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Targeting IGF-1/2 with xentuzumab plus enzalutamide in metastatic castration-resistant prostate cancer after progression on docetaxel chemotherapy and abiraterone: Randomized phase II trial results

#5030

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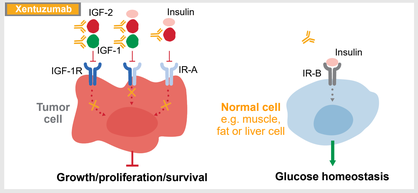
Introduction

- Enzalutamide (Enza) is a potent, second-generation androgen antagonist that has shown efficacy in CRPC[1,2]
  - However, most patients develop resistance to treatment[3]
- IGF-1R signaling activates the PI3K/AKT pathway and may lead to androgen receptor transactivation and progression to endocrine treatment resistance[4–6]
  - Thus, there is a rationale for combining IGF-targeted and anti-androgen therapy to improve treatment outcomes
- Xentuzumab (Xent) is a humanized monoclonal antibody that binds to, and neutralizes signaling by, IGF-1 and IGF-2 ligands[7]



- This phase II trial (NCT02204072) evaluated the anti-tumor activity of Xent plus Enza vs Enza alone following progression on docetaxel-based chemotherapy and abiraterone in mCRPC

AKT, protein kinase B; IGF, insulin-like growth factor; IGF-1R, IGF receptor 1; CRPC, castration-resistant prostate cancer; mCRPC, metastatic CRPC; PI3K, phosphoinositide 3-kinase

Methods

- Multicenter, open-label phase II trial with a two-arm, randomized, parallel design (**Figure 1**)

Figure 1. Study design

- Men aged ≥18 years with histologically/cytologically confirmed mCRPC
- ECOG PS 0/1
- Progression on/after docetaxel* and abiraterone
- PSA ≥20 ng/mL†

Randomized (1:1)

Xent 1000 mg IV QW + Enza 160 mg/day PO N=40 ‡

Enza 160 mg/day PO N=40‡

28-day cycles until progression or intolerable AEs

*Patients must have received ≥12 weeks of docetaxel and be unlikely to derive benefit from additional docetaxel-based therapy, or be intolerant to docetaxel; †Inclusion criterion was later amended to PSA ≥5 ng/mL (31 May 2016). ‡Planned sample size. AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; PO, orally; PSA, prostate-specific antigen; QW, once weekly

Methods (cont'd)

Primary endpoint	• PFS per investigator assessment (PFS-IA)
Secondary endpoints	• PFS by central review (PFS-CR); OS • PSA response; PSA-related endpoints • CTC response • AEs

- PFS was defined as the time from randomization until radiological progression in bone (PCWG2 criteria) or soft tissue (modified RECIST v1.1), or death
- AEs were graded according to NCI CTCAE v4.03

CTC, circulating tumor cell; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; OS, overall survival; PCWG2, Prostate Cancer Clinical Trials Working Group 2; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours

Results - Patients

Patients

- 43 patients were randomized and treated per arm (**Table 1**)
  - All 86 patients were included in the efficacy and safety analyses

Table 1. Baseline characteristics

	Xent + Enza (n=43)	Enza (n=43)	Total (N=86)
Median age, years (range)	68 (46–88)	72 (51–82)	70 (46–88)
Race, n (%)*			
Asian	15 (34.9)	10 (23.3)	25 (29.1)
White	27 (62.8)	33 (76.7)	60 (69.8)
ECOG PS, n (%)			
0	14 (32.6)	21 (48.8)	35 (40.7)
1	29 (67.4)	22 (51.2)	51 (59.3)
Smoking status, n (%)			
Never smoked	22 (51.2)	26 (60.5)	48 (55.8)
Ex-smoker	16 (37.2)	14 (32.6)	30 (34.9)
Current smoker	5 (11.6)	3 (7.0)	8 (9.3)
Median time since first diagnosis, months (range)	69.8 (6–201)	68.5 (22–240)	69.2 (6–240)
Gleason score, n (%)†			
2–6	1 (2.3)	3 (7.0)	4 (4.7)
7	7 (16.3)	15 (34.9)	22 (25.6)
8	10 (23.3)	7 (16.3)	17 (19.8)
9	19 (44.2)	15 (34.9)	34 (39.5)
10	2 (4.7)	2 (4.7)	4 (4.7)
Median PSA level, ug/L (range)	217.6 (7–3617)	147.9 (8–9106)	165.9 (7–9106)
Patients with baseline CTC value, n	36	31	67
≥5 CTCs/7.5 mL blood, n (%)‡	25 (69.4)	19 (61.3)	44 (65.7)
Patients with baseline IGF-1 mRNA,§ n	28	25	53
≤115.3, n (%)‡	6 (21.4)	10 (40.0)	16 (30.2)
>115.3, n (%)‡	22 (78.6)	15 (60.0)	37 (69.8)

- At data cut-off (23 October 2017), 39/43 (Xent + Enza) and 38/43 patients (Enza) had discontinued, mostly due to progression

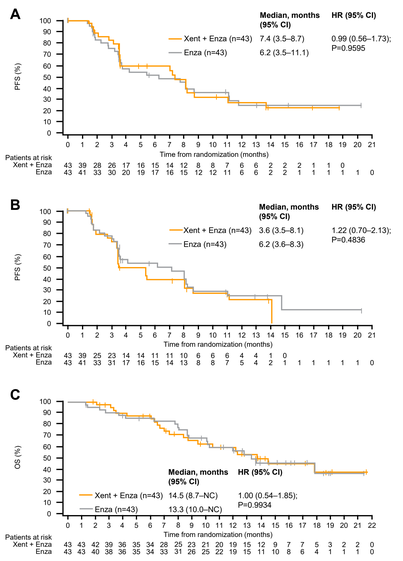
*Missing for one patient in the Xent + Enza arm; †Missing for 4 patients in the Xent + Enza arm and one in the Enza arm; ‡Percentage based on patients with baseline value available; §Missing for >35% in both arms

Efficacy

PFS

- Median PFS-IA was similar for Xent + Enza vs Enza (**Figure 1A**)
  - Results were similar after post-hoc adjustment for imbalances in baseline ECOG PS and Gleason score (HR 0.86 [95% CI 0.47, 1.55]; p=0.6113)
  - There was some evidence of improved PFS with Xent + Enza in patients with IGF-1 mRNA >115.3 (HR 0.48 [95% CI 0.20, 1.16], vs 4.44 [1.20, 16.48] for patients with IGF-1 mRNA ≤115.3), albeit based on small sample sizes
- There was also no meaningful difference in PFS-CR between the two arms (**Figure 1B**)
- OS data were immature at the time of analysis (**Figure 1C**)

Figure 1. (A) PFS-IA; (B) PFS-CR; (C) OS

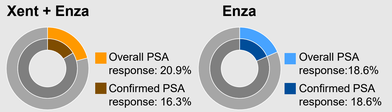


CI, confidence interval; HR, hazard ratio; NC, not calculable

Efficacy (cont'd)

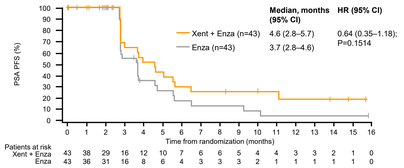
PSA response

- PSA response rates were comparable between the two arms



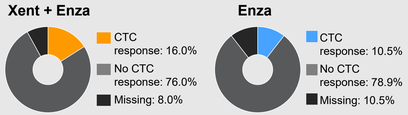
- Median (range) maximum PSA decline from baseline was
  - 20.4 ug/L (–2803.8, 1210.2) with Xent + Enza vs –9.0 ug/L (–5857.0, 1646.2) with Enza
  - Median (range) % change in PSA at Week 12 was comparable, at 18.6% (–99.2, 251.1%) vs 18.3% (–94.8, 360.7%)
- Median time to PSA progression was similar for Xent + Enza and Enza alone (**Figure 2**)

Figure 2. Time to PSA progression



CTC response

- 4/25 and 2/19 patients with ≥5 CTCs per 7.5 mL blood at baseline had a CTC response in the Xent + Enza and Enza arms, respectively (i.e. a reduction to <5 CTCs per 7.5 mL on treatment)



Odds ratio: 1.579 (95% CI 0.269, 12.515)

- At Week 12, 25.6% vs 37.2% of patients had <5 CTCs per 7.5 mL blood (odds ratio 1.891 [95% CI 0.727, 5.059])
- Maximum median (range) decline in CTC counts was –52.4% (–100.0, 1153.4%) vs –34.5% (–100.0, 933.3%)

Exposure and Safety

- Median (range) duration of treatment was 3.2 (0.5–19.1) months with Xent + Enza and 3.7 (0.5–23.0) months with Enza
- All patients had ≥1 AE; the most common are shown in **Table 2**

Table 2. AEs occurring in ≥30% of patients in either arm

AE (preferred term), n (%)	Xent + Enza (n=43)	Enza (n=43)
Fatigue	29 (67.4)	21 (48.8)
Decreased appetite	24 (55.8)	23 (53.5)
Weight decreased	16 (37.2)	5 (11.6)
Anemia	14 (32.6)	19 (44.2)
Back pain	13 (30.2)	16 (37.2)
Musculoskeletal pain	11 (25.6)	14 (32.6)
Arthralgia	7 (16.3)	13 (30.2)

- TRAEs occurred in 41 patients (95.3%) in the Xent + Enza arm and 35 patients (81.4%) in the Enza arm; the most common were fatigue (55.8% vs 39.5%) and decreased appetite (41.9% vs 27.9%)
- Nine patients discontinued Xent due to AEs
- Two patients in the Xent + Enza arm had an AE resulting in death (respiratory failure and general physical health deterioration); these were not considered to be related to study treatment

TRAE, treatment-related adverse event

Key findings and conclusions

- Addition of Xent to Enza did not prolong PFS in mCRPC compared with Enza alone, even after adjustment for imbalances in baseline characteristics
- There were no notable differences in PSA-related endpoints and CTC response between treatment arms
- OS data were still immature at the time of analysis
- The safety profile was generally similar between treatment arms and was in line with the known safety profile of Enza

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Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, IL, USA, 31 May–4 June

This study was funded by Boehringer Ingelheim. The authors were fully responsible for all content and editorial decisions, were involved at all stages of poster development and have approved the final version.
Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Fiona Scott, of GeoMed, an Ashfield company, part of UDG Healthcare plc, during the development of this poster.

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