Great Debates
Solid Tumors

Anal Squamous Cell Carcinoma: Enhancing Outcomes with Immune Checkpoint Inhibitors

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Disclosures

- **Cathy Eng, MD, FACP, FASCO:** Consultant—Abbvie, Amgen, Elevation, GSK, GE, IGM, Merck, Natera, Pfizer, Seagen, Takeda, Taiho

This CME activity includes brand names for participant clarity purposes only.
No product promotion or recommendation should be inferred.

Learning Objectives

- Evaluate the efficacy and safety of ICIs in anal SCC, focusing on the latest clinical trial data
- Assess current challenges and unmet needs in the standard of care for patients with anal SCC, including management of comorbidities and immune-related adverse events
- Discuss strategies to enhance interdisciplinary collaboration and engage patients in shared decision-making discussions about therapy options for anal SCC

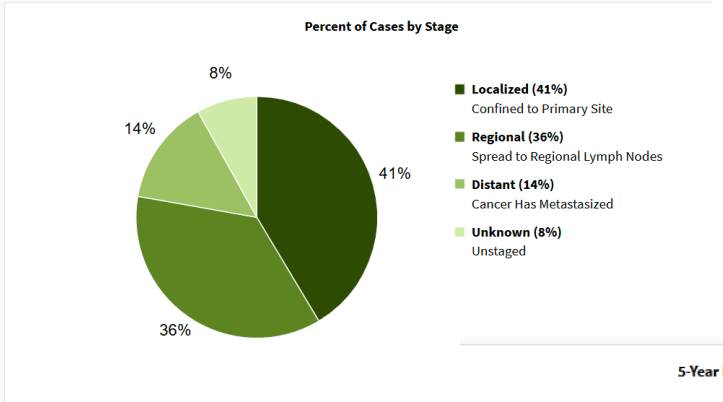
ICI = immune checkpoint inhibitor; SCC = squamous cell carcinoma.

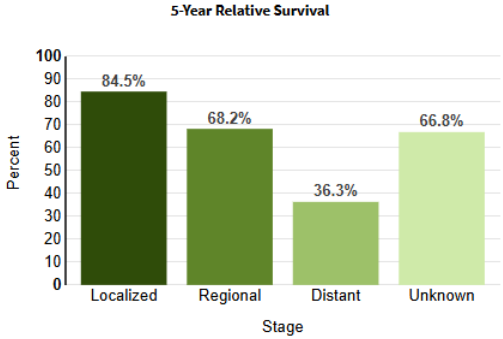
Incidence of Anal Cancer

At a Glance

Estimated New Cases in 2024	10,540
% of All New Cancer Cases	0.5%
Estimated Deaths in 2024	2,190
% of All Cancer Deaths	0.4%

Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Anal Cancer





National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program [seer.cancer.gov]. https://seer.cancer.gov/statfacts/html/anus.html.

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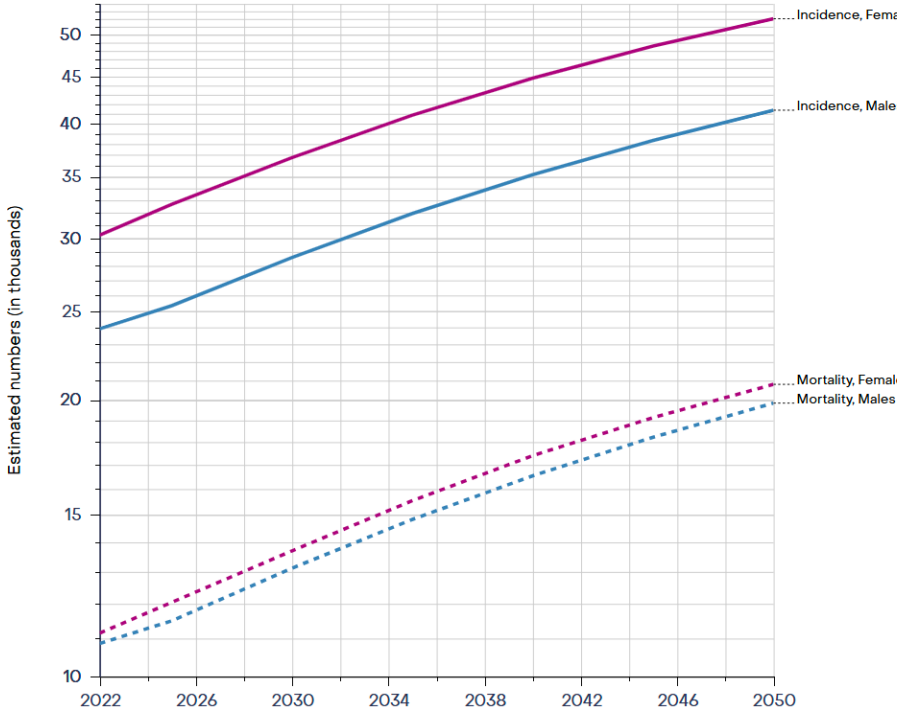
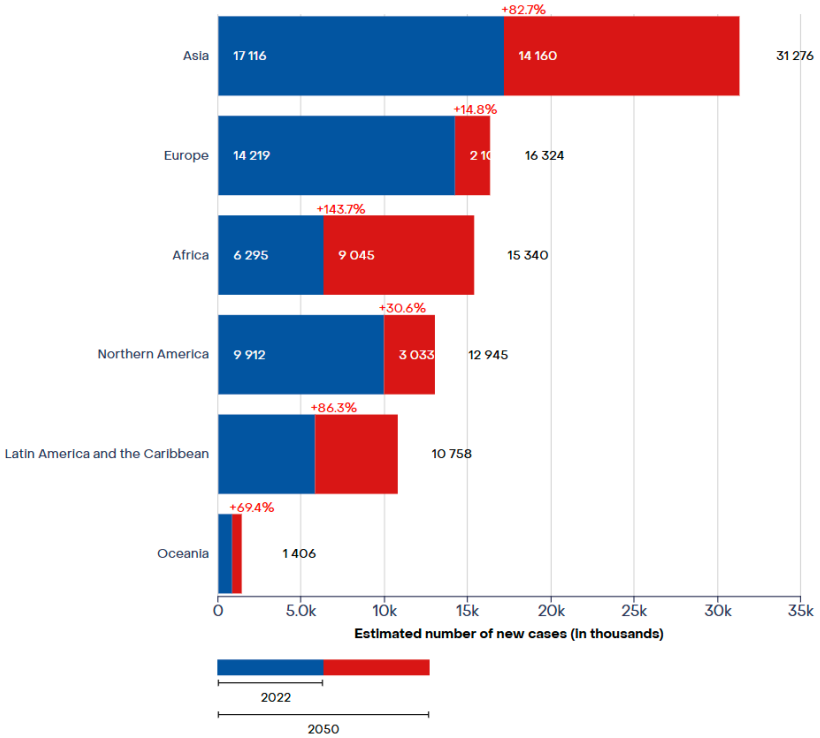
Global Incidence

Global incidence: 54.1K (2022) to 93.4K (2050)





World Health Organization (WHO) International Agency for Research on Cancer (IARC) [gco.iarc.who.int]. https://gco.iarc.who.int/en.

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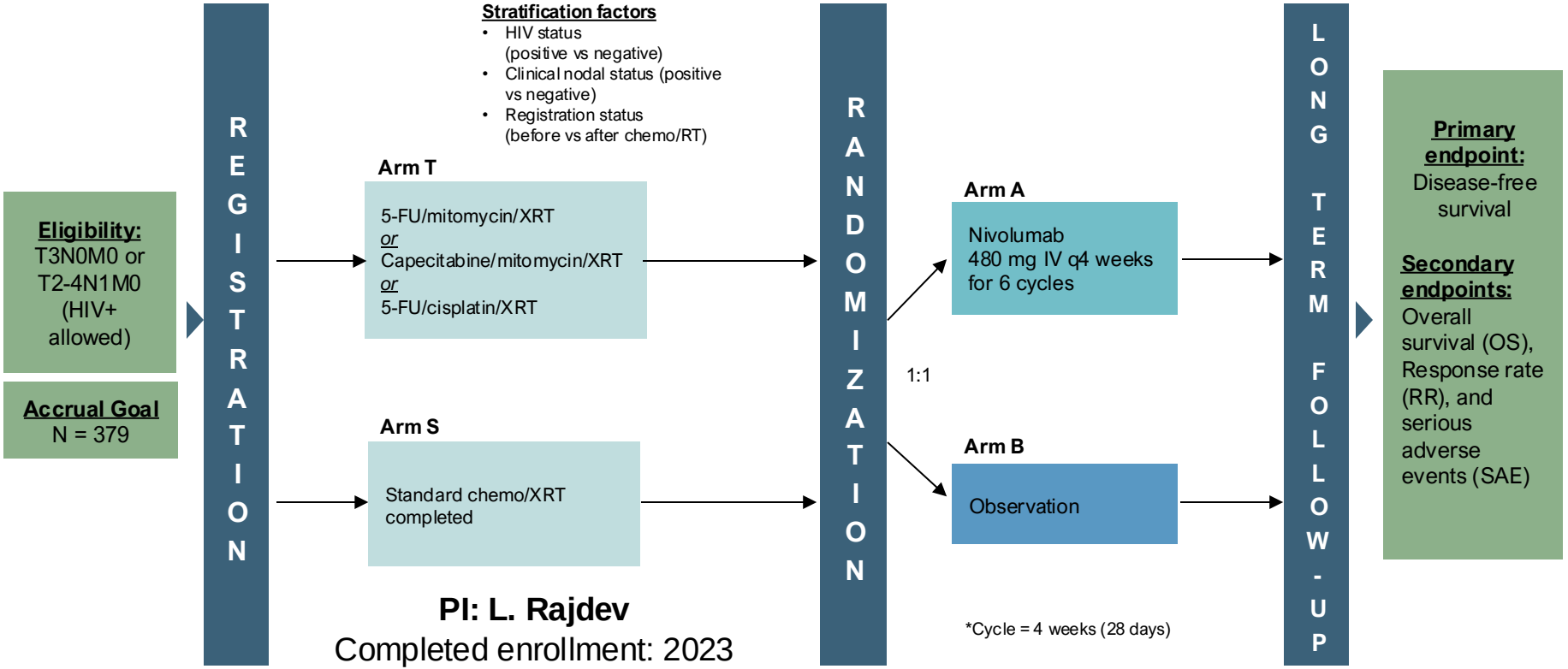
Historic Immunotherapy Trials in Met Anal CA

Drug	Phase	N	Dose	Primary endpoint	Secondary Endpoints
NCI9673: Nivolumab (Part A)	II	34	3 mg/kg IV q2 wks	ORR: 24% (2CR's)	PFS: 4.1M OS: 11.5M
Pembrolizumab (KN 158)	I/II	112	200 mg IV q3 wks	ORR:11% (No CR's)	PFS: 2.0M OS: 11.9M
Retifanlimab (POD1UM-202)	II	94	500 mg IV q 4 wks	ORR: 14% (1CR)	PFS: 2.3M OS:10.1M

CA = cancer; ORR = objective response rate; PFS = progression-free survival; OS = overall survival.

Morris VK, et al. *Lancet Oncol*. 2017;18(4):446-453. Marabelle A, et al. *Lancet Oncol*. 2020;21(10):1353-1365. Rao S, et al. ESMO Open. 2022;7(4):100529.

EA2165: A Randomized Phase III Study of Nivolumab after Combined Modality Therapy (CMT) in High-Risk Anal Cancer



PI: L. Rajdev

Completed enrollment: 2023

Final results pending

XRT = radiotherapy.

ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated April 22, 2024. https://clinicaltrials.gov/study/NCT03275311.

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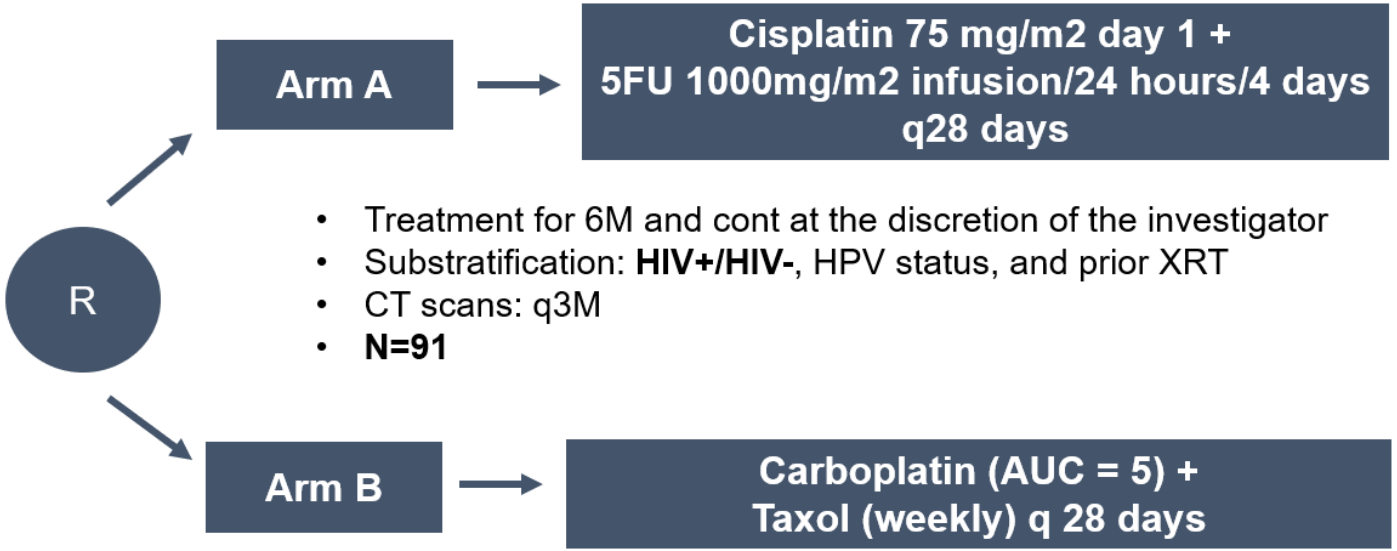
International Rare Cancer Initiative (IRCI)/ECOG EA#2133 InterAACT: Treatment-Naïve Met SCCA

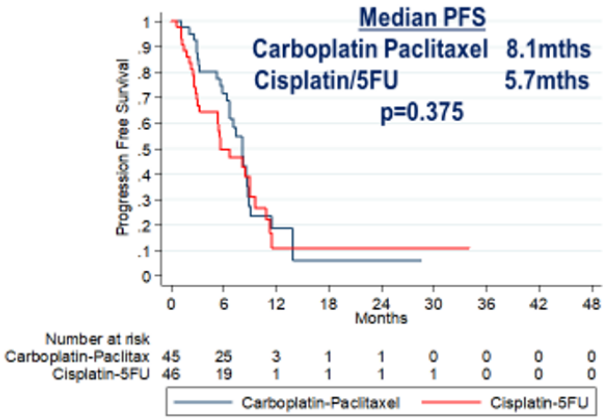


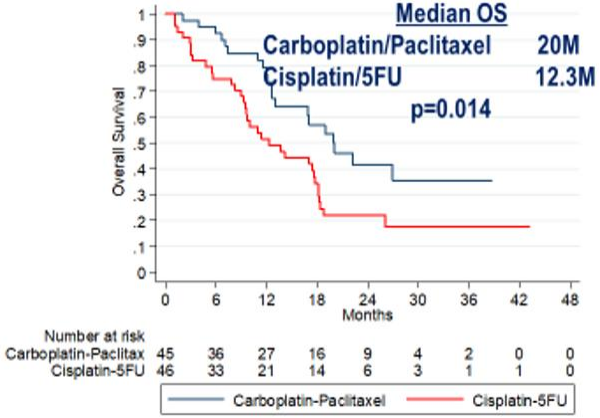
- Treatment for 6M and cont at the discretion of the investigator
- Substratification: **HIV+/HIV-**, HPV status, and prior XRT
- CT scans: q3M
- **N=91**

ECOG = Eastern Cooperative Oncology Group; SCCA = squamous cell carcinoma of the anus; HPV = human papillomavirus; CT = computed tomography; AUC = area under the curve.

Rao S, et al. *J Clin Oncol*. 2020;38(22):2510-2518.

International Rare Cancer Initiative (IRCI)/ECOG EA#2133 InterAACT: Treatment-Naïve Met SCCA





Response (RECIST)	Carboplatin-Paclitaxel N=39		Cisplatin-5FU N=35	
	N	(%) CI	N	(%)
CR	5	12.8	5	14.3
PR	18	46.2	15	42.9
SD	10	25.6	7	20.0
PD	6	15.4	8	22.9
CR/PR	23	59	20	57
		95% CI: [42.1-74.4]		*95% CI: [39.4-73.7]*

RECIST = response evaluation criteria in solid tumors; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

Rao S, et al. *J Clin Oncol*. 2020;38(22):2510-2518.

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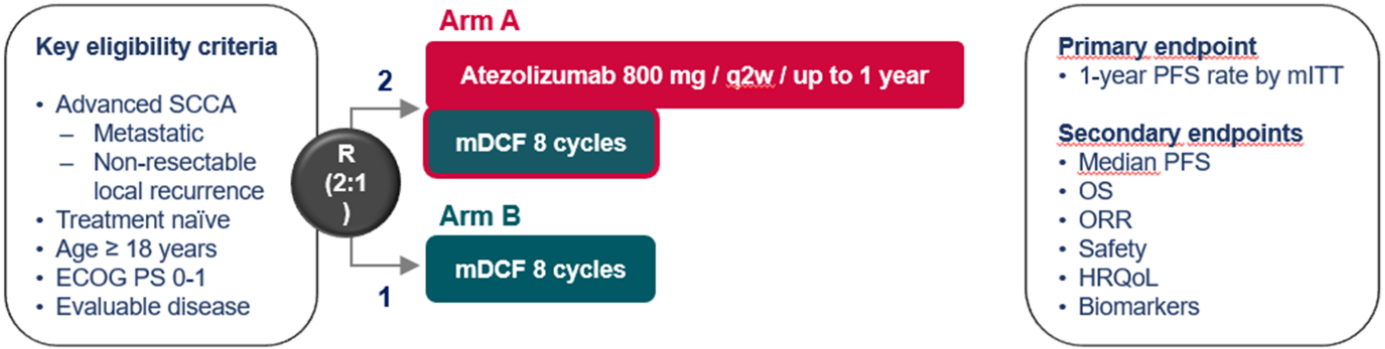
Other Chemotherapy Backbone

Atezolizumab plus modified DCF (docetaxel, cisplatin, and 5-fluorouracil) as first-line treatment for metastatic or locally advanced squamous cell anal carcinoma (SCCA). A SCARCE-PRODIGE 60 randomized phase II study

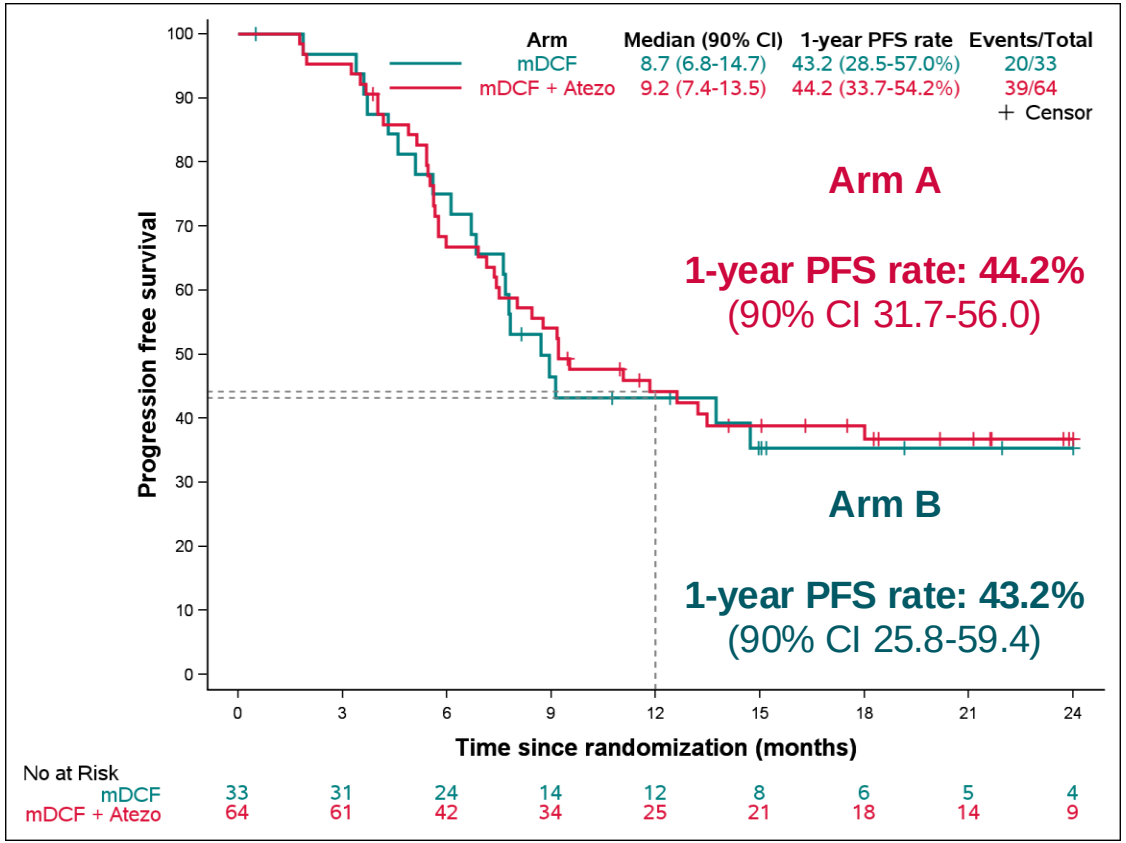


Stratification: age (<65 vs ≥65 years), stage (synchronous metastatic vs metachronous metastatic vs locally advanced unresectable disease without metastasis)

PS = performance status; mDCF = modified docetaxel, cisplatin, and fluorouracil; mITT = modified intention to treat; HRQOL = health-related quality of life.

Kim S, et al. *Lancet Oncol*. 2024;25(4):518-528. Kim S, et al. *J Clin Oncol*. 2022;40(16 Suppl):3508.

Other Chemotherapy Backbone



Kim S, et al. *Lancet Oncol*. 2024;25(4):518-528. Kim S, et al. *J Clin Oncol*. 2022;40(16 Suppl):3508.

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SCARCE: Secondary Endpoint

	All (N=97)	Arm A (N=64)	Arm B (N=33)
Objective response, n (%)	72 (**75.8**)	47 (**74.6**)	25 (**78.1**)
Complete response	34 (35.8)	19 (30.2)	15 (46.9)
Partial response	38 (40.0)	28 (44.4)	10 (31.3)
Stable disease	20 (21.1)	14 (22.2)	6 (18.8)
Progression disease	3 (3.2)	2 (3.2)	1 (3.1)
Missing	2	1	1
1-year OS rate, % (95% CI)		**77.7** (68.1-88.7)	**80.8** (68.1-95.9)

Kim S, et al. *Lancet Oncol*. 2024;25(4):518-528. Kim S, et al. *J Clin Oncol*. 2022;40(16 Suppl):3508.

SCARCE: Adverse Events

	All (N=97)	Arm A (n=64)	Arm B (n=33)
Grade 3-4 AE, n (%)	48 (51.1)	36 (**59.0**)	12 (**36.4**)
Most frequent (≥ 5%) grade 3-4 AE, n (%)			
Diarrhea	8 (8.5)	7 (**11.5**)	1 (3.0)
Fatigue	7 (7.4)	3 (4.9)	4 (**12.1**)
Anemia	11 (11.7)	10 (**16.4**)	1 (3.0)
Neutropenia	14 (14.9)	9 (14.8)	5 (15.2)
Febrile neutropenia	2 (2.1)	1 (1.6)	1 (3.0)
Treatment-related SAE	20 (20.6)	16 (**25.0**)	4 (12.1)

Kim S, et al. *Lancet Oncol*. 2024;25(4):518-528. Kim S, et al. *J Clin Oncol*. 2022;40(16 Suppl):3508.

Comparison of the Two Phase II Trials

	IRCI InterAACT (EA2133)	EPITOPES HPV-02
Study design	**Randomized phase II**	**Single arm**
Chemotherapy	5-FU/cisplatin vs carbo/paclitaxel (C/P)	Docetaxel/cisplatin/5-FU
Primary endpoint	RR (or least toxic)	12M PFS
Sites	31 centers (global)	25 centers (France)
N	**91**	66 [**30** pts (mDCF)]
Median follow-up	28.6 M	19.8 M
RR	57%-58% (CR: 13%-17%)	89% [CR (45%)]; mDCF [ORR: 83%; CR (47%)]
Grade ¾ toxicities	62% (5-FU/Cis) vs **36% (C/P)** P < 0.016	83% DCF; **53% mDCF** (myelosuppression, n/v/d, asthenia, mucositis, etc.)
12M PFS	N/A	47% (N=66)
PFS	8.1M (C/P) vs 5.7M (5-FU/Cis; NS)	11M
OS	20M (C/P) vs 12.3M (5-FU/Cis; *P*=0.014)	N/A
Outcome: New Standard	Carbo/paclitaxel (global)	France

RR = response rate; n/v/d = nausea, vomiting, diarrhea.

Eng C. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; June 3-7, 2022; Chicago, Illinois.

Combination of Nivolumab/Ipilimumab

NCI9673 (Part B) Study Design

Primary Endpoint:
- Progression-free survival (PFS)

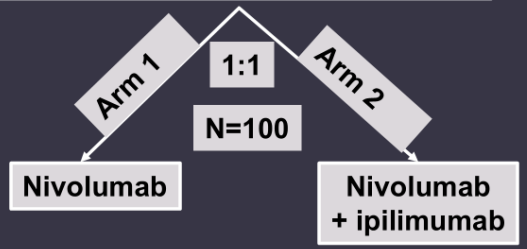
Secondary Endpoints:
- Overall response (RECIST 1.1)
- Overall survival (OS)
- Safety/toxicity (CTCAE v5)

Statistical Design:
- H_0: Median $PFS_{Arm2} \leq PFS_{Arm1}$
  H_a: Median $PFS_{Arm2} > PFS_{Arm1}$
- At a one-sided α=.10 and 90% power, 100 participants are needed to observe an improvement in median PFS from 4 to 7 months.

NCT02314169

Participants with:

- Unresectable or metastatic SCCA
- ≥1 prior line of systemic treatment

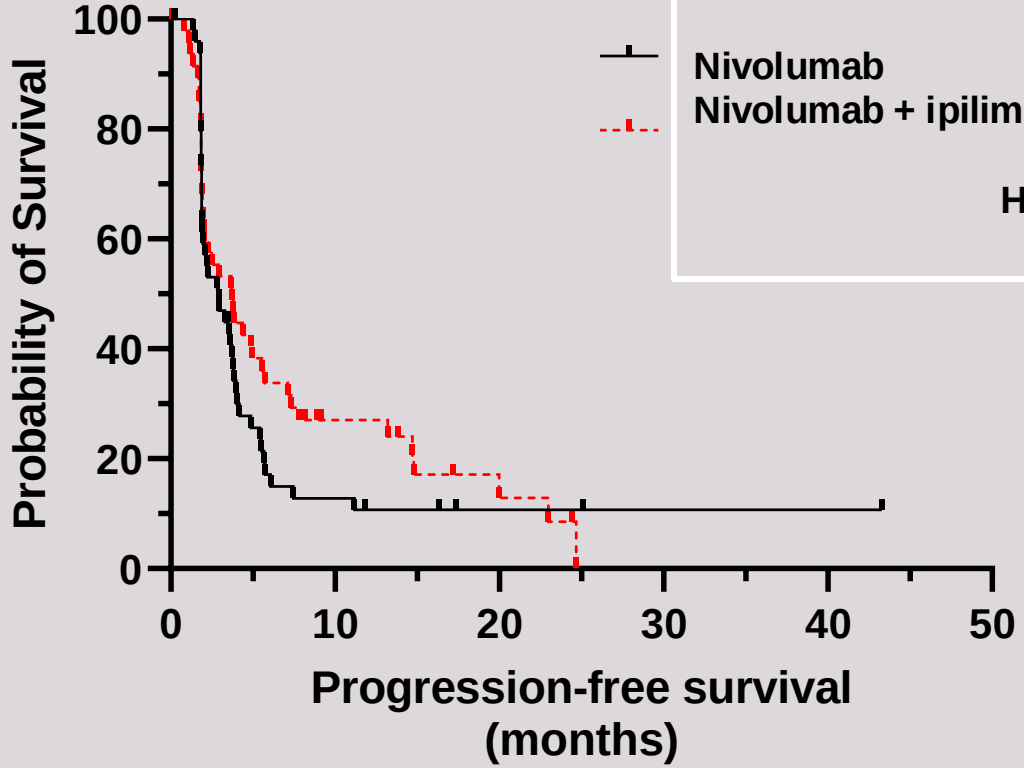


Study Treatment:

- **Nivolumab: 480 mg IV every 4 weeks**
- **Ipilimumab 1 mg/kg IV every 8 weeks (Arm 2 only)**

CTCAE = Common Terminology Criteria for Adverse Events.
Morris VK, et al. Presented at: European Society for Medical Oncology (ESMO) World Congress on Gastrointestinal Cancers; June 28-July 1, 2023; Barcelona, Spain. Abstract O-12.

Combination of Nivolumab/Ipilimumab



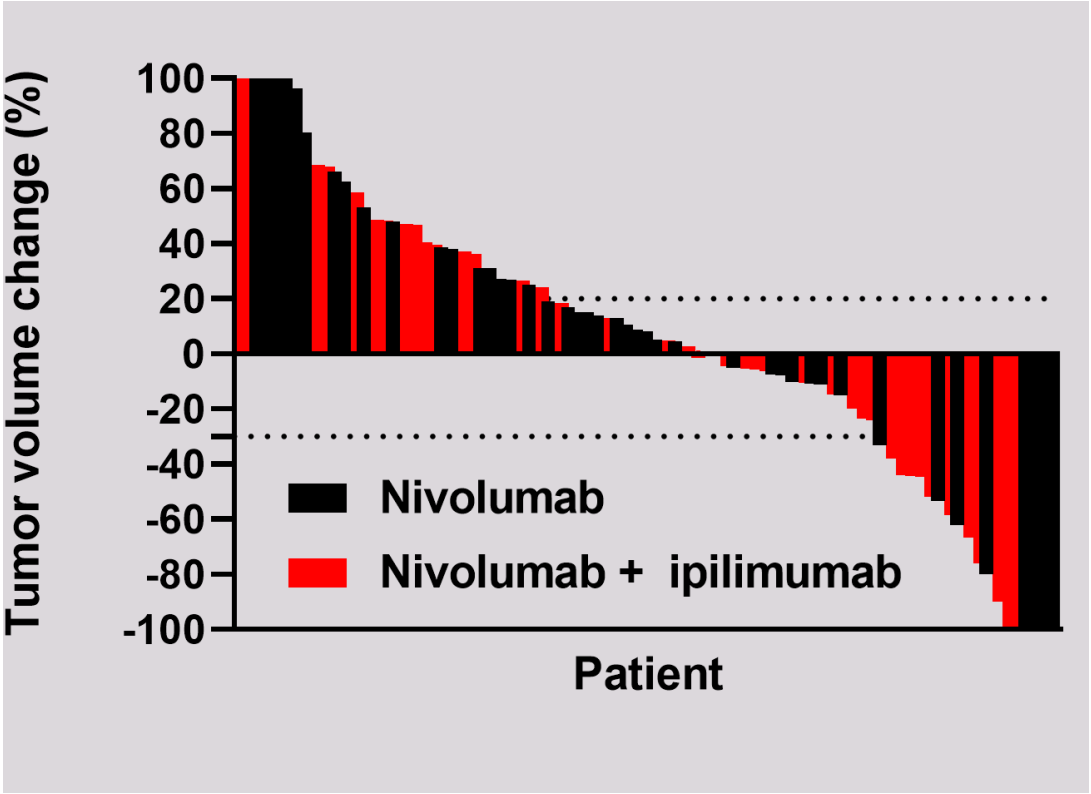
Median PFS (95% CI):

Nivolumab	2.9 months (1.9-4.0)
Nivolumab + ipilimumab	3.7 months (2.0-7.1)

HR 0.80 (95% CI, .52-1.2)
P=.16

Morris VK, et al. Presented at: ESMO World Congress on Gastrointestinal Cancers; June 28-July 1, 2023; Barcelona, Spain. Abstract O-12.

Combination of Nivolumab/Ipilimumab



Overall Response Rate (95% CI):

Nivolumab	17.4% (9.1-31)
Nivolumab + ipilimumab	21.5% (12-36)

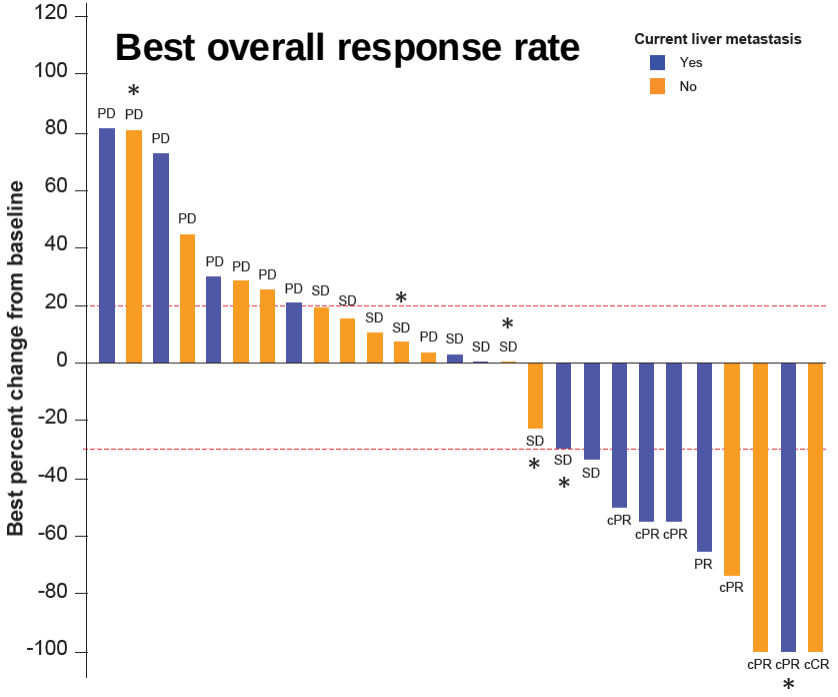
Disease Control Rate (95% CI):

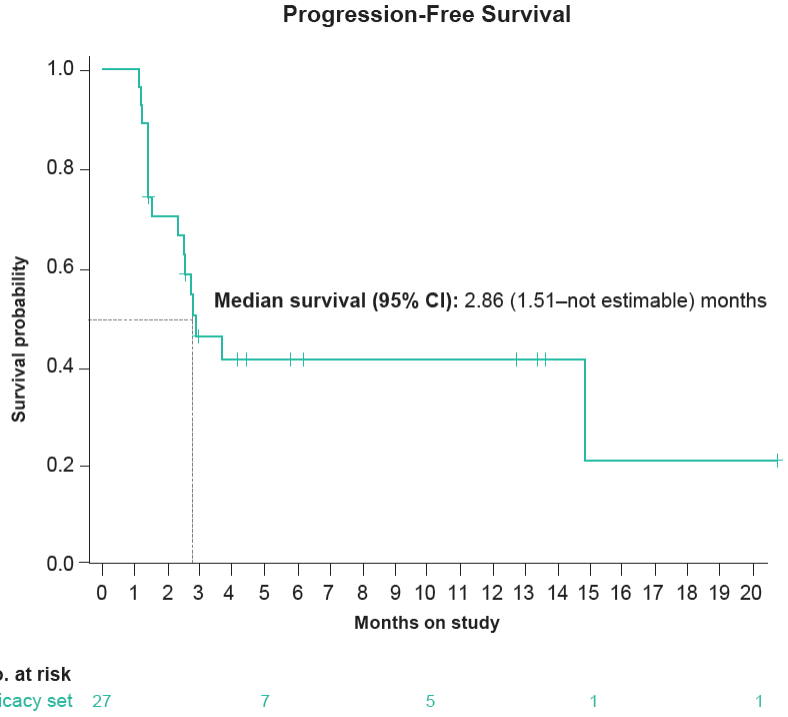
Nivolumab	43.5% (30-58)
Nivolumab + ipilimumab	47.6% (33-62)

	Nivolumab (%)	Nivolumab + Ipilimumab (%)
Complete Response	3 (6.5)	2 (4.8)
Partial Response	5 (10.9)	7 (16.7)
Stable Disease	12 (21.7)	11 (26.2)
Progressive Disease	26 (56.5)	22 (52.3)

Morris VK, et al. Presented at: ESMO World Congress on Gastrointestinal Cancers; June 28-July 1, 2023; Barcelona, Spain. Abstract O-12.

Other Investigational Agents: Bifunctional EGFR/TGF-B (BCA 101) + Pembrolizumab





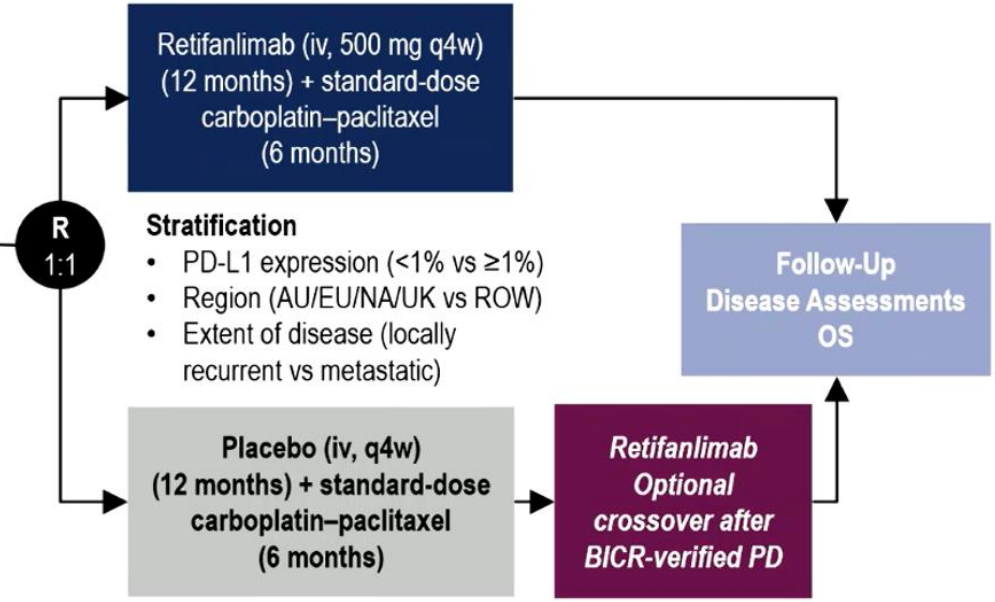
Morris VK, et al. *J Clin Oncol.* 2025;43(4 Suppl):4.

ESMO 2024: POD1UM-303/InterAACT2: Phase III Study of Carboplatin + Paclitaxel +/- Retifanlimab in Treatment-Naive Inoperable or Metastatic SCCA

Patients with locally recurrent or metastatic SCAC

- No prior chemotherapy except as radiosensitising 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



SCAC = squamous cell carcinoma of the anal canal; ROW = rest of the world; BICR = blinded independent central review; DOR = duration of response; PK = pharmacokinetics; PFS2 = PFS on second-line therapy; PROs = patient-reported outcomes.

Rao S, et al. *Ann Oncol*. 2024;35(Suppl 2):1-72.

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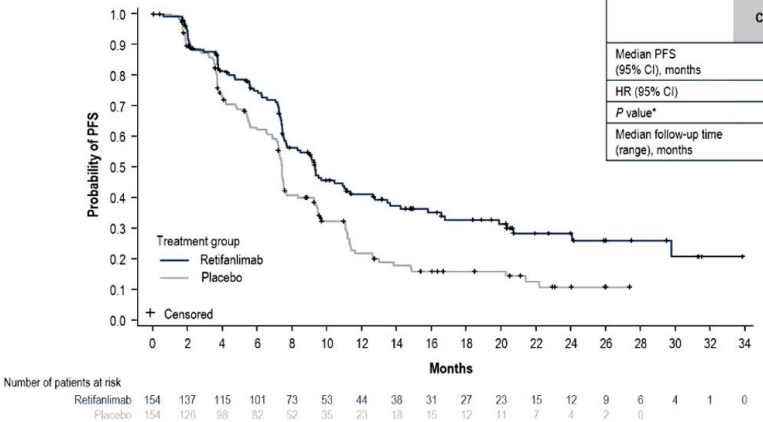
ESMO 2024: POD1UM-303/InterAACT2: Phase III Study of Carboplatin + Paclitaxel +/- Retifanlimab in Treatment-Naive Inoperable or Metastatic SCCA

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*		**0.0006**
Median follow-up time (range), months	7.1 (0.0, 27.4)	7.6 (0.0, 33.9)

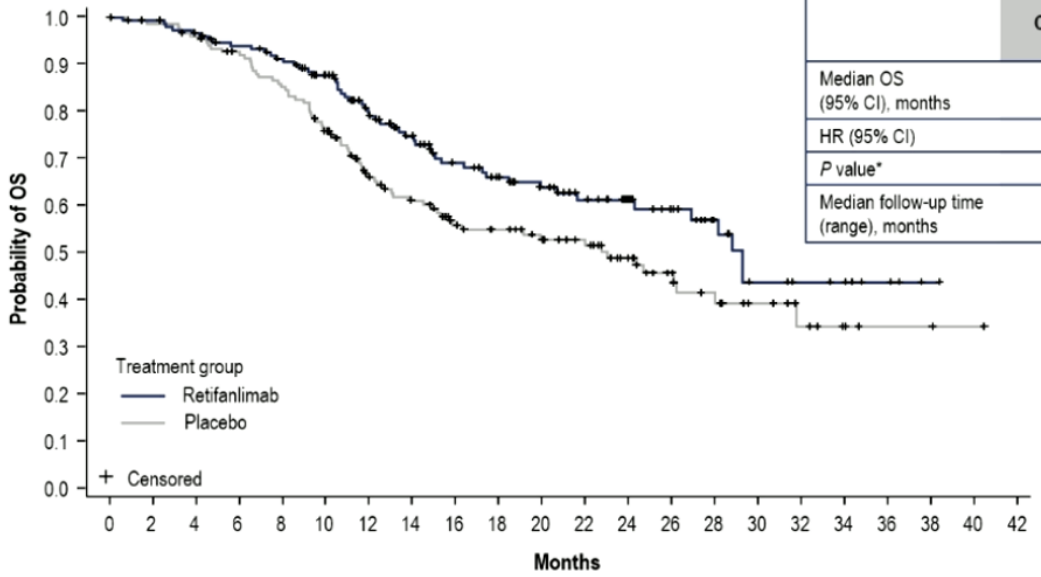
	Placebo + Carboplatin–Paclitaxel (n=154)	Retifanlimab + Carboplatin–Paclitaxel (n=154)
ORR (95% CI), % CR, %	44 (36, 52) 14	56 (48, 64) 22 ***P*=0.0129†**
Median DOR (95% CI), months	7.2 (5.6, 9.3)	14.0 (8.6, 22.2)
DCR (95% CI), %	80 (73, 86)	87 (81, 92)

DCR = disease control rate.

Rao S, et al. *Ann Oncol*. 2024;35(Suppl 2):1-72.

ESMO 2024: POD1UM-303/InterAACT2: Phase III Study of Carboplatin + Paclitaxel +/- Retifanlimab in Treatment-Naive Inoperable or Metastatic SCCA

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*		**0.0273**
Median follow-up time (range), months	12.9 (0.0, 40.4)	14.8 (0.6, 38.3)

Rao S, et al. *Ann Oncol*. 2024;35(Suppl 2):1-72.

ESMO 2024: POD1UM-303/InterAACT2: Phase III Study of Carboplatin + Paclitaxel +/- Retifanlimab in Treatment-Naive Inoperable or Metastatic SCCA

≥ Grade 3 toxicities

- Neutropenia: 17% vs 9%
- Hypothyroidism: 14% vs 3%
- Pruritus: 7% vs 2%
- Adrenal insufficiency: 5% vs 0%

Rao S, et al. *Ann Oncol*. 2024;35(Suppl 2):1-72.

Updated NCCN Anal Cancer Guidelines 2.2025

PRINCIPLES OF SYSTEMIC THERAPY – METASTATIC CANCER

First-Line Therapy	
Preferred Regimens	**Other Recommended Regimens**
• Carboplatin + paclitaxel	• FOLFCIS • mFOLFOX6[a] • 5-FU + cisplatin (category 2B) • Carboplatin + paclitaxel + retifanlimab-dlwr (category 2B) • Modified docetaxel/cisplatin/fluorouracil (DCF) (category 2B)

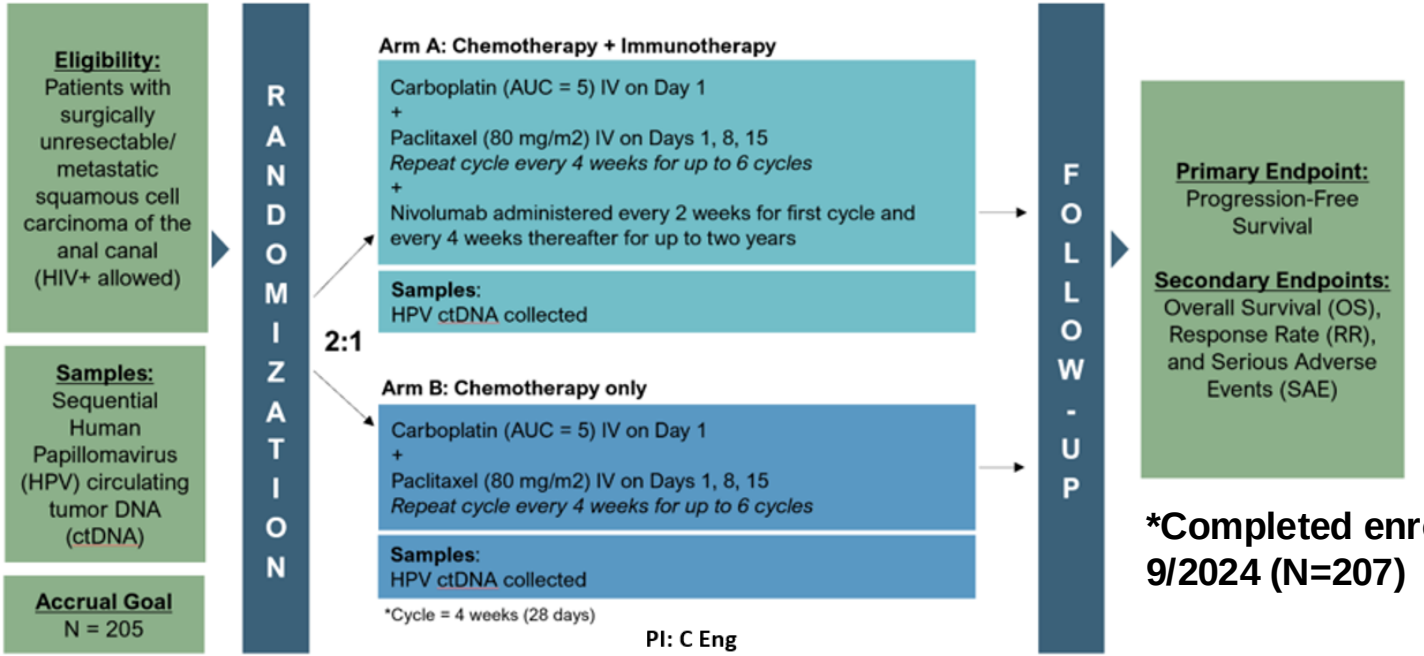
Chemo/RT to the Primary Site for Local Control
• 5-FU + RT • Capecitabine + RT

Second-Line and Subsequent Therapy	
Preferred Regimens (if no prior immunotherapy received)[b]	**Other Recommended Regimens** (if not previously given)
• Cemiplimab-rwlc • Dostarlimab-gxly • Nivolumab[c] • Pembrolizumab • Retifanlimab-dlwr • Tislelizumab-jsgr • Toripalimab-tpzi	• Carboplatin + paclitaxel • FOLFCIS • mFOLFOX6[a] • 5-FU + cisplatin (category 2B) • Modified DCF (category 2B)

FOLFCIS = leucovorin calcium (folinic acid), fluorouracil, cisplatin; mFOLFOX6 = modified leucovorin calcium (folinic acid), fluorouracil, oxaliplatin.

National Comprehensive Cancer Network (NCCN) [www.nccn.org]. Last updated February 2025. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1414

EA2176: Phase 3 Clinical Trial of Carboplatin and Paclitaxel +/- Nivolumab in Treatment-Naïve Metastatic Anal Cancer Patients (NCT04444921)



***Completed enrollment: 9/2024 (N=207)**

*HIV pts are eligible

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

ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated March 21, 2025. https://clinicaltrials.gov/study/NCT04444921.

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EA2176: Phase 3 Clinical Trial of Carboplatin and Paclitaxel +/- Nivolumab in Treatment-Naïve Metastatic Anal Cancer Patients (NCT04444921)

- Patients must have histologically or cytologically confirmed previously untreated surgically unresected metastatic squamous cell carcinoma of the anal canal (SCCA)
- Patients must have measurable disease according to the standard RECIST version 1.1. CT scans or MRIs within 28 days of drug initiation.
- Patients must be of 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

MRI = magnetic resonance imaging; CIS = carcinoma in situ.
ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated March 21, 2025. https://clinicaltrials.gov/study/NCT04444921.

EA2176: Phase 3 Clinical Trial of Carboplatin and Paclitaxel +/- Nivolumab in Treatment-Naïve Metastatic Anal Cancer Patients (NCT04444921)

- 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 0.05 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)
- Exploratory HPV ctDNA and its association with tumor response
- EA2176 investigators, in collaboration with Sysmex, will utilize SafeSEQ NGS to quantify serum HPV ctDNA during treatment at various time points (up to 5 collections per patient)

NGS = next-generation sequencing.

Key Learning Points

- When combined with standard of care (SOC) chemotherapy, retifanlimab has demonstrated a significantly longer PFS compared with chemotherapy alone in patients with previously untreated, locally recurrent or metastatic SCC of the anal canal
- Delayed recognition and management of immune-related adverse events (irAEs) represent a major gap in the management of irAEs in patients receiving ICIs for anal SCC
- Due to the complexity of anal SCC, actively integrating patient preferences, comorbidities, and quality-of-life considerations is an important aspect of care

Acknowledgments

- Drs. Kristen Ciombor (ECOG) and Van Morris (SWOG)
- ECOG and NCI-CTEP
  - Al Benson (Northwestern)
  - Paul Catalano (ECOG statistician)
  - Peter O'Dwyer (ECOG Chair)
  - Howard Streicher (NCI)
  - Jordan Berlin (ECOG GI Chair)
- In memoriam: Michelle Longabaugh, RN, NCI patient advocate, author, blogger, and friend as well as many other beloved patients
- Various foundations for their continued support of this rare cancer
  - ECOG-ACRIN
  - Vanderbilt-Ingram Cancer Center
  - NIH NCI DCTD CTEP
  - Sysmex
  - Anal Cancer Foundation
  - HPV Cancers Alliance
  - Farrah Fawcett Foundation

Thank You!

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