Abstract #9534: Phase 1b trial of IFx-Hu2.0, a novel personalized cancer vaccine, in checkpoint inhibitor resistant Merkel cell carcinoma and cutaneous squamous cell carcinoma

Andrew S. Brohl[1*], Joseph Markowitz[1], Zeynep Eroglu[1], Ann W. Silk[2], John Hyngstrom[3], Nikhil Khushalani[1], Ahmad A. Tarhini[1], Deanryan De Aquino[1], Edith Abraham[1], Kenneth Tsai[1], Jacob Thomas[4]

[1]Moffitt Cancer Center, Tampa, FL, USA; [2]Dana-Farber Cancer Institute, Boston, MA;[3]Huntsman Cancer Institute, Salt Lake City, UT; [4]USC Norris Comprehensive Cancer Center, Los Angeles, CA; *contact: andrew.brohl@moffitt.org

H. LEE MOFFITT CANCER CENTER & RESEARCH INSTITUTE, AN NCI COMPREHENSIVE CANCER CENTER – Tampa, FL
1-888-MOFFITT (1-888-663-3488) www.MOFFITT.org

Background

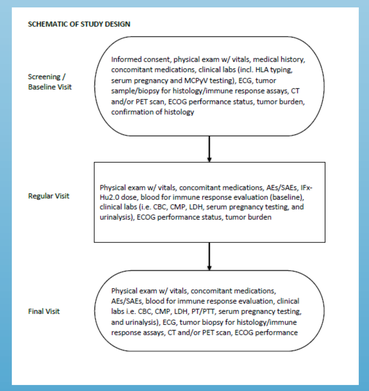
Background: Merkel cell carcinoma (MCC) and cutaneous squamous cell carcinoma (cSCC) exhibit high response rate to immune checkpoint inhibitor (ICI).[1,2] However, patients with advanced disease who fail initial ICI therapy have limited treatment options. IFx-Hu2.0 (IFx) is a plasmid DNA encoding for an immunogenic bacterial protein, Emm55, formulated with a transfection agent for direct intratumoral injection. In a phase 1 study in advanced melanoma, biomarker analyses demonstrated robust immune priming effects of IFx administration.[3] As part of an ongoing Phase 1b study, we evaluated the safety and immunologic response of different schedules of IFx intratumoral administration in patients with advanced MCC or cSCC. We report the initial results of the first stage of this study. Clinicaltrials.gov Identifier NCT04160065.

Methods

Methods: In the first trial stage (n=9), IFx was administered intratumorally in up to 3 lesions on 3 schedules; weekly x 1, 2, or 3. We report safety and efficacy data for these patients as well as preliminary correlative studies. Given the proposed potential for immune priming effects of IFx, we performed an unplanned exploratory analysis of post-protocol treatment efficacy to evaluate for response to ICI rechallenge if given. Data cutoff for clinical outcomes was February 2023.

Trial Design

Trial Design: This study follows a two-stage design with primary goal to assess the safety and feasibility of repeated dosing schemas of the study agent. In the first trial stage (exposure escalation), a 3+3 trial design was utilized to assess safety of repeated weekly intratumoral vaccinations using a fixed dose of IFx (Cohort 1 = single dose; Cohort 2 = 2 doses, 1 week apart; Cohort 3 = 3 doses, weekly). If successful, the second trial stage (expansion) would be conducted to increase the total study sample size to 20.



Study Timeline:

1 week (screening to treatment)

1-3 weeks (treatment visits)

4 weeks (DLT window and time from last dose to final trial assessment)

Total on-protocol time = 6-8 weeks.

Results

Patient Demographics

Five patients with advanced MCC and four with cSCC were enrolled. Prior to trial enrollment, all patients with MCC received ICI with pembrolizumab (4) or avelumab (1), all had progressive disease with median 3 months treatment (2.0-4.5mo). All 4 patients with cSCC previously received cemiplimab with median 6 months treatment (3.0-11.5mo).

Patient Demographics (N=9)		
Sex		
	Male	6
	Female	3
Age		
	Min	57
	Max	74
	Avg	67.4
Race		
	White/Not Hispanic or Latino	7
	Hispanic or Latino	1
	Asian	1
Histology		
	Merkel Cell (MCC)	5
	Squamous Cell (cSCC)	4
Prior lines of therapy		
	1	6
	2	1
	≥3	2

Toxicity

IFx was well tolerated at all dose schedules evaluated with no treatment-related significant adverse events (SAEs) observed. As per protocol, 3 patients were enrolled in each predefined study cohort and cohort #3 (weekly dosing x 3) was selected for the second stage of the study (expansion).

Treatment related Adverse Events		
Adverse Event Term	G1-2	≥G3
Injection site reaction/erythema	2 (22%)	0
Tumor related bleeding	1 (11%)	0
Aspartate aminotransferase increased	1 (11%)	0
Any TRAE	3 (33%)	0

Only 3 patients (33%) experienced any adverse events that were felt by treating investigator to be treatment related. Two patients experienced G1 injection site reaction and/or G1 tumor related bleeding at the injection site and in both cases this local adverse event was self-limiting. One patient developed new G1 AST elevation in the following up period post-injection that was considered possibly treatment related given the timing and lack of alternate etiology identified. No patients experienced a G2 or higher adverse event during the study window that was felt to be treatment related.

Efficacy

Best response to trial therapy was SD in 2 patients and PD in seven. One MCC patient experienced complete clinical response in 2 injected lesions, but had progression of disease overall with development of new disease areas. Both patients with SD (one MCC, one cSCC) had only the injected site as a known disease area and experienced a clinical response in injected site (not meeting RECIST criteria for PR).

Results: Post-protocol ICI Rechallenge

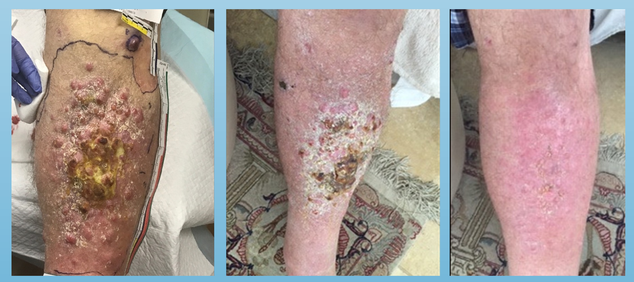
Following completion of protocol therapy, all 5 MCC patients and 2 of 4 cSCC patients were treated with anti-PD(L)1 monotherapy as the immediate post-protocol therapy: pembrolizumab (3) or avelumab (2) in MCC and cemiplimab (2) in cSCC. **Four of 5 MCC patients and 1 of 2 cSCC patients, or 5 of 7 total (71%), experienced objective response to ICI rechallenge** in this setting, with duration of response ongoing in 4 patients (7+, 8+, 9+, 20+ months) and one response lasting 23 months. All 4 MCC patients with post-protocol response to anti-PD(L1) therapy had previously experienced progression to this same drug class prior to treatment on protocol.

Merkel Cell Carcinoma (MCC) patients								
Patient ID	Cohort (1-3)	Pre-trial CPI	Pre-trial CPI Best Response	Pre-trial CPI Tx Duration (months)	Additional Treatments between CPI and IFx trial	Post-protocol Treatment after IFx-Hu2.0	Treatment Response	DOR
MCC-02	1	Pembrolizumab	PD	3.0	None	Avelumab	CR	23 months
MCC-03	2	Pembrolizumab	PD[1]	4.5	Surgery + XRT	Avelumab	PR	20+ months
MCC-04	2	Pembrolizumab	PD[1]	4.0	None	Pembrolizumab	Radiographic PR, then surgical CR (with pCR)	9+ months
MCC-05	3	Avelumab	PD	2.5	None	Pembrolizumab	PR	8+ months
MCC-07	3	Pembrolizumab	PD	2.0	MDM2 inhibitor trial (PD), carboplatin + etoposide (PD), sandostatin (PD)	Pembrolizumab	PD	N/A

[1]Progressed while on adjuvant therapy; CPI = checkpoint inhibitor; DOR= duration of response

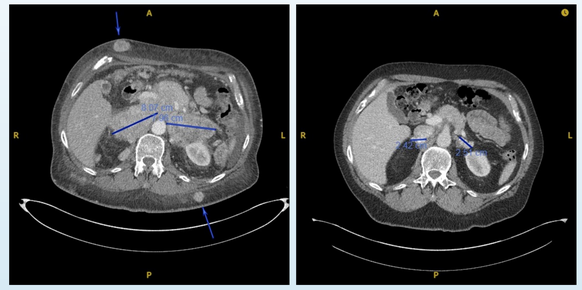
Cutaneous Squamous Cell Carcinoma (cSCC) patients								
Patient ID	Cohort (1-3)	Pre-trial CPI	Pre-trial CPI Best Response	Pre-trial CPI Tx Duration (months)	Additional Treatments between CPI and IFx trial	Post-protocol Treatment after IFx-Hu2.0	Treatment Response	DOR
MCC-01	1	Cemiplimab	SD	11.5	XRT	Cetuximab	PD	N/A
USC-01	1	Cemiplimab	PD	4	Cetuximab, XRT	Carboplatin + cetuximab	PD	N/A
USC-02	2	Cemiplimab	PD	2.5	XRT, carbo/cetuximab, carboplatin + capecitabine + cetuximab	Cemiplimab	PD	N/A
MCC-06	3	Cemiplimab	PR	8.0	None	Cemiplimab	PR	7+ months

CPI = checkpoint inhibitor; DOR= duration of response

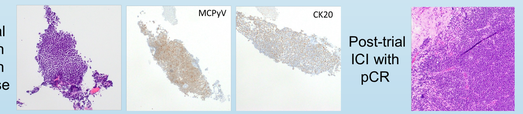


Case study (MCC-005): Patient was treated for multifocal in-transit recurrence of MCC in L leg with avelumab x 6 doses with continued rapid clinical progression as well as development of liver metastatic disease on this therapy. Subsequently enrolled on protocol and received 3 weekly injections of IFx without complication but continued clinical progression (additional in-transit sites). Disease status at time of last injection shown on Left. Following completion of protocol therapy, subject was rechallenged with ICI with pembrolizumab and experienced an obvious clinical response initially apparent approximately 3-4 weeks into therapy. Clinical response at 3 months (middle) and 6 months (right) are show. Concordant (near-complete) radiographic response of liver metastases has also been observed and response has been maintained to date (7+ months).

Results: Post-protocol ICI Rechallenge



Case study (MCC-002): Subject was treated with adjuvant pembrolizumab for stage II MCC on the STAMP trial but developed (nodal) progression after receiving 6 doses. Underwent salvage surgery/XRT but developed widespread metastatic disease ~3months later (nodal, dermal, and intramuscular sites of disease). Subject was then enrolled on IFx protocol and received 2 weekly injections to 3 nodal/dermal metastatic sites but experienced continued rapid progression (both injected and non-injected sites) including bulky diffuse adenopathy and numerous widespread subcutaneous/dermal nodules. Representative imaging from the time of completion of protocol therapy is shown on Left including several subcutaneous sites (arrows) and bulky RP conglomerate LN metastases. Post-protocol was started on ICI rechallenge with avelumab and experienced deep partial response that has been maintained to date (20+ months). Representative images from post-ICI rechallenge restaging shown on Right (complete remission of subcutaneous nodules, partial response in RP sites).



Case study (MCC-003): Subject was previously treated for resectable stage IV MCC on a neoadjuvant/adjuvant protocol utilizing pembrolizumab + lenvatinib. Following 6 weeks of neoadjuvant therapy (2 doses of pembrolizumab), patient underwent resection of an isolated distant dermal metastasis. Pathology from this specimen revealed a viable tumor no evidence of pathological response (Left figures). The subject continued on adjuvant pembrolizumab monotherapy and received two additional cycles before developing clinically evident progression with growth of an epitrochlear node confirmed by imaging and biopsy. Subject was then enrolled on the IFx trial and received injections x 2 to this isolated site of disease with clinical stabilization/minor regression of this lesion. After completion of the IFx trial, subject was rechallenged with pembrolizumab and achieved radiographic partial response at next restaging with no further metastatic progression. Subject subsequently had surgical excision of this isolated disease site with pathology demonstrating complete pathological response (Right figure) with no residual cells staining for CK20 or MCPyV large T antigen (not shown). Subject continues on therapy and is without evidence of disease at 9+ months following post-protocol ICI rechallenge.

Conclusions

IFx-Hu2.0 is safe and well tolerated at weekly dosing repeated up to 3 weeks. In an exploratory post-hoc analysis, five of seven patients (71%) treated with standard of care ICI agents immediately following protocol therapy experienced a durable objective response despite prior failure of this same drug class prior to protocol enrollment, suggesting an “immune priming” effect of study therapy. An additional 11 patients are planned for enrollment in the expansion stage of the study using the weekly x 3 dosing schedule. Exploratory/biomarker analyses are ongoing.

References

1 Kim, S. *et al.* Combined nivolumab and ipilimumab with or without stereotactic body radiation therapy for advanced Merkel cell carcinoma: a randomized, open label, phase 2 trial. *Lancet* **400**, 1008-1019 (2022). https://doi.org/10.1016/S0140-6736(22)01659-2

2 Migden, M. R. *et al.* PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma. *N Engl J Med* **379**, 341-351 (2018). https://doi.org:10.1056/NEJMoa1805131

3 Markowitz, J. *et al.* IFx-Hu2.0 phase I first in human study for unresectable melanoma for an intralesional "in-situ vaccine" approach. *Journal of Clinical Oncology* **40** (2022).