showed a raw association with DFS (Table 1, unadjusted analysis), while propensity score analysis did not show statistically significant effects for chemotherapy regimens (anthracycline/taxane versus anthracycline) and hormone therapy. Of note, patients who were both ER-negative and lymph node-positive (ER~N+) were identified as those at highest risk of relapse (Table 1, adjusted analysis) with the 3-year DFS of 0.76 [95% confidence interval (CI) 0.63–0.85] versus 0.96 (95% CI 0.93–0.98) in the non-ER~N+.

Thus, according to results by Rodrigues et al. indicating that tumor size is not associated to relapse in T1a, bN0 population treated with trastuzumab-adjuvant therapy, we found the same lack of association when considering all the T1 subgroups. These findings support the notion that the clinical decision to treat small tumors with trastuzumab should be dictated more by pathological tumor characteristics than by tumor size.

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funding
This work was supported by Associazione Italiana per la Ricerca sul Cancro (AIRC) (grant no. 1224) (SM) and Roche s.p.a (no. INT02/07). The sponsor has no role in study design, collection analysis, interpretation of the data, in the writing of the manuscript or in the decision to submit the manuscript.

disclosure
The authors have declared no conflicts of interest.

references
doi: 10.1093/annonc/mdu058
Published online 20 February 2014

The histone deacetylase inhibitor panobinostat is active in patients with advanced pretreated ovarian sex-cord tumors

Ovarian sex cord tumors (OSCT) account for only 7% of ovarian malignancies and include granulosa cell tumor (GCT), Sertoli–Leydig cell tumor, fibrothecomatos tumor and OSCT not otherwise specified. These tumors often have an indolent clinical behavior and are generally associated with favorable prognosis. However, once the tumor has spread outside the pelvis (stages III and IV), 5-year survival is limited and varies between 0 and 20% depending on histological subgroups [1]. Surgery is the cornerstone of therapy for localized disease and probably has a role in advanced disease as well. Patients with metastatic and/or recurrent disease that are not amenable to complete surgical excision are usually treated with first-line cisplatin-based chemotherapy (bleomycin, etoposide and cisplatin or carboplatin and paclitaxel) [2]. However, data to guide further therapy beyond are limited. Aside from the recently reported FOXL2 mutation found in GCT, knowledge regarding the biology of OSCT is limited, although their natural history suggests a different biology from that of carcinomas.

We report here on the interesting activity of the histone deacetylase (HDAC) inhibitor panobinostat (formerly LBH589, Novartis, Basel, Switzerland) in this rare disease. HDACs were discovered through their HDAC activity, but other substrates include the chaperone protein HSP90, p53 and tubulins. Activity of vorinostat, an HDAC inhibitor, had been observed in a patients with granulosa cell tumor treated in a phase 1 trial [3] and prompted us to further explore the activity of this class of compound in OSCT.

The patients were enrolled in a phase II trial and provided written informed consent before any trial-related procedure. This trial enrolled mainly patients with soft tissue sarcoma and has been published elsewhere [4], but also allowed the enrollment of patients with advanced OSCT tumors previously treated with at least one line of cisplatin-containing chemotherapy (trial number NCT01136499). Details regarding trial design were previously described [4]. Briefly, patients were required to have RECIST-defined disease progression before study entry. Computed tomography scans were repeated every 6 weeks for the first 12 weeks and every 8 weeks thereafter. Panobinostat (LBH589) was administered orally, at doses of 40 or 20 mg thrice a week (Monday, Wednesday, Friday) on 28-day cycles. Dose interruption and dose reductions were allowed to manage toxicity.

Five patients with advanced pretreated OSCT were recruited, their age ranged from 35 to 65 years (Table 1). All patients had recurrent disease following surgery and had received at least one line of prior chemotherapy for advanced disease (number of prior lines of chemotherapy: 1–4, Table 1). Safety of panobinostat was not different from that observed in patients with sarcoma and adverse events consisted mainly of hematological toxicity (anemia, thrombocytopenia), gastrointestinal disorders (nausea and diarrhea) and fatigue. All five patients required at least one dose reduction at some point in the study, mostly because of thrombocytopenia. None of these patients had significant electrocardiogram (ECG) findings (e.g. corrected QT
interval prolongation). All patients were assessable for response: there was one complete and one partial response, which both lasted over a year, and three other patients had stable disease as their best response (Table 1). Both cases of granulosa cell tumors where positive for FOXL2, while two cases of Sertoli–Leydig cell tumors were negative for FOXL2, while analysis was not possible in one case. Three patients had tumor samples available for further molecular analysis (patient # 1-01, 1-10 and 1-15). Interestingly, all three patients, despite differences in histological diagnosis, displayed relatively similar and monotonous comparative genomic hybridization (CGH) profile with loss of chromosome 16q, and partial (22q) or complete loss of chromosome 22 was also seen in all three patients. Monosomy 22 was previously described in granulosa cell tumors of the ovary, together with trisomy 14 (which we also detected in one patient) [5]. Other alterations included gain of 1q (two patients) and loss of 8p (one patient). No homozygous gene deletion or gene amplification was seen in any patient. No conclusion could be drawn regarding the correlation of cytogenetic alterations and response or outcome.

Our data suggest that panobinostat may have interesting activity in patients with advanced OSCT and confirm the preliminary signs of activity seen with vorinostat in this rare disease. Based on these promising results, a larger trial assessing an HDAC inhibitor in patients with advanced OSCT is currently in preparation.

Table 1. Characteristics and outcome of the five patients with ovarian sex cord tumor treated with panobinostat

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Diagnosis</th>
<th>Age (years)</th>
<th>Dose reduction</th>
<th>Cause for dose reduction</th>
<th>Number of previous line of chemotherapy</th>
<th>Best response</th>
<th>Progression-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-1</td>
<td>Adult granulosa</td>
<td>61.8</td>
<td>30 mg × 3/week</td>
<td>thrombopenia</td>
<td>4</td>
<td>SD</td>
<td>2.7</td>
<td>24.3</td>
</tr>
<tr>
<td>1-10</td>
<td>Sertoli–Leydig</td>
<td>40.7</td>
<td>20 mg × 2/week</td>
<td>thrombopenia</td>
<td>2</td>
<td>PR</td>
<td>12.7</td>
<td>30.4</td>
</tr>
<tr>
<td>1-15</td>
<td>Adult granulosa</td>
<td>44.7</td>
<td>20 mg × 2/week</td>
<td>diarrhea</td>
<td>1</td>
<td>CR</td>
<td>24.6</td>
<td>28.3</td>
</tr>
<tr>
<td>2-1</td>
<td>Sertoli–Leydig</td>
<td>64.9</td>
<td>15 mg × 2/week</td>
<td>thrombopenia</td>
<td>2</td>
<td>SD</td>
<td>4.9</td>
<td>33.0</td>
</tr>
<tr>
<td>4-1</td>
<td>Sertoli–Leydig</td>
<td>35.8</td>
<td>20 mg × 3/week</td>
<td>thrombopenia</td>
<td>2</td>
<td></td>
<td>8.4</td>
<td>17.4</td>
</tr>
</tbody>
</table>

Table 1. Characteristics and outcome of the five patients with ovarian sex cord tumor treated with panobinostat

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disclosure

This study was supported by an unrestricted research grant from Novartis Pharma, who also provided the study drug free of charge. PAC has received honoraria and travel reimbursement from Novartis. JYB and IRC have received honoraria, travel reimbursement and research funding from Novartis. CES was an employee of Novartis at the time the study was designed and during the enrollment period. JYB also received honoraria and research funding Merck Sharp Dohme and Glaxo Smith Kline. PAC, JYB and IRC have received honoraria from Servier and CES is currently an employee of Servier.

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doi: 10.1093/annonc/mdu045
Published online 20 March 2014

Medical oncology: in search of a definition

As every evolving science, medical oncology (MO) needs a continuous effort in setting an evolving definition. MO is under a tremendous tension. On one side, the increasing number of cancer patients and complexity of care are dramatically expanding the request for services and knowledge. On the other side,