BARCELONA 2024 ESMO congress

A Podium for Pod1um-303

POD1UM-303/InterAACT 2: Phase 3 Study of Retifanlimab With Carboplatin-Paclitaxel (C-P) in Patients (Pts) With Inoperable Locally Recurrent or Metastatic Squamous Cell Carcinoma of the Anal Canal (SCAC) Not Previously Treated With Systemic Chemotherapy

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Barcelona, 14.09.2024

DECLARATION OF INTERESTS

Honoraria
Servier, Amgen, Merck, Sanofi, BMS, MSD, AstraZeneca, Pierre Fabre, GSK, Seagen, G1, IKF GmbH, Onkowissen, COR2ED, Taiho, Takeda, Incyte, Cureteq, 21up, Medscape, Aptitude Health, Regeneron

Research funding (inst)
Servier, Amgen

Travel support
Servier, Amgen

SCAC incidence in different regions

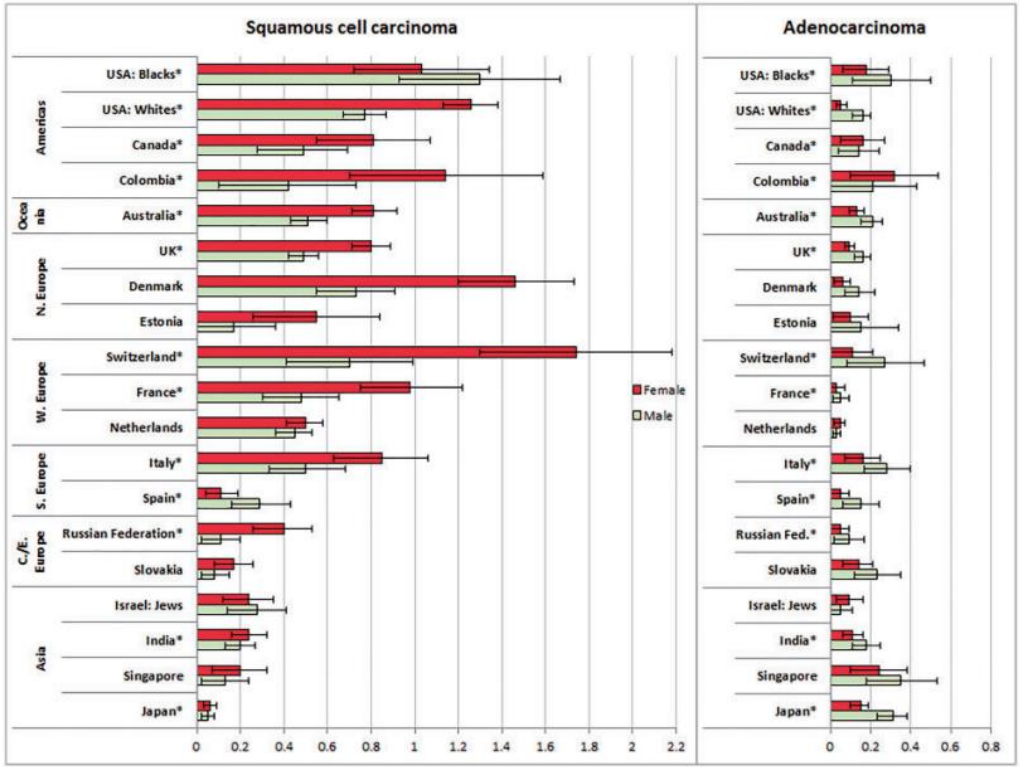


Figure 1. Age-standardized incidence rates for all ages combined (95% confidence intervals) of anal squamous cell carcinoma and adenocarcinoma by sex in 2006–2007

C./E., Central and Eastern; N., Northern; S., Southern; W., Western. Incidence rates are per 100,000 and standardized to the 1960 World standard population. * Regional data.

→The majority of anal cancers are squamous cell carcinomas.

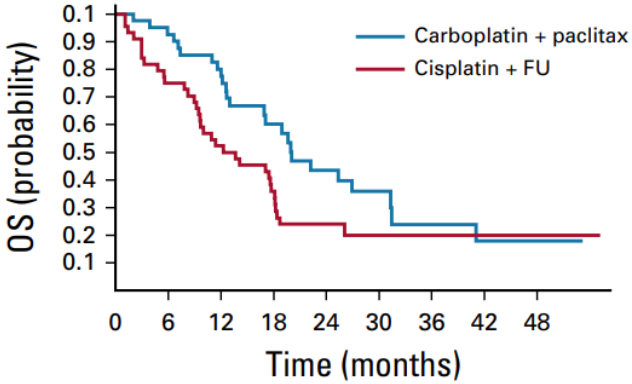
→The overall incidence is low with 1-2/100.000 per year.

→Human papilloma virus (HPV16 in particular) is a known risk factor.

→HIV infection also increases the risk of anal cancer.

Islami F et al. International Journal of Epidemiology 2017

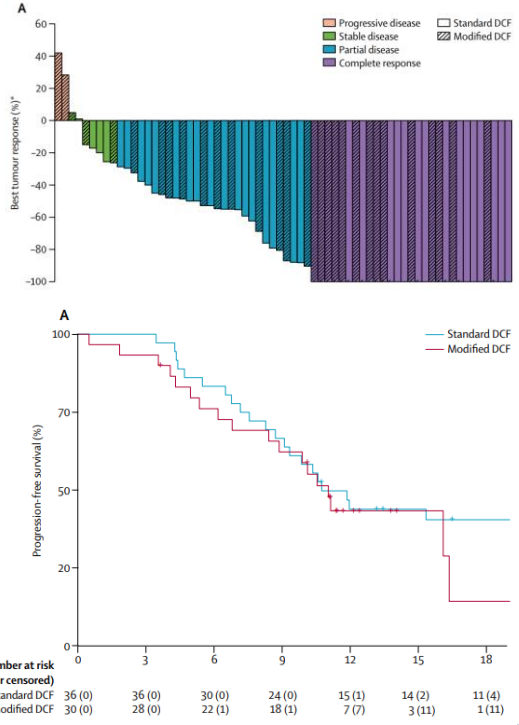
Chemotherapy backbone for Pod1um



No. at risk:

Carboplatin + paclitax	45	37	31	18	12	7	4	2	1
Cisplatin + FU	46	33	23	15	8	4	3	2	2

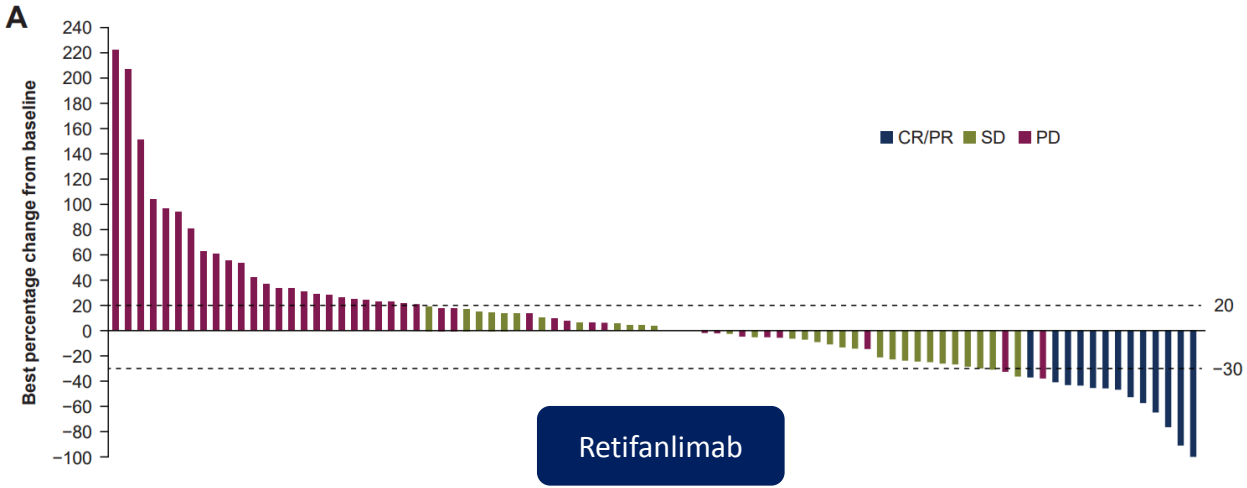
VS.

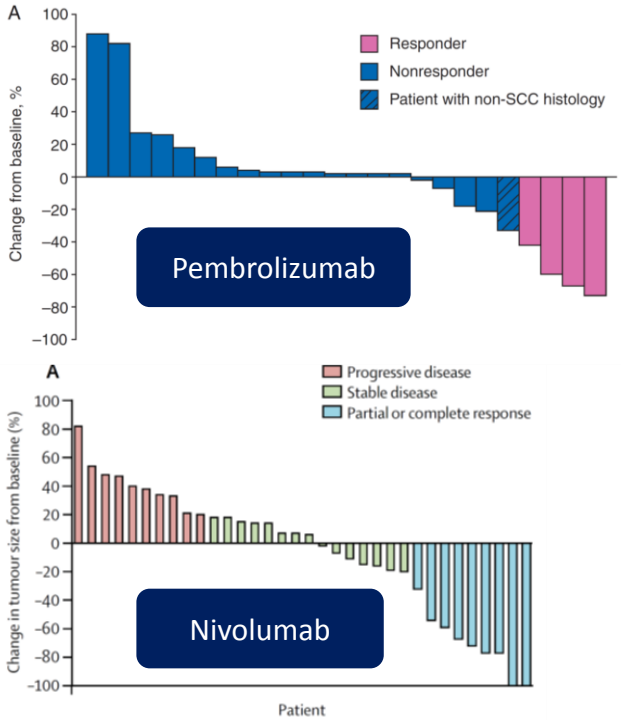


→InterAAct reported less toxicity and longer survival with carboplatin+paclitaxel as compared to cisplatin+FU and is the preferred choice in 1L therapy according to current ESMO guidelines

Rao S et al J Clin Oncol 2020, Kim S et al. Lancet Oncol 2018 and Rao S et al Ann Oncol 2021

Experience with anti-PD-1 in pretreated SCAC





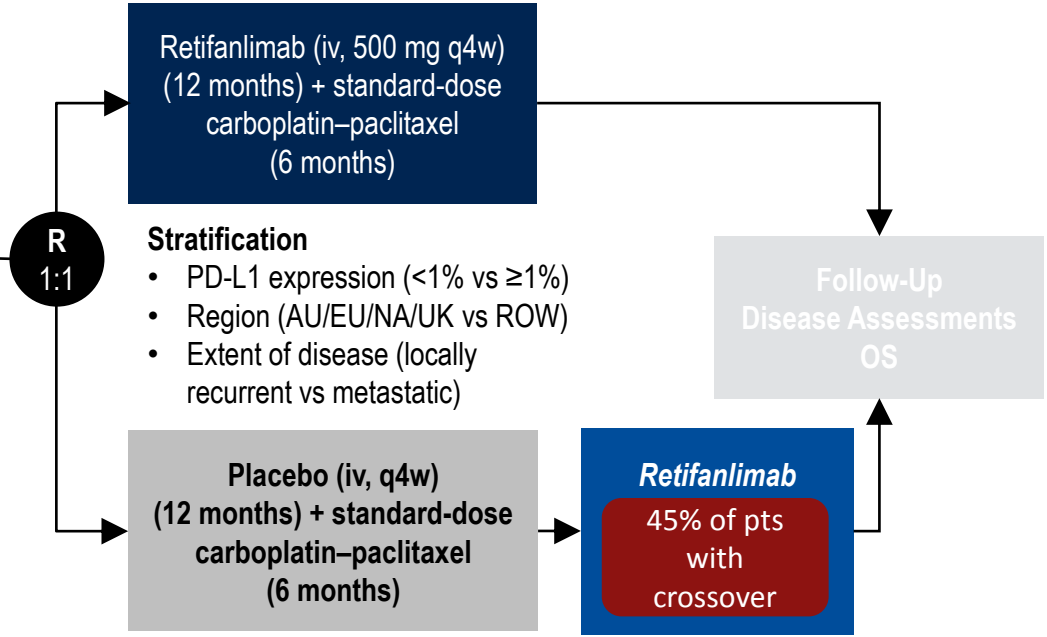
Ott PA et al Ann Oncol 2017, Rao S et al ESMO open 2022, Van Morris K et al Lancet Oncol 2017

POD1UM-303/InterAACT 2 study design

Patients with locally recurrent or metastatic SCAC

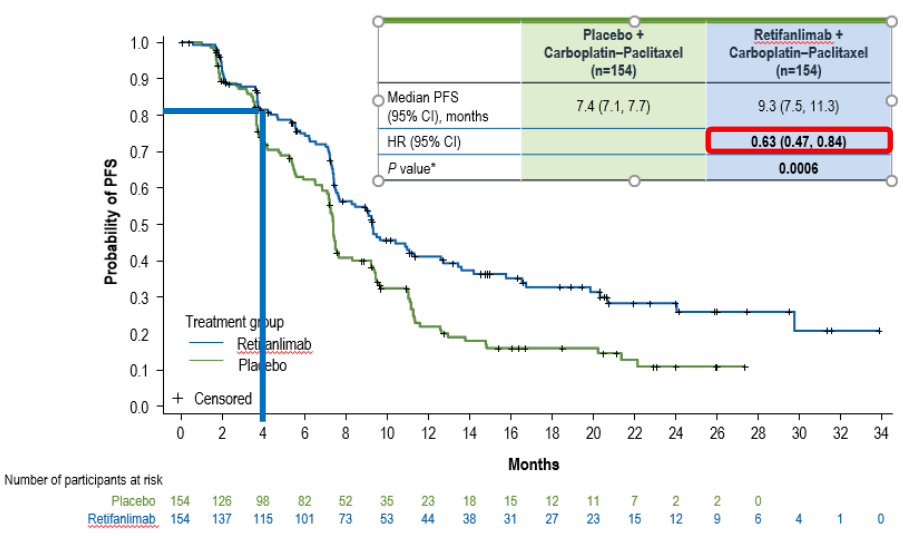
- No prior chemotherapy except as radiosensitising treatment or (neo) adjuvant therapy ≥6 months prior to study entry
- Patients with HIV and well-controlled infection were eligible
- **Planned enrolment: N=300**

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, PRO, HIV control, immunogenicity

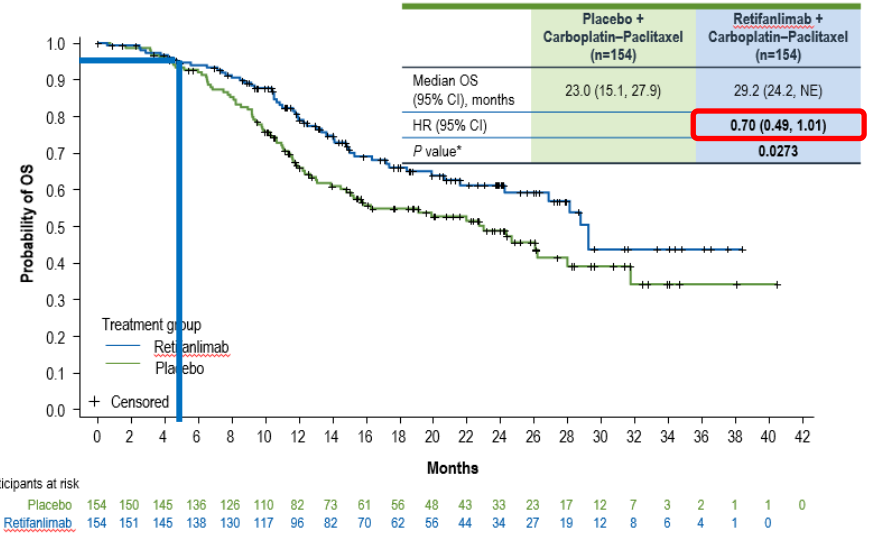


Standard-dose carboplatin–paclitaxel: carboplatin AUC5 iv: day 1. Paclitaxel 80 mg/m^2 iv: days 1, 8 and 15. Each cycle = 28 days. 6 months/24 weeks (6 cycles).
AU, Australia; AUC, area under the curve; BICR, blinded independent central review; DOR, duration of response; EU, European Union; HIV, human immunodeficiency virus; HR, hazard ratio; iv, intravenous; NA, North America; ORR, overall response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PK, pharmacokinetics; PRO, patient-reported outcomes; q4w, every 4 weeks; R, randomisation; ROW, rest of the world; SCAC, squamous cancer of the anal canal; UK, United Kingdom.

Efficacy (PFS & OS)



	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**



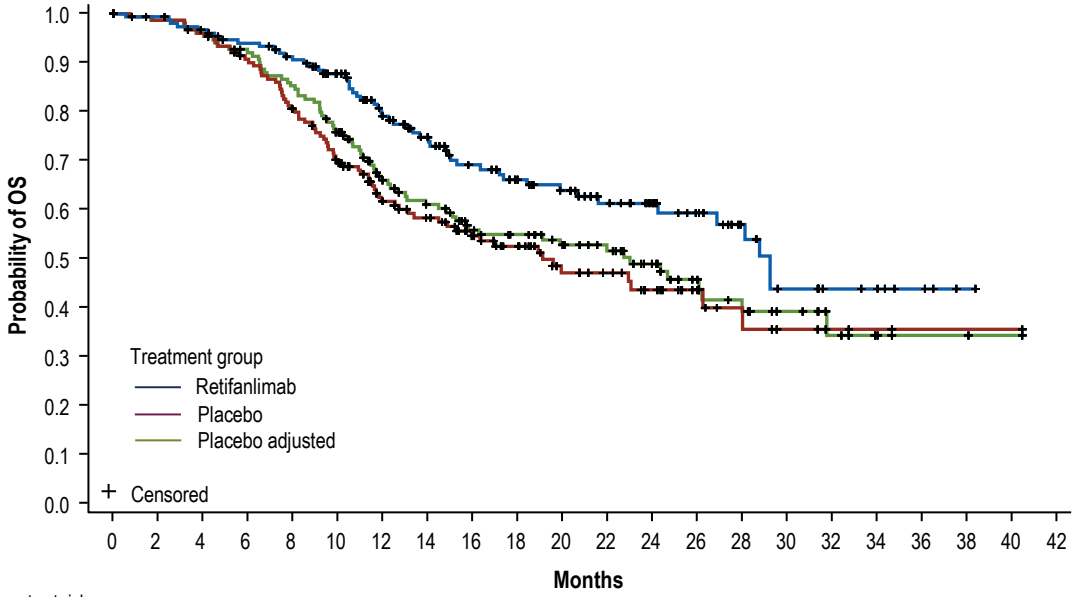
	Placebo + Carboplatin–Paclitaxel (n=154)	Retifanlimab + Carboplatin–Paclitaxel (n=154)
Median OS (95% CI), months	23.0 (15.1, 27.9)	29.2 (24.2, NE)
HR (95% CI)		**0.70 (0.49, 1.01)**
P value*		**0.0273**

→ The benefit of added retifanlimab appears rather early in the PFS curve while >80% of patients are still at risk. The OS observation is consistent.

→ Subgroup analyses, particularly according to PD-L1 and clinical stage (advanced/relapsed vs. metastatic) would have further supported the data (but not changed the perspective)

Graphs according to Rao S et al ESMO 2024

Crossover-effect on OS?



Number of participants at risk

Placebo unadjusted	154	150	145	136	126	110	82	73	61	56	48	43	33	23	17	12	7	3	2	1	1	0
Placebo adjusted	154	150	145	133	117	99	76	67	54	45	33	29	22	14	8	5	3	2	1	1	1	0
Retifanlimab	154	151	145	138	130	117	96	82	70	62	56	44	34	27	19	12	8	6	4	1	0	

Graphs according to Rao S et al ESMO 2024

- → Crossover of patients to retifanlimab had no or minor influence on OS
- → ***Late*** introduction of checkpoint- inhibition in SCAC may not add substantial benefit
- → The mediocre crossover effect compares well to the monotherapy data* in pretreated pts (speculation).
- → Which therapies were used in patients not receiving retifanlimab after progressive disease in the control arm?

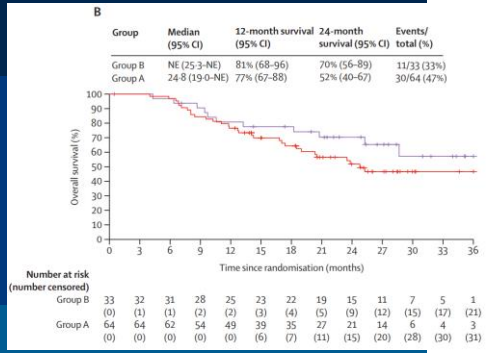
*Ott PA et al Ann Oncol 2017, Rao S et al ESMO open 2022, Van Morris K et al Lancet Oncol 2017

Consistency with other cohorts in terms of prognosis

Study	Study arms	Patients	ORR	PFS	OS
InterAAct	5FU/ Cisplatin	N=46	57%	5.7mo	12.3mo
	Carboplatin/ Paclitaxel	N=45	59%	8.1mo	20.0mo
SCARCE C17-02 Prodige 60	Docetaxel/Cisplatin/ 5-FU	N=33	78%	8.7mo	n.r.
	Docetaxel/Cisplatin/ 5-FU/Atezolizumab	N=64	75%	9.4mo	24.8mo
POD1UM-303	Carboplatin/ Paclitaxel	N=154	44.2%	7.4mo	23.0mo
	Carboplatin/Paclitaxel /Retifanlimab	N=154	55.8%	9.3mo	29.2mo

Kim S et al Lancet Oncol 2024, Rao S et al J Clin Oncol 2020 and Rao S et al ESMO 2024

Consistency with other cohorts in terms of checkpoint-inhibitor efficacy

Study	Study arms	Patients	ORR	PFS	OS
SCARCE C17-02 Prodige 60	Docetaxel/Cisplatin/ 5-FU	N=33	-3% P=ns	HR= 0.837 (0.501–1.398)	
	Docetaxel/Cisplatin/ 5-FU/Atezolizumab	N=64			
POD1UM-303	Carboplatin/ Paclitaxel	N=154	+11.6% P=0.013	HR= 0.63 (0.47-0.84) P=0.0006	HR=0.70 (0.49, 1.01) P=0.0273
	Carboplatin/Paclitaxel/ Retifanlimab	N=154			

→ The inconsistency between POD1UM and SCARCE is hard to explain. Formally, differences in backbone chemotherapy and the checkpoint-inhibitor might be reasons.

Kim S et al Lancet Oncol 2024, and Rao S et al ESMO 2024

Summary

- POD1UM-303/InterAACT 2 is a positive phase-3 trial in a rare cancer entity demonstrating superior efficacy in an acceptable primary endpoint (PFS)
    - The trial provides consistent efficacy data in secondary endpoints (ORR, OS)
    - The gain of benefit in this first-line trial is greater than expected based on monotherapy with checkpoint-inhibitors in pretreated patients
    - Crossover rates of retifanlimab did not impact on OS (due to only 45% exposition but likely also due to lack of efficacy)
    - With a PFS of 7.4 months and an OS of 23 months in the control arm, more information on the use of further-line therapy might help to understand the role of sequential therapy in SCAC
- Safety and tolerability are as expected, retifanlimab adds some immune-related events, but the regimen is manageable
- The external consistency of the trial is limited by lacking availability of randomized trials in this disease or their result (SCARCE C17-02/ Prodige 60)

What we would (have) like(d) to see…

1. PD-L1 expression, clinical subgroups, mature OS data.

2. Data from other trials, i.e. EA2176 (carboplatin + paclitaxel + nivolumab or placebo), NCT 04444921

3. Further developments/challenge of this new regimen
    1. more immuno-oncologic therapy
    2. other chemotherapy backbones (triplet?)

Conclusion

Carboplatin, paclitaxel and retifanlimab should be considered a new SOC in advanced/metastatic squamous cell anal carcinoma

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Thank you very much for your kind attention

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