Dana-Farber Cancer Institute

Research To Practice
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Discussion Question

What type of genetic testing (eg, germline versus somatic, panel versus one-off, homologous recombination deficiency) should be ordered for patients with newly diagnosed advanced ovarian cancer? Which patients should be offered PARP inhibitor maintenance therapy? How do you choose among olaparib, olaparib/bevacizumab and niraparib?

1. What type of genetic testing (eg, germline versus somatic, panel versus one-off, HRD) should be ordered for patients with newly diagnosed advanced ovarian cancer?

Newly diagnosed ovarian cancer:

- Germline sequencing via a panel test as soon as the diagnosis is made: we do rapid genetic testing, and I can get a germline test ordered and done within one day
  Allows patient and her family to start planning for cascade testing and then consider risk reducing measures
  Patient: if +, additional testing (i.e.MMG) and getting ready to add PARPi after completion of chemotherapy

- If adequate tissue on the initial biopsy: I will order NGS and Myriad HRD
  If not enough tissue from initial biopsy: I order using the cancer tissue from cytoreductive surgery

1. Who should be offered PARP inhibitor maintenance?

- BRCA+ (either germline or somatic): everyone – 2 yrs of olaparib,
  if on bev, then olaparib/bev if bev is planned to be continued as maintenance
- BRCA neg and HRD+: will discuss with patient, but lean towards recommending PARPi
- BRCA neg and HRP: will discuss with patient, tend to move to bev alone in this setting unless dramatic response to platinum chemotherapy or perhaps HRD score is just under ”+.”
- BRCAneg and HRD test not able to be done: will discuss risks and benefits with patient

ESMO 2022 and J Clin Oncol 41:609-617, 2022

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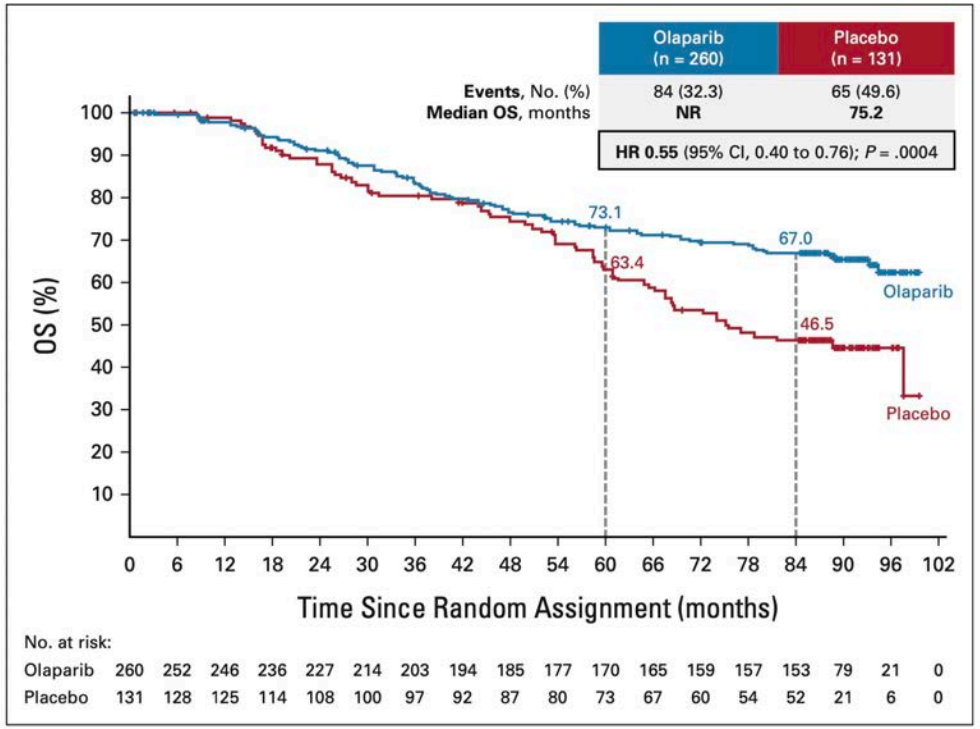

<u>For BRCAm ovarian cancer</u>

SOLO1: Standard of care to use olaparib maintenance for 2 yrs in BRCAm ovarian ca

PRIMA: tested 3 yrs of niraparib; OS data not available yet

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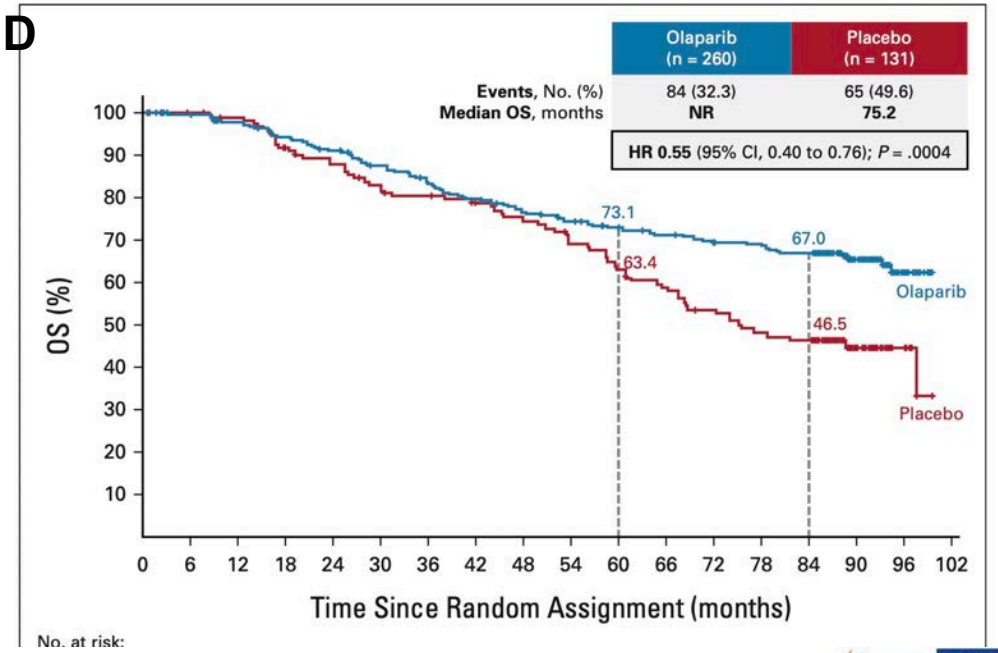

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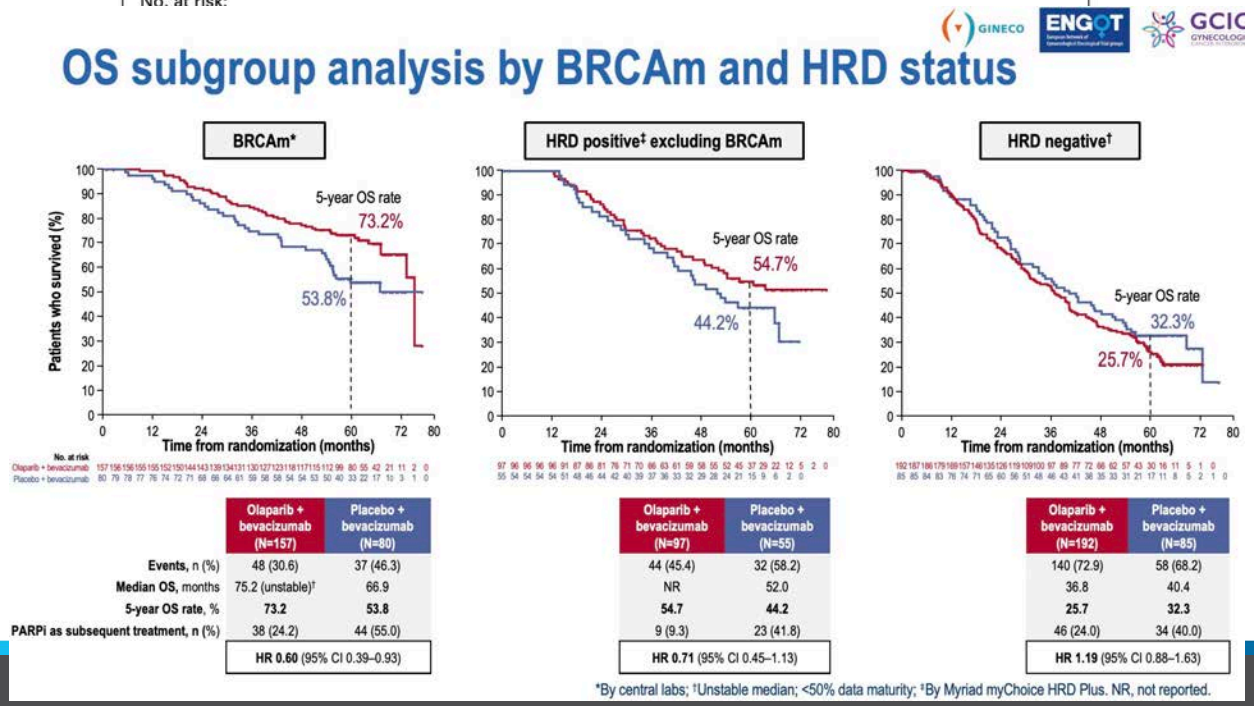


PAOLA-1:
OS improvement trend for olaparb/bev vs bev alone in BRCAm and HRD+/BRCAwt:
Recommend adding olaparib to bev in these situations

Poorer OS trend for olaparib/bev in HRP patients:
no FDA approval: do not use!

ESMO 2022 and J Clin Oncol 41:609-617, 2023

Discussion Question

What role, if any, do PARP inhibitors have in the management of relapsed ovarian cancer? What do you make of the recent withdrawal of various later-line indications for PARP inhibitors? Do you ever rechallenge with a PARP inhibitor in patients who have experienced disease progression on or after PARP inhibition?

2. What role, if any, do PARP inhibitors have for patients with relapsed ovarian cancer? What do you make of the recent withdrawal of various later-line PARP inhibitor indications?

Drug	upfront maintenance, single agent	upfront maintenance, with bev	platinum sensitive relapse	Treatment for relapsed BRCAm ov ca
olaparib	YES: BRCAm	YES: only for BRCAm and HRD+	YES: all patients	Rescinded in 2022
niraparib	YES: all comers	No FDA approval	YES: Just BRCAm BRCAwt and HRD rescinded in 2022	Rescinded in 2022
rucaparib	No FDA approval	No FDA approval	YES: just BRCAm BRCAwt and HRD rescinded in 2022	Rescinded in 2022

Dear health care provider letters: Olaparib 8/10/22, Rucaparib June 2022, Niraparib 9/22
ARIEL4, ESMO 2022; SOLO3, IGCS 2022, NOVA OS SGO 2022, ARIEL3 IGSC 2022

Question 2 continued: Do you ever rechallenge with a PARP inhibitor in patients who have experienced disease progression on or after prior PARP inhibition?

OReO study: Despite + PFS results in both BRCAm and BRCAwt patients, no OS data is available and there are now risks of inducing treatment resistance mechanisms and toxicity risks of AML/MDS

Would not rechallenge with a PARPi in patients whose cancer progressed on a PARPi.

Discussion Question

Do you anticipate that PARP inhibitor/immune checkpoint inhibitor combination strategies will eventually have a role in the treatment of advanced ovarian cancer? If so, how do you anticipate that these combinations will eventually be used?

3. Do you anticipate that PARP inhibitor/immune checkpoint inhibitor combination strategies will eventually have a role in advanced ovarian cancer? If so, how do you anticipate that these combinations will eventually be used?

Trial and NCT#	Phase	Drug combination	Patient group	ORR	median PFS	median OS
Platinum sensitive recurrence						
Mediola[1,2]	II	durvalumab/ olaparib	non-gBRCA	34.4% (95% CI 18.6-53.2)	5.5 months (95% CI 3.6-7.5)	26.1 months (95% 18.7-non-calculable)
		durva/olaparib/bev		87.1% (95% CI 70.2-96)	14.7 months (95% CI 10.0–18.1)	31.9 months (95% CI 22.1-non-calculable)
		durvalumab/ olaparib	gBRCA	DCR at 12 wks: 81.3% (90% CI 66.3, 91.5).	11.1 months (95% CI 8.2, 15.6)	NR
Javelin PARP Medley[3]	II	Talazoparib/ Avelumab	non-gBRCA	20% (5.7-43.7)	7.2 (4-9.1)	NR
			gBRCA	63.6% (30.8-89.1%)	NR (7.2-NE)	NR

1.Drew et al, ESMO 2020 2. Banerjee et al, ESMO 2022
3. Yap et al, JAMA Oncology 2023

NE= not estimable
NR = not reported

Platinum resistant recurrence

Study	Phase	Drugs tested	Patient group	ORR	Median PFS	Median OS
TOPACIO[1]	I/II	niraparib and pembrolizumab	62 pts, non-gBRCA needed a response lasting at least 6 months to first-line platinum-based therapy but were considered to have platinum-resistant disease; up to 4 prior lines of tx	18% (90% CI, 11%-29%)	3.4 months (95% CI, 2.1-5.1 months	NR
OPAL[2]	II	niraparib/ dostarlimab/ bevacizumab	non-gBRCA up to 2 prior lines of tx no prior PARPi or ICI	17.9% [90% CI, 8.7%-31.1% Prior Bev: 6%	7.6 months (95% CI, 4.2-10.6	Not reported
MOONSTONE[3]	II	niraparib and pembrolizumab	non-gBRCA up to 3 prior lines	12%	2.1 (95% 2.0–2.2)	not reported

1.Konstantinopoulos et al, JAMA Onc 2019, 2. Liu et al, SGO 2021, 3. Randall et al, ASCO 2022

Phase III upfront treatment studies testing PARPi/ICI and all awaiting read-outs

ATHENA	Newly diagnosed, advanced EOC, FTC, PPC	Rucaparib + nivolumab vs rucaparib vs nivolumab vs placebo 1LM	PFS	NCT03522246
KEYLYNK-001	1LM in *BRCA*^{wt} EOC	Pembrolizumab + CT ± olaparib vs CT	PFS, OS	NCT03740165
DUO-O	Newly diagnosed, advanced high-grade EOC, FTC, PPC	CT ± bev + durvalumab followed by durvalumab + bev + olaparib	PFS (non-t*BRCA*m)	NCT03737643
FIRST	Advanced nonmucinous EOC, FTC, PPC	CT ± bev + niraparib vs CT ± bev + dostarlimab + niraparib	PFS (all) PFS (PD-L1+)	NCT03602859

Discussion Question

Given its recent FDA approval, how are you incorporating mirvetuximab soravtansine into the treatment of advanced ovarian cancer? How do you monitor for and manage common adverse events, including ocular toxicity, with this drug?

4. Given its recent FDA approval, how are you incorporating mirvetuximab soravtansine into the treatment of your patients with advanced ovarian cancer?

SORAYA: 106 pts enrolled; Mirvetuximab tested as a single agent; dose is 6 mg/kg by adjusted ideal body weight

Mirvetuximab is an antibody-drug conjugate comprised of an FRα-binding antibody, cleavable linker, and a maytansinoid DM4 payload, a potent tubulin-targeting agent

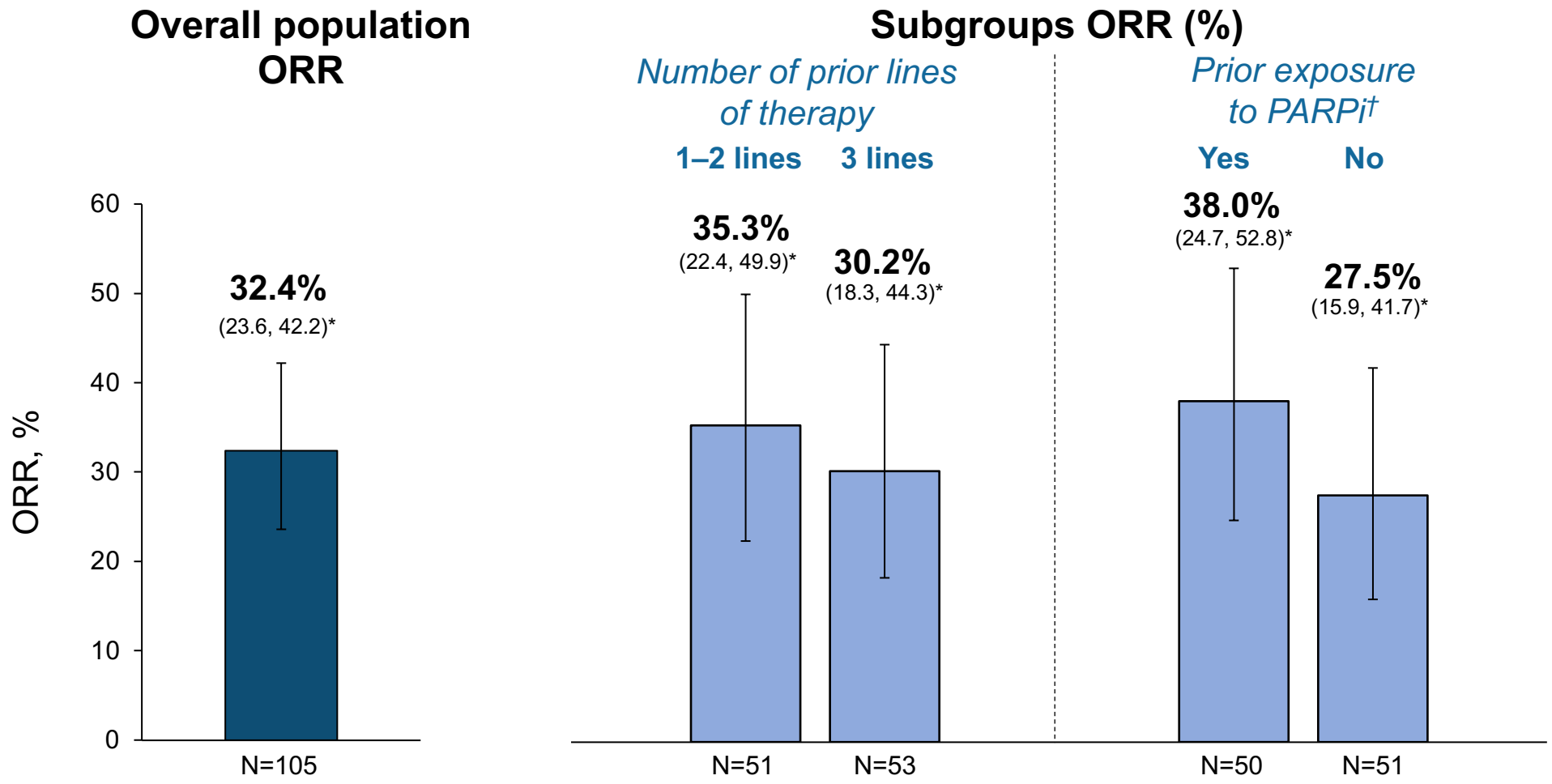
Eligibility: Platinum resistant ovarian cancer, high grade serous histology, all had received prior bevacizumab and had received up to 3 prior lines of chemotherapy: cancers had to be folate receptor alpha +, i.e. IHC ≥75% 2-3+ FR alpha + (testing available thru Caris, LabCorp, and Neogenomics)

ORR confirmed response rate: 32.4%
Median Duration of response: 6.9 months

Subset analyses: 1-2 or 3 prior lines of treatment and prior PARPi use
Neither impacted the ORR or DOR

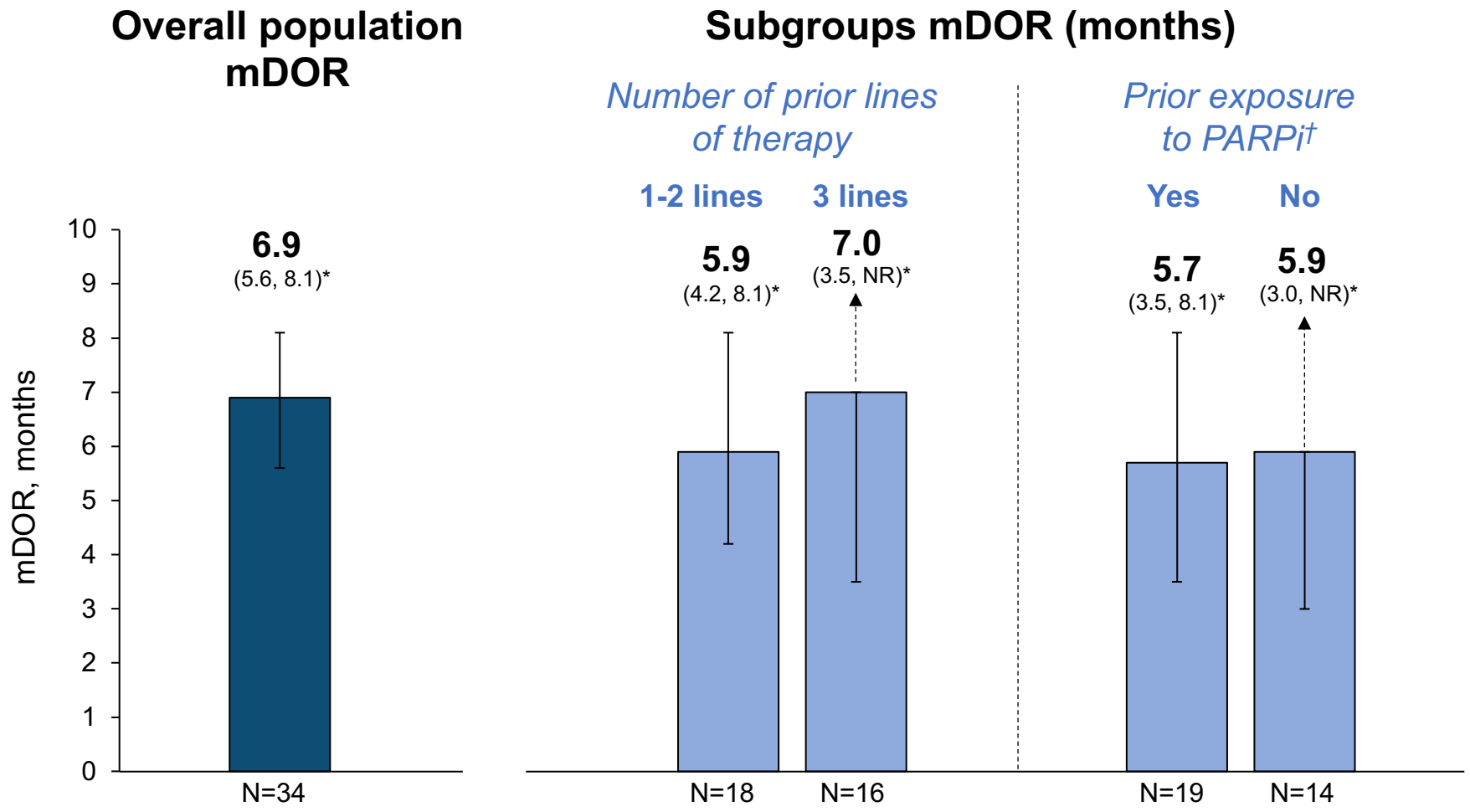
Matulonis et al, JCO 2023

Investigator-Assessed Objective Response Rate by Prior Therapy



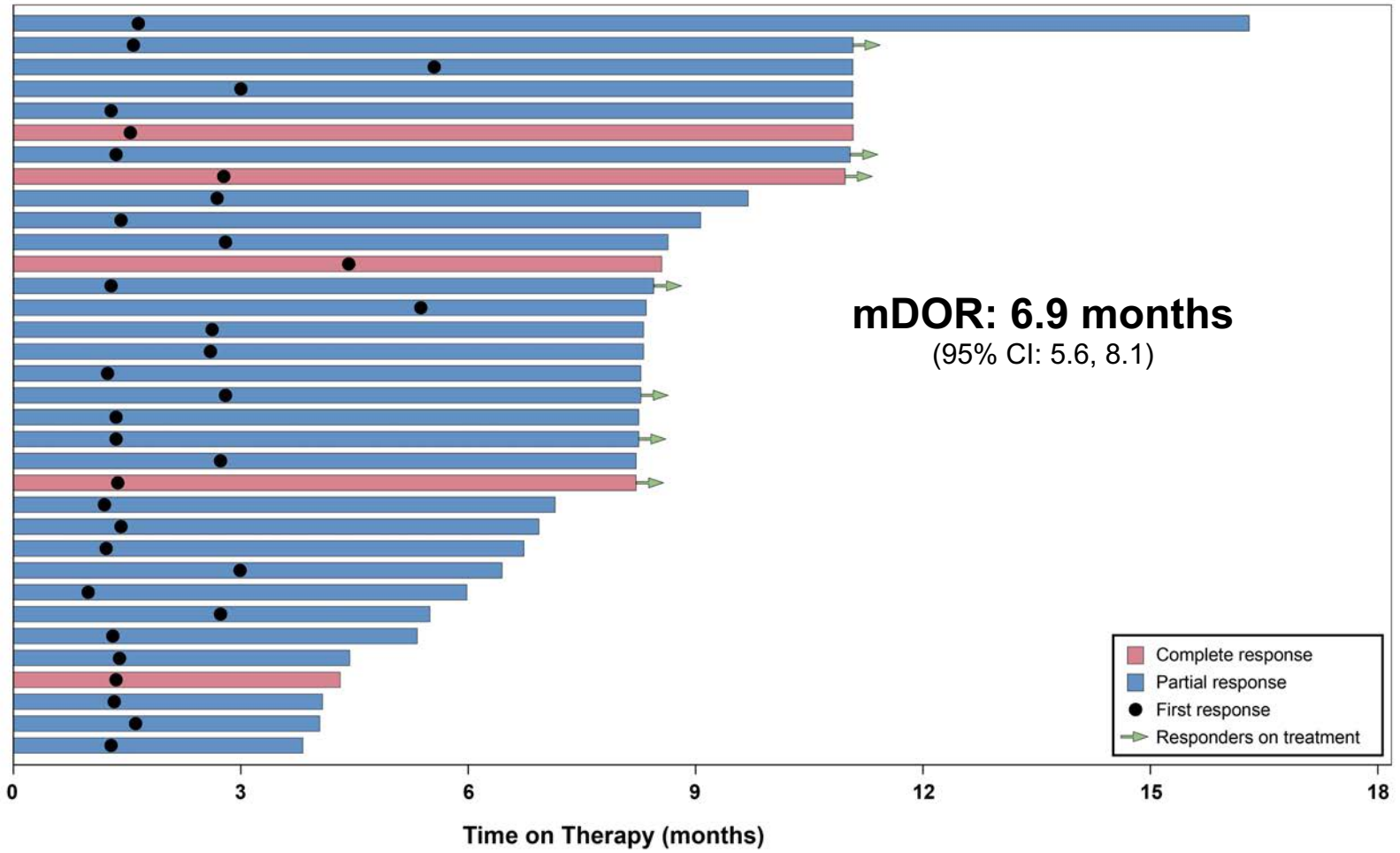
Matulonis et al, SGO 2022, ASCO 2022, IGCS 2022

Investigator-Assessed Duration of Response by Prior Therapy



Matulonis et al, SGO 2022, ASCO 2022, IGCS 2022

Investigator-Assessed Duration of Response for Patients With Complete and Partial Responses: Most responses occurred at first radiographic assessment



Data cutoff: March 3, 2022.
CI, confidence interval; mDOR, median duration of response.

Matulonis et al, SGO 2022, ASCO 2022, IGCS 2022, JCO 2023

Chalk Talk -- Ursula Matulonis, MD

How do you monitor for and manage common adverse events, including ocular toxicity, with this drug?

Treatment-Related Adverse Events

- Adverse events were primarily low-grade, reversible ocular and gastrointestinal events

  No alopecia, 13% grade 1 or 2 neuropathy
  13% risk of neutropenia, grade 1 or 2; 2% gr 3

- Ocular toxicities occur because of off-target effects on the cornea, with primary involvement of the corneal epithelium which leads to blurred vision and can be associated with microcystic keratopathy
- Eye exam, including slit lamp exam and visual acuity, needs to be done prior to receiving mirvetuximab and then every 2 cycles by either optometrist or an ophthalmologist, for the first 8 cycles, then as clinically indicated.
- ~9% risk of infusion related reaction

Premedication	**Route of Administration**	**Examples (or equivalent)**	**Administration Time Prior to ELAHERE Infusion**
Corticosteroid	intravenous	dexamethasone 10 mg	At least 30 minutes prior
Antihistamine	oral or intravenous	diphenhydramine 25 mg to 50 mg	
Antipyretic	oral or intravenous	acetaminophen 325 mg to 650 mg	
Antiemetic	oral or intravenous	5-HT_3 serotonin receptor antagonist or appropriate alternatives	Before each dose and thereafter as needed

Matulonis et al, SGO 2022, ASCO 2022, IGCS 2022, JCO 2023, Mirv PI

Chalk Talk -- Ursula Matulonis, MD

PRINCIPLES OF SYSTEMIC THERAPY

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

Recurrence Therapy for Platinum-Resistant Disease (alphabetical order)

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Cytotoxic Therapy Cyclophosphamide (oral)/ bevacizumab[i,35] Docetaxel[36] Etoposide, oral[37] Gemcitabine[38,39] Liposomal doxorubicin[38,39] Liposomal doxorubicin/ bevacizumab[i,q,40] Paclitaxel (weekly)[f,41] Paclitaxel (weekly)/ bevacizumab[f,i,q,40] Topotecan[42,43] Topotecan/bevacizumab[i,q,40] Targeted Therapy (single agents) Bevacizumab[i,q,17,18] Mirvetuximab soravtansine-gynx (for *FRα*-expressing tumors)[x,44]	Cytotoxic Therapy[s] Capecitabine Carboplatin[*] Carboplatin/docetaxel[*] Carboplatin/paclitaxel (weekly)[f,*] Carboplatin/gemcitabine[10] ± bevacizumab[i,q,r,11,*] Carboplatin/liposomal doxorubicin[12] ± bevacizumab[i,q,13,*] Carboplatin/paclitaxel[f,14] ± bevacizumab[i,q,r,15,*] Cyclophosphamide Doxorubicin Gemcitabine/cisplatin[16,*] Ifosfamide Irinotecan Ixabepilone/bevacizumab (category 2B)[i,y,46] Melphalan Oxaliplatin Paclitaxel Paclitaxel, albumin bound Pemetrexed Sorafenib/topotecan[45] Vinorelbine Targeted Therapy (single agents) Niraparib (category 3)[u,23] Olaparib (category 3)[v,24] Pazopanib (category 2B)[25] Rucaparib (category 3)[w,26] Hormone Therapy Aromatase inhibitors (anastrozole, exemestane, letrozole) Leuprolide acetate Megestrol acetate Tamoxifen	Carboplatin/paclitaxel (for age >70)[f,t,*] Carboplatin/paclitaxel, albumin bound (for confirmed taxane hypersensitivity)[*] Immunotherapy Dostarlimab-gxly (for dMMR/MSI-H recurrent or advanced tumors)[x,32] Pembrolizumab (for patients with MSI-H or dMMR solid tumors, or TMB-H tumors ≥10 mutations/ megabase)[x,33] Hormone Therapy Fulvestrant (for low-grade serous carcinoma) Targeted Therapy Dabrafenib + trametinib (for *BRAF* V600E-positive tumors)[x,28] Entrectinib or larotrectinib (for *NTRK* gene fusion positive tumors)[x] Mirvetuximab soravtansine-gynx/bevacizumab (for *FRα*-expressing tumors) (category 2B)[i,x,47, 48] Selpercatinib (for *RET* gene fusion-positive tumors)[x,29] For low-grade serous carcinoma: • Trametinib[30] • Binimetinib (category 2B)[31,32]

* Do not use in platinum-refractory disease.

NCCN Ovarian cancer guidelines 1.23

Mirvetuximab combined with bevacizumab

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journal homepage: www.elsevier.com/locate/ygyno

Safety and efficacy of mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients with platinum-resistant ovarian cancer

Lucy Gilbert [a], Ana Oaknin [b], Ursula A. Matulonis [c], Gina M. Mantia-Smaldone [d], Peter C. Lim [e], Cesar M. Castro [f], Diane Provencher [g], Sanaz Memarzadeh [h], Michael Method [i], Jiuzhou Wang [i], Kathleen N. Moore [j,k], David M. O'Malley [l,*]

Table 1
Patient demographics and baseline characteristics.

Characteristic	$N = 94$
Age, years	
Median (range)	62 (39–81)
Primary diagnosis, n (%)	
Epithelial ovarian cancer	72 (77)
Fallopian tube cancer	17 (18)
Primary peritoneal cancer	5 (5)
ECOG PS, n (%)	
0	60 (64)
1	34 (36)
No. of prior systemic therapies, n (%)	
1–2	45 (48)
≥3[a]	49 (52)
FRα expression,[b] n (%)	
≥75%	44 (47)
50–74%	39 (42)
25–49%	11 (12)
Prior exposure, n (%)	
Taxane	91 (97)
Bevacizumab	55 (59)
PARP inhibitor	25 (27)

ECOG PS, Eastern Cooperative Oncology Group performance status; FRα, folate receptor alpha; PARP, poly (ADP-ribose) polymerase; PS2+, positive staining 2 +.

[a] One patient had 4 prior lines of therapy.

[b] ≥75%, 50–74%, 25–49% of tumor cells with FRα membrane staining of ≥2+ intensity using PS2+ scoring methodology.

Chalk Talk -- Ursula Matulonis, MD

Combined Mirvetuximab and Bevacizumab for platinum resistant ovarian cancer with varying levels of Folate receptor alpha

Summary of efficacy measures.

Endpoint	N = 94
Confirmed objective response rate, n (%)	41 (44)
95% CI	(33, 54)
Best overall response, n (%)	
Complete response	5 (5)
Partial response	36 (38)
Stable disease	44 (47)
Progressive disease	8 (9)
Not evaluable	1 (1)
Median duration of response, (months)	9.7
95% CI	(6.9, 14.1)
Median progression-free survival, (months)	8.2
95% CI	(6.8, 10.0)

44% confirmed ORR , median DOR 9.7 months, and mPFS 8.2 months

Efficacy was also seen at lower levels of FR alpha expression

Results have led to a 2B recommendation by the National Comprehensive Cancer Network (NCCN) ovarian cancer committee Jan 2023

Table 3
Summary of efficacy in patients by subgroups.

Endpoint	FRα ≥ 75% (*n = 44*)	FRα 50–74% (*n = 39*)	FRα 25–49% (*n = 11*)	BEV-naïve (*n = 39*)	BEV-pretreated (*n = 55*)
Confirmed objective response rate, n (%)	21 (48)	16 (41)	4 (36)	22 (56)	19 (35)
95% CI	(33, 63)	(26, 58)	(11, 69)	(40, 72)	(22, 49)
Median duration of response, (months)	9.7	9.7	18.5	10.4	9.7
95% CI	(6.0, 12.0)	(3.0, NR)	(NE)	(6.9, 14.5)	(4.2, NR)
Median progression-free survival, (months)	9.7	6.9	8.6	10.6	6.8
95% CI	(6.8, 11.0)	(5.1, 9.9)	(1.3, NR)	(8.2, 14.5)	(5.3, 8.2)

BEV, bevacizumab; FRα, folate receptor alpha; NE, not evaluable; NR, not reached.

O'Malley et al, Gyn Onc 2023

Discussion Question

Based on available data, do you anticipate that upifitamab rilsodotin will eventually receive regulatory approval for the treatment of advanced ovarian cancer? If so, how do you envision sequencing this drug relative to currently available therapies?

5. Based on available data, do you anticipate that upifitamab rilsodotin will eventually receive regulatory approval for the treatment of advanced ovarian cancer?

Depends on the outcomes of ongoing trials

Upifitamab rilsodotin is an ADC that targets NaPi2b and is being tested in relapsed high grade serous ovarian cancer

Payload of UpRi is auristatin F-HPA (proprietary dolalock payload)
High levels expression of NaPi2b probably have higher ORR; ongoing studies will help solve this

SGO 2022 presentation showed data from Phase I expansion cohorts: 36 versus 43 mg/m2 dosing
43 mg/m2 had higher toxicities: ~15% rate of pneumonitis
36 mg/m2: ~7% rate of grade I or II pneumonitis

Efficacy data on 25 pts (36 mg/m2): confirmed ORR 44% NaPi2b high and 36% RR in all comers
DOR ~5 months

Richardson et al, SGO 2022

Open UpRi trials

UPLIFT (ENGOT-ov67/GOG-3048)
NCT 03319628
UpRi 36 mg/m2 IV every 4 weeks
Platinum resistant, high grade serous ovarian cancer, up to 4 lines of prior treatment
enrollment: 100 pts NaPi2b-high; 80 pts with lower levels of NaPi2b
Primary endpoint: confirmed ORR, secondary endpoints DOR and safety

UPNEXT (GOG-3049/ENGOT-OV71-NSGO-CTU)
NCT05329545
Randomized phase III study of UpRi versus placebo
Platinum sensitive recurrence, NaPi2b expression high, HGSC, requires CR, PR or SD as best response following platinum

UPGRADE
NCT04907968
Phase I study that combines different agents with UpRi (carboplatin)

If multiple ADCs are approved, how do you envision sequencing this drug relative to currently available therapies?

Will test all cancers for various markers at initial diagnosis:
i.e. Folate receptor alpha, NaPi2b (if approved), HER2 (if approved)

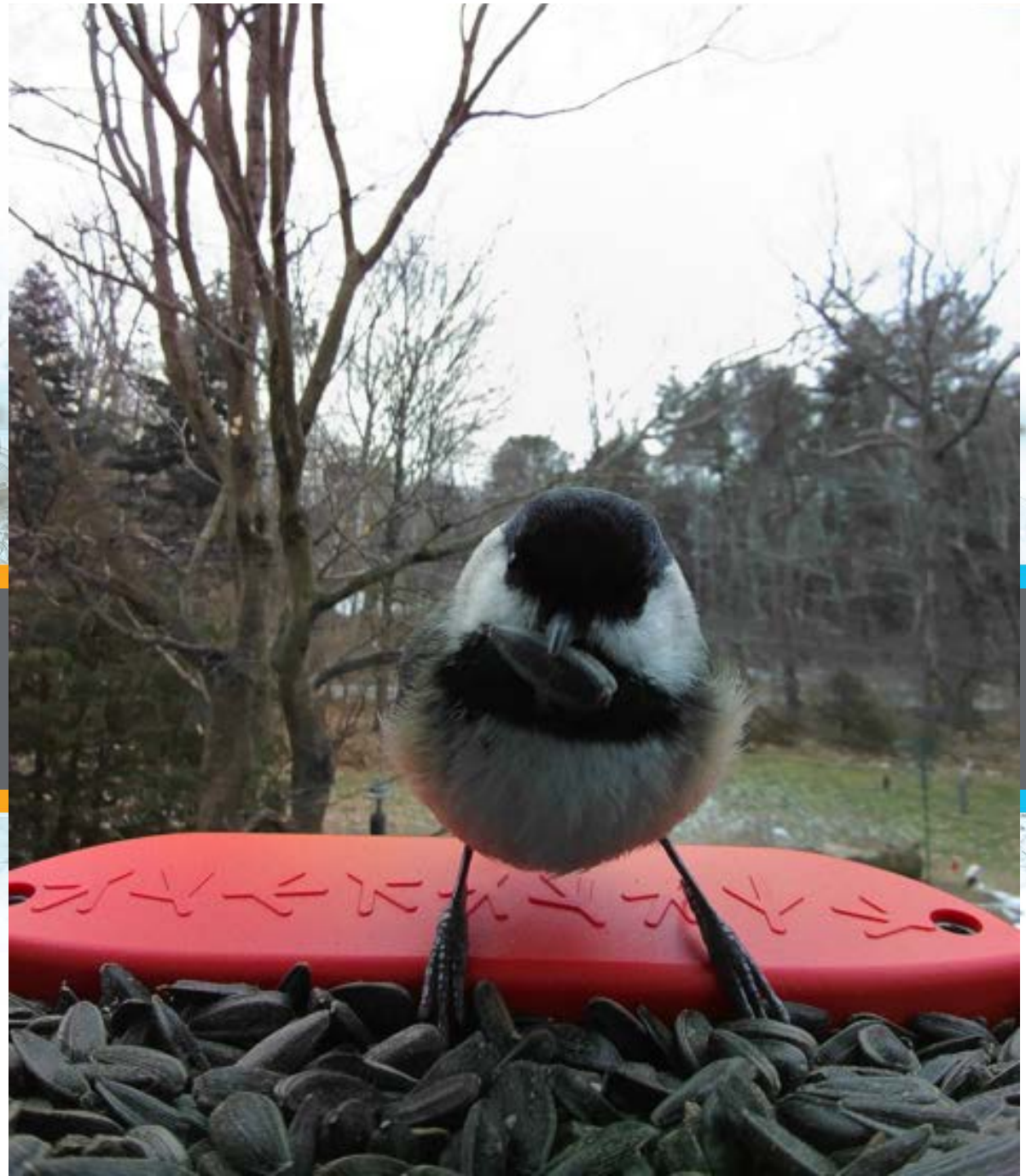
Need to determine if marker expression changes from new dx to recurrent dx (FR alpha does not change, NaPi2b appears not to)

Determine biomarker expression levels and match appropriate drug(s) to the patient

Avoid overlapping toxicities that the patient already has, exhibited in the past, and toxicities you want to avoid: i.e. neuropathy, myelosuppression, pneumonitis

Trials will need to be done to understand ADC resistance mechanisms and to test sequencing. Will using an anti-microtubule agent (MMAF, MMAE, DM1, DM4) impact use of a future anti-microtubule drug? the same with a Topoisomerase inhibitor agent (DXd, SN-38)?

Thank you!!!



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