



Prostate cancers that 'Wnt' respond to abiraterone

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Prostate cancers that 'Wnt' respond to abiraterone

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Wnt/ β -catenin (Wnt) signalling is involved in cancer cell self-renewal, epidermal to mesenchymal transition and growth signalling. Furthermore the interplay between Wnt pathway components and androgen receptor (AR) signalling have been well documented [1]. Linkage studies in prostate cancer have demonstrated an association between Wnt pathway genes and reduced PSA-free survival [2] and prostate cancer progression [3]. RNA-Sequencing of circulating tumour cells has implicated non-canonical Wnt pathway activation in resistance to AR antagonism [4] and large scale sequencing efforts have revealed genomic aberrations in the Wnt signalling pathway in approximately 20% of castration-resistant prostate cancer (CRPC) metastases obtained by biopsy or at rapid autopsy [5, 6]. In this edition of Annals of Oncology, Wang et al report the PROMOTE single-centre trial designed to identify associations with primary resistance to abiraterone using molecular analyses of tumor biopsies obtained prior to treatment from progressing pre-chemotherapy metastatic CRPC patients [7]. This prospectively defined and well-characterised study population is an important resource. Specifically, Wang et al enrolled 92 men and succeeded in performing a combination of whole exome and/or whole transcriptome sequencing on tumours from 86. Of note, 72% of biopsies were from bone metastases, putatively more clinically representative than most recent endeavours that were enriched for soft tissue disease. Patients were dichotomised by progression at 12 weeks of therapy (non-responders vs responders) and associations with mutated genes, copy number aberrations and transcriptional profiles were determined. For these analyses, the authors selected 98 genes with recurrent mutations in two or more tumours in their and the Grasso and Robinson data sets. They also restricted copy number evaluation to tumours with a minimum 15% tumour purity and transcriptomic analyses to skeletal metastases. Activating mutations in the Wnt pathway were enriched in abiraterone non-responders compared to responders (56.3 vs 17.1%, $p=0.001$) and patients were twice as likely (HR 2.07, CI 1.08-3.97, $p=0.03$) to be resistant to abiraterone if they had gene expression aberrations of the pathway.

Another strength of the current study is that the investigators functionally tested chemical inhibition of Wnt signalling in combination with abiraterone in abiraterone-sensitive and resistant patient-derived prostate cancer organoids. In keeping with their prediction, inhibition of Wnt had little effect in the abiraterone-sensitive (normal Wnt) model but in the abiraterone-

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3 resistant model (aberrant Wnt), cell death was seen with Wnt inhibitor monotherapy and partial
4 induction of sensitivity when combined with abiraterone. Future work could further support the
5 association between aberrant Wnt signalling and abiraterone resistance using an orthogonal
6 approach such as CRISPR-CASP9 genome editing to activate the Wnt pathway. It should also
7 be noted that abiraterone may be acting as an AR antagonist in *in vitro* models, rather than by
8 inhibiting androgen synthesis [8], in this case also competing with pregnenolone added as a
9 CYP17 substrate. These findings nonetheless still implicate Wnt pathway signalling in
10 resistance to AR inhibition. The results of drug screens in organoid or patient-derived xenograft
11 models have been correlated with clinical responses [9, 10], but the lack of stromal and
12 immunological interactions are a limitation that could be overcome by developing co-culture
13 systems or using the next generation of humanised mouse models.
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18 Low tumour purity can markedly reduce the detection of mutations and copy number changes
19 in clinical samples. Traditional visual or image analysis of tumour purity is being replaced by
20 computational methods. In the current study, the inferred tumour purity was low (median 33%)
21 although the high mean sequencing coverage of 258x should help to limit the false negative
22 rate. Low tumour purity has previously been correlated to some clinicopathological entities in
23 prostate cancer [11] and Wang et al build on this by presenting a trend to higher tumour purity
24 in non-responders compared to responders (36% vs 22%, p=0.09). Low tumour purity implies
25 that non-tumour cells or tumour microenvironment (TME) predominates in the sample. It is well
26 recognised that paracrine Wnt signals from the TME can contribute to prostate tumour
27 progression [4]. In mouse models, Wnt signalling has been implicated as modulating the TME-
28 inflammatory response, [12] and similarly, we have recently demonstrated in a cohort of high-
29 risk localised or hormone-naïve metastatic prostate cancer patients that activated Wnt
30 signalling correlated with low CD8/FoxP3 ratio, consistent with a dysfunctional T-cell response
31 and tumour escape[13].
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36 While a convincing association between Wnt signalling and abiraterone primary resistance is
37 reported in this discovery cohort, the negative predictive value, even if confirmed in
38 independent validation sets, is insufficient for clinical decision making. Moreover, nearly one-in-
39 five Wnt aberrant patients responded. Prostate cancer mouse models suggest that Wnt/ β -
40 catenin signalling requires additional events (for example PTEN loss) for oncogenesis [14] and
41 similarly, abiraterone resistance may also be multi-genomic. AR aberrations detected in blood,
42 both genomic (copy number gain or point mutations) and splice variants (mRNA or protein),
43 have shown strong associations with primary resistance [15-17]. In the current study, tumour
44 biopsy AR-V7 transcript levels also associated with primary resistance. It is therefore probable
45 that a biomarker suite would provide the most accurate prediction of response. Overall, the
46 PROMOTE data provide a strong rationale for testing of Wnt inhibitors (several agents
47 currently in early clinical trial testing) alone or in combination with abiraterone in abiraterone-
48 resistant biomarker-selected patients.
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53 **Conflict of Interest Disclosures**

54 The ICR developed abiraterone and therefore has a commercial interest in this agent. G.A. is
55 on the ICR list of rewards to inventors for abiraterone. M.L. has received educational grants
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3 from BMS & Sanofi, travel support from Janssen, Astellas, Bayer and MSD and honorarium
4 from Janssen. G.A. has received honoraria, consulting fees or travel support from Astellas,
5 Medivation, Janssen, Millennium Pharmaceuticals, Ipsen, Ventana, ESSA Pharmaceuticals
6 and Sanofi-Aventis and grant support from Janssen, AstraZeneca and Arno.
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