Trial of Sacituzumab Govitecan (IMMU-132) in Patients with Pretreated Metastatic Urothelial Cancer (PRUC): Interim Results

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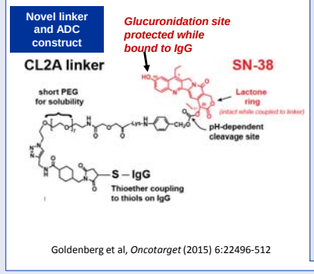
Background

- Most pts with metastatic urothelial carcinoma (mUC) pre-treated with standard 1st line therapy have limited options
- Five immune checkpoint inhibitors (I-O's) are now approved for patients with advanced bladder cancer following platinum chemotherapy, but only 15-25% respond.
- Sacituzumab govitecan (IMMU-132), an anti-Trop-2-SN-38 antibody-drug conjugate (ADC), has shown activity in many chemotherapy-pretreated cancers expressing Trop-2, as reported previously (Goldenberg et al, 2015) with promising initial signal in mUC (Faltas et al, 2016)
- Here we present an interim update of the safety and activity of IMMU-132 as therapy for chemotherapy-pretreated mUC patients (ClinicalTrials.gov, NCT01631552)

IMMU-132: Anti-Trop-2-SN-38 ADC

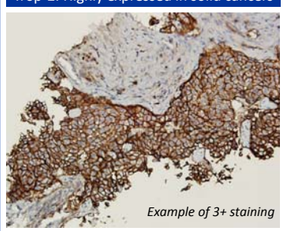


Goldenberg et al, *Oncotarget* (2015) 6:22496-512

- CL2A linker stabilizes lactone ring
  - pH-dependent release of SN-38
- IgG shields glucuronidation site
  - SN-38G serum levels << irinotecan, reducing diarrhea
- Site-specific coupling to 8 interchain thiols delivers high doses of SN-38
  - Average 7.6 SN-38 molecules/IgG

Trop-2 Expression Levels in This Study

Trop-2: Highly expressed in solid cancers



Example of 3+ staining

- Immunohistology (IHC) used polyclonal goat anti-human Trop-2 antibody
- Positive staining (>10% tumor cells) scored as 3+ (strong), 2+ (moderate), 1+ (weak), 0 (<10% stained)
- Archived tumor samples from 19 mUC patients scored as 3+ (74%), 2+ (16%), 1+ (5%), 0 (5%)
- Overall 90% of mUC patients had moderate-to-strong Trop-2 expression

Study Design

- Single arm, open-label study evaluating IMMU-132 in PRUC
- Patients (Key Entry Criteria)
  - Histologically confirmed urothelial cancer
  - Stage IV (metastatic) disease
  - Measurable disease by CT or MRI
  - Progressed during or after >1 prior therapies
  - ECOG: 0 or 1
- IMMU-132 administered at 10 mg/kg on days 1 and 8 every 21 days, repeated until PD or unacceptable toxicity
  - Toxicity managed by dose delay/reduction guidelines
  - G-CSF given at Investigators discretion
- Scan images for tumor response every 8 weeks
- Response evaluation as per RECIST v1.1 by Investigators. All responses had to be confirmed by scan at least 4 weeks later.
- Other evaluations: safety, immunogenicity to IMMU-132, PK (not reported here), Trop-2 expression in available tumor specimens by IHC staining

Demography & Baseline Characteristics (N=41)

Age, median (range)	68 years (50 to 91)
Gender M/F	38/3
ECOG (0/1)	9/32
Prior lines, median (range)	3 (1 to 6)
1	8 (20%)
2	8 (20%
3	15 (37%)
≥ 4	10 (24%)
Platinum combinations	38 (93%)
Immune checkpoint inhibitors (I-O's)	14 (34%)
Metastatic Sites	
Liver	13 (32%)
Bone	11 (27%)
Any visceral disease	29 (71%)

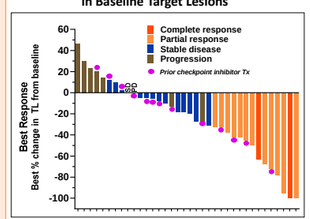
Best Response By RECIST 1.1

Response Assessments

ORR (ITT): 34% (14/41)

- 2 CR (confirmed)
- 12 PR (confirmed)
- 13 Stable Disease
  - (1 pt >30% and 3 pts ≥20% shrinkage)
- 9 Progression
- 5 inevaluable for response (withdrew early with no CT assessment; included as non-responders in ITT analysis)

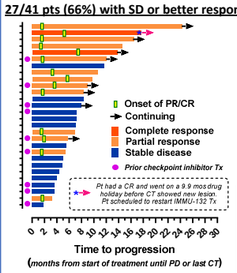
Waterfall Plot: Percent Reduction in Baseline Target Lesions



72% (26/36) of patients with at least one CT response assessment had reduction of target lesions (sum of diameters)

Long Term Disease Control

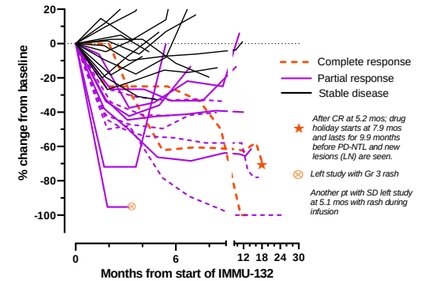
27/41 pts (66%) with SD or better response



- 14 Objective Responses (OR)
- Median Time to OR Onset 1.9 mos (range, 1.7 to 7.4 mos)
- K-M Median Duration of OR 12.6 mos (95% CI = 7.5, 12.9)
- 4 Long-Term ORs (> 1 yr), including 2 ongoing at 15 – 22 mos

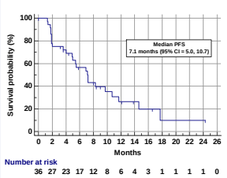
One pt, after achieving a CR at 5.2 mos, started a drug holiday at 7.9 mos, lasting 9.9 mos, until recently, 1 non-target LN progressed and 2 new LN were discovered. Patient is now scheduled to restart IMMU-132

Depth of Response Increases with Treatment



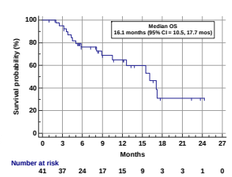
Progression-Free and Overall Survival (N=41)

Median PFS 7.1 months



80% Data Maturity (8/41 pts still on study and progression-free)

Median OS 16.1 months



46% Data Maturity (22/41 pts still alive on study)

Subgroup Response to IMMU-132

Prior Therapy	Best Response	Clinical Benefit Rate	Survival (Months)	
	ORR	(CR+PR+ SD ≥6 mos)	PFS Median (95% CI)	OS Median (95% CI)
Overall (N=41)	34% (14/41)	49% (20/41)	7.1 (5.0, 10.7)	16.1 (10.5, 17.2)
2nd line (N=8)	50% (4/8)	63% (5/8)	14.6 (5.5, 17.7)	Not met
≥ 3rd line (N=33)	30% (10/33)	45% (15/33)	6.9 (4.0, 9.7)	15.5 (8.9, 17.2)
Prior I-O (N=14)*	29% (4/14)	43% (6/14)	5.4 (1.9, 7.2)	Not met

*IMMU-132 was given as ≥ 4th line in 11/14 pts receiving checkpoint inhibitors (I-O's) including all 4 responders

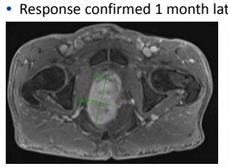
Adverse Events >15% (Regardless of Causality)

Event	All Grades (%)	Grades 3/4 (%)
Diarrhea	63	7
Nausea	56	-
Neutropenia	49	39
Fatigue	49	7
Constipation	37	-
Rash	32	2
Anemia	29	10
Anorexia	27	-
Alopecia	27	-
Back Pain	20	-
Vomiting	17	2
Fever	17	-
UTI	17	2

Serious Events
9/41 pts (22%) had ≥ 1 SAEs considered at least possibly treatment related
Febrile neutropenia (n=2)
Neutropenia (n=2)
Diarrhea (n=2)
Bacteremia (n=1)
UTI (n=1)
Sepsis (n=1)
Pouchitis (n=1)
Fatigue (n=1)

Partial Response After 4 Prior Lines (2 I-O's)

- 58 y-o male with inoperable, high-grade papillary UC, treated with cisplatin/ gem/paclitaxel (1st), gemcitabine (2nd), atezolizumab (3rd), nivolumab (4th)
- Non-responsive to both I-Os
- Responded to IMMU-132 with 72% shrinkage
- Response confirmed 1 month later (Jan. 2017)

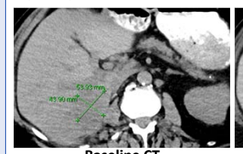


Baseline MRI
Pelvic Tumor: 6.4 cm

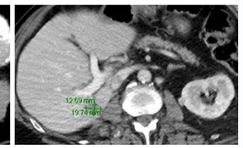
1st Response Assessment
Pelvic Tumor: 1.6 cm

31% Reduction After Failing 4 Prior Lines (1 I-O)

- 83 y-o male with high-grade metastatic UC, primarily invading perinephric soft tissue and surgically resected in September 2015
- Unresponsive to all prior lines (carboplatin & gemcitabine, paclitaxel, pembrolizumab, and investigational adenosine A2A receptor)
- Responded to IMMU-132 with liver (5.4 & 1.7 cm), lung (2.0 cm) and bone (6.0 cm) metastases reduced by 31% in February 2017



Baseline CT
Liver tumor: 5.4 cm



Confirmatory CT
Liver tumor 2.0 cm

Summary

- 41 patients enrolled (80% ≥ 2 lines of prior therapy)
- 10 mg/kg IMMU-132 given days 1 & 8 of 21-day repeated cycles
- Median number of doses received: 12 (range, 1-58)
- Best response: 2 CR, 12 PR, 13 SD, 9 PD, 5 IE
- Objective Response Rate (ITT): 34% (14/41)
  - 1 prior chemotherapy: 50% (4/8)
  - 2 to 6 prior chemotherapies: 30% (10/33)
  - Prior I-O: 29% (4/14)
- Median duration of response: 12.6 months (95% CI: 7.5, 12.9)
- Clinical benefit rate (CR+PR+SD≥6 months): 49%
- Median PFS: 7.1 months (95% CI, 5.0, 10.7)
- Median OS: 16.1 months (95% CI, 10.5, 17.7)
- Major Grade ≥ 3 toxicity: neutropenia, 39%; anemia, 10%; fatigue, 10%; diarrhea, 7%
- No immune reaction to ADC or antibody response

Conclusions

- **Sacituzumab govitecan (IMMU-132) is an active and promising agent with ORR of 34% in ITT population (response duration 12.6 mo), good overall tolerance, median PFS 7.1 mo, median OS 16.1 mo in patients relapsed/refractory to chemotherapy and immune checkpoint inhibitors**

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Sacituzumab govitecan (IMMU-132) is an investigational agent. Drs. Wegener, Maliakal, Mudenda, Sharkey and Goldenberg are or were employees of Immunomedics which provided funding for the other investigators for the conduct of this trial.