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Mechanism of Action for Antitumoral Activity of Autologous Heterotopic Transplant of Peripheral Blood in Non-Small Cell Lung Cancer

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Background: Autologous Heterotopic Transplant of Peripheral Blood (AHTOPB) is a medical procedure of autologous immunotherapy operated by blood-cells *ex vivo* processed with an adjuvant system and pulsed with an autologous plasma fraction enriched for polyvalent tumour antigens (PTA). Lately, antitumour activity of AHTOPB and other autologous immunotherapies upon different malignancies was reported. Here we study the mechanism of action involved in Non Small Cell Lung Cancer (NSCLC) patients.
Methods: NSCLC patients, adenocarcinoma, to be submitted to neoadjuvant chemotherapy (NCH) were 2-arm randomized: G1, NCH, 4 series; G2, NCH plus AHTOPB. After surgery, all patients received 4 additional series of adjuvant chemotherapy. Selection criteria: patients reaching surgery, recurrence post-surgery with measurable M1. Exclusion criteria: M1 brain, unaccomplished programmed treatments. All assessments were performed at the time of diagnostic-biopsies (TOD), before any treatment, and at the time of resection-surgery (TOR), after neoadjuvant treatment. Assessment in tumour samples T-Regulatory cells (CD4+CD25+FOXP3+), Dendritic cells (CD1a+/CD83+) and neovessell density (CD34+) by IMC. In peripheral venous blood, VEGF and Angiostatin dosification by ELISA method. Toxicity (CTCAE), 30-day tumour-growth (30d-TG) in measurable M1 and Overall survival (OS) were registered.
Results: See Table 1.
Conclusions: In these patients, as shown in other models, the activity of AHTOPB when added to chemotherapy was confirmed: significant slow of tumour growth and OS advantage. These results were associated to a profile of angiogenesis and immunity mediators compatible with AHTOPB mechanism of autologous immunotherapy plus antiangiogenic/antitolerogenic conditioning of tumour-elicited biological response.

Table 1. Results

		Pre-treatment sample	Post-Neoadjuvant sample	
			G1: Chemotherapy	G2: Chemotherapy + AHTOPB
T-Reg (CD4+CD25+FOXP3+)	% CD4+ % TOD	25.8±4.2 100	18.2±3.1 76	6.3±2.6 24
Dendritic (CD1a+/CD83+)	by HPF % TOD	2.3±1.1 100	2.7±0.9 116	14.2±2.7 640
VEGF	pg/ml %TOD	146±6.3 100	158±5.5 102	66±3.8 55
Angiostatin	µg/ml %TOD	0.07±0.02 100	0.09±0.02 98	0.38±0.08 210
CD34+ vessels	%TOD	100	84	22
Clinical results				
Maximal toxicities	CTCAE		Hemo 2.8±0.6 Nephro 2.2±0.5	Hemo 2.6±0.9 Nephro 2.3±1.0
30 day tumour growth	%		15.6±2.1	8.4±1.4
Overall Survival	mo		9.6±1.8	14.2±2.0

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Activity of Ixabepilone and Cisplatin Combination in Chemo-naive Stage IIIB/IV NSCLC − a Phase Ib Study

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Background: Randomized trials have shown that platinum-based (carboplatin or cisplatin (cis)) drug combinations as primary therapy for non-small cell lung cancer (NSCLC) significantly increase survival. However, no single regimen incorporating platinums is recommended for routine use.
The primary objective of this phase I trial was to establish the maximum tolerated dose (MTD) and recommend a phase II dose of ixabepilone and cisplatin given every 3 weeks. Secondary objectives included preliminary evaluation of safety and efficacy.
Methods: This was a phase I dose escalation trial with expansion at the MTD dose level in patients with advanced NSCLC. The escalation phase was a standard 3+3 design with no more than 25% increase in only one of the 2 compounds at each dose escalation step. Treatment was given every 3 weeks, starting with 32 mg/m^2 ixa and 60 mg/m^2 cis. At the MTD, 18 chemo-naive patients (pts) with NSCLC were accrued to the expansion phase. A maximum of 6 cycles was planned unless there was progressive disease (PD), or unacceptable toxicity. Tumour assessments were done every 2 cycles in the expansion phase.
Results: A total of 29 pts were enrolled (12 females and 17 males, median age 63 years with age range 30−77 years); 11 pts in escalation phase and 18 pts in expansion phase. Starting dose level was 32 mg/m^2 ixa and 60 mg/m^2 cis and none of the 6 pts treated had a dose-limiting toxicity (DLT). At the next level, two out of five pts treated at 32 mg/m^2 ixa and 80 mg/m^2 cis had DLTs, one with grade 4 neutropenic sepsis and another with grade 3 abdominal pain. The MTD was defined as 32 mg/m^2 ixa and 60 mg/m^2 cis. The median cycles of ixa at the MTD was 6 (2−23). Most frequent grade 3 or 4 adverse event at the MTD was neutropenia (50%). Severe non-hematologic toxicities at the MTD were infrequent and included 1 pt with grade 3 neuropathy and 2 pts with grade 3 vomiting and no grade 4 adverse events. In the expansion phase, 7/18 pts with NSCLC achieved PR, 9/18 pts with stable disease, and 2/18 pts with PD.
Conclusions: The combination of ixa 32 mg/m^2 and cis 60 mg/m^2 every 3 weeks is feasible in chemonaive NSCLC. This experimental combination may warrant further investigation.

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Network Meta-analysis of Second and Third-line Treatments on Overall Response and Overall Survival in Patients With Metastatic Non-small Cell Lung Cancer

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Objective: To perform a network meta-analysis of recommended 2nd/3rd line treatments for overall response and survival in metastatic non-small cell lung cancer (mNSCLC).
Methods: A systematic literature review identified phase III trials of drugs approved for 2nd/3rd line treatment of patients with mNSCLC in the US and EU-5. A network analysis was performed on hazard ratios (HRs) for overall survival and odds ratios (ORs) of overall response using a Bayesian approach assuming fixed-effects. Heterogeneity was assessed across the 3 studies comparing gefitinib to docetaxel with Q- and I^2 statistics. Sensitivity analyses around network composition and sub-group analyses by performance status (PS) were conducted.
Results: A network of 7 trials (JMEI, TAX 317, V-15−32, INTEREST, ISTANA, ISEL, BR21) of N = 5564 patients was identified covering 4 drugs and placebo/BSC. Drugs(# arms) were: docetaxel(4), pemetrexed(1), erlotinib(1), gefitinib(4) and placebo/BSC(3). Heterogeneity in treatment effects across trials comparing gefitinib and docetaxel was acceptable (Q-statistic=1.385, p = 0.24; I^2=27.81%). A significant improvement in overall response was estimated for all therapies compared with placebo/BSC (Table 1). Ranking by effect on overall response estimated erlotinib as most effective, then gefitinib, docetaxel75, pemetrexed, docetaxel60 and BSC. Estimated effects on survival were suggestive of benefit but credible intervals were relatively wide. Only erlotinib demonstrated a significant effect on survival compared with placebo − thus no ranking was done. Results generally improved with initial PS and were stable in sensitivity analyses.

Table 1: Treatment Effects on Overall Response and Survival

Treatment	Response		Treatment	Survival	
	Mean OR	95% CrI		Mean HR	95% CrI
Placebo	1		Placebo	1	
BSC	1.389	(0.02, 8.71)	BSC	1.949	(0.9, 3.72)
Docetaxel60	4.531	(1.54, 10.48)	Gefitinib	0.888	(0.77, 1.02)
Docetaxel75	6.133	(2.23, 13.62)	Docetaxel75	0.886	(0.74, 1.06)
Pemetrexed	6.808	(2.01, 17.04)	Pemetrexed	0.883	(0.67, 1.14)
Gefitinib	8.751	(3.47, 18.48)	Docetaxel60	0.800	(0.6, 1.04)
Erlotinib	15.090	(2.78, 48.15)	Erlotinib	0.705	(0.58, 0.85)