PARIS 2022 ESMO congress

EO2401 therapeutic vaccine for patients with adrenocortical carcinoma (ACC) and malignant pheochromocytoma/paraganglioma (MPP):

Phase 1/2 SPENCER study, NCT04187404

Publication number: 2MO

Eric Baudin on behalf of the investigators of the EOADR1-19/SPENCER trial

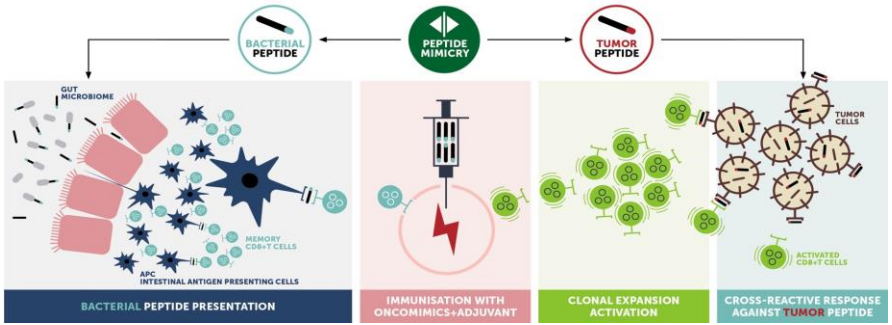
Gustave Roussy, Villejuif, France

Background

- Adrenal tumors are ultra rare cancers with contrasted therapeutic results
- No significant progress in the field of adrenocortical carcinoma (ACC) in the last 3 decades (no targetable alteration)
- Personalized strategy “in progress” in patients with malignant pheochromocytoma/paraganglioma (MPP): 30-60% of targetable alterations (best evidence with sunitinib provided by FIRSTMAPPP trial)
- Overall limited response to immune check point inhibitors currently reported in both ACC and MPP*

EO2401 was designed to activate commensal memory T cells with non-self, microbiome-derived peptides mimicking tumor associated antigens (TAAs : IL13Rα2, BIRC5 and FOXM1) upregulated in ACC/MPP (HLA 2 restricted) and the CD4 peptide UCP2.

Nivolumab is utilized to support T cell expansion and T cell infiltration of tumor.



** Fassnacht M, Assie G, Baudin E, et al. Adrenocortical carcinomas and malignant phaeochromocytomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2020; 11 (31): 1476-1491*

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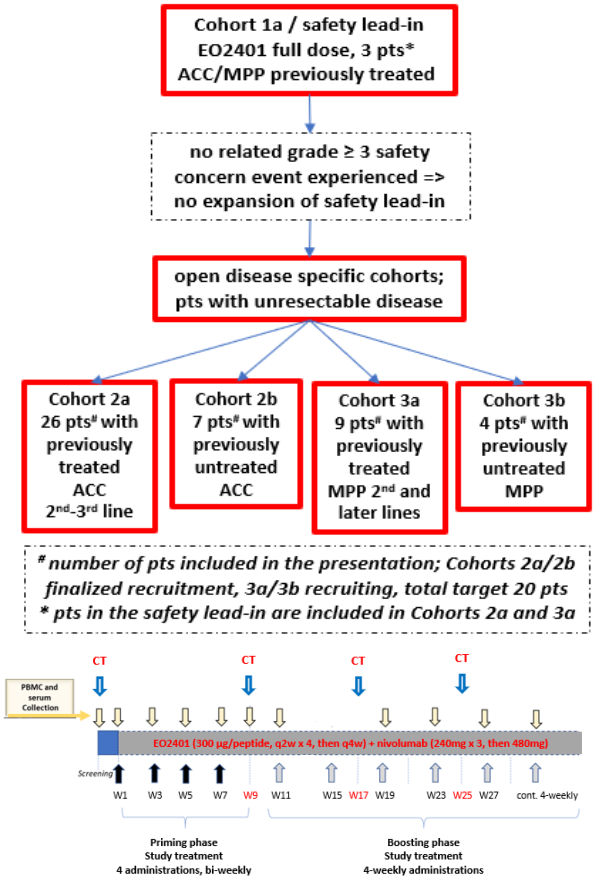
Design



Safety as primary objective
(ACC & MPP combined, n=46)

- *The combination of EO2401 (administered SC with the adjuvant Montanide ISA 51 VG) and nivolumab is well tolerated.*
  - *The safety profile is consistent with the profile of nivolumab, except the addition of local administration site reactions.*
  - *Any local administration site event (i.e., any term) was seen in 25 (54%) patients. Distribution of Grades among the 63 events was, 67% Grade 1, 22% Grade 2, and 11 % Grade 3.*
  - *The most common AEs, irrespective of relationship, were pyrexia (33%), diarrhea (33%), injection site reaction (28%), anemia (24%), fatigue (22%), and back pain (22%).*

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Adrenocortical Carcinoma: efficacy as secondary objective

ACC population: stage IV 94%, adrenalectomy 82%, post MP 73%*, prior mitotane 88%*, mitotane continued post PD 58%

Cohorts 2a* (2nd/3rd line, n=26) & 2b (1st line, n=7)

- objective response rate (ORR) = 12.1%
  (95% CI 3.4; 28.2)
  - median time to response = 4.6 months
  - median duration of response = 9.6 months
- disease control rate (ORR + SD) = 36.4%
  (95% CI 20.4; 54.9)
- median progression-free survival = 1.9 months
  (95% CI 1.8; 2.3)
- median survival = 13.0 months
  (95% CI 5.7; ne) / median follow-up 14.0 months
- **12-months survival rate = 57.2%**
  (95% CI 38.7%; 72.1%)

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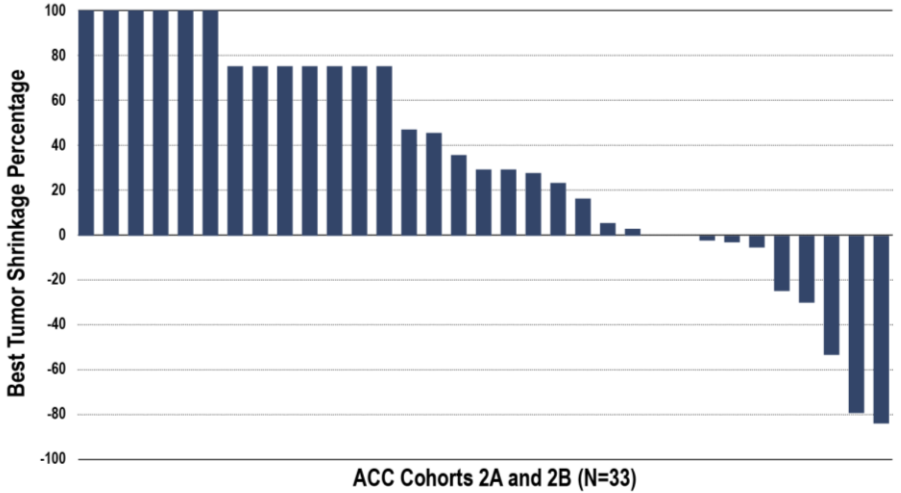

Best tumor percentage change versus baseline in individual patients; note, two patients have 0% change as the best outcome; 100% = death without on study assessment; 75% = progression including new lesions.

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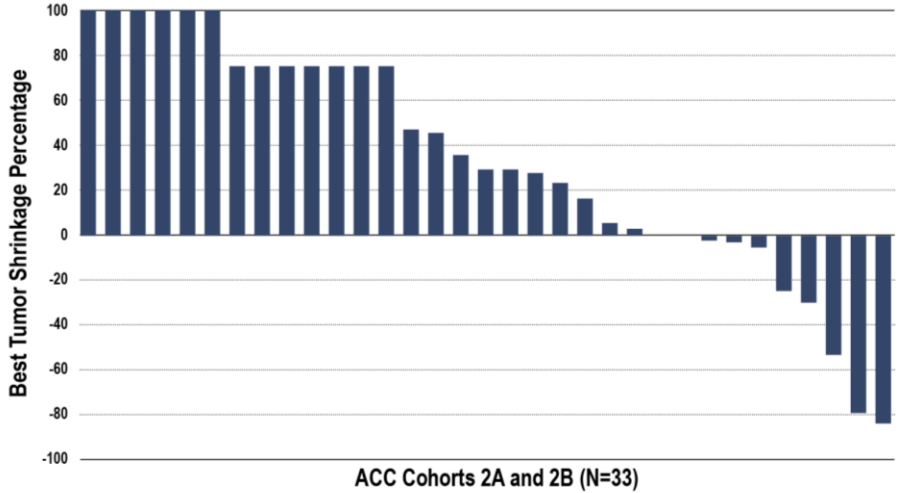

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No correlation found between outcome and baseline tumor mutational burden, MSI-status, PD-L1 expression, serum cytokines (IL-1β, IFN-α, IFN-γ, TNF-α, IL-6, IL-10, IL-12, IL-17A, IL-18, IL-23, IL-33, MMP2), chemokines (MCP-1, RANTES, IP-10, Eotaxin, TARC, MIP-1α, MIP-1β, MIG, MIP-3α, ENA-78, GROα, I-TAC, IL-8), or hormonal levels (cortisol, IGF2)

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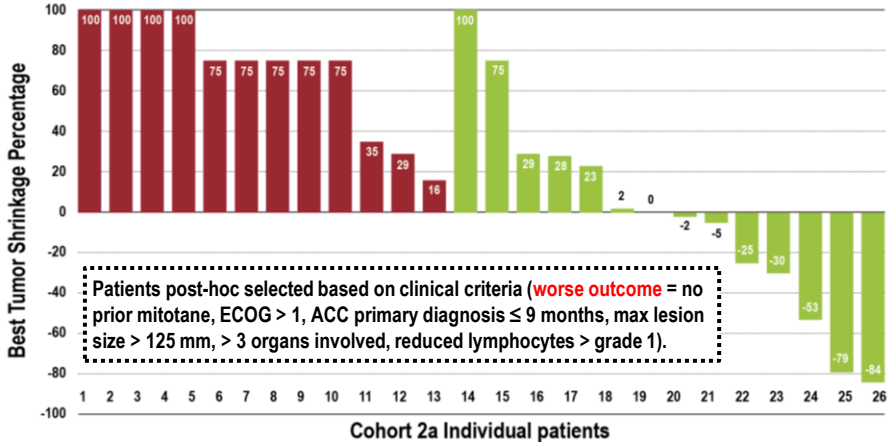
  (95% CI 5.7; ne) / median follow-up 14.0 months
- **12-months survival rate = 57.2%**
  (95% CI 38.7%; 72.1%)

Cohort 2a (2nd/3rd line, n=26): best tumor shrinkage

Clinical Criteria Positively Selected Patients (#13-26): ORR 28.6% (95% CI 8.4; 58.1), DCR 64.3% (95% CI 35.1; 87.8)



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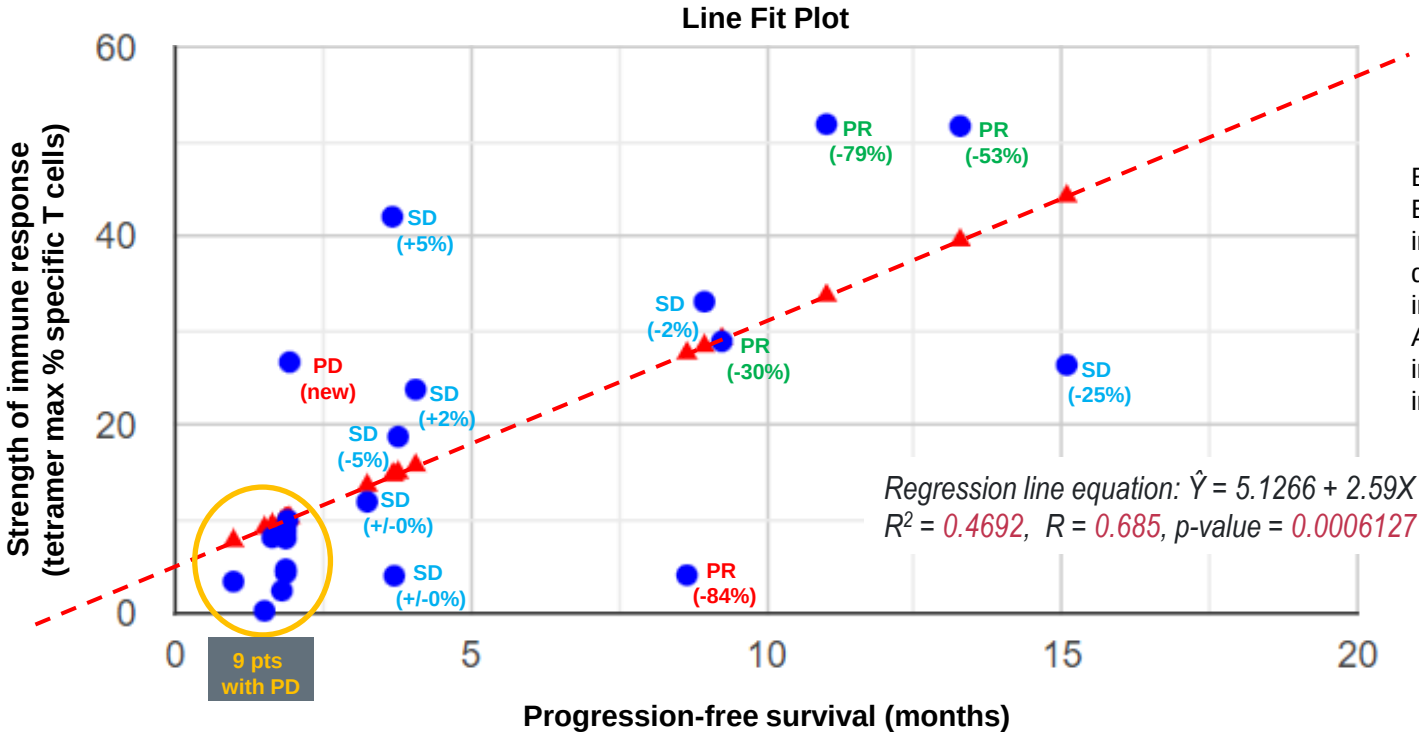
Adrenocortical Carcinoma: immune response as secondary objective

relationship between immune response and PFS/ORR



Best tetramer (EO2316, EO2317, or EO2318) % after in vitro amplification for 12 days (IVS) versus PFS in individual patient's vid ACC. All 21 patients with available immune test results included in the correlation.

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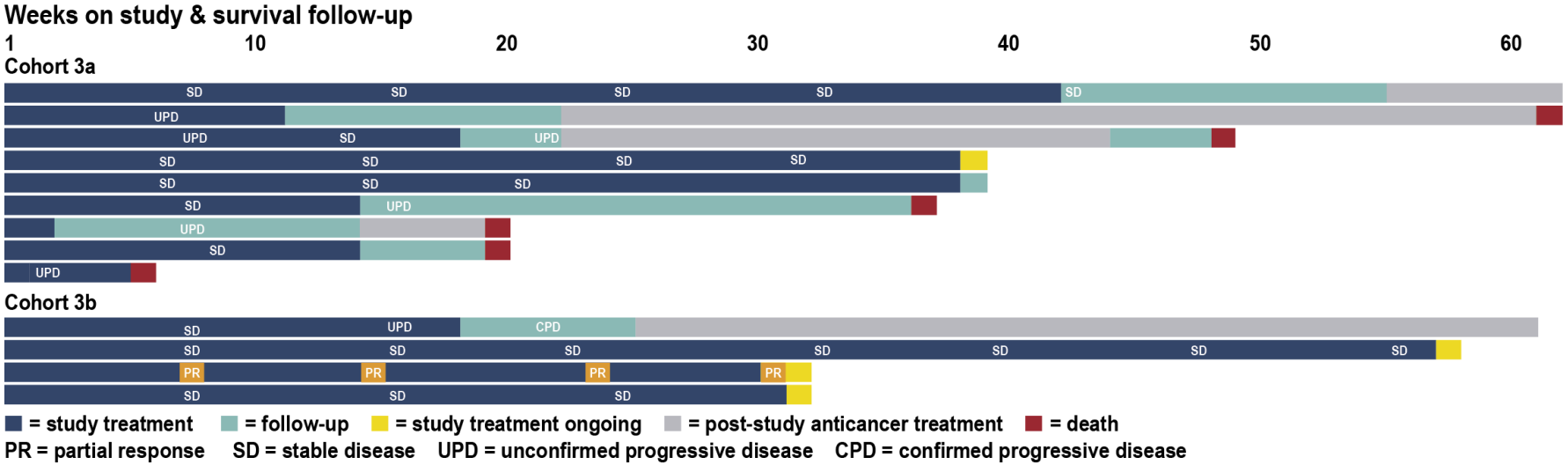
Metastatic Pheo/Paraganglioma: efficacy as secondary objective

- *N=13, including 9 patients with previously treated (2nd and later lines), and 4 patients with systemically previously untreated, MPP*
- objective response rate (ORR) = 8% (95% CI 0.2; 36.0)
- disease control rate (ORR + SD) = 77% (95% CI 46.2; 95.0)
- median progression-free survival = 5.2 months (95% CI 1.9; ne)
- median survival = 14.3 months (95% CI 4.7; ne) at a median follow-up of 13.2 months



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Conclusions

- EO2401/nivolumab was well tolerated with a safety profile consistent with the safety profile of nivolumab monotherapy, except the addition of local administration site reactions
- ACC
  - Clinical efficacy was observed that correlate with the strength of generated immune responses
  - Better efficacy observed in a post-hoc defined subgroup of patients
    - Prolonged duration partial responses (ORR 29%)
    - 12-months survival rate 78.6%
    - *Currently best post-MP results*
  - A randomized study is started to evaluate the finding; EO2401/nivolumab vs EO2401 vs nivolumab (NCT04187404)
- MPP
  - Recruitment still ongoing, no firm conclusion can be drawn

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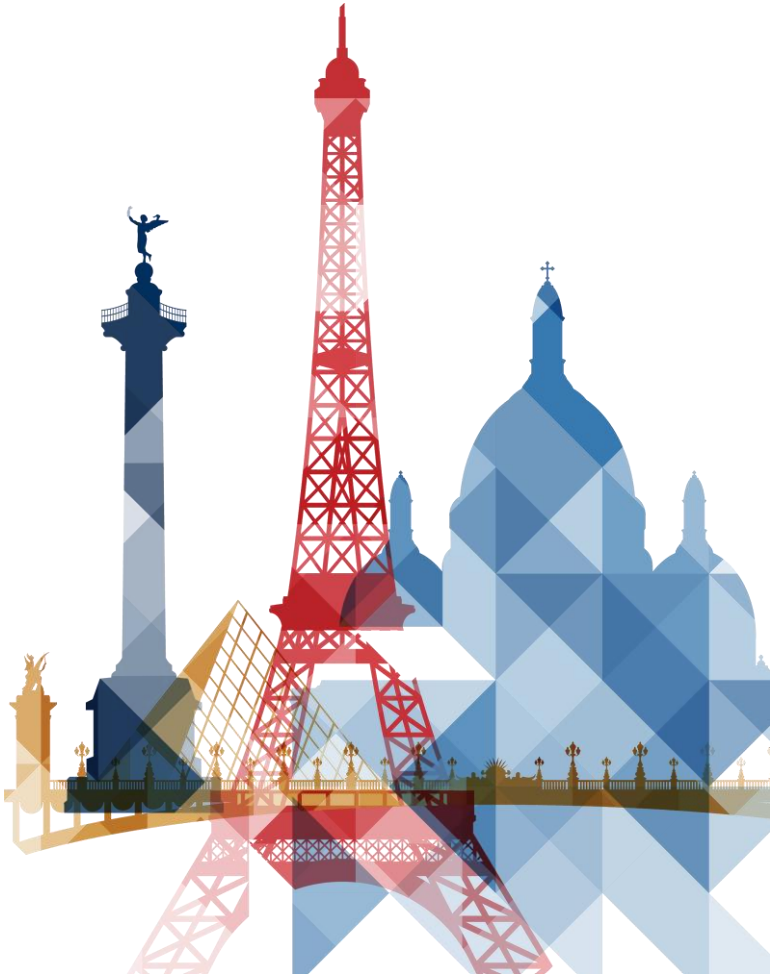
Thank you!



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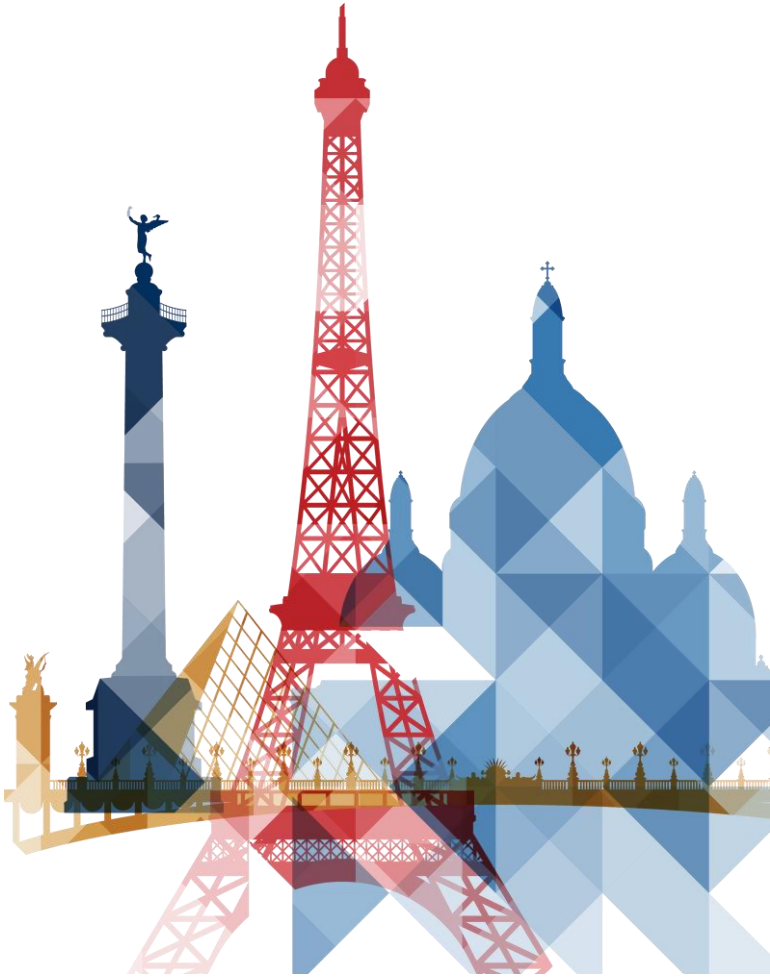
Back-up’s



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Objectives

- The primary objective of the trial is to evaluate safety and tolerability of EO2401 in combination with nivolumab in patients with unresectable, previously treated, and previously untreated, locally advanced or metastatic ACC, and progressive MPP.
- Secondary objectives include:
  - immunogenicity in relation to T cells of EO2316, EO2317, EO2318, and UCP2 that compose EO2401; T cell cross-reactivity with the human TAAs IL13Rα2, FOXM1, and BIRC5/survivin will also be evaluated,
  - efficacy via objective response rate (ORR), time to response, and duration of response (DOR), and
  - progression-free survival (PFS) and overall survival (OS).

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ACC literature survival rate at 12-months

OS (%) and 95% CI	12 Months
EDP-Mitotane (1st line, N=151) Fassnacht (2012)	57.0 (49.1-64.9)
Nivolumab (1st -2nd line, N=10) Carneiro (2019)	56.0 (14.0-90.0)* **mFU 4.5 mo*
EDP-Mitotane (2nd line, N=101) Fassnacht (2012)	55.0 (45.3-64.7)
Streptozocin-Mito. (2nd line, N=84) Fassnacht (2012)	55.0 (44.4-65.6)
Pembrolizumab (1st- 2nd line, N=39) Raj (2019)	52.0 (35.0-63.0)
Streptozocin-Mito. (1st line, N=153) Fassnacht (2012)	50.0 (42.1-57.9)
Lisitinib (≥2nd line, N=90) Fassnacht (2015)	49.0 (38.7-59.3)
Placebo (≥2nd line, N=49) Fassnacht (2015)	45.0 (31.1-58.9)
Avelumab (≥2nd line, N=50) Le Tourneau (2018)	43.4 (27.9-57.9)

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Adrenocortical Carcinoma

Microbiome Derived Therapeutic Vaccine EO2401 + nivolumab

Cohorts 2a (2nd/3rd line) & 2b (1st line) (n=33)

- objective response rate (ORR) = 12.1% (95% CI 3.4; 28.2)
  - median time to response = 4.6 months
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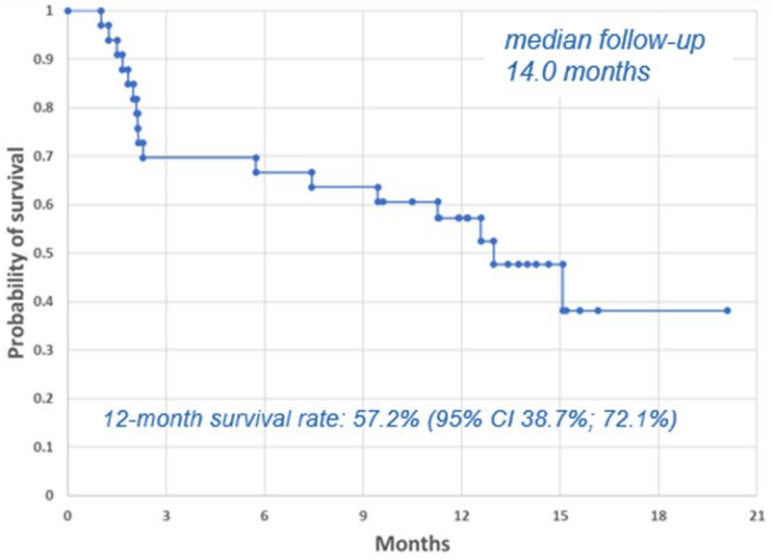
- disease control rate (ORR + SD) = 36.4% (95% CI 20.4; 54.9)
- median progression-free survival = 1.9 months (95% CI 1.8; 2.3)
- median survival = 13.0 months (95% CI 5.7; ne)

Survival of whole AAC population (n=33)



Literature 12 mo survival rate (95% CI)

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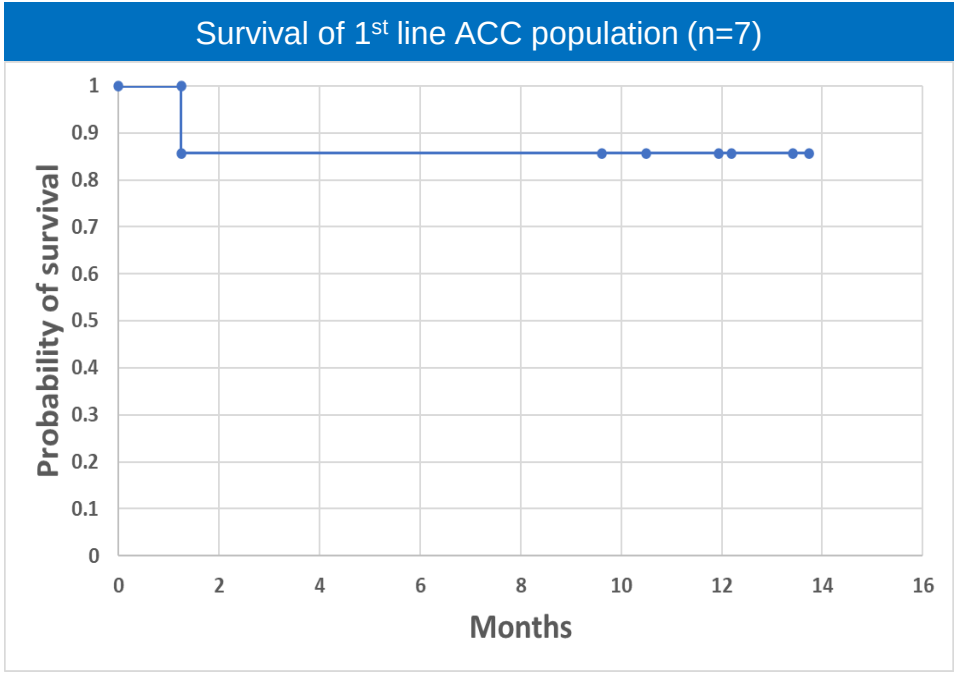
Adrenocortical Carcinoma (1st line)

- *N=7, patients with systemically previously untreated ACC (1st line treatment)*
- objective response rate (ORR) = 0% (95% CI 0.0%; 41.0%)
- disease control rate (ORR + SD) = 29% (95% CI 3.7%; 71.0%)
- median progression-free survival = 1.9 months (95% CI 1.2; 3.2)
- median survival = not reached (95% CI 1.2; ne)
- at a median follow-up of 12.1 months



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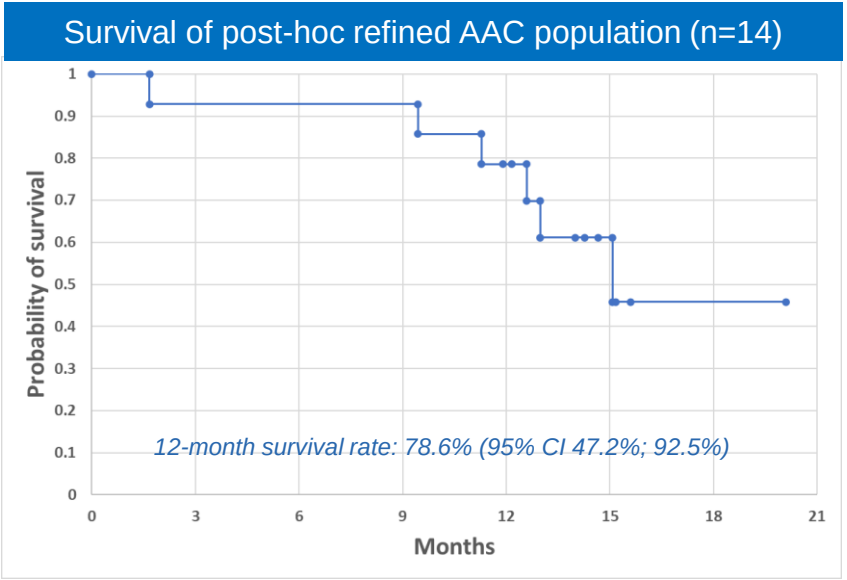
Adrenocortical Carcinoma (2nd-3rd line): post-hoc analysis

- Patients in Cohort 2a had either a good outcome or no noticeable benefit by tumor response/time to progression

- Post-hoc selection with clinical criteria to achieve refined population:
  - A set of clinical criteria (no prior mitotane, ECOG > 1, ACC primary diagnosis ≤ 9 months, max lesion size > 125 mm, > 3 organs involved, reduced lymphocytes > grade 1) was associated with poor outcome
  - Post-hoc remaining population (n=14 of 26 patients) with good outcome:
    ORR 29% (95% CI 8%; 58%)
    DCR 64% (95% CI 35%; 82%)
    median PFS 3.9 months (95% CI 1.9; 13.3)
    median Survival 15.1 months (95% CI 11.3; ne)
    at a median follow-up of 14.7 months



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