ManagingAML

A Phase I Study of IMGN632, a Novel CD123-Targeting Antibody-Drug Conjugate, in Patients with Relapsed/Refractory Acute Myeloid Leukemia, Blastic Plasmacytoid Dendritic Cell Neoplasm, and Other CD123-Positive Hematologic Malignancies

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I am Dr. Naval Daver, and I'm live at the 61st ASH conference in Orlando, Florida. Today, I will be reviewing the results of a phase 1b study of single-agent CD123-targeting antibody-drug conjugate IMGN632, in relapsed/refractory acute myeloid leukemia and relapsed-refractory BPDCN patients. CD123 is a very important target for acute myeloid leukemia. It's expressed in more than 90% of patients who have AML, both newly diagnosed as well as relapsed/refractory AML, and it is a well-differentiated target expressed heavily on the surface of AML cells as compared to healthy normal progenitor cells and stem cells making this an attractive target. IMGN632 is a novel CD123-targeting antibody-drug conjugate, which uses a unique DNA alkylating payload of a recently developed IGN class of cytotoxic compounds. The thing about this DNA alkylating payload that we believe is different and may make this drug better tolerated is that it induces single-strand DNA breaks rather than the usual double-stranded DNA breaks that we see with most other alkylating agents such as BBD, and the hope is that the single-strand DNA break will allow for earlier recovery of neutrophils and platelets. So, this trial is currently ongoing. The trial is evaluating relapsed/refractory patients with acute myeloid leukemia of all ages and there's a second cohort looking at relapsed/refractory BPDCN, which is a myeloid-based disease called blastic plasmacytoid dendritic neoplasm. The trial has two different treatment schedules. We did a dose escalation looking at the different dose levels of IMGN632 given on a q.21 dosing. The dosing is outpatient, it's a 30-minute infusion. In general, this single agent has been well tolerated, especially at the dose levels A1 through A3, which are the lower dose levels. We did see three DLTs. These were VOD (veno-occlusive disease) which is basically an inflammation of the liver resulting from obstruction of the hepatic veins. These were all seen at higher dose levels at dose levels A4, A5, which we are no longer evaluating. So, the focus going forward is going to be looking at the dose levels A1, A2, A3 on a q.21-day schedule, and these seemed to be quite well tolerated. The main side effect that we see in dose days levels is infusion-related reactions. These are in the form of itching, flushing, nausea, rarely drop in blood pressure, usually fully reversible and we have not had to discontinue any patients due to this.

In total, we have enrolled at this time 91 patients of which 80 patients are AML and 10 patients are BPDCN. The response rate at this time is about 22% in the relapsed/ refractory AML as a single agent. What's encouraging is that we do see responses even

in people who have adverse cytogenetics as well as in post-transplant setting. And especially when we look at the relapsed population, not the refractory one, we see response rates of about 35% to 40% at the A2, A3 doses, which are the doses that we will be taking forward. So, we believe that this is an active agent, overall well tolerated, can be given outpatient every 21 days. We don't see CRS that may be seen with some of the other antibody constructs and bispecifics; and we feel that there's a role for this to move forward but mainly as a combination. And so we now will be proceeding with a combination approach. We have a poster here, Abstract 2601, that will show the schema of the combination study that has just started looking at three different combinations: azacitidine with IMGN632; venetoclax with IMGN632, these are both in relapsed AML; and then a frontline cohort of azacitidine-venetoclax with IMGN632 as well as an MRD eradication cohort. So, I think this study will be very critical to see if we can improve the response duration MRD negativity and survival over azacitidine-venetoclax in a similar older patient population not fit for induction, as well as potentially see if there's a role for these combinations of immunogen with venetoclax or with azacitidine relapsed AML, and a lot of preclinical data done by Marina Konopleva in our group suggest that there is very potent synergy between the venetoclax and the IMGN. So, we are hoping to have some data for this hopefully by next year's ASH.

Reference: Daver NG, et al. A Phase I Study of IMGN632, a Novel CD123-Targeting Antibody-Drug Conjugate, in Patients with Relapsed/Refractory Acute Myeloid Leukemia, Blastic Plasmacytoid Dendritic Cell Neoplasm, and Other CD123-Positive Hematologic Malignancies. Abstract 1334. ASH 2019. https://ash.confex.com/ash/2019/webprogram/Paper128275.html

For additional information, see Encouraging Clinical Profile of IMG632 Supplemental Slides

Updated Results from the Venetoclax (Ven) in Combination with Idasanutlin (Idasa) Arm of a Phase 1b Trial in Elderly Patients (Pts) with Relapsed or Refractory (R/R) AML Ineligible for Cytotoxic Chemotherapy

Elderly patients in general are very difficult to treat. They have AML phenotype that is often associated with adverse cytogenetics or complex cytogenetics, higher frequency of TP53, and drug resistant. They also don't tolerate high-dose chemotherapy well and have more toxicity and early mortality with high-intensity induction. It's even more difficult in elderly patients who are relapsed AML because now you have two highly risky features, which is one being older and one being relapsed, and so there is a dearth of available options for this population. We do have FLT3 inhibitors and IDH inhibitors that can still be given in older relapsed AML and are quite effective if one has those mutations, but this makes up about 30% to 35% of the total population. So for the remaining relapsed/refractory AML, we are still looking for good options. This combination of venetoclax and BCL-2 inhibitor and idasanutlin an MDM2 inhibitor is

showing some early encouraging response data and tolerability data. So, this study is basically allowing patients who are 60 years of age and above and have relapsed/refractory acute myeloid leukemia, and importantly, they should not be considered candidates for cytotoxic intensive chemotherapy or transplant at the time of enrollment. This study is a phase 1b study so the goal is really to identify the maximum tolerated dose, select the recommended phase 2 dose, as well as evaluate safety. What we are seeing is that the recommended phase 2 dose will likely be a combination of venetoclax 600 mg with either idasanutlin 150 mg days 1-5 of each cycle or idasanutlin 200 mg days 1-5, and the ongoing expansion of these two arms will help us finalize which of these two can be the recommended phase 2 dose. What we are seeing at this time is that overall the therapy is quite well tolerated. In general, we see the most common side effect, which is a well-known one with MDM2 inhibitor, is GI toxicity, diarrhea, and nausea. This is seen in about 50% to 70% of patients, but the good thing is that the grade 3 and 4 diarrhea and nausea rates are only 3% to 4%. And actually once we started implementing routine antidiarrheal prophylaxis for the first 48 hours of idasanutlin in cycle 1, we have seen no grade 3 or higher diarrhea. So, it is quite manageable with some proactive interventions for the first one or two days of treatment. The early mortality in this relapsed older population with AML is 6%, which is quite acceptable in the elderly high-risk relapsed group and this population, in general, does have multiple high-risk features including adverse cytogenetics in about 40% to 50%, secondary AML features in 50%, and others.

Now getting, of course, to the response data that we have presented here at the recommended phase 2 dose cohorts, which are the venetoclax 600 either with idasanutlin 150 or with idasanutlin 200 on days 1-5, we have 33 patients enrolled at the time of presentation and we see an overall response rate, which includes CR/CRi/MLFS, of about 50% to 55%. This is quite encouraging putting it into perspective. Historically, in this older population with AML relapsed disease, response rates are about 15% to 20% with standard chemotherapy or epigenetic therapy, usually with higher early mortality. So, small numbers, but we think this is quite a promising strategy and the study will be going into expansion with one of these two dose levels. The other important thing that we do see is that in patients who have achieved a remission, but have not had count recovery, often allowing interruption of the venetoclax for 7 to 10 days under close monitoring after confirmation of bone marrow remission, thus allow for count recovery and a number of the MLFS's we showed will actually get upgraded to CR/CRp. So, we are now looking at schedules of either 21 days or 14 days venetoclax, which we think will allow for better CR/CRp rates. We've done a lot of baseline molecular profiling. What we find is that there are particular mutation groups such as IDH1, IDH2, RUNX1 that are associated with high response rates to this combination. These are similar biomarkers that predicted for higher response to venetoclax with HMA as well. And then there are certain mutations such as the ASXL1, FLT3, NF1 signaling kinase mutations that predict for resistance. Importantly, we did see that TP53 clonal selection was noted as it has been seen and shown in lab with MDM2 inhibitors and about 30% of patients had a detectable FLT3 allele burden at the

time of progression. When we went back and looked at those patients, almost all of them did have a low level TP53 clone, and so basically we are seeing TP53 clonal selection over time rather than an emergence of a new clone; and I think we do need to monitor the TP53 allele on these treatments as patients continue. So, the next steps for this are importantly there is a parallel study that has recently been completed, a phase 3 randomized study in relapsed AML of the same MDM2 inhibitor, idasanutlin, with Ara-C versus Ara-C alone. This is the MIRROS study. We expect readout of this in the next few months.

Reference: Daver NG, et al. Updated Results from the Venetoclax (Ven) in Combination with Idasanutlin (Idasa) Arm of a Phase 1b Trial in Elderly Patients (Pts) with Relapsed or Refractory (R/R) AML Ineligible for Cytotoxic Chemotherapy. Abstract 229. ASH 2019. https://ash.confex.com/ash/2019/webprogram/Paper123711.html

Encouraging Clinical Profile of IMG632 Supplemental Slides

IMGN632 in R/R AML and BPDCN, abstract #734

Encouraging Clinical Profile of IMGN632, a Novel CD123-Targeting Antibody-Drug Conjugate, in Patients with Relapsed/Refractory Acute Myeloid Leukemia or Blastic Plasmacytoid Dendritic Cell Neoplasm

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IMGN632 in R/R AML and BPDCN, abstract #734

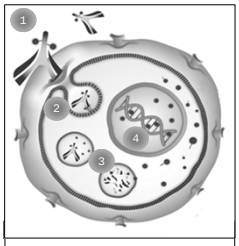
CD123 as a Therapeutic Target

- CD123, the alpha-subunit of interleukin-3 receptor (IL-3Rα), is expressed in >90% of AML, ~100% of blastic plasmacytoid dendritic cell neoplasm (BPDCN), as well as >90% of B-ALL and >75% of T-ALL and early thymic progenitor (ETP) ALL cases[1,2]
- IL3R/CD123 is a clinically-validated target in BPDCN
- CD123 expression is increased on AML blasts and leukemic stem cells compared with normal hematopoietic stem and progenitor cells[3]
- CD123-directed therapy may be able to de-bulk and potentially eliminate the source of disease
- CD123 is rapidly internalized making it well suited for antibody-drug conjugate (ADC)-based therapeutic strategies

[1]Testa 2014 *Biomarker Res* 2:4; [2]Angelova 2018 *Haematologica*; [3]Ehninger 2014 *Blood Cancer J* 4:e218

IMGN632 in R/R AML and BPDCN, abstract #734

IMGN632: A Novel CD123-Targeting ADC



1 - ADC binds target
2 - ADC internalized
3 - Payload released
4 - Payload alkylates DNA

- **Novel Anti-CD123 Antibody**
  - High affinity binding to CD123
  - Unique epitope in extracellular domain
- **Novel IGN Payload (DGN549)**
  - DNA-alkylating activity, single strand DNA breaks (vs. double strand)
  - Uniform drug antibody ratio (DAR=2)
- **Novel Peptide Linker**
  - Confers greater stability in circulation
  - Efficient intracellular payload release
- Pre-clinical efficacy in AML, BPDCN, and B-ALL models
- Pre-clinical evidence for broad combination potential: Increased anti-tumor activity in combination with cytarabine, venetoclax, azacitidine and the triplet of IMGN632, venetoclax and azacitidine (2019 ASH Abstract #1375)

Kovtun 2018 *Blood Adv* 2:848-858

Encouraging Clinical Profile of IMG632 Supplemental Slides

IMGN632 in R/R AML and BPDCN, abstract #734

Study Objectives

Primary

- Establish maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), and optimal schedule of IMGN632 monotherapy in relapsed and refractory AML and BPDCN

Secondary

- Determine safety and tolerability of IMGN632, including dose-limiting toxicities (DLTs)
- Characterize preliminary antileukemia activity (ORR) and pharmacokinetic (PK) profile of IMGN632 in AML and BPDCN

IMGN632 in R/R AML and BPDCN, abstract #734

Study Design

- Patients ≥18 years with CD123-positive (local lab, any level by flow or IHC), relapsed or refractory AML or BPDCN, with no more than 3 prior lines of therapy
- 3+3 escalation, with ability to expand multiple dose-levels to optimize RP2D selection
- IMGN632 administered IV on two schedules:
  - A: Day 1 of a 3 week cycle (D1 Q3W)
  - B: Days 1, 4 and 8 of a 3 week cycle (D1,4,8 Q3W)
    - Fractionated schedule from Schedule A
- Starting dose 0.015 mg/kg, with escalation using a modified Fibonacci schema

IMGN632 in R/R AML and BPDCN, abstract #734

Enrollment (n=95)

Patients dosed	Schedule A D1 Q3W		Schedule B D1,4,8 Q3W	Patients dosed
2	A6 0.45 mg/kg x1			
5	A5 0.3 mg/kg x1			
7	A4 0.18 mg/kg x1	=	B3 0.06 mg/kg x3	14
17*	A3 0.09 mg/kg x1	=	B2 0.03 mg/kg x3	6
38**	A2 0.045 mg/kg x1	=	B1 0.015 mg/kg x3	3
3	A1 0.015 mg/kg x1			

equivalent cumulative dose per cycle

- Two schedules were explored
  - A: 6 dose levels given D1 Q3W (n=72, 62 AML, 10 BPDCN)
  - B: 3 dose levels given fractionated on D1,4,8 Q3W (n=23, AML only)

* includes 16 AML and 1 BPDCN patient; ** includes 29 AML and 9 BPDCN patients

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IMGN632 in R/R AML and BPDCN, abstract #734

Patient Characteristics (N=95)

Age, years [range]*		66 [33-83]
		% (n)
Gender*	Male	59% (56)
	Female	41% (39)
Disease	AML	n=85
	De novo AML	53% (45)
	Secondary AML/incl. therapy-related AML	47% (40)
	BPDCN	n=10
ELN Risk Category (AML only)	Favorable/Intermediate	35% (30)
	Adverse	49% (42)
	Not determined	15% (13)
Prior therapy*@	Non-intense only (e.g. HMA, IDHi)	26% (25)
	Intense (e.g. 7+3, HiDAC, SCT)	73% (69)
	Prior SCT	24% (23)
Disease status*	Primary refractory	25% (24)
	Relapsed	
	First relapse	33% (31)
	Second or greater relapse	42% (40)

*All patients (AML and BPDCN) are combined for some demographics
@Data incomplete for 1 patient

IMGN632 in R/R AML and BPDCN, abstract #734

Treatment-Emergent Adverse Events
(TEAEs >15%) (N=95)

Adverse Event	Any Grade %	Treatment-Related Any Grade %	Grade ≥3 %	Treatment-Related Grade ≥3 %
Nausea	34	11	2	1
Diarrhea	31	3	0	0
Febrile Neutropenia	25	10	25	10
Infusion Related Reaction	25[#]	24	8	8
Constipation	24	2	0	0
Lung Infection	24	1	22	1
Peripheral Edema	22	3	1	0
Chills	21	8	0	0
Pyrexia	21	4	1	0
Fatigue	19	3	5	1
Insomnia	19	1	0	0
Dyspnea	17	3	3	2
Epistaxis	17	0	0	0
Abdominal Pain	16	2	1	1
ALT Increase	16	2	5	0
Decreased Appetite	16	2	1	0

Possibly/Probably related TEAEs ≥10% highlighted in yellow

[#] one unrelated platelet transfusion IRR

IMGN632 in R/R AML and BPDCN, abstract #734

Safety Summary (n=95)

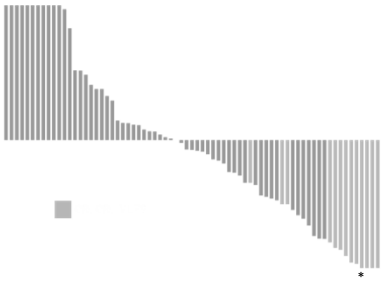
- Overall well tolerated in relapsed/refractory AML and BPDCN patient population
- Most frequent treatment-related AEs were infusion-related reactions (24%; chills, tachycardia, nausea/vomiting, diarrhea). IRRs were reversible, did not require IMGN632 discontinuation in any patient
- Single DLTs seen at higher dose levels (n=4)
  - Reversible veno-occlusive disease (VOD) (n=3), two had prior SCT
    - All occurred at cumulative doses ≥0.18 mg/kg per cycle
    - Abdominal pain, ascites, variable LFT elevation
    - Liver biopsies consistent with sinusoidal obstruction
    - All reversible, improved in 1-2 weeks
    - Fractionated Schedule B did not appear to improve safety margin for VOD
  - Prolonged neutropenia (n=1): 0.3 mg/kg after 2 cycles
- Deaths: 30 day any cause mortality (6%)
  - 5 unrelated (progressive disease x2, lung infection, respiratory failure, sepsis)
  - 1 possibly related (cause unknown)

Encouraging Clinical Profile of IMG632 Supplemental Slides

IMGN632 in R/R AML and BPDCN, abstract #734

AML Efficacy

BM-evaluable patients (n=71)



- 54% of BM-evaluable patients had a reduction in BM blasts
- 13 responses (2 CR, 10 CRi, 1 MLFS*) observed across both schedules and at multiple dose levels
- Fractionated Schedule B did not appear to provide increased efficacy

BM evaluable: patients who had at least one post-dosing BM evaluation

IMGN632 in R/R AML and BPDCN, abstract #734

AML Responder Analysis

Of 13 responders

- 92% had prior intense therapy, including 3 with prior SCT
- 69% had 2-3 prior lines of therapy
- 54% had ELN Adverse Risk

Response by subgroups

- Relapsed AML (excluding primary refractory AML)
  - 26% (6/23) overall response rate (ORR) in relapsed AML patients at 0.045 mg/kg
- Relapsed/refractory De novo AML (excluding secondary AML)
  - 40% (6/15) ORR in relapsed and refractory de novo AML patients at 0.045 mg/kg
  - 46% (6/13) ORR in relapsed de novo AML at 0.045 mg/kg
- ELN Adverse Risk (excluding ELN Fav/Int): 20% (7/35) ORR across all dose levels
- Prior SCT: 18% (3/17) ORR across all dose levels

Pharmacokinetics and pharmacodynamics

- Efficacy observed was independent of CD123 expression levels or CD123 saturation
- Efficacy observed was independent of PK parameters (Cmax, AUC)

Based on safety and efficacy data

- 0.045 mg/kg Q3W (Dose level A2) selected as the RP2D for IMGN632 monotherapy
- 0.015-0.09 mg/kg (Dose levels A1-A3) selected for continued development in combinations

IMGN632 in R/R AML and BPDCN, abstract #734

BPDCN experience

Nine of ten BPDCN patients were evaluated for response

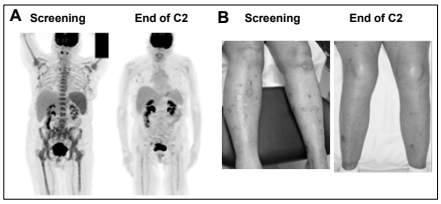
- Three responders (CR, CRi, PR)
  - All three had prior SL-401
  - Two also had prior intense chemotherapy and/or alloSCT
  - All three had skin, PET and BM disease
  - All three achieved their response with 1-2 doses of IMGN632 at dose level 0.045 mg/kg
  - BM cleared to 0% from baseline 28%, 37%, and 84% at screening, respectively

Encouraging Clinical Profile of IMG632 Supplemental Slides

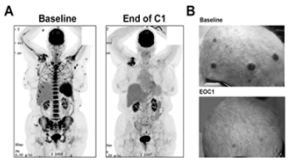
IMGN632 in R/R AML and BPDCN, abstract #734

Responses in refractory BPDCN

63yo female with BPDCN, refractory to SL-401 x2 presented with extensive marrow and skin involvement. After 1 dose, BM cleared from 84% to 0%. After 2 cycles, skin cleared active lesions and "Partial Remission" based on lymph nodes reduction.



69yo female with MDS/BPDCN, refractory to SL-401, CLAG-M, CLAG and presented with extensive skin/PET/BM involvement. After 1 cycle, in CRi, BM cleared from 37% to 0%.



IMGN632 in R/R AML and BPDCN, abstract #734

Conclusions

- **IMGN632 is well tolerated at dose levels 0.015-0.09, including the RP2D 0.045 mg/kg Q3W**
  - Manageable IMGN632-related infusion related reactions in 24% of patients, none requiring IMGN632 discontinuation
  - Most doses given as outpatient with <30 minute IMGN632 infusion Q3W
- **Responses in R/R AML**
  - The majority of AML responders were ELN Adverse risk with 2-3 prior lines of therapy, including three with prior SCT
  - 26-46% ORR in R/R AML at the RP2D in subgroups of de novo and relapsed patients
- **Responses in R/R BPDCN**
  - BPDCN responses in 3 of 9 patients; all with prior SL-401 and two with intense chemo
- **This trial continues to enroll AML, BPDCN, and recently opened to ALL patients**
- **Further development of IMGN632 includes an open Phase Ib/II trial (TiP abstract 2601 ASH 2019)**
  - Combinations with AZA, with VEN and with AZA+VEN (supported by pre-clinical abstract 1375 ASH 2019)
  - IMGN632 monotherapy in MRD+ frontline patients