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Controlled IL-12 in combination with a PD-1 inhibitor subjects with recurrent glioblastoma
Poster Discussion Transcript: ASCO 2020 Virtual Meeting
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00:00
Good morning. On behalf of my co-authors, it is my pleasure to present initial findings from a completed Phase I clinical trial where we combined controlled IL-12 gene therapy with a PD-1 inhibitor in subjects were occurring glioblastoma.

00:21
The background the study is the following. Controlled IL-12 gene therapy consists of a gene therapy vector where an IL-12 cDNA is regulated by a promoter that is switched off. To switch on transcription of the delivered IL-12 cDNA, the promoter has to bind to a small activator ligand veledimex.

00:45
In the previously published Phase I clinical trial, we injected the IL-12 gene therapy vector directly into the cavity wall of the resected glioblastoma. The patient then injected-- or ingested oral for 14 days. And the drug crossing to the tumor bound to the promoter, turning on IL-12 gene expression.

01:12
The rationale for combining the IL-12 gene therapy with a PD-1 inhibitor is presented here in the poster. The previous Phase I of IL-12 gene therapy alone showed it to be well tolerated, showed encouraging survival benefits, and showed increasing in infiltrates with CA-plus TILs between baseline and day 175 in post-treatment biopsies. But it also showed that there was increased expression of both PD-1 and PD-L1.

01:46
The study design is shown here in the top center. This is a combined Phase I, single arm, open label, dose escalation, multi-center study. After determination of eligibility, the subject was treated to one dose of neoadjuvant nivolumab on day minus 7 before surgery.

02:10
Three hours before the scheduled craniotomy, the patient ingested one dose of oral veledimex. After tumor resection, the neurosurgeon free-hand injected the gene therapy vector, indicated here with the name Ad-RTS-hIL-12.

02:29
The patient then took all of the veledimex for 14 days post-operatively to turn on IL-12 gene expression in the tumor, and then continued intravenous nivo.

02:41
The dose escalation consists of escalating both VDX and nivolumab separately until the final third cord when more drugs were administered at the MDD.

02:55
The safety results are shown here at the bottom left of the poster. The safety results show that a combination of IL-12 gene therapy and nivolumab was just as well tolerated as when we administered the IL-12 gene therapy alone in the previous trial. When there were toxicities they were predictable, they were dose-related, and reversible.

03:19
The subject characteristics as shown here in the table in the poster-- in the center of the poster. And at the bottom we see the plasma pharmacokinetics. We showed dose response relationship with veledimex.

03:36
Now serum cytokines are shown here in the upper right. The previous shown that VDX does cross the blood brain barrier, gets into the tumor, and turns on transcription of IL-12.

03:49
Here we show that this was also true in the trial. IL-12 can be measured three days in serum after the craniotomy. And there was a peak at three days with a decline over the following week.

04:06
One of the downstream effects of IL-12 is to stimulate interferon gamma production by immune cells. And here we show that interferon gamma levels also increased in peak by seven days after surgery with a decline over the next two weeks.

04:22
As shown in the middle right, in some patients there was evidence of increased enhancement on MRI scans after therapy, which then spontaneously regressed, consistent when inflammatory pseudoprogression.

04:36
Therefore, median overall survival has not been reached yet with a mean follow-up time of 8.3 months. Addition of serum IL-12 was detecting subjects following the start of IL-12 plus veledimex followed by an increase in interferon gamma.

04:52
We are now in the midst of a Phase II trial where we're combining in a multi-institutional fashion IL-12 gene therapy with have another checkpoint inhibitor, cemiplimab. Thank you.