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Abstract No: 10505

LMS-02: A phase II single-arm multicenter study of doxorubicin in combination with trabectedin as a first-line treatment of advanced uterine leiomyosarcoma (u-LMS) and soft tissue LMS (ST-LMS): First results in patients with u-LMS

Patricia Pautier, Anne Floquet, Didier Cupissol, Benjamin Lacas, Emmanuelle Bompas, Christine Chevreau, Frédéric Selle, Beatrice E. Weber, Cecile Guillemet, Nicolas Penel, Florence Duffaud

Background: U-LMS and ST-LMS are rare tumours with poor prognosis when metastatic or locally advanced, presenting moderate chemosensitivity mainly to doxorubicine (doxo), ifosfamide (ifo), cisplatin, gemcitabine (gem) and trabectidine (trab). Response rates (RR) in combination therapies (1st line) does not exceed 50% for U-LMS and 35% for ST-LMS. The most active ones are doxo combinations (most of the time with ifo or dacarbazine) and gem + docetaxel (in particular in U-LMS) with a mean response durations of 3 to 6 months. Trab was demonstrated a definite activity on pre-treated LMS (RR of approximately 20% in LMS overall [U-LMS in particular]). In view of these encouraging results on LMS, a study combining trab with doxo as first line therapy for LMS is of interest. **Methods:** Patients (pts) received every 3 weeks, 6 cycles of doxo 60 mg/m^2 followed by trab 1.1 mg/m^2 3-h at day 1, and pegfilgrastim 6 mg on Day 2. Study primary objective: to determine the disease control rate (DCR) (ORR+SD). Secondary objectives: PFS 12 wks, RR by RECIST and duration, OS and toxicities. Patients were stratified into U-LMS *(n* = 5) and ST-LMS *(n* = 62) group. Herein, we report the first results in pts with U-LMS; mature data will be shown in ASCO Meeting. **Results:** 45 pts with U-LMS have been enrolled until November 2012. Median age is 58 years, 38 where of with data collected for at least 1 cycle, 85% had metastatic disease (mostly lung 30/33, liver and bone), and 26 pts have received 6 cycles. For 33 pts with at least 1 disease assessment (every 2 cycles), the ORR was 55% (18 PR) and 13 SD (39%) had SD disease for a DCR of 94% at that time. Presently, the median PFS at 12 weeks is 94,3% [95% IC: 86-100]. Main grade 3-4 toxicities in 187 cycles were neutropenia (51%), febrile neutropenia (7%), thrombopenia (14%), anemia (7%), fatigue (5%), vomiting (6%) and transiet transaminase increase (22%). **Conclusions:** The combination of trab plus doxo seems to be an effective first-line treatment for pts with U-LMS, with meaningful clinical benefits and an acceptable and manageable safety profile. Clinical trial information: 2009-012430-70.

Abstract No: 10517

Results of the randomized phase III trial of trabectedin (T) versus doxorubicin-based chemotherapy (DXCT) as first-line therapy in patients (pts) with translocation-related sarcoma (TRS)

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Background: T is the first of a new class of anticancer agents with a transcription-targeted mechanism of action. In vitro,T interferes with the aberrant transcription factors binding to DNA promoters in TRS. **Methods:** Pts with advanced TRS of the subtypes: myxoid liposarcoma (ML), alveolar soft part sarcoma, angiomatoid fibrous histiocytoma, clear cell sarcoma, desmoplastic small round cell tumor, low grade endometrial stromal sarcoma**,** low grade fibromyxoid sarcoma, myxoid chondrosarcoma and synovial sarcoma, stratified by performance status (0 vs 1-2) and subtype (ML *vs* other TRS) were randomized (1:1 ratio) to T (1.5 mg/m^2 in 24h iv infusion q3wk) or doxorubicin, either single agent 75 mg/m^2 q3wk, or 60 mg/m^2 combined with ifosfamide (6-9 g/m^2 q3wk) as 1st line treatment. Primary endpoint: efficacy of T vs DXCT by comparing progression-free survival (PFS). Secondary: PFS at 6 months (PFS6), response rate (RR), PFS/RR by subtype (ML vs other TRS); overall survival (OS), safety. **Results:** 121 pts enrolled from 22 centers, 88 were confirmed by central pathology review and evaluable for the primary efficacy endpoint by independent review assessment (IR), and all 121 pts randomized were evaluable by investigators' assessment (IA). The main limitation of the study analyses in both arms was high censoring rate (70% IR; 61% IA) mostly due to surgery (~30%) or chemotherapy/ radiotherapy (~30%). PFS results are shown in the Table. PFS6 was not different between arms (IR: 66.4% vs 80.8% p = 0.18/IA: 60.7% vs 62.4% p = 0.88). Current median OS: not reached (NR) for T (24.1-NR) and 21.7 mo. for DXCT (21.2-NR). Safety: Most frequent AEs in both arms were nausea (70% vs 65%), vomiting (44% vs 26%) and fatigue (64% vs 63%). ALT increase G4 occurred in 10% pts treated with T and neutropenia G4 in 25% of pts in the T arm vs 52% in the DXCT arm. **Conclusions:** Although with a high censoring rate, this prospective study suggests that PFS/OS with trabectedin are not significantly different from DXCT in first-line treatment. Clinical trial information: NCT00796120.

	Median PFS (mo.) 95% CI			
	Efficacy population IR *n* = 88		All randomized pts IA *n* = 121	
T	18.8	8.6-NR	17.2	5.9-NR
DXCT	NR	7.1-NR	8.8	5.7-12.7
P value	0.79		0.47	

NR: not reached

Abstract No: 10563

A large retrospective analysis of trabectedin in 885 patients with advanced soft tissue sarcoma

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Background: Trabectedin (Yondelis) is the first marine-derived antineoplastic drug approved in Europe for the treatment of patients with recurrent ASTS or for patients unsuited to receive anthracyclines and ifosfamide. We retrospectively analyzed the RetrospectYon database with patients' data treated with trabectedin between Jan 2008 - Dec 2011. **Methods:** Trabectedin was given at the approved dose of 1.5 mg/m^2 as a 24-h infusion every 3 weeks. Patients who achieved partial response (PR) or stable disease (SD) after 6 cycles could receive maintaining trabectedin treatment. Uni- and multivariate analyses of prognostic factors were performed. **Results:** 885 patients (486 women) from 26 centers in France with ASTS with a median age of 54 years (range 12-84) were included. Most had leiomyosarcoma (36%), liposarcoma (18%) or synovial STS (11%). At baseline, performance status (PS) was 0 in 26%, 1 in 47% and > 1 in 27% of patients. A median of 4 trabectedin cycles (range 1-28) was given as a 2nd (41%), 3rd (39%) or ≥ 4th (20% of patients) treatment line. Toxic death and unscheduled re-hospitalization occurred in 0.5% and 8% of patients, respectively. The objective response rate was 15% (6 complete and 127 PR), and SD rate was 45.5% (*n* = 403). After a median follow-up of 22.6 months (range 0.03-51.2), the patients who received trabectedin as 2nd, 3rd or ≥4th line had the median PFS of 4.3, 4.2 and 3.4 months, respectively, and the median OS of 12.9, 12.3 and 9.5 months. Multivariate analysis identified liposarcoma, leiomyosarcoma, angiosarcoma, undifferentiated pleomorphic sarcoma (UPS) and trabectedin line as independent prognostic factors for PFS, and UPS, angiosarcoma, rhabdomyosarcoma, gender, PS and trabectedin line for OS. After 6 cycles, 205 of the 273 patients with non-progressive disease received trabectedin as maintenance treatment and obtained a superior PFS (median 11 *vs.* 7.2 months, $p = 0.0001$) and OS (median 25.1 *vs.* 16.9 months, $p < 0.0001$) that those who stopped trabectedin after 6 cycles. **Conclusions:** Patients with ASTS treated with trabectedin had PFS and OS comparable or better to those observed in phase II/III trials. Trabectedin maintenance beyond 6 cycles is associated with improved OS and warrants further exploration.

Abstract No: 10576

Safety of trabectedin (T) in elderly patients (pts) with advanced soft tissue sarcoma (STS)

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Background: T is a marine-derived cytoxic alkaloid approved in the European Union for further-line chemotherapy of advanced STS. Most common side effects are fatigue, neutropenia and transient transaminitis. Overall the drug is well tolerated with no cumulative toxicity. Studies in elderly pts are lacking. **Methods:** We retrospectively reviewed all pts ≥65 year-old, with pre-treated advanced STS, who received T at our Institution from January 2002 to January 2013, focusing on tolerability. All patients received premedication with dexamethasone 4 mg p.o. bid 24 hours prior to T administration. Treatment toxicity was graded according to CTCAE (v 4.0). **Results:** Fourty-two pts were identified (males = 22, females = 20; median age = 69 years, range 65-82; ECOG PS 0 = 1 pt, 1 = 38 pts and 2-3 = 3 pts; main histotypes = 22 liposarcoma: 12 myxoid-round cell liposarcoma, 10 well/dedifferentiated liposarcoma, 17 leiomyosarcoma, 2 synovial sarcoma, 4 others; disease extent = 34 metastatic and 8 locally advanced; median line of administration of T = 3rd, range 1st-5th; median T dose = 2.2 mg, range = 2.7-1.7 mg). A total of 319 cycles were administered (median 6, range = 1-23). Starting dose was 1.3 mg/mq in 37 pts and 1.1 mg in 5 pts. The most common side effects were: fatigue (all grades: 19% of cycles), reversible myelosuppression, mainly neutropenia (grade 3-4: 50%), transient transaminitis (grade 3-4: 21%). Eighteen pts needed a dose reduction: inter-cycle transient transaminitis (3 pts), neutropenia (13 pts), asthenia (2 pts). In 7 patients, cycles needed to be delayed as well. Three pts interrupted T due to toxicity: grade 3 thrombocytopenia in 1 pt and grade 4 neutropenia in 2 pts. **Conclusions:** This retrospective analysis confirms that T is well tolerated in elderly pts. No major differences were found in the safety profile compared to historical controls, except a higher incidence of myelosuppression, which however was not influential on subsequent T administration.

Abstract No: e21509

Efficacy of trabectedin for advanced soft tissue sarcoma (ASTS): A retrospective single center analysis

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Background: Trabectedin (Yondelis) is the first marine-derived antineoplastic drug approved in Europe for the treatment of patients with recurrent ASTS or for patients unsuited to receive anthracyclines and ifosfamide. We retrospectively analyzed patients with ASTS treated with trabectedin from Nov. 2006 to April 2012. **Methods:** Trabectedin was given at the approved dose of 1.5 mg/m^2 as a 24-h infusion every 3 weeks. An analysis of response rate, time to progression (TTP) and overall survival (OS) and univariate analyses of prognostic factors were performed. **Results:** Overall, 39 patients (24 men) with mostly high-grade *(n* = 29) ASTS with a median age of 57 years (range 20-81) were analyzed. Most had L-type STS (leiomyosarcoma *n* = 10; liposarcoma *n* = 3), undifferentiated pleomorphic sarcoma *(n* = 11), sarcoma NOS *(n* = 5), or synovial STS *(n* = 2). Eight had one of 6 very rare STS. At baseline patients had metastatic *(n* = 21), bulky *(n* = 4) or metastatic/bulky *(n* = 14) disease and were pretreated with a median of 2 prior chemotherapy lines (range: 0-3; 4 patients received adjuvant chemotherapy only), including anthracycline-based chemotherapy (*n* = 30), gemcitabine plus dacarbazine (GEM-DTIC; *n* = 18), other (*n* = 20). Patients received a median of 4 trabectedin cycles (range 1-34). Among 37 evaluable patients best responses as per RECIST were partial response (PR, *n* = 7), stable disease (SD > 3 months, *n* = 9, 5 had SD > 6 months) and disease progression (*n* = 19), and 5 patients had a decrease in tumor density. Responses to trabectedin and GEM-DTIC did not exclude responses to the other regimen suggesting the feasibility of sequential treatment. After a median follow-up of 9.37 months, median TTP and OS were 4.4 months (95% CI: 3.5-5.4) and 9.7 months (95% CI: 4.5-14.9), respectively. Univariate analyses identified low/medium-grade STS and growth modulation index > 1.13 as favorable prognostic factors for TTP, and retroperitoneal/visceral localization, L-type and rare STS and low/medium-grade STS for OS. **Conclusions:** The results of this real-life retrospective analysis confirmed the findings of previous trials showing that trabectedin is active drug for ASTS.

Abstract No: e13540

Heat-shock (H-S) and trabectedin efficacy in human soft-tissue sarcoma (STS) cells in vitro

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Background: Regional hyperthermia improves response and survival when combined with chemotherapy in patients with high-risk STSs (Issels, R.D. Lancet Oncol 2010). Trabectedin is the first marine-derived antineoplastic drug approved in Europe for the treatment of advanced STS after failure of anthracyclines and ifosfamide, or for patients who are unsuited to receive these drugs. Trabectedin's cytotoxicity is associated with the induction of lethal DNA double-strand breaks (DSB). The rationale to combine trabectedin with H-S is that heat-exposure sensitizes tumor cells by inhibiting the repair of induced DSBs (Krawczyk, P.M. PNAS 2011). **Methods:** Combinations of trabectedin and H-S at clinically relevant temperatures were examined in 3 different human cell lines: Osteosarcoma (U2Os), liposarcoma (SW872) and synovial sarcoma (SW982). Cells were treated with trabectedin at the dose of 500-4000 pM for 3 hours. H-S was applied in an incubator at 41.8°C and 43°C for 90 or 150 min before, during or after trabectedin incubation. Cytotoxicity was assessed measuring clonogenic survival of cells. Expression of BRCA2, which recruits homologous recombination repair recombinase Rad 51 to DSBs, was measured by Western Blot (WB). Recruitment of Rad 51 and the amount of gH2AX positive DSB-repair-foci were analysed by immunocytochemistry (ICC). **Results:** All cell lines showed reduced viability after increasing doses of trabectedin at 37°C. Combined treatment with trabectedin and H-S additionally enhanced cytotoxicity of trabectedin with strongest effects observed after simultaneous administration of both. WB-analysis showed strong heat-dependent reduction of BRCA2 expression. ICC revealed that recruitment of Rad 51 to DSBs was reduced after heat exposure at 41.8°C and abolished after exposure at 43°C. Accordingly, combined treatment significantly increased the amount of cells with severe DNA damage (> 50 DSBs). **Conclusions:** Combined treatment with trabectedin and H-S *in vitro* resulted in significantly enhanced cytotoxicity that was accompanied by elevated DNA-damage in term of DSB-accumulation. The mechanisms of interaction between trabectedin and H-S concerning DNA repair are under investigation.

Abstract No: e21517

Tumor response assessment in locally unresectable or metastatic soft tissue sarcoma (aSTS) patients (pts): A three-year Regina Elena Cancer Institute (IRE) experience with trabectedin therapy

Carmen Nuzzo, Vincenzo Anelli, Silvia Carpano, Angela Torsello, Domenico Sergi, Renato Covello, Carmine Zoccali, Vanja Vaccaro, Franco Di Filippo, Diana Giannarelli, Virginia Ferraresi, Francesco Cognetti

Background: Trabectedin has emerged as an effective agent for aSTS pts pretreated with anthracyclines and ifosfamide. Recent data suggest that RECIST criteria could underestimate tumor response. **Methods:** ASTS pts who received trabectedin as 2nd or further line of treatment were retrospectively reviewed. Tumor response was assessed using RECIST, mChoi and MASS criteria. A good response according to mChoi Criteria was defined as ≥ 10% mean decrease in tumor size or a ≥ 15% decrease in tumor attenuation on contrast-enhanced CT images. Predominantly solid enhancing target lesions were evaluated for marked central necrosis or marked decreased attenuation on axial contrast-enhanced CT images by MASS Criteria. **Results:** From May 2009 to December 2012, 30 pts with aSTS received trabectedin; pts characteristics are summarized in the table. Median number of previous treatment lines was 2 (range 1-5); median number of cycles administered was 4 (range 1–22 cycles). Treatment was well tolerated; main causes of dose-reduction were hematological and liver toxicities. Median progression free survival (PFS) was 8 wks (95% CI: 2-14); median overall survival (OS) was 44 wks (95% CI: 18-94). According to RECIST, 4 pts (15.4%) obtained a partial response (PR)), 9 pts (34.6%) achieved a stable disease (SD); tumor control rate was 50%. 13 pts (43%) obtained a progression of disease (PD). CT Scans of 13 pts were available for comparison of different response assessment methods (2 RP, 5 SD, and 6 PD). In our small series of pts concordance between the three radiologic methods tested was 90%. **Conclusions:** In aSTS patients treated with trabectedin, there is substantial concordance between mChoi, MASS and RECIST criteria. Prospective validation of the potential role of mChoi and MASS criteria in this setting is warranted.

Abstract No: e16543

Prolonging the platinum-free interval (PFI) with trabectedin to allow retreatment with platinum-based chemotherapy in patients with platinum-refractory and -resistant recurrent ovarian cancer (PROC)

Antonio Casado Herraez, Hector Callata, Aranzazu Manzano, Pluvio Coronado, Teresa Alonso, Barbara Sanchiz, Pablo Gajate, Santiago Cabezas, Jose Antonio Vidart, Eduardo Diaz Rubio

Background: Dose-dense therapy and administration of sequential non-platinum agents in PROC plays a role in reverting platinum-resistance and may improve the prognosis of such patients over years (Bamias A, 2013). The PFI extension is one of the current strategies to improve survival in partially platinum-sensitive (PPS) ROC, with a PFI 6-12 months (Poveda A, 2011). Trabectedin is a minor groove DNA-binder, which may play a role in reverting platinum resistance in patients with PROC and PPS ROC. **Methods:** Trabectedin 1.1-1.5 mg/m^2 as single agent was given as a 3-h infusion every 3 weeks with antiemetic and steroid premedication. Tumor response was assessed every 12 weeks. **Results:** Overall, 27 patients (24 with PROC and 3 with PPS ROC) treated from 2003 to 2013 in a single institution were included in the analysis. The patients had a median age of 63 years (range 45-81), most had serous-papillary (67%), clear-cell (11%), endometrioid (7%) and other (15%) histological subtypes and received a median of 5 prior chemotherapy lines (range: 1-9), 89% of whom also received other non-platinum agents. A median of 4.9 trabectedin cycles (range 1-14) was given. The overall response rate (ORR) was 15%, with a median duration of response of 16.5 weeks (range 5.86-44.43), while 41% of patients achieved stable disease (SD) lasting ≥4 months as best response. Thirteen of 27 patients were retreated with platinum-based chemotherapy after progression with trabectedin treatment. The ORR to platinum retreatment was 54% (n = 7) and SD was achieved in 8% (n = 1) of these patients, for an overall clinical benefit of 61%. **Conclusions:** Intercalation of a non-platinum therapy with trabectedin prior to subsequent platinum rechallenge may contribute to prolong PFI and to re-sensitize the patients with PROC and PPS ROC to further platinum-based therapies leading to a significant clinical benefit. Further prospective studies are warranted to determine the contribution of sequential treatments with trabectedin in patients with PROC and PPS ROC.

Abstract No: e16538

Efficacy and safety outcomes in heavily pretreated patients (pts) with relapsed ovarian cancer (ROC) after single-agent trabectedin

Vanda Salutari, Gabriella Ferrandina, Bruno Vincenzi, Marco Marinaccio, Emanuele Naglieri, Vera Loizzi, Silvia Carpano, Domenica Lorusso, Rosa Pasqualina De Vincenzo, Distefano Maria Grazia, Giulia Amadio, Giuseppe Tonini, Giovanni Scambia

Background: Trabectedin is a marine-derived antineoplastic agent, initially isolated from the tunicate *Ecteinascidia turbinata* and currently produced synthetically. In combination with pegylated liposomal doxorubicin, trabectedin is approved in Europe for the treatment of pts with platinum-sensitive (PS) ROC. The aim of this multicenter, retrospective study was to evaluate the efficacy and safety of single agent trabectedin in the palliative treatment of heavily pretreated patients with ROC. **Methods:** Patients with measurable ROC and at least 2 prior treatments were eligible. Patients received single agent trabectedin (1.3 mg/m^2, n = 56; 1.1 mg/m^2, n = 42) as a 3-hour i.v. infusion every 3 weeks. An analysis of the overall response rate (ORR; primary end point) as per RECIST, time to progression (TTP) and overall survival (OS) were performed. **Results:** Overall, 98 pts were enrolled: median age at diagnosis of recurrence was 53 years (range: 29-79). Forty-four pts (44.9%) were fully PS, while 23 (23.5%) were partially PS and 31 (31.6%) were platinum-resistant. Median number of previous chemotherapy regimens was 4 (range: 2-6). The ORR was 28.6% (5 complete and 23 partial responses); 32 pts (32.6%) experienced stabilization of disease, which lasted ≥6 months in 2 pts, while 38 (38.8%) pts progressed during treatment. The ORR was higher in PS pts (38.6%) compared to partially PS (26.1%) and platinum resistant cases (16.1%), although the statistical significance was not reached (p = 0.071). No difference in the ORR was found according to number of prior treatments or trabectedin dose. After a median follow-up of 8 months, median TTP and OS were 5 and 13 months, respectively. The most common grade 3/4 toxicities were transient and non-cumulative anemia and neutropenia in 6.1% and 17.5% of cases, respectively. AST and ALT were increased in 7.1% and 13.3% of pts. Cardiac toxicity was documented in 4 anthracycline pretreated pts, of whom one died due to acute arrhythmia. **Conclusions:** Single agent trabectedin represents a valid approach in the palliative treatment of pts with heavily pretreated ROC with meaningful clinical benefit and acceptable and manageable safety profile.

Abstract No: 5559

Phase II study of trabectedin in pretreated patients with recurrent epithelial ovarian cancer (REOC)

Marco Marinaccio, Emilia Mele, Vito Lorusso, Valeria Vincenza Fumarulo, Fausta Sozzi, Ettore Cicinelli

Background: The prognosis of patients with REOC is extremely poor after several lines of chemotherapy. The choice and timing of therapies must be individualized to optimize survival and quality of life. This open-label, nonrandomized, phase II study was aimed at evaluating efficacy and toxicity of Trabectedin as a single-agent therapy in patients with preteated Recurrent Epithelial Ovarian Cancer (REOC). **Methods:** Sixteen patients (median age 51 yrs, range 44 – 71) with REOC who progressed after 2 (18.7%), 3 (56.3%) or 4 (25.0%) previous lines of chemotherapy were treated with Trabectedin at the dose of 1.1 mg/m^2 via a 3-hour i.v. infusion with dexamethasone pretreatment every 3 weeks until disease progression, unacceptable toxicity or when a stability of disease was reached. Clinical objective response was the primary efficacy endpoint; the secondary one was safety. Response to treatment was assessed according to Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1), and toxicities were graded according to NCI Common Toxicity Criteria, version 2.0. **Results:** The median number of treatment cycles per patients was 5 (range, 2-9 cycles). A total of 81 cycles were administered. A dose reduction was never required. Main toxicities included anemia (20.9%), leucopenia (15.0%), thrombocytopenia (4.5%) and asthenia (22.2%). No deaths were attributable to therapy. No one showed complete response, while 9/16 partial response (56.2%) and 4/16 stable disease (25.0%) were observed. 3/19 pts (18.8%) progressed on therapy. The median progression-free interval was 18 weeks in patients with partial response; stable disease was maintained for a median time of 12 weeks. **Conclusions:** Trabectedin 1.1mg/m^2 given as a 3-hour i.v. infusion every 3 weeks was well tolerated and has confirmed a very interesting antitumor activity in this heavily pretreated population and it seems also to be a very tolerable regimen. The co-treatment with dexamethasone improves the safety of Trabectedin by reducing drug-induced myelosuppression and hepatotoxicity. Trabectedin has a manageable toxicity profile, and can be safely administered thanks to its secure action profile also in patients with no other viable therapeutic options.

Abstract No: 5566

Exploratory analysis of nibrin in advanced ovarian cancer (AOC) patients treated in the phase III OVA-301 trial

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Background: Nibrin (p95/NBS1) is a protein with an essential function in DNA double-strand break repair by homologous recombination. Therefore, we have investigated its value as a possible biomarker in patients with AOC by immunohistochemistry (IHC). **Methods:** IHC staining was performed in 138 samples from a subset of patients that have participated in the phase III OVA-301 trial, in which the combination of trabectedin plus pegylated liposomal doxorubicin (PLD) or PLD alone were randomly administered for advanced disease after failure of platinum-based chemotherapy (Monk 2010; Monk 2012). A computerized image analysis system was used to calculate the total percentage of nibrin-positive cells. Nibrin expression was considered as a continuous variable. The analysis of overall response rate (ORR) and progression-free survival (PFS) was based on independent oncologist assessment. Overall survival (OS) was defined from randomization to death/last contact. All the comparisons had an exploratory nature; an alpha cut-off value of 0.05 (two-sided) was established as statistically significant. **Results:** For PFS, there was a statistically significant correlation between high levels of nibrin and short PFS (HR = 1.014, 95% CI: 1.004-1.024, $p = 0.0047$). Similarly, for OS, there was a statistically significant correlation between high levels of nibrin and worse OS (HR = 1.009, 95% CI: 1.001-1.017, $p = 0.0295$). A multivariate analysis showed that high levels of nibrin were independently correlated to a worse PFS (HR = 1.012, 95% CI: 1.002-1.022, $p = 0.0147$) and to a worse OS (HR = 1.010, 95% CI: 1.002-1.018, $p = 0.0192$). After stratification according to platinum-sensitivity, high nibrin showed a significant correlation with lower ORR (ORR = 1.02, 95% CI: 1.01-1.03, $p = 0.0009$), short PFS and OS values only in the platinum-sensitive patients. **Conclusions:** The results point out the potential importance of nibrin expression in the clinical outcome of patients with AOC. In particular, high protein expression of nibrin seems to be associated with a worse clinical outcome. Prospective clinical trials evaluating the clinical usefulness of this marker with other standard of care treatments are warranted. Clinical trial information: NCT00113607.

Abstract No: e16519

Combination chemotherapy with temsirolimus and trabectedin in patients with heavily pretreated clear cell carcinoma of the ovary

Masashi Takano, Hiroko Kouta, Naoki Sasaki, Kazuya Kudoh, Tsunekazu Kita, Ryoko Kikuchi, Katsutoshi Oda, Tomoko Goto, Kenichi Furuya, Yoshihiro Kikuchi

Background: Clear cell carcinoma (CCC) of the ovary showed exceedingly chemo-resistant phenotype, especially in the case with recurrent or refractory to previous therapy. An inhibitor against the mammalian target of rapamycin (mTOR), temsirolimus, has been reported to be effective in renal CCC. Additionally, a marine natural product, trabectedin, had activity against recurrent ovarian cancers. We evaluated the effect of combination therapy with temsirolimus and trabectedin for patients with recurrent/refractory CCC of the ovary. **Methods:** Patients with recurrent/refractory CCC of the ovary were treated with weekly regimen using two drugs: 10mg/m^2 of temsirolimus and 0.15mg/m^2 of trabectedin (3 weeks, one week rest) with written informed consents. Treatment was continued until development of progressive disease (PD) or unmanageable adverse effects. Responses were evaluated by RECIST criteria, and adverse effects were analyzed by NCI-CTCAE v4.0. **Results:** A total of 12 patients treated with the regimen, and there were no cases that discontinued the therapy due to toxicities. Median age was 60 years (range: 42-69), and median number of previous chemotherapy was 3 (range: 1-5). All cases were assessable by RECIST and CTCAE. One patient (8%) had a complete response (CR), and another (8%) achieved a partial response (PR), and 4 patients (33%) had stable disease (SD) beyond three months, resulting in clinical benefit rate (CBR; CR+PR+SD > 3 month) of 50%. Median response duration in CBR case was 3.5 months (range: 3-12+). There were no cases that developed toxicities more than grade 2. **Conclusions:** The present preliminary study demonstrated combination therapy with temsirolimus and trabectedin was effective in patients with recurrent/refractory CCC of the ovary. These results warrant further study in such clinical settings.

Abstract No: e13512

Phase I/IIa, randomized, open-label, drug-drug interaction study of trabectedin and rifampin in patients with advanced cancer

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Background: Trabectedin (Yondelis; T) is a tetrahydroisoquinoline compound initially isolated from the marine tunicate, *Ecteinascidia turbinata,* and currently produced synthetically. It is primarily metabolized by the cytochrome P450 (CYP)3A4 enzyme. Thus, potent inducers or inhibitors of this enzyme may alter the plasma concentrations of T. This study assessed the effects of rifampin (R), a strong CYP3A4 inducer, on the pharmacokinetics (PK) and safety of T. **Methods**: In this 2-way crossover study, patients (≥18 years of age) with locally advanced or metastatic disease were randomized (1:1) to receive one of the 2 treatment sequences: sequence 1: R plus T followed 28 days later by T; sequence 2: T followed 28 days later by R plus T. During each sequence, R (600 mg/day) was administered for 6 consecutive days and T (1.3 mg/m^2, IV) was administered over a 3 hour infusion. Dexamethasone (20 mg, IV) was administered before T administration. PK and safety of T were evaluated with and without coadministration of R. **Results:** Of the 11 enrolled patients, 8 were PK evaluable. Coadministration of R with T decreased mean maximum plasma concentration (C_{max}) by approximately 22% and mean area under the plasma concentration-time curve from time 0 to the last quantifiable concentration (AUC_{last}) by approximately 31% (Table 1). Coadministration of R with T also resulted in 23% shorter elimination half-life. Overall, the safety profile of T was comparable when administered alone or with R. **Conclusions:** In comparison with T alone, coadministration of R resulted in reduced systemic exposure of T in these 8 patients, as measured by C_{max} and AUC_{last}. The coadministration of potent inducers of CYP3A4 with T may increase the metabolic clearance of T. Clinical trial information: NCT01273480.

Relative bioavailability of trabectedin when administered with and without rifampin.

Parameters	Treatment (n = 8)	Geometric mean	Ratio of geometric means (90% CI[a]) (R + T/T alone)	Intrapatient CV%
C_{max} (ng/mL/mg)	R+T	2.937	78.48 (70.65 - 87.17)	10.85%
	T	3.743		
AUC_{last} (ng/mL/mg)	R+T	15.194	68.51 (60.57 - 77.49)	12.73%
	T	22.178		

Abbreviations: T, trabectedin; R, rifampin. a Ratio parameter means (expressed as percent) transformed back to linear scale. T used as reference.

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