111P - Neoadjuvant high-dose vitamin C (HDVC) combined with ipilimumab and nivolumab in proficient mismatch repair (pMMR) colon cancer (CC): first safety analysis of ALFEO pilot study

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BACKGROUND

Neoadjuvant immunotherapy with immune checkpoint inhibitors (ICI) ipilimumab (I) + nivolumab (N) can induce pathological responses in stages II-III pMMR CC (Chalabi et al, 2020). Preclinical data (Magrì et al, 2020) showed improvement in the efficacy of I + N when combined with HDVC. ALFEO is a window-of-opportunity trial for stages II-III and resectable oligometastatic stage IV CC candidates to R0 surgery, to test if HDVC can increase the efficacy of I + N by improving major pathological responses (MPR).

METHODS

Efficacy and the safety endpoints were assessed using the Bayesian optimal phase 2 (BOP2) design (Zhou, Lee and Yuan, 2017), with a fixed maximum sample size of 24 patients. Patients received HDVC 70 mg/m^2 on D1-D3 and D15-D17, and I 1 mg/Kg on D2 + N 3 mg/Kg on D2, D16. Assuming an MPR of 23% (H_0) vs 75% (H_1), and monitoring responses after the accrual of 12, 18, and 24 patients (stop and not refuse H_0 if MPR <3, 6and 10), such design held a 99% power and 3% type I error. Safety monitoring requires check after 6,12, and 18 patients enrolled, to stop the trial if key adverse events (AEs) exceeded 2, 2, and 3 patients, respectively. Key AEs are defined as any AE G4 or preventing/delaying curative surgery.

Inclusion criteria and the treatment schedule are summarized in **Figure 1**, and futility and toxicity boundaries in **Table 1**.

TRANSLATIONAL ENDPOINTS

Peripheral blood samples were collected at different time points: before treatment (baseline), during therapy, and after its completion. They will be used to investigate T cell immunosenescence and exhaustion within peripheral blood mononuclear cells (PBMCs), as well as to analyze cell-free DNA, cytokine profiles involved in systemic and tumor immunity, and markers of immunogenic cell death (ICD) in plasma. Trial workflow and sample collection are summarized in **Figure 2**.

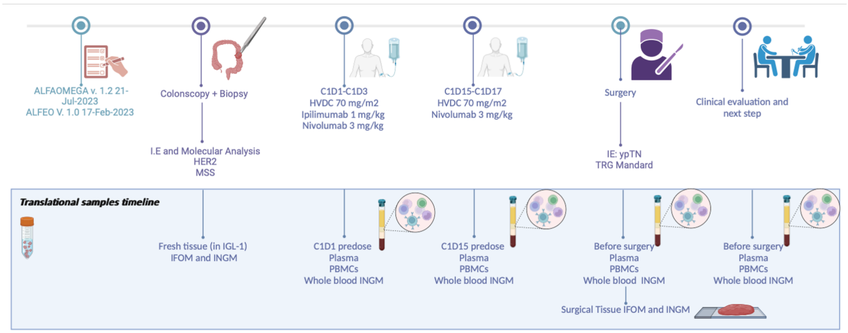

Figure 2. Trial workflow with samples collection during treatment/surgery/EOT.

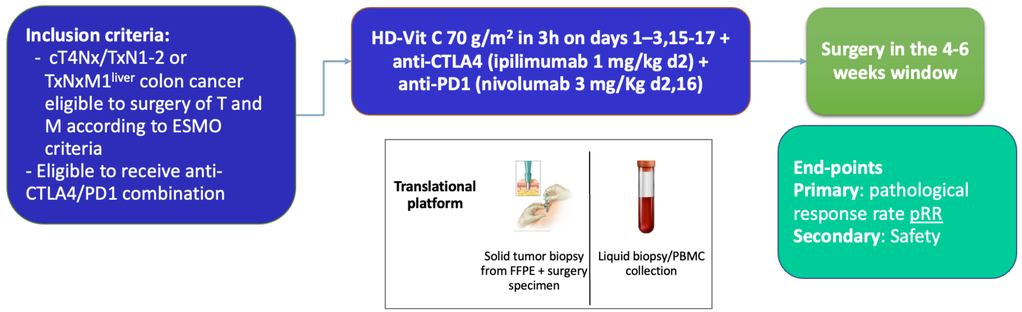

Figure 1. Study design.

RESULTS

To date, the first cohort of 6 patients completed the treatment. One MPR in the first 6 evaluable patients was observed at the cut-off date. Characteristics and pathological responses are shown in **Table 2**. No key AEs have occurred. **Figure 3** shows type of AE according with causality (**A**), and grading according to experimental treatment relationship (**B**).

ALFEO ID#	TRG DWORAK	TRG Mandard	Patological stage	CT adjuvant	Relapse	F-UP (months)
A01-02	1	4	ypT3N0 (0/37)	YES- 5FU	YES (liver)	19,6
A01-03	0	5	ypT1N0 (0/35)	NO	No	18,2
A01-05	1	4	ypT2N1c (0/41)	YES - XELOX	No	15,2
A01-06	4	1	ypT0N0 (0/38)	No	No	15,5
A01-08	1	4	ypT3N0 (0/29)	YES - XELOX	No	12,5
A01-09	1	4	ypT3N1b (2/61) ypM1a	YES - XELOX	No	11,5

Table 2: Patient clinical and pathological characteristics. pStage: pathological stage. TRG: Mandard tumor regression score

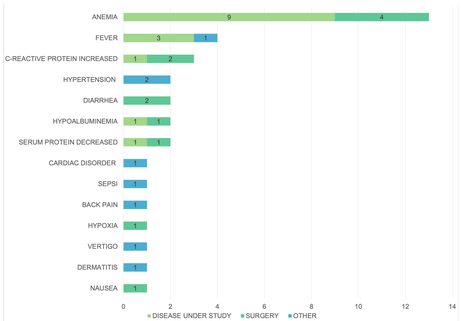

Figure 3A: AEs according to causality.

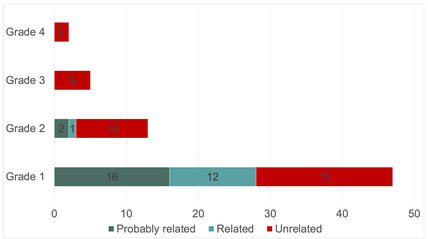

Figure 3B: Number of AE according to grading and experimental treatment relationship.

# PATIENTS	STOP if # responses ≤	STOP if # toxicity ≥
6	NA	2
12	2	2
18	5	3
24	9	3

Table 1. Pathological response rate and futility/toxicity boundaries. Any G3/4 toxicity related to study treatment preventing surgery or delaying surgery >4 weeks will be counted as critical toxicity.

CONCLUSIONS

At the first safety analysis, treatment with HDVC and I + N has proven to be safe. No AEs ≥G3 have been observed and all patients received curative surgery as scheduled.

References

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ACKNOWLEDGEMENTS

EudraCT n. 2022-502101-15-00. Funded by EU NextGenerationEU, "Valorizzazione e potenziamento della Ricerca Biomedica nel SSN", M6, C2, I2.1; CUP H43C21000130006, and Fondazione Oncologia Niguarda ETS

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