Eradication of AR and MYC Amplifications, and Re-Sensitization to Abiraterone, by High Dose Testosterone in a CRPC Patient

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Increasingly AR amplification and a variety of other amplifications, deletions, and mutations are implicated in the resistance to newer hormonal agents such as abiraterone (abi) and enzalutamide (enza). Over coming this resistance is a significant current problem. Preliminary data are available that support use of PARP inhibitors, taxanes, various platin-based treatments, PSMA-targeted radiopharmaceuticals, and PD1 inhibitors. Additional maneuvers capable of overcoming abi/enza resistance are clearly needed.

A patient with CRPC was previously treated with ADT, abi, dexamethasone, radium-223, enza, DES, docetaxel, and a single dose of docetaxel/carboplatin (33 mg/M2 and AUC 3.3) given at low doses due to due to persistent thrombocytopenia (see below). A bone marrow 9/24/15 demonstrated a hypoplastic marrow. Conventional chemotherapy ceased as his platelet count on May 17, 2016 were 26,000 and his PSA was 530 ng/ml and rapidly rising with a castrate testosterone for over 3 years.

In desperation, high dose testosterone was started May 20, 2016 at a dose of 87.5 mg given daily as a 1% testosterone gel applied to the skin. Concomitant medications included LHRH agonist (ongoing >3 years) and 0.75 mg/day dexamethasone which had been ongoing for >6 months. The PSA declined one week later and nadired at 45.8 on June 21, 2016. Thereafter the PSA began to rise and on August 24, 2016, the PSA was 280. Abiraterone was restarted and the PSA declined reaching a level of 65.5 on Sept 20, 2016.

Circulating free (cf) DNA was measured by Guardant assays. These assays revealed marked AR and MYC amplification at baseline with a dominant p53 mutation. Post-T, there was restoration of normal AR and MYC copy number and over 90% reduction in the p53 R273H mutations. Though it is conceivable that a single reduced dose of docetaxel + carboplatin could have such an effect, we think that is unlikely and attribute the changes in AR and MYC copy number to high T doses.

Date	PSA ng/ml	T (ng/dL)	Platelets $X10^3$	Hgb	AR Amplification	MYC Amplification	P53 R273H	Rx
4/5/16	268	<10*	46	8.4	15.9X	3.7X	9.8%**	
4/26/16	333	ND	48	7.5				Doc/ Carbo
5/17/16	530	ND	27	9.5				T***
5/31/16	207	1462	41	7.9				T
6/21/16	46	1056	41	8.2				T
7/12/16	78	1332	51	8.9	1.4X	0	0.6%	T
7/26/16	131	1387	56	9.4	0	0	0.5%	T
8/24/16	280	ND	65	9.9				Abi
9/6/16	99	24	82	10.6				Abi
9/20/16	65	<10	78	10.8				Abi

*T was measured 2 months previously with LHRH agonist maintained
**p53R273H mutation expressed as % of total cfDNA
*** High dose T started 5/20/16

Summary: Sporadic cases of CRPC patients with responses to high dose T have been reported but the dramatic loss of AR and MYC amplification shown here is to our knowledge unprecedented. Additional studies, such as the TRANSFORMER trial, are required to better understand the molecular changes we have observed in this single patient.