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BACKGROUND & METHODS

EO4010 was designed to expand pre-existing memory CD8 T cells recognizing non-self protein sequences from gut bacteria which cross-react with tumor associated antigens (TAAs) (**Figure 1**).

EO4010 includes 5 synthetic HLA-A2 CD8-epitopes (EO2317, EO2318, OMP10, OMP11, and OMP12) with mimicry to BIRC5, FOXM1, UBE2C, CDC20 and KIF2C (**Figures 2 and 3**), upregulated in mCRC, and a CD4 epitope UCP2.

The current phase 1/2 trial investigated EO4010 + nivolumab (EN) +/- bevacizumab (**Figure 4**) in patients with unresectable pMMR mCRC previously treated with oxaliplatin, irinotecan, fluoropyrimidines and anti-VEGF/EGFR, with HLA-A2, EOCG 0-1, measurable disease (RECIST 1.1), and progression during or within 3 months following the latest therapy. Final study data is presented.

CD8 T cells specific for EO4010- and TAA target-peptides were assessed directly ex vivo on cryopreserved PBMCs either by flow cytometry using tetramers or by IFN-γ ELISPOT after restimulation for 24 hours.

Survival was estimated with the Kaplan-Meier method; hazard ratios are from univariate Cox regression with log-rank p-values (**Figures 6, 7, 9, 10**) or Firth-penalized Cox regression (**Figure 8**); all p-values are nominal. NR = not reached / not estimable.

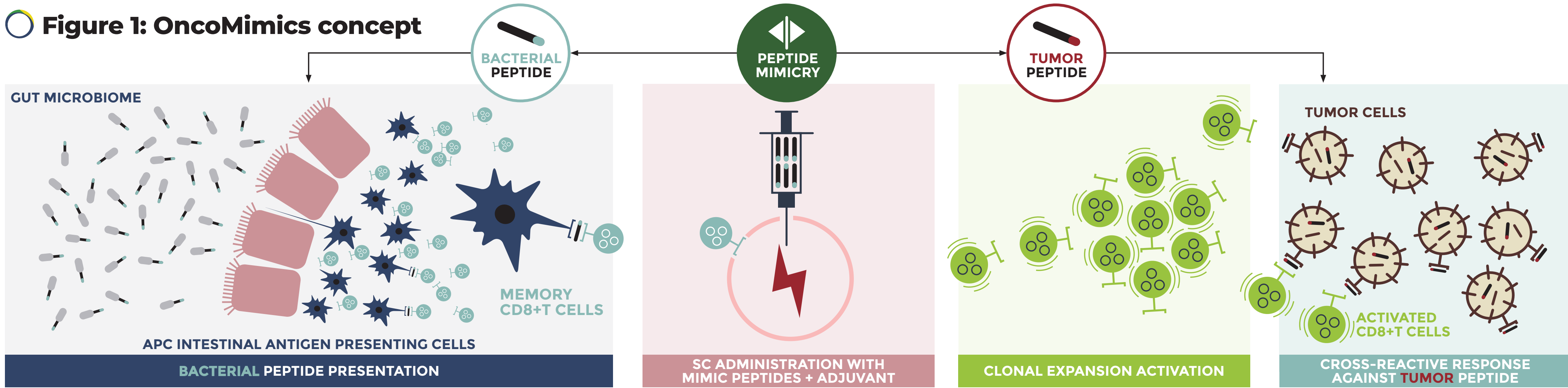


Figure 2: EO4010 targeted cell-cycle function TAAs

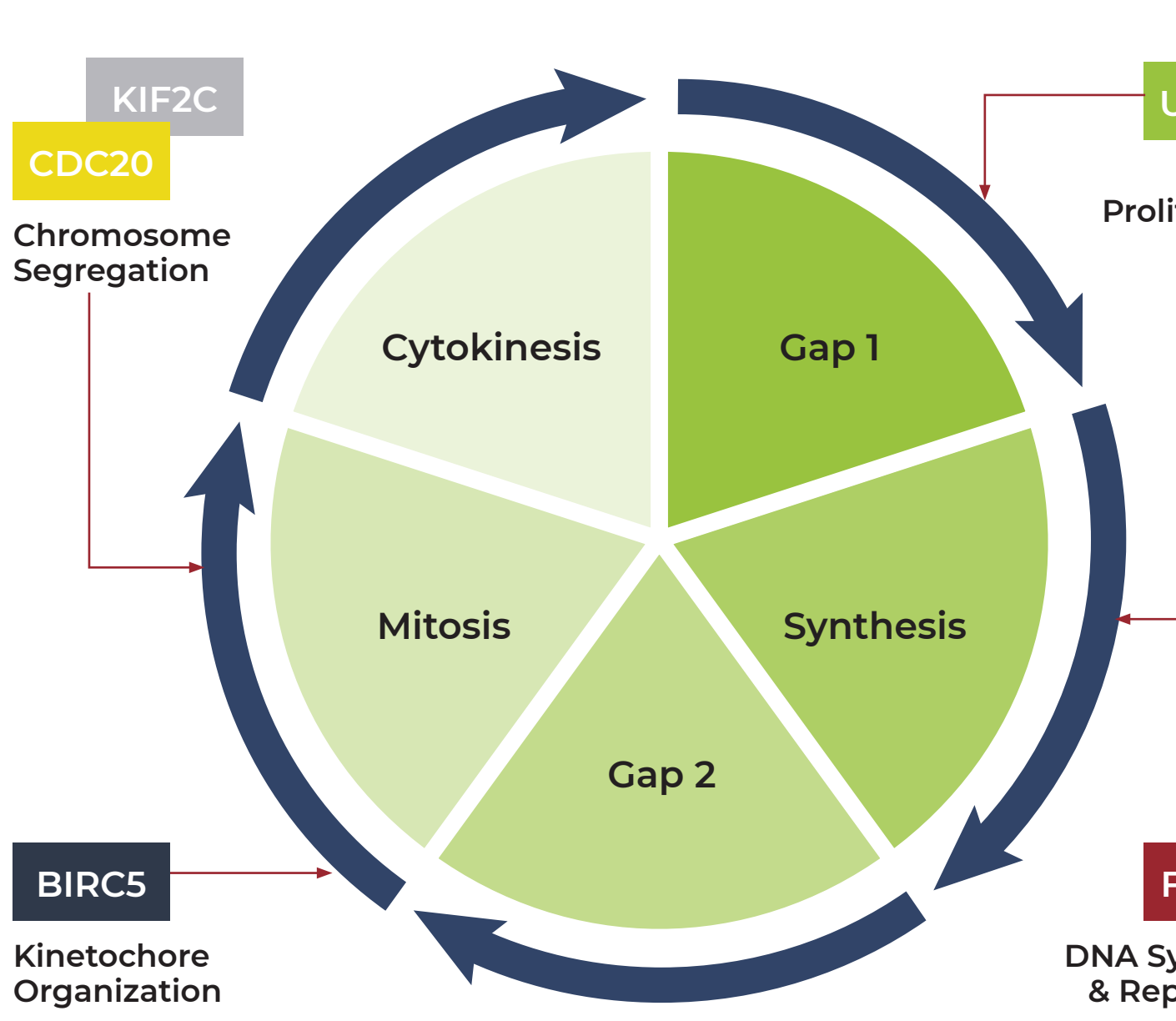


Figure 3: Expression of EO4010 targeted TAAs in different tumor types

Indications	#new cases / y ww	BIRC5	FOXM1	UBE2C	CDC20	KIF2C
Breast	2.2M					
Lung	2.2M					
Colorectal	1.9M					
Prostate	1.4M					
Gastric	1.1M					
Liver	0.9M					
Cervical	0.6M					
Oesophagus	0.6M					
Thyroid	0.6M					
Bladder	0.6M					
Pancreas	0.5M					
Ovarian	0.3M					

High gene overexpression
log2FC ≥ 1.0 - median tumour ≥ 10 TPM - tumours > P95 normal ≥ 50% - q<0.01

Intermediate gene overexpression
log2FC ≥ 0.5 - median tumour ≥ 5 TPM - q<0.05

Limited gene overexpression
log2FC = log2(median tumour) - log2(median normal), computed on log2 (TPM + 0.0001) values; +1 = 2-fold

P95 normal = 95th percentile of the matched normal samples; the criterion counts the share of tumours above it

q = p-value (Mann-Whitney U) adjusted for multiple testing across the 60 cells of this figure (Benjamini-Hochberg)

UCSC Xena TCGA recompute, in which TCGA tumours and CTCs normal tissues are quantified through a single pipeline; values are log2(TPM + 0.0001). Vivian et al. Nat Biotechnol 2017; Goldman et al. Nat Biotechnol 2020.

Figure 4: Treatment schedules

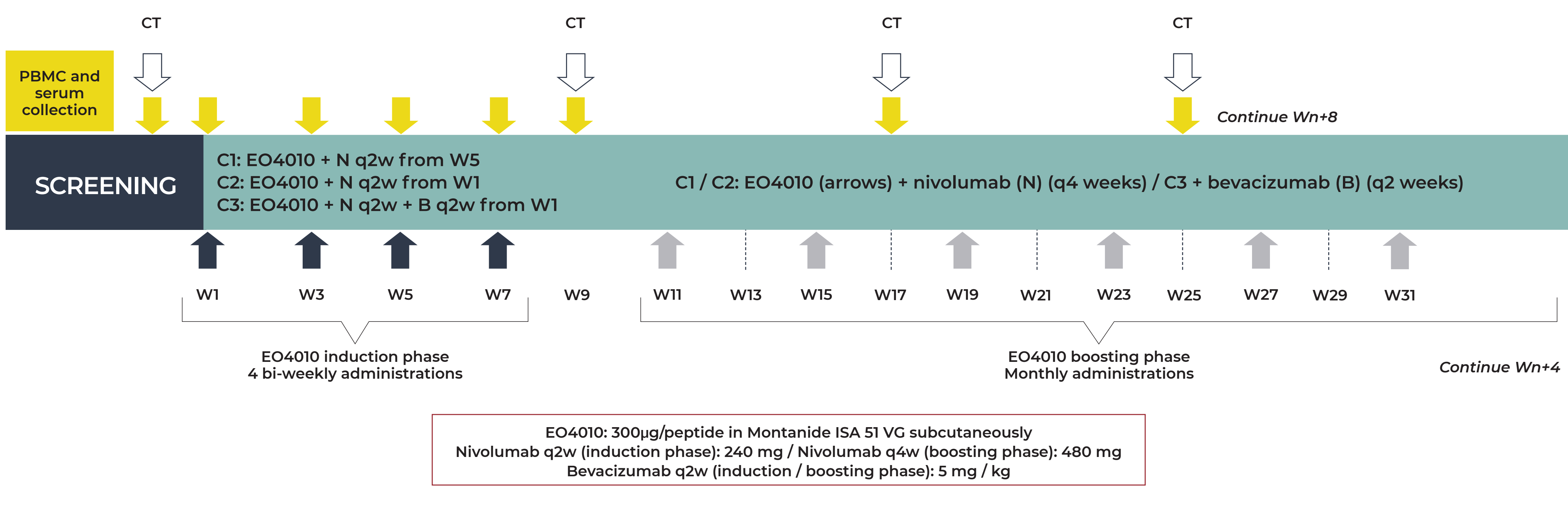


Table 1: Baseline characteristics

Baseline characteristics	EO4010 + nivolumab (n=20)	EO4010 + nivolumab + bevacizumab (n=5)
Age [years] median (min-max)	57.5 (45-80)	42.0 (38-72)
Gender [n(%)] female / male	11 (55) / 9 (45)	3 (60) / 2 (40)
EOCG [n(%)] 0 / 1 performance status	14 (70) / 6 (30)	3 (60) / 2 (40)
Time from primary diagnosis [years] median (min-max)	2.9 (0.9-7.8)	2.0 (1.2-5.3)
Time from diagnosis of metastatic disease [years] median (min-max)	2.4 (0.6-6.8)	1.9 (0.4-5.3)
Primary tumor location [n(%)] proximal / distal / rectum	7 (35) / 7 (35) / 6 (30)	0 (0) / 0 (0) / 5 (100)
Primary diagnosis stage [n(%)] Stage III / IV	5 (25) / 15 (75)	0 (0) / 5 (100)
Mismatch repair status [n(%)] proficient	20 (100)	5 (100)
Microsatellite [n(%)] stable / instable low	18 (90) / 2 (10)	5 (100) / 0 (0)
KRAS [n(%)] wildtype / mutation / unknown	7 (35) / 13 (65) / 0 (0)	2 (40) / 2 (40) / 1 (20)
NRAS [n(%)] wildtype / mutation / unknown	11 (55) / 2 (10) / 7 (35)	4 (80) / 1 (20) / 0 (0)
Any RAS mutation [n(%)] any KRAS or NRAS mutation	15 (75)	3 (60)
BRAF [n(%)] wildtype / mutation / unknown	17 (85) / 0 (0) / 3 (15)	5 (100) / 0 (0) / 0 (0)
Number of organs with mets [n(%)] 1 / 2 / ≥3 organs	3 (15) / 8 (40) / 9 (45)	1 (20) / 2 (40) / 2 (40)
Liver mets [n(%)] present	10 (50)	4 (80)
Number of prior systemic lines of treatment for mCRC median (min-max)	3 (1-5)	2 (2-6)

Table 2: Safety

Safety / Treatment emergent events (TEAE) N = 25 patients	TEAE, any grade ≥10%, irrespective of relationship	TEAE, any grade ≥10%, related to any study drug
Local administration site reaction (LASR)	21 (84%)	21 (84%)
Asthenia	8 (32%)	5 (20%)
Fatigue	5 (20%)	2 (8%)
Anemia	5 (20%)	0 (0%)
Diarrhea	5 (20%)	1 (4%)
Transaminase elevation	4 (16%)	1 (4%)

- Median treatment duration 14 months (range 10-101 months).
- There were no grade 4 or 5 events.
- All 14 grade 3 events included LASR (2), pyelonephritis (2), and the following with 1 event each: asthenia, fatigue, anemia, transaminase elevation, respiratory tract infection, acute myocardial infarction, gastrointestinal obstruction, wrong medication administered, acute kidney injury, and pelvic pain.
- The only related grade 3 events were 2 LASRs.
- Study treatment discontinuation: progressive CRC = 23, death AMI = 1 (not related to study treatment), withdrawn consent = 1.

POST-STUDY TREATMENT SYSTEMIC ANTI-CANCER THERAPY

Overall, any post-study treatment systemic anti-cancer treatment was administered in 18/25 (72%) patients. The median number of lines post-study treatment was 1 (range 1-4), starting at median 32 days (range 15-296 days) after the last EO4010 administration.

Three complementary exploratory analyses converge and support the conclusion that post-study anti-cancer treatments do not account for the survival signal observed in the study: i) landmark analyses at day 90 and day 180 by post-study treatment status, ii) a Cox model with post-study treatment as time-dependent covariate (HR 0.47, p=0.19), and iii) a comparison of survival across the dominant post-study regimens (irinotecan-based vs TAS-102-based).

CONCLUSIONS

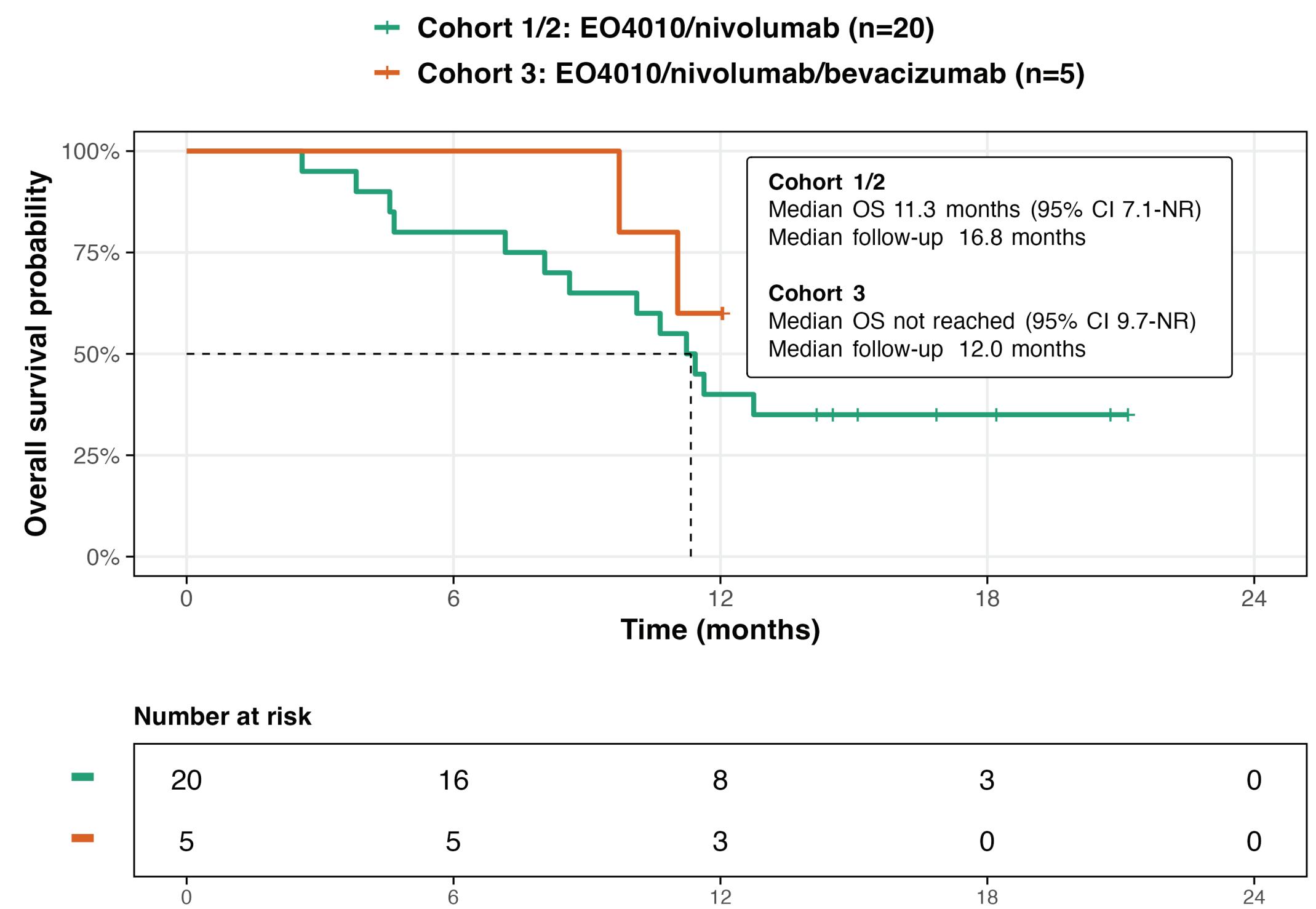
- EO4010 + nivolumab +/- bevacizumab is well tolerated in patients with mCRC.
- EO4010 promotes expansion of CD8 T cells specific for EO4010- and TAA target-specific epitopes.
- Fast and high level of EO4010 induced expansion of specific tumor targeting CD8 T cells is associated with longer survival.
- The survival advantage driving epitope seems to be located on BIRC5.
- Continued clinical evaluation of EO4010 in pMMR mCRC is warranted.

EFFICACY BY RECIST 1.1

EO4010/nivolumab (n=20)

- Objective response rate 5.0% (95% CI 0.1-24.9).**
 - One partial response max tumor shrinkage week 33 with shrinkage of liver (2 lesions minus 47%) and lung (2 lesions minus 34%) mets; normalization of baseline pathologic CEA. Time to response 1.9 months, duration of response 8.7 months.

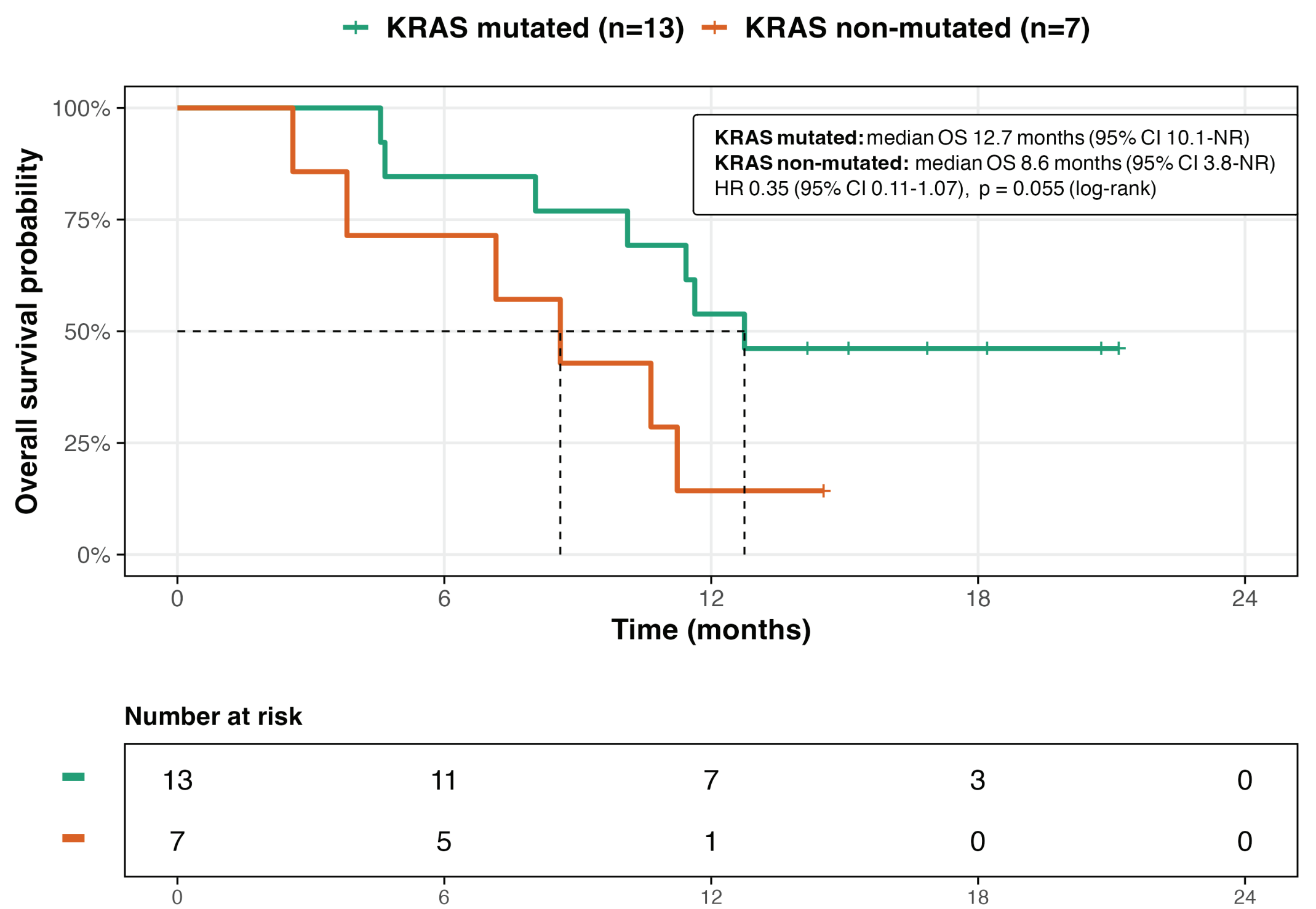
Figure 5: Overall survival (OS) by cohort for EO4010/nivolumab (Cohort 1/2) and EO4010/nivolumab/bevacizumab (Cohort 3)



Two patients' stabilization of disease:

- tumor shrinkage minus 7% week 8, CEA decrease minus 68%; severe cardiosclerosis, AMI at weeks 12.9, 15.6, and died of AMI week 17 without known tumor progression.
- treatment for 10.4 weeks before withdrawn consent; patient died at 8.6 months, primary cause complications at tumor surgery attempt.

Figure 6: Overall survival (OS) by KRAS mutation status, patients with tumors with (n=13) and without (n=7) KRAS mutation treated with EO4010/nivolumab (Cohort 1/2)



EO4010/nivolumab/bevacizumab (n=5)

- Three patients' stabilization of disease.

EO4010/nivolumab +/- bevacizumab (n=25)

- Disease control rate 6/25 (24%); duration of disease control 5.5 months (95% CI 2.4-not reached).
- Median time to progression 1.9 months (95% CI 1.8-2.2).

Figure 7: Overall survival (OS) by liver metastatic status, patients having (n=10) and not having (n=10) liver metastases treated with EO4010/nivolumab (Cohort 1/2)

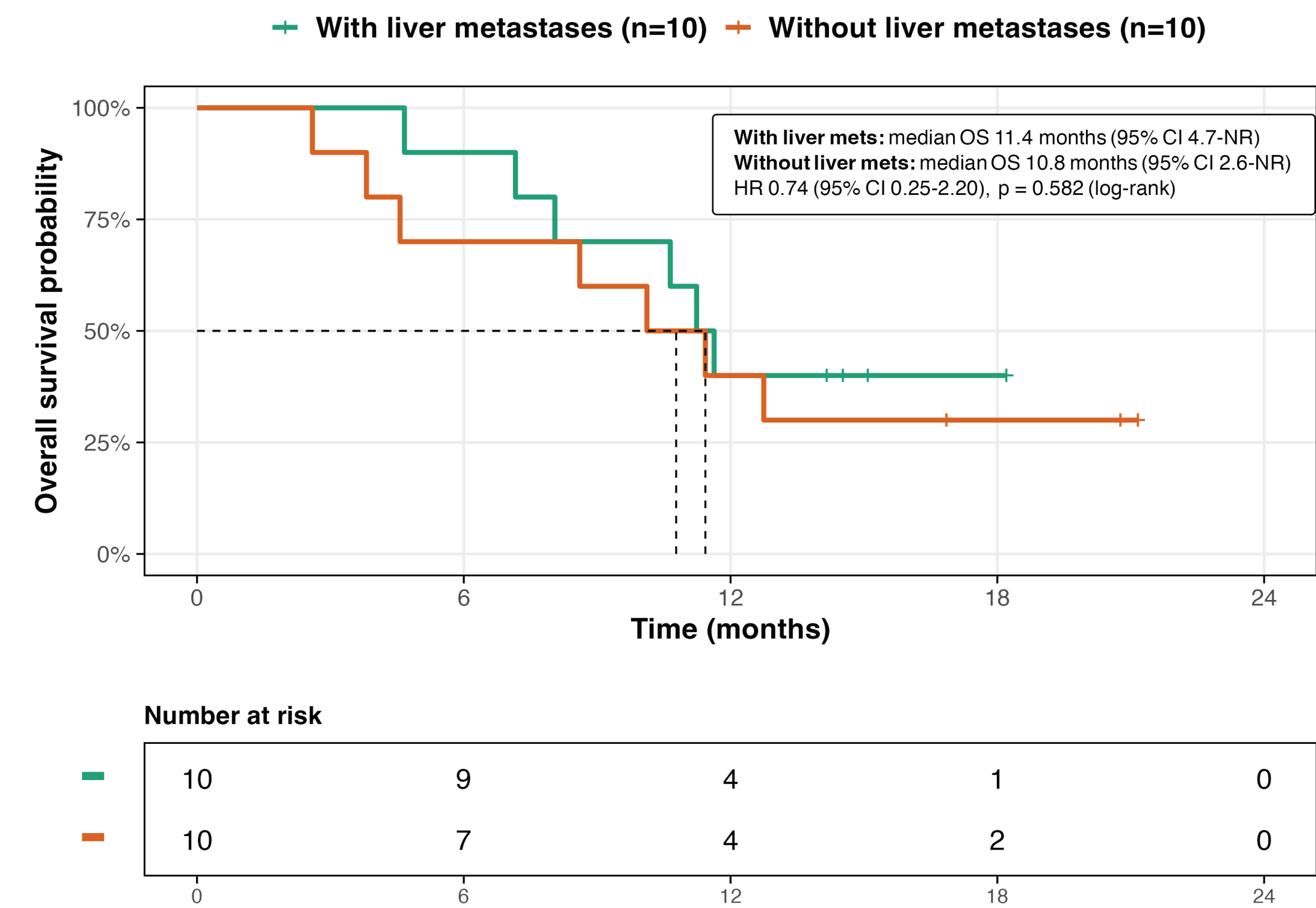


Figure 8: Univariate Cox-analyses of EO4010 induced expansions of specific CD8 T cells impact on overall survival (Cohort 1/2, n=20).

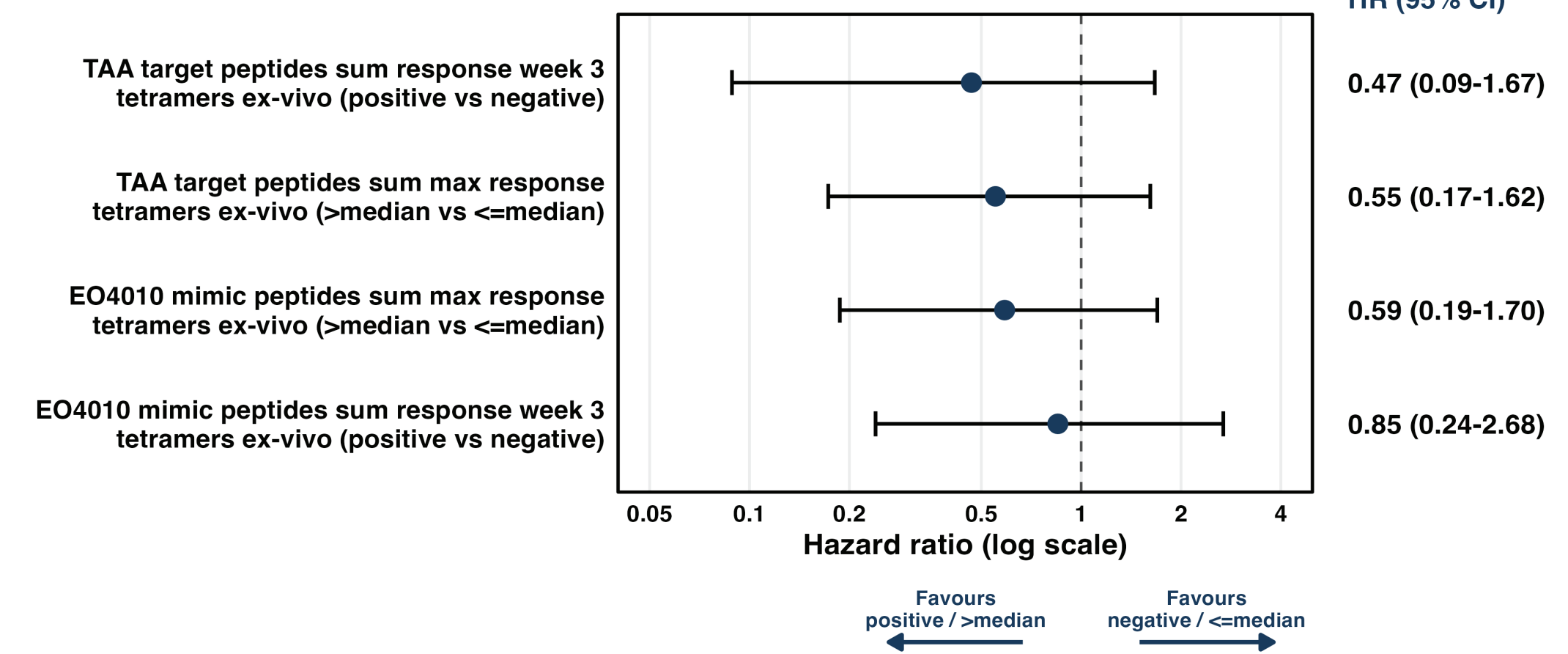


Figure 9: Overall survival (OS) by EO2317 specific CD8 T cell expansion, patients with (n=9) and without (n=12) EO2317 expansion at week 5 (Cohort 1/2/3)*

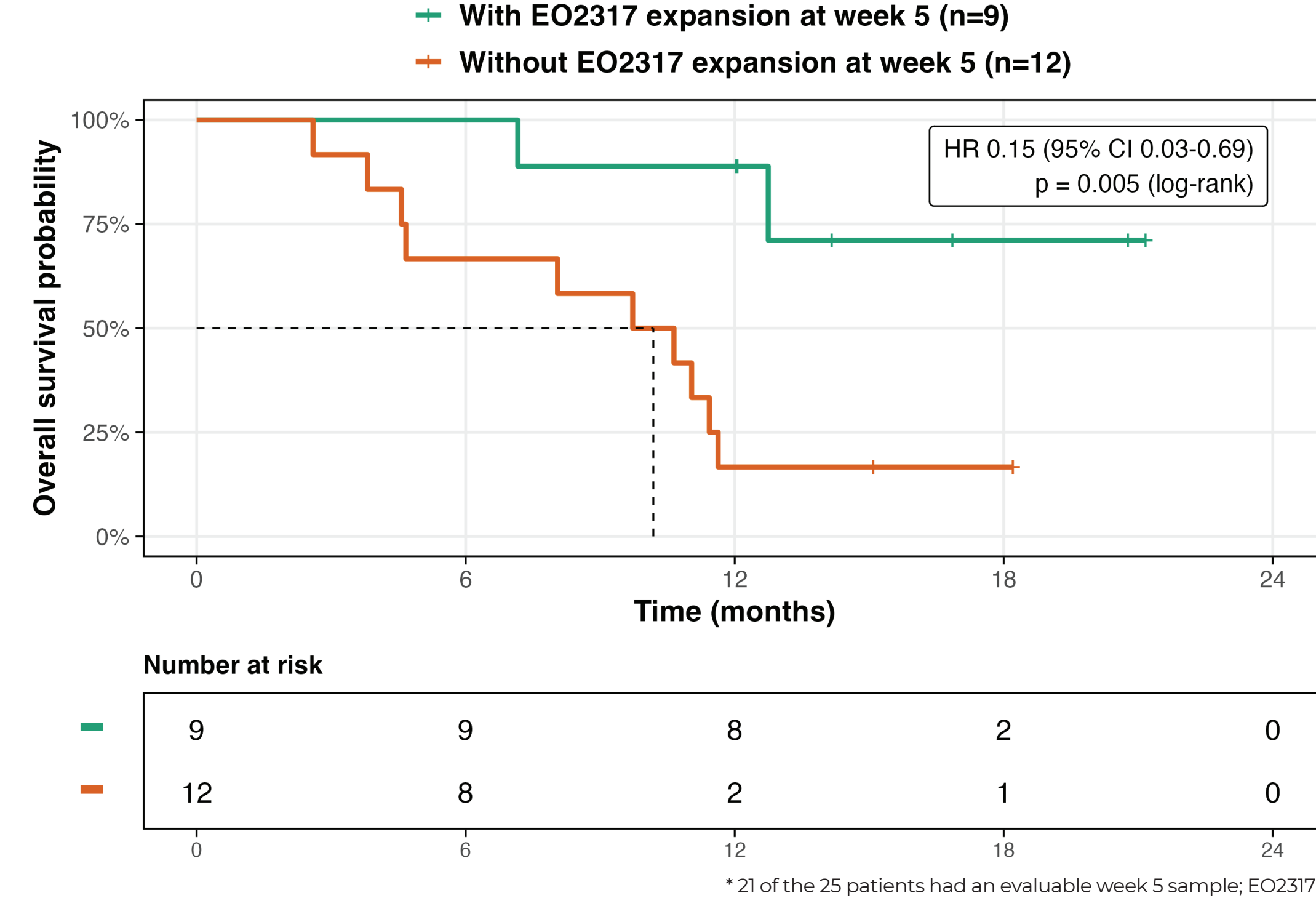


Figure 10: Overall survival (OS) by BIRC5 specific CD8 T cell expansion, patients with (n=11) and without (n=10) BIRC5 expansion at week 5 (Cohort 1/2/3)*

