Metastasis Free Survival - A Novel Endpoint in nmCRPC

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Disclaimer

This presentation reflects my personal views and not necessarily those of Bayer

The focus of this presentation is on key factors contributing to the establishment of a novel endpoint in nmCRPC and not on specific treatment options/products

Objectives

- Discuss key factors that led to the establishment of metastasis free survival as a novel endpoint for regulatory approval in non-metastatic castration resistant prostate cancer

- Discuss applicability to other tumor types/settings

Non-Metastatic Castration Resistant Prostate Cancer and Metastasis Free Survival

Non-metastatic CRPC is a disease state defined by rising levels of prostate-specific antigen (PSA) despite castrate levels of testosterone and the absence of radiographic evidence of distant metastatic disease.

Metastasis Free Survival (MFS) definitions have been designed to ensure that metastatic events exclude local progression, which is not considered as likely to cause illness and death as are distant bone or visceral metastatic disease

Novel endpoint of MFS was confirmed to be meaningful by 3 prospective, randomized trials; by using this earlier endpoint it was possible to bring new therapies providing improvement in morbidity and mortality to patients earlier

Three new drugs have been approved recently in the US and the EU (as well as other regions/countries) based on MFS as the primary endpoint and OS as either co-primary or secondary endpoint

- ERLEADA (apalutamide), XTANDI (enzalutamide) and NUBEQA (darolutamide)
- All three drugs demonstrated substantial improvement in MFS and following approval, demonstrated an improvement in Overall Survival as well

Key factors contributing to the establishment of MFS as an endpoint in nmCRPC

Considerations regarding the target patient population

Natural history of disease and biological plausibility

OS no longer a practical primary endpoint for approval in the target indication

Multi-stakeholder engagement and sustained efforts in the drug development community

Considerations regarding the target patient population

Prior to 2018, there were no drugs approved for the nmCRPC population

Men with nmCRPC with rising PSA levels are generally not considered disease-free[1]

Patient anxiety regarding rising PSA levels often lead to earlier use of ADT[2]

- Androgen deprivation therapy (ADT) with either a gonadotropin-releasing hormone agonist/antagonist or surgical orchiectomy offered in the setting of rising PSA levels
- While ADT induces PSA decline, many patients eventually develop nonmetastatic castration-resistant prostate cancer (nmCRPC),
- Significant heterogeneity within the nmCRPC population in terms of risk levels and progression to metastatic disease which in turn leads to increased morbidity and risk of death

Addressing the unmet need[3]

Reducing anxiety of patients and unease of physicians with rising PSA levels and fast PSA doubling time

Anticipation of a substantial risk for metastases in the very near future

Concerns with complications and symptoms that metastases would give rise to: pain, skeletal events and medical interventions

Concerns that the window of opportunity to improve outcome may be lost

1. Beaver et al, *NEJM* (2018)
2. Dale, *J Clin Oncol* (2009)
3. De Santis and Steuber, ESMO Open (2019)

Key factors contributing to the establishment of MFS as an endpoint in nmCRPC

Considerations regarding the target patient population

Natural history of disease and biological plausibility

OS not considered to be a practical primary endpoint for approval in the nmCRPC population

Multi-stakeholder engagement and sustained efforts in the drug development community

Natural history of disease and biological plausibility

Long survival in many cases with risk of recurrence and metastasis based on risk factors

In the era of PSA testing, many patients can be detected early with the chance for potential cure with either surgery or radiation

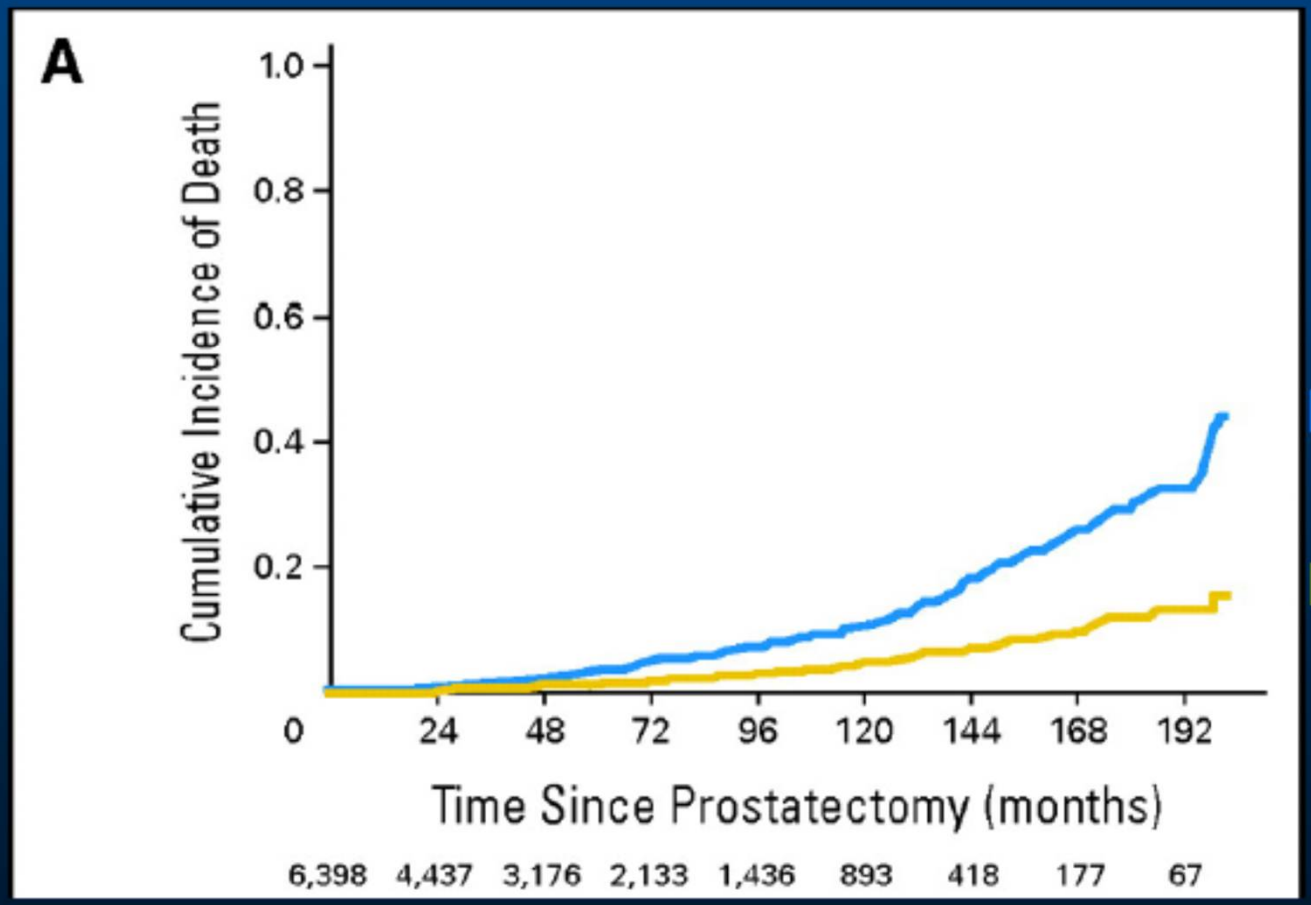
Despite early detection and advances in surgical and radiation techniques, prostate cancer can recur, and many patients continue to have rising PSA levels after salvage local therapy and subsequent androgen-deprivation therapy.

Many years may elapse between detection of rising PSA levels and metastasis or death.

However, in some nmCRPC patients, specific risk factors contribute to earlier progression to metastatic disease and death

- For example, patients with a more rapid rise in PSA levels (short PSA doubling time), the risk of death within the next few years is high

Prostate Cancer-Specific Mortality After Radical Prostatectomy



Stephenson AJ, et al: JCO 27:4300-4305, 2009

Source:
FDA Archives
MFS ODAC 2011

Prostate Cancer-Specific Mortality After Radical Prostatectomy

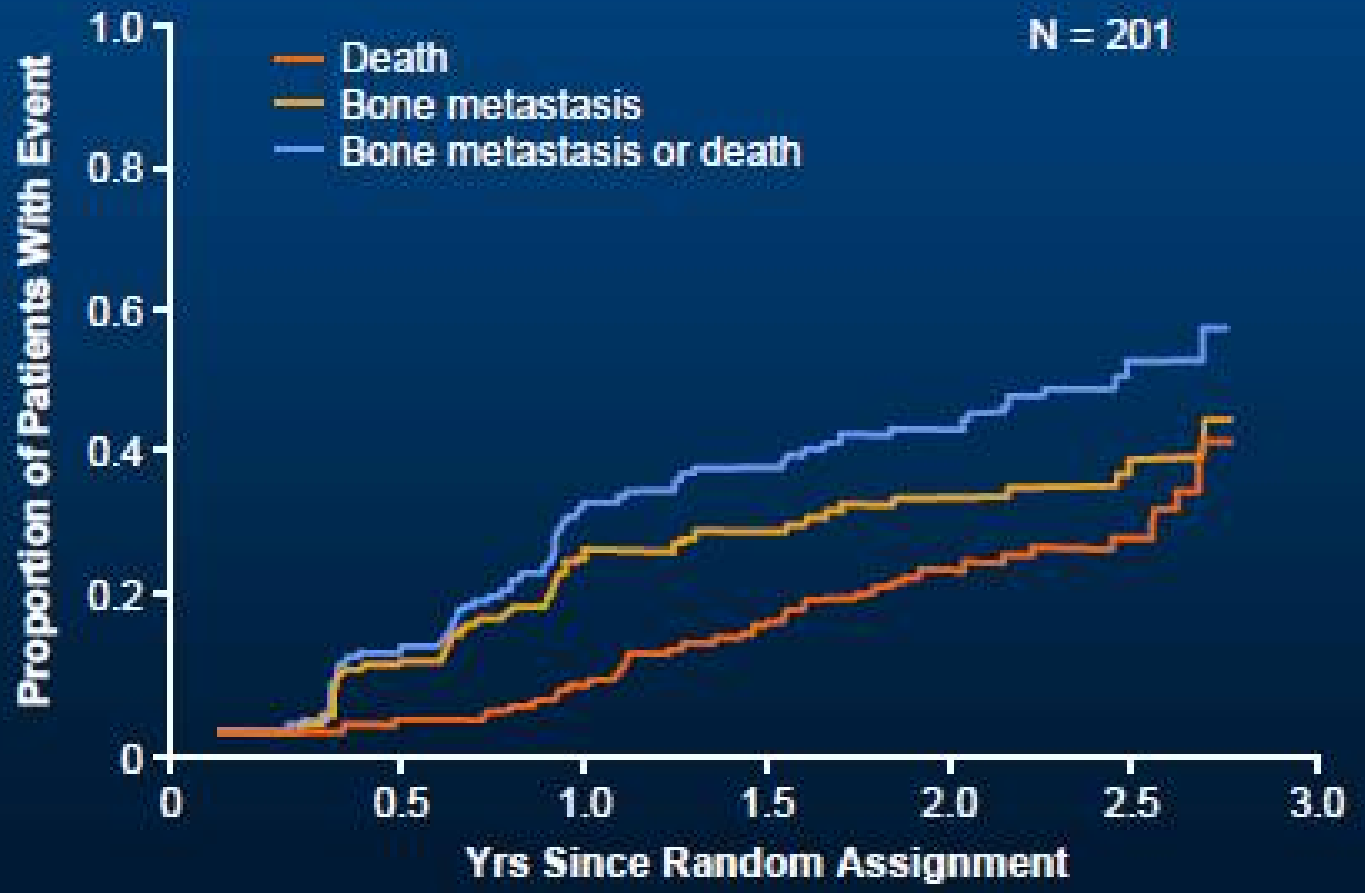
Variable	15 yr PCSM	% Pts
Gleason 8-10	34%	6%
T3	38%	2%
PSA 20-50	22%	6%
"High Risk"	19%	17%

Adverse clinical features are rare and most patients do not die of PCa

Stephenson AJ, et al: JCO 27:4300-4305, 2009

Source:
FDA Archives
MFS ODAC 2011

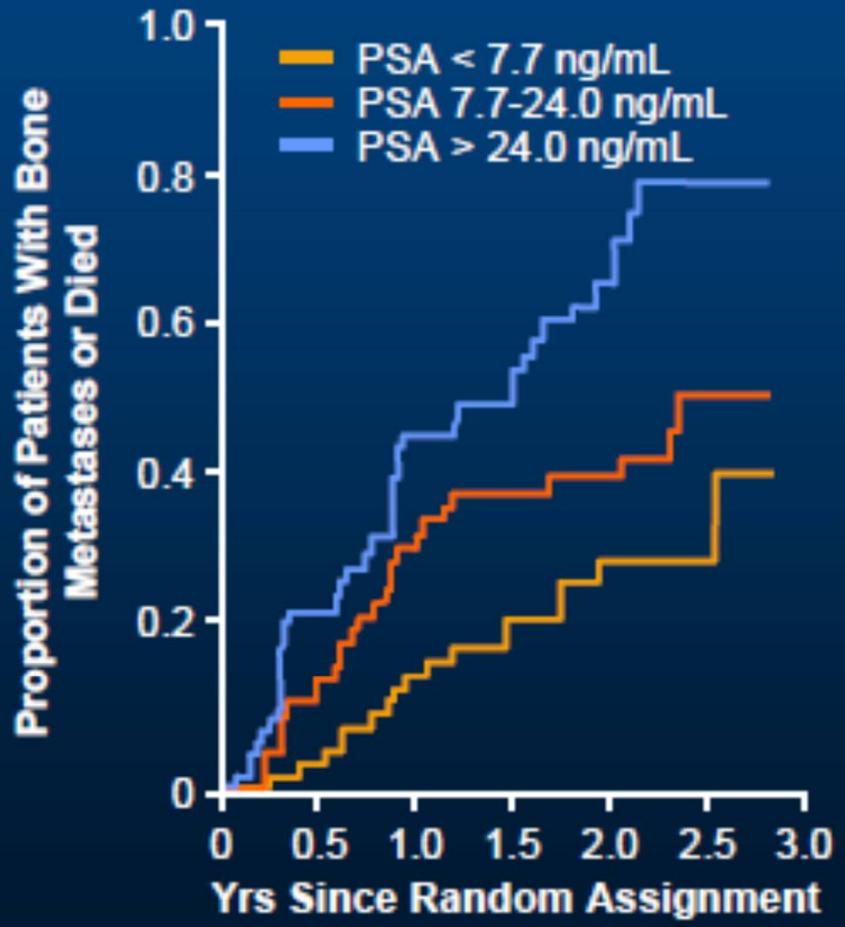
Time to Bone Metastasis and/or Death in Nonmetastatic HRPC

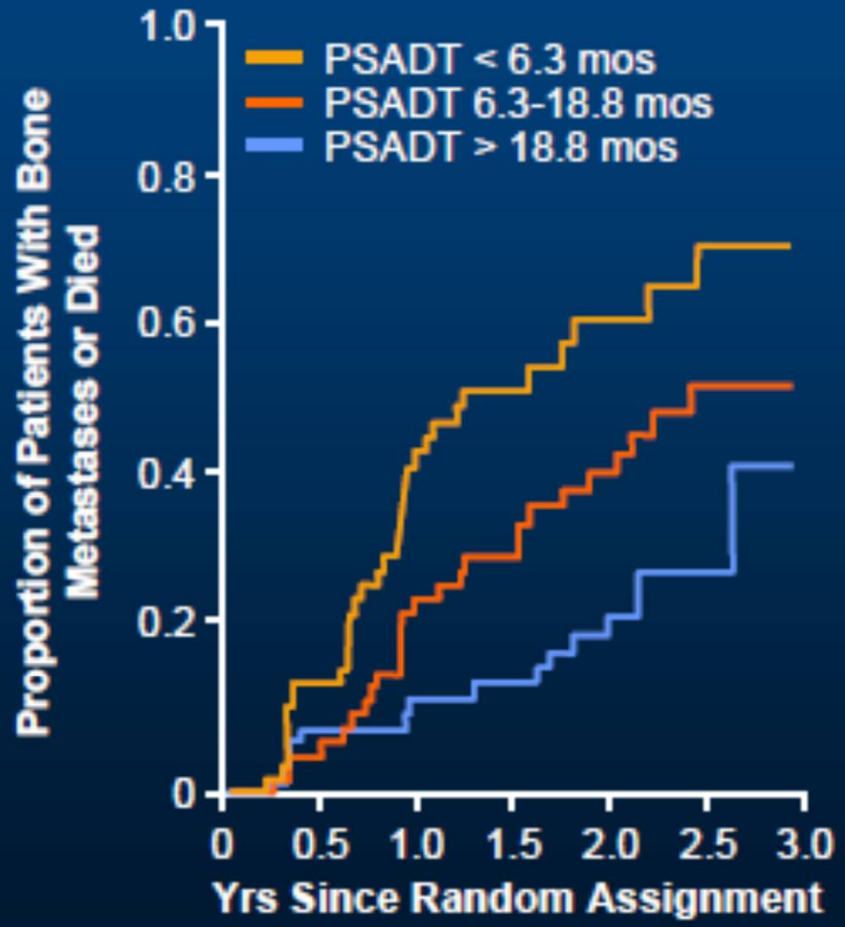


Smith MR, et al. J Clin Oncol. 2005;72:2918-2925.

Source:
FDA Archives
MFS ODAC 2011

PSA Level and Doubling Time Define Shift From M0 to M+ in CRPC

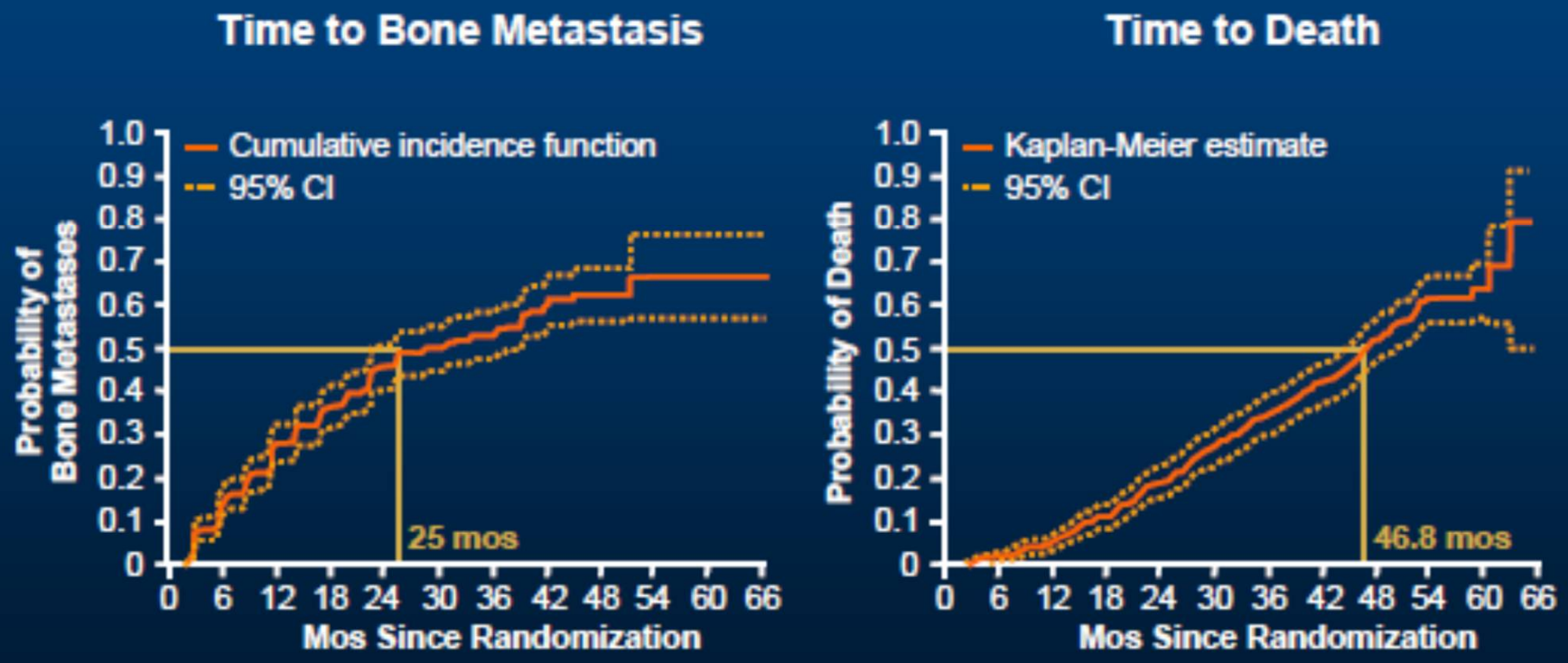




Smith MR, et al. J Clin Oncol. 2005;72:2918-2925.

Source:
FDA Archives
MFS ODAC 2011

Time of M0 to M1 and Death in Progressive, Non-metastatic CRPC



Smith MR, et al. Cancer. 2010;117:2077-2085

Source:
FDA Archives
MFS ODAC 2011

Key factors contributing to the establishment of MFS as an endpoint in nmCRPC

Considerations regarding the target patient population

Natural history of disease and biological plausibility

OS not considered to be a practical primary endpoint for approval in the nmCRPC population

Multi-stakeholder engagement and sustained efforts in the drug development community

Challenges with OS as a primary endpoint in nmCRPC

Prior to consideration of MFS as a novel endpoint in nmCRPC, there were approved therapies in the US and EU for metastatic CRPC based on improvement in overall survival (e.g. Docetaxel, Cabazitaxel, Abiraterone acetate)

Transition from nmCRPC to detectable metastatic disease is a clinically relevant event that can be associated with pain and morbidities, resulting in the need for additional interventions

Relatively long survival periods in nmCRPC patients along with the availability of multiple subsequent therapies that can confound results rendered overall survival an impractical end point and spurred interest in earlier efficacy end points.

References:
- Brave et al, 2020, Clinical cancer Research
- Beaver, Kleutz and Pazdur, 2018, NEJM
- Kleutz, P, ODAC 2011

Key factors contributing to the establishment of MFS as an endpoint in nmCRPC

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Multi-stakeholder engagement and sustained efforts in the drug development community

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Key multi-stakeholder meetings

In recognition of the increased interest in developing therapies for the nmCRPC population, the FDA convened a non-product specific ODAC in September 2011 to discuss clinical trial end points and trial designs that might be used to support drug approval

- ODAC emphasized that though metastasis-free survival is a reasonable end point, ensuring clinical benefit of a drug would require a substantial magnitude of improvement and a favorable benefit–risk evaluation.

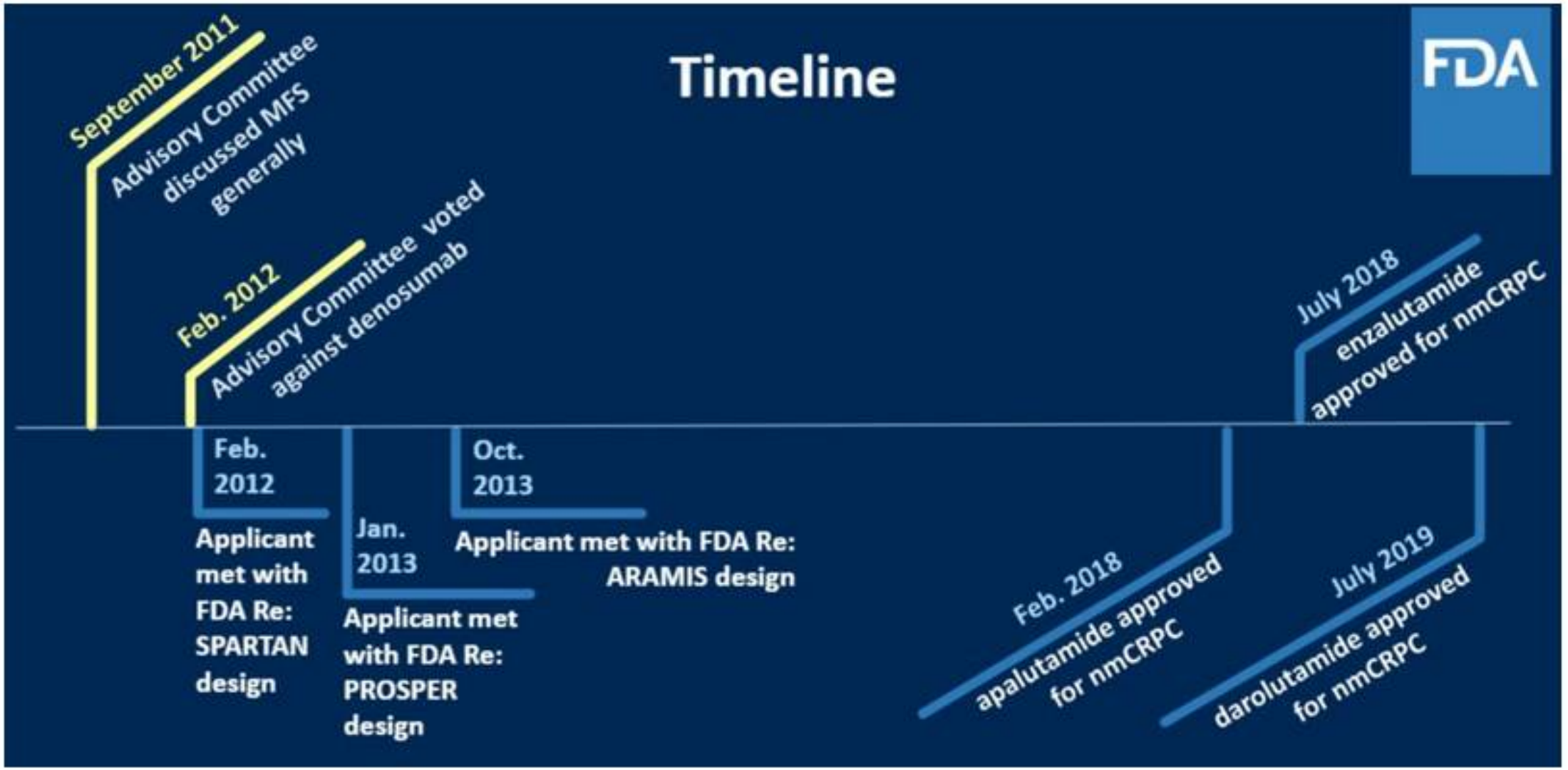
In 2012, another FDA ODAC examined the results of denosumab in a randomized, placebo-controlled trial involving men with nmCRPC and BMFS as primary endpoint.

- Although the study was positive, given benefit-risk considerations, ODAC members recommended that longer metastasis-free survival would be required to justify approval.

Following these meetings, multiple companies designed trials examining systemic therapies in nmCRPC using metastasis-free survival as the primary end point with overall survival as a co-primary or secondary end point.

BMFS: bone metastasis-free survival

Timeline to US approvals in nmCRPC using MFS as endpoint



ASCO GU 2020: Meet the Regulators: History of Metastasis-Free Survival and Drug Development in Nonmetastatic Castrate-Resistant Prostate Cancer

Timeline to EMA approvals in nmCRPC using MFS as endpoint

Significant interactions between the EMA/CHMP and the Sponsors over a similar timeframe as in the US

CHMP also obtained input from external scientific experts*

All three drugs are also approved in the EU for nmCRPC based on MFS

- Enzalutamide (Type II variation) Oct 2018
- Apalutamide (MAA) Jan 2019
- Darolutamide (MAA) March 2020

**Advice sought from SAG Oncology for first regulatory decision making based on MFS in EU*

- *Clinical relevance of the new endpoint which was considered indicative of clinical benefit in the disease setting by experts*
- *Importance of magnitude of effect and provision of follow-up OS data*

Pivotal trials in nmCRPC using MFS as endpoint

Each of the three sponsor companies conducted a randomized, double blind, placebo-controlled trial designed to demonstrate an improvement in MFS.

- Regulatory approvals of enzalutamide, apalutamide, and darolutamide for patients with nmCRPC were supported by the pivotal trials SPARTAN, PROSPER, and ARAMIS respectively.

Key common design features included stratification of patients at randomization by PSADT, blinded independent central review (BICR) of imaging studies and the scheduling of an interim analyses of OS.

In the US, the companies sponsoring each trial worked with the FDA to refine their clinical trial designs under FDA's Special Protocol Assessment mechanism.

In the EU, the companies obtained CHMP Scientific Advice on pre-clinical, clinical and quality aspects of the dossier

References:
- Brave et al, 2020, Clinical cancer Research
- EPAR ERLEADA
- EPAR XTANDI
- EPAR NUBEQA

FDA nmCRPC draft guidance document 2018

Nonmetastatic, Castration-Resistant Prostate Cancer: Considerations for Metastasis-Free Survival Endpoint in Clinical Trials, November 2018

Considerations on MFS as acceptable endpoint for approval

- large magnitude of treatment effect on MFS with an acceptable safety profile could be used to demonstrate clinical benefit and support product approval
- the sponsor should conduct a formal interim analysis of OS (at the time of final MFS analysis) - to support a favorable benefit-risk assessment, this analysis should demonstrate a favorable trend and provide assurance that OS is not adversely affected by the treatment. In addition, FDA expects continued follow-up for final OS.
- the acceptable magnitude of improvement in MFS required to support drug approval will depend primarily on the trial design (e.g., add-on design, active control versus placebo control), toxicity profile, enrolled population, and overall benefit-risk evaluation
- the sponsor should establish the definition of MFS before initiation of the trial, need to clearly describe methodology for assessing, measuring, and analyzing MFS (local progression events should be excluded)

https://www.fda.gov/media/117792/download

EU Anticancer guideline

EMA Appendix 4 to Anticancer guideline includes guidance regarding the design of prostate cancer trials

While not specific to nmCRPC, the guideline discusses:

- Cancer prevention studies
- Minimally Invasive treatment
- Neoadjuvant and adjuvant therapy
- Therapy for high-risk localized disease and locally advanced disease (Distant Metastasis Free Survival is discussed in this context)
- Therapy for metastatic disease

version 1: https://www.ema.europa.eu/en/documents/scientific-guideline/appendix-4-guideline-evaluation-anticancer-medicinal-products-man-condition-specific-guidance_en.pdf

Summary & Applicability to Other Tumor Types/Settings

Summary: New endpoint for nmCRPC

Factors that supported development of the new regulatory endpoint

- **Unmet medical need**: ongoing discussions among oncology experts/academia/regulators/industry sponsors to address development of new therapies for patients in the pre-metastatic stage
- **Condition: long natural history of disease**, transition from nmCRPC to detectable metastatic disease was recognized as a clinically relevant event (ODAC 2011) that can be associated with morbidity and the need for additional medical interventions
- **Choice of endpoint**: OS was considered not feasible in this setting (long survival periods, multiple subsequent therapies could confound OS results), need for a clinically meaningful endpoint especially in view of asymptomatic patients, time to metastases alone was considered less relevant as primary endpoint since MFS would also cover a survival benefit and take into account toxicities
- **Measurable**: Prolonged delay of metastatic disease is an objective and clinically relevant measure
- **Benefit-Risk:** a substantial effect of MFS is expected**,** absence of detrimental toxicity, and positive trend for OS

Future considerations

- Heterogeneity of disease, novel imaging methods (PSMA-PET) might change definition of disease and assessment of MFS
- Due to long term use of approved drugs based on MFS, need to better understand impact on overall long-term safety and QoL

Potential considerations for other cancer types/settings

- Need to understand target patient population and natural history of disease, knowledge will evolve over time based on emerging biomarker (e.g., CTC, ctDNA) or new diagnostic tools
- When looking at opportunities to move into earlier lines of disease or even disease interception this would results in trials with very extended times, so novel (surrogate) endpoints will be important
- Surrogate endpoint can bring higher uncertainty, and require best available evidence (biological plausibility), relevant magnitude of effect, understanding of association with OS or impact on QoL
- Important to integrate patients' perspective and outcome measures in trial design especially when moving into earlier line or a largely asymptomatic disease stage
- Overall, developing and validating a novel endpoint this will be a collaborative and multi-stakeholder effort in the anticancer drug development community

Acknowledgements

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