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NCCN
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NCCN Breast Cancer Guideline Panel:

On behalf of R-Pharm US, I respectfully request the NCCN Panel to review the enclosed data and information to support the inclusion of the combination of ixabepilone/capecitabine as a treatment option for HER2-negative, ER/PR-negative recurrent or metastatic Stage IV Breast Cancer.

Specific Changes

We respectfully suggest the following changes for NCCN consideration:

- **BINV Q (1 of 6) in Table for Chemotherapy Regimens under HER2-negative for Recurrent or Stage IV (M1) Disease:** Please add ixabepilone/capecitabine under "Useful in Certain Circumstances" as a therapeutic option with new footnote below.
- **New footnote:** "Ixabepilone/capecitabine provides an additional chemotherapy option for patients with Triple Negative Breast Cancer (TNBC) after the failure of anthracycline and taxane therapy."

FDA Clearance

IXEMPRA (ixabepilone), a microtubule inhibitor, in combination with capecitabine is indicated for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated. IXEMPRA as monotherapy is indicated for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine (1).

Rationale

A recently (2018) published pooled analysis (2) by Rugo et al combined two large randomized trials (3,4) comparing ixabepilone/capecitabine to capecitabine. The purpose of the study was to evaluate the safety and efficacy of the ixabepilone/capecitabine combination in patients with metastatic or locally advanced triple-negative breast cancer (TNBC) who had been previously been treated with anthracyclines and taxanes. Data were pooled from 2 randomized Phase III trials. Major findings and conclusions from this study were as follows:

- For the TNBC patients, there was a statistically significant improvement in progression-free survival (4.2 mo. vs 1.7 mo; $P < .0001$) for the combination over capecitabine monotherapy representing a 36% reduction in the estimated risk of disease progression;
- For the TNBC patients, the objective response rate (ORR) was doubled (31% vs 15%) for the combination over capecitabine monotherapy;
- For the TNBC patients, there was a non-statistically significant trend toward improvement in median overall survival (OS) (10.4 mo vs 9.0 mo; $P = .1802$) for the combination vs capecitabine monotherapy.

Safety

- Adverse events observed with the combination were adjudged to be "generally manageable" and consistent with the safety profiles of the individual agents;
- Drug discontinuation due to study drug toxicity occurred in 21.1 % of TNBC patients receiving the combination vs 6.6% of the patients receiving the capecitabine monotherapy;

- Dose reductions due to toxicity occurred in 43.1 % of patients receiving the combination vs 22.1% of the patients receiving the capecitabine monotherapy;
- A frequent cause of dose reduction was peripheral neuropathy (PN). Following a dose reduction or delayed dose, resolution of PN occurred within a median of 5.7 weeks (in TNBC patients).

The authors concluded that the management of toxicity with dose reductions resulted in no impact on efficacy.

The authors further concluded that for patients with TNBC previously treated with an anthracycline and with a taxane:

- It is important to optimize the use of available chemotherapy agents for patients with resistant TNBC.
- Ixabepilone added to capecitabine is effective at improving PFS and increasing response rates for patients with limited treatment options who have failed anthracycline and a taxane.
- Ixabepilone/capecitabine provides an additional important chemotherapy treatment option for patients with TNBC after the failure of anthracycline and of taxane therapy.

Ixabepilone/capecitabine continues to be used in practice

NCCN Panels provide the most authoritative guidance on the appropriate and effective use of drugs and biologics in cancer care. The combination of ixabepilone/capecitabine is considered and listed as a therapeutic option for invasive breast cancer in current pathways and protocols in some cancer centers, including the MD Anderson Invasive Breast Cancer Algorithm. Prescribing of the ixabepilone/capecitabine combination is occurring as indicated by separate, independent survey and analysis. A survey of 150 medical oncologists found that among those prescribing chemotherapy and targeted agents, 80% had prescribed ixabepilone for 1 -20 patients in the previous 12 months; 30.7% indicated they prescribed the combination ixabepilone/capecitabine and another 30.0% specified prescribing both the monotherapy and the combination (5). In addition, an analysis of Medicare census level data over a 3-year period (2015 – 2017) indicated 13% - 17%* of the ixabepilone utilization was in combination with capecitabine (6).

Given the results and conclusions of the pooled trial data, the FDA labeled indication, and the documented ongoing prescribing of the ixabepilone/capecitabine combination, it is important to specify and provide guidance on the combination as a chemotherapeutic option for TNBC patients who have failed an anthracycline and a taxane. Such NCCN expert guidance is important to enable access for the practice community that integrates NCCN recommendations into their pathways and prescribing decisions, and for payers that apply NCCN recommendations in setting coverage policy and approving reimbursement.

Thank you for your consideration.

Sincerely,

Amit Patel, PharmD
R-Pharm US, Medical Affairs

Behshad Sheldon
R-Pharm US, Executive VP, Head of Development

*****Based on the window of treatment for Medicare claims associated with ixabepilone and capecitabine.

References:

1. IXEMPRA [ixabepilone] prescribing information. R-Pharm US Operating, LLC.
2. Rugo, HS, Roche, H, et al. Clinical Breast Cancer, 18 (6): 489-497. 2018.
3. Thomas, ES, Gomez, RK, et al. JCO, 25 (33): 5210-5217, 2007.
4. Sparano, JA, Vrdojak, E, et al. JCO, 28 (20): 3256-3262, 2010.
5. Primary Quantitative Market Research conducted by an independent third party on behalf of R-Pharm US April 2019.
6. Sourced through the CMS Virtual Research Data Center (VRDC) by CareSet Systems July 2019.