Abstract Number 2020

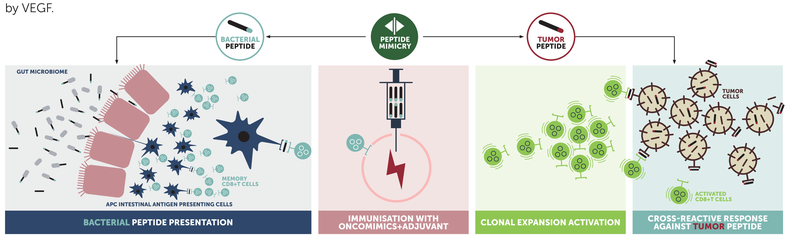
EO2401 (E) peptide immunotherapy + nivolumab (N) +/- bevacizumab (B) in recurrent glioblastoma (GB): EOGBM1-18/ROSALIE

ASCO Annual Meeting, June 2-6, 2023, Chicago, IL, USA . Poster Discussion Session - Central Nervous System Tumors
Poster Display (poster board 377): June 3, 1:15 PM-4:15 PM | Poster Discussion: June 3, 4:30 PM-6:00 PM

Authors: Wolfgang Wick[1], Ahmed Idbaih[2], Maria Vieito Villar[3], François Ghiringhelli[4], Agostina Stradella[5], Ghazaleh Tabatabai[6], Michael C. Burger[7], Iris Mildenberger[8], Ulrich Herrlinger[9], Patrick Y. Wen[10], Mehdi Touat[2], Antje Wick[1], Macarena González[3], Alice Hervieu[4], Marta GilMartin[5], Mirjam Renovanz[6], Ana Maia[11], Christophe Bonny[12], Jan Fagerberg[12], David A. Reardon[10]
1 Universitätsklinikum Heidelberg and German Cancer Research Center, Heidelberg, Germany 2 Sorbonne Université, AP-HP, ICM, Hôpital Universitaire La Pitié-Salpêtrière, Paris, France, 3 Hospital Universitari Vall d'Hebron, Barcelona, Spain, 4 Centre Georges-François Leclerc, Dijon, France, 5 Institut Català d'Oncologia - Hospital Duran i Reynals, Barcelona, Spain, 6 Universitätsklinikum, Tübingen, Germany, 7 Universitätsklinikum Frankfurt Goethe-Universität, Frankfurt, Germany, 8 Medizinische Fakultät, Mannheim, Germany, 9 Universitätsklinikum, Bonn, Germany, 10 Dana-Farber Cancer Institute, Boston, MA, USA, 11 Department of Immunology, Eberhard-Karls-University, Tübingen, Germany, 12 Enterome, Paris, France

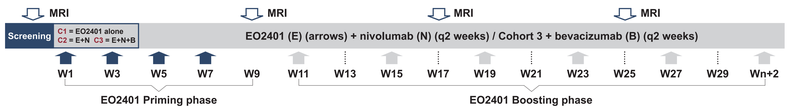
BACKGROUND

Recurrent GB has an expected median survival around 8-9 months on standard of care treatments (Wick W et al. Lomustine and bevacizumab in progressive glioblastoma (EORTC 26101). N Engl J Med. 2017; 377: 1954-1963).
EO2401 was designed to expand pre-existing memory cytotoxic T cells recognizing specific protein sequences from gut bacteria with high prevalence in the population, which cross-react with tumor associated antigens (TAAs). EO2401 contains 3 synthetically produced CD8 HLA-A2 epitopes with mimicry to GB-TAAs (IL13Rα2, BIRC5/survivin, and FOXM1) and the CD4 epitope UCP2. The EO2401 mimic peptides are non-self, high affinity and stable MHC class I binders.
Nivolumab supports T cell expansion and infiltration of tumor. Bevacizumab has anti-edema properties and can counteract immunosuppression by VEGF.



METHODS

This ongoing phase 1/2 trial (NCT04116658) investigates EO2401 (E) + nivolumab (N) +/- bevacizumab (B) in patients with GB at first progression after surgery and adjuvant radiotherapy/temozolomide.
Patients were HLA-A2, and had KPS ≥70, ≤ dexamethasone 2 mg/day within 14 days before study, normal organ functions, no contraindications, and had measurable disease in all cohorts except C2b (adjuvant treatment after re-surgery).
Treatment is given until toxicity or tumor progression using the iRANO criteria.
Patients received EO2401 (300 µg/peptide, q2 weeks x 4, then every 4 weeks; administered SC with adjuvant Montanide ISA 51 VG) with nivolumab (3mg/kg, q2 weeks) in cohorts: C1a (E x2 ➝ EN; after 3 patients in safety lead-in, option for symptom directed low-dose bevacizumab [sLDB; 5mg/kg, q2w] as anti-edema treatment), C2a/1 (EN), C2a/2 (EN + sLDB), C2b (adjuvant EN; + sLDB for last 3 patients in cohort), C2c (neoadjuvant EN x2 ➝ surgery ➝ adjuvant EN; + sLDB), C3/1 and C3/2 (EN + bevacizumab, every 2 weeks, 10 mg/kg; C3/1 recruited at DFCI only, C3/2 recruited at all sites for validation).



BASELINE CHARACTERISTICS

E = EO2401 N = nivolumab B = bevacizumab sLDB = sLDB = symptom directed low-dose B DB 2023-04-14	Cohort 1a E+EN + sLDB (n=21)	Cohort 2a/1 EN (n=23)	Cohort 2a//2 EN+ sLDB (n=15)	Cohort 2b EN adjuvant (n=6)	Cohort 2c EN + sLDB neoadjuvant – surgery – adjuvant (n=9)	Cohort 3/1 ENB (n=11)	Cohort 3/2 ENB (n=15)	Total All Cohorts (n=100)
Age, median (range), years	58 (19-73)	58 (37-78)	60 (18-76)	54 (46-70)	53 (41-67)	64 (24-72)	59 (43-73)	**58 (18-78)**
Gender, female - male	33% - 67%	35% - 65%	47% - 53%	50% - 50%	33% - 67%	64% - 36%	20% - 80%	**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)	9 (6-98)	11 (7-25)	**12 (5-98)**
MGMT promoter methylation (% pts yes - % pts no)	35% - 65%	36% - 64%	36% - 64%	40% - 60%	38% - 62%	80% - 20%	15% - 85%	**38% - 62%**
IDH1 mutation (no (%) pts yes)	0	1 (4%)	0	1 (17%)	1 (11%)	2 (18%)	0	**5 (5%)**
Baseline target lesion seize, median (range), mm2	645 (97-2017)	952 (169-4290)	617 (220-2808)	21 (0-80)	433 (132-858)	939 (110-4780)	1100 (170-2961)	**672 (0-4780)**
Baseline KPS ≥ 90% (% pts yes - % pts no)	67% - 33%	43% - 57%	53% - 47%	83% - 17%	100% - 0%	36% - 64%	67% - 33%	**60% - 40%**
Baseline steroid use (0 < DEX ≤ 2 mg) (% pts yes)	24%	26%	47%	50%	0%	36%	27%	**29%**
Baseline s-cortisol (% pts < LLN% - % pts > ULN)	24% - 0%	17% - 4%	53% - 0%	17% - 0%	22% - 11%	27% - 0%	0% - 0%	**23% - 2%**
Baseline decreased lymphocytes (Gr 1 % - Gr 2 % - Gr 3%)	29% - 29% - 5%	30% - 22% - 0%	27%- 27% - 0%	33% - 0% - 0%	22% - 11% -11%	0% - 0% - 0%	20% - 13% - 0%	**24% - 18% - 2%**

SAFETY

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

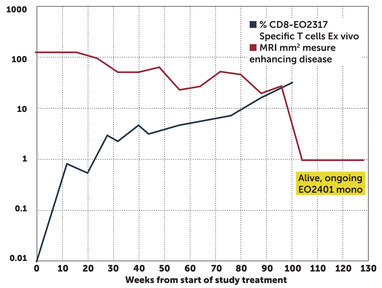
- Most common treatment-related AEs (any grade) were fatigue (19%), injection site reaction (18%), ALT increase (10%), AST increased (9%), headache (9%), nausea (7%), pyrexia (7%), hyperthyroidism (6%), hypothyroidism (6%), diarrhea (6%), gamma-GT increased (6%), pruritus (6%), vaccination complication (6%), injection site induration (5%), and white blood cell count decreased (5%)
- Any local administration site event (main erythema, induration, pain) in 39% of patients; 96% of events Grade 1/2 and 4% Grade 3; median time to event onset 45 days (range 1-629); KM analysis median event duration 58 days (range 1-934)
- Grade ≥3 treatment-related events in 16% of patients; most common were increased gamma-GT (3%), ALT/AST (2% each), and injection site reaction, aseptic meningitis, and brain edema (all 2%)
- Ten AEs leading to treatment discontinuation: transaminitis (3), aseptic meningitis, creatinine increased/somnolence, adenocarcinoma liver metastases, alteration general status, ataxia/apraxia/alexia, seizures, and intracranial hemorrhage
- Two AEs leading to death: status epilepticus, and urosepsis

IMMUNE RESPONSE

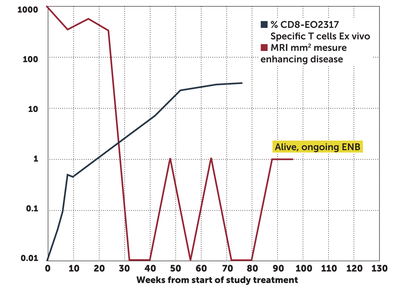
Immune monitoring in peripheral blood demonstrates the ability of EO2401 to expand mimic specific CD8 T cells with cross-reactivity against the targeted human TAAs in a significant portion of patients (Table).
Clinical responders with major tumor shrinkages have gradually increasing number of specific T cells in peripheral blood as the tumors diminish (Figure Pat #1, #2, and #3; Pat #4 illustrates that an early strong immune response measured in peripheral blood is not enough for tumor shrinkage). In C3/1 there is no correlation between strength of the immune response and PFS taking peripheral blood early during study treatment; adding later measures there is a strong significant direct relationship between strength of immune response and PFS (Table).

DB 2023-04-14 Cohort	Patients currently tested for immune response	Patients with expansion of CD8 T cells specific for microbiome peptides*	Patients with expansion of T cells cross reacting with peptides corresponding to human targets*	Correlation (regression line equation) for strength of immune response (Y) and progression-free survival (X) (C2a/1 = mimic tetramers after IVS; C3/1 & C3/2 = EO2317/mimic for BIRC5 tetramer ex vivo)
C2a/1 (n=23)	19 (83%)	17 (74%) [89% of tested]	16 (70%) [84% of tested]	Max individual immune response, any time: Ŷ = 12.1174 x + 0.08311X R = 0.436, R2 = 0.19, p = 0.062
C3/1 (n=11)	10 (91%)	9 (82%) [90% of tested]	9 (82%) [90% of tested]	**Max individual immune response, early (<16 weeks):** Ŷ = 0.6016 + 0.00218X R = 0.231, R2 = 0.053, **p = 0.521** **Max individual immune response, any time:** Ŷ = -6.7371 + 0.05148X R = 0.7595, R2 = 0.58, **p = 0.011**
C3/2 (n=15)	11 (73%)	11 (73%) [100% of tested]	11 (73%) [100% of tested]	Max individual immune response, early (<16 weeks): Ŷ = 0.9769 - 0.001715X R = -0.112, R2 = 0.013, p = 0.743

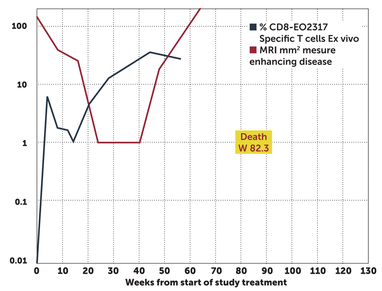
Pat #1 (E=>EN, C1a/1)



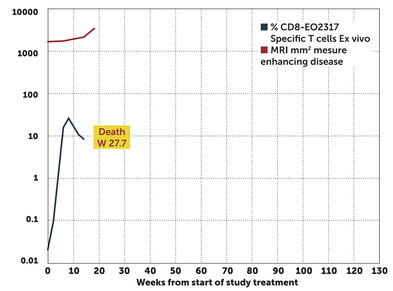
Pat #2 (ENB, C3/1)



Pat #3 (ENB, C3/1)



Pat #4 (E=>EN, C1a/2)



MRI: 0.01 = measure 0; 1 = "too small to measure"
Tetramer: 0.01 = analysis 0

CLINICAL OUTCOME

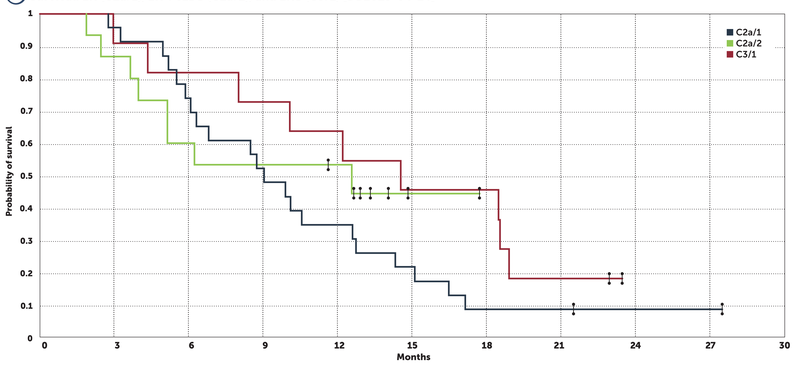
Addition of sLDB as anti-edema treatment to EN (C2a/2) prolonged treatment duration and increased efficacy vs. EN alone (C2a/1); the risk of early termination of study treatment due to neurological symptoms was high in C2a/1, assumed at least partially due to infiltration of tumor by immune cells causing edema. Direct use of ENB ameliorates the risk of missing the opportunity of rescuing patients with sLDB; assumed reason for the further increased efficacy in C3/1.
Another mitigation strategy for early neurological symptoms was delayed addition of N to E (C1a), with the assumption of a slower immune response and thereby slower tumor infiltration of immune cells. The strategy was not as advantageous as the addition of B, even if minor improvements vs C2a/1 was seen for median treatment duration (C1a vs C2a/1: 2.8 vs 1.4 months), disease control rate (33% vs 22%), and median duration of disease control (4.2 vs 2.8 months), the median survival was similar (9.5 vs 9.0 months).

EOGBM1-18/ROSALIE: EN vs EN + sLDB vs ENB

E = EO2401 N = nivolumab B = bevacizumab sLDB * ne = not estimable DB 2023-04-14	Treatment duration Median months (95% CI)	Patients with ongoing treatment	Disease control rate; iRANO SD+PR+CR % (95% CI)	Duration of disease control Median months (95% CI)	Progression-free survival Median months (95% CI)	Survival Median months (95% CI)	Survival rate at 12-months % (95% CI)	Patients alive	Follow-up for survival Median months
EN Cohort 2a/1 (n=23)	1.4 (0.9-2.3)	0	22% (8%-44%)	2.8 (1.8-11.9)	1.6 (1.1-1.8)	9.0 (6.1-12.6)	35% (16%-57%)	2 (9%)	24.5
EN + sLDB* Cohort 2a//2 (n=15)	3.2 (1.1-7.3)	1 (7%)	40% (16%-68%)	9.1 (5.3-ne)	3.6 (1.8-10.8)	12.6 (3.6-ne)	53% (27%-79%)	7 (47%)	13.3
ENB Cohort 3/1 (n=11)	5.0 (2.3-14.5)	1 (9%)	82% (48%-98%)	7.3 (3.6-15.4)	6.0 (1.8-15.4)	14.5 (4.3-18.8)	64% (31%-89%)	2 (18%)	23.2
ENB Cohort 3/2 (n=15)	5.1 (3.2-ne)	8 (53%)	93% (68%-100%)	5.4 (3.4-ne)	5.4 (2.8-ne)	Too early	Too early	11 (73%)	5.5

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

Survival: EN (C2a/1), EN + sLDB (C2a/2), and ENB (C3/1) [DB2023-04-14]



EOGBM1-18/ROSALIE: Integration of surgery and EN; Cohorts 2b and 2c

E = EO2401 N = nivolumab B = bevacizumab sLDB* ne = not estimable DB 2023-04-14	Patients with surgery per treatment plan	Treatment duration Median months (95% CI)	Patients with ongoing treatment	Progression-free survival Median months (95% CI)	Survival Median months (95% CI)	Survival rate at 12-months	Patients alive	Follow-up for survival Median months
EN* surgery – adjuvant Cohort 2b (n=6)	4 (67%)	7.7 (3.1-ne)	1 (17%)	8.4 (2.7-ne)	13.2 (12.2-ne)	100%	2 (33%)	15.4
EN* neoadjuvant – surgery – adjuvant Cohort 2c (n=9)	7 (78%)	7.4 (0.5-ne)	4 (44%)	5.8 (2.7-ne)	ne (9.0-ne)	Too early	7 (78%)	7.8

* symptom driven low-dose bevacizumab as time-limited anti-edema treatment, median 3 administrations, was given to 1 patient in C2b and 3 patients in C2c.
All outcome parameters also include surgery; meaning durations in C2c starts from surgery (25-40 days before the first dose of EN).

CONCLUSIONS

- Trial EOGBM1-18/ROSALIE finalized recruitment December 2, 2022, with the 100th patient starting treatment.
- EO2401/nivolumab +/- bevacizumab was well tolerated and generated fast, extensive, and durable immune responses which correlates with efficacy; outcomes support a hypothesis that the tumor function as a "sink" for tumor specific T cells.
- EO2401/nivolumab without efficacious supportive anti-edema treatment (leading to short treatment duration; median 1.4 months) show efficacy like current standards; survival around 9 months.
- Starting with EO2401 monotherapy and then adding nivolumab (delayed nivolumab) was not significantly advantageous for outcome (vs EO2401/nivolumab from start); but still showing efficacy like current standards with survival around 9.5 months.
- Addition of symptom directed low-dose bevacizumab to EO2401/nivolumab increased treatment duration and improved all efficacy parameters (survival around 12.5 months).
- EO2401/nivolumab with bevacizumab added from start showed further improved efficacy (survival around 14.5 months).
- Integration of surgery and EO2401/nivolumab as adjuvant and neoadjuvant/adjuvant treatment have been shown feasible; further follow-up will tell if there is any efficacy gain versus the ENB triplet.
- Cohort C3/2 (n=15; ENB) was initiated to validate the intriguing data from C3/1 (n=11; ENB); the follow-up is too short for a full assessment. However, current early data gives hope regarding a validation of the ENB outcome, paving the way for a next step in the development of EO2401 in glioblastoma.

Contact info: medicalmonitoring@enterome.com, and Wolfgang.Wick@med.uni-heidelberg.de