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Targeting NaPi2b in ovarian cancer

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ABSTRACT

Novel biomarkers are needed to direct new treatments for ovarian cancer, a disease for which the standard of care remains heavily focused on platinum-based chemotherapy. Despite the success of PARP inhibitors, treatment options are limited, particularly in the platinum-resistant setting. NaPi2b is a cell surface sodium-dependent phosphate transporter that regulates phosphate homeostasis under normal physiological conditions and is a lineage marker that is expressed in select cancers, including ovarian, lung, thyroid, and breast cancers, with limited expression in normal tissues. Based on its increased expression in ovarian tumors, NaPi2b is a promising candidate to be studied as a biomarker for treatment and patient selection in ovarian cancer. In preclinical studies, the use of antibodies against NaPi2b showed that this protein can be exploited for tumor mapping and therapeutic targeting. Emerging data from phase 1 and 2 clinical trials in ovarian cancer have suggested that NaPi2b can be successfully detected in patient biopsy samples using immunohistochemistry, and the NaPi2b-targeting antibody-drug conjugate under evaluation appeared to elicit therapeutic responses. The aim of this review is to examine literature supporting NaPi2b as a novel biomarker for potential treatment and patient selection in ovarian cancer and to discuss the critical next steps and future analyses necessary to drive the study of this biomarker and therapeutic targeting forward.

NaPi2b function and tissue expression

NaPi2b (encoded by *SLC34A2*) is one of three members of the SLC34 family of type-2 sodium-dependent phosphate transporters. The SLC34 family, including NaPi2a (*SLC34A1*), NaPi2b, and NaPi2c (*SLC34A3*), plays a critical role in whole-body phosphate homeostasis by transporting phosphate across epithelial membranes [1,2]. Whereas NaPi2a and NaPi2c are confined to the kidneys and regulate renal phosphate reabsorption, NaPi2b mRNA expression was identified in various tissues including lung, small intestine, salivary glands, mammary glands, liver, and kidney [3–9]. Consequently, NaPi2b has been associated with various roles in physiological processes, including absorption of dietary phosphate in the small intestine, secretion and reabsorption of phosphate in saliva in the salivary gland, and regulation of phosphate in intraalveolar fluid and surfactant production in the lungs [2,10,11]. NaPi2b genetic knockout is embryonically lethal, although conditional knockout of NaPi2b in adult mice has revealed that loss of NaPi2b impairs intestinal phosphate uptake and can induce alveolar microlithiasis, a rare lung disorder characterized by accumulation of calcium phosphate deposits [12–14].

Role of NaPi2b in disease

NaPi2b has been linked to several diseases, including pulmonary alveolar microlithiasis, inflammatory bowel disease, and cancer (Fig. 1) [14–17].

Preclinical and early clinical evidence suggest that NaPi2b is expressed in high-grade serous epithelial ovarian, fallopian tube, and primary peritoneal cancers, as well as in thyroid, breast, and non-squamous non–small cell lung cancers, with limited expression in normal tissues [18–22]. The first evidence for high expression of NaPi2b in tumors came from studies in the 1980s and 1990s, which showed that the monoclonal antibody MX35 had high reactivity in ovarian tumors, although the identity of the antigen at the time was unknown [23–25]. In 2008, the epitope targeted by the MX35 antibody was discovered to be NaPi2b, which showed reactivity in 90 % of epithelial ovarian cancer

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cell lines [26]. Subsequent findings have confirmed high expression of NaPi2b and its *SLC34A2* gene in benign fallopian tube epithelium and well-differentiated serous, endometrioid, and to a lesser extent, mucinous ovarian carcinomas, but absent from normal ovary epithelium [18,20,27–29].

Several studies have suggested that NaPi2b plays a role in tumorigenesis of ovarian, lung, and breast cancers, likely resulting from dysregulation of phosphate homeostasis [30–33]. Interestingly, expression of *SLC34A2* is driven by PAX8, a master transcription factor that is highly expressed and required for the development of the female reproductive system and survival of ovarian cancer cells [34–36]. A loss-of-function screen assessing possible dependencies in ovarian cancer revealed that inactivation of XPR1, a phosphate exporter enriched in ovarian and uterine cancers, in cells with high expression of *SLC34A2* resulted in toxic accumulation of intracellular phosphate [30]. The study concluded that high levels of PAX8 increase expression of *SLC34A2* and lead to dependency on XPR1 in ovarian cancer. Through its regulation by PAX8, a lineage-specific transcription factor, NaPi2b itself is a lineage marker that appears to remain expressed in the PAX8-positive secretory cells of the fallopian tube and their malignant counterparts [18,34].

Ovarian cancer: Disease background and role of NaPi2b as a biomarker

Ovarian cancer is the fifth most lethal type of cancer in women in the United States, with nearly 20,000 new cases and 13,000 deaths estimated in 2022 [37,38]. Worldwide, there were 314,000 new cases and 207,000 deaths in 2020 [39]. The 5-year survival rate was approximately 50 % among all cases diagnosed in the United States between 2012 and 2018 [37,38]. However, more than 70 % of cases are diagnosed at an advanced stage, and metastatic disease has a 5-year survival rate of 31 %, which has remained consistent for several decades [37,40,41]. Cytoreductive surgery, with or without neoadjuvant therapy, followed by platinum-based doublet chemotherapy (typically carboplatin/paclitaxel) with or without bevacizumab is the standard-of-care frontline therapy [41–44]. Standard frontline maintenance therapy consists of PARP inhibitors and/or bevacizumab, depending on the presence of *BRCA* mutations or homologous recombination deficiency (HRD) [41,45,46]. Tumors harboring HRD, largely caused by somatic or

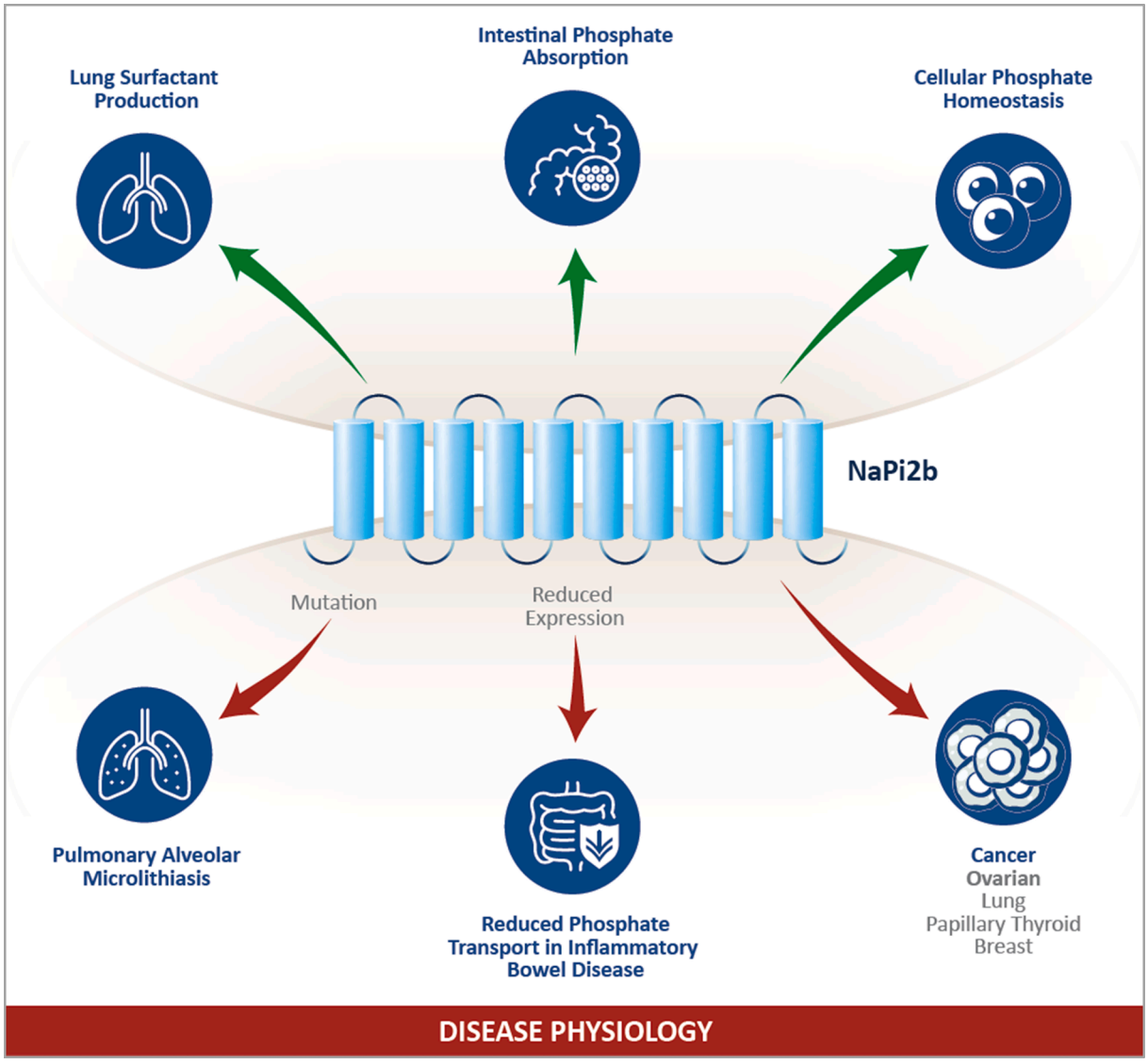

Fig. 1. NaPi2b sodium-dependent phosphate transporter regulates the normal physiological processes of surfactant production in the lungs, intestinal phosphate absorption, and whole-body cellular phosphate homeostasis. NaPi2b is also implicated in various disease areas, including pulmonary alveolar microlithiasis due to mutations in the *SLC34A2* gene, inflammatory bowel disease due to reduced NaPi2b expression and subsequent decreased phosphate transport in the intestine, and several types of cancer (ovarian, lung, breast, and papillary thyroid).

germline *BRCA1/2* mutations, are more susceptible to PARP inhibitors. *BRCA1/2* and HRD testing have improved patient selection and treatment decision making, which underscores the clinical value of biomarker testing and biomarker-directed treatment [41,42,45,47].

Unfortunately, most patients with advanced ovarian cancers are estimated to experience recurrence during or after frontline treatment [41,44]. Depending on the duration of the treatment-free interval before disease recurrence, the disease is defined as either platinum-sensitive (>6 months after the last platinum-containing treatment), primary platinum refractory due to intrinsic resistance (<1 month after the last platinum-containing treatment), or platinum-resistant (1–6 months from last platinum dose) and reflects the likelihood of further response to platinum-based chemotherapy [41,44]. To date, recurrent disease remains incurable, and treatments are aimed at controlling disease-related symptoms, prolonging treatment-free intervals, and delaying disease progression without compromising quality of life. In the past decade, approval of PARP inhibitors as part of maintenance therapy for patients with recurrent disease has transformed the treatment landscape, as evidenced by improved prognosis of patients with platinum-sensitive ovarian cancer [46,48]. However, treatment options in platinum-resistant disease remain limited. When progression occurs within 6 months of receiving platinum-based therapy, standard-of-care for patients historically has consisted of single-agent non-platinum chemotherapy, which is associated with considerable toxicity and has limited efficacy, with response rates of 4 %–12 %, progression-free survival (PFS) of 3–4 months, and overall survival of approximately 12 months [42,44,49–52]. Some progress has been made in the platinum-resistant space with the addition of bevacizumab to single-agent chemotherapy, resulting in significantly improved PFS (median of 6.7 months vs 3.4 months) and response rates (31 % vs 13 %) [53]. Nonetheless, some patients may be ineligible for bevacizumab-containing therapy or discontinue bevacizumab due to the risk of complications including bowel perforation, uncontrolled hypertension, proteinuria, and posterior reversible encephalopathy syndrome [53,54]. Consequently, there remains a high unmet need for new therapies with improved efficacy and tolerability in platinum-resistant patients. Biomarker testing and subsequent expansion of personalized, biomarker-directed treatment, particularly in the platinum-resistant space, could help the strategic selection of patients who would benefit from treatment and potentially improve their survival [47,55,56].

Because ovarian cancer is a heterogeneous disease that comprises several distinct histological subtypes, identification of a biomarker that is subtype-agnostic and has stable expression over time would be clinically relevant [47,50,55]. Considering that NaPi2b is highly expressed in serous ovarian tumor tissues (Fig. 2), it represents a valid lineage biomarker to be explored in ovarian cancer.

Accordingly, NaPi2b (through interaction with the MX35 antibody) has been evaluated as a tumor-selective marker, and early studies showed that MX35 antibody could be used to identify ovarian tumor micrometastases and minimal residual disease [58]. In addition, results from a translational study showed that a humanized monoclonal anti-NaPi2b antibody (Rebmab200) induced considerable cell death mediated by antibody-dependent cellular cytotoxicity in ovarian cancer cell lines [59]. More recently, several analyses of ovarian serous carcinoma tissue samples have provided important insights into NaPi2b expression throughout disease course. In a longitudinal tissue series, samples were collected from 11 patients with high-grade serous ovarian cancer across multiple time points throughout their disease and treatment course (prior to neoadjuvant chemotherapy, after adjuvant chemotherapy, at time of recurrence), and NaPi2b expression was assessed via an immunohistochemistry (IHC) GLP assay to calculate a tumor proportion score (TPS) [60]. Overall, 73 % of patients maintained their same NaPi2b TPS over the course of disease and treatment (positive/positive or negative/negative) and 86 % of patients with NaPi2b-positive tumors (established previously as TPS $\geq$ 75 % [57]) at the initial sample maintained high expression across matched samples [60].

In a separate study, NaPi2b expression was evaluated in samples collected from primary versus metastatic sites, and from fresh versus archival ovarian cancer tissues [61]. In 18 pairs of synchronous primary and metastatic samples procured from tissue banks, a high concordance (72 %) was observed between collection sites. In a second set including paired fresh and archival specimens (all sampled prior to drug administration) from 56 patients enrolled in a phase 1b trial of a NaPi2b-targeting antibody-drug conjugate (ADC), upifitamab rilsodotin (UpRi), high concordance was noted across fresh and archival samples for both NaPi2b-positive samples (76 %) and NaPi2b-negative samples

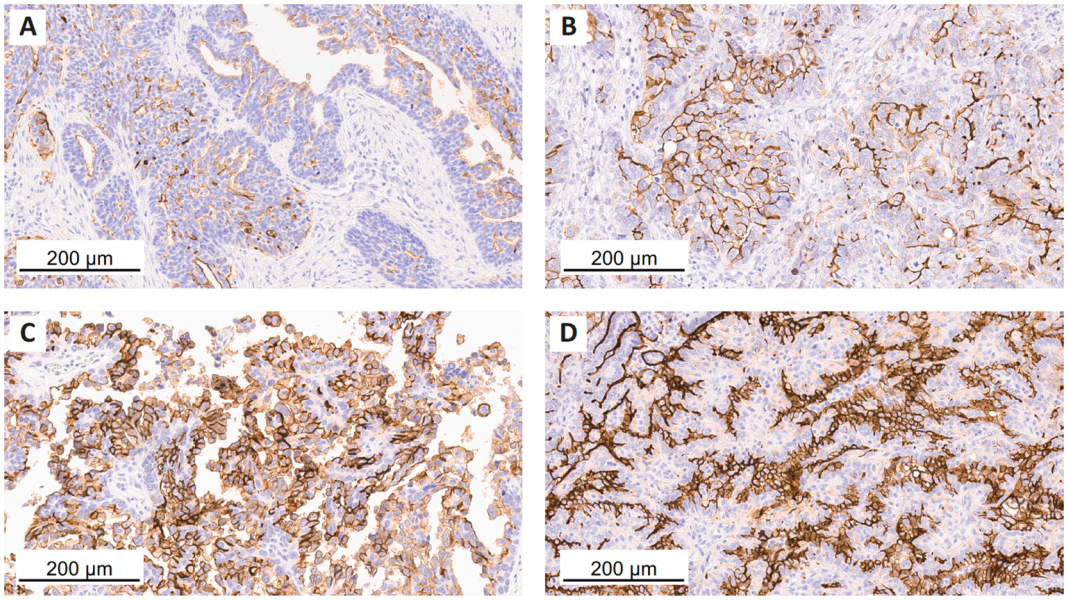

Fig. 2. NaPi2b immunohistochemistry (IHC) staining in high-grade serous ovarian cancer samples, displaying variation in proportion of NaPi2b positive cells. All images were provided by Leica Biosystems and were scanned at 20 × magnification using an Aperio AT2 scanner. A novel human-rabbit chimeric antibody has been developed and is for investigational use only as an IHC reagent on the BOND-III autostainer for detection of NaPi2b in formalin-fixed, paraffin-embedded serous ovarian cancer tissue [57]. **A.** Weak NaPi2b plasma membrane staining. **B.** Moderate plasma membrane staining. **C.** Strong membrane staining. **D.** Strong mix of aggregate and membrane staining.

(74 %), suggesting that archival tissue is sufficient for biomarker testing [61]. Taken together, these analyses suggest that NaPi2b status is stable through disease and treatment course and does not vary significantly across collection sites or in fresh versus archival biopsy specimens. The latter is particularly notable, as NaPi2b biomarker screening is less likely to significantly increase the burden on patients. While these are small sample sets and further evaluation is warranted, the stability of NaPi2b over time, sample location, and specimen type provide additional rationale for the use of NaPi2b as a biomarker and confidence in the robustness of NaPi2b as a biomarker for ovarian cancer.

While personalized, biomarker-directed therapy has the potential to guide identification of patients who may benefit from treatment, effective biomarker detection can present challenges. In a recent example, the ADC mirvetuximab soravtansine, which targets folate receptor α (FRα), was evaluated in patients with platinum-resistant ovarian cancer in the randomized, phase 3 FORWARD I trial versus investigator's choice of chemotherapy. Disappointingly, the trial did not meet the primary endpoint of PFS in either the intention-to-treat population (HR 0.981, $P = 0.897$) or the prespecified FRα-high population (HR 0.693, $P = 0.049$) [51,62]. The study investigators have attributed this to the way in which patients were assessed for FRα positivity. In FORWARD I, FRα positivity was assessed by the 10 × scoring method, in which tumors with membrane staining in ≥ 50 % of cells were considered FRα-positive, and those with membrane staining in ≥ 75 % of cells were considered FRα-high [51]. However, in all prior mirvetuximab soravtansine studies, FRα positivity was assessed using PS2 + scoring, which takes into account both staining intensity and percentage of tumor cells with staining; tumors were FRα-positive if ≥ 25 % of tumor cells stained with medium or high intensity and were considered FRα-high if ≥ 75 % of tumor cells stained with medium or high intensity [62,63]. Exploratory analyses rescoring the FORWARD I samples using PS2 + revealed that 34 % of patients enrolled in FORWARD I had FRα levels that would not have met inclusion criteria. Therefore, the change in scoring method from PS2 + to 10 × introduced a population of patients into FORWARD I with lower levels of FRα expression than intended, including in the predefined FRα-high subset (FRα-high using 10×: 60 % [n = 198]; FRα-high using PS2+: 35 % [n = 116]) [63]. Reanalysis of outcomes using PS2 + scoring demonstrated improved PFS with mirvetuximab soravtansine versus chemotherapy in the FRα-high subgroup (median PFS, 5.6 months vs 3.2 months; HR 0.549, $P = 0.015$). This has led to the randomized phase 3 MIRASOL trial (NCT04209855, ENGOT OV-55), which is evaluating mirvetuximab soravtansine versus investigator's choice of chemotherapy in patients with platinum-resistant ovarian cancer whose tumors are FRα-high via PS2 + scoring [64].

The development of mirvetuximab illustrates the importance of biomarker detection and thresholding which is critical for the success of personalized biomarker-directed strategies. Therefore, clinical development of a biomarker-based therapeutic strategy requires an optimized, robust, predictive, and reproducible diagnostic assay for detection. Robust assays must have a broad dynamic range that allows for clear distinctions to be made between low, medium, and high expressors. Moreover, a clinically useful diagnostic assay must have the ability to predict and enrich for outcomes, thus potentially identifying patients who are most likely to respond to therapy. Finally, it must be possible for the assay to be reliably reproduced in any laboratory, regardless of location, based on clear guidelines on how to perform it and read and consistently interpret the results [65].

The success of a companion diagnostic used to detect biomarkers relies on a widely available assay, a precise scoring system, and a cutoff. IHC-based diagnostic assays have become broadly used to detect tumor biomarkers, such as HER2 or programmed death-ligand 1 (PD-L1), and use common and well-defined scoring systems, including the H-score, the PS2 + method, and the TPS [66,67]. These scoring methods are associated with various benefits and challenges. The H-score accounts for intensity of staining and proportion of positive cells [68]. Although it provides the most information in terms of percentage of cells at given intensities, the H-score is a relatively complex scoring system, which may lead to difficulties with reproducibility; therefore, it might be better applied to clinical research and centralized reading than routine practice. The PS2 + scoring system accounts only for the proportion of higher-intensity staining [69]. Using this method, the pathologist identifies all cells with medium and high staining and distinguishes them from those with low staining. This distinction requires the pathologist to apply a threshold to a continuous spectrum from dark to light brown, which may be highly subjective and could lack reproducibility across laboratories worldwide. Finally, the TPS is defined as percentage of positive tumor cells within the viable tumor cells counted [66]. The TPS system requires the pathologist to distinguish between the absence of staining and any intensity of positive staining, and therefore, may be more reproducible. Testing for NaPi2b in this way could help identify patient populations most likely to benefit from selective NaPi2b targeted therapies.

Antibody-drug conjugates as a therapeutic modality to target NaPi2b

A critical challenge in developing effective cancer treatments is the ability to deliver targeted therapy to tumor tissue while sparing healthy tissue. Because NaPi2b is a lineage marker and not an oncogene, it is not a candidate for targeted inhibition; however, the expression profile of NaPi2b in ovarian cancer presents a unique opportunity to preferentially deliver cytotoxic treatment to tumor cells using ADCs. ADCs are emerging biomarker-based therapeutic approaches developed to direct potent cytotoxic agent with high selectivity in various tumor types [43,70]. Structurally, an ADC is composed of an antigen-targeted monoclonal antibody coupled to a cytotoxic payload via a cleavable or non-cleavable linker [43,70]. The binding of the antibody to its tumor antigen results in internalization of the complex and release of the cytotoxic payload into the targeted tumor cells [43,70].

To date, there are 13 US FDA-approved ADC therapies, of which six are approved in solid tumors, including breast, urothelial, cervical, and ovarian cancers [43,70]. In addition to mirvetuximab soravtansine (targeting FRα), several other ADCs are in various stages of clinical development in ovarian cancer, including anetumab ravtansine (targeting mesothelin), tisotumab vedotin (targeting tissue factor), and UpRi (targeting NaPi2b) [43,44]. Using ADCs to target NaPi2b in ovarian cancer is an attractive strategy to minimize the occurrence of toxicities such as peripheral neuropathy and neutropenia, which are typically associated with standard-of-care chemotherapy [18,44,51].

Clinical potential of NaPi2b

To date, two NaPi2b targeting ADCs have been investigated in early phase studies in ovarian cancer (Table 1). The first of these, lifastuzumab vedotin (LIFA), was an ADC comprising a humanized anti-NaPi2b monoclonal antibody conjugated to monomethyl auristatin E [71,72]. In the phase 2 trial in patients with platinum-resistant ovarian cancer, treatment with LIFA resulted in a median PFS of 5.3 months compared with 3.1 months ($P = 0.34$) with standard-of-care pegylated liposomal doxorubicin in the overall study population [71]. In patients with high NaPi2b-expressing tumors (as determined by an H-score IHC-based assay), the median PFS was 5.3 versus 3.4 months ($P = 0.24$), and the objective response rate (ORR) was 36 % versus 14 % in patients treated with LIFA versus pegylated liposomal doxorubicin [71]. Commonly reported adverse events with LIFA included fatigue, gastrointestinal adverse events, and peripheral neuropathy [72]. Although the overall data in ovarian cancer looked promising and supported the feasibility of ADCs to target NaPi2b, the PFS differences were not statistically significant, and the sponsor made the decision to discontinue LIFA development [73]. Of note, 93 % of patients treated with LIFA were determined to have high NaPi2b levels, which suggests the diagnostic

Table 1
Clinical activity of NaPi2b ADCs in ovarian cancer.

NaPi2b ADC	Payload	Study	Patient population	Enrollment/dose groups/treatment arms	Efficacy	Top 3 AEs with ADC	
						Any grade	Grade ≥ 3
Lifastuzumab vedotin (LIFA)	Monomethyl auristatin E	Phase 1b NCT01363947 [73]	Recurrent PSOC	$N = 41$ LIFA 1.2 mg/kg + carboplatin LIFA 2.4 mg/kg + carboplatin ± bevacizumab	**All patients** ORR: 59 % Median PFS: 10.7 mo	Neutropenia (78 %) Peripheral neuropathy (63 %) Thrombocytopenia (61 %)	Neutropenia (59 %) Thrombocytopenia (31 %) Anemia (15 %)
		Phase 2 (terminated) NCT01991210 [71]	PROC Median of 2 prior systemic therapies	$N = 95$ NaPi2b high: 93 % LIFA 2.4 mg/kg Total: $n = 47$ NaPi2b high: $n = 42$ PLD 40 mg/kg Total: $n = 48$ NaPi2b high: $n = 43$	**ITT** ORR: 34 % LIFA vs 15 % PLD Median PFS: 5.3 vs 3.1 mo ($P = 0.34$) **NaPi2b high** ORR: 36 % LIFA vs 14 % PLD Median PFS: 5.3 vs 3.4 mo ($P = 0.24$)	Abdominal pain (46 %) Nausea (46 %) Fatigue (44 %)	Neutropenia (13 %) Abdominal pain (9 %) Anemia (7 %)
Upifitamab rilsodotin (UpRi)	Auristatin F-HPA	Phase 1b NCT03319628 [76]	HGSOC progressing after standard treatment 1–3 prior lines in platinum-resistant patients 4 prior lines regardless of platinum status	Total enrolled: $N = 97$ Response evaluable: $n = 75$ NaPi2b positive: $n = 50$ (64 %) UpRi 36 mg/m^2 UpRi 43 mg/m^2	**All dose levels ITT** ORR: 23 % (CR 3 %) **NaPi2b positive** ORR: 34 % (CR 5 %)	**UpRi 36 mg/m^2** Fatigue (79 %) Nausea (59 %) AST increased (38 %)	**UpRi 36 mg/m^2** Transient AST increased (21 %) Transient thrombocytopenia (14 %) Fatigue (10 %)

assay used in this study may not have been optimized to distinguish responders from non-responders [71].

UpRi is a first-in-class NaPi2b-targeting ADC with a novel scaffold-linker-payload [74]. The design of this ADC enables a high drug-to-antibody ratio of approximately 10, which is hypothesized to improve drug concentration at the tumor and result in a lower dose or less frequent administration, especially in tumors with low antigen expression [43,70]. In addition, to limit potential off-target toxicity, UpRi has been designed with an auristatin F-HPA payload with a controlled bystander effect, in which auristatin F-HPA has a limited diffusion capacity that reduces its potential action on neighboring, healthy cells [74–77]. The safety and preliminary efficacy of UpRi were recently investigated in a phase 1/1b study of 97 patients with high-grade serous ovarian cancer [76]. Data from this trial suggested that UpRi has clinical activity at the 36 mg/m^2 dose, with a differentiated safety profile, showing no reports of grade ≥ 3 cases of neutropenia, peripheral neuropathy, or ocular toxicity [76]. The most frequently reported treatment-related adverse events were low-grade and included fatigue, nausea, transient aspartate aminotransferase increase, transient thrombocytopenia, and decreased appetite [76]. Using an immunostaining protocol for NaPi2b, it was established that a TPS cut-off ≥ 75 % could be used in a clinical setting to detect samples with NaPi2b-high expression and identifies a population similar to that for the previously used H-score [57]. Overall, of 78 patients who had NaPi2b expression determined by TPS, 50 (64 %) had NaPi2b-positive (TPS ≥ 75) ovarian tumors. These patients achieved an ORR of 34 % vs 23 % in those with any level of NaPi2b expression and had a trend toward longer time on treatment than patients with low NaPi2b expression [76]. The aforementioned phase 1/1b efficacy and tolerability data support the investigation of the potential clinical benefit with UpRi in three ongoing clinical trials: the phase 2 registrational UPLIFT trial (NCT03319628), designed to evaluate UpRi monotherapy in patients with platinum-resistant, high-grade serous ovarian cancer who have received up to four prior lines of therapy; the phase 1/2 UPGRADE trial (NCT04907968), an umbrella study investigating UpRi in combination with other agents in patients with platinum-sensitive ovarian cancer; and the phase 3 randomized UP-NEXT trial (NCT05329545) evaluating UpRi maintenance monotherapy vs placebo in patients with recurrent, platinum-sensitive high-grade ovarian cancer with NaPi2b-positive disease [78–83].

Future considerations and conclusions

Studies using NaPi2b for patient selection and therapeutic targeting in ovarian cancer are promising; however, several important considerations remain. Emerging evidence suggests that patients who express high levels of NaPi2b at the time of diagnosis continue to maintain high levels of expression over the course of their disease. This indicates that timely biomarker testing would be of value to patient care, especially in later-line and platinum-resistant settings; however, these findings were based on analyses with limited sample sizes, thus larger studies are warranted to fully elucidate NaPi2b expression though disease and treatment course. In addition, anticipating and uncovering potential mechanisms of resistance to anti-NaPi2b ADCs, particularly in patients with platinum-resistant disease, could further inform treatment sequencing in patients with advanced/recurrent ovarian cancer. It is also currently unknown how NaPi2b expression may be correlated with or impacted by the presence of other biomarkers, including *BRCA1/2* or HRD; understanding the relationship between these biomarkers and NaPi2b would support future studies exploring anti-NaPi2b ADCs in combination with other therapies. Finally, because NaPi2b expression is not confined to ovarian cancer, further exploration of anti-NaPi2b ADCs in other cancers, including lung, endometrial and thyroid cancers, is of interest. Additional studies with larger cohorts of patients are

warranted.

Biomarker-directed treatment is an important area of clinical focus in ovarian cancer, and there is a need to identify patients who would benefit from selected therapies. The key to personalized care in ovarian cancer is the identification of a biomarker that can be used for patient selection using accessible IHC-based robust diagnostic assays. NaPi2b is a promising novel therapeutic target due to its high expression in ovarian cancer and low expression in normal tissues. Moreover, because NaPi2b is highly expressed on the cell surface, it is an ideal candidate for an IHC-based diagnostic assay for effective patient selection and for ADC-based therapy. Accordingly, encouraging early findings with anti-NaPi2b ADCs suggest promise in further development of these therapies as a valid approach for personalized medicine. Based on the body of literature summarized here, NaPi2b has the potential to be a clinically relevant biomarker for patient selection and treatment in ovarian cancer.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [**S. Banerjee:** research funding: AstraZeneca, GlaxoSmithKline, Verastem; advisory boards: Amgen, AstraZeneca, GlaxoSmithKline, Immunogen, Merck & Co., Mersana, Novartis, OncXerna, Regeneron, Seagen, Shattuck; honoraria: Amgen, AstraZeneca, Clovis, GlaxoSmithKline, Immunogen, Merck & Co., Mersana, Pfizer, Roche, Takeda; stock or other ownership: Perci Health. **R. Drapkin:** advisory boards: Repare Therapeutics and VOC Health, Inc. **D. Richardson:** Consultancy/advisory role with Mersana, AstraZeneca, Genentech, GlaxoSmithKline, Immunogen, and Deciphera; research funding from GlaxoSmithKline, Celsion, Roche, Aravive, Shattuck, Mersana, Syros, Arch Oncology, Harpoon, Hookipa, Clovis, and Karyopharm. **M. Birrer:** advisory boards: AstraZeneca, Merck.].

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