NaPi2b (SLC34A2) is a multi-transmembrane, sodium-dependent phosphate transporter (Xu et al., 1999) normally expressed in lungs, testis, salivary gland, thyroid gland, small intestine, mammary gland, and uterus (Nakamura and Naito, 2008) and is involved in transcellular absorption of inorganic phosphate.

NaPi2b is highly expressed in non-squamous non-small cell lung cancer (NSCLC) and non-mucinous ovarian cancer (OC).

NaPi2b-positive tissue immunoreactivity is present in 81% of NSCLC, and 95% OC cancer specimens.

Mutations in NaPi2b have been associated with clinical syndromes of alveolar and testicular microthrombosis.

DNIB0600A is a monoclonal antibody conjugated to the cytotoxic agent monomethyl auristatin E (MMAE) via a protease-cleavable peptide linker (v-MAFA platform, Seattle Genetics).

This study evaluated safety, pharmacokinetics (PK), and pharmacodynamics of DNIB0600A (0.2–2.8 mg/kg) given every 3 weeks (q3w) to patients with non-square NSCLC or platinum-resistant, non-mucinous OC.

A traditional 3+3 design was used for dose escalation followed by expansions in NSCLC and OC at the recommended Phase 2 dose (RP2D).

No pre-medication was required or recommended prior to study drug treatment, but was instituted per study guidelines in the event of infusion-related reactions or onset of AEs.

Pharmacokinetic and Pharmacodynamic Evaluations

PK analysis was performed for total antibody, antibody-conjugated MMAE (ac/MMAE) and unconjugated MMAE.

Tumor NaPi2b expression was evaluated in archival tissue by immunohistochemistry (IHC).

Clinical Evaluations

Anti-tumor activity was evaluated per RECIST 1.1 every 6 weeks.

RESULTS

- As of 18 September 2013, 73 patients have enrolled (43 NSCLC; 30 OC).
- Forty-one patients have discontinued due to progressive disease, 13 based on physician decision, 9 due to any AEs, and 1 patient with consent withdrawal.

Patient Characteristics, Patient Status

- Patients received a median of 4 (range 1–28) doses of DNIB0600A.
- Ten patients (14%) experienced Grade 1–2 infusion-related reactions, defined as any AE occurring within 24 hours of study drug infusion (most commonly nausea, vomiting or fatigue). Generally, these resolved within 24–48 hours with observation or symptomatic management.
- Four patients reported serious AEs considered related to study treatment; dyspnea (Grade 3) in 1 patient at 1.8 mg/kg (DLT), upper abdominal pain, headache, and nausea (each Grade 2) in 1 patient at 2.4 mg/kg, hypokalemia and hyperglycemia (each Grade 3) in 1 patient at 2.4 mg/kg, and upper respiratory tract infection and pneumonia (each Grade 3) in 1 patient at 2.4 mg/kg. No deaths occurred on study or were related to study treatment.

Pharmacokinetics

Nine (13%) of 36 patients (56%) developed an antibody response to DNIB0600A with no impact on exposure or AE. Linear pharmacokinetics were observed for total antibody, ac/MMAE, and unconjugated MMAE. PK characteristics support the regimen with minimal accumulation of either analyte over dosing cycles. PK is comparable in NSCLC and OC patients.

Safety

- Of the 65 patients with NaPi2b/ICH Score of 2+ or 3+, treated at dose levels 1.8–2.8 mg/kg, 14 patients had a confirmed partial response (PR), 3 of 26 (12%) NSCLC and 11 of 22 (50%) OC patients, respectively.
- Three NSCLC patients had unconfirmed PRs.
- No patient was enrolled with NaPi2b/ICH Score of 1+. No responses were reported among the 13 patients with NaPi2b/ICH Score of 0 or unavailable, at any dose level.

CONCLUSIONS

- DNIB0600A administered every 3 weeks has an encouraging safety, tolerability, and PK profile and evidence of anti-tumor activity in NSCLC and OC, with pts whose tumors express NaPi2b detectable by IHC.
- This data supports further clinical evaluation of DNIB0600A in NSCLC and OC together with a companion diagnostic.

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