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EO2401, a novel microbiome-derived therapeutic vaccine for patients with recurrent glioblastoma: **ROSALIE study.**

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on behalf of the EOGBM1-18/ROSALIE investigators

Declaration of conflict of interest

Type of affiliation / financial interest	Company
Receipt of travel fundings	Enterome, Novocure, Leo Pharma, Carthera
Receipt of grants/research supports:	Carthera, Sanofi, Nutrithéragène, Servier, Transgene
Receipt of honoraria or consultation fees:	Novocure, Leo Pharma, Novartis, Boehringer Ingelheim

ROSALIE clinical trial

NCT04116658

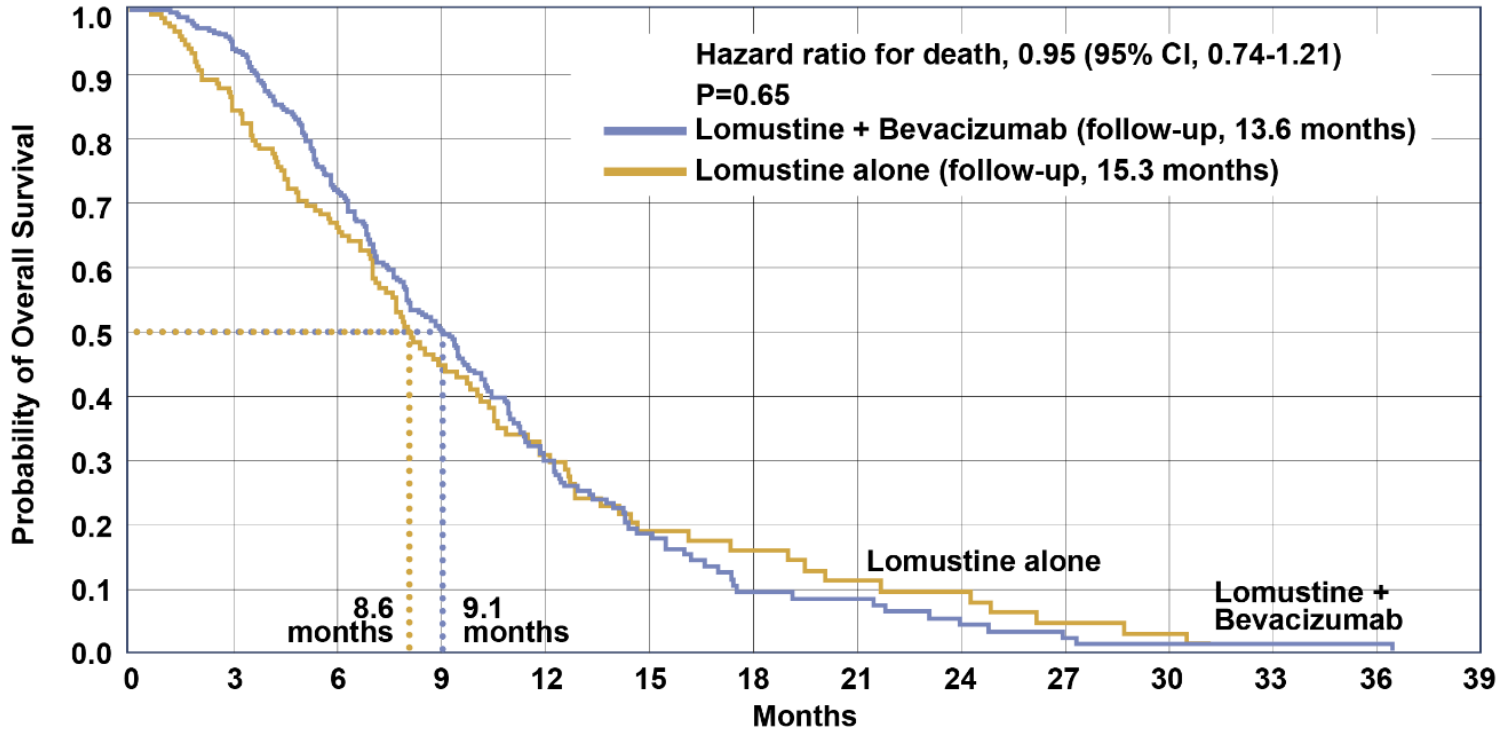
- **A MulticenteR, Open-Label, First-in-Human, PhaSe I/II Trial of**
- **EO2401, a Novel Multipeptide Therapeutic VAccine,**
- **with PD-1 Check Point Inhibitor,**
- **with or without bevacizumab,**
- **FoLlowing Standard Treatment in PatIents with first ProgrEssion Glioblastoma**

First recurrence glioblastoma

Target population

Second line treatment

- Surgery and/or radiotherapy and/or
- Lomustine, or lomustine + bevacizumab, or bevacizumab
- Median OS between 6 and 12 months



Stupp et al., 2005; Stupp et al., 2017; Wick et al., 2017

EO2401, Nivolumab and Bevacizumab

Experimental treatment

EO2401 is a therapeutic vaccine including

- 3 synthetic microbial-derived peptides mimicking (non-self-nature) cytotoxic T cell HLA-A2 restricted epitopes from the 3 TAAs
  - IL13Rα2
  - BIRC5/survivin
  - FOXM1
- the peptide UCP2, a helper CD4+ derived from hTERT
- the adjuvant Montanide

Nivolumab

- T cell expansion
- T cell infiltration

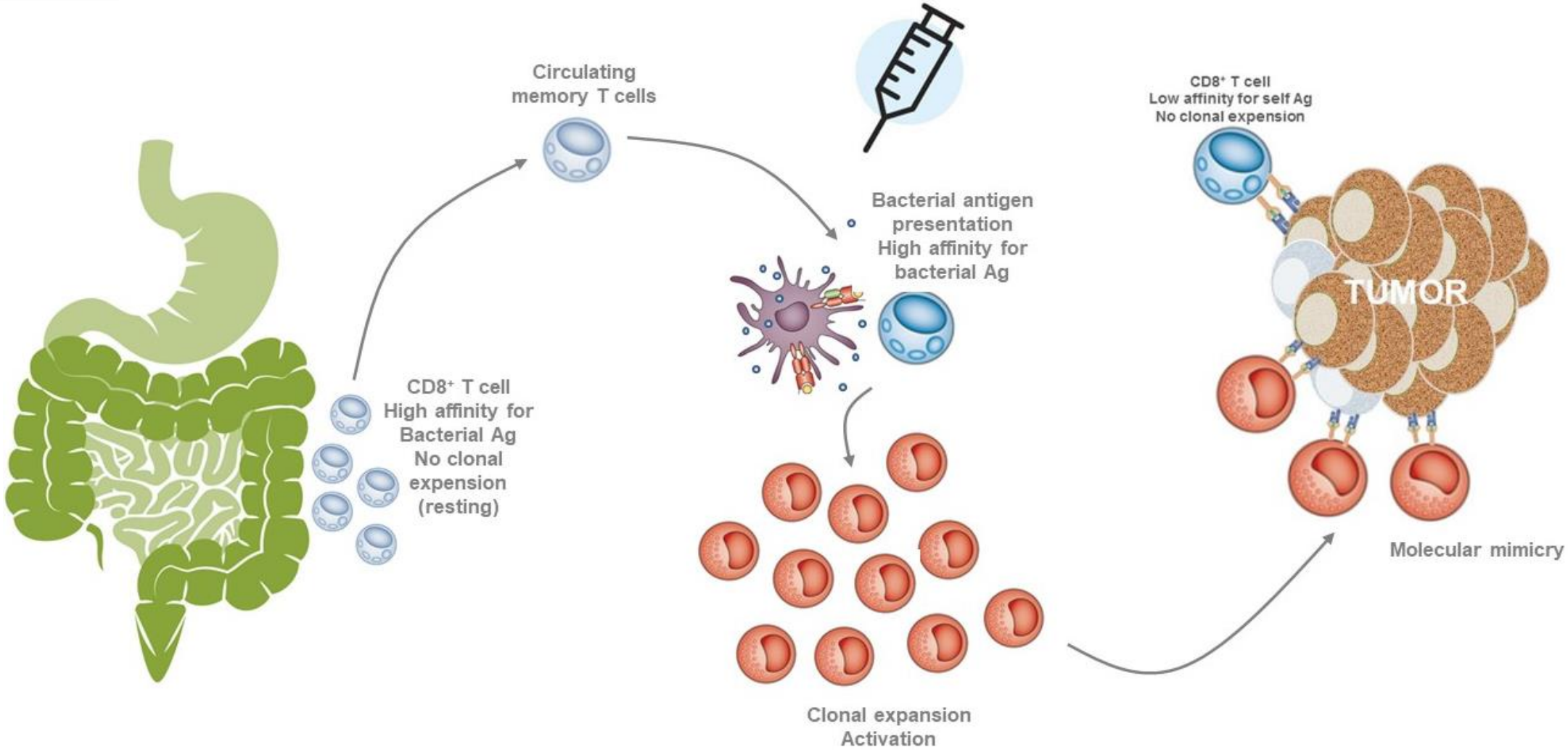
Bevacizumab

- Anti-edema : reduces the use of steroids
- Counteract immunosuppression induced by VEGF

EO2401

Principles

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



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Endpoints and Inclusion criteria

Main Endpoints

- Primary: Safety
- Secondary: Clinical and biological efficacies

Main inclusion/exclusion criteria

- First recurrence glioblastoma after SOC
- HLA-A2 positive
- Karnofsky Performance Status ≥ 70 %
- Dexamethasone ≤ 2 mg/day within 14 days before study

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Design, cohorts and treatment

Treatment Cohort	Study part 1	Study part 2; symptom driven low-dose bevacizumab** as time-limited anti-edema treatment	Total
Cohort 1 (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

Treatment is given until toxicity or tumor progression using the iRANO criteria.

Bevacizumab:

* Standard dose = 10 mg/kg every 2 weeks starting at day 1, until PD ** Low dose = 5 mg/kg every 2 weeks starting at neurological symptoms

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Results 1/6: Baseline characteristics

Baseline Characteristics	Cohort 1 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%
Progression free survival #1 median (range), months	11.9 (4.5-36.9)	10.7 (5.0-54.1)	12.3 (4.6-33.0)	7.5 (3.7-95.2)	11.1 (3.7-95.2)

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Results 2/6: Safety

EO2401 (3 OncoMimics + 1 UCP2 + Montanide) SC + Nivolumab IV +/- Bevacizumab IV

- Well tolerated
- Safety profile consistent with the profile of nivolumab monotherapy, and bevacizumab when applicable
- Except the addition of local administration site reactions
  - 4% of patients Grade 3

AE in the 76 patients enrolled:

- Grade 3 AEs : 30% (14% possibly related)
- Grade 4 AEs : 4% (3% possibly related)
  - increased AST and ALT, resolved without sequalae
  - prolonged repetitive seizures, resolved without sequelae
  - diagnosis of adenocarcinoma of colon
- Grade 5 AE : 1%
  - non-related status epilepticus

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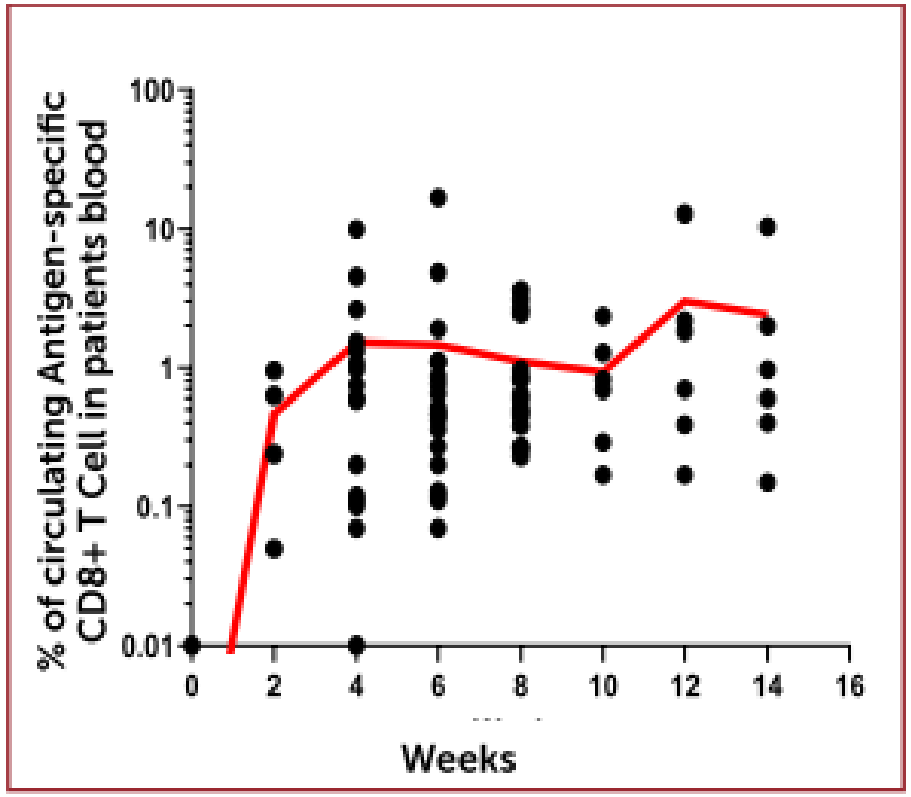
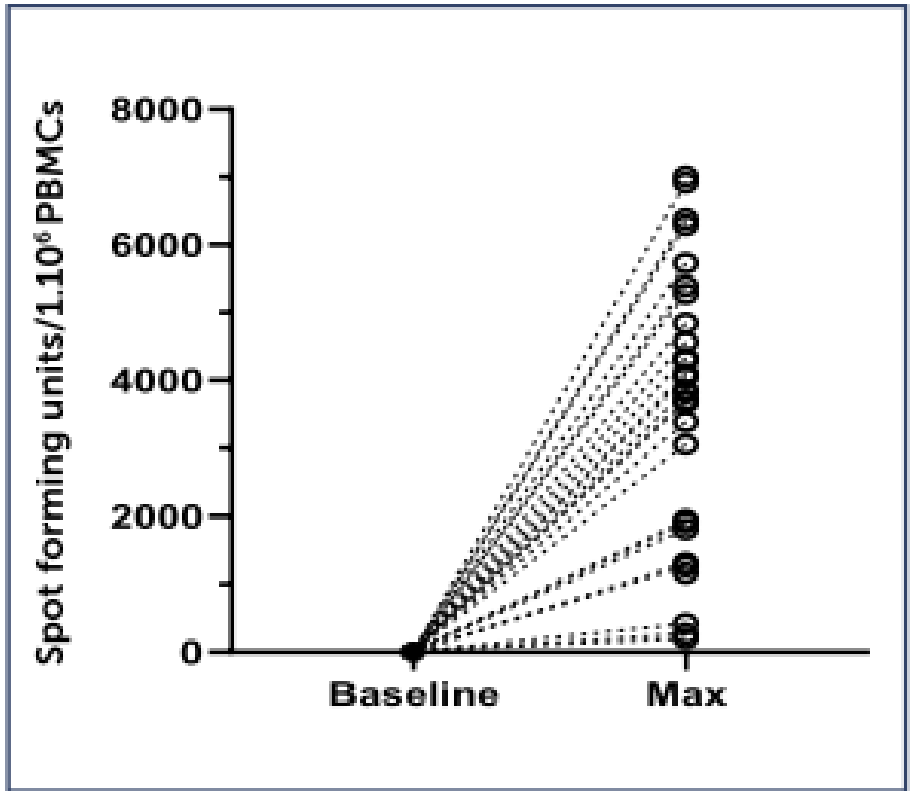
Results 3/6: Immune response

Fast, durable, and strong CD8+ T cell response (28/29 patients) with strong cross-reactivity against human selected TAAs (27/28 patients)



Effector function
(ex vivo assay, Tetramer analyze)



Robust TAA-specific CD8 T cell IFN-γ Response ELISpot assay after IVS; data from max response study weeks 8-16)

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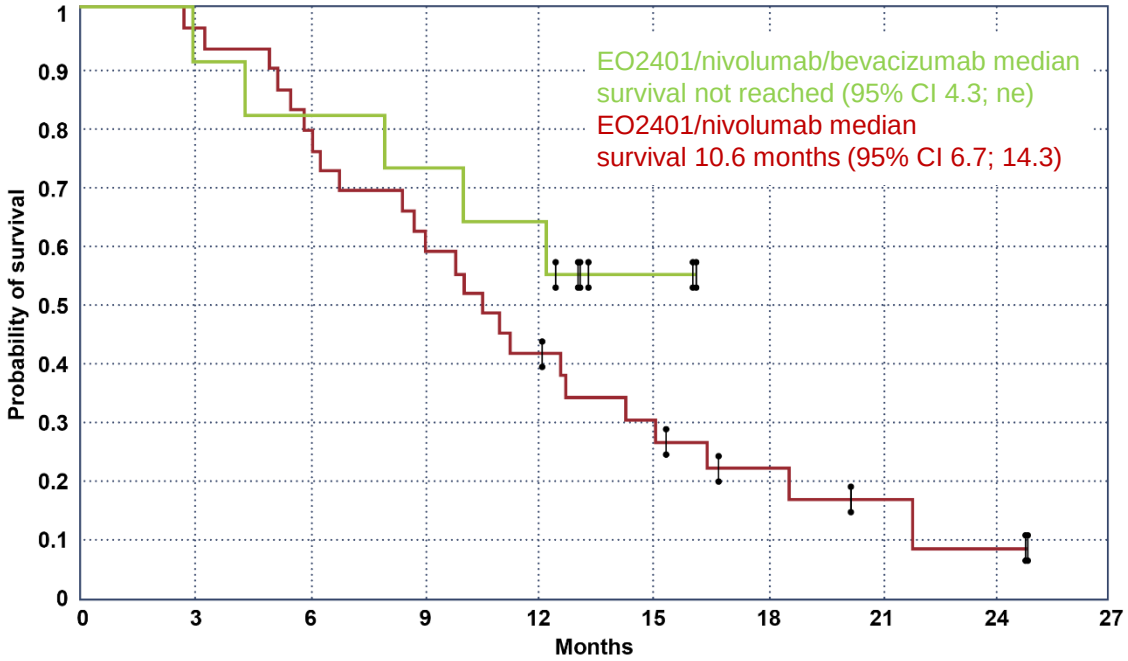
Results 4/6: Outcome

	Study Part 1 Cohorts 1/2a/2b (n=29) EN	Study Part 1 Cohort 3 (n=11) ENB
Objective response rate (CR+PR)	13.8% (95% CI 3.9; 31.7)	54.5% (95% CI 23.4; 83.3)
Disease control rate (ORR+SD)	34.5% (95% CI 17.9; 54.3)	81.8% (95% CI 48.2; 97.7)
Median PFS	1.8 months (95% CI 1.3; 2.8)	5.5 months (95% CI 1.8; ne)

Survival study part 1*

Cohorts 1/2a/2b (n=29, median follow-up 20.1 months, 24 events, 5 censored)
Cohort 3 (n=11, median follow-up 13.1 months, 5 events, 6 censored)



* Median survival for Part 2: Cohorts 1/2a/2b too early to assess.

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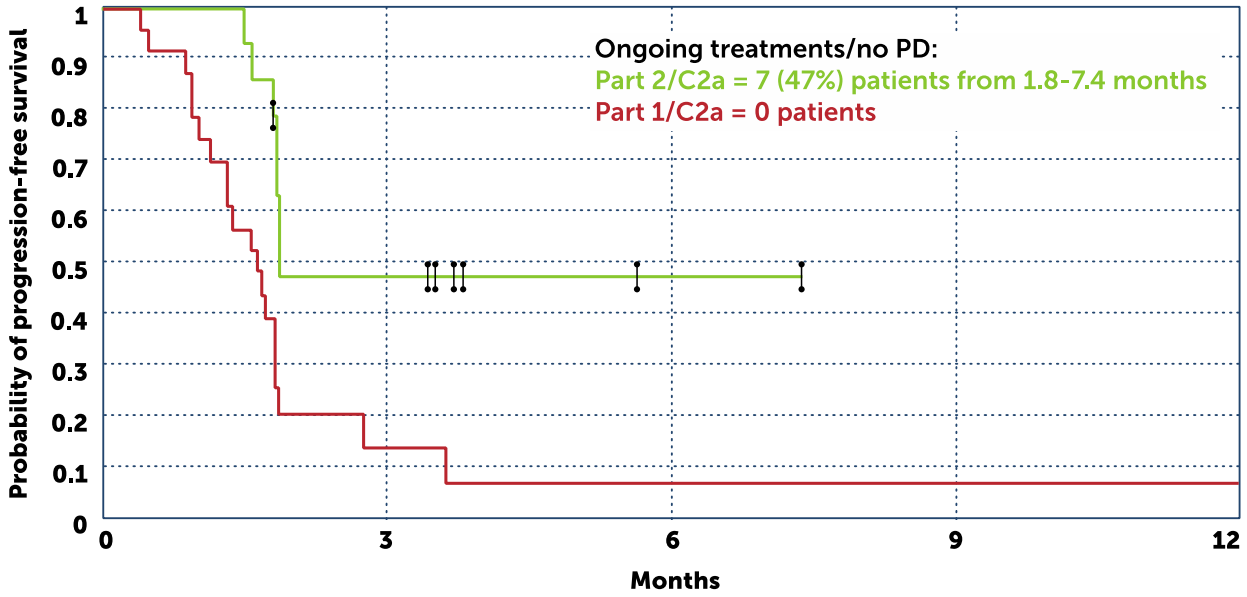
Results 5/6: Outcome

Median treatment durations in Cohort 2a

- Study Part 1 (n=23)
  - 6.1 weeks (95% CI 4.0; 10.0)
  - 0 of 23 on treatment
- Study Part 2 (n=15)
  - 14.1 weeks (95% CI 4.9; ne)
  - 7 of 15 on treatment



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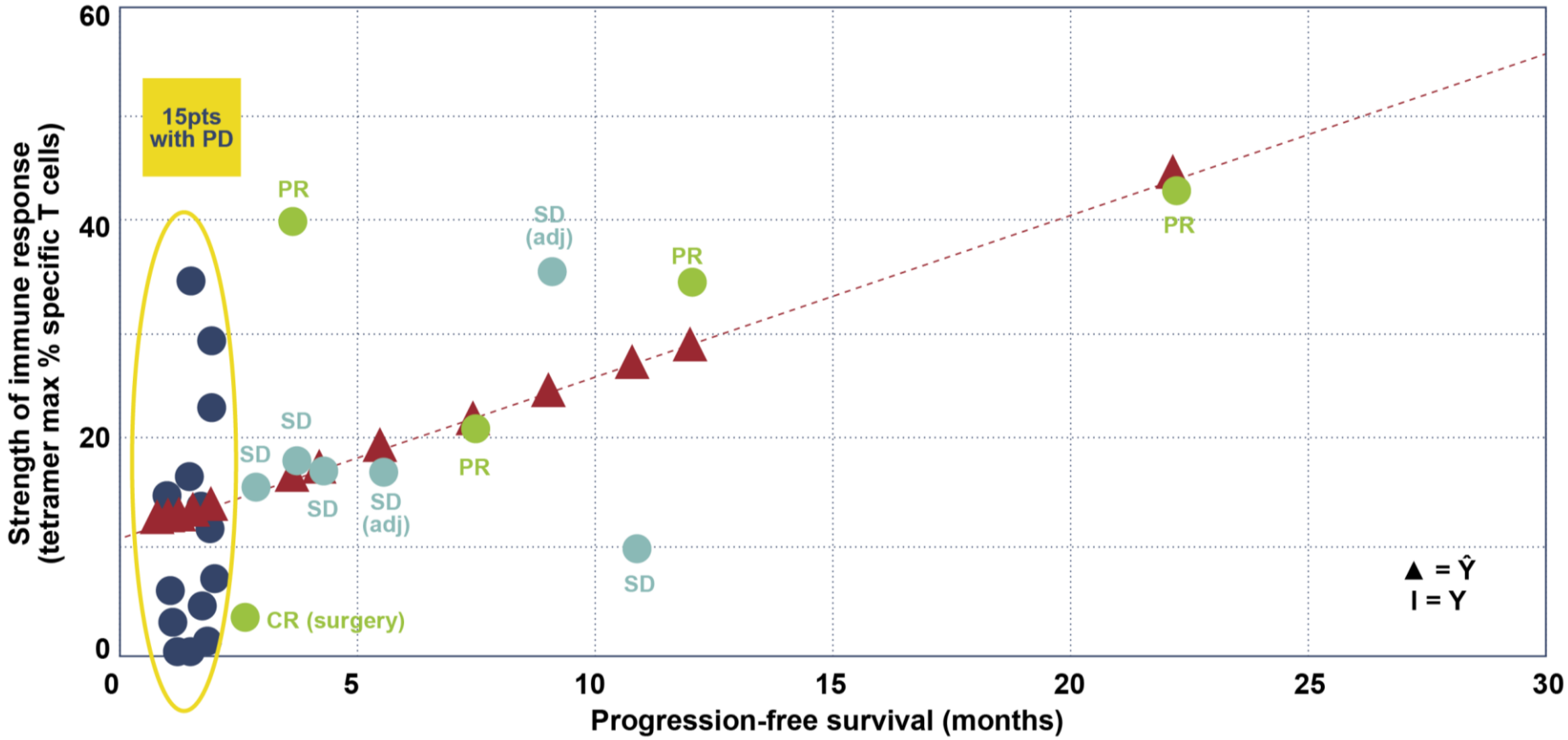
Results 6/6: Correlation immune response with clinical response

EO2401/nivolumab (Cohorts 1/2a/2b)



Regression line equation

Ŷ = 10.963 + 1.4772X
R2 = 0.3003
R = 0.548
p-value = 0.004

Cohorts C1a/2a/2b

Best tetramer (EO2316, EO2317, or EO2318) % after IVS for 12 days versus PFS in individual patients. All 26 patients with available immune test results included in the correlation.

ROSALIE clinical trial: EO2401 with nivolumab +/- bevacizumab

Conclusions

1. **Well tolerated; safety as nivolumab and bevacizumab with added local administration site reactions**
2. **Strong systemic immune responses**
3. **Addition of Bevacizumab**

- Low-dose, time-limited, symptoms driven
  - longer treatment durations, efficacy to be assessed (too early)
- Standard-dose
  - improved ORR/DCR, and PFS
  - signal of efficacy OS

4. **Clinical efficacy correlates with immune efficacy**

Additional patients are now treated with ”the triplet” EO2401/nivolumab/bevacizumab to support selection of final regimen for further studies.

Thank you

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