Updates in Gynecologic Oncology

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LOS
LOUISIANA ONCOLOGY SOCIETY

Disclosure of Conflicts of Interest

Agustin A. Garcia, MD has no relevant financial relationships to disclose.

What is new in ovarian cancer (fallopian tube and primary peritoneal carcinoma)

- **Upfront management of Ovarian cancer**
  - Surgery
    - Pafolacianine Sodium (OTL 38)
- HIPEC
- Neoadjuvant Chemotherapy
- Maintenance thereapy
- **Management of Recurrent Disease**
  - Surgery
  - Systemic Therapy
- Novel agents
- Screening, Genetics, Nutrition

Upfront management of Ovarian cancer

1970s	
	OS
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Combination	14.2 m

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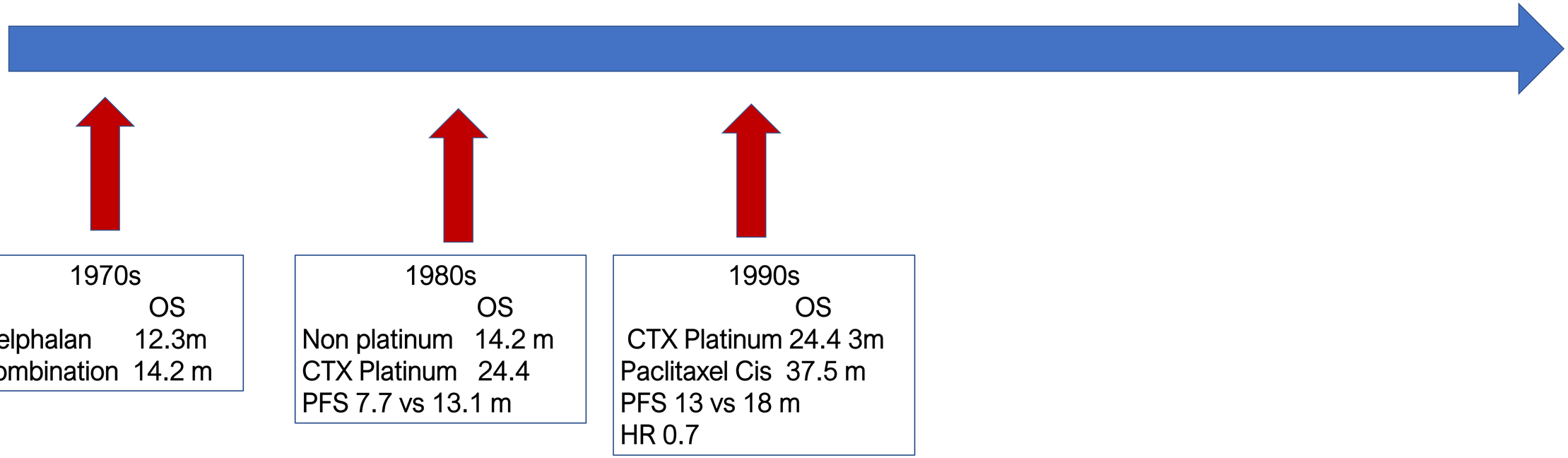
Upfront management of Ovarian cancer



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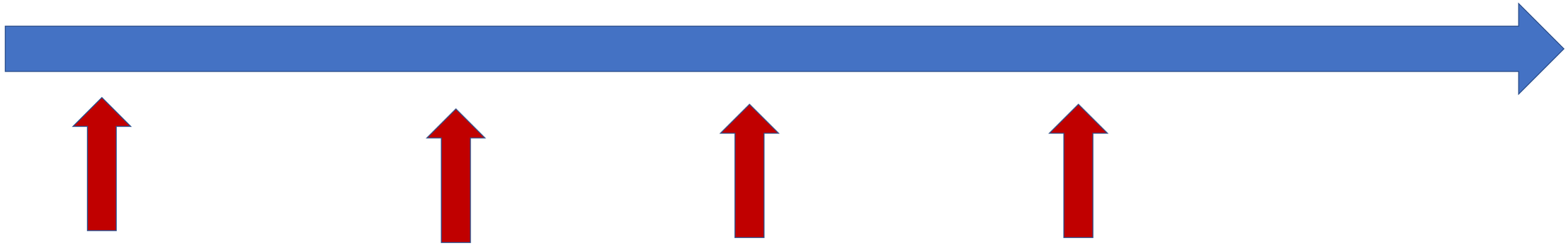
Upfront management of Ovarian cancer



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Chemo	41.1 m
Bev Conc	40.8 m
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PFS 10.3 vs 11.2 vs 14.1	
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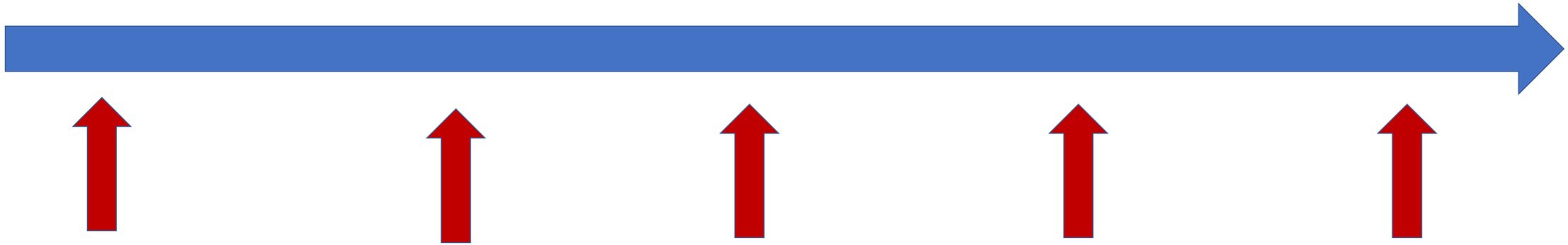
Upfront management of Ovarian cancer



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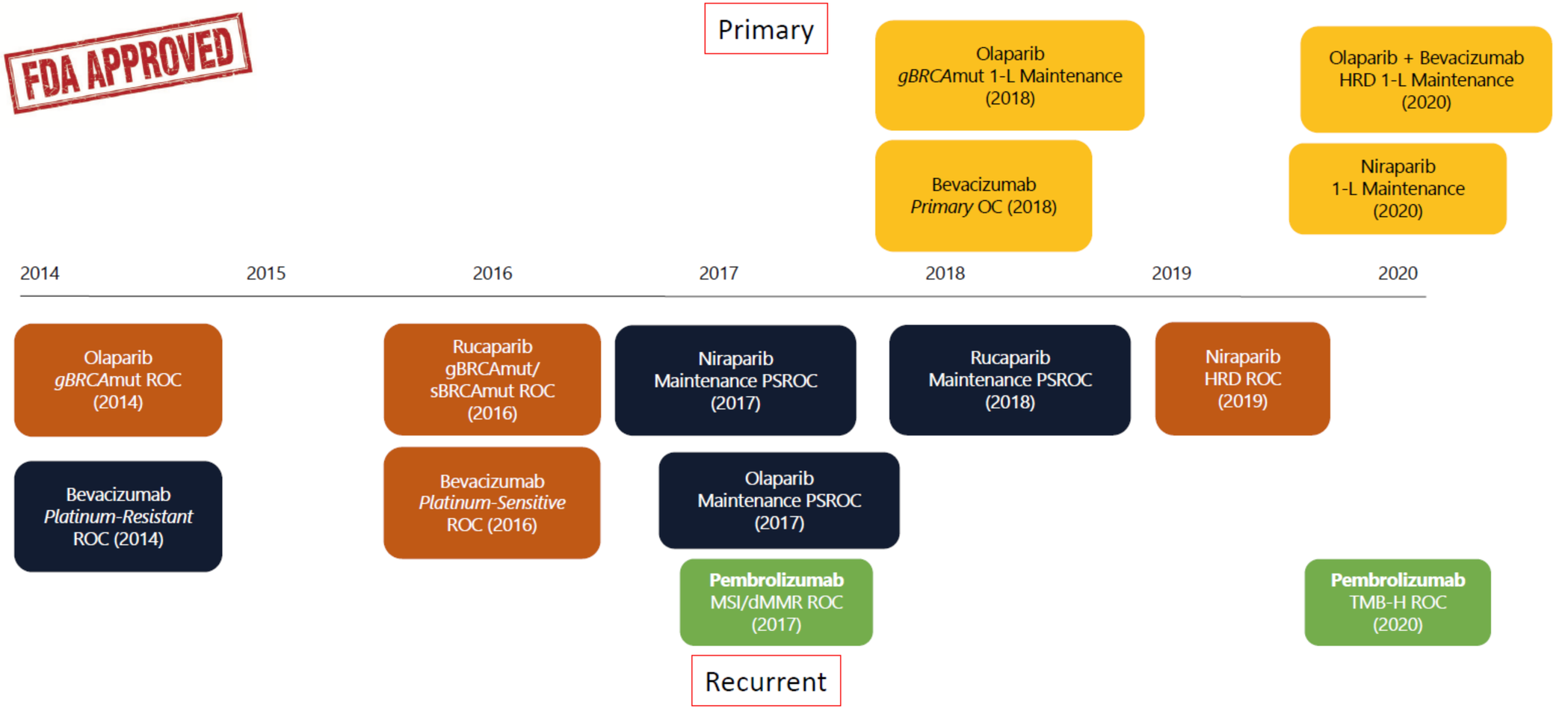
New Drugs for Ovarian cancer

Fourteen Approvals In The Last 6 Years!



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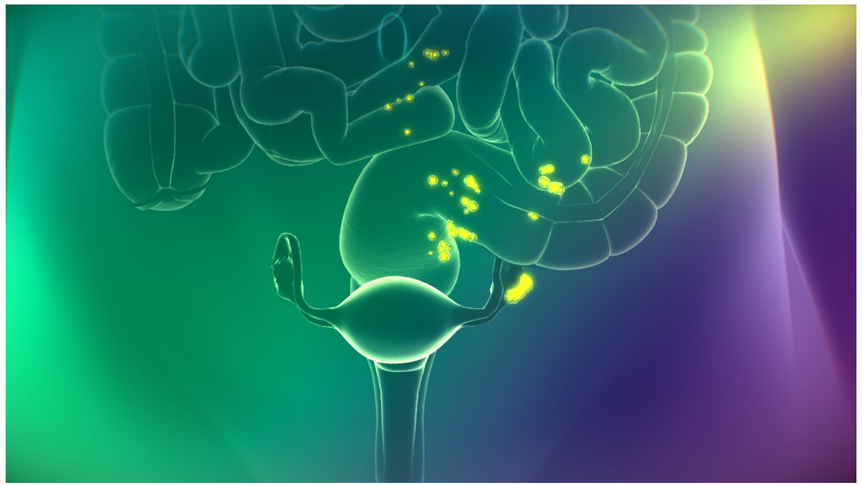
Pafolacianine Sodium (OTL 38, Cytalux)



- Recent FDA Approval
- Infusion 1-9 hours prior to surgery
- Near infrared imaging
- Phase II & III data:
  - 33% of women with additional lesions identified (39.7% if interval cytoreduction)
  - 30% adverse events (nausea, vomiting, abdominal pain), most mild
  - >half of surgeons revised plan
  - 33% false positive rate

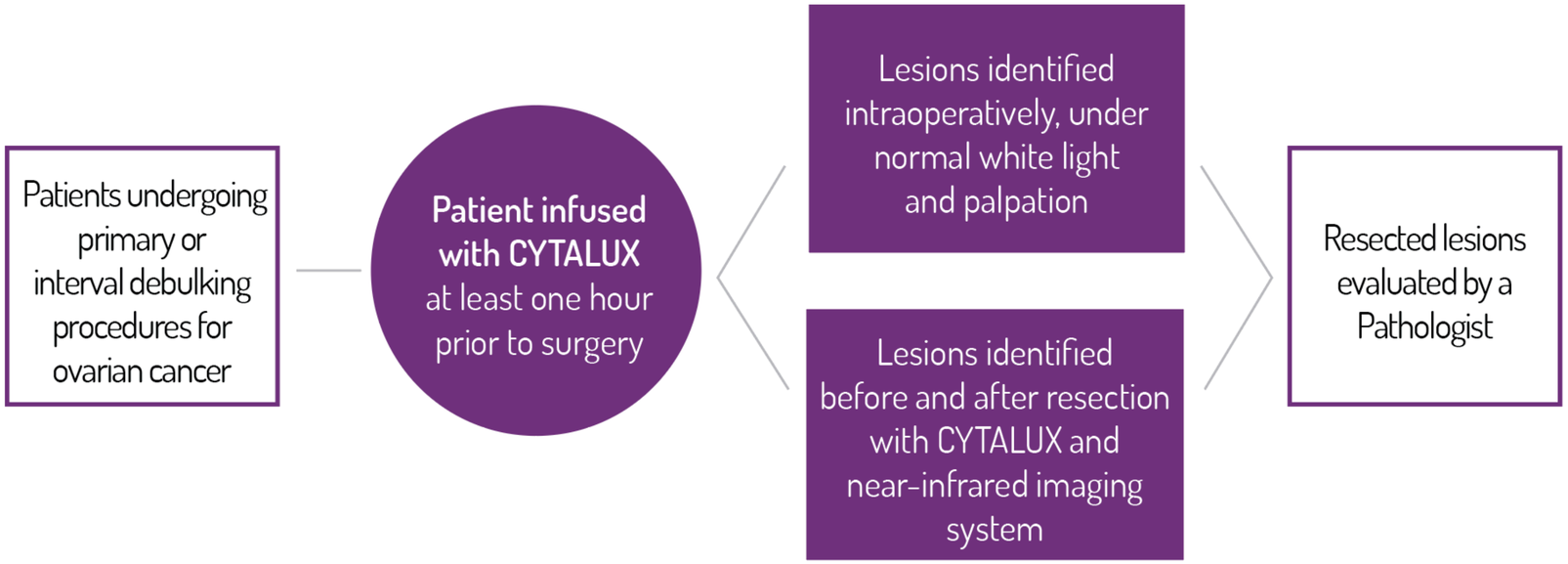
Voelker *JAMA* 2022; FDA; Randall *Gyn Onc* 2019; ASCO 2021

PHASE 3 CLINICAL STUDY

DESIGN

PHASE 3 (006 STUDY): CYTALUX FOR FR+ OVARIAN CANCER

A Phase 3, Randomized, Single Dose, Open-Label Study to Investigate the Safety and Efficacy of CYTALUX (OTL38) for Intraoperative Imaging of Folate Receptor Positive Ovarian Cancer



Primary Endpoint:
Proportion of patients with at least one evaluable FR+ ovarian cancer lesion confirmed by central pathology that was detected using the combination of CYTALUX and fluorescent light but not under normal light or palpation.

N=150 patients infused with CYTALUX; N=134 patients analyzed for primary and secondary endpoints

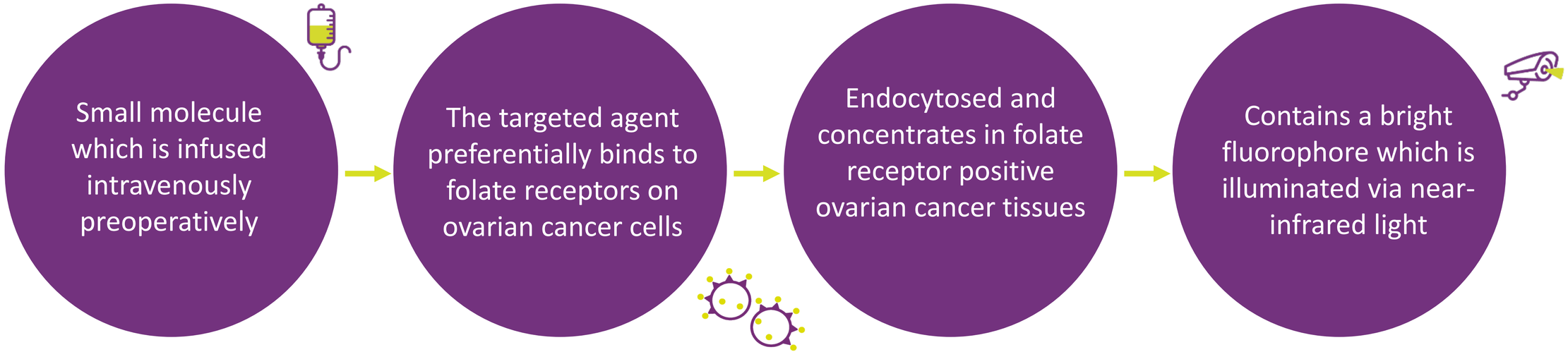
Tanyi JL, ASCO 2021

MECHANISM OF ACTION

FOLATE

- Folate is an essential vitamin required for **cell growth and DNA replication**[1]
- Rapidly dividing cancer cells **consume folate in elevated quantities**[1]
- Most of ovarian cancers over-express high-affinity folate receptors **to increase folate uptake for tumor growth**[2]

OTL-38 is a folic acid analog conjugated with a fluorescent dye which binds to folate receptor positive ovarian cancer cells.



Tanyi JL, ASCO 2021

1. Markert S, et al. Alpha-folate receptor expression in epithelial ovarian carcinoma and nonneoplastic ovarian tissue. Anticancer Res. 2008 (28): 3568-3572.
2. Kalli KR, Oberg AL, Keeney GL, et al. Folate receptor alpha as a tumor target in epithelial ovarian cancer. Gynecologic Oncology. 2008;108(3):619-626.

PHASE 3 CLINICAL STUDY

EFFICACY

WITH CYTALUX™, ADDITIONAL LESIONS WERE FOUND IN

27%

OF PATIENTS*

* On tissue not planned for resection in women highly suspicious for or with confirmed ovarian cancer who underwent both normal and fluorescent light evaluation (Intent-to-Image set); N=134, 95% CI [0.196, 0.352]

In a subgroup analysis of patients with confirmed FR+ ovarian cancer who underwent interval debulking surgery

ADDITIONAL LESIONS WERE FOUND IN 40% OF INTERVAL DEBULKING PATIENTS**

** Phase 3 (006 Study): CYTALUX FOR FR+ OVARIAN CANCER; N=58, 95% CI [0.270, 0.534] This subgroup analysis utilized a smaller analysis set than the primary endpoint and was not adjusted to control for error, so the results are not conclusive and should be interpreted cautiously.

- Patient-level false positive rate with respect to the detection of ovarian cancer lesions confirmed by central pathology was 20% (95% CI [0.137, 0.280])
- Most common sites: paracolic gutter, pelvic area, sigmoid/rectosigmoid epiploica, and omentum

Tanyi JL, ASCO 2021

PHASE 3 CLINICAL STUDY

SPECIMEN SIZE

In 70% of patients, specimen size was >1cm

Lesions identified by CYTALUX and Near-Infrared Imaging ONLY

Specimen Size*	# Subjects
< 0.5 cm	4
0.5-1.5 cm	13
> 1.5 cm	24

N=34 patients and 55 lesions; 7 patients had more than one lesion identified

*Categories based on Griffiths 1975 paper evaluating mean survival outcomes by amount of gross residual disease remaining after surgery[1]

Tanyi JL, ASCO 2021

1. Griffiths CT. Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma. Natl Cancer Inst Monogr. (1975) Oct;4: 101-4

PHASE 3 INVESTIGATOR REPORTED OUTCOMES

In a post-procedural questionnaire (n=109), investigators reported information gained from use of CYTALUX™ with near-infrared fluorescence imaging yielded the following:

56%
of patients

surgical plan was revised due to use of intraoperative fluorescence

51%
of patients

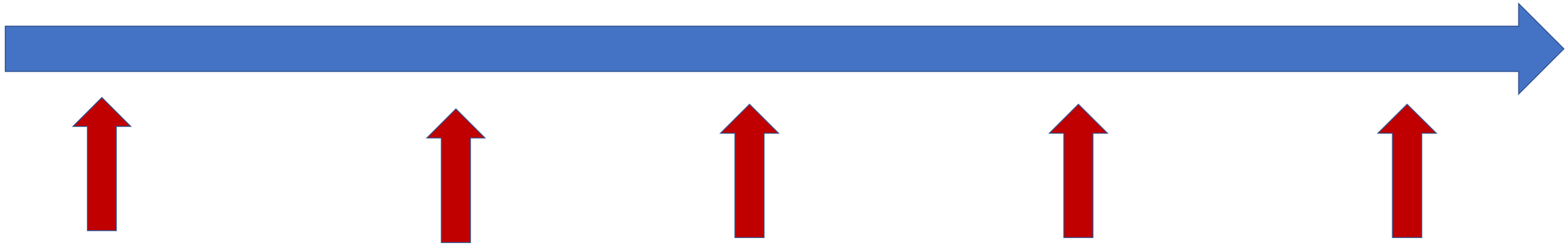
more complete debulking achieved

62%
of patients

complete resection (R0) achieved

Tanyi JL, ASCO 2021

Upfront management of Ovarian cancer



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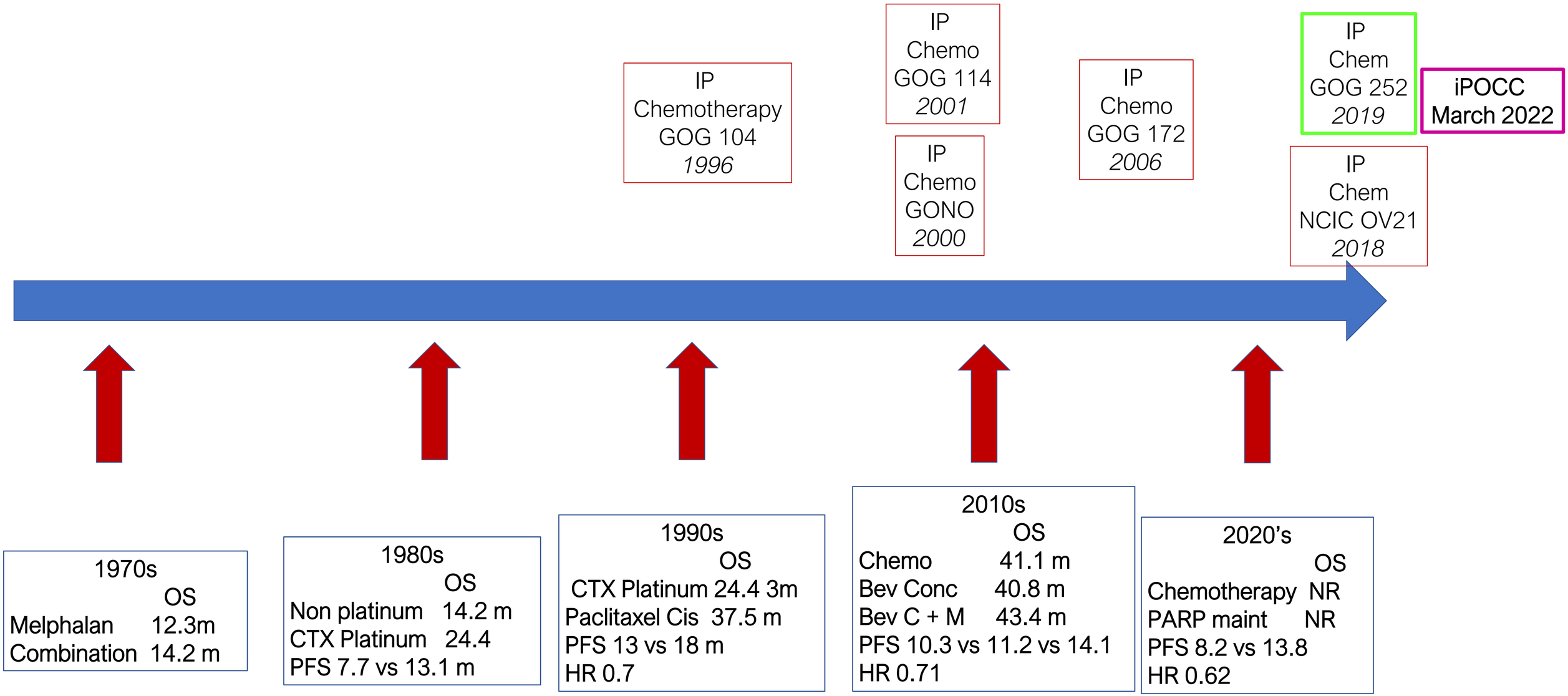

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iPocc trial: Intraperitoneal therapy for ovarian cancer with carboplatin

- Phase 3 randomized trial
  - Arm A: IV paclitaxel weekly + IV Carbo AUC 6
  - Arm B: IV paclitaxel weekly + IP Carbo AUC 6
- Results

	IV chemo N=299	IP chemo N=303	
PFS	20.0 m	22.9 m	HR 0.78 P=0.009
OS	64.0 m	64.9 m	HR 0.91 P=0.403
Grade ≥ 3 toxicities	96%	93.2%	

Fujiwara K et al. SGO 2022

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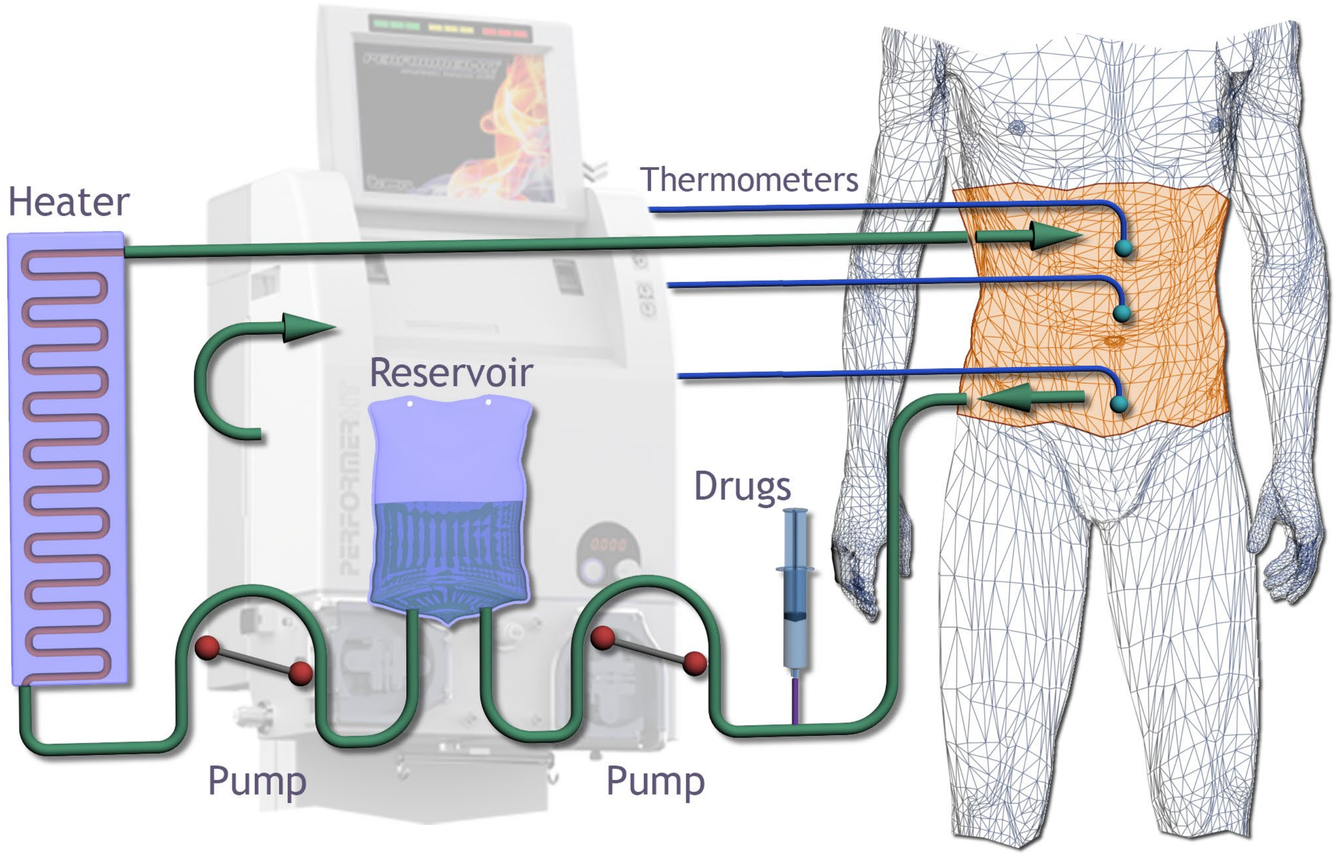
HIPEC In Ovarian Cancer



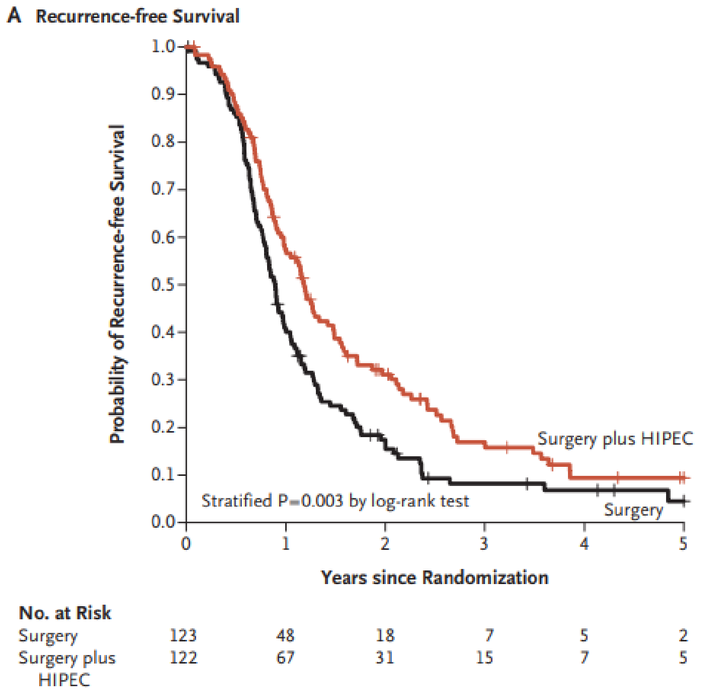
Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC)

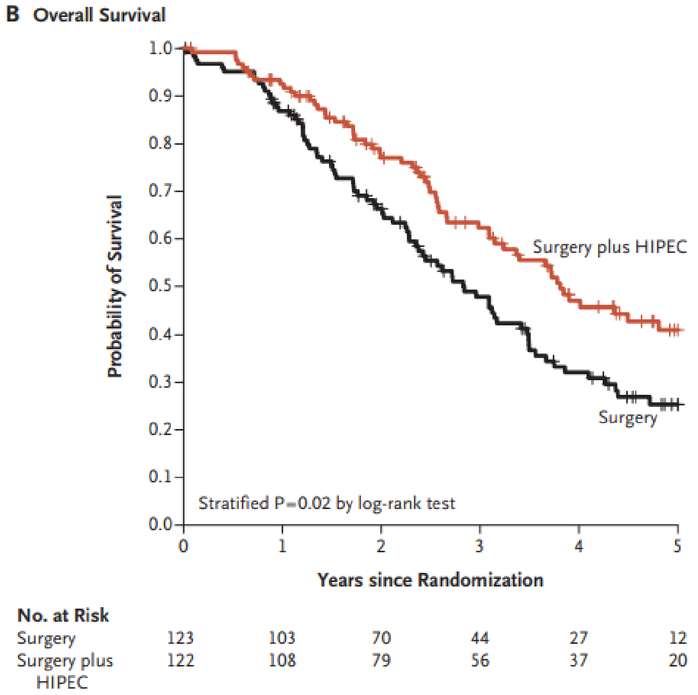
Rationale for HIPEC

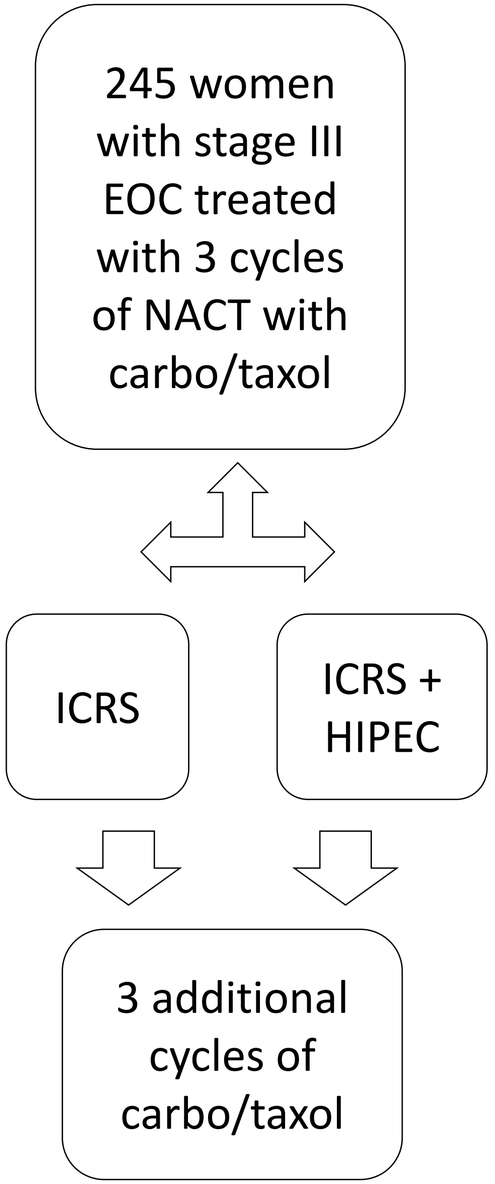
- IP Chemotherapy
  - Major route of tumor dissemination through peritoneal cavity
  - Pharmacokinetic advantage for IP administration
- HIPEC
  - Standard IP chemo: Delay of IP Therapy: adhesions, poor peritoneal distribution
  - Intraoperative perfusion: no adhesion barriers
  - Hyperthermia enhances chemotherapy effects
    - Direct Cytotoxic effects
    - Protein denaturation, induction of apoptosis, inhibition of angiogenesis
  - Hemodynamic changes
    - Vasodilatation, increase blood loss, fluid shifts → increase peritoneal penetration

HIPEC

- Median RFS 10.7 vs 14.2 months
- Median OS 33.9 vs 45.7 months
- Grade 3-4 adverse events similar between groups (25 vs 27%)







Van Driel *NEJM* 2018

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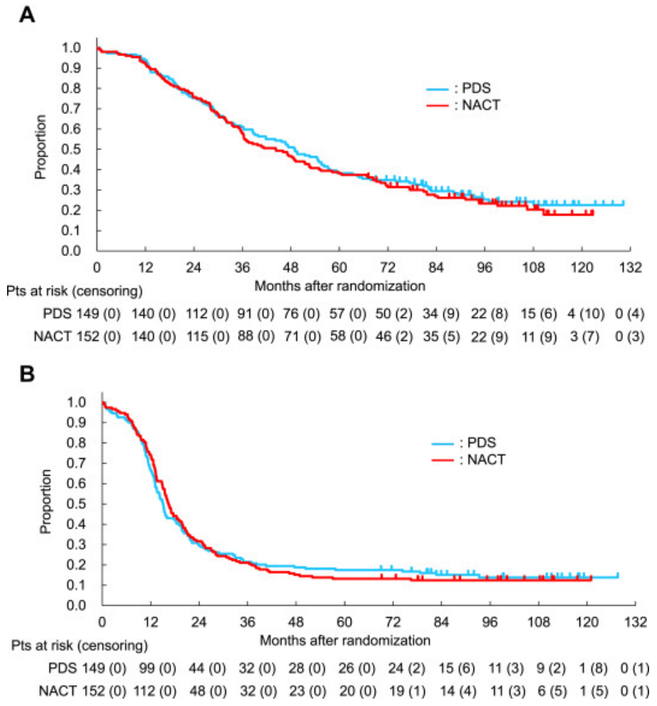
Randomized Trials of Neoadjuvant Chemotherapy for Ovarian Cancer

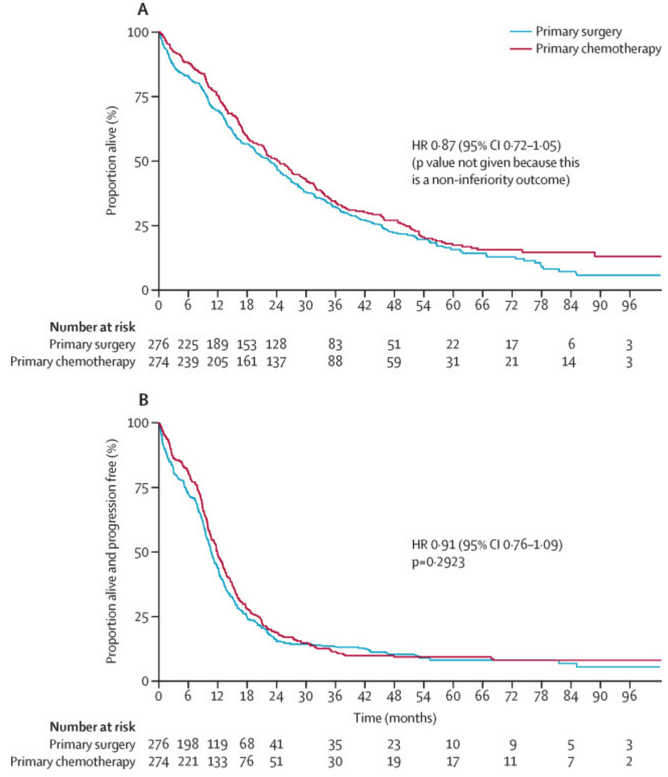
	Onda et al. 2020		Fagotti et al. 2020 SCORPION		Kehoe et al 2015 CHORUS		Vergote et al. 2010	
Cases	NACT N= 149	PDS N=152	NACT N= 87	PDS N=84	NACT N=274	PDS N=276	NACT N=334	PDS N=336
Stage IV	49 (32..9)	47 (30.9)	8 (9.2)	13 (15.5)	68 (24.8)	70 (25.4)	81 (24.3)	77 (22.9)
PS 0-1	131 (86.2)	130 (87.2)	80 (92.0)	75 (89.3)	221 (80.1)	221 (86.8)	290 (86.8)	294 (87.5)
PS > 2	21 (13.8)	19 (12.8)	7 (8.0)	9 (10.7)	53 (19.3)	54 (19.6)	44 (13.2)	40 (11.9(
Surgical Time (mins)	302	240	253	460	120	120	180	165
R0	83 (63.8)	17 (11.6)	57 (77.0)	40 (47.6)	79 (39.3)	39 (16.7)	151 (51.2)	61 (19.4)
Periop Mortality	0	1 (0.7)	0	3 (1.7)	1 (0.5)	14 (5.5)	2 (0.7)	8 (2.5)
G 3-4 AE	7 (5.4)	25 (17.0)	7 (9.5)	39 (46.4)	30 (14)	60 (24)	17 (5.3)	56 (18.1)
DFS	15.1 m	16.4 m	14 m	15 m	12.0m	10.7m	12m	12m
OS	49.0 m	44.3 m	43 m	41 m	24.1m	22.6m	30 m	29 m

Adapted from Patel A et al. 2021

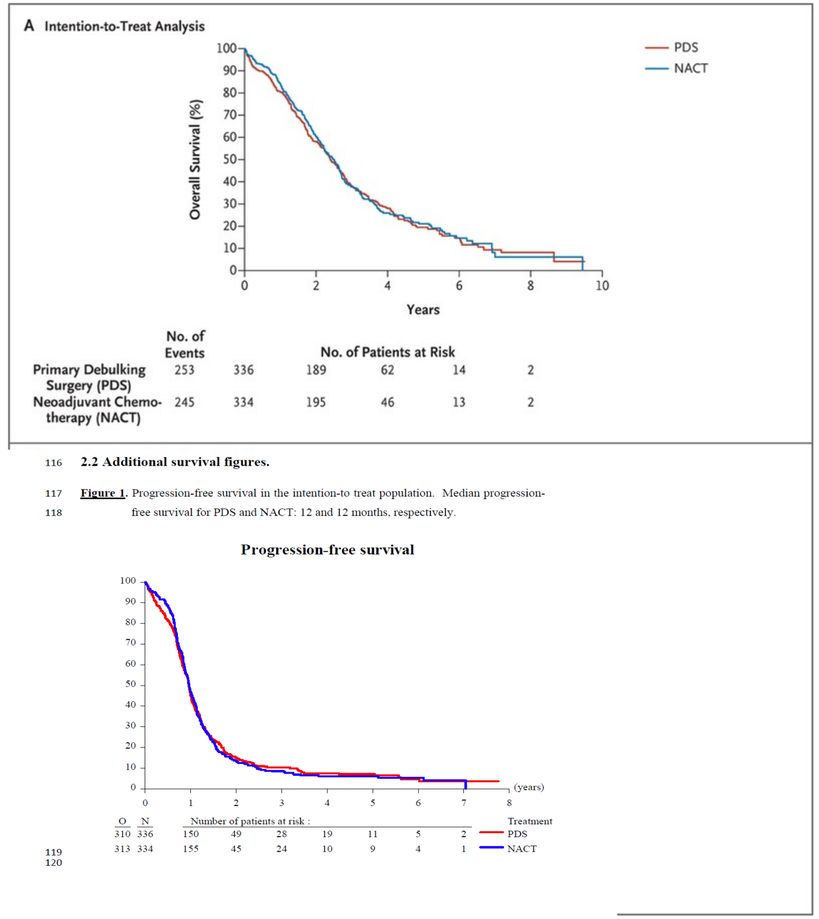
Neoadjuvant Chemotherapy in Ovarian Cancer: PFS and OS



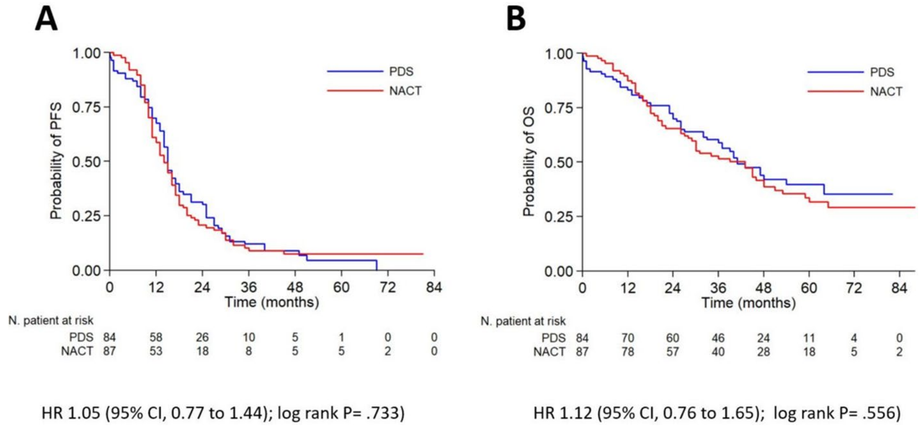
Onda 2020



Kehoe 2015 2010



Vergote 2010



HR 1.05 (95% CI, 0.77 to 1.44); log rank P= .733)

HR 1.12 (95% CI, 0.76 to 1.65); log rank P= .556)

Fagotti 2020

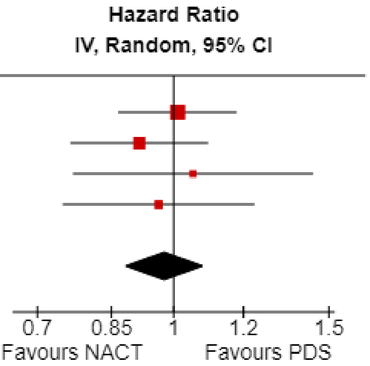
Neoadjuvant chemotherapy before surgery versus surgery followed by chemotherapy for initial treatment in advanced ovarian epithelial cancer
Coleridge SL, et al. Cochrane Database Syst Rev 2021

4 Randomized Controlled Trials; N= 1774

PFS

Study or Subgroup	log[Hazard Ratio]	SE	NACT Total	PDS Total	Weight	Hazard Ratio IV, Random, 95% CI
Vergote 2010 (1)	0.01	0.079	334	336	42.3%	1.01 [0.87 , 1.18]
Kehoe 2015 (2)	-0.09	0.092	274	276	31.2%	0.91 [0.76 , 1.09]
Fagotti 2016	0.05	0.16	87	84	10.3%	1.05 [0.77 , 1.44]
Onda 2016	-0.04	0.128	152	149	16.1%	0.96 [0.75 , 1.23]
Total (95% CI)			**847**	**845**	**100.0%**	**0.98 [0.88 , 1.08]**

Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 3 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.49 (P = 0.62)
Test for subgroup differences: Not applicable

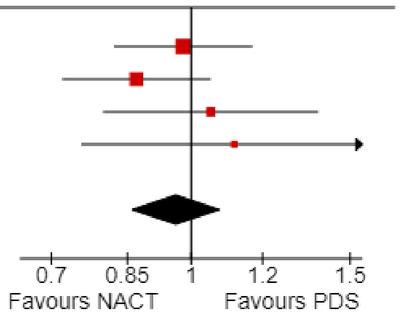


Footnotes
(1) We have applied 95% CIs (Investigators used 90% CIs)
(2) 0.09

OS

Study or Subgroup	log[Hazard Ratio]	SE	Favours NACT Total	PDS Total	Weight	Hazard Ratio IV, Random, 95% CI
Vergote 2010 (1)	-0.0202	0.09	334	336	40.2%	0.98 [0.82 , 1.17]
Kehoe 2015	-0.1393	0.0966	274	276	34.9%	0.87 [0.72 , 1.05]
Onda 2016	0.05	0.14	152	149	16.6%	1.05 [0.80 , 1.38]
Fagotti 2016	0.11	0.199	87	84	8.2%	1.12 [0.76 , 1.65]
Total (95% CI)			**847**	**845**	**100.0%**	**0.96 [0.86 , 1.08]**

Heterogeneity: Tau² = 0.00; Chi² = 2.09, df = 3 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



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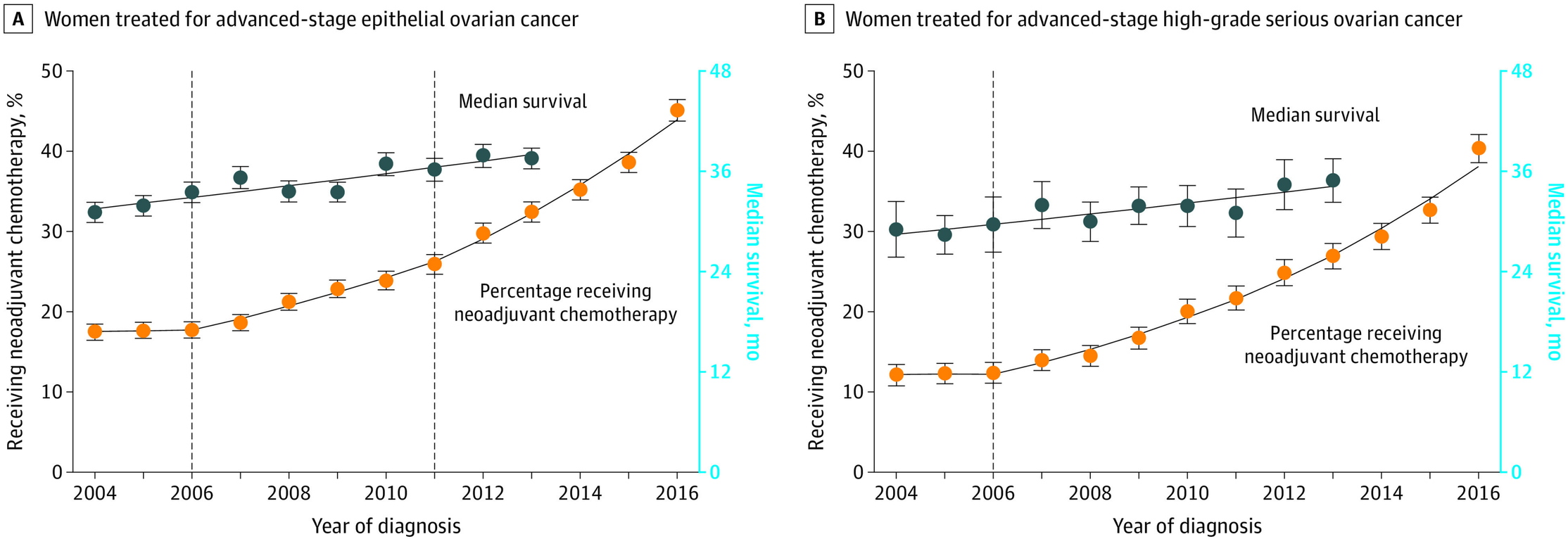
Neoadjuvant Chemotherapy for Newly Diagnosed, Advanced Ovarian Cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline 2016

- For women who are fit for PCS, with potentially resectable disease, either NACT or PCSmay be offered based on data from phase III RCTs that demonstrate that NACT is non- inferior to PCS with respect to progression-free and overall survival.
- NACT is associated with less peri- and postoperative morbidity and mortality and shorter hospitalizations
- For women with a high likelihood of achieving a cytoreduction to < 1 cm (ideally to no visible disease) with acceptable morbidity, PCS is recommended over NACT.
- For women who are fit for PCS but are deemed unlikely to have cytoreduction to < 1 cm (ideally to no visible disease) by a gynecologic oncologist, NACT is recommended over PCS.

Neoadjuvant Chemotherapy for Newly Diagnosed, Advanced Ovarian Cancer: NCCN 2022

- For women who are fit for PCS, with potentially resectable disease PCS is recommended
- For women who are poor surgical candidates or are deemed unlikely to have cytoreduction to < 1 cm (ideally to no visible disease) by a gynecologic oncologist, NACT is recommended over PCS.

Trends in Primary Treatment and Median Survival in Advanced Ovarian Cancer



Knisely AT et al JAMA Netw Open 2020

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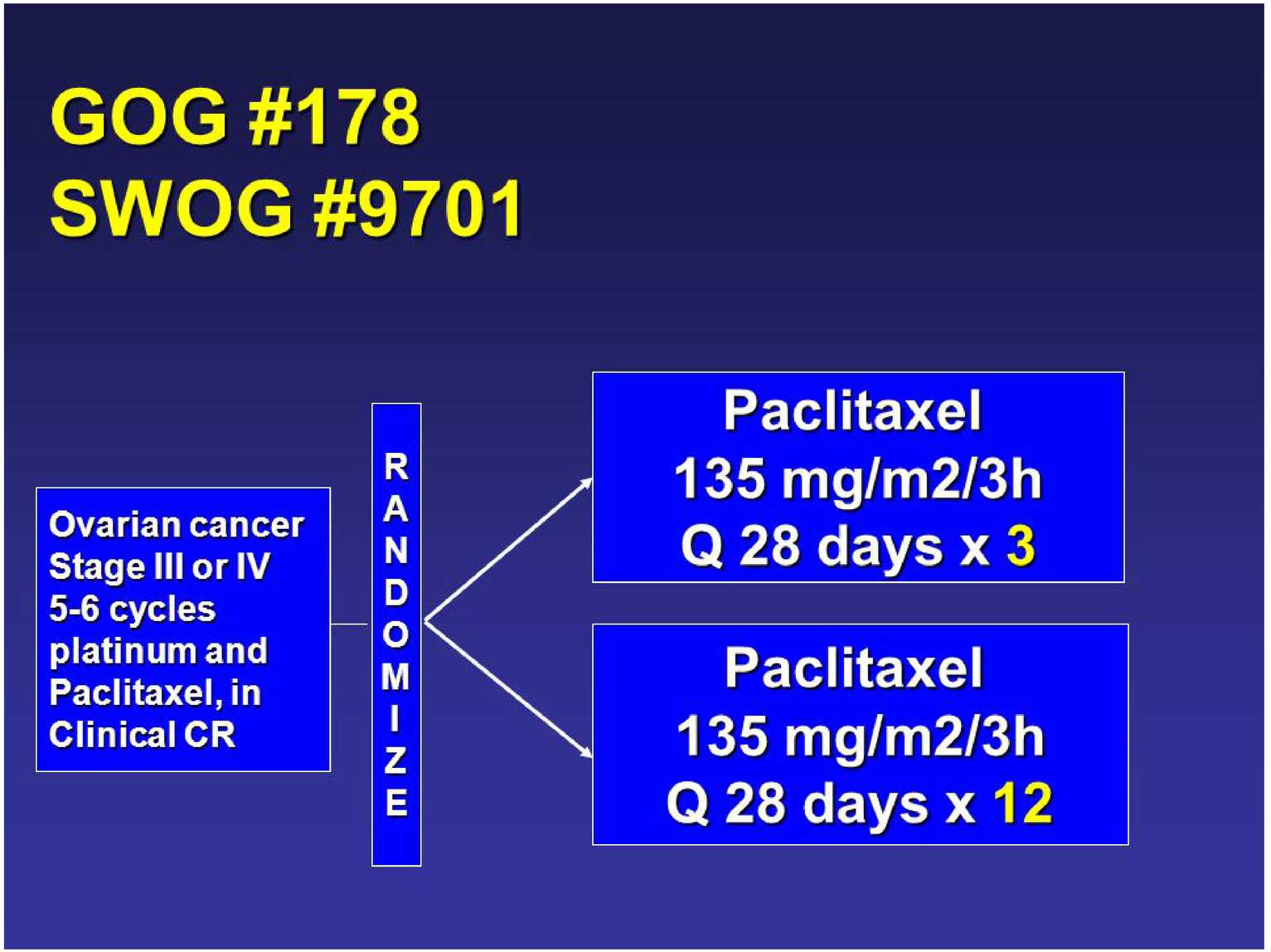
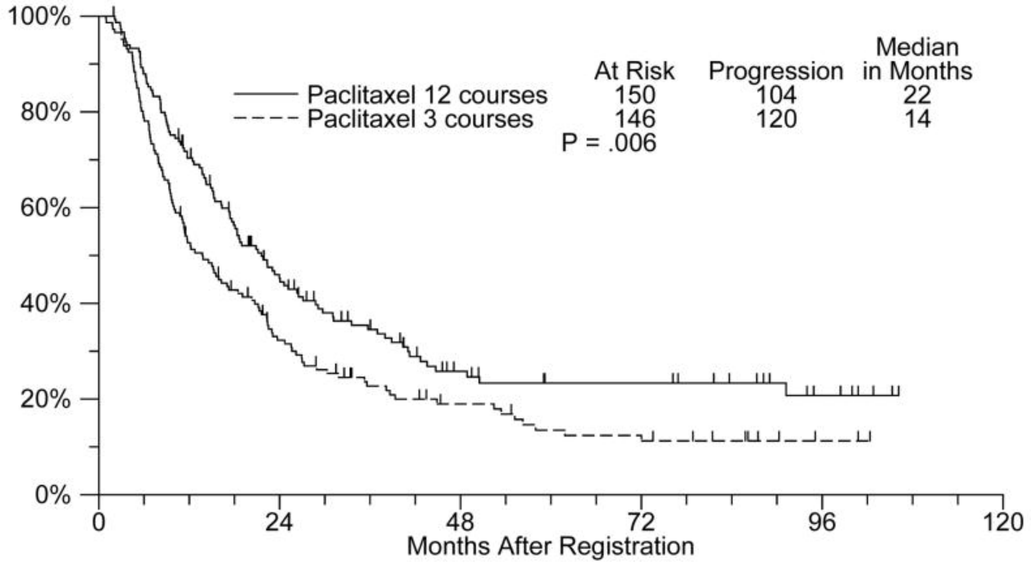
Maintenance Therapy for Ovarian cancer: Not a New Idea



Markman M, Gynecol Oncol 2003, 2009

12 versus 3 monthly cycles of paclitaxel (175 mg/m2) maintenance in advanced ovarian cancer



PFS

HR 0.68

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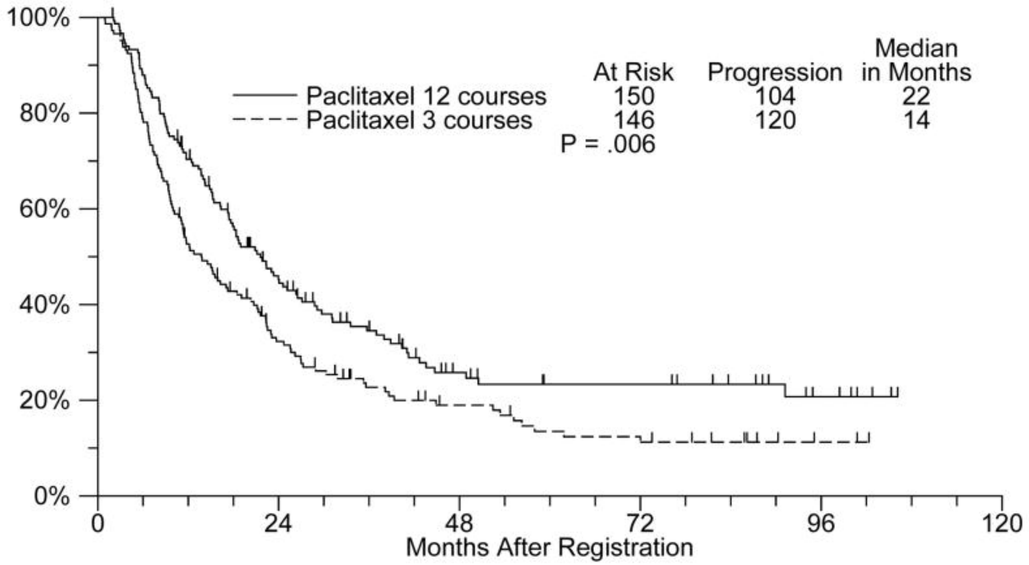

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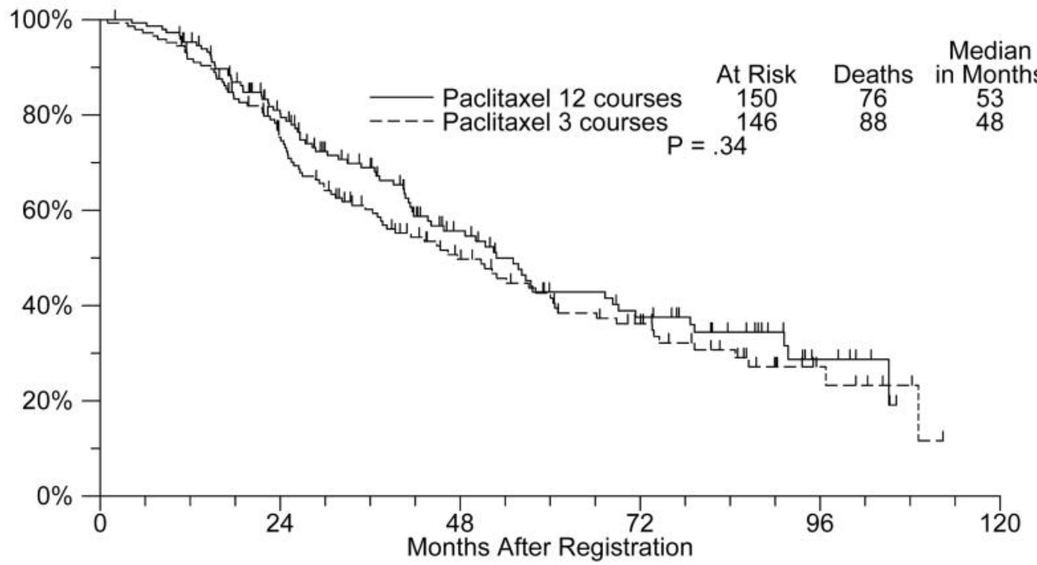


OSS

HR 0.88

2009

FDA-Approved PARP Inhibitors as Maintenance Therapy after 1st Line Chemotherapy for Ovarian Cancer

Agents	Initial Approval	Indication
Olaparib	2018	Maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic $BRCA^{mut}$ advanced epithelial ovarian, fallopian tube or primary peritoneal carcinoma who are in CR or PR after 1st line Platinum based chemotherapy
Olaparib + Bevacizumab	2020	Maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal carcrinoma who are HRd positive and in CAR or PR after 1st line Platinum based chemotherapy
Niraparib	2020	Maintenance treat of adult patients with advance epithelial ovarian , falloptian tube or primary peritoneal cancer who are in CR or PR after 1st line Platinum based chemotherapy

Maintenance PARP after 1st line Platinum Based Chemotherapy PFS (months)

Patient Population	PRIMA (N=733) Niraparib	PAOLA-1 (N=806) Bev + Olaparib	SOLO-1 (N=391)
All patients	13.8 vs 8.2 HR 0.62	22.1 vs 16.6 HR 0.59	
BRCA ^{mut}	22.1 v 10.9 HR 0.40	37.2 vs 21.7 HR 0.31	56 vs 13.8 HR 0.33
BRCA ^{WT}/HRd	19.6 vs 8.2 HR 0.50	28.1 vs 16.6 HR 0.43	
BRCA ^{WT}/HRp	8.1 vs 5.4 HR 0.68	16.9 vs 16.0 HR 0.92	

What is new in ovarian cancer (fallopian tube and primary peritoneal carcinoma)

- **Upfront management of Ovarian cancer**
  - Surgery
    - Pafolacianine Sodium (OTL 38)
- HIPEC
- Neoadjuvant Chemotherapy
- Maintenance therapy
- **Management of Recurrent Disease**
  - Surgery
  - Systemic Therapy
- Novel agents
- Screening, Genetics, Nutrition

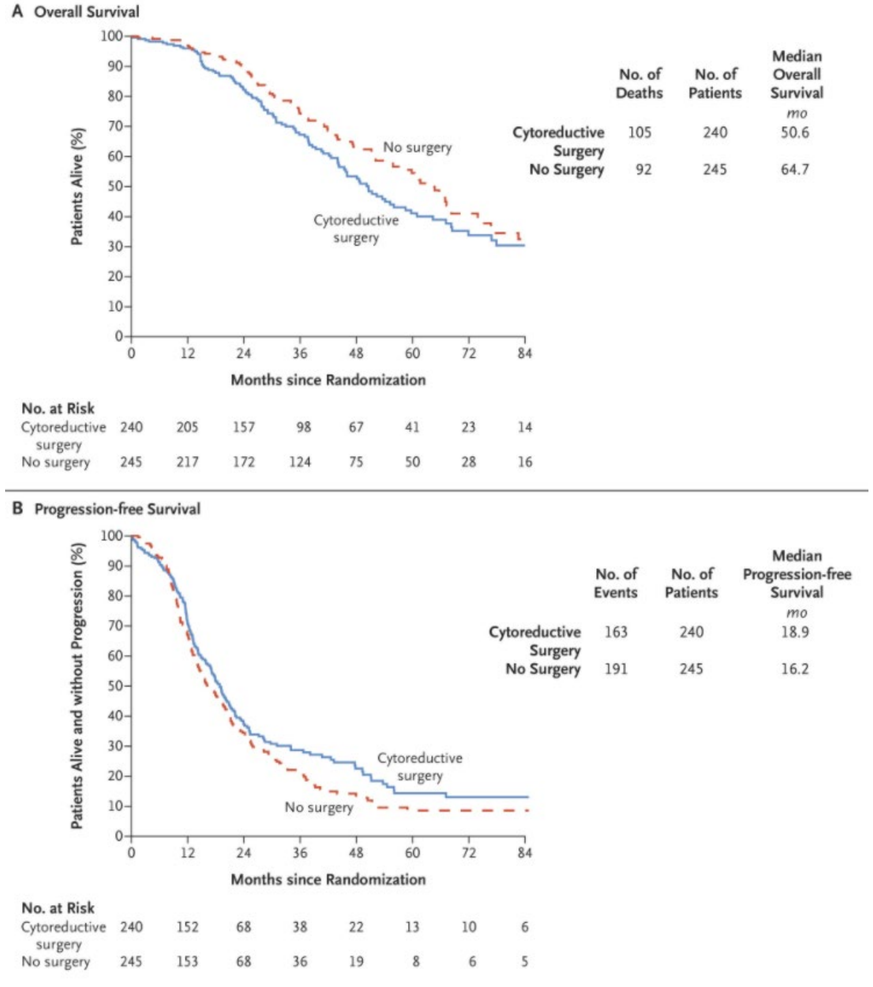
Role of Secondary Cytoreductive Surgery in Platinum Sensitive Ovarian Cancer: Traditional Approach

DFI	Single Site	Multiple Sites: No carcinomatosis	Diffuse Carcinomatosis
6-12 months	**Offer SC**	**Consider SC**	**No SC**
12-30 months	**Offer SC**	**Offer SC**	**Consider SC**
> 30 months	**Offer SC**	**Offer SC**	**Offer SC**

Adapted from Chi DS,, et al. Guidelines and selection criteria for secondary cytoreductive surgery in patients with recurrent, platinum-sensitive epithelial ovarian carcinoma. Cancer. 2006

Secondary Cytoreduction?

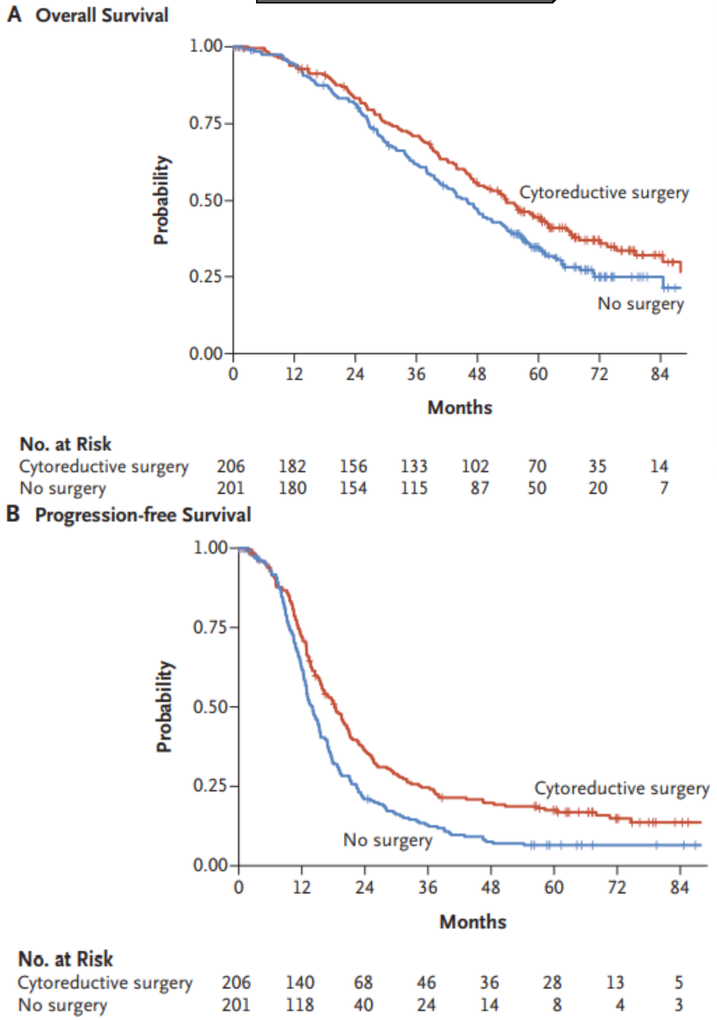
GOG213



	No. of Deaths	No. of Patients	Median Overall Survival (mo)
Cytoreductive Surgery	105	240	50.6
No Surgery	92	245	64.7

	No. of Events	No. of Patients	Median Progression-free Survival (mo)
Cytoreductive Surgery	163	240	18.9
No Surgery	191	245	16.2

DESKTOP III



SOC1

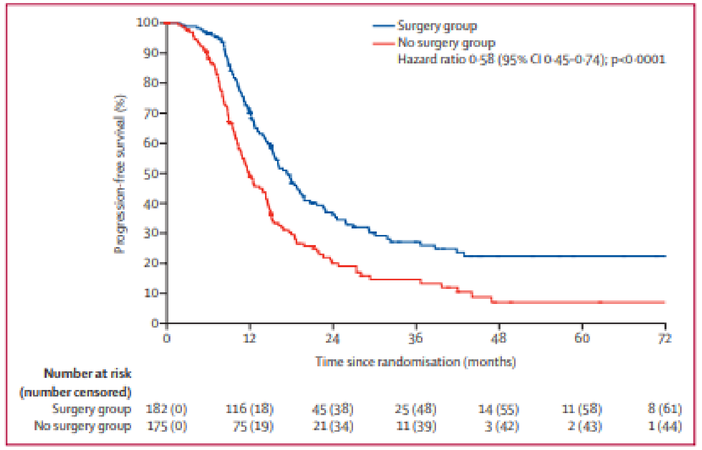


Figure 2: Progression-free survival in the intention-to-treat population

NCCN: **Consider** Secondary Cytoreduction in Selected patients with Platinum Sensitive Disease

GOG213, Dubuois *JCO* 2020, Harter P *NEJM* 2021 Shi T *Lancet Oncol* 2021; Coleman NEJM 2019

What is new in ovarian cancer (fallopian tube and primary peritoneal carcinoma)

- **Upfront management of Ovarian cancer**
  - Surgery
    - Pafolacianine Sodium (OTL 38)
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- **Management of Recurrent Disease**
  - Surgery
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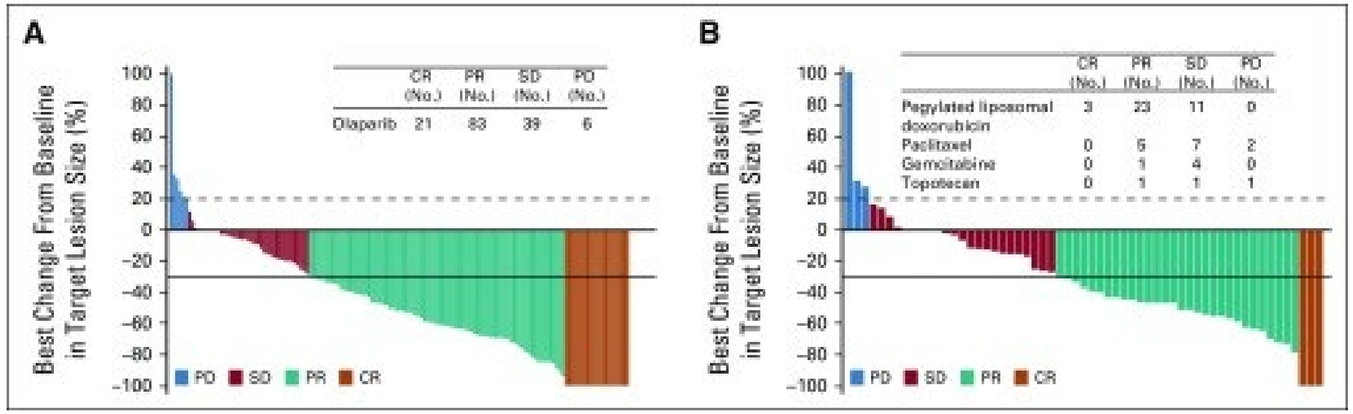
Maintenance PARP for Platinum Sensitive Recurrent Ovarian Cancer PFS (months)

Patient Population	ENGOT-OV16/NOVA (N=553) Niraparib	ARIEL 3 (N=564) Rucaparib	SOLO-2 (N=264) Olaparib
All patients		10.8 vs 5.4 HR 0.36	19.1 VS 5.5 HR 0.30
BRCA ^{mut}	21 vs 5.5 HR 0.27	16.6 vs 5.4 HR 0.23	
BRCA ^{WT}/HRd	12.9 vs 3.8 HR 0.38	13.6 vs 5.4 HR 0.32	
BRCA ^{WT}/HRp	9.3 vs 3.9 HR 0.34		
OS All patients			29.8 vs 27.8 HR0.73
OS BRCA ^{mut}			34.9 vs 32 0.62
OS BRCA ^{WT}			24.5 vs 26.6 HR 0.83

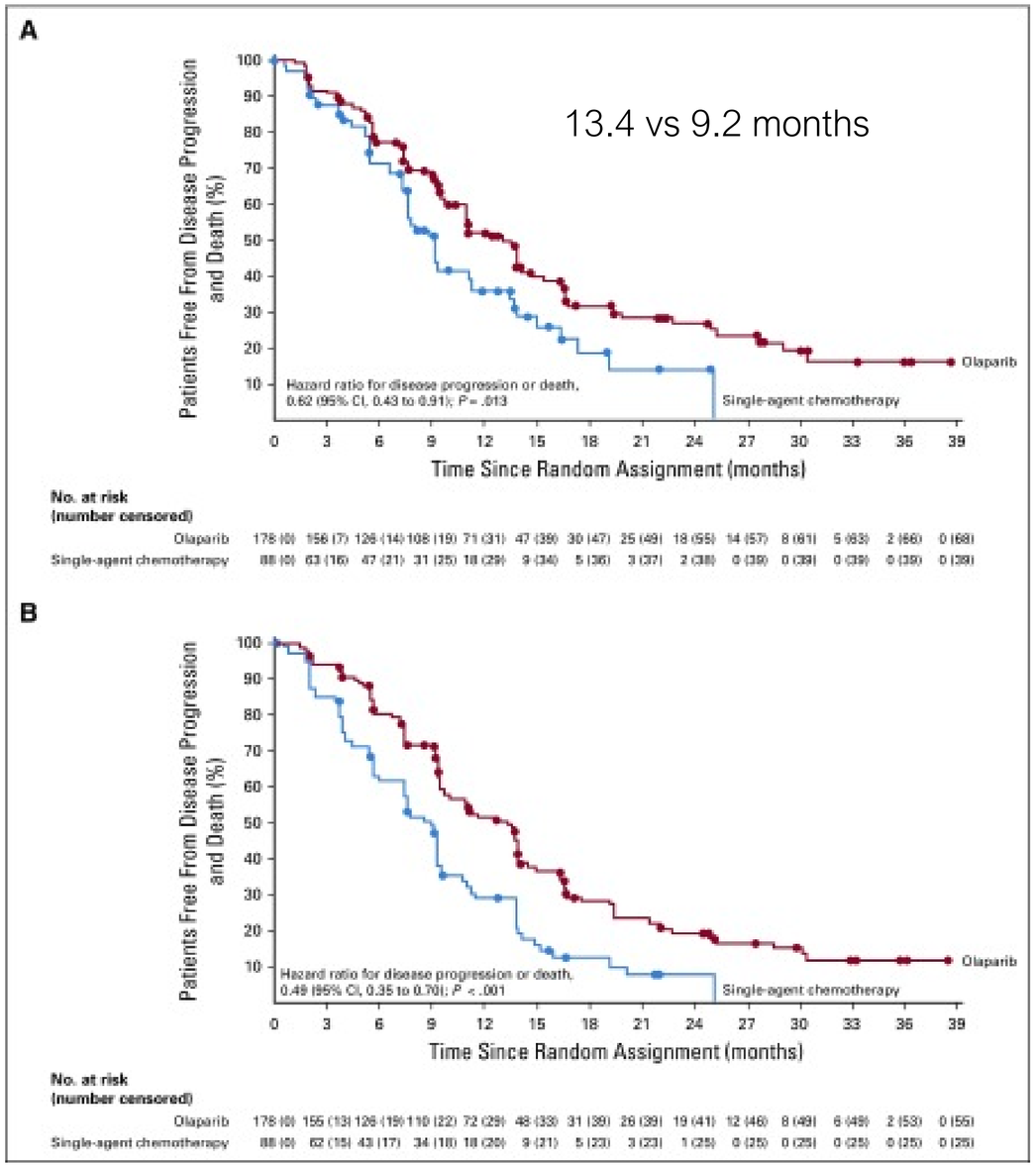
SOLO-3 Olaparib vs Chemotherapy in Recurrent Ovarian Cancer

Best Response Olaparib (A)
and Chemotherapy (B)
72% vs 51%



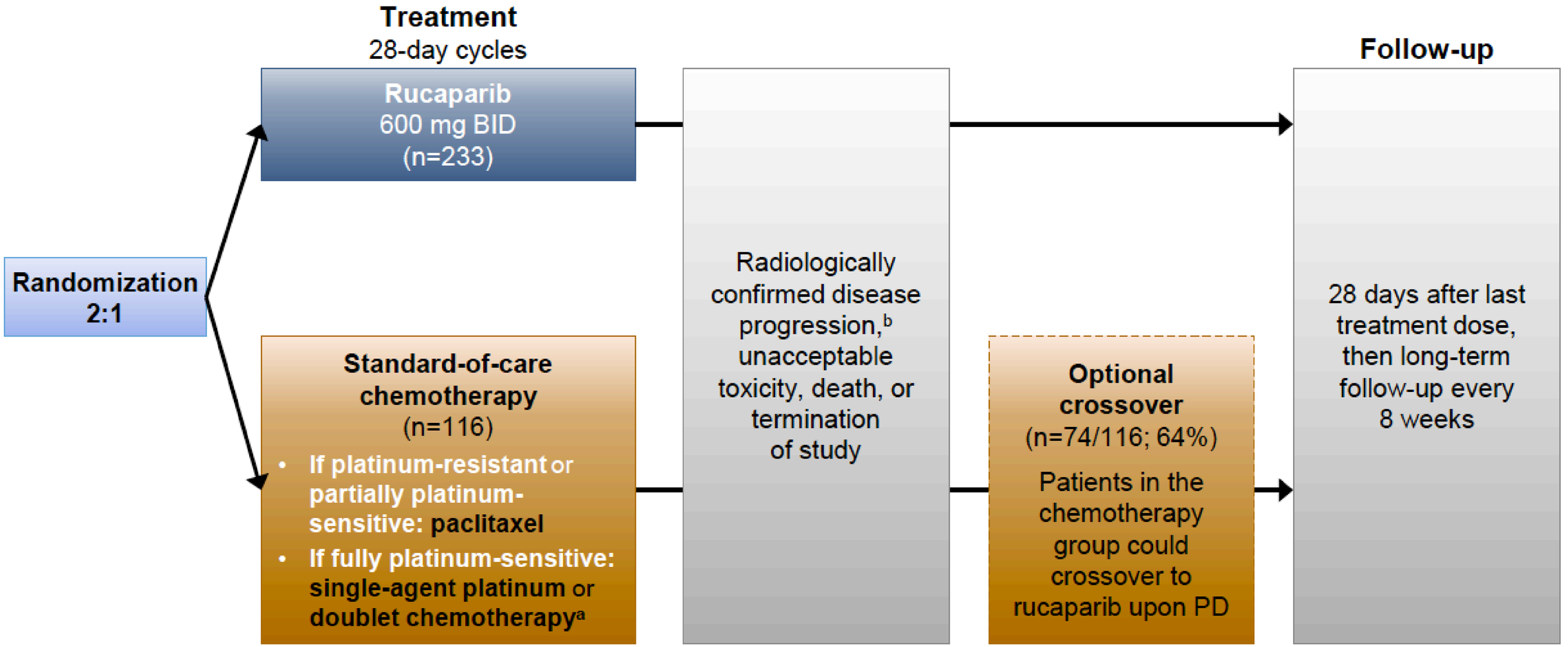
OS
Olaparib 34.9 m
Chemotherapy 32.9 m
P=0.714

Penson SGO 2022

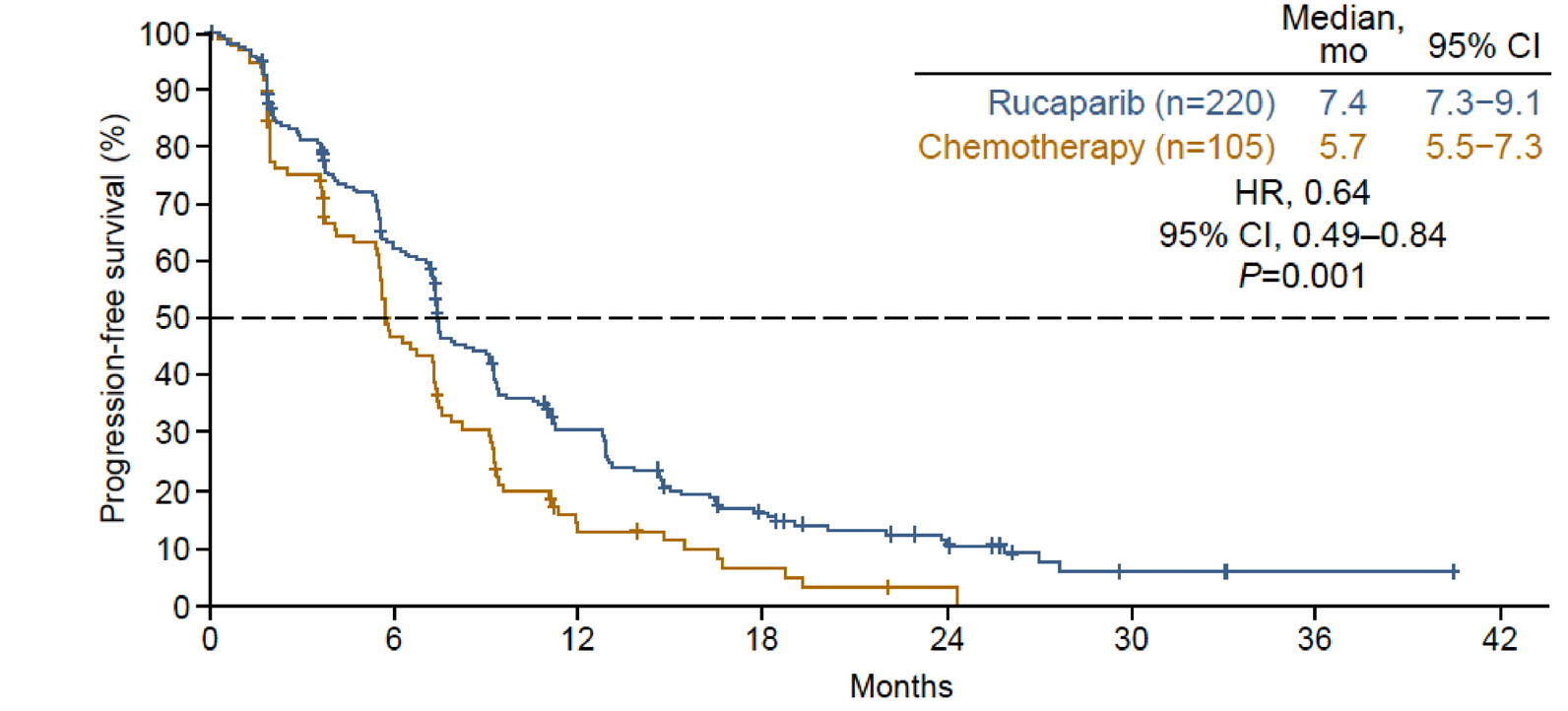


Penson et al J Clin Oncol 2020

Rucaparib vs Chemoterapy in Recurrent Ovarian cancer: Ariel 4



Kristeleit R, et al SGO 2021



At risk (events)								
Rucaparib	220 (0)	121 (75)	53 (134)	23 (158)	11 (165)	3 (168)	1 (168)	0 (168)
Chemotherapy	105 (0)	42 (50)	9 (78)	4 (82)	1 (84)	0 (85)		

What is new in ovarian cancer (fallopian tube and primary peritoneal carcinoma)

- **Upfront management of Ovarian cancer**
  - Surgery
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- Neoadjuvant Chemotherapy
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- **Management of Recurrent Disease**
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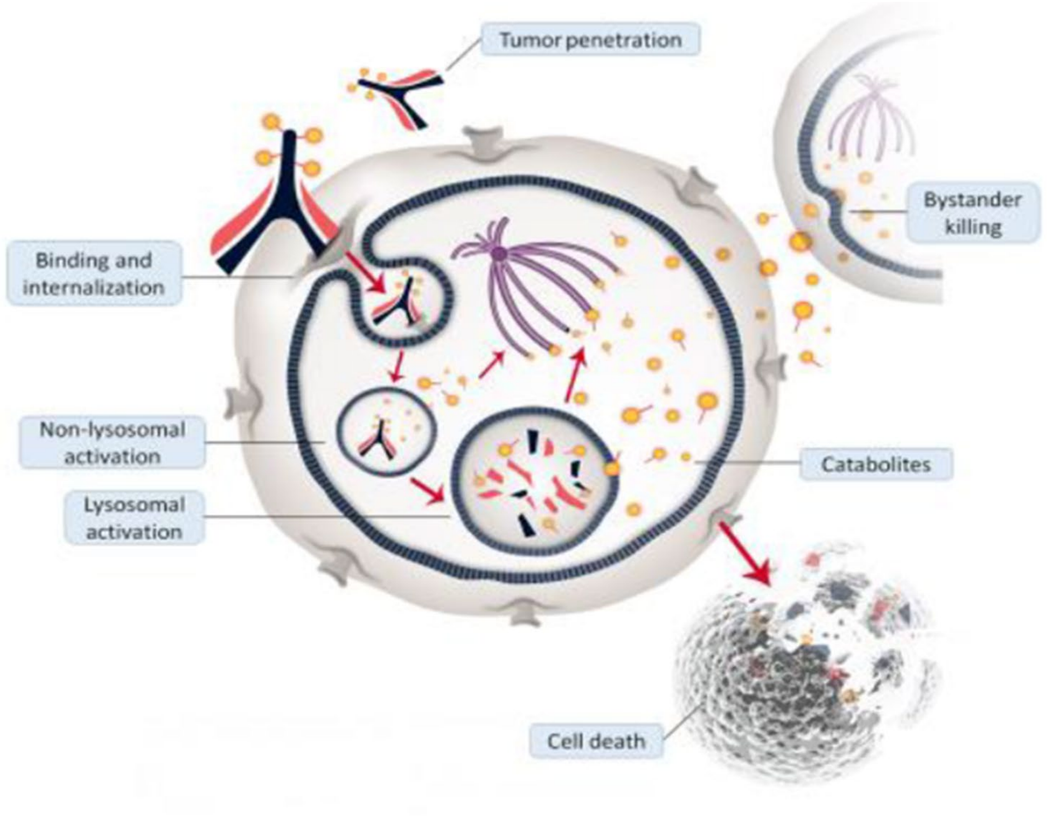
Mirvetuximab Soravtansine

- Antibody-drug conjugate comprising a folate receptor alpha (FRα)-binding antibody, cleavable linker, and the maytansinoid DM4, a potent tubulin-targeting agent.



Moore KN, et al. Ann Oncol 2021

Mirvetuximab Soravtansine

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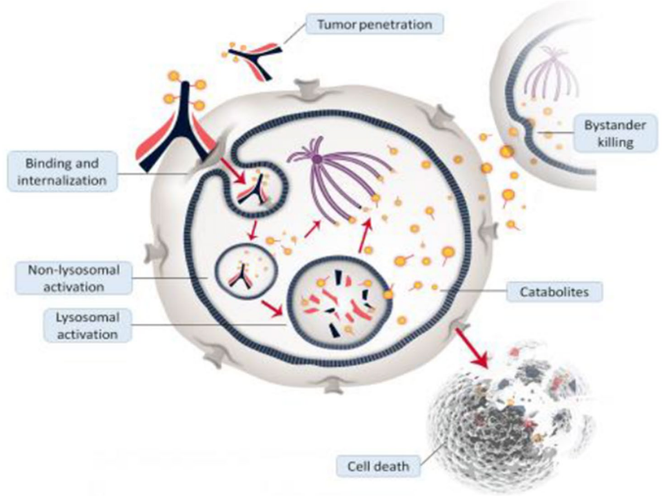
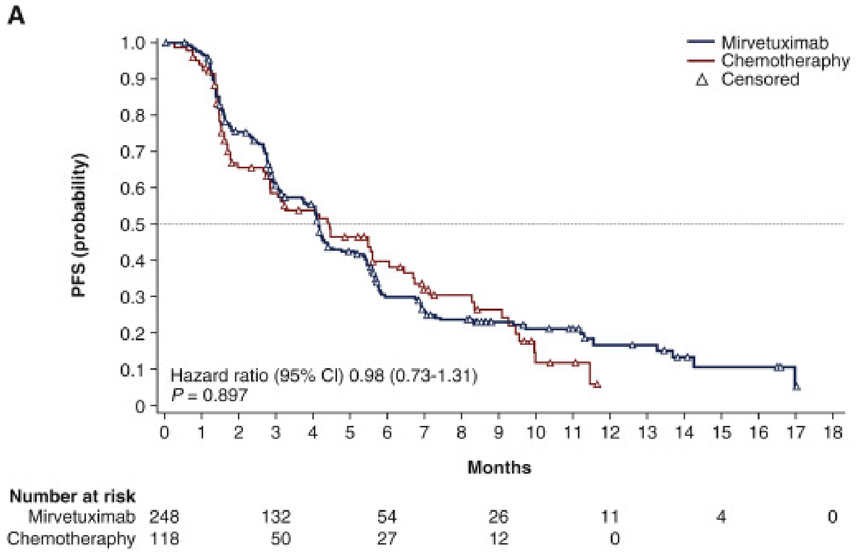


- Forward 1: Phase III randomized trial platinum resistant ovarian cancer vs SOC N= 366 patients
- Primary Endpoint PFS in all patients (ITT) and high FRα

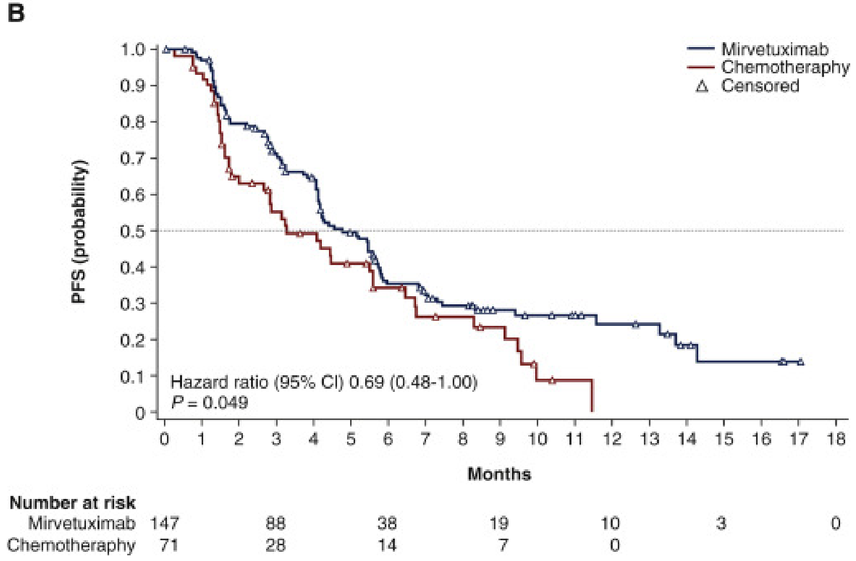
Moore KN, et al. Ann Oncol 2021

FORWARD I: PFS Results

PFS
ITT



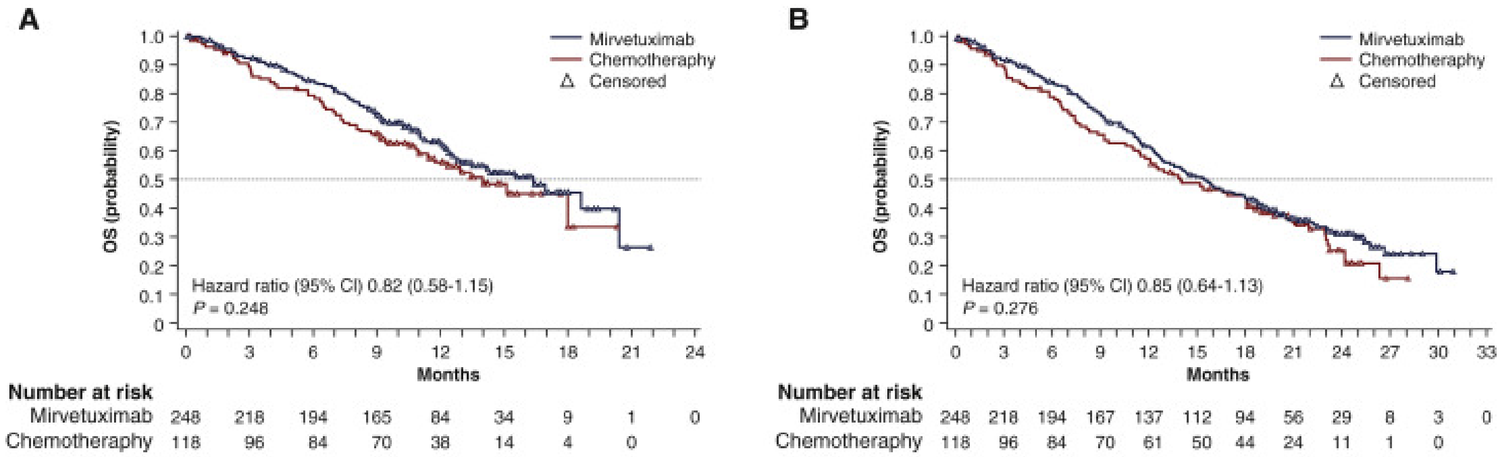
PFS
High FRα



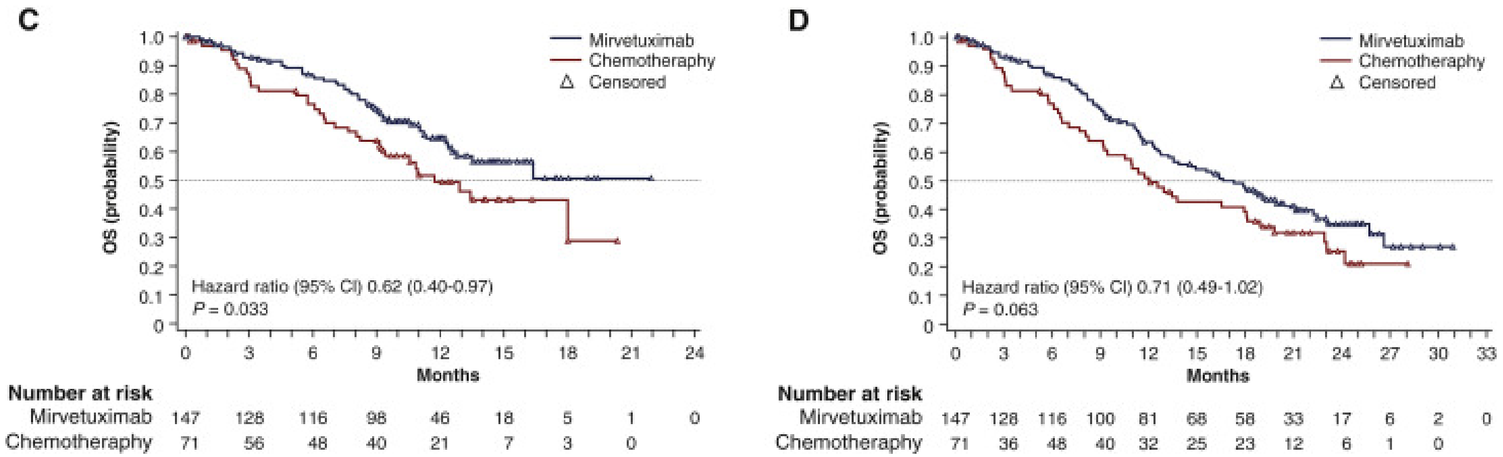
Moore KN, et al. Ann Oncol 2021

FORWARD I: OS Results

OS ITT



OS
High FRα



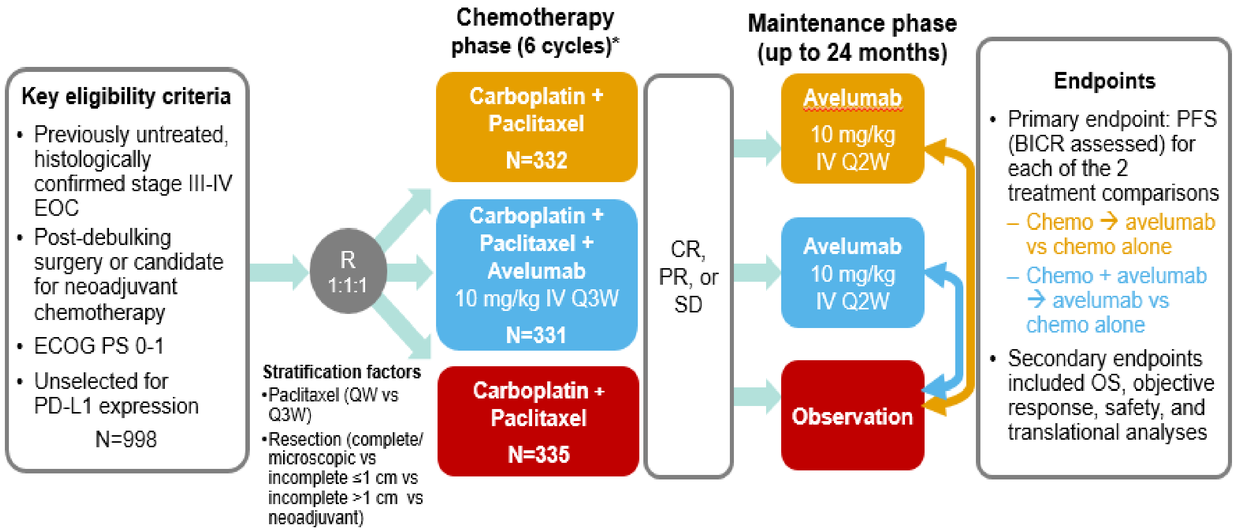
Efficacy and Safety of Mirvetuximab Soravtansine in Patients with Platinum-Resistant Ovarian Cancer with High Folate Receptor Alpha Expression: Results from the SORAYA Study

- Phase II study. N=106
- Platinum resistant ovarian cancer, HighFRα expression, up to 3 prior regimens
- All patients prior Bev, 48% PARP inhibitor
- ORR 32.4% independent of pior lines of therapy or prior PARP
- Median DOR 5.9 months
- Ocular toxicity
  - Blurred vision 41% (grade $\geq$ 3: 6 %)
  - Keratopathy 35% (grade > 3: 9 %)

Matulonis U, et al SGO 2022

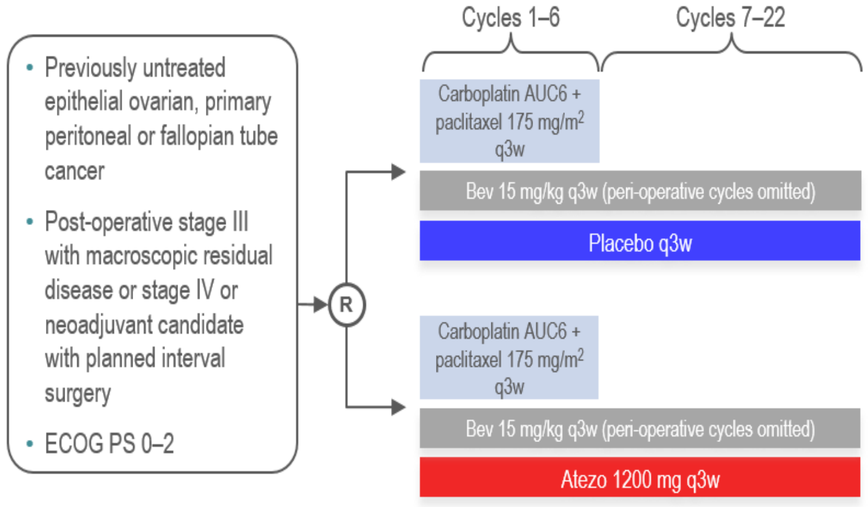
Randomized Phase 3 Trials of Immune Checkpoint Inhibitors in Front Line Ovarian Cancer: A Tale of Two Trials

JAVELIN OVARIAN 100



PFS	Chemo → Avel (N=332)	Chemo + Avel → Avel (N=331)	Chemo → Obs (N=335)
Events, n (%)	99 (29.8)	88 (26.6)	70 (20.9)
Median (95% CI), months	16.8 (13.5, NE)	18.1 (14.8, NE)	NE (18.2, NE)
Stratified HR vs control (95% CI)	1.43 (1.051, 1.946)	1.14 (0.832, 1.565)	–
p value vs control*	0.9890	0.7935	–

IMagyn050



PFS	ITT population	
	Placebo + CP + bev (n=650)	Atezo + CP + be
Patients with events, n (%)	341 (52.5)	323 (49.[illegible])
Median PFS, months (95% CI)	18.4 (17.2–19.8)	19.5 (18.1–20.8)
Stratified HR (95% CI)	0.92 (0.79–1.07)	
Stratified log-rank p-value	0.2785	
2-year event-free rate (95% CI)	29.1 (23.9–34.3)	35.1 (30.0–40.3)

Ledermann et al. SGO Annual Meeting (virtual) 2020); Moore et al. J Clin Oncol 2021

Courtesy of Kathleen Moore, MD

Ongoing Randomized Trials of Immunotherapy

Trial	Size	Anti-angiogenic	PARPi	ICI	Start	Estimated Primary Completion
FIRST[a] ENGOT OV-44	1405	± Bevacizumab	Niraparib	Dostarlimab	Oct 2018	Jan 2023
DUO-O[b] ENGOT OV-46	~1254	Bevacizumab	Olaparib	Durvalumab	Jan 2019	June 2023
ATHENA[c] GOG-3020 ENGOT OV-45	~1000	-	Rucaparib	Nivolumab	May 2018	Dec 2024
ENGOT OV-43[d] KEYLYNK-001	~1086	± Bevacizumab	Olaparib	Pembrolizumab	Dec 2018	Aug 2025

What is new in Cervical Cancer

- **Upfront management**
- **Management of Recurrent Disease**
  - Novel agents
- Screening, Surveillance, Genetics, Nutrition

original report

Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Cervical Cancer: Results From the Phase II KEYNOTE-158 Study

Hyun Cheol Chung, MD, PhD[1]; Willeke Ros, MSc[2]; Jean-Pierre Delord, MD, PhD[3]; Ruth Perets, MD, PhD[4]; Antoine Italiano, MD, PhD[5]; Ronnie Shapira-Frommer, MD[6]; Lyudmila Manzuk, MD[7]; Sarina A. Piha-Paul, MD[8]; Lei Xu, PhD[9]; Susan Zeigenfuss, RN[9]; Scott K. Pruitt, MD, PhD[9]; and Alexandra Leary, MD, PhD[10]

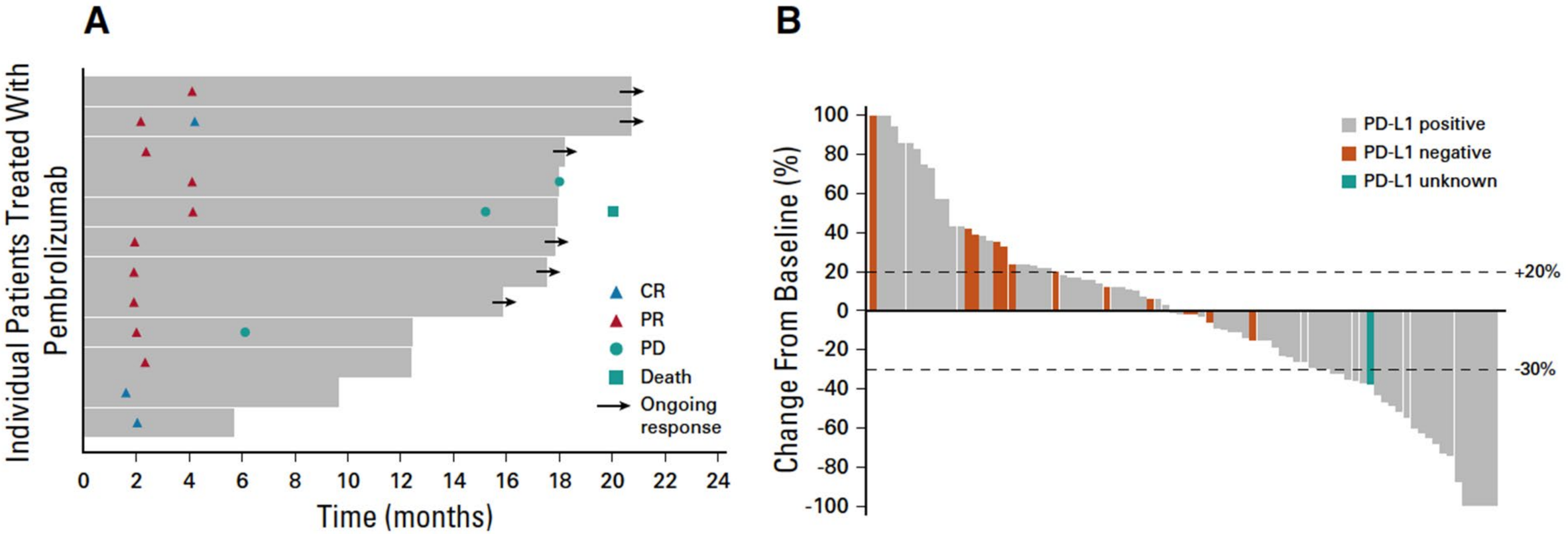
J Clin Oncol 2019;37(17):1470-8

KeyNOte-158 Objective Response Rate

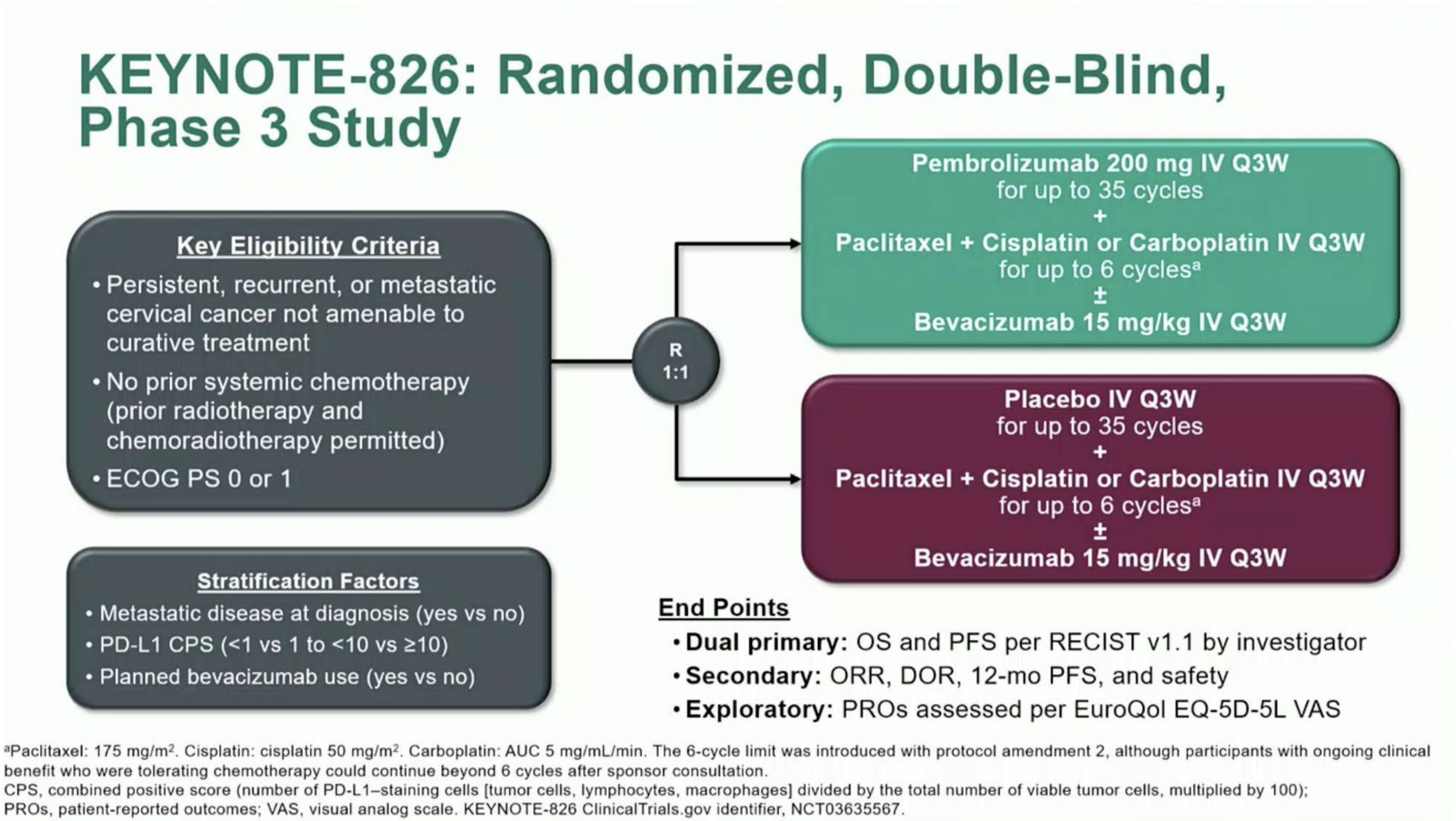
Antitumor Activity	Total Population (N = 98)*	Total (n = 82)	Previously Treated (n = 77)†	PD-L1–Negative Population (n = 15)
ORR	12 (12.2)	12 (14.6)	11 (14.3)	0 (0.0)
95% CI	6.5 to 20.4	7.8 to 24.2	7.4 to 24.1	0.0 to 21.8

Chung HC, et al. J Clin Oncol 2019;37(17):1470-8

Duration of Response

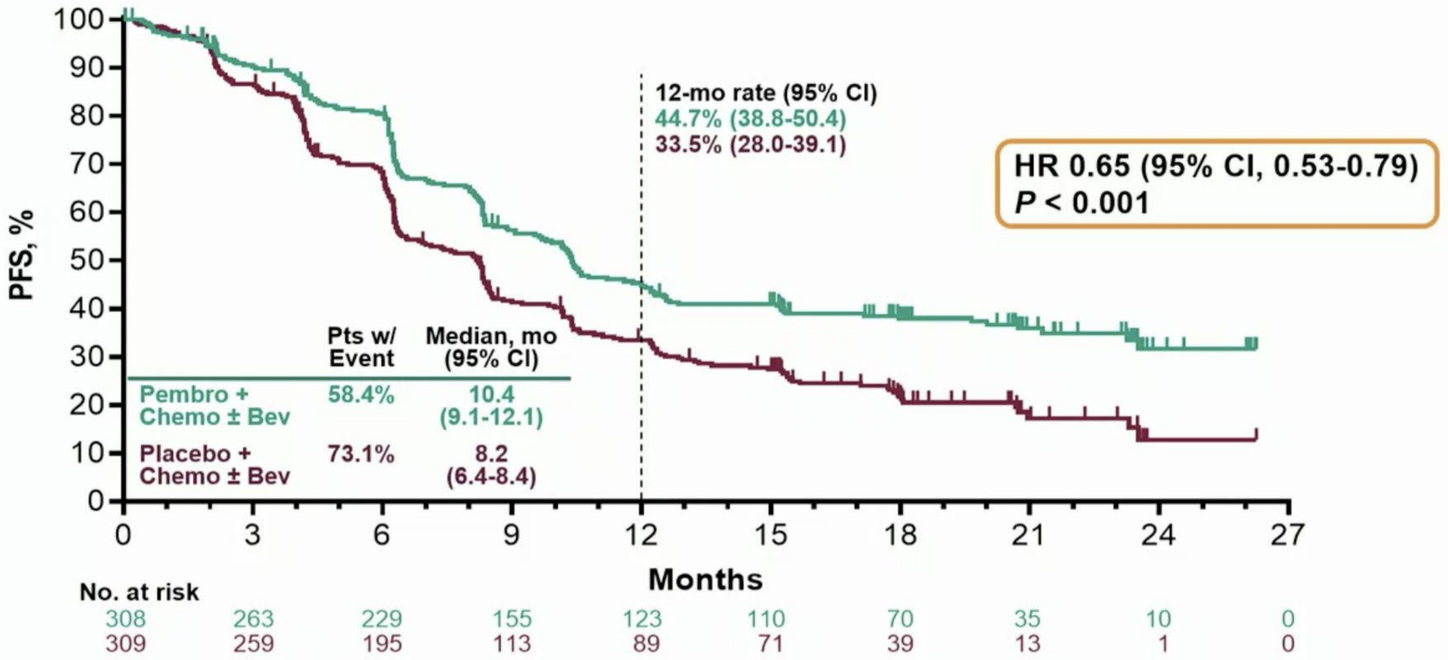


Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer



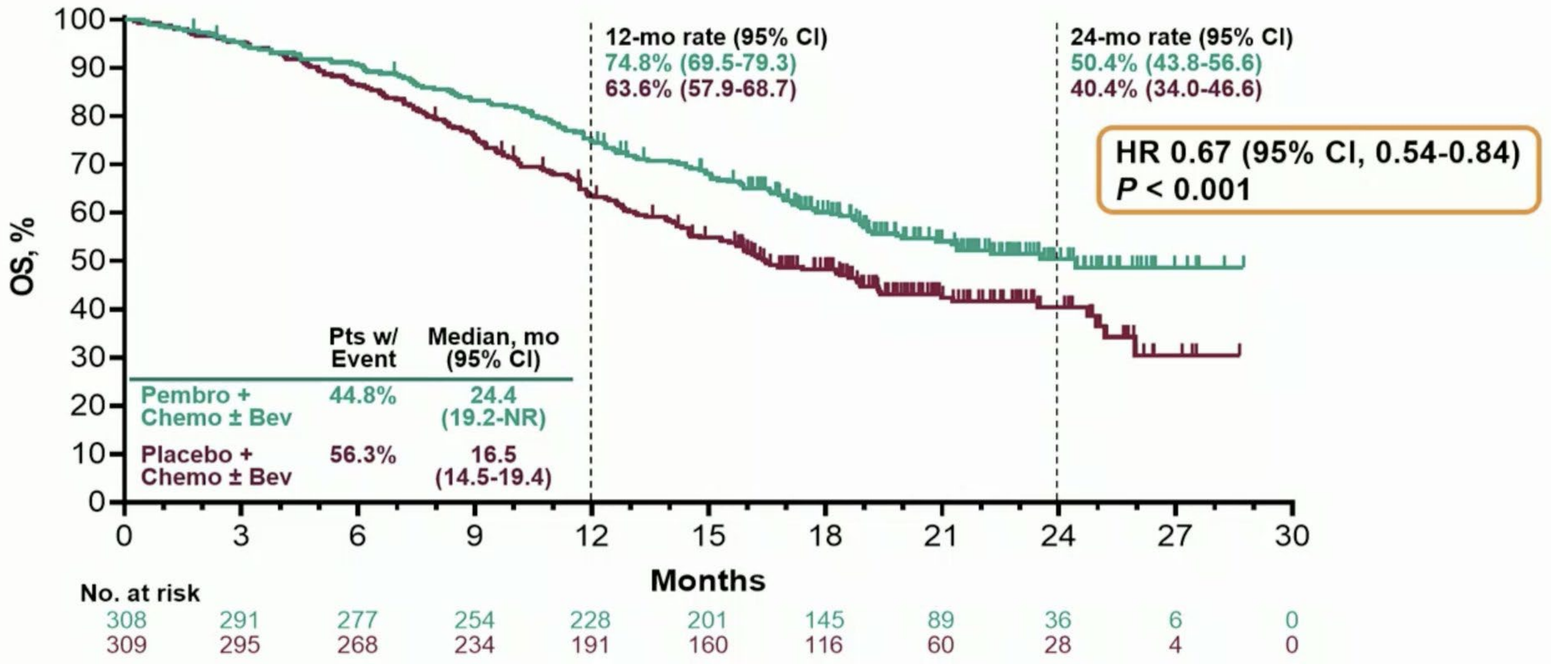
Colombo et al. Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer New Engl J Med 2021

PFS: All-Comer Population



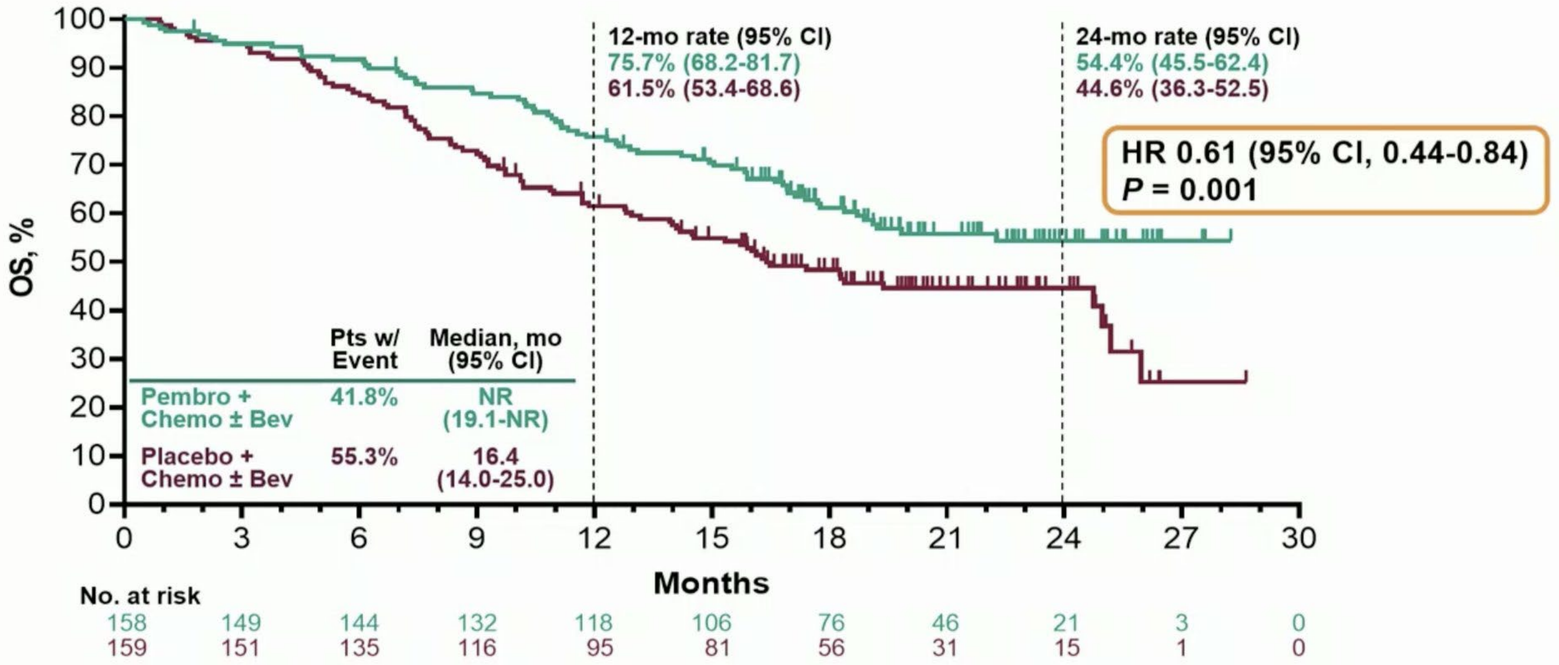
Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: May 3, 2021.

OS: All-Comer Population



Data cutoff date: May 3, 2021.

OS: PD-L1 CPS ≥10 Population



Data cutoff date: May 3, 2021.

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

Tisotumab Vedotin in Previously Treated Recurrent or Metastatic Cervical Cancer AC

David S. Hong[1], Nicole Concin[2], Ignace Vergote[2], Johann S. de Bono[3], Brian M. Slomovitz[4], Yvette Drew[5], Hendrik-Tobias Arkenau[6], Jean-Pascal Machiels[7], James F. Spicer[8], Robert Jones[9], Martin D. Forster[10], Nathalie Cornez[11], Christine Gennigens[12], Melissa L. Johnson[13], Fiona C. Thistlethwaite[14], Reshma A. Rangwala[15], Srinivas Ghatta[16], Kristian Windfeld[17], Jeffrey R. Harris[18], Ulrik Niels Lassen[19], and Robert L. Coleman[20]

Clin Cancer Res 2020;26:1220–8

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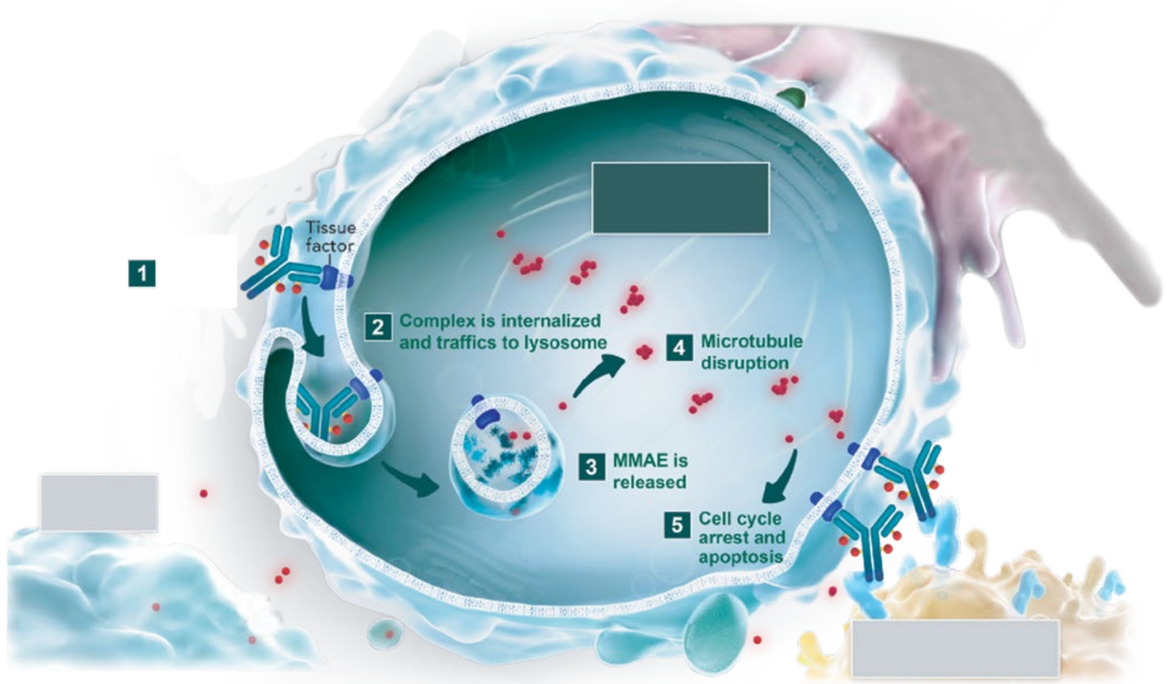
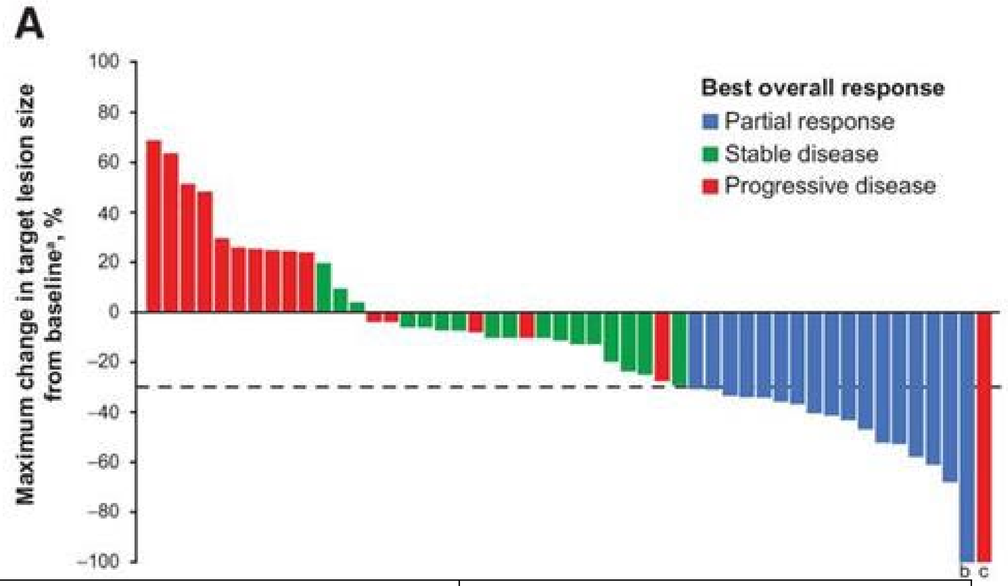
FDA grants accelerated approval to tisotumab vedotin-tftv for recurrent or metastatic cervical cancer
September 2021

Clin Cancer Res 2020;26:1220–8

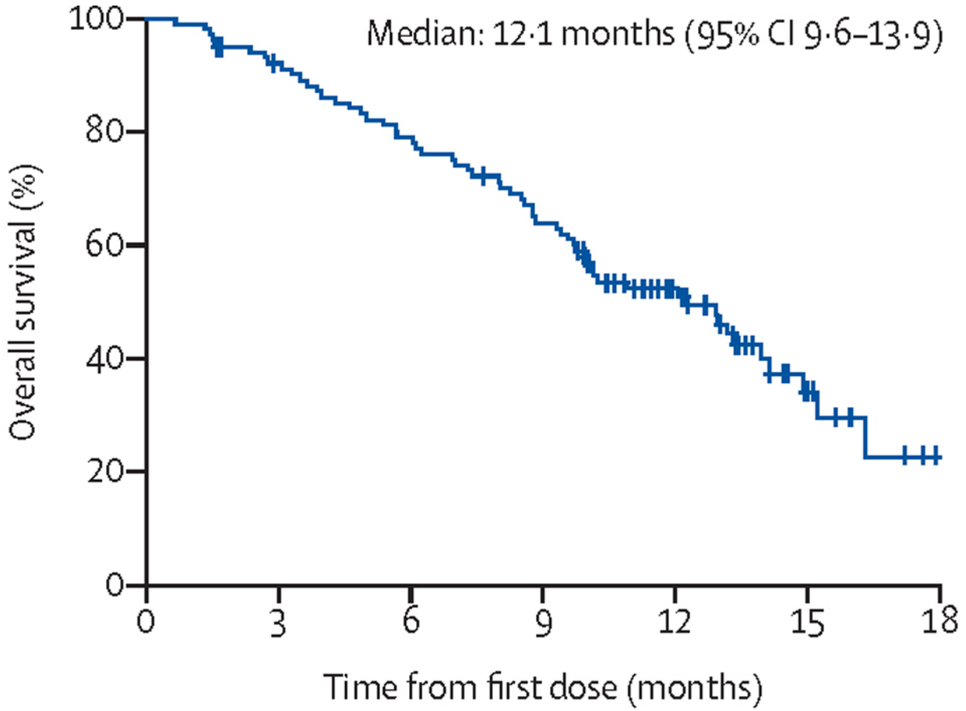
Tisotumab Vedotin

- Tissue factor (TF) is aberrantly expressed in a broad range of solid tumours, including cervical cancer,[1,2] and TF expression has been associated with higher tumour stage and grade, higher metastatic burden and poor prognosis[2]
- TF expression in cervical cancer makes TF a novel target for patients with cervical cancer
- ADC targets TF
  - Monoclonal Antibody targets TF
  - Payload: Microtubule disrupting MMAE
- Allowing for direct cytotoxicity and bystander killing, as well as antibody-dependent cellular cytotoxicity[3,4]





Antitumor Activity	
ORR	24%
CR	0%
PR	24%
Median DOR	4.2 m
Median PFS	4.2 m
6-month PFS	29%



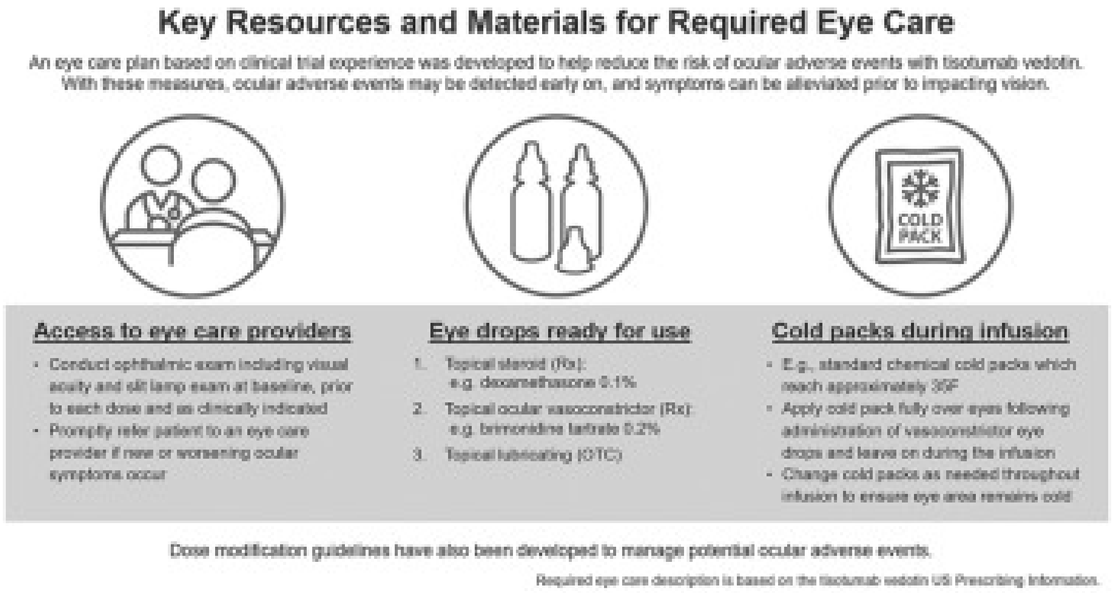
Overall Survival	
Median	12.1 m
6 month OS	79%
12- month OS	51%

Lancet Oncol 2021

Ocular Toxicity

Incidence, n (%)	*N* = 101	
	Any grade	Grade 3
Patients with ≥ 1 ocular AE	55 (54)	3 (3)
Ocular AE in ≥ 2 patients		
Conjunctivitis	31 (31)	0
Dry eye	25 (25)	0
Keratitis	11 (11)	0
Blepharitis	7 (7)	0
Punctate keratitis	6 (6)	0
Increased lacrimation	4 (4)	0
Ocular hyperemia	4 (4)	0
Blurred vision	3 (3)	0
Entropion	3 (3)	0
Meibomitis	3 (3)	0
Ulcerative keratitis	3 (3)	3 (3)
Cataract	2 (2)	0
Conjunctival hemorrhage	2 (2)	0
Conjunctival hyperemia	2 (2)	0
Eye discharge	2 (2)	0
Trichiasis	2 (2)	0

No Grade 4 adverse events were reported.



What is new inEndometrial Cancer

- **Upfront management**
  - **Surveillance**
- **Management of Recurrent Disease**
  - Novel agents
- Screening, Genetics, Nutrition

Surveillance in Endometrial Cancer

TOTEM Study: Intensive versus minimalist follow-up in patients treated For endometrial cancer

- 1800 patients with endometrial cancer randomized to minimalist vs intensive surveillance
- Low Risk Patients (Stage IA, G1-2)
  - Minimalist: Clinical exam every 6 months
  - Intensive: Minimalist + PAP and CT scans every 12 months
- High Risk Patient (Stage 1A G3 or ≥ 1B
  - Minimalist: Clinical exam every 4 months * and CT scans every 12 months
  - Intensive: Minimalist + CA125 and US every 4 months and PAP every 12 m

Zola P, ASCO 2021

TOTEM Results

	Intensive	Minimalist	
5 year OS %	90.6	91.9	HR 1.12 P=0.429
Low Risk	94.1	96.8	HR 1.48 P= 0.104
High Risk	85.3	84.7	HR 0.96 P= 0.814

What is new in Endometrial Cancer?

- **Upfront management of Ovarian cancer**
- **Management of Recurrent Disease**
  - Surgery
  - Systemic Therapy
- Novel agents
- Screening, Genetics, Nutrition

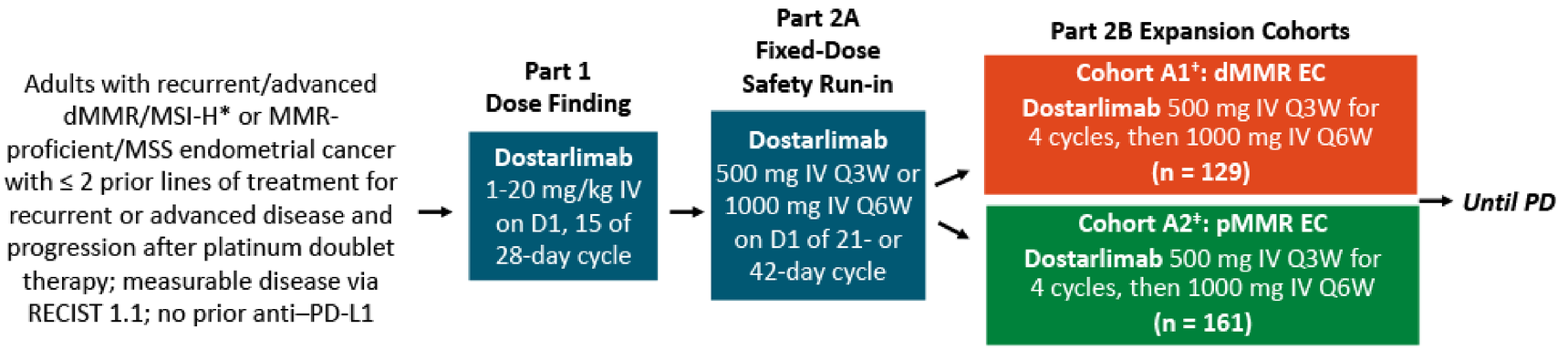
FDA grants accelerated approval to dostarlimab-gxly for dMMR endometrial cancer

April 2021

GARNET Trial: Safety and antitumor activity of dostarlimab in patients with advanced or recurrent DNA mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) or proficient/stable (MMRp/MSS) endometrial cancer

GARNET: Dostarlimab (TSR-042) Monotherapy in Endometrial Cancer

- Multicenter, open-label, single-arm phase I study



*Tumor MMR/MSI screening based on local MMR/MSI testing results using IHC, PCR, or NGS performed in a certified local laboratory, but patient eligibility needs to be confirmed by MMR IHC results.
†Includes 3 patients with MMRunk/MSI-H disease.
‡Includes 16 patients with MMRunk/MSS disease.

- Primary endpoint: ORR
- Secondary endpoints: DoR, DCR

Oaknin. ESMO 2020. Abstr LBA36. Oaknin. JAMA Oncol. 2020;6:1. NCT02715284.

GARNET Results

Cohort A1 Median FU 16.3m	dMMR (N=106)	MSI-H and MMRunk (N=2)	Overall N=108
ORR (%)	43.4	50	43.5
Best Response (%)			
CR	10.4	0	10.2
PR	33.0	50	33
Median DUR	NR	NR	NR

Cohort A2 Median FU 11.5 m	MMRp (N=142)	MSS and MMRunk (N=14)	Overall (N=156)
ORR (%)	13.4	21.4	11.5
Best Response (%)			
CR	2.1	0	1.9
PR	11.3	21.4	12.2
Median DUR	NR	NR	NR

J Immunother Cancer 2022

Specific learning objectives

Use new knowledge about the complementary and alternative supplements to conduct discussions with patients about their use and potential interactions with cancer treatment

Complementary and Alternative Medicine in Gynecological Cancers

- Nutrition
  - Prevention
  - Therapy
- Herbal and Dietary Supplements:
    - Curcumin, Mistletoe, Ginger, Agaricus, Gingko, Ginseng
    - Selenium, Probiotics
  - Mostly preclinical
- Lifestyle Changes
  - Exercise
  - Weight loss
- Acupuncture
  - Pain, CINV
- Massage/Touch Therapies
- Mind Body Therapies

Ben-Arye E, et al. Integrative Medicine for Female Patients with Gynecologic Cancer J Altern Compl Med 2018

Society of Integrative Oncology

- 2009 SIO Guidelines, Evidence-Based Clinical Practice Guidelines for Integrative Oncology: Complementary Therapies and Botanicals.
- 2013 SIO Guidelines, Complementary therapies and integrative medicine in lung cancer: Diagnosis and Management of Lung Cancer.
- 2014 SIO Guidelines, Clinical Practice Guidelines on the Use of Integrative Therapies as Supportive Care in Patients Treated for Breast Cancer as Supportive Care in Patients Treated for Breast Cancer
- 2017 Clinical practice guidelines on the evidence-based use of integrative therapies during and after breast cancer treatment.

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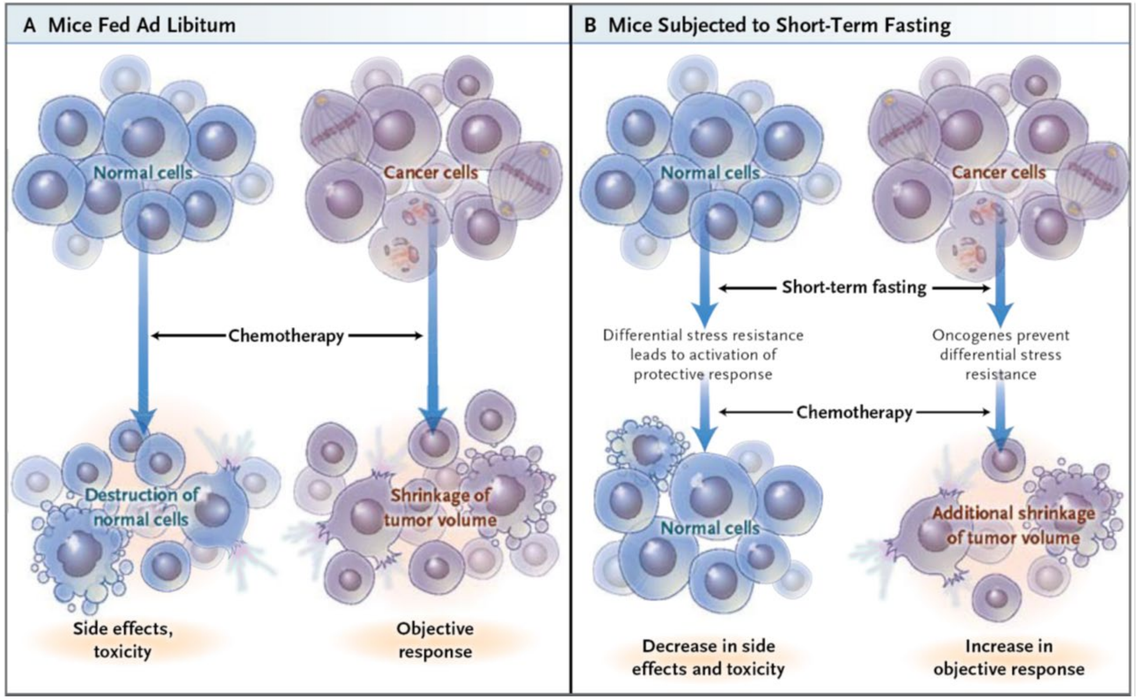
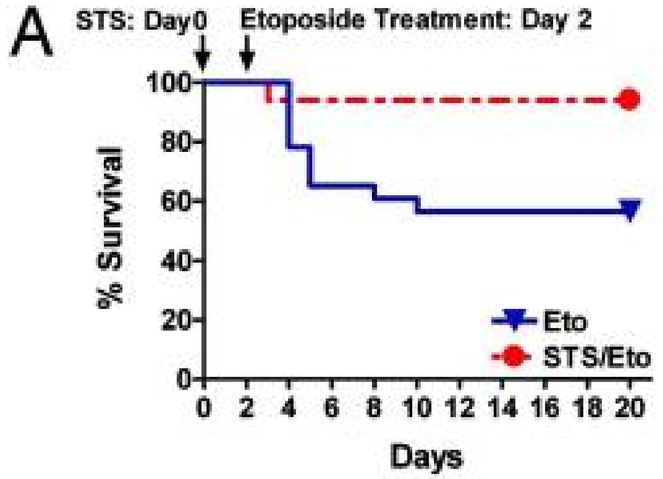
Effects of Fasting on Chemotherapy

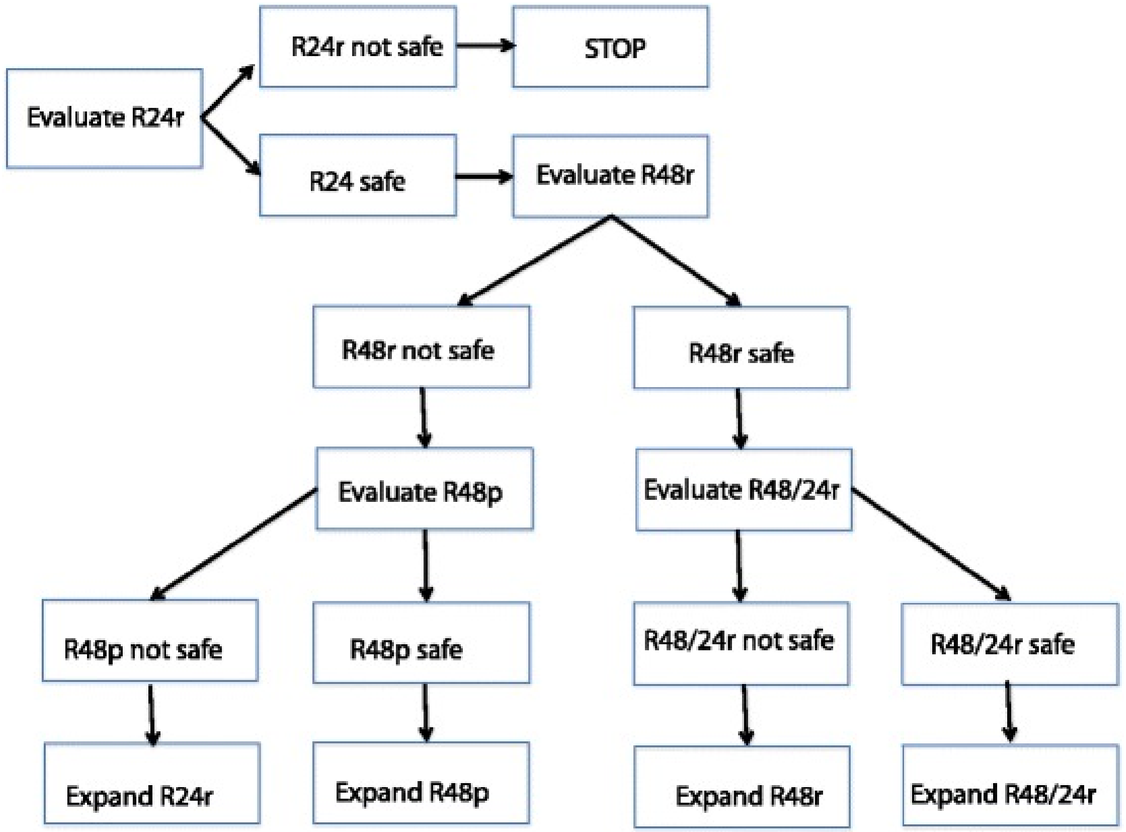
Raffaghello et al Proc Natl Acad Sci 2008





Safety and feasibility of fasting in combination with platinum-based chemotherapy

Fasting = < 200 kcal/day



Dorff TB, Groshen S, Garcia A, et al. BMC Cancer 2016

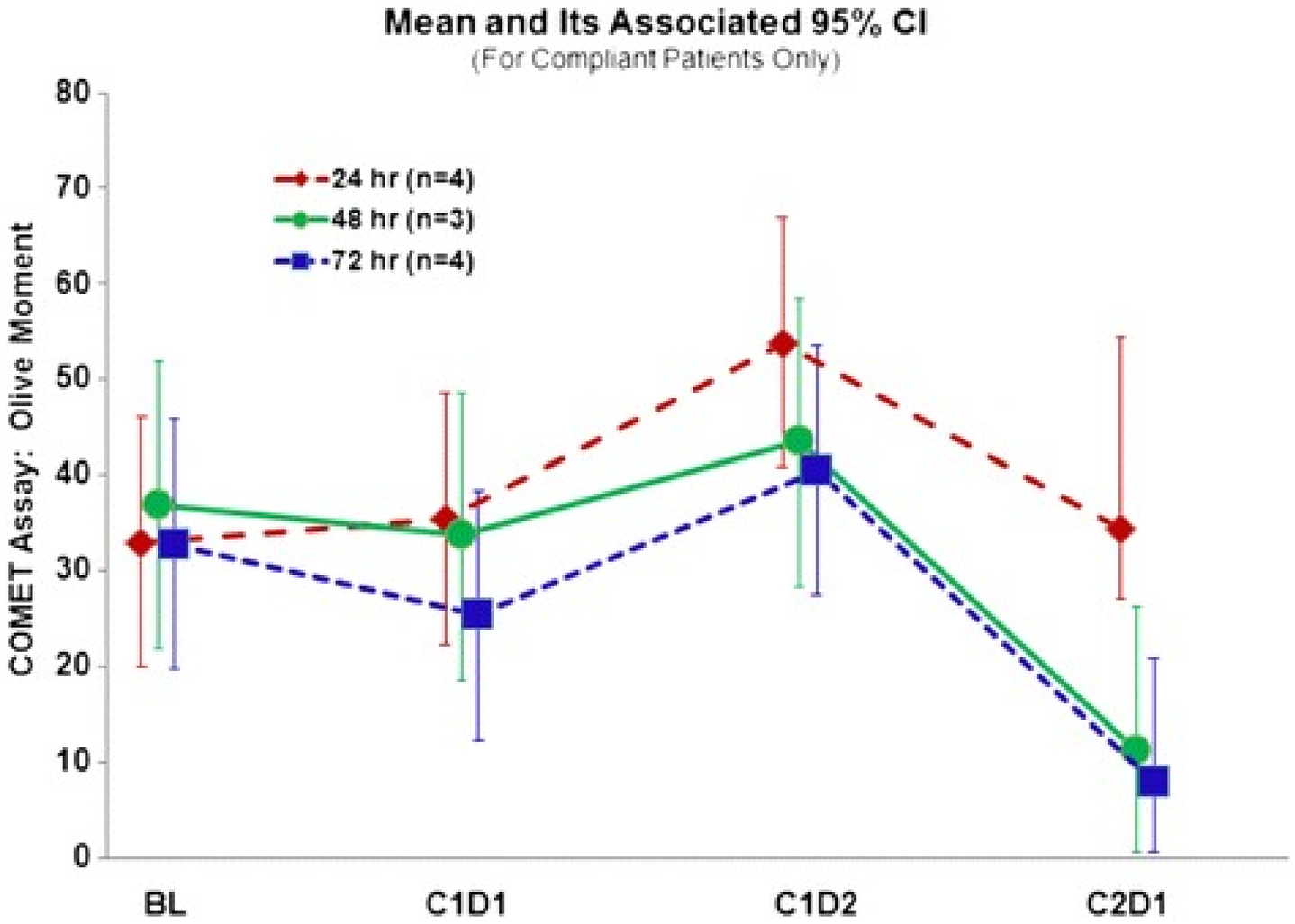
Patient Characteristics

Cancer Type	Chemotherapy Regimen	Disease State
24 hr cohort		
Urothelial (3)	Gemcitabine/Cisplatin	Adj, Neoadj, Metastatic (1 each)
Ovarian (1)	Carbo Paclitaxel	Adjuvant
Endometrial (1)	Carbo nab Paclitaxel	Metastatic
Lung (1)	Gemcitabine/Cisplain	Metastatic
48 hr cohort		
Ovarian (2)	Carbo Paclitaxel	Adjuvant, Metastatic (1 each)
Breast (4)	Docetaxel/Carbo/Trastuzumab	Adjuvant
Urothelial (1)	Gemcitabine/Cisplatin	Neoadjuvant
72 hr cohort		
Ovarian (3)	Carbo Paclitaxel	Adjuvant (1), Metastatic (2)
Uterine (1)	Carbo Paclitaxel	Adjuvant
Breast (1)	Docetaxel/Carbo/Trastuzumab	Neoadjuvant
Urothelial (2)	Gemcitabine/Cisplatin	Neoadjuvant

Toxicities

Toxicity	Cohort 24 hr %	Cohort 48 hr %	Cohort 72 hr %
Fatigue Gr 1/2	100	71	86
Nausea Gr 1/2	100	86	43
Vomiting Gr 1/2	83	43	0
Diarrhea Gr 1/2 **Gr 3/4**	33 0	0 14	57 0
Neutropenia Gr 1/2 **Gr 3/4**	17 67	43 14	14 29
Thrombocytopenia Gr 1/2 **Gr 3/4**	67 0	14 14	14 0
Peripheral Neuropathy G 1	50	14	14

DNA damage in peripheral lymphocytes by COMET assay



Chemotherapy and Fasting

- A Randomized, Phase II Clinical Trial of a Controlled Diet Prior to Selected Chemotherapy Treatment in Breast and Prostate Cancer to Evaluate the Impact on Toxicity and Efficacy. Ongoing
- DIetary REstriction as an Adjunct to Neoadjuvant ChemoTherapy for HER2 Negative Breast (DIRECT): De Groot et al. Nat Commun 2020

Bariatric surgery in patients with breast and endometrial cancer Lee E, Kawaguchi ES, Zhan J, Kim SE, Deapen D, Liu L, Sheidaee N, Hwan AE, Kan I, Sandthu K, Ursin G, Wu AH, Garcia AA. Surg for Obesity and Related Diseases 2022

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Association between WLS and time to death among obese (BMI ≥30) breast cancer and endometrial cancer patients

Cancer site	WLS (after cancer diagnosis)	Total N	Death N	HR (95% CI)[¶]	P-value
Breast cancer					
	No	9091	967	1 (ref)	
	Yes	60	<15[§]	0.52 (0.17 to 1.61)	0.25
Endometrial cancer					
	No	3343	451	1 (ref)	
	Yes	46	<15[§]	0.21 (0.030 to 1.50)	0.12
Combined[†]					
	No	12434	1417	1 (ref)	
	Yes	106	<15[§]	0.37 (0.14 to 0.99)	0.049

Abbreviation: HR, hazard ratio; CI, confidence interval; NHW, non-Hispanic white; NHB, non-Hispanic black; API, Asian/Pacific Islander; SES, socioeconomic status

[*] WLS group had a diagnosis code for obesity or morbid obesity. Excluding those who had undergone WLS prior to cancer diagnosis.

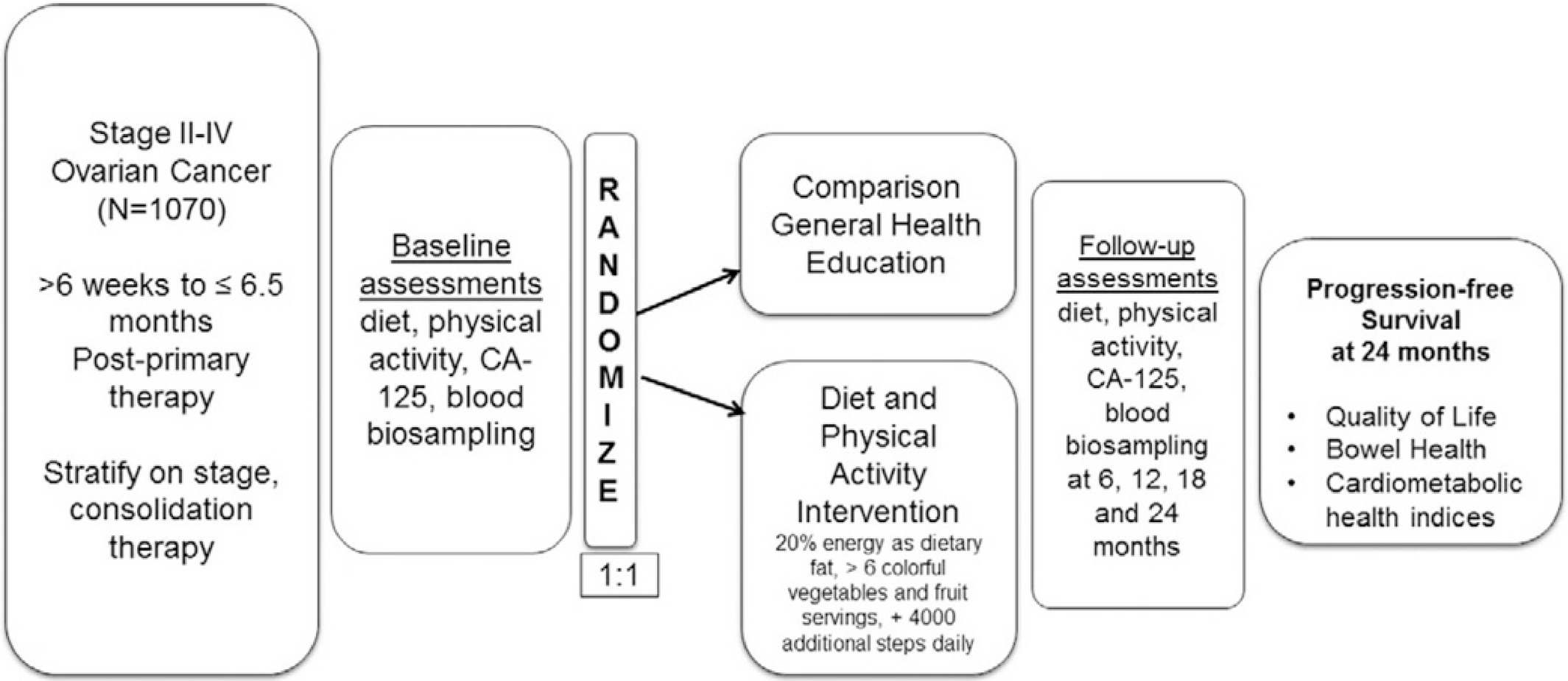
[§] Suppressed due to the OSHPD small cell suppression policy.

[¶] Adjusted for stage (localized, regional), age at cancer diagnosis (<40, 40-49, 50-59, 60-69, 70-79, ≥80), Charlson Comorbid Index (0, ≥1, unknown), race/ethnicity (NHW, NHB, Hispanic, Asian/Pacific Islanders/Other), SES (quintiles).

[**] Adjusted for quintiles of propensity score.

[†] Combined analysis of breast cancer and endometrial cancer patients was stratified by cancer site.

NRG/GOG 225: Randomized trial of diet and physical activity in women treated for stage II—IV ovarian cancer: Lifestyle Intervention for Ovarian Cancer Enhanced Survival (LIVES)



780/857 Events

THANK YOU

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