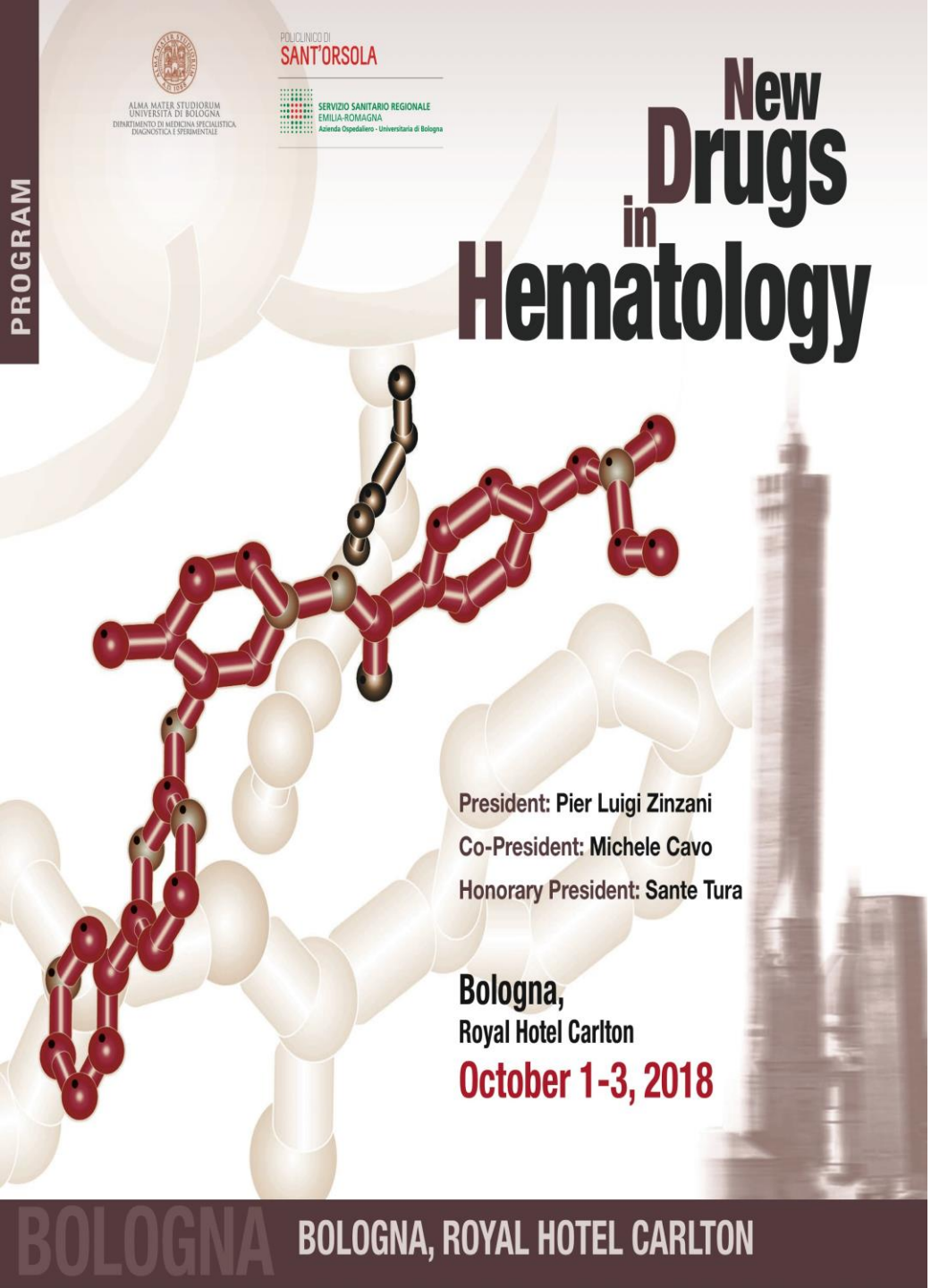

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

Idasanutlin

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Institute of Hematology
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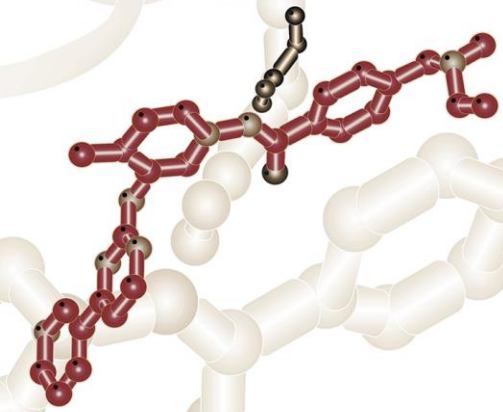
University of Bologna



New Drugs in Hematology

President: Pier Luigi Zinzani
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Bologna,
Royal Hotel Carlton
October 1-3, 2018

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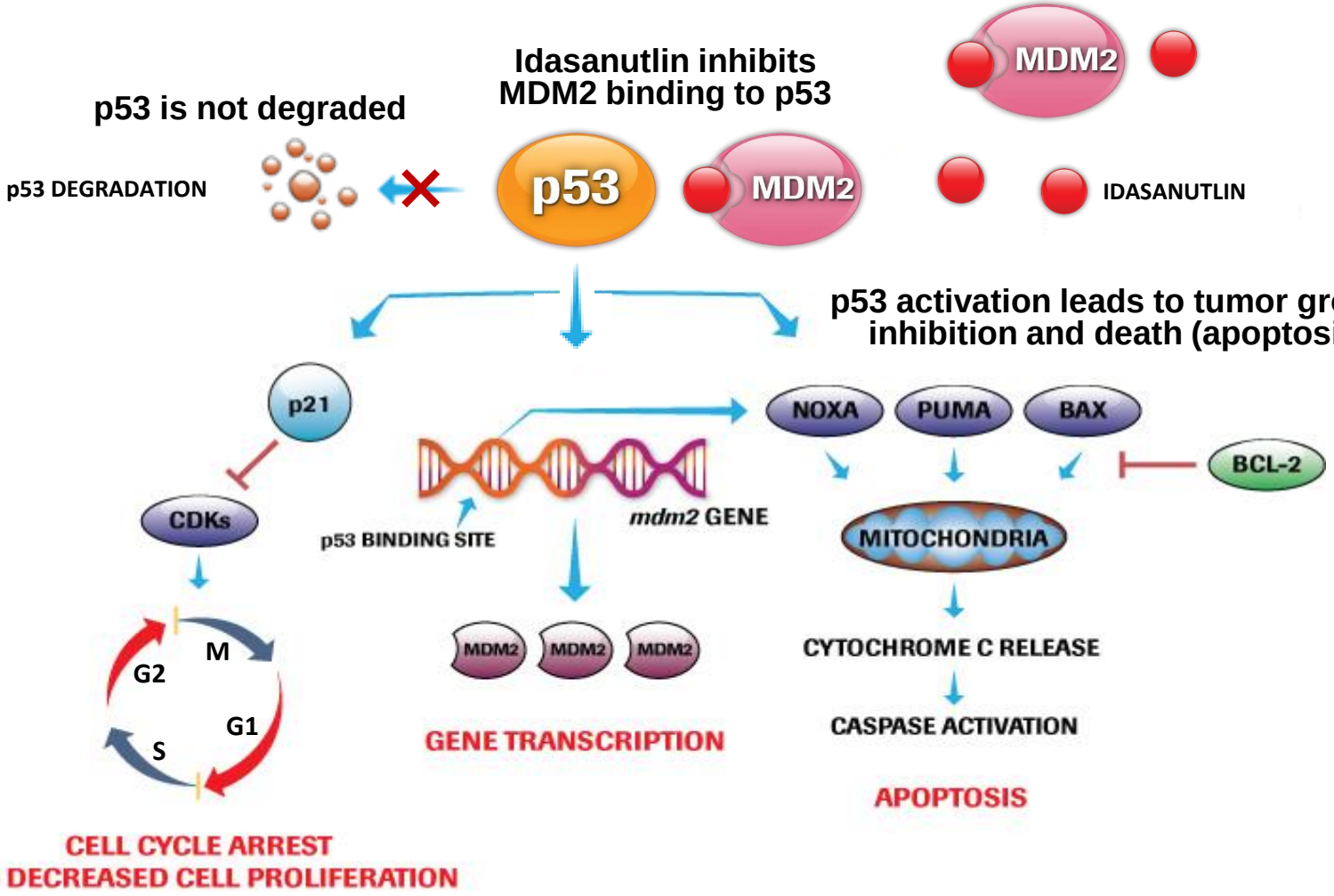
Disclosures of Cristina Papayannidis

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
TEVA						X	
NOVARTIS						X	

Idasanutlin is a first-in-class MDM2 inhibitor in clinical development

Mechanism of action: p53 activation by inhibition of negative regulator

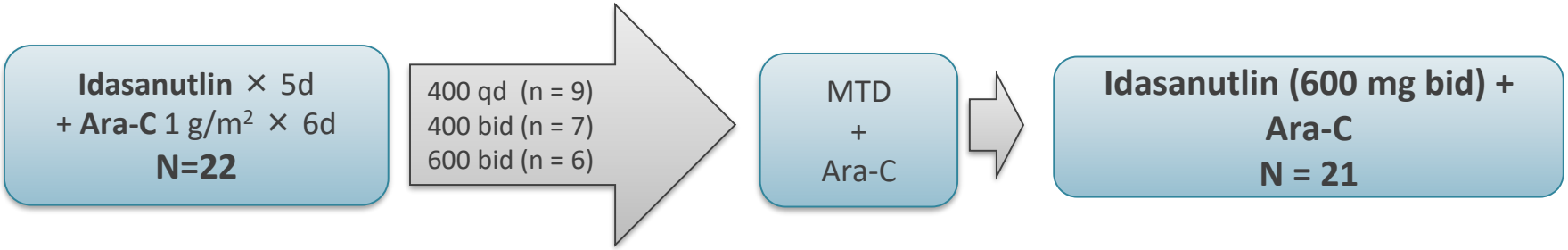


Phase 1/1b Study design in R/R AML

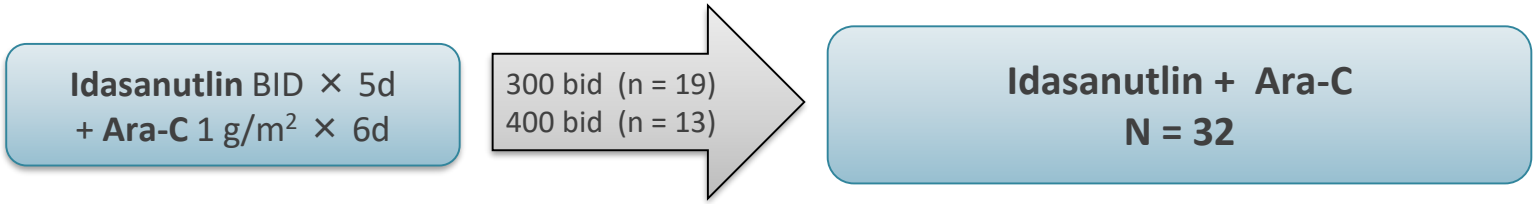
Objectives

- Determine the maximum tolerated dose (MTD) of idasanutlin microprecipated bulk powder (MBP) with Ara-C
- Confirm PK and safety of optimized spray-dried powder (SDP) formulation
- Focus on **relapsed/refractory AML** (≤ 3 prior regimens)

Dose Escalation MBP **Expansion MBP**



Optimized SDP formulation (Bridging)



Martinelli G et al, EHA 2016

Key inclusion and exclusion criteria

Patients enrolled regardless of TP53 mutational status

	Dose Escalation	Expansion	Bridging
ECOG PS	0-2	0-1	0-1
Age	> 18 y	> 18 y	> 18 y
Prior therapies for AML[1]	No restrictions	≤ 2 prior regimens	≤ 3 prior regimens
Prior allogeneic transplant	Permitted	Excluded	Permitted (> 4 months prior)
2° AML/t-AML	Permitted	Excluded	Permitted

General Criteria:

- *TP53* was not a selection marker
- Inclusion: willingness to undergo blood and bone marrow assessments
- Exclusion: uncontrolled medical conditions; 14 d since last therapy except HU; CNS leukemia; HIV on anti-retrovirals; unwillingness to use contraception; unwillingness to undergo transfusions

[1] Hypomethylating agents (azacitidine, decitabine) permitted for antecedent hematologic disorders (CMML, ET, PMF, MDS, etc).

Majority of patients had prior Ara-C regimens

Many received Ara-C > 1g/m²

Idasanutlin arm and dose	Dose Escalation (n = 23)[2] 400 mg QD to 600 mg BID MBP	Expansion (n = 21) 600 mg BID MBP	Bridging (n = 32) 300 and 400 mg BID SDP
Median age (range)	64 y (32-76)	64 y (45-74)	61 y (32-79)
Male:female	11:12	12:9	19:13
ECOG PS 0, n (%)	5 (22)	11 (52)	11 (34)
1, n (%)	13 (56)	10 (48)	21 (66)
2, n (%)	5 (22)	0	0
Prior MPN, MDS[1], n (%)	5 (22)[2]	1 (5)	5 (16)
Prior treatment with			
Ara-C, %	19 (83)	18 (86)	29 (91)
Ara-C[3] > 1 g/m², %	15 (65)	14 (67)	26 (81)
Hypomethylator, %	7 (30)	3 (14)	8 (25)

MBP, microprecipated bulk powder; SDP, spray-dried powder.[1] Includes CMML, MDS, MPN, ET, PV, atypical CML.[2] 1 CMML pt did not have AML, safety evaluable but not response evaluable. [3] Approximate numbers based on regimen as doses not provided for some treatments.

Idasanutlin + Ara-C AML Ph 1/1b patients' characteristics

Majority of patients are poor risk with short-duration CR1

Idasanutlin arm and dose	Dose Escalation (n = 22[1]) 400 mg QD to 600 mg BID MBP		Expansion R/R AML (n = 21) 600 mg BID MBP		Bridging (n = 32) 300 and 400 mg BID SDP	
ELN risk at diagnosis, n (%)						
Favorable	1 (5)		2 (10)		3 (9)	
Intermediate 1 & 2	12 (55)	96%	14 (67)	91%	14 (44)	91%
Adverse	9 (41)		5 (24)		15 (47)	
No prior therapy[2]	1 (5)		0		1 (3)	
Refractory[2]	7 (32)	87%	10 (48)	96%	15 (47)	84%
Duration of CR1[3,4], n (%)						
< 3 months	1 (5)		1 (5)		4 (12)	
3-12 months	11 (50)		9 (43)		8 (25)	
≥ 12 months	2 (9)		1 (5)		4 (12)	

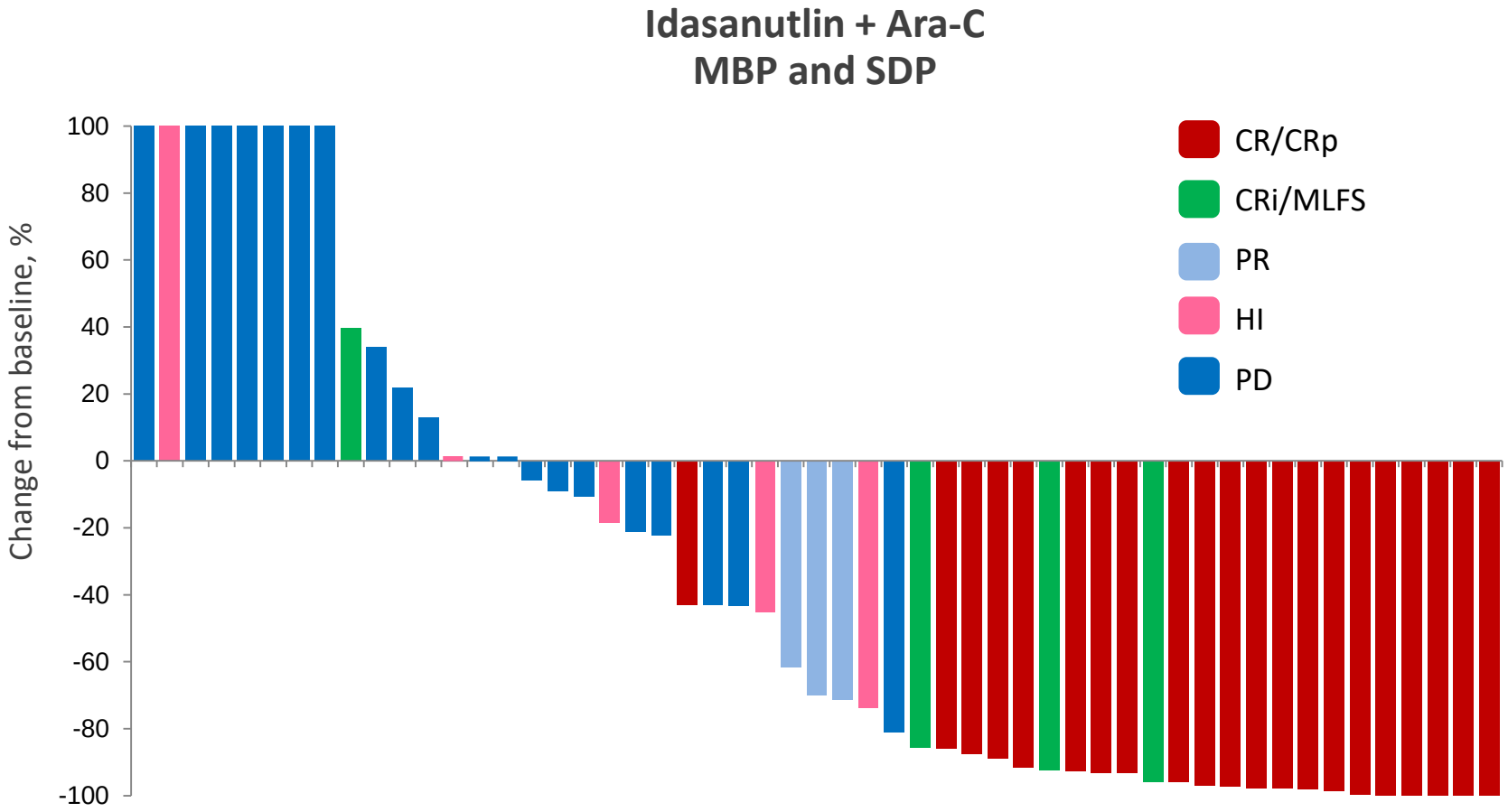
ELN, European LeukaemiaNet; MBP, microprecipated bulk powder; SDP, spray-dried powder.
[1]1 pt in dose escalation had CMML, not AML and is not included here.
[2] Estimates based on response to initial therapy for AML
[3] CR1 < 12 months is associated with poor response rates in relapse.
[4] Duration of CR1 are estimates as exact start of initial response and end of response were not always available and are approximate.

Most patients who achieve a response have a CR

Idasanutlin arm and dose	Dose Escalation (n = 22)[1] 400 mg QD to 600 mg BID	Expansion Arm (n = 21) 600 mg BID	Bridging (n = 19) 300 mg BID SDP	Bridging (n = 13) 400 mg BID SDP
Response evaluable, n	21	16	19	12
CR, n (%)		**20/75 (27)**		
CR + CRp, n (%)		**21/75 (28)**		
CR + CRp + CRi, n (%)		**22/75 (29)**		
CR + CRp + CRi + MLFS, n (%)		**25/75 (33)**		
Best response, n (%)[2]				
CR	6 (27)	5 (24)	7 (37)[3]	2 (15)
CRp	0	0	0	1 (8)
CRi	0	0	1 (5)	0
MLFS	1 (5)[4]	0	1 (5)	1 (8)
PR	2 (9)	1	0	0
HI/SD	2 (9)	0	1 (5)	2 (15)
PD	10 (45)	10 (70)	9 (47)	6 (46)

MBP, microprecipated bulk powder; SDP, spray-dried powder; [1] 1 patient did not have AML and is not included; [2] CR and CRp were confirmed ~28d following initial assessment; [3] 1 pt was a CRi at D29 and went immediately to allo-SCT without waiting for count recovery; in CR post-transplant; [4] Assessment performed on SD18.

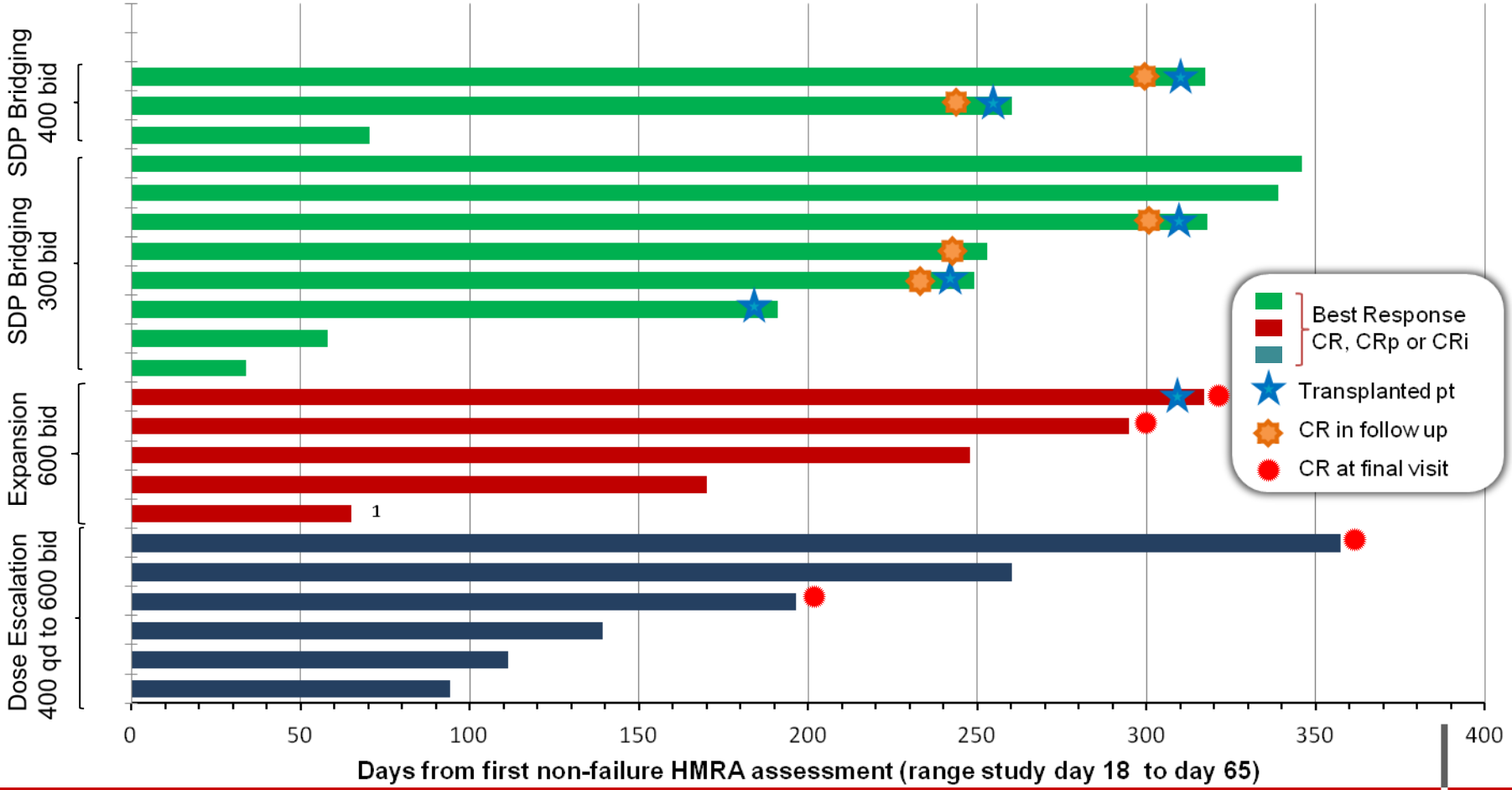
Idasanutlin + Ara-C: waterfall plot



MBP, microprecipated bulk powder; SDP, spray-dried powder.
CR/CRp: < 5% marrow blasts with complete recovery of peripheral counts/incomplete platelet recovery.
CRi/MLFS: < 5% marrow blasts with incomplete/no recovery of peripheral counts.
PR: > 50% decrease in marrow blasts.

Responses are deep and prolonged: Median duration of response for pts with CR, CRp and CRi > 8 mo

Responders (CR, CRi, CRp, MLFS) followed until relapse or up to 1 year from start of treatment; 5 patients remain in CR and in 1yr follow up period



MBP, microprecipated bulk powder; SDP, spray-dried powder.
[1]Received second cycle at relapse and achieved a CR prior to final discontinuation.

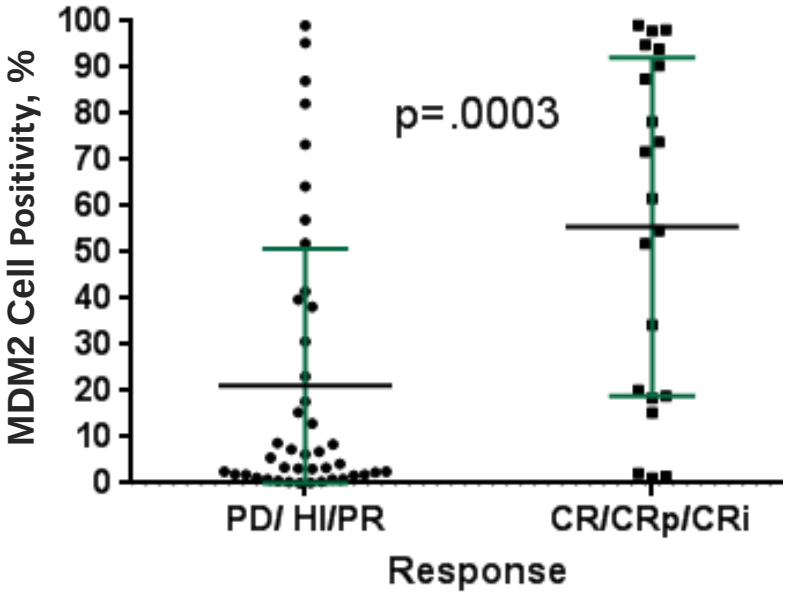
Most responder patients are *TP53* WT

Idasanutlin arm and dose	Dose Escalation (n = 22)	Expansion R/R AML (n = 21)	Bridging (n = 32)	Totals
Patients with *TP53* results, n (%)	22 (100)	21 (100)	32 (100)	75 (100)
Wild type, n (%)	18 (82)	17 (81)	25 (78)	60 (79)
Mutant, n (%)	5 (18)	4 (19)	7 (22)	16 (21)

- TCGA/COSMIC databases report 10-15% AML pts are *TP53* mutant (high preponderance of de novo AML samples)
- All responders were *TP53* wild type except for 1 patient with an M243R mutation in exon 7

MDM2 protein expression in leukemic blasts by flow cytometry is associated with response

Idasanutlin + Ara-C Treatment
***TP53* wild type and mutant**
(flow cytometry CD45dim blast cells)



- High association of response (CR, CRp or CRi) with MDM2 protein expression on blast cells
- Promising biomarker distinct from TP53 mutation status
  - p = 0.0003 for all patients (n = 64)
  - p = 0.0019 for *TP53* WT-only patients (n = 50)
  - Potential complementary diagnostic

Reis et al. *Haematologica,* 2016.

Poor-prognosis patients can achieve CR with Idasanutlin + Ara-C and proceed to successful allo-transplant

Molecular/cytogenetic/risk factors in patients achieving bone marrow clearance (CR, CRp, CRi or MLFS)		
600 mg MBP BID	**300 mg SDP BID**	**400 mg SDP BID**
t(6;9); FLT3-ITD[2] →allo-SCT	**FLT3-TKD + NPM1 mt → allo-SCT**	**t(3;3)[2] → allo-SCT**
t(1;21); t(7;19); FLT3-ITD[1,2]	**TP53WT, IDH1 WT, IDH2 mt[2] → allo-SCT**	**NPM1 mt[1] → allo-SCT**
Treated simultaneous cervical cancer[2] (normal cytogenetics)	**FLT3-ITD[2] → allo-SCT**	MF with FLT3-ITD[1,2]
Normal cytogenetics (n = 3)[1,2]	DLBCL x 2; t(2;4)[2]	Normal cytogenetics[1,2]
	AML M5 2001; +8[1,2]	
	Early stage prostate Ca > 5yrs; del7, FLT3-ITD[1,2]	
	Normal cytogenetics[2]	
	Normal cytogenetics[1]	
	CEBPalpha +[2]	

MBP, microprecipated bulk powder ; MF, myelofibrosis; SDP, spray-dried powder; [1] Patients aged ≥ 60y. [2] 1° refractory or CR1 < 12 mos. Additional responders at 400 mg QD MBP (1) or 400 mg BID MBP (5) characteristics: ring 17p; inv(16) with prior cecal cancer; del 5; t(4;11); +8 with NPM1mutation; t(1;11).

GI effects are common but manageable

Idasanutlin arm and dose	Expansion (n = 21) 600 mg BID MBP		Bridging (n = 19) 300 mg BID SDP		(n = 13) 400 mg BID SDP	
n (%)	Total	Gr 3/4	Total	Gr 3/4	Total	Gr 3/4
Diarrhea	19 (90)	3 (14)	17 (89)	4 (21)	12 (92)	5 (38)
Nausea	17 (81)	1 (5)	10 (53)	2 (11)	11 (85)	2 (15)
Vomiting	11 (52)	1 (5)	7 (37)	0	8 (62)	0
Decreased appetite	6 (29)	2 (10)	5 (26)	0	3 (23)	0
Hypokalemia	7 (33)	5 (24)	7 (37)	2 (11)	8 (62)	6 (46)
Fatigue	4 (19)	2 (10)	8 (42)	1 (5)	4 (31)	1 (8)
Asthenia	7 (33)	2 (10)	2 (11)	0	5 (38)	1 (8)
Tumor lysis syndrome	1 (5)	0	0	0	0	0

MBP, microprecipated bulk powder; SDP, spray-dried powder.
Diarrhea prophylaxis was not regularly given until late in the study.

Low 30-days mortality

Idasanutlin arm and dose	Expansion (n = 21) 600 mg BID MBP	Bridging (n = 19) 300 mg BID SDP	Bridging (n = 13) 400 mg bid SDP
30-days mortality	5 (23.8)	1 (5.3)	1 (7.7)
AE, n	4	0	1
Disease, n	1	1	0
Time to recovery (d)			
Neutrophils	30 (34 for SDP only)		44.5
Platelets	29 (34 for SDP only)		47.5

Grade 3 and higher hematologic and infection-associated adverse events

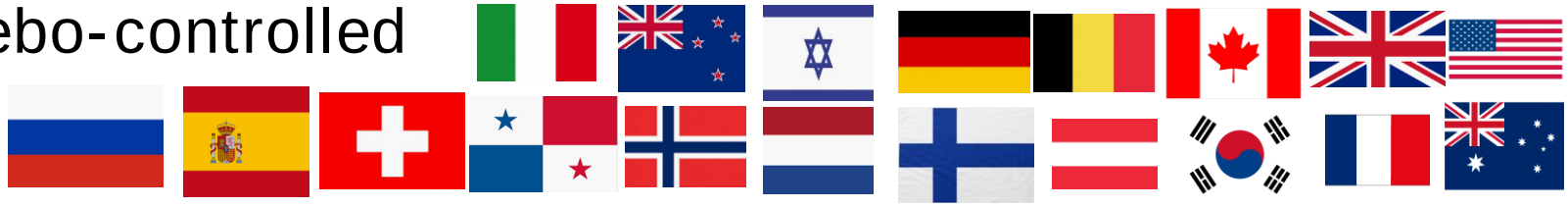
n (%)	Gr 3/4	Gr 5	Gr 3/4	Gr5	Gr 3/4	Gr5
Febrile aplasia or neutropenia	5 (24)	0	6 (32)	0	6 (46)	0
Sepsis	2 (10)	2 (10)	1 (5)	0	1 (8)	1 (8)
Neutropenic sepsis	1 (5)	0	0	0	0	1 (8)
Pneumonia	2 (10)	0	3 (16)	0	1 (8)	0
C. difficile	0	1 (5)	0	0	0	0

MBP, microprecipated bulk powder; SDP, spray dried powder.

Idasanutlin + Ara-C is a promising option for R/R AML

- Idasanutlin + Ara-C can induce durable CRs in R/R AML
  - 22/75 (29%) patients had CR (20), CRp (1) or CRi (1)
  - At the 300 mg BID SDP dose, 8/19 (42%) patients had CR (7) or CRi (1)
- Patients achieve rapid and durable responses
  - Most responses occurred after only one cycle of therapy
  - Median duration of response for patients with CR, CRp or CRi followed up to 1 year is > 8 months
- 6 patients with CR underwent allogeneic transplant
- MDM2 expression by flow (on blast cells) may be predictive for response
- Phase 3 MIRROS study is ongoing and accruing (1st or 2nd relapsed/refractory AML→ Idasanutlin +Ara-C vs Placebo+Ara-C)

WO29519 Phase III design in R/R AML
Idasanutlin + cytarabine, randomised, double-blind, placebo-controlled



AML R/R*

Randomisation

Arm A: placebo po bid + cytarabine 1 g/m^2 iv

Arm B: idasanutlin 300 mg po bid + cytarabine 1 g/m^2 iv

Stratification:
- Age (≥60 vs <60 years)
- Cyto/molecular risk category
- Length of 1st remission (refractory or CR <3 months vs CR >3 months <1 year vs CR >1 year
- Prior HSCT vs no prior HSCT

- 2:1 randomisation from the beginning
- Decision at IA requires 120 p53 wt patients (p53 mut will also be assessed)

IA (n=120 p53 wt patients): IDMC recommends Go/No Go based on pre-specified criteria

(OR, CR & EFS, safety)

OS also assessed

Go

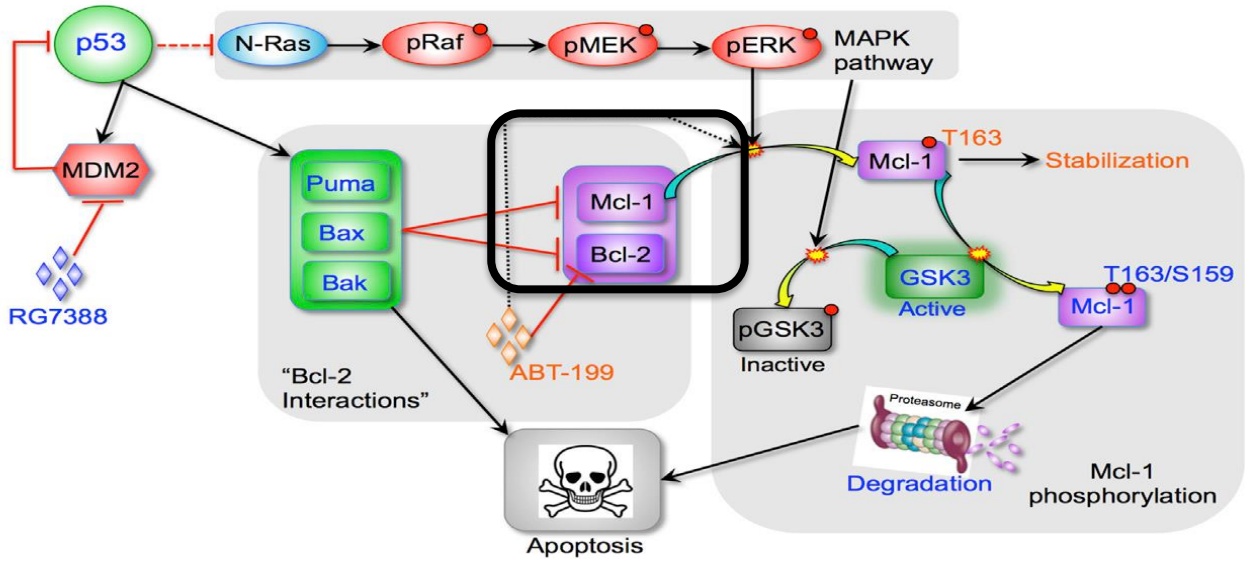
Phase III endpoints (n=440 total)

- Primary: OS in wt
- Secondary: OS in all-comer, CR, 'bridge to transplant', EFS, PRO

*1st or 2nd relapse, excludes 1st relapse age <60 with CR >1 year, excludes R/R patients having intermediate- or high-dose cytarabine–containing regimen in prior 3 months. CR rate at interim will be assessed locally and independently; CR defined as confirmed CR and CRp.

Synthetic Lethality of Combined Bcl-2 Inhibition and p53 Activation in AML: Mechanisms and Superior Antileukemic Efficacy

Rongqing Pan,[1,5,6] Vivian Ruvolo,[1] Hong Mu,[1] Joel D. Leverson,[2] Gwen Nichols,[3] John C. Reed,[4] Marina Konopleva,[1] and Michael Andreeff[1,7,*]



Pan et al., 2017, Cancer Cell 32, 748–760
December 11, 2017
https://doi.org/10.1016/j.ccell.2017.11.003

Preliminary Results from a Phase Ib Study Evaluating BCL-2 Inhibitor Venetoclax in Combination with MEK Inhibitor Cobimetinib or MDM2 Inhibitor Idasanutlin in Patients with Relapsed or Refractory (R/R) AML

Naval Daver, Daniel A. Pollyea, Karen W.L. Yee, Pierre Fenaux, Joseph M. Brandwein, Norbert Vey, Giovanni Martinelli, Kevin R Kelly, Gail J. Roboz, Jacqueline S. Garcia, Arnaud Pigneux, Smita Kshirsagar, Monique Dail, Jue Wang, Mehrdad Mobasher, Lin-Chi Chen, Wan-Jen Hong, Marina Konopleva, and Michael Andreeff

Blood 2017 130:813;

AIM of the trial: to evaluate the safety, tolerability and efficacy of VEN + cobi or idasa in pts ≥60 yrs old with R/R or secondary AML not eligible for cytotoxic therapy **(NCT02670044)**.

Arm A: VEN PO daily + cobi PO on Days 1-21
Arm B: VEN PO daily + idasa PO on Days 1-5 in 28-day cycles

Table 1. Summary of Adverse Events

Adverse Event	Arm A: VEN + Cobi (N=22)		Arm B: VEN + Idasa (N=20)	
	All Grade AE ≥30% pts* (%)	Grade ≥3 (%)	All Grade AE ≥30% pts* (%)	Grade ≥3 (%)
Diarrhea	82	36	80	10
Nausea	64	0	70	5
Vomiting	41	0	40	0
Fatigue	41	9	20	10
Peripheral edema	41	0	20	0
Febrile neutropenia	23	23	30	30
Decreased appetite	23	5	30	15
Hypokalemia	18	5	35	10

* Occurring in either treatment arm
No events of clinical tumor lysis syndrome were reported

Daver et al, ASH 2017

Table 2. Mutation Profile at Baseline for Responders

VEN + Cobi			
VEN dose (mg)	Cobi dose (mg)	Best Response	Key Mutations*
600	40	CR	JAK2, NOTCH1, NOTCH3, PTCH1
800	40	CR	IDH1, CEBPA, NRAS**
400	60	CRp	EGFR, FGFR1
400	40	CRi	DMNT3A**
VEN + Idasa			
VEN dose (mg)	Idasa dose (mg)	Best Response	Key Mutations*
600	200	CR	IDH2, JAK2, SFSR2, ASXL1, RUNX1, NTRK1, CALR, CSF1R
600	200	CRp	TYK2
600	200	CRi	IDH2, MPL, CEBPA, NTRK1, CALR, CSF1R, STAT5A
400	400	PR	IDH2, DMNT3A, NPM1, NRAS, CSF3R, DOT1L

*Mutation profiling was performed by FoundationOne Heme panel or Investigator reported.
**Investigator reported

VEN+ COBI:
ORR 18%

VEN+ IDA:
ORR 20%

VEN 600 mg+ IDA 200 mg:
0RR 38%

Daver et al, ASH 2017

Thank you!

All the centers involved in the phase 1 trial and in the phase 3 MIRROS trial

Institute "L. and A. Seràgnoli", Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna

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