Utah IRB. R. Martinez-Monge: None. A. Berlin: Vaccinex Inc. D.E. Spratt: Advisory Board; Daniel Spratt. R.T. Dess: None. T. Romero: None.

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10-Year Results of a Phase III Randomized Trial of High-Dose Radiotherapy and Risk-Adapted Androgen Deprivation in Localized Prostate Cancer

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Purpose/Objective(s): The optimal duration of androgen deprivation (AD) combined with high-dose radiotherapy (HDRT) in prostate cancer remains a matter of controversy. We did a phase 3 trial designed to determine whether long-term AD (LTAD) is superior to short-term AD (STAD) when combined with HDRT. In this report, we present the 10-year survival results. The hypothesis is that long-term AD (LTAD) compared to short-term AD (STAD) improves overall survival among high-risk patients receiving HDRT.

Materials/Methods: This open-label, phase 3 randomized controlled trial, recruited patients from ten university hospitals throughout Spain. Eligibility included patients with cT1c-T3aN0M0 adenocarcinoma of prostate with intermediate and high-risk factors according to NCCN criteria and PSA less than 100 ng/ml. All patients received 4 months of neoadjuvant and concomitant AD (STAD) + HDRT (median radiation dose 78 Gy) before randomization to adjuvant goserelin for two years (LTAD). Stratification was performed according to risk group (intermediate risk [IR] versus high risk [HR]). Study endpoints included overall survival (OS), metastasis free survival (MFS), disease free survival (DFS) and biochemical-disease free survival (bDFS). Survival analyses were done with Kaplan-Meier (KM) curves. Fine & Gray (F&G) regression was used for the adjusted analyses.

Results: From 2005 to 2010, 355 patients were randomly assigned to the treatment groups and included in the analysis (178 to STAD and 177 to LTAD). The median follow-up was 119 months (IQR 101-124). The 10-year bDFS for LTAD and STAD was 70.2% and 62.3% respectively (hazard ratio [HR] 1.19, 95% CI, 0.71 to 2.01). The 10-year OS was 78.4% for LTAD and 73.3% for STAD (HR 1.20, 95% CI, 0.79 to 1.82), and the corresponding figure for MFS was 76.0% and 70.9% for LTAD and STAD respectively (HR 1.12, 95% CI, 0.46 to 2.73). For high-risk patients treated with LTAD, the 10-year bDFS was 67.2% compared to 53.7% for STAD (log rank $P = 0.03$; F&G $P = 0.147$, HR 1.12 95% CI 0.61 to 2.04). The 10-year OS was 78.5% compared to 67.0% for STAD (log rank, $P = 0.056$; F&G $P = 0.786$, HR, 1.18, 95% CI, 0.36 to 3.84) and the 10-year MFS was 76.6% versus 65.0% for LTAD and STAD respectively (log rank $P = 0.069$; F&G $P = 0.057$, HR, 1.12, 95% CI, 0.46 to 2.73). Only 11 patients died from PCa, all of them in the high-risk subgroup.

Conclusion: Long term results failed to show a significant benefit with LTAD compared to STAD in patients treated with HDRT. The subgroup of patients with high-risk PCa treated with LTAD had a non-significant improvement in bDFS, MFS and OS compared with STAD. The relatively small simple size, a low number of events and an effective salvage treatment could be responsible for the lack of a statistical significance. The trial is registered at ClinicalTrials.gov, number NCT 02175212.

Author Disclosure: A. Zapatero: Research Grant; AstraZeneca. Honoraria; Astellas Pharma, Janssen-Cilag. Travel Expenses; Ipsen Pharma. A.D. Guerrero Grande: None. X. Maldonado: None. A. Alvarez: None. C. González San Segundo: None. M. Cabeza: None. J.M. Solé: None. A. Pedro Olive: None. F. Casas Duran: None. A. Boladeras: None. C. Martín de Vidales: None. M. Vázquez de la Torre: None. S. Varas: None. F.A. Calvo: None.

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A Prospective Trial of Aggressive Therapy Consisting of Neoadjuvant Chemotherapy and Androgen Deprivation Followed by Prostatectomy and Adjuvant Radiation in High/Very High-Risk Prostate Cancer

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Purpose/Objective(s): Prostatectomy (RP) is a treatment (tx) option even for high-risk prostate cancer (PC) per the NCCN guidelines. We report the long-term follow-up of a pilot clinical trial using an aggressive multimodal approach integrating chemo-hormone tx, prostatectomy (RP) and adjuvant radiation (RT) in men with high/very high-risk PC.

Materials/Methods: Preoperative tx entailed 6 months (mo) of chemo-hormones consisting of LHRH agonist (6 mo) integrated with adriamycin (A) and docetaxel (T). Two dose levels of A and T were incorporated with LHRH agonist tx: a higher dose (HD) of A (50mg/m2) and T (70mg/m2), and a lower dose (LD) of A (15mg/m2) and T (30mg/m2). HD chemo was given on 2 separate occasions (3 days post LHRH injection) in an effort to take advantage of the expected testosterone surge that occurs 3-5 days post LHRH agonist tx, while LD chemotherapy was given at other time points during the 6-month neoadjuvant period. This was followed by RP. The median post-op RT dose was 70.2 Gy (whole pelvis, with cone downs; range: 64.8-70.2) via 3D-CRT/IMRT. Three patients did not undergo RP after neoadjuvant chemo-hormone tx and went on to receive definitive RT (75.6 Gy). The overall survival (OS), disease-free survival (DFS), freedom from PSA failure (bNED, PSA > 0.2), and late GI/GU toxicity rates were calculated using the Kaplan-Meier method.

Results: A total of 22 men were enrolled from 2002-2006. Median pre-tx age, PSA and Gleason score were 61 years (range, 43-70), 24.1 ng/ml (range, 1.6-168.3) and 7 (range, 6-10), respectively. A total of 77% of patients received all therapy as planned. Median follow-up for the entire cohort and those alive were 10.9 years (range, 3.4-18.4) and 16.8 years (range, 15-18.4), respectively. The 15-year OS, DFS and bNED rates were 31.2%, 22.7% and 46.2%, respectively. Six patients (27%) never achieved PSA < 0.2. Worst acute grade 3 and 4 toxicity rates were 68% and 32%, respectively. The 15-year actuarial grade 3 or worse late GU toxicity rate was 13%. There was no grade 3 or worse late GI toxicities and no grade 5 acute or late toxicity.

Conclusion: Despite an aggressive multimodal regimen that incorporated chemo-hormones, RP and adjuvant RT for high/very high-risk prostate cancer, the 15-year bNED rate was only 46.5%. Therefore, the role of RP and neoadjuvant chemo-hormone therapy remains questionable among high-risk patients in light of superior long-term outcomes demonstrated in trials like ASCENDE-RT that incorporated brachytherapy boost with RT and androgen deprivation.

Author Disclosure: Y. Kwok: None. N. Mirkheshti: None. M. Naslund: None. A. Hussain: None.