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Biomarker analyses from the phase II PT-112 monotherapy study in late-line metastatic castration-resistant prostate cancer (mCRPC)

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Background

PT-112, an inhibitor of ribosome biogenesis, induces robust signals of immune activation and was evaluated as monotherapy in a 111-patient phase 2 study in late-line mCRPC (median 4 prior lines of therapy), where it demonstrated good tolerability and showed multiple efficacy signals with encouraging overall survival. This report details a biomarker analysis to explore baseline profiles and on-treatment dynamics with PT-112.

Methods

Blood samples were collected pre- and on-treatment (multiple timepoints). CD45- CK+ CTCs, ALP, LDH, and ctDNA (fraction, mutations, and copy number variations) were assessed. Hazard ratios for survival were calculated via Cox proportional hazards regression.

Results

Baseline CTCs, ALP, LDH, and ctDNA fraction were elevated and were significant prognostic factors for overall survival. CTC reductions to 0.0 CTCs/mL (CTC0) and declines of ≥10% of ALP and LDH were seen in 31%, 53% and 39% of patients respectively. Quantitative measurement of ctDNA fraction showed 8/36 patients (22%) experienced relative ctDNA reductions of >25%. Monoallelic and biallelic copy number alterations were frequent and included amplifications in mCRPC drivers, e.g., *AR* (54%) and *MYC* (24%), and loss of tumor suppressor genes, e.g., *RB1* (45%), *TP53* (32%), and *PTEN* (30%).Table: 2462P

Cox proportional hazards regression of baseline factors for survival

Baseline factor	Evaluable patients (n)	Median baseline value	Hazard ratio for survival (below vs above baseline median)	p value
Circulating tumor cells (CTCs)	86	1.1 CTCs/mL blood	0.54	0.01
Alkaline phosphatase (ALP)	108	119 U/L	0.56	0.008
Lactate dehydrogenase (LDH)	104	219 U/L	0.52	0.003
Circulating tumor DNA (ctDNA) fraction	42	21%	0.12	<0.0001

Conclusions

Prognostic factors (CTCs, ALP, LDH, and ctDNA fraction) were significant and showed treatment-induced reductions, suggestive of benefit to PT-112 therapy in certain patients. High baseline values for these factors, particularly ctDNA fraction, indicate extensive disease burden and poor prognosis. The observed copy number variations were suggestive of highly aggressive, heterogenous, and multi-treatment resistant disease at study entry. Taken together, these data support PT-112 benefit in a markedly disease burdened patient population with poor survival prognosis.

Clinical trial identification

Trial protocol number: NCT02266745.

Release date: October 2020.

Legal entity responsible for the study

Promontory Therapeutics Inc.

Funding

Promontory Therapeutics Inc.

Disclosure

A.H. Bryce: Financial Interests, Personal, Advisory Board: Johnson & Johnson, Astellas, Merck, Tolmar, AstraZeneca, Pharma&, Lantheus, Pfizer; Financial Interests, Personal, Invited Speaker: Pfizer, Tolmar; Financial Interests, Personal, Steering Committee Member: Lantheus; Financial Interests, Trial Chair: PharmaMar, promontory; Financial Interests, Personal, Other, Research Project lead for the analysis of cardiovascular outcomes in men with prostate cancer: Astellas. A.W. Wyatt: Financial Interests, Personal, Other, Advisory Board and/or received honoraria: AstraZeneca, Astellas, Bayer, EMD Serono, Janssen, Merck, Pfizer; Financial Interests, Institutional, Research Funding: ESSA Pharma, Tyra Biosciences, Promontory Therapeutics. G. Roubaud: Financial Interests, Personal, Advisory Board: Janssen, Astellas, Bayer; Financial Interests, Institutional, Advisory Board: Pfizer, AstraZeneca; Financial Interests, Institutional, Invited Speaker: Novartis; Financial Interests, Institutional, Coordinating PI: Bayer. C.Y. Yim: Financial Interests, Personal, Full or part-time Employment: Promontory Therapeutics; Financial Interests, Personal, Stocks/Shares: Promontory Therapeutics. T.D. Ames: Financial Interests, Institutional, Full or part-time Employment, I'm a full time employee of Promontory Therapeutics: Promontory Therapeutics; Financial Interests, Institutional, Stocks/Shares, I own stocks in Promontory Therapeutics: Promontory Therapeutics; Non-Financial Interests, Leadership Role, I'm an SVP at Promontory Therapeutics: Promontory Therapeutics. J. Baeck: Financial Interests, Personal, Full or part-time Employment: Promontory Therapeutics; Financial Interests, Personal, Stocks/Shares: Promontory Therapeutics. M. Price: Financial Interests, Institutional, Officer, Salaried officer, and non-compensated director.: Promontory Therapeutics; Financial Interests, Institutional, Stocks/Shares: Promontory Therapeutics; Non-Financial Interests, Institutional, Proprietary Information: Promontory Therapeutics. H.I. Scher: Financial Interests, Personal, Other, Consultant: Bayer, Pfizer, Regeneron Pharmaceuticals, Sanofi (Genzyme Corporation); Financial Interests, Personal, Invited Speaker: Physician Education Resource; Financial Interests, Personal, Other, Intellectual Property Rights: Elucida Oncology; Financial Interests, Institutional, Funding, Research Funds to Institution - Memorial Sloan Kettering Cancer Center: AIQ Pharma, Astrin Biosciences, Biodesix; Financial Interests, Institutional, Research Grant, Research Funds to Institution - Memorial Sloan Kettering Cancer Center: Janssen; Non-Financial Interests, Other, Uncompensated Consultant: AIQ Global Inc, Promontory Therapeutics, Janssen Research & Development LLC; Non-Financial Interests, Member: American Society of Clinical Oncology, American Association for Cancer Research, American College of Physicians, American Medical Association. All other authors have declared no conflicts of interest.