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Unmet Needs in Gynecologic Oncology: Advancing the Management of Rare Tumors

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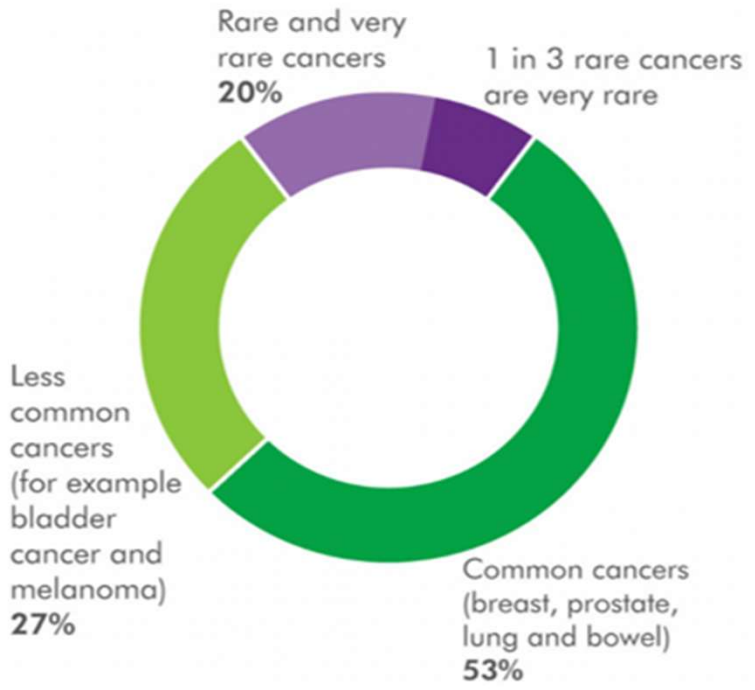
GOG Highlight Reel

Rare Cancers Add Up

- Although the incidence of rare malignancies is a fraction of that of the leading cancer types, the aggregate impact is significant

- Individuals with rare gynecologic cancers represent 25-30% of all survivors of GYN malignancies but:
  - Tumors are more challenging to treat
  - Have fewer treatment options
  - **Experience 30-40% of all gynecologic cancer-related deaths**



The Decade of Rare Gynecologic Cancer Advances

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A Phase Ii Trial Of Selumetinib (Azd6244) In Women With Recurrent Low-Grade Serous Carcinoma Of The Ovary Or Peritoneum: A Gynecologic Oncology Group Trial

John Farley, MD[1], William E. Brady, PhD[2], Vinod Vathipadiekal, PhD[3], Heather A. Lankes, PhD[2], Robert Coleman, MD[4], Mark A. Morgan, MD[5], Robert Mannel, MD[6], S. Diane Yamada, MD[7], David Mutch, MD[8], William H. Rodgers, MD[9], Michael Birrer, MD, PhD[3], and David M. Gershenson, MD[4]

[1]Professor, Creighton University School of Medicine at St. Joseph's Hospital and Medical Center

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Efficacy and Safety of Bevacizumab in Recurrent Sex Cord-Stromal Ovarian Tumors: Results of a Phase II Trial of the Gynecologic Oncology Group

Jubilee Brown, MD[1] [Associate Professor], William E. Brady, PhD[2] [Statistician], Julian Schink, MD[3] [Professor], Linda Van Le, MD[4] [Professor], Mario Leitao, MD[5] [Assistant Member], S. Diane Yamada, MD[6] [Professor], Koen de Geest, MD[7] [Clinical Professor], and David M. Gershenson, MD[8] [Professor]

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Adjuvant Gemcitabine Plus Docetaxel Followed by Doxorubicin Versus Observation for High-Grade Uterine Leiomyosarcoma: A Phase III NRG Oncology/Gynecologic Oncology Group Study

Martee L. Hensley, Danielle Enserro, Helen Hatcher, Petronella B. Ottevanger, Anders Krarup-Hansen, Jean-Yves Blay, Cyril Fisher, Katherine M. Mackey, Shashikant B. Lele, Jayanthi S. Lea, Krishnansu S. Tewari, Premal H. Thaker, Oliver Zivanovic, David M. O'Malley, Katina Robison, and David S. Miller

Trametinib versus standard of care in patients with recurrent low-grade serous ovarian cancer (GOG 281/LOGS): an international, randomised, open-label, multicentre, phase 2/3 trial

David M Gershenson, Austin Miller, William E Brady, James Paul, Karen Carty, William Rodgers, David Millan, Robert L Coleman, Kathleen N Moore, Susana Banerjee, Kate Connolly, Angeles Alvarez Secord, David M O'Malley, Oliver Dorigo, Stephanie Golland, Hani Gabra, Brian Slomovitz, Pamela Hanjani, John Farley, Michael Churchman, Alitia Ewing, Robert J Hollis, C Simon Herrington, Helen Q Huang, Lori Wenzel, Charlie Gourley

original reports

MILO/ENGOT-ov11: Binimetinib Versus Physician's Choice Chemotherapy in Recurrent or Persistent Low-Grade Serous Carcinomas of the Ovary, Fallopian Tube, or Primary Peritoneum

Bradley J. Monk, MD[1]; Rachel N. Grisham, MD[2]; Susana Banerjee, PhD[3]; Elsa Kalbacher, MD[4]; Mansoor Raza Mirza, MD[5]; Ignacio Romero, MD[6]; Peter Vuylsteke, MD[7,8]; Robert L. Coleman, MD[9]; Felix Hilpert, MD[10]; Amit M. Oza, MD[11]; Anneke Westermann, MD, PhD[12]; Martin K. Oehler, MD, PhD[13]; Sandro Pignata, MD, PhD[14]; Carol Aghajanian, MD[2]; Nicoletta Colombo, MD[15]; Esther Drill, DrPH[2]; David Cibula, MD, PhD[16]; Kathleen N. Moore, MD[17]; Janna Christy-Bittel, MSN[18]; Josep M. del Campo, MD[19]; Regina Berger, PhD[20]; Christian Marth, MD, PhD[21]; Jalid Sehouli, MD[22]; David M. O'Malley, MD[23]; Cristina Chumuca, MD[24]; Adam P. Boyd, PhD[18]; Gunnar Kristensen, MD, PhD[25]; Andrew Clamp, MD, PhD[26]; Isabelle Ray-Coquard, MD, PhD[27]; and Ignace Vergote, MD, PhD[28]

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Randomized Phase III Trial of Paclitaxel and Carboplatin Versus Paclitaxel and Ifosfamide in Patients With Carcinosarcoma of the Uterus or Ovary: An NRG Oncology Trial

Matthew A. Powell, MD[1]; Virginia L. Filiaci, PhD[2]; Martee L. Hensley, MD[3]; Helen Q. Huang, MS[2]; Kathleen N. Moore, MD[4]; Krishnansu S. Tewari, MD[5]; Larry J. Copeland, MD[6]; Angeles A. Secord, MD[7]; David G. Mutch, MD[8]; Alessandro Santin, MD[9]; David P. Warshal, MD[10]; Nick M. Spirtos, MD[11]; Paul A. DiSilvestro, MD[12]; Olga B. Ioffe, MD[13]; and David S. Miller, MD[14]

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Phase II Study of Single-Agent Cabozantinib in Patients with Recurrent Clear Cell Ovarian, Primary Peritoneal or Fallopian Tube Cancer (NRG-GY001)

Panagiotis A. Konstantinopoulos, MD, PhD[1], William E. Brady, PhD[2], John Farley, MD[3], Amy Armstrong, MD[4], Denise S. Uyar, MD[5], and David M. Gershenson, MD[6]

Clinical Trial > Gynecol Oncol. 2022 Jan;164(1):12-17. doi: 10.1016/j.ygyno.2021.10.087. Epub 2021 Nov 8.

Phase II study of enzalutamide in androgen receptor positive, recurrent, high- and low-grade serous ovarian cancer

Beryl L Manning-Geist [1], Sushmita B Gordhandas [1], Dilip D Giri [2], Alexia Iasonos [3], Qin Zhou [4], Jeffrey Girshman [5], Roisin E O'Cearbhaill [6], Dmitriy Zamarin [6], Stuart M Lichtman [6], Paul J Sabbatini [6], William P Tew [6], Karen Li [7], Autumn S McDonnell [8], Emeline M Aviki [9], Dennis S Chi [9], Carol A Aghajanian [6], Rachel N Grisham [10]

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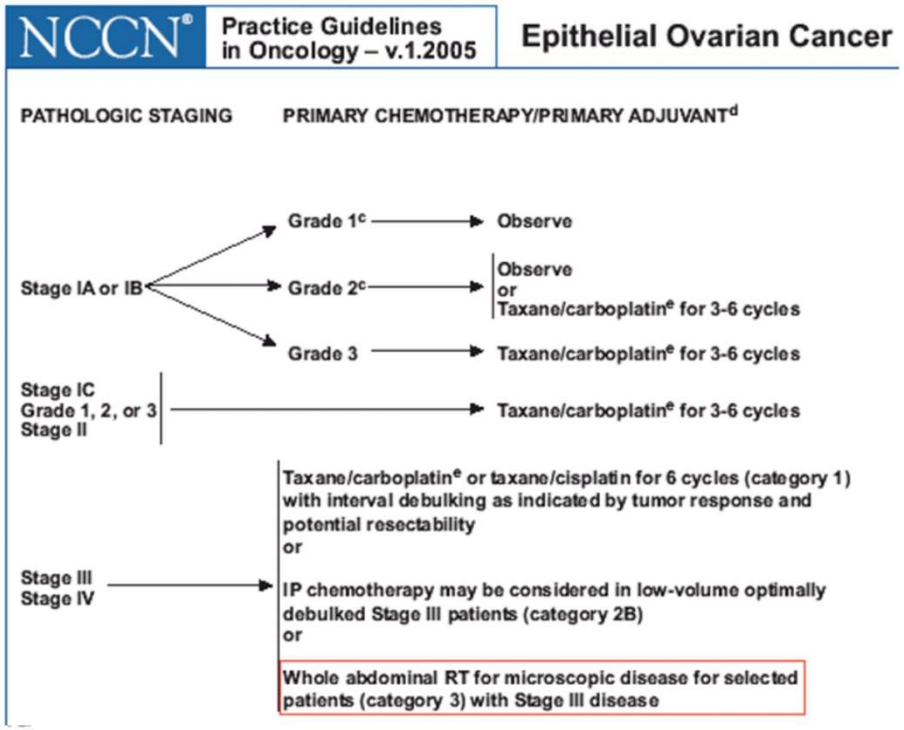
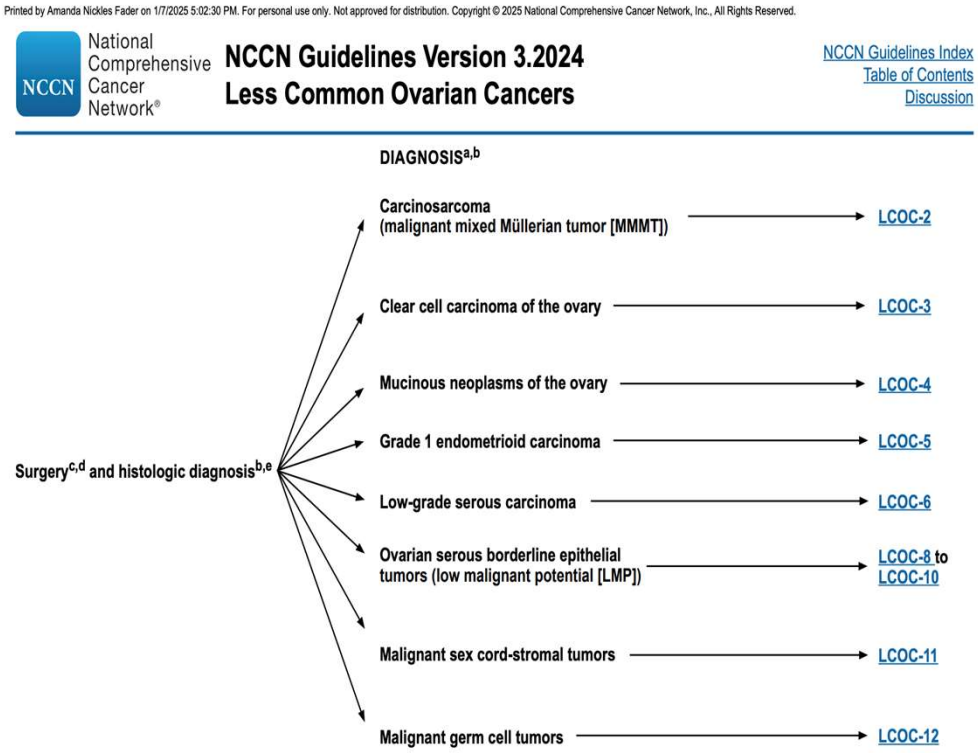
Randomized phase II trial of carboplatin-paclitaxel compared to carboplatin-paclitaxel-trastuzumab in advanced (stage III-IV) or recurrent uterine serous carcinomas that overexpress Her2/Neu (NCT01367002): updated overall survival analysis

Amanda N. Fader[1], Dana M. Roque[2], Eric Siegel[3], Natalia Buza[4], Pei Hui[4], Osama Abdelghany[4], Setsuko Chambers[5], Angeles Alvarez Secord[6], Laura Havrilesky[6], David M. O'Malley[7], Floor J. Backes[7], Nicole Nevadunsky[8], Babak Edraki[9], Dirk Pikaart[10], William Lowery[11], Karim ElSahwi[12], Paul Celano[13], Stefania Bellone[4], Masoud Azodi[4], Babak Litkouhi[14], Elena Ratner[4], Dan-Arin Silasi[4], Peter E. Schwartz[4], Alessandro D Santin[4,*]

NCCN Ovarian Cancer Guidelines Progress in Rare Epithelial OC



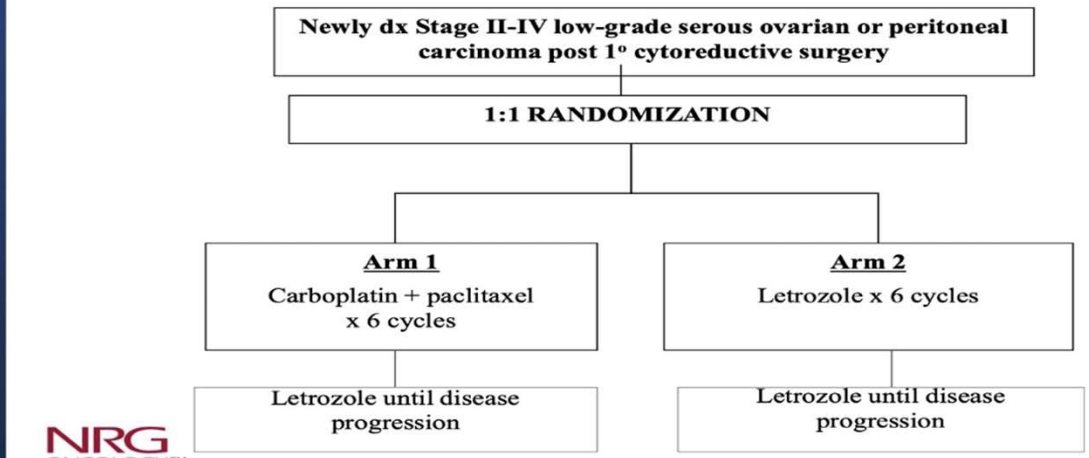


NRG-GY019: One of the first adjuvant trials in advanced ovarian cancer without platinum/taxane in one of the treatment arms

- Moving beyond the “Add on" clinical trial design model (i.e., building upon a chemo backbone)
- NRG-GY019 overcomes that limitation
- 92% of patients enrolled to date

NCT04095364

Study Schema



*Strata: Residual Disease and Country

NRG ONCOLOGY™

NCI National Clinical Trials Network
a National Cancer Institute program

NRG-GY019

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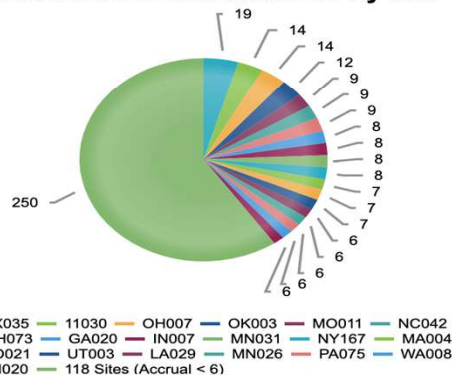
A Randomized Phase III, Two-Arm Trial of Paclitaxel/Carboplatin/Maintenance Letrozole Versus Letrozole Monotherapy in Patients with Stage II-IV, Primary Low-Grade Serous Carcinoma of the Ovary or Peritoneum

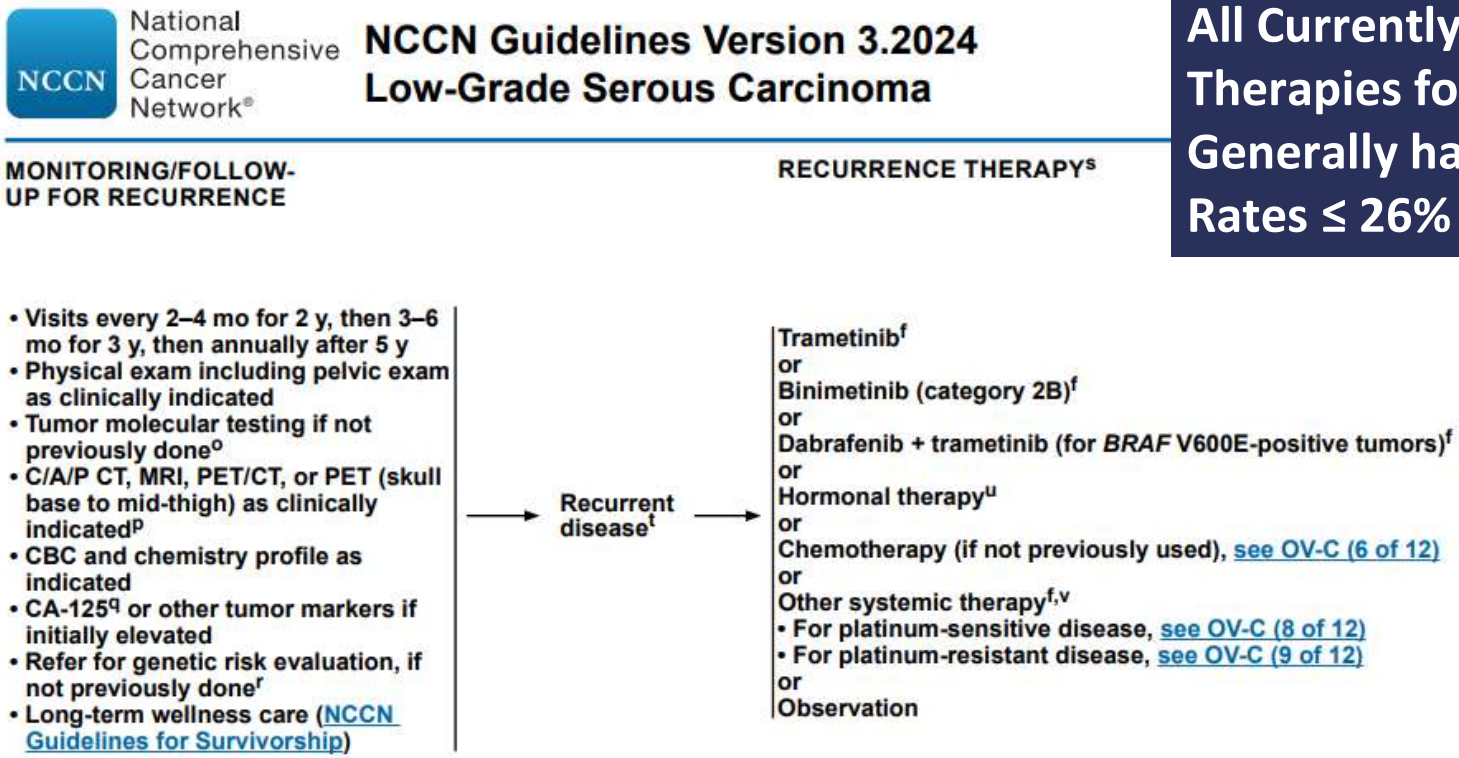
Protocol Status:	**ACTIVE**
Protocol Status Date:	26-Aug-2019
Activation Date:	26-Aug-2019
Lead Organization:	**NRG**
NCI Program:	**NCTN**
Phase:	**III**
Country Participation:	
ClinicalTrials.gov Link:	NCT04095364
Patient Accrual:	As of 17-Jan-2025 12:30:15 AM

Step Type	Step(s)	Planned	Actual
Intervention	1	457	419

Patient Intervention Accrual by site



No FDA-Approved Regimens Specifically for LGSOC



All Currently Available Therapies for LGSOC Generally have Response Rates ≤ 26%

Studies Recently Completed in LGSOC

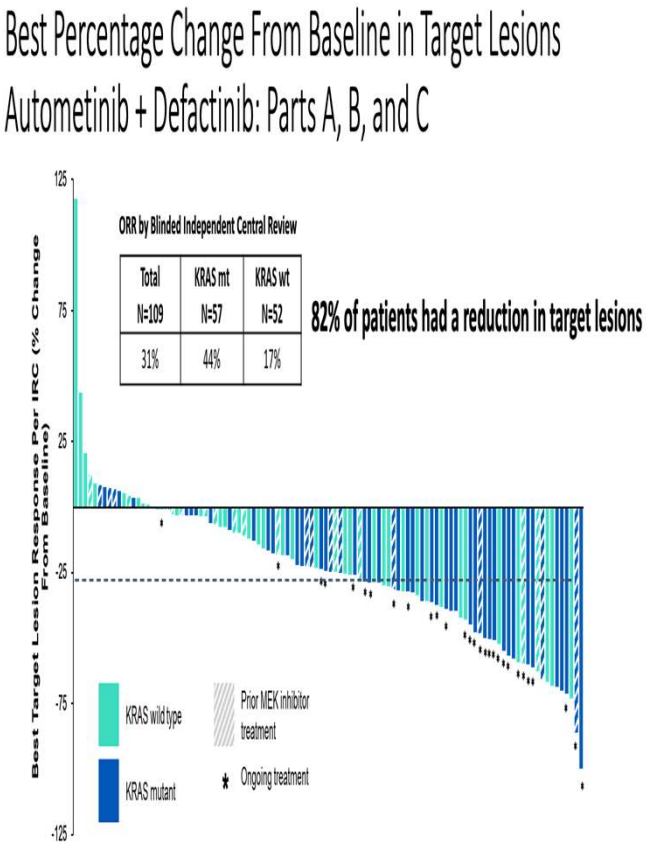
Study	Phase	Treatment	Efficacy Outcome
NCT01974765[1]	II	Enzalutamide for AR+ LGSOC	1/14 unconfirmed PR, 4.6 mo mPFS, 38.5% PFS6 mo
PARAGON[2] **(ANZGOG-0903)**	II	Anastrazole for ER+ LGSOC	14% ORR (5/26)
GOG 3026[3] **(NCT03673124)**	II	Ribociclib + Letrozole	23% ORR, 19.1 mo mDOR, 19.1 mo mPFS
FRAME[4] **(NCT03875820)**	I	Avutometinib + Defactinib	46% ORR (64% KRAS mt, 44% KRAS wt), 23 mo mPFS
RAMP 201[5] **(NCT04625270)**	II	Avutometinib + Defactinib	45% ORR (60% KRAS mt, 29% KRAS wt)
NCT03905148	I	Lifirafenib + Mirdametinib	58.8% ORR (10/17) [BIOMARKER SELECTED]
SOLAR[6] **(NCT03162627)**	I/II	Olaparaib + Selumetinib	44% ORR (4/9) [BIOMARKER SELECTED]
EMR 20006-012[7] **(NCT01936363)**	II	Pimasertib ± SAR245409	9.4% (combo) and 12.1% (mono) ORR
NCT03909152[8]	II	Onapristone ER + Anastrozole	50% CBR (2/4), 75% PFS3

[1] Manning-Geist *Gynecol Oncol* 2020; [2]Tang *Gynecol Oncol* 2019; [3]Slomovitz SGO 2023; [4]Banerjee ESMO 2021 #799; [5]Banerjee ASCO 2023 #5515; [6]Westin SGO 2023; [7]Arend *Gynecol Oncol* 2020; [8]Grisham ASCO 2022 #5521

Courtesy of David Gershenson, MD

RAMP 201 Summary and Conclusions

- Avutometinib 3.2 mg BIW + defactinib 200 mg BID resulted in clinically meaningful responses, duration of response, and progression-free survival
- **ORR:** 31% overall; 44% in KRASmt and 17% in KRASwt
- **Median DOR:** 31 months overall
- **Median PFS**: 12.9 months overall; 22.0 months in KRASmt and 12.8 months in KRASwt
- The majority of adverse events were grade 1 and 2 and managed by dose interruptions or reductions.
- A new drug application for this combination in recurrent, KRASmut LGSOC granted FDA priority review with a Prescription Drug User Fee Act (PDUFA) action date of June 30, 2025

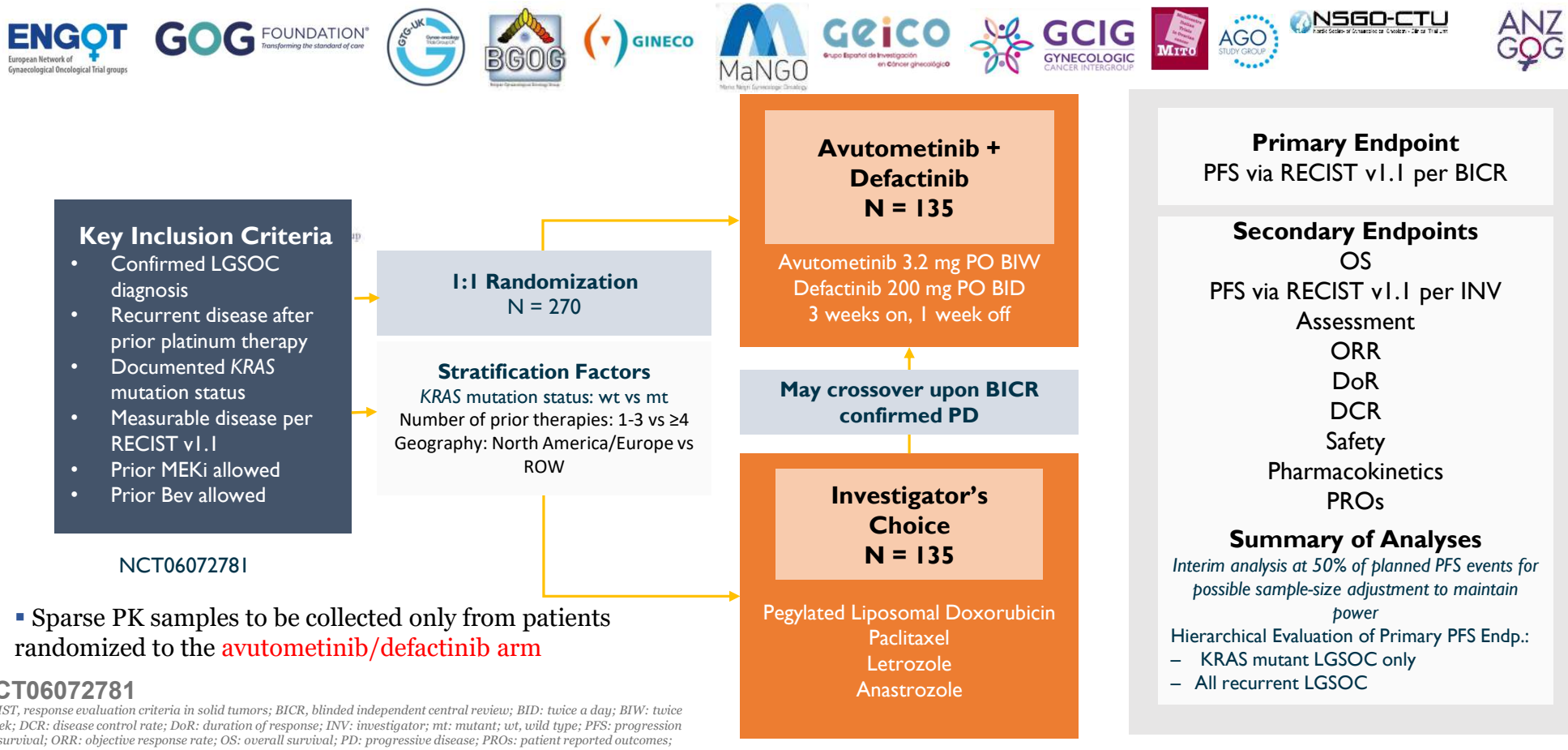


NCT04625270

Courtesy of Rachel Grisham, MD

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 (LGSOC)



- Sparse PK samples to be collected only from patients randomized to the avutometinib/defactinib arm

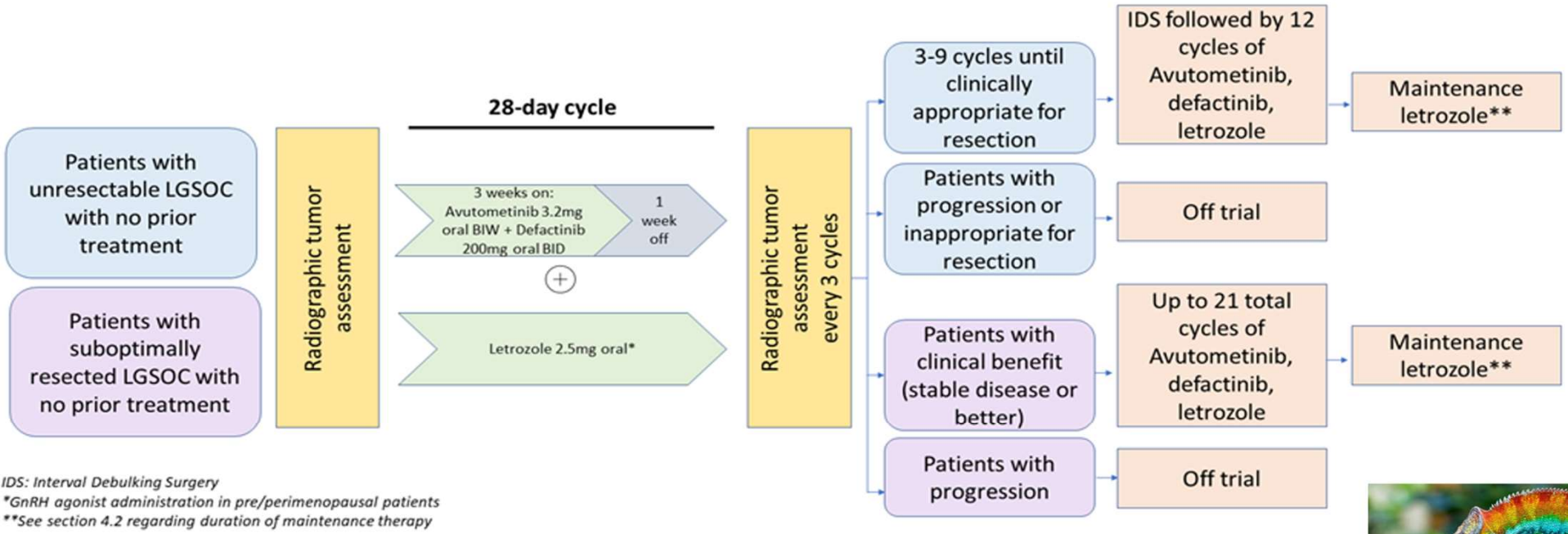
NCT06072781

RECIST, response evaluation criteria in solid tumors; BICR, blinded independent central review; BID: twice a day; BIW: twice a week; DCR: disease control rate; DoR: duration of response; INV: investigator; mt: mutant; wt, wild type; PFS: progression free survival; ORR: objective response rate; OS: overall survival; PD: progressive disease; PROs: patient reported outcomes; ROW: rest of world

Avutometinib and defactinib are investigational drugs and have not been approved for use by any regulatory health authority. Safety and efficacy have not been established.

Combination targeted and Hormonal treAtMENt of Low-gradE serous Ovarian cancer in the upfroNt setting (CHAMELEON) Study Schema

NCT06394804



IDS: Interval Debulking Surgery
**GnRH agonist administration in pre/perimenopausal patients*
***See section 4.2 regarding duration of maintenance therapy*

Courtesy of Rachel Grisham, MD

Ongoing Studies in Recurrent LGSOC

Study	Phase	Treatment	Est. Completion
PARAGON II (ACTRN12621000639820)	II	Letrozole+alpelisib (PIK3CAi); Letrozole+ ribociclib (CDK4/6i) based on presence of PIK3CA mutation status	
ALEPRO* (NCT05872204)	II	Abemaciclib + Letrozole	10/2026
NCT05113368	II	Regorafenib + Fulvestrant	6/2023
BOUQUET* (NCT04931342)	II	Biomarker Selected Treatments	12/2026
PERCEPTION (NCT04575961)	II	Pembrolizumab + Chemotherapy	11/2023
FUCHSia	II	Fulvestrant	4/2022
ComboMatch* (NCT05554367)	II	Palbociclib + Binimetinib	8/2026
NCT04092270*	I	Peposertib + Chemotherapy	
NCT04739800*	II	Durvalumab + Olaparib + Cediranib	12/2023
NCT02923934*	II	Ipilimumab + Nivolumab	12/2023

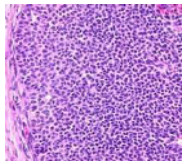
*Basket Trial with LGSOC Cohort

Courtesy of David Gershenson, MD

GOG-0264: Randomized phase II trial of paclitaxel and carboplatin versus bleomycin, etoposide and cisplatin for newly diagnosed and recurrent, chemonaive stromal ovarian tumors

PI: Jubilee Brown, MD

- **Granulosa cell tumors**
- 2-5% of all ovarian cancers, most common sex-cord stromal tumor
- Indolent growth
- ER/PR positivity is common
- Somewhat chemoresistant



SCHEMA

Patients diagnosed with histologically confirmed ovarian stromal tumor
Newly diagnosed, Stage IIA – IVB disease and must be entered within eight weeks from surgery
OR biopsy-proven recurrent disease with no prior chemotherapy

↓

Randomization (1:1)

↙ ↘

Arm I	Arm II
Treatment: • Paclitaxel 175 mg/m2 IV over 3 hours • Carboplatin AUC = 6 IV over 1 hour • Every 3 weeks x 6 cycles (=18weeks)	Treatment: • Bleomycin 20 units/m2 IV Push day 1 (MAX 30 units/cycle; Total lifetime cumulative dose should not exceed 120 units) • Etoposide** 75 mg/m2 IV Day 1,2,3,4,5 • Cisplatin 20 mg/m2 IV Day 1,2,3,4,5 • Every 3 weeks x 4 cycles (=12 weeks)

NCT01042522

Primary endpoint: PFS

Non-inferiority design

Opened in 2010; majority with granulosa cell tumor and measurable disease

Closed due to futility

Futility analysis was supported by an estimated HR = 1.11 [95% CI: 0.57 to 2.13] which exceeded the pre-determined threshold for non-inferiority (1.10). Median PFS was 27.7 months [11.2 to 41.0] for PC and 19.7 months for BEP [95% CI: 10.4-52.7].

PC patients had fewer grade 3 or higher adverse events (PC 77% vs BEP 90%).

Brown et al, Gynecol Oncol, Nov 2024

Study to Determine the Safety, Tolerability, Pharmacokinetics and Recommended Phase 2 Dose (RP2D) of Livmoniplimab (ABBV-151) as a Single Agent and in Combination With Budigalimab (ABBV-181) in Participants With Locally Advanced or Metastatic Solid Tumors

- **Livmoniplimab** a monoclonal antibody against **GARP/TGF-β1** that can inhibit the release of active TGF-**β1**
- **Budigalimab,** a humanized, recombinant immunoglobulin G1 monoclonal antibody targeting programmed cell death protein 1 (PD-1)

NCT03821935

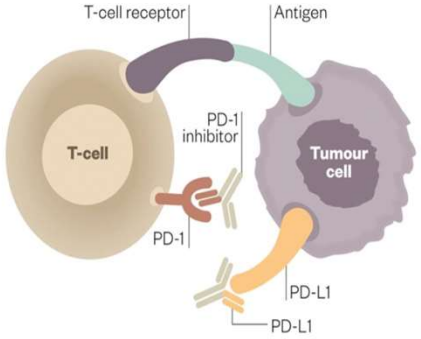
Experimental: Dose Expansion: Cohort 12A Livmoniplimab + Budigalimab Participants with PD-1-naïve ovarian granulosa (OG) cell tumors will receive livmoniplimab at the Dose B Q3W plus budigalimab Dose B administered Q3W.	Drug: Livmoniplimab • Liquid for intravenous infusion. • Other Names: ◦ ABBV-151 Drug: Budigalimab • Lyophilized powder for solution for intravenous infusion. • Other Names: ◦ ABBV-181
Experimental: Dose Expansion: Cohort 12B Livmoniplimab + Budigalimab Participants with PD-1-naïve ovarian granulosa (OG) cell tumors will receive livmoniplimab at the Dose C Q3W plus budigalimab Dose B administered Q3W.	Drug: Livmoniplimab • Liquid for intravenous infusion. • Other Names: ◦ ABBV-151 Drug: Budigalimab • Lyophilized powder for solution for intravenous infusion. • Other Names: ◦ ABBV-181

Clear Cell Carcinoma of the Ovary

Recurrent Ovarian Clear Cell Carcinomas

- Chemoresistant, response rates <10%
- Limited options

- Studies of PD-1 inhibition in epithelial ovarian cancers (all histologic types): ORR 15%



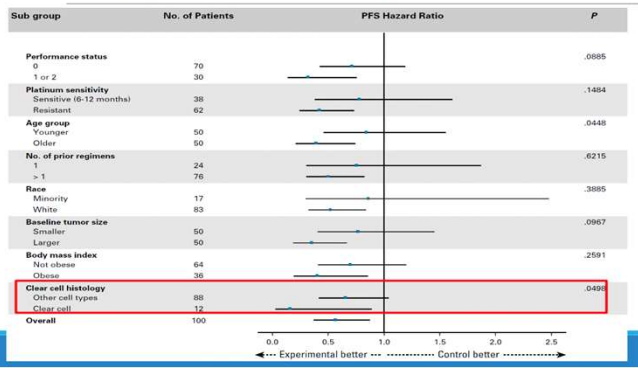
CCC Ovary Negative Trials

- GOG 268: Temsirolimus + C/P ->Temsirolimus
- GOG 254: Sunitinib
- GOG 283: Dasatanib
- GY-001: Cabozantinib
- ENGOT/ov36: Nintedanib

Randomized Phase II Trial of Nivolumab Versus Nivolumab and Ipilimumab for Recurrent or Persistent Ovarian Cancer: An NRG Oncology Study

NRG-GY003

Dmitriy Zamarin, MD, PhD[1]; Robert A. Burger, MD[2]; Michael W. Sill, PhD[3]; Daniel J. Powell Jr, PhD[4]; Heather A. Lankes, PhD, MPH[3]; Michael D. Feldman, MD, PhD[4]; Oliver Zivanovic, MD, PhD[1]; Camille Gunderson, MD[5]; Emily Ko, MD, MSCR[6]; Cara Mathews, MD[7]; Sudarshan Sharma, MD[8]; Andrea R. Hagemann, MD[9]; Samir Khleif, MD[10]; and Carol Aghajanian, MD[1]



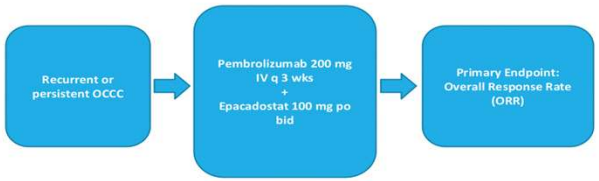
5-fold increased odds of response in clear cell histology (n=12)

J Clin Oncol 38:1814-1823. © 2020

O014/#415

PHASE II TRIAL OF PEMBROLIZUMAB AND EPACADOSTAT IN RECURRENT CLEAR CELL CARCINOMA OF THE OVARY: AN NRG ONCOLOGY STUDY

[1]Lilian Gien*, [2]Danielle Enserro, [3]Matthew Block, [4]Steven Waggoner, [5]Linda Duska, [3]Andrea Wahner Hendrickson, [6]Premal Thaker, [7]Floor Backes, [8]Justin Bottsford-Miller, [9]Carolyn Muller, [10]Paul Disilvestro, [1]Allan Covens, [11]David Gershenson, [12]Kathleen Moore, [13]Carol Aghajanian, [14]Robert L Coleman.



NRG-GY016
Abstract presented at IGCS Oct 2022

Results: n=14 at first stage, rapid accrual: 2.3 pts per month
ORR=21% (95% CI 0.05-0.51)
Median DOR: 6.9 months
4 patients with SD, DCR 50%

Median PFS 4.8 mos (95% CI 1.9-9.6),
Median OS 18.9 mos (95% CI 1.9-NR)

Met criteria for 2nd stage, but study closed prematurely (insufficient drug supply)

Clear Cell Carcinoma Trials

Clear Cell Carcinoma: - BrUOG 354 Ipi/Nivo

LEGORRETA CANCER CENTER
BROWN UNIVERSITY

Lifespan
Delivering health with care

Top Line Conclusions

For people with ovarian or gynecologic clear cell carcinoma, the clinical activity and survival outcomes are greater when nivolumab is given with ipilimumab vs. as a single agent.

Treatment	ORR (%)	Median PFS (range, months)	Median OS (range, months)
Nivolumab	14.3	2.2 (1.2-3.4)	17.3 (2.1-42.7)
Nivolumab/Ipilimumab	33.3	5.6 (1.6-29.1)	24.7 (5.7-NR)

There were no new safety signals identified among volunteers with gynecologic clear cell cancer treated with immunotherapy.

Immunotherapy represents an important and available treatment option for people with these rare and aggressive malignancies.

Dizon D, ASCO Abstracts, 2024

Neuroendocrine Carcinoma of the Cervix (NECC)

- <2% of all cervical malignancies
  - An extrapulmonary variant of small cell lung cancer (SCLC)
- The mean annual incidence according to SEER data is 0.06 per 100,000 women[3]
- In the setting of improved diagnostic testing, the incidence has increased
- Median age at diagnosis: 40-45

Unique Genomic Landscape of High-Grade Neuroendocrine Cervical Carcinoma: Implications for Rethinking Current Treatment Paradigms

Ramez N. Eskander, MD[1,2]; Julia Elvin, MD, PhD[3]; Laurie Gay, PhD[3]; Jeffrey S. Ross, MD[3,4]; Vincent A. Miller, MD[3]; and Razelle Kurzrock, MD[2,5]

TABLE 1. Molecular Features of High-Grade Neuroendocrine Cervical Cancers

	Patients With ≥ 1 Oncogenic Alteration (N = 97)			
Altered Gene	Total	HPV Positive (n = 83)	HPV Negative (n = 14)	P
PIK3CA	19.6	17	36	.0037
MYC	15.5	17	7	.0484
TP53	15.5	11	43	.0001
PTEN	14.4	8	50	.0001
ARID1A	9.3	5	36	.0001
RB1	8.2	4	36	.0001

- PIK3CA[6]
- KRAS
- TP53 mutations
- MYC
- Mismatch repair deficiency
- ARID1A
- PTEN
- BRCA2
- VEGF
- HER2
- TMB
- RB1

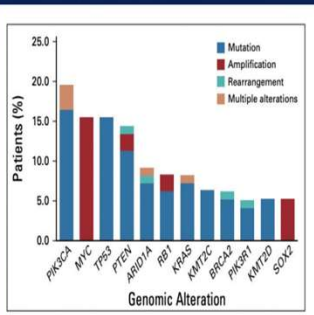


FIG 1. Most common genomic alterations in patients with high-grade neuroendocrine cervical cancer (HGNECC), reflected as percentage of patients (N = 97). Only genes altered in > 5% of samples are depicted. Variants of unknown significance excluded.

2024 ASCO ANNUAL MEETING #ASCO24

PRESENTED BY: Amanda Fader, MD

Eskander et al, JCO Precis Oncol

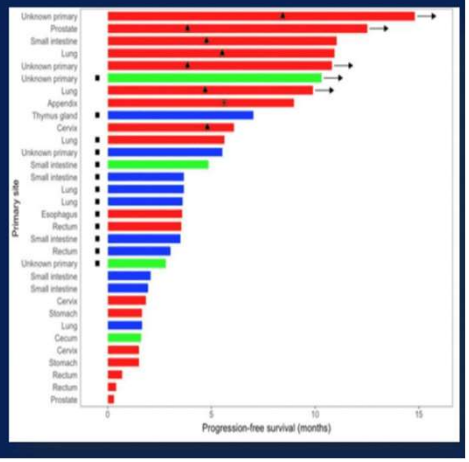
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

NECC and Checkpoint Inhibition

A Phase II Basket Trial of Dual Anti–CTLA-4 and Anti–PD-1 Blockade in Rare Tumors (DART SWOG 1609) in Patients with Nonpancreatic Neuroendocrine Tumors

Sandip P. Patel[1], Megan Othus[2], Young Kwang Chae[3], Francis J. Giles[3,4], Donna E. Hansel[5], Preet Paul Singh[6], Annette Fontaine[7], Manisha H. Shah[8], Anup Kasi[9], Tareq Al Baghdadi[10], Marc Matrana[11], Zoran Gatalica[12], W. Michael Korn[12,13], Jourdain Hayward[14], Christine McLeod[14], Helen X. Chen[15], Elad Sharon[15], Edward Mayerson[2], Christopher W. Ryan[16], Melissa Plets[2], Charles D. Blanke[17], and Razelle Kurzrock[1]

- Ipilimumab + Nivolumab
- ORR in High Grade Lesions: 44%
- 3 patients with cervix cancer, 1 responded



Meeting Abstract: 2024 ASCO Annual Meeting I
FREE ACCESS | Gastrointestinal Cancer—Gastroesophageal, Pancreatic, and Hepatobiliary | May 29, 2024

SWOG S2012: Randomized phase II/III trial of first line platinum (P)/etoposide (E) with or without atezolizumab (NSC #783608) in patients with advanced or metastatic poorly differentiated extrapulmonary neuroendocrine carcinomas (NEC).

Authors: David Bing Zhen, Anna Moseley, E. Gabriela Chiorean, Earle F Burgess, Elizabeth M. Swisher, Carl Michael Gay, Lauren Averett Byers, Ignacio Ivan Wistuba, Haider Mahdi, Jason S. Starr, Megan Othus, Young Kwang Chae, and Razelle Kurzrock SHOW FEWER | AUTHORS INFO & AFFILIATIONS

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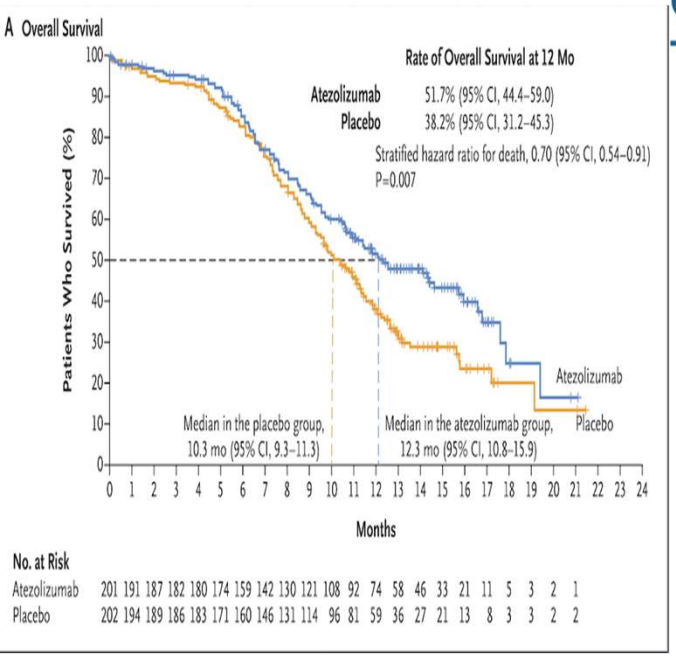
ARM I: During induction phase, patients receive atezolizumab intravenously (IV) over 30-60 minutes on day 1 of each cycle, carboplatin IV over 30 minutes or cisplatin IV over 60 minutes on day 1 of each cycle, and etoposide IV on days 1-3 of each cycle. Treatment repeats every 21 days for 4 cycles in the absence of disease progression or unacceptable toxicity. During maintenance phase, patients receive atezolizumab IV over 30-60 minutes on day 1 of each cycle. Treatment repeats every 21 days for up to 17 cycles in the absence of disease progression or unacceptable toxicity.

ARM II: During induction phase, patients receive atezolizumab IV over 30-60 minutes on day 1 of each cycle, carboplatin IV over 30 minutes or cisplatin IV over 60 minutes on day 1 of each cycle, and etoposide IV on days 1-3 of each cycle. Treatment repeats every 21 days for 4 cycles in the absence of disease progression or unacceptable toxicity. Patients then undergo observation for 1 year.

ARM III: During induction phase, patients receive carboplatin IV over 30 minutes or cisplatin IV over 60 minutes on day 1 of each cycle and etoposide IV on days 1-3 of each cycle. Treatment repeats every 21 days for 4 cycles in the absence of disease progression or unacceptable toxicity. Patients then undergo observation for 1 year.

Neuroendocrine carcinoma of the cervix (NECC)



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Cervical Cancer

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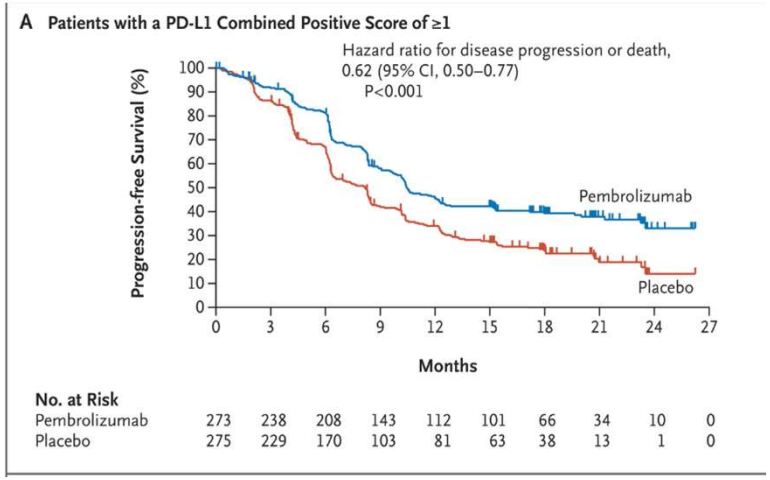
SYSTEMIC THERAPY FOR CERVICAL CANCER[a,b]

Small Cell NECC[n]		
Chemoradiation[o]	Recurrent or Metastatic Disease	
	First-line Therapy[g]	Second-line or Subsequent Therapy[g]
Preferred Regimens • Cisplatin + etoposide[26,27] **Other Recommended Regimens** • Carboplatin + etoposide if patient is cisplatin intolerant	**Preferred Regimens** • Cisplatin/etoposide • Carboplatin/etoposide **Other Recommended Regimens** • Cisplatin/etoposide + atezolizumab (or durvalumab)[e,f,i,28,29] • Carboplatin/etoposide + atezolizumab (or durvalumab)[e,f,i,28,29] • Topotecan/paclitaxel/bevacizumab[e,30] • Cisplatin/paclitaxel • Carboplatin/paclitaxel (for patients who have received prior cisplatin therapy)	**Other Recommended Regimens** • Bevacizumab • Albumin-bound paclitaxel • Docetaxel • Topotecan • Topotecan/paclitaxel • Cisplatin/topotecan • Cisplatin • Carboplatin • Paclitaxel • Irinotecan

Horn et al, NEJM, 2018

NCCN Vaginal Cancer Update

Keynote 826 Phase III Trial



Colombo et al, NEJM, 2021

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SYSTEMIC THERAPY FOR PRIMARY VAGINAL CANCER (REGIMENS ARE EXTRAPOLATED FROM CERVICAL CANCER)[a,b,c]

Squamous Cell Carcinoma, Adenocarcinoma		
Chemoradiation[d]	Recurrent or Metastatic Disease	
	First-Line Therapy[d,e]	Second-Line or Subsequent Therapy[e]
Preferred Regimens • Cisplatin • Carboplatin if patient is cisplatin intolerant **Other Recommended Regimens (if cisplatin and carboplatin are unavailable)** • Capecitabine/mitomycin[1] • Gemcitabine[2] • Paclitaxel[3,4]	**Preferred Regimens** • PD-L1–positive tumors ▸ Pembrolizumab + cisplatin/paclitaxel ± bevacizumab[f,g,h,5] ▸ Pembrolizumab + carboplatin/paclitaxel ± bevacizumab[f,g,h,5] • Cisplatin/paclitaxel/bevacizumab[h,6] • Carboplatin/paclitaxel/bevacizumab[h,6] **Other Recommended Regimens** • Cisplatin/paclitaxel[7,8] • Carboplatin/paclitaxel[9,10] • Topotecan/paclitaxel/bevacizumab[h,6,11] • Topotecan/paclitaxel[11] • Cisplatin/topotecan[11] • Cisplatin[8] • Carboplatin[12,13]	**Preferred Regimens** • Pembrolizumab[f] for TMB-high (TMB-H) tumors[i] or PD-L1–positive[g] or MSI-H/mismatch repair deficient (dMMR) tumors[14] **Other Recommended Regimens** • Bevacizumab • Paclitaxel[13,15] • Albumin-bound paclitaxel • Docetaxel • Fluorouracil • Gemcitabine • Pemetrexed • Topotecan • Vinorelbine • Irinotecan • Tisotumab vedotin-tftv[16] • Cemiplimab[f,17] **Useful in Certain Circumstances** • PD-L1–positive tumors ▸ Nivolumab[f,g,18] • HER2-positive tumors (IHC 3+ or 2+) ▸ Fam-trastuzumab deruxtecan-nxki[19] • *RET* gene fusion-positive tumors ▸ Selpercatinib • *NTRK* gene fusion-positive tumors ▸ Larotrectinib ▸ Entrectinib • Repotrectinib[j,20]