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NGR-hTNF, a vascular targeting agent (VTA), in previously treated patients with malignant pleural mesothelioma (MPM): a phase II study

V. Gregorc[1], G.L. Ceresoli[2], P.A. Zucali[2], F.G. De Braud[3], E. Bajetta[4], A. Santoro[2], M.G. Viganò[1], F. Caligaris Cappio[1], A. Lambiase[5], C. Bordignon[5]. [1]*Istituto Scientifico San Raffaele, Department of Oncology, Milan, Italy;* [2]*Istituto Clinico Humanitas, Department of Oncology, Milan, Italy;* [3]*Istituto Europeo di Oncologia, Clinical Pharmacology and New Drugs Unit, Milan, Italy;* [4]*IRCCS Fondazione Istituto Nazionale dei Tumori, Department of Oncology, Milan, Italy;* [5]*MolMed, Clinical Development, Milan, Italy*

Background: NGR-hTNF is a VTA exploiting a tumor-homing peptide (NGR) that selectively binds an aminopeptidase N overexpressed on tumor blood vessels. In preclinical models, NGR-hTNF has shown antitumor activity even at low doses.
Methods: MPM patients (pts) with radiologically-documented progression after a pemetrexed-based chemotherapy were treated with low-dose NGR-hTNF given intravenously as 1-hour infusion at 0.8 μg/m^2 every 3 weeks (q3w; triweekly cohort). The trial had a 2-stage design with 16 and 27 patients to be enrolled. Primary study aim was progression-free survival (PFS) with restaging performed q6w according to MPM-modified RECIST criteria. Subsequently, an additional 14 pts were treated at 0.8 μg/m^2 on a weekly basis (weekly cohort).
Results: In the triweekly cohort, 43 pts were evaluated over 170 cycles (range, 1−18). Patient characteristics were: median age 64 years (range, 54−80); male/female 27/16; epithelial/nonepithelial histology 34/9; PS 0/1/2 24/10/9; EORTC score good/poor 34/9. Only one grade 3 drug-related toxicity was observed. Main grade 1−2 toxicities were short-lived chills (71%), arising during the first infusions. The median and 3-month PFS were 2.8 months (95% CI, 1.9−3.7) and 43% (95% CI, 28−58), respectively. The disease control rate (DCR) was 44%. One patient (2%) had a partial response lasting 10.0 months and 18 patients (42%) maintained stable disease (SD) for a median time of 4.3 months (range, 2.2−13.7 months). With a median follow-up of 19.6 months, the median and 1-year overall survival (OS) were 11.6 months and 48%, respectively. Median OS in pts who achieved DCR and in those who did not were 13.3 and 8.3 months, respectively. In the weekly cohort, 242 infusions were delivered (range, 4 to 45 cycles) and 5 pts (36%) received ⩾30 weekly cycles. There was no toxicity exacerbation. Seven pts (50%) experienced SD for a median time of 8.1 months (range, 2.4−11.4+). The 6- and 12-month PFS rates were 36% and 19%, respectively. In the overall study population (n = 57), the DCR was 46% (95% CI, 34−59), the median duration of DCR was 4.7 months (95% CI, 4.0−5.3), and the median OS was 13.1 months (95% CI, 9.1−17.1).
Conclusion: NGR-hTNF 0.8 μg/m^2 weekly is well tolerated, showing promising disease control in previously treated MPM patients, and will be further developed in this setting.

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Volumetric helical perfusion CT and FDG-PET/CT as prognostic biomarkers in operable non-small cell lung cancer: correlation with clinico-pathological parameters

Q.S. Ng[1], H. Mandeville[2], W.L. Wong[3], J. Chambers[3], M.M. Burke[4], A. Bell[4], E. Townsend[5], M.I. Saunders[2], P.J. Hoskin[2], V. Goh[3]. [1]*National Cancer Centre, Department of Medical Oncology, Singapore, Singapore;* [2]*Mount Vernon Cancer Centre, Marie Curie Research Wing, Northwood, United Kingdom;* [3]*Mount Vernon Hospital, Paul Strickland Scanner Centre, Northwood, United Kingdom;* [4]*Royal Brompton and Harefield Hospitals, Department of Pathology, Middlesex, United Kingdom;* [5]*Royal Brompton and Harefield Hospitals, Department of Thoracic Surgery, Middlesex, United Kingdom*

Background: Elevated tumor angiogenesis may be associated with poor prognosis in lung cancer. The aim was to investigate the role of volumetric helical perfusion CT and FDG-PET/CT as prognostic biomarkers in patients with operable lung cancer.
Patients and Methods: Following IRB approval and informed consent, 20 prospective patients (14 males 6 females, mean age 64 years) with proven non-small cell lung cancer undergoing curative surgery underwent dynamic contrast enhanced CT in addition to standard pre-operative FDG-PET/CT staging. Multiple dynamic helical CT acquisitions comprising an unenhanced and 8 post contrast breath-hold studies (80 kV, 120 mAs, 2 mm collimation) encompassing the entire tumour were performed following intravenous injection of 108 mls 300 iobitridol; 4 ml/s decreasing bolus injection. Following ROI definition, mean tumor permeability surface area product (PS; ml/100 ml/min), blood volume (BV; ml/100 ml) and blood flow (BF; ml/100 ml/min) were derived on a pixel-by-pixel basis. Tumor SUV_{max} and SUV_{mean} were derived from FDG-PET/CT studies. Correlation was assessed by Spearman rank correlation. Mann-Whitney was used to compare group means. ROC analysis was used to correlate perfusion CT parameters to nodal status.
Results: Mean (±SD) values for PS, BV, BF, SUVmean, and SUVmax were 17.5±12.5, 8.1±3.4, 56.4±18.8, 10.4±5.4, and 17.6±10.1 respectively. PS correlated inversely with SUVmax (r = −0.54, p = 0.050). Tumor size correlated inversely with PS (r = −0.73, p = 0.004), but not with SUVmax (r = 0.47, p = 0.09). PS was significantly lower in squamous cell compared to adenocarcinoma (11.3 vs 17.8; p = 0.043); SUVmax (18.0 vs 12.3, p = 0.043) and SUVmean (12.6 vs 7.5, p = 0.039) were significantly higher. Mean BF was significantly lower in stage I versus II/III tumors (42.2 vs 63.5, p = 0.028), and node negative (N0) versus node positive (N1/2) tumors (44.3 vs 65.1, p = 0.048). ROC analysis for predicting node positivity showed significant AUC of 0.86. Using a BF cut-off of 53.4, sensitivity for predicting node positivity was 71.4% and specificity 100%.
Conclusions: Volumetric helical perfusion CT and FDG-PET/CT correlate with clinico-pathological parameters and show potential as prognostic biomarkers in operable lung cancer.

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Phase II results of ABT-869 treatment in patients with non small cell lung cancer (NSCLC)

E. Tan[1], G. Goss[2], R.R. Salgia[3], B. Besse[4], D.R. Gandara[5], N. Hanna[6], J.L. Ricker[7], J. Qian[8], D.M. Carlson[7], R. Soo[9]. [1]*National Cancer Centre, Medical Oncology, Singapore, Singapore;* [2]*The Ottawa Hospital Regional Cancer Centre, Division of Medical Oncology, Ottawa ON, Canada;* [3]*University of Chicago Medical Center, Oncology Research Program, Chicago IL, USA;* [4]*Institut Gustave Rousse, Dept of Medicine, Villejuif, France;* [5]*UC Davis Cancer Center, Clinical Research, Sacramento CA, USA;* [6]*Indiana University Cancer Center, School of Medicine, Indianapolis IN, USA;* [7]*Abbott Laboratories, Oncology, Abbott Park IL, USA;* [8]*Abbott Laboratories, Global Statistics & Data Management, Abbott Park IL, USA;* [9]*National University Hospital, Dept. of Haematology-Oncology, Singapore, Singapore*

Background: ABT-869, a novel orally active, potent and specific inhibitor of VEGF and PDGF receptor tyrosine kinases, showed single-agent activity in early-phase clinical trials, in a variety of advanced solid-tumor patients (pts) including those with NSCLC.
Materials and Methods: This open-label, multicenter trial assessed antitumor activity and toxicity of ABT-869. Pts, randomized 1:1 to 0.10 mg/kg (Arm A) or 0.25 mg/kg (Arm B), self-administered the daily dose until progressive disease (PD) or intolerable toxicity. Eligibility criteria included locally advanced or metastatic NSCLC; 1 or 2 prior systemic treatment, and ⩾1 measurable lesion (RECIST). Primary endpoint was progression free (PF) rate at 16 wks. Secondary endpoints were objective response rate (ORR), time to progression (TTP), progression free survival (PFS), overall survival (OS). All efficacy results are based on radiographic assessment by the central imaging center (except as noted) and clinical assessment by the investigator. Trial abbreviation: *ABT-869 in subjects with NSCLC*. Trial registry: NCT00716534. Trial status: ongoing; recruiting; sponsored by Abbott Laboratories. ABT-869 is being developed in collaboration with Genentech.
Results: Of 139 pts enrolled from 08/07−10/08, all received prior systemic therapy; 83 (60%) had ⩾2 prior regimens; 17 (12%) had squamous cell carcinoma at screening. Median age was 62y.

Efficacy Results	Arm A n = 65 [95% CI]	Arm B n = 74 [95% CI]
PF rate at 16 wks, %	32.3 [21.2, 45.1]	36.5 [25.6, 48.5]
ORR, %	0	2.7 [0, 9.4]
ORR, % per site	4.6 [1.0, 12.9]	10.8 [4.8, 20.2]
TTP*, m	3.6 [2.1, 4.3]	3.7 [3.1, 5.3]
PFS*, m	3.5 [2.0, 4.3]	3.7 [3.1, 4.9]
OS*, m	10.7 [6.9, –]	8.6 [5.6, 12.8]

ORR per RECIST; − not reached; *Median

The most common AEs were fatigue (45%), hypertension (HT) (37%), anorexia (35%), diarrhea (35%), nausea (33%); rates for HT, diarrhea, proteinuria and hand-foot syndrome were significantly lower in Arm A. The most common AE ⩾Grade 3 (NCI toxicity criteria) was HT (13%). 57% of pts (34% Arm A, 77% Arm B, p < 0.001) had dose interruptions due to AEs and 25% required dose reductions (6% Arm A, 41% Arm B, p < 0.001). The most common reasons for dose interruption included HT (14%), hand-foot syndrome (9%), and proteinuria (7%), which were reversible. 20 pts (10 Arm A, 10 Arm B) remained on study at the time of analysis. 95 pts had