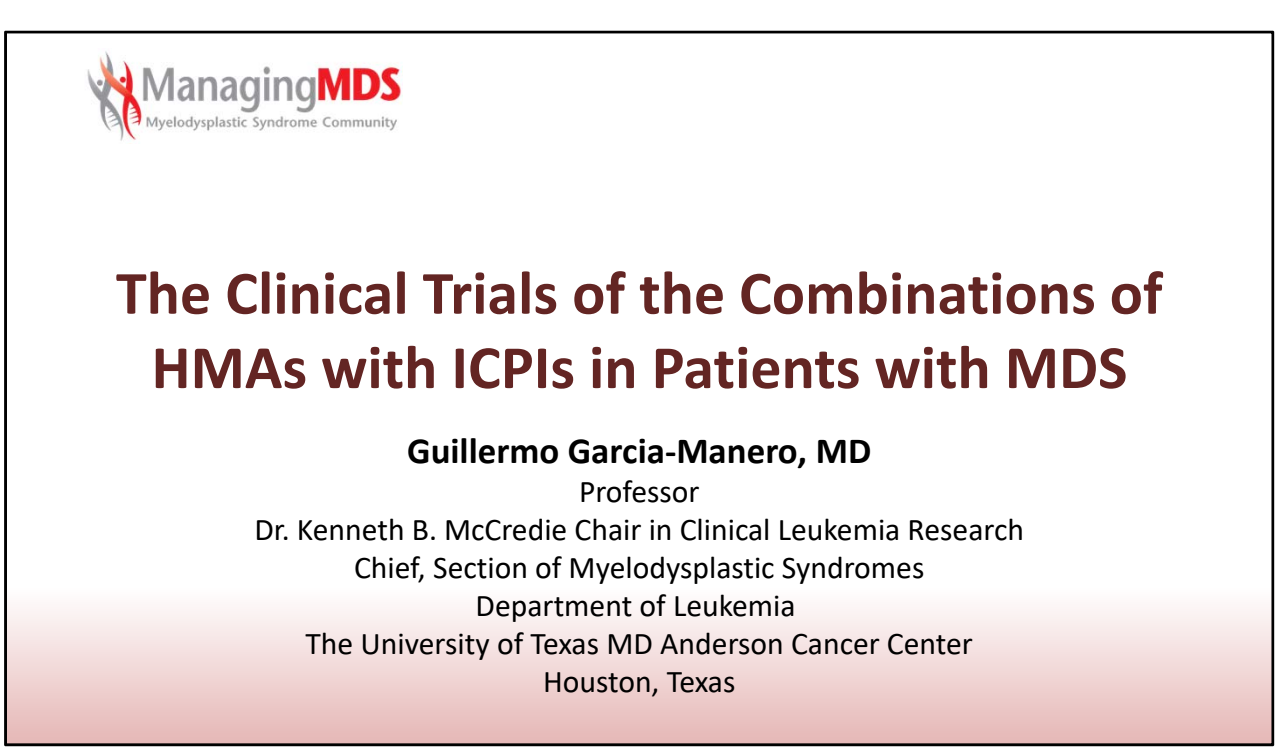
The Clinical Trials of the Combinations of HMAs with ICPIs in Patients with MDS



Hello. I am Guillermo Garcia-Manero, professor in the Department of Leukemia at the University of Texas MD Anderson Cancer Center in Houston. Thank you for this opportunity.

I'm going to discuss today a presentation that I had the opportunity to give at the bi-annual MDS meeting in Copenhagen. The topic was, *Studies of Clinical Trials of the Combination of Hypomethylating Agent with Immune Checkpoint Inhibitors in Patients with MDS*. The first question is, if there is a rationale for the use of these compounds in patients with MDS? As the audience probably very well knows, these immune checkpoint inhibitors, like CTLA-4 inhibitors, PD-1, PD-L1 inhibitors, are approved for a number of solid tumor malignancies. The question is why to use it in MDS and potentially, acute myelogenous leukemia?

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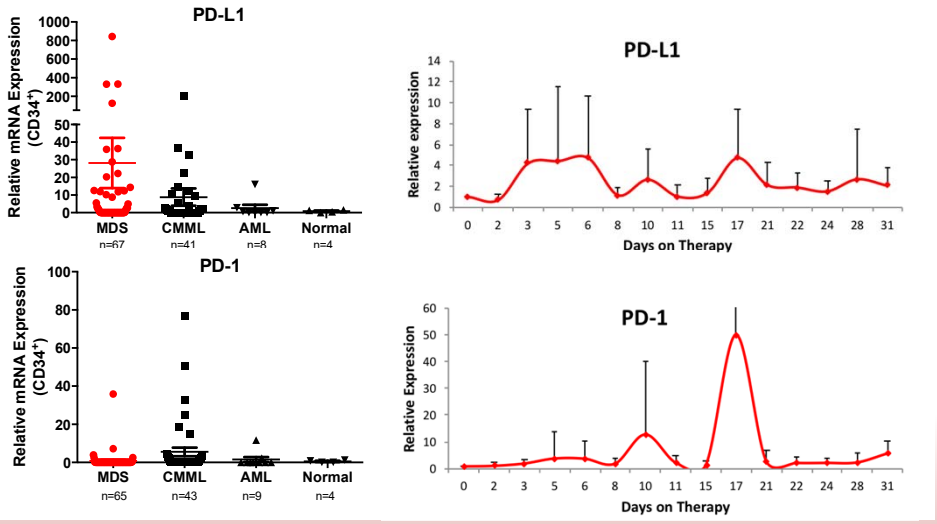
Sequential PD1/PDL1 Activation Post HMA



Yang H, et al. *Leukemia*. 2014;28(6):1280-1288.

A number of years ago, we conducted a very simple experiment where we studied the expression, both at the RNA and at the protein level of PD-1, PD-L1, PD-L2, and CTLA-4 in patients with MDS and AML. We found that indeed, these targets are expressed in the myeloid compartment of this disease, and what was more important, was in patients that had been treated with a hypomethylating agent like azacitidine or decitabine, there was a significant overexpression of these molecules. Meaning that treatment with these hypomethylating agents could indeed actually prime these patients to subsequent benefit from the immune checkpoint inhibitor. That data was published in the *Journal of Leukemia* a few years ago and has served as the basis for multiple clinical trials, not only here at MD Anderson but in multiple other centers.

The Clinical Trials of the Combinations of HMAs with ICPIs in Patients with MDS

Safety of Pembrolizumab in Patients With Myelodysplastic Syndrome After Failure of Hypomethylating Agents: A Phase 1b Study

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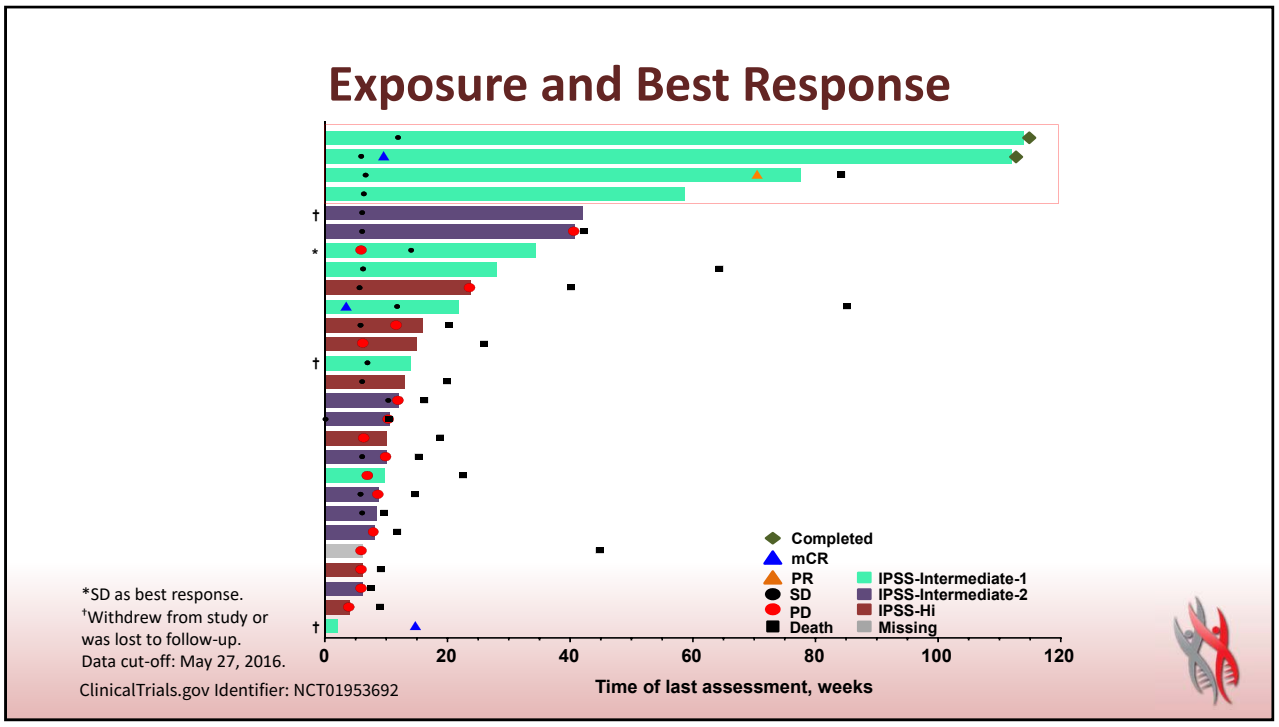
Garcia-Manero G, et al. *Blood*. 2016;128:345.

The very first study that we conducted was with a compound known as pembrolizumab, that is again a compound accepted and approved for multiple solid tumor malignancies, not for MDS or AML. This was a proof of principle trial using monotherapy with these immune checkpoint inhibitors in patients with hypomethylating agent failure high-risk myelodysplastic syndrome. What we observed in this trial was around 20 patients, this was a multicenter trial, that the toxicity profile of the single agent immune checkpoint inhibitor was quite acceptable.

The Clinical Trials of the Combinations of HMAs with ICPIs in Patients with MDS



Interestingly, even if we did not see any clear responses following a standard criteria, there are two patients that I am aware of that are long-term survivors of this approach in this context of HMA failure that as the audience knows, carries a survival of around four to six months. So, we were intrigued by the signal in terms of duration of survival and the tolerability of this compound, at least as monotherapy, in patients with MDS.

The Clinical Trials of the Combinations of HMAs with ICPIs in Patients with MDS

A Phase II Study of Nivolumab or Ipilimumab with or without Azacitidine for Patients with Myelodysplastic Syndrome

Guillermo Garcia-Manero, Koji Sasaki, Guillermo Montalban-Bravo, Naval G. Daver, Elias J. Jabbour, Yesid Alvarado, Courtney D. DiNardo, Farhad Ravandi, Gautam Borthakur, Prithviraj Bose, Naveen Pemmaraju, Kiran Naqvi, Jorge E. Cortes, Tapan M. Kadia, Marina Y. Konopleva, Simona Colla, Hui Yang, Caitlin R. Rausch, Yvonne Gasior, Carlos E. Bueso-Ramos, Rashmi Kanagal-Shamanna, Keyur P. Patel, Hagop M. Kantarjian

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Garcia-Manero G, et al. *Blood*. 2018;132:465.

With that data, we embarked in a much more aggressive clinical trial that was the focus of the presentation in Copenhagen where we showed more updated results of the combination of azacitidine with either nivolumab or ipilimumab for patients with MDS. This is a complex phase I, II clinical trial that has six cohorts.

The Clinical Trials of the Combinations of HMAs with ICPIs in Patients with MDS

ICPI in MDS: Eligibility Criteria

- Age ≥18 years with WHO MDS
- Both untreated and HMA failure disease
- Acceptable PS, renal and hepatic functions
- No prior history of inflammatory or autoimmune disease
- HIV disease or active hepatitis C
- For HMA failure cohort:
  - No more than four months since last cycle of HMA
  - No other therapy after HMA exposure

ClinicalTrials.gov Identifier: NCT01953692

They are divided into groups, one for patients that had not received prior therapy and a group for patients that had already been exposed to hypomethylating agents, the so called “HMA failure” patients.

The Clinical Trials of the Combinations of HMAs with ICPIs in Patients with MDS

ICPI in MDS: Study Design

HMA failure cohorts	Previously untreated cohorts
Cohort #1: Single-agent nivolumab	Cohort #4: 5-azacitidine + nivolumab
Cohort #2: Single-agent ipilimumab	Cohort #5: 5-azacitidine + ipilimumab
Cohort #3: Ipilimumab + nivolumab	Cohort #6: 5-azacitidine + ipilimumab + nivolumab

- Each cohort max of N=20 patients
- In HMA failure cohorts: add back azacitidine after 6 cycles of ICPI if no response
- Stopping rules for toxicity and response

ClinicalTrials.gov Identifier: NCT01953692

Then, each of these two subsets is divided into three cohorts. In one cohort, we are going to try nivolumab alone for HMA failure or ipilimumab alone for HMA failure, and then a final cohort of combination of nivolumab and ipilimumab for the hypomethylating failure. For the patients that had not been previously treated, we had again three cohorts: azacitidine/nivolumab, azacitidine/ipilimumab, and then finally azacitidine/nivolumab/ipilimumab. Basically, we started with one, completed the cohort with 20 patients and then moved to the second cohort and third cohort, and the studies in the frontline and in the relapsed setting were in parallel. The study now is completed, and we are expanding this cohort and we think that the data is of great interest. So, the first thing of interest was with those patients with relapsed/ refractory disease to hypomethylating agent. What we saw with nivolumab was very similar to what we had seen with pembrolizumab was very limited activity and we could not complete that cohort because we had predefined stopping rules for the nivolumab cohort.

The Clinical Trials of the Combinations of HMAs with ICPIs in Patients with MDS

ICPI in MDS: Response Rates

Response	Frontline		HMA failure	
	Nivo + AZA N = 20	Ipi + AZA N = 21	Nivo N = 15	Ipi N = 20
ORR	14 (70)	13 (62)	0 (0)	6 (30)
CR	8 (40)	3 (14)	0 (0)	0 (0)
mCR + HI	2 (10)	0 (0)	0 (0)	1 (5)
mCR	3 (15)	7 (33)	0 (0)	3 (15)
HI	1 (5)	3 (14)	0 (0)	3 (15)
SD	0 (0)	1 (5)	0 (0)	0 (0)
NR	5 (25)	5 (24)	15 (100)	13 (65)

- Not evaluable: three patients
- Median number of cycles: 4 (range 1-29)
- Median number of cycles to response: 3 (range 1-15)

ClinicalTrials.gov Identifier: NCT01953692

Interestingly though, when we treated the cohort with patients with ipilimumab, we actually saw a response rate of around 30% and a duration of response that was along the lines with what we have seen before with pembrolizumab or potentially even longer, and potentially longer than expected compared to the prior experience in patients with HMA failure. Now, we had also performed a combination of nivolumab-ipilimumab in the HMA failure. This data is not that mature. We have seen responses but of course, additive toxicity when combining both immune checkpoint inhibitors.

When we move to the frontline setting, we saw a very interesting signal. We saw very high response rates with both the combination of azacitidine and nivolumab cohort, a very high response rate also with the combination of azacitidine and ipilimumab, but what was more intriguing from this initial clinical trial, was that the median survivor of those patients with high-risk disease that were treated with azacitidine and ipilimumab, had not been reached and the follow up at that time of presentation in Copenhagen, was close to two years. The follow up is quite prolonged for this group of patients, yet the survival was probably the best that we have seen at MD Anderson with this type of doublets. We have a high response rate and duration of those responses.

The Clinical Trials of the Combinations of HMAs with ICPIs in Patients with MDS

ICPI in MDS: Toxicities

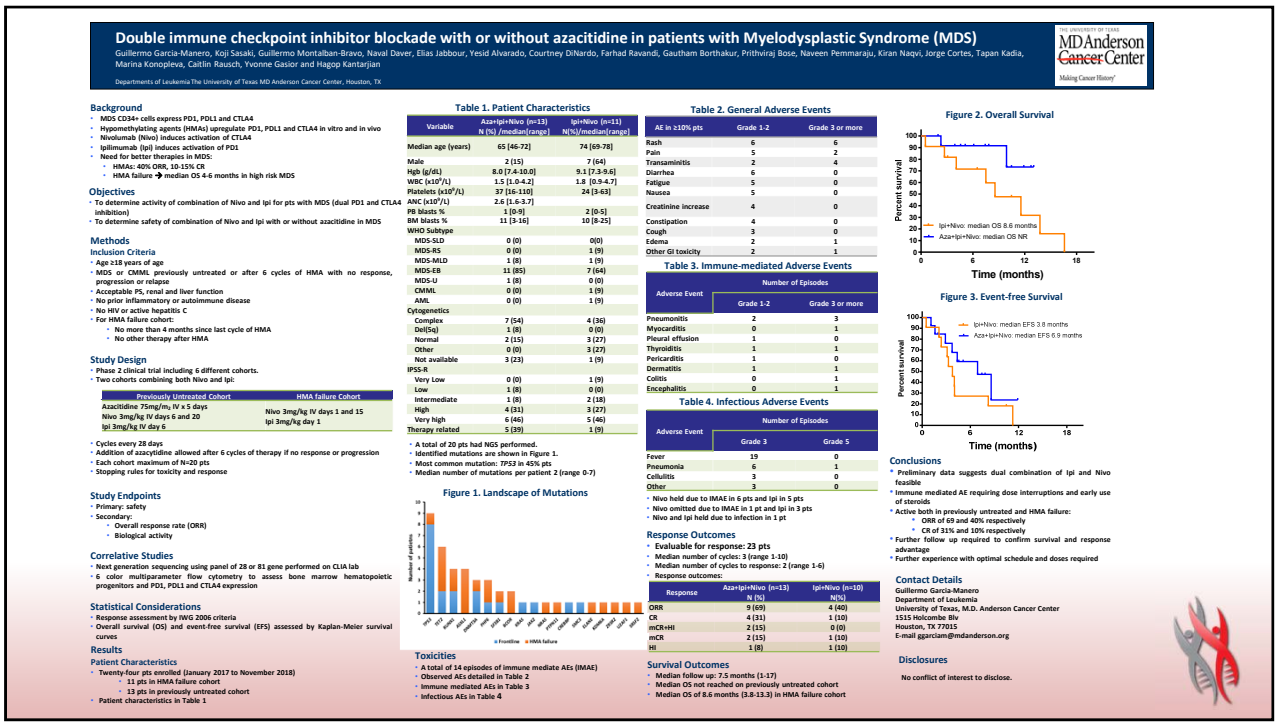
	Frontline				HMA failure			
	Nivo + AZA N = 20		Ipi + AZA N = 21		Nivo N = 15		Ipi N = 20	
	All	G3/4	All	G3/4	All	G3/4	All	G3/4
Infection	6 (30)	5 (25)	5 (24)	4 (19)	6 (40)	6 (40)	7 (35)	6 (30)
Rash	5 (25)	0	8 (38)	1 (5)	1 (7)	0	7 (35)	1 (5)
Fatigue	6 (30)	0	1 (5)	0	6 (40)	0	5 (25)	0
Musculoskeletal pain	7 (35)	0	4 (19)	2 (10)	0	0	4 (20)	0
Pruritus	1 (5)	0	4 (19)	0	1 (7)	1 (7)	5 (25)	0
Transaminitis	2 (10)	2 (10)	2 (10)	2 (10)	1 (7)	0	3 (15)	2 (10)
Constipation	3 (15)	0	4 (19)	0	1 (7)	0	0	0
Diarrhea	1 (5)	0	3 (14)	0	1 (7)	0	2 (10)	0
Nausea	2 (10)	0	3 (14)	0	1 (7)	0	1 (5)	0
Anorexia	3 (15)	0	1 (5)	0	0	0	2 (10)	0

- Other G3/4: AKI, 2 in Ipi; hemolysis, 1 in Ipi; colitis, 1 in Nivo
- Grade 2 hypophysitis: 1 in Ipi, Ipi + AZA, and Novo + AZA, respectively

ClinicalTrials.gov Identifier: NCT01953692

That said, there are things that are still limiting. They brought applicability of this experience and mainly, that these combinations can have significant toxicities that are referred by the experts sometimes as ITs. Basically, immune reactions to these immune checkpoint inhibitors that can be quite toxic if the doctor is not alert and starts preventive approaches like high-dose steroids fast in the course of this disease. In our experience, the most common toxicity was actually pneumonitis. Sometimes, this can be difficult to assess because it can be compounded with pneumonia or infectious complications. Many times, physicians will hesitate before starting steroids and in our experience, what these patients need that may be a little bit different than the standard of care is actually to start these steroids early on as soon as you have some type of unusual inflammatory complication or pneumonitis. Other inflammatory conditions could be colitis, diarrhea, thyroiditis, but there are sometimes neurotoxicity that is not very frequent but could be quite severe. The data shows a very high response rate, long survival compared to our historical experience, but the toxicity profile that requires some experience and potentially education if this is going to move forward.

The Clinical Trials of the Combinations of HMAs with ICPIs in Patients with MDS



Double immune checkpoint inhibitor blockade with or without azacitidine in patients with Myelodysplastic Syndrome (MDS)

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Background

- MDS CD34+ cells express PD1, PDL1 and CTLA4
- Hypomethylating agents (HMAs) upregulate PD1, PDL1 and CTLA4 in vitro and in vivo
- Nivolumab (Nivo) induces activation of CTLA4
- Ipilimumab (Ipi) induces activation of PD1
- Need for better therapies in MDS:
  - HMAs: 40% ORR, 10-15% CR
  - HMA failure → median OS 4-6 months in high risk MDS

Objectives

- To determine activity of combination of Nivo and Ipi for pts with MDS (dual PD1 and CTLA4 inhibition)
- To determine safety of combination of Nivo and Ipi with or without azacitidine in MDS

Methods

Inclusion Criteria

- Age ≥18 years of age
- MDS or CMML previously untreated or after 6 cycles of HMA with no response, progression or relapse
- Acceptable PS, renal and liver function
- No prior inflammatory or autoimmune disease
- No HIV or active hepatitis C
- For HMA failure cohort:
  - No more than 4 months since last cycle of HMA
  - No other therapy after HMA

Study Design

- Phase 2 clinical trial including 6 different cohorts.
- Two cohorts combining both Nivo and Ipi:

Previously Untreated Cohort	HMA failure Cohort
Azacitidine 75mg/m^2 IV x 5 days Nivo 3mg/kg IV days 6 and 20 Ipi 3mg/kg IV day 6	Nivo 3mg/kg IV days 1 and 15 Ipi 3mg/kg day 1

- Cycles every 28 days
- Addition of azacytidine allowed after 6 cycles of therapy if no response or progression
- Each cohort maximum of N=20 pts
- Stopping rules for toxicity and response

Study Endpoints

- Primary: safety
- Secondary:
  - Overall response rate (ORR)
  - Biological activity

Correlative Studies

- Next generation sequencing using panel of 28 or 81 gene performed on CLIA lab
- 6 color multiparameter flow cytometry to assess bone marrow hematopoietic progenitors and PD1, PDL1 and CTLA4 expression

Statistical Considerations

- Response assessment by IWG 2006 criteria
- Overall survival (OS) and event-free survival (EFS) assessed by Kaplan-Meier survival curves

Results

Patient Characteristics

- Twenty-four pts enrolled (January 2017 to November 2018)
  - 11 pts in HMA failure cohort
  - 13 pts in previously untreated cohort
- Patient characteristics in Table 1

Table 1. Patient Characteristics

Variable	Aza+Ipi+Nivo (n=13) N (%) /median[range]	Ipi+Nivo (n=11) N(%)/median[range]
Median age (years)	65 [46-72]	74 [69-78]
Male	2 (15)	7 (64)
Hgb (g/dL)	8.0 [7.4-10.0]	9.1 [7.3-9.6]
WBC (x10^9/L)	1.5 [1.0-4.2]	1.8 [0.9-4.7]
Platelets (x10^9/L)	37 [16-110]	24 [3-63]
ANC (x10^9/L)	2.6 [1.6-3.7]	
PB blasts %	1 [0-9]	2 [0-5]
BM blasts %	11 [3-16]	10 [8-25]
WHO Subtype		
MDS-SLD	0 (0)	0(0)
MDS-RS	0 (0)	1 (9)
MDS-MLD	1 (8)	1 (9)
MDS-EB	11 (85)	7 (64)
MDS-U	1 (8)	0 (0)
CMML	0 (0)	1 (9)
AML	0 (0)	1 (9)
Cytogenetics		
Complex	7 (54)	4 (36)
Del(5q)	1 (8)	0 (0)
Normal	2 (15)	3 (27)
Other	0 (0)	3 (27)
Not available	3 (23)	1 (9)
IPSS-R		
Very Low	0 (0)	1 (9)
Low	1 (8)	0 (0)
Intermediate	1 (8)	2 (18)
High	4 (31)	3 (27)
Very high	6 (46)	5 (46)
Therapy related	5 (39)	1 (9)

- A total of 20 pts had NGS performed.
- Identified mutations are shown in Figure 1.
- Most common mutation: *TP53* in 45% pts
- Median number of mutations per patient 2 (range 0-7)

Figure 1. Landscape of Mutations

Toxicities

- A total of 14 episodes of immune mediate AEs (IMAE)
- Observed AEs detailed in Table 2
- Immune mediated AEs in Table 3
- Infectious AEs in Table 4

Table 2. General Adverse Events

AE in ≥10% pts	Grade 1-2	Grade 3 or more
Rash	6	6
Pain	5	2
Transaminitis	2	4
Diarrhea	6	0
Fatigue	5	0
Nausea	5	0
Creatinine increase	4	0
Constipation	4	0
Cough	3	0
Edema	2	1
Other GI toxicity	2	1

Table 3. Immune-mediated Adverse Events

Adverse Event	Number of Episodes	
	Grade 1-2	Grade 3 or more
Pneumonitis	2	3
Myocarditis	0	1
Pleural effusion	1	0
Thyroiditis	1	1
Pericarditis	1	0
Dermatitis	1	1
Colitis	0	1
Encephalitis	0	1

Table 4. Infectious Adverse Events

Adverse Event	Number of Episodes	
	Grade 3	Grade 5
Fever	19	0
Pneumonia	6	1
Cellulitis	3	0
Other	3	0

- Nivo held due to IMAE in 6 pts and Ipi in 5 pts
- Nivo omitted due to IMAE in 1 pt and Ipi in 3 pts
- Nivo and Ipi held due to infection in 1 pt

Response Outcomes

- Evaluable for response: 23 pts
- Median number of cycles: 3 (range 1-10)
- Median number of cycles to response: 2 (range 1-6)
- Response outcomes:

Response	Aza+Ipi+Nivo (n=13) N (%)	Ipi+Nivo (n=10) N(%)
ORR	9 (69)	4 (40)
CR	4 (31)	1 (10)
mCR+HI	2 (15)	0 (0)
mCR	2 (15)	1 (10)
HI	1 (8)	1 (10)

Survival Outcomes

- Median follow up: 7.5 months (1-17)
- Median OS not reached on previously untreated cohort
- Median OS of 8.6 months (3.8-13.3) in HMA failure cohort

Figure 2. Overall Survival

Figure 3. Event-free Survival

Conclusions

- Preliminary data suggests dual combination of Ipi and Nivo feasible
- Immune mediated AE requiring dose interruptions and early use of steroids
- Active both in previously untreated and HMA failure:
  - ORR of 69 and 40% respectively
  - CR of 31% and 10% respectively
- Further follow up required to confirm survival and response advantage
- Further experience with optimal schedule and doses required

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Disclosures

No conflict of interest to disclose.

It is also important to say that the characteristics of this group of patients were quite severe in terms of poor prognosis, so there was a very significant group of patients with very complex karyotype and with mutations on p53 that, as the audience knows, are associated with very poor outcomes in this context. We believe that this data is again of interest and our plans are as follows right now:

1. In collaboration with the immune therapy platform here at MD Anderson with Dr. Allison, we're trying to develop immune biomarkers to identify potential patients that may benefit more or less, from this kind of therapy. That effort now is basically ongoing.
2. We have developed sophisticated flow cytometry assays to see if we can distinguish whether the therapy is affecting or not the stem cell compartment in this disease. This will be very important data to have, of course, as sequential cytogenetic and genomic analysis.
3. We have also completed the third cohort of patients with azacitidine, nivolumab, and ipilimumab. This is actually extremely powerful, but again, with potential very severe toxicities but we had used the nivolumab and ipilimumab at higher doses.

The protocol at MD Anderson right now is amended to use in the combination of nivolumab and ipilimumab both in the frontline and in relapse, a lower dose of this immune checkpoint inhibitor, so instead of using 3 mg/k down to 1 mg/k and we're doing the same thing when using this drugs as monotherapies in combination with the hypomethylating agent. We're going to expand this cohort with the support of BMS to an additional 80 patients and we're going to take the winner in terms of whether we use azacitidine-nivolumab, azacitidine-ipilimumab, or potentially the triplet of azacitidine-nivolumab-ipilimumab expanded cohorts depending on the data that we're going to generate hopefully, in the next coming months.

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ICPI in MDS: Conclusions

- Incorporation of ICPI in MDS feasible
- Single-agent activity of ipilimumab after HMA failure
- High response rates of nivolumab + AZA: 40% CR, 70% ORR
- Median OS not reached with ipilimumab + AZA
- Immune mediated toxicity → need for early steroids
- Toxicity profiles differ for different agents
- More experience and randomized studies are needed

ClinicalTrials.gov Identifier: NCT01953692

In summary, we think the disease, a potential new therapeutic approach for our patients, I think we need to understand a little better the toxicity profile and potentially be able to develop some type of biomarker that could allow us to target this therapy better, but I think that this early data in terms of response and survival is quite exciting and it deserves to be explored in larger, longer trials. Thank you for this opportunity to present this data.