130708

Emerging Biomarkers in Metastatic Castration Resistant Prostate Cancer as Evaluated in Early Phase Clinical Trials: A Targeted Literature Review

Lauren J. Lee,[1] Michael Jones,[2] Emma Timmel,[3] Leslee Masten,[3] Li Liu,[4] Claudia Andreu-Vieyra,[5] Lucile Serfass[6]

[1]Pfizer, Inc., New York, NY, USA; [2]Evidera, Inc., Toronto, ON, Canada; [3]Evidera, Inc. Waltham, MA, USA; [4]Pfizer. Inc., San Diego, CA, USA; [5]Pfizer, Inc., Collegeville, PA, USA; [6]Pfizer International Operations, Paris, France

Objective

The objective of this targeted literature review was to investigate emerging biomarkers that have been evaluated in recently published early clinical studies of metastatic castration-resistant prostate cancer (mCRPC), with a focus on how those biomarker data were analyzed in relation to trial outcomes.

Conclusions

- Trends in more 'Established Biomarkers' (see Table 1) were generally consistent over time, while the use of 'Emerging Biomarkers' (e.g., PI3K/AKT) has increased in early mCRPC studies by approximately 60% over the past 7 years, with decline in most recent years (2019-2021).
  - Among Emerging Biomarkers, whole genome/transcriptome-based biomarkers have emerged as a notable approach for efficacy analyses, potentially resulting from greater access to next generation sequencing.
- The total number of studies with outcomes (e.g., PK/PD, survival outcomes) related to biomarkers increased from 2007 to a peak between 2016–2018, with publication delays likely driving the observed decline in the last 2–3 years.
  - Efficacy outcomes including PFS and OS were commonly found to be modulated by biomarker status in Phase 1 and 1/2 trials in mCRPC, although none of the studies examined the relationship between biomarker subgroups and PK/safety.

Background

- Metastatic prostate cancer (mPC) is a highly heterogenous disease with a complex set of factors associated with disease initiation, progression, and treatment resistance.[1,2]
- Multiple clinical studies in mPC have been designed to assess biomarker status to optimize treatment outcomes, with circulating tumor deoxyribonucleic acid (ctDNA) and androgen receptor (AR) pathway genetic alterations being well-known prognostic indicators in mCRPC.[1,3]
- However, many potential therapeutically relevant biomarkers have not been explored in a clinical study setting, limiting the potential impact of these targets on wider clinical practice.[2-3]

Materials and Methods

- Electronic databases (Embase, MEDLINE, Cochrane Library) and key conference proceedings were evaluated. Searches were limited to studies published in English from January 2017 to November 2022.
  - The search was performed according to publication year, but this review used the year of study initiation for analysis (i.e., start year of patient recruitment, protocol publication year, or the year of first entry on clinicaltrials.gov.co, whichever was earliest.
- Studies were included if they recruited men with mCRPC, used systemic treatments, and reported outcomes that utilized patient biomarker data in analyses of PK/PD, efficacy, and/or safety outcomes.
- Articles that met the criteria but were Phase 3+, in metastatic hormone-sensitive prostate cancer (mHSPC), or tested chemotherapy monotherapy regimens were excluded to focus on emerging targets in early mCRPC trials.
- To summarize the findings, we defined AR and DNA damage and repair (DDR) pathways, circulating tumor cells (CTCs) and circulating DNA as **'Established Biomarkers'** based on their history as predictive factors in mCRPC,[1 3] and the rest as **'Emerging Biomarkers'** as their history as predictive factor is less prevalent.

Results

- Sixty-one studies across 78 publications were included (Figure 1), with starting years ranging from 2007–2021 (50% of studies started in 2016+) and 77% of the studies being Phase 2 or Phase 1/2 (the remainder being Phase 1).
  - The trend in study initiation year increased from 2007 up to a peak in 2017; although the number of studies decreased after 2017. This decrease is likely driven by the delay between study initiation and publication date.
- Forty-seven different treatments were investigated in the studies (alone or as part of a combination therapy), with the most common classes of drugs being anti-androgen and immune-oncology agents.
- The included studies reported 131 specific biomarkers related to study outcomes, with 52 studies (85%) reporting ≥1 Established Biomarkers and 31 studies (51%) reporting ≥1 Emerging Biomarkers.

Figure 1. PRISMA Diagram

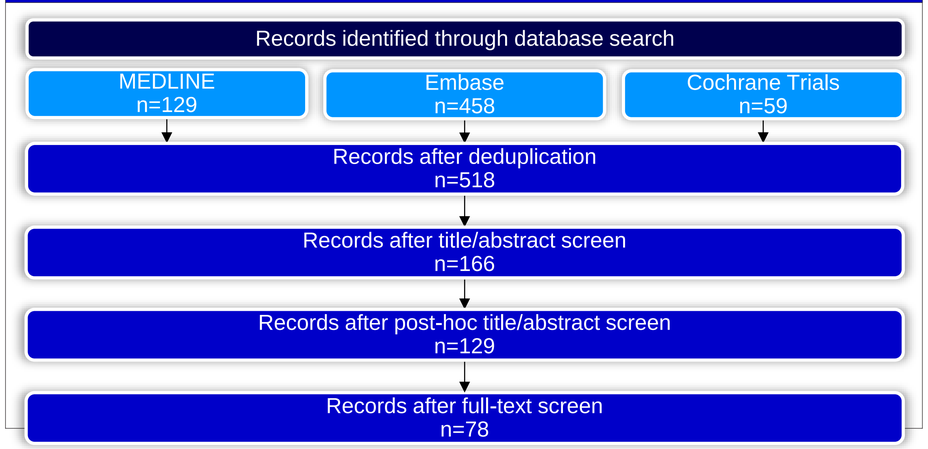
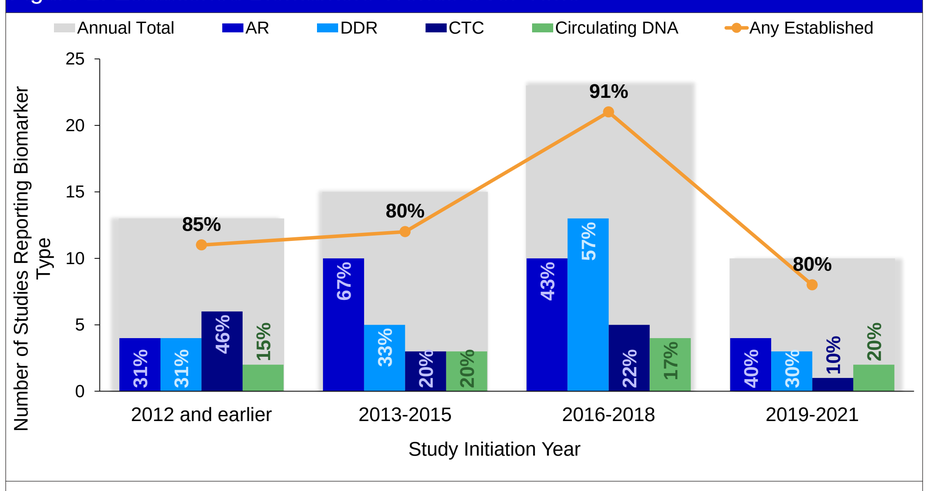


Table 1. Established and Emerging Biomarker Categories

Biomarker	# of Studies		Brief Description
	Phase 1	Phase 2 or 1/2	
Established Biomarker Types			
AR	4	24	Androgen receptor (mutations, gene amplification and gene fusions), key oncogenic driver for mCRPC
DDR	4	21	DNA damage and repair pathway (e.g., BRCA1/2, PALB2), also includes studies that reported DDR biomarkers but did not specify specific gene targets, a common oncogenic driver for many cancers
CTCs	3	12	CTCs (as a standalone biomarker) e.g., CTC enumeration
Circulating DNA	2	9	ctDNA or cfDNA markers not related to specific genes
Emerging Biomarkers of Interest			
PI3K/AKT	7	9	Common oncogenic drivers, include mTOR and PTEN
TP53	3	8	Tumor suppressor gene implicated in several adenocarcinomas
Immune	2	8	Immune pathway, including PD-1/PD-L1, T-cell antigens, CBP/p300, and cytokines/chemokines associated with immune response
Genetic	0	5	Whole genome/transcriptome profile biomarkers (e.g., TMB, GEP)
MMR/MSI	0	4	MSI and deficiency of the DNA MMR, involved in DDR and IO efficacy
PSMA + Imaging	2	2	Surface antigen for prostate cancer, as well as other targets used for imaging-related outcomes (e.g., CD8)

TRENDS IN BIOMARKER RESULTS

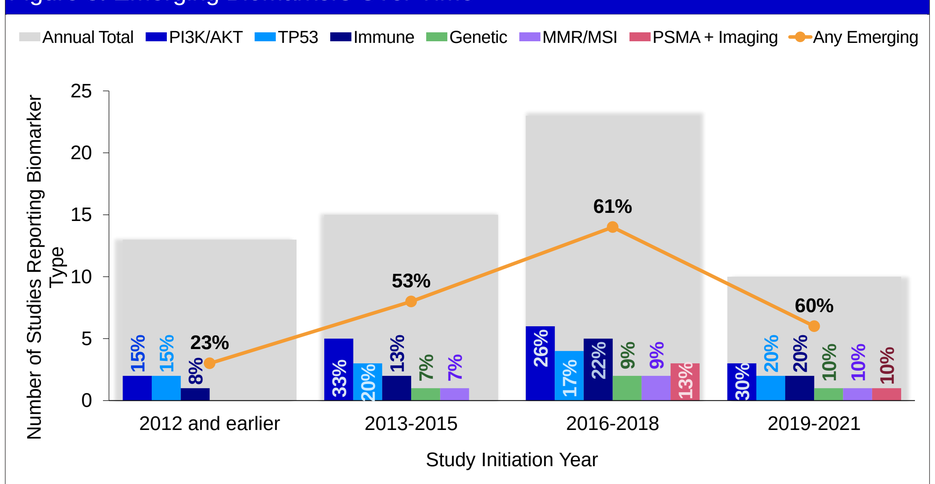
Figure 2. Established Biomarkers Trends Over Time



Bars: Number of studies with a specific Established Biomarker category; **Orange line:** Percent of studies with Established Biomarkers; **Gray bar:** Total number of studies in the analysis

- Established Biomarkers remained targets for biomarker analyses in the majority of early mCRPC biomarkers over the 13-year period (60–100% of studies per year starting between 2007–2021).
  - The AR pathway and DDR biomarkers were generally the most common established biomarkers used each year, with the AR pathway largely driven by studies on abiraterone or enzaluatmide.
  - Before 2015, 53% of studies included CTCs as biomarkers themselves while after 2015, they were collected for subsequent imaging or sequencing for other biomarkers.

Figure 3. Emerging Biomarkers Over Time



Bars: Number of studies with a specific Emerging Biomarker category; **Orange line:** Percent of studies with Emerging Biomarkers; **Gray bar:** Total number of studies in the analysis

- Proportion of studies including Emerging Biomarkers slowly increased starting 2011 with a peak at 88% of total number of studies in 2016.
- This rising trend was largely driven by an increase in studies with PI3K/AKT biomarkers, with 14% (n=2/14) before 2013 and 33% between 2013–2021.
  - Whole genome/mismatch repair (MMR)/microsatellite instability (MSI) increased in usage from no studies before 2014 to 20% of studies between 2020–2021.
  - Tumor protein 53 (TP53) first appeared in biomarker analyses in 2011 in this review and remained consistently used in approximately 20% of studies across the entire review period.
  - Immune biomarkers as well as prostate specific membrane antigen (PSMA) and Imaging-based biomarkers also increased in usage over time, which aligned with the concomitant increase in trials that examined immunotherapy and PSMA-based treatments, respectively.

OUTCOMES RELATING TO BIOMARKER STATUS

- None of the studies used biomarker status for subgroup analyses of safety or PK endpoints; only efficacy-related endpoints were analyzed in relation to biomarker status.
- Over half of the clinical trials (n=34/61, 56%) reported survival outcomes in relation to biomarkers, with all but one study finding trends between progression-free survival (PFS)/overall survival (OS) and ≥1 biomarker.
  - The biomarker types most commonly related to survival outcomes were AR (n=12 studies, 35%) and DDR (n=8, 24%), as well as CTCs, circulating DNA, and PI3K/AKT pathway markers (n=5, 15% for each).
- While most of biomarkers were directly related to mechanism of action of treatments in the trials (e.g., AR pathway for antiandrogen treatments), 33% (n=20) of biomarkers were used only for their prognostic/predictive value, mostly in the DDR (25%) and/or PI3K/AKT (15%) pathways.

Limitations

- There is some uncertainty in the index study start dates due to variability in the information available in publications and clinical trial registries.
- There could be publication bias: Authors being disinclined to share exploratory biomarker analyses unless the data show a clear trend.

Abbreviations: AACR=American Association for Cancer Research; AI=antiandrogen; AKT=protein kinase B; AR=androgen receptor; AR=androgen receptor; ASCO=American Society of Clinical Oncology; ASCO-GU=American Society of Clinical Oncology-Genitourinary; AUA=American Urological Association; BRCA1/2=breast cancer gene 1/2; cfDNA=cell-free DNA; CTC=circulating tumor cell; ctDNA=circulating tumor DNA; DDR=DNA damage and repair; DNA=deoxyribonucleic acid; EAU=European Association of Urology; ECCO=European Chron's and Colitis Organization; EMUC=European Multidisciplinary Congress on Urological Cancers; ESMO=European Society for Medical Oncology; ESOU=European Society of Oncological Urology; GEP=gene expression profile; IO=immuno-oncologic; ISPOR=International Society for Pharmacoeconomics and Outcomes Research; mCRPC=metastatic castration-resistant prostate cancer; mHSPC=metastatic hormone-sensitive prostate cancer; MMR=mismatch repair; mPC=metastatic prostate cancer; MSI=microsatellite instability; mTOR=mammalian target of rapamycin; NCCN=National Comprehensive Cancer Network; OS=overall survival; PALB2=partner and localizer of BRCA2; PD=pharmacodynamic; PD-1=programmed death-1; PD-L1=programmed death-ligand 1; PFS=progression-free survival; PI3K=phosphoinositide 3-kinase; PK=pharmacokinetic; PSMA=prostate specific membrane antigen; PTEN=phosphatase and tensin homolog; SUO=Society of Urologic Oncology; TMB=tumor mutational burden; TP53=tumor protein 53

Electronic Poster

An electronic version of this poster may be obtained by scanning this QR code with your smartphone app. Copies of this poster obtained through the QR Code are for personal use only and may not be reproduced without permission from ISPOR® and the author of this poster. To request permission or to ask questions about the poster please contact Jiyoung.Lee@pfizer.com.

References: 1. Mizuno K, Beltran H. *Prostate*. 2022;82:S86-S96. doi:10.1002/pros.24354. **2.** Adamaki M, Zoumpourlis V. *Pharmacol Ther*. 2021;228:107932. doi:10.1016/j.pharmthera.2021.107932. **3.** Couñago F, et al. *Cancers (Basel)*. 2020;12(6):1550. doi:10.3390/cancers12061550

Acknowledgments: The authors would like to acknowledge Dr. Karen Sandman for her support in reviewing the content of this poster.