PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

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New Cell Surface Targets in Prostate Cancer

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H&O Could you provide a brief overview of cell surface targets in cancer treatment?

AJA Cell surface targets are very accessible and engageable, and therapies based on these targets have been successful in both solid tumors and hematologic malignancies. An ideal cell surface target is highly expressed by cancerous cells and absent in normal cells, so that targeted treatment does not damage normal tissue. Right now, we have 8 validated cell surface targets that have led to US Food and Drug Administration (FDA) approvals of agents in solid tumors on the basis of improved survival. These targets consist of human epidermal growth factor receptor 2 (HER2), trophoblast cell surface antigen 2 (TROP2), nectin cell adhesion molecule 4 (NECTIN4), folate receptor 1 (FOLR1), prostate-specific membrane antigen (PSMA), somatostatin receptor 2 (SSTR2), delta-like protein 3 (DLL3), and glycoprotein 100 (gp100). Although PSMA is the only one of the targets that currently applies to prostate cancer, other cell surface receptors are abundant in prostate cancer. Some of the validated targets are overexpressed in different subtypes of prostate cancer, such as DLL3 in small cell/neuroendocrine prostate cancer (NEPC).

Of the 200,000 or so known human proteins, we have insight into what approximately 21,000 do, and only 3000 to 5000 are present on the cell surface. Fewer than 100 drugs or antibodies are being studied to target these cell surface proteins, which means a great opportunity exists for drug development. The hope is that in the future, researchers will make use of cell surface targets to develop new antibody-drug conjugates, radioligand therapies, bispecific or trispecific antibodies, and chimeric antigen receptor (CAR) T-cell or natural killer/myeloid cell therapies.

H&O What new cell surface targets are being investigated in advanced prostate cancer?

AJA Multiple targets are being investigated for each of the 3 different biological disease states in prostate cancer: (1) adenocarcinoma; (2) NEPC/small cell prostate cancer; and (3) poorly differentiated prostate cancer. The last is also known as anaplastic, aggressive variant, or double-negative prostate cancer because it lacks androgen receptor (AR) and neuroendocrine differentiation markers (Figure). Each of these disease states has different cell surface proteomes, so traditional measures for one type may not work in another. To add complexity, the heterogeneity characteristic of these subtypes (and therefore, of their markers) can increase over time because of clonal selection, lineage plasticity, and divergent evolution. We need biomarkers for these states—detected through positron emission tomography (PET) or tissue—to tailor treatments more effectively.

Typical prostate adenocarcinoma, which is AR-positive, is the most common type of prostate cancer. Most cases of newly diagnosed prostate cancer and 60% to 70% of cases of metastatic castration-resistant prostate cancer (mCRPC) fall into this category. PSMA is an especially useful target in this type of prostate cancer, with proven survival benefits. In the VISION trial, radioligand therapy with lutetium 177

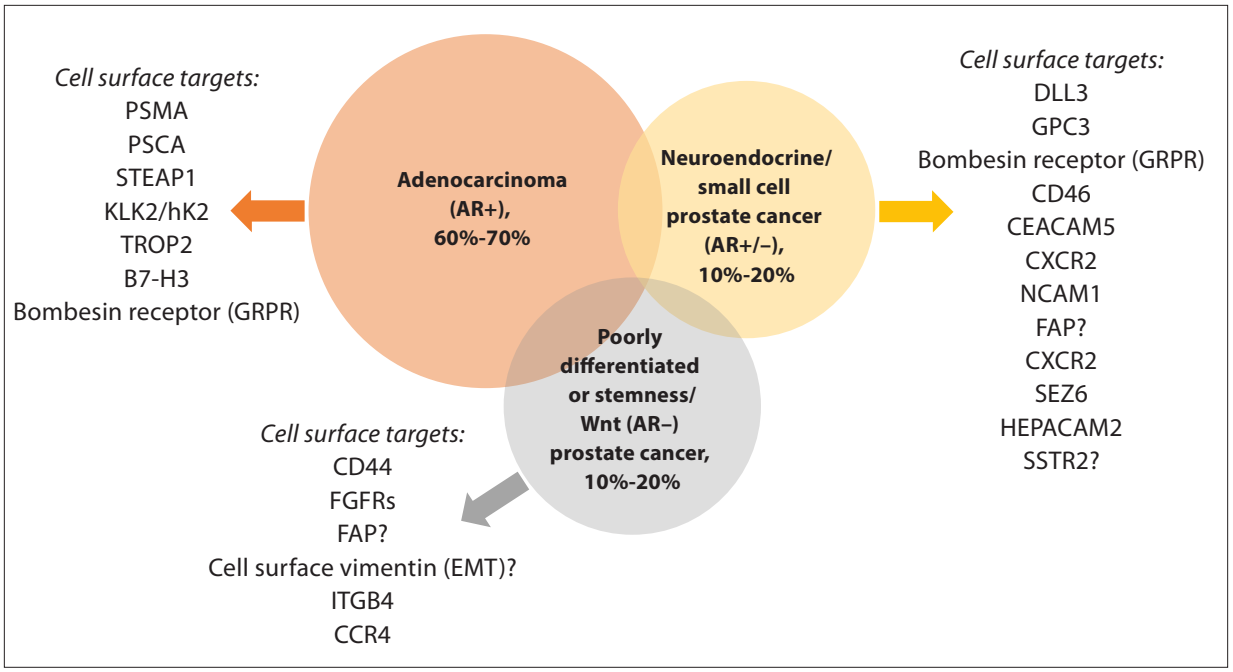

Figure. Potential cell surface targets according to prostate cancer subtype: adenocarcinoma, neuroendocrine/small cell prostate cancer, or poorly differentiated prostate cancer. Percentages refer to those seen in metastatic prostate cancer. Because of tumor heterogeneity, more than one subtype may occur in a single tumor. Only 8 cell surface targets validated by trial success have led to US Food and Drug Administration approvals in solid tumors: HER2, TROP2, NECTIN4, FOLR1, PSMA, SSTR2, DLL3, and gp100.

AR, androgen receptor; CCR4, C-C chemokine receptor type 4; CEACAM5, CEA cell adhesion molecule 5; CXCR2, C-X-C motif chemokine receptor 2; DLL3, delta-like protein 3; EMT, epithelial-mesenchymal transition; FAP, fibroblast activation protein alpha; FGFRs, fibroblast growth factor receptors; FOLR1, folate receptor 1; gp100, glycoprotein 100; GPC3, glypican 3; GRPR, gastrin releasing peptide receptor; HEPACAM2, HEPACAM family member 2; HER2, human epidermal growth factor receptor 2; hK2, hexokinase 2; ITGB4, integrin subunit beta 4; KLK2, kallikrein-related peptidase 2; NCAM1, neural cell adhesion molecule 1; NECTIN4, nectin cell adhesion molecule 4; NEPC, neuroendocrine prostate cancer; PSCA, prostate stem cell antigen; PSMA, prostate-specific membrane antigen; SEZ6, seizure related 6 homolog; SSTR2, somatostatin receptor 2; STEAP1, STEAP family member 1; TROP2, trophoblast cell surface antigen 2.

(^{177}Lu)-PSMA-617 was shown to improve progression-free survival and overall survival in patients with advanced PSMA-positive mCRPC.[1]

Approximately 15% of patients with adenocarcinoma are PSMA-negative and most others will acquire PSMA resistance within 6 to 24 months, so having other targets is essential. STEAP1 is targeted by the bispecific antibody AMG 509, also known as xaluritamig. In a first-in-human study, step-dosed xaluritamig produced encouraging and often durable responses as late-line treatment in patients with mCRPC.[2] Hexokinase 2 (hK2) is targeted by an antibody conjugated to an alpha-emitting radioligand therapy delivering actinium 225 (^{225}Ac) that has shown safety and achieved response at the correct dose.[3] Another promising target is B7-H3, an immune checkpoint expressed in many prostate cancer cells that can be targeted by radiotherapy or an antibody-drug conjugate. These are just a few of the cell surface–targeting therapies currently in clinical trials.

NEPC contains neuroendocrine markers and is typically AR-negative, whereas poorly differentiated prostate cancer lacks neuroendocrine markers and is AR-negative. NEPC and poorly differentiated prostate cancer have a whole host of targets, including DLL3, glypican 3 (GPC3), C-X-C motif chemokine receptor 2 (CXCR2), fibroblast activation protein alpha (FAP), CD46, and gastrin-releasing peptide receptor (GRPR). These are unique and specific cell surface targets with varying distribution in normal tissue; however, all are expressed in NEPC and double-negative prostate cancer. Drugs are in development for each of these targets, including antibody-drug conjugates, radioligand therapies, and bispecific antibodies. Toxicities may be anticipated because of the distribution of these proteins in normal tissue.

The advantage of radioligand therapies is that radiation can be delivered even to negative cells nearby if

the radiation penetrates into the tissue deeply enough, addressing some heterogeneity. The downside is that heterogeneity still exists, so resistance is generally expected to emerge with any therapy that targets a single antigen. I anticipate that drug development will pursue bispecific agents that target 2 molecules, or combinations of radioligands with antibody-drug conjugates.

The University of Wisconsin operates a useful resource that allows users to input RNA sequencing data on a public website so that tumor cell surface target expression can be predicted (https://www.humonc.wisc.edu/cell-surface-target-expression; password: zona-gale). This information can be helpful in designing a clinical trial or identifying important cell surface markers for a specific disease under study.

H&O What are some of the limitations of therapies that target the cell surface?

AJA When these trials are interpreted, the goal is not just to see a short-term prostate-specific antigen or radiographic response but also to ensure that the response is durable and results in improved patient-reported outcomes. A nice minimum benchmark for the durability of progression-free survival in a population of patients with highly refractory mCRPC is 6 months, and we ultimately aim to improve overall survival. Controlled studies to establish the benefits of cell surface–targeting therapies must include careful monitoring for safety because the targeted cell surface markers may also be expressed in normal tissues. For example, targeting PSMA can cause dry mouth, dry eyes, and some kidney toxicity because PSMA is also expressed in those organs. Targeting glypican 3 (GPC3) and kallikrein-related peptidase 2/hexokinase 2 (KLK2/hK2), which are not found in noncancer tissues, may reduce these toxicities. Monitoring long-term toxicity is critical to balancing the benefits vs the risks of treatment.

H&O What are the challenges in developing new agents alone or in combination to target cell surface antigens?

AJA The first challenge is finding an adequate biomarker, one that has both analytic and clinical validity. Treating all patients who have prostate cancer with the same cell surface–targeting strategy likely will not succeed. For example, GPC3 is expressed in only one-third of NEPC cases, and PSMA-dim/-low disease does not respond well to PSMA-targeted radioligand therapies. Some markers, like CD46, are more common, but others may appear in only a minority of cells or patients. We need PET-based imaging or tissue-based biomarkers, like DLL3 immunohistochemistry or DLL3 PET, to select the patients most likely to benefit. We have seen this with the phase 1 data reported by Dr Rahul Aggarwal at the 2024 American Society of Clinical Oncology Annual Meeting, in which the DLL3-bispecific antibody agent tarlatamab (Imdelltra, Amgen) demonstrated encouraging antitumor activity in patients with DLL3-expressing NEPC, but not in all comers.[4] Responses to treatments such as tarlatamab are not as robust in NEPC as they are in small cell lung cancer, however, because NEPC is more heterogeneous and likely requires more biomarkers. Developing combination strategies to anticipate heterogeneity and resistance will improve success rates.

H&O What steps should be taken to ensure the appropriate use of biomarkers?

AJA Biomarker development needs to be intentional from the start because biomarkers must go through phases 1, 2, and 3 as a companion diagnostic, in line with drug development. Biomarkers should be an integral part of the studies submitted for FDA approval to optimize dosing and patient benefit while minimizing toxicity and exposure to potentially harmful therapies in patients for whom treatment will be ineffective.

Disclosures

Dr Armstrong has consulting or advising relationships with Astellas, Pfizer, Bayer, Janssen, Bristol Myers Squibb, AstraZeneca, Merck, Forma Therapeutics, Celgene, Myovant Sciences, Exelixis, GoodRx, Novartis, Medscape, MJH Life Sciences, and Telix Pharmaceuticals; and has received research support (to institution) from the National Institutes of Health/National Cancer Institute, the Prostate Cancer Foundation, Movember, the US Department of Defense, Astellas, Pfizer, Bayer, Janssen, Bristol Myers Squibb, AstraZeneca, Merck, Pathos Therapeutics, Celgene, Amgen, and Novartis.

References

Sartor O, de Bono J, Chi KN, et al; VISION Investigators. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2021;385(12):1091-1103.

Kelly WK, Danila DC, Lin CC, et al. Xaluritamig, a STEAP1 × CD3 XmAb 2+1 immune therapy for metastatic castration-resistant prostate cancer: results from dose exploration in a first-in-human study. *Cancer Discov*. 2024;14(1):76-89.

Morris MJ, Wong JY, Nordquist L, et al. A phase 1 study of JNJ-69086420 (JNJ-6420), an actinium-225 (^{225}Ac) -labeled antibody targeting human kallikrein 2 (hK2), for metastatic castration-resistant prostate cancer (mCRPC) [ASCO abstract 5010]. *J Clin Oncol*. 2024;42(16)(suppl).

Aggarwal RR, Rottey S, Bernard-Tessier A, et al. Phase 1b study of tarlatamab in de novo or treatment-emergent neuroendocrine prostate cancer (NEPC) [ASCO abstract 5012]. J Clin *Oncol*. 2024;42(16)(suppl).