Ovarian Cancer: Targeted Therapy, Angiogenesis, and Immunotherapy

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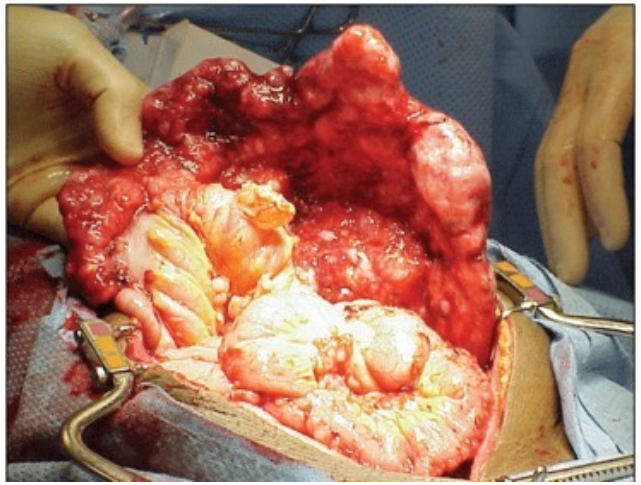
Still… Surgery and Chemo (plus some)

Include a Gyn Oncologist in the care team starting at diagnosis because survival is improved[1,2]

- Data continues to show that those good candidates who get upfront R0 surgery **DO BETTER**
- NACT on the rise, so is survival
  - Our treatments are better
  - Our informed decision making is better on selecting appropriate surgical candidates



(1)Gynecol Oncol. 2021 Jun;161(3):852-857. doi: 10.1016/j.ygyno.2021.04.021. Epub 2021 Apr 20. PMID: 33888339 (2) Obstet Gynecol. 2007 Jun;109(6):1342-50. doi: 10.1097/01.AOG.0000265207.27755.28. PMID: 17540806.

HIPEC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer

W.J. van Driel, S.N. Koole, K. Sikorska, J.H. Schagen van Leeuwen, H.W.R. Schreuder, R.H.M. Hermans, I.H.J.T. de Hingh, J. van der Velden, H.J. Arts, L.F.A.G. Massuger, A.G.J. Aalbers, V.J. Verwaal, J.M. Kieffer, K.K. Van de Vijver, H. van Tinteren, N.K. Aaronson, and G.S. Sonke

HOTT trial opening here at UMCNO

- Multicenter open label phase III tha
- 245 women w/ >/= stable disease after carbo/t iCRS to R0/R1
  - Randomized to +/- HIPEC with cisplatin 100 mg/msq
  - All got carbo/taxol x 3 postop
- mRFS: 10.7 vs 14.2 months in favor of HIPEC (p=0.003)
- mOS: **33.9 vs 45.7** months in favor of HIPEC (p=0.02)
- Grade 3-4 adverse events: 25 vs 27% (similar)

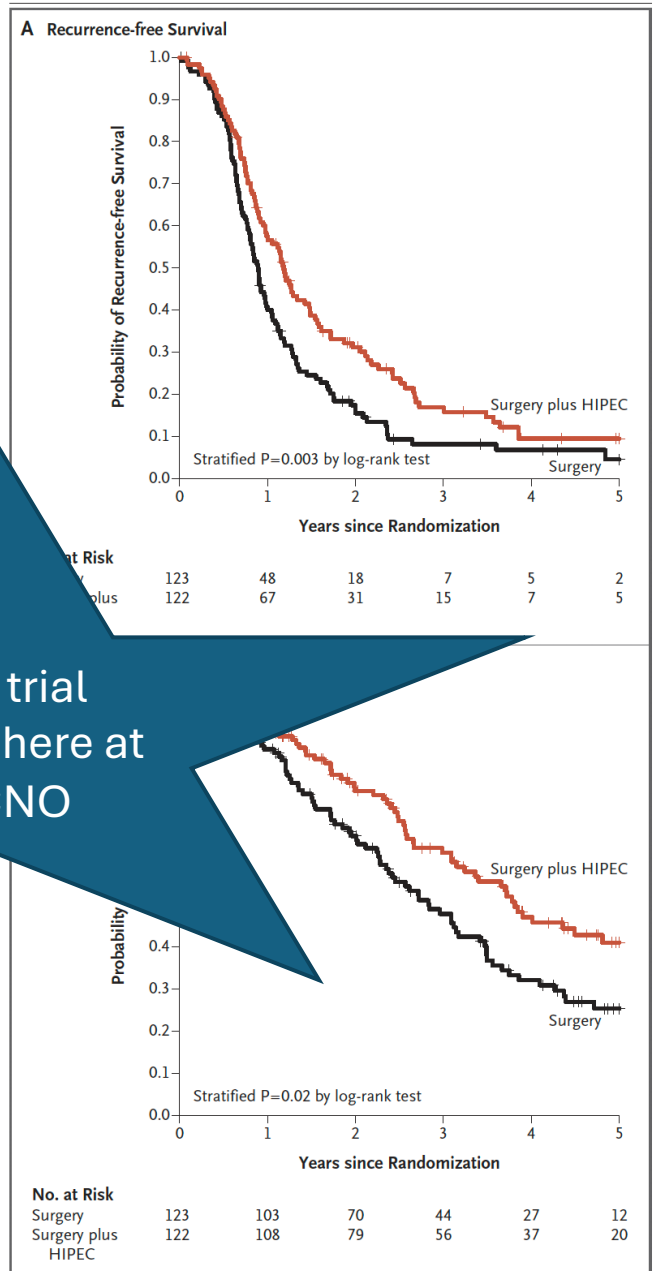


Figure 2. Kaplan–Meier Estimates of Recurrence-free Survival and Overall Survival.
Panel A shows Kaplan–Meier estimates of recurrence-free survival among patients in the intention-to-treat population. Events of disease recurrence or death were observed in 110 patients (89%) in the surgery group and in 99 patients (81%) in the surgery-plus-HIPEC group. Panel B shows Kaplan–Meier estimates of overall survival among patients in the intention-to-treat

HOTT

GOG-3068

(Hyperthermic Ovarian Treatment Trial)

HIPEC: A phase III randomized superiority trial of heated intraperitoneal chemotherapy (HIPEC) with cisplatin versus "cold" intraperitoneal chemotherapy versus heated intraperitoneal saline at the time of optimal interval cytoreductive surgery followed by niraparib maintenance in patients with newly diagnosed stage III and IV ovarian, primary peritoneal, and fallopian tube cancer

GOG FOUNDATION Transforming the standard of care

GOG PARTNERS

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THE HIPEC PROCEDURE | CANCERS TREATED | RESOURCES | HIPEC SURGEONS & HOSPITALS

University Medical Center New Orleans
LCMC Health

University Medical Center New Orleans
2020 Gravier Street, 5th Floor
New Orleans, LA 70112

LSU Health NEW ORLEANS

Dr. Kevin Sullivan
Assistant Professor, Surgical Oncology

United States, LA 70112 US
LSU Health, University Medical Center New Orleans
Schedule Conversation

Dr. Omeed Moaven
Surgical Oncologist, Assistant Professor

United States, New Orleans, LA 70112
LSU Health New Orleans
Schedule Conversation

Dr. Amelia Jernigan
Gynecologic Oncologist

USA, New Orleans, LA 70112
University Medical Center New Orleans
Schedule Conversation

Paclitaxel 175 mg/m² IV over 3 hours or Docetaxel at 60-75 mg/m² every 3 weeks and Carboplatin AUC 6 IV on Day 1 every 21 days for 3-4 cycles

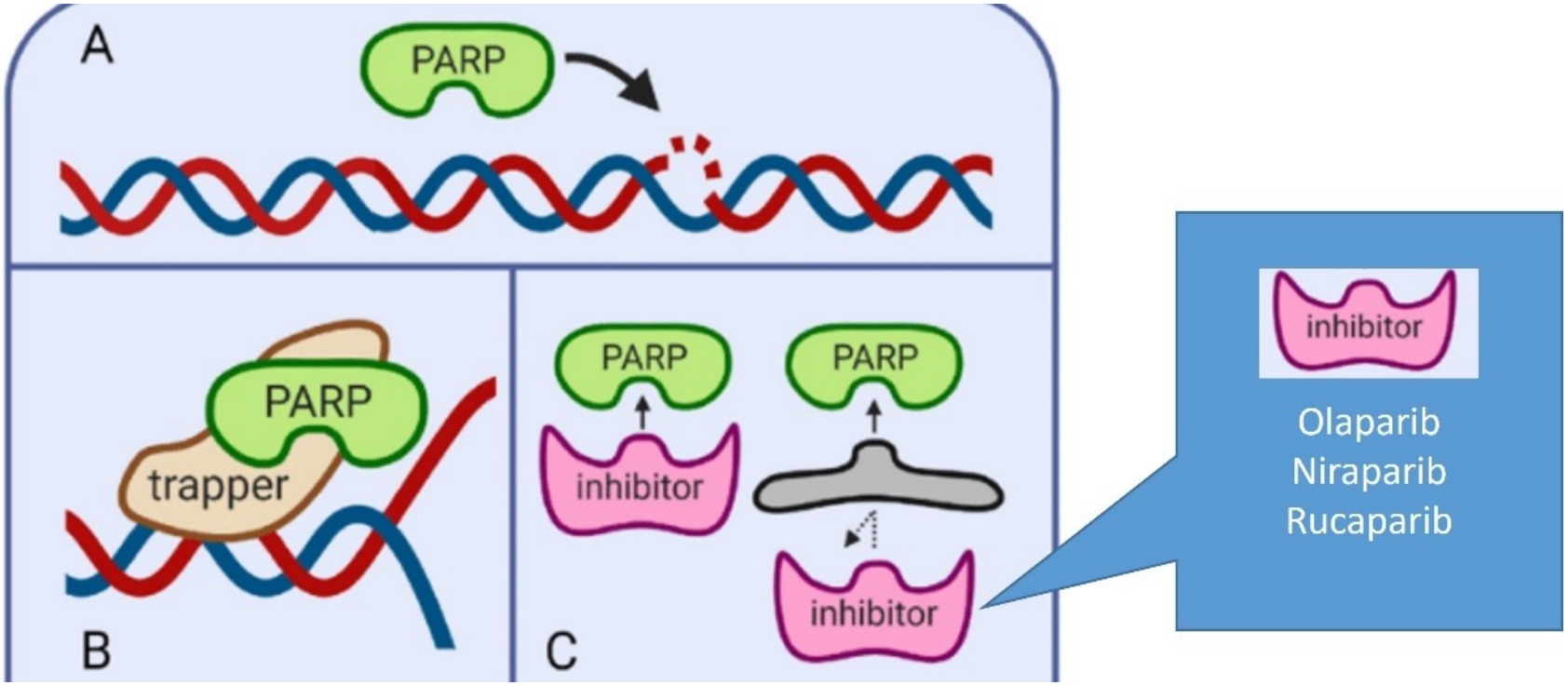
→ Optimal ICRS → RANDOMIZE

- HIPEC: Cisplatin 100 mg/m² IP over 90 minutes at 42°C
- NO HIPEC

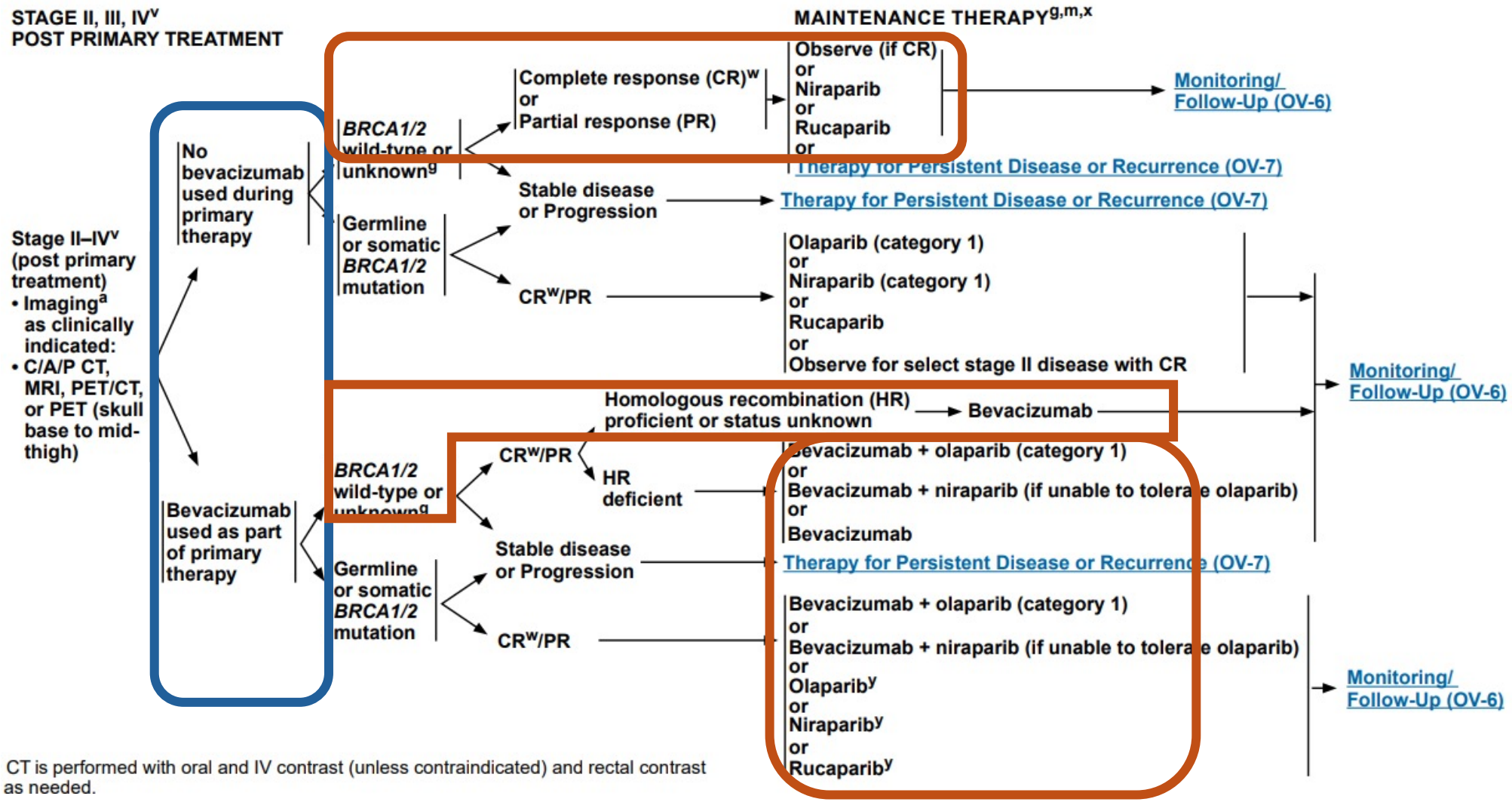
→ Paclitaxel 175 mg/m² IV over 3 hours or Docetaxel at 60-75 mg/m² Carboplatin AUC 6 IV on Day 1 every 21 days for 2-3 cycles (6 cycles max neoadjuvant and post-op chemotherapy)

→ **Niraparib Maintenance**
300mg PO daily on a 28-day cycle (200mg PO daily if weight > 77 kg and/or platelet count , 150,000)
Treatment until disease progression or 36 months (if no evidence of disease)

What about PARPi!?

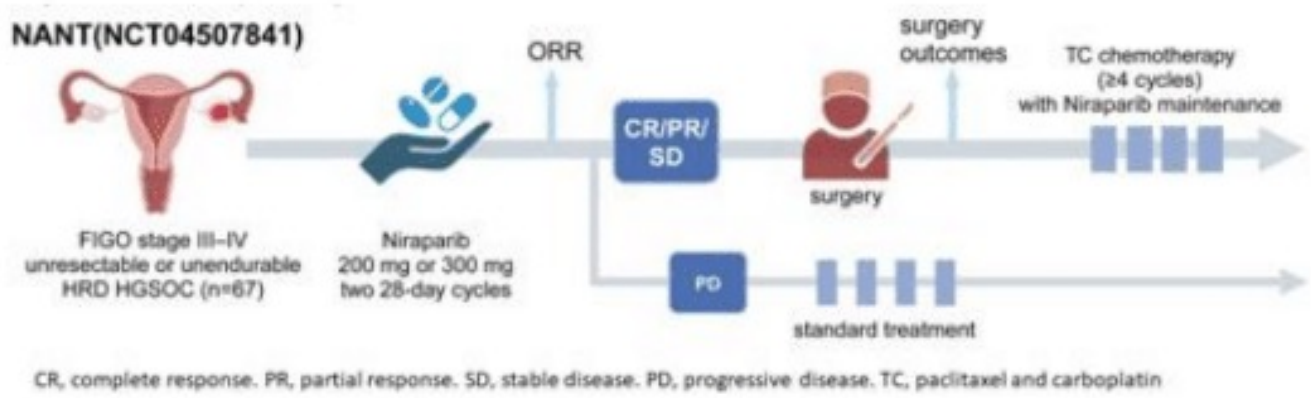


Probably not (now), so how to maximize PARP



Can PARPi replace upfront chemo before surgery

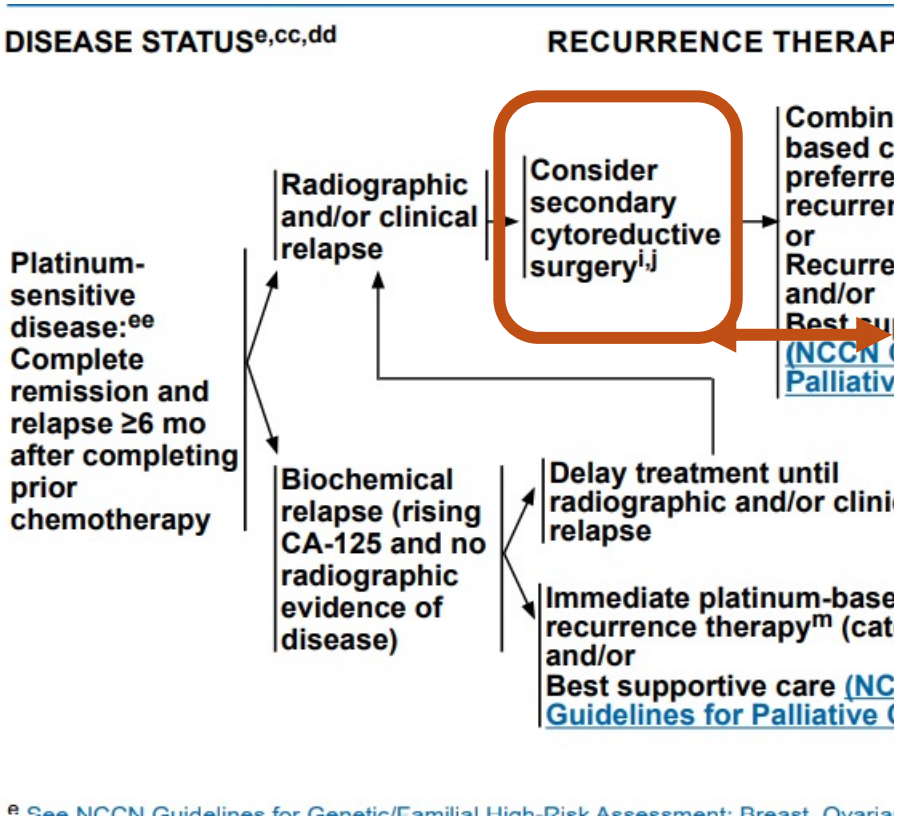
- NOW (SGO 2023)
  - HGSOC for NACT, BRCA mut
  - Olaparib until response or PD → Surgery or chemo
  - N=15, 86% surgery directly
  - ORR:53%, 1/15 pCR, 12/15 R0
- NANT (ASCO 2024)
  - Stage III-IV unresectable, HRD
  - Niraparib x 2 cycles → surgery or chemo
  - N=67, n=48 evaluable
  - 62.5% PR, 25% SD
    - 80% R0 resection, 95% optimal debulk

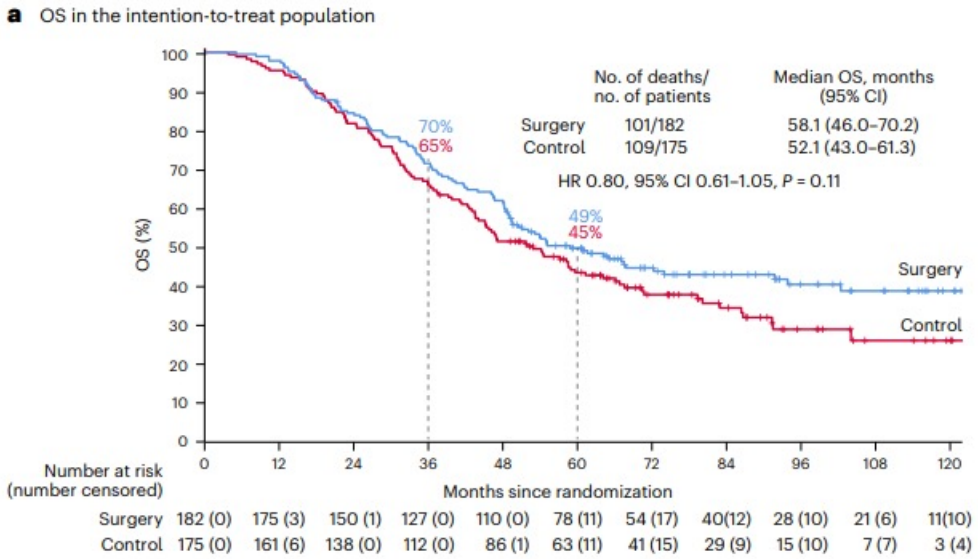


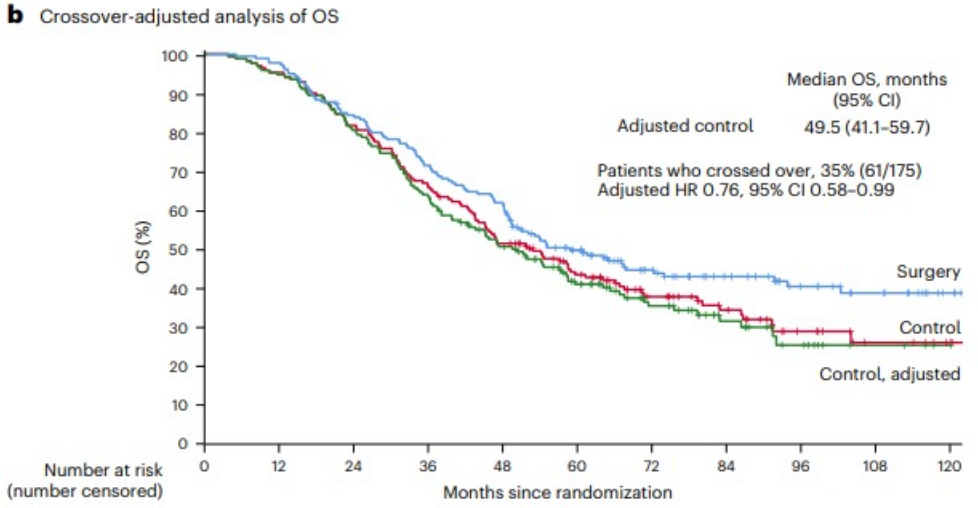
- Harano, et al (ASCO 2024)
  - Stage III-IV HGSOC, endometrioid, HR
  - Niraparib with ICPC (pembrolizumab) x 2 cycled → surgery or chemo
  - N=20, n=17 had surgery, n=15 required more chemo
  - 70% ORR – No CRs
    - 88%R0

(1)Westin et al. SGO 2023 (2)Gao et al. ASCO 2024 abstract 5549 (3) Harano et al. ASCO 2024 abstract 5545

PARPi now or PARP



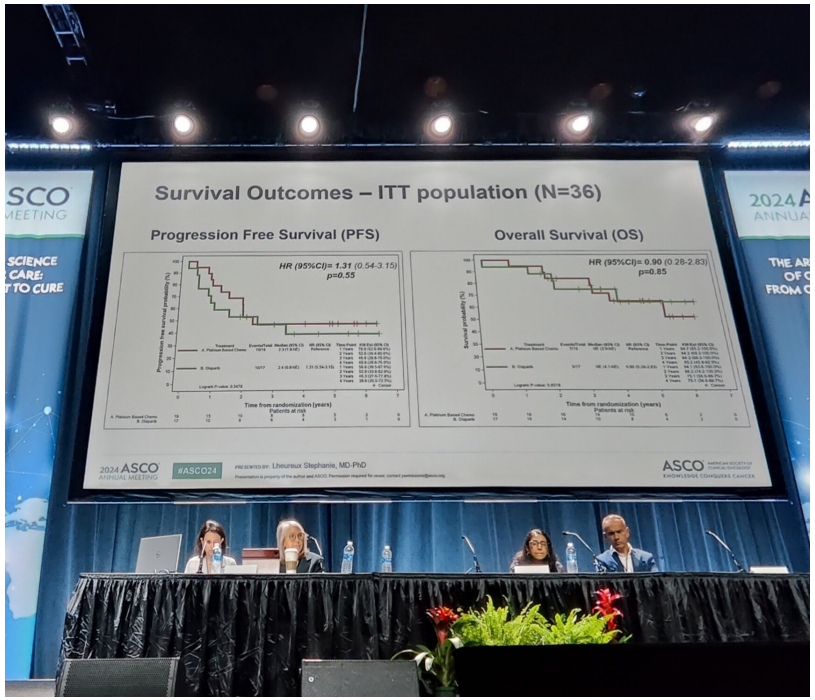




(1) Current use, NCCN July 2024 (2) Zhang et al. ASCO 2024 abstract 5520

Can PARPi Replace Chemo at recurrence

- NEO trial: rPSOC 44 patients with rec HGSOC >/= 6 m after plat.
  - Pts naïve to PARPi and were suitable for 2CRS
  - Neoadjuvant olaparib at 300 mg twice daily for 6 weeks (± 2 weeks
- No significant difference in PFS (2.3 months in the chemo arm and 2.4 months in the olaparib-alone arm)
  - (hazard ratio [HR], 1.31; 95% CI, 0.54-3.15; *P* =.5478).
- No significant difference in OS between the arms.
  - (HR, 0.90; 95% CI, 0.28-2.83; *P* =.8518).
- Very select population
  - 31% had a known germline *BRCA1/2* mutation.



Lheureuxet al. ASCO 2024 abstract 5506

Recurrent disease

- Does platinum sensitive hold the same meaning as before?
  - “Those for which platinum is an option”
  - Use of maintenance treatments prolong clinical benefit of platinum therapy, and the evolving definition of platinum resistance has shifted the characteristics of patients with PROC toward a population that is later in the disease course and more heavily pretreated
- In a phase 2 RCT[1], ORR for cisplatin plus gemcitabine in patients with PROC was 57%, with 3 of 14 patients reaching a complete response.
- Accordingly, the European Society for Medical Oncology guidelines8 now recommend the use of platinum-based therapies until platinum is no longer appropriate
- GCIG: Recs PFI or TFI

(1) Gynecol Oncol. 2022;165(1):97-104. doi:10.1016/j.ygyno.2022.02. 002

Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)[p]/Fallopian Tube/Primary Peritoneal Cancer[q]

Recurrence Therapy for Platinum-Resistant Disease (alphabetical order)

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Cytotoxic Therapy Cyclophosphamide (oral)/ bevacizumab[k,40] Docetaxel[41] Etoposide (oral)[42] Gemcitabine[43,44] Liposomal doxorubicin[43,44] Liposomal doxorubicin/ bevacizumab[k,s,45] Paclitaxel (weekly)[g,46] Paclitaxel (weekly)/ bevacizumab[g,k,s,45] Topotecan[47,48] Topotecan/bevacizumab[k,s,45] Targeted Therapy (single agents) Bevacizumab[k,s,21,22] Mirvetuximab soravtansine-gynx (for FRα-expressing tumors [≥75% positive tumor cells])(category 1)[z,49,50]	Cytotoxic Therapy[u] Capecitabine Carboplatin[*] Carboplatin/docetaxel[*] Carboplatin/paclitaxel (weekly)[g,*] Carboplatin/gemcitabine[14] ± bevacizumab[k,s,t,15,*] Carboplatin/liposomal doxorubicin[16] ± bevacizumab[k,s,17,*] Carboplatin/paclitaxel[g,18] ± bevacizumab[k,s,t,19,*] Cyclophosphamide Cyclophosphamide (oral)/pembrolizumab/bevacizumab[k,52,53] Doxorubicin Gemcitabine/bevacizumab[k,54] Gemcitabine/cisplatin[20,*] Ifosfamide Irinotecan Ixabepilone/bevacizumab (category 2B)[k,aa,55] Melphalan Oxaliplatin Paclitaxel Paclitaxel, albumin bound Pemetrexed Sorafenib/topotecan[51] Vinorelbine Targeted Therapy (single agents) Niraparib (category 3)[v,27] Olaparib (category 3)[w,28] Pazopanib (category 2B)[29] Rucaparib (category 3)[x,30] Hormone Therapy Aromatase inhibitors (anastrozole, exemestane, letrozole) Goserelin acetate Leuprolide acetate Megestrol acetate Tamoxifen[i]	Carboplatin/paclitaxel (for age >70)[g,y,*] Carboplatin/paclitaxel, albumin bound (for confirmed taxane hypersensitivity)[*] Immunotherapy Dostarlimab-gxly (for dMMR/MSI-H recurrent or advanced tumors)[z,38] Pembrolizumab (for patients with MSI-H or dMMR solid tumors, or TMB-H tumors ≥10 mutations/megabase)[z,39] Hormone Therapy Fulvestrant (for low-grade serous carcinoma) Targeted Therapy Dabrafenib + trametinib (for *BRAF* V600E-positive tumors)[z,32] Entrectinib or larotrectinib (for *NTRK* gene fusion-positive tumors)[z] Fam-trastuzumab deruxtecan-nxki (for HER2-positive tumors [IHC 3+ or 2+])[56] Mirvetuximab soravtansine-gynx/bevacizumab (for FRα-expressing tumors)[k,z,33,57,58] Selpercatinib (for *RET* gene fusion-positive tumors)[z,34] For low-grade serous carcinoma: • Trametinib[35] • Binimetinib (category 2B)[36,37]

* Platinum agents have limited activity when the disease has demonstrated growth through a platinum-based regimen, and platinum rechallenge is generally not recommended in this setting.

Footnotes

Anti-

- NRG
  - **Ne**
- AGO-
  +cher
  recur
  - **Ne**
  - mC
- ENGC
  paclit
  - On
  - Pac

+ Atezo +/- Bev in PROC

zolizumab +bevacizumab
zumab +chemotherapy in

placebo), NS diff in PFS ~6.5m

3 pembro vs placebo plus
b for PROC

giogenic property)

(1) MarmeF et al. ASCO 2024 LBA 5501 (2) O'cearbhailet al. IGCS 2023 (3) Colombo et al, ASCO 2022 TIP

Other promising new approaches

Pembrolizumab, oral cytoxan, bevacizumab

JAMA Oncology | Original Investigation

Efficacy and Safety of Pembrolizumab in Combination With Bevacizumab and Oral Metronomic Cyclophosphamide in the Treatment of Recurrent Ovarian Cancer
A Phase 2 Nonrandomized Clinical Trial

Emese Zsiros, MD, PhD; Sarah Lynam, MD; Kristopher M. Attwood, PhD; Chong Wang, MA; Shanmuga Chilakapati, PhD; Eduardo Cortes Gomez, MS; Song Liu, PhD; Stacey Akers, MD, MBA; Shashikant Lele, MD; Peter J. Frederick, MD; Kunle Odunsi, MD, PhD

Figure 2. Tumor Response and Survival Data Among Evaluable Patients Receiving Combination Pembrolizumab With Bevacizumab and Oral Cyclophosphamide

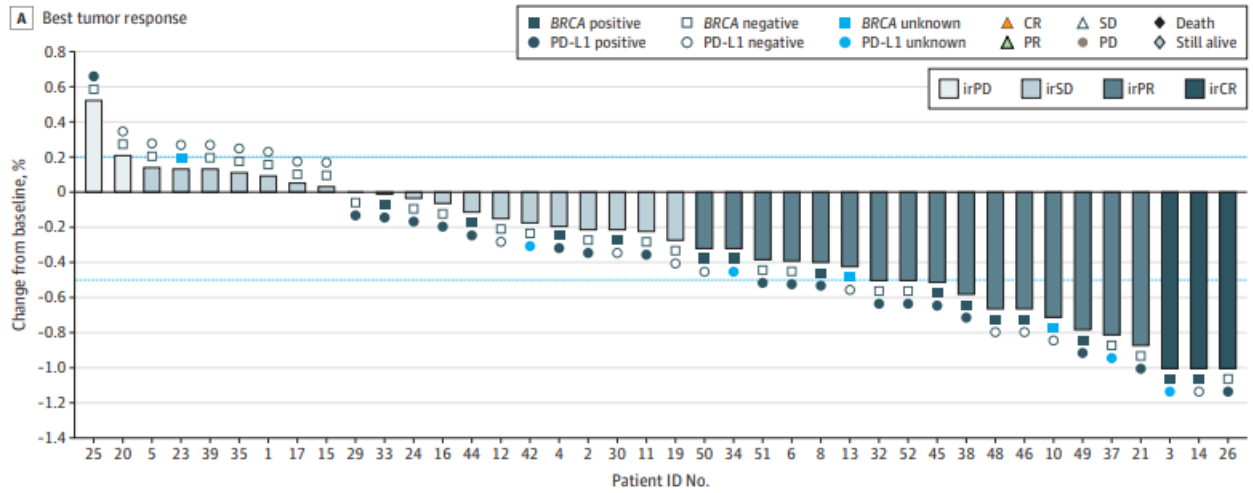


Table. Best Responses to Efficacy Measures

Best response	Patient group[a] Platinum-sensitive disease (n = 10)	Platinum-resistant disease (n = 30)	All (n = 40)
Unevaluable	0	0	0
Complete response	0	3 (10.0)	3 (7.5)
Partial response	6 (60.0)	10 (33.3)	16 (40.0)
Stable disease only, wk			
≥24	3 (30.0)	8 (26.7)	11 (27.5)
<24	1 (10.0)	7 (23.3)	8 (20.0)
Progressive disease	0	2 (6.7)	2 (5.0)
Objective response rate (complete plus partial responses)	6 (60.0)	13 (43.3)	19 (47.5)
Total clinical benefit rate (complete plus partial responses plus stable disease)	10 (100)	28 (93.3)	38 (95.0)
DOR, median (IQR) [range], mo[b]	11.5 (4.1-16.3) [1.6-21.3]	5.5 (2.4-8.7) [0-26.4]	5.8 (3.1-10.7) [0-26.4]

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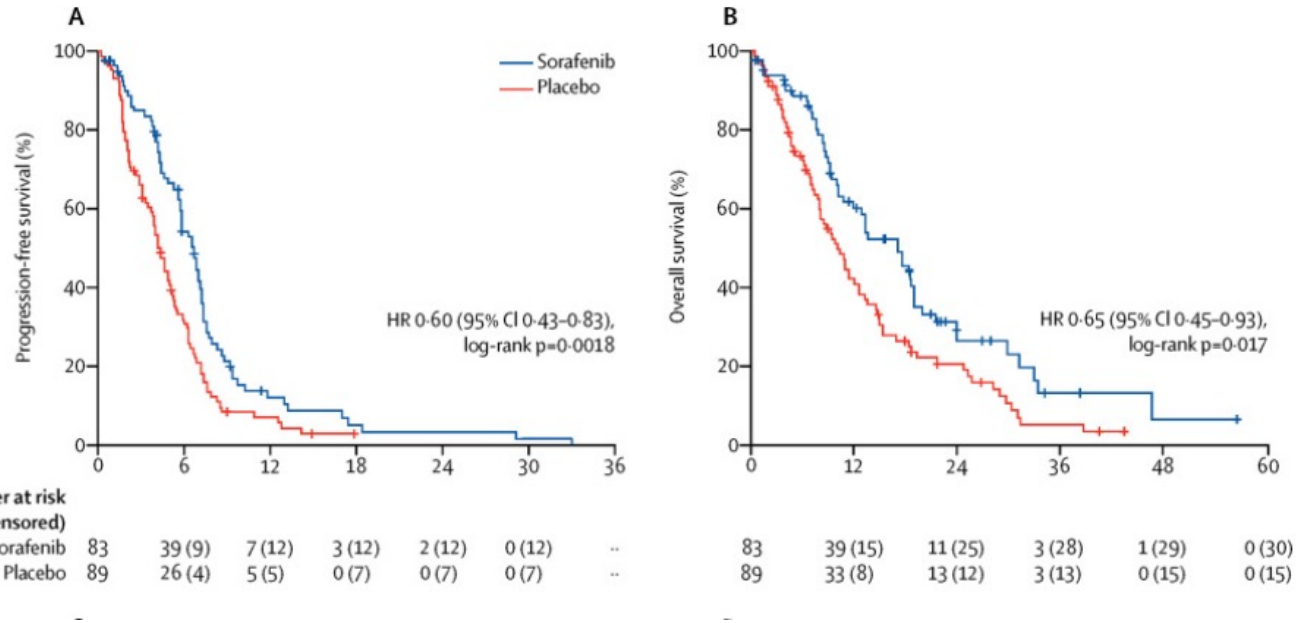
TRIAS TRIAL: Topotecan / Sorafenib

Topotecan (1·25 mg/m ^{2} on days 1–5) plus PO sorafenib 400 mg or placebo BID days 6–15, repeated every 21 days for six cycles, followed by daily maintenance sorafenib or placebo for up to 1 year in patients without progression.

- Sorafenib, a non-selective oral multi-kinase inhibitor
- Gr3-4 leukopenia, Hand/foot rxn
- No Gr3-4 HTN
- mOS was 17·1 mos sorafenib group

Vs 10·1 mos placebo group (HR 0.65)



Lancet Oncology, The, 2018-09-01, Volume 19, Issue 9, Pages 1247-1258,

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Where are the TARGETs at?

Antibody Drug Conjugates

- FOLR1
- HER2
- CDH6 IgG1
- NaPi2b (UPLIFT, UP NEXT)
- Many More

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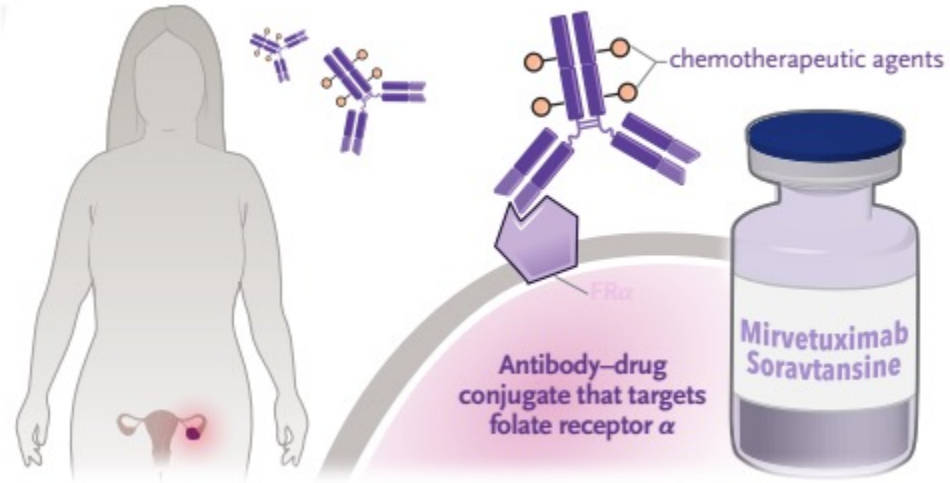
Mirvetuximab soravtansine-gynx

	Progression-free survival	Overall survival	Patients with tumor shrinkage
Elahere	5.6 months	16.5 months	42%
Chemotherapy	4.0 months	12.8 months	16%

Blurred vision	89 (40.8)	17 (7.8)
Keratopathy	70 (32.1)	20 (9.2)
Abdominal pain	66 (30.3)	6 (2.8)
Fatigue	66 (30.3)	5 (2.3)
Diarrhea	64 (29.4)	3 (1.4)
Dry eye	61 (28.0)	7 (3.2)
Constipation	59 (27.1)	0
Nausea	58 (26.6)	4 (1.8)
Peripheral neuropathy	47 (21.6)	3 (1.4)
Neutropenia	24 (11.0)	2 (0.9)
Anemia	21 (9.6)	2 (0.9)



DOI: 10.1056/NEJMoa2309169

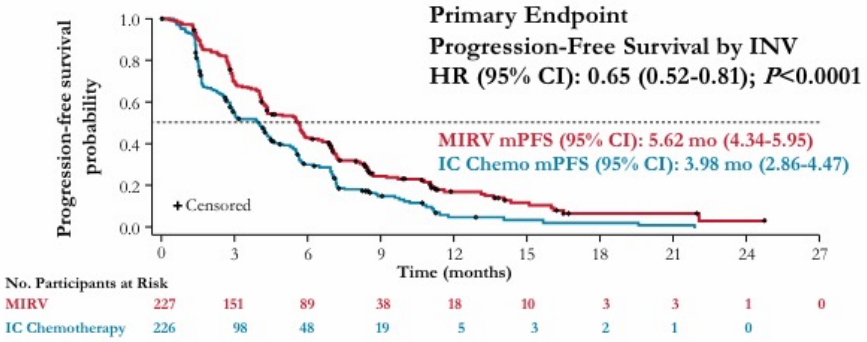
Patient-Reported Outcome Results from Phase III MIRASOL Trial of Mirvetuximab Soravtansine vs. Investigator's Choice of Chemotherapy in FRα Positive Platinum-Resistant Ovarian Cancer

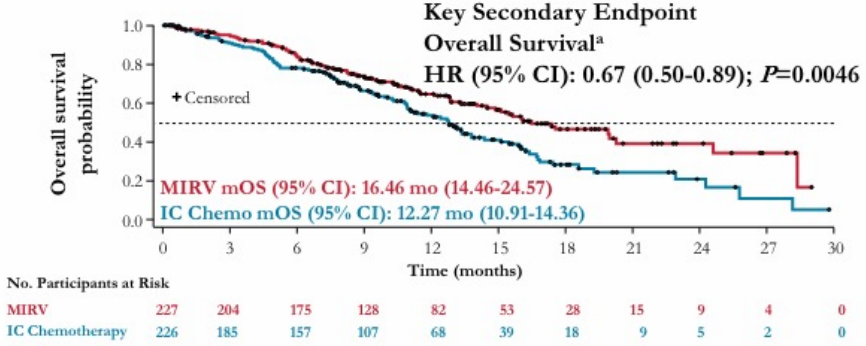
Gottfried E. Konecny[1], Kathleen N. Moore[2], Coriolan Lebreton[3], Saravut Weroha[4], Margarita Romeo[5], Lucy McAvan[6], Nicoletta Colombo[7], David M. O'Malley[8], Lan Coffman[9], Andrzej Roszak[10], Ronnie Shapira-Frommer[11], Roy Lalisang[12], David Cibula[13], Aranzazu Barquin[14], Ros Glasspool[15], James Stec[16], Lingling Li[16], Michael Method[16], Anne-Claire Hardy-Bessard[17], Toon Van Gorp[18]

SGO QoL updates: Patients on MIRV with better ovarian cancer specific measures of HRQoL and better abdominal & GI symptoms

Mirvetuximab ASCO Updates: Long term updates. Among 682 participants, longterm survival (defined as >15 months) was observed in 34% with a median OS of 28.35m

Topline MIRASOL Results[1,2]





Key Secondary Endpoint: Objective Response Rate by INV

	MIRV (n=227)	IC Chemotherapy (n=226)
ORR by INV, (%)[b] n (95% CI)	42.3% 96 (35.8-49.0)	15.9% 36 (11.4-21.4)
ORR Difference (95% CI), 26.4% (18.4-34.4)		
Odds Ratio (95% CI), 3.81 (2.44-5.94)		
P<0.0001		

Safety Findings:

- Fewer grade ≥3 AEs occurred with MIRV (41.7%) versus IC chemotherapy (54.1%)
- Fewer participants discontinued MIRV treatment due to AEs (9.2%) versus IC chemotherapy treatment (15.9%)

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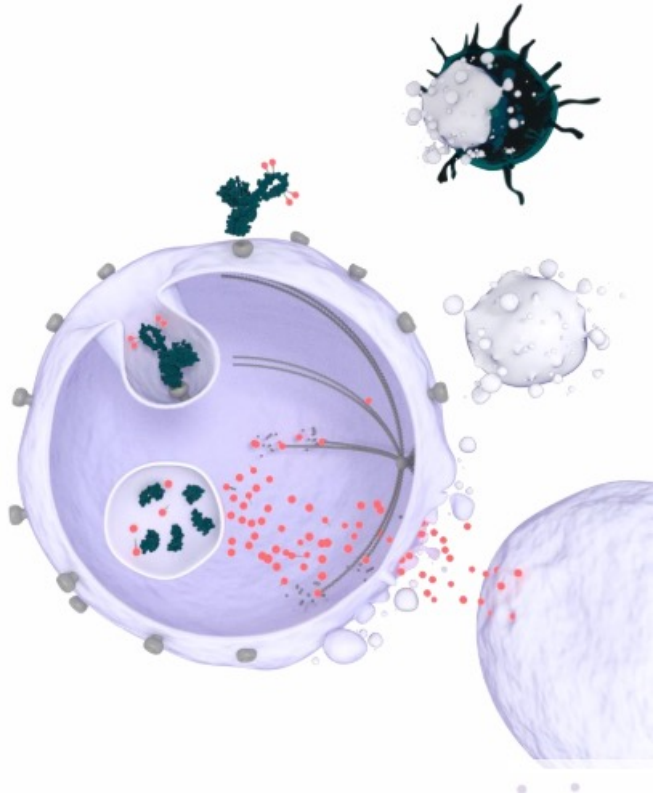


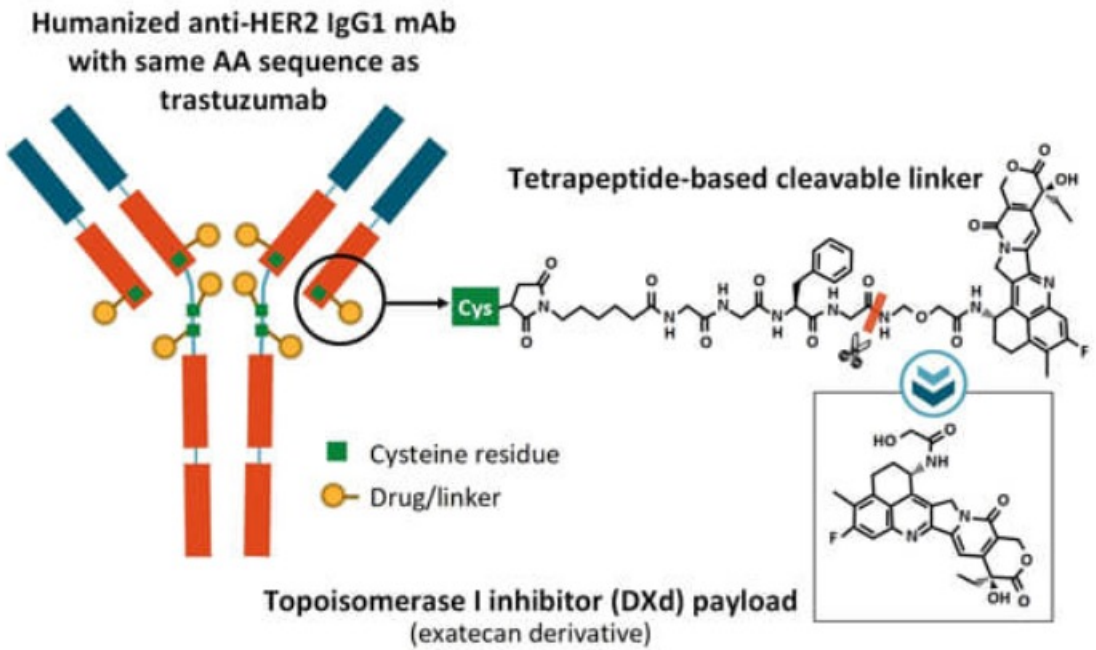
Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Cytotoxic Therapy Cyclophosphamide (oral)/ bevacizumab[k,40] Docetaxel[41] Etoposide (oral)[42] Gemcitabine[43,44] Liposomal doxorubicin[43,44] Liposomal doxorubicin/ bevacizumab[k,s,45] Paclitaxel (weekly)[g,46] Paclitaxel (weekly)/ bevacizumab[g,k,s,45] Topotecan[47,48] Topotecan/bevacizumab[k,s,45] Targeted Therapy (single agents) Bevacizumab[k,s,21,22] Mirvetuximab soravtansine-gynx (for FRα-expressing tumors [≥75% positive tumor cells])(category 1)[z,49,50]	Cytotoxic Therapy[u] Capecitabine Carboplatin[*] Carboplatin/docetaxel[*] Carboplatin/paclitaxel (weekly)[g,*] Carboplatin/gemcitabine[14] ± bevacizumab[k,s,t,15,*] Carboplatin/liposomal doxorubicin[16] ± bevacizumab[k,s,17,*] Carboplatin/paclitaxel[g,18] ± bevacizumab[k,s,t,19,*] Cyclophosphamide Cyclophosphamide (oral)/pembrolizumab/bevacizumab[k,52,53] Doxorubicin Gemcitabine/bevacizumab[k,54] Gemcitabine/cisplatin[20,*] Ifosfamide Irinotecan Ixabepilone/bevacizumab (category 2B)[k,aa,55] Melphalan Oxaliplatin Paclitaxel Paclitaxel, albumin bound Pemetrexed Sorafenib/topotecan[51] Vinorelbine Targeted Therapy (single agents) Niraparib (category 3)[v,27] Olaparib (category 3)[w,28] Pazopanib (category 2B)[29] Rucaparib (category 3)[x,30] Hormone Therapy Aromatase inhibitors (anastrozole, exemestane, letrozole) Goserelin acetate Leuprolide acetate Megestrol acetate Tamoxifen[j]	Carboplatin/paclitaxel (for age >70)[g,y,*] Carboplatin/paclitaxel, albumin bound (for confirmed taxane hypersensitivity)[*] Immunotherapy Dostarlimab-gxly (for dMMR/MSI-H recurrent or advanced tumors)[z,38] Pembrolizumab (for patients with MSI-H or dMMR solid tumors, or TMB-H tumors ≥10 mutations/megabase)[z,39] Hormone Therapy Fulvestrant (for low-grade serous carcinoma) Targeted Therapy Dabrafenib + trametinib (for *BRAF* V600E-positive tumors)[z,32] Entrectinib or larotrectinib (for *NTRK* gene fusion-positive tumors)[z] Fam-trastuzumab deruxtecan-nxki (for HER2-positive tumors [IHC 3+ or 2+])[56] Mirvetuximab soravtansine-gynx/bevacizumab (for FRα-expressing tumors)[k,z,33,57,58] Selpercatinib (for *RET* gene fusion-positive tumors)[z,34] For low-grade serous carcinoma: • Trametinib[35] • Binimetinib (category 2B)[36,37]

* Platinum agents have limited activity when the disease has demonstrated growth through a platinum-based regimen, and platinum rechallenge is generally not recommended in this setting.

Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: biomarker and subgroup analyses from the cervical, endometrial, and ovarian cancer cohorts of the DESTINY-PanTumor02 study

Vicky Makker,[1,2] Ana Oaknin, Luis Manso, Antonio González-Martín, Iwona Ługowska, Funda Meric-Bernstam, Domenica Lorusso, Susana Banerjee, John B Liao, Salvatore Siena, Chien-Hsing Lu, Naiyarat Prasongsook, Bohuslav Melichar, Anitra Fielding, Lindsey Jung, Soham Puvvada, Flavia Michelini, Jung-Yun Lee

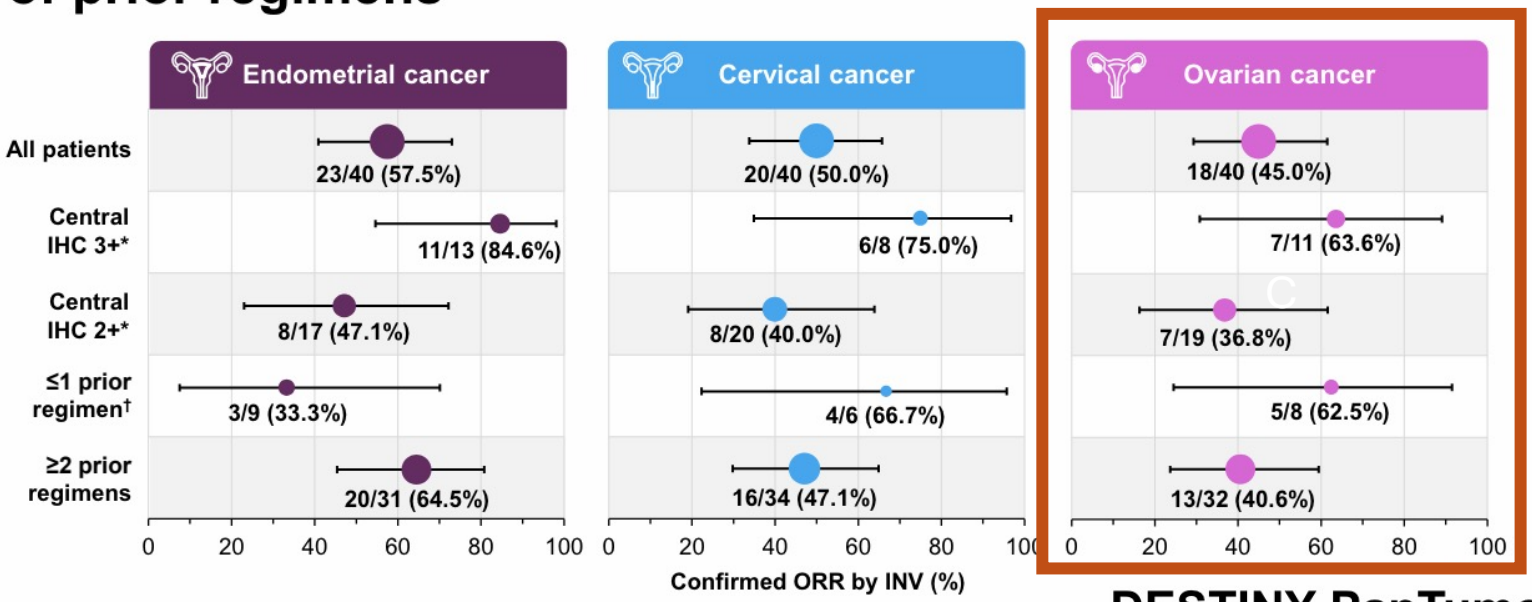
HER2-Targeted ADC: Trastuzumab Deruxtecan



- High drug:antibody ratio: ~8
- Stable linker-payload
- Tumor-selectable cleavable linker
- High potency, membrane-permeable payload with short systemic half-life
- Bystander killing effect

Nakada. Chem Pharm Bull (Tokyo). 2019;67:173. Trail. Pharmacol Ther. 2018;181:126. Ogitani. Cancer Sci. 2016;107:1039.

ORR in all patients, and by central IHC status and number of prior regimens



THE POWER OF SHARED PURPOSE: Transforming Gynecologic Cancer Care

*In patients with IHC 1+/0/unknown by central testing, responses were observed in 4/10 patients cervical cancer, and 4/10 patients with ovarian cancer; †one patient with endometrial cancer was IHC, immunohistochemistry; INV,

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DESTINY-PanTumor02: T-DXd for HER2-expressing solid tumors

A Phase 2, open-label, multicenter study (NCT04482309)

Key eligibility criteria

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)*
  - Cervical cohort was expanded to include five IHC 1+ patients†
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1

T-DXd 5.4 mg/kg Q3W

n≈40 per cohort‡

Primary endpoint

- Confirmed ORR (investigator)

Secondary endpoints

- DOR, DCR, PFS, OS
- Safety

Exploratory analyses

- Subgroup analyses by HER2 status§
- Subgroup analyses by biomarkers§

Primary analysis DCO

- June 8, 2023

- Endometrial
- Cervical
- Ovarian
- Bladder
- Other tumors¶
- Biliary tract
- Pancreatic

*Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer scoring[1]); patients were eligible for either test. All patients were centrally tested; †if ≥3 objective responses were observed in the first 15 patients in any of the tumor-specific cohorts (with IHC 3+ or 2+ confirmed by central testing), confirmed on repeat scan 4 weeks or later after first response documented, subsequent patients with IHC 1+ were also eligible for recruitment, up to a maximum of 10 patients with IHC 1+ per cohort; ‡planned recruitment; cohorts with no objective responses in the first 15 patients were to be closed; §subgroup analyses were based on central HER2 testing ¶patients with tumors that express HER2 (IHC 3+ or 2+), excluding tumors in the tumor-specific cohorts, and breast cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer. 2L, second line; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; DCO, data cutoff; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization. 1. Hofmann M, et al. *Histopathology*. 2008;52:797–805

THE POWER OF SHARED PURPOSE: Transforming Gynecologic Cancer Care

SGO ANNUAL MEETING ON WOMEN'S CANCER

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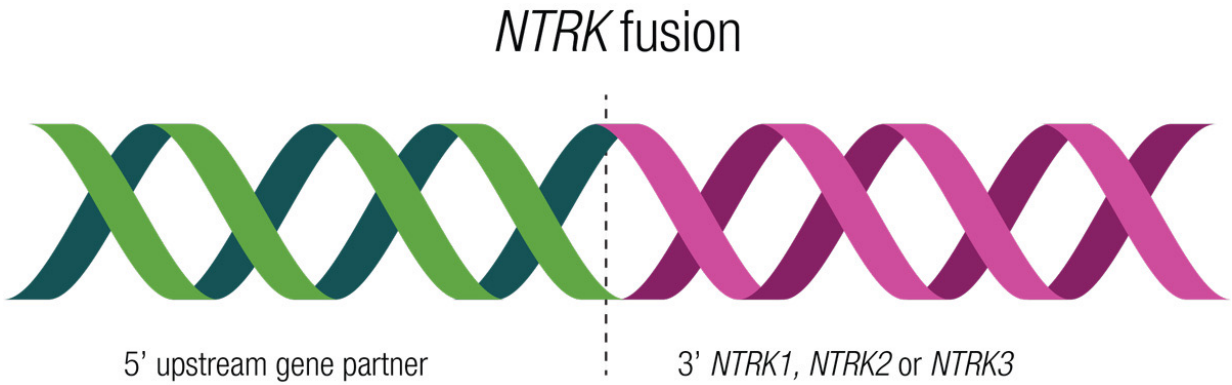


- Fusions of NTRK genes oncogenic activation through tyrosine receptor kinases (TRK) associated with downstream signaling pathways like Ras, MAPK, and PI3K.
  - **Likely <1 % of ovarian cancers, but represents a target for precision therapy**
- Entrectinib, N= 54 adult patients with advanced or metastatic NTRK fusion-positive solid tumor with 31 (57%) having an OR[1]
- Larotrectinib, N = 194 adult pts enrolled, with 180 eligible for efficacy analyses by IRC; 22 pts had known brain metastases at baseline, 57% ORR[2]

(1) Lancet Oncol. 2020 February ; 21(2): 271–282. doi:10.1016/S1470-2045(19)30691-6
(2) (2) Hong et al, ASCO 2023 Lancet Oncol. 2020 February ; 21(2): 271–282. doi:10.1016/S1470-2045(19)30691-6.

Other ADCs in the Pipeline

- ADC targeting sodium-dependent phosphate transport protein (NaPi2b) UPLIFT/UP NEXT → terminated
- ADC targteting mesolthelin
  - RC88 (anti-MSLN ADC) cORR 42%, N=83 w/ovary
- HumanCadherin-6(CDH-6)
  - REJOICE

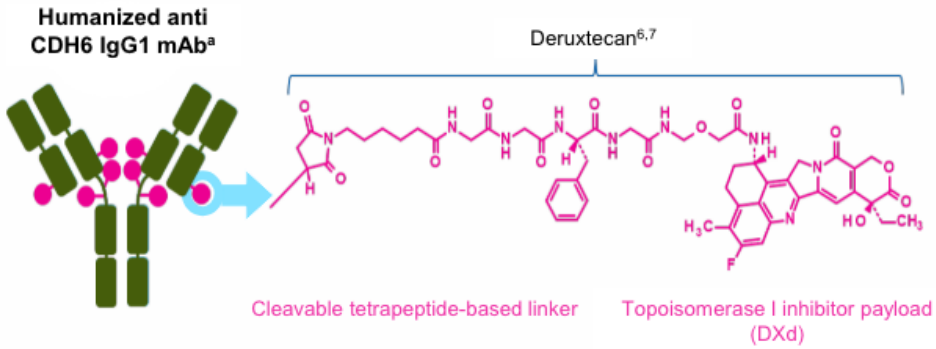
Bispecific Abs

- MUC16 × CD3 bispecific antibody (REGN4018)
- MUC16 × CD28 bispecific antibody (REGN5668) in combination with cemiplimab or REGN4018

REJOICE-Ovarian01

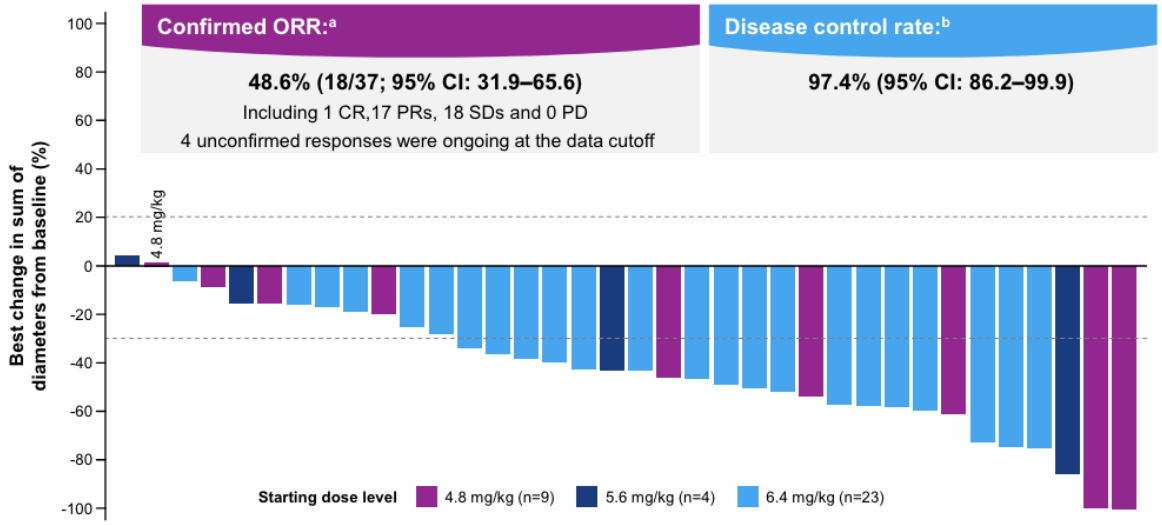
Phase I
RP2D 4.8-6.5 months
Overall response rate 48.6% with median DOR 11.2 months

R-DXd was designed with 7 key attributes



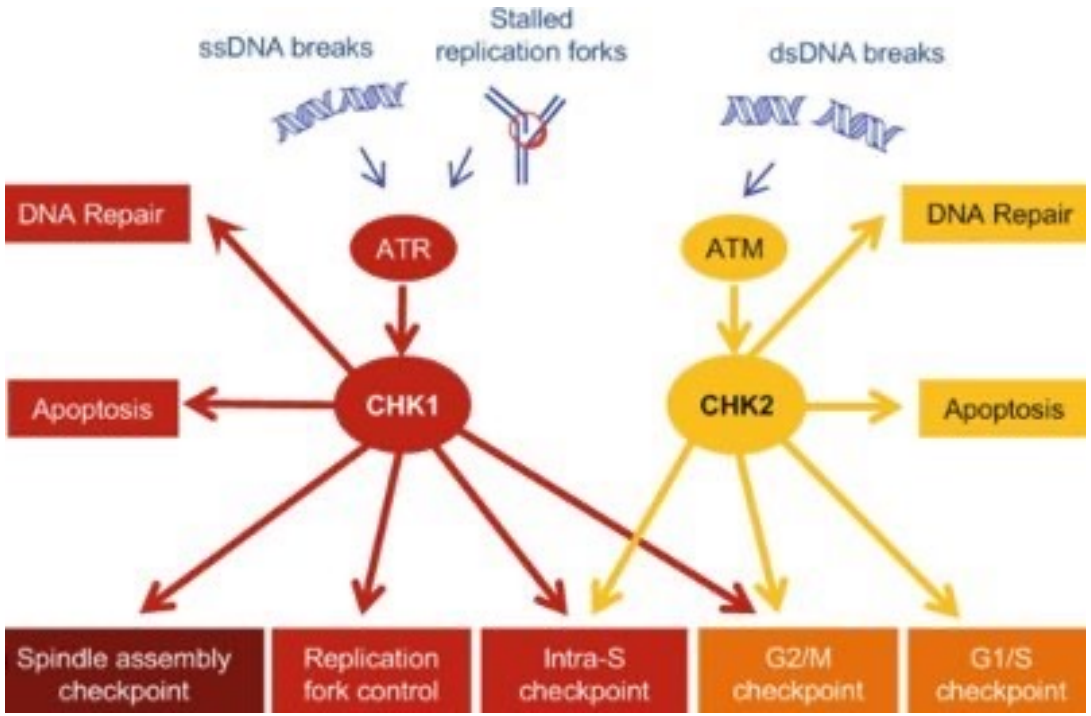
Payload mechanism of action: topoisomerase I inhibitor[4,b]
High potency of payload[5,8,b]
High drug-to-antibody ratio of ≈8[4,b]
Payload with short systemic half-life[5,b,c]
Stable linker-payload[5,8,b]
Tumor-selective cleavable linker[4,5,8,b]
Bystander antitumor effect[4,b]

R-DXd (4.8–6.4 mg/kg)
Recurrent ovarian cancer, heavily pretreated



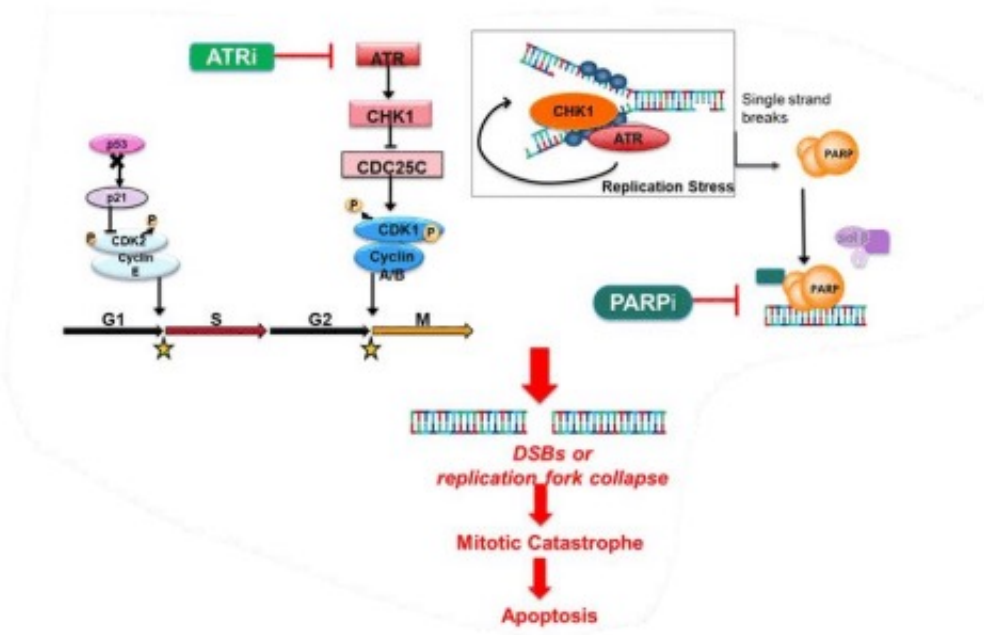
Raludotadug deruxtican: ADC made of humanized anti CDH6 IgG1 mAb covalently linked to a topoisomerase I inhibitor payload via a tetrapeptide based cleavable linker

Replicative Stress....



DNA replication/repair targets

- **Prexasertib** (CHEK1); ORR in platinum resistant patients (Cohorts 1--3) was 12.1%, and 6.9% in platinum refractory patients[1]
- **ACR-138** (CHEK1/2): ACRIVON
- **Ceralasertib**/ATR and RAD-3 inhibitor
  - CAPRI Trial[2] (ASCO 2024); Celasertib + Olaparib with 16/18 observed response
    - COHORT A (platinum sensitive, HRD agnostic, no prior PARPi progression
- Elimusertib and camonsertib (ATR inhibitors)
- Peposertib (DNA-PK inhibitor)

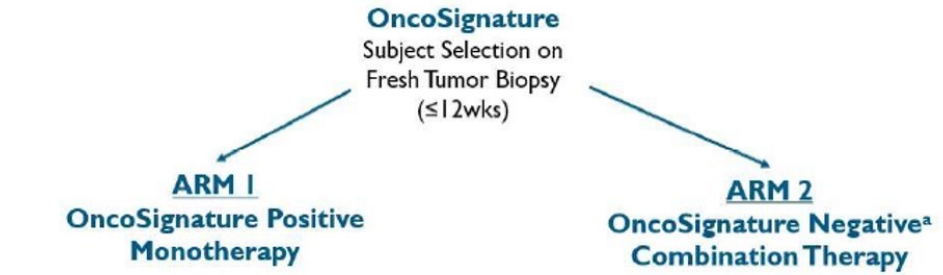


(1) Konstantinopoulos et al, Gynecol Oncol. 2022 Nov;167(2):213-225. doi: 10.1016/j.ygyno.2022.09.019. Epub 2022 Sep 30. PMID: 36192237; PMCID: PMC10673677.

(2) Simpkins et al. ASCO 2024 abstract 5510

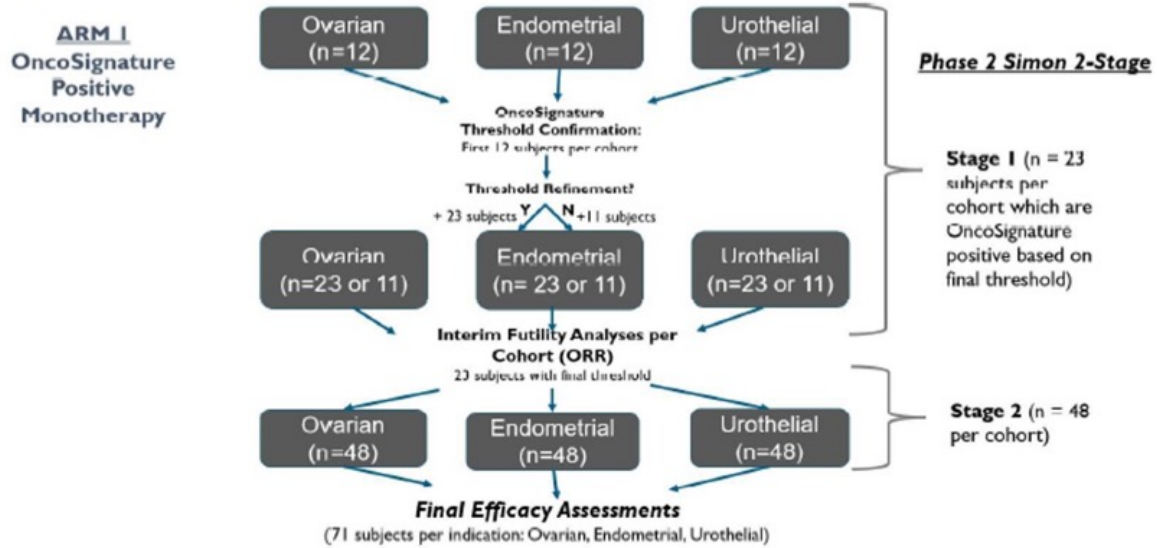
ACRIVON/GOG-3082

Figure 1: Overview of Study Design



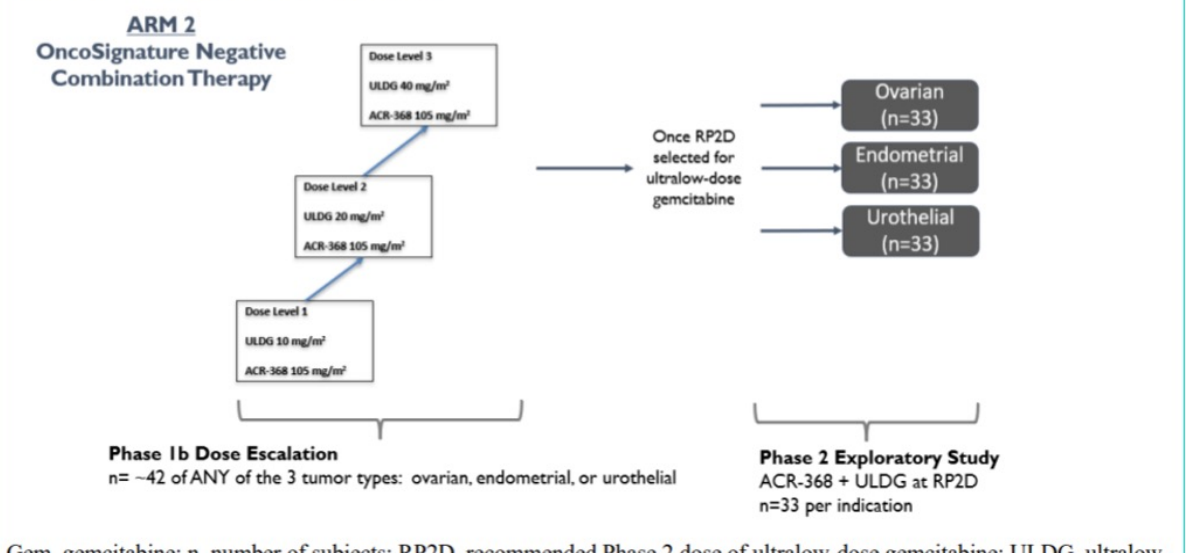
[a] OncoSignature Unevaluable subjects are allowed in the Phase 1b portion.

Figure 2: Study Schema for Arm 1



N, no; ORR, objective response rate; Y, yes

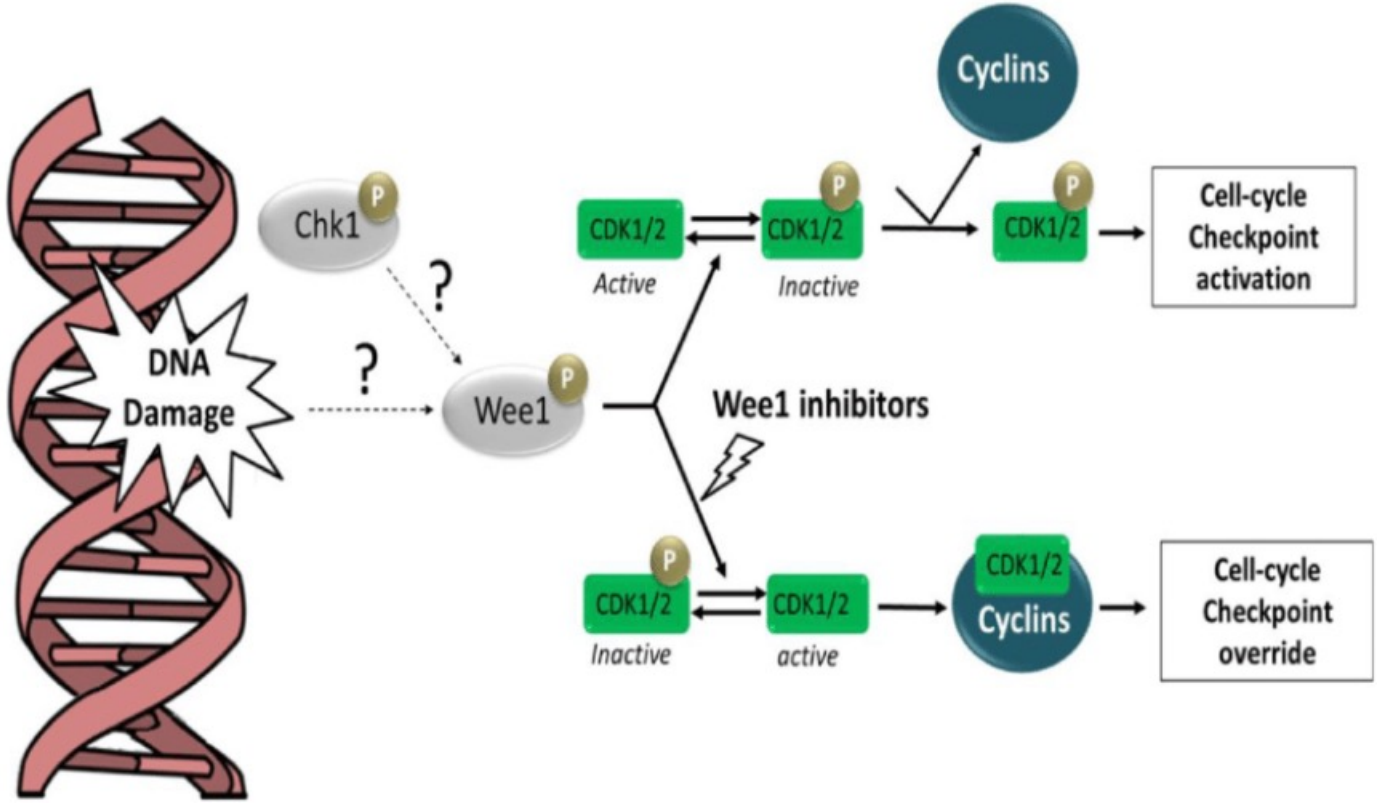
Figure 3: Study Schema for Arm 2



Gem, gemcitabine; n, number of subjects; RP2D, recommended Phase 2 dose of ultralow-dose gemcitabine; ULDG, ultralow-dose of gemcitabine

Cell Cycle CPI

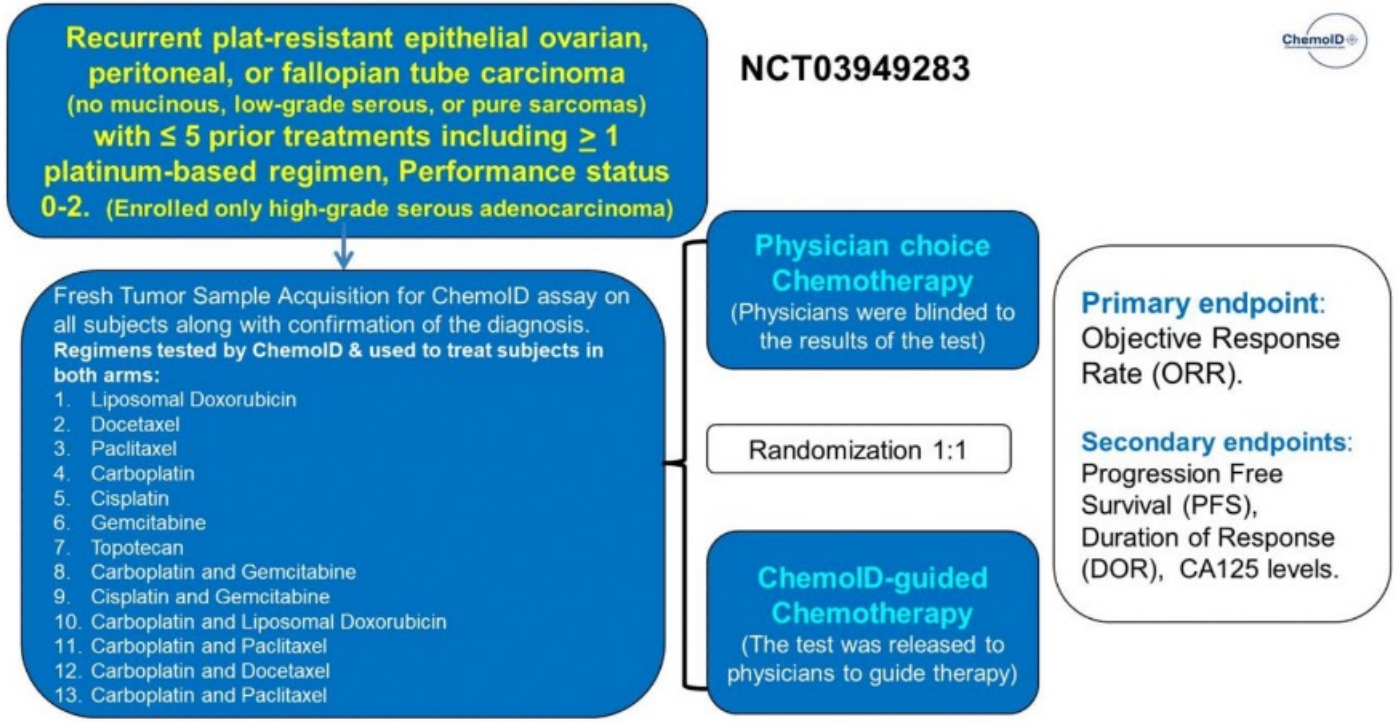
- AKT inhibitor (afuresertib)
- AXL decoy protein (batiraxcept)
- WEE1 inhibitor (ZN-c3)



Ghelli Luserna di Rora'et al. Journal of Hematology & Oncology (2017) 10:77
DOI 10.1186/s13045-017-0443-

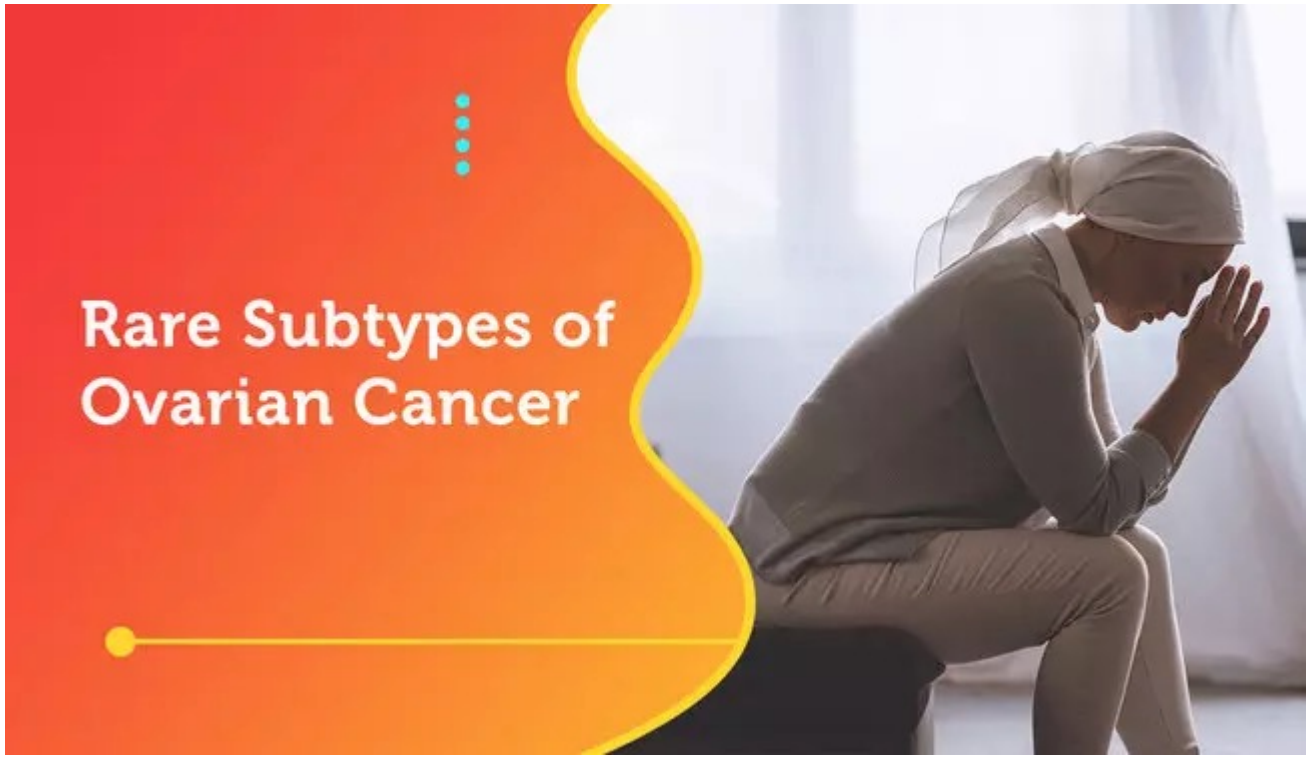
Chemo-ID

- Cancer Stem Cell Assay Directed Chemotherapy in Recurrent Platinum Resistant Ovarian Cancer
  - Patients with PROC who had failed standard of care (SOC) therapy → (1:1) given one of thirteen mono or combination chemotherapies based on the results of a ChemoID assay or physician choice.
  - Fresh biopsy were used to determine the sensitivity of CSCs and the bulk of tumor cells to the same panel of chemotherapies.
  - **mORR of Tx guided by the ChemoID assay was 55%, compared to 5% for those treated with physician's choice chemo, p<0.0001.**
  - **mOS 3mo vs 11mo**
  - **mDOR of 5.5mo vs 8mo**



Herzog et al. ASCO 2024 abstract 5518

Rare Ovarian Therapies

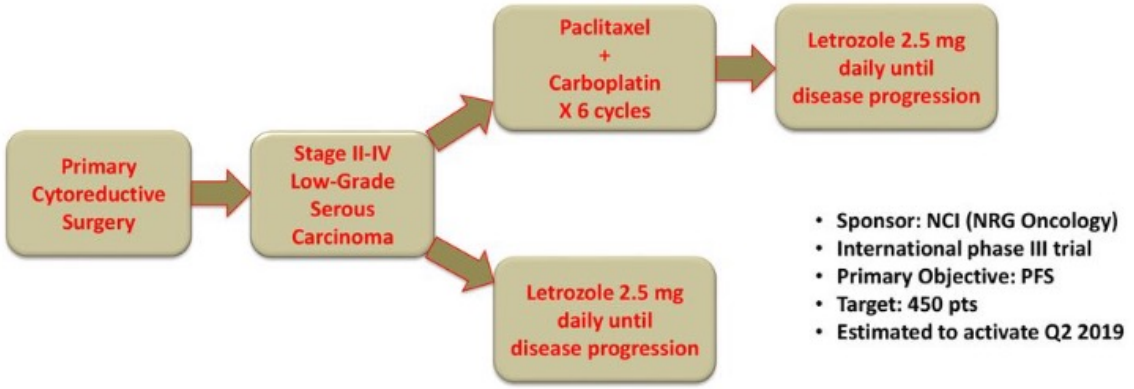


Low grade ovary: NRG GY019

Retrospective multi-institutional series

- Low grade serous ovarian cancer with response rates as low as 4% to carbo/taxol
- CRS followed by HT associated with excellent responses
  - Fader et al :41 months, only 22% with recurrence and 2 deaths from disease, median PFS and OS not reached, 2 year PFS 82.8%, 2 year OS 96.3%

NRG GY019



Avutometinib + Defactinib in Recurrent Low-Grade Serous Ovarian Cancer (LGSOC): A Subgroup Analysis of ENGOT-ov60/GOG-3052/RAMP 201 Part A

- **Avutometinib** is a first-in-class oral R… activity, while also block…
- **Defa…**

…tly inhibits MEK kinase …EK by upstream RAF[5-8]

…as been shown to

ENGOT-ov60/GOG-3052/RAMP 20…
Trial of Avutometinib + D…

GOG-3097/ENGOT-ov81/NCRI/RAMP 301: A Phase 3, Randomized, Open-Label Study of Combination Therapy with Avutometinib plus Defactinib Versus Investigator's Choice of Treatment in Patients with Recurrent Low-Grade Serous Ovarian Cancer Grisham RN et al, SGO 2024. Poster 2120

International Coordinating Investigator: Rachel N. Grisham, MD
ENGOT Lead: Susana N. Banerjee, MBBS, MA, FRCP, PhD

Key Inclusion Criteria
- Confirmed LGSOC diagnosis
- Recurrent disease after prior platinum therapy
- Documented *KRAS* mutation status
- Measurable disease per RECIST v1.1
- Prior MEKi allowed[a]
- Prior Bev allowed

1:1 Randomization
N ~ 270

Stratification Factors
- *KRAS* mutation status: wt vs mt
- Geography: North America/Europe vs rest of the world
- Number of therapies: 1-3 vs ≥4

Avutometinib + Defactinib
n ~ 135
Avutometinib 3.2 mg PO BIW
Defactinib 200 mg BID
3 weeks on, 1 week off

Investigator's Choice of Therapy
n ~ 135
Pegylated liposomal doxorubicin
Paclitaxel
Topotecan
Letrozole
Anastrozole

May crossover upon BICR-confirmed PD

Primary Endpoint: PFS
per BICR by RECIST v1.1

Secondary Endpoints[b]
- OS
- PFS via RECIST v1.1 by investigator assessment
- ORR
- DOR
- DCR
- Safety
- Pharmacokinetics
- PROs

Primary Analysis: Hierarchical Evaluation
1. *KRAS* mutant LGSOC only
2. All recurrent LGSOC

Participating Countries: United States (GOG Foundation), United Kingdom (NCRI), Spain (GEICO), Belgium (BGOG), France (GINECO), Italy (MaNGO, MITO), Canada (GOG Foundation), Germany (AGO), Denmark (NSGO), South Korea (KGOG), Australia (ANZGOG)

Bev, bevacizumab; BICR, blinded independent central review; BID, twice daily; BIW, twice weekly; DCR, disease control rate; DOR, duration of response; *KRAS*, Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; MEKi, MEK…

…ients treated with …+%) prior LoT[2]

…% of patients treated with avutometinib + …

Confirmed responses in 3/4 patients previously treated with MEKi[1]

- Of the 13 patients with SD, 10 achieved tumor shrinkage, 6 with ≥15% tumor regression[c]
  - Median time from last LoT = 1.84 mo
  - Last LoT for 13 patients with SD included chemotherapy (n=2), bevacizumab ± chemotherapy (n=2), hormonal therapy (n=7), MEKi (n=1), and everolimus (n=1)

Best …
-100
…KRAS mt
Previous Treatment with MEKi
Patient experienced 120% increase from baseline
* Still on treatment at time of data cutoff

Clear Cell Ovarian Carcinoma

BrUOG 354

- Non-renal CCC with >/=1 prior line of treat with PD, no prior I/O
- Nivo +/- Ipi
- N=30, The majority (83%) had CCC of the ovary (n=24)
- ORR with N and N+I was 14.2 and 26.7%, respectively
- There were no treatment-related deaths and no new safety signals

	Nivolumab n=14	Nivolumab/Ipilimumab n=30
Complete Response (n, %)	**0**	**5 (16.7)**
Partial Response (n,%)	**2 (14.3)**	**5 (16.7)**
Complete + Partial Response	**2 (14.3)**	**10 (33.3)**
Stable Disease	5 (35.7)	10 (33.3)
Progression	7 (50)	10 (33.3)
Duration of Response (months, median ± SD)	30.6 ± 4.5	22.4 ± 11.8

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Thank you!

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