IDH1 and *IDH2* Mutations in Prostate Cancer

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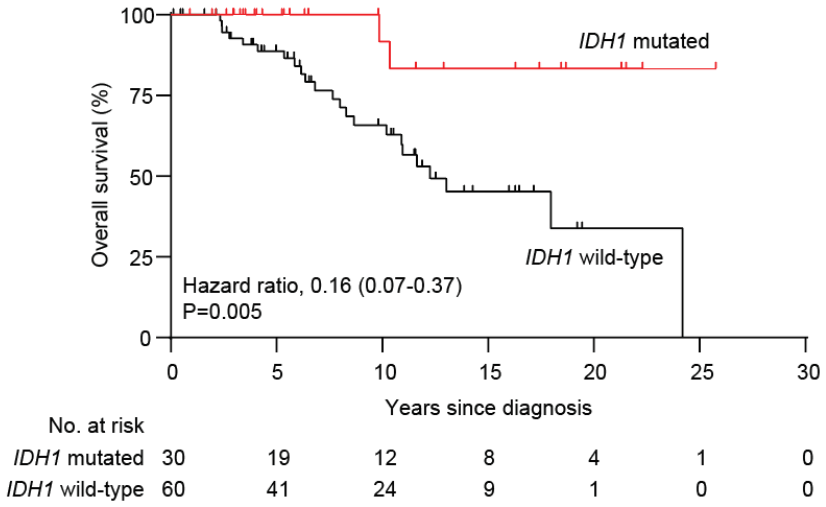
Background: Prostate cancer with *IDH1* or *IDH2* hotspot mutation is a unique molecular subclass of prostate cancer, but its clinical features are unknown. Here we describe clinical, genomic, and transcriptomic features of prostate cancer with *IDH1* p.R132 or *IDH2* p.R172 mutation.

Methods: A series of 99 cases of prostate cancer with *IDH1* mutation and 12 cases of *IDH2* mutation was identified using genomics databases at multiple academic institutions and Caris Life Sciences. A control cohort of *IDH1/2* wild-type cases was generated with matched features at diagnosis. Clinical, genomic, and transcriptomic features were assessed by retrospective review.

Results: *IDH1* mutation occurred in 0.6-0.8% and *IDH2* mutation in less than 0.1% of localized prostate cancer cases included in publicly available genomic databases. In our case-control series, patients with *IDH1*-mutated prostate cancer experienced longer overall survival (hazard ratio, 0.16; 95% CI, 0.07-0.37; P=0.005), metastasis-free survival (hazard ratio, 0.32; 95% CI, 0.17-0.63; P<0.001), and progression-free survival on hormonal therapies (hazard ratio, 0.35; 95% CI, 0.16-0.76; P=0.036) than controls. *IDH1* and *IDH2* mutations occurred in the absence of a concurrent pathogenic driver mutation in 16% of cases and frequently in the absence of concurrent common early genomic alterations including *TMPRSS2-ERG* fusions (5% *IDH1* versus 26% controls, P<0.001), *SPOP* (4% *IDH1* versus 20% controls, P=0.002), and *RB1* (0% *IDH1* versus 6% controls, P=0.015). In contrast, *IDH1* and *IDH2* mutations frequently co-occurred with activating mutations of *FOXA1* (34% *IDH1* versus 8% controls, P=0.003) and *CTNNB1* (17% *IDH1* versus 4% controls, P=0.013). Transcriptomic analyses demonstrated that *IDH1*-mutant cases had more differentially expressed genes downregulated rather than upregulated, and differentially expressed genes were enriched for involvement in metabolic pathways of lipids and nucleotides.

Conclusions: Prostate cancer with *IDH1* or *IDH2* mutation constitutes a rare but unique molecular subtype associated with favorable outcomes. These findings may enable more personalized treatment of patients with *IDH1* and *IDH2* mutant prostate cancer and identify molecular features of prostate cancer associated with lower rates of metastasis and treatment resistance.



Funding Acknowledgements: This work was funded by the National Institutes of Health grant R21CA292179 to LAS.

Conflicts of Interest Disclosure Statement: SSN, MGE, NS, and EA are employed by and may hold stock in Caris Life Sciences. JFC provides consultation to AstraZeneca outside the scope of this study. NA has received honorarium before May 2021 and during his lifetime for consulting to Astellas, AstraZeneca, Aveo, Bayer, Bristol Myers Squibb, Calithera, Clovis, Eisai, Eli Lilly, EMD Serono, Exelixis, Foundation Medicine, Genentech, Gilead, Janssen, Merck, MEI Pharma, Nektar, Novartis, Pfizer, Pharmacyclics, and Seattle Genetics; and NA's institution has received research funding during his lifetime from Arnivas, Astellas, AstraZeneca, Bavarian Nordic, Bayer, Bristol Meyers Squibb, Calithera, Celldex, Clovis, CRISPR Therapeutics, Eisai, Eli Lilly, EMD Serono, Exelixis, Genentech, Gilead, Glaxo Smith Kline, Immunomedics, Janssen, Lava, Medivation, Merck, Nektar, Neoleukin, New Link Genetics, Novartis, Oric, Pfizer, Prometheus, Rexahn, Roche, Sanofi, Seattle Genetics, Takeda, and Tracon. WA received speaking honoraria from Roche, Pfizer, Medscape, Aptitude Health, Clinical Education Alliance, theMedNet, the Prostate Cancer Foundation, touchIME and Onclive/MJH Life Sciences, consulting fees from Clovis Oncology, Janssen, ORIC Pharmaceuticals, Daiichi Sankyo, MOMA Therapeutics, Laekna Therapeutics, Endeavor Biomedicines, AstraZeneca, Boundless Bio, K36 Therapeutics, DualityBio, Tolmar and IDEOlogy and Research Funding (to his institution) from AstraZeneca, Zenith Epigenetics, Clovis Oncology, ORIC Pharmaceuticals, Epizyme/Ipsen, Transthera, Merus, MOMA Therapeutics and Nuvation Bio. ESA reports grants and personal fees from Janssen, Johnson & Johnson, Sanofi, Bayer, Bristol Myers Squibb, Convergent Therapeutics, Curium, MacroGenics, Merck, Pfizer, and AstraZeneca; personal fees from Aadi Bioscience, Abeona Therapeutics, Aikido Pharma, Astellas, Amgen, Blue Earth, Boundless Bio, Corcept Therapeutics, Duality Bio, Exact Sciences, Hookipa Pharma, Invitae, Eli Lilly, Foundation Medicine, Menarini-Silicon Biosystems, Tango Therapeutics, Tempus, Tolmar Scientific, VIR Biotechnology, and Z-alpha; grants from Novartis, Celgene, and Orion; and has a patent for an AR-V7 biomarker technology that has been licensed to Qiagen. LAS has received funding to her institution from Panbela Therapeutics.