Risk of Second Primary Malignancies (SPMs) Following Bortezomib (Btz)-Based Therapy: Analysis of Four Phase 3 Randomized Controlled Trials in Previously Untreated or Relapsed Multiple Myeloma (MM)

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**Background:** MM patients have a significantly increased risk of developing certain SPMs subsequent to their initial diagnosis, including a 3.49-fold increased risk of leukemia and, specifically, an 8.32-fold increased risk of acute non-lymphocytic leukemia (but no overall increased risk of solid tumor SPMs; Surveillance, Epidemiology and End Results [SEER] data 1973–2000). The relative SPM risk increases with age and time after initial diagnosis; the risk of leukemia rises from a 1.22-fold increase within 1 year after diagnosis to 3.12-fold, 7.01-fold, and 5.45-fold increases at 1–4, 5–9, and ≥10 years, respectively. An elevated risk of SPMs may be particularly associated with the use of specific therapeutic agents, including conventional or high-dose cytotoxic chemotherapy. Here we report an analysis of data from four phase 3, randomized, controlled trials of Btz alone or in combination to determine whether Btz treatment is associated with an increased SPM risk.
Methods: Data were reviewed from: 1) the APEX study of Btz versus high-dose dexamethasone (Dex), and 2) the MMY-3001 study of Btz plus pegylated liposomal doxorubicin (PLD) versus Btz in patients with relapsed or refractory MM after 1–3 prior therapies; 3) the VISTA study of Btz plus melphalan-prednisone (VMP) versus MP in previously untreated transplant-ineligible patients; and 4) the HOVON65/GMMG-HD4 study of Btz, doxorubicin, and Dex (PAD) induction plus Btz maintenance post-transplant versus vincristine, doxorubicin, and Dex (VAD) induction plus thalidomide (Thal) maintenance in previously untreated transplant-eligible patients. Planned duration of Btz therapy was 39 weeks in APEX, 24 weeks in MMY-3001, 54 weeks in VISTA, and 9 weeks induction plus 2 years of maintenance in HOVON65/GMMG-HD4. For APEX, MMY-3001, and VISTA, clinical trial databases were reviewed for events within the MedDRA system organ class of ‘neoplasms’, and new malignancies developing during or after treatment were recorded (excluding non-melanomatous skin cancers and in situ malignancies). In addition, for VISTA, data were obtained from an SPM survey after a median follow-up of 5 years. For HOVON65/GMMG-HD4, data were prospectively collected; median follow-up was 42 months. The incidence rate (IR) of SPMs was expressed as the number per 100 patient-years (pt-yrs).

Results: The risk of SPMs with Btz-based therapy appeared uniformly low across all four phase 3 studies in different MM patient populations (Table). A total of 25 SPMs were seen in 1718 Btz-treated patients, including three cases of acute myeloid leukemia/myelodysplastic syndromes, one B-cell malignancy, and one case of cutaneous T-cell lymphoma (in a patient with substantial prior alkylating agent exposure for treatment of MM), plus 20 reports of solid tumors (reflecting the higher overall incidence of these tumors). The IR ranged from 0 in the single-agent Btz arm of MMY-3001 to 1.66 with VMP in VISTA, with an IR of 0.88 in APEX and 0.3 in the PAD arm of HOVON65/GMMG-HD4; median age of Btz-treated patients was highest in VISTA, at 71 years. Overall rates (%) also appeared higher in VISTA, probably due to the longer follow-up and older population, plus the potential effects of concomitant chemotherapy. In the three studies with non-Btz control arms, the IR did not appear to be increased with Btz-based therapy versus the control arm, and across all Btz-containing arms in the four studies, the IRs for hematologic malignancies and solid tumors were consistent with SEER estimates (2004–2008 data) of the overall incidence of malignancies in the US population, of 1.1, 1.9, and 2.4 per 100 pt-yrs in individuals aged 55–64, 65–74, and 75–84 years, respectively.

Conclusions: Btz-based therapy for MM does not appear to be associated with an increased risk of either hematologic or solid tumor SPMs, with IRs consistent with SEER data for IRs in the overall US population.
ASH 996

Second Primary Malignancies in Newly Diagnosed Multiple Myeloma Patients Treated with Lenalidomide: Analysis of Pooled Data in 2459 Patients

Data in 2459 Patients

Program: Oral and Poster Abstracts
Type: Oral
Session: 653. Myeloma - Therapy, excluding Transplantation: Prospective Trials in Plasma Cell Disorders
Tuesday, December 13, 2011: 7:30 AM
Ballroom 20BC (San Diego Convention Center)

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Background: The risk of developing a tumor is 2.1% per year of life in the general population older than 65 years. In MGUS, the incidence of AML/MDS is increased 8 fold compared with normal population, this observation supports a role for non-treatment related factors in the causation of AML/MDS in plasma-cell dyscrasias (Blood, July 27, 2011). In multiple myeloma (MM) patients, the risk of second primary malignancy (SPM) is influenced by age and the use of alkylating agents.

Methods: We examined SPM incidence rates (IRs) per 100 person-years in 2459 newly diagnosed MM patients, enrolled in 9 experimental trials of the European Myeloma Network (RVMM EMN 01, RVMM EMN 441, RVMM PI 026, RVMM PI 302, RVMM PI 209, GIMEMA MM 03 05, GIMEMA MM 04 05, GISMM 2001, HOVON 87). 287 patients received cyclophosphamide-lenalidomide-corticosteroids (CRC), 685 melphalan-prednisone-lenalidomide (MPR), 484 high-dose melphalan followed by lenalidomide maintenance (MEL200-R), 164 melphalan-prednisone (MP), 328 MP-thalidomide (MPT), 257 MP-bortezomib (MPV), 254 MP-bortezomib-thalidomide (VMPT). This post hoc analysis was restricted on pooled data from 1798 patients with at least 1 year of follow-up.

Results: As of March 2011 cut-off, median follow-up was 28 months. Median age was 69 years, 49% of patients were aged 65-74 years, and 19% aged ≥75 years. Total cases of SPMs were 30/1798 (IR 0.72), including 8 hematologic (acute leukemia) and 22 solid cancers (gastrointestinal, lung, breast, skin, gynecologic). No cases of SPMs were reported in patients receiving cyclophosphamide and lenalidomide.

<table>
<thead>
<tr>
<th></th>
<th>CRC/MPR (N=534)</th>
<th>MEL200-R (N=366)</th>
<th>MP/MPT/MPV/VMPT (N=898)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Invasive SPM</strong></td>
<td>6</td>
<td>7</td>
<td>17</td>
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<tr>
<td><strong>Hematologic SPM</strong></td>
<td>1</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td><strong>Solid tumor SPM</strong></td>
<td>5</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td><strong>Incidence rate</strong></td>
<td>0.66</td>
<td>0.87</td>
<td>0.67</td>
</tr>
<tr>
<td><strong>Incidence rate</strong></td>
<td>0.11</td>
<td>0</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Incidence rate</strong></td>
<td>0.55</td>
<td>0.87</td>
<td>0.39</td>
</tr>
</tbody>
</table>

* Incidence rate per 100 person-years;
In patients receiving lenalidomide and alkylating agents (CRC/MPR/MEL200-R), the cumulative incidence of death for MM and diagnosis of SPMs at 3 years was 13.8% and 2.0%, respectively. In patients not receiving lenalidomide (MP/MPT/MPV/VMPT), the cumulative incidence of death and SPMs at 3 years was 26.1% and 1.1%, respectively. In the analysis restricted to Italian patients treated with lenalidomide and alkylating agents, we report 11 cases of SPMs. This figure is lower than the 15.6 cases expected from the age/sex adjusted incidence derived from the Italian Cancer Registry, with a standardized incidence ratio of 0.70.

**Conclusions:** SPM incidence was lower than expected in all treatment groups. At present, the benefits of continuous therapy with lenalidomide outweigh the potential risk of SPMs. Longer follow-up is needed to definitively assess the risk of SPMs in patients receiving lenalidomide with alkylating agents. With the limitation of a short follow-up, the numbers currently support a role for non-treatment related factors as causes of SPMs. Updated data will be presented at the meeting.

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**FDA Drug Safety Communication: Safety review update of cancer drug Revlimid (lenalidomide) and risk of developing new types of malignancies**

**Safety Announcement**

The U.S. Food and Drug Administration (FDA) is informing the public of an increased risk of second primary malignancies (new types of cancer) in patients with newly-diagnosed multiple myeloma who received Revlimid (lenalidomide). Clinical trials conducted after Revlimid was approved showed that newly-diagnosed patients treated with Revlimid had an increased risk of developing second primary malignancies compared to similar patients who received a placebo. Specifically, these trials showed there was an increased risk of developing acute myelogenous leukemia, myelodysplastic syndromes, and Hodgkin lymphoma.
This safety information has been added to the Warnings and Precautions section of the Revlimid drug label. The patient Medication Guide is also being updated to inform patients about this risk.

Healthcare professionals should consider both the potential benefit of Revlimid and the risk of second primary malignancies when deciding to treat patients with this drug, and monitor patients for this risk.

Patients should contact their healthcare professional if they have any questions or concerns about Revlimid.

In April 2011, FDA announced an ongoing safety review to evaluate the possible increased risk of second primary malignancies with Revlimid. FDA performed a comprehensive review of this safety issue.

**Data Summary**

FDA reviewed controlled clinical trials of Revlimid as maintenance therapy in patients with newly-diagnosed multiple myeloma and for the treatment of relapsed/refractory multiple myeloma, to evaluate the risk of developing a second primary malignancy with Revlimid.

**Second primary malignancies in patients with newly diagnosed multiple myeloma**

In three prospective, randomized trials, patients with newly-diagnosed multiple myeloma received initial chemotherapy or chemotherapy plus blood stem cell transplantation followed by treatment with Revlimid or a placebo. This treatment protocol was used to study the effect of Revlimid as maintenance therapy. A pooled analysis of the three ongoing trials, as of February 28, 2011, showed 65 second primary malignancies among 824 patients in the Revlimid treatment arms compared to 19 second primary malignancies among 665 patients in the treatment arms that did not include Revlimid maintenance (7.9% vs. 2.8%; p<0.001). This difference is almost a three-fold increase in new malignancies for the groups receiving Revlimid versus the groups that did not receive Revlimid. The second primary malignancies noted included acute myelogenous leukemia (AML), myelodysplastic syndromes (MDS), and B-cell malignancies. Overall, 30 (3.6%) second primary hematologic malignancies were reported in the Revlimid treatment arms (22 MDS/AML, 5 Hodgkin lymphoma, 3 B-cell acute lymphoblastic leukemia) compared with 2 (0.3%) cases of AML in the study arms not receiving Revlimid. The median time from start of Revlimid to a diagnosis of a second primary malignancy was two years. Based on the available data, there appears to be no difference in the incidence of non-melanoma skin cancers or of solid tumors between the patients who received Revlimid and those who did not.

**Second primary malignancies in patients with relapsed/refractory multiple myeloma**

A retrospective pooled analysis of second primary malignancies also was conducted on data derived from the two clinical trials that supported the initial FDA approval for relapsed multiple myeloma. These were multicenter, double-blind, placebo-controlled, parallel-group trials of
Revlimid plus high-dose dexamethasone therapy versus dexamethasone alone in the treatment of patients with relapsed or refractory multiple myeloma. The incidence rates of developing a second primary malignancy during the treatment phase of these trials were 3.98 and 1.38 per 100 person-years for patients in the Revlimid/dexamethasone and the placebo/dexamethasone groups, respectively. The higher incidence rate of second primary malignancies in the Revlimid/dexamethasone group was largely accounted for by the higher incidence of non-melanoma skin cancers with Revlimid (2.4 vs. 0.91 per 100 person-years for the Revlimid/dexamethasone and placebo/dexamethasone groups, respectively). The patients in the Revlimid/dexamethasone group had longer on-study treatment time compared to the placebo/dexamethasone group (467 person-years vs. 218.7 person-years, respectively). When adjusted for the differences in observation time on-study, the incidence rate of invasive non-melanoma skin cancers was not substantially different between the two groups (1.71 vs. 0.91 per 100 person-years, respectively).