significant in all subgroups, with the exception of the CK sub-population (the larger sample).
Conclusions: Although the overall negative impact of adjuvant treatment upon the natural history of RCC, the significant 'qualitative' interaction between VAX and CK suggests an underlying differential effect, which requires deeper investigations.

7165 POSTER

Sunitinib (SU) Pharmacokinetic (PK)–Pharmacodynamic (PD) Modeling With Respect to Safety and Efficacy Endpoints in Asian Patients With Gastrointestinal Stromal Tumour (GIST) or Renal Cell Carcinoma (RCC) in Pursuit of a Therapeutic Window

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Background: SU (SUTENT®) is an oral multitargeted tyrosine kinase inhibitor, approved multinationally for the treatment of advanced RCC, imatinib-resistant or -intolerant GIST, and well-differentiated pancreatic neuroendocrine tumour. We explored SU PK–PD relationships with respect to safety and efficacy endpoints to determine a therapeutic window for SU in Asian patients with GIST and RCC.
Methods: We analyzed pooled PK–PD data from two completed Japanese phase 2 studies (N = 81 combined; NCT 00457743, NCT00254540; Pfizer) in patients with GIST (SU 25 mg, 50 mg or 75 mg on intermittent schedule) and RCC (SU 50 mg on intermittent schedule) using NONMEM® V7.0. We initially built a PK model (2-compartments with 1st order absorption and elimination) to describe SU PK data. Subsequently, different sequential semi-mechanistic or mechanism-based (i.e., transit compartments with feedback loop [TCF] or indirect response [IDR] with E_{max} or sigmoid E_{max} drug effect) PK–PD models were built and compared for selection of a PK–PD model to describe each PD endpoint; these models were internally validated by Visual Predictive Check using PsN and Xpose.
Results: Key PK–PD model characteristics or parameter estimates are shown in the table below. There appeared to be great inter-patient variability in, and overlap between, the exposure–response curves for safety endpoints and that of the efficacy endpoint.
Conclusions: We could not identify a therapeutic window for SU in Asian patients with GIST and RCC. SU dose modification based on individual ppatient safety/tolerability appears to be the best approach to ensure maximum SU plasma exposure and efficacy, consistent with the SUTENT® label recommendation.

PD Endpoint	PK-PD Model	EC_{50} Mean (CV) ng/mL (%)	g Mean
Safety			
Absolute neutrophil count	TCF	6.91 (146)	1(F)
Platelet count	TCF	55.7 (27)	5.22
Lymphocyte count	IDR	98.6 (NE)	3.09
LVEF	IDR	1050 (180)	1(F)
Diastolic blood pressure	IDR	318 (44)	1(F)
AST	TCF	74.7 (NE)	4.66
Efficacy			
SLD	IDR	80.1 (248)	1(F)

CV: coefficient of variation; EC_{50}: SU concentration at which 50% of the maximum effect is achieved; F: fixed; g (Gamma): Hill coefficient; LVEF: left ventricular ejection fraction; NE: not estimable; SLD: sum of the largest diameters of target tumours.

7166 POSTER

Validation of the Prognostic Score System for Survival in Patients (pts) With Relapses of Metastatic Nonseminomatous Germ Cell Tumours (mNGCT) After Induction Chemotherapy (iCT)

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Background: The International Prognostic Factors Study Group published a new prognostic classification for pts with relapses of GCT at the end of 2010. Scores prognostic system is presented at JCO 2010;28:4906–4911. This classification was validated on the data of 138 pts with relapses of NGCT.
Materials and Methods: We analyzed the data of 698 CT-näive pts with mNSGCT, who were treated in our department from 1986 to 2006 with etoposide- and cisplatin-based regimens (EP, BEP, C-BOP-3BEP and T-BEP) followed by resection of residual tumours. Pts with mature teratoma syndrome were excluded from analysis. With median follow-up time 32 (range, 3–215) months 181 (26%) pts had relapsed. The salvage CT was administered in 138 pts. 71 (51.7%) out of 138 were treated with ifosfamide-cisplatin-based CT. Mediastinal localization of primary GCT was revealed in 10.1% pts. According to the IGCCCG criteria: 26/138 (18.8%) pts had good prognosis, 47/138 (30.4%) − intermediate prognosis, and 65/138 (47.1%) − poor prognosis. One metastatic site was revealed in 71/138 (51.1%) pts. Complete and marker-negative response reached in 101/138 (73.2%) pts, 51/138 (36.9%) pts underwent surgical resection of residual masses.
Results: Early relapses (<2 years) were seen in 121/138 (87.7%) pts (the most of them was cisplatin-sensitive − 81/121 (67%) pts), 17/138 (12.3%) pts had late relapses (all of them were marker-positive). Median f.-up after relapse was 19 months (range 3–191). According new prognostic classification for pts with relapses: 33/138 (23.9%) pts were in the low risk group (0 scores), 44/138 (31.9%) − intermediate risk group (1 score), 18/138 (13%) − high risk group (2 scores), 43/138 (31.2%) − very high risk group (3 cores). Two-year PFS and 3-year OS for each group are presented in the table. The classification properly distributed pts into prognostic groups. However pts outcome in our study was worse than originally reported. That could be explained by differences in pts' characteristics: only half of them received ifosfamide in salvage CT and 28% of relapses were platinum resistant.

Prognostic category	Score	N = 138 (100%)	HR (95% CI)	P	2-Year PFS	3-Year OS
Low	0	33 (23.9%)			30%	43%
Intermediate	1	44 (31.9%)	1.1 (0.6−1.9)	0,13	18%	29%
High	2	18 (13%)	1.4 (0.7−3.1)	0,02	6%	24.5%
Very high	3	43 (31.2%)	2.6 (1.6−4.8)	<0.0001	0%	7.2%

Conclusion: The International Prognostic Factors Study Group classification for patients with relapsed mNGCT was successfully validated in independent pts cohort and recommended to use in daily practice.

7167 POSTER

Prognostic Factors for Overall Survival (OS) of Patients (pts) With Locally Advanced (LA) or Metastatic (m) Urothelial Carcinomas (UC) Following Platinum-based Combination Chemotherapy (CT) at Georges Pompidou Hospital (GPH) Between 2001 and 2009

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Background: The study was undertaken to identify clinical and biological pre-treatment prognostic factors of OS after platinum-based combination CT in LA or mUC pts.
Materials and Methods: A retrospective study was designed and clinical, biological, histopathological and therapeutic data were recorded before CT of 77 LA or mUC pts at GPH, Paris, France. Objective responders (OR) were defined as those with complete or partial response and non-responders (NR) as those with progressive or stable disease at the end of first-line CT in the metastatic setting. OS was estimated between date of initiation of first-line CT and date of last follow-up or death. Correlations with OS after CT were analysed using univariate and multivariate analyses.
Results: Sex ratio was 4 men/1 woman, mean age±SD: 66±8.7 years. Median (Range) OS: 11.0 (0.2–59.8) months. 85% of pts had ECOG PS <1. Mean ± SD of haemoglobin was 12.0±1.8 g/dl. Median (Range) of AST, ALT, Alkalin Phosphatase and CRP was 20 (10–132) U/L, 20 (1–172) U/L, 75 (7–320) U/L and 36.5 (1–273.3) mg/l, respectively. 83% pts had mUC and others had a LAUC disease. Among pts, 36 received CT in either neoadjuvant/adjuvant setting (n = 9/27 pts). Type of metastasis was liver, lung, bone and lymph nodes in 22, 32, 22 and 54% of pts, respectively. OR were 33%. With univariate analysis, response to CT, AST level, presence of metastasis and number of organ involved (in mUC pts) were significantly associated with OS. Other biological factors and ECOG PS were not significantly associated with OS because pts had mainly normal values at the initiation of CT. Upon multivariate analysis, only presence of metastasis [HR = 5.0, CI95% (1.2–21.2)], abnormal AST [HR = 2.4, CI95% (1.11−5.0)] and lack of response to the first-line CT [HR = 3.2, CI95% (1.4−7.7)] were main adverse prognostic factors (APF) for OS. Pts with more than 1 APF had significant poorer OS (8.8 vs 24.1 months, p < 0.001) [HR = 5.6, CI95% (2.7–11.9)].
Conclusion: Presence of metastasis, abnormal AST and lack of response at the first-line of CT can predict poor prognostic of LA or mUC pts. Compared to pts with 0−1 APF, those with more than 1 APF had a worse OS. These factors could be used to stratify pts in prospective clinical trials.