Immunotherapy and Other Systemic Therapies in Gynecologic Malignancies

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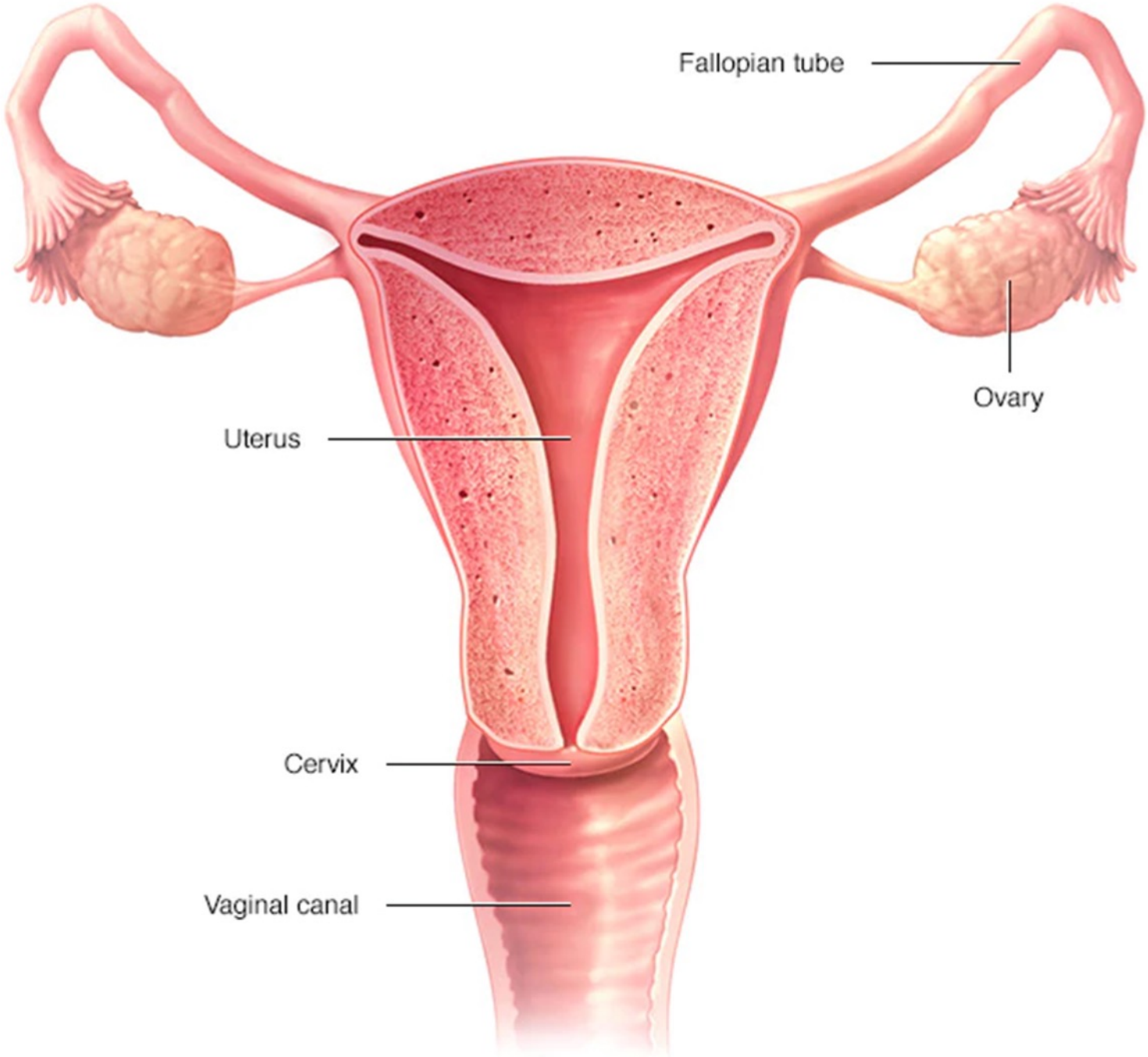
July 2023



OVERVIEW

- IMPORTANT PRACTICE CHANGING PRESENTATIONS AT SGO AND ASCO

OVERVIEW

- RUBY and GY018 ENDOMETRIAL CANCER
- UPDATE ON HIPEC IN OVARIAN CANCER
- DESTINY-PANTUMOR-02
- MIRASOL TRIAL

ORIGINAL ARTICLE

Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer

Mansoor R. Mirza, M.D., Dana M. Chase, M.D., Brian M. Slomovitz, M.D., René dePont Christensen, Ph.D., Zoltán Novák, Ph.D., Destin Black, M.D., Lucy Gilbert, M.D., Sudarshan Sharma, M.D., Giorgio Valabrega, M.D., Lisa M. Landrum, M.D., Ph.D., Lars C. Hanker, M.D., Ashley Stuckey, M.D., et al., for the RUBY Investigators*

June 8, 2023
N Engl J Med 2023; 388:2145-2158
DOI: 10.1056/NEJMoa2216334

40 References 2 Citing Articles

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer

Ramez N. Eskander, M.D., Michael W. Sill, Ph.D., Lindsey Beffa, M.D., Richard G. Moore, M.D., Joanie M. Hope, M.D., Fernanda B. Musa, M.D., Robert Mannel, M.D., Mark S. Shahin, M.D., Guilherme H. Cantuaria, M.D., Eugenia Girda, M.D., Cara Mathews, M.D., Juraj Kavecansky, M.D., Charles A. Leath, III, M.D., M.S.P.H., Lilian T. Gien, M.D., Emily M. Hinchcliff, M.D., M.P.H., Shashikant B. Lele, M.D., Lisa M. Landrum, M.D., Floor Backes, M.D., Roisin E. O'Cearbhaill, M.D., Tareq Al Baghdadi, M.D., Emily K. Hill, M.D., Premal H. Thaker, M.D., Veena S. John, M.D., Stephen Welch, M.D., Amanda N. Fader, M.D., Matthew A. Powell, M.D., and Carol Aghajanian, M.D.

June 8, 2023
N Engl J Med 2023; 388:2159-2170
DOI: 10.1056/NEJMoa2302312

Chinese Translation 中文翻译

30 References 2 Citing Articles

Phase 3, randomized, double-blind, multicenter study of dostarlimab plus carboplatin-paclitaxel versus placebo plus carboplatin/paclitaxel in patients with primary advanced or recurrent EC

Eligible patients

- Histologically/cytologically proven advanced or recurrent EC
- Stage III/IV disease or first recurrent EC with low potential for cure by radiation therapy or surgery alone or in combination
  - Carcinosarcoma, clear cell, serous, or mixed histology permitted[a]
- Naïve to systemic therapy or systemic anticancer therapy and had a recurrence or PD ≥6 months after completing treatment
- ECOG PS 0-1
- Adequate organ function

Stratification

- MMR/MSI status[b]
- Prior external pelvic radiotherapy
- Disease status

R1:1

Dostarlimab IV 500 mg
Carboplatin AUC 5 mg/mL/min
Paclitaxel 175 mg/m^2 Q3W for 6 cycles

Dostarlimab IV 1000 mg Q6W up to 3 years[c]

Placebo
Carboplatin AUC 5 mg/mL/min
Paclitaxel 175 mg/m^2 Q3W for 6 cycles

Placebo IV Q6W up to 3 years[c]

Follow-up

Primary endpoint

- PFS by INV per RECIST v1.1
- OS

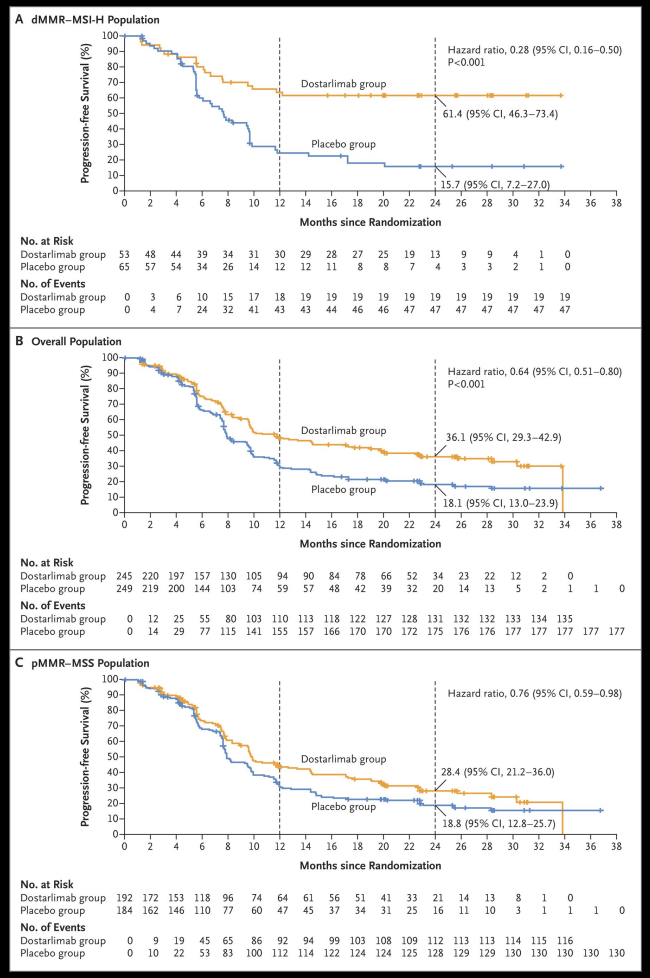
Secondary endpoints

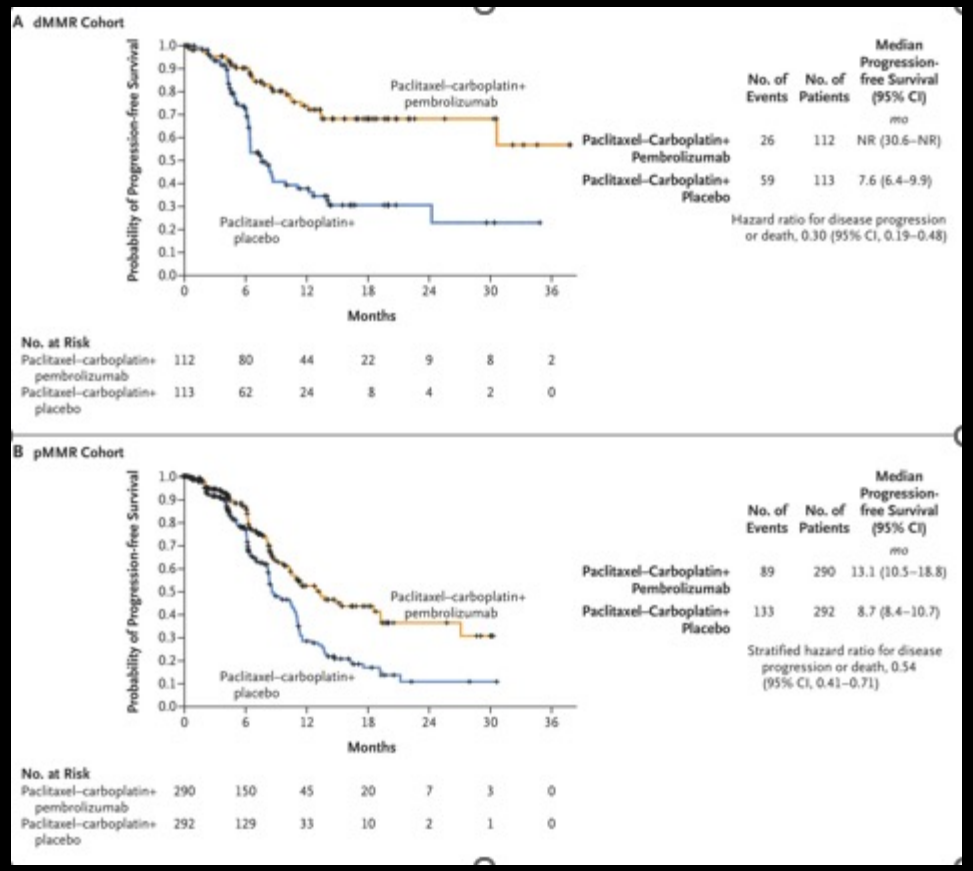
- PFS by BICR per RECIST v1.1
- PFS2
- ORR
- DOR
- DCR
- HRQOL/PRO
- Safety

On-study imaging assessments are to be performed Q6W (±7 days) from the randomization date until Week 25 (Cycle 8), followed by Q9W (±7 days) until Week 52. Subsequent tumor imaging is to be performed every 12 weeks (±7 days) until radiographic PD is documented by Investigator assessment per RECIST v1.1 followed by one additional imaging 4-6 weeks later, or subsequent anticancer therapy is started, whichever occurs first. Thereafter, scans may be performed per standard of care.
[a]Mixed histology containing at least 10% carcinosarcoma, clear cell, or serous histology. [b]Patients were randomized based on either local or central MMR/MSI testing results. Central testing was used if local results were not available. For local determination of MMR/MSI status, IHC, next generation sequencing, and polymerase chain reaction assays were accepted. For central determination of MMR/MSI status IHC per Ventana MMR RxDx panel was used. [c]Treatment ends after 3 years, PD, toxicity, withdrawal of consent, investigator's decision, or death, whichever occurs first. Continued treatment with dostarlimab or placebo beyond 3 years may be considered following discussion between the Sponsor and the Investigator. AUC, area under the plasma or serum concentration-time curve; BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response, EC, endometrial cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; HRQOL, health-related quality of life; IHC, immunohistochemistry; INV, investigator assessment; MMR, mismatch repair; MSI, microsatellite instability; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PRO, patient-reported outcome; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Dr. Matthew A. Powell

RUBY vs NRG-GY018

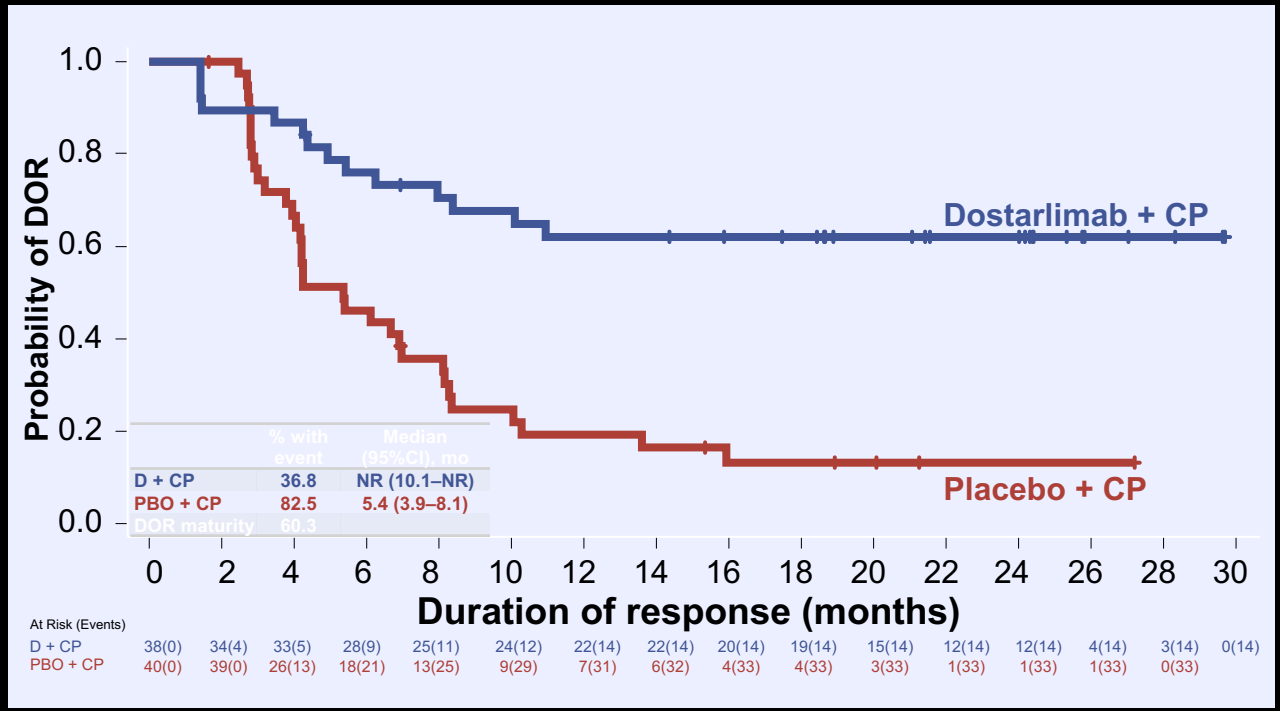




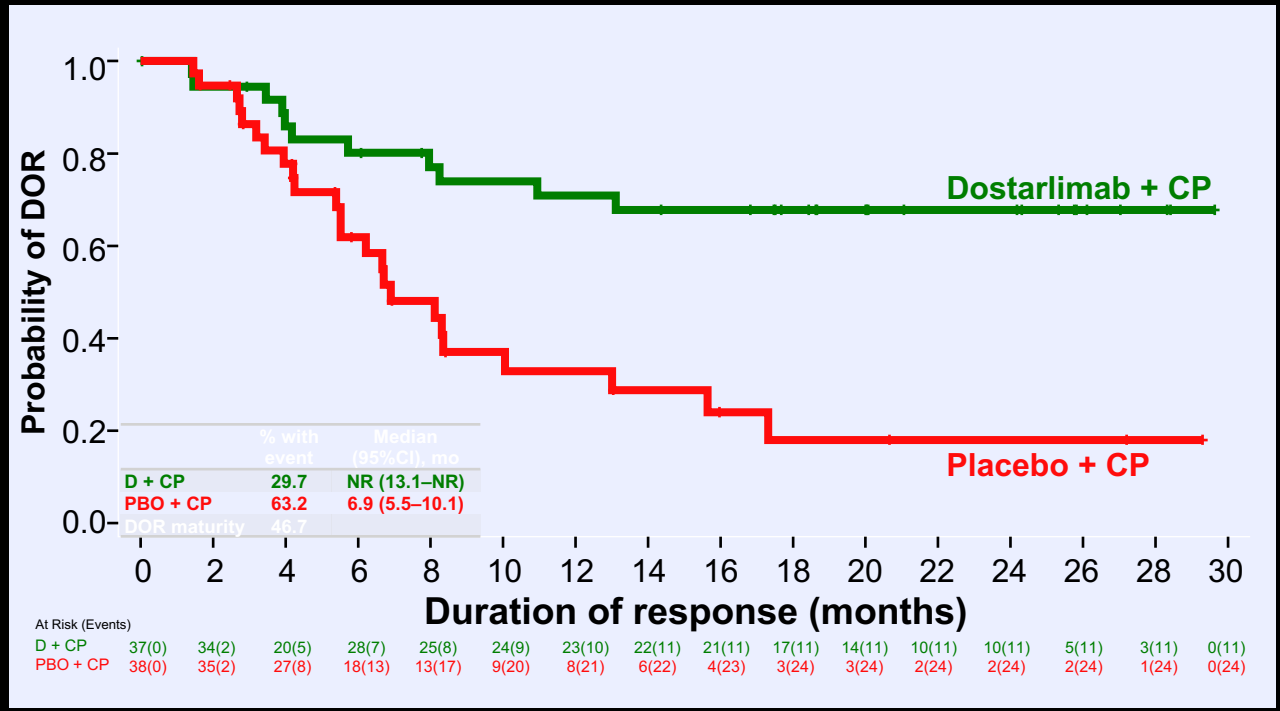
Dostarlimab+CP Led to More Durable Responses than CP Alone

Consistent Duration of Response by INV and by BICR in dMMR/MSI-H Population

INV



BICR



From New England Journal of Medicine, Mirza MR, Chase DM, Slomovitz MD, et al, Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. DOI: 10.1056/NEJMoa2216334. Copyright © 2023 Massachusetts Medical Society.
BICR, blinded independent central review; CP, carboplatin/paclitaxel; DOR, duration of response; INV, investigator assessment; NR, not reached.

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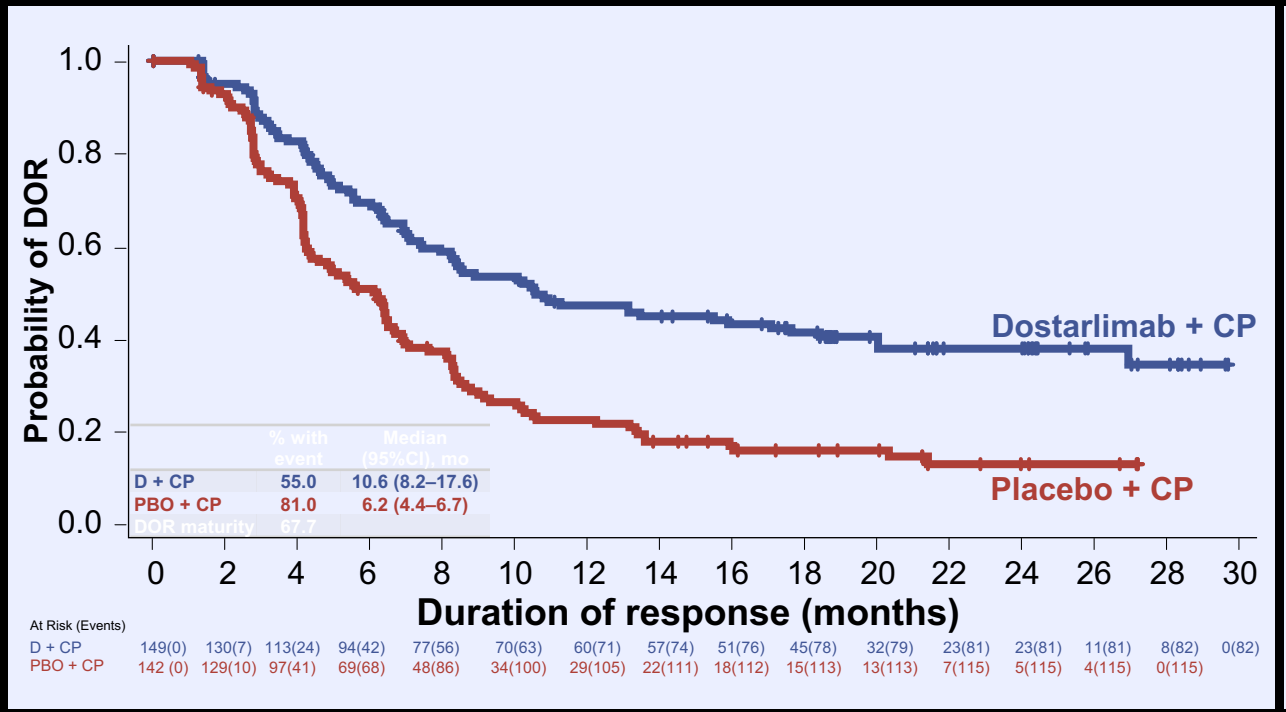
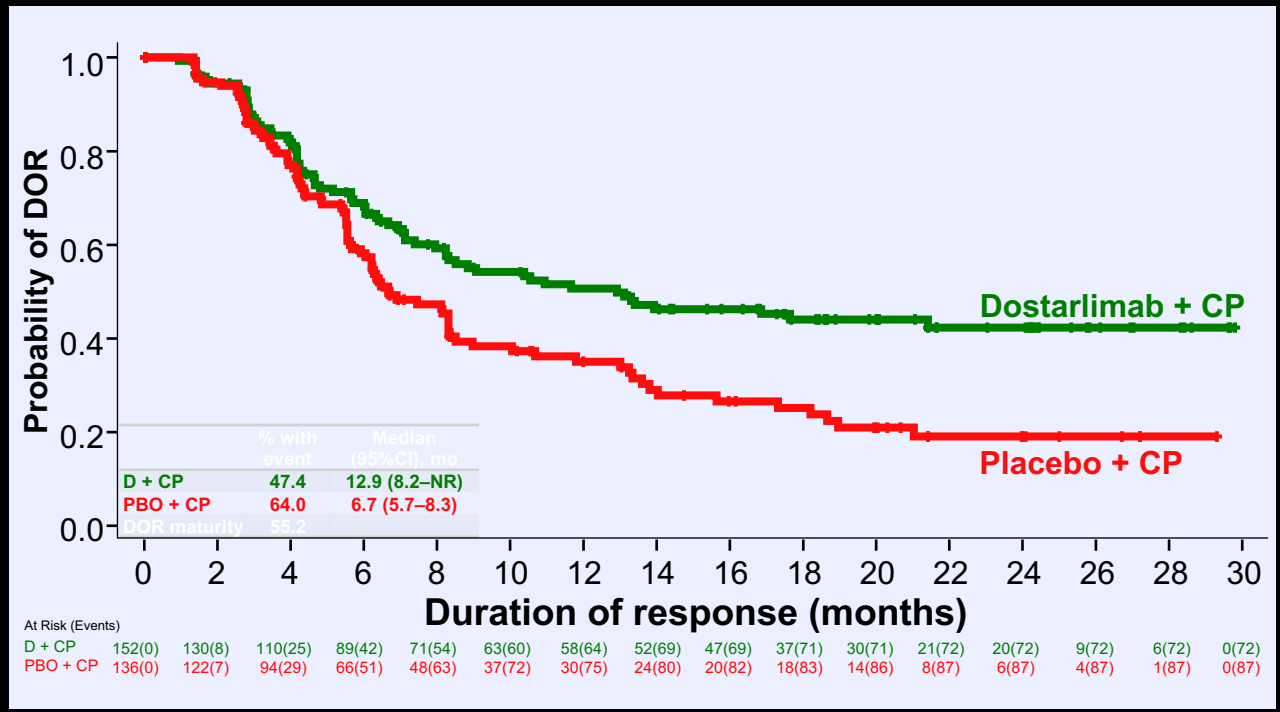
Dostarlimab+CP Led to More Durable Responses than CP Alone

Consistent Duration of Response by INV and by BICR in Overall Population

INV



BICR



From New England Journal of Medicine, Mirza MR, Chase DM, Slomovitz MD, et al, Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. DOI: 10.1056/NEJMoa2216334. Copyright © 2023 Massachusetts Medical Society.
BICR, blinded independent central review; CP, carboplatin/paclitaxel; DOR, duration of response; INV, investigator assessment; NR, not reached.

Dr. Matthew A. Powell

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Endometrial Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

Primary or Adjuvant Therapy (Stage I-IV)	
Chemoradiation Therapy	**Systemic Therapy**
Preferred Regimens • Cisplatin plus RT followed by carboplatin/paclitaxel[1,2]	**Preferred Regimens** • Carboplatin/paclitaxel[3] • Carboplatin/paclitaxel/pembrolizumab (for stage III-IV tumors, except for carcinosarcoma) (category 1)[a,b,4] • Carboplatin/paclitaxel/dostarlimab-gxly (for stage III-IV tumors) (category 1)[b,c,5] • Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive uterine serous carcinoma)[d,e,6] • Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive carcinosarcoma) (category 2B)[d,e,6]

SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

RECURRENT DISEASE[f,g]	
First-Line Therapy for Recurrent Disease[h]	**Second-Line or Subsequent Therapy**
Preferred • Carboplatin/paclitaxel (category 1 for carcinosarcoma)[i,3] • Carboplatin/paclitaxel/pembrolizumab (except for carcinosarcoma) (category 1)[b,4] • Carboplatin/paclitaxel/dostarlimab-gxly (category 1)[b,5] • Carboplatin/paclitaxel/trastuzumab[e] (for HER2-positive uterine serous carcinoma)[d,6] • Carboplatin/paclitaxel/trastuzumab[e] (for HER2-positive carcinosarcoma) (category 2B)[d,6] **Other Recommended Regimens** • Carboplatin/docetaxel[j] • Carboplatin/paclitaxel/bevacizumab[k,7,8] **Useful in Certain Circumstances (Biomarker directed: after prior platinum-based therapy including neoadjuvant and adjuvant)** • Lenvatinib/pembrolizumab (category 1) for mismatch repair proficient (pMMR) tumors[b,9] • Pembrolizumab[b] for TMB-H[l,10] or MSI-H/dMMR[m] tumors[11] • Dostarlimab-gxly for dMMR/MSI-H tumors[b,12]	**Other Recommended Regimens** • Cisplatin/doxorubicin[13] • Cisplatin/doxorubicin/paclitaxel[n,13] • Cisplatin • Carboplatin • Doxorubicin • Liposomal doxorubicin • Paclitaxel[14] • Albumin-bound paclitaxel[o] • Topotecan • Bevacizumab[k,p,15] • Temsirolimus[16] • Cabozantinib • Docetaxel[f] (category 2B) • Ifosfamide (for carcinosarcoma) • Ifosfamide/paclitaxel (for carcinosarcoma)[17] • Cisplatin/ifosfamide (for carcinosarcoma) **Useful in Certain Circumstances (Biomarker directed therapy)** • Lenvatinib/pembrolizumab (category 1) for mismatch repair proficient (pMMR) tumors[b,9] • Pembrolizumab[b] for TMB-H[l,8] or MSI-H/dMMR tumors[m,11] • Dostarlimab-gxly for dMMR/MSI-H tumors[b,12] • Larotrectinib or entrectinib for NTRK gene fusion-positive tumors (category 2B) • Avelumab for dMMR/MSI-H tumors[b] • Nivolumab for dMMR/MSI-H tumors[b,18]

2023 ASCO® ANNUAL MEETING

Hyperthermic intraperitoneal chemotherapy in ovarian cancer

Final survival analysis of the phase III OVHIPEC-1 trial

S.L. Aronson, M.I. Lopez-Yurda, S.N. Koole, J.H. Schagen van Leeuwen, H.W. Schreuder, R.H. Hermans, I.H. de Hingh, M.D. van Gent, H.J. Arts, M.A. van Ham, P.A. van Dam, P. Vuylsteke, A.G. Aalbers, V.J. Verwaal, K.K. Van de Vijver, N.K. Aaronson, **G.S. Sonke***, W.J. van Driel*

*shared last author

PRESENTED BY: Prof. Gabe S. Sonke, MD, PhD – contact: ovhipec@nki.nl

ORIGINAL ARTICLE

Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer

Willemien J. van Driel, M.D., Ph.D., Simone N. Koole, M.D., Karolina Sikorska, Ph.D., Jules H. Schagen van Leeuwen, M.D., Ph.D., Henk W.R. Schreuder, M.D., Ph.D., Ralph H.M. Hermans, M.D., Ph.D., Ignace H.J.T. de Hingh, M.D., Ph.D., Jacobus van der Velden, M.D., Ph.D., Henriëtte J. Arts, M.D., Ph.D., Leon F.A.G. Massuger, M.D., Ph.D., Arend G.J. Aalbers, M.D., Victor J. Verwaal, M.D., Ph.D., Jacobien M. Kieffer, Ph.D., Koen K. Van de Vijver, M.D., Ph.D., Harm van Tinteren, Ph.D., Neil K. Aaronson, Ph.D., and Gabe S. Sonke, M.D., Ph.D.

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

23 References 806 Citing Articles

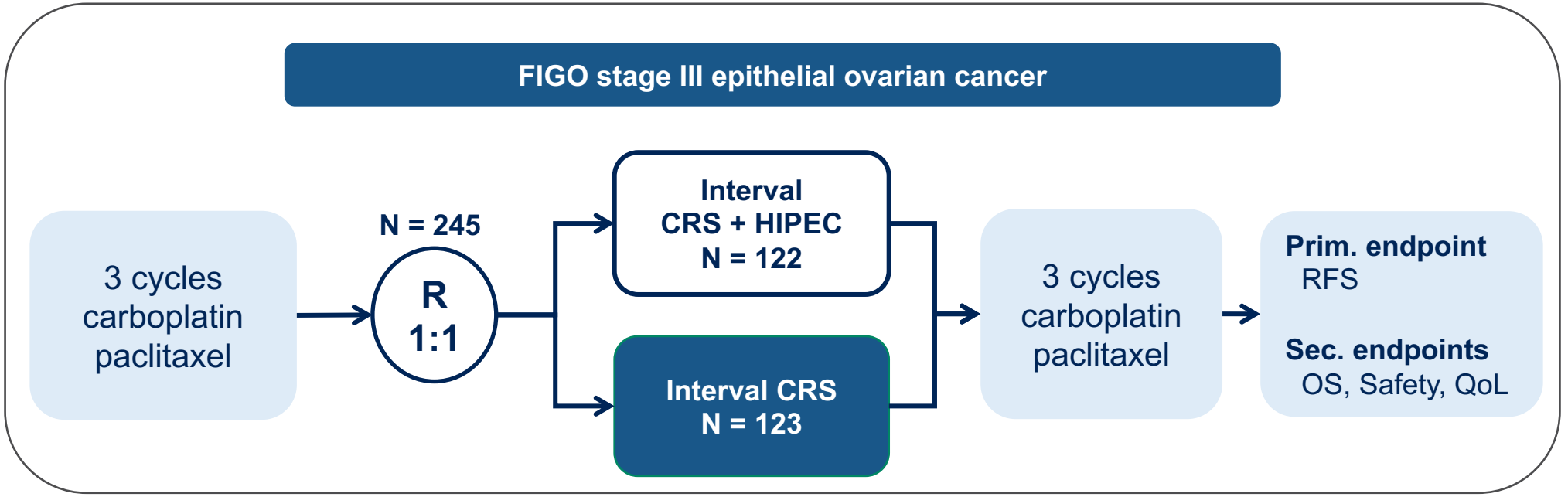
Background OVHIPEC-1 trial

- First RCT to evaluate HIPEC in ovarian cancer
- Improved recurrence-free and overall survival at 4.7 years of follow-up[1]
- No increase in adverse events or delayed start of adjuvant chemotherapy[1]
- Significantly fewer peritoneal recurrences[2]
- No negative impact on quality of life[3]
- Cost-effective[4]

PRESENTED BY: Prof. Gabe S. Sonke, MD, PhD – contact: ovhipec@nki.nl

1. van Driel et al, N Engl J Med, 2018
2. Koole et al, Int J Gynecol Cancer, 2020
3. Koole et al, Eur J Surg Oncol, 2021
4. Koole et al, J Clin Oncol, 2019

Study design



- Accrual between 2007-2016 in 8 centers in the Netherlands and Belgium
- Patients required neo-adjuvant chemotherapy due to extensive disease
- Follow-up visits every 3 months in year 1-2, every 6 months thereafter

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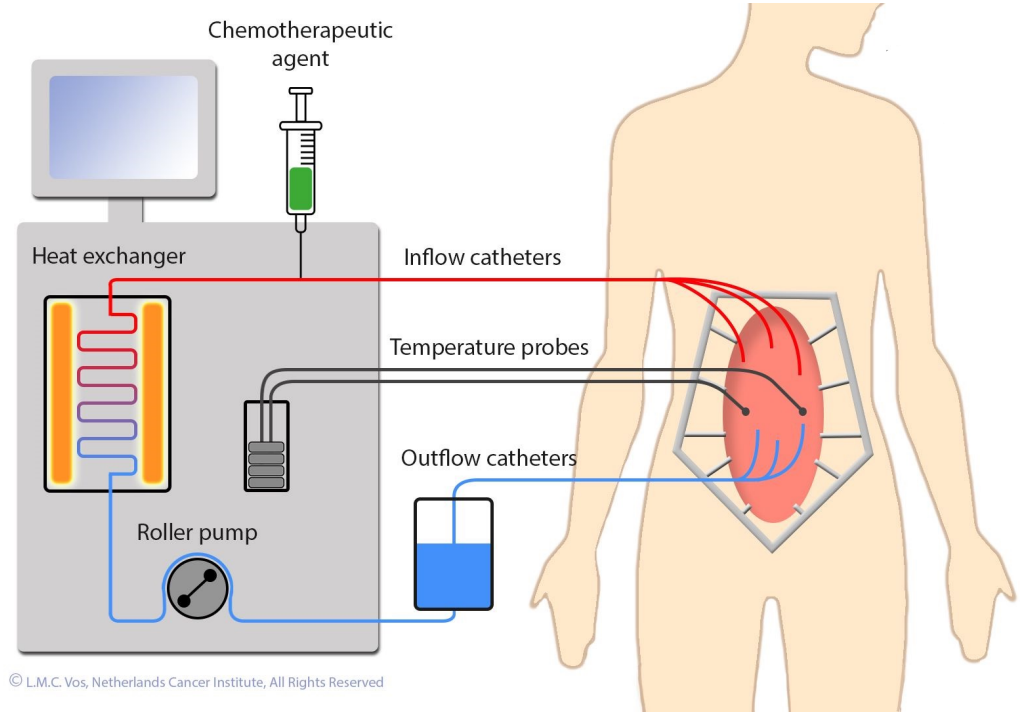
HIPEC procedure

- Open ‘colosseum’ technique
- Cisplatin 100 mg/m^2
  - 50% at the start
  - 25% after 30 min
  - 25% after 60 min
- Heated to 42°C, min flow of 1L/min
- Sodium thiosulfate for renal protection



Key eligibility criteria

- Newly diagnosed stage III epithelial ovarian, fallopian tube, or peritoneal cancer
- At least stable disease after 3 cycles of neo-adjuvant chemotherapy
- Adequate renal and bone marrow function
- Treated with interval cytoreductive surgery with residual disease <1 cm
- No history of previous malignancy within 5 years prior to inclusion

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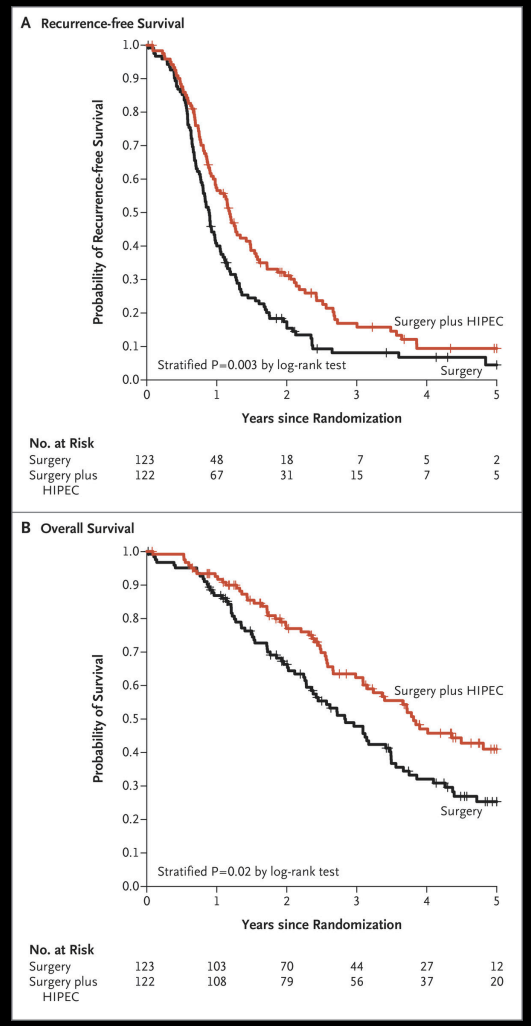
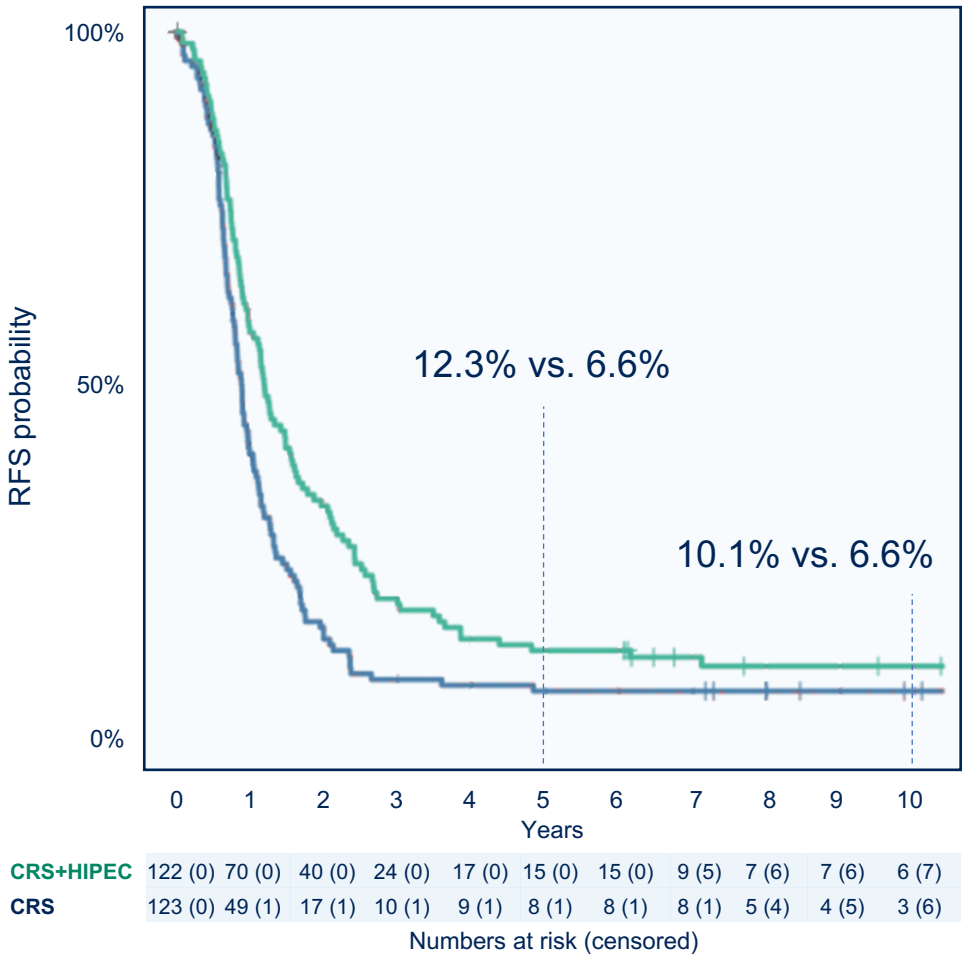
Kaplan–Meier Estimates of Recurrence-free Survival and Overall Survival.



WJ van Driel et al. N Engl J Med 2018;378:230-240.

The NEW ENGLAND JOURNAL of MEDICINE

RFS after ten years follow-up



	CRS-HIPEC	CRS
Median RFS, mo	14.3	10.7
HR (95%CI)	**0.63 (0.48 – 0.83)**	
Stratified log-rank p	0.0008	

HIPEC delays recurrences

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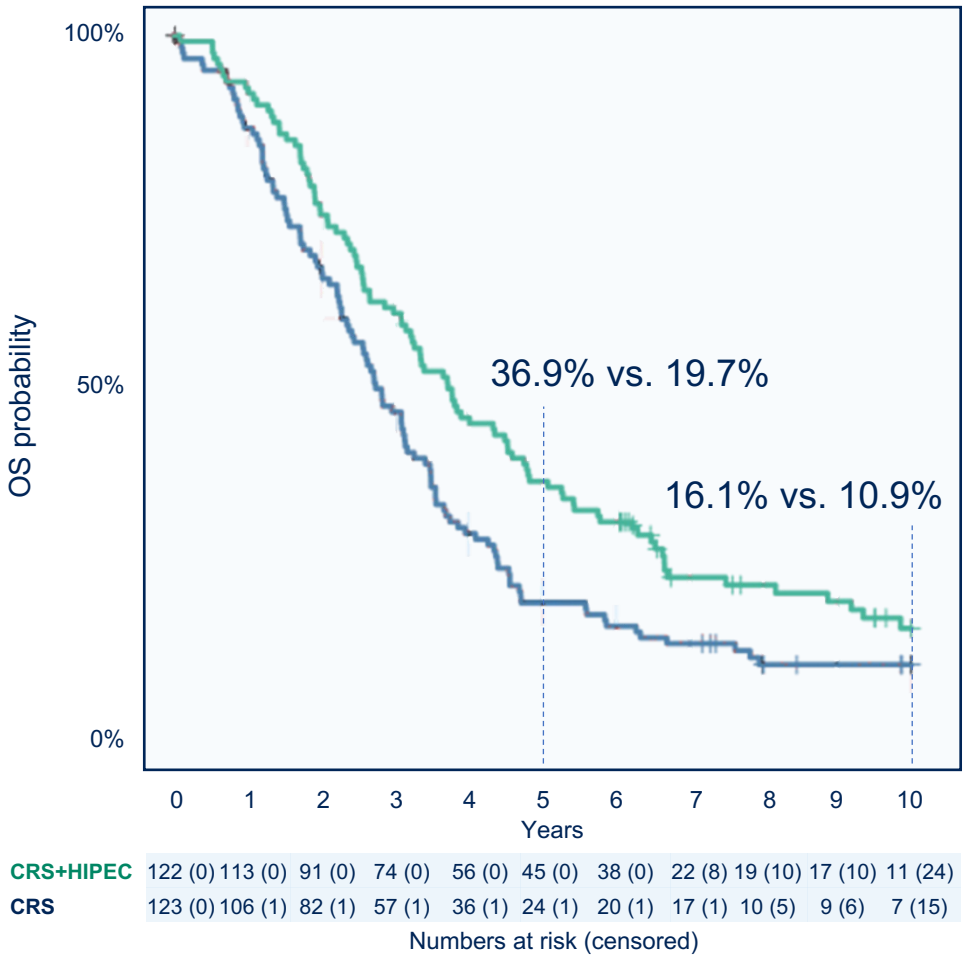
OS after ten years follow-up

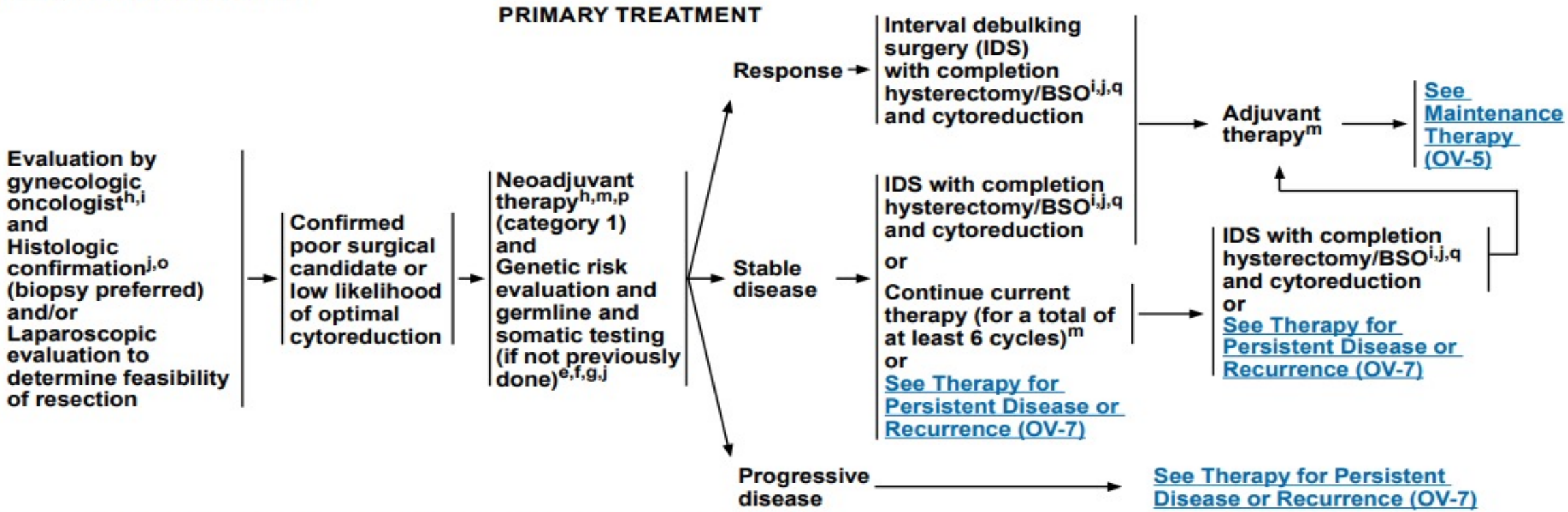


	CRS-HIPEC	CRS
Median OS, mo	44.9	33.3
HR (95%CI)	**0.70 (0.53 – 0.92)**	
Stratified log-rank p	0.0113	

HIPEC improves long-term overall survival

PRESENTED BY: Prof. Gabe S. Sonke, MD, PhD – contact: ovhipec@nki.nl

POOR SURGICAL CANDIDATE OR LOW LIKELIHOOD OF OPTIMAL CYTOREDUCTION NEOADJUVANT THERAPY



[e] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.

[f] Germline and somatic *BRCA1/2* status informs maintenance therapy.

[g] In the absence of a *BRCA1/2* mutation, HRD status may provide information on the magnitude of benefit of PARPi therapy (See OV-B).

[h] Evaluation by a gynecologic oncologist is recommended for:

- All patients with suspected ovarian malignancies; published data demonstrate that primary assessment and debulking by a gynecologic oncologist results in a survival advantage.
- Patients being evaluated for neoadjuvant therapy prior to being considered a poor surgical candidate.
- Management of occult STICs.
- Consideration of laparoscopic evaluation to determine feasibility of debulking surgery in select patients.
- Endometrial biopsy as clinically indicated.

[i] See Principles of Surgery (OV-A).

[j] See Principles of Pathology (OV-B).

[m] See Principles of Systemic Therapy (OV-C) and Management of Drug Reactions (OV-D).

[o] If biopsy is not feasible, cytopathology from ascites or pleural effusion combined with CA-125:CEA ratio of >25 can be used.

[p] Completion surgery after 3–4 cycles is preferred; however, surgery may be performed after 4–6 cycles based on the clinical judgment of the gynecologic oncologist.

[q] Hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin (100 mg/m^2) can be considered at the time of IDS for stage III disease.

2023 ASCO ANNUAL MEETING

DESTINY-PanTumor02

Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: DESTINY-PanTumor02 interim results

Funda Meric-Bernstam

The University of Texas MD Anderson Cancer Center, Houston, TX, USA

June 5, 2023

Additional authors: Vicky Makker, Ana Oaknin, Do-Youn Oh, Susana Banerjee, Antonio González-Martín, Kyung Hae Jung, Iwona Ługowska, Luis Manso, Aránzazu Manzano, Bohuslav Melichar, Salvatore Siena, Daniil Stroyakovskiy, Chiedozie Anoka, Yan Ma, Soham Puvvada, Jung-Yun Lee

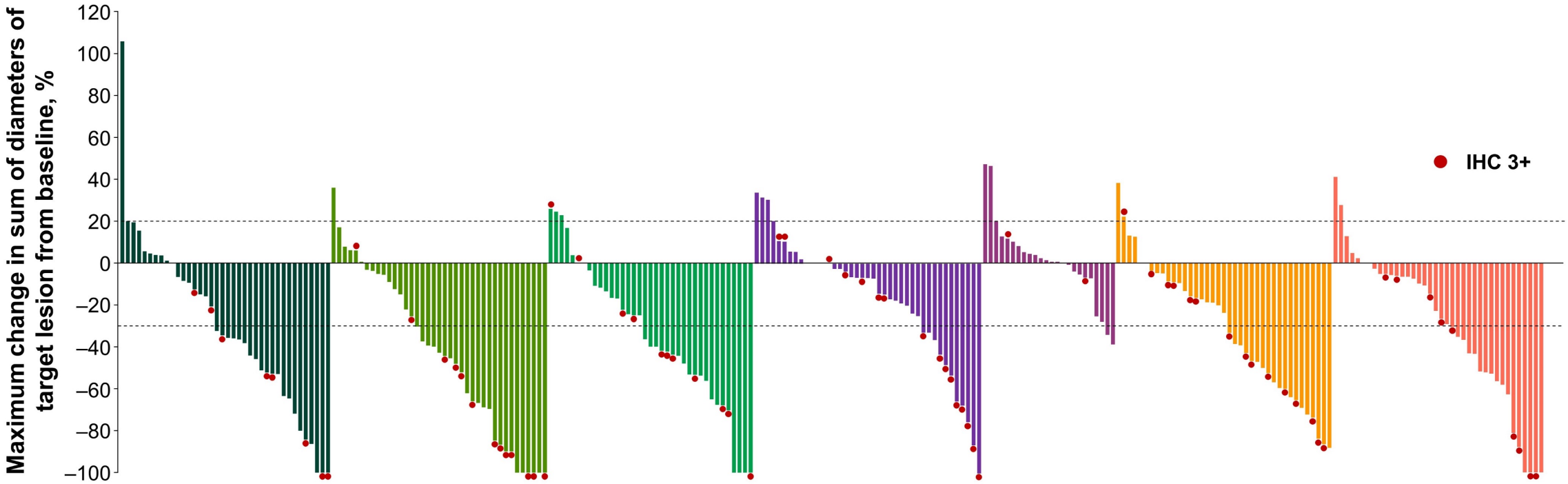
On behalf of the DESTINY-PanTumor02 investigators

Efficacy endpoints: ORR, DCR and DOR

		Cervical (n=40)	Endometrial (n=40)	Ovarian (n=40)	BTC (n=41)	Pancreatic (n=25)	Bladder (n=41)	Other (n=40)	All patients (N=267)
Investigator assessment									
ORR, n (%)		**20 (50.0)**	**23 (57.5)**	**18 (45.0)**	**9 (22.0)**	**1 (4.0)**	**16 (39.0)**	**12 (30.0)**	**99 (37.1)**
Best overall response, n (%)	Complete response	2 (5.0)	7 (17.5)	4 (10.0)	1 (2.4)	0	1 (2.4)	0	15 (5.6)
	Partial response	18 (45.0)	16 (40.0)	14 (35.0)	8 (19.5)	1 (4.0)	15 (36.6)	12 (30.0)	84 (31.5)
	Stable disease	12 (30.0)	13 (32.5)	14 (35.0)	25 (61.0)	17 (68.0)	18 (43.9)	24 (60.0)	123 (46.1)
	PD	7 (17.5)	4 (10.0)	7 (17.5)	7 (17.1)	7 (28.0)	7 (17.1)	3 (7.5)	42 (15.7)
	Not evaluable	1 (2.5)	0	1 (2.5)	0	0	0	1 (2.5)	3 (1.1)
DCR[a] at 12 weeks, n (%)		27 (67.5)	32 (80.0)	28 (70.0)	27 (65.9)	9 (36.0)	29 (70.7)	30 (75.0)	182 (68.2)
Median DOR, months (95% CI)		9.8 (4.2–NE)	NR (9.9–NE)	11.3 (4.1–NE)	8.6 (2.1–NE)	NR	8.7 (4.3–11.8)	NR (4.1–NE)	11.8 (9.8–NE)
Independent central review: ORR, n (%)		16 (40.0)	21 (52.5)	17 (42.5)	11 (26.8)	3 (12.0)	17 (41.5)	13 (32.5)	98 (36.7)

Analysis of response and DCR was performed in patients who received ≥1 dose of T-DXd (n=267). Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd (n=99).
[a]Confirmed complete response, confirmed partial response or stable disease.
BTC, biliary tract cancer; CI, confidence interval; DCR, disease control rate; DOR, duration of response; NE, not estimable; NR, not reached; ORR, objective response rate; PD, progressive disease.

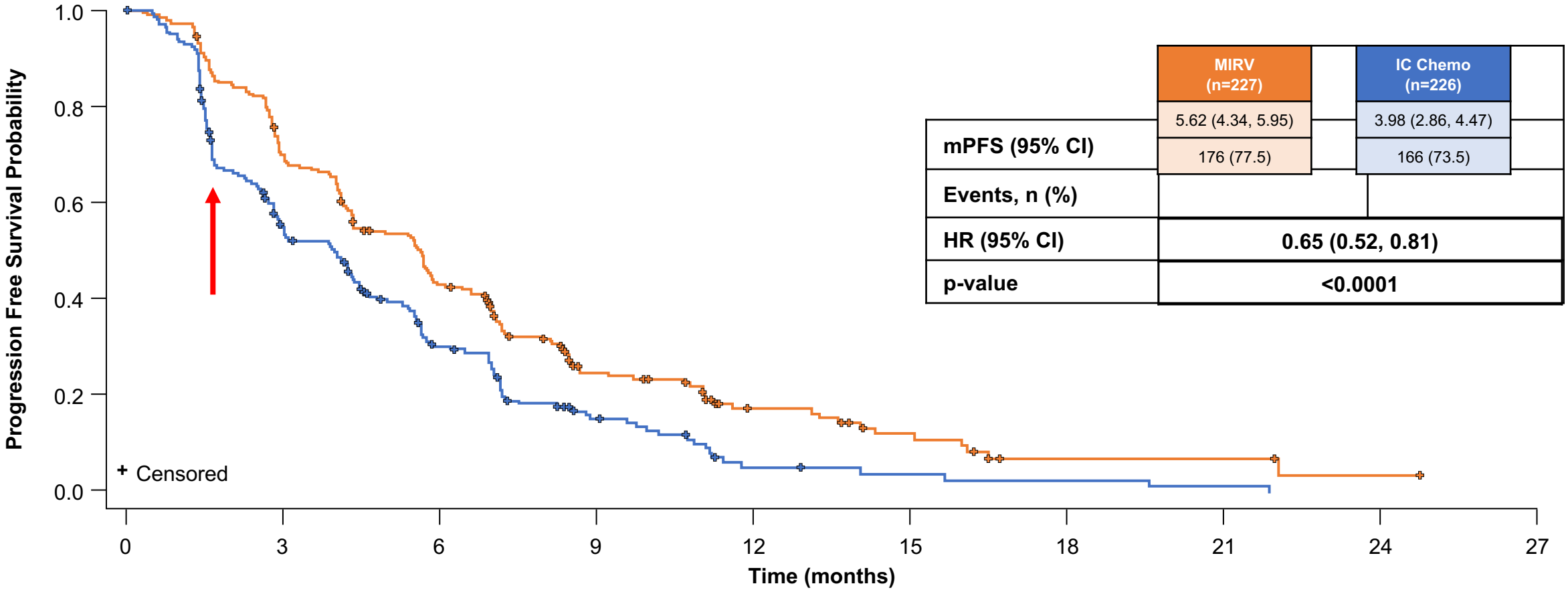
Best Percentage Change in Target Lesion From Baseline



ORR in IHC 3+	Cervical (n=8)	Endometrial (n=13)	Ovarian (n=11)	BTC (n=16)	Pancreatic (n=2)	Bladder (n=16)	Other[a] (n=9)
n (%)	6 (75.0)	11 (84.6)	7 (63.6)	9 (56.3)	0	9 (56.3)	4 (44.4)

Analyses were performed in patients who received ≥1 dose of T-DXd (n=267). Analysis of ORR in IHC 3+ was performed in patients with centrally confirmed HER2 status (n=75).
[a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.
BTC, biliary tract cancer; IHC, immunohistochemistry; ORR, objective response rate.

Primary Endpoint: Progression-Free Survival by Investigator



	MIRV (n=227)	IC Chemo (n=226)
mPFS (95% CI)	5.62 (4.34, 5.95)	3.98 (2.86, 4.47)
Events, n (%)	176 (77.5)	166 (73.5)
HR (95% CI)	0.65 (0.52, 0.81)	
p-value	<0.0001	

No. Participants at Risk

MIRV	227	151	89	38	18	10	3	3	1	0
IC Chemo	226	98	48	19	5	3	2	1	0	

Data cutoff: March 6, 2023
MIRV, mirvetuximab soravtansine; IC Chemo, investigator's choice chemotherapy; mPFS, median progression-free survival; CI, confidence interval; HR, hazard ratio.

PRESENTED BY: Kathleen Moore, Associate Director of Clinical Research, Stephenson Cancer Center University of Oklahoma College of Medicine

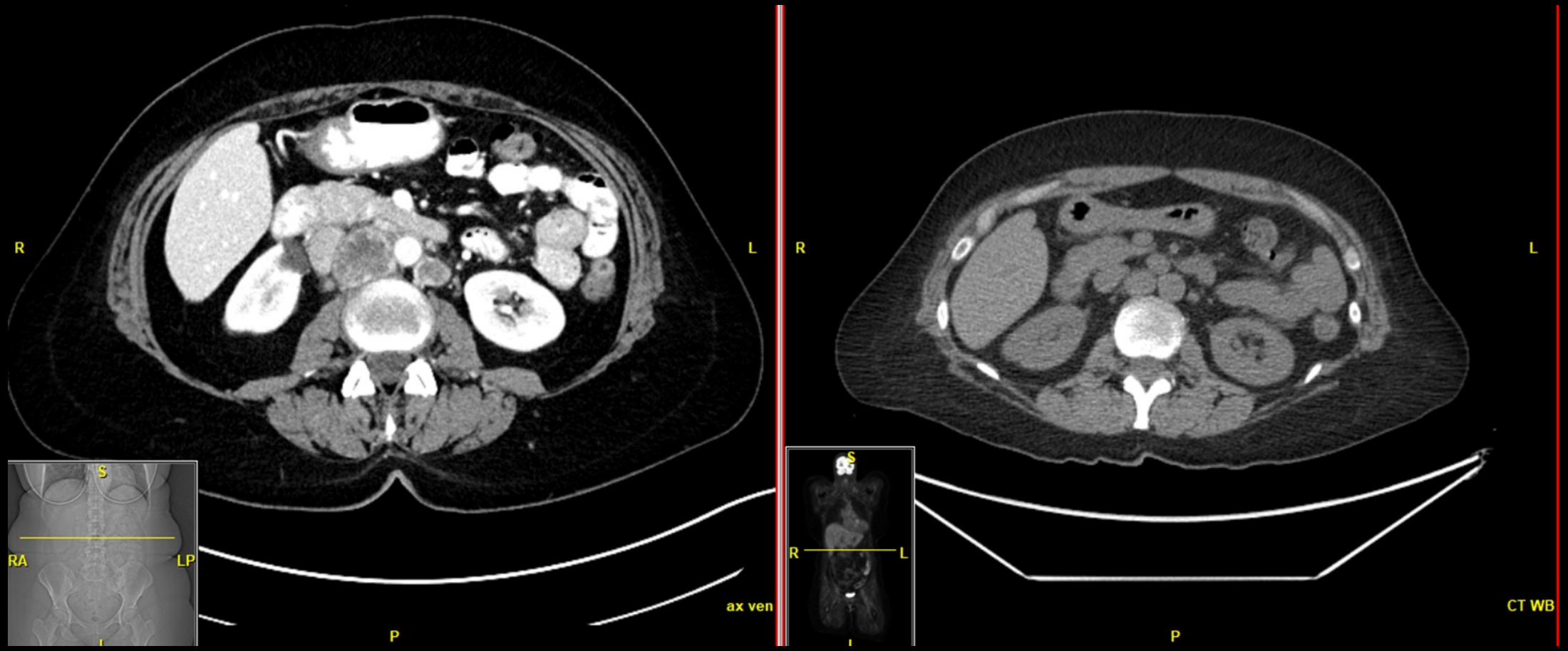
Patient Case Vignette
64 y/o female

- *February 2022: Laparoscopic TAH-BSO. Path: T1aN0Mo grade 2 endometrioid carcinoma, extensive LVS, positive washings, ER negative. MMR-IHC: deficient.*

- *March 2022: Headaches. MRI brain: multiple metastasis (6). Gamma knife. PET: omental, pelvic and RP mets. Biopsy: g3 carcinoma with necrosis. Treatment with pembrolizumab.*

- *May 2022: Repeat CT with progression*

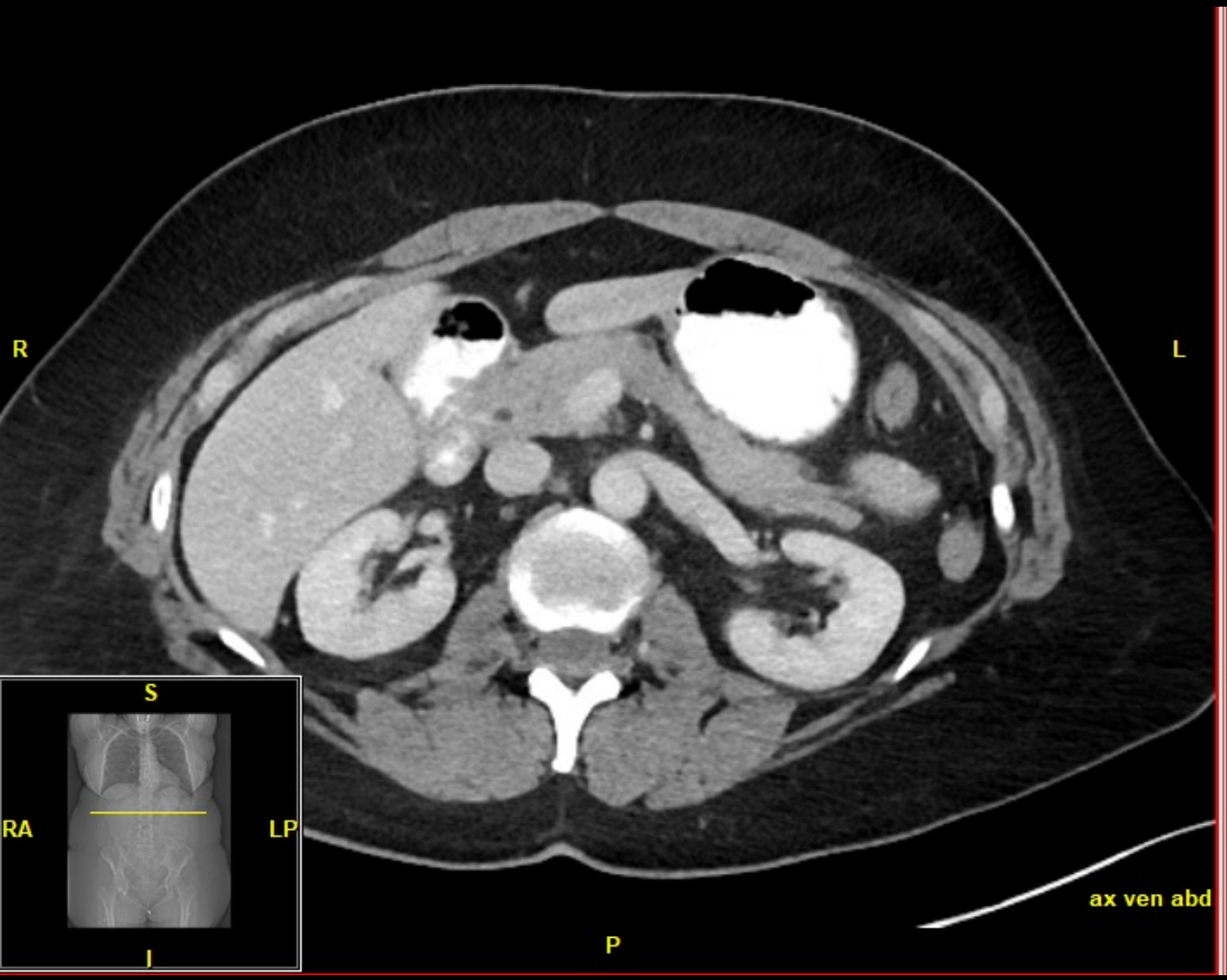
CT SCANS

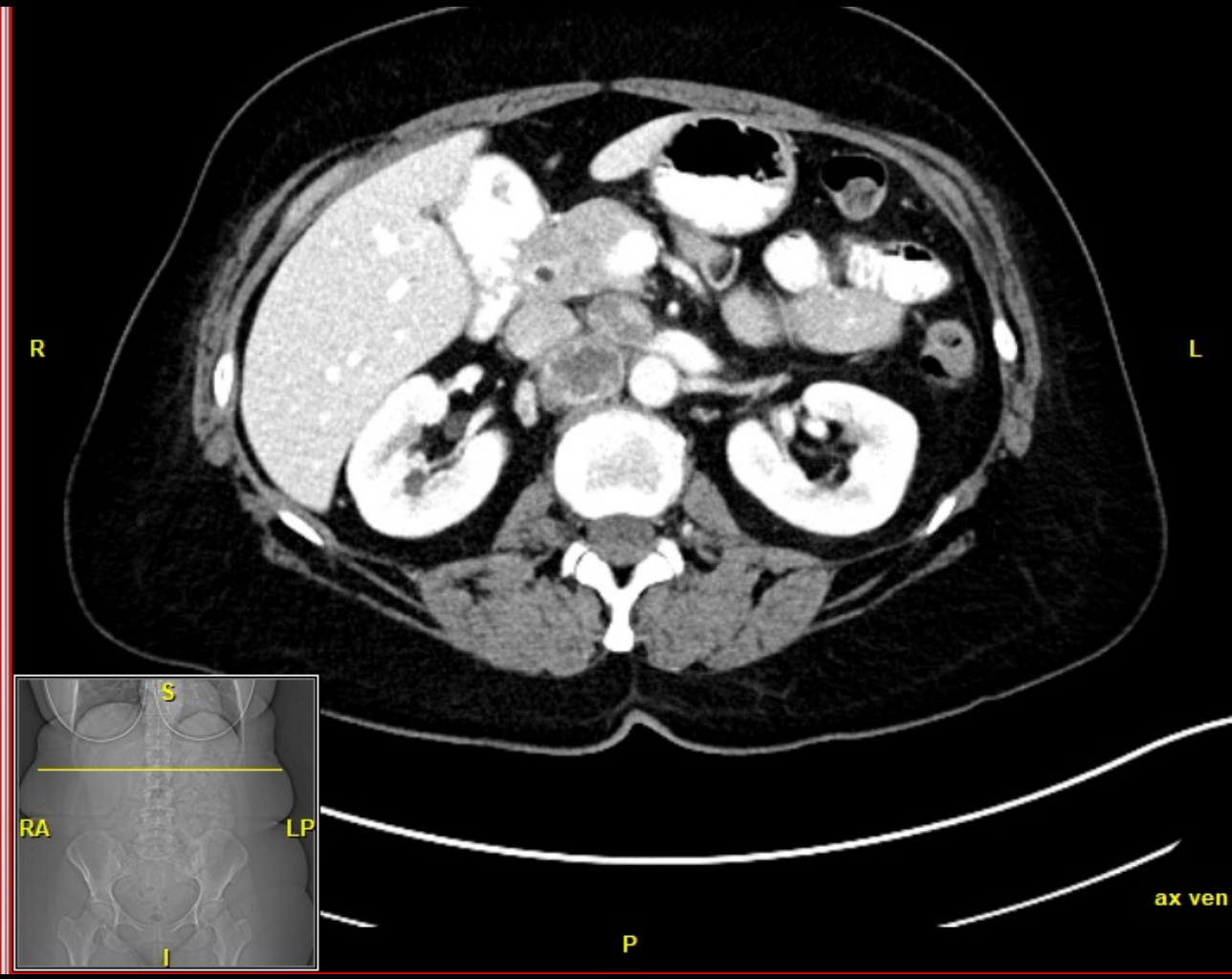


Case Question: What would you recommend?

- Switch to chemotherapy given progression
- Refer to hospice
- Continue treatment with pembrolizumab
- Add lenvatinib to pembrolizumab

CT RESULTS- FOLLOW UP





Key Take Home Messages (4)

- New standard of care for Stage 3-4 or recurrent endometrial cancer (MMR deficient): Dostarlimab or pembrolizumab and paclitaxel and carboplatin.
- HIPEC improves 10-year OS in ovarian cancer treated with neo-adjuvant chemotherapy.
- Trastuzumab deruxtecan is active in cervical, endometrial and ovarian cancers with positive HER2 IHC (2+ and 3+).
- Mirvetuximab improves PFS and OS in FOLR1 IHC positive platinum resistant ovarian cancer.