The objective of this study was to assess physical, chemical and biological stabilities of diluted rtx (1 and 4 mg/ml) for six months at 4ºC.
Materials and Methods: Three batches were prepared under aseptic conditions in normal saline for each concentration in Feeflex® bags and stored at 4ºC during 6 months. Samples were withdrawn and analysed at days D0, D14, D30, D90 and D180. Results obtained at different times of storage were compared to those at day 0. Various complementary qualitative and quantitative analytical methods were used to determine changes in physicochemical properties of rtx including size exclusion (SEC) and cation exchange HPLC (CEX), dynamic light scattering (DLS) and turbidimetry, UV spectrometry and peptide mapping HPLC after trypsin/ endopeptidase digestion. Tertiary structure destabilisation was studied by examining aggregation vs temperature curves and determining the corresponding melting point. Biological stability was assessed by comparison of the rtx-induced cytotoxicity curves using CD-20 expressing RAJI lymphoma cells.
Results: No modification of chemical, physical and biological properties of rtx was observed after 6 months of storage whatever the methods used. By CEX, SEC and peptide mapping, no significant change in chromatographic profiles was detected. The mean hydrodynamic diameter stayed unchanged (11.5±1.0 nm) without additional populations. The melting point remained unchanged at 72.6ºC. No increase in absorbance at 350 nm was noticed indicating the absence of aggregation. The IC_{50} and the area under the cytotoxicity curves (AUC) were not significantly different (IC_{50}: 137 vs 126 μg/ml; AUC: 25334 vs 25077 $\mu g/ml.days^{-1}$; D0 and D180 respectively).
Conclusion: Contrary to the manufacturer claims, diluted rtx is stable up to 6 months at 4ºC. This longer stability could authorize the anticipated preparation or batches by pharmacy centralized units which could also induce an important decrease of costs.

1306 POSTER

Accuracy of Clinical Judgment of Progressive Disease in Phase II Trials

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Background: The diagnosis of progressive disease (PD) is a key element for assessment of clinical activity of new drugs in contemporary phase II trials. In some cases, PD is assessed by the physician before the planned imaging. In this study, we attend to analyze the value of the PD based on clinical judgment.
Materials and Methods: We have conducted a single-center retrospective study to analyze the diagnostic performance of clinical judgment compared to planned imaging with respect with PD. The medical records of all patients enrolled in our institution in phase II trials investigating systemic treatments for advanced solid tumours between January 2008 and November 2010 were independently reviewed. Diagnostic accuracy of the clinical judgment of PD was examined as a diagnostic test, in comparison to PD diagnosed by imaging according to RECIST.
Results: 84 from 129 patients (65%) included in 32 different and consecutive phase II trials experienced PD during trials and 27 discontinued trials for reasons other than PD. Eighteen patients are currently treated according to these phase II trials. 47 PDs were documented by planned imaging without clinical signs of progression. One patient experienced biological PD without radiological confirmation. Out of the 36 patients who experienced clinical PD, imaging was not available at clinical progression in 7 cases. In 29 cases where imaging was available at clinical PD, radiologic PD was confirmed in 28 cases. The positive predictive value (PPV) and the specificity of clinical judgment of progression was very high (>90%). Conversely, sensibility and the negative predictive value (NPV) were low (<40%). As a result, and since most PDs were asymptomatic, the accuracy of clinical judgment of PD was 49%. We have conducted a sensitivity analysis (worst-case and best-case scenario) to take into account the 6 clinical suspicion of PD without confirmatory imaging; the PPV range from 77% to 97% and the NPV range from 33% to 46%.
Conclusions: According to this study, the clinical judgment of PD is highly predictive of radiological PD assessed by RECIST. By default, clinical judgment of PD appears as an acceptable criteria defining tumour progression.

1307 POSTER

European Consensus Conference on the Practical Stability of Anticancer Drugs

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Background: Stability studies performed by the pharmaceutical industry are only designed to fulfill licensing requirements. Thus, post-dilution or -reconstitution stability data are frequently limited to 24h only for bacteriological reasons regardless of the true chemical stability which could be largely longer. In practice, the pharmacy-based centralized preparation may require in advance preparations for several days, filling of ambulatory devices for continuous infusions or batch preparations for dose banding. Furthermore, a non justified limited stability for expansive products is obviously very costly. Thus, there is a strong need for additional stability data covering practical uses of anticancer drugs.
Method: A European conference consensus was held in France, May 2010, under the auspices of the French Society of Oncology Pharmacy (SFPO) to propose adapted rules on stability in practical situations and guidelines to perform corresponding stability studies.
Results: For each anticancer drug, considering their therapeutic index, PK/PD variability, specific clinical use and risks related to degradation products, the limit of 10% of degradation can be inappropriate. Therefore, acceptance limits must be clinically relevant and should be defined drug by drug. Design of stability studies has to reflect the different needs of the clinical practice (preparation for the week-ends, outpatient transportations, implantable devices, dose banding. . .). It is essential to use validated stability-indicating methods, separating degradation products being formed in the practical use of the drug. Sequential temperatures design should be encouraged to mimic problems seen in daily practice such as rupture of the cold-chain. Stressed conditions are recommended to evaluate not only the role of classical variability factors (i.e. pH, temperature, light) but also the mechanical stress. Physical stability (particles formation) should be systematically evaluated. Consensus conference focused on the need to perform more studies on the stability of biotherapies including a minimum of 3 complementary separative methods, careful evaluation of sub-micronic aggregates. The determination of the biological activity could be useful.
Conclusion: A guideline on the practical stability of anticancer drugs has been proposed to covert the current clinical and pharmaceutical practices. It should contribute to improve their security of use, to optimize centralized handling and to reduce costs.

1308 POSTER

Paclitaxel-related Interstitial Lung Disease − Implication of Mediastinal Lymphadenopathy

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Background: Drug-related interstitial lung disease (ILD) is rare but serious adverse reaction in patients with solid tumours treated with cytotoxic systemic chemotherapy. Paclitaxel (PTX) is widely used worldwide against solid tumours, including lung, breast, gastric, and ovarian cancer. However little is known about PTX in regard to the risk factors for developing ILD.
Material and Methods: We reviewed patients treated with PTX at our institute between January 2007 and December 2008. Clinicopathological data was retrieved from medical records. Chest CT prior to the administration of PTX was reviewed and evaluated whether the patient had pre-existing ILD and mediastinal lymphadenopathy. PTX-related ILD was defined as the bilateral interstitial shadow developed during the course of PTX administration and lack of evidence for other cause. Correlation with PTX-related ILD and clinicopathological data was investigated.
Results: A total of 192 patients were included. Median age was 66 years (range 33–86) and 99 patients (52%) were female. Primary site of disease was lung (n = 83; 43%), breast (n = 34; 18%), stomach (n = 31; 16%), ovary (n = 30; 16%), and others (n = 14; 7%). Median number of PTX administration was 8.5 doses (1−56). PTX was administered weekly in

most patients (n = 133; 69%). Seven patients (4%) developed ILD and one of them died of it. Among these seven patients, six were affected by lung cancer and the other breast cancer. However multivariate analysis showed disease site was not significantly correlated with ILD (p = 1.00); while the presence of mediastinal lymphadenopathy was significantly correlated with ILD (odds ratio 6.96, p = 0.037).
Conclusion: Mediastinal lymphadenopathy was significantly correlated with developing paclitaxel-related ILD. Further investigation is warranted to validate this findings.

1309 POSTER

How Much is the Likelihood of Being Helped or Harmed (LHH) When Adopting Oral Targeted Agents (OTA) in the Treatment of Advanced Solid Tumours (AST) − Comprehensive Assessment of Their Clinical Overall Impact According to FDA/EMEa Regulatory Approvals

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Background: The number needed to treat or to harm (NNT/NNH) represents a practical tool to quantify the clinical impact of TA for the treatment of AST. LHH, a quality-adjusted ratio between NNT and NNH, is an Evidence-Based-Medicine patient-centered measure. With a purely speculative intent for trial design, the aim of this analysis was to have a general overview upon the LHH provided by OTA in AST.
Methods: Randomized clinical trials (RCTs) providing registration of OTA by FDA/EMEA were eligible if data for efficacy (PFS, OS), activity (ORR) and safety (Grade 3−4 specific toxicities) were available. PFS and OS rates were extracted/derived from curves; absolute differences were determined and NNT or NNH (derived according to the worst drug-specific toxicity) were calculated. LHH was calculated for PFS, and additionally for OS whereas that OTA was registered for a significant survival advantage.
Results: Ten RCTs and settings were gathered (see table); 3 trials compared the OTA versus active treatment, 2 RCTs as add-on to chemo versus the same chemo, and 5 versus placebo. 6 and 3 OTA were registered for a significant PFS and OS advantage, respectively.

Comparator	Setting	Specific Toxicity	LHH	
			PFS	OS
Chemo	Gefitinib [*EGFR-MT-NSCLC*]	Rash	14.9	–
Immuno	Sunitinib [*RCC*]	Hypertension	6.4	–
	Sorafenib [*RCC*]	Hand-Foot Syndrome	3.4	–
Chemo + OTA	Lapatinib [*HER2+MBC*]	Diarrhea	2.7	–
	Erlotinib [*PDAC*]	Rash	2	0.1
Placebo	Sunitinib [*GIST*]	Hypertension	4.9	–
	Pazopanib [*RCC*]	High-transaminase	3.2	–
	Sorafenib [*HCC*]	Diarrhea	2.2	0.1
	Erlotinib [*NSCLC*]	Rash	1.8	0.8
	Everolimus [*RCC*]	High-glycemia	1.5	–

FDA/EMEA registered OTA exert a potential LHH in the range of 1.5−6.5 (these are 1.5−6.5 times more likely to benefit than to provide drug-specific toxicities); the exception is Gefitinib for patients with EGFR mutation, specific target of an oncogene-addicted disease.
Conclusions: Although the limitations of a derived-by-curve determination at various time-points weighted with an arbitrary-chosen drug-toxicity, and the unreliability of a formal comparison between OTA-LHH based on different drug-toxicities, the benefit obtained by OTA seems related to the identification of the tumour-driven target. Three scenarios appear: 1) drugs targeting a target-dependent malignancy (LHH > 10); 2) drugs targeting 1 among multiple tumour-driving pathways (LHH 2−7); 3) drugs definitively requiring a biomarker-driven development (LHH <2). A cost analysis is mandatory to put these data in context with the general health care system.

1310 POSTER

Adequacy of Prognostic Markers Reporting Based on NCI-EORTC REMARK Guideline − a Comparison Between Pre- and Post-REMARK Eras

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Background: Lack of data reporting is a well-known issue and an obstacle to the applicability of prognostic biomarker studies (PBS) in clinical practice. REMARK guideline (J Clin Oncol, Vol 23, No 36, 2005: pp 9067−72) was developed in order to standardize information in such trials. We sought to compare the fairness of PBS regarding REMARK recommendations pre- and post-guideline publication.
Material and Methods: We systematically searched PubMed for PBS from Jan 1, 2004 to Dec 31, 2005 (pre-REMARK), and from Jan 1, 2009 to Oct 31, 2010 (post-REMARK). Inclusion criteria: 1) one biomarker per study; 2) validation in a multivariate model; 3) correlation between biomarker and overall, disease-free, or progression-free survival. Exclusion criteria: 1) gene expression arrays; 2) proteomic analysis; 3) biophysical features; and 4) predictive biomarkers. Fifty-two REMARK recommendations were assessed. The rate of reported recommendations (RRR) was compared between the periods (chi-square test) and correlated with journal impact factor of publications (Spearman's test).
Results: 1,208 articles were retrieved, 110 of which met the eligibility criteria (52 and 58, pre- and post-REMARK, respectively). A total of 82 biomarkers were investigated in 19 types of cancers. The median number of studied patients size was 135 (range 21–1984). The overall RRR was 61.8% and 62.7% for the pre- and post-REMARK periods, respectively. Low reporting was found in the following REMARK recommendations: exclusion criteria [25% (pre-), 32.8% (post-); p = 0.371]; preservation of biological material [19.2% (pre-), 25.9% (post-); p = 0.407]; blinded analysis of the biomarker [34.6% (pre-), 34.5% (post-); p = 0.988]; overall [59.6% (pre-), 63.8% (post-); p = 0.653] and subgroup number of events [32.7% (pre-), 25.9% (post-); p = 0.431]; discussion about study limitations [55.8% (pre-), 58.6% (post-); p = 0.763]; and future research implications [57.7% (pre-), 58.6% (post-); p = 0.921]. There was a correlation between the overall RRR and the probability to be published in a higher impact factor journal (p = 0.001).
Conclusions: Reporting of key information in PBS remains poor. More efforts from authors and editors in using REMARK recommendations should be considered to improve the quality of studies on prognostic markers.

1311 POSTER

Written Information for Research Participants in Randomized Cancer Clinical Trials − a Study of Compliance With Good Clinical Practice Regulations

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Background: Development of oncology treatments requires patients' participation in clinical trials. Informed consent from participants is mandatory according to guidelines and laws. Before signing the consent form, potential participants should get oral and written information and have the opportunity to get unclear points resolved. According to Good Clinical Practice (GCP) important aspects should be described in the written information. Studies have revealed deficient understanding of clinical trials among participants. Therefore, consent forms were studied regarding the level of compliance with GCP.
Material and Methods: All consent forms for phase III trials open for inclusion in May 2009 at the Department of Oncology were included. Consent forms (n = 30) were evaluated regarding GCP § 4.8.10 that demands written information to include explanations of 20 items, e.g. that the trial involves research, the purpose of the trial, treatments and the probability for random assignment to each treatment, procedures to be followed and subject's responsibilities. In addition, 5 clarifying items were reviewed, e.g. clarification of randomization and that the study have been approved by the Regional Ethical Review Board (RERB). Explanation of the items were scored in the following way; clearly explained = 5, explained to a high degree = 4, partly explained = 3, mentioned but not explained = 2, the item is not included = 0. The scores for all 25 items were summarized for each consent form making a maximum score of 125 if all items were clearly explained.
Results: Three consent forms got scores over 100 and 4 consent forms scored between 91–100, 12 forms scored between 71−90 and 11 forms got scores of 70 or below. In 2 consent forms 15 items were clearly explained and 5 forms showed compliance with all 25 items in varying degrees. The form with the highest score (107), explaining all 25 items of which 15 items were clearly explained, used 10 pages. The consent form with the highest score within the limitations to 5 pages, as recommended by the RERB, reached a score of 90 and explained 24 items out of which 12 were clearly explained.
Conclusions: In terms of written information, a great variation in compliance to GCP was found. Efforts are needed to clarify the randomisation procedure and expectations on research participants. The results show that it might be possible to produce condensed clearly written information to patients considering participation in a phase III cancer clinical trial.