Bristol Myers Squibb™

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**NCCN Guidelines® Panel:** Multiple Myeloma

On behalf of Bristol Myers Squibb, we respectfully request the NCCN Panel to review new recently presented data at the American Society of Clinical Oncology (ASCO) 2021 Annual Meeting on the use of REVLIMID®(lenalidomide) for the treatment of patients with multiple myeloma.

**Specific Changes:** We respectfully request the panel's consideration of the enclosed data for an update to the Primary Therapy for Transplant Candidates: Maintenance Therapy Useful in Certain Circumstances (MYEL-G 1 of 3) and Primary Therapy for Non-transplant Candidates: Maintenance Therapy Useful in Certain Circumstances (MYEL-G 2 of 3) as well as an update to the discussion section (MS-25 – MS-27) to include lenalidomide in combination with carfilzomib as Category 2A with a footnote for patients with high-risk chromosomal abnormalities.

**FDA Clearance:**

REVLIMID® is a thalidomide analogue indicated for the treatment of adult patients with multiple myeloma (MM):

- in combination with dexamethasone
- as maintenance following autologous hematopoietic stem cell transplantation (auto-HSCT).[1]

KYPROLIS®(carfilzomib) is a proteasome inhibitor that is indicated:[2]

- for the treatment of adult patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy in combination with lenalidomide and dexamethasone; or dexamethasone; or daratumumab and dexamethasone.
- as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy.

Lenalidomide in combination with carfilzomib is not FDA approved for maintenance therapy.

**Rationale:** This data is being submitted in response to a standing request from the NCCN® for consideration of new data.

Study Summary:

Gay et al. presented randomized Phase 2 data on the impact of carfilzomib-based induction and consolidation treatment with or without autologous transplant (ASCT) followed by Lenalidomide (R) or Carfilzomib-Lenalidomide (KR) maintenance in high risk patients with chromosomal abnormalities based on progression-free survival (PFS) and 1-year sustained MRD negativity rates.[3]

474 newly diagnosed multiple myeloma patients that were transplant eligible and ≤ 65 years of age were randomized at first randomization (R1) 1:1:1 to receive Carfilzomib, cyclophosphamide, dexamethasone (KCd) induction followed by ASCT and KCd consolidation (KCd_ASCT), or Carfilzomib, lenalidomide,

dexamethasone induction (KRd) followed by ASCT and KRd consolidation (KRd_ASCT), or 12 cycles of KRd with no ASCT.
At second randomization (R2) patients were randomized 1:1 to receive maintenance treatment with R or KR. High-risk chromosomal abnormalities determined by fluorescence in situ hybridization (FISH) included t(4;14), t(14;16), del(17p), del(1p), gain(1q), amp(1q). Standard risk was absence of any chromosomal abnormalities, high risk ≥1 chromosomal abnormalities, and double hit ≥2 chromosomal abnormalities.

Patients in R1 with complete cytogenetic data included: KCd_ASCT (N=138), KRd_ASCT (N=132), and KRd12 (N=126); median age was 57 years, ISS stage III was 19%, 15% and 19% for KCd_ASCT, KRd_ASCT, and KRd12; respectively. FISH Status for standard risk were 33% KCd_ASCT, 39% KRd_ASCT, 44% KRd12, high risk 67% KCd_ASCT, 61% KRd_ASCT, 56% KRd12, and double hit 30% KCd_ASCT, 34% KRd_ASCT, 25% KRd12. The breakdown of single chromosomal abnormalities can be found in the table **Patient characteristics: Random 1**, in the attached presentation.

At median follow up of 51 months (IQR 46-55) from R1, KRd_ASCT improved PFS significantly vs KCd_ASCT (HR 0.54, 95% Confidence Interval (CI) 0.38-0.78, p<0.001) and KRd12(HR 0.61, 95% CI 0.43-0.88, p=0.0084), while KRd12 vs KCd_ASCT was not statistically significant (HR 0.88, 95% CI 0.64-1.22, p=0.45). 4-year PFS rates for KRd_ASCT, KRd12, and KCd_ASCT were 69%, 56%, and 51%; respectively. At median follow up of 37 months (IQR 33-42) from R2 PFS was statistically significant for KR vs R (75% vs 65%, HR 0.64, 95% CI 0.44-0.94, p=0.02294).

PFS was significantly prolonged in R1 for KRd_ASCT vs KCd_ASCT across standard risk, high risk and double hit chromosomal abnormalities and KRd12 for standard risk and high risk, see table below for 4-year PFS rates.

4-year Progression free survival rates across chromosomal abnormalities: R1[3]

| | Standard risk (N=153) | High risk (N=243) | Double hit (N=105) |
|---|---|---|---|
| KRd_ASCT vs KCd_ASCT | 82% vs 62%<br>HR 0.44, **p=0.04** | 62% vs 45%<br>HR 0.57, **p=0.01** | 55% vs 33%<br>HR 0.49, **p=0.03** |
| KRd_ASCT vs KRd12 | 82% vs 67%<br>HR 0.46, **p=0.04** | 62% vs 45%<br>HR 0.6, **p=0.04** | 55% vs 31%<br>HR 0.53, p=0.07 |
| KRd12 vs KCd_ASCT | 67% vs 62%<br>HR 0.96, p=0.9 | 45% vs 45%<br>HR 0.95. p=0.8 | 31% vs 33%<br>HR 0.91, p=0.75 |

Due to the small number of patients, analysis by single chromosomal abnormalities was limited. Despite this limitation, PFS benefit was observed for KRd_ASCT vs KRd12 across del(17p), gain(1q), and t(4;14). KRd_ASCT vs KCd_ASCT and KRd12 demonstrated statistically significant longer PFS for gain(1q). Amp(1q) patients observed lower PFS regardless of treatment. For full analysis on 4-year PFS rates, see table below.

4-year Progression free survival rates across single chromosomal abnormalities: R1[3]

| | KRd_ASCT vs KCd_ASCT | KRd_ASCT vs KRd12 | KRd12 vs KCd_ASCT |
|---|---|---|---|
| del(17p) | 52% vs 43%<br>HR 0.57, p=0.185 | 52% vs 40%<br>HR 0.61, p=0.28 | 40% vs 43%<br>HR 0.94, p=0.89 |
| del(1p) | 82% vs 41%<br>HR 0.24, p=0.06 | 82% vs 72%<br>HR 0.73, p=0.72 | 72% vs 41%<br>HR 0.33, p=0.09 |
| gain(1q) | 71% vs 38%<br>HR 0.35, **p=0.001** | 71% vs 45%<br>HR 0.45, **p=0.02** | 45% vs 38%<br>HR 0.78, p=0.38 |
| t(4;14) | 50% vs 43%<br>HR 0.73, p=0.44 | 50% vs 29%<br>HR 0.59, p=0.19 | 29% vs 43%<br>HR 1.23, p=0.57 |
| amp(1q) | 33% vs 32% | 33% vs 18% | 18% vs 32% |

| | | | |
|---|---|---|---|
| | HR 1.16, p=0.72 | HR 0.87, p=0.73 | HR 1.34, p=0.46 |

Pre-maintenance MRD negativity rates in high risk and double hit were: KRd_ASCT (N=132, 59% and 44%), KCd_ASCT (N=138, 47% and 39%), and KRd12 (N=126, 62% and 50%). In high risk patients, the 1-year MRD negativity rates were 50% (KRd_ASCT), 29% (KCd_ASCT), and 39% (KRd12). In double hit patients, the 1-year MRD negativity rates were 47% (KRd, ASCT), 17% (KCd, ASCT), and 25% (KRd12). 4-year PFS in 1- year sustained MRD-negative patients with high risk and double hit were 87% and 84%, respectively.

Patients in R2 with complete cytogenetic data were KR (N=140) and R (N=152); median age was 57 years; ISS stage III was 19% and 11%; respectively. FISH Status for KR & R were the following: standard risk was 37% and 45%, high risk 63% and 55%, and double hit 20% and 23%, respectively. The breakdown of single chromosomal abnormalities can be found in the table **Patient characteristics: Random 2**, in the attached presentation.

At median follow up of 37 months (IQR 33-42) for R2, the 3-year PFS rate was statistically significant for KR vs R in standard and high risk patients, see table below.

Progression free survival across chromosomal abnormalities: R2[3]

| | Standard risk (N=120) | High risk (N=172) | Double hit (N=105) |
|---|---|---|---|
| KR vs R | 90% vs 73%<br>HR 0.4, **p=0.05** | 69% vs 56%<br>HR 0.6, **p=0.04** | 67% vs 42%<br>HR 0.53, p=0.1 |

Due to the small number of patients, analysis by single chromosomal abnormalities was limited. Despite this limitation, PFS benefit was observed for KR vs R across del(17p), del(1p), gain(1q), and t(4;14), and was not prolonged for amp(1q).

Progression free survival across single chromosomal abnormalities: R2[3]

| | KR | R |
|---|---|---|
| del(17p) | 60% | 57% |
| | HR 0.59, p=0.38 | |
| del(1p) | 86% | 57% |
| | HR 0.23, p=0.07 | |
| gain(1q) | 72% | 53% |
| | HR 0.54, p=0.07 | |
| t(4;14) | 71% | 53% |
| | HR 0.59, p=0.31 | |
| amp(1q) | 46% | 45% |
| | HR 0.83, p=0.72 | |

Safety was not reported in this most recent presentation however has been previously described for the maintenance phase of the trial at the 62nd American Society of Hematology (ASH) 2020 Annual Meeting.[3]

The REVLIMID®(lenalidomide) full prescribing information, includes boxed WARNINGs for embryo-fetal toxicity, hematologic toxicity, and arterial thromboembolism. Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of

two reliable methods of contraception. Lenalidomide is available only through a restricted distribution program, called the REVLIMID REMS® program. Lenalidomide can cause significant neutropenia and thrombocytopenia. In the maintenance therapy trials, Grade 3 or 4 neutropenia was reported in up to 59% of lenalidomide treated patients and Grade 3 or 4 thrombocytopenia in up to 38% of lenalidomide treated patients. Venous thromboembolic events (deep vein thrombosis and pulmonary embolism) and arterial thromboembolic events (myocardial infarction and stroke) are increased in patients treated with lenalidomide and dexamethasone. In patients receiving lenalidomide maintenance therapy following high dose intravenous melphalan and auto-HSCT, hematologic secondary primary malignancies (SPMs) occurred in 7.5% of patients compared to 3.3% in patients receiving placebo.[1]

For safety information regarding KYPROLIS®(carfilzomib) please refer to the full Prescribing Information.[2]

As part of the submission, a copy of the ASCO 2021 presentation (Gay 2021 et al.) is enclosed for your review.

Thank you for your consideration of this request.

Sincerely,

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Director| Worldwide Scientific Content & US Market Capabilities, Hematology/Cell Therapy

Fiona An, MD
Executive Director| US Medical Hematology

References:


1. Revlimid® (lenalidomide) capsules, for oral use [Package Insert]. Summit, NJ: Celgene Corporation. October 2019.
2. Kyprolis® (carfilzomib) for injection, for intravenous use [Package Insert]. Thousand Oaks, CA: Onyx Pharmaceuticals. March 2021.
3. Gay F, Mina R, Rota-Scalabrini D, et al. Carfilzomib-based induction/consolidation with or without autologous transplant (ASCT) followed by Lenalidomide (R) or Carfilzomib-lenalidomide (KR) maintenance: efficacy in high risk patients [Oral]. Oral presented at: American Society of Clinical Oncology (ASCO) Annual Meeting 2021; June 4-8, 2021; Virtual Meeting.