

POSTER PRESENTATION

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# Inflammatory status affects the antitumor activity of poly-epitope-peptide vaccination against the thymidylate synthase in metastatic colo-rectal cancer patients enrolled in TSPP/VAC-1 Phase Ib trial

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Thymidylate synthase (TS) is a tumor-associated-enzyme crucial for DNA replication and inhibited by 5'-fluorouracil. TSPP is a previously characterized anticancer poly-epitope peptide vaccine to TS (Correale P, *JNCI* 2005 97:1437). TSPP/VAC-1 is a three-arm dose-finding Phase-Ib trial aimed to test in pretreated-advanced cancer patients, TSPP-vaccination alone (arm A), together with GM-CSF and low dose Aldesleukine (arm B), or together with chemo-immunotherapy according to the GOLFIG regimen (Correale P, *JCO*, 2005, 23:8950) (arm C). TSPP resulted safe, its MTD was not achieved, while its most-effective-biological-dose was 300µg. As the most promising antitumor effects of TSPP were observed in colo-rectal cancer (mCRC) patients (Cusi MG, *CIIT*, 2015, *epub*), we decided of carrying-out a new study to evaluate in this subset of patients, the potential ability of a predefined panel of markers to predict their antitumor response to TSPP. We thus evaluated 41 mCRC patients, 20 males and 21 females, with a good performance status, enrolled between May 2011 and Jan 2013. Our parameters were correlated with progression free survival (PFS) and overall survival (OS) by performing a Kaplan Meier analysis. The baseline marker values were divided in two groups according to their median values, while the changes relative to

baseline values (post-treatment values) were divided according to a fold ratio  $\leq$  or  $>1$ . Patients' PFS and OS were 6.9 and 11.3 months, respectively; there were no significant differences in PFS and OS correlated with treatment arm (A vs. B vs. C), number and type of previous treatments, sex, age, TS expression, HLA2.1 haplotype or expression of peripheral CTLs, regulatory-T cells, central- and effector-memory-T cells. Patients bearing K-ras mutations, showed a trend to a shorter PFS (p:0.051) and no differences in OS (p=0.16). Patients' outcome was instead, inversely correlated with performance status (ECOG 0-1 vs. 2; PFS, p1, OS, p:0.039). These results suggest that inflammatory status and autoimmunity may affect TSPP antitumor activity in mCRC patients. These results deserve to be considered for the design of new studies.

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Parameter	Endpoint	Number of patients	Mean Value	Significance
ECOG	PFS	ECOG 0-1: 29	ECOG 0-1: 9.31 +/- 2.27	p<0.001
		ECOG 2: 12	ECOG 2: 2.41 +/- 0.43	
KRAS	PFS	Wild Type: 22	WT: 8.77 +/- 2.29	P:0.051
		Mut: 19	Mut: 4.68 +/- 1.58	
NLR	PFS	Under median value :20	Under: 11.1 +/- 3.18	p:0.010
		Over median value: 20	Over: 3.80 +/- 0.6	
CRP	PFS	Under median value :20	Under: 11.25 +/- 3.17	p:0.005
		Over median value: 20	Over 3.65 +/- 0.54	
Post-treatment neutrophil count changes	PFS	Ratio ≤ 1: 16	Ratio<1: 9.06 +/- 3.12	p:0.011
		Ratio >1: 11	Ratio>1: 2.36 +/- 0.59	
CEA	OS	Under median value :19	Under: 19.10 +/- 4.19	p:0.021
		Over median value: 19	Over: 7.42 +/- 1.14	
ECOG	OS	ECOG 0-1: 29	ECOG 0-1: 17.04 +/- 2.9	p<0.001
		ECOG 2: 12	ECOG 2: 3.91 +/- 0.74	
NLR	OS	Under median value :20	Under: 19.01 +/- 3.97	p:0.011
		Over median value: 20	Over: 7.40 +/- 1.04	
CRP	OS	Under median value :20	Under: 19.75 +/- 4.1	p:0.002
		Over median value: 20	Over: 7.40 +/- 1.48	
ESR	OS	Under median value :20	Under: 18.92 +/- 3.69	p:0.002
		Over median value: 19	Over: 7.52 +/- 1.97	
LDH	OS	Under median value :20	Under: 19.64 +/- 3.88	p:0.001
		Over median value: 20	Over: 6.60 +/- 0.84	
ENA	OS	Under median value : 22	Under: 17.30 +/- 3.52	p:0.023
		Over median value: 17	Over: 8.58 +/- 2.11	
IL17	OS	Under median value :18	Under: 10.61 +/- 2.82	p:0.074
		Over median value: 18	Over: 17.83 +/- 3.36	
IL4	OS	Under median value :18	Under: 10.33 +/- 2.8	p:0.049
		Over median value: 18	Over: 17.49 +/- 3.31	
Post-treatment neutrophil Count changes	OS	Ratio ≤ 1: 25	Ratio<1: 18.51 +/- 3.38	p:0.001
		Ratio >1: 14	Ratio>1: 5.85 +/- 1.29	
Post-treatment c-ANCA changes	OS	Ratio ≤ 1: 8	Ratio<1: 6.12 +/- 1.67	p:0.039
		Ratio >1: 13	Ratio>1: 16.76 +/- 4.22	

Figure 1

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