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

E. Lasalvia-Prisco[1], E. Garcia-Giralt[2], P. Goldschmidt[2], S. Cucchi[1], J. Vazquez[1], R. Galmarini[3]. *[1]Interdoctors, Oncology, Montevideo, Uruguay; [2]Interdoctors, Oncology, Paris, France; [3]Interdoctors, Oncology, Buenos Aires, Argentina*

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

D. Amadori[1], C. Milandri[1], E.M. Ruggeri[2], E. Baldini[3], L. Moscetti[2], P. Mukhopadhyay[4], B. Mudenda[4], J. Marshal[5], A.R. Tan[6]. *[1]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (I.R.S.T.), U.O. Oncologia Medica, Meldola, [2]Ospedale Belcolle, Viterbo, [3]Ospedale Campo Di Marte, Lucca, Italy; [4]Bristol-Myers Squibb, Wallingford, Wallingford CT, [5]Georgetown University, Lombardi Cancer Center, Washington DC, [6]The Cancer Institute of New Jersey, New Brunswick NJ, USA*

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

F. Bianic[1], N. Despiegel[2], S. Cure[1], J. Campbell[3], Z. Wang[4], J.C. Cappelleri[5], R. Govindan[6]. *[1]Innovus, Health Economics and Outcomes Research, Uxbridge, United Kingdom; [2]Innovus, Health Economics and Outcomes Research, Nanterre, France; [3]Innovus, Health Economics and Outcomes Research, Medford, [4]Pfizer Inc, Oncology BU, New York, [5]Pfizer Inc, Statistics, Groton, [6]Washington University School of Medicine in St. Louis, Medical Oncology, St. Louis, USA*

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)

Conclusions: Given the lack of head-to-head research with active treatments, meta-analyses provide needed comparative information on treatment options in a coherent framework. Evidence for 2nd/3rd line mNSCLC treatment effects on response is stronger than evidence for survival. The exceptions are targeted therapies − this class is likely to be the most promising source for badly needed new therapies.

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Febrile Neutropenia (FN) in Lung Cancer Patients

E. Morocz[1], G. Lupkovics[1], E. Tolnay[1]. [1]*Pest County Hospital of Pulmonology, Oncology, Törökbálint, Hungary*

Background: Neutropenia and related complications represent the most common dose limiting toxicity of cancer chemotherapy. Only few data are available about FN in lung cancer patients treated with chemotherapy.
We investigated the incidences and characteristics of febrile neutropenic events in lung cancer patients receiving chemotherapy at our institute.
Material and Methods: All lung cancer patients treated with standard chemotherapy between 01.10.2005 and 30.09.2010 were included in our retrospectiv analysis. Patients with concurrent radiotherapy were excluded. Febrile neutropenia was defined as any febrile episode (38.5ºC once or 38ºC twice) occurring during neutropenia (neutrophil count ⩽500/mm3).
Results: During the analysed period 1757 patients (1425 NSCLC and 332 SCLC) received chemotherapy. Febrile neutropenia were developed in 85 patients. Males were 70.6%, females were 29.4%. Overall incidence of FN was 4.8%: in SCLC was higher, than in NSCLC (13% versus 3%). FN mortality was 8%, 7 patients (6 SCLC, 1 NSCLC) died. In fatal cases absolut neutrophil count was <100/ul. Important factors associated with risk of febrile neutropenia included platinum based and taxan contained chemotherapy, 1< comorbidities (COPD, cardiovascular diseases, diabetes mellitus, alcoholism), low baseline haemoglobin level (<11.5 g/dl), previous chemo/radiotherapy and advanced stadium of disease.
Prophyilactic G-CSF was not given in any of the patients in FN groups. Some of our fatal cases belongs not to the known high risk protocols.
Conclusions: Treatment, patient and cancer-related factors resulted in the FN in lung cancer patients. Frequency and mortality of FN in SCLC was significantly higher than in NSCLC. According to the 2010 EORTC guidelines the risk assessment for FN before each cycle of chemotherapy is clinically relevant. Profilactic use of G-CSF has a clinical benefit in high risk patients.

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Pemetrexed (PEM) Plus Platinum-based Regimen as First Line Treatment in Unselected Patients Affected With Non-squamous Non-small-cell Lung Cancer (NSCLC): a Retrospective Multicenter Analysis

L. Moscetti[1], M.A. Fabbri[1], F. Narducci[2], G. Mansueto[2], F. Longo[3], O. Martelli[4], F. Angelini[5], I. Pavese[6], E.M. Ruggeri[7]. [1]*Ospedale Belcolle, Division of Oncology, Viterbo,* [2]*Oncologia Medica, Ospedale SS Trinità, Sora,* [3]*Oncologia Medica A, Experimental Medicine Pol Umberto I, Rome,* [4]*Oncologia Medica, Ospedale San Giovanni Addolorata, Rome,* [5]*Oncologia Medica, Ospedale Reginae Apostolorum, Albano,* [6]*Oncologia Medica, Ospedale San Pietro Fatebenefratelli, Rome,* [7]*Ospedale Belcolle, Division of Oncology, Rome, Italy*

Background: PEM plus platinum-based regimen is considered a standard regimen for first-line treatment in non-squamous NSCLC patients. This retrospective multicenter analysis was performed to evaluate the outcomes in an unselected population treated in various oncologic centers.
Methods: Data were obtained by reviewing the clinical chart of pts, affected with advanced non-squamous NSCLC, treated from 2009 to 2010 with first line PEM and platinum-based regimen. One-hundred-twenty three pts were retrieved. Main patient characteristics were: median age 63 years (range 37−79); one-hundred twenty pts were adenocarcinoma, male/female: 67%/33%; ECOG PS 0−1: 94%; weight loss >5%: 21%; current smoker: 31%. Stage IV disease was present in 81% of pts and 79% of pts had ⩾1 site of metastasis. Brain metastasis were present in 14% of pts.
Results: All 123 pts were evaluable for response. The PEM + Cisplatin combination have been used in 81% of pts while 19% of pts received PEM + Carboplatin. Maintenance treatment with P alone was administered to 21% of pts. Objective responses included partial response (PR) in 44 pts (36%) and stable disease in 36 (29%) for an overall disease control rate of 65%. The 1-yr Overall Survival (OS) and the 1-yr Progression-Free Survival (PFS) were 51.4% and 17.4% respectively. At a median follow up of 6.7 months (range 1−22) the median OS was 13 mo (IC95%: 9−16) and the median PFS was 6 mo (IC: 95% 5−8). No differences were seen in PFS and OS according to the type of response (PR or SD), type of platinum-based regimen, smoking status and maintenance treatment (yes vs not). A significant difference in 1-yr OS (63% vs 21%, $p < 0.0001$) and in 1-yr PFS (28.5 vs 6%, $p = 0.007$) was observed for weight loss <5% vs >5%. In the Cox multivariate analysis, the following factors were significant: sex (M vs F, HR 2.1 IC95% 1.17−3.8, $p = 0.01$); PS (0 vs ⩾1, HR 2.12, IC95% 1.24–3.64, $p = 0.006$); sites of disease (1 vs ⩾2, HR 2.38, IC95% 1.07–5.29, $p = 0.03$); type of response (PR vs no response, HR 3.48, IC95% 1.98–6.14, $p < 0.0001$). Regardless to PEM maintenance treatment a trend in improvement in the 1-yr OS was seen (72% vs 55%, $p = 0.07$) whereas not for 1-yr PFS (29% vs 22%, p = ns). Moreover no differences in outcome were seen for patients achieving a PR or SD after the first line treatment and receiving PEM maintenance or in pts with brain metastases. No unexpected toxicity were observed.
Conclusion: This retrospective analysis compares favourably with the data achieved in the registration study and confirms the activity of the PEM + platinum-based regimen also outside clinical studies.

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A Global Phase 2 Study Including Efficacy, Safety and Patient-reported Outcomes (PROs) With Crizotinib in Patients (Pts) With ALK-positive Non-small Cell Lung Cancer (NSCLC)

D.W. Kim[1], F. Blackhall[2], J.C. Soria[3], B. Solomon[4], D.R. Camidge[5], G.J. Riely[6], A. Bottomley[7], V. Tassell[8], A. Polli[9], A. Shaw[10]. [1]*Seoul National University Hospital, Internal Medicine, Seoul, South Korea;* [2]*Christie Hospital NHS Foundation Trust, Medical Oncology, Manchester, United Kingdom;* [3]*Institut Gustave-Roussy, Medical Oncology, Villejuif, France;* [4]*Peter MacCallum Cancer Centre, Medical Oncology, Melbourne, Australia;* [5]*University of Colorado at Denver, Medical Oncology, Aurora,* [5]*Memorial Sloan-Kettering Cancer Center, Medical Oncology, New York, USA;* [7]*European Organisation for Research and Treatment of Cancer, Quality of Life, Brussels, Belgium;* [8]*Pfizer Oncology, Oncology Business Unit, La Jolla, USA;* [9]*Pfizer Oncology, Statistics, Milan, Italy;* [10]*MGH Cancer Center, Medical Oncology, Boston, USA*

Background: Crizotinib is an ATP-competitive, small molecule ALK inhibitor. We present open-label efficacy, safety and pt-reported outcome (PRO) data from an ongoing multicenter Phase 2 study of crizotinib in pts with advanced *ALK*-positive NSCLC (PROFILE1005, NCT00932451; Pfizer).
Materials and Methods: Pts with *ALK*-rearranged NSCLC (by centralised FISH test) that progressed after ⩾1 chemotherapy regimen for recurrent/advanced/metastatic disease (including treated brain metastases) received oral crizotinib 250 mg BID in continuous 3-week cycles. Disease response was evaluated by RECIST v1.1 every 6 weeks. Adverse events (AEs) and PRO (EORTC QLQ-LC13 v3/QLQ-C30) were assessed every 3 weeks.
Results: On 29 October 2010, 136 pts were evaluable for safety, 109 for PRO and 76 for tumour response. Pts' median age was 52 years, 94% had adenocarcinoma, 68% had never smoked, and 53% were female. Most had ⩾2 prior systemic therapy regimens (93%; range 1−11). Pts received a median 9 weeks' treatment (range 1−13 cycles started) and 88% remain on therapy. Of 76 evaluable pts, most had target lesion shrinkage (63/76 pts [83%]; 41 pts had ⩾30% shrinkage), and seven pts had objective progression. Common treatment-related AEs (nausea [46%], vision disorder [45%], vomiting [39%], and diarrhoea [29%]) were mostly Grade 1/2. Treatment-related Grade 3/4 AEs were reported in 15% of pts (mostly dyspnoea [3%], increased ALT [4%], and neutropaenia [2%]). Two of 9 on-study deaths were considered treatment-related (1 pneumonitis, 1 unknown cause). At cycle 4, most pts (71/136 pts [52%]) had completed 4 PRO assessments; clinically significant (⩾10 point mean change from baseline) improvements in pain, cough, fatigue, insomnia, dyspnoea (by QLQ-C30), and alopecia were reported as early as cycle 2. Of reported increases in constipation, diarrhoea, and nausea/vomiting, only increase in constipation was clinically significant over the course of therapy. Mean quality of life (QoL) did not deteriorate during treatment. Updated data will be presented.
Conclusions: Preliminary Phase 2 data suggest crizotinib in pts with *ALK*-positive advanced NSCLC was safe and well tolerated with antitumour activity and symptom improvement, while QoL was maintained.