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NCCN Guidelines Panel: Prostate Cancer

On behalf of Sanofi US Medical Information Services, and in response to your submission request process, I respectfully request the NCCN Prostate Cancer Panel to review the enclosed data for inclusion of docetaxel in combination with androgen deprivation therapy (ADT) as a treatment option for hormone-sensitive metastatic prostate cancer patients with high volume disease. High-volume disease is defined as visceral metastases with or without ≥ 4 bone metastases with at least one lesion outside of the vertebral column and pelvis.

Clinical Evidence in Support of Docetaxel/ADT in Hormone-sensitive Metastatic Prostate Cancer Patients with High-volume Disease

A randomized, multi-center, phase 3 clinical trial, evaluated 790 men with hormone-sensitive metastatic prostate cancer.^{1,2} Patients were stratified according to age (≥ 70 yrs vs. < 70 yrs), ECOG PS 0–1 vs. 2, combined androgen blockade > 30 days (yes vs. no), duration of prior adjuvant hormonal therapy (> 12 months vs. ≤ 12 months), skeletal-related events prevention (yes vs. no) and low or high volume disease (high volume disease was defined as visceral metastases with or without ≥ 4 bone metastases with at least one lesion outside of the vertebral column and pelvis). Median overall survival (OS) was 57.6 months for the group that received ADT plus docetaxel and 44.0 months for ADT alone (HR=0.61, 0.47-0.80, $P=0.0003$). In patients with high volume disease median OS was 49.2 months and 32.2 months (HR=0.60, 0.45-0.81, $P=0.0006$) for the ADT plus docetaxel and ADT alone arms, respectively. Hematologic and non-hematologic toxicity for all patients treated with ADT plus docetaxel was 16% for grade 3 and 12% for grade 4. Grade 3/4 hematologic toxicity for ADT plus docetaxel treated patients included anemia (1% / $< 1\%$), neutropenia (3% / 9%), febrile neutropenia (4% / 2%), and infection with grade 3/4 neutropenia (1% / 1%). Grade 4 thrombocytopenia occurred in $< 1\%$ of patients. The rate of grade 3 non-hematologic toxicity for ADT plus docetaxel treated patients included allergic reaction (2%), fatigue (4%), colitis/diarrhea (1%), stomatitis (1%), neuropathy-motor (1%), neuropathy-sensory (1%), and thromboembolism ($< 1\%$). Grade 4 allergic reaction and thromboembolism occurred in $< 1\%$ and 1% of patients, respectively. There was 1 treatment-related death. The authors concluded that ADT in combination with docetaxel significantly improved OS compared to standard treatment of ADT alone in patients with hormone-sensitive metastatic prostate cancer.

Other Relevant Evidence

A medical literature search was performed, using pubmed.gov, to identify other clinical studies that evaluated the use of docetaxel in combination with ADT for hormone-sensitive metastatic prostate cancer. One study was identified. A randomized, multi-center, open-label, phase 3 study, evaluated docetaxel in combination with ADT compared with ADT alone in 385 metastatic non-castrate prostate cancer patients.³ No specification of volume of disease was made with regards to eligibility. Median OS was 58.9 months (95% CI 50.8-69.1) in the ADT plus docetaxel group and 54.2 months (42.2-not reached) for ADT alone (HR=1.01, 95% CI 0.75-1.36, $P=0.995$). The most common grade 3/4 adverse events in the docetaxel plus ADT group were neutropenia (32%), febrile neutropenia

(7%), erectile dysfunction (8%) and fatigue (7%). Four treatment-related deaths occurred in the ADT plus docetaxel group (2 of which were neutropenia-related). No serious adverse events were reported in the ADT alone group. The authors concluded that docetaxel should not be used as part of first-line treatment for patients with non-castrate metastatic prostate cancer.

Disclosure: Both studies received financial support from a Sanofi group member company.

Specific Changes Recommended within the Guidelines

Please update the following algorithms to include docetaxel in combination with ADT as a treatment option for high-volume, hormone-sensitive metastatic prostate cancer, including:

- PROS-5, under risk group metastatic, any T, any N, M1, high volume disease, initial therapy
- PROS-9, advanced disease: systemic therapy, M1, high-volume disease

FDA Status

Docetaxel is not FDA-approved for use in hormone-sensitive metastatic prostate cancer. Docetaxel in combination with prednisone is FDA-approved for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.

Rationale for Recommended Change

In a phase 3 clinical trial, a 17-month improvement in median OS (HR=0.60, $P=0.0006$) was observed with docetaxel in combination with ADT compared to ADT alone in hormone-sensitive metastatic prostate cancer patients with high-volume disease, while hematologic and non-hematologic toxicity was 16% for grade 3 and 12% for grade 4 for all patients receiving docetaxel in combination with ADT.

Literature Support

1. Sweeney C, Chen Y-H, Carducci MA, et al. Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mPrCa): An ECOG-led phase III randomized trial [abstract]. *J Clin Oncol*.2014; 32 (5 suppl). Abstract LBA2.
2. Sweeney C, Chen Y-H, Carducci M, et al. Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mPrCa): An ECOG-led phase III randomized trial. Presented at: 50th Annual Meeting of the American Society of Clinical Oncology, Chicago II, USA, May 30-June 3, 2014. Oral LBA2.
3. Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomized, open-label, phase 3 trial. *Lancet*. 2013.14(2);149-158.

We appreciate the opportunity to provide this information for consideration by the NCCN Prostate Cancer Panel. If you have any questions or require additional information, please do not hesitate to contact me at (800) 633-1610, option 1 or via e-mail at MED.INFO@sanofi.com. Thank you for your time and consideration.

Sincerely,



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Enclosures: Copies of referenced primary literature. Reference 2 is available at www.asco.org.