Phase I dose escalation study of immunoconjugate L-DOS47 in combination with pemetrexed/carboplatin in non-squamous non-small cell lung cancer (NSCLC) patients.

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Background:
L-DOS47, a cancer therapeutic designed to exploit the acidic tumour extracellular environment, consists of urease conjugated to an anti-CEACAM6 camelid monoclonal antibody. The antibody serves as a targeting agent to deliver urease to tumor sites, while the urease enzyme converts urea, an abundant natural metabolite, into ammonia and generates a local pH increase. The combined effect of ammonia toxicity and pH increase is cytotoxic to cancer cells. An additive cytotoxic effect of L-DOS47 and pemetrexed/carboplatin has been observed against the A549 human lung adenocarcinoma cell line. L-DOS47 has been shown in a previous phase I clinical trial to be safe and well tolerated at doses up to 13.55 µg/kg. The current phase I study was designed to define the maximum tolerated dose of L-DOS47 in combination with pemetrexed/carboplatin.

Methods:

Stage IV (TNM M1a and M1b) histologically confirmed non-squamous NSCLC patients (aged ≥18 yrs, ECOG PS ≤1) received up to four cycles of L-DOS47 in combination with standard of care doses of pemetrexed/carboplatin. L-DOS47 was administered weekly over 21 days in each treatment cycle. Seven planned dosing cohorts (0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 μg/kg) employed a standard 3+3 design for the first two and the last two cohorts, and an accelerated 1 + 2 design for the middle three cohorts. Dose levels of L-DOS47 were escalated following a review of safety data by the Trial Steering Committee.

Results:

Fourteen (14) patients were enrolled across 6 dosing cohorts before recruitment was halted. Median age was 65.1 years, with 50.0% male and 78.6% Caucasian. 57.1% of patients had an ECOG score of 0, and 42.9% had an ECOG score of 1. The maximum tolerated dose (MTD) could not be determined as none of the patients experienced a dose limiting toxicity (DLT). 50.0% of patients experienced at least one treatment emergent adverse event (TEAE) assessed as study drug-related, with 14.3% of patients experiencing at least one grade 3/4 drug-related toxicity. Of 12 patients evaluable for efficacy, 5 patients (41.7%) had a partial response (PR), 4 patients (33.3%) experienced stable disease (SD) and 3 patients (25.0%) had progressive disease (PD). The objective response rate is 41.7%. The clinical benefit rate is 75.0%.

Conclusions:

L-DOS47, in combination with pemetrexed/carboplatin, appears to be well tolerated with promising anti-tumor activity against non-squamous NSCLC. Clinical trial information: NCT02309892