

**Interleukin-21(IL-21) has activity in patients (pts) with metastatic melanoma (MM).**

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**Background:** IL-21 is a T-cell derived cytokine with anti-tumor activity shown to be dependent on NK cells or CD8+ T cells through induction of central and effector memory cells. Two previous phase I studies suggested activity in MM.

**Methods:** We conducted a phase II study of IL-21 evaluating the response rate (ORR) by RECIST, toxicity, progression free survival (PFS) and biomarker profile. Pts with no prior systemic therapy for MM were treated with IL-21 using 3 different dosing regimens. The initial cohort received 50µg/kg/day by outpatient intravenous bolus injection daily x 5, weeks 1, 3, 5 q 8 wks. Cohort 2 received 30µg/kg/day in the same schedule and Cohort 3 received 50µg/kg/day daily x 5, weeks 1, 3 q 6 wks.

**Results:** 40 pts were enrolled: 3 in cohort 1, 30 in cohort 2, 7 in cohort 3. Two pts in cohort 1 had dose limiting toxicity (DLTs) and 4 in cohort 3, thus all other pts were treated with the 30ug/kg/day dose. The most common adverse events were fatigue, rash, diarrhea and myalgia. 37 pts are evaluable for response: 9 had a PR (ORR = 24.3%; median duration 5 mo), 16 had stable disease (median 5.1 mo, 95% C.I. (2.17, 5.95)) and 12 had PD. ORR was not dependent on dose, IL-21 receptor expression or BRAF mutation status (3 of the PRs were BRAF positive, 5 were BRAF negative, 1 was BRAF inconclusive). The median PFS is 5.19 mo. The encouraging PFS result was examined further by comparing the outcome of this study to historical NCIC CTG phase II melanoma trials in those patients who matched the IL-21 trial entry criteria (n = 68). The PFS in the historical group was 1.58 mo (95% C.I. (1.22, 1.87)). A multivariate analysis comparing PFS of IL-21 treated patients to the historical group to adjust for prognostic factors (age, gender, perf status, liver mets, number of metastatic sites) revealed that age (HR=0.97, p=0.0008), performance status (1 vs. 0: HR=1.497 and 2 vs. 0: HR = 8.091, p= 0.0026) and treatment with IL-21 (HR=0.584, p=0.0198) were significant predictors of PFS.

**Conclusions:** The ORR to IL-21 is 24% for first line MM and warrants further investigation. A median PFS of 5.19 months is superior to that observed in historical NCIC CTG data even when adjusted for prognostic variables. We plan a randomized phase II study of IL-21 to confirm and extend these observations.