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NCCN Guidelines Panel: Prostate Cancer Panel

On behalf of *Vi3c*, we respectfully request the *NCCN Prostate Cancer Guideline Panel* to amend the NCCN guidelines to include the non-FDA-approved option of using **Abiraterone Acetate (AA), in all its approved indications, at a dose of 250mg/day following a low-fat breakfast, as an alternative to the dose of 1000mg/day after an overnight fast, in those patients in whom financial toxicity is felt to be a major concern and/or is felt to be a potential impediment to compliance**. We note that the NCCN evidence blocks would appear to be uniquely well suited to allow for clear communication of the relative strengths and weaknesses of these two different AA administration strategies.

In support of this request we submit for your consideration the randomized phase II study, recently published in JCO, supporting this lower dose with food.[1] This randomized controlled trial of 75 patients with mCRPC comparing 1000mg/day AA fasting with 250mg/day after a low-fat breakfast had a primary clinical endpoint of log change in PSA, with secondary endpoints of PSA response (≥ 50%) and Progression-Free Survival (PFS). In this trial, the **primary endpoint favored the low-dose arm** (log change in PSA: -1.59 vs. -1.19), as did the PSA response rate (58% vs. 50%) with equal PFS of 9 months in both arms. ***These trends make it very unlikely that a larger study would disclose poorer outcomes with use of low-dose 250mg/day AA with food as compared to the full dose (1000mg/day) after an overnight fast.***

As a matter of precedent, we note that the formulation of AA marketed as YONSA (500mg fine particle formulation to be given with methylprednisolone) was FDA-approved (May 2018) based on a phase 2 trial of 53 patients (the STARR trial[2]), which used a primary endpoint of fall in serum testosterone. The NCCN prostate panel voted approval (24 to 0 with 1 abstention) as part of their Guidelines Prostate Cancer V4 on 07/11/2018. ***The evidence to support our current request for low dose AA (250mg/day after a low fat breakfast) is considerably stronger.***

We also submit the following supportive materials:

Rationale:

Pharmacokinetics (PK): Several studies have shown that the bioavailability of abiraterone acetate (AA) is increased substantially if taken after a meal as compared to when taken after an overnight fast[3-6]. In 73 healthy men[5,6] there was a mean 12.5-fold increase in maximum serum concentration (C_{max}) AA, and a mean 7.1-fold increase in area under the time-concentration curve (AUC) if AA was given after food (mostly after a moderate of high-fat breakfast) than after an overnight fast. In about 60 men with metastatic castration-resistant prostate cancer (mCRPC)[3-5] the mean increases were

lower: 2.6-fold in C_{max} and 3.8-fold in AUC when AA was taken after food. In a randomized controlled trial (RCT) of 75 patients with mCRPC that compared 100mg AA fasting with 250mg AA after a low-fat breakfast[1], maximum and trough levels of AA in serum were higher in the standard dose arm but there was less inter-patient variability among subjects who took the drug after food than in the fasting state.

Pharmacodynamics (PD): More important than PK is PD: effectiveness in inhibiting the target CYP17 enzymes responsible for the formation of testosterone, and the adrenal androgens: androstenedione, dehydroepi-androsterone (DHEA) and its sulfate (DHEA-S), which stimulate the growth of prostate cancer. In a Phase I study of 21 patients with mCRPC[3], all doses of AA from 250 - 2000mg/day (fasting or not) suppressed serum testosterone to undetectable levels and reduced the adrenal androgens to low levels. Another phase I study of 33 men with mCRPC[4] gave similar results: doses of AA (fasting or not) of 250mg, 500mg, 750mg and 1000mg were equally effective in suppressing testosterone and DHEA-S to undetectable or very low levels. *Thus a clear relationship between AA dose and target inhibition has not been established*. In the RCT[1], serum testosterone and DHEA-S fell to equally low levels in the standard (1000mg/day fasting) and low-dose (250mg after a low fat breakfast) arms.

Clinical Outcomes: PSA declines were observed in both phase I trials with no trends for a relationship with dose of AA[3,4].

References:

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3. **A**ttard G, Reid AH, Yap TA. Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acet[ate], *c*onfirms that castration-resistant prostate cancer commonly remains hormone driven. J Clin Oncol 26:4563-71, 2008
4. Ryan CJ, Smith MR, Fong L et al. Phase I clinical trial of the CYP17 inhibitor abiraterone acetate demonstrating clinical activity in patients with castration-resistant prostate cancer who received prior ketoconazole therapy. J Clin Oncol 28: 1481-1488, 2010
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6. Innoue K, Shishido A, Vaccaro N et al. Pharmacokinetics of abiraterone in healthy Japanese men dose proportionality and effect of food timing. Cancer Chemother Pharmacol 75:49-58, 2015