MADRID 2023 ESMO congress

EO2401 (E) peptide immunotherapy + nivolumab (N) in adrenocortical carcinoma (ACC) and metastatic pheochromocytoma /paraganglioma (MPP); EOADR1-19/SPENCER

Publication number: 7240

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

Gustave Roussy, Villejuif, France

Declaration of interests

Eric Baudin

Personal financial interests

- Expert board: Ipsen, Novartis, AAA, Pfizer, Hutchinson Pharma, Enterome

Institutional financial interests

- Research grant: Novartis, HRA
- Principal investigator: Ipsen
- Drug supply: Pfizer, AAA

Non-financial interests, Leadership role:

- Past-president of the French group of endocrine tumors (GTE)
- Coordinator of the French ENDOCAN network (TUTHYREF, COMETE, RENATEN)
- Advisory board/EC of ENSAT/ENETS

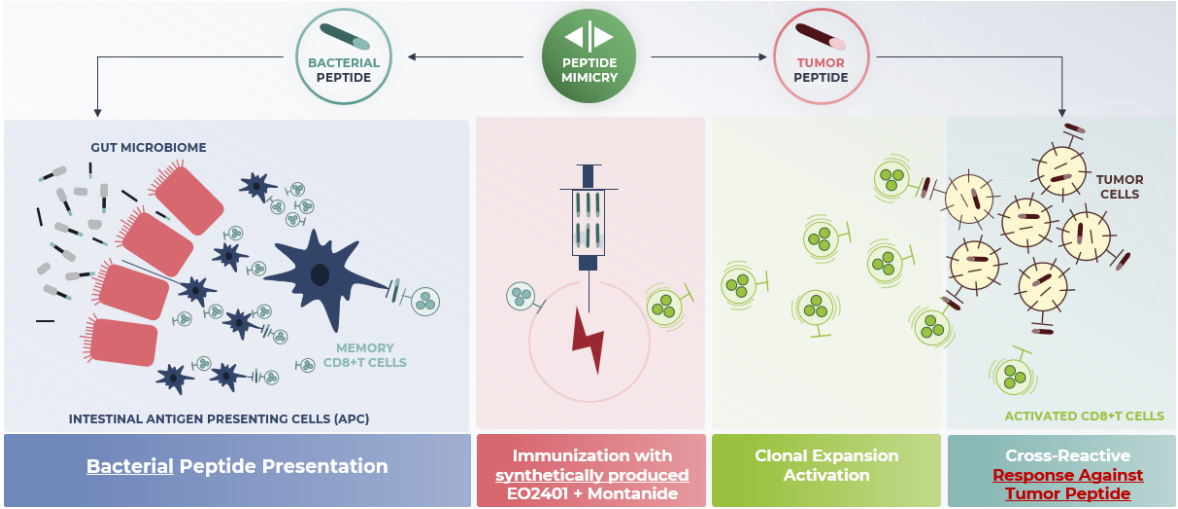
Background

- Adrenal tumors are ultra rare cancers with highly variable therapeutic results
- No significant progress in the field of ACC in the last 3 decades (no targetable alteration)
- Personalized strategy “in progress” in patients with 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 memory CD8 T cells targeting tumor associated antigens (TAAs) upregulated in ACC/MPP

- EO2401 = Three non-self, synthetically produced microbiome-derived HLA-A2 restricted peptides mimicking TAAs (IL13Rα2, BIRC5 and FOXM1) 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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EOADR1-19/SPENCER: Phase 1/2 trial in adrenal tumors

NCT04187404

Cohort 1
Safety lead-in

EO2401/ nivolumab

n=3 (pts included in Cohorts 2a and 3a)

Cohort 2a
EO2401/nivolumab
Previously systemically treated locally advanced/metastatic ACC (2nd-3rd line)
Final n=26

Cohort 2b
EO2401/nivolumab
Previously systemically untreated for established locally advanced/metastatic ACC
Final n=7

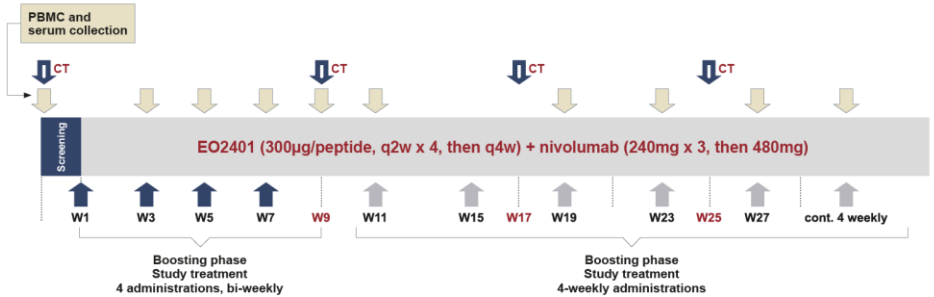
Cohort 3a
EO2401/nivolumab
Previously systemically treated MPP
Final n=13

Cohort 3b
EO2401/nivolumab
Previously systemically untreated MPP
Final n=5

Randomized Cohort 2a
EO2401/nivolumab vs EO2401 vs nivolumab
Previously systemically treated locally advanced/metastatic ACC (2nd-3rd line) - *Inclusion criteria updated based on data from the non-randomized Cohort 2a*
n=65; RND 4:1:1
Current n=16

1st objective phase 2: effect of EO2401/nivolumab on PFS-rate at 6 months, per investigator/local site assessments

2nd objectives: as for phase 1, and in addition, effect of EO2401/nivolumab PFS-rate at 6 months per independent review



1st objective phase 1: safety and tolerability of EO2401/nivolumab
2nd objectives: immunogenicity of EO2401, objective response rate, time to response, duration of response, progression-free survival, overall survival

EOADR1-19/SPENCER: primary objective - safety

Adrenocortical carcinoma & pheochromocytoma/paraganglioma [DB 2023-08-21; n = 51]

- The safety profile of EO2401 (administered SC with the adjuvant Montanide ISA 51 VG) in combination with nivolumab is consistent with the profile of nivolumab monotherapy, except the addition of local administration site reactions
- Most common related AEs of any Grade: injection site reaction (37%), injection site pain (20%), fatigue (18%), asthenia (14%), pyrexia (14%), diarrhea (12%)
  - Overall Grade ≥ 3 in 27 (53%) patients
- Local administration site events (pooled AE terms for event type, n=29 [57%]), Grades:
  - 19 (37%) patients with a max Grade 1
  - 7 (14%) patients with a max Grade 2
  - 3 (6%) patients with a max Grade 3
- Systemic related Grade 3 events in 6 (12%) patients (no related Grade 4/5 events)
  - 1 pat with pyrexia, 1 pat with asthenia, 1 pat with increased ALP, 1 pat with autoimmune hepatitis, 1 pat with rash, and 1 pat with pyrexia/stomatitis
- No main differences in the safety profile between ACC and MPP; and no severe hypertension during or immediately after study treatments in patients with MPP

EOADR1-19/SPENCER: Adrenocortical Carcinoma

Baseline characteristics: 2/3 of patients with ≥ 3 tumor sites

Group	Age Median (range)	Gender		ECOG			Glucocorticoid secretion	Baseline Ki67 index		Modified ENSAT * at study start			Adrenalectomy
		F	M	0	1	2	(any time)	Median (range)	Ki67 ≥ 20%	IVa	IVb	IVc	
C2a ^ ***2nd/3rd line*** (n=26)	46 (20-78)	69%	31%	54%	38%	8%	46%	25 (7-90)	72%	32%	40%	28%	85%
C2b ***1st line*** (n=7)	47 (38-85)	100%	0%	71%	29%	0%	43%	20 (10-50)	60%	57%	29%	14%	71%
All C2 (n=33)	***47 (20-85)***	***76%***	***24%***	***58%***	***36%***	***6%***	***45%***	***25 (7-90)***	***70%***	***38%***	***37%***	***25%***	***82%***

*** Stage IVa, IVb, and IVc according to the number of tumor-involved organs (including the primary tumor and the "N" as "organ"): 2, 3, or >3, respectively.**
^ 22 (85%) of the patients in C2a had received prior platinum-containing treatment regiments, most commonly (14 patients) EDP-M (etoposide, doxorubicin, cisplatin, mitotane); 15 (58%) patients received study treatment as 2nd line, and 11 (42%) received study treatment as 3rd line

EOADR1-19/SPENCER: secondary objective - efficacy

Adrenocortical carcinoma: 11 pts (33%) experienced PR or SD with mDDC of 9 months

Cohort 2 [DB 2023-08-25]

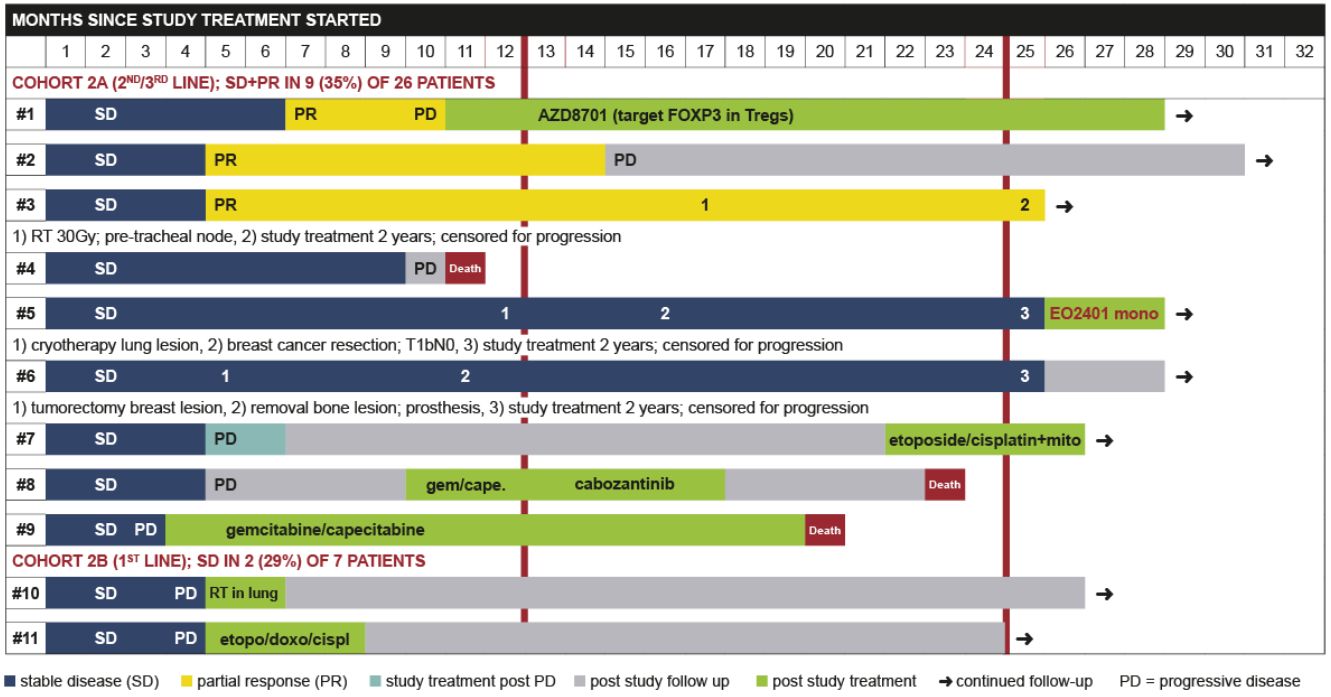
Study Treatment
- 26 (79%) pts 2/3rd line
- 7 (21%) pts 1st line

Tumor response
- ORR = 3 (9%), mDOR 9.6 mo
- DCR = 11 (33%), mDDC 9.0 mo

Progression-free survival
- mPFS 1.9 mo

Survival (mFU 25.8 mo)
- mSurvival 13.8 mo
- 12-mo survival rate 58%
- 18-mo survival rate 45%
- 24-mo survival rate 36%

ORR = objective response rate RECIST 1.1
DCR = disease control rate (OR+SD)
DOR = duration of objective response
DDC = duration of disease control
PFS = progression-free survival
FU = follow-up
m = median



EOADR1-19/SPENCER: Pheochromocytoma/paraganglioma

Baseline characteristics: classical malignant population

Group	Age Median (range)	Gender		ECOG		Tumor type		Tumors over-secreting catecholamines	Dominant secretion				Hypertension at study BL	Bone metastases	Number of organs involved Median (range)
		F	M	0	1	Pheo	Para		dopa	nor-epi	epi	epi & nor-epi			
C3a* ≥ 2nd line (n=13)	55 (39-74)	31%	69%	38%	62%	46%	54%	54%	40%	40%	-	20%	46%	77%	3 (2-4)
C3b 1st line (n=5)	63 (3-68)	80%	20%	20%	80%	40%	60%	60%	33%	33%	33%	-	80%	60%	3 (1-4)
All C3 (n=18)	***57 (33-74)***	***44%***	***56%***	***33%***	***67%***	***44%***	***56%***	***56%***	***38%***	***38%***	***12%***	***12%***	***56%***	***72%***	***3 (1-4)***

*** 3 (23%) patients received study treatment as 2nd line, 8 (62%) patients received study treatment as 3rd line, and 2 (15%) received study treatment as ≥ 4th line**

EOADR1-19/SPENCER: secondary objective - efficacy

Pheochromocytoma/paraganglioma: 12 pts (75%) experienced PR or SD with mDDC of 19.6 months

Cohort 3 [DB 2023-08-25]

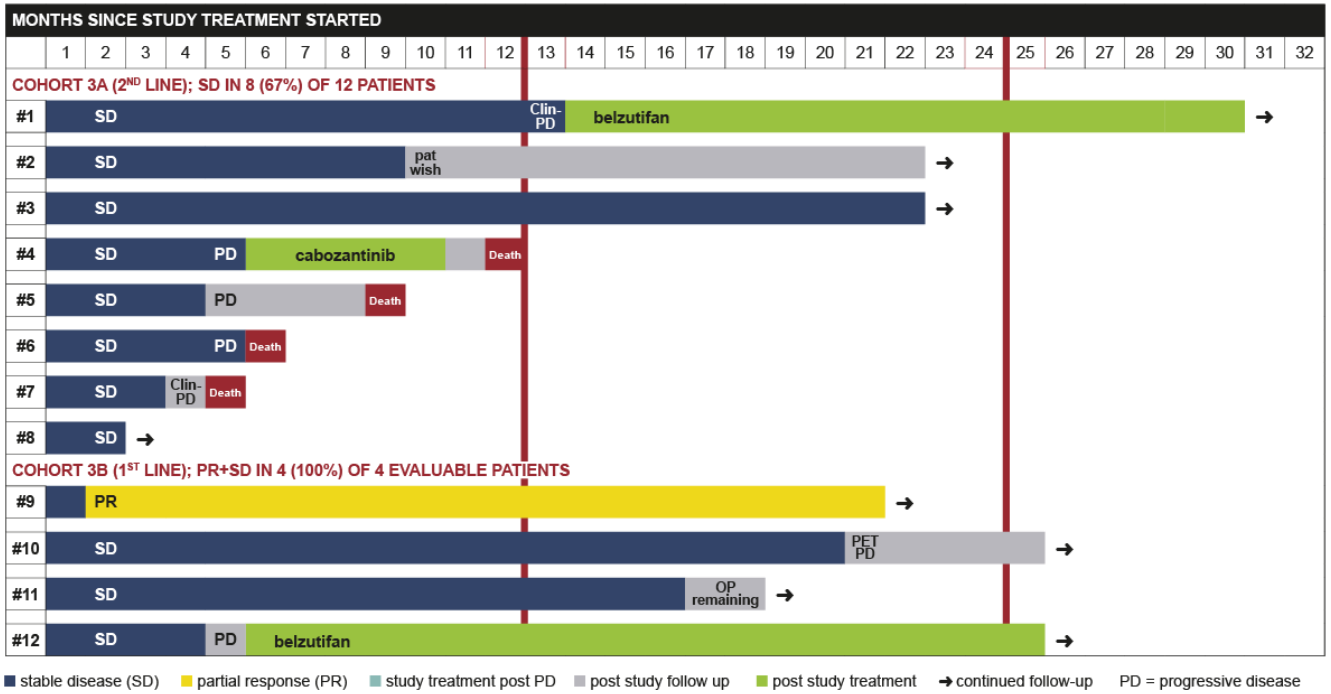
Study Treatment
- 13 (72%) pts ≥ 2nd line
- 5 (28%) pts 1st line

Tumor response (2pts too early)
- ORR = 1 (6%), DOR 18.4 mo
- DCR = 12 (75%), mDDC 19.6 mo

Progression-free survival
- mPFS 1.52 mo
- 12-mo progression-free rate 44%
- 18-mo progression-free rate 44%

Survival (mFU 21.6 mo)
- mSurvival not reached
- 12-mo survival rate 59%
- 18-mo survival rate 52%
- 24-mo survival rate 52%

ORR = objective response rate RECIST 1.1
DCR = disease control rate (OR+SD)
DOR = duration of objective response
DDC = duration of disease control
PFS = progression-free survival
FU = follow-up
m = median

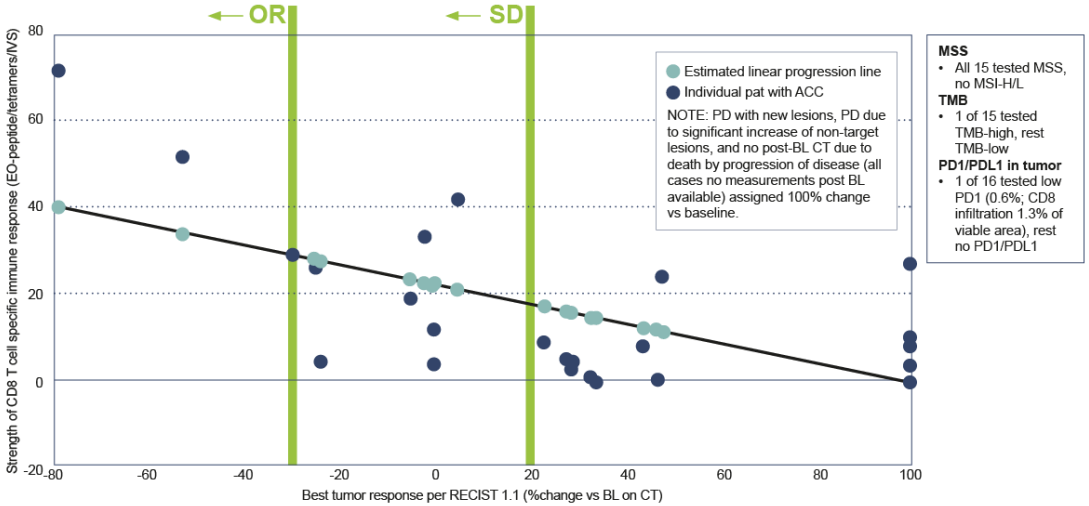


EOADR1-19/SPENCER: ACC patients secondary objective – immune response

There seems to be an **inverse relationship by linear regression** between **Degree of tumor shrinkage** and **Strength of CD8 T cell specific immune response** (assayed by tetramers after in vitro stimulation of PBMC; max response during treatment)

- *R^2 = 0.4048, R = -0.6362; overall regression p = 0.0005 [*
- *DB 2023-08-25; https://www.statskingdom.com/linear-regression-calculator.html]*

The above results are corroborated by **Mann Whitney U tests (Wilcoxon rank-sum)** showing that **patients with PR/SD on EO2401/nivolumab have significantly stronger CD8 specific T cell immune response against EO2401 than patients without a PR/SD (p = 0.002), and the same for patients with PR on EO2401/nivolumab vs patients without a PR (p = 0.01).**



Overall immune testing adrenocortical carcinoma:

- 28 (85%) of 33 patients tested, 23 (82% of tested/70% of all) had specific CD8 T cell response against microbiome derived peptides after study treatment start.
- 20 of 22 tested with an immune response also had CD8 T cells cross-reactive with the targeted TAAs.

Overall immune testing pheochromocytoma/paraganglioma

- 13 (72%) of 18 patients tested, 11 (85% of tested/61% of all) had specific CD8 T cell response against microbiome derived peptides after study treatment start.
- All tested (10 of the 11 with an immune response) had also CD8 T cells cross-reactive with the targeted TAAs.
- One patient had baseline detectable specific CD8 T cell responses against both microbiome derived peptides and the targeted TAAs

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EOADR1-19/SPENCER: Phase 1/2 trial in adrenal tumors

Conclusions

- **EO2401 in combination with nivolumab was generally well tolerated in patients with advanced/metastatic adrenal tumors**
- **Encouraging results in pretreated patients with ACC; median duration of disease control of 9 months, and 3 of 26 patients stopped study treatment at 2 years only due to protocol**
    - *A randomized study part for patients with previously treated adrenocortical carcinoma started recruiting patients July 2022 (EO2401/nivolumab vs EO2401 monotherapy vs nivolumab monotherapy; randomization 4:1:1; primary endpoint 6-months progression-free rate); outcome of a futility assessment after approx. 20 patients is awaited Q4-2023/Q1-2024*
- **EO2401 in combination with nivolumab achieved long term stabilizations of "cold tumors" (TMB-low, MSS, PDL1-low ACC)[1,2]**
    - **Specific CD8 T cell immune responses could be a biomarker**
- **Longer follow-up needed to interpret results in pheochromocytoma/paraganglioma patients**

1. Fassnacht M, 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.
2. Bratslavsky et al. Clinically Advanced Pheochromocytomas and Paragangliomas: Comprehensive Genomic Profiling Study. Cancers 2021, 13, 3312. https://doi.org/10.3390/cancers13133312

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Thank you!

- **Patients and families**
- **All involved staff at 10 sites in 8 countries**
- **All principal investigators**

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  - *Jaume Capdevila (Barcelona, Spain)*
  - *Martin Fassnacht (Würzburg, Germany)*
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  - *Christelle de la Fouchardière (Lyon, France)*
  - *Jeffrey Yachnin & Dan Granberg (Stockholm, Sweden)*
  - *Matthias Kroiss (Munich, Germany)*
  - *Gedske Daugaard (Copenhagen, Denmark)*

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Back-ups

- *Slides 15, 17-20 also provided to the discussant of the ESMO oral presentation*

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EOADR1-19/SPENCER: Adrenocortical carcinoma

SECONDARY OBJECTIVE – IMMUNE RESPONSE

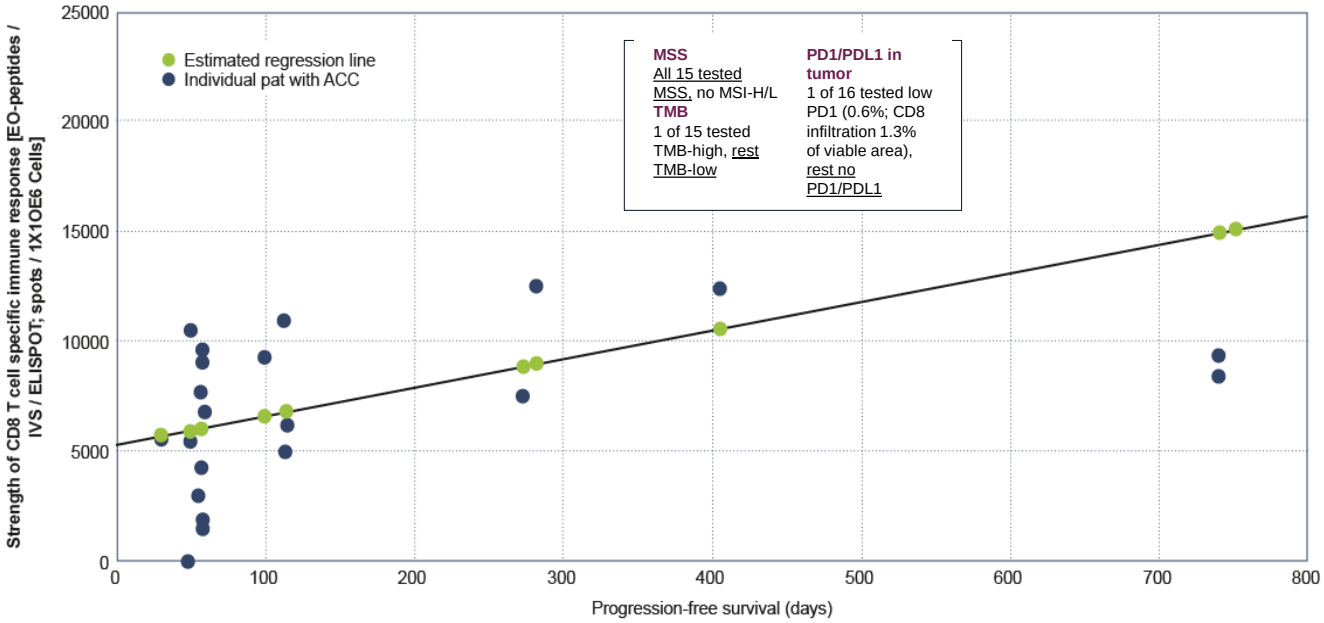
Overall immune testing adrenocortical carcinoma

- 28 (85%) of 33 patients tested, 23 (82% of tested/70% of all) had specific CD8⁺ T cell response against microbiome derived peptides after study treatment start.
- 20 of 22 tested with an immune response also had CD8⁺ T cells cross-reactive with the targeted TAAs.

Mann-Whitney U tests (two sided) of correlations immune response vs PFS (IFN-γ ELISPOT assay after in vitro stimulation; max response during treatment)

- patients with a PFS > median PFS of the total group have significantly stronger CD8+ specific T cell immune response against EO2401 than patients with a PFS ≤ than the median (p = 0.0192)
- patients with a PFS > 6 months have significantly stronger CD8+ specific T cell immune response against EO2401 than patients with a PFS ≤ 6 months (p = 0.0104)
- No difference in response to CEF 32 peptide pool recall antigens between groups per above, either at baseline or during study treatment (p-values 0.25-1.00)

LINE FIT PLOT



There seems to be direct relationship by linear regression between **PFS** and **Strength of CD8⁺ T cell specific immune response** (assayed by IFN-γ ELISPOT after in vitro stimulation of PBMC; max response during treatment)

$R^2 = 0.3781$, $R = 0.6149$; overall regression $p = 0.0023$

[DB 2023-08-25; https://www.statskingdom.com/linear-regression-calculator.html]

Data presented at oral session, ENSAT meeting 2023

European Network for the Study of Adrenal Tumors (ENS@T) Conference Dubrovnik, Croatia, October 11-13, 2023

EOADR1-19/SPENCER: secondary objective – immune response

Adrenocortical carcinoma: specific controls for correlations regarding strength of immune response and efficacy outcome

- CEF peptide pool including 32 defined CD8+ T cell epitopes of CMV, EBV, and flue virus [NIH AIDS Reagent Program. CEF Control Peptide Pool NIH, Ed. 2018. Available online: aidreagent.org/ referenced in Cells 2021, 10, 248. https://doi.org/10.3390/cells10020248]
- CEF responses were assayed by IFN-γ ELISPOT
- **Linear regression**
  - Best tumor response according to RECIST 1.1 (% change on CT vs BL)
    - Baseline CEF response: R2 = 0.067, R = 0.259; overall regression p = 0.300
    - Max CEF response during study treatment: R2 = 0.041, R = 0.202; overall regression p = 0.379
  - Progression-free survival according to RECIST 1.1 (days)
    - Baseline CEF response: R2 = 0.031, R = -0.177; overall regression p = 0.483
    - Max CEF response during study treatment: R2 = 0.032, R = -0.178; overall regression p = 0.439
- **Mann-Whitney U test (two-tailed)**
  - Patients with PFS > median vs patients with PFS ≤ median
    - Baseline CEF response: p = 1.0
    - Max CEF response during study treatment: p = 0.82
  - Patients with PFS > 6 months vs patients with PFS ≤ 6 months
    - Baseline CEF response: p = 0.25
    - Max CEF response during study treatment: p = 0.55
  - Patients with PR/SD (disease control) vs patients without disese control
    - Baseline CEF response: p = 0.93
    - Max CEF response during study treatment: p = 0.97
  - Patients with PR (objective response) vs patients without objectve response
    - Baseline CEF response: p = 0.82
    - Max CEF response during study treatment: p = 0.26

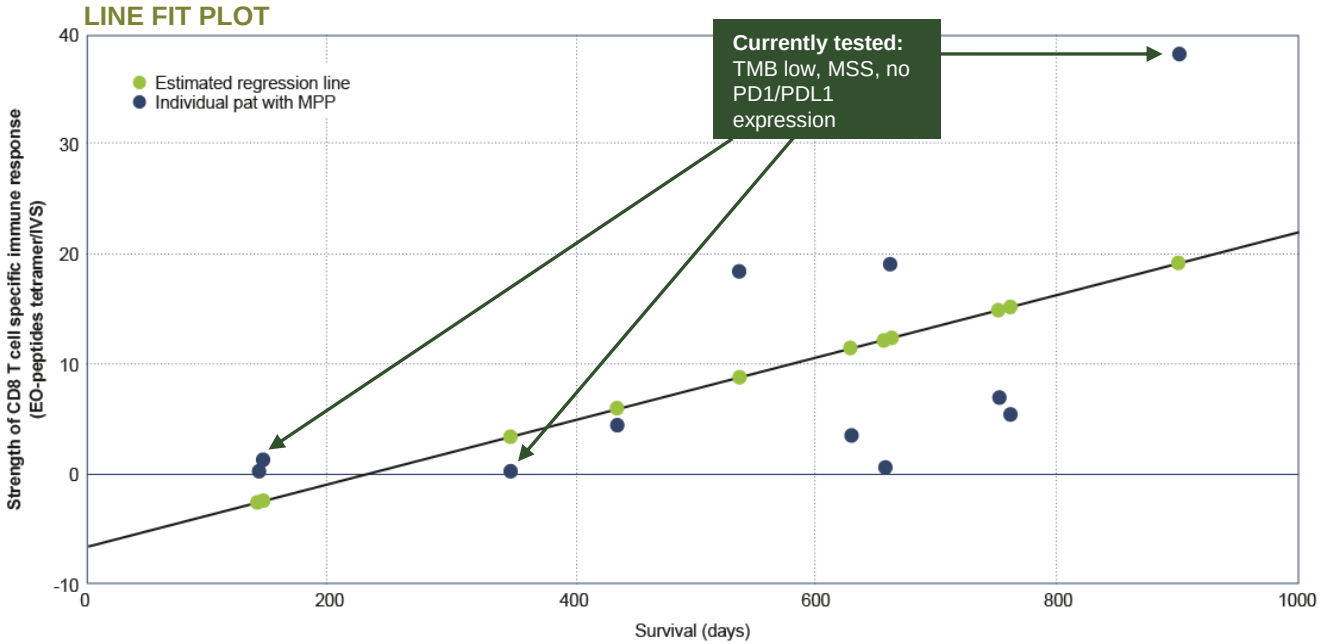
Conclusion (ACC):
There is NO correlation between a good efficacy outcome on EO2401/nivolumab and the ability for patients to respond to common recall antigens, either at baseline or during study treatment

EOADR1-19/SPENCER: Pheochromocytoma/Paraganglioma

SECONDARY OBJECTIVE – IMMUNE RESPONSE

Overall immune testing pheochromocytoma / paraganglioma

- 13 (72%) of 18 patients tested, 11 (85% of tested/61% of all) had specific CD8+ T cell response against microbiome derived peptides after study treatment start.
- All tested patients with an immune response also had CD8+ T cells cross-reactive with the targeted TAAs.
- One patient had baseline detectable specific CD8+ T cell responses against both microbiome derived peptides and the targeted TAAs



There seems to be direct relationship by linear regression between **Survival** and **Strength of CD8$^+$ T cell specific immune response** (assayed by tetramers after in vitro stimulation of PBMC; max response during treatment)

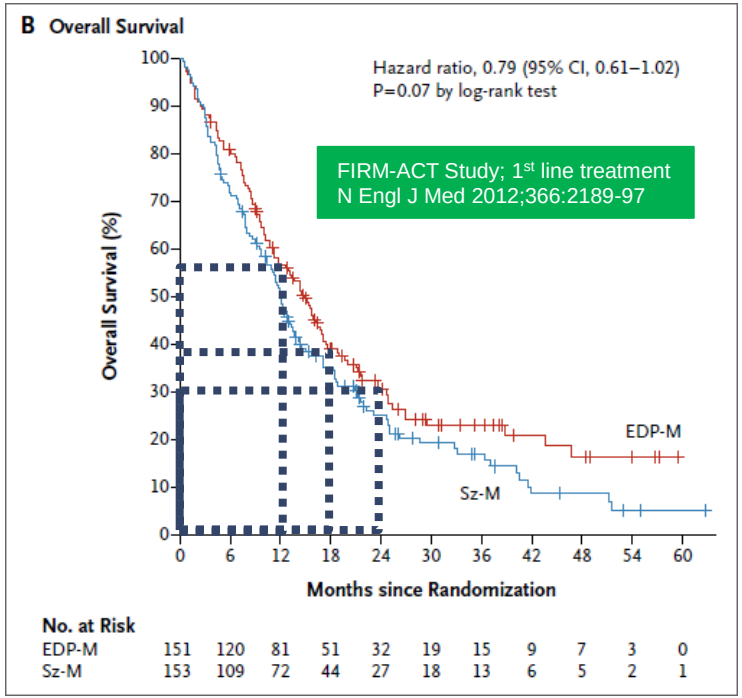
$R^2 = 0.3627$, $R = 0.6022$; overall regression $p = 0.05$

[DB 2023-08-25; https://www.statskingdom.com/linear-regression-calculator.html]

Data presented at oral session, ENSAT meeting 2023

EOADR1-19/SPENCER: Efficacy in context

Adrenocortical carcinoma historical context; 1st line treatment



Survival	EDP-M *	EO2401 + nivolumab	EO2401 + nivolumab	EO2401 + nivolumab
	N=151	N=33	N=7	N=26
	100% 1st line	21% 1st line & 79% 2nd/3rd line	100% 1st line	100% 2nd/3rd line
12 months	57%	58%	86%	50%
18 months	38%	45%	71%	38%
24 months	31%	36%	57%	31%

** EDP-M = etoposide/doxorubicin/cisplatin/mitotane*

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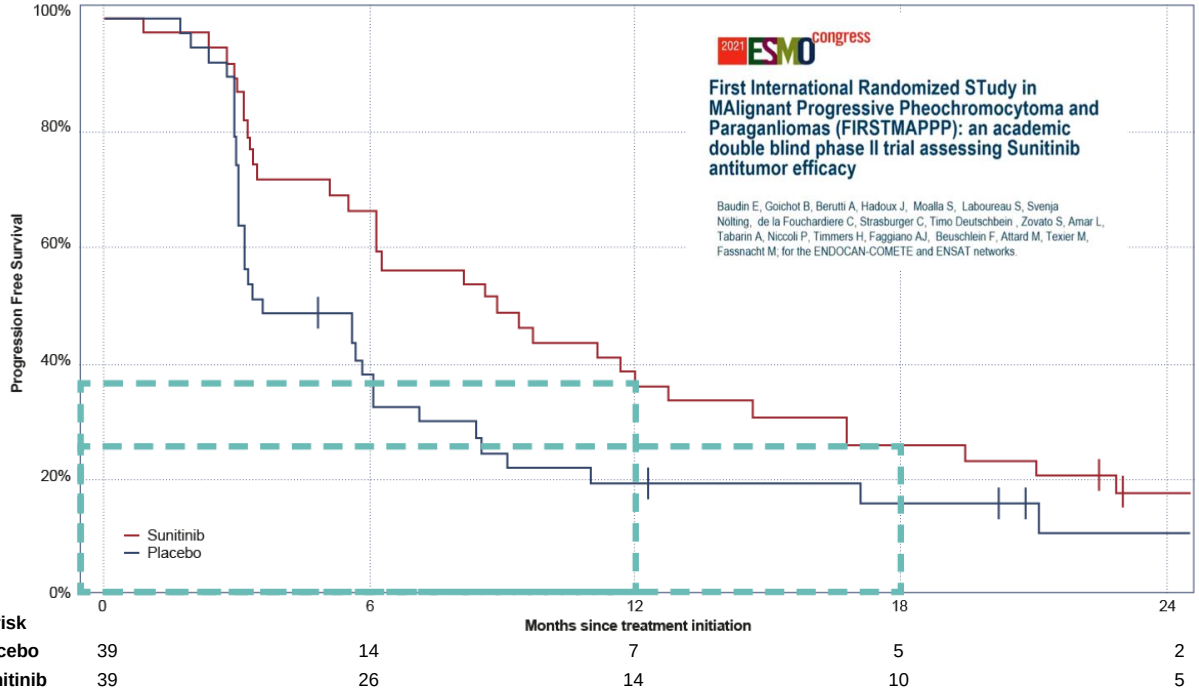
EOADR1-19/SPENCER: Pheochromocytoma/Paraganglioma

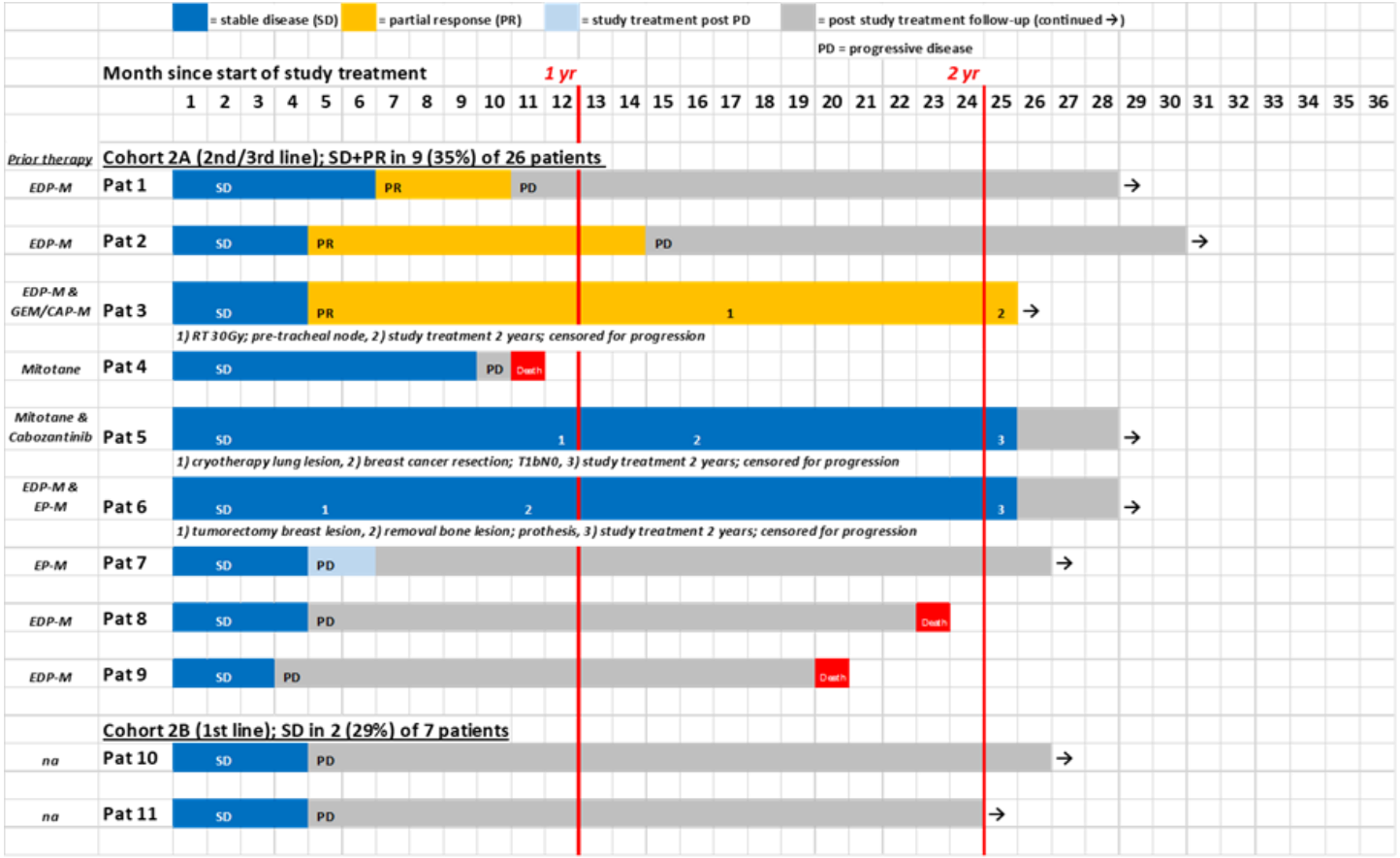
EFFICACY OUTCOME IN A HISTORICAL CONTEXT



Baseline	Sunitinib (n=39)	EO2401/ nivolumab (n=18)
1st line	44%	28%
Pheo/ Para	44%/56%	44%/56%
Hypertension	41%	56%
Bone met	67%	72%
Progression-free survival	**Sunitinib**	**EO2401 + nivolumab**
	N=39	N=18
12 months	36%	44%
18 months	26%	44%

EOADR1-19/SPENCER: secondary objective - efficacy

Adrenocortical carcinoma: prior therapies



EOADR1-19/SPENCER: secondary objective - efficacy

Pheochromocytoma/paraganglioma: last prior treatment before study treatment