**6515** POSTER DISCUSSION

**Continuous sunitinib treatment in patients with unresectable hepatocellular carcinoma (HCC): A multicenter phase II trial (SAKK 77/06 and SASL 23)**

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**Background:** Sunitinib (SU) is a multitargeted tyrosine kinase inhibitor with antitumor and antiangiogenetic activity. Evidence for clinical activity in HCC was reported in 2 phase II trials [Zhu et al and Faivre et al, ASCO 2007] using either a 37.5 or a 50 mg daily dose in a 4 weeks on, 2 weeks off regimen. The objective of this trial was to demonstrate antitumor activity of continuous SU treatment in patients (pts) with HCC.
**Methods:** Key eligibility criteria included unresectable or metastatic HCC, no prior systemic anticancer treatment, measurable disease and Child-Pugh A or B liver dysfunction. Pts received 37.5 mg SU daily until progression or unacceptable toxicity. The primary endpoint was progression free survival at 12 weeks (PFS12) defined as 'success' if the patient was alive and without tumor progression assessed by 12 weeks ($\pm$7 days) after registration. A PFS12 of $\leqslant$20% was considered uninteresting and promising if $\geqslant$40%. Using the Simon-two minimax stage design with 90% power and 5% significance the sample size was 45 pts. Secondary endpoints included safety assessments, measurement of serum cobalamin levels and tumor density.
**Results:** From September 2007 to August 2008 45 pts, mostly male (87%), were enrolled in 10 centers. Median age was 63 years, 89% had Child-Pugh A and 47% had distant metastases. Median largest lesion diameter was 84 mm (range: 18–280) and 18% had prior TACE. Reasons for stopping therapy were: PD 60%, symptomatic deterioration 16%, toxicity 11%, death 2% (due to tumor), and other reasons 4%; 7% remain on therapy. PFS12 was rated as success in 15 pts (33%) (95% CI: 20%, 49%) and failure in 27 (60%); 3 were not evaluable (due to refusal). Over the whole trial period 1 CR and 40% SD as best response were achieved. Median PFS, duration of disease stabilization, TTP and OS were 2.8, 3.2, 2.8 and 9.3 months, respectively. Grade 3 and 4 adverse events were infrequent and all deaths due to the tumor.
**Conclusions:** Continuous SU treatment with 37.5 mg/d daily is feasible and demonstrates moderate activity in pts with advanced HCC and mild to moderately impaired liver dysfunction. Under this trial design the therapy is considered promising (>13 PFS12 successes).

**6516** POSTER DISCUSSION

**A scoring system in predicting the risk of hepatocellular carcinoma in chronic hepatitis B carrier**

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**Background:** The risk of hepatocellular carcinoma (HCC) is variable among hepatitis B viral (HBV) carriers. Universal surveillance is costly thus it is important to identify the high risk population. We have reported a prospective intensive surveillance study in 1018 HBV carriers (Mok TS et al. J Clin. Oncol. 05). The aim of current study is to develop a scoring system from this prospective cohort that predicts the risk of HCC according to simple clinical parameters.
**Materials and Methods:** HBV carriers were recruited at the Prince of Wales Hospital between Oct 1997 and Nov 2000. We updated the database in Dec 2008 and performed univariate and multivariate analyses on clinical factors (gender, age, ascites, cirrhosis, albumin, bilirubin, ALT, AFP, HBV DNA, antiviral treatment). A scoring system is developed according to the top independent predictive factors. Scoring system is validated in a separate non-overlapping prospective cohort (Chan HL et al. Hepatology 00).
**Results:** Data of 1005 HBV carriers was updated in Dec 2008 (13 excluded because HBV DNA results were unavailable). After median follow-up of 9.95 years, we confirmed diagnosis of 105 HCC by histology. By multivariate analysis, 5 variables including age >50 years, albumin $\leqslant$35 g/l, bilirubin >18 $\mu$mol/l, high HBV DNA ($\leqslant$4, 4−6, >6 log) and sonographic evidence of cirrhosis were independently predictive of HCC. We developed the scoring from these factors (Table 1) by applying an integral weight to each factor. The rate of HCC development for low risk (CU score <0.0001). The validation works in separate prospective cohort are ongoing and will be available at the meeting.
**Conclusions:** We have successfully stratified the risk of HCC among HBV carriers by a simple scoring system. Surveillance may not be indicated for the low risk population while more intensive surveillance is warranted for the high risk group.

Table 1

| Variable | Score |
|---|---|
| Albumin (g/l) | |
| $\leqslant$35 | 20 |
| >35 | 0 |
| Cirrhosis | |
| Yes | 15 |
| No | 0 |
| Log HBV DNA | |
| $\leqslant$4 | 0 |
| 4−6 | 1 |
| >6 | 4 |
| Age (year) | |
| >50 | 3 |
| $\leqslant$50 | 0 |
| Bilirubin ($\mu$mol/l) | |
| >18 | 1 |
| $\leqslant$18 | 0 |
| **CU Score (Total score)** | |
| Low risk | <4 |
| Intermediate risk | 4−<20 |
| High risk | $\geqslant$20 |

**6517** POSTER DISCUSSION

**International phase 2 trial of ABT-869 in patients with advanced hepatocellular carcinoma (HCC)**

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**Background:** ABT-869 is a novel orally active, potent and selective inhibitor of the VEGF and PDGF platelet derived growth factor families of receptor tyrosine kinases, designed to inhibit angiogenesis, tumor growth, and metastasis.
**Material and Methods:** This was an open-label, multicenter trial of oral ABT-869 at 0.25 mg/kg QD in Child-Pugh A (C-PA) or QOD in Child-Pugh B (C-PB) patients (pts) until progressive disease (PD) or intolerable toxicity. Key eligibility criteria included unresectable or metastatic HCC; up to one prior line of systemic treatment; and at least one measurable lesion by computed tomography (CT) scan. Primary endpoint was the progression free (PF) rate at 16 weeks. Secondary endpoints included objective response rate (ORR), time to progression (TTP), progression free survival (PFS) and overall survival (OS). All efficacy results are based on radiographic assessment by the central imaging center and clinical assessment by the investigator. Trial abbreviation: *Phase 2 trial of ABT-869 in HCC*. Trial registry number: NCT00517920. Trial status: ongoing; not recruiting; sponsored by Abbott Laboratories. ABT-869 is being developed in collaboration with Genentech.
**Results:** Of the 44 pts enrolled from 09/07 to 08/08, 84% received no prior systemic therapy. Median age was 62 y (range 20−81). The most common AEs were fatigue (57%), diarrhea (43%), hypertension (HT) and rash (39% each), and oedema peripheral (25%). The most common AEs $\geqslant$Grade 3 were HT (16%) and fatigue (14%). 61% of pts had dose interruptions due to AEs and 30% of pts required dose reductions. The most common reasons for dose interruption included HT (16%), proteinuria (9%), and skin reaction

(9%), which were reversible. 10 pts (all CP-A) remained on study at the time of the analysis. 21 pts had discontinued due to PD (clinical, radiographic or AE related to PD), 9 due to AEs not related to PD, and 4 for other reasons. There was one death possibly related to ABT-869 (intracranial hemorrhage, Day 111, CP-B).

| | Point estimate [95% CI] | | |
|---|---|---|---|
| | CP-A N = 38 | CP-B N = 6 | All N = 44 |
| PF rate at 16 weeks, % | 34.2 [19.6, 51.4] | 16.7 [0.4, 64.1] | 31.8 [18.6, 47.6] |
| ORR, % | 7.9 [1.7, 21.4] | 0 | 6.8 [1.4, 18.7] |
| Estimated median TTP, mo | 5.4 [3.6, 14.1] | 3.7 [0.7, NR] | 3.7 [3.6, 7.3] |
| Estimated median PFS, mo | 5.4 [3.6, 14.1] | 1.3 [0.7, 3.7] | 3.7 [2.0, 5.5] |
| Estimated median OS, mo | 9.7 [8.7, NR] | 2.5 [1.1, 4.5] | 9.3 [6.0, 11.0] |

ORR per RECIST; NR = not reached.

**Conclusions** ABT-869 is clinically active in advanced HCC, with an acceptable safety profile. Further study of ABT-869 in this setting is warranted.

**6518** POSTER DISCUSSION

**Evaluation of vandetanib in patients with inoperable hepatocellular carcinoma (HCC): a randomized, double-blind, parallel group, multicentre, Phase II study**

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**Background:** Vandetanib is a once-daily oral anticancer agent that targets VEGFR, EGFR and RET signalling. The efficacy and safety of vandetanib was investigated in Taiwanese patients with inoperable HCC (study codes D4200C00072; NCT00508001).
**Materials and Methods:** Eligible patients with Child–Pugh class A, inoperable HCC were randomized 1:1:1 to receive vandetanib 300 mg/day + best supportive care (BSC), vandetanib 100 mg/day + BSC or placebo + BSC until disease progression. Patients receiving vandetanib 100 mg or placebo were eligible to receive open-label vandetanib 300 mg after progression. The primary objective was to evaluate tumour stabilization rate (complete response + partial response + stable disease $\geqslant$4 months). Secondary assessments included progression-free survival (PFS), overall survival (OS) and safety.
**Results:** Between July 07–Nov 08, 67 patients (55 male/12 female; mean age, 58 years) were randomized to vandetanib 300 mg (n = 19), vandetanib 100 mg (n = 25) or placebo (n = 23). At data cut-off, 59 patients had progressed, 40 had died and 28 had entered treatment with vandetanib 300 mg after progression. In both vandetanib arms, the primary endpoint of tumour stabilization rate was not significantly different from placebo; however, vandetanib treatment showed positive trends for PFS and OS, including significant prolongation of OS versus placebo in patients randomized to vandetanib 100 mg (see Table).

Table. Efficacy summary (intent-to-treat population)

| | Vandetanib | | Placebo |
|---|---|---|---|
| Efficacy assessment | 300 mg N = 19 | 100 mg N = 25 | N = 23 |
| Tumour stabilization rate | 5.3% | 8.0% | 4.3% |
| Odds ratio vs placebo | 1.22 | 1.98 | – |
| *P* value | 1.00 | 1.00 | – |
| Median PFS (weeks) | 7.0 | 7.1 | 4.0 |
| PFS hazard ratio vs placebo | 0.557 | 0.643 | – |
| *P* value | 0.0898 | 0.158 | – |
| Median OS (months) | 6.0 | 5.6 | 3.9 |
| OS hazard ratio vs placebo | 0.481 | 0.447 | – |
| *P* value | 0.077 | 0.037 | – |

Treatment was generally well tolerated, with a median duration of 5.6 weeks (vandetanib 300 mg), 6.1 weeks (vandetanib 100 mg) and 4.3 weeks (placebo). The most common adverse events were diarrhoea and rash, which occurred more frequently in the vandetanib 300 mg arm (42% and 47%, respectively) compared with vandetanib 100 mg (28% and 20%) or placebo (30% and 26%). Four adverse events led to treatment discontinuation: hepatic failure (vandetanib 300 mg), and diarrhoea, hyperbilirubinaemia and upper gastrointestinal haemorrhage (all placebo).
**Conclusions:** In this small study of Taiwanese patients with advanced inoperable HCC, the primary endpoint of improved tumour stabilization rate was not met with vandetanib (100 or 300 mg) versus placebo. However, the PFS and OS results suggest vandetanib has clinical activity in this patient population that may warrant further investigation. The safety profile was consistent with previous studies of vandetanib in patients with advanced cancer.

**6519** POSTER DISCUSSION

**Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma (HCC): collective results from the phase III sorafenib HCC assessment randomized protocol (SHARP) and Asia-Pacific (AP) trials**

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**Background:** The frequency of viral etiologies of hepatocellular carcinoma (HCC) varies between geographic populations. The hepatitis virus B predominates in many Asian populations, while hepatitis virus C underlies most HCCs in Western countries. Whether these different etiologies result in tumors that respond differently to treatment is unknown. Here, we compared results of the SHARP and AP trials to evaluate the effectiveness of sorafenib in patients worldwide with advanced HCC. SHARP enrolled patients from Europe, North/South America, and Australia; the AP trial enrolled patients from the AP region.
**Methods:** Eligibility criteria were similar for the two trials. Patients had advanced HCC, Child-Pugh A, ECOG PS 0−2, and no prior systemic therapy for HCC. Patients were randomized to sorafenib 400 mg BID or placebo, at a 1:1 (SHARP) or 2:1 (AP) ratio. Endpoints included overall survival (OS), time to progression (TTP), and safety.
**Results:** Efficacy and safety results are summarized in the table below. AP patients had more advanced disease (eg, more extrahepatic spread, poorer ECOG PS) than SHARP patients at baseline. OS and TTP hazard ratios were similar between SHARP/AP studies, despite more advanced disease in AP patients. The incidence of grade 3/4 adverse events (AEs) was similar in all sorafenib populations and included hand-foot skin reaction (HFSR), diarrhea, fatigue, and hypertension. When comparing all grades of AEs, HFSR was more common in the AP population and diarrhea in the SHARP trial. The treatment discontinuation rates were similar in both trials.
**Conclusions:** Sorafenib was effective and safe for the treatment of advanced HCC regardless of etiology, despite a more evolved HCC stage in Asia.

| | SHARP Study | | AP Study | |
|---|---|---|---|---|
| Endpoint | Sorafenib/Placebo median (months) (N = 299)/(N = 303) | Hazard Ratio (95% CI) | Sorafenib/Placebo median (months) (N = 150)/(N = 76) | Hazard Ratio (95% CI) |
| Overall survival | 10.7/7.9 | 0.69 (0.55−0.87) | 6.5/4.2 | 0.68 (0.50−0.93) |
| Time to progression | 5.5/2.8 | 0.58 (0.45−0.74) | 2.8/1.4 | 0.57 (0.42−0.79) |

Incidence of drug-related AEs in Sorafenib and Placebo groups

| Drug-related AE | Incidence, Sorafenib/Placebo (%) | | | |
|---|---|---|---|---|
| | SHARP Study | | AP Study | |
| | All Grades (N = 297)/(N = 302) | Grade 3/4 (N = 297)/(N = 302) | All Grades (N = 149)/(N = 75) | Grade 3/4 (N = 149)/(N = 75) |
| HFSR | 21/3 | 8/<1 | 45/3 | 11/0 |
| Diarrhea | 39/11 | 8/2 | 26/5 | 6/0 |
| Fatigue | 22/16 | 4/4 | 20/8 | 3/1 |
| Hypertension | 5/2 | 2/1 | 19/1 | 2/0 |