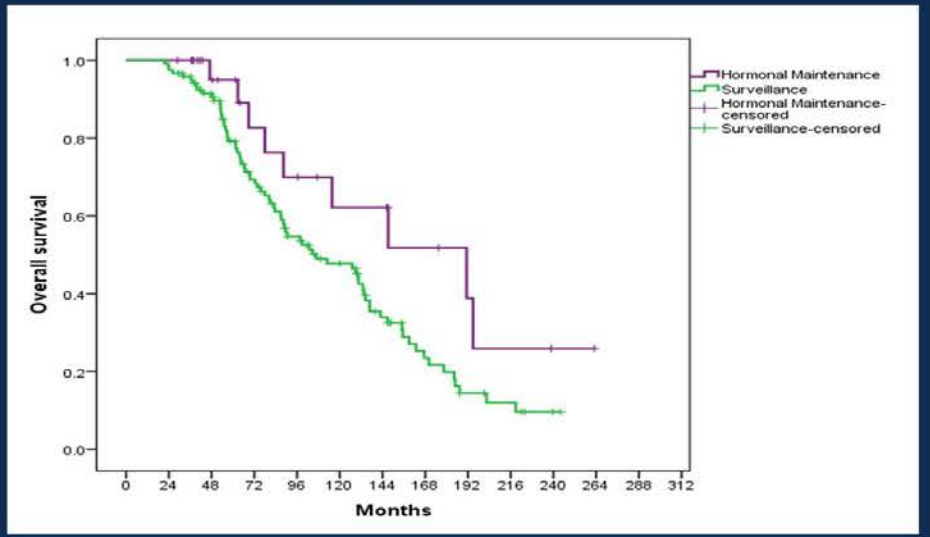
Results: PFS in Patients NED at Completion of Chemotherapy

Group	Median PFS (mo)	95% CI	P-Value
SURV (n = 121)	29.9	24.5, 35.2	
			< .001
HMT (n = 27)	81.1	55.2, 106.9	
ALL (N = 148)	33.0	28.4, 37.7	



Results: OS in Patients NED at Completion of Chemotherapy

Group	Median OS (mo)	95% CI	P-Value
SURV (n = 121)	106.8	72.8, 140.7	
			.04
HMT (n = 27)	191.3	93.5, 289.1	
ALL (N = 148)	115.7	86.5, 144.9	



Results: Multivariable Analysis for PFS

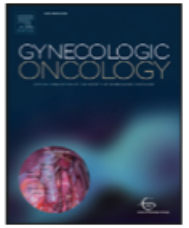
Characteristic	HR	95% CI	P-Value
Group SURV (ref) HMT	.23	0.11, 0.51	< .001
Primary site Ovary (ref) Peritoneum	.45	0.27, 0.76	.003
Residual disease Gross (ref) No gross	.49	0.28, 0.87	.02
Disease status at completion of chemo Persistent disease (ref) NED	.42	0.18, 0.96	.04

Gynecologic Oncology 146 (2017) 64–68

Contents lists available at ScienceDirect

Gynecologic Oncology

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



Phase 2 trial of everolimus and letrozole in relapsed estrogen receptor-positive high-grade ovarian cancers

Gerardo Colon-Otero [a,*], S. John Weroha [b], Nathan R. Foster [c], Paul Haluska [b,1], Xiaonan Hou [b], Andrea E. Wahner-Hendrickson [b], Aminah Jatoi [b], Matthew S. Block [b], Tri A. Dinh [d], Matthew W. Robertson [d], John A. Copland [e]

[a] Division of Hematology and Medical Oncology, Mayo Clinic, Jacksonville, FL, United States
[b] Division of Medical Oncology, Mayo Clinic, Rochester, MN, United States
[c] Division of Biomedical Statistics and Informatics, Rochester, MN, United States
[d] Department of Medical & Surgical Gynecology, Mayo Clinic, Jacksonville, FL, United States
[e] Department of Cancer Biology, Mayo Clinic, Jacksonville, FL, United States

HIGHLIGHTS

- AI therapy is associated with limited clinical activity in high-grade ovarian cancer.
- Combination of everolimus and letrozole is associated with a promising12-week PFS.
- PDX tumor models can be generated from biopsies of ovarian tumors.

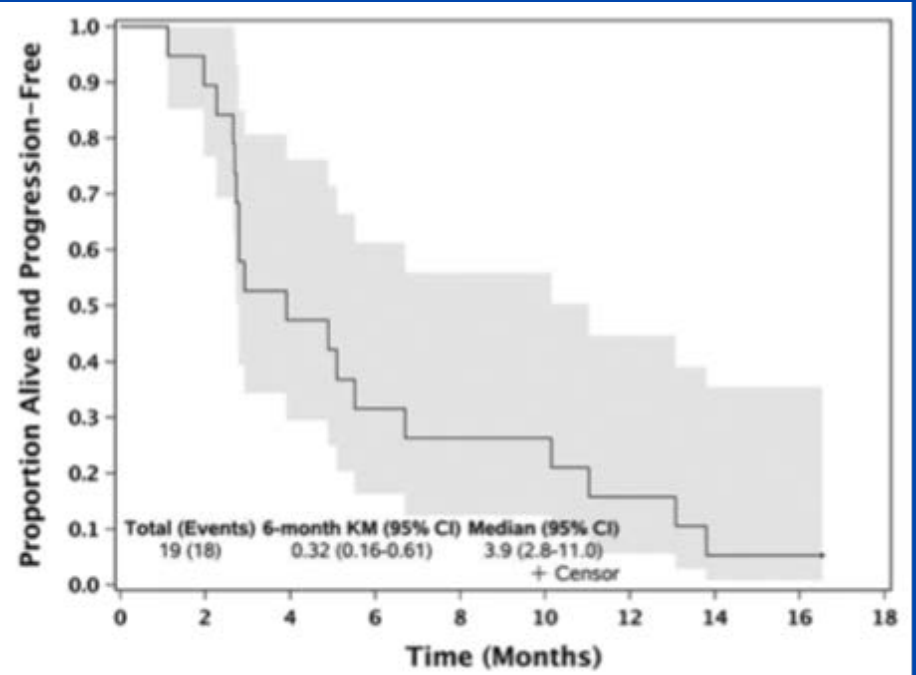


Fig. 1. Progression-Free Survival. CI, confidence interval; KM, Kaplan-Meier method.

ESR1 Alteration in Metastatic ER-Positive Breast Cancer

- 10–40% prevalence of *ESR1* LBD mutations in patients with metastatic ER+ breast cancer
- *ESR1* mutations are associated with prior exposure to AI treatment
- After first line treatment with non-steroidal AI, patients with *ESR1* mutation have worse PFS with steroidal AI compared to patients with WT *ESR1*
- *ESR1*-mutant metastatic breast cancer patients seem to benefit from fulvestrant +/- palbociclib

Jeselson R, et al. *Curr Oncol Rep* 2017;35

MAYO CLINIC

Clinical Cancer Research DOI: 10.1158/1557-3265.OVCASYMP16-MIP-056 Published June 2017

- Abstract MIP-056: CONSTITUTIVELY ACTIVE ESTROGEN RECEPTOR–ALPHA LIGAND BINDING DOMAIN (ERA–LBD) MUTATIONS IN OVARIAN CARCINOMA

- J. A. Elvin, L. Gay, G. Colon-Otero, M. Jorgensen, L. Havrilesky, D. Zajchowski, L Shawver, F. A. Valea, S Aithal, J. S. Ross, M. Markman, and S. Gaillard

MAYO CLINIC

Elvin J et al: Clinical Cancer Research June 2017

- CGP of 3641 ovarian and peritoneal tumors
- 31/3641 (0.9%) amplifications of ESR1 and 16 (0.4%) with ESR1 LBD mutations
- 10/16 (Y537S); 4/16 (D638G); 1/16 (S341L); 1/16 (Y537N)
- 8 patients: 3/3 patients responded to fulvestrant

MAYO CLINIC

Gynecologic cancers 2018

- Ovarian cancer
- 22,240 new cases
- 14,070 deaths
- Endometrial cancer
- 63, 230 new cases
- 11, 350 deaths
- Cervical, vaginal, vulvar cancers
- 24,800 new cases
- 6,700 deaths

Total Gyn cancers

110,000 new cases

32,000 deaths

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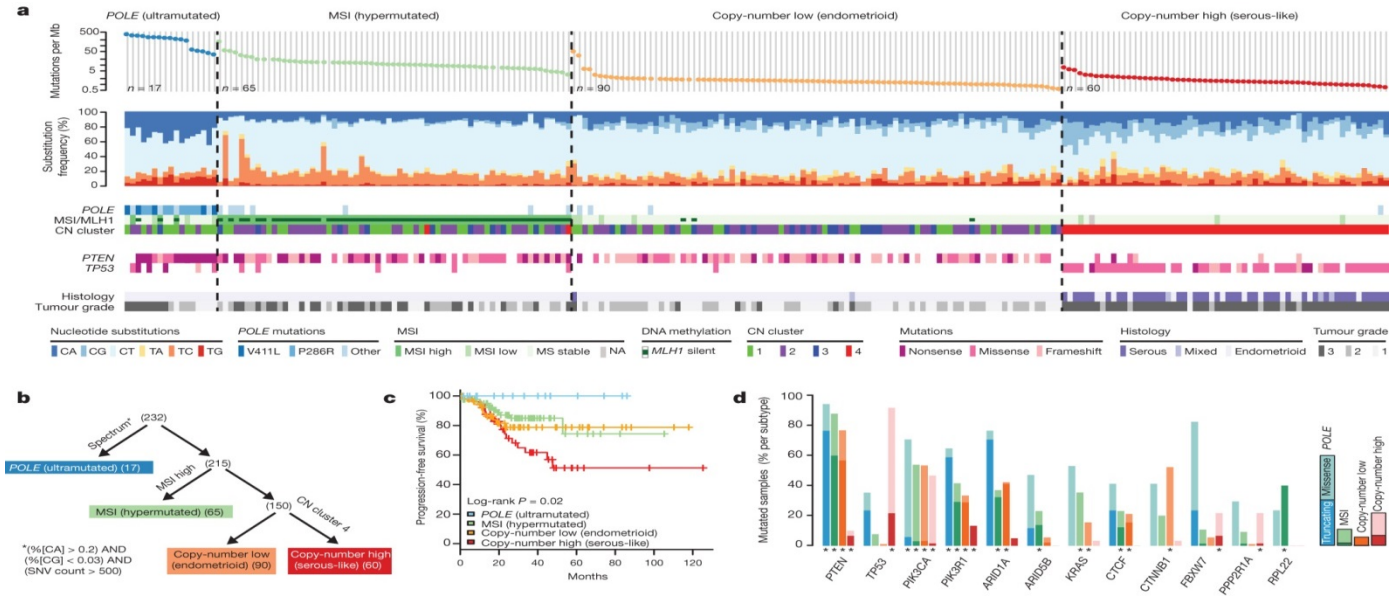
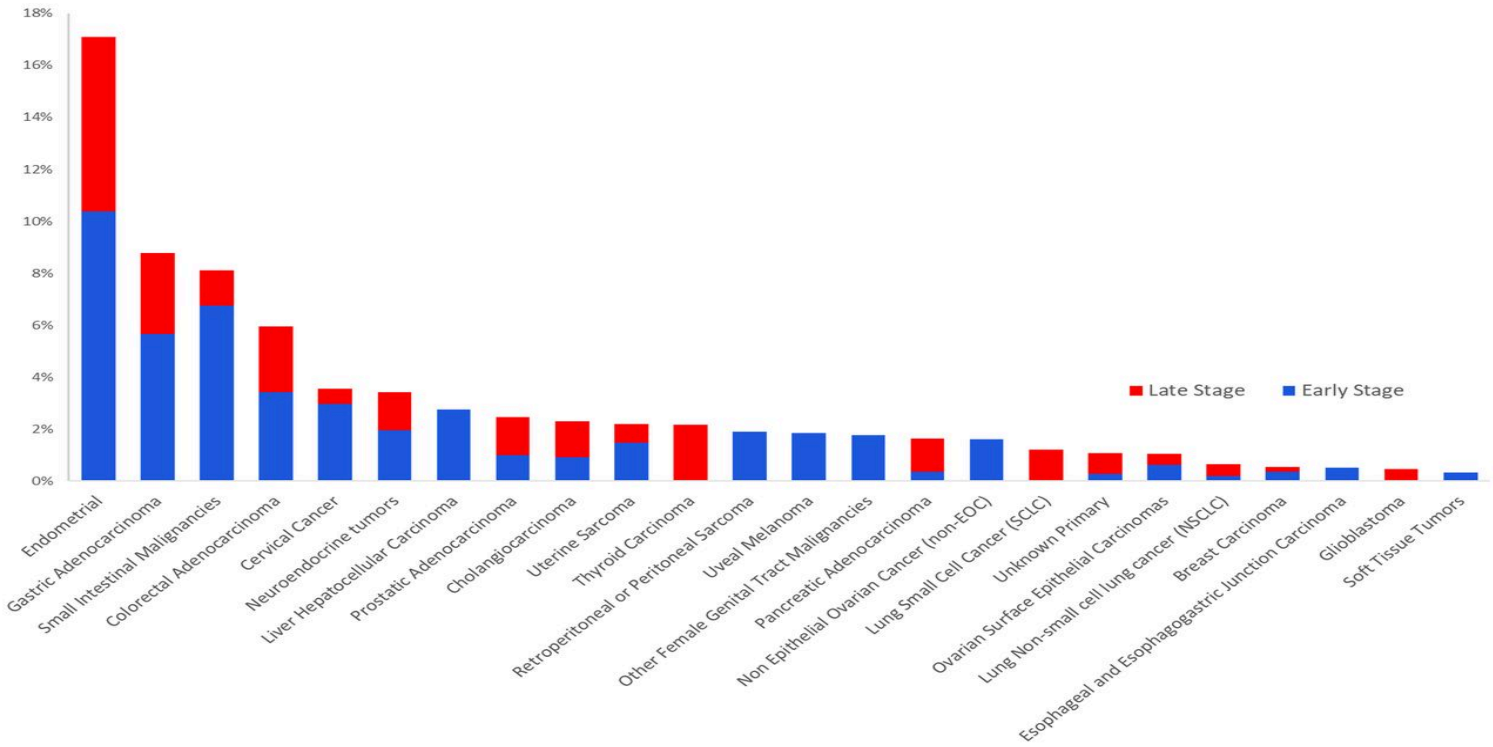
Mutation spectra across endometrial carcinomas.



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

nature

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



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

Target Lesions

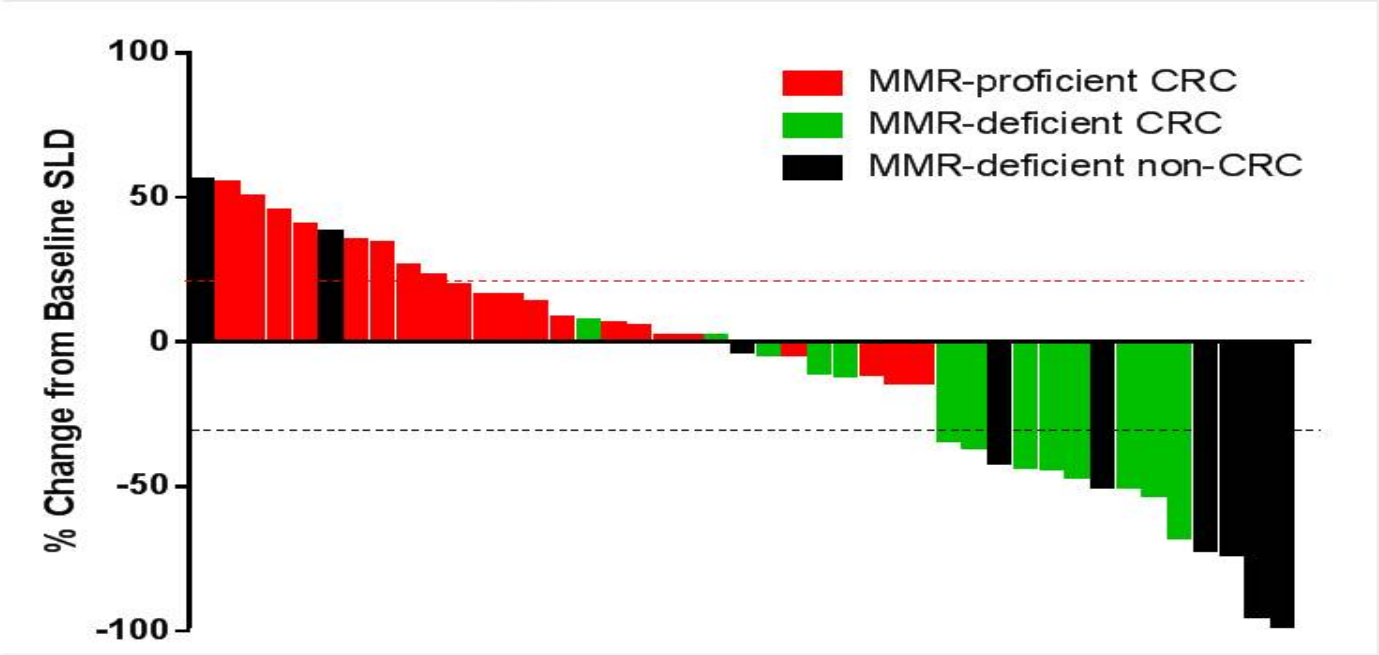
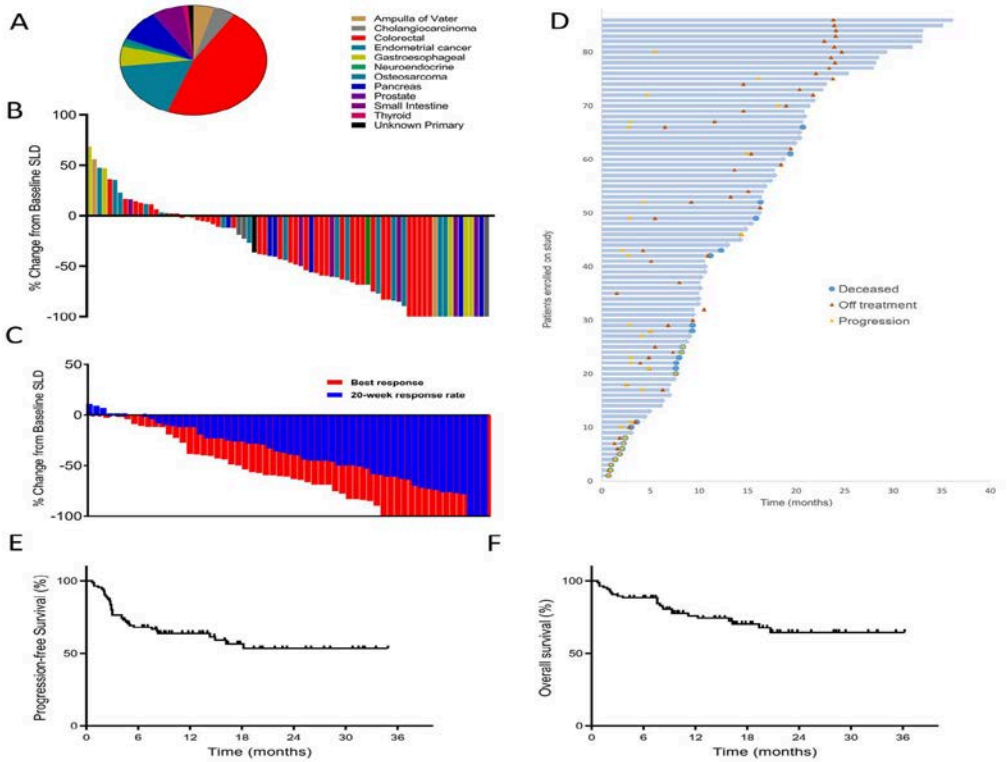


Fig. 1 Patient survival and clinical response to Pembrolizumab across 12 different tumor types with mismatch repair deficiency.



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

Metastatic Endometrial cancer

- Letrozole and everolimus vs Tamoxifen alternating with Medroxyprogesterone acetate
- Pembrolizumab in MMR deficient tumors
- Pembrolizumab plus ipilimumab in MMR deficient tumors
- Trastuzumab in HER2 amplified high grade serous tumors
- Bevacizumab and temsirolimus as potential Rx

MAYO CLINIC

Slomovitz BM et al: GOG3007: SGO 2018

- Randomized phase 2 trial: Everolimus and letrozole vs alternating Tamoxifen with medroxyprogesterone acetate (PT)
- 74 patients: February 2015 through April 2016
- RR: 24% with everolimus and letrozole (EL)
- Upfront setting: RR 53% EL vs 43% PT; PFS : 6.4 m v 3.8 m; grade 3-4 SAE: 0% vs 8.3%

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Metastatic Endometrial cancer

- Letrozole and everolimus vs Tamoxifen alternating with Medroxyprogesterone acetate
- Pembrolizumab in MMR deficient tumors
- Pembrolizumab plus ipilimumab in MMR deficient tumors
- Trastuzumab in HER2 amplified high grade serous tumors
- Bevacizumab and temsirolimus as potential Rx

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Santin AD and Fader AN: SGO 2018

- 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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Metastatic Endometrial cancer

- Letrozole and everolimus vs Tamoxifen alternating with Medroxyprogesterone acetate
- Pembrolizumab in MMR deficient tumors
- Pembrolizumab plus ipilimumab in MMR deficient tumors
- Trastuzumab in HER2 amplified high grade serous tumors
- Bevacizumab and temsirolimus as potential Rx in subsets

MAYO CLINIC

Levine D et al: SGO 2018: NRG/GOG 86P trial

- Phase 2 randomized trial of TC bevacizumab vs TC temsirolimus vs Ixabepilone CBDCA bevacizumab
- 349 patients: advanced stage or recurrent endometrial Ca
- TSC2 somatic mutations in 5.8%; associated with improved PFS in temsirolimus arm (HR 0.11)
- CTNNB1 mutations were associated with improved PFS if bevacizumab was given.

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Gynecologic cancers 2018

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- 11, 350 deaths
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- 24,800 new cases
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Total Gyn cancers

110,000 new cases

32,000 deaths

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Cervix cancer

- Data from Australia on prevention of cervical cancer with vaccination

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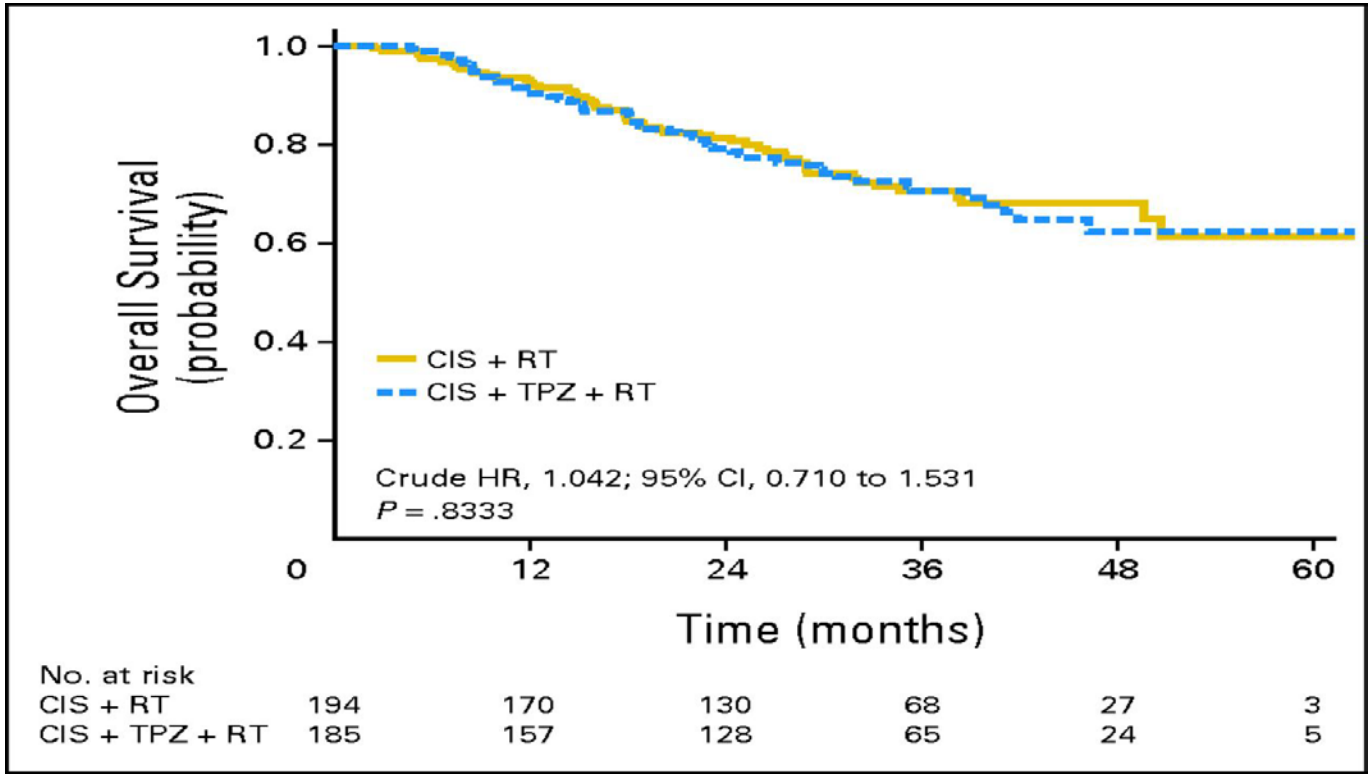
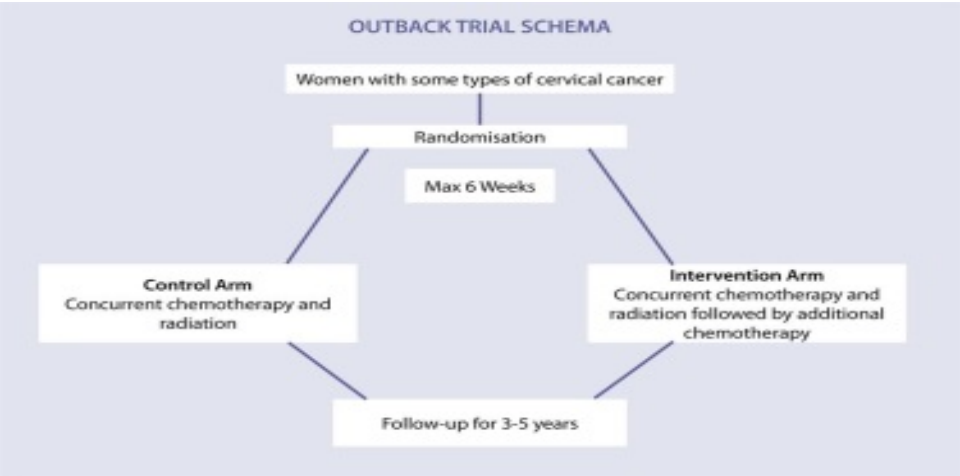
Overall survival by treatment (log-rank P = .8333).

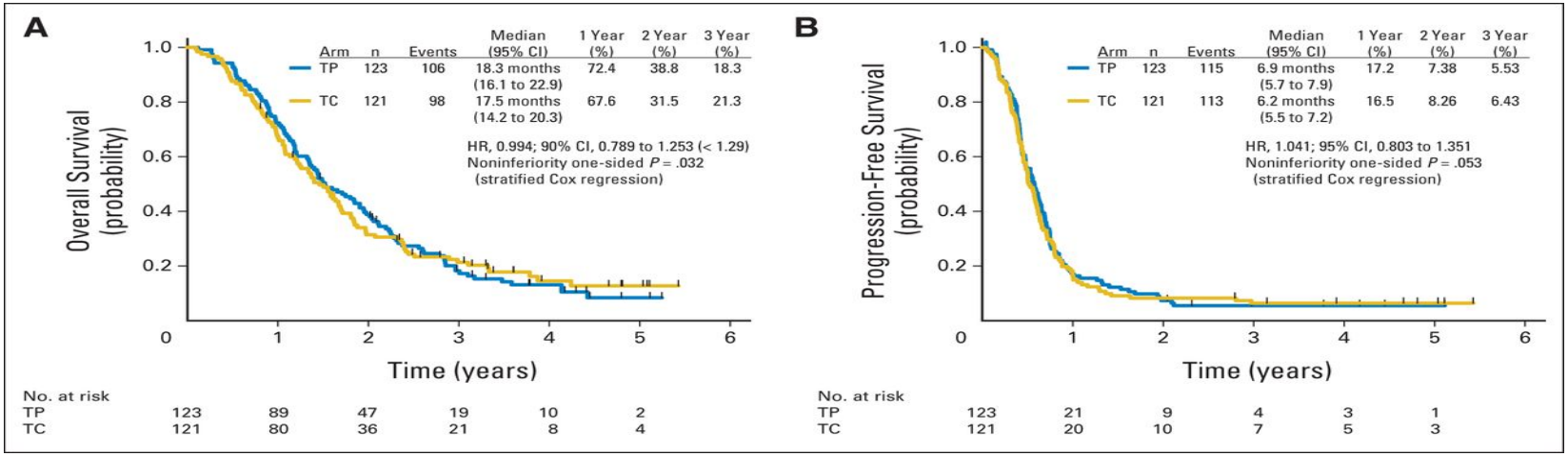


DiSilvestro P A et al. JCO 2014;32:458-464

MAYO CLINIC


OUTBACK TRIAL SCHEMA
Women with some types of cervical cancer
Randomisation
Max 6 Weeks
Control Arm
Concurrent chemotherapy and radiation
Intervention Arm
Concurrent chemotherapy and radiation followed by additional chemotherapy
Follow-up for 3-5 years

(A) Overall and (B) progression-free survival.



Ryo Kitagawa et al. JCO 2015;33:2129-2135

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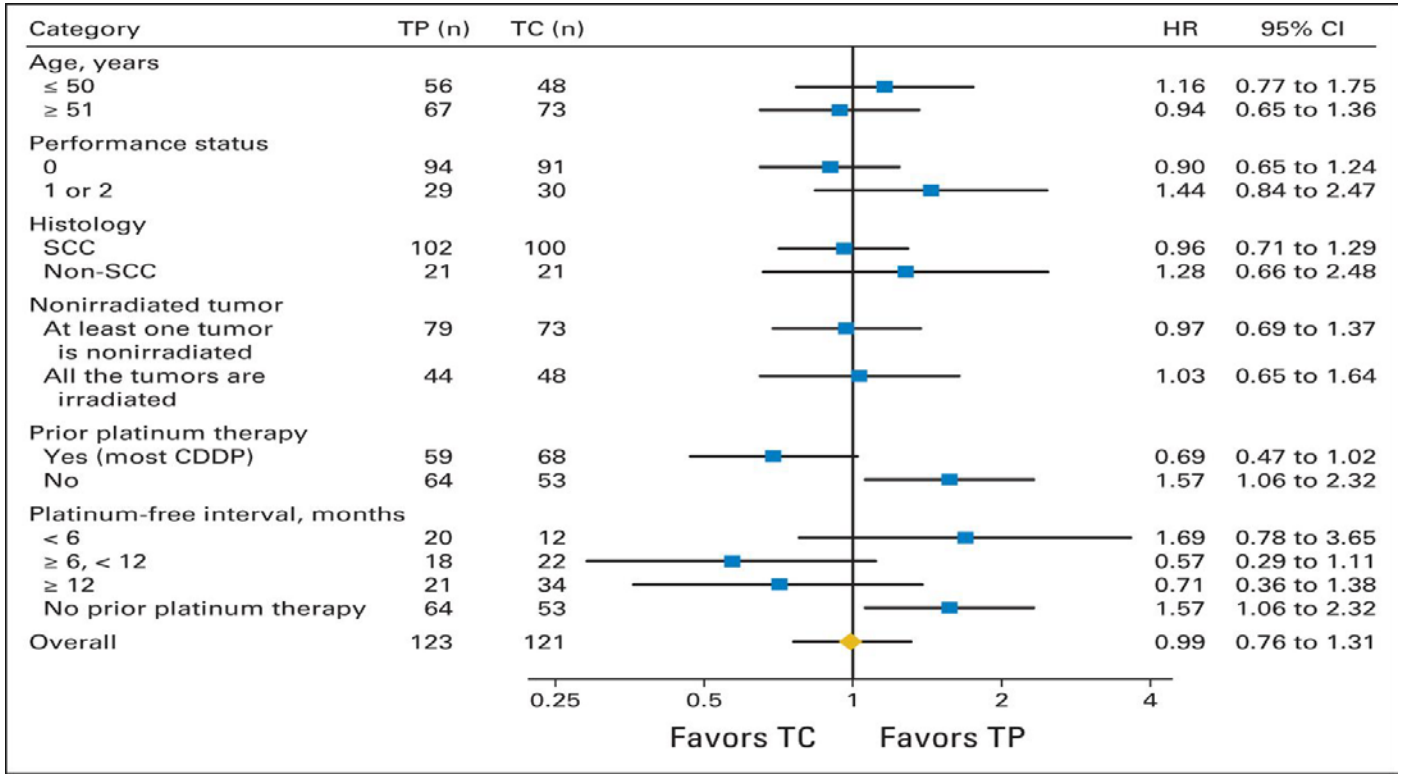
Subgroup analysis of overall survival.



Ryo Kitagawa et al. JCO 2015;33:2129-2135

JOURNAL of CLINICAL ONCOLOGY ASCO

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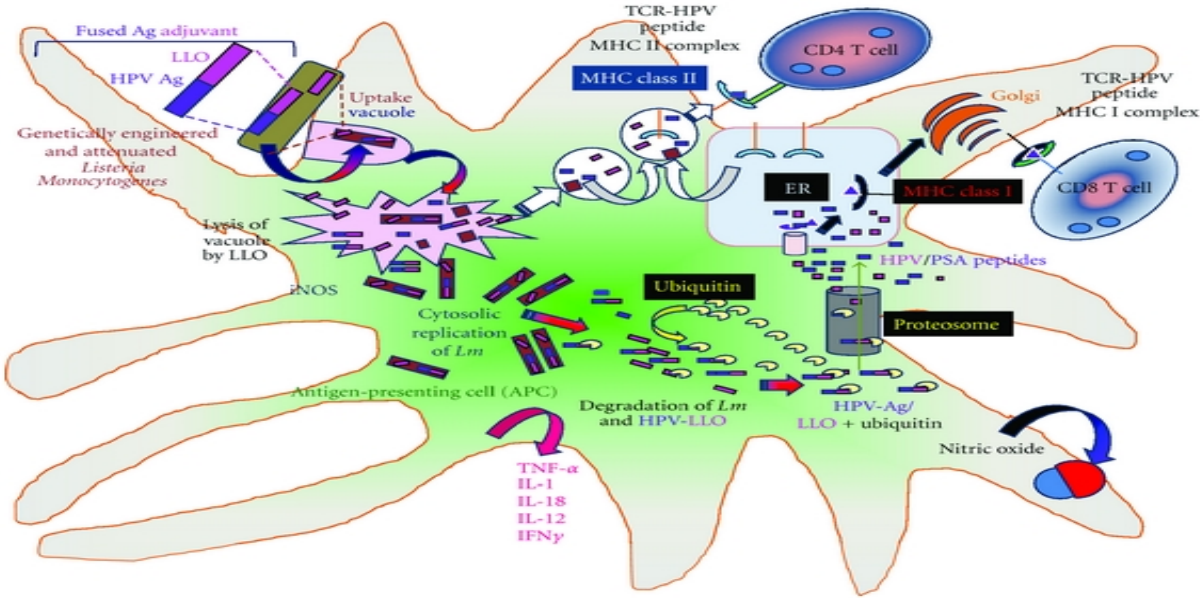
GOG 3009: ADXS001-02
GOG Foundation Trial



CONCLUSIONS: What is new in 2018

- Heterogeneous nature of ovarian cancers; most of fallopian tube origin
- Neo-adjuvant chemotherapy is an increasingly used option for ovarian cancer. More research studies in this setting. Promise of neo-adjuvant immuno-chemo.
- Debate on roles of dose dense IV paclitaxel vs IP regimens persists. Less toxicity with dose dense IV.
- Potential role of aromatase inhibitors in low grade ovarian cancer and endometrial cancer with everolimus and less so in high grade ER positive ovarian cancers.
- Potential expanded indications for upfront PARP inhibitors in HRD ovarian cancer (still under study).
- Potential for immuno-conjugates in ovarian ca and checkpoint inhibitors +/- PARP in ovarian cancers, MMR-deficient ovarian-endometrial ca and cervical cancer.

Thank you!

Gerardo Colon-Otero, M.D.

Mayo Clinic

Jacksonvile, Florida

Cell 904-742-6002

Email: gcolonotero@mayo.edu

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Questions & Discussion