ABSTRACT # CTIM-25

EO2401 peptide immunotherapy + nivolumab +/- bevacizumab in first recurrent glioblastoma: the phase 1/2 EOGBM1-18/ROSALIE* study

(NCT04116658)

Society for Neuro-Oncology (SNO) Annual Meeting, November 15-19, 2023, Vancouver, British Columbia, Canada
Abstract Concurrent Session:
Clinical Trials - Immunologic
Friday, November 17, 2023, 7:15 am – 8:45 am

** Rosalie is a musical with music by George Gershwin and Sigmund Romberg, lyrics by Ira Gershwin and P.G. Wodehouse. The name of this study has been established in tribute of George Gershwin who died of glioblastoma in 1937: he was 38 years old.*

Declaration of conflict of interests

DAVID REARDON, DANA-FARBER CANCER INSTITUTE, BOSTON, MA, USA

Honoraria

Advantagene; Agenus; Anheart Therapeutics; Bayer; Bristol-Myers Squibb; Deciphera; DelMar Pharmaceuticals; Ellipses Pharma; EMD Serono; Genenta Science; Imvax; Inovio Pharmaceuticals; Kintara Therapeutics; KIYATEC; Medicenna; Merck; Merck KGaA; NEUVOGEN; Novocure; Oncorus; Regeneron; Sumitomo Dainippon Pharma; Taiho Pharmaceutical; Vivacitas Oncology; Y-mAbs Therapeutics

Consulting or Advisory Role

Advantagene; Agenus; Agios; Anheart Therapeutics; Bayer; Bristol-Myers Squibb; Delmar Pharmaceuticals; Ellipses Pharma; EMD Serono; Genenta Science; Imvax; Kintara Therapeutics; Kiyatec; Medicenna; Merck; Merck KGaA; Novocure; Oncorus; Regeneron; Taiho Pharmaceutical; Vivacitas Oncology

Research Funding

Acerta Pharma (Inst); Agenus (Inst); Celldex (Inst); EMD Serono (Inst); Enterome (Inst); Incyte (Inst); Omniox

Phase 1/2 EOGBM1-18/ROSALIE study

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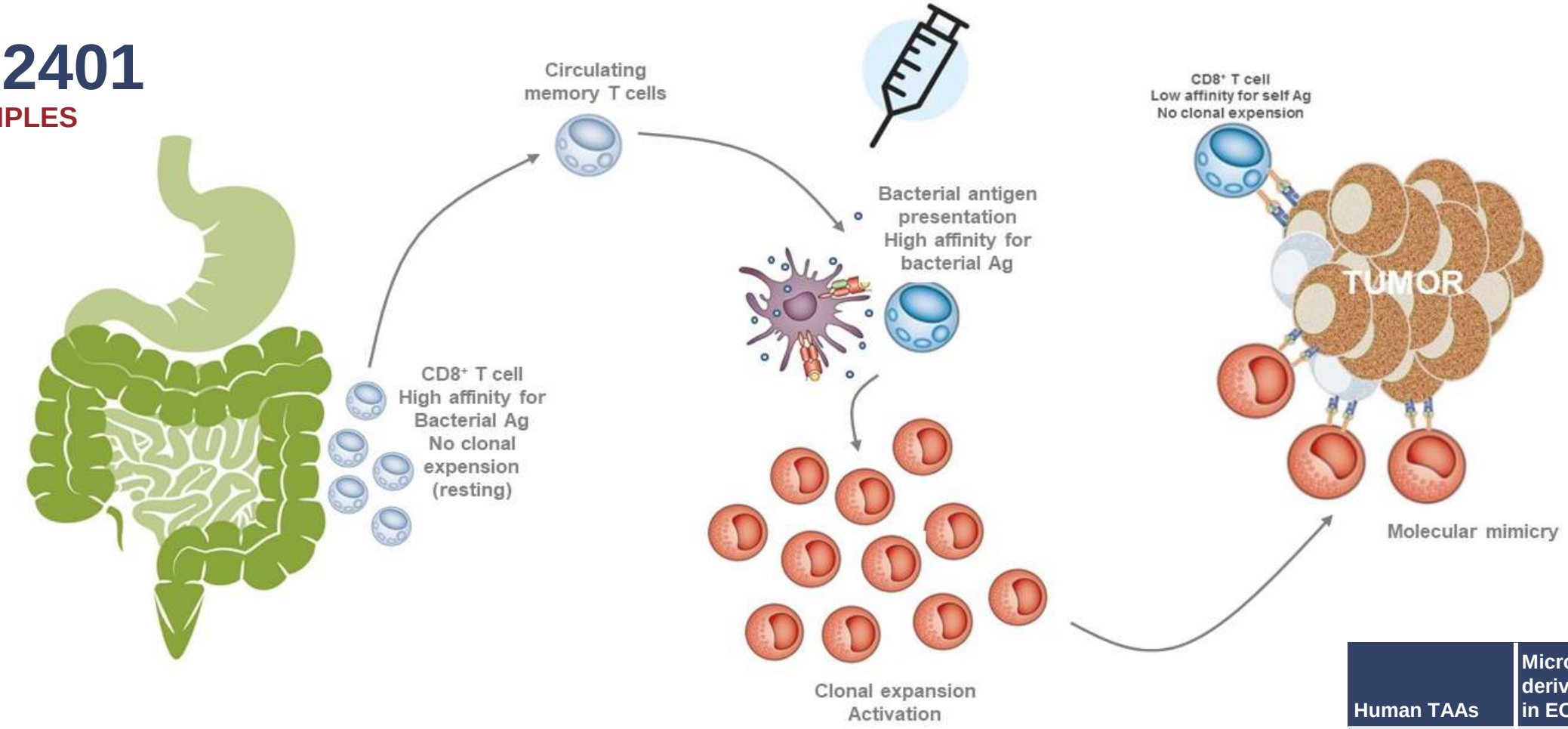
12 Enterome, Paris, France

EO2401

PRINCIPLES

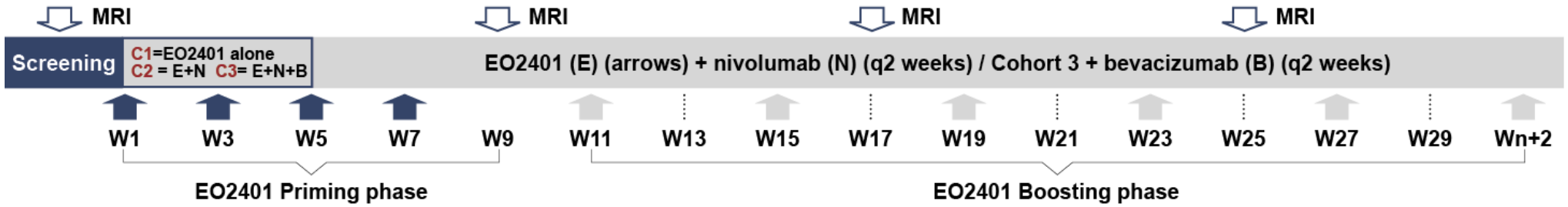


Human TAAs	Microbiome derived peptide in EO2401
BIRC5	EO2317
FOXM1	EO2318
IL13Rα2	EO2316

The microbiome-mimicry concept utilizing high affinity MHC class I, non-self-microbiome-derived peptides mimicking TAAs exhibited by tumor cells to expand pre-existing memory cytotoxic T cells cross-reacting with the selected TAAs

ROSALIE study

COHORTS, TREATMENTS, AND SCHEDULES



EO2401 in combination with nivolumab +/- bevacizumab

- **Nivolumab:** support fast and extensive T cell expansion and T cell infiltration of tumor
- **Bevacizumab:** anti-edema properties, counteract immunosuppression by VEGF

Endpoints:

- Safety and tolerability
- Immunogenicity, clinical efficacy, extensive exploratory endpoints

FIRST RECURRENT GLIOBLASTOMA

Cohort 1a
EO2401 → EO2401/nivolumab
Measurable disease
Study part 1, n=3*
Study part 2 /sLDB**, n=18
** pts from safety lead-in*

Cohort 2a
EO2401/nivolumab
Measurable disease
Study part 1, n=23
Study part 2/sLDB**, n=15

Cohort 2b
EO2401/nivolumab
Non-measurable disease (intended post-surgery)
Study part 1, n=3
Study part 2 /sLDB**, n=3

Cohort 2c
EO2401/nivolumab
Peri-operative treatment
Study part 2 /sLDB**, n=9

Cohort 3
EO2401/nivolumab/ bevacizumab*
Measurable disease
Study part 1, n=11 (DFCI)
Study part 2, n=15 (all sites)

EOGBM1-18
EO2401/nivolumab +/- bevacizumab
Total study n=100

EO2401:
300 µg/peptide, every 2 weeks x 4, then every 4 weeks; administered SC with adjuvant Montanide ISA 51 VG

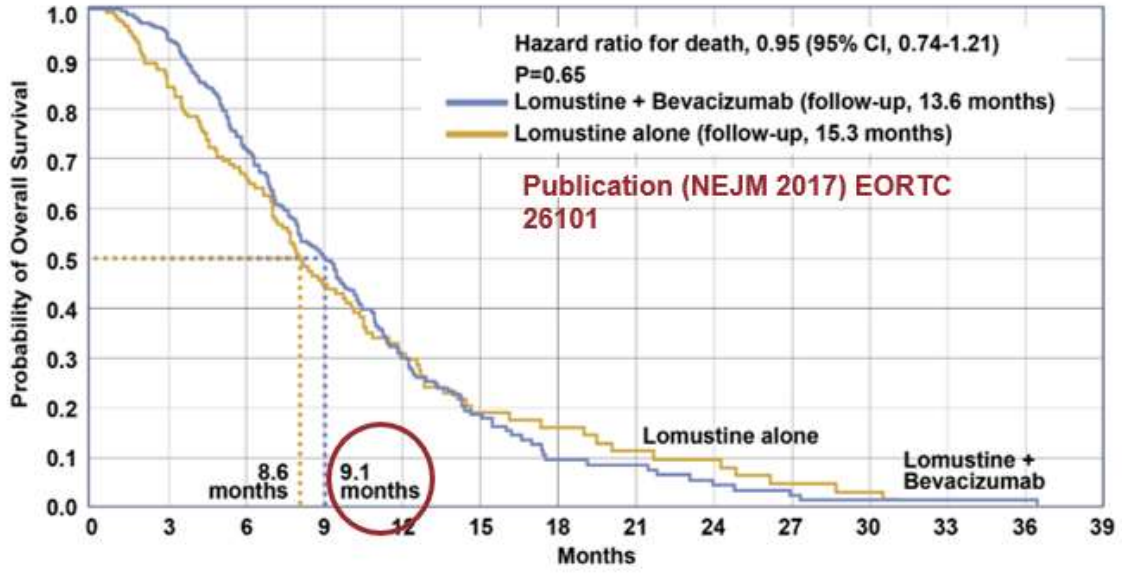
Nivolumab:
3 mg/kg every 2 weeks (Cohort 1 start week 5, other Cohorts start week 1)

Bevacizumab:
* Standard dose (Cohort 3) = 10 mg/kg every 2 weeks start week 1, until PD
** symptomatic low dose (sLDB) = 5 mg/kg every 2 weeks start at neurological symptoms

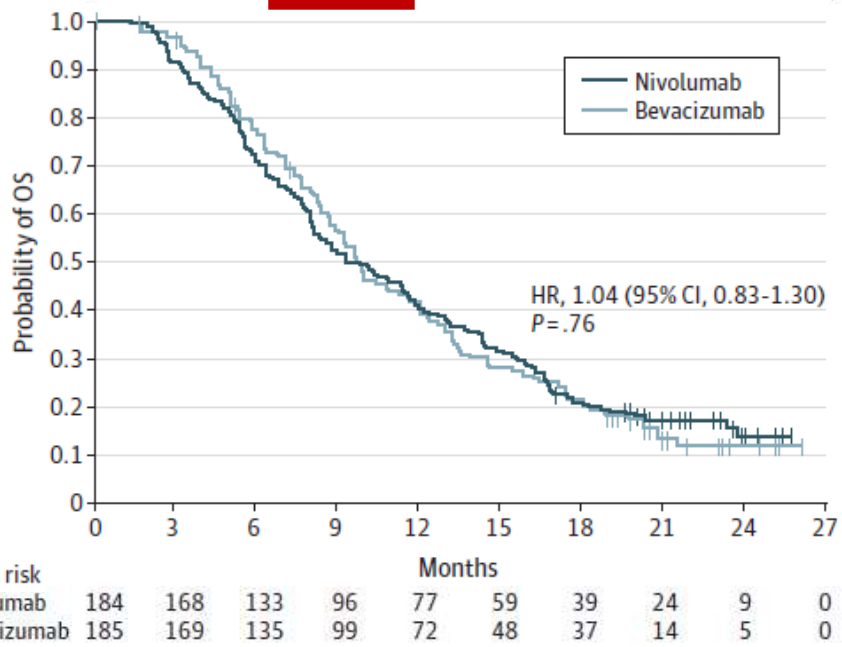
This presentation is dedicated to efficacy outcomes for patients treated with EO2401/nivolumab/bevacizumab (n=26)

ROSALIE study

HISTORICAL PERSPECTIVE



Intervention	Events, No.	Median OS (95% CI), months	OS Rate (95% CI), %		
			6 Months	12 Months	18 Months
Nivolumab	154	9.8 (8.2-11.8)	72.3 (65.2-78.2)	41.8 (34.7-48.8)	21.7 (16.1-27.9)
Bevacizumab	147	10.0 (9.0-11.8)	78.2 (71.2-83.6)	42.0 (34.6-49.3)	21.6 (15.8-28.0)

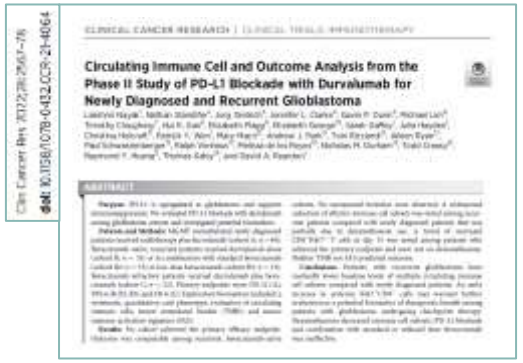


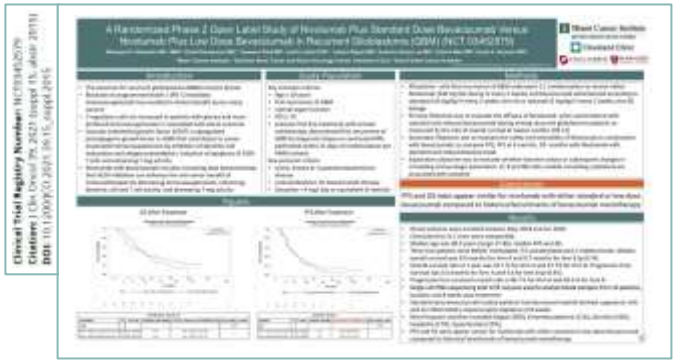
Publication (JAMA 2020) CheckMate-143

Median (range) follow-up 9.8 (1.3-26.3) months in nivolumab group and 9.4 (0-26.8) months in bevacizumab group

No additional efficacy benefits from adding pembrolizumab, durvalumab, or nivolumab to bevacizumab in glioblastoma:


Randomized Phase II and Biomarker Study of Pembrolizumab plus Bevacizumab versus Pembrolizumab Alone for Patients with Recurrent Glioblastoma


Circulating Immune Cell and Outcome Analysis from the Phase II Study of PD-L1 Blockade with Durvalumab for Newly Diagnosed and Recurrent Glioblastoma



ROSALIE study

BASELINE CHARACTERISTICS

E = EO2401 N = nivolumab B = bevacizumab sLDB = symp. directed low B **DB 2023-10-28**	**Cohort 1a E→EN + sLDB (n=21)**	**Cohort 2a/1 EN (n=23)**	**Cohort 2a//2 EN + sLDB (n=15)**	**Cohort 2b EN + sLDB adjuvant (n=6)**	**Cohort 2c EN + sLDB neoadjuvant → surgery → adjuvant (n=9)**	**Cohort 3 ENB (n=26)**	**Total All Cohorts (n=100)**
Age, median (range), years	58 (19-73)	58 (37-78)	60 (18-76)	54 (46-70)	53 (41-67)	61 (24-73)	58 (18-78)
Gender, female - male	33% - 67%	35% - 65%	47% - 53%	50% - 50%	33% - 67%	38% - 62%	38% - 62%
Time from initial diagnosis to study start, median (range), months	13 (7-39)	14 (7-54)	12 (6-28)	14 (6-36)	12 (5-59)	11 (6-98)	12 (5-98)
MGMT promoter methylation (% pts yes - % pts no)	35% - 65%	36% - 64%	36% - 64%	40% - 60%	38% - 62%	43% - 57%	38% - 62%
IDH1 mutation (no (%) pts yes)	0	1 (4%)	0	1 (17%)	1 (11%)	2 (8%)	5 (5%)
Baseline target lesion size, median (range), mm^2	645 (97-2017)	952 (169-4290)	617 (220-2808)	21 (0-80)	433 (132-858)	947 (110-4780)	672 (0-4780)
Baseline KPS (% pts ≥ 90% - % pts 70 to 80)	67% - 33%	43% - 57%	53% - 47%	83% - 17%	100% - 0%	54% - 46%	60% - 40%
Baseline steroid use (0 < DEX ≤ 2 mg) (% pts yes)	24%	26%	47%	50%	0%	31%	29%
Measurable enhancing disease (≥ 1x1 cm in maximum bi-perpendicular plane)	100%	100%	100%	0%	100%	100%	94%
Baseline decreased lymphocytes (Gr 1 % - Gr 2 % - Gr 3%)	29% - 29% - 5%	30% - 22% - 0%	27%- 27% - 0%	33% - 0% - 0%	22% - 11% -11%	15% - 8% - 0%	25% - 18% - 2%

ROSALIE study

SAFETY IN ALL PATIENTS IN ALL COHORTS

EO2401 + nivolumab +/- bevacizumab safety profile is consistent with the previously established profile of nivolumab, and when applicable bevacizumab, except the addition of local administration site reactions [DB 2023-03-16; n = 100]

- **Most common treatment-related AEs* (any grade) were**
  - fatigue (19%)
  - ALT increase (10%)
  - AST increased (9%)
  - headache (9%)
  - nausea (7%)
  - pyrexia (7%)
  - hyperthyroidism (6%)
  - hypothyroidism (6%)
  - diarrhea (6%)
  - gamma-GT increased (6%)
  - pruritus (6%)
  - vaccination complication (6%)
  - white blood cell count decreased (5%)

**local administration site reactions presented combined below*

- **Grade ≥3 treatment-related events* in 16% of patients**
- **most common were**
  - increased gamma-GT (3%)
  - ALT/AST (2% each)
  - aseptic meningitis, and brain edema (all 2%)

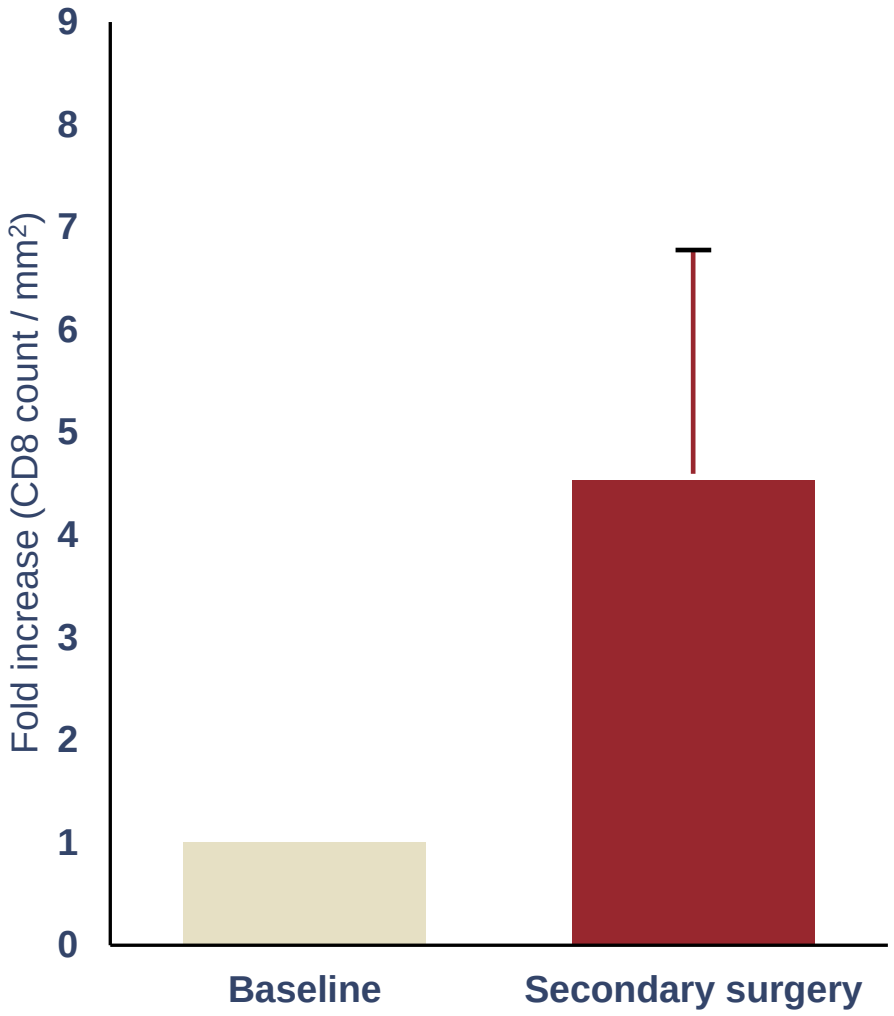
**local administration site reactions presented combined below*

- **Ten AEs leading to treatment discontinuation:**
  - transaminitis (3)
  - aseptic meningitis
  - creatinine increased/somnolence
  - adenocarcinoma liver metastases
  - alteration general status
  - ataxia/apraxia/alexia
  - seizures
  - intracranial hemorrhage
- **Two AEs leading to death**
  - status epilepticus
  - urosepsis

- **Any local administration site reaction (combined term of all types of reactions): 39% of patients**
  - Grade 1-2: 96% of events; grade 3: 4%; grade 4: 0%
  - Median time to event onset: 45 days (range 1-629);
  - Median event duration: 58 days (range 1-729)

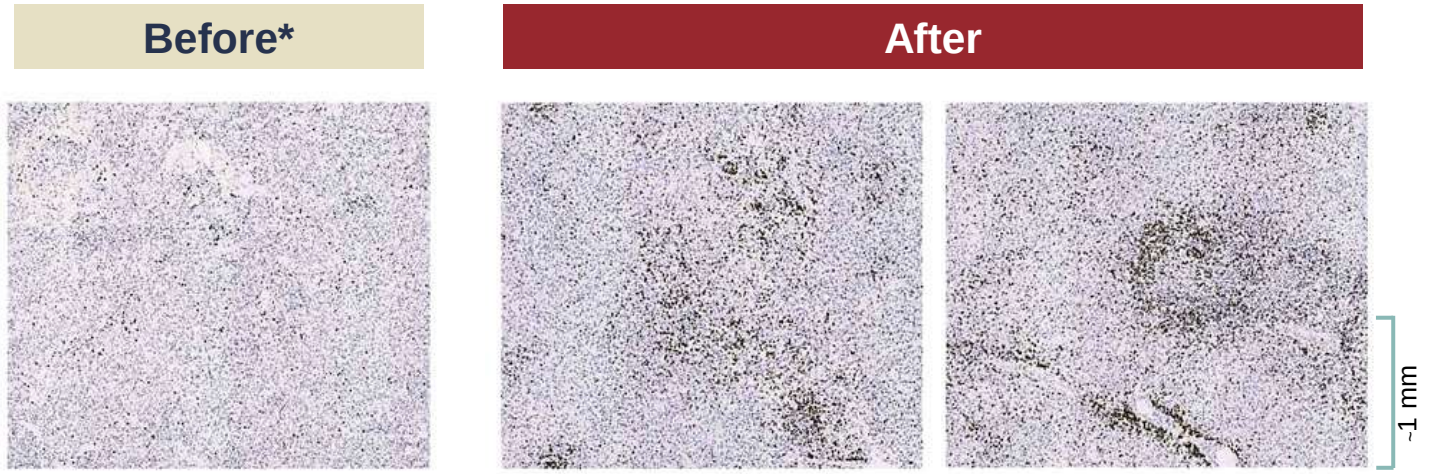
ROSALIE study

T CELLS EXPANDED WITH EO2401 INFILTRATE GLIOBLASTOMA



In **COHORT 2C** (*EN/sLDB neoadjuvant → surgery → EN/sLDB adjuvant*), brain tissue samples from 6 patients were collected after 2 administrations of EO2401/nivolumab prior to surgery (median treatment duration 20 days)

CD8⁺ T cell Influx
(Patient From Cohort 2C)



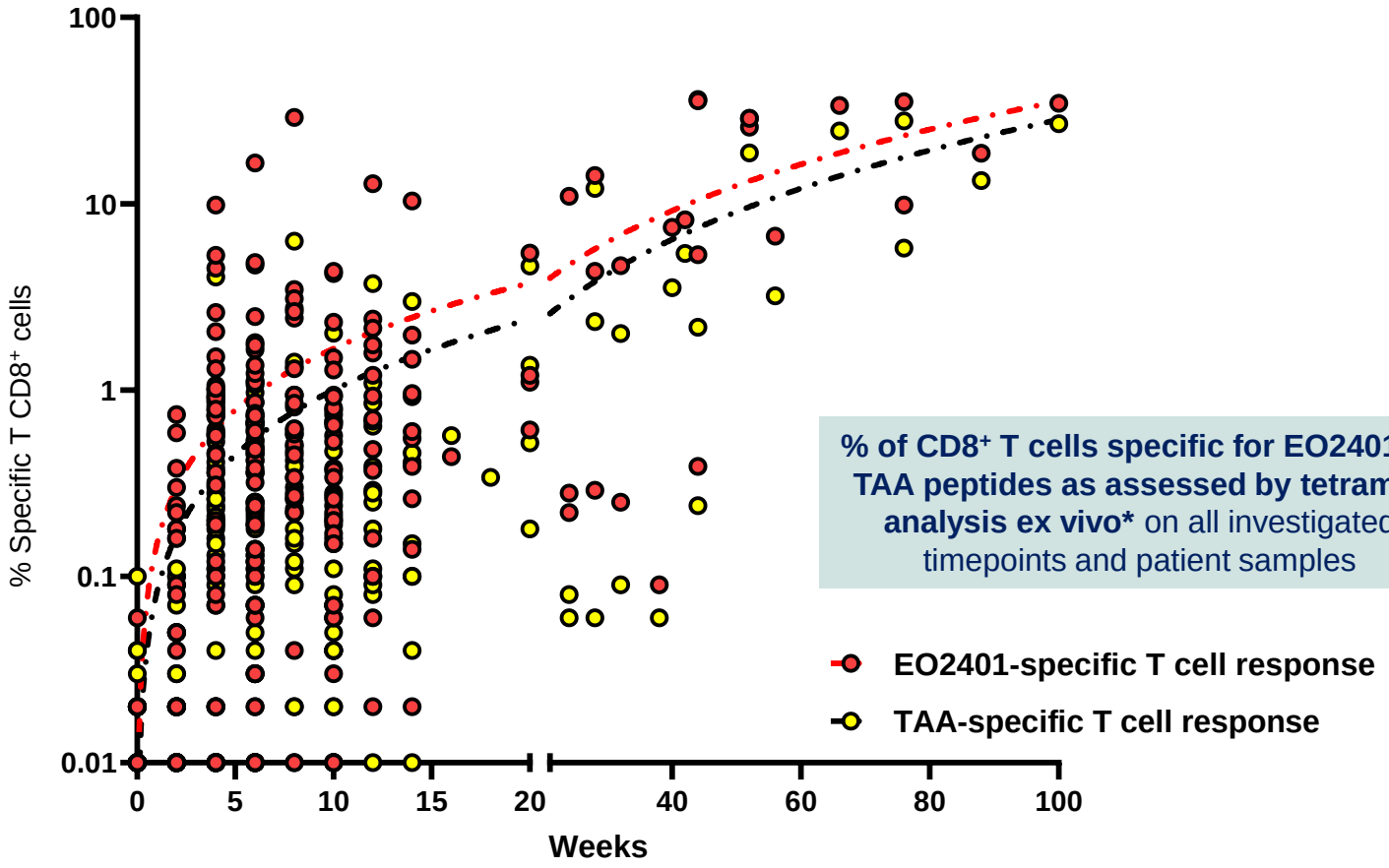
** Baseline/before = tissue sample from primary surgery*

ROSALIE study

IMMUNE RESPONSE

MAGNITUDE OF RESPONSE INCREASES OVER TIME IN ALL EVALUABLE PATIENTS

Expansion of effector memory T cells



% of CD8⁺ T cells specific for EO2401 or TAA peptides as assessed by tetramer analysis ex vivo* on all investigated timepoints and patient samples

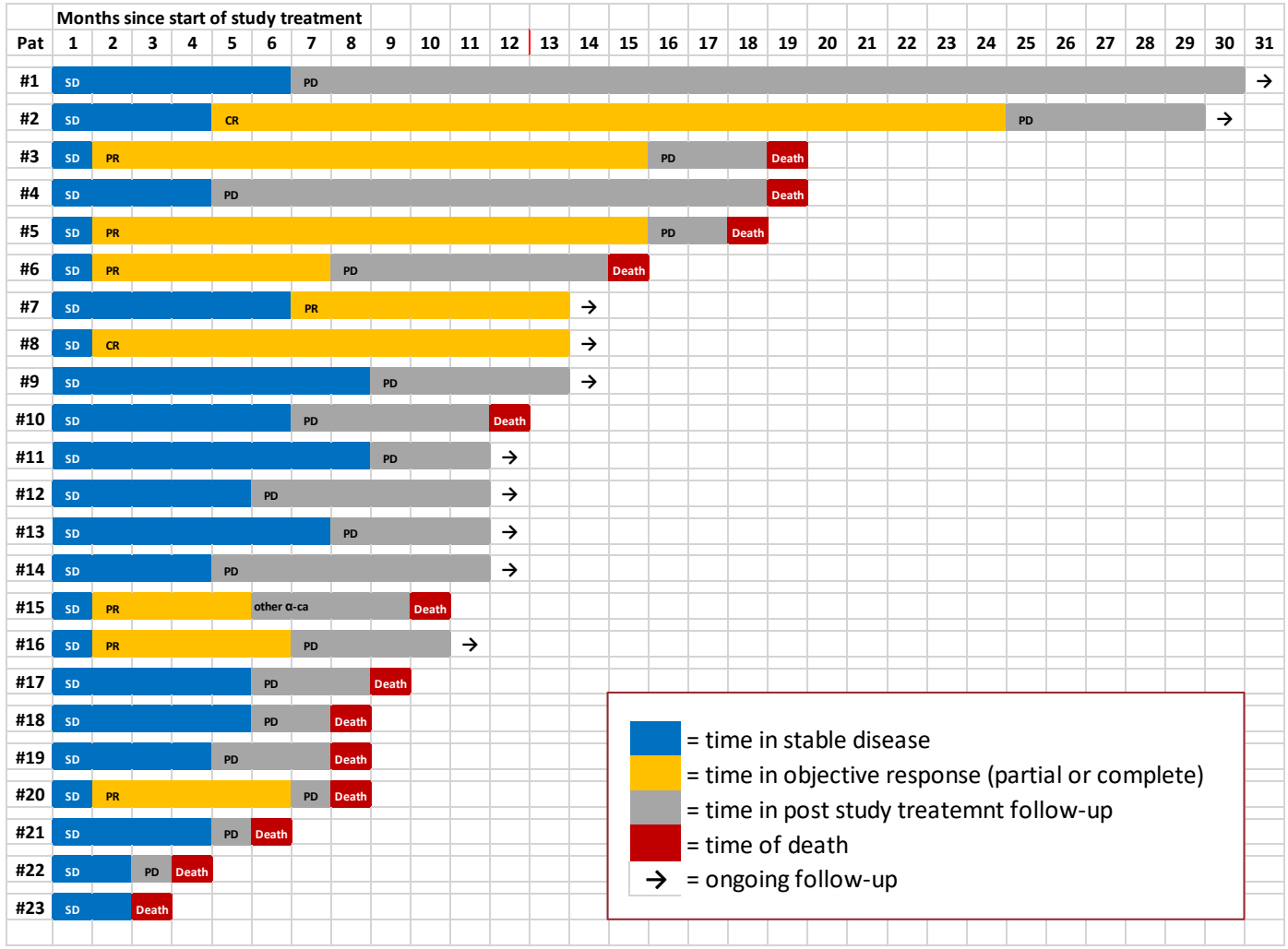
Immune testing Cohort 3*

- 25 (96%) of 26 patients tested (1 early drop-out)
- 23 (92% of tested / 88% of all) had a specific CD8+ T cell response against microbiome derived EO-peptides after study treatment start
- 23 (100%) of the immune response positive patients had CD8+ T cells cross-reactive with the targeted TAAs, i.e., recognizing IL13Rα2, BIRC5/survivin, and/or FOXM1

ex vivo assay: PBMC separated from peripheral blood directly analyzed by flow cytometry for CD8+ cells using specific tetramers staining without any prior in vitro stimulation
Quadratic regression fitting curves are used to highlight specific immune response over the course of the study

ROSALIE study

EO2401/NIVOLUMAB/BEVACIZUMAB (COHORT 3; N=26*) [DB 2023-10-28]



Objective response rate (CR + PR) = 9 pts
34.6% (95% CI; 17.2 – 55.7%)

Median time to objective response =
1.9 months (95% CI; 1.3 – 4.5 months)

Median duration of objective response =
13.1 months (95% CI; 3.7 – 18.5 months)

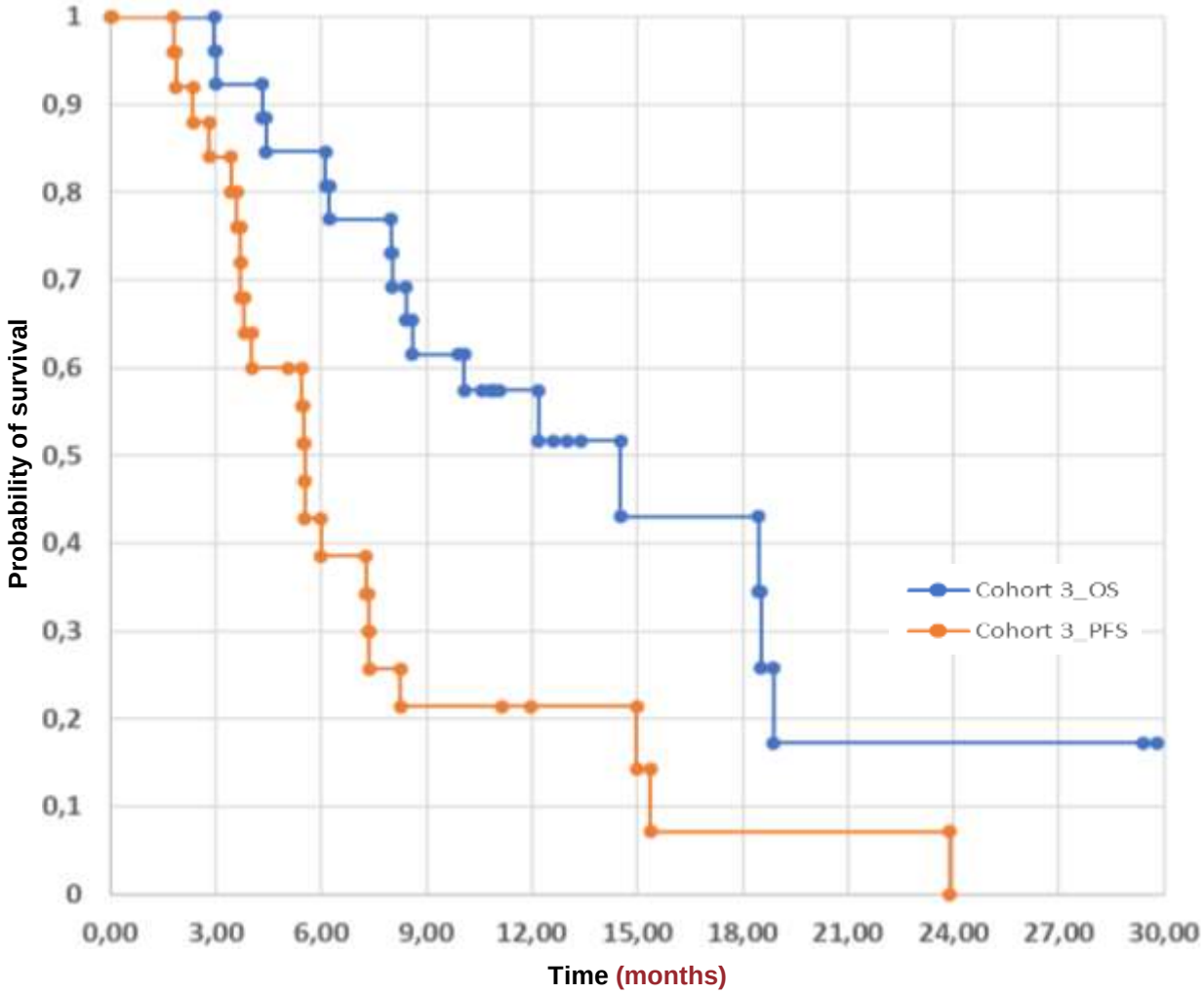
Disease control rate (CR + PR + SD) = 23 pts
88.5% (95% CI; 69.8 – 97.6%)

Median duration of disease control =
5.5 months (95% CI; 3.8 – 7.4 months)

iRANO:
CR = complete response;
PR = partial response;
SD = stable disease;
PD = progressive disease;
UPD = unconfirmed progressive disease
** Three patients not included in figure: two pts UPD at 1st assessment, survival 4.3 and 6.1 months, and one pat non-evaluable, off study treatment due to G4 transaminitis, survival 3.0 months*

ROSALIE study

EO2401/NIVOLUMAB/BEVACIZUMAB (COHORT 3; N=26) [DB 2023-10-28]



	Median (months)	6 months (%)	12 months (%)	18 months (%)	24 months (%)
Progression-free survival (95% CI)	5.5 months (3.7 – 7.3 months)	42.9% (23.2 – 61.1%)	21.4% (7.9 – 39.3%)	7.1% (0.6 – 26.0%)	0.0%
Overall survival (95% CI)	14.5 months (8.0– 18.5 months)	84.6% (64.0 – 93.9%)	57.4% (36.4 – 73.8%)	43.1% (20.6 – 63.9%)	17.2% (3.1 – 41.6%)

Median follow-up for survival: 13.4 months; 10 (38%) of patients alive in follow-up

ROSALIE study

HISTORICAL PERSPECTIVE

Parameter	Bevacizumab Checkmate-143*	Bevacizumab + lomustine EORTC-26101^	EO2401/nivolumab + cont. bevacizumab EOGBM1-18/ROSALIE**
Number of patients	185	288	26
Median follow-up	9.4 months	13.6 months	13.4 months
ORR	23.1% (16.7-30.5)	41.5% (35.5-47.8)	**34.6%** (17.2-55.7)
Median Duration of OR	5.3 months	NR	**13.1 months** (3.7-18.5)
DCR (CR+PR+SD)	69.9%	NR	88.5% (69.8-97.6)
Median Duration of DC	NR	NR	5.5 months (3.8-7.4)
Median PFS	3.5 months (2.9-4.6)	4.2 (3.7-4.3) / local 3.8 (3.0-4.2) /central	**5.5 months** (3.7-7.3)
Median survival	10.0 (9.0-11.8)	9.1 (8.1-10.1)	**14.5 months** (8.0-18.5)
Survival rate			
6-months	78.2% (71.2-83.6)	72% (NA)	**84.6%** (64.0-93.9)
12-months	42.0% (34.6-49.3)	31.5% (25.7-37.6)	**57.4%** (36.4-73.8)
18-months	21.6% (15.8-28.0)	~10% (NR)	**43.1%** (20.6-63.9)
24-months	*[~12% (NR)]*	*[~5% (NR)]*	*[17.2% (3.1-41.1)]*
	**JAMA Oncol. doi:10.1001/jamaoncol.2020.1024; 95% CI's given when available*	*^N Engl J Med 2017;377:1954-63. DOI: 10.1056/NEJMoa1707358 95% CI's given when available*	*** Database 2023-10-28; fixed median survivals is not reached (10 pts alive); 95% CI's given*

NR = not reported

ORR = objective response rate

OR = objective response

DCR = disease control rate

CR = complete response

PR = partial response

SD = stable disease

DC = disease control

PFS = progression-free survival

ROSALIE study: EO2401 with nivolumab and bevacizumab

CONCLUSIONS

- EO2401/nivolumab/bevacizumab was well tolerated with a safety profile consistent with the safety profiles of nivolumab and bevacizumab, except the addition of local administration site reactions
- EO2401/nivolumab generated fast, strong, and durable systemic immune responses against the targeted tumor associated antigens IL13Rα2, BIRC5/survivin, and FOXM1
- The addition of bevacizumab with strong anti-edema properties, and possibility to counteract immunosuppression by VEGF, to EO2401/nivolumab has overcome short treatment durations due to neurologic decline from ongoing tumor progression during initiation of immunologic effect generated by EO2401/nivolumab
- Efficacy of EO2401/nivolumab/bevacizumab seems encouraging in a historical perspective, including a median survival of 14.5 months and an 18-months survival rate of 43% in patients with first recurrent glioblastoma
- ***Evaluation of "the triplet" EO2401/nivolumab/bevacizumab (ENB) in a randomized study seems a logical next step***

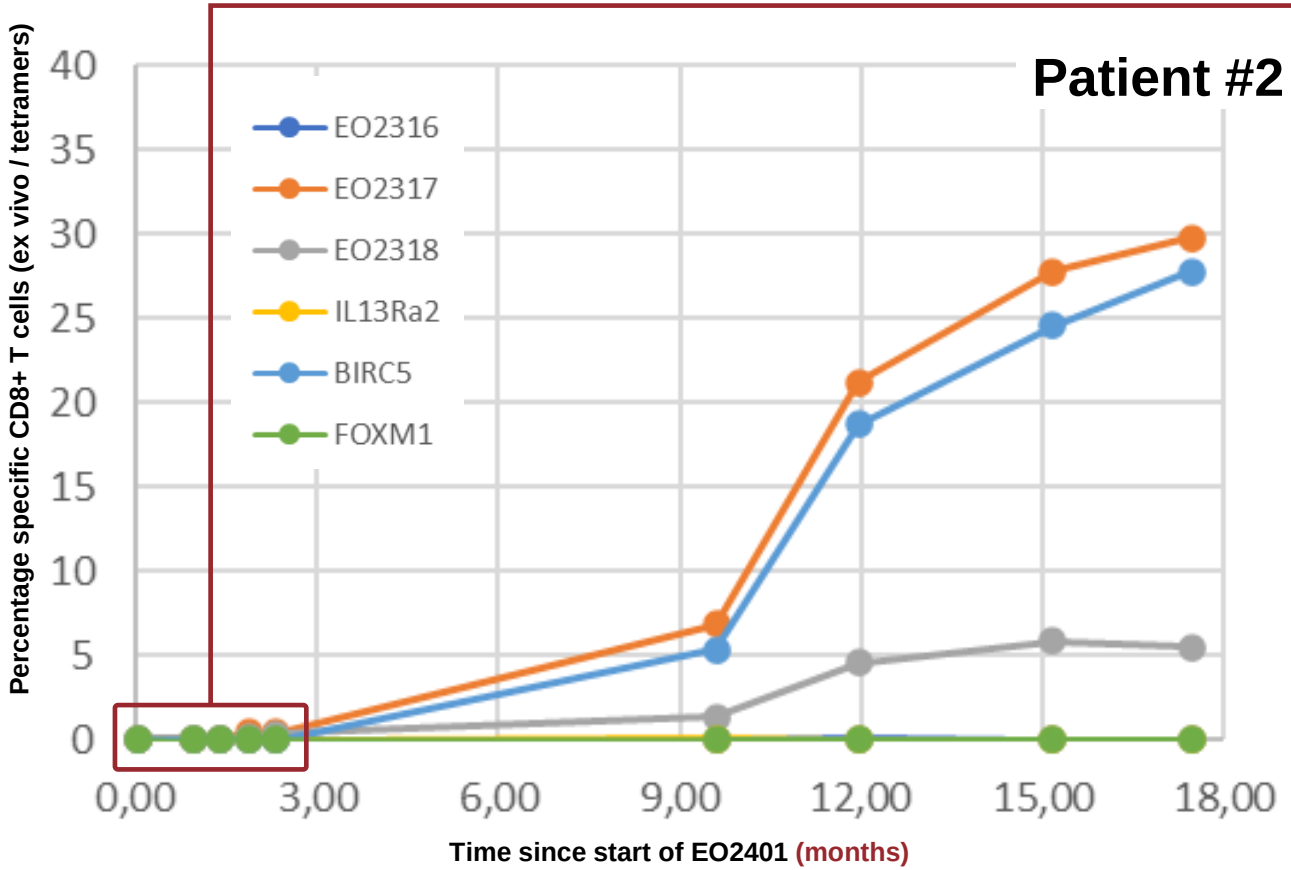
Thank you

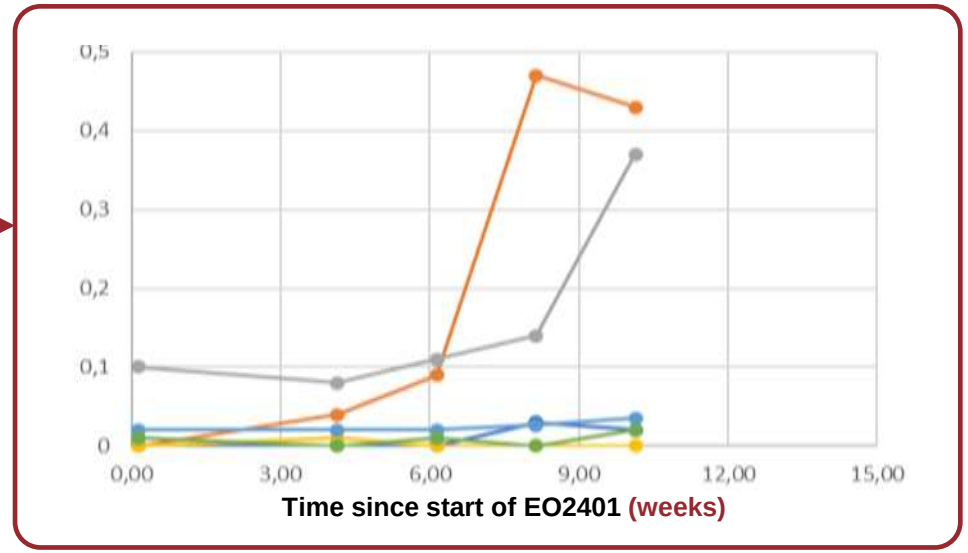
Patients and Families
Clinical research assistants
Co-investigators

Back-up’s

ROSALIE study

EO2401/NIVOLUMAB/BEVACIZUMAB IMMUNE RESPONSE





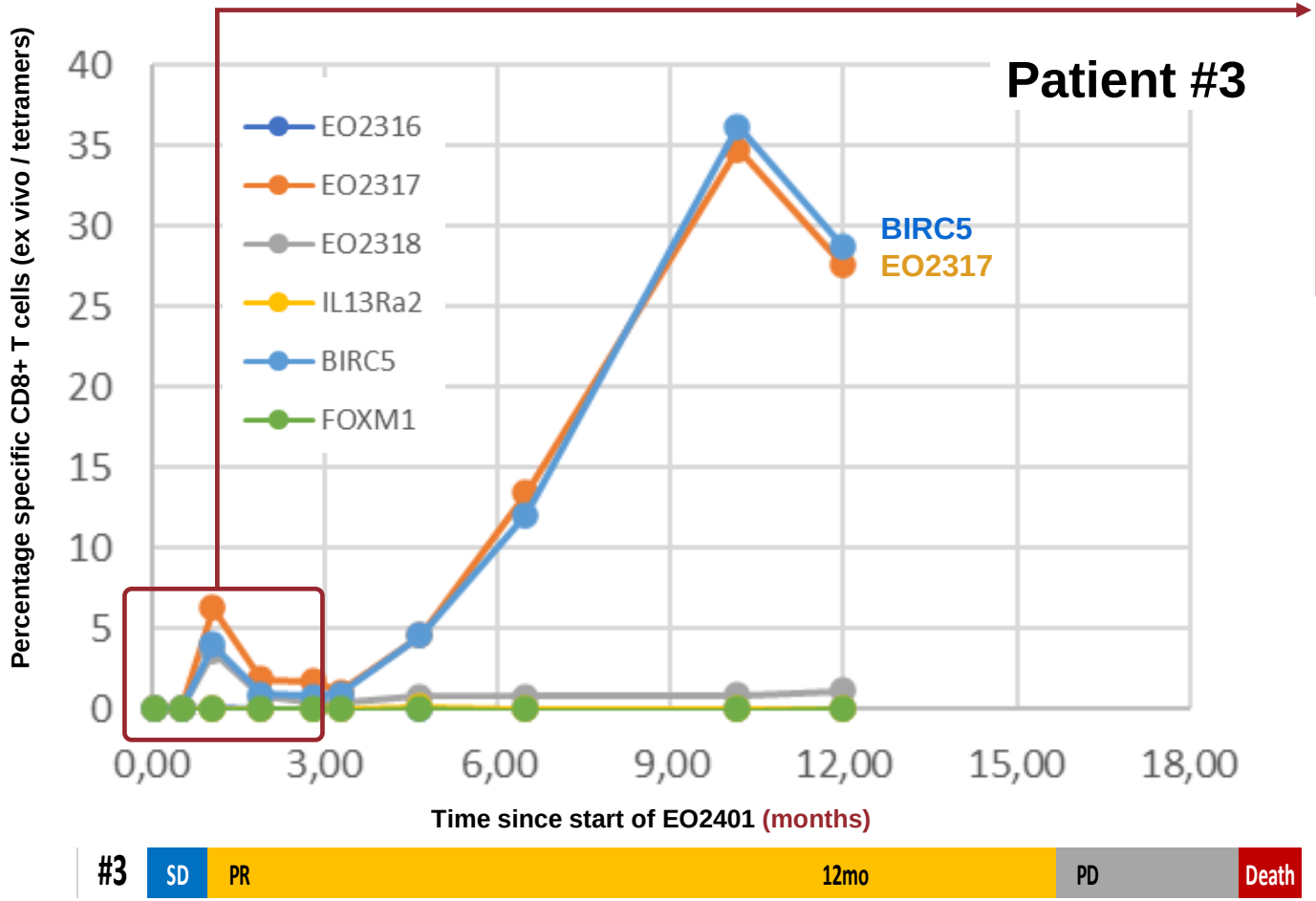
Immune testing Cohort 3*

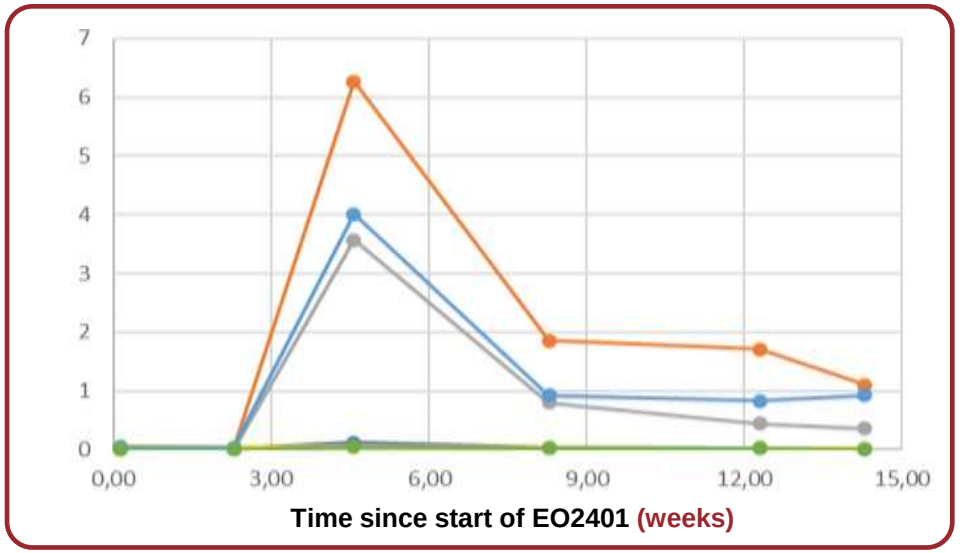
- 25 (96%) of 26 patients tested (1 early drop-out)
- 23 (92% of tested / 88% of all) had a specific CD8+ T cell response against microbiome derived EO-peptides after study treatment start
- 23 (100%) of the immune response positive patients had CD8+ T cells cross-reactive with the targeted TAAs, i.e., recognizing IL13Rα2, BIRC5/survivin, and/or FOXM1
- **At early time points (week 2-15; 72% <week10); all tested**
  - median % of EO-peptide specific CD8+ T cells (max per pat) = **0.75% (range 0.03-9.96%) / mean 1.41%**
  - median % of TAA-peptide specific CD8+ T cells (max per pat) = **0.25% (range 0-4.1%) / mean 0.53%**

** Ex vivo assay: PBMC separated from peripheral blood directly analyzed by flow cytometry for CD8+ cells using specific tetramers staining without any prior in vitro stimulation*

ROSALIE study

EO2401/NIVOLUMAB/BEVACIZUMAB IMMUNE RESPONSE





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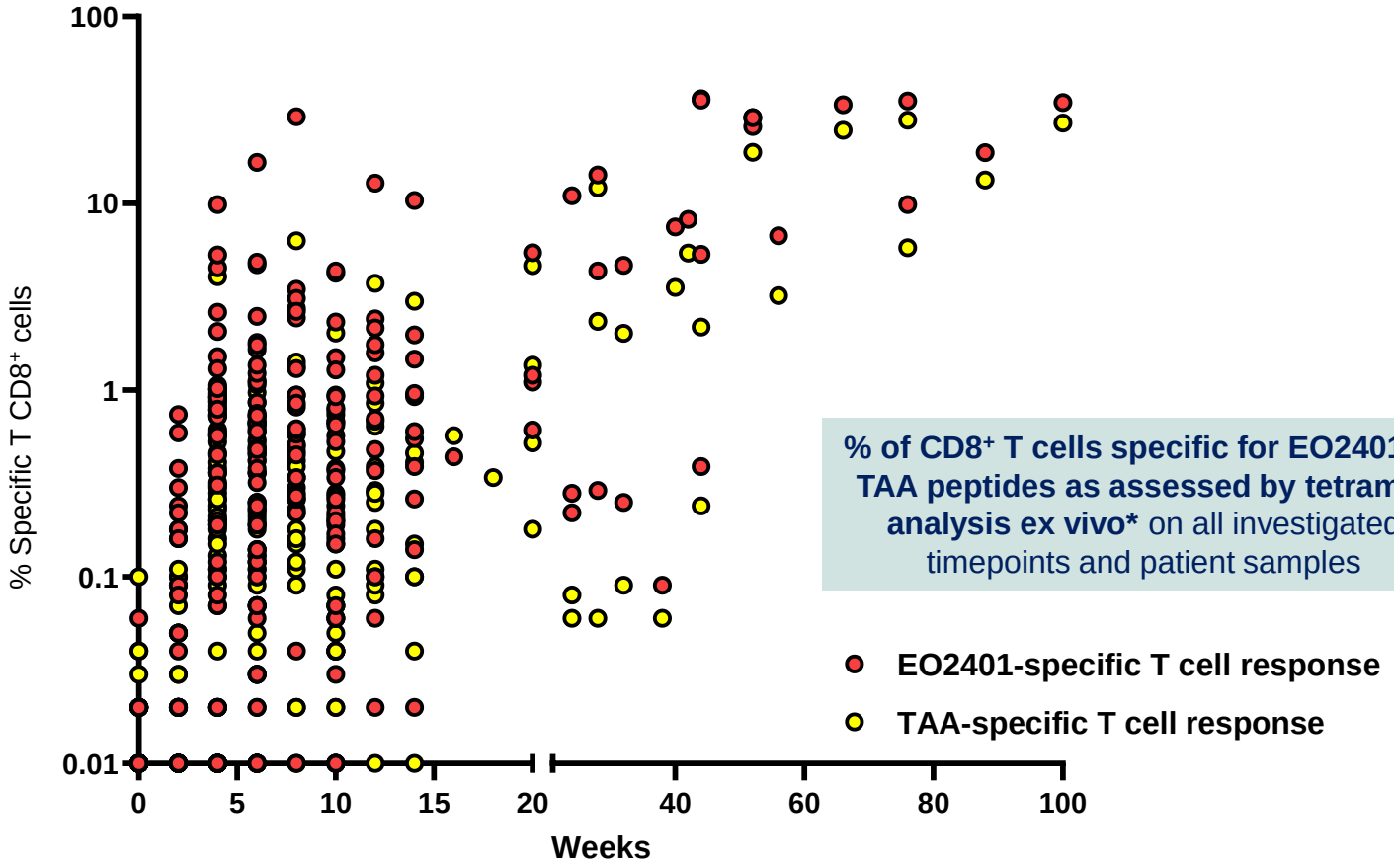
ROSALIE study

IMMUNE RESPONSE

MAGNITUDE OF RESPONSE INCREASES OVER TIME IN ALL EVALUABLE PATIENTS

Expansion of effector memory T cells



% of CD8⁺ T cells specific for EO2401 or TAA peptides as assessed by tetramer analysis ex vivo* on all investigated timepoints and patient samples

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  - median % of EO-peptide specific CD8+ T cells (max per pat) = **0.75% (range 0.03-9.96%) / mean 1.41%**
  - median % of TAA-peptide specific CD8+ T cells (max per pat) = **0.25% (range 0-4.1%) / mean 0.53%**

ex vivo assay: PBMC separated from peripheral blood directly analyzed by flow cytometry for CD8+ cells using specific tetramers staining without any prior in vitro stimulation