

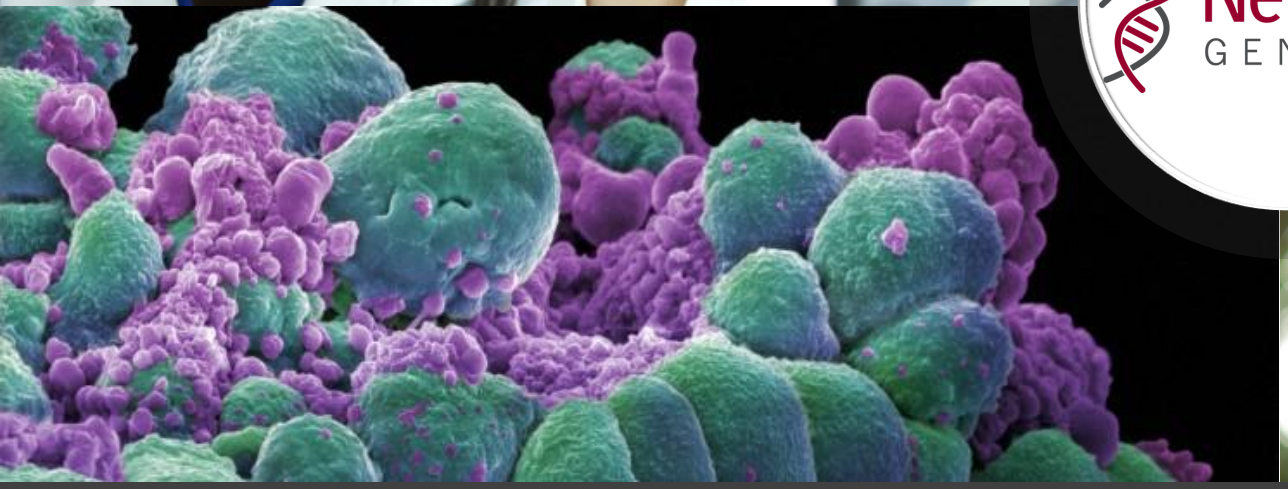


Indoximod Combined with Standard Induction Chemotherapy Is Well Tolerated and Induces a High Rate of Complete Remission with MRD-Negativity in Patients with Newly Diagnosed AML: Results from a Phase 1 Trial

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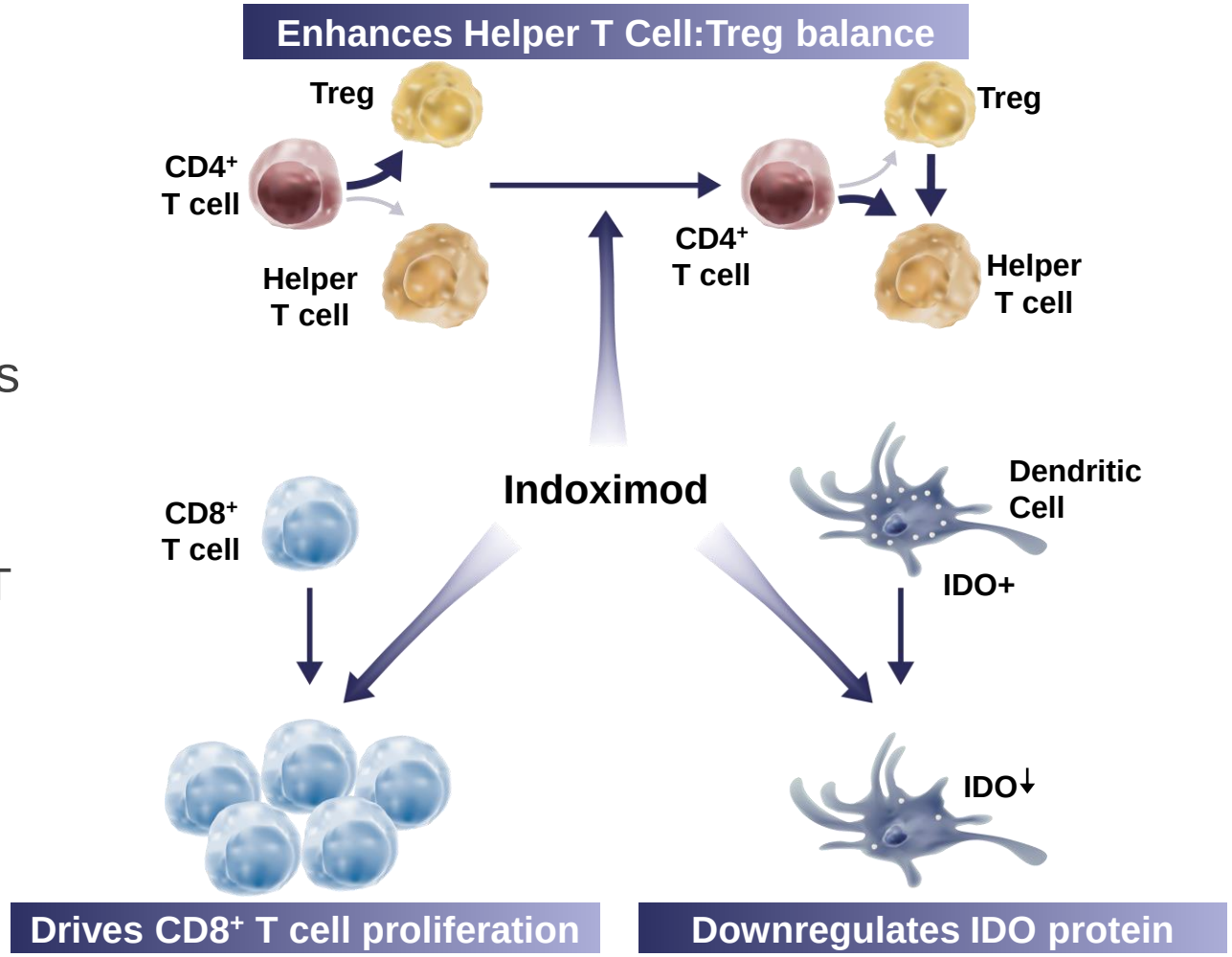
Background

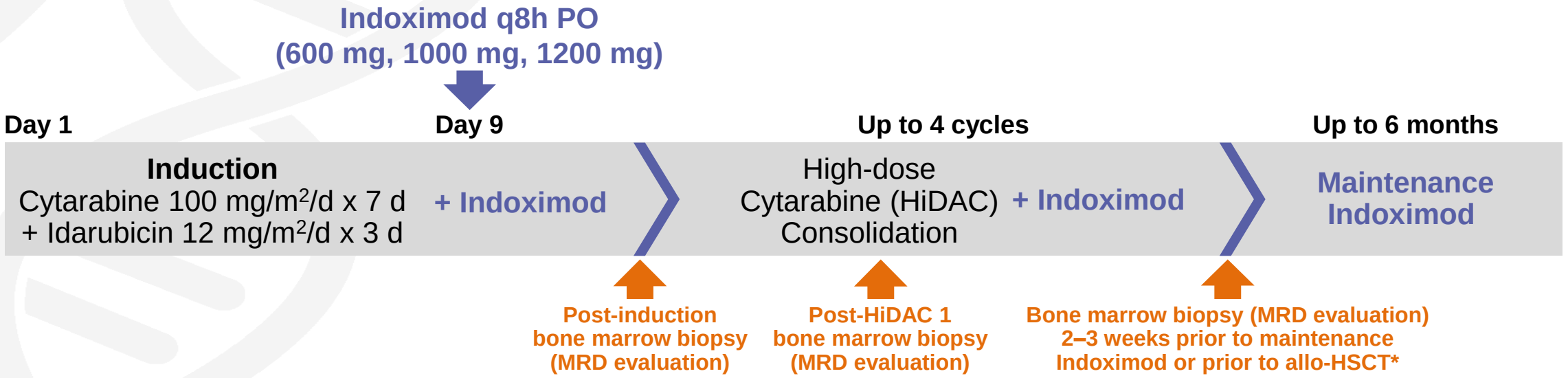
- Indoximod is an orally administered, small-molecule IDO pathway inhibitor that reverses the immunosuppressive effects of low tryptophan and high kynurenine that result from IDO activity
- Indoximod has immunostimulatory effects mainly by:
  - reversing the effects of low tryptophan by increasing proliferation of effector CD8+ T cells
  - directly reprogramming T regulatory cells into helper T cells
  - downregulating IDO expression in dendritic cells



Brincks EL, et al. AACR 2018, poster 3753.

Study Objectives and Design

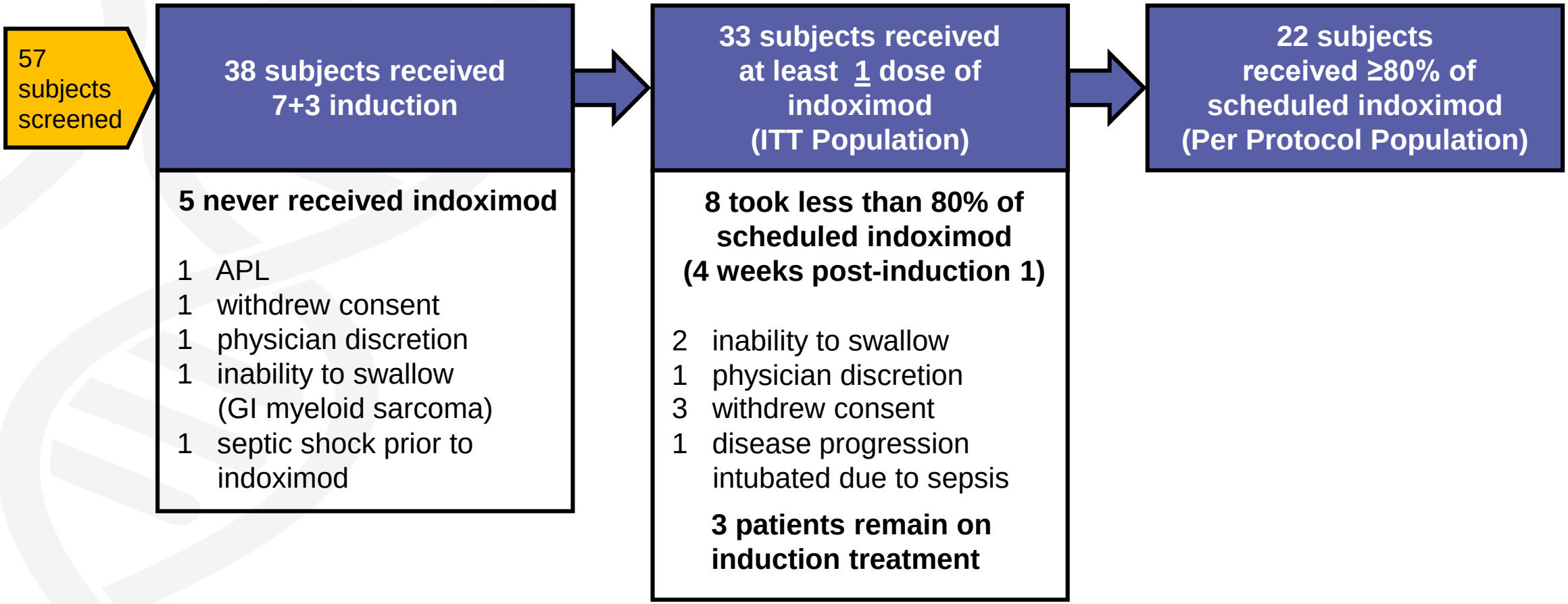
- **Primary objective:** To assess the safety and preliminary efficacy of indoximod in combination with standard induction chemotherapy in adult patients with newly diagnosed AML
- **Key eligibility:** ≥18 years, confirmed diagnosis of AML, ECOG PS ≤2
- Open-label, multicenter Phase 1 study, 3+3 design



- Regimen-limiting toxicity (RLT): any ≥Grade 3 non-hematologic AE unrelated to underlying AML, cytarabine or idarubicin
- Indoximod is discontinued 3–4 weeks before allo-HSCT and not resumed post-allo-HSCT

*Patients may undergo allo-HSCT post consolidation at discretion of MD.

Patient Disposition



Baseline demographics and disease characteristics (N = 33)

Age	
Median years (range)	54 (18–72)
Sex, n (%)	
Male	22 (67%)
Race, n (%)	
White	26 (79%)
African American	4 (12%)
Asian	3 (9%)
ECOG performance n (%)	
0	22 (67%)
1	8 (24%)
2	3 (9%)
ELN risk classification, n (%)	
Favorable	13 (39%)
Intermediate	1 (3%)
Adverse	**19 (58%)**

Mutational panel, n	
FLT3-ITD	3
FLT3-TKD	4
NPM1	10
DNMT3A	7
IDH1/IDH2	7
NRAS/KRAS	12
RUNX1/ASXL1	8
TP53	**7**
Baseline CBC	
White cell count (x10^3/µL), median	6.95 (0.7–65.6)
Absolute neutrophil count (k/µL), median	1.38 (0–17.38)
Hemoglobin (g/dL), median	8.3 (6.4–12.2)
Platelet count (x10^6/µL), median	49 (11–160)

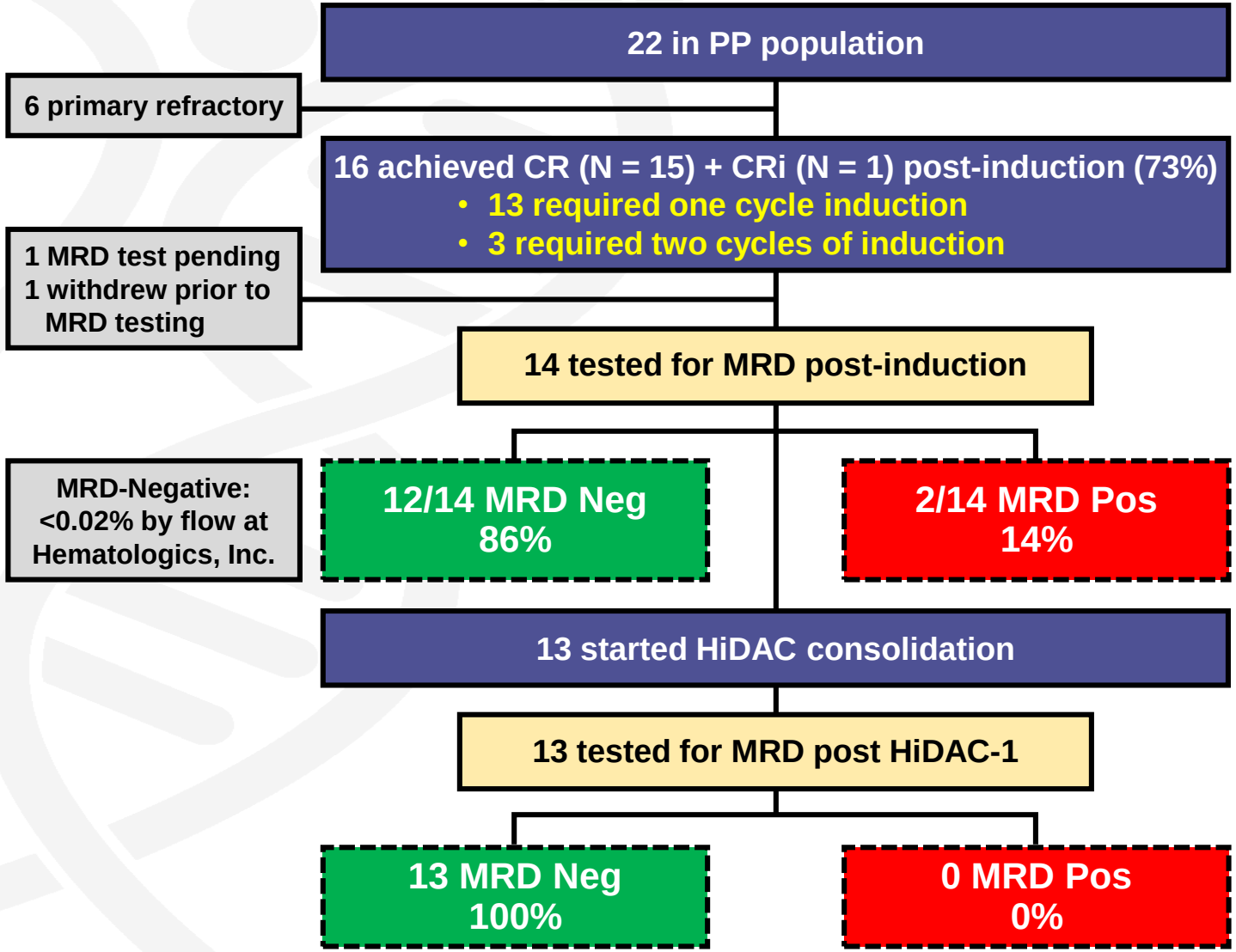
Adverse Events

Grade ≥3 AE (occurring in ≥9%, regardless of attribution)	N = 33 (%)
Hematologic	
Febrile neutropenia	27 (82%)
Anemia	4 (12%)
Thrombocytopenia	3 (9%)
Non-hematologic	
Hypoxia	5 (15%)
Hypotension	3 (9%)
Pneumonia	3 (9%)

- Hematologic toxicities, in line with expected disease and chemotherapy related toxicities, were the most frequently reported adverse events
- 94% of participants experienced at least one grade ≥3 adverse event
- Three participants experienced fatal adverse events during the study—all deemed unrelated or unlikely related to indoximod by the treating MD

- **No regimen limiting toxicities were observed when indoximod was combined with 7+3 induction and HiDAC consolidation chemotherapy in patients with newly diagnosed AML**
- **The RP2D of indoximod was determined to be 1200 mg q8h PO in combination with 7+3 induction and HiDAC consolidation chemotherapy**

Clinical Activity (Per Protocol population, N = 22)



Results Summary

Per protocol population	N=22
Achieved CR/CRi post-induction	16/22 (73%)
MRD negative post-induction	12/14 (86%)
MRD negative post-consolidation	13/13 (100%)

MRD in AML post-induction—Literature review

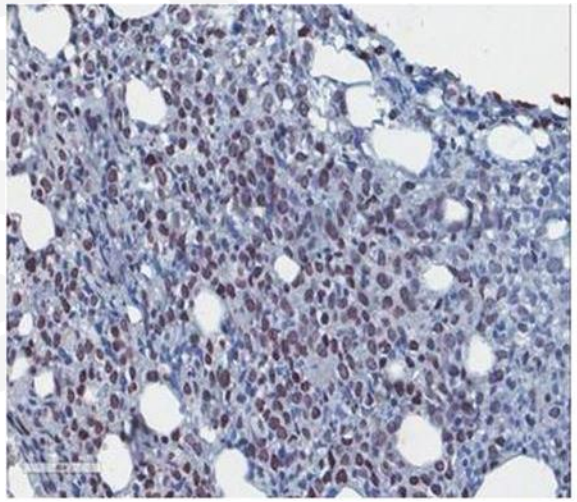
	Newly Dx AML pts (n)	MRD Methodology	CR rate, n (%)	Post Induction MRD-Neg in pts achieved CR, n (%)	Commentary
Buccisano 2006[1]	135	MRD by flow (<0.035%)	100/135 (83%)	35/100 **(35%)**	
Chen 2015[2]	165	MRD by flow	133/165 (81%)	112/133 **(84%)**	heterogenous chemotherapy regimens (high intensity, standard, low intensity)
Jongen-Lavrencic 2018[3]	340	Next-generation sequencing (MRD by flow as comparison)	Not reported	269/340 **(79%)**	MRD negative rate after two cycles of induction
Freeman 2018[4]	1443	MRD by flow (<0.02%–0.05%)	1023/1443 (71%)	446/1023 **(44%)**	NPM1-mutated pts excluded, younger patients (<60)

- Currently collecting more contemporaneous multi-institutional dataset to optimize comparison of individual patient characteristics

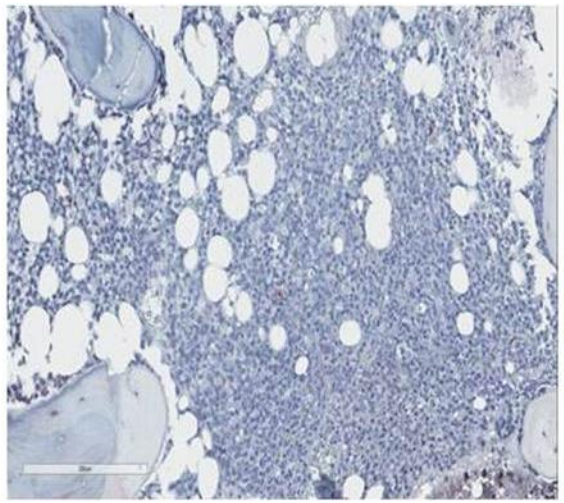
1. Buccisano F, et al. Leukemia 2006:20:1783-9; 2. Chen X, et al. J Clin Oncol 2015:33:1258-64;
3. Jongen-Lavrencic M, et al. N Engl J Med 2018:378:1189-99; 4. Freeman SD, et al. J Clin Oncol 2018:36:1486-97.

IDO expression in initial diagnostic bone marrow

Composite IDO scoring system



Strong expression



Minimal expression

- Published data predict a higher IDO score is associated with more refractory disease and greater early mortality[1]
- 17 patients had diagnostic marrow biopsies available for IDO staining
- All patients expressed IDO in bone marrow as determined by IHC (composite score) and mRNA
- Due to small sample size, there is not yet statistical correlation between IDO expression and clinical outcome

1. Mangaonkar A, et al. Sci Rep 2017;7:12892.

Conclusions

- Indoximod in combination with standard 7+3 chemotherapy was well tolerated and the overall adverse event profile observed in this small sample size was consistent with the profile of 7+3 chemotherapy alone
- No regimen limiting toxicities were observed and the RP2D of indoximod was determined to be 1200 mg q8h PO in combination with 7+3 induction therapy
- Evidence of clinical activity was observed as supported by a post induction MRD negativity (<0.02% by flow) rate of 86% and post-HiDAC1 MRD negativity of 100%
- Given the well characterized role of IDO as a marker of poor prognosis in AML, this study supports targeting the IDO pathway as a potentially beneficial approach in frontline AML