receptor (ER) and hormone resistance biology. Because of a very low tumor take in immunodeficient mice, most *in vivo* models of estrogen-dependent human breast tumors are derived from human cancer cell lines. We report here the establishment and the characterization of new primary human luminal breast cancer xenografts directly obtained from fresh human tumor samples.

Methods: As of December 2009, 453 fresh human BC samples have been engrafted in the interscapular fatpad of *nude* mice, of which 405 were retained for further studies (32 were non infiltrating or non-breast carcinoma, and 16 were axillary metastatic lymph node from a simultaneously engrafted primay tumor). ER was expressed in 313 tumors (77.3%), progesterone receptor in 175/291 informative tumors (60.1%), Her2 in 39/315 tumors (12.4%), and overall 60 tumors were triple negative. Validation of the xenografts was obtained by a large phenotypic and genotypic profiling including: pathological and immunohistochemical (IHC) examination, dedicated gene expression (RT-qPCR), genomic (BAC CGH arrays) and transcriptomic (Affymetrix u133 RNA chips) analyses, and therapeutic assessment (estrogen deprivation, ovariectomy, LHRH agonists, letrozole, tamoxifen, fulvestrant).

Results: Among the 405 human xenografted tumors, 8 luminal models have been established (2%), 7 from ER+/PR+ tumors and 1 from an axillary relapse of an ER−/HER2+ tumor. In all tumor/xenograft pairs, histopathological analyses showed an impressive morphological concordance. One had a strong mucinous component, and all of them were grade II/III tumors. Out of the 7 ER+/PR+ models, 3 were also HER2 positive. RNA expression by RT-qPCR confirmed ER, PR and HER2 status for the 7 ER+/ER+ tumors, and confirmed the ER+ status of the ER-/HER2+ derived tumorgraft. CGH arrays analyses demonstrated striking similarities of the genomic profile between the original tumors and their corresponding xenografts. Array CGH analyses were also performed at several passages, showing stable profile of the tumors during sequential *in vivo* passages. Transcriptomic profiling is ongoing. Therapeutic characterization of the xenografts showed that tamoxifen had a delayed but significant anti-tumor effect, whereas fulvestrant was the most efficient hormone therapy with durable complete responses observed in 3/3 evaluable models. Updated and extended results will be presented during the meeting.

Conclusions: We have durably established and characterized 8 primary human luminal BC xenografts. In order to identify new therapeutic approaches of hormone resistant BC, we have now planed to decipher in these well-defined preclinical models the molecular variations associated with emergence of resistance to hormone therapies.

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Preclinical antitumor assessment of bendamustine in human primary uveal melanoma xenografts

F. Némati[1], S. Piperno-Neumann[2], L. Desjardins[3], N. Karboul[1], C. Elbaz[1], A. Dahmani[1], X. Sastra-Garau[4], A. Berniard[1], P. Mariani[5], D. Decaudin[1].
[1]Institut Curie, Translational Research, Paris Cedex 05, France; [2]Institut Curie, Medical Oncology, Paris Cedex 05, France; [3]Institut Curie, Ophthalmological Oncology, Paris Cedex 05, France; [4]Institut Curie, Tumor Biology, Paris Cedex 05, France; [5]Institut Curie, Surgical Oncology, Paris Cedex 05, France

Background: Uveal melanoma (UM) is the most common primary cancer of the eye, with a pejorative outcome due to metastatic death in up to half of the patients. Apart complete resection of metastasis, few alkylating agents such as temozolomide and fotemustine were used in metastatic UM patients with a slight efficacy. Bendamustine hydrochloride, which is both an alkylating and an anti-metabolite cytotoxic drug, has been shown to possess clinical activity in cancer patients refractory to alkylating-based chemotherapy. The purpose of this study was therefore to determine the efficacy of bendamustine in primary human UM xenografts.

Materials and methods: Four well characterized models of human UM, obtained from patients after enucleation (primary tumors)(MP41, MP46, and MP80) or liver surgery (metastatic tumors)(MM26), were used for the *in vivo* experiments (Némati et al, CCR 2010). Bendamustine was administered intraperitoneally (IP) at a dosage of 11 mg/kg day 1 to 5 every 28 days; temozolomide was administered IP at a dose of 40 mg/kg day 1 to 5 every 28 days and fotemustine was administered IP at a dosage of 30 mg/kg every three weeks. Tumor growth inhibition (TGI) was calculated to measure the efficacy of various tested compounds.

Results: Bendamustine induced a TGI between 44% and 49% in the four human UM xenografts, as shown in the Table 1. Moreover, when bendamustine was compared to temozolomide and fotemustine, it appears less efficient than fotemustine in all tested tumors and more efficient than temozolomide in 2/4 xenografts.

Conclusions: Using 4 human UM models, bendamustine was less efficient than standard chemotherapies administered in metastatic patients. These data are correlated to the results of the only one clinical study evaluating bendamustine efficacy in relapsed or refractory metastatic UM patients and showing 11/11 progressive diseases (Schmidt-Hieber et al, Melanoma Res 2004). These data also suggest that human primary UM xenografts constitute relevant preclinical models for pharmacological assessment of new therapeutic compounds and new combination of treatments.

UM models	Bendamustine	Temozolomide	Fotemustine
MP41	49	38	64
MP46	46	93	94
MP80	49	14	75
MM26	48	95	96

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Myxoid liposarcoma tumors with different chimera subtypes xenografted in nude mice are characterized by different response to trabectedin and gene expression profile

S. Marchini[1], R. Frapolli[1], I.F. Nerini[1], S. Pilotti[2], P. Casali[3], F. Grosso[3], R. Sanfilippo[3], A. Gronchi[4], J.C. Tercero[5], M. D'incalci[1]. *[1]Mario Negri, Oncology, Milano, Italy; [2]Fondazione IRCCS Istituto Nazionale Tumori, Pathology, Milano, Italy; [3]Fondazione IRCCS Istituto Nazionale Tumori, Cancer Medicine, Milano, Italy; [4]Fondazione IRCCS Istituto Nazionale Tumori, Surgery, Milano, Italy; [5]PharmaMar, Scientific Development, Madrid, Spain*

Background: Trabectedin is a marine alkaloid isolated from Ecteinascidia turbinata, that is approved in Europe for the 2nd line of therapy in soft tissue sarcomas (STS). Among different STS, myxoid liposarcomas (MLS) are particularly sensitive to trabectedin, a clinical finding possibly related to the drug ability to block the trans-activating activity of the FUS-CHOP chimera gene, that represents the MLS pathogenic lesion. Different chimera subtypes seem to share different response to trabectedin in clinical setting. To define if this can be related to a different pattern of sensitivity to trabectedin tumor myxoid liposarcomas type II and type III were xenografted in nude mice, treated with trabectedin and analyzed for their gene expression profile.

Material and Methods: Fragments of type II and type III MLS were transplanted s.c. in female athymic NCr-nu/nu mice. Xenografts were established and characterized by morphology and molecular biology. Trabectedin 0.15 mg/kg was injected i.v. weekly for three times. The growing tumor masses were measured with a Vernier caliper. Drug efficacy was calculated as T/C %, where T and C are the mean tumor weights of treated and control groups, respectively. Whole gene expression experiments were performed with dual color labeling protocols and hybridized onto 44K oligos-array platforms commercially available. Analysis was performed with "R" package software. Pathway analysis was performed using Metacore software. qRT-PCR was used for data validation. Statistical analysis was performed using *Graphpad software.*

Results: The responsiveness to trabectedin in type II MLS xenografts was very high (T/C = 8%) whereas type III MLS xenografts appeared much less sensitive (T/C = 42%) to trabectedin. Gene expression analysis of both type II and type III subtypes identified a large subset of genes which expression is modulated by trabectedin in a dose dependent manner. Pathway analysis revealed that trabectedin treatment modulated different molecular pathways in the two FUS-CHOP subtypes models.

Conclusions: The overall data suggest that nude mice xenografted with different FUS-CHOP subtypes are associated with different sensitivity to trabectedin, mirroring clinical evidence. The differences appear to be related to a different modulation of gene expression by trabectedin.

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NC-001 induces tumor growth discontinuation and necrosis in a xenograft renal cancer rat model

H. Hedman[1], L. Buvall[1], U. Nilsson[1], J. Nystrom[1], B. Haraldsson[1].
[1]University of Gothenburg, Molecular and clinical medicine, Gothenburg, Sweden

Of all cancer malignancies in the world, renal cancer constitutes about 3%, which corresponds to 100,000 cases annually worldwide. The majority of renal cancer (75%) starts in the proximal tubular epithelial cells in the kidney, and is referred to as clear cell renal cell carcinoma (CCRCC). At diagnosis, about one third of the patients are presented with metastases. Subsequently, half of the patients who seemed to have a localized disease initially, will develop metastases even if the original tumor is successfully removed. Several new therapies are emerging in clinical trials, with mainly anti-angiogenic properties. These are combined and compared with conventional therapies, explicitly interferon-alfa and interleukin-2. However, none of these show true curative potential, although significant retardation of the disease have been reported for specific patient categories.