Ongoing Investigation and Potential Integration of Secondary Hormonal Therapy, Immunotherapy or Cytotoxic Therapy into the Management of Earlier Stage Disease

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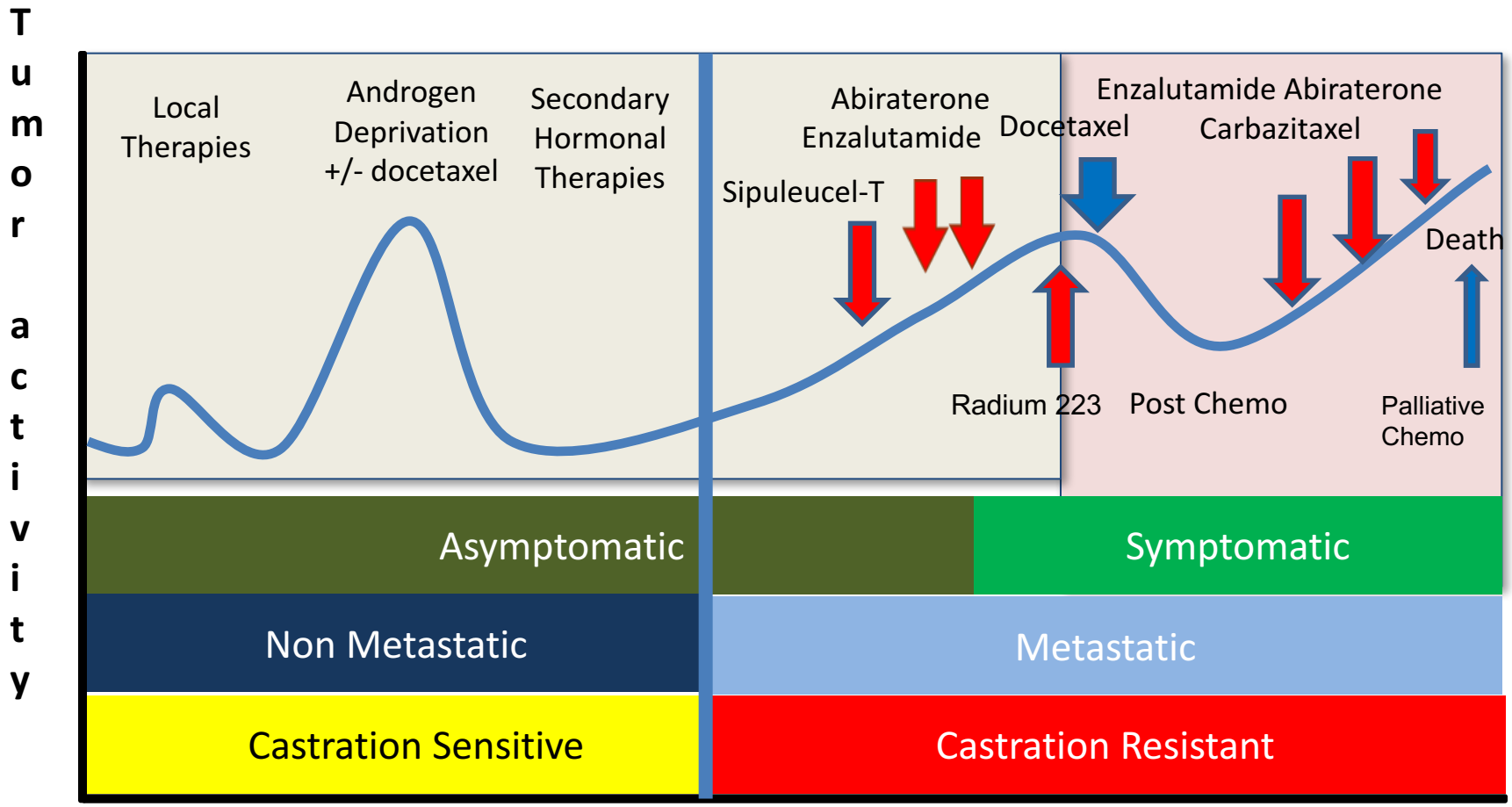
Disclosures

Advisory Committee	Abbott Laboratories, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Janssen Biotech Inc, Merck, Pfizer Inc

Novel Agents in Early Stage Prostate Cancer

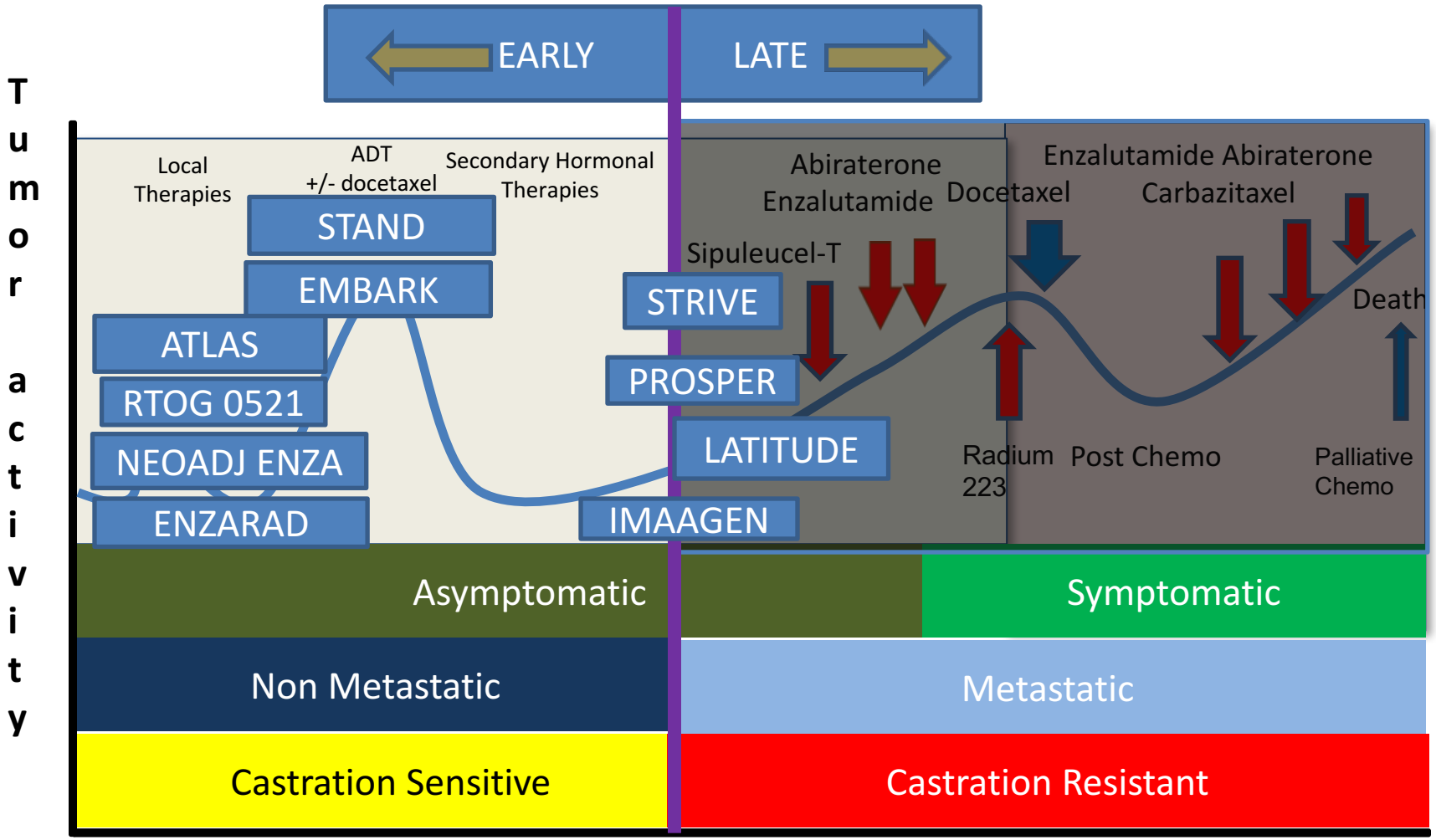
- Since 2010, 5 new agents have been approved in the mCRPC space
- Increasing interest in using new approaches in earlier high risk, non-metastatic disease
  - Existing and newer androgen biosynthesis pathway inhibitors
  - Immunotherapy
  - Chemotherapy

2017 Prostate Cancer Landscape



Red arrows indicate new agents and indications since 2010.

Evolving Interest in Early Stage High Risk Disease



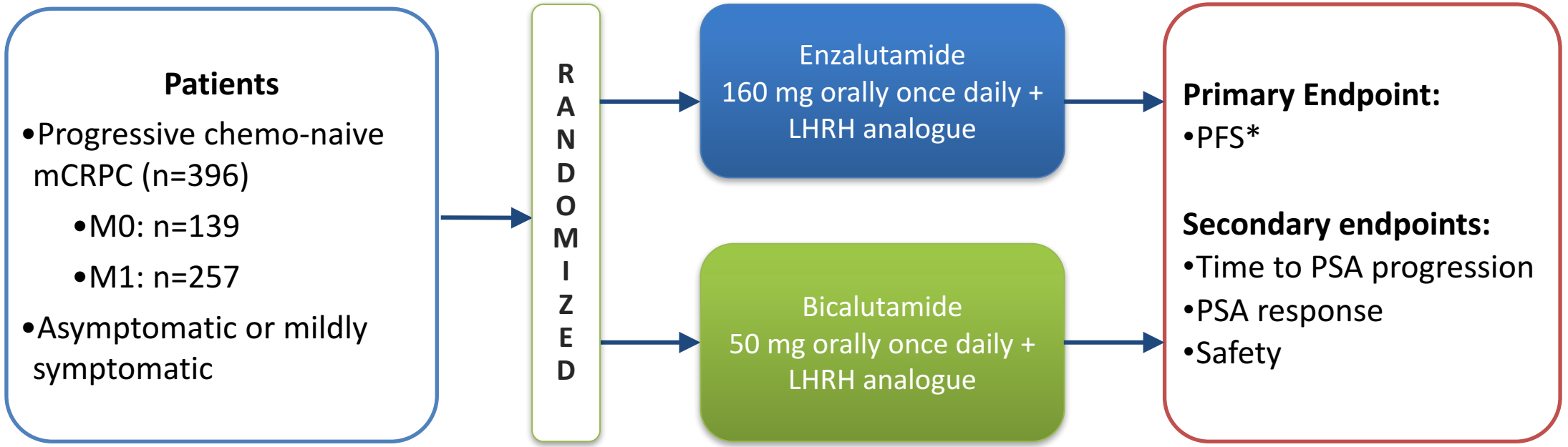
Selected clinical trials completed and ongoing in “early” disease

Select Clinical Trials In Earlier Stage Prostate Cancer Using Approved Agents

Clinical trial	Phase	Study description	N	Status
STRIVE NCT01664923	2	ENZA vs. bicalutamide after ADT in M0/M1 CRPC	400	Data available
Neoadjuvant Enzalutamide NCT01547299	2	Randomized, open-label ENZA neoadj therapy for patients undergoing RP for localized PC	52	Data available
EMBARK NCT02319837	3	Randomized, 3-arm trial of ENZA vs. ENZA + Leuprolide vs. Placebo + Leuprolide with non-metastatic prostate cancer and rapidly rising PSA after initial local therapy	1860	Enrolling
Enzarad NCT02446444	3	RT + Adjuvant LHRH + Enzalutamide in High-Risk Clinically Localized Prostate Cancer	800	Enrolling
PROSPER NCT02003924	3	ADT ± ENZA in M0 CRPC without prior chemotherapy	1560	Enrolling
RTOG 0521 NCT00288080	3	ADT and radiotherapy vs ADT and RT followed by chemotherapy with docetaxel and prednisone for localized, high-risk prostate cancer	563	Data Available
LATITUDE NCT01715285	3	ADT alone vs Abiraterone/prednisone newly diagnosed high risk metastatic hormone naïve	1200	Data pending

STRIVE
Study Design

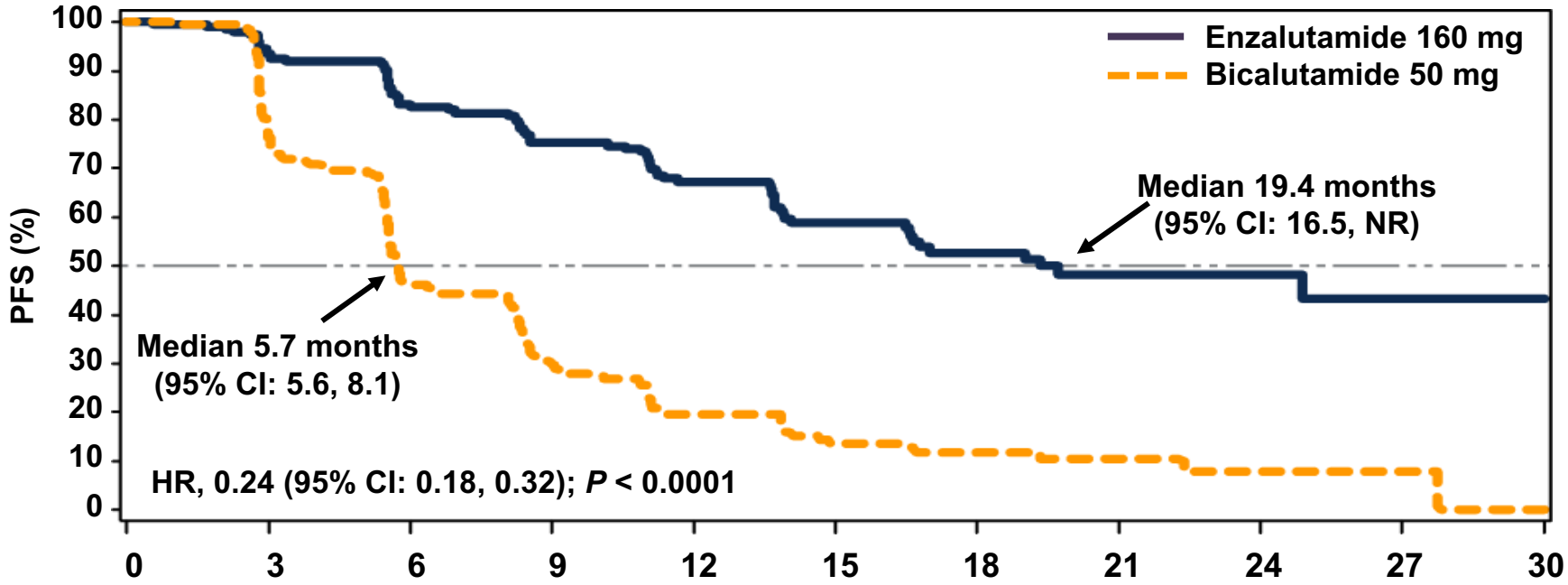
Phase 2, randomized, double-blind, parallel study



*PFS was defined as time from randomization to radiographic (bone or soft tissue) progression, PSA progression (defined by Prostate Cancer Working Group 2 criteria), or death due to any cause, whichever occurred first.[3]

1. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT01664923?term=strive+enzalutamide&rank=1. Accessed April 7, 2015.
2. Penson D et al. Presented at: AUA Annual Meeting; May 15-19, 2015: New Orleans, LA.

STRIVE: Progression-Free Survival

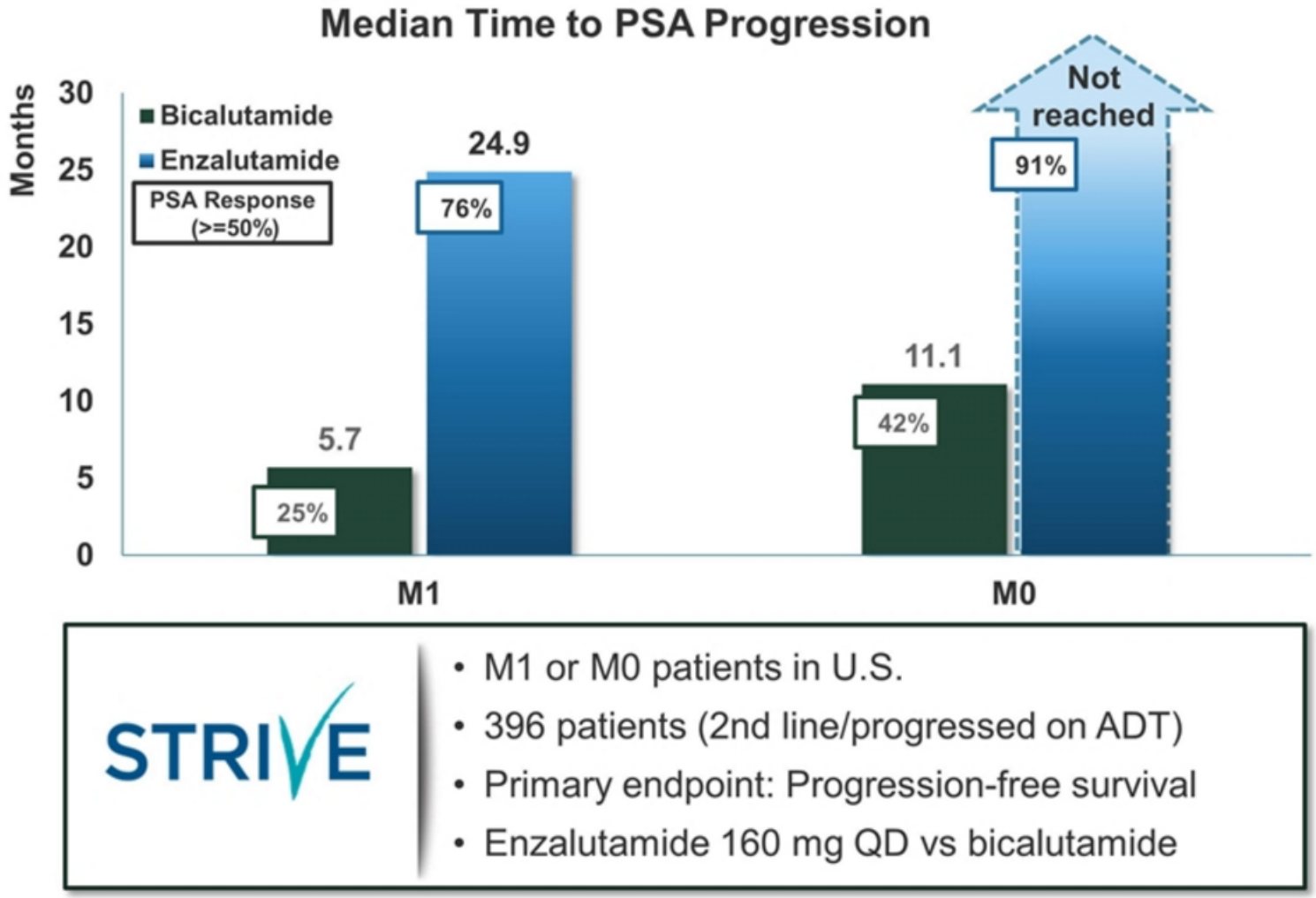


Patients at Risk

Enzalutamide	198	171	150	131	101	66	43	24	16	5	0
Bicalutamide	198	138	80	51	29	17	9	5	3	1	0

CI = confidence interval; HR = hazard ratio; NR = not reached

Penson D et al. AUA Annual Meeting. May 15 -19, 2015; New Orleans

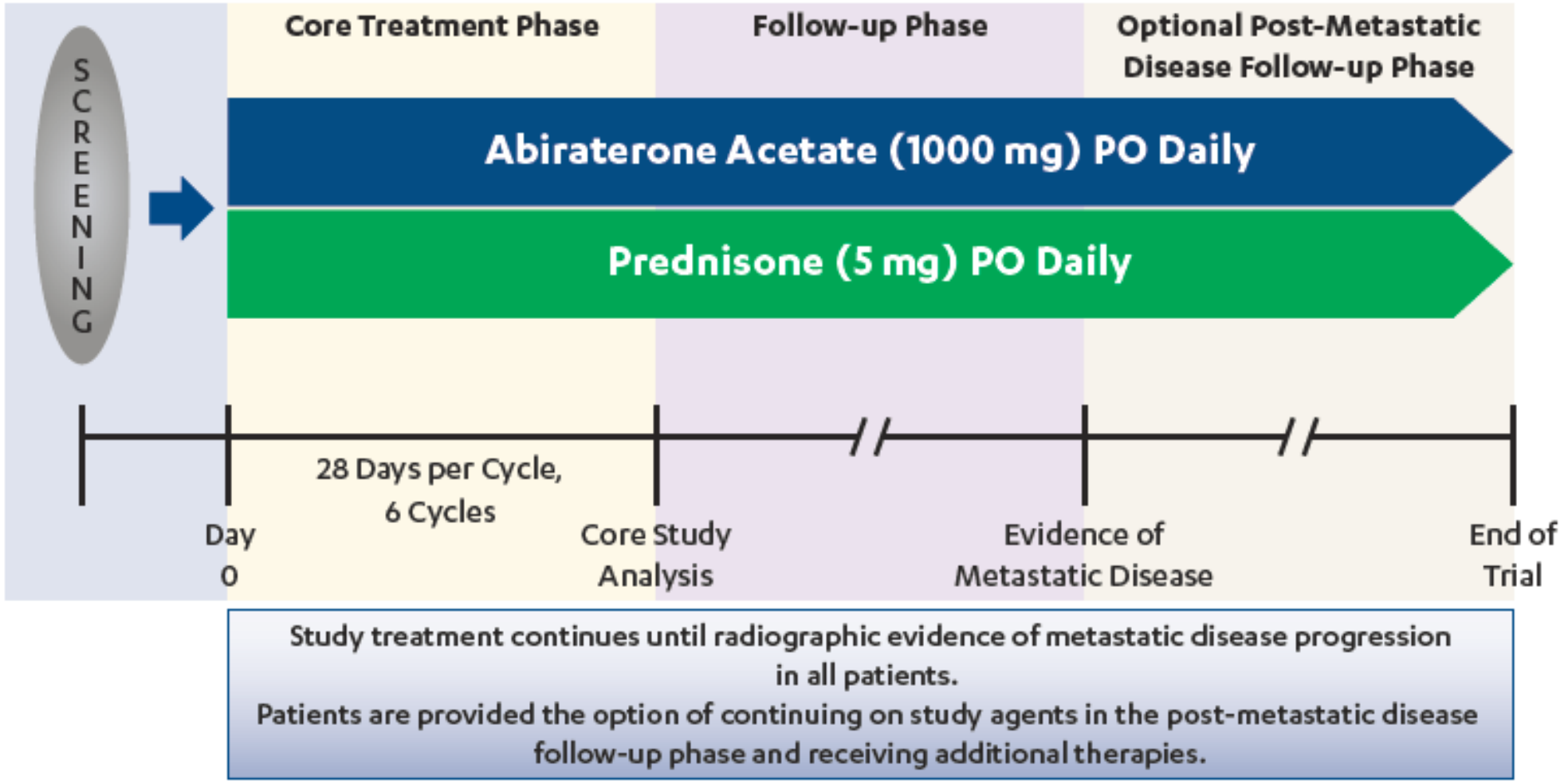


Data from the STRIVE trial indicate that enzalutamide significantly reduced the risk of prostate cancer progression or death compared with bicalutamide in patients with nonmetastatic or metastatic CRPC.

Penson D, et al. AUA Congress. May 15-19, 2015; New Orleans, LA, USA. Publication: Penson D, Armstrong A, Concepcion R, et al. Enzalutamide Versus Bicalutamide in Castration-Resistant Prostate Cancer: The STRIVE Trial. Journal of Clinical Oncology. January 25, 2016, doi: 10.1200/JCO.2015.64.9285.

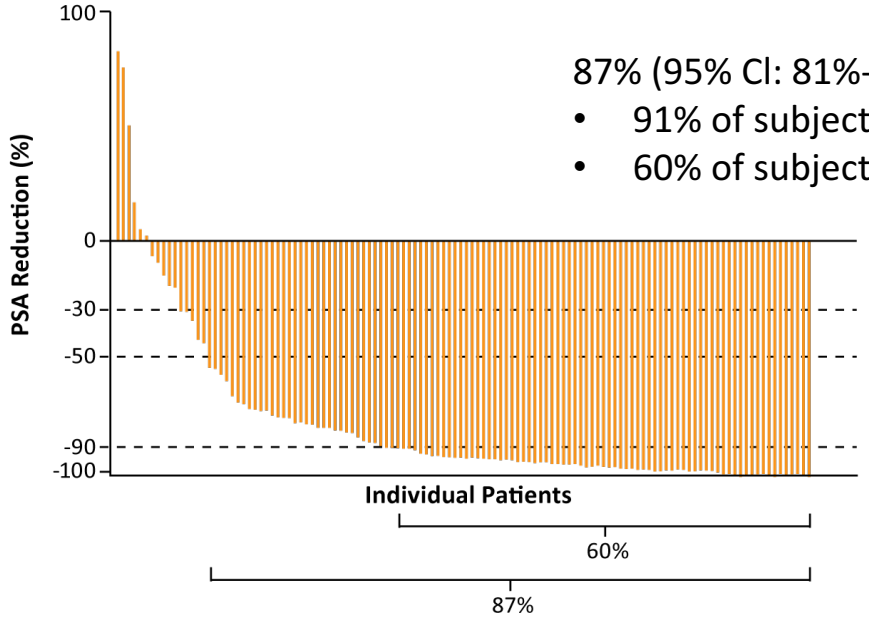
IMAAGEN Study: **IM**pact of **A**biraterone **A**cetate in Prostate-Specific Anti**GEN**

Safety/efficacy of AA + prednisone in nmCRPC with rising PSA and castrate testosterone



Ryan CJ, et al. ASCO Annual Meeting; June 3-7, 2016; Chicago, IL.

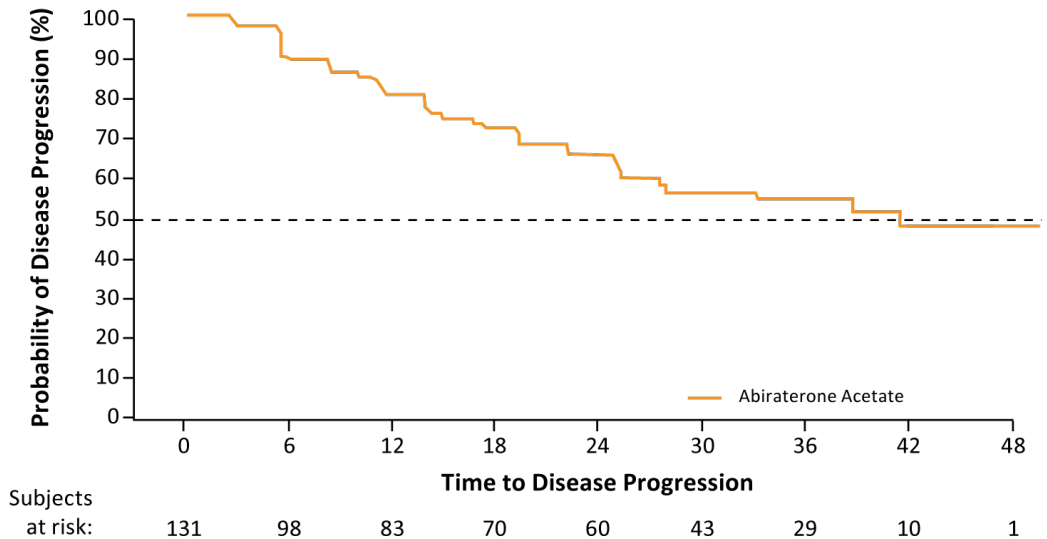
Maximum PSA Reduction During Cycles 1-6



87% (95% CI: 81%-93%) of subjects achieved a ≥50% PSA reduction

- 91% of subjects achieved a ≥30% PSA reduction
- 60% of subjects achieved a ≥90% PSA reduction

Radiographic Evidence of Disease Progression*



* Additional analysis including 31 confirmed and 15 with unconfirmed progression that led to discontinuation from the trial

IMAAGEN data presented by Ryan CJ, et al. ASCO Annual Meeting; June 3-7, 2016; Chicago, IL

IMAAGEN Conclusions

- Treatment of high-risk nmCRPC patients with AA (1000mg) + P (5mg) resulted in a median time to PSA progression of 28.7 months
- The median time to radiographic disease progression was not reached at the data cut-off
- The safety profile was consistent with the safety profile from previously reported studies

Ryan CJ, et al. ASCO Annual Meeting; June 3-7, 2016; Chicago, IL.

Sequencing of Sipuleucel-T and Androgen Deprivation Therapy **(STAND)** in Men with Hormone-Sensitive Biochemically-Recurrent Prostate Cancer: A Phase II Randomized Trial

- M0 following RP or RT, PSADT < 12 months
- Sipuleucel-T w/12 mo ADT vs 12 mo ADT→Sipuleucel-T
- Endpoint was PA2024-specific T cell response
- Results: responses were higher with sipuleucel-T→ADT versus ADT→sipuleucel-T; longer time to PSA progression
- **Conclusions:** Sipuleucel-T→ADT appears to induce greater antitumor immune responses than the reverse sequence.

Antonaarakis, Clin Can Res Published Online November 10, 2016

Neoadjuvant Enzalutamide Prior to Prostatectomy

- Combo therapy with enza/dutasteride/LHRHa resulted in pCR and MRD rates similar to historical controls.
  - 0/25 enza pCR or MRD
  - 1/23 enza/dutasteride/LHRHa pCR (4.3%)
- Continued AR activity in residual tumor suggests that AR signaling may contribute to survival. Strategies to more effectively ablate AR activity are warranted to determine whether more substantial antitumor effects are observed.

Montgomery, B et al. Clin Ca Res May 2017

AR antagonists: Central to Next Phase of Early Trials

First Generation	Type	Action	FDA Approved
Flutamide	Non-steroidal phenylamine	Binds AR LBD and inhibits AR activation by androgens	1989
Bicalutamide	Non-steroidal phenylamine	Binds AR LBD and inhibits AR activation by androgens	1995
Nilutamide	Non-steroidal phenylamine	Binds AR LBD and inhibits AR activation by androgens	1996
Second Generation	**Type**	**Action**	**FDA Approved**
Enzalutamide (MDV3100)	Non-steroidal diarylthiohydantoin	Binds AR LBD, inhibits AR activation by androgens, inhibits AR nuclear translocation, inhibits AR DNA binding	2012
Apalutamide (ARN-509)	Non-steroidal diarylthiohydantoin	Binds AR LBD, inhibits AR activation by androgens, inhibits AR nuclear translocation, inhibits AR DNA binding	Phase III
Darolutamide (ODM-201)	Non-steroidal carboxamide	Binds AR LBD, inhibits AR activation by androgens, inhibits AR nuclear translocation	Phase III

Select Phase III Clinical Trials in Earlier-Stage Prostate Cancer Using Investigational Agents

Trial Identifier	Target Accrual	Eligibility Setting	Randomization
ATLAS	1,500	High-risk clinically localized PCa receiving primary radiation therapy	• Apalutamide (ARN-509) x 30 mos + Placebo + GnRH agonist x 30 mos + Radiation therapy (74-80 Gy) • Bicalutamide x 30 mos + Placebo + GnRH agonist x 30 mos + Radiation therapy (74-80 Gy)
SPARTAN	1,200	M0 CRPC at high risk of progression (PSADT ≤ 10 mos)	• Apalutamide + ADT • Placebo + ADT
ARAMIS	1,500	M0 CRPC at high risk of progression (PSADT ≤ 10 mos and PSA > 2 ng/ml)	• Darolutamide (ODM-201) • Placebo
ARASENS	1,300	Metastatic hormone-sensitive PCa	• Darolutamide + ADT + docetaxel • Placebo + ADT + docetaxel

Management of Early Stage Prostate Cancer: Conclusions

- Recent advances have focused on metastatic CRPC disease
- Renewed attention on the management of early stage high risk disease in current clinical trials
- Newer less toxic agents combined with advances in genomic and genetic biomarkers will redefine the approach to early high risk disease

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The Role of Genetic Testing for Inherited Prostate Cancer Risk

Consensus Conference

Sidney Kimmel Cancer Center, Thomas Jefferson University

and

The Foundation for Breast and Prostate Health

Philadelphia, Pennsylvania

March 3 & 4, 2017

SELECT PHILADELPHIA PROSTATE CANCER CONSENSUS 2017 CONCLUSIONS

- Factor in BRCA2 mutation status into PCA screening discussions.
- Test men with suspected HPC (hereditary prostate cancer) for HOXB13, with suspected hereditary breast and ovarian cancer (HBOC) for BRCA1/2, and suspected Lynch Syndrome for DNA mismatch repair (MMR) gene mutations.
- When considering management, BRCA2 achieved moderate consensus for factoring into early-stage management discussion, and strong consensus in high-risk/metastatic setting.
- There was moderate agreement to test all men with metastatic castration-resistant PCA, with strong agreement to test BRCA1/2 and moderate agreement to test ATM to guide targeted therapy.

Giri, et al Submitted JCO May, 2017