Plasma androgen receptor (pAR) status at emergence of metastatic castration-resistant prostate cancer (mCRPC)

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Background:

pAR gene aberrations in mCRPC patients (pts) may be associated with worse outcome with drugs targeting the AR.

Methods:

We studied plasma from a multi-institutional, open-label phase 2 study of abiraterone acetate (1000mg QD) in asymptomatic, chemo-naïve mCRPC pts (NCT01867710). Pre-defined objectives were to evaluate the association of pAR status and radiographic progression-free survival (rPFS), PFS and PSA decline. Pre-defined exploratory end-points were to ascertain more accurately the relationship between pAR copy number (CN) and worse outcome and interrogate the association between pAR status at development of CRPC (defined as the time at randomization for first-line mCRPC treatment) with duration of benefit to androgen deprivation therapy (ADT). We used a validated droplet digital PCR assay to study pAR.

Results:

Pre-treatment pAR status was defined for 135 pts from the NCT01867710 cohort. These were pooled with data from 3 independent trial cohorts (N=369:as described previously[1,2]) and a non-linear relationship between pAR and outcome was identified, where for small incremental increases in CN up to 1.93 there was a large added Hazard Ratio (HR). Using an AR CN cut-off for defining gain of 1.93, we confirmed in the NCT01867710 cohort a significant association between pAR gain (21 pts, 15%) and shorter rPFS (median 5.7 months [m]: pAR gain vs 23.7m pAR normal; HR: 2.78; 95% CI 1.34 - 4.6; p = 0.004) and PFS (median, 4.90m: pAR gain vs 16.2m: pAR normal; HR: 2.28; 95% CI 1.3 - 4;

p = 0.004). In multivariate analysis, pAR gain remained significantly associated with rPFS and PFS (Table 1). The median time from start of long-term ADT to randomisation, was significantly shorter in pAR gain at castration resistance (8m pAR gain vs 29.5m pAR normal; p = 0.004). This was validated in the primary, PREMIERE and Vancouver cohorts (primary cohort: median 9.5 m pAR Gain versus 22.5m pAR normal, p=0.0026; PREMIERE cohort: 22.7m pAR gain vs 46m pAR normal; p=0.0016; Vancouver cohort median 9.5m pAR Gain versus 17m pAR normal, p=0.003)

Conclusions:

pAR gain chemo-naïve mCRPC pts, defined as CN > 1.93, have a significantly worse outcome on drugs targeting AR. A novel observation is that pts progressing after a short duration of ADT are enriched for pAR gain.

Table 1

	rPFS		**PFS**	
	HR[95% CI]	**p**	**HR[95% CI]**	**p**
AR Gain (yes vs no)	2.54[1.20-5.30]	0.01	2.13[1.10-4.14]	0.03
Pre-treatment LDH (>ULN versus <ULN)	1.12[0.62-2.04]	0.07	1.14[0.67-1.93]	0.63
Pre-treatment ALP (> ULN versus <ULN)	0.90[0.50-1.70]	0.8	1.05[0.61-1.79]	0.87
Disease Site				
Bone/bone +LN versus LN	0.53[0.24-1.14]	0.10	0.56[0.27-1.16]	0.12
Visceral versus Bone/Bone+LN	1.07[0.14-8.16]	0.95	1.30[0.17-9.78]	0.80
Visceral versus LN	0.49[0.06-3.87]	0.50	0.43[0.06-3.39]	0.43
≥ 5 Bone Mets versus < 5 Bone Mets	1.04[0.52-2.09]	0.12	1.28[0.69-2.36]	0.44
Pre-treatment PSA (continuous)	1.00[1.00-1.00]	0.17	1.00[1.00-1.00]	0.66

References:
1. Conteduca et al Ann Oncol 2017
2. Annala et al Cancer Discovery 2018

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