Immunotherapy in Ovarian Cancer

Is there a role for it? For whom?

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Epidemiology and Standard of Care

Ovarian cancer is the most fatal of all gynecologic cancers

- Each year, impacts almost 20K in the US and kills >12K
- Early detection remains the holy grail in gynecologic oncology

Standard of care:

- Surgery to complete resection (R0)
- If concerns around surgery, neoadjuvant therapy is appropriate
- Total of 6 cycles of chemotherapy (carboplatin/paclitaxel) is recommended

Is there a role for immunotherapy?

TRIAL (checkpoint inhibitor)	TREATMENTS	OVERALL RESPONSE RATE (%)	PROGRESSION-FREE SURVIVAL (mos)	REFERENCE
JAVELIN-100 (Avelumab)	C/T+Av vs C/T+Av→Av vs C/T alone	36 30 30	18.1 (HR 1.14) 16.8 (HR 1.43) **NE**	52
DUO-O (Durvalumab)	C/T/B → B+D+Ol vs C/T/B → B+D vs C/T/B → B	NA	24.2 20.6 19.3	84
IMagyn50 (Atezolizumab)	C/T/B→B+At vs C/T/B→B	93 89	19.5 (HR 0.92) 18.4	55

Clear cell carcinoma

- Extra-renal clear cell cancer (CCC) are rare tumors that can arise from any organ
  - 10% ovarian | 3-4% cervix | Up to 6% uterine
- Compared to serous carcinomas, CCC is associated with:
  - Lower Overall Response Rate
  - Worse survival

Gadducci A, et al. Gynecol Oncol 2021; 163:741; DeLair DF, et al. J Pathol 2017; 243:230; Olawaiye AB and Boruta DM, Gynecol Oncol 2009; 113:277.

Nivolumab/Ipilimumab for Recurrent Clear Cell Cancer of the ovary

NRG GY003 (n=100)

- **Nivolumab monotherapy: ORR 12.2%**
  - 3 CR
- **N + Ipilimumab (4 doses) → N alone: ORR 31.4%**
  - 3 CR
- *5-fold higher ORR in clear cell vs. other histologies (n=12)*

SWOG S1609 (n=19 with ovarian CCC):

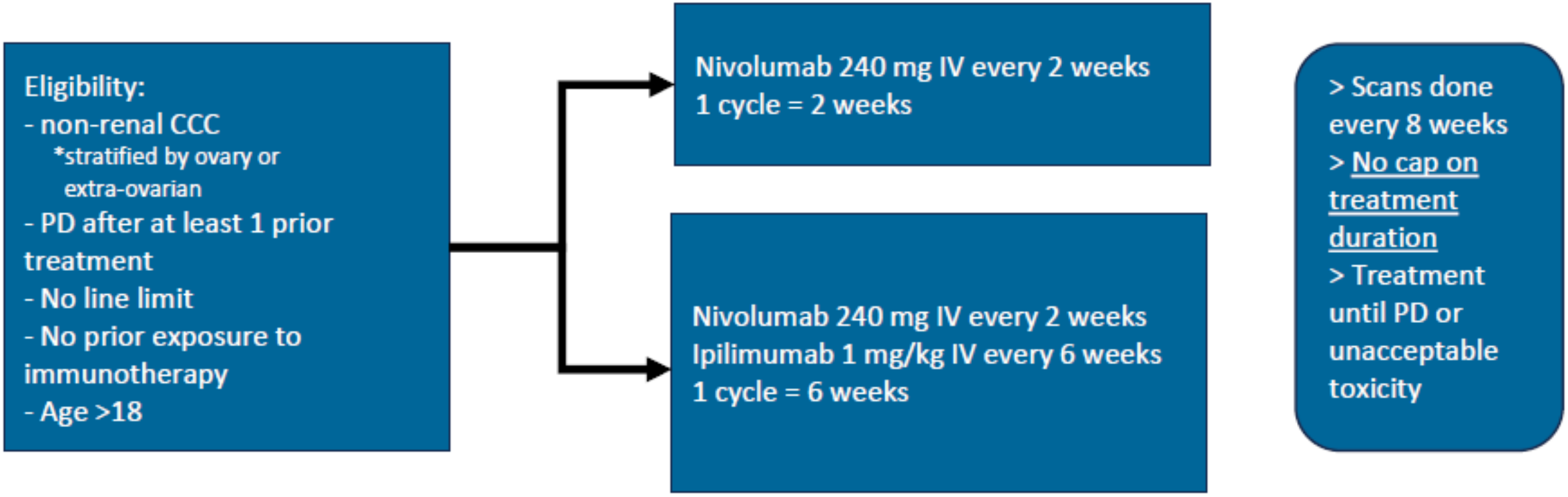
- **Nivolumab plus Ipilimumab up to 2y → N alone: ORR 21.1%**
  - 3 CR
- No responses in volunteers with endometrial CCC (n=8) or cervical CCC (n=5)

Zamarin D, et al. J Clin Oncol 2020; 38:1814; Chae YW, et al. Cancer Res 2023; 83:8_suppl; Abstr CT162

ASCO 2024: Final results of BrUOG 354:

A randomized phase II trial of nivolumab alone or in combination with ipilimumab for people with ovarian and other extra-renal clear cell carcinomas

BrUOG 354



Data cut-off: December 31, 2023
Median Follow-up: 11.3 months (range, 1.6 to 46.4 months)

Objectives and Statistics

- Randomized, non-comparative, phase 2
  - Primary Objective: Overall Response Rate (ORR)
  - Secondary Objectives: PFS and OS, Adverse Events
  - Exploratory: Molecular characteristics for response or non-response
- Simon's two-stage minimax design, true ORR = 30%, poor ORR = 10%
  - 86% power, alpha = 0.03

Enrollment during COVID-19

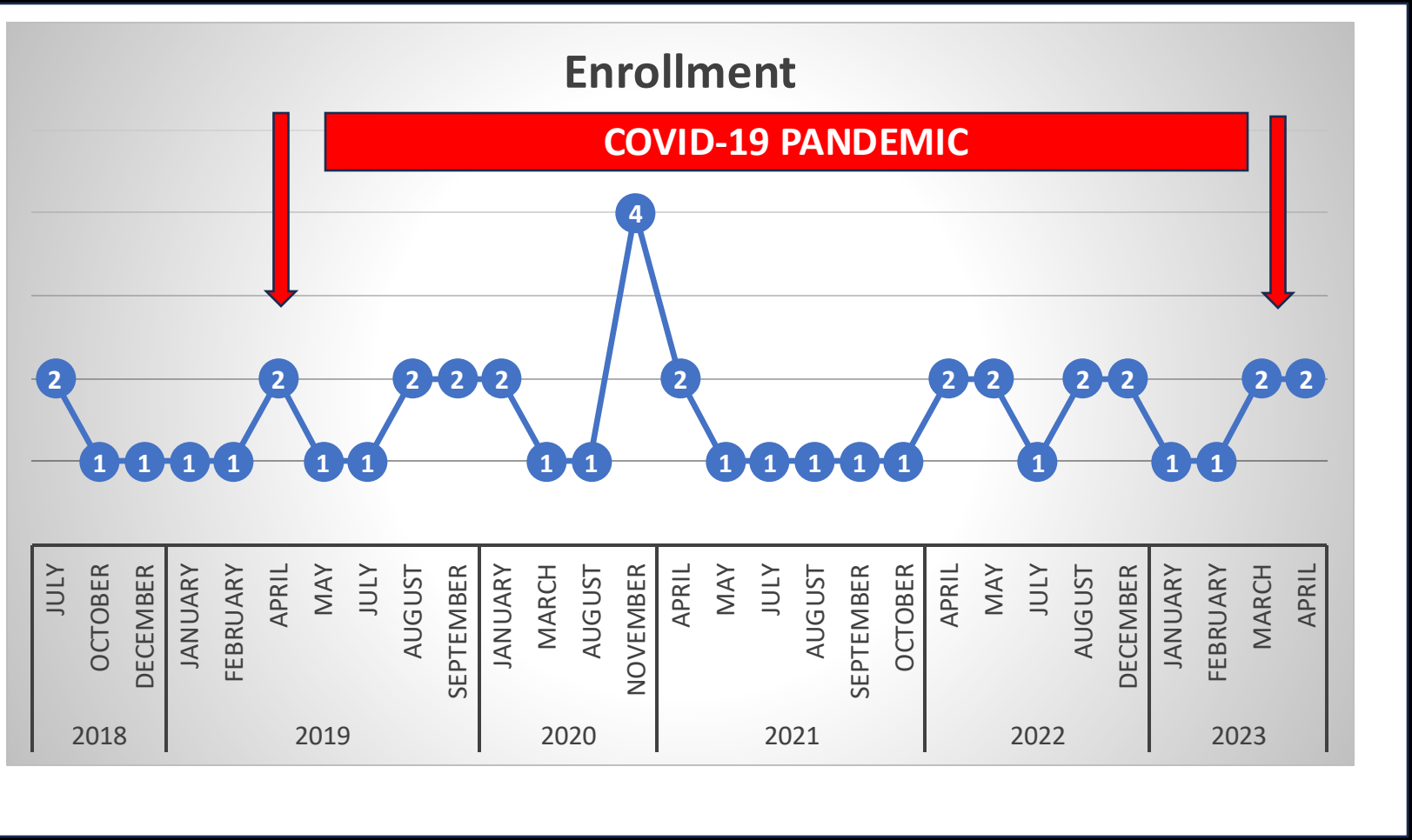
First patient in: June 2018
Last patient in: April 2023

No pause during lockdown
46 enrolled; 2 withdrew informed consent

44 treated on trial

During COVID-19, **decentralization** was key

- Dizon, et al. JCO Oncol Pract 2023; 19(suppl 11; abstr 100)



Demographics, n=44

	Nivolumab (n=14)	Nivolumab/Ipilimumab (n=30)	Total (n=44)	Incidence (SEER, 2008)
Age (median, range)	54.5 (18-74)	58 (22-75)	57 (18-75)	
Diagnosis (n,%)				
Ovarian	11 (78.6)	25 (83.3)	36 (81.2)	
Uterine	3 (21.4)	3 (10)	6 (13.6)	
Other	0	2 (6.7)	2 (4.5)	
Race (n, %)				
White	12 (85.7)	21 (70)	33 (75)	**82.5%**
Black	1 (7.1)	3 (10)	4 (9)	**3.6%**
Asian	1 (7.1)	1 (3.3)	2 (4.5)	**11.7%**
Not Answered	0	5 (16.6)	5 (11.4)	
Ethnicity (n,%)				
Hispanic	1 (7.1)	4 (13.3)	5 (11.4)	
Not Hispanic	12 (85.7)	22 (73.3)	34 (77.3)	
Not Answered	1 (7.1)	4 (13.3)	5 (11.4)	
Prior lines (median, range)	1 (1-7)	1.5 (1-4)		

Response Data

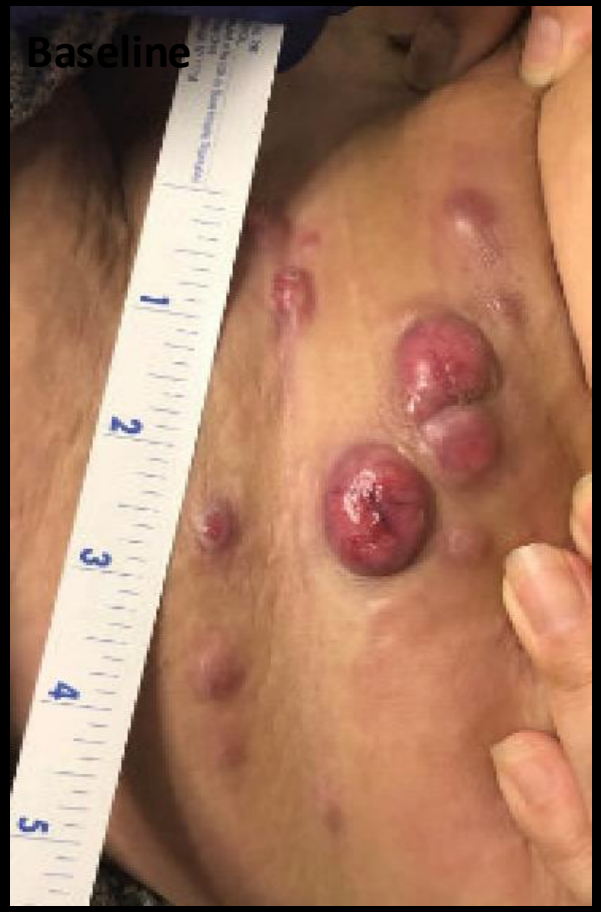
	Nivolumab n=14	Nivolumab/Ipilimumab n=30
Complete Response (n, %)	**0**	**5 (16.7)**
Partial Response (n,%)	**2 (14.3)**	**5 (16.7)**
Complete + Partial Response	**2 (14.3)**	**10 (33.3)**
Stable Disease	5 (35.7)	10 (33.3)
Progression	7 (50)	10 (33.3)
Duration of Response (months, median ± SD)	30.6 ±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

Nivo/Ipi Response in dermal metastases

50 year-old woman

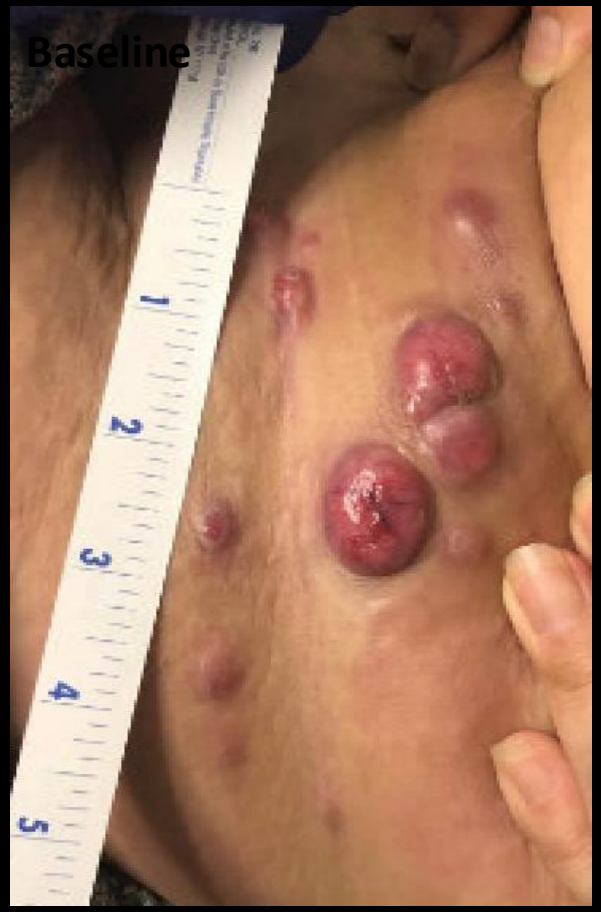
- Diagnosed with CCC of the abdominal wall 3y prior
  - Surgery → Adjuvant carboplatin + paclitaxel
  - PD 12 months later → inguinal/pelvic adenopathy
    - chemoradiation
  - PD 11 months later
    - Carboplatin + Liposomal doxorubicin
  - PD after 2 months
- On exam: dermal metastases

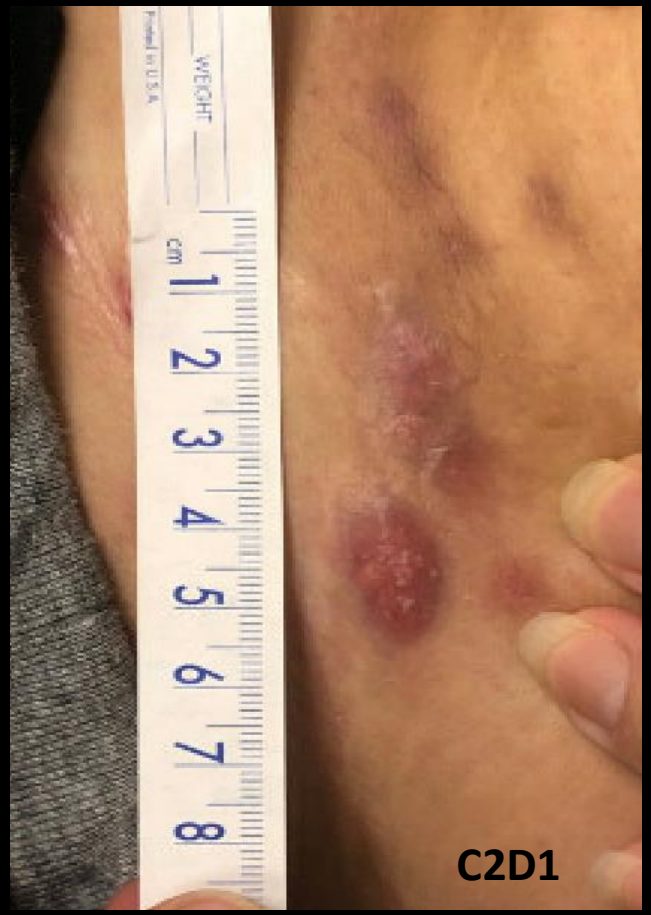
Response in dermal metastases



Study volunteer provided authorization to use images.

Response in dermal metastases





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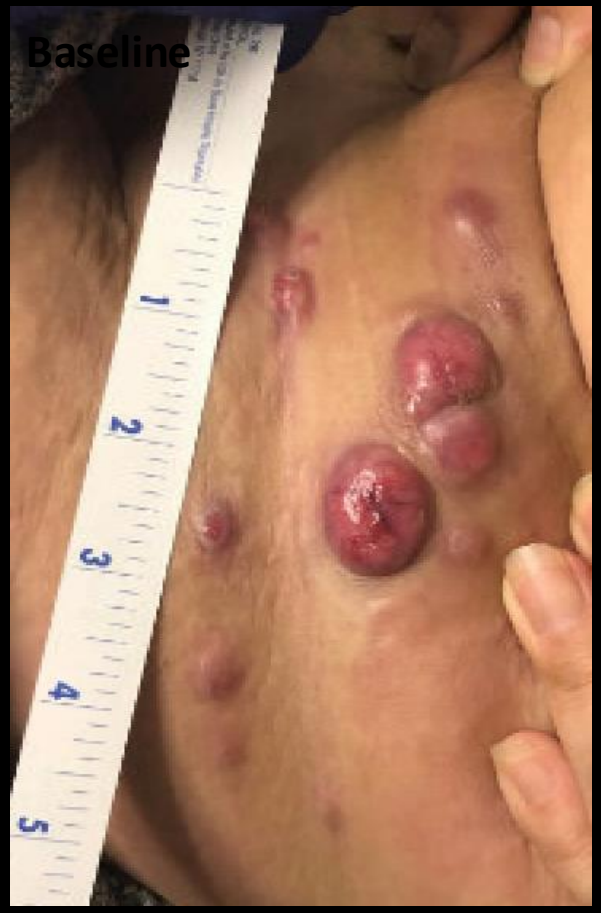
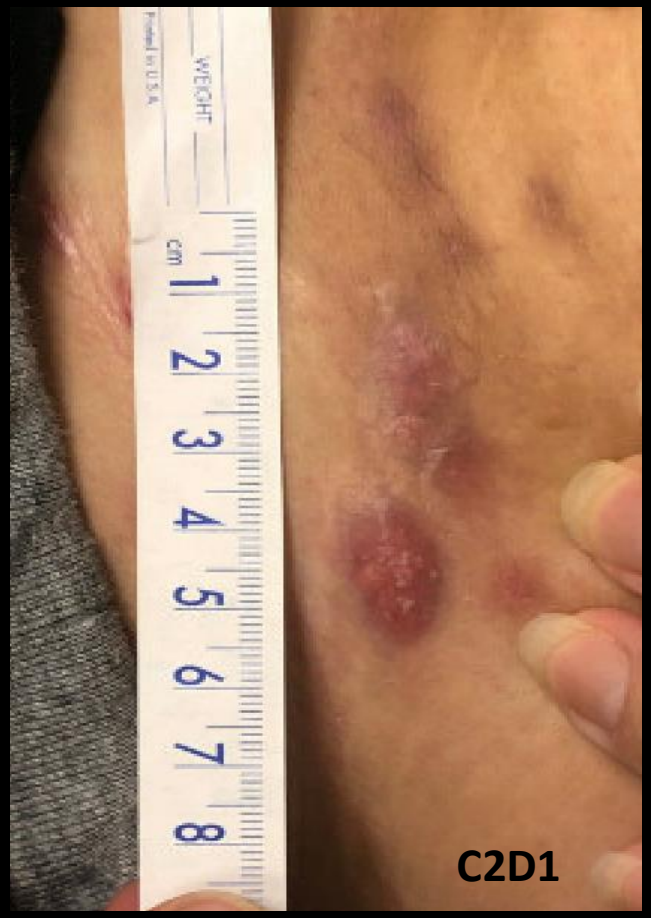
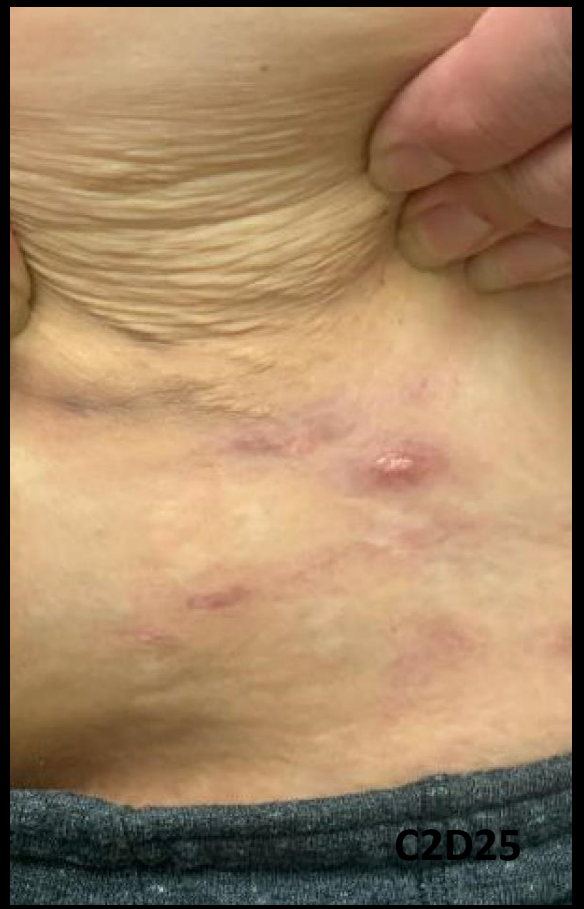
Response in dermal metastases







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Clinical course

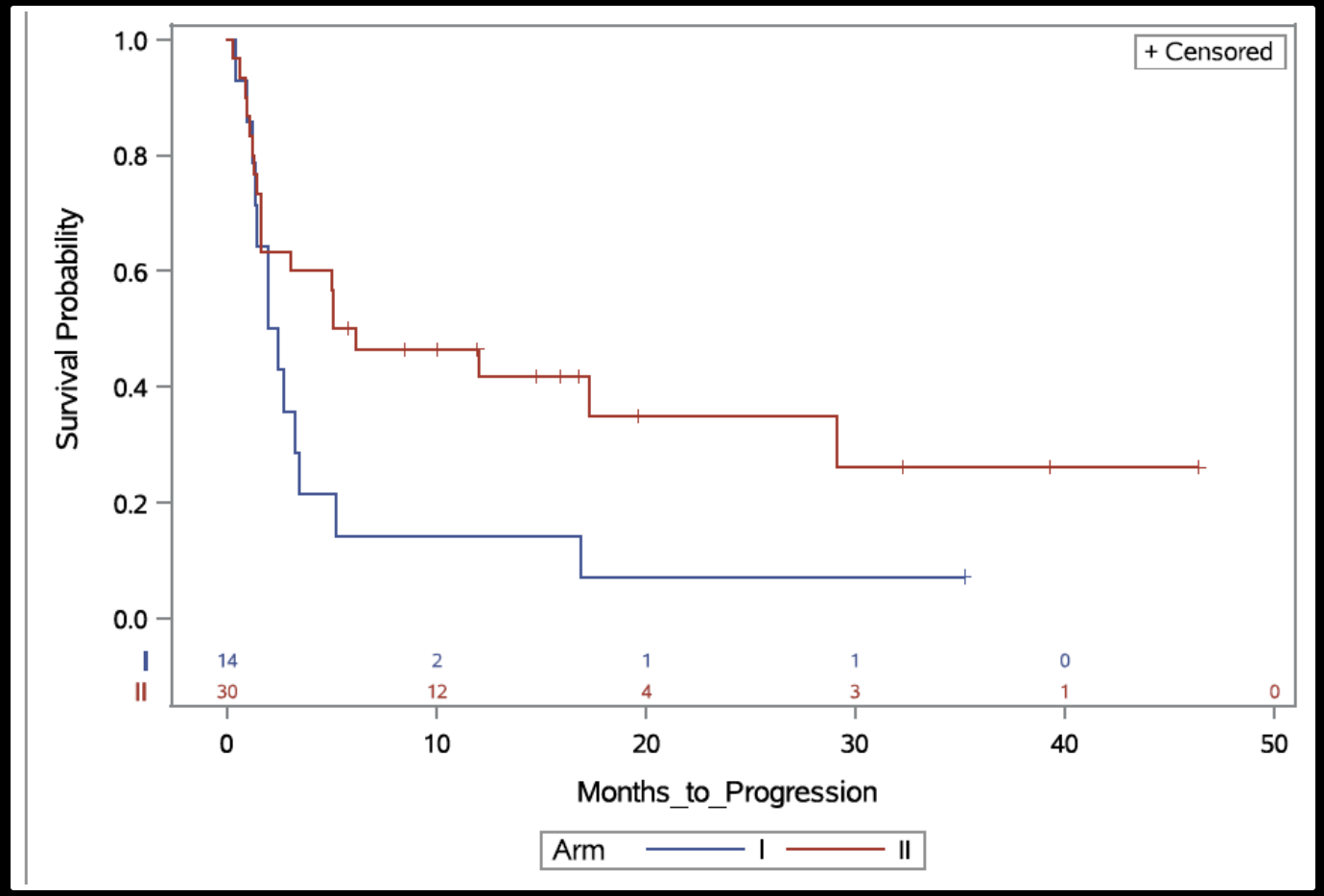
- Achieved partial response
- Time on study = 1 year → PD in lungs
- Treated with cisplatin/gemcitabine → CR after 4 cycles
- **No evidence of disease at 1-year post-chemotherapy**

Treatment-Related Toxicity

Nivolumab (n=14)				Nivolumab-Ipilimumab (n=30)			
Toxicity	Grade	N	%	Toxicity	Grade	N	%
Hypothyroidism	**All**	**5**	**35.7**	Fatigue	All	9	22.5
Maculopapular rash	All	2	14.2	Pruritis	All	8	26.7
Thromboembolism	3	1	7.1	**Hypothyroidism**	**All**	**6**	**20.0**
Diarrhea	3	1	7.1	Elevated Amylase Elevated Lipase	3/4 3/4	2/1 2/3	5/2.5 5/7.5
				Elevated creatinine Decreased magnesium Hypocalcemia	3 3 4	**1***	3.3

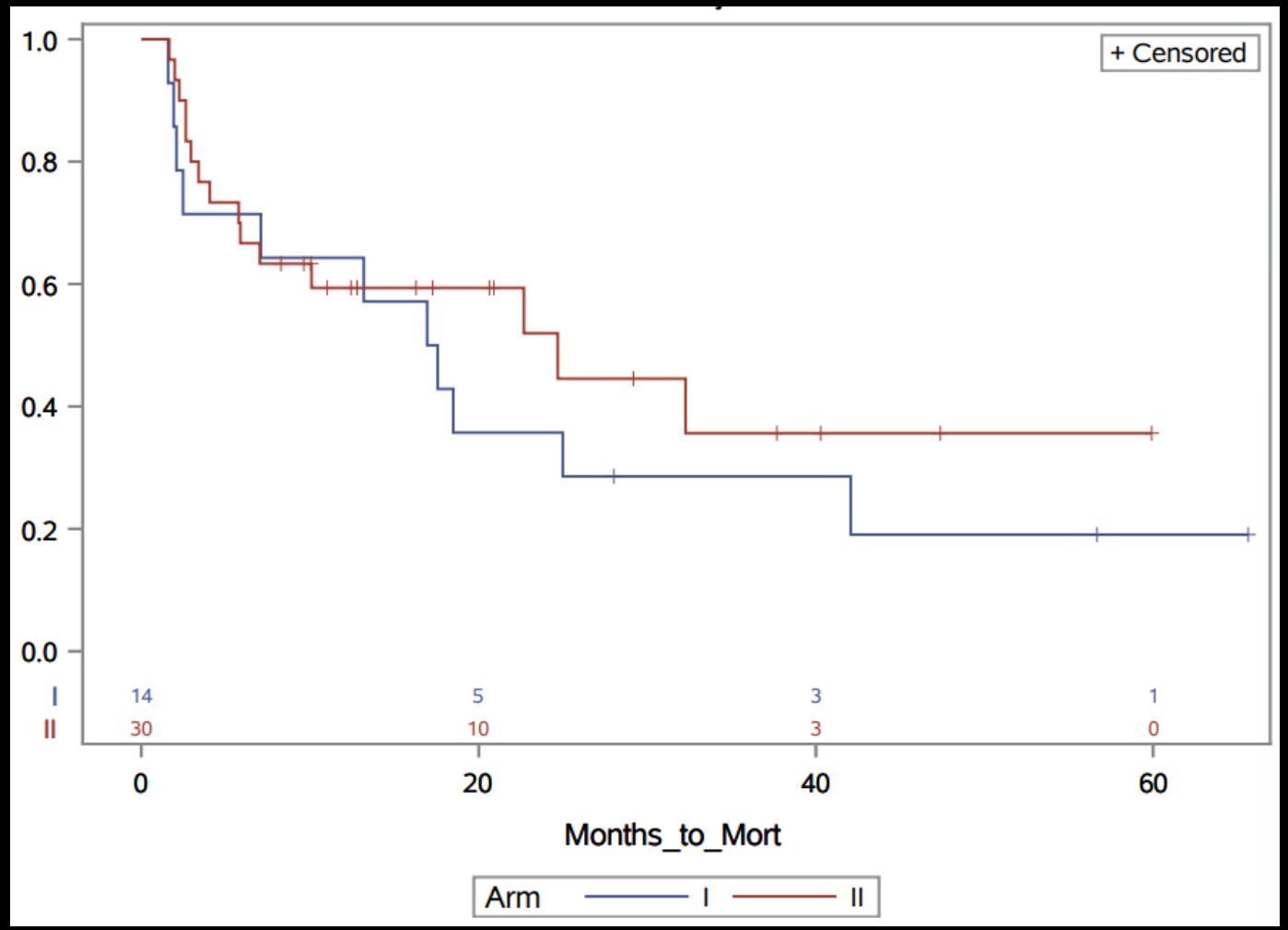
* No clinical symptoms but volunteer taken off-study due to persistent G3 creatinine
  - Biopsy of kidney → **interstitial nephritis consistent with drug-induced reaction**
  - Treated with steroids
  - CT 6 weeks **after** end of treatment → **Partial response**

Progression-Free Survival



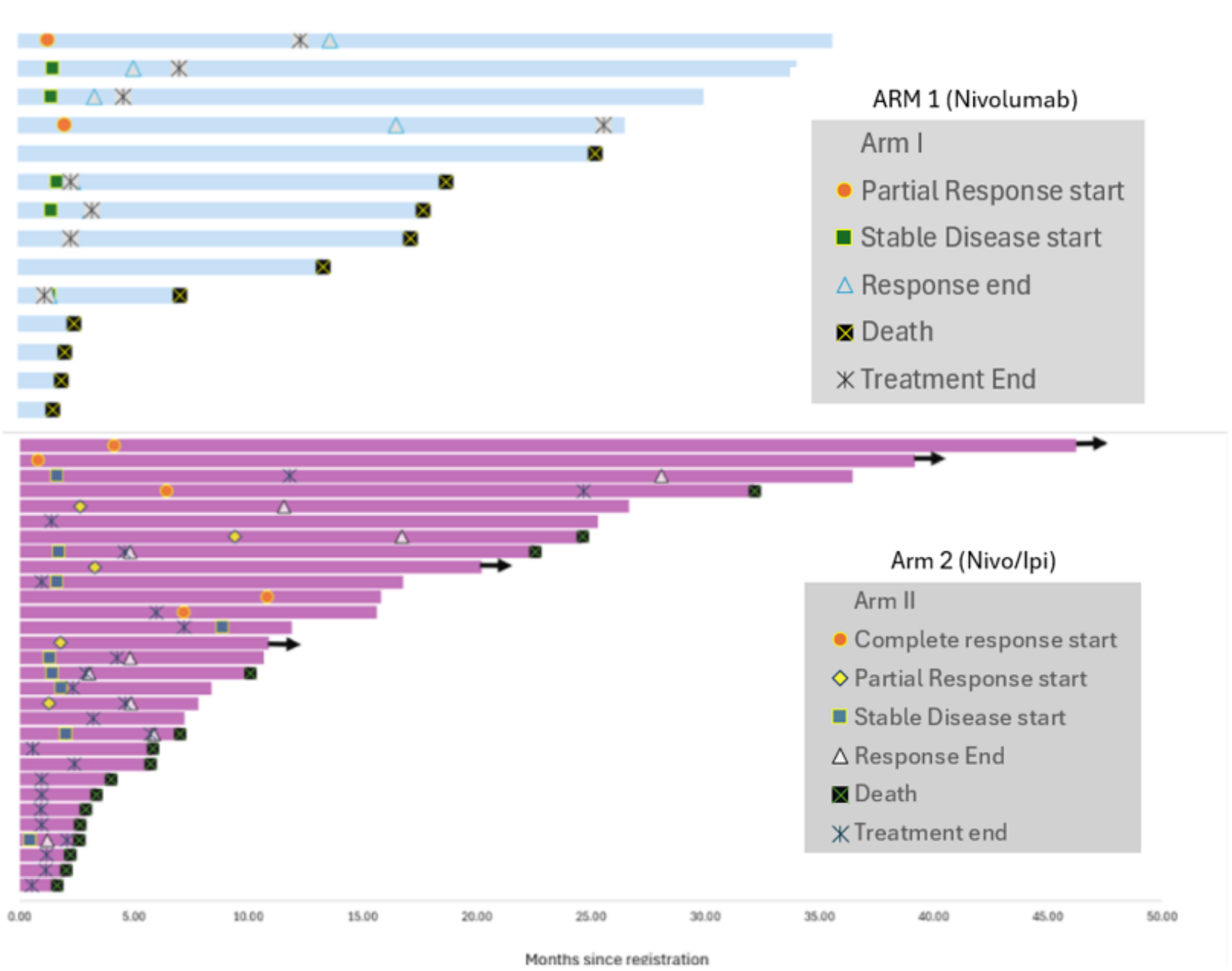
Arm	Median (months)	95%CI
I (Nivo)	2.2	1.2-3.4
II (Nivo/Ipi)	5.6	1.6-29.1

Overall Survival



Arm	Median (months)	95%CI
I (Nivo)	17.3	2.1-42.7
II (Nivo/Ipi)	24.7	5.9-NR

Timecourse on BrUOG 354



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.

Decentralized Trials Work

Study volunteers

Women and Infants Hospital of RI:
Katina Robison, Cara Mathews, and Paul DiSilvestro

Univ Illinois at Chicago
Shannon MacLaughlan

Brown University Oncology Group
Roxanne Wood, Amy Webber, Ashlee Sturtevant, Alicia Friedlander

Pelvic Malignancies Program, Legorreta Cancer Center and Lifespan Cancer Institute
Howard Safran, Rochelle Strenger, Mary Lopresti, Christina Bandera, Tarra Evans, Faith Hassinger, Sopha Dionson, Janine Guglielmo, Adam Braga, Denise Luppe, Kelly Mitchell, Andrew Schumacher, Jason Machan

Harvard Comprehensive Cancer Center
Michael Birrer, Ursula Matulonis, Susana Campos, Alexi A. Wright, Oledepu Yeku, Sarah Bouberhan

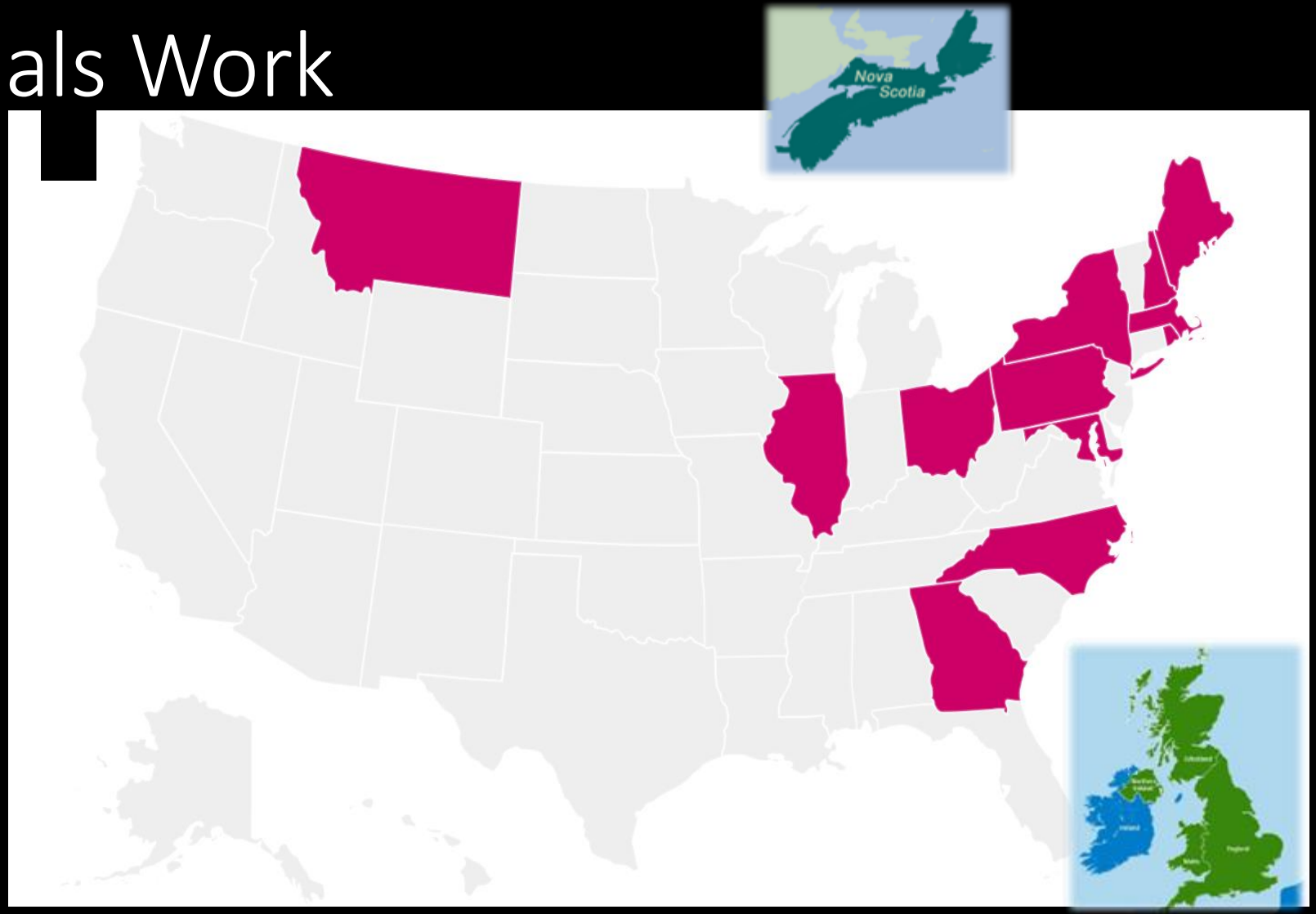
Medical University of South Carolina:
Whitney Graybill

University Hospitals Cleveland
John Nakayama, Amy Armstrong, Nancy Fusco

Emory Healthcare
Jane Meisel

Fox Chase Cancer Center
Gina Mantia-Smaldone

Johns Hopkins Kimmel Cancer Center
Anna Beavis, Deborah Armstrong



Thank you

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