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A phase I study of axitinib (AG-013736) combined with paclitaxel/carboplatin (P/C), gemcitabine/cisplatin (Gem/Cis) or pemetrexed/cisplatin (Pem/Cis) in patients (pts) with solid tumours, including advanced non-small cell lung cancer (NSCLC)

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Background: Axitinib is a potent and selective inhibitor of VEGFRs 1, 2, and 3. In pts with advanced solid tumours, anti-VEGF therapy + chemotherapy (CT) improves survival vs. CT. We evaluated safety and tolerability of axitinib + CT regimens used to treat NSCLC (NCT00454649; sponsor: Pfizer Oncology).
Material and Methods: Pts without prior platinum or taxane treatment received P (200 mg/m^2)/C (AUC 6 mg$\times$min/mL) every 3 weeks (q3w) + axitinib at lead-in doses of 1, 3, or 5 mg BID increasing to 5 mg BID after 3–5 days (d). Pts exposed to any prior CT received axitinib 5 mg BID + either Gem (1,250 mg/m^2 on d1 + d8)/Cis (80 mg/m^2 on d1) or Pem (500 mg/m^2 on d1)/Cis (75 mg/m^2 on d1) q3w. Pts receiving Pem/Cis were given vitamin B_{12} and folic acid per standard of care. After determination of dose-limiting toxicities (DLTs) with axitinib + P/C, 15 pts with squamous cell (sq) NSCLC were enrolled into an expansion cohort (prior anti-VEGF therapy excluded) and received axitinib 5 mg BID + P/C. DLTs, adverse events (AEs), objective response rate (ORR) and pharmacokinetics (PK) were evaluated.
Results: 55 pts enrolled; all were evaluable for safety: axitinib + P/C (n = 28), axitinib + Gem/Cis (n = 21) and axitinib + Pem/Cis (n = 6). DLTs in the initial six pts of each cohort comprised fatigue (n = 2) and proteinuria (n = 1). Treatment-related AEs included hypertension (39%), diarrhoea (36%) and fatigue (36%) for axitinib + P/C; nausea (33%), headache (29%) and hypertension (29%) for axitinib + Gem/Cis; hypertension (33%), transaminase elevation (33%) and venous thrombosis (17%) for axitinib + Pem/Cis. No grade $\geqslant$3 haemoptysis occurred in 15 pts with sq NSCLC. ORR was 41%, 26% and 0% for axitinib + P/C (n = 27), Gem/Cis (n = 19) and Pem/Cis (n = 5), respectively. Mean [%CV] exposure (AUC_{inf}, μg·h/mL) was similar +/− axitinib for P (20.8 [21] vs. 20.6 [21]; n = 11)/C (45.7 [26] vs. 40.5 [30]; n = 12), Gem (12.4 [32] vs. 12.7 [32]; n = 17)/Cis (3.6 [24] vs. 3.5 [27]; n = 13) and Pem (159 [16] vs. 138 [27], n = 4)/Cis (3.0 [39] vs. 3.4 [35]; n = 4), respectively.
Conclusion: Axitinib 5 mg BID can be combined with standard P/C, Gem/Cis or Pem/Cis with acceptable tolerability, no apparent overlapping toxicities and unaltered PK. Axitinib + P/C was well tolerated in pts with sq NSCLC with no grade $\geqslant$3 haemoptysis. Axitinib + P/C or Gem/Cis has antitumour activity. Phase II studies of axitinib + CT in pts with NSCLC are ongoing.

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Impact of age on the outcome of cancer patients treated in phase I trials between 2005 and 2008

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Background: Phase I trials enrolls higly selected patents. Elderly or very young patients are frequently underrepresented in these studies. We evaluated the outcome and the propensity to present severe toxicities in a population of patients included in phase I trials according to the age.
Materials and Methods: We reviewed 400 consecutive cancer patients treated in the phase I unit of Institut Gustave Roussy, from 2005 to 2008. The cohort was stratified into three groups according to the age: (i) Young group: <35 years; (ii) Intermediate: $\geqslant$35 and $\leqslant$65 years; (iii) Elderly: >65 years. Univariate analyses were conducted to identify the impact of the age on OS, PFS, 90-day-mortality rate and the occurrence of severe toxicity.
Results: The distribution of the population according to the age identified 25 patients (6.3%) in the young group; 297 patients (74.3%) in the intermediate group and 78 pts (19.5%) in the elderly group. Among the entire cohort, median OS and PFS were respectively 358 days [IC95% = 303; 412] and 85 days [IC95% = 71; 98]. 64 patients (16%) died within the 90 days after inclusion. 88 patients (22%) presented severe toxicities.
Median OS of young, intermediate and elderly groups were respectively: 355 days [IC95%= 266; 443]; 373 days [IC95% = 274; 471] and 314 days [IC95% = 218; 409]. There was no significant difference between the different groups in term of OS (p = 0.078). Respectively 4 out 25 patients (16%) from the young group; 47 out of 297 patients (15.8%) from the intermediate group and 13 pts out of 78 patients (16.7%) from the elderly group died within the 90 days. There was no significant association between the age group and the 90 days mortality rate (Fisher exact test = 0.970).
Median PFS of young, intermediate and elderly groups were respectively: 126 days [IC95% = 61; 191]; 85 days [IC95% = 69; 101] and 85 days [IC95% = 39; 101]. There was no significant difference between the different groups in term of PFS (p = 0.442).
There was no significant association between the occurrence of severe toxicity and the belonging to a particular age group (Fisher exact test = 0.291).
Conclusion: Patients below 35 years or above 65 years represent about 25% of phase I patients in our center. These “extreme age” populations do not differ from the 35−65 years old group in term of outcome (OS, PFS, 90 days mortality rate) neither in the risk of developing severe toxicities. Investigators should not discriminate patients to be included in phase I trials on the basis of the age factor alone.

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A phase I dose escalation study with sorafenib (Sor) in combination with sirolimus (Sir) in patients (pts) with solid tumors

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Background: Combining Sor, a Raf kinase/VEGFR2 inhibitor with mammalian target of rapamycin (mTOR) inhibitor Sir may have synergistic activity. We therefore studied the feasibility and pharmacokinetics (PK) of the combination of Sor and Sir in a phase I study. The primary objective was to identify the maximum tolerated dose (MTD) of the combination of Sor and Sir. Secondary endpoints were to determine the safety profile, pharmacokinetic (PK) profile and efficacy.
Materials and Methods: Pts $\geqslant$18 years with advanced solid tumors, ECOG status 0−1, normal liver, kidney and bone marrow function and not previously treated with Sor or Sir were enrolled to determine the MTD of the combination. Sor bid and Sir oid were administered with a run in period for optimal PK analysis (single doses Sir on day 1 and 16, continuous dosing (CD) Sir as of day 21, Sor CD as of day 5). PK sampling was performed on cycle 1 day 1−5, day 15−20 and cycle 2, day 1 and 15. The DLT period was the first 50 days (3 wks CD of the combination).
Results: 20 pts were included; mean age 52 years, 8 sarcoma, 3 CRC, 2 melanoma, 2 lung cancer, 2 hepatocellular carcinomas, 3 others. On DL 1, sor 200 mg bid and sir 2 mg oid, 3 DLTs in 3 out of 5 pts were observed: gr 3 elevated transaminases (in all 3 pts), gr 3 fatigue (1 pt) and gr 3 weight loss (1 pt). At DL 0, sor 200 mg bid and sir 1 mg oid, 1 DLT in 6 pts occurred (cardiac ischemia). We amended the protocol to have an intermediate DL with sor 400 mg bid and sir 1 mg. Three out of 4 pts experienced a DLT (gr 3 hand-foot syndrome (HFS) in all 3 pts), gr 3 fatigue (1 pt), rash (in 2 pts). The most frequent reported AEs were (CTC gr 1/2/3/all %): elevated transaminases (42/32/16/89%), fatigue (16/42/21/79%), anorexia (37/21/11/68%), diarrhea (32/26/5/64%), nausea (37/26/0/63%), rash (21/10/10/41%) and HFS (18/6/16/40%). Sir did not change the Sor PK. Unexpectedly, Sor induced a decrease of $AUC_{(0-96)}$ (37%) and of C_{max} (55%) of Sir following the combination of Sor 200 mg bid and Sir 2 mg oid, while mean $t_{1/2}$ of Sir were unchanged. After Sor 200 mg bid and Sir 1 mg oid, $AUC_{(0-96)}$ of Sir was not altered and C_{max} of Sir decreased by only 18%. No objective responses were observed; 7 pts showed SD (8−24 wks).
Conclusions: The MTD of the combination of Sor and Sir is Sor 200 mg bid and Sir 1 mg oid. Combination of Sor with Sir showed enhanced hepatic and dermatological toxicity, which could not be explained by the PK of both drugs. The relative low doses at the MTD in combination with the PK results does not warrant further development of this combination in phase II study.

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Prognosis of patients enrolled in phase I clinical trials admitted in intensive care unit

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Background: Phase I clinical trials usually include patients for whom standard therapies have failed. These patients are expected to be at higher risk for treatment-related morbidities eventually requiring admission to intensive care unit (ICU). Admission of these patients in ICU remains controversial because there are thought to have poor survival. To date,

there is no clear data regarding the frequency and outcome of patients admitted in ICU while included in phase I clinical trials.
Methods: We conducted a retrospective study evaluating all patients admitted in ICU among the 270 consecutive patients enrolled in phase I clinical trials at Institut Gustave Roussy over a 2-year period. We assessed the characteristics and outcome of the patients admitted in ICU. The study endpoints were frequency of ICU admission and 2-month mortality rate.
Results: A total of 270 patients were enrolled in phase I clinical trial between January 2007 and January 2009. Only 11 patients required ICU admission (4.0%). Median age was 54 (48−70) and 5 (45%) were male. The most common cancer was non-small cell lung cancer (n = 5; 45%). Admission occurred within the first month following inclusion for 54% of patients (median = 26 days). The most common reason for ICU transfer was respiratory failure (6/11; 54%). The majority of patients required ventilation support (6/11; 54%) and 4 patients (36%) required vasopressors drugs. The ICU transfer was due to toxicity in 5 patients (45%). The majority of patients had progressive-disease (6/11; 54%) at the time of transfer to ICU. In-ICU mortality was 45%. The 2-month mortality rate was 54%.
Conclusion: ICU admission is rare in patients enrolled in phase I clinical trial. Around 50% of patients admitted in ICU are alive 2 months after discharge. Drug-related toxicity is the reason of admission for 45% of patients. Hence, early collaboration with ICU physicians is mandatory in this setting and ICU admission should be favourably considered for patients enrolled in phase I clinical trial.

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A phase-I study of the combination of intravenous reovirus (REOLYSIN ®) and gemcitabine in patients with advanced cancer

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Background: Reovirus serotype 3 (REO) is a Dearing strain, non-enveloped virus with limited pathogenicity in humans. REO is an oncolytic virus that specifically targets cells with activated Ras signalling and gemcitabine (GEM) has shown efficacy in a wide range of tumors commonly driven by activated Ras signalling. Moreover, multiple pre-clinical experiments suggest that REO is able to synergize with GEM.
Materials and Methods: This open-label, dose-escalating phase-I trial studied the combination of intravenous (iv) REO, starting at 3×10^9 $TCID_{50}$ d1−5 and iv GEM, 1000 mg/m^2 d1 and 8 in a 3 week cycle. We planned to dose escalate Reo. Primary endpoints were: the maximum tolerated dose (MTD), dose limiting toxicity (DLT), safety profile of REO/GEM and to establish a recommended phase 2 dose (RP2D). Secondary endpoints were: evaluation of the immune response, evaluation of pharmacokinetic profiles of both REO and GEM and to describe any anti-tumor activity.
Results: Since July 2007, 16 heavily pre-treated patients entered this trial. The first 2 patients on study both had a DLT (patient 1: transaminase increase; patient 2: Troponin-I increase) probably related to both drugs. The protocol was amended and the dose of REO was adjusted to 1×10^9 $TCID_{50}$, d1 of each cycle and increased in subsequent cohorts to 3×10^9, 1×10^{10}, and 3×10^{10} $TCID_{50}$, d1. In total 47 cycles were administered resulting in multiple expected toxicities including fever, headaches, rhinorrhea, fatigue and myelosupression. In the cohort with 3×10^{10} $TCID_{50}$ we observed 1 DLT in a 3 patient cohort, being a transient grade 3 transaminase rise probably related to REO. Of the 11 pts evaluable for response, 2 pts (breast and nasopharyngeal) had PR and/or clinical response and 5 pts had SD for up to 4−8 cycles, amounting for a total disease control rate (CR+PR+SD) of 64%. Interestingly, the pharmacodynamic parameters showed significant abrogation of the neutralising anti-reoviral antibody (NARA) response (<50-fold increase) when compared to our previous experience with single agent intravenous REO.
Conclusion: REO and GEM could not be combined at full dose but after dose reduction of the REO the combination is well-tolerated and results in disease control for 64% of patients. We did not establish an MTD but REO 1×10^{10} $TCID_{50}$ d1 combined with GEM would be acceptable as RP2D.

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Assessment of pharmacodynamic effect in a Phase I study of NPI-2358, an IV administered vascular disruptive agent, using dynamic contrast-enhanced MRI

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Background: NPI-2358 is a vascular disrupting agent that inhibits tubulin polymerization, leading to endothelial cell swelling, increased vascular permeability, and disruption of blood flow. It was an aim of this study to measure this effect in humans using dynamic contrast-enhanced MRI (DCE-MRI), and to determine whether NPI-2358 shows a dose-dependent treatment effect.
Materials and Methods: DCE-MRI data were acquired at two time points (baseline and 4 hours post-dose) for 17 patients with advanced solid tumors enrolled in clinical trial NPI-2358–100 (Nereus Pharmaceuticals) using a standardized protocol at three imaging sites. Imaged subjects were arranged into 8 cohorts, with doses ranging from 2 mg/m^2 to 30 mg/m^2. A 12 slice, 10 cm slab was imaged, with spatial resolution of 2 mm in-plane and 8 mm between images. Images were acquired in the coronal plane, with TE/TR/FA of 1.3/5.3/30 and temporal resolution of approximately 8 s per slab. K^{trans} and AUCBN(90), both of which are dependent on blood flow and vascular permeability, were measured at each pixel within each target tumor, and mean and median values were reported for each parameter.
Results: Objective vascular response (reduction >20%, based on previously measured uncertainty of $\pm$10%) was seen in 0/3 patients dosed at 6 mg/m^2 and 9 mg/m^2, in 2/5 patients dosed at 13.5 mg/m^2 and 20 mg/m^2, and in 7/9 patients dosed at 30 mg/m^2. At the highest dose level a statistically significant reduction was seen in both K^{trans} (μ = −18.4%, 95% CI = −27% to −9.6%, p = 0.006) and AUCBN(90) (μ = −17.7%, 95% CI = −24% to −11%, p = 0.001). The largest decrease in K^{trans} was 82%. CT contrast enhancement disappeared in this lesion and the patient has remained with stable disease for 15 months and continuing. No reduction was seen in the lower dose cohorts in either K^{trans} (μ = 11.2%, 95% CI = −12% to 34%, p = 0.472) or AUCBN(90) (μ = 0.38%, 95% CI = −12% to 13%, p = 0.964).
Conclusions: NPI-2358 does have a measurable effect on tumor microvasculature at the 30 mg/m^2 dose, inducing a reduction in blood flow that is reflected in reductions in both K^{trans} and AUCBN(90). This effect is dose dependent, as increasing levels of reduction are seen at higher doses. It is interesting to note that the results of this study are very similar to the previously published results for other VDAs. This consistency lends additional credibility to these results, partially offsetting the fact that they are based on a small number of patients.

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Is it ethical to enrol patients with advanced solid tumor in first line therapy in Phase 1 trials?

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Background: The oncology community usually perceives phase I oncology trials as associated with poor or limited benefits and substantial risks. There is limited data concerning outcome and survival of patients treated in first line therapy within phase I trials.
Patients and Methods: We reviewed all medical charts of patients with advanced solid tumors treated in fisrt line treatment within a phase 1 trial at Institut Gustave Roussy between January 2007 and January 2008.
Results: Between January 2007 and January 2008, 58 out of 250 were enrolled in first line therapy phase I trial in organ oriented phase 1 (4) or not (2). Median age was 54 years (33−73), with 35 men and 23 women. The histological cancer types were NSCLC (35 pts), breast cancer (5 pts), SCLC (5 pts), and others (pancreas, oesophagus, thyroid, cervical cancers). Patients received a median number cycles of 6 (1−23), with investigational agents (antiangiogenic therapies: 4; apoptotic induceres: 1; mTOR inhibitor: 2) in combination in standard first line chemotherapy. Partial response was observes in 19 pts and stable disease in 38 patients. Eight patients were enrolled in a further phase 1 after progression. The median PF was 5 months. According to cancer subtype, the mPFS and OS were very similar that those reported in large phase III trials.
Conclusion: This study shows that pts with advanced solid tumor treated in first line therapy enrolled in phase I trials could benefit from such trials. The PFS observed in this cohort of pts is very similar to the one reported in first line regimens.