ManagingMDS
Myelodysplastic Syndrome Community

SGI-110 + Atezolizumab in Relapsed/Refractory MDS

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Hi there, my name is Casey O'Connell and I am an Associate Professor with the Jane Anne Nohl Division of Hematology at the Keck School of Medicine of USC. I'm also the Director of the Gehr Cures Myeloid Malignancy program there. Today I have the pleasure of presenting to you some data that we presented at the International MDS meeting in Denmark Copenhagen last month.

Disclosures

- Astex/Otsuka: Scientific Advisory Board honoraria
- Astex/Otsuka: Research support (study drug)
- Genentech: Research support (study drug)

STUDY FUNDING

- Van Andel Research Institute-Stand Up to Cancer (S↑2C) Collaboration

Here are my disclosures. I have done scientific advisory boards with Otsuka, Astex, and both Astex and Genentech have provided a drug for the research I'm about to go through with you. Our study is funded by the Van Andel Research Institute in collaboration with Stand Up to Cancer.

Relapsed/Refractory MDS: An Unmet Need

No FDA-approved therapies for MDS after HMAs fail

- **5- to 6-month median overall survival in this patient population**

Why do HMAs fail?

- **Rapid endogenous deamination? Or…**
- **Is immune exhaustion an issue in MDS?**

Relapsed/refractory MDS or myelodysplastic syndrome is really an unmet need in cancer therapy. There are no FDA-approved treatments for MDS after hypomethylating agents fail, and as you know our patients have only a 5-6 month median overall survival expectation after HMAs fail. So one of the questions we wanted to address is why did they fail? One idea is that the body rapidly deaminates the hypomethylating agents and therefore, does not allow them to get to the developing cancer cell in the bone marrow. Another thought is that immune exhaustion occurs over time in patients with MDS.

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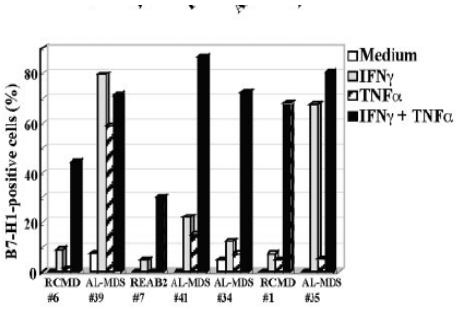
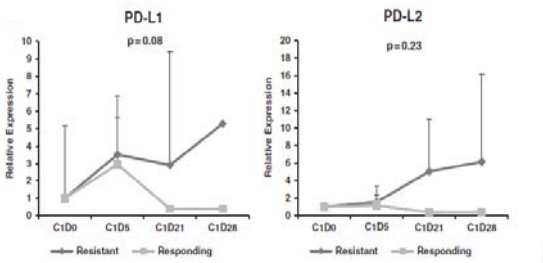
PD-L1/PD-L2 Expression in MDS

***PD-L1* expression on MDS blasts induced by interferon g and TNFa**



***PD-L1* and *PD-L2* expression on MDS blasts induced by DNMTi in vivo**



Kondo A, et al. *Blood.* 2010;116(7):1124-1131.; Yang H, et al. *Leukemia*. 2014;28(6):1280-1288.

With regard to immune exhaustion for patients with MDS, there are published data suggesting PDL1 and PDL2 expression is present on MDS and AML blasts. In the left-hand column you see data showing MDS blasts expressing PDL1 after exposure to interferon and TNF alpha. On the right you see expression of both PDL1 and PDL2 on MDS blasts after exposure to hypomethylating agents.

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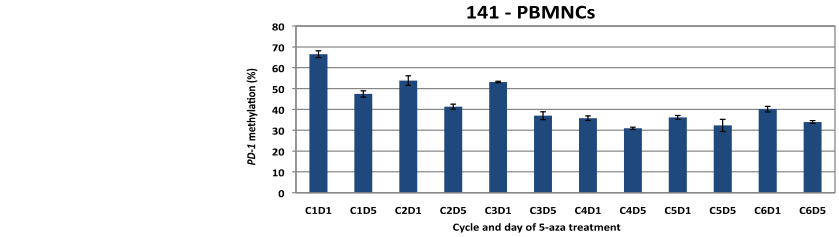
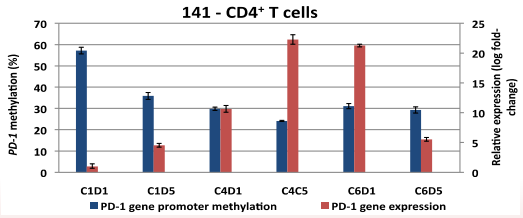
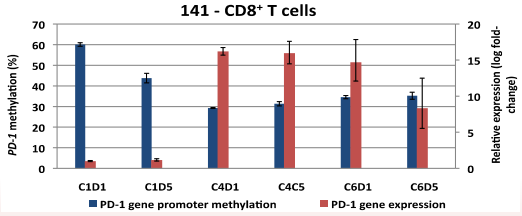
PD-1 Methylation and Expression Before/During AZA







Genome Laboratory, Dept. of Hematology, Rigshospitalet.
Ørskov AD, et al. *Oncotarget.* 2015;6(11):9612-9626.

My colleagues in Denmark have studied PD1 methylation and T cells and have demonstrated that exposure to azacitidine does appear to result in increased PD1 expression which correlates with promoter methylation. This is captured on the lower with CD4+ T cells where PD1 gene expression is represented by the red bars and promoter methylation by the blue bars. On the right lower aspect of the slide, you see the same appearance of gradual increased expression of PD1 with decreased promoter methylation induced by azacitidine in CD8+ T cells.

Immune Checkpoint Inhibitors (ICI): Monotherapy in MDS

Drug (N)	ORR (CR + Other)	TEAEs	Survival	Mechanism
Nivolumab (15)[1]	13% (0%)	Grouped	25% 1 year	Anti-PD1
Pembrolizumab (28) - KEYNOTE[2]	26% (4%)	36%	49% 6 months	Anti-PD1
Ipilimumab (29)[3]	7% (3%)	21% (≥2)	Median 294 d	Anti-CTLA4
Ipilimumab (20)[1]	35% (15%)	Grouped	45% 1 year	Anti-CTLA4

[1]Garcia-Manero G, et al. *Blood*. 2018;132:465. [2]Garcia-Manero G. *Blood.* 2016;128:345. [3]Zeidan A, et al. *Clin Can Res*. 2018;24 (15):3519-3522.

So, based on these data, other investigators have initiated clinical trials and the summary is here showing monotherapy with immune checkpoint inhibitors for patients with myelodysplastic syndrome. There have been four studies with nivolumab in the top row, pembrolizumab in the second row, that's the keynote study that was presented by Dr. Garcia-Manero with updates at this last meeting as well, ipilimumab, a CTL4 inhibitor, shown in the bottom two rows. The responses have been quite modest, ranging from 7% to 35%, and there has been the suggestion that perhaps these would do better if combined with hypomethylating agents.

SGI-110 + Atezolizumab in Relapsed/Refractory MDS

ICI in Combination with HMAs in R/R MDS

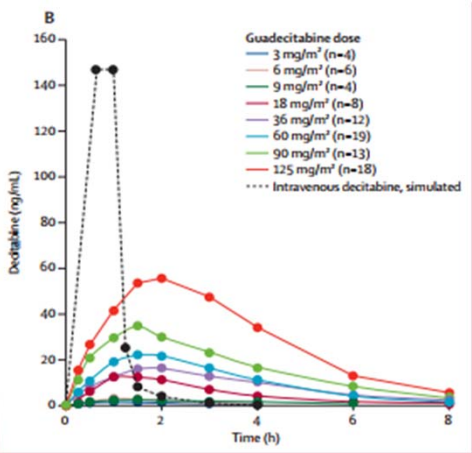
HMA	ICI	N/ORR%	AEs	Biomarkers
5-azacitidine[1]	Atezolizumab	21 U/**62**	29% fatal	CD34+ and T cell PD-L1 – No correlation
5-azacitidine[1]	Atezolizumab	11 R/R/**9**	18% fatal	CD34+ and T cell PD-L1 – No correlation
5-azacitidine[2]	Nivolumab Ipilimumab	20 U+R/**75** 21 U+R/**71**	One fatal AE	Not published R/R mos 8 mos
Guadecitabine[3]	Atezolizumab	21 R/R/**33**	Two fatal AE	Pending

[1]Gerds, et al. *Blood*. 2018;132. [2]Garcia-Manero G, et al. *Blood*. 2018;132:465. [3]O'Connell, et al. 2019 MDSF-Copenhagen.

Here is a table showing the current data that we have using immune checkpoint inhibitors in combination with hypomethylating agents, particularly focusing on relapsed and refractory MDS patients. In the first row we see 5 azacitidine with atezolizumab, these were untreated patients actually, showing 62% overall response rate but a very high rate of fatal adverse events. In the second row, the same combination with relapsed/refractory MDS patients showing only a 9% overall response rate but a much lower incidence of fatal adverse events. In the last two rows, you'll see the 5 azacitidine combined with nivolumab or ipilimumab, and then guadecitabine, our study, combined with atezolizumab. Interestingly that third row shows some very promising overall response rates when untreated and relapsed/ refractory patients were combined, but these data are not yet published.

SGI-110 + Atezolizumab in Relapsed/Refractory MDS

SGI-110 (Guadecitabine)



- Decitabine prodrug
- **Resists deamination**
  - Longer half-life
- Myelosuppressive
- Studies ongoing in R/R AML and R/R MDS

We sought to combine a more durable hypomethylating agent known as guadecitabine, originally SGI-110, that is a prodrug for decitabine. It resists deamination resulting in a longer half-life for the drug, and as you can see here, the black dotted line shows us the half-life of traditional decitabine at 20 mg/m^2 and the colored dots show different doses of guadecitabine. The biologically effective dose for guadecitabine appears to be 60 mg/m^2 shown in the turquoise line, and this also appeared to have a very good demethylation profile as evidenced by line 1 demethylation in published studies.

SGI-110 (Guadecitabine): Clinical Experience in MDS

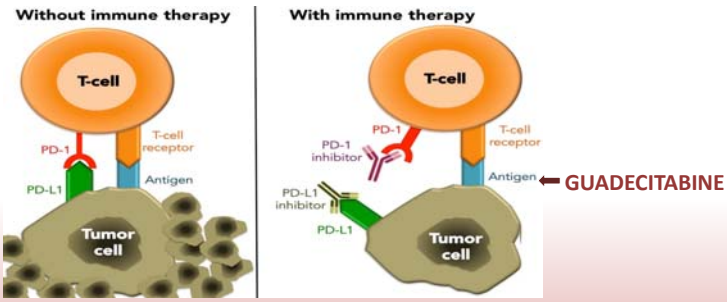
- SGI-110 phase II in HMA-naive (51) and R/R MDS (53):
  - Median age 72
- For R/R MDS patients:
  - ORR: 23 (43%)
  - CR: 2 (4%)
  - Median OS: 352 days (11.7 months)
  - 24% drug-related SAEs, two fatal

Garcia-Manero G, et al. *Lancet.* In press 2019.

So the clinical experience of this drug as a monotherapeutic approach to myelodysplastic syndrome is now published or in press in *Lancet*. The phase 2 study of guadecitabine in HMA-naïve patients and relapsed/refractory patients demonstrated an overall response rate among the relapsed/refractory group of 43% with two patients achieving a complete remission for a complete remission rate of only 4%. Median overall survival is almost one year, and there were 24% patients experiencing drug related SAEs, two of which were felt to be fatal.

Background: Atezolizumab

- Monoclonal antibody targets PD-L1 (programmed death receptor ligand-1)
- FDA approved for urothelial, NSCLC, small-cell lung cancer
- Cytopenias, infections not a significant toxicity



Now we wanted to take the drug a step further by impacting this concept of immune exhaustion and adding atezolizumab, this is a monoclonal antibody that targets PDL1, programmed death receptor ligand-1. This is thought to interact, as shown in the cartoon below, with T cells expressing PD1 and turning those T calls off to put them in a senescence or quiescence state. The drug is approved by the FDA for urothelial, non-small cell, and small cell lung cancer. Since cytopenia and infections are not a significant toxicity of the drug, we felt there would be no significant overlapping issues.

Phase I/II Trial: SGI-110 + Atezolizumab in Relapsed/Refractory MDS

- Safety and tolerability of the combination atezolizumab + guadecitabine in patients with R/R MDS
  - DLTs
- Efficacy of the combination in R/R MDS
  - ORR (mCR + CR + HI)
  - OS
- REMOVED: Phase II cohort two untreated MDS
- Sponsor: Van Andel Research Institute and Stand Up to Cancer (S↑2C)
  - Sites: University of Southern California, Temple/Fox Chase Cancer Center, University of Maryland, Righospitalet/Epi-Genome Lab

We designed a phase 1/2 trial with SGI-110 and atezolizumab only for relapsed/refractory myelodysplastic syndrome patients, and we sought to look at safety and tolerability of the combination as measured by dose-limiting toxicities. We are also interested, of course, in the efficacy of this combination as measured by the overall response rate as well as overall survival. We were going to have an untreated cohort which has subsequently been removed. The sponsor of this study as mentioned, is the Van Andel Research Institute in conjunction with Stand Up to Cancer and it is a multi-center study with our patients here at University of Southern California as well as enrollment at Temple/Fox Chase, the University of Maryland, and Rigshospitalet in Copenhagen, Denmark which is doing the correlative studies.

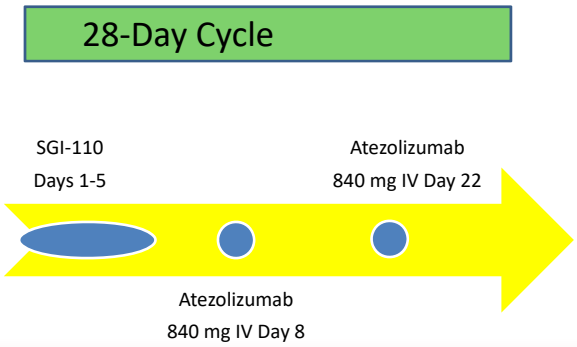
SGI-110 + Atezolizumab in Relapsed/Refractory MDS

Phase I/II Trial: SGI-110 + Atezolizumab in Relapsed/Refractory MDS

Phase I design:

- Atezolizumab
  - Fixed dose 840 mg q 2 weeks
- SGI-110 30 mg/m^2 in three patients
- If no toxicity escalate to
  - SGI-110 60 mg/m^2 in three patients
- If no toxicity confirm with
  - SGI 110 60 mg/m^2 with three patients

Phase II Design (n=30)



The trial design has a standard phase 1 aspect with the fixed dose of atezolizumab at 840/mg every two weeks with the dose minus one level of SGI-100 at 30 mg/m^2. This was given to three patients and since there was no toxicity, we escalated to the biologically effective dose of SGI-110 at 60 mg/m^2 in conjunction with the same fixed does of atezolizumab in three additional patients. There was no toxicity, so we confirmed with an additional three patients before moving into phase 2.

SGI-110 + Atezolizumab in Relapsed/Refractory MDS

Patient Characteristics, N=21 (6 Phase I, 15 Phase II)

Median Age	73 (range, 55-86)
Female	10 (48%)
Prior HMA:	
5-azacitidine	19
Decitabine	5
Guadecitabine (SGI-110)	1
Prior lines of therapy	
1	17
2	4
Primary Refractory to HMA	9 (42.8%)

At this point, we have 21 patients who have enrolled in the trial, six in phase 1 and 15 that are included as phase 2 treated patients. The median age of our cohort is 73, with a range of 55-86 years old; 48% of the patients are female. In terms of prior therapies in our patient cohort, 19 received 5-azacitidine, five had received decitabine, and one had actually received guadecitabine on a clinical trial; 17 of the 21 patients had one line of prior therapy and four had two lines. Approximately 43% of our group had primary refractoriness to the hypomethylating agent they were treated with.

Adverse Events (Possibly, Probably, or Definitely Delated) or Death

	Non-Immune	Immune-Related
Related Grade 3	12	5
Related Grade 4	12	1
FATAL Adverse Event	1	1
FATAL Disease Progression	1	

No DLTs in Phase I

Immune AEs:

- Grade 2: arthritis (1)
- Grade 3: diarrhea (1), encephalitis (2), pneumonitis (1)
- Grade 5: One brainstem herniation (unlikely related)
- One respiratory failure (possibly related, autoimmune pneumonitis)

Adverse events or death. We had no DLTs in phase 1. In terms of related grade 3 events, there were12 non-immune and five immune related. In terms of related grade 4 events, there were 12 non-immune and one immune related. There was one non-immune fatal adverse event and one fatal disease progression, with one patient having an immune related fatal adverse event that was felt to be possibly related due to autoimmune pneumonitis.

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SGI-110 + Atezolizumab Best Responses

	N=21 (%)
ORR	**7 (33.3)**
CR	1 (4.8)
mCR	3 (14.3)
HI-E	2 (9.5)
HI-P	0
HI-N	1 (4.8)
Stable disease	5 (23.8)

In terms of response to the combination of SGI or guadecitabine with atezolizumab, our overall response rate in this pretreated MDS population was 33%, we had one patient who has achieved a true CR and three patients who achieved a marrow CR. In terms of hematologic responses, there were three patients with a hematologic improvement and five patients, or 24%, with stable disease.

Correlative Data

- RNA sequencing of upregulated genes
- T cell repertoires
- T cell receptor antigen recognition epitopes
- T cell and marrow methylation patterns
- IHC evaluation of bone marrows – three hematopathologists reviewing and scoring

We are pursuing correlative data, including RNA sequencing of upregulated genes, T cell repertoires, T cell receptor antigen recognition epitopes, T cell and marrow methylation patterns, and immunohistochemical evaluation of bone marrow biopsies. We hope that this will help us identify the patients that may benefit from a combination like this, particularly those patients that we have seen, as have colleges on other clinical trials, who have very long-term stable disease which may not count as a complete remission or within the IWG criteria for remission, but which may in fact ultimately translate to improved median overall survival for this patient population.

Thank You

- VARI-SU2C team
- Grønbæk lab and collaborators
- Co-Authors: Grønbæk, Kropf, Baer, Duong, Syed, Buit, Rogers
- Astex & Genentech – provision of study drugs
- OUR PATIENTS

I'd like to thank you for your attention. I am very grateful to the Van Andel Research Institute/Stand Up to Cancer team, as well as Dr. Grønbæk and her colleagues, my co-authors on this abstract who helped to enroll patients, and of course to our patients who are living with this disease that we are trying so hard to fight. Thank you.