Prostate Cancer - Newer Antiandrogens & Emerging Therapies Targeting a “Watchful Waiting” and Resistance Population

Description: Increase in prevalence of Prostate cancer and availability of new treatment options (Zytiga, Xtandi, Cabazitaxel and Xofigo) in last few years has extended the role of newer oral Antiandrogens to treat metastatic CRPC patient populations where the unmet need was high. This has expanded WW market size of Prostate cancer drugs to $7b in 2016 from $2.5b in 2011. Now nmCRPC, HSPC and Xtandi/Zytiga resistance population are the markets where in new pipeline drugs are under development.

Reported PhII clinical data of Xtandi, ARN-509 and ODM-201 in nmCRPC when indirectly compared demonstrate the bar is high for ARN-509 to compete against Xtandi in nmCRPC market and while ODM-201 is few years behind in clinical development. While in mHSPC reported clinical results of STAMPEDE study opens door for docetaxel combination approach as standard of care in first line setting.

Around 8 plus drugs are in PhIII development for Prostate cancer treatment and 26 plus drugs are in PhII development (21 small molecules) - success of a few (ARN-509, ODM-201, AZD 5363, GX301) in coming years will expand nmCRPC ($3.5b), mHSPC market ($1b) and Xtandi/Zytiga resistant population ($1b) market by 2023. Longer duration of therapy and high prevalence makes earlier setting market more attractive and bigger for newer options than the late stage if they succeed.

For drugs targeting through androgen pathway - Now trials and clinical development is underway for second and third generation androgen receptor inhibitors (ARN-509, ODM-201, ODM-204, EPI-506, VT-464, TAS-3681 and DR103). While androgen synthesis inhibitors still needs a proof of concept in clinic due to failure of TAK-700 & TOK-001. Expected data from VT-464 (Apr 2017) & ASN-001 will be important to watch to taste the success for this class. Androgen receptor degrader is another MoA in development from a decade and success of in clinic compound GTX-758 (Data expected anytime from now as study completed in March 2016 - less likely to succeed) will decide the proof of concept.

Other than pipeline drugs targeting androgen pathway, NCE targeting AKT pathway (AZDS363, Ipatasertib) appears to be more promising to succeed in late stage, while drugs acting through PARP inhibition (Olaparib, Niraparib) still needs a taste of success. Other interesting pipeline asset is LHRH agonist LMIS 50 mg, which is designed to overcome the drawbacks of the commercial depot products containing GnRH agonists by using a proprietary delivery system.

Also 6 therapeutic vaccines are in clinical development to treat prostate cancer. Recently launched PD-L1 IO therapy has increased hope of treating cancer in much safer way. Current ongoing studies of late stage IO mab are in Ph I/II clinical development and would be able to answer of PTEN hypothesis for role of PD-1, PD-L1 inhibitor to treat prostate cancer in coming years.

Resistant development is another challenge with long term use of Xtandi/Zytiga and needs to be addressed by pipeline second/third generation Antiandrogens/ combination approach with IO/PARP/AKT inhibitors to treat mCRPC. Increase in pricing pressure in developed market again put inference on Combination approach unless the advantage is significant and improve the QoL in earlier setting. Due to that, drugs targeting adjuvant setting has high bar to deliver (Atezolizumab, GX301, Mipsagargin and Olaparib) in the clinical development to add significant value.

This report details current unmet need, changing regulatory requirement, reimbursement challenges & market dynamics of Prostate Cancer drugs. Report mention pipeline Antiandrogens, late stage prostate cancer pipeline drugs/new Mechanism of action & major companies developing Prostate cancer drugs. It also provides insight on clinical development strategy of combination pipeline/marketed drugs & therapeutic competitive landscape to find treatment paradigm fit & market potential of new drugs for treatment of Prostate Cancer.

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- Use patents of Zytiga : the 438 Patent
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  - ARN-509- A better Xtandi is in making

- Ongoing Clinical trials of ARN-509 and our expectations
- ARN-509- Clinical data comparison vs. Xtandi and other pipeline candidates

- ODM-201- Does its safety differentiate it against ARN-509/Xtandi?
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- EPI-001 and EPI-506
- SH3680
- GT0918 (Proxalutamide)
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- Other early stage pipeline Antiandrogens and our view –
- DR103
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- HE3232 (Apoptone)
- BMS-641988

- Androgen Synthesis inhibitors: TAK-700 and TOK-001 Failure in clinical trials creates “No hope” for VT-464 & other Cyp17 lyase inhibitor?
- TAK-700- How it is different from Zytiga?
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7. Combination of drugs with IO therapy

- Pembrolizumab
- Durvalumab with or without Tremelimumab
- Atezolizumab (Tecentriq)
- Nivolumab

8. New pipeline drugs
- AZD 5363
- ADXS31-142 (ADX-PSA)
- [68Ga]RM2 or Ga-bombesin
- Recombinant adenovirus (Ad5-SGE-REIC/Dkk3)
- SM-88
- Mobilan (M-VM3)
- Dendritic cells DCVAC
- LMIS 50 mg
- NBTXR3
- Niraparib
- GX301
- ODX (Osteodex)
- BHR-200 (transdermal estradiol gel)
- Mipsagargin (G-202)
- PROSTVAC-V/F
- ProstAtakÂ
- 99mTc-MIP-1404 injection
- PectaSol –C Modified Citrus Pectin
- ATL-101
- MVI-816
- Olaparib (Lynparza)
- TAK-385 (Relugolix)
- Ipatasertib (GDC-0068, RG7440)
- LY3023414
- PSMA ADC
- Zoptrex (Zoptarelin doxorubicin)

Companies mentioned:

- Pfizer
- Medivation
- Astellas
- Valeant pharmaceuticals
- Turing pharmaceuticals
- Abbott
- Johnson & Johnson
- Tokai pharmaceuticals
- Bayer pharmaceuticals
- AstraZeneca
- Teva pharmaceuticals
- Mylan
- Bind therapeutics
- NanoString Technologies
- Zenith Technologies
- Actavis
- Apotex
- Par pharmaceuticals
- Citron pharma
- Dr. Reddy's Laboratories
- Sun pharma
- Wockhardt
- Amneal pharmaceuticals
- West-ward pharmaceuticals (Hikma pharmaceuticals)
- Hetero Labs.
- BTG International Ltd.
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- Allchem pharma
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