ABSTRACT # 642:

EO2401 microbiome derived therapeutic vaccine + nivolumab, with/without standard continuous, or low-dose symptom directed, bevacizumab, in recurrent glioblastoma

Phase 1-2 EOGBM1-18 / ROSALIE* study

[NCT04116658]

Society for Immunotherapy of Cancer (SITC) 37th Annual Meeting, November 10-12, 2022, Boston, MA, USA

Concurrent Session 105: Rapid Oral Abstracts – Clinical, November 10, 2022, 11:55 am – 12:55 pm

** 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 interest

David Reardon

Type of affiliation / financial interest	Company
Honoraria	Advantagene; Agenus; Anheart Therapeutics; Bayer; Bristol-Myers Squibb; Deciphera; DelMar Pharmaceuticals; Ellipses Pharma; EMD Serono; Genenta Science; Imvax; Inovio Pharmaceuticals; Kintara Therapeutics; Kintara Therapeutics; KIYATEC; Medicenna; Merck; Merck KGaA; NEUVOGEN; Novocure; Oncorus; Regeneron; Sumitono Dainippon Pharma; Taiho Pharmaceutical; 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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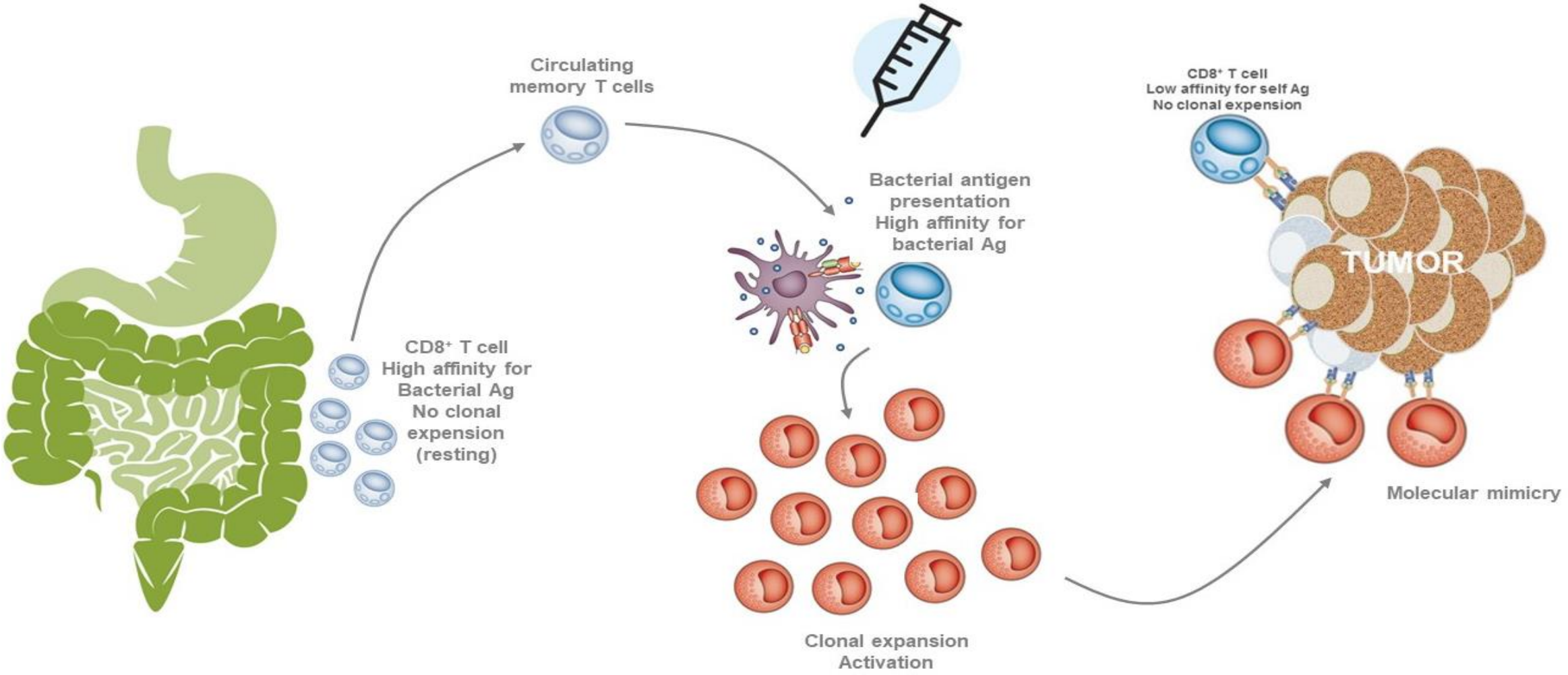
EO2401

Principles

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

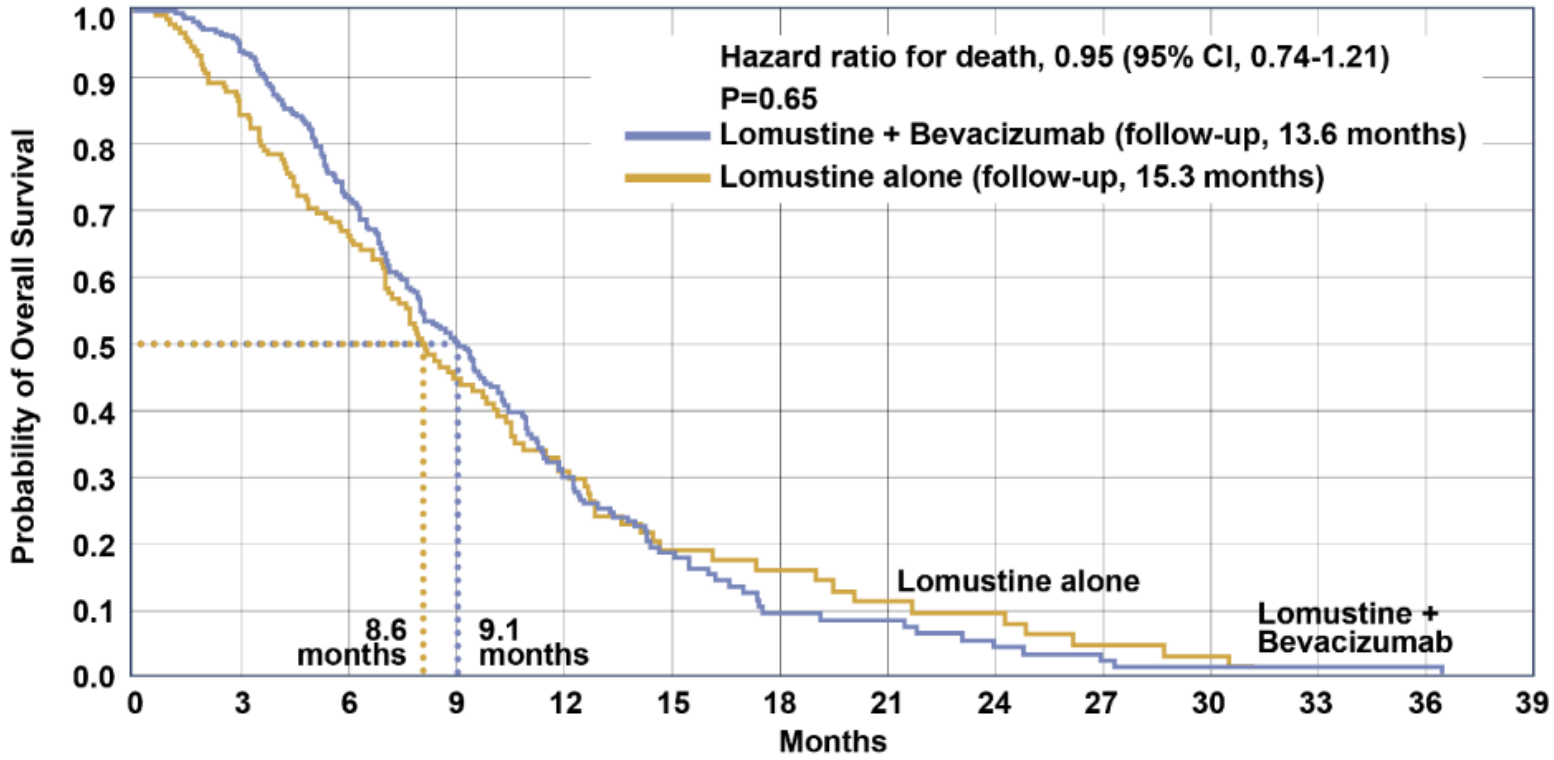


ROSALIE study

First recurrent glioblastoma

- Recurrent glioblastoma (GB) has a poor prognosis and a limited number of treatment options, with an expected median survival around 8-9 months in trials with longer follow-up[1].

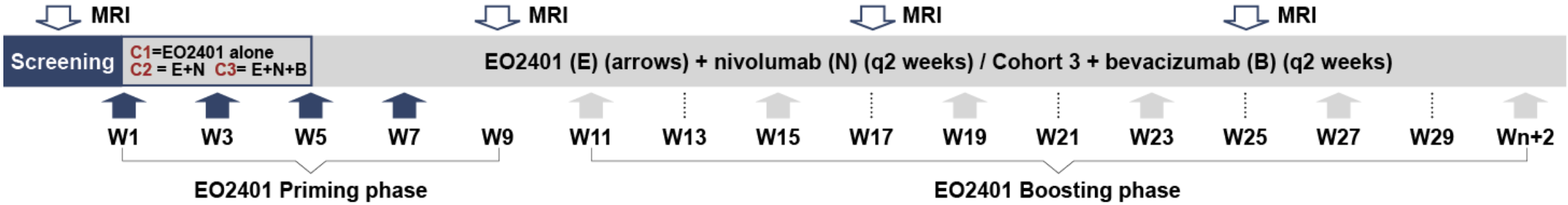
[1] Wick W, Gorlia T, Bendszus M, et al. Lomustine and bevacizumab in progressive glioblastoma (EORTC 26101). N Engl J Med. 2017;16;377(20):1954-1963



- EO2401 is composed of three high-affinity microbial-derived synthetically produced peptides mimicking $CD8^+$ T cell HLA-A2 epitopes from the tumor associated antigens IL13Rα2, BIRC5/survivin, and FOXM1, and the helper $CD4^+$ peptide UCP2; EO2401 is administered SC with the adjuvant Montanide ISA 51 VG.
- Nivolumab supports T cell expansion and infiltration of tumor.
- Bevacizumab has anti-edema properties and can counteract immunosuppression by VEGF.
- Patients with glioblastoma at first progression / recurrence after standard of care surgery, concurrent RT/TMZ, and adjuvant TMZ.
- Patients were HLA-A2, and had KPS ≥70, dexamethasone ≤2 mg/day within 14 days before study, normal organ functions, no contraindications.
- Treatment given until toxicity or tumor progression using the iRANO criteria.

ROSALIE study

Cohorts, treatments, and schedules



Treatment Cohort	Study part 1	Study part 2; symptom driven low-dose bevacizumab** as time-limited anti-edema treatment	Total
Cohort 1a (E→EN): EO2401 mono x2 (4 weeks), followed by EO2401/nivolumab (measurable disease)	3 patients	18 patients	21 patients
Cohort 2a (EN): EO2401/nivolumab (measurable disease)	23 patients	15 patients	38 patients
Cohort 2b (EN): EO2401/nivolumab adjuvant after surgery for recurrence (non-measurable disease)	3 patients	3 patients	6 patients
Cohort 3 (ENB): EO2401/nivolumab/bevacizumab* (measurable disease)	11 patients	No added patients	11 patients

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
** Low dose = 5 mg/kg every 2 weeks start at neurological symptoms

ROSALIE study

Baseline characteristics

Baseline Characteristics	Cohort 1a E→EN (n=21)	Cohort 2a EN (n=38)	Cohort 2b EN (n=6)	Cohort 3 ENB (n=11)	Total (n=76)
Age, median (range), years	58.0 (19-73)	59.0 (18-78)	53.5 (46-70)	64.0 (24-72)	58.5 (18-78)
Gender, female/male	33% / 67%	40% / 60%	50% / 50%	64% / 36%	42% / 58%
KPS ≥ 90% (Yes/No)	67% / 33%	39% / 61%	83% / 17%	36% / 64%	50% / 50%
***MGMT* promoter methylation (Yes/No)**	35% / 65%	36% / 64%	40% / 60%	80% / 20%	43% / 57%
***IDH1* mutation (Yes)**	0	1 (3%)	1 (17%)	2 (18%)	4 (5%)
Baseline steroid use (0 < dexamethasone ≤ 2 mg)	23%	34%	50%	36%	33%
Time from initial diagnosis of glioblastoma to study treatment start, median (range), months	12.6 (6.3-38.3)	12.0 (6.0-54.5)	13.25 (6.0-36.0)	7.7 (0.7-96.6)	12.2 (0.7-96.6)

ROSALIE study

Safety

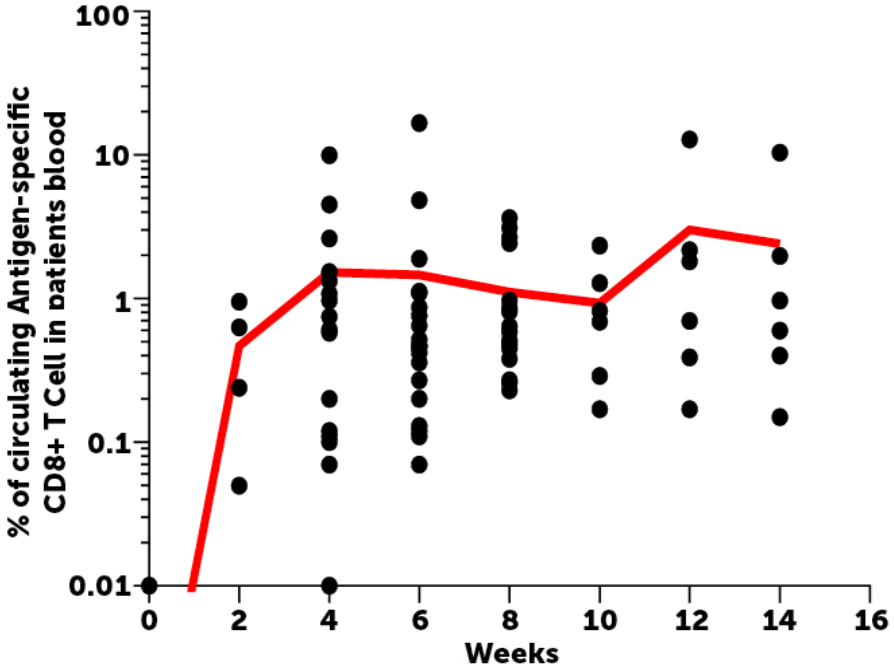
EO2401 + nivolumab +/- bevacizumab safety profile consistent with the profile of nivolumab, and when applicable bevacizumab, except the addition of local administration site reactions

- **Grade 3/4 related events in 17% of patients**
- **Most common treatment-related AEs** were fatigue (22%), injection site reaction (16%), and ALT increase (11%)
- Five **AEs leading to treatment discontinuation:** transaminitis (2), aseptic meningitis, newly diagnosed CRC, alteration general status
- **Immune mediated AEs necessitating action:** transaminitis (2), hypothyroidism (2), aseptic meningitis (2), rash (2)
- Any **local administration site event** (main erythema, induration, pain) in 45% of patients:
  - severity of events 70% Grade 1, 26% Grade 2, and **4% Grade 3**
  - median time to event onset 38 days (range 1-446)
  - KM analysis median event duration 28 days

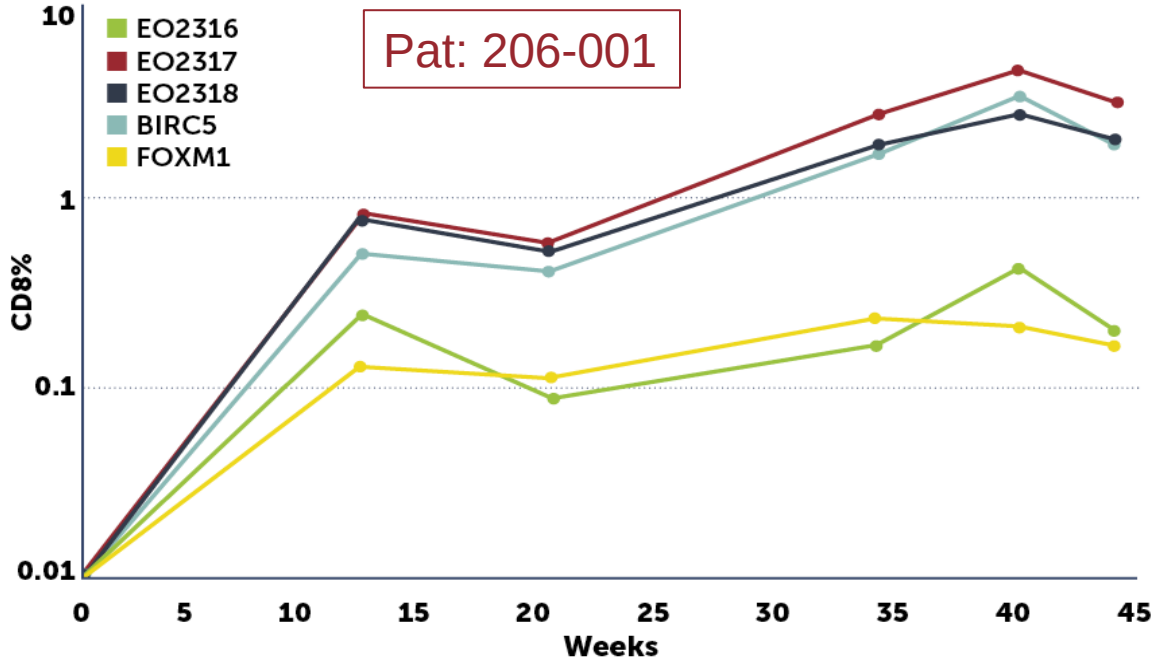
ROSALIE study

Immune response

Fast, strong, and durable CD8⁺ T cell response with strong cross-reactivity against human TAAs



% of CD8+ T cells specific for EO2316, EO2317, and EO2318 as assessed with tetramer analysis ex vivo

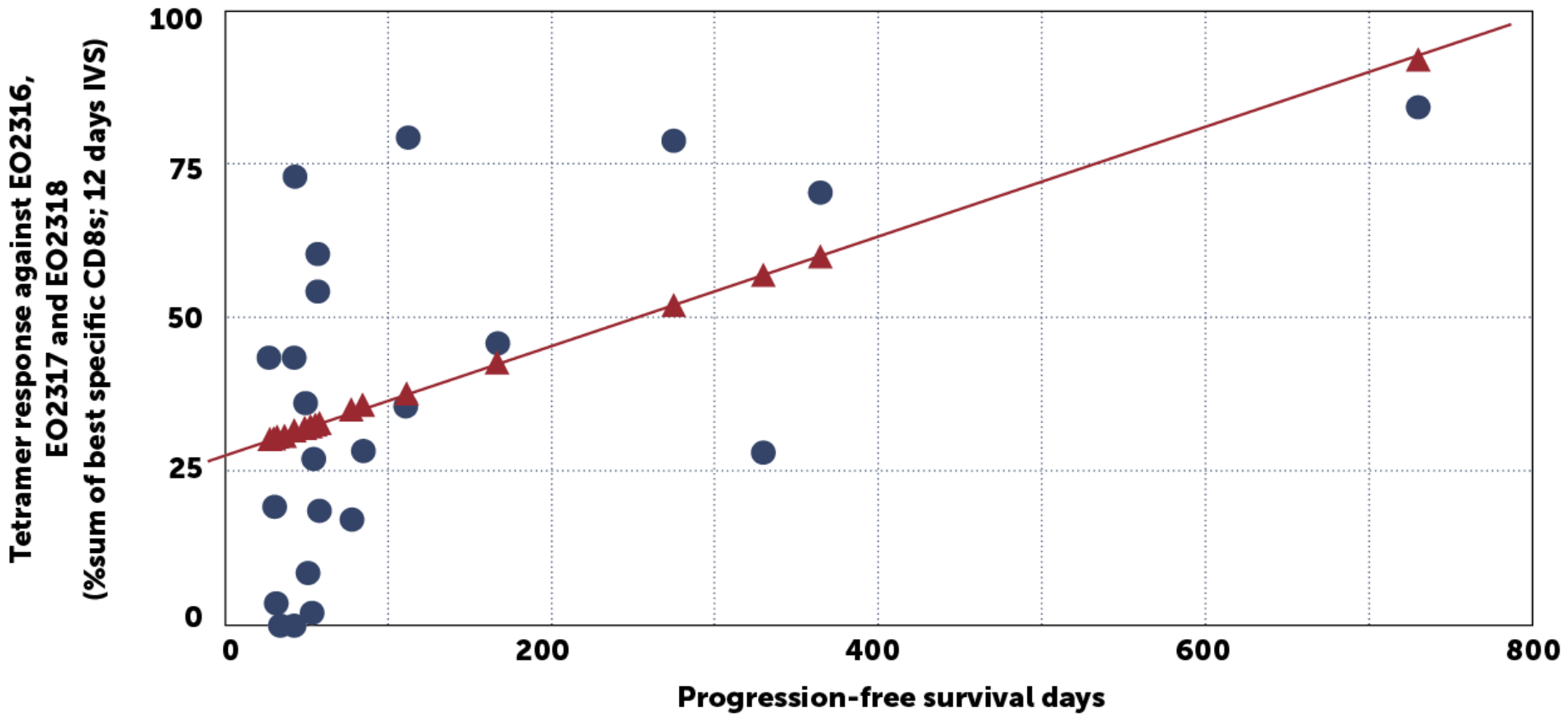


% of CD8+ T cells specific for EO2316, EO2317, EO2318, and the human TAAs BIRC5 and FOXM1 as assessed with tetramer analysis ex vivo

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

ROSALIE study

Strength of immune response direct correlating with clinical outcome



Regression line

Individual patient

Regression line equation:

$\hat{Y} = 27.8078 + 0.08774X$

$R^2 = 0.2669$

$R = 0.5166$

p-value = 0.010

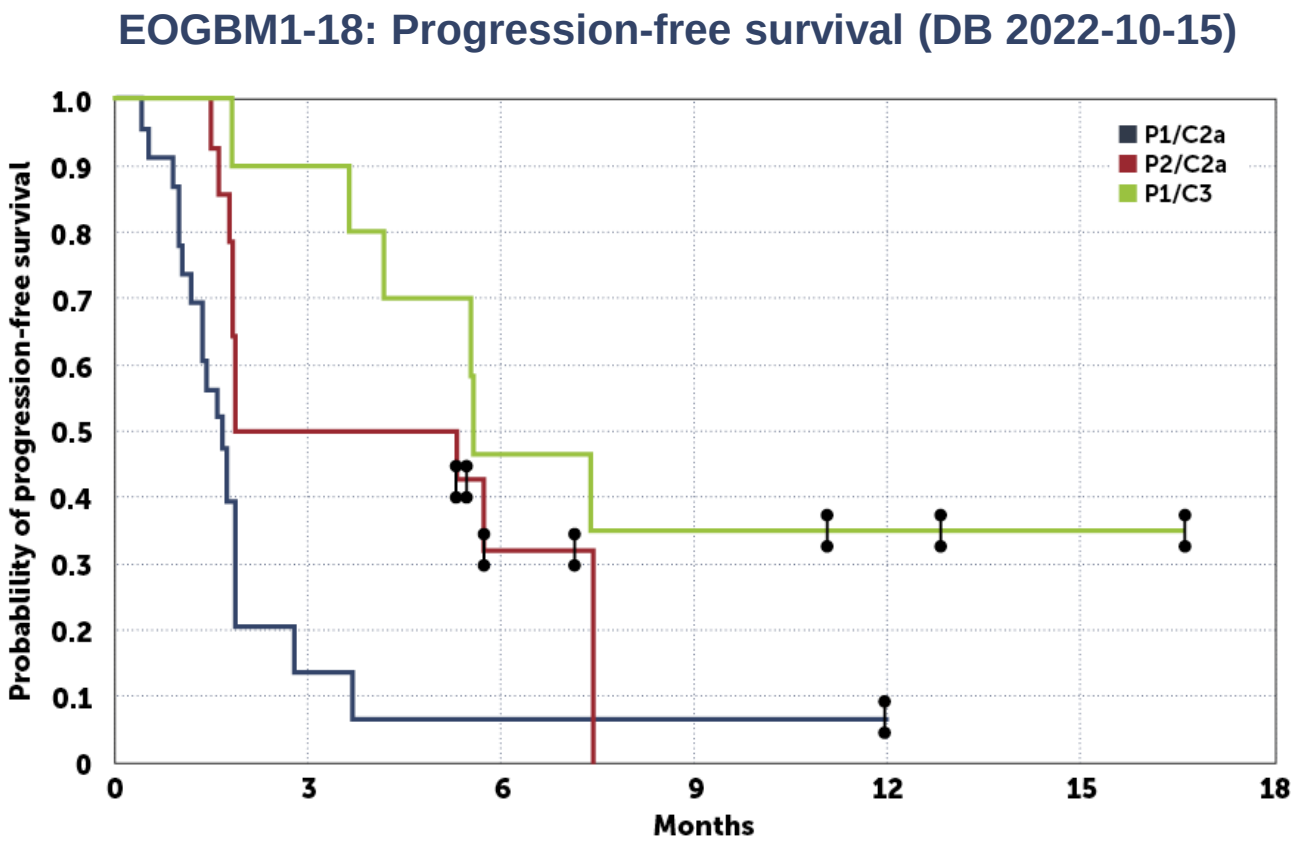
Study Part 1, Cohorts C1a/2a/2b (EO2401/nivolumab): analysis includes all 24 tested pts (of total 29 pts); 2 pts planned to be tested, and 3 not planned (e.g. lack of samples)

ROSALIE study

EO2401 treatment duration, ORR, and PFS; impact of bevacizumab

	Study Part 1 Cohort 2a (n=23) EN (no B)	Study Part 2 Cohort 2a (n=15) EN + symp. LDB*	Study Part 1 Cohort 3 (n=11) ENB**
median treatment duration (95% CI)	1.4 months (95% CI 0.9; 2.3)	3.2 months (95% CI 1.1; 8.3)	5.0 months (95% CI 2.3; ne)
objective response rate (95% CI)	13.0% (95% CI 2.8; 33.6)	20.0% (95% CI 4.3; 48.1)	54.5% (95% CI 23.4; 83.3)
median PFS (95% CI)	1.6 months (95% CI 1.1; 1.8)	3.6 months (95% CI 1.8; 8.4)	5.5 months (95% CI 1.8; ne)
pts on study treatment	0 (0%)	4 (27%)	3 (27%)

** symptom driven low-dose bevacizumab as time-limited anti-edema treatment, median 3 administrations, was given to 5 (33%) patients in Cohort 2a*
*** standard US PI continuous dose bevacizumab*



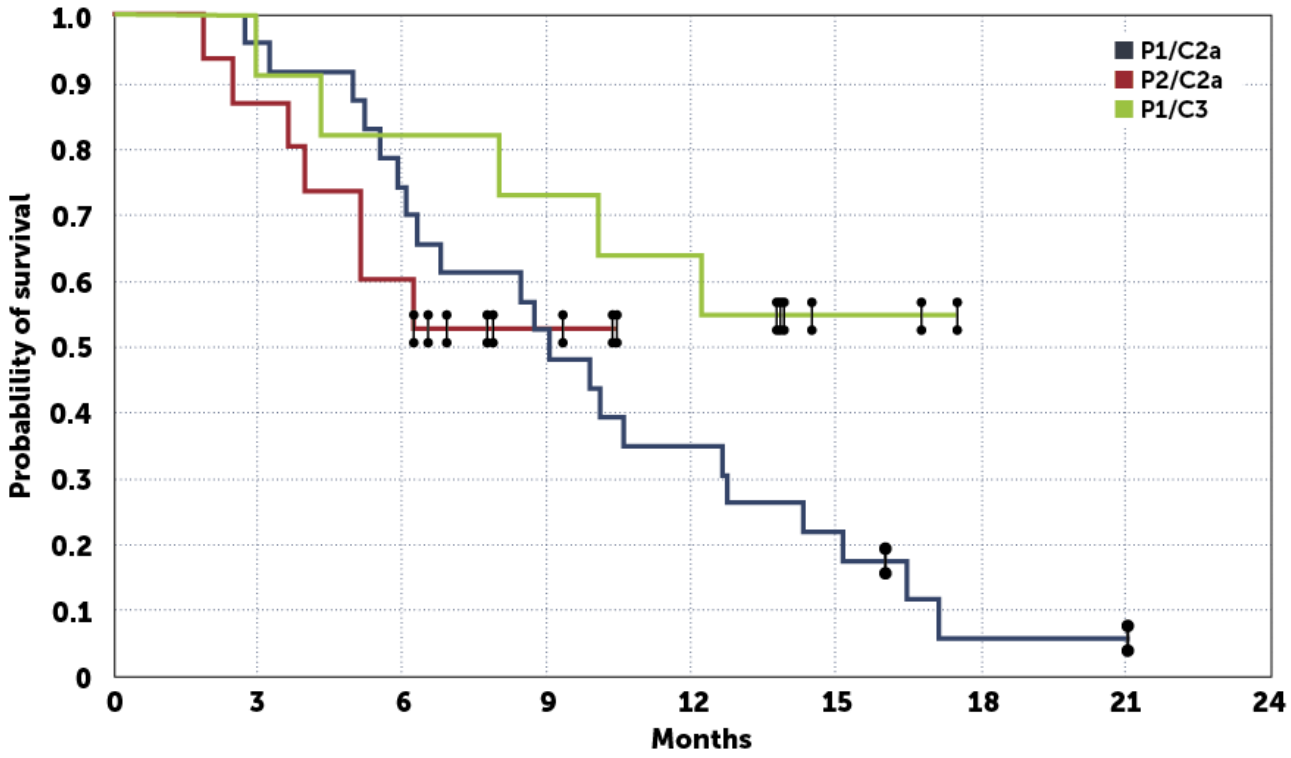
ROSALIE study

EO2401 overall survival; impact of bevacizumab

	Study Part 1 Cohort 2a (n=23) EN (no B)	Study Part 2 Cohort 2a (n=15) EN + symp. LDB*	Study Part 1 Cohort 3 (n=11) ENB**
median follow-up for survival	21.0 months	7.8 months	14.1 months
median survival (95% CI)	9.0 months (95% CI 6.1; 12.6)	not reached (95% CI 3.6; ne)	not reached (95% CI 4.3; ne)
pts alive	2 (9%)	8 (53%)	***6 (55%) all followed beyond 13.8 months***

** symptom driven low-dose bevacizumab as time-limited anti-edema treatment, median 3 administrations, was given to 5 (33%) patients in Cohort 2a*
*** standard US PI continuous dose bevacizumab*

EOGBM1-18: Overall survival (DB 2022-10-15)

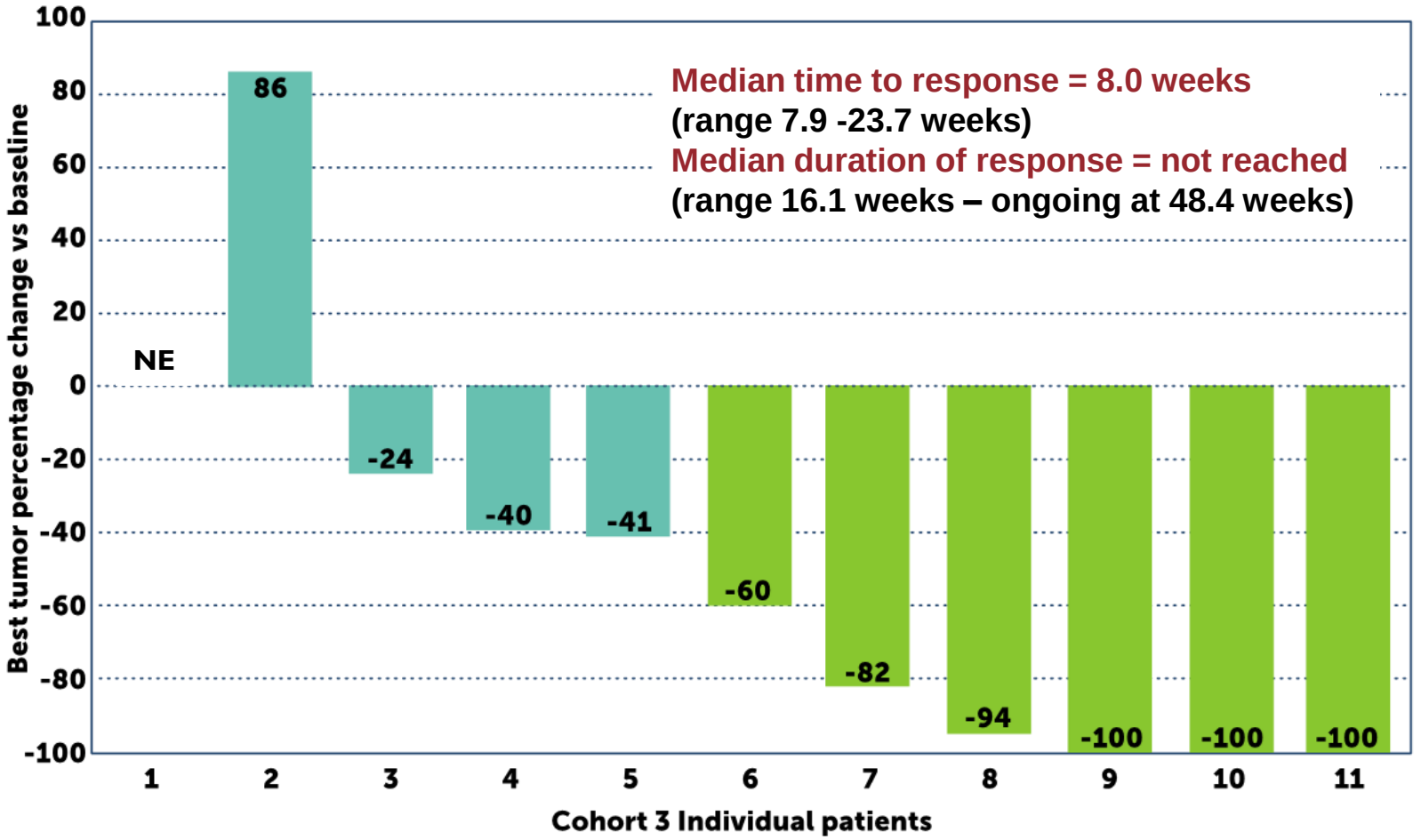


ROSALIE study

Cohort 3: EO2401 + nivolumab + bevacizumab (ENB)

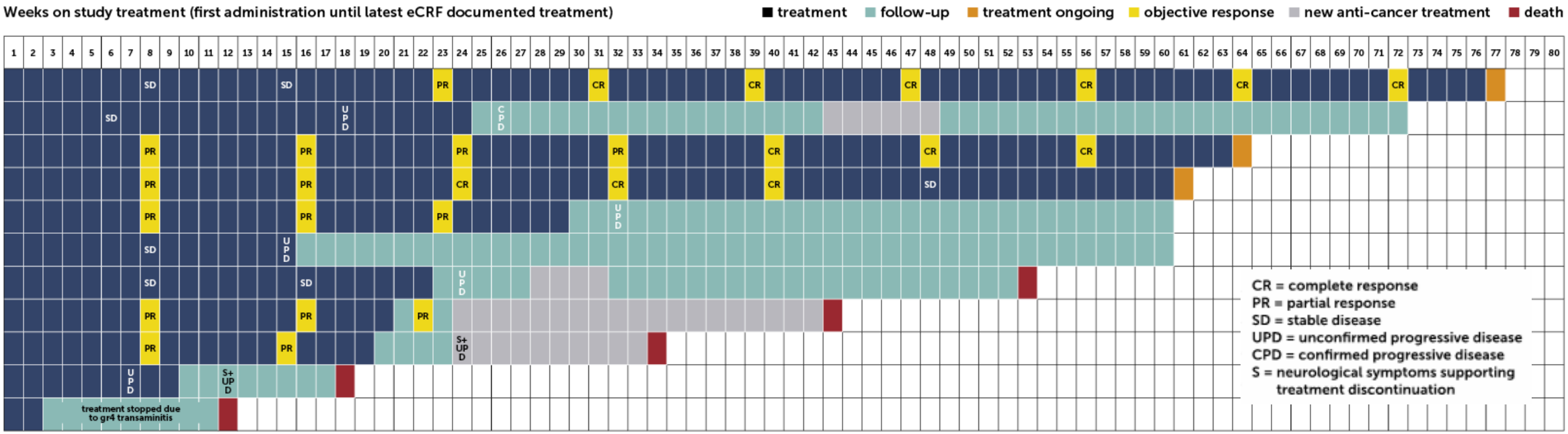
Maximum tumor shrinkage by MRI vs baseline

Pat #1 non-evaluable, no MRI on study (stop study treatment due to transaminitis)



ROSALIE study

Cohort 3: EO2401 + nivolumab + bevacizumab (ENB)



Correlations between efficacy parameters for the ENB regimen

Strong inverse relationship between time to progression/death and percentage of tumor change (inverse relation since shrinkage)
[R^2=0.5447, R=-0.7381, p = 0.009505]

Strong inverse relationship between survival and percentage of tumor change (inverse relation since shrinkage)
[R^2=0.466, R=-0.6826, p = 0.02063]

Strong direct relationship between survival and time to progression/death
[R^2=0.4983, R=0.7059, p = 0.01521]

ROSALIE study: EO2401 with nivolumab +/- 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 strong systemic immune responses correlating with efficacy**
- **Symptom driven use of low-dose, time-limited, bevacizumab supported longer treatment durations of EO2401/nivolumab, and some improvement of efficacy**
- **Addition of standard bevacizumab to EO2401/nivolumab improved efficacy**
- ***Additional patients are treated with "the triplet" EO2401/nivolumab/ bevacizumab (ENB) to support final regimen selection for further studies***

See also ABSTRACT #641:

- *Hall C, Thursday, November 10, 2022, 9am – 9pm*
- Strong immune response to therapeutic vaccination EO2401 microbiome-derived vaccine + nivolumab Interim report of the EOGBM1-18/ROSALIE study

Thank you

- Patients and Families
- Clinical research assistants
- Co-investigators

EOGBM1-ROSALIE:

BACKGROUND bevacizumab

BEVACIZUMAB ACCORDING TO US PI:

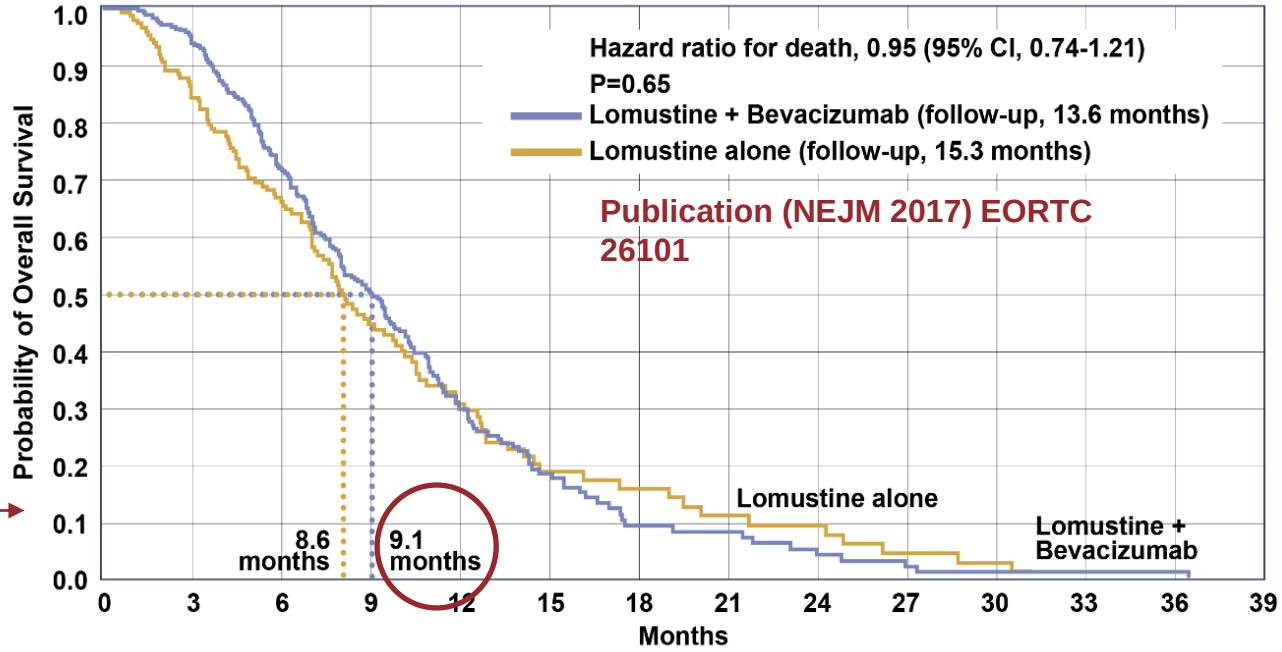
ORR (monotherapy)
AVF3708g: **25.9%** (95% CI: 17, 36.1)
NCI 06-C-0064E: **19.6%** (95% CI: 10.9, 31.3)

DOR (monotherapy)
AVF3708g: **3.9 months** (95% CI: 2.4, 17.4)
NCI 06-C-0064E: **4.2 months** (95% CI: 3, 5.7)

PFS (combination lomustine)
EORTC 26101: Avastin with lomustine vs lomustine
[HR 0.52 (95% CI: (0.41, 0.64)],
median **PFS 4.2** vs 1.5 mo

PUBLICATIONS:
AVF3708g (JCO 2009/n=85): **mPFS 4.2 mo** (95%CI: 2.9-5.8), **mSurvival 9.2 mo** (95% CI: 8.2-10.7)

NCI 06-C-0064E (JCO 2008/n=48): **mPFS 3.7 mo** (95%CI: 2.8-6.0), **mSurvival 7.1 mo** (95% CI: 4.8-12.4)



NEWER CONTROLLED TRIALS:

Bevacizumab in Checkmate-143* [bev = 185 RND pts, 20 pts (10.8% dropped out/censored before treatment start) => 165 pts treated / median follow-up 9.4 months[#]]:
- ORR 23.1% (95% CI: 16.7-30.5), median PFS 3.5 months (95% CI: 2.9-4.6), median survival 10.0 months (95% CI: 9.0-11.8)

RND Ph2 Pembrolizumab plus Bevacizumab vs Pembrolizumab** [bev+pembro = 50 RND/treated pts / median follow-up 48.6 months]:
- ORR 20% (95% CI: not reported), median PFS 4.1 months (95% CI: 2.8-5.5), median survival 8.8 months (95% CI: 7.7-14.2)

RND Ph2 NRG Oncology/RTOG 1205 re-RT & bev vs bev*** [bev = 84 analyzed / median follow-up 12.8 months]:
- ORR 18% (95% CI: not reported), median PFS 3.8 months (95% CI: not reported), median survival 9.7 months (95% CI: 9.0-11.2)

[JAMA 2020, ** Clin Cancer Res 2020, *** JCO 2022]*

Bevacizumab assumed efficacy = ORR 18-26%, median PFS 3.5 - 4.2 months, median OS 7.1 – 10.0[#] months