MINI30.01 - Oncolytic Reovirus in Combination with Paclitaxel/Carboplatin in NSCLC Patients with Ras Activated Malignancies, Long Term Results (ID 500)

Background

Reovirus is a naturally occurring virus which preferentially infects and causes oncolysis in tumor cells with a *Ras*-activated pathway. Cells that express high levels of EGFR are also susceptible to reovirus infection. In preclinical studies, reovirus induces host immunity and cell cycle arrest, acting synergistically with standard cytotoxic agents. Its adverse effects are mild to moderate flu-like symptoms. We have hypothesized those patients with EGFR-mutated, EGFR-amplified, or *Kras*-mutated NSCLC through a common downstream activated *Ras* pathway should be susceptible to treatment with reovirus

Methods

We designed a Fleming, single-arm, phase II study to evaluate the objective response rate (CR + PR RECIST, or >40% PET SUV decrease) of reovirus in combination with paclitaxel-carboplatin as first-line therapy in patients with metastatic NSCLC. Secondary endpoints included progression free and overall survival. Eligible patients had ECOG PS 0-2, adequate organ function, no prior systemic chemotherapy for metastatic disease, and tumors with the specified genotype, as per CLIA certified testing. Adjuvant chemotherapy, or erlotinib/gefitinib for pts with EGFR mutant tumors was permitted.

Results

Thirty-seven patients were enrolled. Molecular tumor demographics included 20 pts with Kras mutations; 10 with EGFR amplification alone; 3 patients with EGFR mutations and four patients with BRAF V600E mutations.

Overall, 258 cycles (median 4, range 1-47) were administered. Initial doses used were C AUC 6 on day 1, and P 200 mg/m^2,on day 1 of each 21-day cycle. Due to unacceptable toxicities (grade 3 diarrhea and febrile neutropenia [1 each]) in the first two patients, doses were reduced to P 175 mg/m-m^2 and C AUC 5..

Common toxicities considered at least possibly related to the therapy included fatigue (30 pts); diarrhea (21 pts); nausea (19 pts); arthralgia-myalgia (15 pts); and anorexia (9 pts). Grade 3-4 adverse events included neutropenia (7 Gr3, 1 Gr4), anemia (2 Gr3), fatigue (9 Gr3), diarrhea (3 Gr3), nausea/vomiting (3 Gr3) and a single case of sepsis.

Response evaluation showed 11 PR (5 Kras mutant), 20 SD, 4 PD and 2 NE patients by RECIST (ORR: 31%, 90% one-sided lower CI: 21%). Four of the SD patients had >40% PET SUV reductions after two cycles. Three patients opted to switch to pemetrexed maintenance after 4 cycles without disease progression or moderate/severe toxicity. Median PFS, OS and 12 month overall survival rates were: 4 months (95% CI: 2.9-6.1), 13.1 months (95% CI: 9.2-21.6) and 57% (95% CI: 39-72%), respectively. Seven patients are alive after a median follow up of 34.2 months (range: 26.9-71.5), including two patients with no evidence of disease progression to date (50 and 37 months).

Conclusion

Oncolytic reovirus administration in combination with paclitaxel and carboplatin was well tolerated. The RECIST response rate (11/35 [31%]; 28% of Kras mutants)(15/35; 43% if PET is considered) is not conclusive, nor excludes additional benefit of the reovirus to chemotherapy. However, the number of patients surviving longer than 2 years (11; 30%) is substantial, suggesting either effect of second/third line post paclitaxel/carboplatin/reolysin treatment or perhaps the triggering of an immune response following tumor reovirus infiltration. The latter concept merits further investigation.