Bayer HealthCare

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11-May-2020

Prostate Cancer Guidelines Panel:
Submission Request: c/o Doreen Walker
National Comprehensive Cancer Network (NCCN)
3025 Chemical Road, Suite 100
Plymouth Meeting, PA 19462

On behalf of Bayer HealthCare Pharmaceuticals Inc., I respectfully request the NCCN Prostate Cancer Guideline Panel to review the enclosed data to support the inclusion of Nubeqa® (darolutamide) a structurally unique high affinity androgen-receptor (AR) inhibitor as a therapeutic option for metastatic castration resistant prostate cancer based on the study results presented. We believe that the data, although limited, indicate that Nubeqa® (darolutamide) would be a reasonable treatment option, particularly for those patients who might not tolerate and/or be appropriate for the currently approved abiraterone or enzalutamide. Since Nubeqa® (darolutamide) is neither a potent inhibitor or inducer of CYP3A4, it may be suitable for patients who are on other drugs that are metabolized by this pathway.

FDA Clearance: Nubeqa® (darolutamide) is an FDA approved androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer (nmCRPC).[1]

Rationale: Pre-clinical studies indicate that Nubeqa® (darolutamide) is a potent androgen-receptor inhibitor, capable of inhibiting CRPC. During clinical development, Nubeqa® (darolutamide) was investigated in two studies that enrolled men with progressive metastatic castration-resistant prostate cancer (mCRPC) comprising bone, visceral and soft tissue disease.

In pre-clinical studies, Nubeqa® (darolutamide) was found to have a Ki for competitive AR binding of 11 nM (the comparable value for enzalutamide was 86 nM); the IC_{50} for the cell line AR-HEK293 of 26 nM (the comparable value for enzalutamide was 219 nM)[2]. Potent AR inhibition is obviously a pre-requisite for efficacy in CRPC.

In the nmCRPC indication, Nubeqa® (darolutamide) was tested in the ARAMIS phase III study, which led to its approval in nmCRPC[3]. The values for the baseline median PSA was 9.0, ≥50% PSA decline was 83%, ≥90% PSA decline was 51% , OS was .71 , and the median MFS was 40.4 months. The comparable reported values for enzalutamide in the PROSPER trial[4] were 11.1, 76%, 56% .80 and 36.6 months. The data indicate that Nubeqa® (darolutamide) is an effective drug for patients with nmCRPC.

The Nubeqa® (darolutamide) clinical development plan included mCRPC patients in the Phase I ARAFOR trial, as well as the phase I/II ARADES trial.

ARADES was a phase 1/2 open-label non-randomized multicenter dose escalation trial.[5] Phase 1 (n=24) assessed safety, tolerability, pharmacokinetics (PK) and maximum tolerated dose. The phase 2 expansion evaluated the antitumor activity of darolutamide based on the following criteria: serum prostate-specific antigen (PSA) response at week 12 (defined as a decrease of 50% or more from baseline), objective disease response as assessed by RECIST (v.1.1) criteria for soft tissue and by PCWG2 criteria for bone. Additional criteria included time to PSA and radiographic disease progression and changes in circulating cell counts. The phase 1 patients were allocated to

predefined sequential dose escalation starting with 200 mg/d, increasing to 400 mg, 600 mg, 1000 mg, 1400 mg and maximum 1800 mg/day. No dose limiting toxicity or dose reduction observed and a maximum tolerated dose was not reached. The results of the PK analysis led to three (200mg, 400mg and 1400 mg/day) daily doses for testing in the phase 2 dose expansion [n=110 patients randomly assigned (1:1)] cohorts of 35 patients who were further stratified based on previous treatment with chemotherapy and CYP17 inhibitor.

Antitumor activity was observed in all doses of darolutamide tested and all treatment stratification subgroups.[5] A PSA response was observed in 17 (81%) of 21 patients who had PSA samples at baseline and week 12. The best PSA response was observed in those patients who received 1400 mg/day and were naïve to chemotherapy and CYP17i whereas the lowest PSA response was observed in those patients who had prior treatment with CYP17 inhibitors. The median time to PSA progression including all dose level was 72.3 weeks (95% CI 24.3 – not reached) for chemotherapy and CYP17i naïve and the median time to radiological progression was not reached for this treatment group (95% CI 36.4-NR). Soft tissue and bone lesion data also showed promising results. The highest complete or partial responses or stable disease in soft tissue and stable disease in bone was observed in patients who were chemotherapy and CYP17i-naïve.

Extended follow-up of 77 CYP17i naïve patients of which 42 (54.5%) were chemotherapy naïve and 35 (45.5%) had received prior chemotherapy.[6] Median time to PSA progression was 25.2 mo (95% CI 11.2-25.2, IQR 6.5-25.2) for all patients, 25.2 mo (95% CI 11.3-25.2, IQR 11.0-25.2) for chemotherapy naïve patients and was not reached (NR) for chemotherapy pretreated patients (95% CI 5.5-NR, IQR 4.7-NR). The HR for PSA progression was 0.55 (95% CI 0.23-1.33 p=0.1854) and although there was no statistical difference between treatment groups, there was a trend for improved antitumor activity among chemotherapy naïve patients. Median time to radiographic progression was longer in the chemotherapy-naïve than in the chemotherapy-pretreated group (14.0 mo, vs 7.2 mo).

The ARAFOR randomized open-labelled phase 1 study enrolled 30 chemotherapy naïve mCRPC patients to assess the PK of two different tablet formulations of a 600 mg dose of darolutamide compared to the existing capsule and the effect of food on drug absorption.[7] Based on the results, the tablet formulation with food was confirmed suitable for further use.

All thirty patients participated in the extension phase that evaluated the long-term safety, tolerability and antitumor activity of darolutamide 600 mg twice daily. Treatment was continued until disease progression or development of an intolerable AE and antitumor activity was assessed by PSA levels and imaging.[7] The PSA response (≥50% decrease) at 12 wk was 83% (25 of 30); of these patients, nine or 30% had a PSA reduction ≥ 90%.[6] The median time to PSA progression was 54 wks. (95% CI, 23-NR) whereas the median time to radiographic progression was 66 wks. (95% CI, 41-79).[8]

A separate analysis was conducted of 41 chemotherapy and CYP17i-naïve patients with progressive mCRPC after extended follow up from the ARADES (11 or 26.8%) and ARAFOR (30 or 72.3%) trials.[9] The analysis indicated that for up to 25.7 mo (median 15.3), treatment with high doses of darolutamide (1200, 1400 and 1800 mg/d) was well tolerated and continued to show encouraging antitumor activity. A decrease in PSA level from baseline was maintained over time in most chemotherapy and CYP17i naïve patients at all dose levels and were similar with the finding reported for the earlier stages of the two trials.

In summary, treatment with darolutamide in both ARADES and ARAFOR trials demonstrated encouraging antitumor activity in mCRPC patients with progressive disease.. To summarize some key demographic data from ARAFOR, the median PSA at baseline was 18.2 (compared to 54 for enzalutamide in the PREVAIL trial)[10] with 47% of patients having only bone metastases (versus 40% for enzalutamide in the PREVAIL trial)[10], a ≥50% PSA decline of 83% (compared to 78% on enzalutamide in the PREVAIL trial)[10], and a median time to PSA progression of 12.5 months (versus 11.2 months on enzalutamide in the PREVAIL trial)[10]. Thus, the sustained PSA reduction and the prolonged time to PSA progression support the antitumor activity of Nubeqa® (darolutamide) in patients with mCRPC.

Sincerely,

Bayer HealthCare

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