Results of the OPAL Study: A Phase II Study to Evaluate the Efficacy, Safety and Tolerability of Tosedostat (CHR-2797) in Elderly Subjects with Treatment Refractory or Relapsed Acute Myeloid Leukemia

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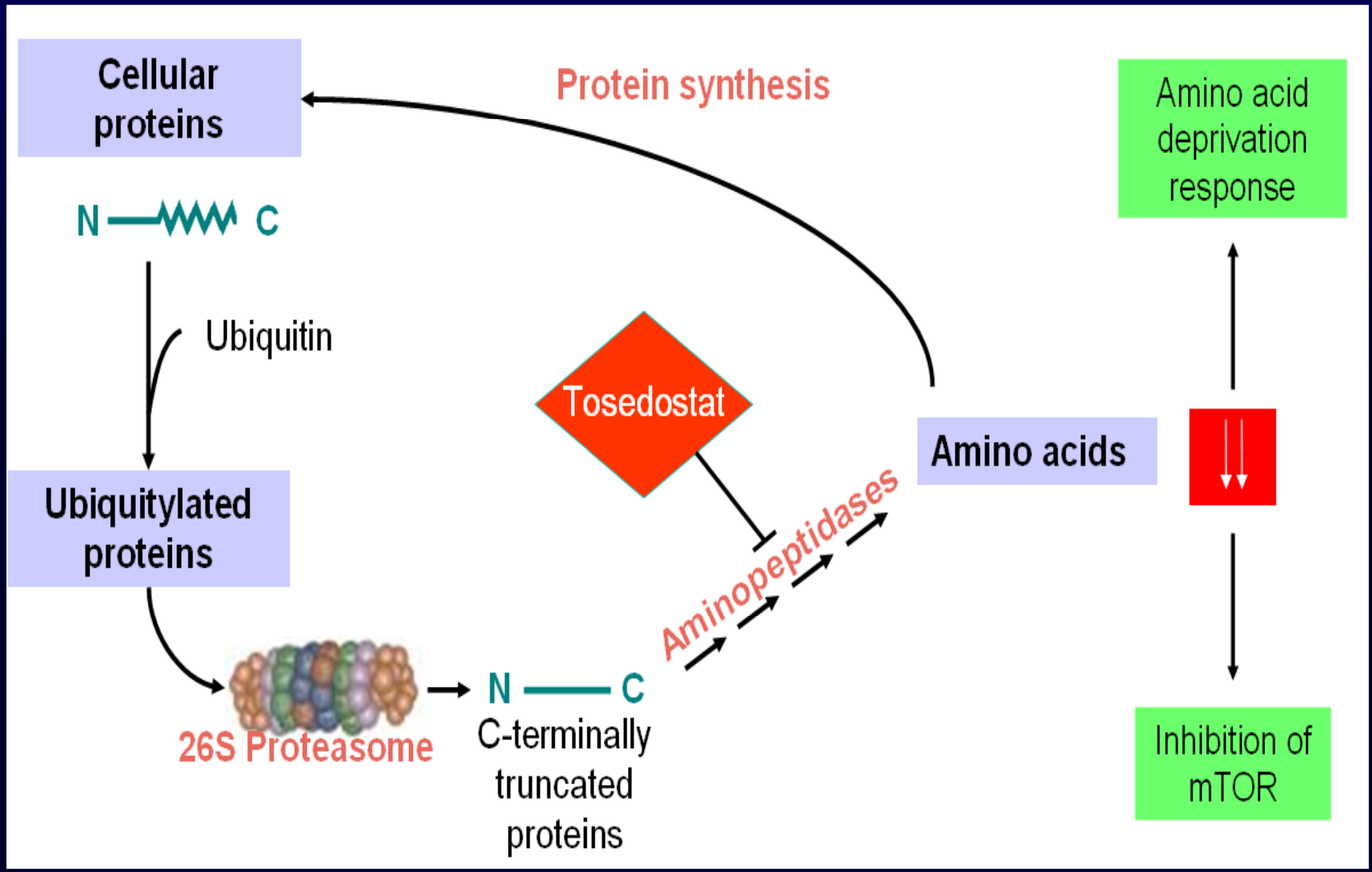
Aminopeptidase Inhibiton



Tosedostat

- Targets aminopeptidases
  - Induces Amino Acid Deprivation Response selectively in cancer cells
- Pleiotropic effects against cancer cells in vitro and in vivo
- Orally administered as ester moiety
- Hydrolysed to polar acid moiety CHR-79888 and trapped inside cells
- Linear PK without accumulation

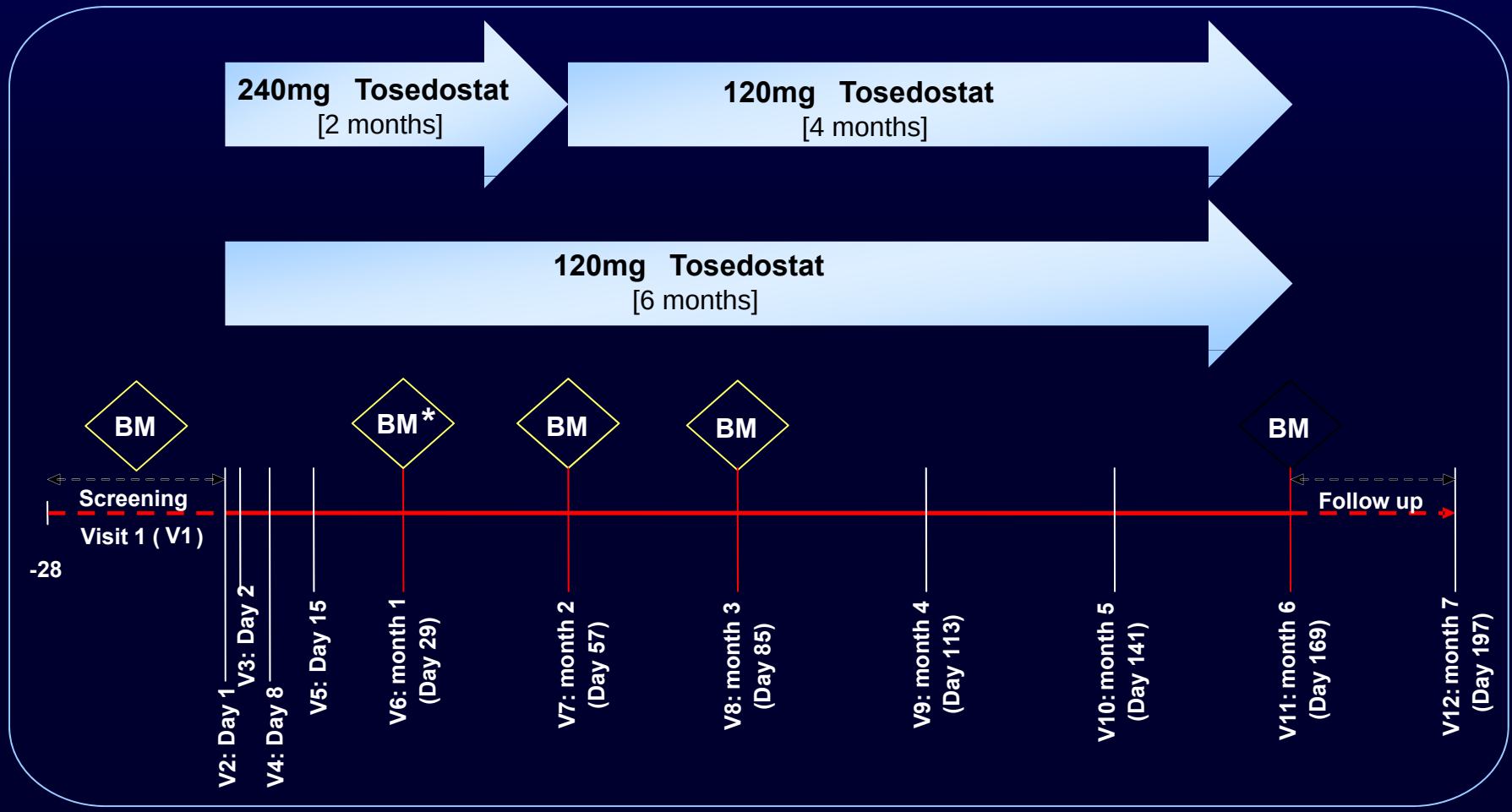
Tosedostat Clinical Experience

- CHR-2797-001 (Reid et al, Clin Cancer Res, 2009)
  - Phase I/II study in solid tumours
  - MTD 320 mg, MAD 240 mg
  - 40 patients: 1 durable PR and 7 confirmed SDs
- CHR-2797-002 (Lowenberg et al, JCO, 2010)
  - Phase I/II study in hem-onc tumours
  - MTD 180 mg, MAD 120 mg
  - 51 AML patients: 14 (28%) response (14% CR)
  - R/R AML subset (N=35): 11 (31%) PR or better

MTD, maximally tolerated dose; MAD, maximum acceptable dose

OPAL
Study Design

- Randomized phase II: ~35 patients per arm
- Primary objective: safety, efficacy, determine optimal dose



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Eligibility Criteria

- Age ≥ 60 years
- Refractory/relapsed AML (WHO classification) with 1st CR <12 months or no CR
- No prior salvage therapy
- Bone marrow aspiration within 4 weeks not in CR or CRp.
- Adequate hepatic and renal function, PS ≤ 2, LVEF ≥ 50%
- <u>Exclusion Criteria</u>
  - Anti-cancer therapy within 2 weeks prior to study entry (except hydroxyurea)
  - Serious co-existing medical conditions

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Patient Characteristics

	No. (%), or Median [range]		
	Overall (N = 73)	120 mg (n = 38)	240 mg (n = 35)
Demographics			
Median age (range)	72 [65 – 86]	73 [64 – 86]	71 [65 – 86]
>75 years	23 (32)	14 (37)	14 (37)
Male	43 (59)	26 (68)	17 (49)
Median days since AML Dx	211	226	154
Cytogenetics*			
Poor	28 (39)	13 (35)	15 (44)
Intermediate	42 (59)	23 62)	19 (56)
Better	1 (1)	1 (3)	0

*2 patients have no cytogenetic data

OPAL
Prior Therapy

	Overall (N = 73)	120 mg (n = 38)	240 mg (n = 35)
Prior AML therapy, n (%)			
Ara-C + anthracycline	28 (38)	14 (37)	14 (42)
Other Ara-C regimens	18 (25)	8 (21)	10 (30)
Hypomethylating agents	25 (34)	15 (39)	10 (29)
Other regimens	2 (3)	1 (3)	1 (3)
Remission experience, n (%)			
Refractory (no CR)	38 (52)	18 (47)	20 (57)
Mean CR duration, days	83	99	66

OPAL
Patient Disposition

	No. (%)		
	Overall (N = 73)	120 mg (n = 38)	240 mg (n = 35)
Completed Rx to week 24	10 (14)	5 (13)	5 (14)
Completed Rx to week 12	25 (34)	12 (32)	13 (37)
Completed Rx to week 4	56 (77)	29 (76)	27 (77)
Reason for withdrawal:			
Adverse event	14 (19)	9 (24)	5 (14)
Disease Progression	35 (48)	20 (53)	15 (43)
Withdrawal of consent	7 (10)	2 (5)	5 (14)
Death	7 (10)	2 (5)	5 (14)

OPAL
Overall Response

Response	No. (%)		
	Overall (n=73)	120mg (n=38)	240mg (n=35)
ORR	**16 (22%)**	**8 (21%)**	**8 (23%)**
CR/CRp/MLFS	9 (12%)	4 (11%)	5 (14%)
CR	1	0	1
CRp	6	2	4
MLFS	2	2	0
Partial Remission	7	4	3
SD	21	14	7
PD	13	6	7
Unevaluable*	23	10	13

*Patients with no post-baseline bone marrow assessment

OPAL
Time to Best Response

Response	Median days (range)		
	Overall (n=73)	120mg (n=38)	240mg (n=35)
CR/CRp/MLFS	84 (29, 170) n=9	58 (29, 150) n=4	86 (29, 170) n=5
PR	56 (29, 86) n=7	52 (29, 86) n=4	56 (33, 58) n=3
PR or better	56 (29, 169) n=16	52 (29, 86) n=8	56 (29, 169) n=8

OPAL
Overall Response by Prior AML Rx

Prior Induction Rx	N Response / Total (%)		
	Overall	120mg	240mg
Cytarabine/ anthracycline	4/28 (14)	1/14 (7)	3/14 (21)
Hypomethylator	9/25 (36)	6/15 (40)	3/10 (30)
Other cytarabine	3/18 (17)	1/8 (13)	2/10 (20)
Other	0/2	0/1	0/1
TOTAL	16/73 (22)	8/38 (21)	8/35 (23)

OPAL
Overall Response by AML Type

	N Response / Total (%)		
	Overall	120mg	240mg
Primary AML	9/47 (19)	5/26 (19)	4/21 (19)
2º AML – prior chemotherapy	0/7	0/2	0/5
2º AML – prior MDS	7/19 (37)	3/10 (30)	4/9 (44)

OPAL
Duration of Response

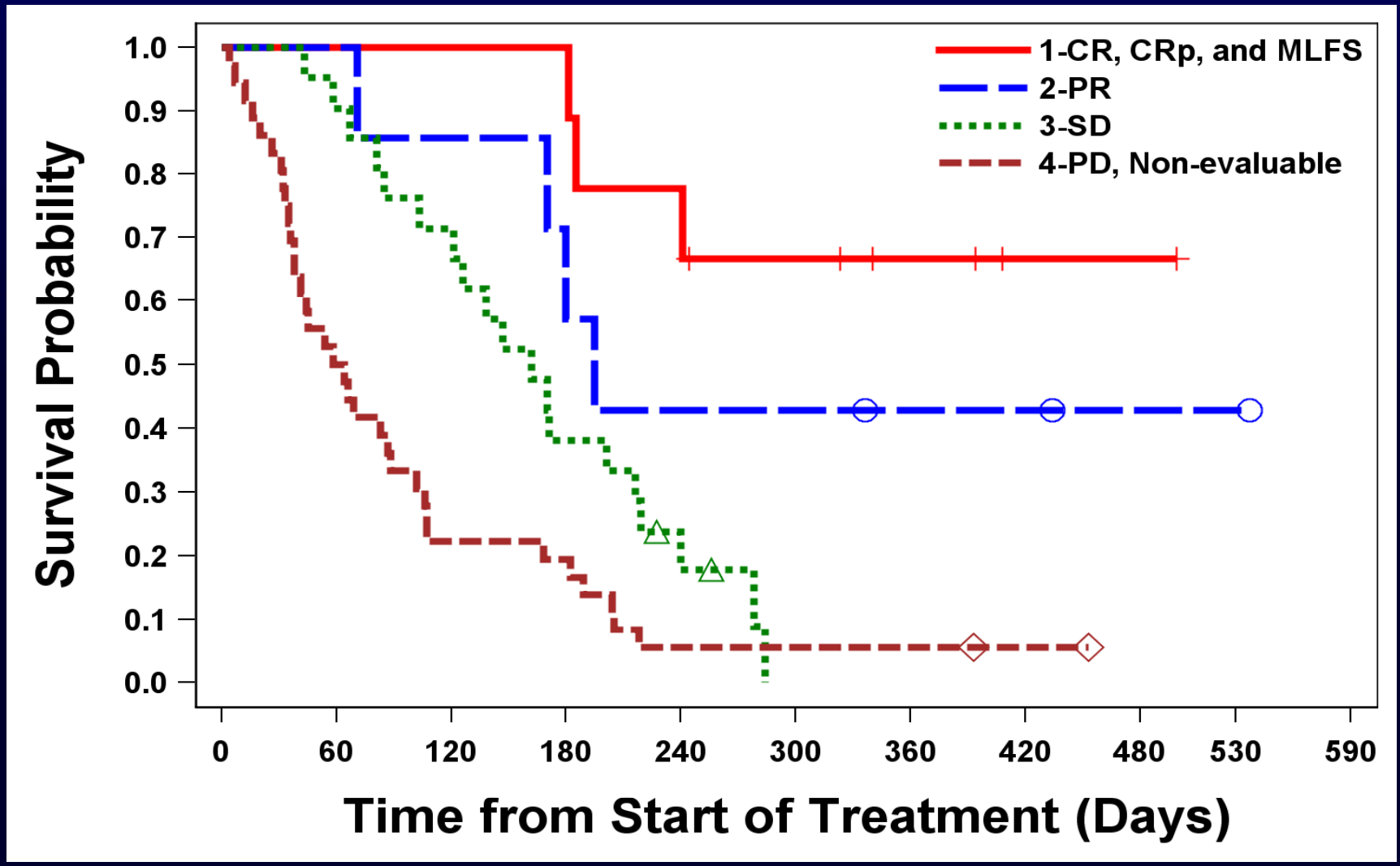
Response	Median days (range)		
	Overall (n=73)	120mg (n=38)	240mg (n=35)
CR/CRp/MLFS	121 (29, 245) n=9	110 (29, 245) n=4	121 (57, 173) n=5
PR	32 (27, 84) n=7	34 (27, 84) n=4	32 (29, 41) n=3
PR or better	84 (27, 331) n=16	62 (27, 331) n=8	103 (29, 245) n=8

OPAL
Overall Survival

Response	Median days (range)		
	Overall (n=73)	120mg (n=38)	240mg (n=35)
Overall	126 (4 - 537)	175.5 (4 - 537)	88 (7 - 434)
CR/CRp/MLFS	323 (181 - 499) n=9	214.5 (181-499) n=4	340 (241 - 408) n=5*
PR	195 (71 - 537) n=7	258 (170 - 536) n=4*	195 (71 - 434) n=3
SD	162 (43 - 284) n=21	166 (43 - 278) n=14	147 (67 - 284) n=7
PD/non-evaluable	61 (4 - 453) n=36	61 (4 - 453) n=16	55.5 (7 - 168) n=20

*some patients in this category still alive at 1 October 2011

Overall Survivall



Includes data from extension study TOPAZ

OPAL
Treatment Emergent Adverse Events

Preferred Term	Percentage	
	Overall	Grade ≥3
Diarrhea	58	4
Edema Peripheral	55	0
Fatigue	49	21
Dyspnea	41	16
Nausea	38	0
Decreased Appetite	37	3
Febrile Neutropenia	36	29
Hypotension	36	10
Dizziness	34	0
Pyrexia	32	3
Cough	32	1

OPAL
Most Common SAEs

Preferred Term	Percentage
Febrile Neutropenia	29
Disease Progression	15
Atrial Fibrillation	8
Pneumonia	8
Pyrexia	6

OPAL: Conclusions

- Significant anti-leukemic activity in relapsed/refractory AML
  - Overall response rate 22%
- Time to response occurred around 56 days of treatment
- Higher responses rate on prior MDS or previous HMA
- Oral tosedostat was well tolerated
- No clear dose difference between 120mg and 240mg
  - 120mg chosen due to good responses, pre-clinical data and safety profile
- Subsequent studies:
  - Combination with HMA, LDAC in AML
  - MDS post HMA failure

OPAL Investigators and sites

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