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**ITTC: a European biology and clinical research network for new drug development for children with cancer within the new European Pediatric Medicine Regulation**

G. Vassal. *On behalf of ITCC European Consortium. Institut Gustave Roussy, Villejuif, France*

Cancer is a rare disease in children. Each year, 12000 children are diagnosed with more than 60 different malignancies in Europe. Pediatric cancers represent 1% of all cancers in humans. 75% of those children will be cured with multimodality treatments that may often induce sequellae in long-term survivors. However, cancer is still the first cause of death by disease in children over one year of age. Innovative and safe therapies are urgently needed to improve further survival and quality of cure.

Many new anticancer compounds with new mechanisms of action are being developed in adults. A global pediatric development strategy needs to be set up considering the limited number of pediatric patients who may participate to early drug trials. The 4 major aims are: (1) *to improve access to new drugs for children:* the new European Regulation (to be launched in 2007) will facilitate the evaluation of anticancer medicines through the obligation to submit a Pediatric Investigation Plan and incitives for Industry which will study their compounds in children. Such a regulation proved to be effective in the USA. (2) *to choose the best candidate drugs:* biological evaluation of the role of therapeutic targets in pediatric tumors along with *in vitro* and *in vivo* evaluation of anticancer compounds in relevant pediatric tumor models will help to identify compounds being developed in adults that deserve evaluation in children. (3) *to speed up the early clinical development* with new trial designs and new pharmacodynamic endpoints through networks of well-qualified clinical centers able to meet the high quality criteria and timely–fashion recruitment. (4) *to consider the unique ethical dimension of testing new drugs in children* by improving information and participation of patients and parents.

The European Consortium for Innovative Therapies for Children with Cancer (ITCC, www.ITCCconsortium.org) is a Biology and Clinical Network that runs a clinical and translation research programm connecting new drugs, biology and the unmet needs of children with cancer. The 5 ITCC goals are: (1) *to select and prioritize adult compounds* through biology and preclinical evaluation. (2) *to identify new pediatric targets* through a fundamental and translational research project untitled KidsCancerKinome in the European Framework Program. (3) *to conduct early drug clinical evaluation* with improved methodology, and to validate the use of new pharmacodynamic endpoints and imaging. (4) to improve parents and patients information, participation and related issues. (5) *to educate and train professionals* who will develop innovative therapies, and to disseminate knowledge and results.

ITTC is composed a consortium of *9 European research laboratories* with expertise in pediatric tumor biology, pharmacology, experimental therapeutics, high-throughput technologies, and with a large mutualized biobank, and a clinical network of *32 centers* in 5 countries (France, United Kingdom, Netherlands, Italy, Germany). In addition, the Internationl Confederation of Children Cancer Parents Organisation (ICCPO) is a full member of ITCC.

Several new anticancer compounds such as imatinib, erlotinib, dasatinib, plitidepsin are currently being evaluated in children in partnership with Pharmaceutical Companies. In addition, ITCC did participate to the definition of the EMEA guidelines for the evaluation of anticancer medicinal products in children, and several ITCC members are EMEA experts.

In conclusion, ITCC is a well-structured clinical and translational research European network for new drug development for children with cancer in partnership with Pharmaceutical Companies and Regulatory Bodies.

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**Approaches to shortening the timeline of paediatric phase I trials**

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The advances in the care of children with cancer have primarily been made through the systematic investigation of a relatively small library of cytotoxic chemotherapeutic drugs and an increased understanding of the heterogeneity of childhood cancers. The past 10 to 15 years, however, have witnessed a relative plateau in outcome for most childhood cancers, and is primarily a reflection of our inability to identify and develop new therapeutic agents. The global landscape of cancer drug development has also changed, with a near logarithmic increase in the number of new agents in the clinical development pipeline. The approach to pediatric phase 1 trials however, has not changed in more than 40 years. Pediatric phase 1 studies follow adult phase 1 studies, accruing patients according to the standard 3 + 3 design. Better utilization of early phase adult trial data can improve the efficiency of pediatric phase 1 trials. The 3 patient cohort approach is inherently inefficient, with the greatest contributor to the prolonged timeline being the multiple periods of time a study remains suspended to accrual awaiting tolerability results form a cohort. Results of analyses exploring alternatives to the 3 + 3 design will be presented, including COG plans that streamline the development of targeted agents from focused phase 1 trials into randomized phase 2 studies.

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**Imatinib mesylate in recurrent solid tumours expressing KIT or PDGFR (phase II)**

B.J. Morland[1], B. Geoerger[2], M.-C. Le Deley[2], F. Doz[3], F. Pichon[4], D. Frappaz[5], J.-C. Gentet[6], J. Landman-Parker[7], P. Berthaud[8], G. Vassal[2]. [1]*Birmingham Children's Hospital, Department of Oncology, Birmingham, United Kingdom;* [2]*Institut Gustave Roussy, Villejuif, France;* [3]*Institut Curie, Paris, France;* [4]*Centre Oscar Lambret, Lille, France;* [5]*Centre Leon Berard, Lyon, France;* [6]*Hopital d'enfants de la Timone, Marseille, France;* [7]*Hopital Trousseau, Paris, France;* [8]*Novartis Pharma, France*

**Background:** Imatinib mesylate (Glivec®) selectively inhibits specific activations of the platelet-derived growth factor receptor (PDGFR), c-KIT and BCR/ABL tyrosine kinases and is approved for the treatment of chronic myeloid leukemia and gastro-intestinal stromal tumors (GIST). This study evaluated efficacy of imatinib in solid childhood tumors.

**Methods:** Phase II study of imatinib as single agent in children and adolescents with refractory or relapsing solid tumor expressing at least one of the receptors. Patients were to be treated at 340 mg/m$^2$, a dose escalation allowed to 440 mg/m$^2$ after 2 months in case of insignificant improvement. C-KIT, PDGFRa and b expression was determined on archive tissue sections by immunohistochemistry prior to study entry. Gene mutations, pharmacokinetics, pharmacogenetics, and positron emission tomography imaging were assessed.

**Results:** 36 patients, 21 boys, median age 13.7 years (2.2–22.5 y), 12 with brain tumors, 6 fibromatosis, 8 mesenchymal/bone tumors, and 10 other solid tumors, including 1 GIST and 3 chordoma, were treated at 340 mg/m$^2$ daily during a total of 168 months (median 1.9 months/patient, range 0.5–19). 18/36 expressed c-KIT, 10 PDGFRa, 21 PDGRb; 12 expressed more than 1 receptor. Ten patients were escalated to 440 mg/m$^2$ due to lack of efficacy. During the 1st month, 17 patients experienced mild toxicity (grade 1 and 2) related to study treatment: gastro-intestinal (n = 22), face edema (n = 7), asthenia (n = 5), tumor induration (n = 2), skin toxicity (n = 2), thrombocytopenia (n = 1). No partial or complete response was observed; 5 patients (2 fibromatosis, 1 GIST, 1 medulloblastoma, 1 pseudo-inflammatory tumor) experiencing durable stable disease have been under treatment for more than 12 months. Interesting tumor stabilization during 10 and 7 months, respectively, was achieved in a brain stem glioma and a renal carcinoma. Glucose uptake on 18FDG PET scan was reduced in a chordoma, although the child progressed and died due to disease. Pharmacokinetic and genetic data are currently evaluated.

**Conclusions:** Imatinib as single agent was well tolerated, but as used in our study failed to show measurable anti-tumor effects according to standard criteria in the pediatric malignancies studied.

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**The development of VEGF blocking therapies for the treatment of pediatric tumours**

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Blockade of vascular endothelial growth factor (VEGF) has been validated as a clinical therapy for adults with metastatic cancer. The prototypic agent is bevacizumab, a high affinity monoclonal VEGF neutralizing antibody, which received FDA approval for use in adult advanced stage colon cancer in early 2004. Despite robust preclinical data supporting the potential for tumor growth inhibition in xenograft models of solid embryonal tumors of childhood, pediatric development of this class of agents has been delayed due to concerns of adverse effects on growth and development: specifically, the preclinical finding of physeal dysplasia in juvenile monkeys. A phase I dose escalation study of bevacizumab administered by IV infusion every 2 weeks in children with clinically refractory solid tumors was conducted through the Children's Oncology Group (COG). Cohorts were enrolled at dose levels of 5, 10, and 15 mg/kg; the final dose level was expanded to include at least 3 children under 6 years of age. Minimal adverse effects were seen, with no dose-limiting toxicities observed and a maximum tolerated dose not reached. Non-dose limiting, grade 1–2 toxicities included infusional reaction (n = 3), rash (n = 3), mucositis (n = 2), and proteinuria (n = 3). There was no hemorrhage or thrombosis reported. Analysis of blood pressures revealed subtle but statistically significant increases in

systolic and diastolic pressures, although not meeting clinical criteria for hypertension. Growth perturbation over a one month term of therapy was not detected. Encouraging disease stabilization was observed in subset of patients with bone and soft-tissue sarcomas. Limited pharmacokinetic data support bevacizumab dosing schedules for children similar to those used in adults. Analysis of apoptotic and viable circulating endothelial cells was feasible in children, and results are promising for mechanistic validation and potential surrogate clinical application. Further evaluation of VEGF blockade therapy in the pediatric population is warranted. Combination studies of bevacizumab with epidermal growth factor receptor inhibition or cytotoxic chemotherapy, and assessment of oral multitargeted small molecular receptor kinase inhibitors BAY 43–9006 and SU11248 are planned or ongoing through the COG.

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**Clinical phase I-II and pharmacokinetic study of plitidepsin in children with malignant tumors**

B. Geoerger[1], F. Doz[2], E. Estlin[3], P. Kearns[4], S. Bezares[5], C. Pico[5], G. Vassal[1]
. *On behalf of ITCC. [1]Institut Gustave Roussy, Department of Pediatrics and "Pharmacology and new treatments in cancer", Villejuif, France; [2]Institut Curie, Department of Pediatrics, Paris, France; [3]Royal Children's Hospital, Oncology, Manchester, UK; [4]Royal Hospital for Children, Oncology, Bristol, UK; [5]PharmaMar SAU, Clinical R&D, Madrid, Spain*

**Background:** Plitidepsin is a cyclic depsipeptide isolated from the tunicate *Aplidium albicans*, nowadays manufactured by synthesis. It is a rapid and potent inducer of apoptosis and preliminary clinical activity has been observed in several adult malignancies. Phase I trials in adults explored 5 different schedules. Muscle and liver toxicities were dose-limiting; haematological toxicity was not observed at the recommended dose (RD). Preclinical data suggest activity in pediatric leukemia.
**Methods:** This is a multicentre, open-label, non-randomized phase I-II study with a dose finding stage in children with solid tumors, and subsequently two expanded cohorts in leukemia and solid tumors at the RD. Plitidepsin was administered as a 3 h iv infusion every 2 weeks (= 1 cycle). The initial dose level was 4 mg/m$^2$ (80% of the RD in adults) with a classic escalation to 5 and 6 mg/m$^2$.
**Results:** 22 patients have been entered to date with median age 7.5 years (range 2–17). 70 cycles in 21 patients were evaluable for toxicity. Eight patients were treated at 4 mg/m$^2$, five at 5 mg/m$^2$, seven at 6 mg/m$^2$, and two in the extension phase at 5 mg/m$^2$. One patient presented dose-limiting G2 myalgia lasting more than 2 weeks at 4 mg/m$^2$. One patient experienced asymptomatic G4 CPK elevation and one other G3 non-transient transaminitis at 6 mg/m$^2$, suggesting 5 mg/m$^2$ as the RD in children. Non-hematological toxicities included muscle side effects (G1–2 myalgia, muscle weakness, muscle cramps and G1–4 CPK elevation), G1–3 fatigue, G1–3 transaminitis, G3 vomiting, G3 hypersensitivity reaction. Pharmacokinetic data are similar to those reported in adult (extensive tissue distribution, a long half-life); if any, clearance was slightly higher and half-life shorter. Partial tumor response was observed in a refractory neuroblastoma and some evidence of activity in a medulloblastoma and a pancreatoblastoma.
**Conclusions:** Plitidepsin was well tolerated in children with muscle side effects being the most relevant toxicity observed. The RD for the pediatric population is equivalent to the RD in adults. The extension phase in solid tumors and leukemia is ongoing.

## Thursday 9 November 14:45–16:15

**PLENARY SESSION 6**

# Proffered Papers

**250** ORAL

**Presurgical treatment of metastatic renal cell carcinoma patients with bevacizumab and erlotinib: preliminary efficacy and biomaker data**

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**Background:** A number of new targeted therapies are being developed for metastatic renal cell carcinoma (mRCC) The role and timing of cytoreductive nephrectomy in patients receiving targeted therapies has not been defined. We have initiated a study investigating the role of presurgical treatment of mRCC patients with bevacizumab and erlotinib, and present data on tumor response and biomarker readouts in the first 19 patients in this protocol.
**Materials and Methods:** Patients were previously untreated, did not have brain metastases, had a performance status of 0 or 1, predominant clear cell histology, and had not undergone cytoreductive nephrectomy. Patients received bevacizumab 10 mg/kg IV every 2 weeks for 4 doses, and erlotinib 150 mg daily for 8 weeks. Two weeks after the last dose of erlotinib, and 4 weeks after the last dose of bevacizumab, patients underwent cytoreductive nephrectomy. Patients who demonstrated disease stability or response were restarted on treatment one month post-surgery and continued until disease progression. Phospho and total EGFR, AKT, S6, FAK and ERK were evaluated by Western blots and by immunohistochemistry on tissue microarrays, and compared to control untreated RCC tissue.
**Results**: Between 3/23/2005 and 6/04/06, 27 patients were enrolled out of a total planned accrual of 50 patients As of June 4, 2006, 19 patients were evaluable. One patient had a CR in target lesion and stability in his nontarget lesion (bone). There were 3 PRs, 13 patients with stable disease and 3 patients with progressive disease.
Evaluation of protein expression of key signaling molecules controlling proliferation, survival and migration (phospho-AKT, total AKT, PTEN, phospho-FAK and phospho-ERK) did not reveal any statistically significant change between the treated and the untreated groups, with the exception of a modest increase in overall AKT expression in the treated group (p value <0.02). p-ERK and p-AKT (and p-FAK less strongly, p value <0.02) correlate with disease grade, regardless of treatment status (increase in grade IV, p value <0.002).
**Conclusions:** Early data suggest presurgical treatment with bevacizumab and erlotinib is safe and efficacious in patients with previously unresected, untreated mRCC, with shrinkage of both metastatic disease and primary tumors. There is previous (pre-clinical) evidence for target inhibition of both VEGFR and EGFR, but key downstream signaling molecules were not affected in this study. Further investigation is required to elucidate the pathways involved in mediating the therapeutic effect of these drugs.

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**The phosphatidylinositide 3-kinase (PI3-kinase) inhibitor PI103 sensitises some ovarian carcinoma (OC) cell lines to paclitaxel or carboplatin**

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PI3-kinase, through phosphorylation of its downstream substrate, AKT, is an important mediator of proliferation and survival signals. Activation of this pathway has been linked to cytotoxic drug resistance and to the ability of PI3-kinase inhibitors, such as LY294002, to sensitise some tumour cell lines to cytotoxic drugs. PI103 is a novel potent inhibitor of the catalytic p110$\alpha/\beta$ catalytic subunits of PI3-kinase and of mTOR. The PI3-kinase/AKT pathway is frequently activated in OC due to aberrations at different points in the pathway. SKOV-3 cells overexpress ErbB2,