1231 POSTER

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)

M.F. Kozloff[1], L.P. Martin[2], M. Krzakowski[3], T.A. Samuel[4], J. Tarazi[5], B. Rosbrook[5], M. Tortorici[5], A.J. Olszanski[6], R.B. Cohen[2]. [1]*Ingalls Hospital, Department of Medicine, Harvey, USA;* [2]*Fox Chase Cancer Center, Department of Medical Oncology, Philadelphia, USA;* [3]*Institute of Oncology, Department of Lung and Thoracic Tumours, Warsaw, Poland;* [4]*Medical College of Georgia, MCG Cancer Center, Augusta, USA;* [5]*Pfizer Oncology, Development, San Diego, USA;* [6]*Pfizer Oncology, Development, New London, USA*

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.

1232 POSTER

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

C. Ferte[1], C. Gomez Roca[1], Y. Loriot[1], R. Bahleda[1], C. Moldovan[1], C. Massard[1], J.C. Soria[1]. [1]*Gustave Roussy, Sitep (Phase I Unit) Medecine Departement, Villejuif, France*

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.

1233 POSTER

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

C. van Herpen[1], I.M.E. Desar[1], R. Verijdt[1], W.T.A. van der Graaf[1], J.N.H. Timmer-Bonte[1]. [1]*Radboud University Nijmegen Medical Centre, Medical Oncology, Nijmegen, The Netherlands*

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.

1234 POSTER

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

Y. Loriot[1], C. Massard[1], C. Moldovan[1], C. Ferte[1], C. Gomez-Roca[1], R. Bahleda[1], J.C. Soria[1], F. Blot[2]. [1]*Institut Gustave Roussy, SITEP (Service des Innovations Thérapeutiques Précoces) Department of Medicine, Villejuif, France;* [2]*Institut Gustave Roussy, Intensive Care Unit, Villejuif, France*

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,