Advances in Ovarian Cancer

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Conflicts of Interest

- **None**

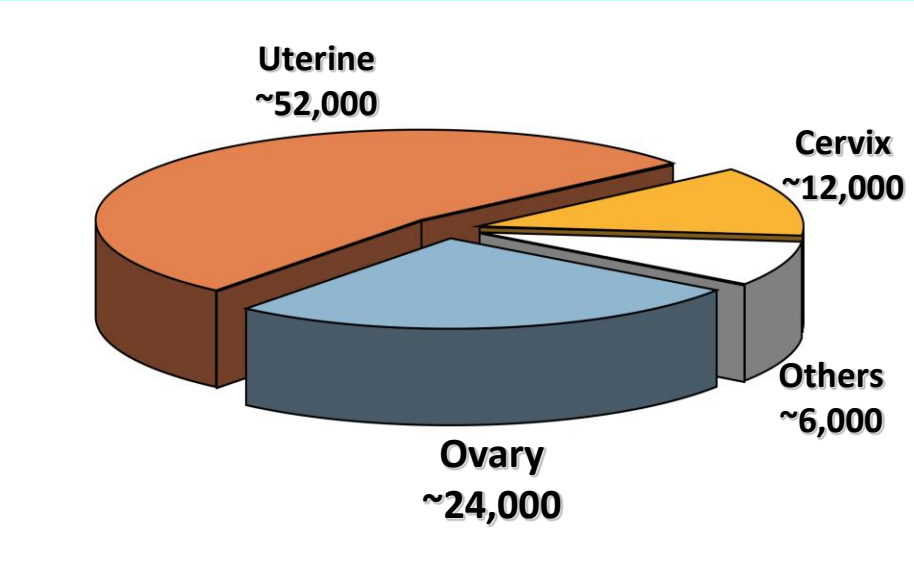
Goals

- Discuss spectrum of ovarian cancer care
  - Prevention → treatment
- Brief review of current treatment paradigms

- Topics with recently updated data
  - Focus:
    - Genomics
    - Targeted therapies
    - Consensus guideline updates

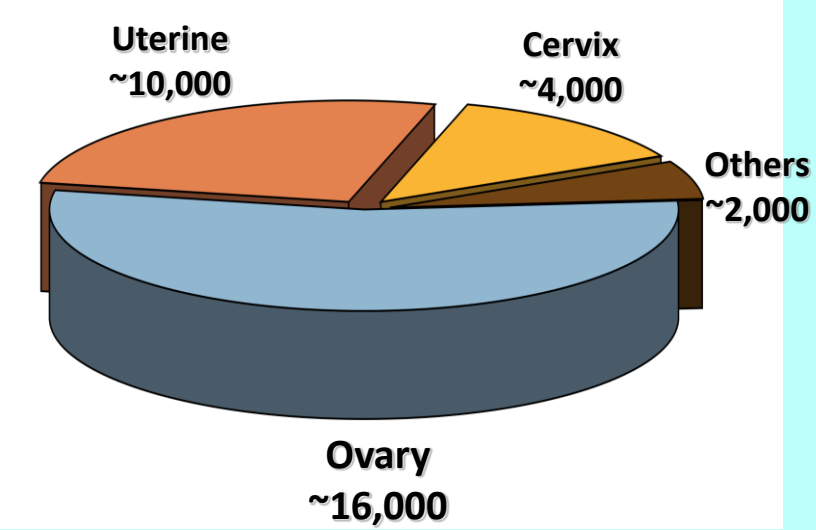
Gynecologic Cancers: Ovary

Estimated New Cases



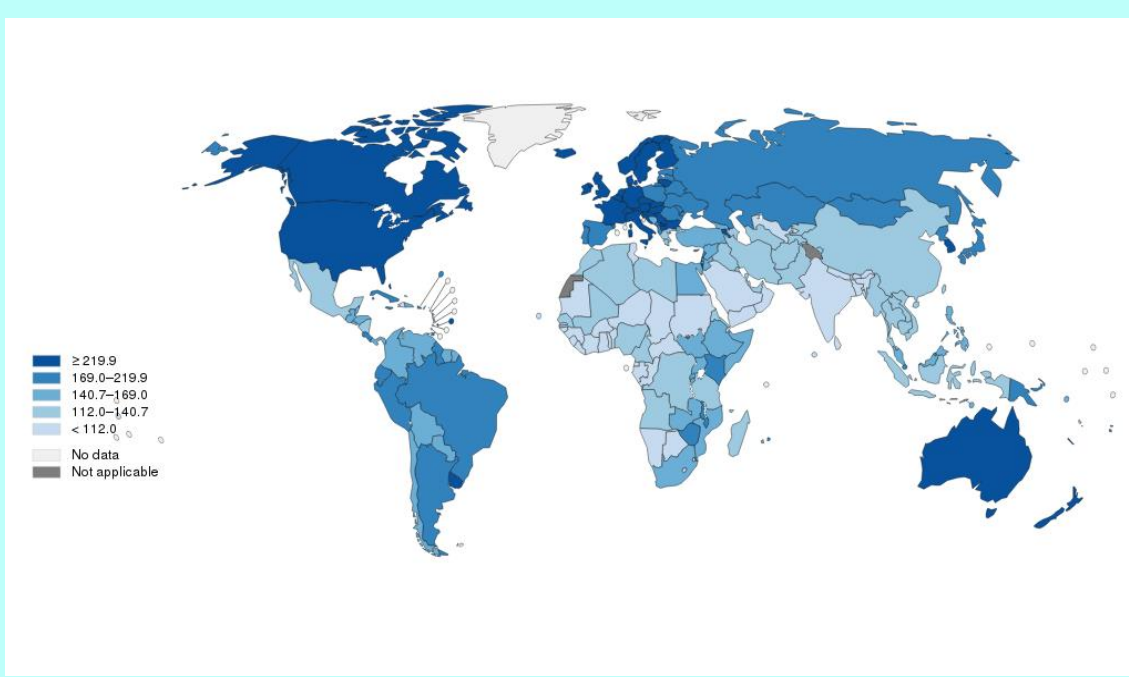
Total = ~84,000

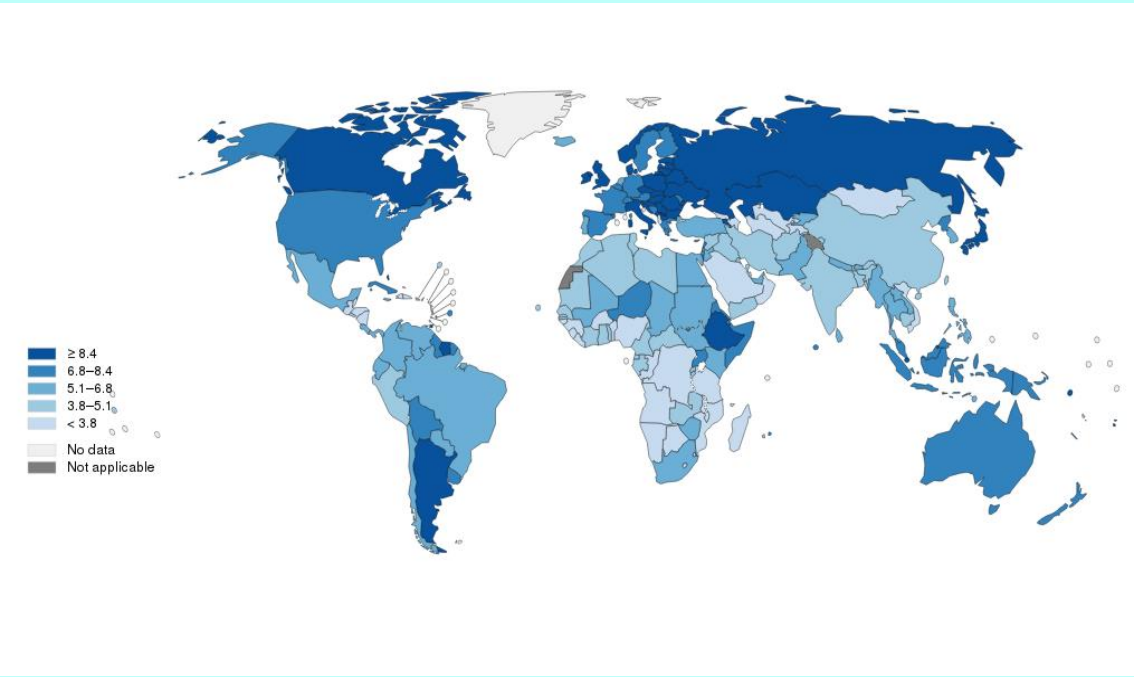
Estimated Cancer Deaths



Total = ~30,000

2012 Age-standardized rates (World) incident cases, females, *all* vs Ovarian cancers





World Health Organization

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Data source: GLOBOCAN 2012
(http://gco.iarc.fr/today)
World Health Organization

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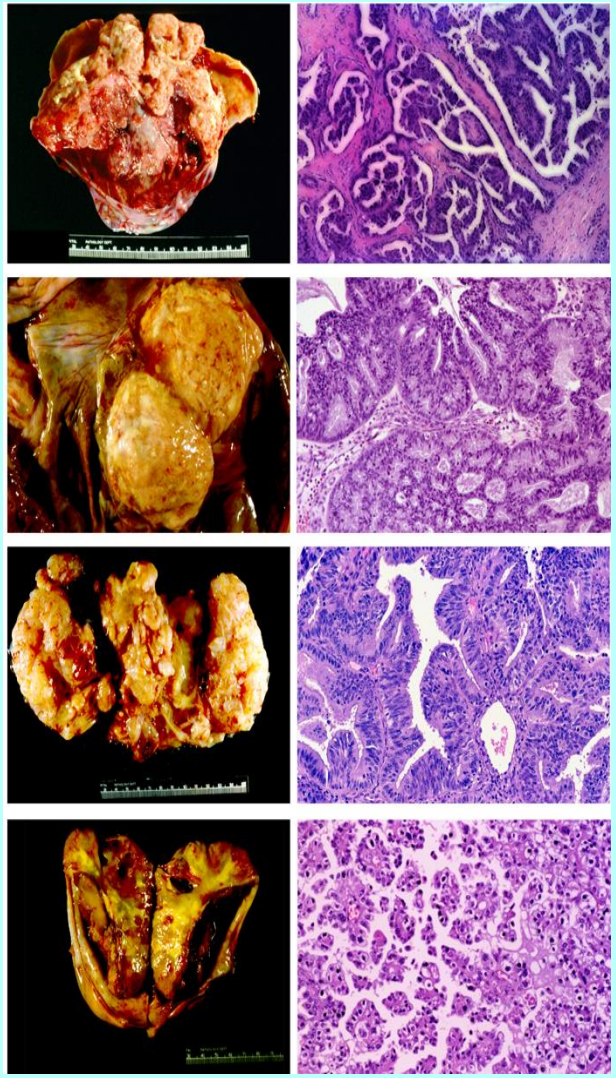
Ovarian cancer subtypes



- Serous
- Mucinous
- Endometriod
- Clear Cell

- A disease of genomic instability
- A disease of aberrant Ras pathway signaling
- A disease of aberrant PTEN,PI-3K, AKT signaling
- A disease of ARID1A

Consensus guidelines in ovarian cancer

- National Comprehensive Cancer Network (NCCN)
  - https://www.nccn.org/professionals/physician_gls/f_guidelines.asp
- Society of Gynecologic Oncology (SGO)
  - https://www.sgo.org/clinical-practice/guidelines/
- American Society of Clinical Oncology
  - http://www.asco.org/practice-guidelines/quality-guidelines/guidelines

Prevention?

Risk factor	Contributory?	Risk factor	Contributory
Age	Yes. 😃😂	Heritable gene mutations	15-25% YES
Obesity	Likely	Oral contraceptives	Decrease risk
Hormone replacement therapy (HRT)	Maybe	Diet and nutrition	Matters – how much unclear
Infertility	Complicated	Exercise and physical activity	Matters – how much unclear
Endometriosis	Likely	Cigarette smoking	Yes – mucinous cancers
Talc	Controversial	Alcohol	Maybe

Cancer Biol Med 2017. doi: 10.20892/j.issn.2095-3941.2016.0084

Screening / Early detection goals

- Cure more patients
- Enable those patients who will not achieve a cure to live longer

- Challenges (Ovarian cancer):
  - Relatively uncommon (1:70 lifetime risk – fewer events)
  - No clearly definable pre-invasive phase
  - Few if any early clinical symptoms
  - Expensive to study (follow-up)

- Important study endpoints: **overall survival (OS),** sens/spec, NNT (# of patients who undergo surgery to find (1) ovarian cancer

Screening / Early detection summary

- Annual Ca-125: NO
- Annual pelvic ultrasound: NO
- Annual Ca-125 and pelvic ultrasound: NO
- Annual pelvic exam: …. Controversial sure why not?
- ROCA: not yet
  - Randomized groups: xxx vs xxx vs xxx
  - No OS improvement (201x)

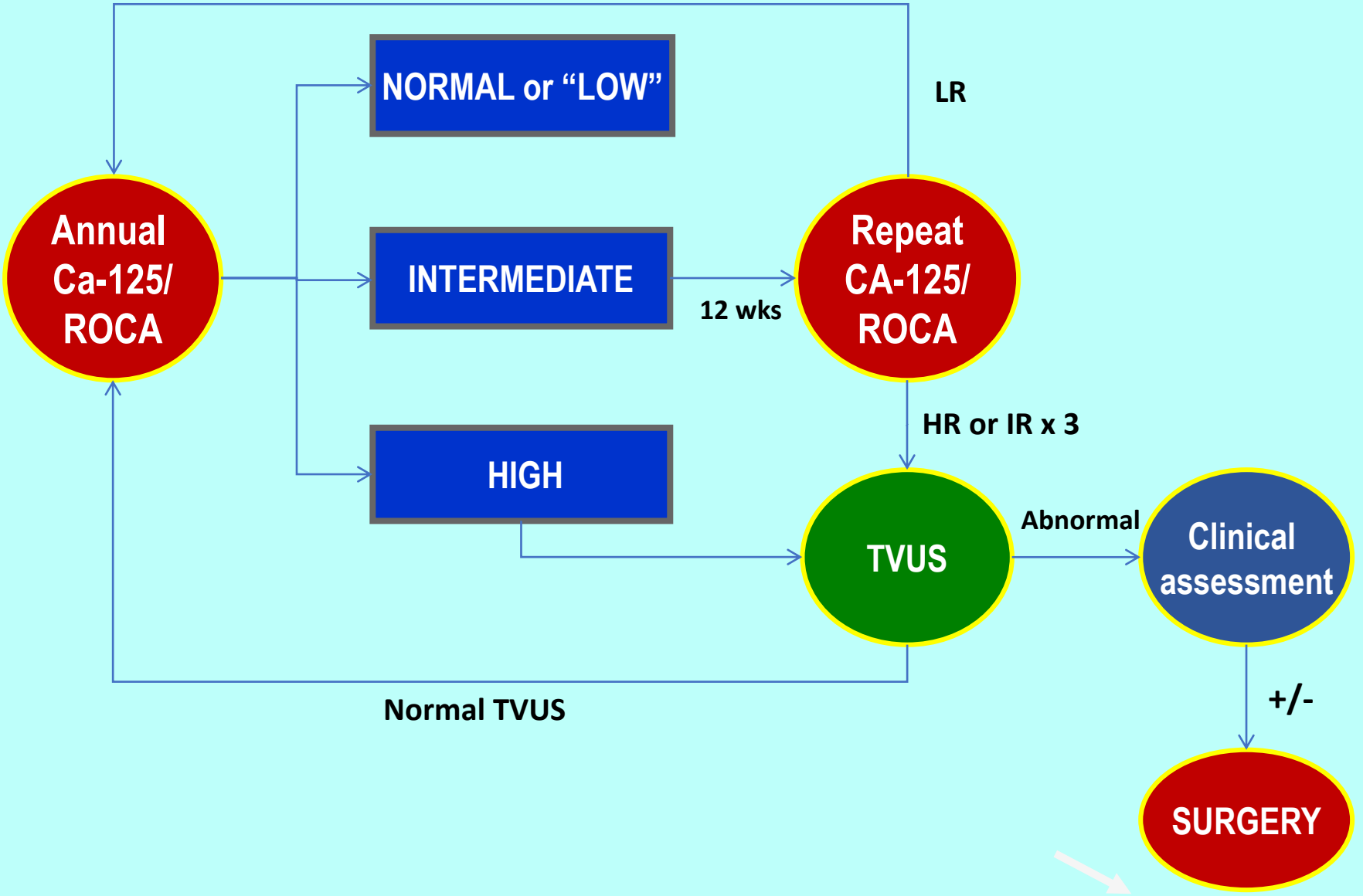
Ovarian cancer screening trials (average risk)

- Prostate, Lung, Breast and Ovarian Cancer (PLCO) trial
  - 78,216 women patients between 1993 and 2001
  - Randomization: annual Ca-125 + pelvic ultrasound vs usual care
  - No OS improvement… (2011)

- UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)
  - 202,000 patients between 2001 and 2015
  - Randomization: usual care vs MMS vs UMS
  - No OS improvement… (2015)

- **Stage I/II diagnoses**: *40% among screened vs 26% non-screened patients*

UKCTOCS Multi-Modal Screening (MMS)



Definitions

- **Primary treatment**
  - Some combination of: surgery + chemotherapy
    - Expectation: remission (~70+%)

- **Recurrent treatment**: *1st question* → how long one remains in remission
  - Platinum sensitive
  - Platinum resistant
  - Platinum refractory

- ***Changing treatment paradigms with genomic / precision oncology***

Initial management

- Surgery + chemo
- Chemo + surgery + chemo
- Both are essential in advanced stage disease

ASCO + SGO guidelines (Aug 2016)

- *All new patients should be evaluated by a gynecologic oncologist prior to initiation of medical therapy*
  - Surgical evaluation: R0 resectable?

- If cannot be optimally resected → chemotherapy (3 cycles) followed by interval surgery and an additional 3 cycles

Quality of surgery matters

- “Optimal vs Sub-optimal”
  - Goal: “R0” resection = no visible disease at completion
  - Optimal = largest remaining diameter < 1 cm
  - Sub-optimal = > 1 cm residual disease

Survival by surgical outcome

Maximal primary cytoreduction

Author	Year	Residual disease	No.	Median survival (mo)	5-yr survival (%)
Hoskins[3]	1994	No gross	41		60
		≤1 cm	62		35
		1-2 cm	12		35
		≥2 cm	65		<20
Chi[6]	2006	No gross	67	106	
		≤0.5 cm	70	66	
		0.6-1 cm	99	48	
		1-2 cm	53	33	
		>2 cm	176	34	
du Bois[8]	2010	No gross	1,046	99.1	
		≤1 cm	975	36.2	
		>1 cm	1,105	29.6	

J Gynecol Oncol. 2010 Jun;21(2):75-80.
https://doi.org/10.3802/jgo.2010.21.2.75

Primary adjuvant treatment

- **Backbone: “Platinum + taxane”**
  - Carboplatin *or* cisplatin + paclitaxel *or* docetaxel
  - Intravenous (IV) only vs IV + intraperitoneal (IP)

+

  - Bevacizumab (complicated)
  - Numerous other candidate drugs… (*clinical trials*)

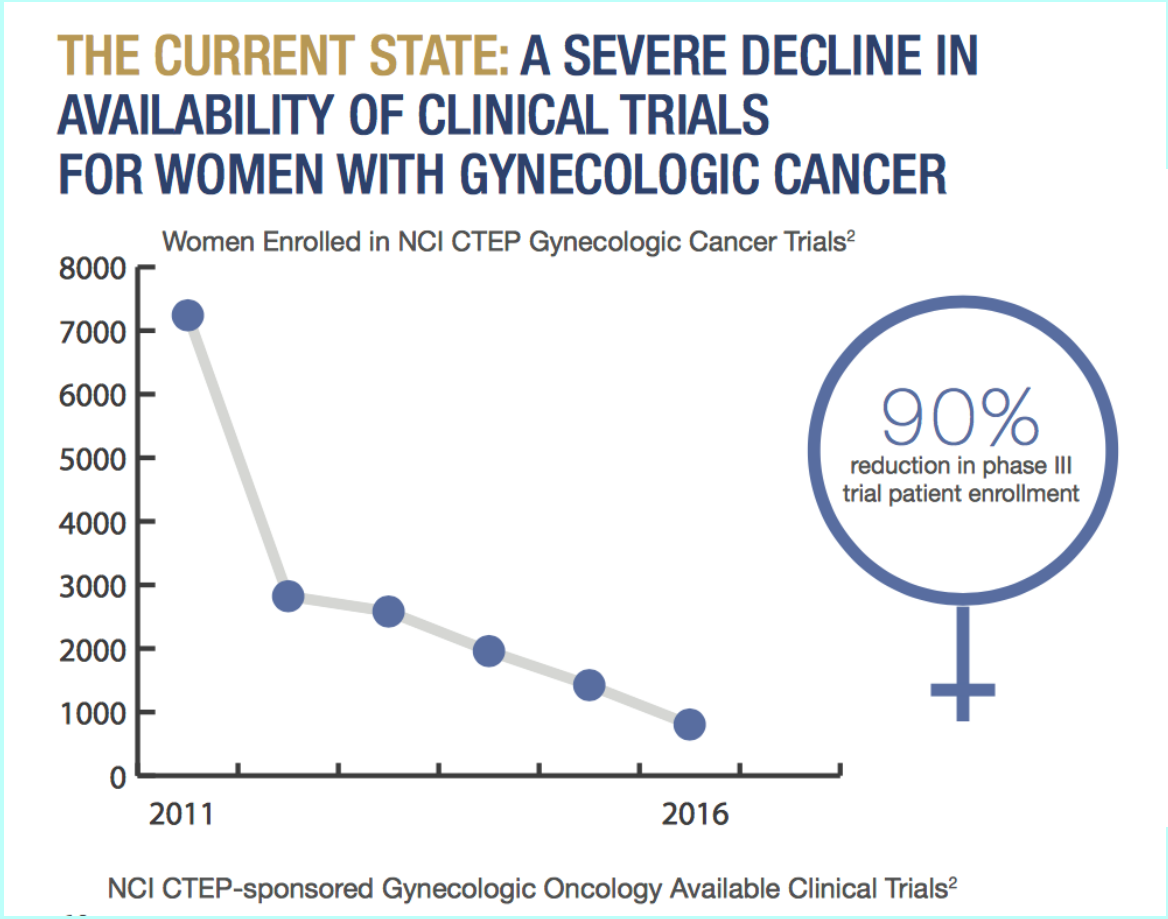
Clinical Trials

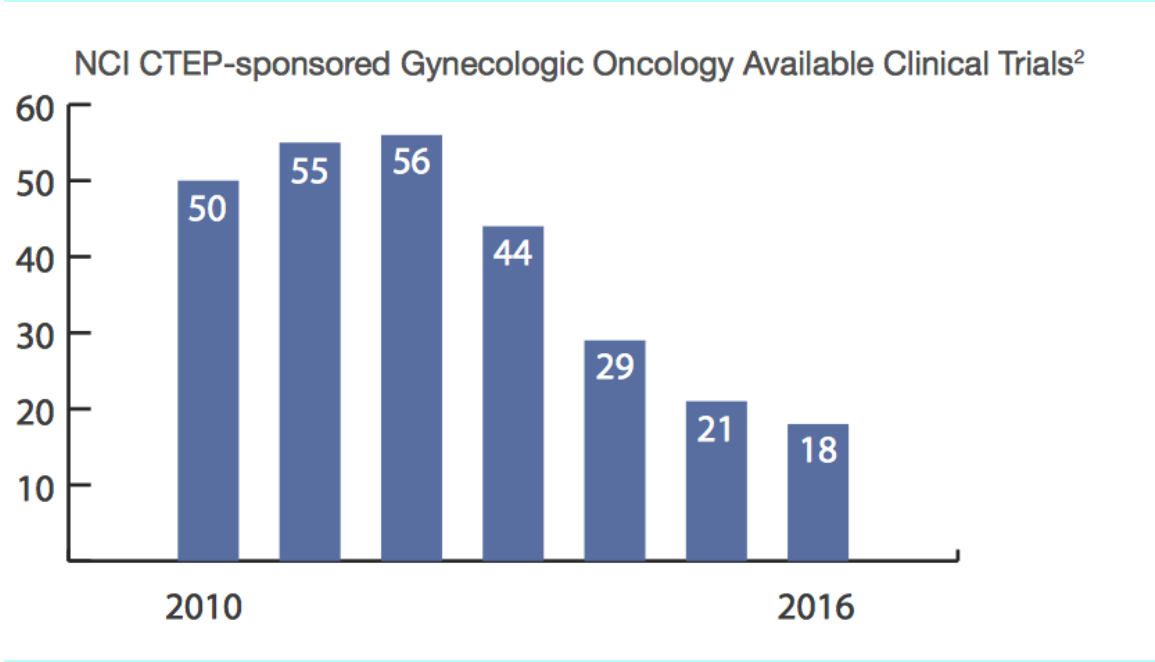
- Patients on clinical trials do ***as well or better*** than patients not enrolled on clinical trials (trials *in general* – including early phase)

- Clinical trials are the primary tool for advancing the treatment of ovarian cancer

- Current crisis: Trial availability and enrollment has precipitously declined since 2011

Not Fake News: Crisis in available clinical trials for women with gynecologic cancers





https://www.sgo.org/wp-content/uploads/2012/09/SGO-Clinical-Trial-Crisis-FINAL.pdf

Hyperthermic Intraperitoneal Extracorporeal Chemotherapy (HIPEC)

- Old concept (1980s)
- Standard therapy for select gastrointestinal cancers
- Numerous small ovarian trials
  - No clear survival advantage
  - Improved IV IV/IP (non-HIPEC) drug options
  - TOXIC!!

- Since: improved technique, expertise, standardization, drug choice…

HIPEC

Phase 3 Trial of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Ovarian Cancer

W.J. van Driel[1,2], K. Sikorska[1], J.H. Schagen van Leeuwen[3], H.W. Schreuder[4], R.H. Hermans[5], I.H. de Hingh[5,6], J. van der Velden[7], H.J. Arts[8], L. Massuger[9], A.G. Aalbers[1,6], V.J. Verwaal[10], K.K. van de Vijver[1], N.K. Aaronson[1], G.S. Sonke[1,2]

[1]Netherlands Cancer Institute, Amsterdam; [2]Dutch Gynecological Oncology Group; [3]Sint Antonius Hospital, Nieuwegein; [4]University Medical Center Utrecht; [5]Catharina Hospital, Eindhoven; [6]The Dutch Peritoneal Oncology Group; [7]Amsterdam Medical Center; [8]University Medical Center Groningen; [9]Radboud University Medical Centre, Nijmegen; [10]Aarhus University Hospital

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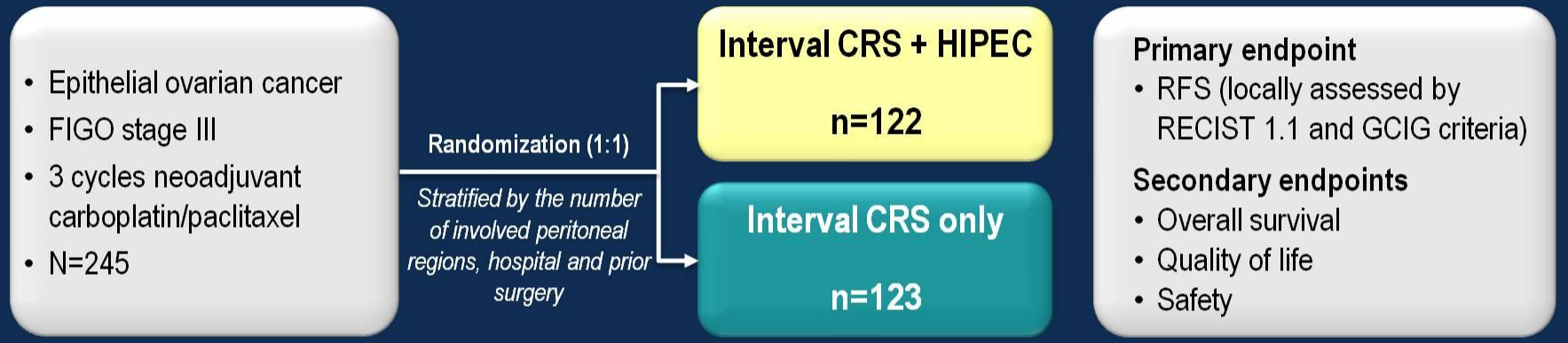
Study Design OVHIPEC



- All patients planned to received three additional cycles of carboplatin/paclitaxel after surgery
- Follow-up visits were performed every 12 weeks for 24 months, then every 26 weeks thereafter
- Tumor assessments with CT scans were performed 26, 52, and 104 weeks after the last chemotherapy
- Final analysis planned after 192 RFS events
  - 80% power to detect a 33% risk reduction (hazard ratio 0.67) with two-sided α=5%

RFS, recurrence-free survival; HIPEC, hyperthermic intraperitoneal chemotherapy; OVIHIPEC is registered at ClinicalTrials.gov (NCT00426257)

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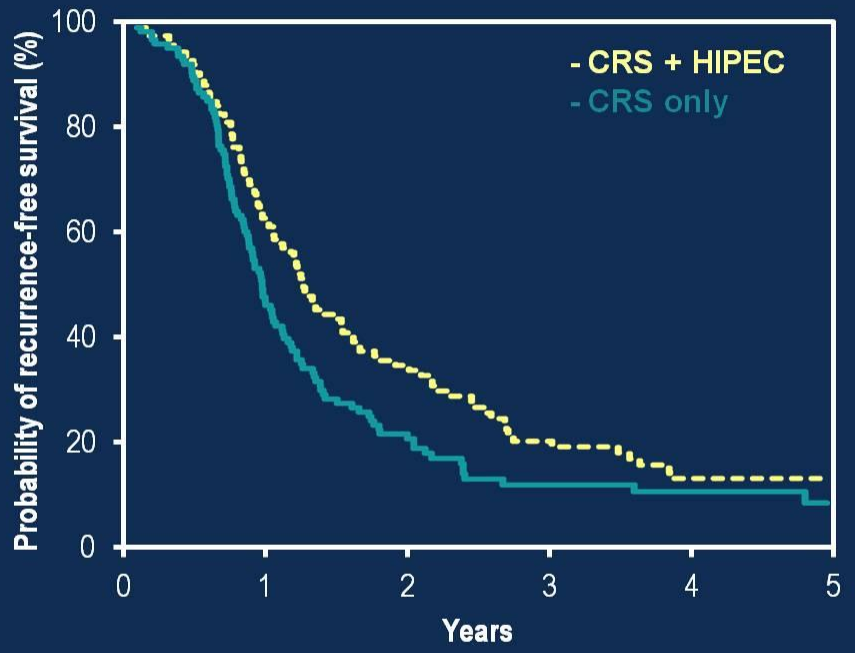
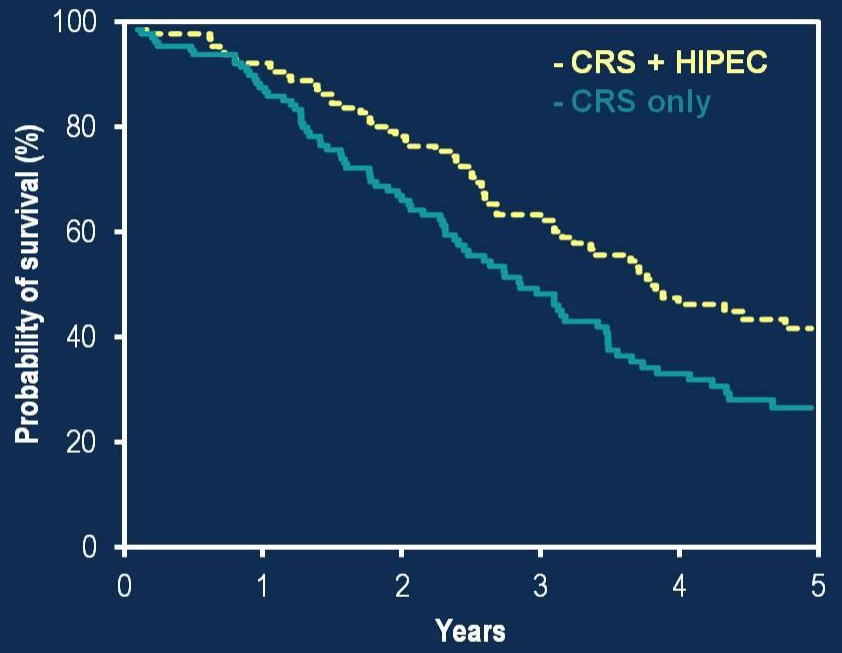
Recurrence-free Survival



RFS	CRS+HIPEC n=122	CRS only n=123
Median RFS, months	14.2	10.7
Hazard Ratio (95% CI)	0.68 (0.51–0.89)	

Overall Survival



OS	CRS+HIPEC n=122	CRS only n=123
Median OS, months	45.7	33.9
Hazard Ratio (95% CI)	0.67 (0.48–0.94)	

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Completion of primary therapy

- Okay – now what?
  - Complete Remission
    - Normal Ca-125, exam, film
  - Partial response
    - Improvement but disease still apparent
  - Progressive disease
    - Cancer worsens during primary treatment

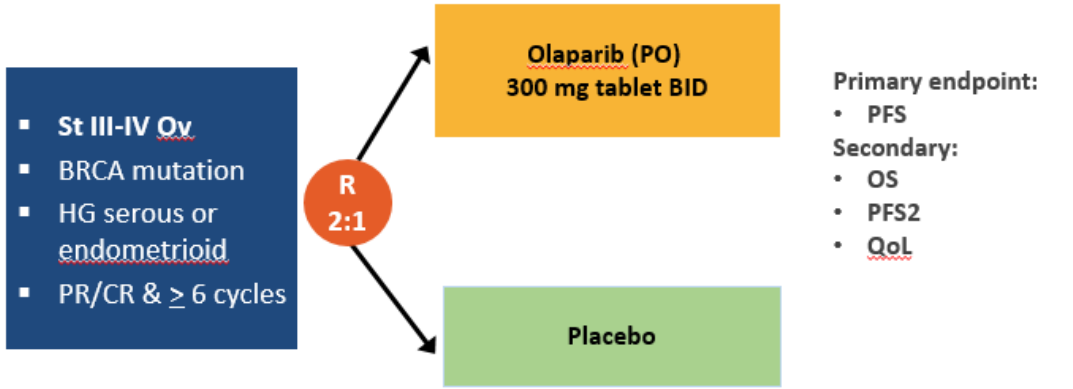
- Maintenance therapy??
  - Must effectively fight cancer and be less toxic

FDA approved maintenance therapies

- ***Primary*** **treatment**
  - None (U.S.); Olaparib in Europe
    - Long list of potentials have been evaluated
  - Off label?: bevacizumab, pazopanib, PARP?
    - Controversial...
- Multiple clinical trials with drugs vying for this space

Front Line Maintenance Clinical Trials: PARPi switch maint

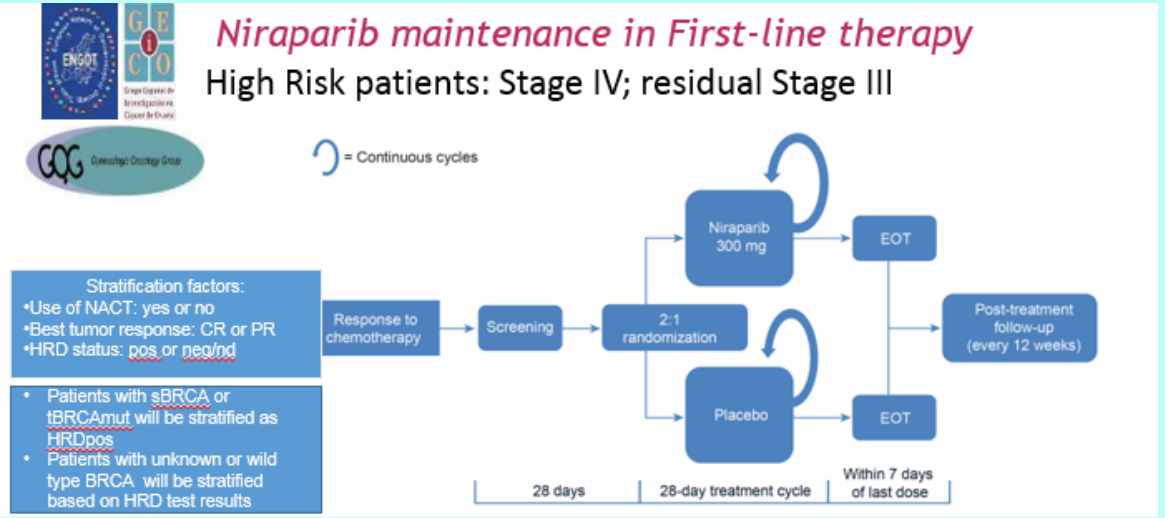
SOLO-1 (Olaparib)



Estimated Enrollment: 397
Study Start Date: Aug 2013
Estimated Study Completion Date: Jan 2022
Estimated enroll Completion: Jul 2016 (Final data)

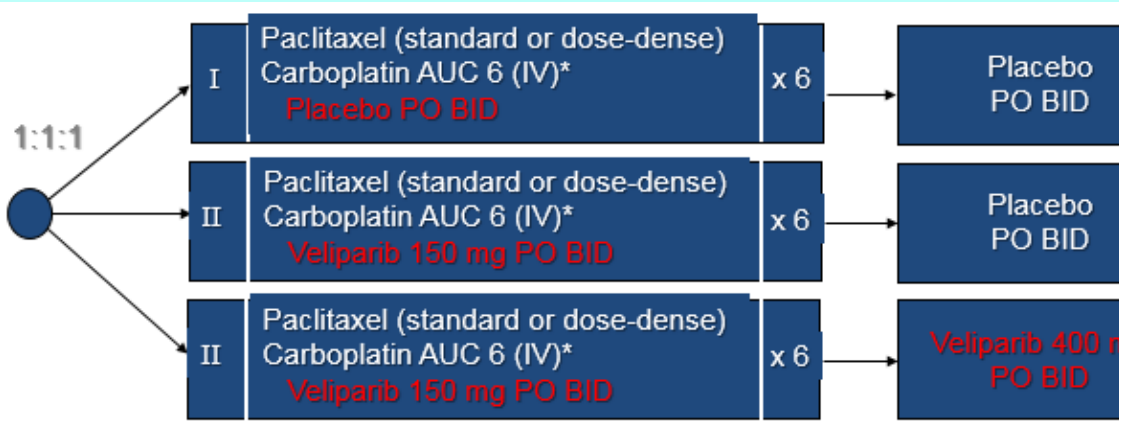
ClinicalTrials.gov Identifier: NCT01844986

PRIMA (Niraparib)



Front Line Maintenance Clinical Trials: PARPi continuous + maint

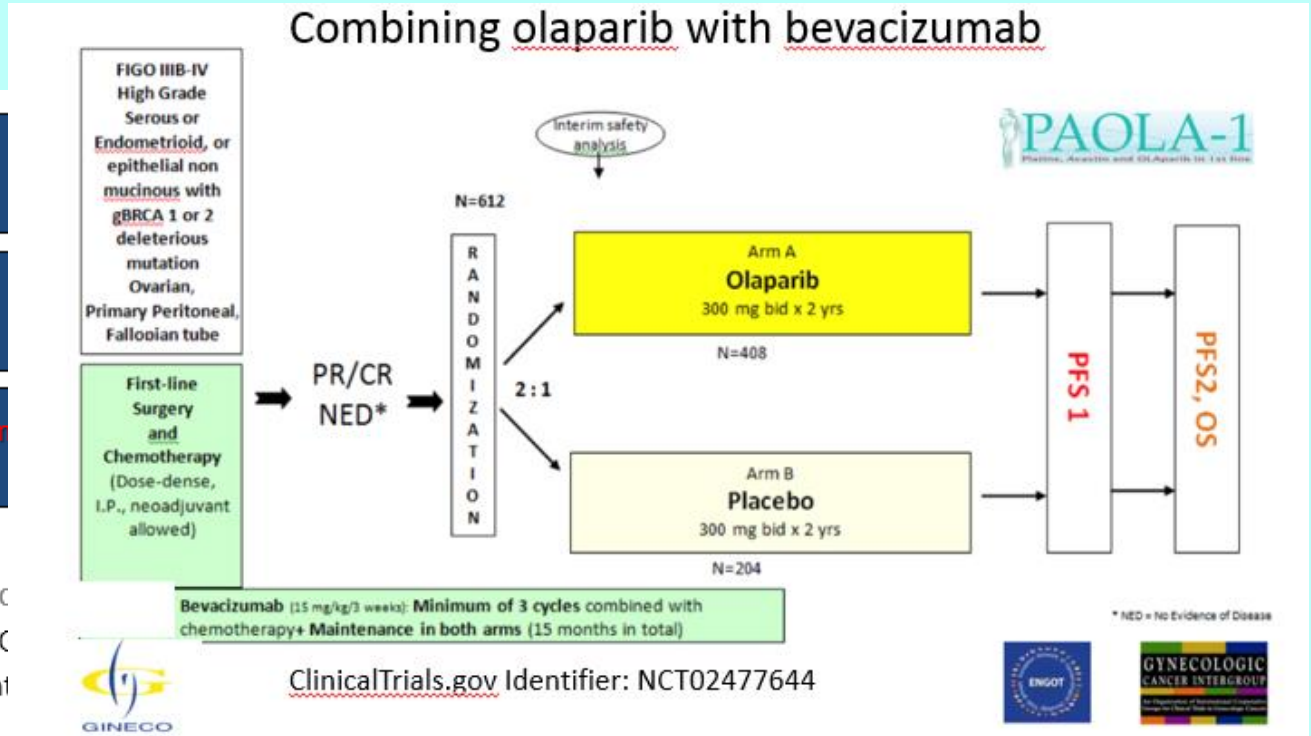
GOG 3005 (Veliparib)



Collaborative development with AbbVie (M13-694) including international participation, seeking EMA and FDA regulatory appro

Open:	JUL 2015 (856 as of 07FEB2017)	Coleman R, for GOC
Closed:		ClinicalTrials.gov Ident
Target Accrual:	~1100 pts (264 BRCA1/2 +)	NCT02470585

PAOLA-1 (Olaparib)



FDA approved maintenance therapies

- ***Relapsed* treatment**
  - Nirapirib (March 2017)
    - Maintenance treatment following a partial or complete response to most recent platinum therapy
      - No biomarker test required

New FDA approvals for recurrent disease

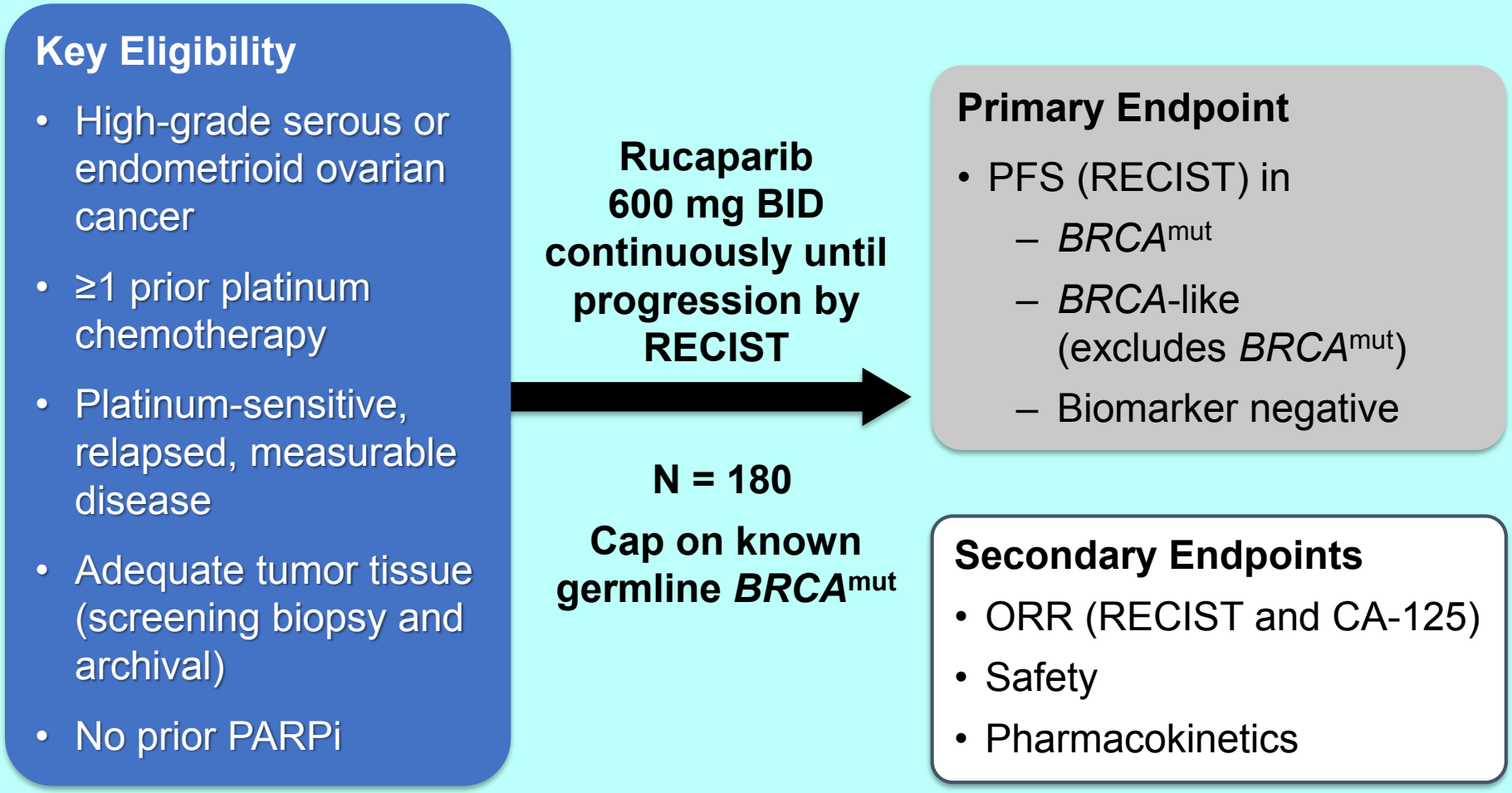
- Bevacizumab (Dec 2016) expanded indication
  - Platinum **sensitive** recurrence in combination with chemotherapy
    - Gemcitabine + Carboplatin
    - Paclitaxel + Carboplatin
      - Followed by bevacizumab maintenance

New FDA approvals for recurrent disease

- Rucaparib (Dec 2016)
  - BRCA mutated (germline or somatic) ovarian cancer treatment
    - 2 or more prior therapies
    - FoundationFocus CDxBRCA test simultaneously approved for assessment of BRCA status (tumor/tissue test)

- *Olaparib (Dec 2014)
  - BRCA mutated (germline) ovarian cancer treatment
    - 3 or more prior therapies
    - BRAC Analysis CDX for BRCA status

ARIEL2: Phase 2 Trial of Rucaparib in Prospectively Defined Molecular Subgroups[1]

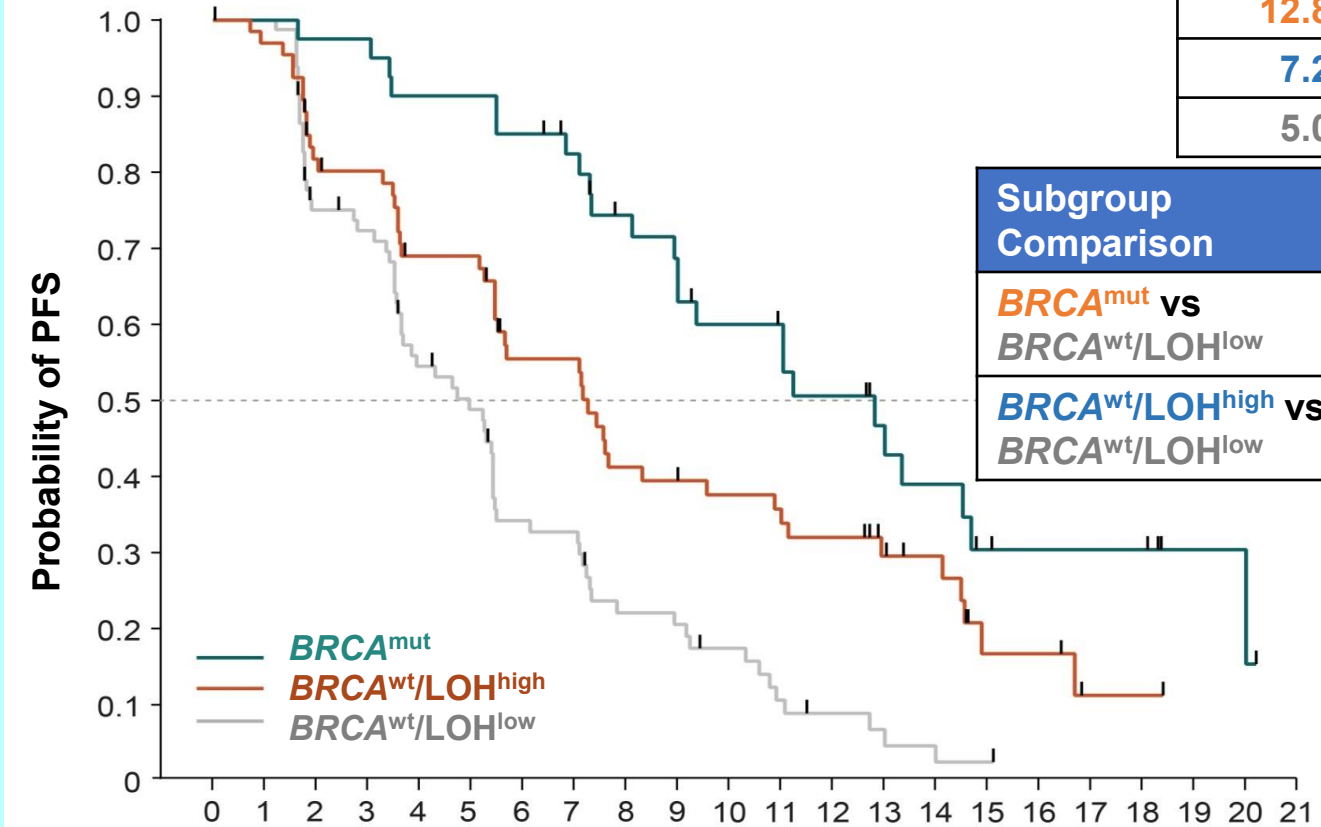


1. McNeish IA et al. 2015 American Society of Clinical Oncology Annual Meeting (ASCO 2015). Abstract 5508.

ARIEL2 (Rucaparib): PFS (2016)

Median, mo (95% CI)
12.8 (9.0-14.7)
7.2 (5.5-9.6)
5.0 (3.6-5.4)

Subgroup Comparison	HR (95% CI)	*P*
BRCA^{mut} vs *BRCA*^{wt}/LOH^{low}	0.25 (0.15-0.42)	< .001
BRCA^{wt}/LOH^{high} vs *BRCA*^{wt}/LOH^{low}	0.51 (0.34-0.74)	< .001



Available

BRCA^{mut}	40	40	39	39	36	36	34	33	27	25	22	20	19	16	12	9	7	5	5	5	2	2	0
BRCA^{wt}/LOH^{high}	69	65	54	50	43	42	36	31	27	23	21	20	18	17	14	10	5	4	3	1	1		
BRCA^{wt}/LOH^{low}	83	81	60	54	42	37	23	22	15	14	12	10	6	4	3	2	1	0					

1. Coleman R et al. ASCO 2016. Abstract 5540. 2. Swisher EM et al. *Lancet Oncol*.2017;18:75-87.

Rucaparib Activity(2016) in BRCA^{mut} and BRCA^{wt}

- ***BRCA*^{mut} patients (n = 40)**
  - **69% ORR (RECIST)**
  - 82% ORR (RECIST and CA-125)
  - 83% of patients continuing on treatment (+)

Responses observed in both germline and somatic *BRCA*^{mut} tumors

***BRCA*-like signature (n = 82)**

- **30% ORR (RECIST)**
- 45% ORR (RECIST and CA-125)
- 52% of patients continuing on treatment (+)

***BRCA*^{wt} patients <u>without</u> *BRCA*-like signature (n = 70)**

- **13% ORR (RECIST)**
- 21% ORR (RECIST and CA-125)
- 38% of patients continuing on treatment (+)

BRCA-like = LOH^{high} by NGS analysis.

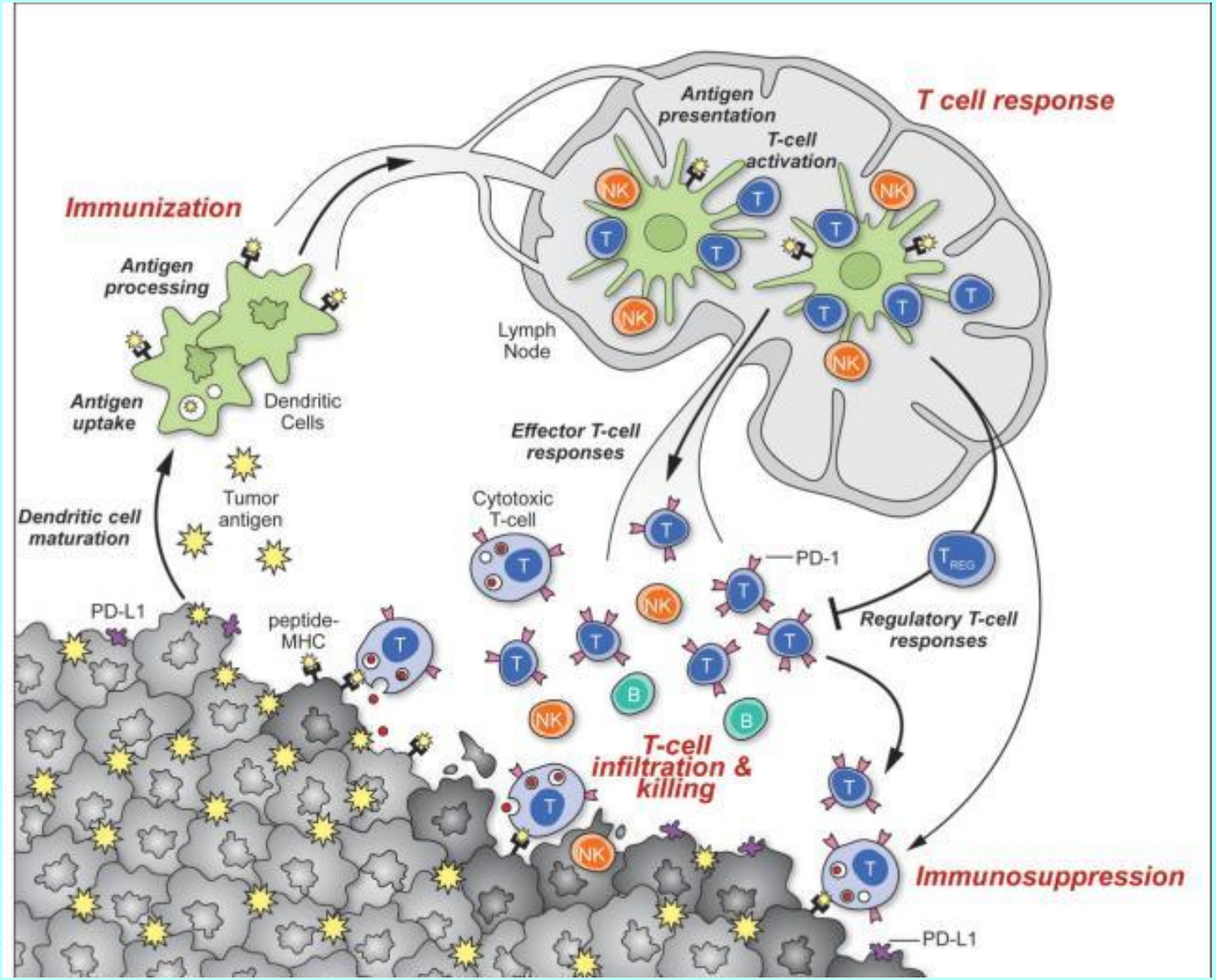
1. Coleman RL et al. ASCO 2016. Abstract 5540.

Immunotherapy

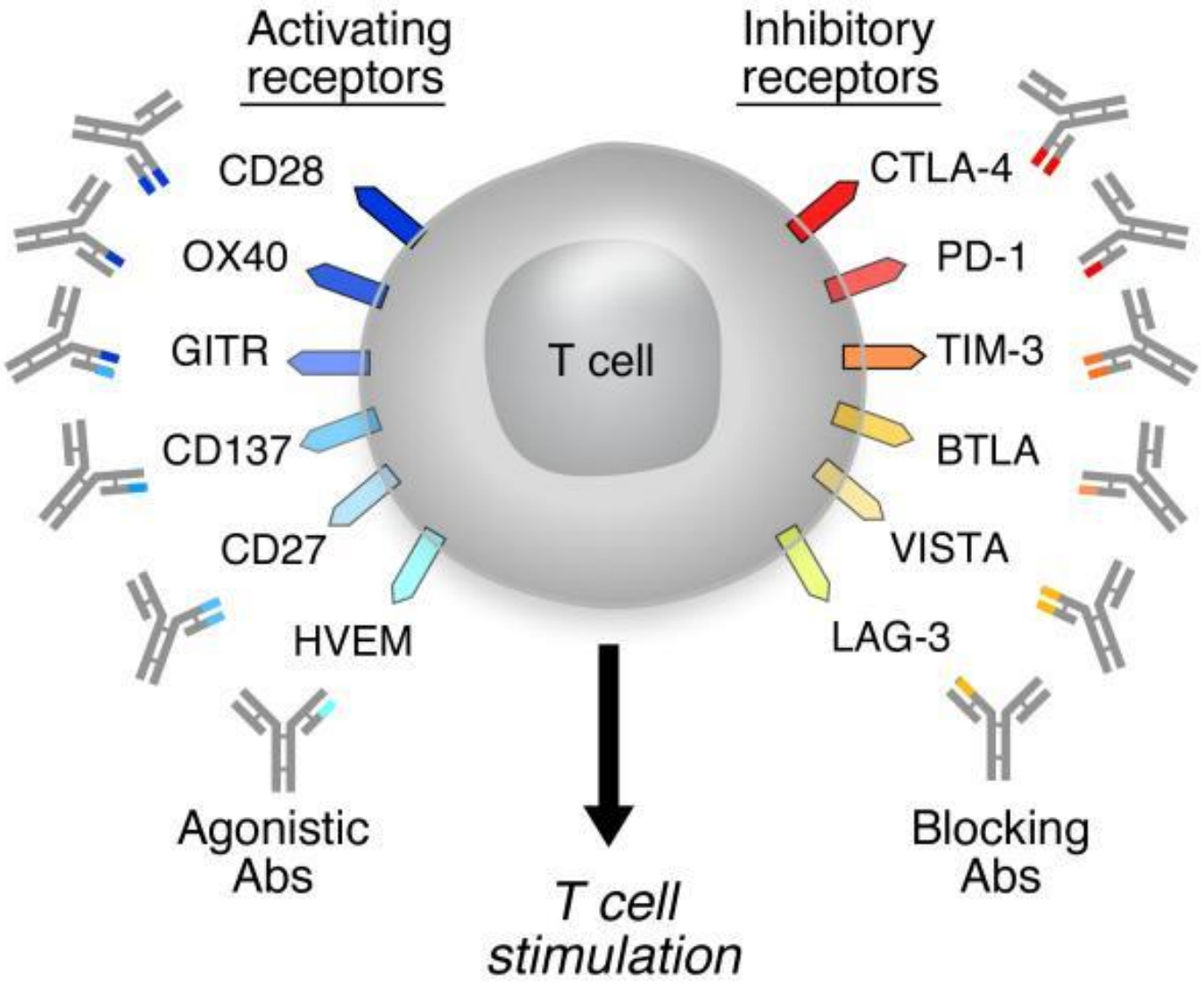
- Broad term – includes numerous different strategies
  - Adoptive T cell transfer
    - Chimeric Antigen Receptor T cell therapy (CAR-T)
  - Bispecific monoclonal antibodies
  - Checkpoint inhibition
    - PD-1
    - CTLA-4

Immunotherapy basic mechanism

- Key concepts:
  - Multiple arms make up immune system, most broadly: innate and adaptive
  - Balance between T cell activation and regulation



Checkpoint inhibitor targets



Pembrolizumab in Patients with PD-L1–positive Advanced Ovarian Cancer: Updated Analysis of KEYNOTE-028

Andrea Varga,[1] Sarina Piha-Paul,[2] Patrick A. Ott,[3] Janice M. Mehnert,[4] Dominique Berton-Riguad,[5] Anne Morosky,[6] Guo Qing Zhao,[6,7] Reshma Rangwala,[6] Daniela Matei[8]

[1]Institut Gustave Roussy, Villejuif, France; [2]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Dana-Farber Cancer Institute, Boston, MA, USA; [4]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [5]ICO Centre René Gauducheau, Saint-Herblain, France; [6]Merck & Co., Inc., Kenilworth, NJ, USA; [7]MRL, MSD China, Beijing, China; [8]Northwestern University Feinberg School of Medicine, Chicago, IL, USA

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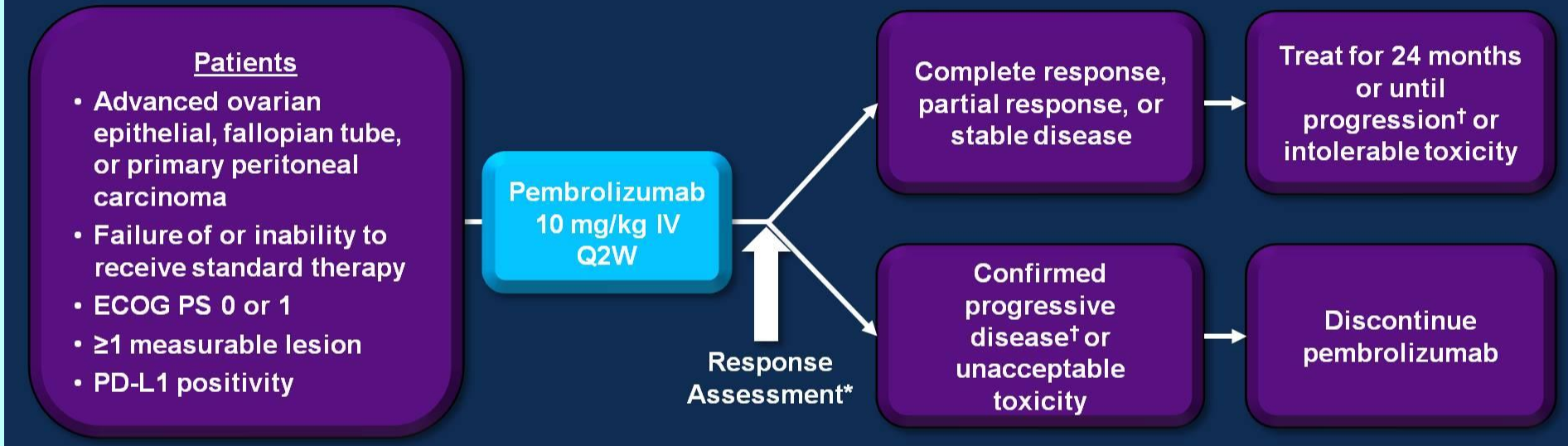
KEYNOTE-028 (NCT02054806): Phase 1b Multicohort Study of Pembrolizumab for PD-L1–positive Advanced Solid Tumors



***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

†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.

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ECOG = Eastern Cooperative Oncology Group; IV = intravenous; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PS = performance status.

Best Overall Response (RECIST v1.1, Investigator Review)

	N = 26		
	n	%	95% CI†
Overall response rate	3	11.5	2.4, 30.2
Complete response	1	3.8	0.1, 19.6
Partial response	2	7.7	0.9, 25.1
Stable disease	7	26.9	11.6, 47.8
Progressive disease	16	61.5	40.6, 79.8

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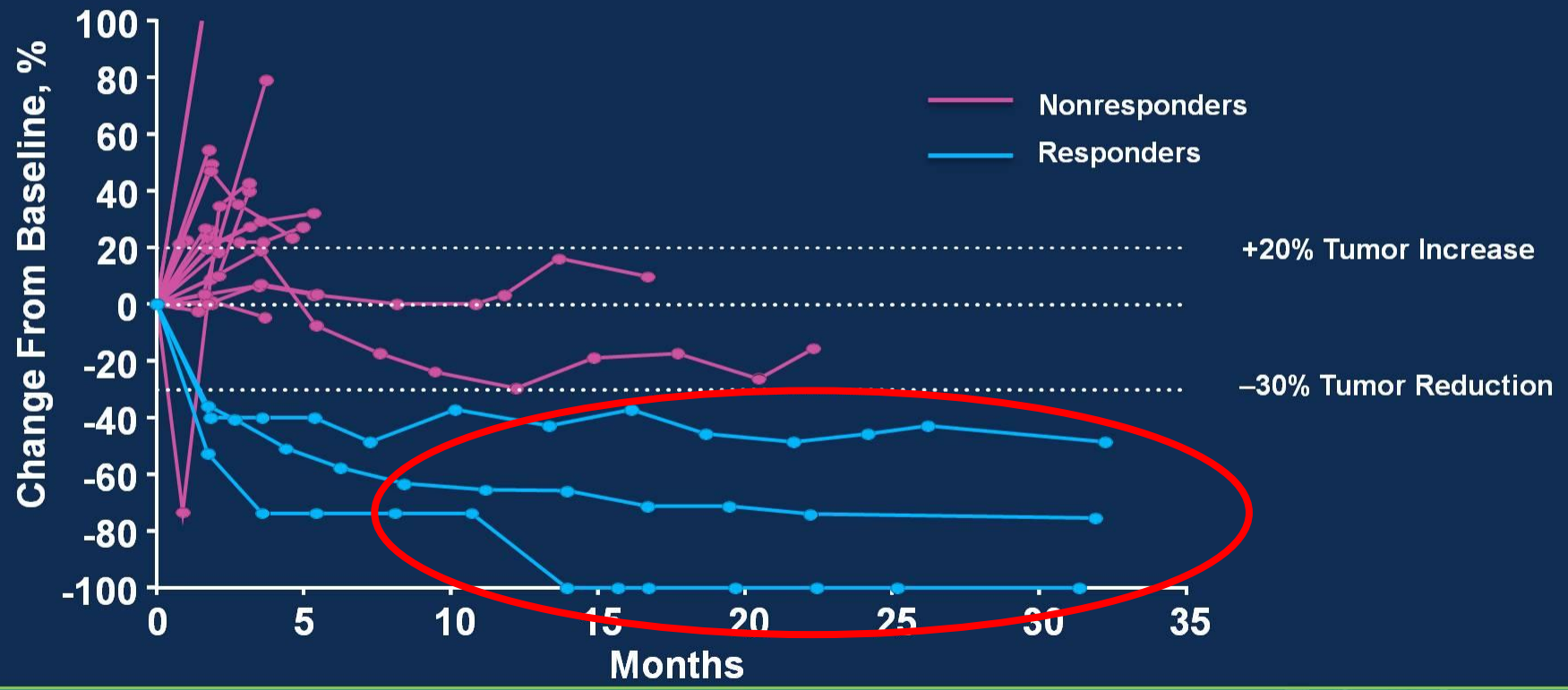
CI = confidence interval. †Based on binomial exact CI method.
Data cutoff date: February 20, 2017.

Longitudinal Change in Tumor Size from Baseline (RECIST v1.1, Investigator Review)



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Data cutoff date: February 20, 2017.

How does this compare with other I/O data in EOC?

Agent	Target	N	Response	Stable Disease
Nivolumab	PD-1	20	10% CR 5% PR	30%
Pembrolizumab	PD-L1	26	4% CR 8% PR	27%
Avelumab	PD-L1	124	10%PR	44%
Durvalumab + Olaparib	PD-L1 + PARP	10	10% PR	70%
Duralumab + Cediranib	PD-L1 + VEGFR	4	25% PR	50%

Hamanishi et al. J Clin Onc 2015, 33; Varga et al. ASCO 2017; Disis et al J Clinic Oncol 34 (suppl): 2016; Lee et al J Clin Onc 34 suppl): 2016 **Table as presented by Paul Sabbatini at ASCO 2017**

Responses to checkpoint inhibitors in ovarian cancer

Table 3 Studies of immune checkpoint inhibitors in ovarian cancer with reported results

Immunotherapy agent(s)	Trial number	Disease status	Phase	N	Results (N; duration)	G3/4 adverse events	Reference
Ipilimumab		recurrent EOC, previously treated with GVAX vaccine	I	9	PR (1; 35+ mos.) SD (3; 1 for 6+ mos.)	diarrhea	Hodi et al. [50]
BMS-936559 (anti-PD-L1)	NCT00729664	recurrent EOC	I	17	6% PR (1; 1.3+ mos.) 18% SD (3; 6+ mos.)	infusion-related reaction, adrenal insufficiency	Brahmer et al. [80]
Nivolumab		platinum resistant EOC	II	20	10% CR (2; 11+ mos.) 5% PR (1; 11+ mos.) 30% SD (6; 1 for 11+ mos.)	lymphocytopenia, hypoalbuminemia, elevated ALT, rash, fever, anemia	Hamanishi et al. [25]
Pembrolizumab	NCT02054806	recurrent EOC, PD-L1 positive	Ib	26	4% CR (1; 6+ mos.) 8% PR (2; 6+ mos.) 23% SD (8; 2 for 6+ mos.)	transaminitis	Varga et al. [26]
Ipilimumab	NCT01611558	recurrent EOC	II	40	10% BRR (4; NA)	NA	clinicaltrials.gov [27]
Avelumab	NCT01772004	recurrent EOC	Ib	124	10% PR (12; 4 for 6+ mos.) 44% SD (55; NA)	rash, edema, elevated amylase/ lipase, arthritis, colitis, hyperglycemia/DM	Disis et al. [28]
Durvalumab + Olaparib	NCT02484404[a]	recurrent EOC	I/II	10	PR (1; 11+ mos.) SD (7; 4+ mos.)	Lymphopenia, anemia	Lee et al. [29]
Durvalumab + Cediranib				4	PR (1; 7 mos.) SD (2; 1 for 6 mos.)	Lymphopenia, anemia, nausea, diarrhea, hypertension, PE, pulmonary hypertension, fatigue, headache	

Future directions

- Promising advances in early detection
- Surgery affirmed as an essential pillar of primary therapy
- Defective DNA repair is achilles heel of ovarian cancer
  - Drugs that exploit this will become increasingly important
- Targeted therapies including coimbinations emerging
  - Includes anti-angiogenesis, PARP-I and immunotherapy agents