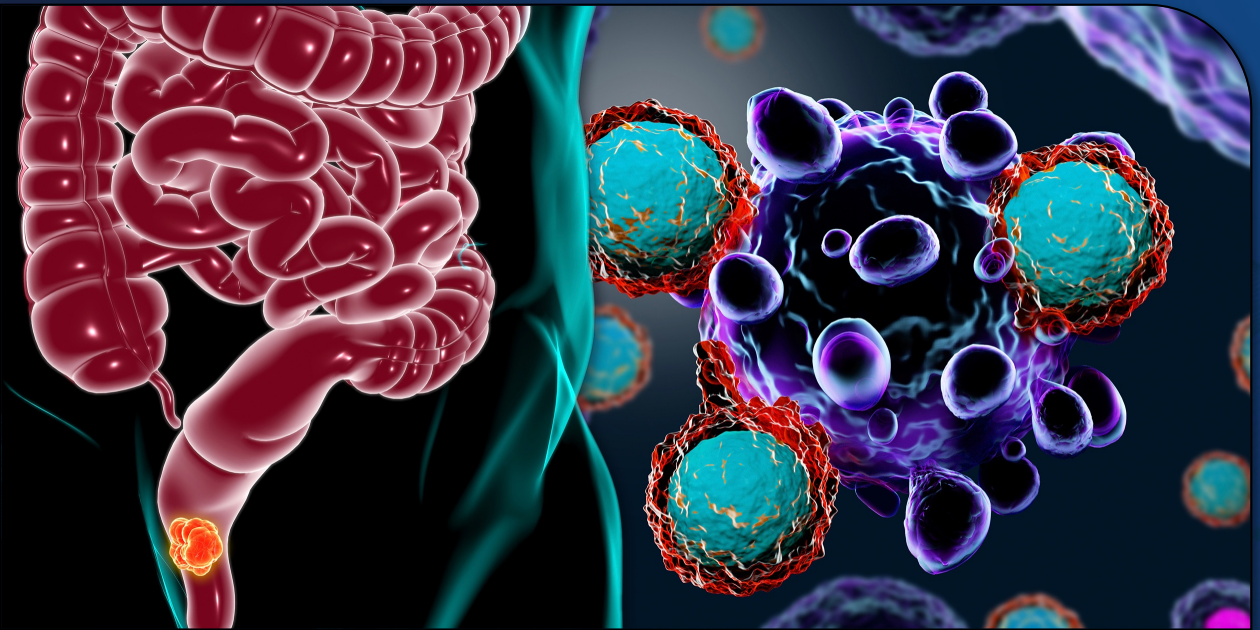
Strengthening the Immunotherapy Paradigm in Advanced SCAC

PeerView Live

Established & Emerging Roles of Immune-Based Platforms Across Lines of Therapy

ACF ANAL CANCER FOUNDATION



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Our Goals for Today

- **Review the latest clinical trial evidence** and guideline recommendations supporting the use of immunotherapy for the management of advanced SCAC
- **Develop personalized treatment plans** for advanced SCAC patients based on guideline recommendations and the latest clinical trial evidence supporting immunotherapy
- **Integrate team-based strategies** to address the nuances of treatment delivery with immunotherapy platforms, including care coordination, patient consultation and engagement, and immune-related adverse event management

Identifying Opportunities To Enhance Care in Anal Cancer

Current Unmet Needs & Solutions To Optimizing Treatment

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Chair of NCRI Anorectal Cancer Subgroup
Member of NCRI Colorectal Cancer Group
Member of International Rare Cancers Initiative (IRCI) for Anal Cancer
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SCAC Statistics: Incidence and Epidemiology

- Incidence of anal carcinoma: <1% of all cancers, <3% of all GI cancers
- Increasing incidence: worldwide, especially in Europe, USA, and Australia
- Profound increase in incidence at younger age: 45-65 years
- More advanced stages at diagnosis: 2001-2015, 30.5% to 44.6% in men and 33.9% to 47% in women
- Increased mortality: 2001-2005 vs 2014-2018
- Advanced disease:
  - ~15% stage IV at diagnosis.
  - ~20% - 37% recurrence after CRT

1. Siegel RL *CA. Cancer J Clin.* 2019;69. 2. Islami Int. *J Epidemiol*. 2017; 46. 3. Lin C. *Lancet Infect Dis*. 2018; 18. 4. Symer MM. F1000Res. 2018;7.

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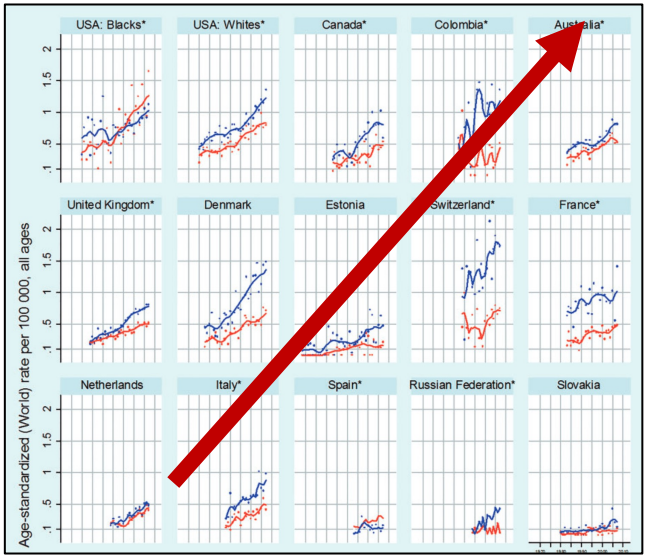

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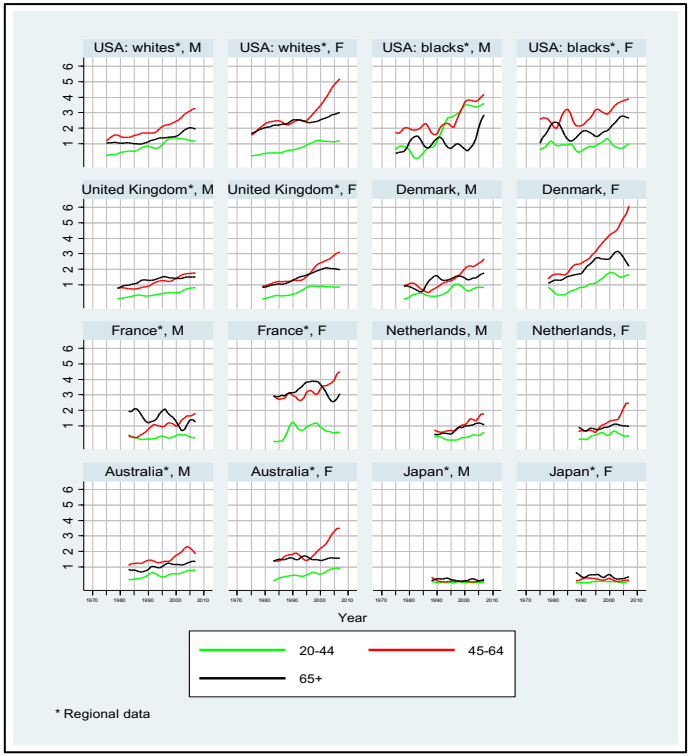

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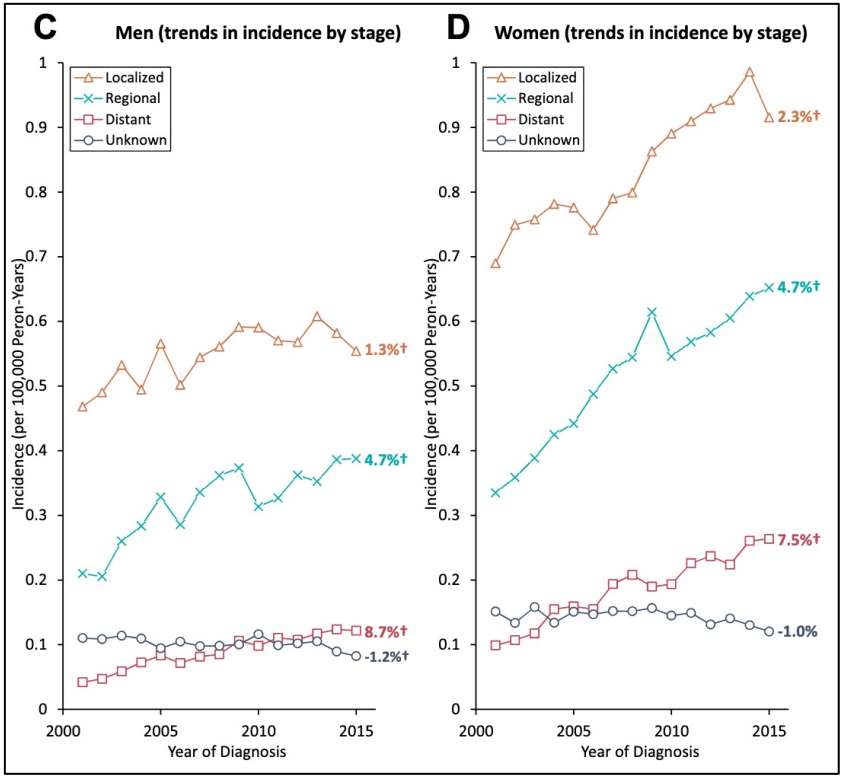

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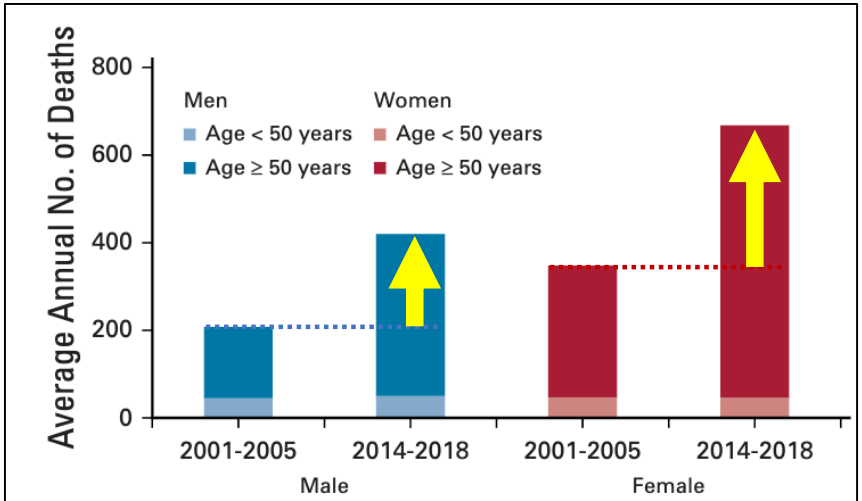

	Male		Female	
Persons age 50 years or older:	78.2%	88.0%	86.5%	93.1%
Mortality rate (per 100,000):				
All age groups	0.16 (0.15 to 0.17)	0.24 (0.23 to 0.25)	0.21 (0.20 to 0.22)	0.31 (0.30 to 0.33)
< 50 years	0.04 (0.04 to 0.05)	0.05 (0.05 to 0.06)	0.04 (0.04 to 0.05)	0.05 (0.04 to 0.05)
≥ 50 years	0.46 (0.43 to 0.49)	0.74 (0.71 to 0.78)	0.65 (0.62 to 0.68)	1.02 (0.98 to 1.05)

1. Siegel RL *CA. Cancer J Clin.* 2019;69. 2. Islami Int. *J Epidemiol*. 2017; 46. 3. Lin C. *Lancet Infect Dis*. 2018; 18. 4. Symer MM. F1000Res. 2018;7.

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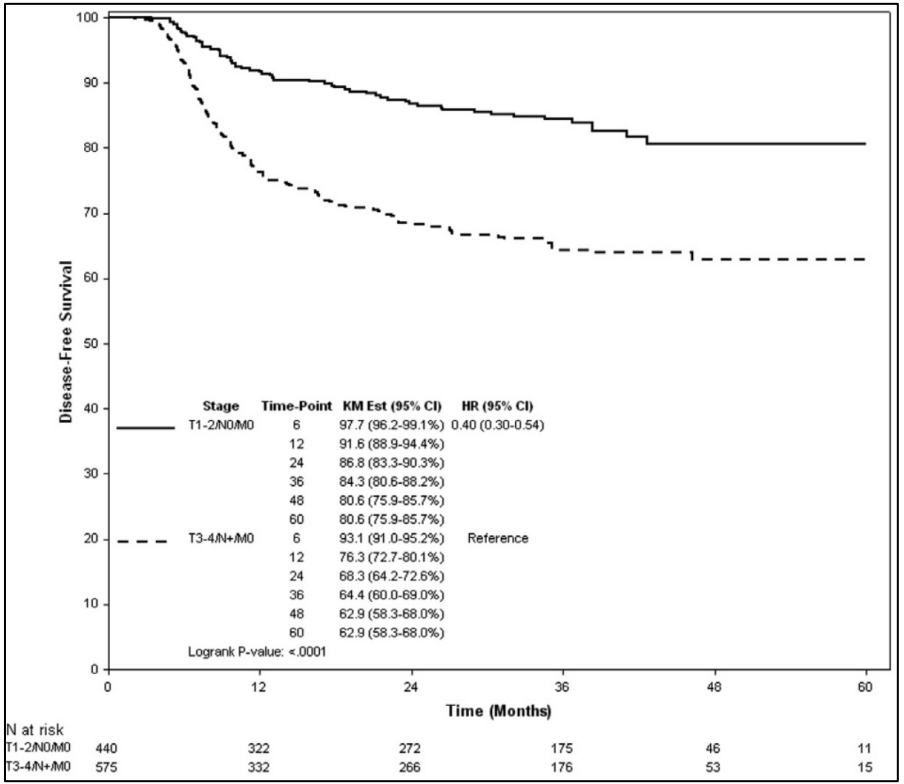

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Trends Associated With SCAC: “The 90’s Rule”

- 90%: Squamous cell carcinoma
- 90% of SCAC is associated with E6 and E7 oncoproteins encoded by Human Papillomavirus (HPV) [2,3]
- 90% of SCAC HPV+ is related to genotype HPV-16[3]
- 90% of SCAC HPV+ is detectable by liquid biopsy (HPV ctDNA)

1. Siegel RL *CA. Cancer J Clin.* 2019;69. 2. Islami Int. *J Epidemiol*. 2017; 46. 3. Lin C. *Lancet Infect Dis*. 2018;18. 4. Symer MM. F1000Res. 2018;7.

Acknowledging Unmet Needs in Advanced SCAC

- SCAC is a neglected orphan disease; incidence is increasing ~3% per year mainly due to endemic HPV, the causative agent for most anogenital cancers[1-4]
  - HIV is an important amplifier of SCAC; people with HIV are 25- to 35-fold more likely to develop SCAC[5,6]
- Relapse after primary therapy (chemo-radiotherapy) is common; standard of care treatment has not changed since the early 1980s[7]
  - Prognosis is poor for patients who relapse or with de novo metastatic disease, and quality of life is greatly diminished[8]

1. Gondal TA et al. *Curr Oncol*. 2023;30:3232-3250. 2. Islami F et al. *Int J Epidemiol*. 2017;46:924-938. 3. Giuliano AR et al. *Int J Cancer*. 2015;136:2752-2760.
4. Morris V, Eng C. *J Gastrointest Oncol*. 2016;7:721-726. 5. Wang C-CJ et al. *Surg Oncol Clin N Am*. 2017;26:17-31. 6. NCCN Clinical Practice Guidelines in Oncology: Cancer in People with HIV. Version 1.2025. https://www.nccn.org/professionals/physician_gls/pdf/hiv.pdf. 7. Pessia B et al. *Ann Med Surg (Lond)*. 2020;55:36-46.
8. Rao S,et al. *Ann Oncol*. 2021;32:1087-1100.

An Excellent Resource for Clinicians and Patients: The Anal Cancer Foundation

Download the Practice Aid for more information

Expert-Hour Webinars

The Anal Cancer Foundation held expert-hour webinars to provide patients the same information as their providers

- **Clinical Trials 101**
- **Immunotherapy 101**
- **Anal Cancer Detection and Prevention**
- **Fertility Preservation Options**
- **The Role of Circulating Tumor DNA**

Scan for More Clinical Trial Information
Types, safety, and how to find them
analcancerfoundation.org/treatment/clinical-trials

Learn more about side effect management

Surgery, Chemo, Radiation, and Recurrent and Advanced Anal Cancer

Anal Cancer Patient Guide

- ✓ Step-by-step guides to the cancer care options likely to have the best results
- ✓ Based on treatment guidelines used by health care providers worldwide
- ✓ Designed to help you discuss cancer treatment with your doctors

Patient Conferences

The Anal Cancer Foundation held patient conferences focused on **living and thriving after anal cancer**, including **information on clinical trials for advanced anal cancer.**

Watch the past presentations on YouTube by scanning the QR code

ACF's closed Facebook group for all cancer thrivers
Connect, communicate, support
https://www.facebook.com/groups/acfsupportgroup

PeerView

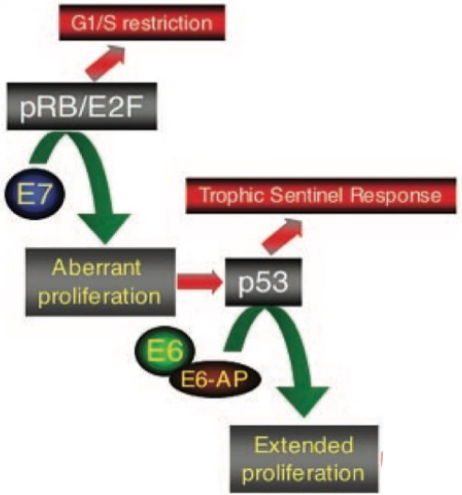
Integrating IO in Advanced SCAC

Evidence-Based Applications in the Second-Line and Beyond

Prof. Stefano Kim, MD, PhD
Medical Oncologist
Sanatorio Allende
Córdoba, Argentina
Associate Professor
University Bourgogne Franche-Comte
Investigator in Immuno-oncology
Clinical Investigational Center, CIC-1431/National Institute of Health and Medical Research (INSERM)
Besancon, France

Rationale for PD-1 Inhibition in SCAC[1-2]

HPV+ SCAC



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Rationale for PD-1 Inhibition in SCAC[1-2]

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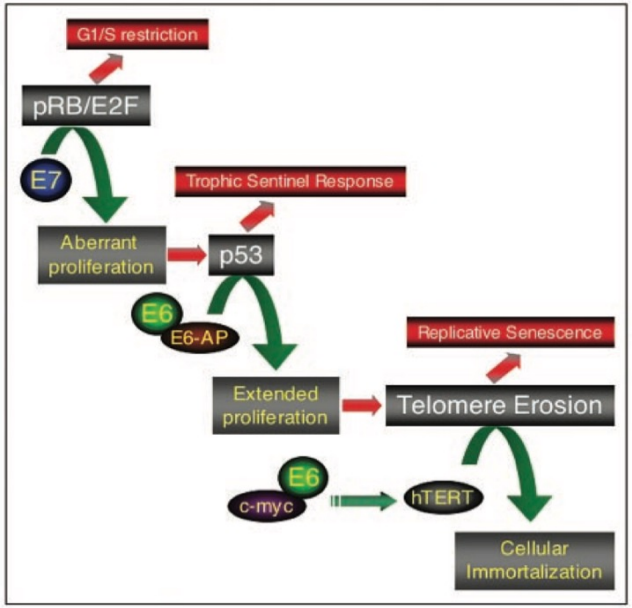

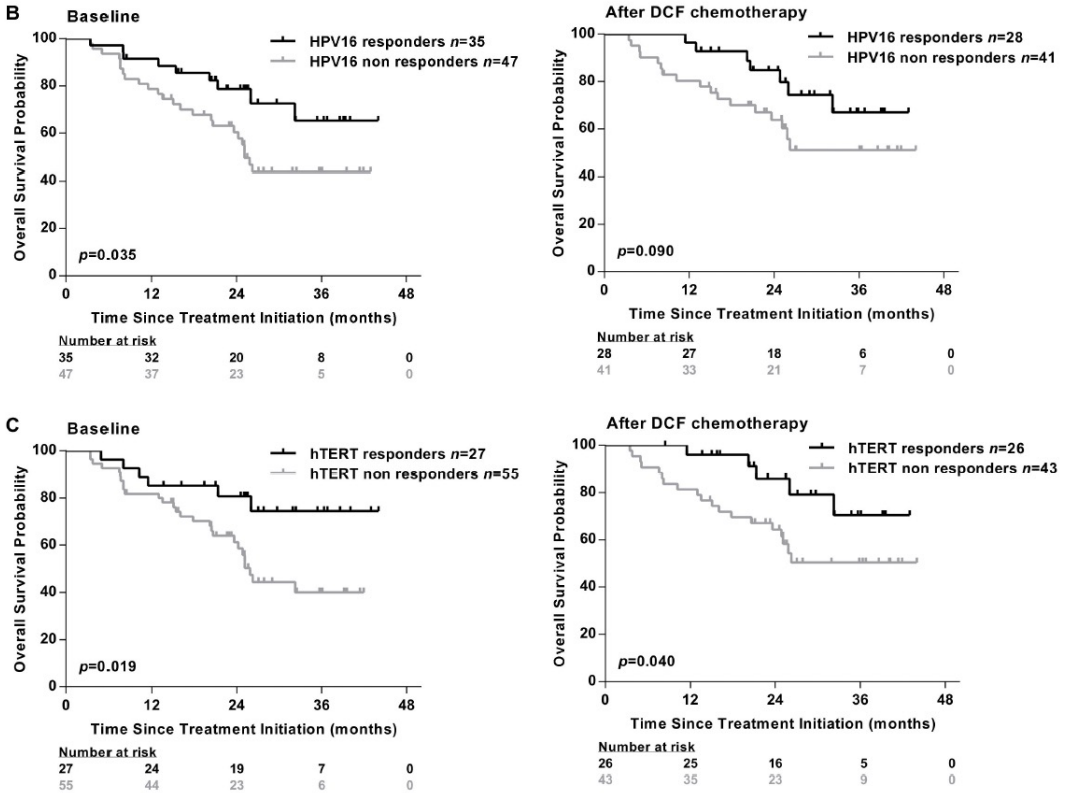

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NCCN Guidelines Include Expanded Immunotherapy Options for Advanced SCAC in the 2L Setting[1]

Principles of Systemic Therapy: Metastatic Cancer

First-Line Therapy

PREFERRED REGIMENS	OTHER RECOMMENDED REGIMENS
• Carboplatin + paclitaxel	• FOLFCIS • mFOLFOX • 5-FU + cisplatin (category 2B) • Carboplatin + paclitaxel + retifanlimab (category 2B) • Modified docetaxel/cisplatin/fluorouracil (DCF) (category 2B)

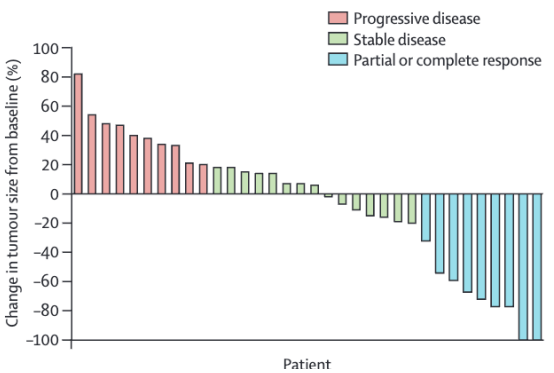
Second-Line Therapy and Subsequent Therapy

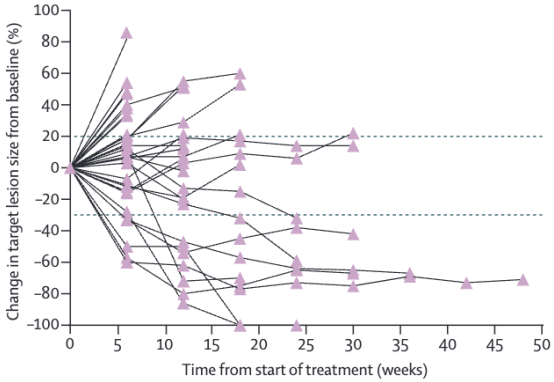
PREFERRED REGIMENS (if no prior immunotherapy received)	OTHER RECOMMENDED REGIMENS (if not previously given)
• Cemiplimab • Dostarlimab • Nivolumab • Pembrolizumab • Retifanlimab • Tislelizumab • Toripalimab	• Carboplatin + paclitaxel • FOLFCIS • mFOLFOX6 • 5-FU + cisplatin (category 2B) • Modified DCF (category 2B)

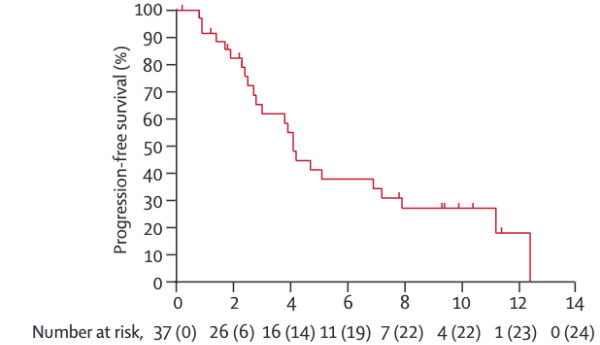
Chemo/RT to the Primary Site for Local Control
• 5-FU + RT • Capecitabine + RT

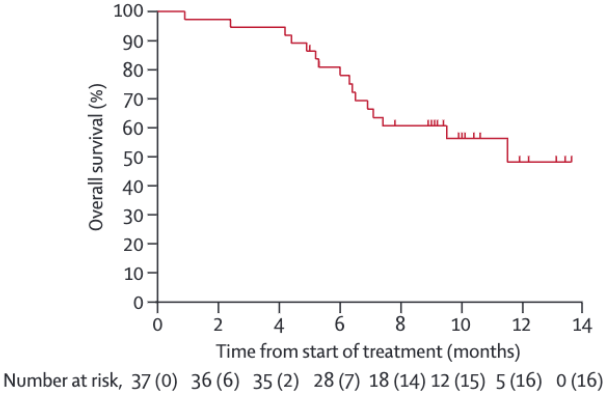
1. NCCN Clinical Practice Guidelines. Anal Carcinoma. Version 1.2025. https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf.

PD1/L1 Inhibitor in Monotherapy: Nivolumab for Previously Treated Advanced SCAC[1]







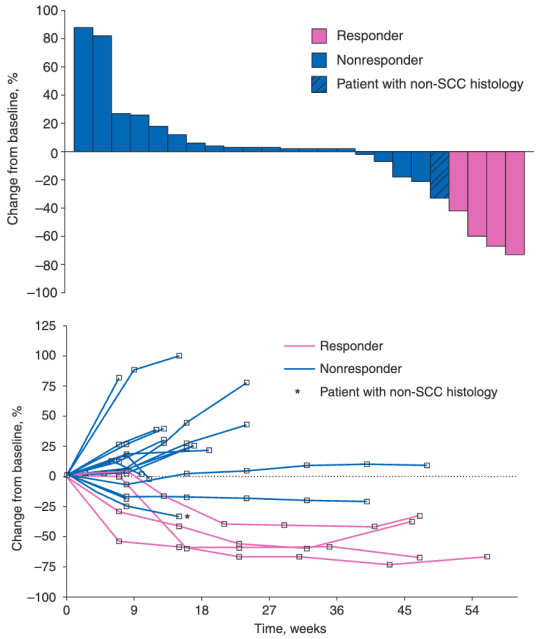


Efficacy Findings (N = 34)
ORR: 24%
CRR: 5%
PFS: 4.1 m
DOR: 5.8 m

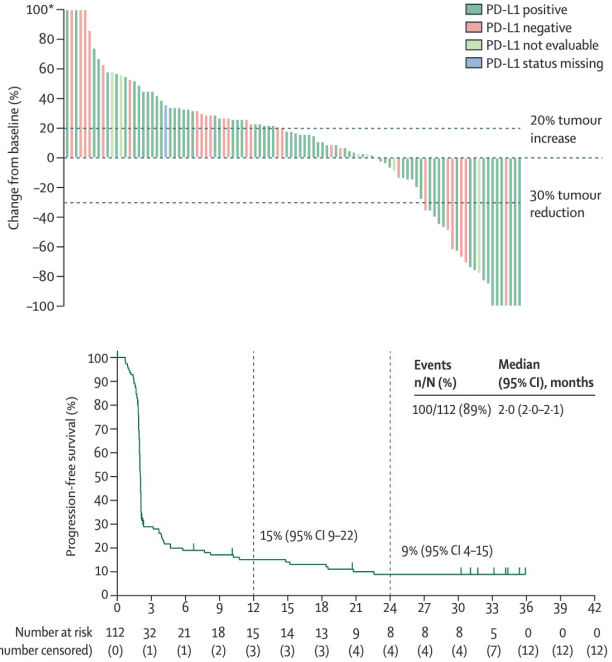
1. Morris VK et al. *Lancet Oncol*. 2017;18:446-453.

PD1/L1 Inhibitor in Monotherapy: Pembrolizumab for Previously Treated Recurrent/Advanced SCAC[1,2]

KEYNOTE-028



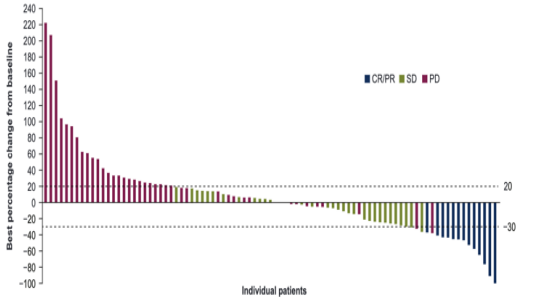
KEYNOTE-158

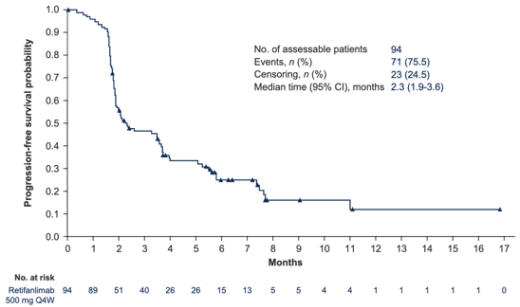


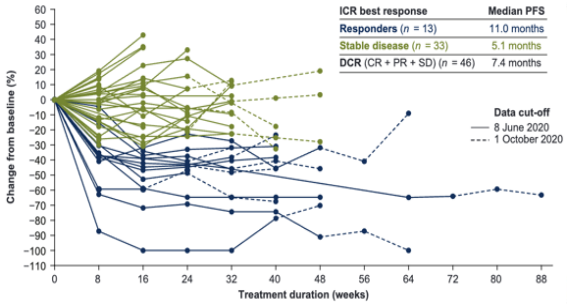
Efficacy Findings (N = 136)
ORR: 12%
CRR: 4% (PDL1+)
PFS: 2 m
DOR: 8.1 m

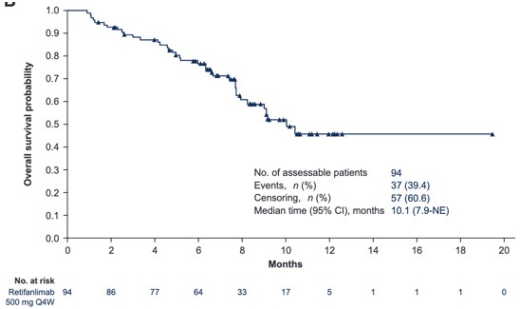
1. Ott PA et al. *Ann Oncol*. 2017. 2. Marabelle A et al. *Lancet Oncol*. 2022.

PD1/L1 Inhibitor in Monotherapy: Retifanlimab Demonstrated Improved Efficacy For 2L Advanced SCAC[1]





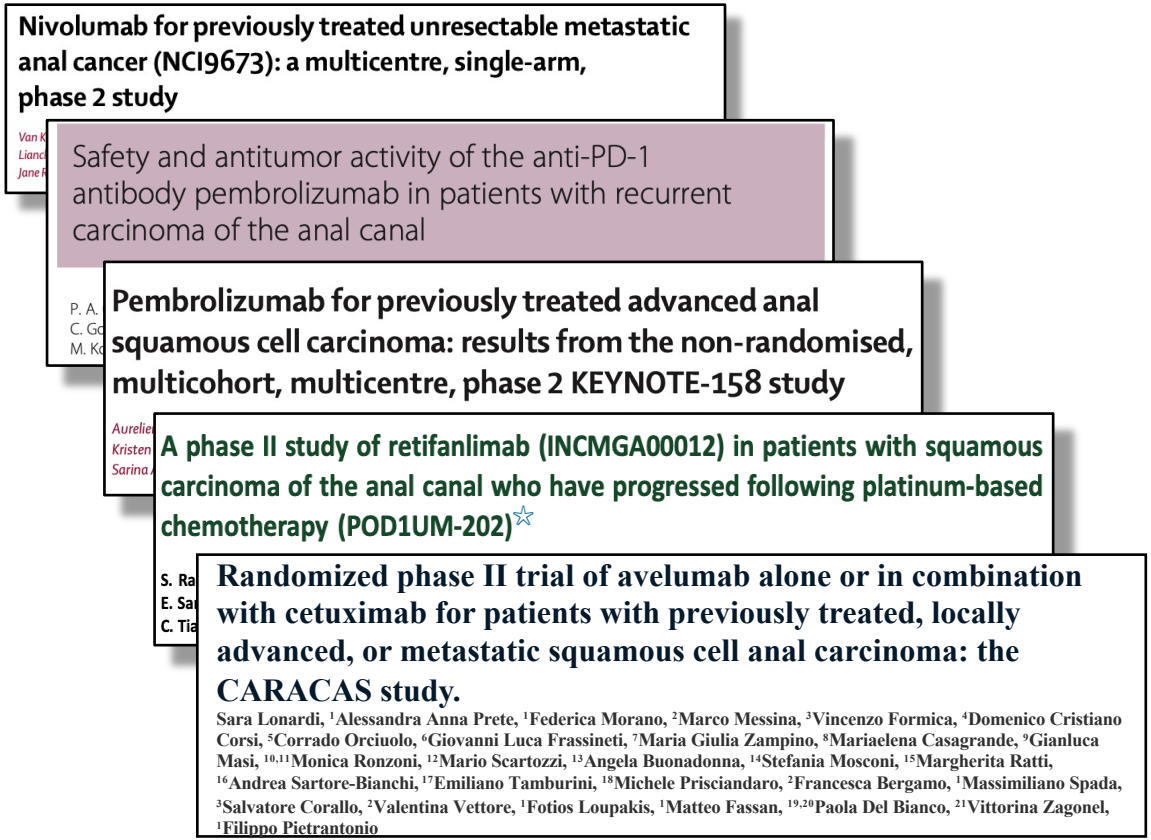




Efficacy Findings (N = 94)
ORR: 14%
CRR: 1%
PFS: 2.3 m
DOR: 11 m

1. Rao S et al. ESMO Open 2022. 7(4):100529.

Progress in Advanced Disease: PD-1/L1 Inhibitor Monotherapy[1-5]



PD1/L1 inhibitor (N = 298)
Nivolumab Pembrolizumab Retifanlimab Avelumab
ORR: 13.8%
CRR: 3%
PFS: 2.0-4.1 m
DOR: 5.5-11.7 m

1. Morris VK et al. *Lancet Oncol.* 2017. 2. Ott PA et al. *Ann Oncol.* 2017. 3. Marabelle A et al. *Lancet Oncol.* 2022. 4. Rao S et al. ESMO Open 2022.
5. Lonardi S et al. *J Immunother Cancer.* 2021;9(11):e002996.

What Does the Evidence Say About PD-1/L1 Inhibitor Combinations for SCAC?

+ anti-CTLA4	+ anti-VEGF	+ anti-EGFR
IPILIMUMAB	BEVACIZUMAB	CETUXIMAB

Phase 2 Studies Evaluating PD-1/L1 Inhibitor Combinations for Advanced SCAC

+ anti-CTLA4 (NCI9673)

Phase II R (1/1)

Nivolumab ± Ipilimumab

(n = 100)

PFS (1º EP): **3.7 m vs 2.9 m**

HR 0.80 (0.51-**1.24**); ***P* = .16**

ORR

21.5% vs **17.4%** (*P* = .89)

OS

20.0m vs **15.4m** (*P* = .59)

Grade ≥3 toxicities

25%[a] vs **12%**

+ anti-VEGF
BEVACIZUMAB

+ anti-EGFR
CETUXIMAB

[a] 1 G5: pneumonitis

1. Morris VK et al. ESMO 2023.

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Grade ≥3 toxicities

25%[a] vs **12%**

+ anti-VEGF

Single-arm Phase II

Bevacizumab + Atezolizumab

(n = 20)

PFS: 4.1 m

12 m PFS: 20%

ORR (1º EP)

10%

OS

11.6 m

Grade ≥3 toxicities

35%[b]

+ anti-EGFR

CETUXIMAB

[a] 1 G5: pneumonitis. [b] 1 G5: bowel perforation.

1. Morris VK et al. ESMO 2023. 2. Morris VK et al. ESMO 2020.

Phase 2 Studies Evaluating PD-1/L1 Inhibitor Combinations for Advanced SCAC

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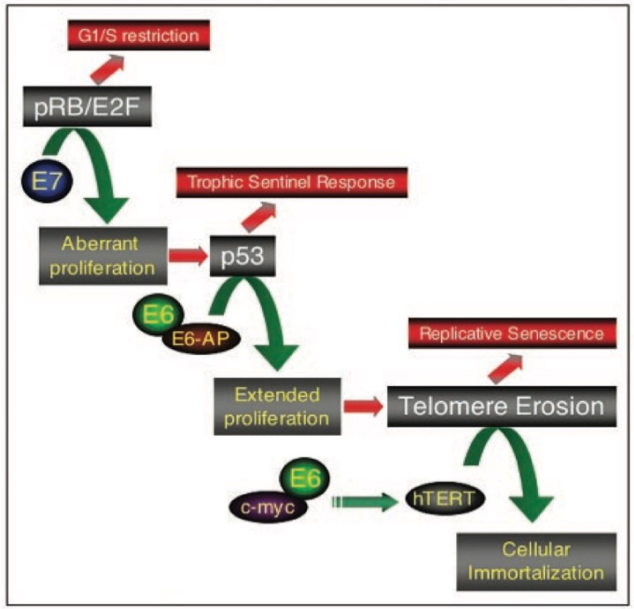
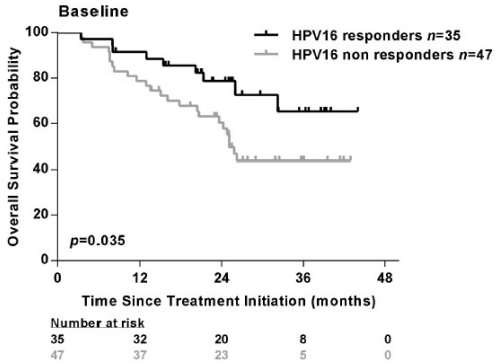
+ anti-VEGF
Single-arm Phase II
Bevacizumab + Atezolizumab
(n = 20)
PFS: 4.1 m
12 m PFS: 20%
ORR (1º EP)
10%
OS
11.6 m
Grade ≥3 toxicities
35%[b]

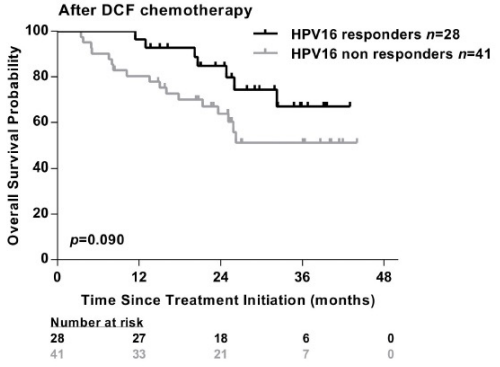
+ anti-EGFR
Non-C Phase II R (1/1)
Avelumab ± Cetuximab
(n = 60)
PFS: **3.9 m vs 2.0 m**
12 m PFS: <15%
ORR (1º EP)
17% vs **10%**
OS
13.9 m vs **7.8 m**
Grade ≥3 toxicities
6% vs **0%**

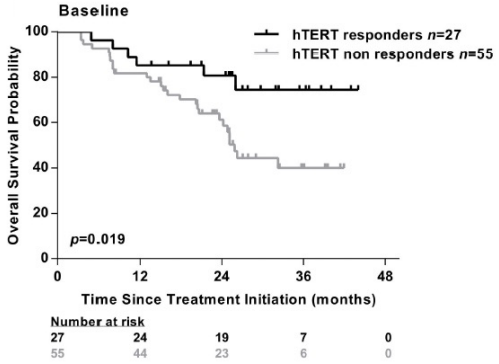
[a] 1 G5: pneumonitis
1. Morris VK et al. ESMO 2023. 2. Morris VK et al. ESMO 2020. 3. Lonardi S et al. *J Immunother Cancer*. 2021;9(11):e002996.

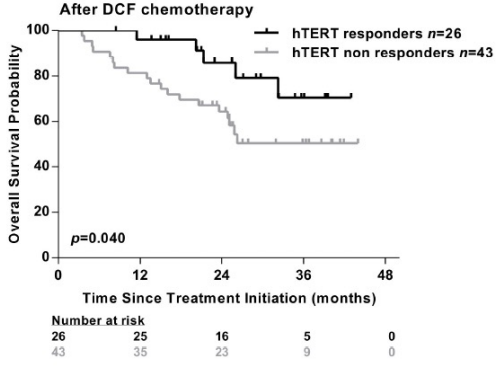
Prognostic Value of Anti-HPV and Anti-hTERT Immunity[1-2]











1. Munger K. et al. *Virol J*. 78(21), 11451-11460. 2. Spehner L. et al. IJMS 2020.

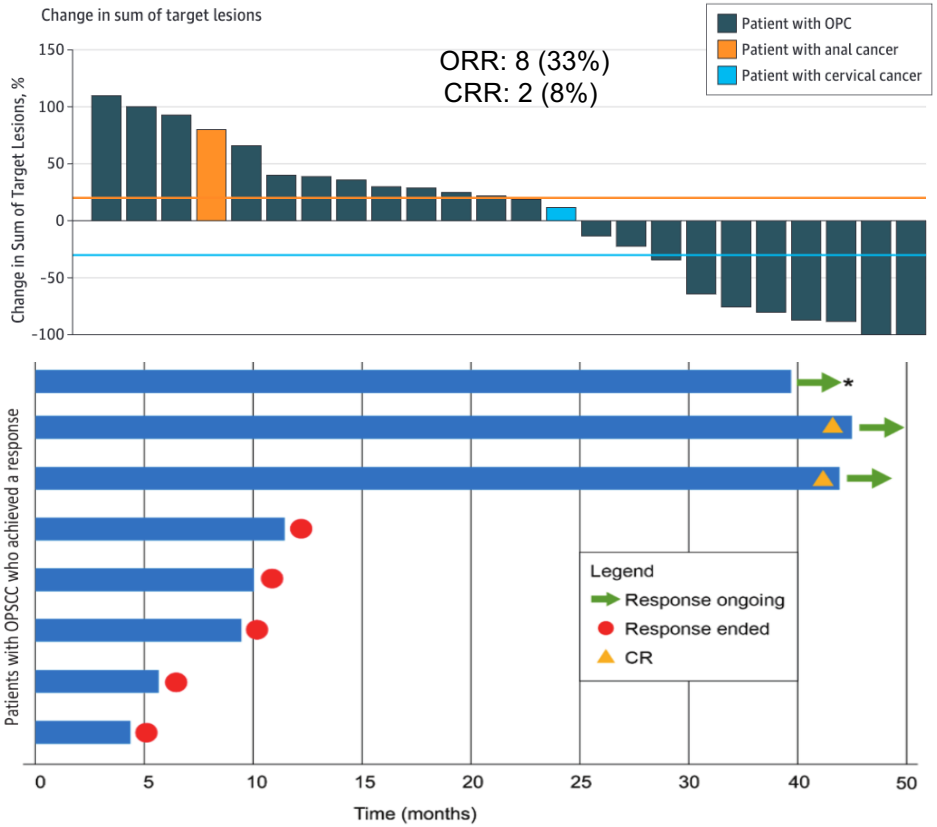
Phase 2 Trial Combining Immunotherapy + Anti-HPV Vaccine[1-2]

34 Patients screened

→ **10** Did not enroll

24 Enrolled

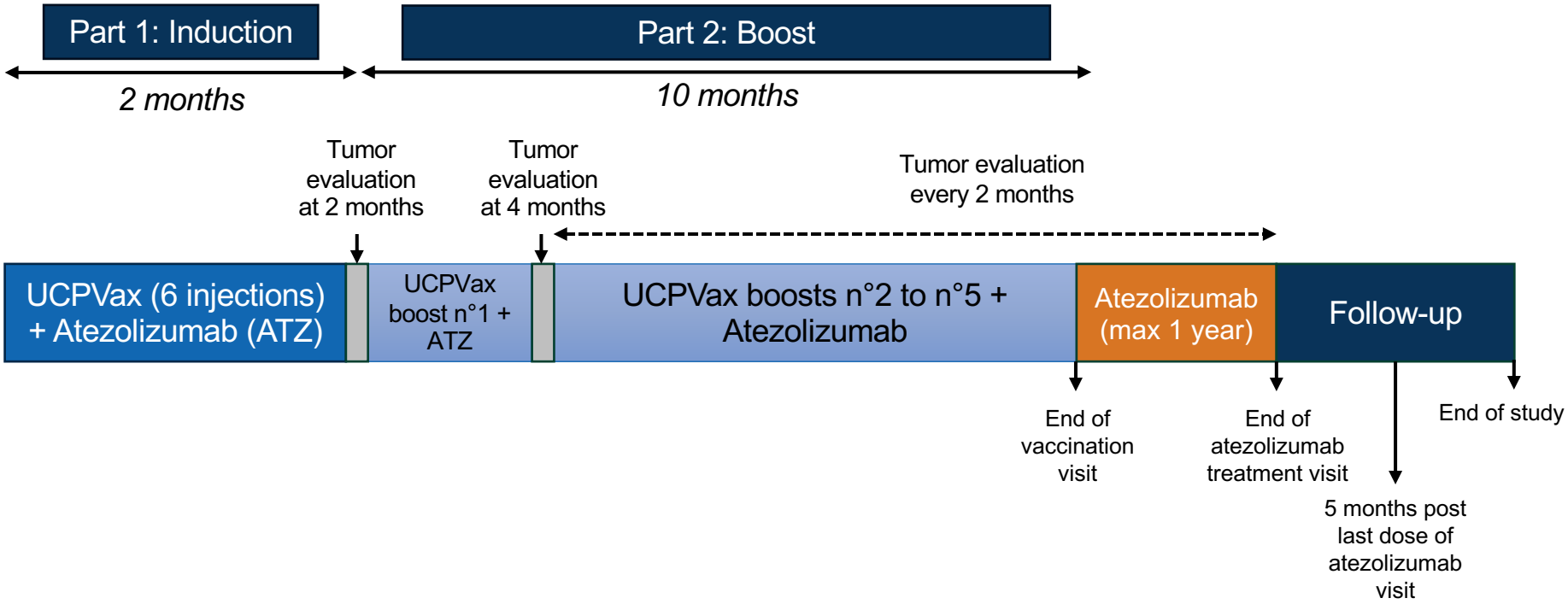
24 Discontinued
- **17** Progressive disease
- **5** Completed 12-mo treatment
- **2** Adverse event



1. Massarelli E et al. *JAMA Oncol*. 2019;5(1):67-73. 2. Guimaraes de Sousa ·L. *Journal for ImmunoTherapy of Cancer*. 10(2):e004232.

PeerView

Phase 2 VolATIL Study: Combining Immunotherapy With An Anti-hTERT Vaccine[1]

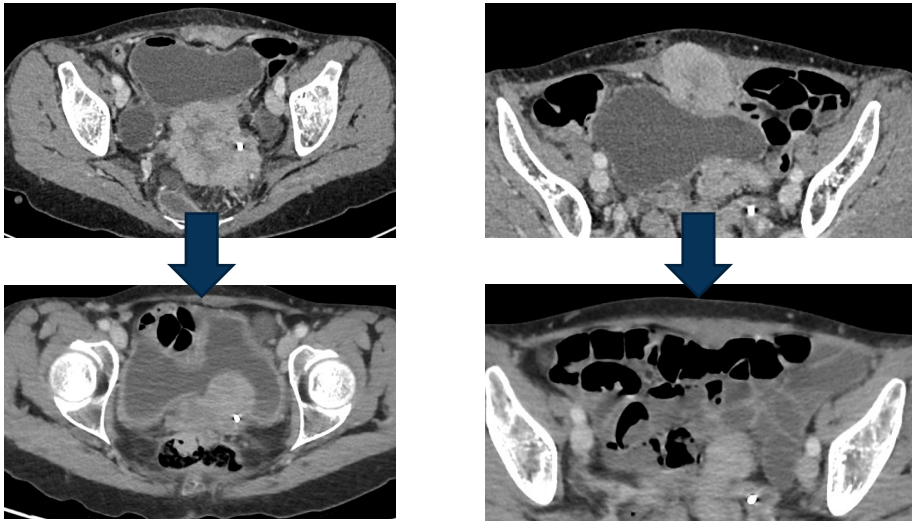


- **Primary endpoint:** Durable response rate (OR > 4 months)

1. Rebucci-Peixoto et al. *Front Oncol.* 2022;12:10.3389/fonc.2022.957580.

Phase 2 VolATIL Study: Efficacy Findings[1,2]

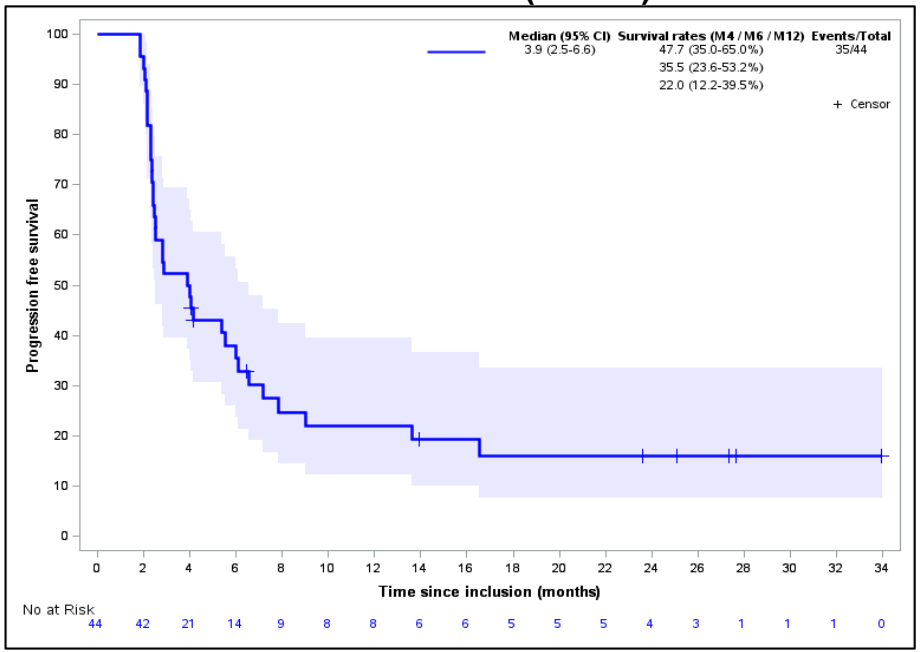
Endpoints	N = 44
Durable ORR	8 (18.2%)
Complete response	6 (13.6%)



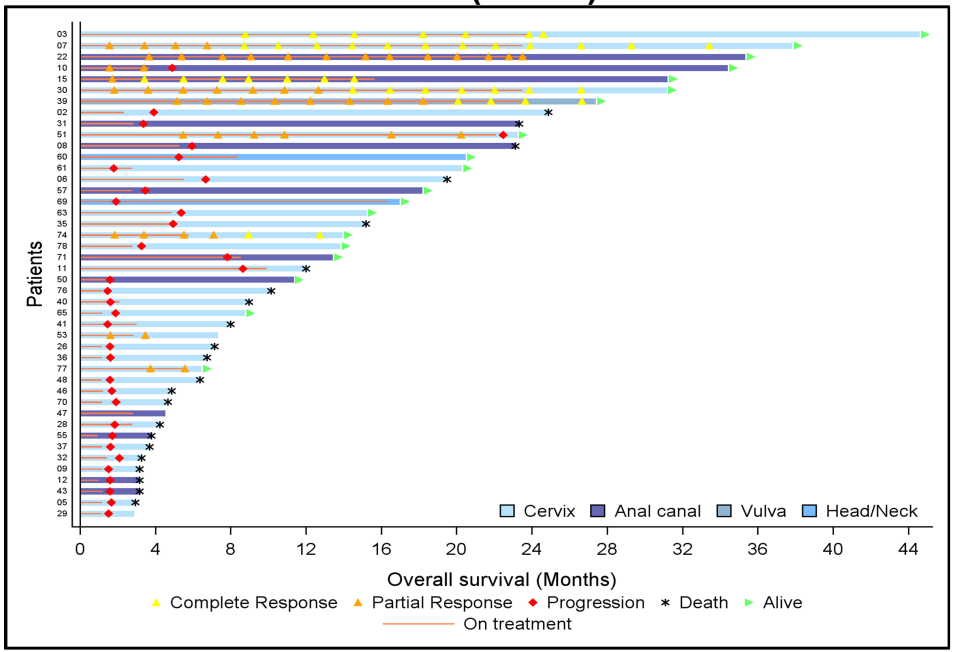
1. Rebucci-Peixoto et al. *Front Oncol.* 2022;12:10.3389/fonc.2022.957580. 2. Zheng M. ESMO 2024. Abstract # 660P.

Phase 2 VolATIL Study: Efficacy Findings[1,2]

12m PFS (24.2%)



12m OS (41.5%)



1. Rebucci-Peixoto et al. *Front Oncol.* 2022;12:10.3389/fonc.2022.957580. 2. Zheng M. ESMO 2024. Abstract # 660P.

Take-Homes for the 2L Immunotherapy for Advanced SCAC

- Anti-PD1 monotherapy: valid option in ≥2 line (durable benefit in ~15%)
- Combination: HPV or hTERT vaccine: durable benefit in ~25%?
- Adoptive T cells: future option?

The Next Generation in SCAC

Moving Immunotherapy To Earlier Lines of Therapy

Sheela Rao, MBBS, MD, FRCP
Consultant Medical Oncologist
Chair of NCRI Anorectal Cancer Subgroup
Member of NCRI Colorectal Cancer Group
Member of International Rare Cancers Initiative (IRCI) for Anal Cancer
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Ingram Associate Professor of Cancer Research
Associate Professor of Medicine
Vanderbilt-Ingram Cancer Center
Nashville, Tennessee

NCCN Guidelines for Advanced SCAC in the Upfront Setting[1]

Principles of Systemic Therapy: Metastatic Cancer

First-Line Therapy

PREFERRED REGIMENS	OTHER RECOMMENDED REGIMENS
• Carboplatin + paclitaxel	• FOLFCIS • mFOLFOX • 5-FU + cisplatin (category 2B) • Carboplatin + paclitaxel + retifanlimab (category 2B) • Modified docetaxel/cisplatin/fluorouracil (DCF) (category 2B)

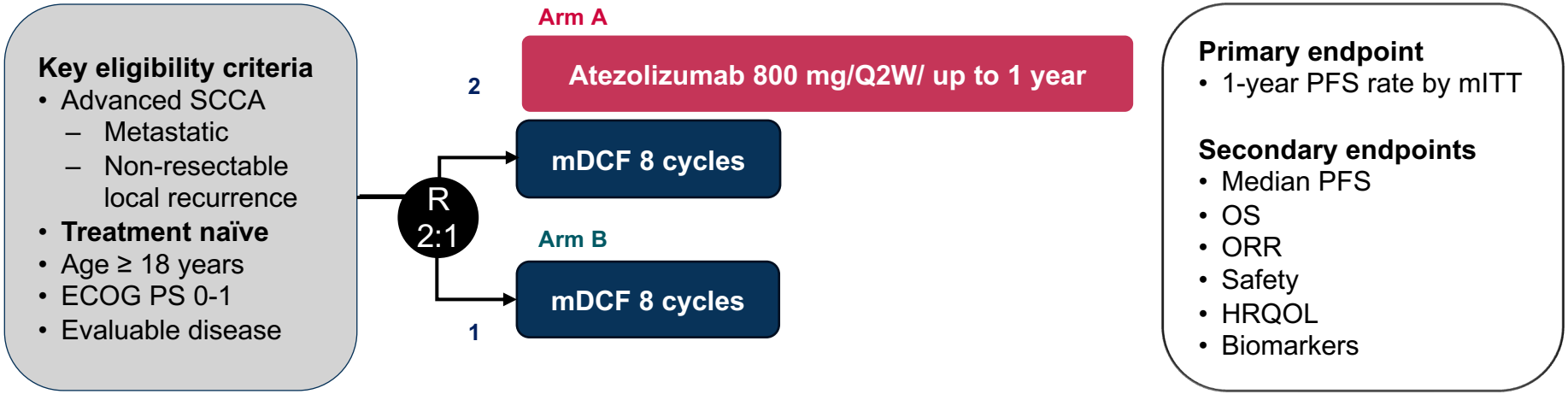
Second-Line Therapy and Subsequent Therapy

PREFERRED REGIMENS (if no prior immunotherapy received)	OTHER RECOMMENDED REGIMENS (if not previously given)
• Cemiplimab • Dostarlimab • Nivolumab • Pembrolizumab • Retifanlimab • Tislelizumab • Toripalimab	• Carboplatin + paclitaxel • FOLFCIS • mFOLFOX6 • 5-FU + cisplatin (category 2B) • Modified DCF (category 2B)

Chemo/RT to the Primary Site for Local Control
• 5-FU + RT • Capecitabine + RT

1. NCCN Clinical Practice Guidelines. Anal Carcinoma. Version 1.2025. https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf.

SCARCE PRODIGE 60: Atezolizumab Plus Modified DCF as 1L Treatment for Metastatic or Locally Advanced SCAC[1]



Stratification: age (<65 vs ≥65 years), stage (synchronous metastatic vs metachronous metastatic vs locally advanced unresectable disease without metastasis)

1. Kim S. *Lancet Oncol*. 2024;25(4):518-528.

SCARCE-PRODIGE 60: Baseline Patient Characteristics[1]

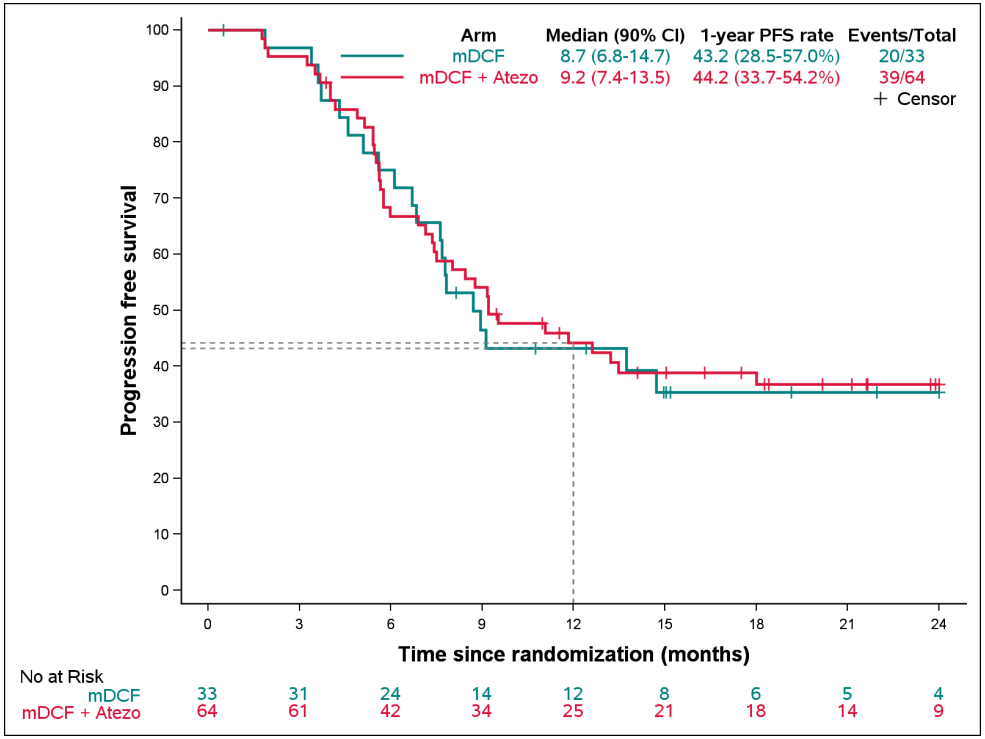
	All (N = 97)	Arm A (n = 64)	Arm B (n = 33)
Age, median (range)	64.1 (40.4-83.3)	63.2 (44.1-83.3)	64.7 (40.4-77.9)
Sex, n (%)			
Female	71 (73.2)	46 (71.9)	25 (75.8)
ECOG PS, n (%)			
0	61 (62.9)	37 (57.8)	**24 (72.7)**
1	36 (37.1)	**27 (42.2)**	9 (27.3)
HIV+, n (%)	4 (4.1)	3 (4.7)	1 (3.0)
Disease stage, n (%)			
Synchronous metastasis	40 (41.2)	26 (40.6)	14 (42.4)
Metachronous metastasis	36 (37.1)	25 (39.1)	11 (33.3)
Locally advanced	21 (21.6)	13 (20.3)	8 (24.2)
Prior treatment, n (%)			
Radio(chemo)therapy	49 (50.5)	34 (53.1)	15 (45.5)
Surgery primary tumor	13 (13.4)	**11 (17.2)**	2 (6.1)

1. Kim S. *Lancet Oncol*. 2024;25(4):518-528.

SCARCE-PRODIGE 60 Primary Endpoint: 1-Year PFS Rate[1]

Arm A

1-year PFS rate: 44.2%
(90% CI: 31.7-56.0)



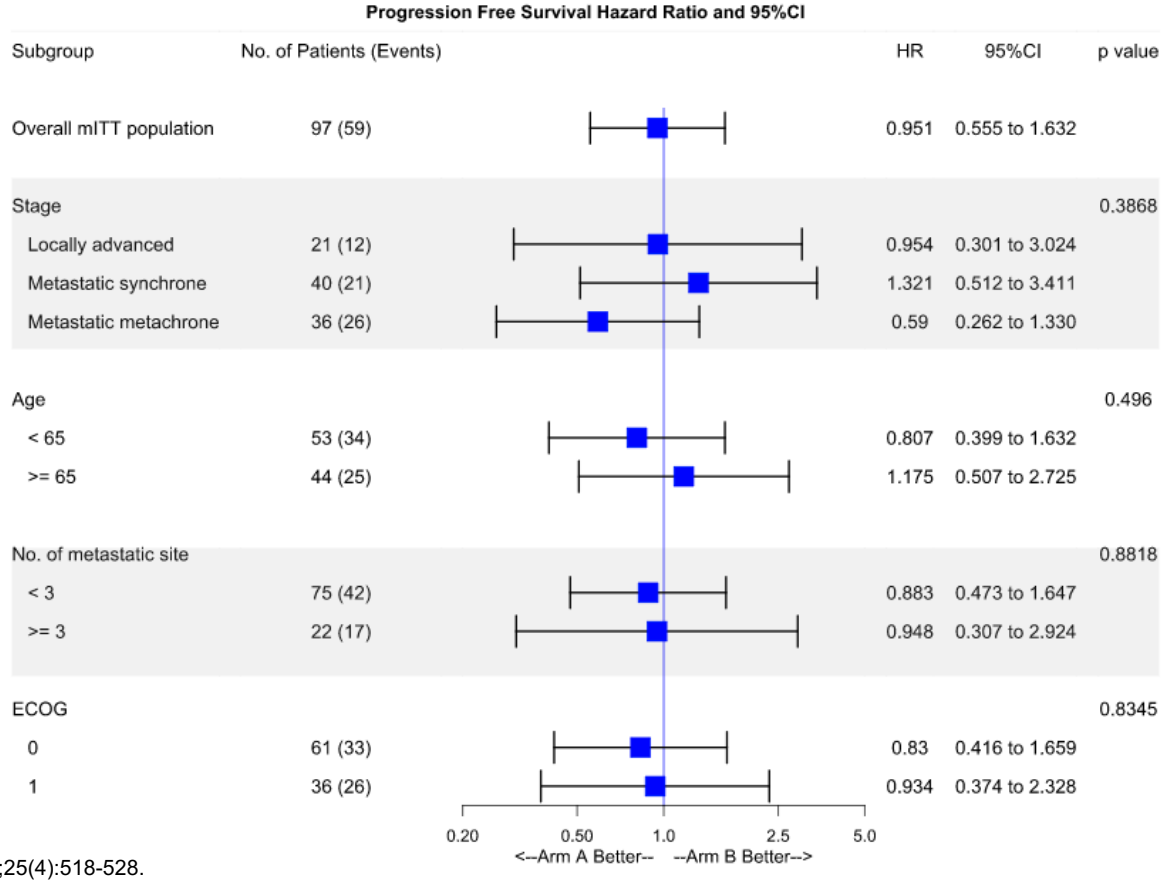
Arm B

1-year PFS rate: 43.2%
(90% CI: 25.8-59.4)

1. Kim S. *Lancet Oncol*. 2024;25(4):518-528.

PeerView

SCARCE PRODIGE 60: Subgroup Analysis[1]



1. Kim S. *Lancet Oncol*. 2024;25(4):518-528.

Phase 3 POD1UM-303/InterAACT 2: Rationale For Retifanlimab For 1L Locally Advanced or Metastatic SCAC

- The InterAACT phase 2 study established carboplatin–paclitaxel as 1L treatment. Responses were meaningful and durable, but overall PFS (8 months) and OS (20 months) remained short[1]

- HPV-driven malignancy is an attractive target for immunotherapy approaches

  – Improved survival in head and neck squamous cell carcinoma[2] and cervical cancer[3] serve as proof of concept for SCAC

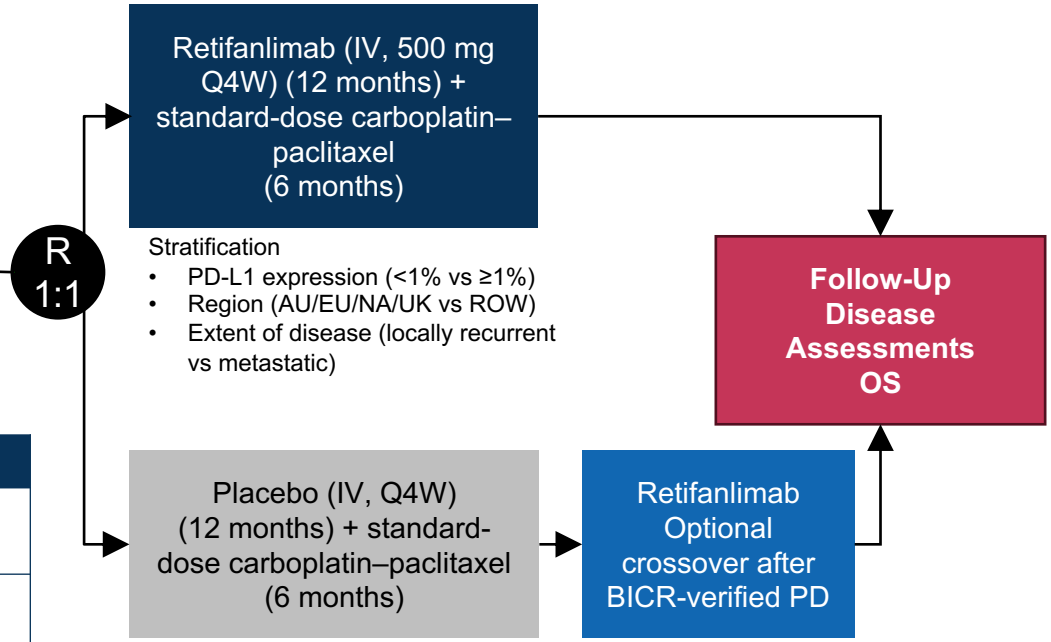
- Retifanlimab, a humanized anti–PD-1 monoclonal antibody, showed anti-tumor activity in platinum-refractory SCAC in the phase 2 POD1UM-202 study[4]

1. Rao S et al. *J Clin Oncol*. 2020;38:2510-2518. 2. Ferris RL et al. *N Engl J Med*. 2016;375:1856-1867. 3. Colombo N et al. *N Engl J Med*. 2021;385:1856-1867.
4. Rao S et al. *ESMO Open*. 2022;7:100529.

POD1UM-303/InterAACT 2 Study Evaluating Retifanlimab for Locally Recurrent or Advanced SCAC

Patients with **locally recurrent or metastatic SCAC**

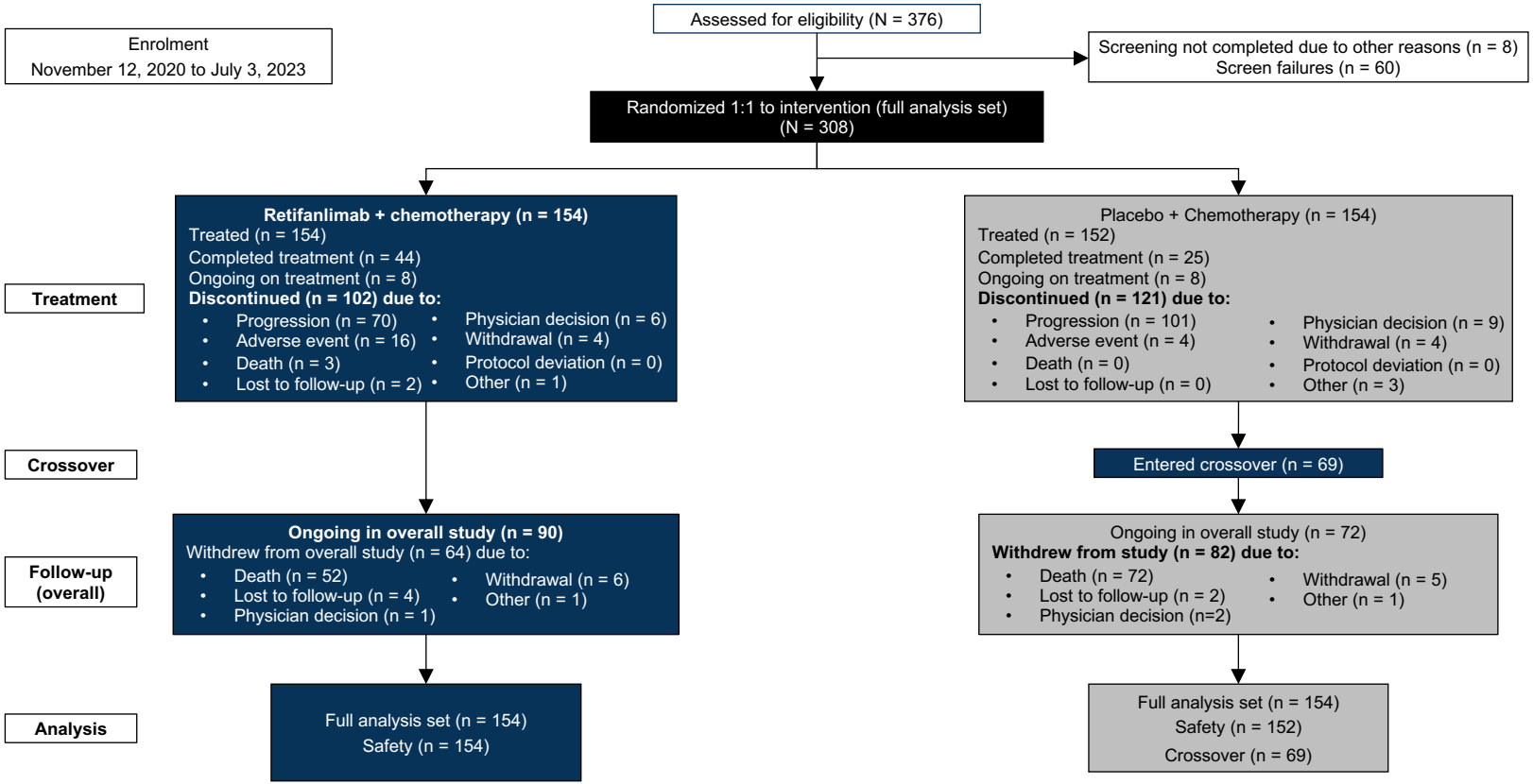
- No prior chemotherapy except as radiosensitizing treatment or (neo) adjuvant therapy ≥6 months prior to study entry
- Patients with HIV and well-controlled infection were eligible
- Planned enrolment: N = 300



Study Endpoints	
Primary	PFS by BICR (HR = 0.67 at >80% power, alpha = 0.025 [1-sided])
Secondary	OS (key secondary, alpha = 0.025 [1-sided] if PFS is statistically significant), ORR, DOR, safety, PK
Exploratory	PFS2, PROs, HIV control, immunogenicity

1. Rao S et al. ESMO 2024. Abstract # LBA2.

Patient Flow



1. Rao S et al. ESMO 2024. Abstract # LBA2.

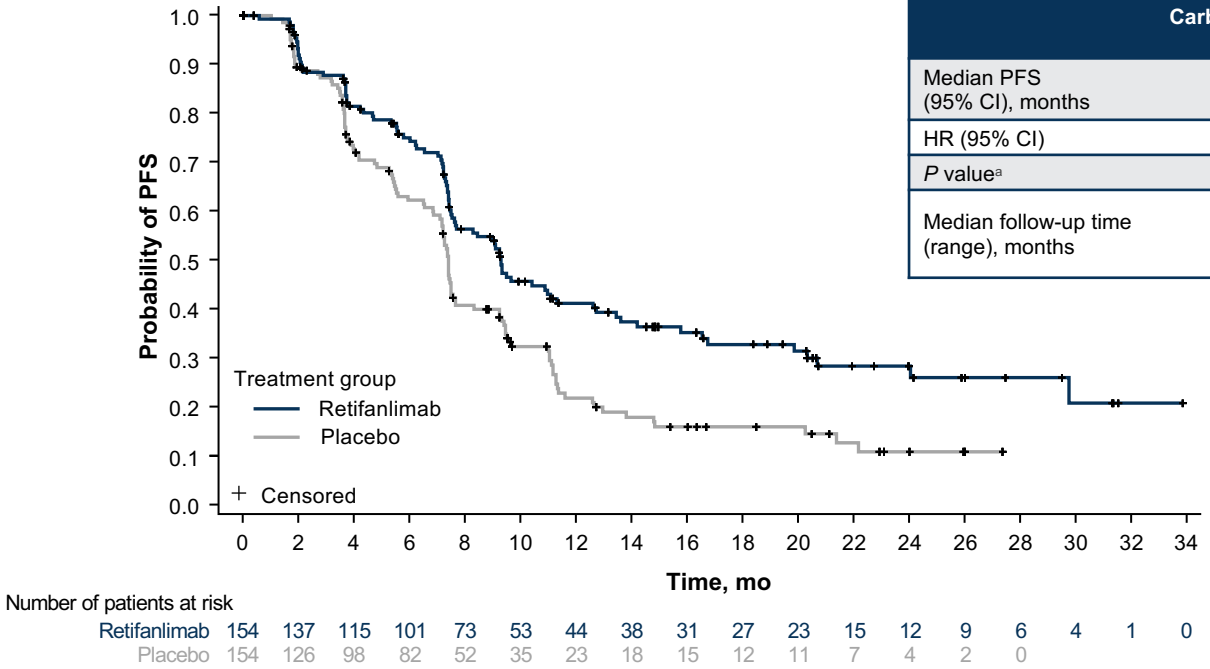
Patient Demographics and Characteristics (ITT Population)

Characteristic	Placebo + Carboplatin–Paclitaxel (n = 154)	Retifanlimab + Carboplatin–Paclitaxel (n = 154)
Median age, years	61	62
Female, %	77	68
White, %	89	86
Prior RT, %	73	68
Metastatic disease, %*	**83**	**82**
Liver, %	36	36
ECOG PS 0, %	56	53
HIV+, %	3	4
PD-L1 expression status ≥1, %[a,b]	**91**	**90**

[a] Stratification factor. [b] PD-L1 expression <1 also includes non-evaluable patients.

1. Rao S et al. ESMO 2024. Abstract # LBA2.

PFS by BICR (Primary Endpoint)

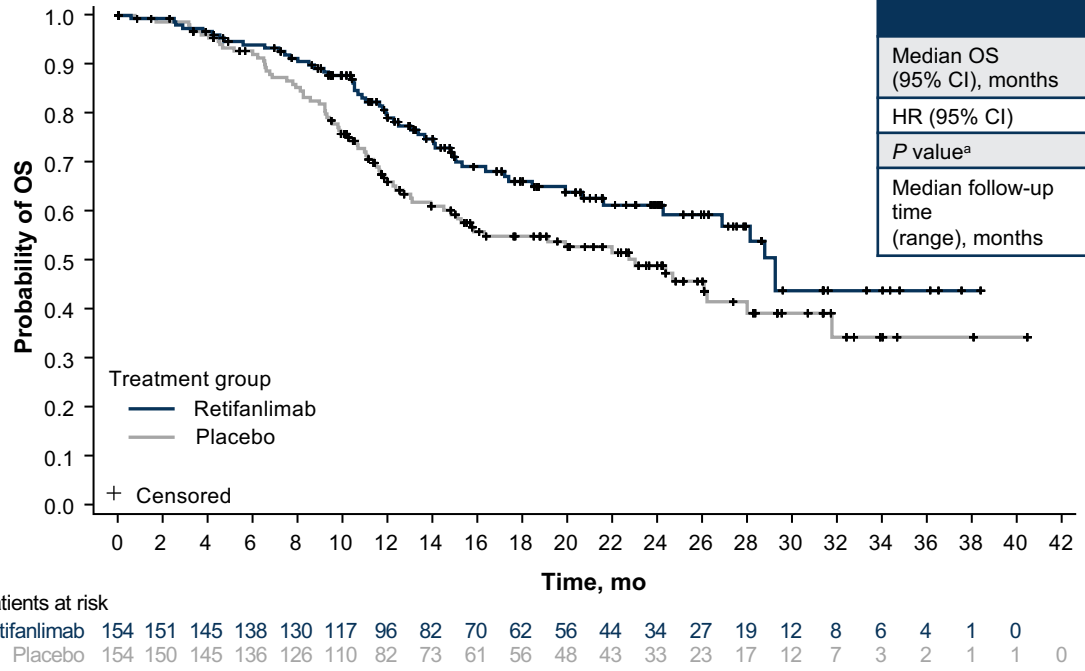


	Placebo + Carboplatin–Paclitaxel (n = 154)	Retifanlimab + Carboplatin–Paclitaxel (n = 154)
Median PFS (95% CI), months	7.4 (7.1, 7.7)	9.3 (7.5, 11.3)
HR (95% CI)		**0.63 (0.47, 0.84)**
P value[a]		**.0006**
Median follow-up time (range), months	7.1 (0.0, 27.4)	7.6 (0.0, 33.9)

[a] Stratified log-rank test with a 1-sided significance level of 2.5%. Stratification factors: region of the world, extent of disease and PD-L1 expression status.

1. Rao S et al. ESMO 2024. Abstract # LBA2.

OS (Interim Analysis)

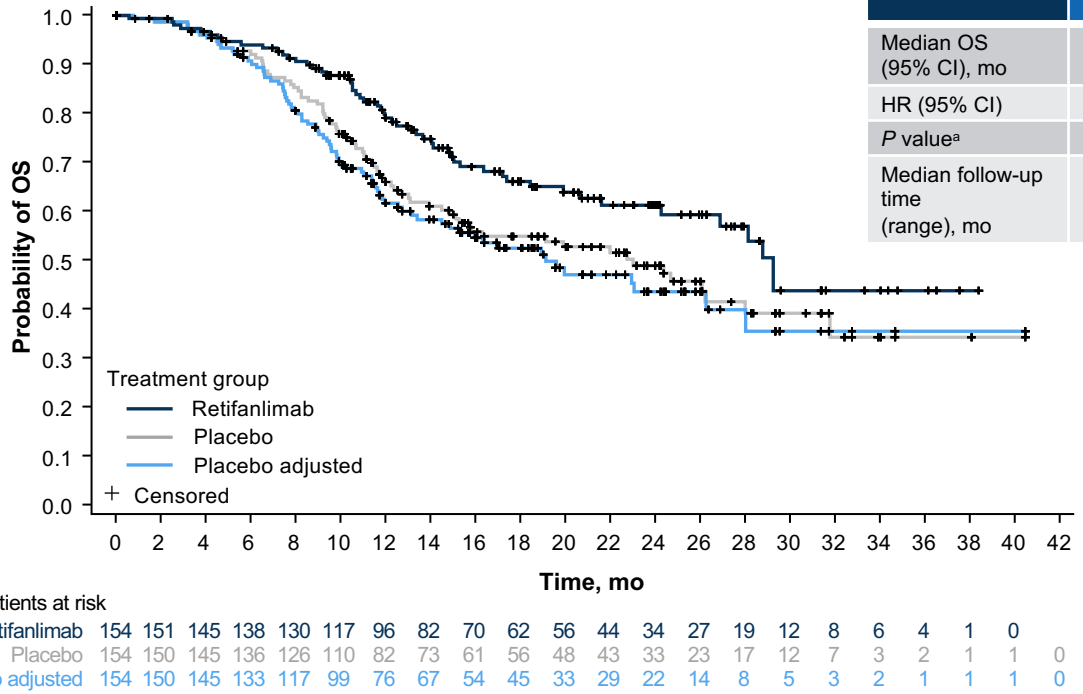


	Placebo + Carboplatin–Paclitaxel (n = 154)	Retifanlimab + Carboplatin–Paclitaxel (n = 154)
Median OS (95% CI), months	23.0 (15.1, 27.9)	29.2 (24.2, NE)
HR (95% CI)		**0.70 (0.49, 1.01)**
P value[a]		**0.0273**
Median follow-up time (range), months	12.9 (0.0, 40.4)	14.8 (0.6, 38.3)

[a] Stratified log-rank test with a 1-sided significance level of 1.2% at this interim look.
Stratification factors: region of the world, extent of disease and PD-L1 expression status.

1. Rao S et al. ESMO 2024. Abstract # LBA2.

OS Adjusted for Crossover



	Placebo + Carboplatin–Paclitaxel (Adjusted; n = 154)	Retifanlimab + Carboplatin–Paclitaxel (n = 154)
Median OS (95% CI), mo	19.1 (13.4, 27.9)	29.2 (24.2, NE)
HR (95% CI)		**0.63 (0.44, 0.90)**
P value[a]		**.0055**
Median follow-up time (range), mo	12.0 (0.0, 40.4)	14.8 (0.6, 38.3)

[a] Nominal *P* value.

1. Rao S et al. ESMO 2024. Abstract # LBA2.

Secondary Efficacy[a]

	Placebo + Carboplatin–Paclitaxel (n = 154)	Retifanlimab + Carboplatin–Paclitaxel (n = 154)
ORR (95% CI), % CR, %	44 (36, 52) 14	56 (48, 64) 22 ***P* = .0129[b]**
Median DOR (95% CI), months	7.2 (5.6, 9.3)	14.0 (8.6, 22.2)
DCR (95% CI), %	80 (73, 86)	87 (81, 92)

[a] Results by BICR. [b] Nominal *P* value for ORR.

1. Rao S et al. ESMO 2024. Abstract # LBA2.

InterAACT vs POD1UM-303/InterAACT 2[1,2]

Treatment	InterAACT 1 (Rao, 2020[1])	POD1UM-303/InterAACT 2	
	Carboplatin–Paclitaxel	Placebo + Carboplatin–Paclitaxel	Retifanlimab + Carboplatin–Paclitaxel
n	91	154	154
Participating countries	UK, AU, Norway, US	EU, AU, JPN, US, PR	
Demographics and disease characteristics[a] Median age, years Female, % White/other, % HIV+, % Metastatic, % ECOG PS 0 or 1	 61 67 NS 5 88 93	 62 72 87/13 4 82 100	
Median number of chemotherapy cycles	6	6	6
ORR, % (95% CI) CR, %	59 (42, 74) 13	44 (36, 52) 14	
Median PFS, months (95% CI)	8.1 (6.6, 8.8)	7.4 (7.1, 7.7)	
Median OS, months (95% CI)	20.0 (12.7, NE)	23.0 (15.1, 27.9)	

[a] Entire study population.

1. Rao S et al. *J Clin Oncol.* 2020;38(22):2510-2518. 2. Rao S et al. ESMO 2024. Abstract # LBA2.

Safety Summary

Variable	Placebo + Carboplatin–Paclitaxel (n = 152)	Retifanlimab + Carboplatin–Paclitaxel (n = 154)	Total (N = 306)
Median treatment duration, months	6.8	7.4	7.2
Patients with any TEAEs, n (%)	152 (100)	154 (100)	306 (100)
Patients with ≥ grade 3 TEAEs, n (%)	114 (75.0)	128 (83.1)	242 (79.1)
Patients with grade 5 TEAEs, n (%)	1 (0.7)[a]	4 (2.6)[b]	5 (1.6)
Patients with SAEs, n (%)	59 (38.8)	73 (47.4)	132 (43.1)
Treatment-related SAEs, n (%)	10 (6.6)	25 (16.2)	35 (11.4)
Immune-related AEs, n (%)	36 (23.7)	71 (46.1)	107 (35.0)
AEs leading to discontinuation, n (%)	4 (2.6)	17 (11.0)	21 (6.9)

- Safety of retifanlimab plus chemotherapy consistent with prior phase 2 data and known CPI literature in SCAC
- No loss of HIV control/viral load observed in patients with HIV
- At data cutoff, 90 patients (58.4%) in the retifanlimab arm remained on study

[a] Patient had a fatal event of pneumonia. [b] 1 patient each had a fatal event of metastases to peritoneum, pancytopenia, pneumonia and sepsis.

1. Rao S et al. ESMO 2024. Abstract # LBA2.

TEAEs by Preferred Term

Most Common (≥3%) Grade 3 or Higher TEAEs

MedRA Preferred Term	Placebo + Carboplatin–Paclitaxel (n = 152)	Retifanlimab + Carboplatin–Paclitaxel (n = 154)	Total (N = 306)
Neutropenia	45 (29.6)	54 (35.1)	99 (32.4)
Anemia	31 (20.4)	30 (19.5)	61 (19.9)
Neutrophil count decreased	13 (8.6)	26 (16.9)	39 (12.7)
White blood cell count decreased	13 (8.6)	14 (9.1)	27 (8.8)
Diarrhea	9 (5.9)	8 (5.2)	17 (5.6)
Leukopenia	6 (3.9)	6 (3.9)	12 (3.9)
Asthenia	5 (3.3)	6 (3.9)	11 (3.6)
Sepsis	6 (3.9)	5 (3.2)	11 (3.6)
Pulmonary embolism	5 (3.3)	5 (3.2)	10 (3.3)
Vomiting	6 (3.9)	4 (2.6)	10 (3.3)

Most Common (≥2%) Immune-Related TEAEs

MedRA Preferred Term	Placebo + Carboplatin –Paclitaxel (n = 152)	Retifanlimab + Carboplatin–Paclitaxel (n = 154)	Total (N = 306)
Peripheral sensory neuropathy	15 (9.9)	17 (11.0)	32 (10.5)
Hypothyroidism	5 (3.3)	22 (14.3)	27 (8.8)
Hyperthyroidism	1 (0.7)	13 (8.4)	14 (4.6)
Pruritus	3 (2.0)	11 (7.1)	14 (4.6)
Adrenal insufficiency	0	8 (5.2)	8 (2.6)
Rash maculo-papular	3 (2.0)	3 (1.9)	6 (2.0)

1. Rao S et al. ESMO 2024. Abstract # LBA2.

Ongoing Plans

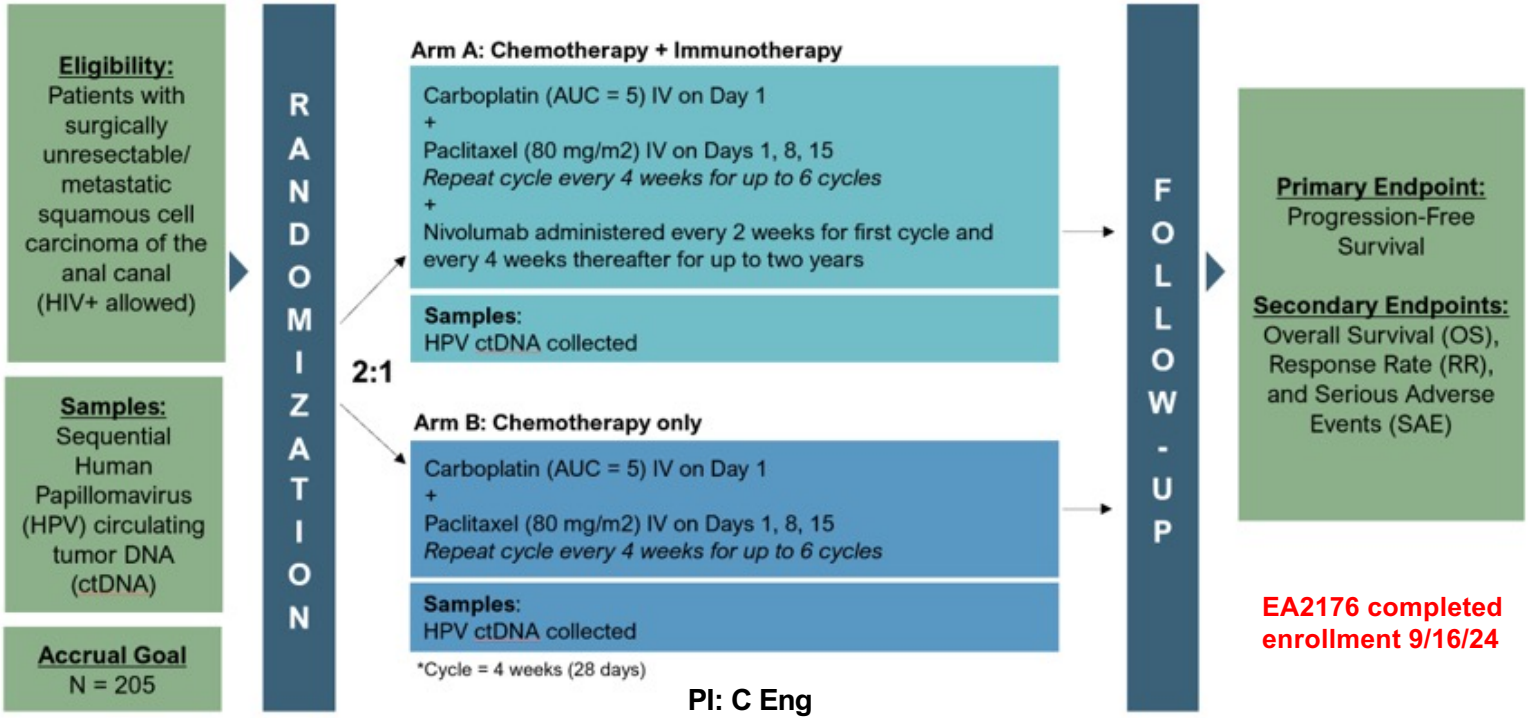
- Translational work from POD1UM 303
- Blood, tissue, and stool collection for analysis
- Correlative work with efficacy endpoints
- Understanding potential resistance mechanisms
- Identify relevant biomarkers

Take-Home Messages

- Advanced SCAC is a rare disease and where possible patients should be entered into clinical trials
- New standard of care in first line with retifanlimab and carboplatin/paclitaxel for patients with advanced or locally recurrent inoperable SCAC
- Immunotherapy combined with chemotherapy appears more effective than monotherapy in advanced anal cancer
- More work on biomarkers of response needed including PD-L1 and CPS
- Patients with metastatic liver disease do benefit form this combination
- Further trials needed in second line setting

Future Directions and Other Exploratory Investigations

EA2176: Phase 3 Clinical Trial of Carboplatin and Paclitaxel +/- Nivolumab in Treatment-Naïve Metastatic Anal Cancer Patients[1]



EA2176 completed enrollment 9/16/24

*HIV pts eligible

PI: C Eng
Co-PI's: Ciombor and A Benson
Statistician: Paul Catalano

1. https://clinicaltrials.gov/study/NCT04444921.

EA2176 Eligibility

- Histologically or cytologically confirmed previously untreated surgically unresected metastatic squamous cell carcinoma of the anal canal (SCCA)
- Measurable disease according to the standard RECIST version 1.1; CT scans or MRIs within 28 days of drug initiation
- Age ≥18 years at the time of study registration
- ECOG performance status 0 or 1 (Karnofsky ≥ 80 %)
- If HIV positive, CD4 ≥ 200
- No prior immunotherapy
- No prior malignancy other than basal cell, SCC, or CIS of the cervix

1. https://clinicaltrials.gov/study/NCT04444921.

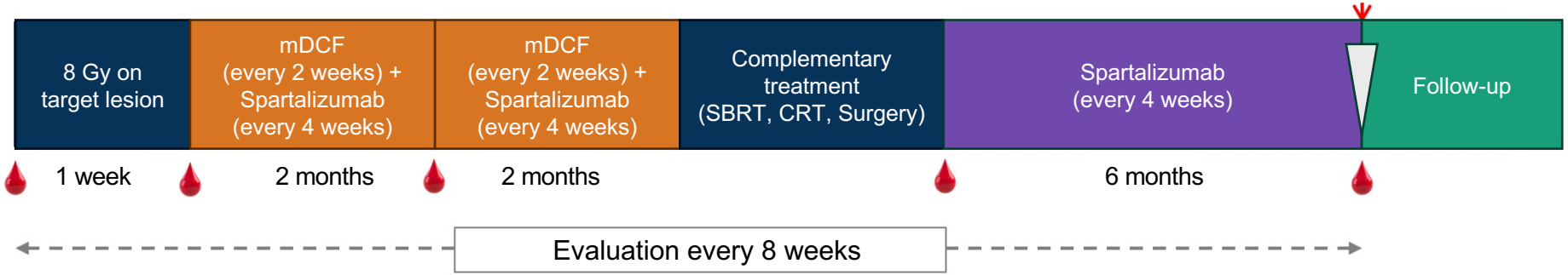
EA2176 Statistical Design and Correlatives

- The study assumes a median PFS of **8** months in the control arm and will target a **PFS hazard ratio** of **0.625** under exponential failure which translates to an experimental PFS median of **12.8** months
- For the PFS endpoint, to maintain at least 80% power using a stratified two-sided overall .05 level log-rank test as the primary analysis will require **160 total PFS events** and accrual of **205** patients (195 patients plus 5% to allow for drop-out) over 26 months with 14 months of follow-up (40 months total)
- HPV ctDNA has been correlated with tumor response in other HPV-driven malignancies
- EA2176 investigators will utilize SafeSEQ NGS to quantify serum HPV ctDNA during treatment at various timepoints (up to 5 collections per patient)

1. https://clinicaltrials.gov/study/NCT04444921.

Phase 2 SPARTANA Study: Spartalizumab, mDCF, and Radiotherapy in Patients With mSCAC[1]

Primary objective
- PFS rate at 12 months



- Primary endpoint: 1-year PFS rate
- Secondary endpoints: OS, RR, safety, HRQOL, biomarkers

1. https://clinicaltrials.gov/study/NCT04894370.

Immunotherapy is Also Being Evaluated for Localized SCAC[1]

Localized Disease			Treatment	Trial Number	Phase
Neoadjuvant	**Concomitant**	**Adjuvant**			
		NCI-EA2165	Nivolumab + IMRT	NCT03233711	III
	INTERACT-ION		Ezabenlimab + mDCF + IMRT	NCT04719988	II
	RADIANCE		Durvalumab + IMRT	NCT04230759	II
	CORINTH		Pembrolizumab + IMRT	NCT04046133	I/II
	BrUOG 276		ADXS11-001 + IMRT	NCT01671488	I/II

1. Spehner et al. *Cancers (Basel).* 2021;13(15):3895.

Take-Homes and Future Directions

- IO is moving to earlier lines and disease settings
- SOC for early-stage anal cancer is established, but has some toxicity concerns
  - Room to improve earlier stages of disease with established agents in mSCAC
- Importance of performing NGS panels in anal cancers
- Future for potential biomarkers
  - Need better biomarkers for response to IO and chemotherapy
  - Necessity for biomarkers to assess for response to treatment
  - Other targets of interest?

Translating Science Into Routine Patient Care

Case-Based Instruction On Integrating Immunotherapies in Metastatic Anal Cancer

Patient Case 1: A 65-Year-Old Patient With Progressive mSCAC

- A 65-year-old female patient with advanced SCAC
- Received upfront carboplatin + paclitaxel
- Upon follow up, imaging reveals increased tumor volume and elevated HPV ctDNA, indicating relapsed disease

Discussion

- How would you approach subsequent treatment selection? Chemotherapy? IO?
- Given you are considering a 2L IO option, what patient-specific factors would you take into account?

Case 1 Continued: Considerations for Immune Checkpoint Inhibitor Monotherapy

- A 65-year-old female patient with advanced SCAC
- Received upfront carboplatin + paclitaxel
- Upon follow up, imaging reveals increased tumor volume and elevated HPV ctDNA, indicating relapsed disease
- **The patient is initiated on retifanlimab**

Discussion

- How would you plan to counsel the patient on potential AEs?
- What AEs should you monitor for?
- What monitoring strategies would you employ?

Case 1 Continued: Strategies for Assessment and Management of irAEs

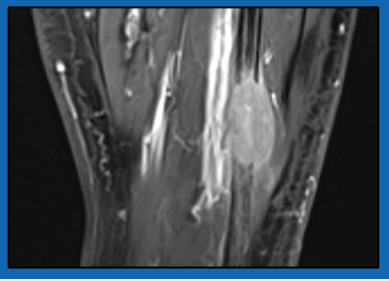
- A 65-year-old female patient with advanced SCAC
- Received upfront carboplatin + paclitaxel
- Upon follow up, imaging reveals increased tumor volume and elevated HPV ctDNA, indicating relapsed disease
- The patient is initiated on retifanlimab
- **Subsequently, the patient reports an itchy skin rash**

Discussion

- How would you initially assess her dermatologic condition?
- Given her pruritis is determined to be immune-related, how would you manage this AE?
- Grade 1 vs 2?
- **Case variation:**
  What if the patient presented with a different AE? How would you approach managing GI symptoms?

Patient Case 2: A 69-Year-Old Patient With Newly Diagnosed mSCAC

- A 69-year-old male patient with a history of HIV
- Biopsy reveals squamous cell histology
- CT/MRI shows a large tumor (8 cm) extending to the lower rectum
  - Bilobar liver nodules (largest is 5 cm)
  - Nodule in the left leg



Discussion

- How would you approach 1L treatment selection for this patient?
- Would you consider biomarker testing prior to selecting therapy?
- Would you consider newer therapeutic combination regimens?
- Given you elect to initiate retifanlimab + carboplatin/paclitaxel, what patient-specific factors would you consider to determine eligibility?
- Unique AEs with this combination?

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- Complete and submit your post-test and evaluation for credit
- Download the slides and Practice Aids
- Watch the replay of this event in the next 24 hours and the online activity in the coming weeks

Thank you for joining us!

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Abbreviations

1L: first line
2L: second line
5-FU: 5-fluorouracil
ACF: Anal Cancer Foundation
ASCO: American Society of Clinical Oncology
AU: Australia
BICR: blinded independent central review
CD4: cluster of differentiation 4
CIS: cisplatin
CP: carboplatin-paclitaxel
CPI: checkpoint inhibitor
CPS: combined positive score
CR: complete response
CRR: complete remission rate
CRT: chemoradiotherapy
ctDNA: circulating tumor DNA
CTLA4: cytotoxic T-lymphocyte–associated protein 4
DCF: docetaxel/cisplatin/fluorouracil
DCR: disease control rate
DOR: duration of response
ECOG PS: Eastern Cooperative Oncology Group performance status
ECOG: Eastern Cooperative Oncology Group
ESMO: European Society for Medical Oncology
EU: European Union
HPV: human papillomavirus
HRQoL: health-related quality of life
hTERT: human telomerase reverse transcriptase
IHC: immunohistochemistry
IJMS: International Journal of Medical Students
IMRT: intensity-modulated radiation therapy
IO: immunotherapy
irAE: immune-related adverse event
JITC: Journal for ImmunoTherapy of Cancer
mDCF: modified docetaxel, cisplatin, fluorouracil
mSCAC: metastatic squamous cell carcinoma of the anal canal
NA: North America
NCCN: National Comprehensive Cancer Network
NE: not evaluable
NGS: next-generation sequencing
NS: not shown
OPC: oropharyngeal cancer
ORR: objective response rate
PD-1: programmed cell death protein 1
PD-L1: programmed death-ligand 1
PD: progressive disease
PK: pharmacokinetics
PRO: patient-reported outcome
Q2W: every 2 weeks
Q4W: every 4 weeks
RECIST: Response Evaluation Criteria in Solid Tumors
ROW: rest of the world
RR: response rate
RT: radiation therapy
SAE: severe/serious adverse event
SBRT: stereotactic body radiation therapy
SCAC: squamous cell carcinoma of the anal canal
SCC: squamous cell carcinoma
SCCA: squamous cell carcinoma antigen
SOC: standard of care
TEAE: treatment-emergent adverse event
UK: United Kingdom
VEGF: vascular endothelial growth factor