PB045

Individualized schedule improves rates and severity of anemia in patients treated with lunresertib, a PKMYT1 inhibitor, and camonsertib, an ATR inhibitor, in the Phase I MYTHIC study (NCT04855656)

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Background

- Lunresertib (lunre), is a first-in-class, membrane-associated tyrosine- and threonine-specific Cdc2-inhibitory kinase inhibitor (PKMYT1i)
- Camonsertib (cam) is an ataxia telangiectasia and Rad3-related inhibitor (ATRi)[1,2]
- The combination of lunre + cam in Module 2 of the MYTHIC study (NCT04855656) has demonstrated promising clinical activity in molecularly selected patients across multiple tumor types[3]
- The combination is well tolerated with the most predominant high-grade toxicity of-on target anemia
  - For lunre monotherapy, Gr3 anemia was reported in 6% of patients[2] and 11% of patients treated at the optimized dose of cam alone[3]
  - Gr3 anemia for the combination was initially reported in 45% of patients treated at RP2D in this heavily pretreated Phase 1 study population[4]
- An in-depth analysis of anemia risk factors and management strategies led to implementation of an individualized schedule and management algorithm in October 2023
- Here, we present the analysis and the effectiveness of the strategy in patients treated at the RP2D for ~9 months since initial implementation

MYTHIC study design

Key inclusion criteria

Module 2: Lunre with cam

- Patients ≥12 years with solid tumors resistant/intolerant to standard therapy
- Local NGS report (tissue or plasma)[a]
- Tumors with *CCNE1* amplifications[b], or deleterious alterations in *FBXW7* or *PPP2R1A*
- ECOG PS of 0–1
- Hgb ≥10 g/dL
- Platelets ≥100 K/µL
- ANC ≥1.5 K/µL

Study ongoing *NCT04855656*

Study timeline and objectives

May 2022: Module 2 initiated
Oct 2023: Schedule optimization implemented
Aug 2024: Data snapshot

✓ **Primary endpoints:**
- Safety and tolerability
- RP2D, schedule

✓ **Other endpoints:**
- Pharmacokinetic
- Preliminary antitumor activity
- Kinetics of ctDNA

Module 2 dose finding and backfill cohorts

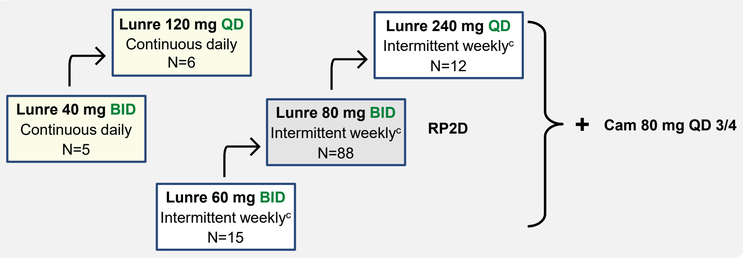

Figure 1. Overview of MYTHIC Module 2 including (upper left) key inclusion criteria, (upper right) study timeline and endpoints, and (lower panel) dose finding cohorts. [a] NGS report centrally reviewed and annotated by Precision Oncology Decision Support (PODS) Group at MDACC. [b] *CCNE1* amplification (copy number ≥6). [c] 3 days on/4 days off (3/4) with 2 weeks on/1 week off (2/1w) or 3 weeks continuous were evaluated.

Analysis population and methods

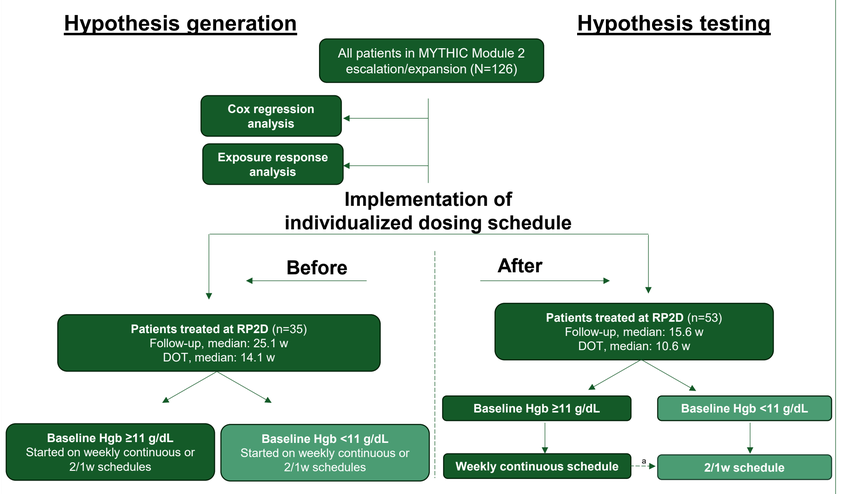

Figure 2. Flowchart of patient populations used for analysis of anemia predictors and comparison populations before (left) and after (right) implementation of anemia management strategy. [a]Patients who switched due to Gr3 anemia or ≥2 g/dL drop in Hgb.

- In MYTHIC (NCT0485565), 126 patients with biomarker-selected solid tumors were treated with lunre + cam; 85 received RP2D (80 mg BID lunre + 80 mg QD cam) given 3/4, either weekly or 2/1w
- Exposure-response analysis assessed daily pharmacokinetic exposures at steady state (AUC and C_{max}) vs. the probability of anemia. Cox regression models assessed baseline predictive factors of Gr3 anemia in patients at RP2D range
- Results of the analysis led to prospective testing of an individualized weekly schedule based on BL and on-study Hgb
  - Schedule determination: Patients with BL Hgb ≥11g/dL received 3w continuous and those with Hgb <11 g/dL received 2/1w
  - On-treatment adjustments (for those starting on weekly dosing): prioritize interruptions over daily dose reductions if Hgb decreases by 2 g/dL or Gr2 anemia
- Overall rates, exposure-adjusted event rate (Gr3 events/patient-month of observation) of anemia as well as other adverse events, RBC transfusions, dose interruptions, and dose reductions were analyzed to assess the impact of the individualized schedule approach
- Anti-tumor activity was assessed radiographically (RECIST v1.1) and by exploratory ctDNA using Tempus xF V3

Results: Anemia risk analysis

Predictor analysis supports baseline marrow function as key reason for Gr3 anemia, with alternate schedule providing potential mitigation

Individual predictor	Univariate analysis: Individual HR (90% CI)	Univariate analysis: Chi-square *P*-value	Multivariate analysis: Adjusted[a] HR (90% CI)	Multivariate analysis: Adjusted *P*-value
Age, years	1.01 (0.97, 1.04)	0.707		
Sex, female vs. male	1.56 (0.55, 4.41)	0.486		
Baseline ECOG PS, 1 vs. 0	1.93 (0.83, 4.47)	0.201		
Baseline weight, kg	1.01 (0.99, 1.04)	0.465		
Lines of prior anti-cancer therapy, n	1.16 (1.00, 1.35)	0.095		
Number of lines of therapy, >3 vs. ≤3	2.95 (1.35, 6.45)	**0.022**	6.82 (2.58, 17.99)	**0.001**
Baseline Hgb, g/dL	0.71 (0.54, 0.94)	**0.048**		
Baseline Hgb category, <11 vs. ≥11 g/dL	2.89 (1.32, 6.37)	**0.027**		
Dose schedule, 3w vs. 2w/1w	8.05 (1.42, 45.50)	**0.048**		
Weekly schedule and baseline Hgb				
3w and BL <11 g/dL vs. 2/1w and any BL Hgb	24.93 (3.8, 164.1)	**0.005**	88.07 (9.11, 851.35)	**0.001**
3w and BL ≥11 g/dL vs. 2/1w and any BL Hgb	5.74 (0.95, 34.51)	0.109	10.06 (1.38, 73.48)	0.056

[a]Adjusted HR and *P*-values are based on the multivariate Cox model adjusting for other factors within the model. Multivariate covariates were selected based on a stepwise model selection method. All patients in RP2D range (60–80 mg BID) and with at least 6 w of follow-up in MYTHIC Module 2 preoptimization were included. Each HR and each Chi-square *P*-value in the univariate analysis are based on the corresponding single predictor model. Additional individual predictors that were nonsignificant included in the analysis but not shown on the table included age range (≥65 vs <65 years), BMI, gynecological tumor (Y vs N), and prior platinum (Y vs N).

Exposure response analysis excluded exposure as a reason for Gr3 anemia and along with predictive factor analysis led to a mechanism-based schedule modification approach

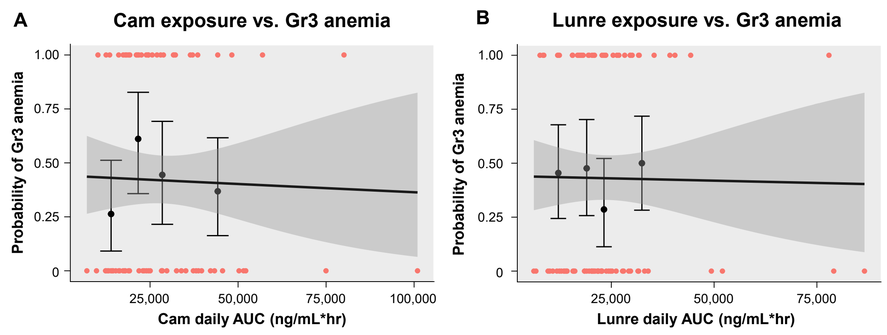

Figure 3. Logistic regression on the relationship between **(A)** cam or **(B)** lunre exposure and the incidence of Gr3 anemia. The solid lines represent logistic regression fit of probability of Gr3 anemia vs. exposure; the shaded areas represent 90% CIs. Solid dots and error bars represent incidence and 95% of CIs of observation at mean exposure within each exposure quartile. All patients enrolled in MYTHIC Module 2 and at least 6 weeks follow-up preoptimization were included.

Results: Individualized schedule implementation

Baseline characteristics are similar for patients enrolled before and after implementation of individualized dosing strategy

Parameter	Before optimization (N=35)	After optimization (N=53)
Sex, n (%)		
Female	25 (71.4)	43 (81.1)
Age (years)		
Median (range)	60 (16–78)	63.0 (29–82)
≥65 years, n (%)	15 (42.9)	23 (43.4)
ECOG PS[a], n (%)		
0	16 (45.7)	26 (49.1)
1	18 (51.4)	27 (50.9)
Prior lines of therapy, n (%)		
1-2	13 (37.1)	21 (39.6)
3-4	16 (45.7)	22 (41.5)
≥5	6 (17.1)	10 (18.9)
Baseline Hgb (g/dL),		
Median (range)	10.9 (8.4–15.5)	11.8 (9.1–16.3)
(Q1, Q3)	(10.3, 12.1)	(10.8, 13.1)
Tumor types, n (%)		
Endometrial	14 (40.0)	17 (32.1)
Colorectal	4 (11.4)	5 (9.4)
Ovarian	6 (17.1)	19 (35.8)
Breast	1 (2.9)	2 (3.8)
Lung	2 (5.7)	2 (3.8)
Other[b]	8 (22.9)	8 (15.1)

Includes patients from MYTHIC Module 2 treated at RP2D: lunresertib 80mg BID + camonsertib 80mg QD at datacut of 22 August, 2024. [a] One adolescent patient in the before optimization group had a Lansky Performance Status score of 90. [b] Other tumor types before optimization: gastroesophageal (n=3); hepatobiliary, melanoma, pancreatic, soft tissue sarcoma, and bone (n=1 each). After optimization: cervical (n=2); bone, gastroesophageal, head and neck, pancreatic, prostate, and anal (n=1 each).

Gr3 anemia frequency was meaningfully reduced in both patient groups after individualized schedule optimization

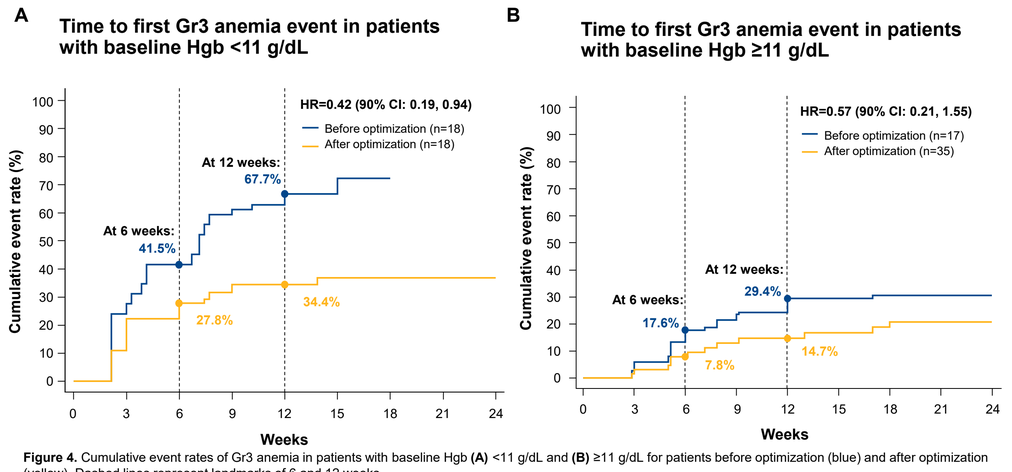

Figure 4. Cumulative event rates of Gr3 anemia in patients with baseline Hgb **(A)** <11 g/dL and **(B)** ≥11 g/dL for patients before optimization (blue) and after optimization (yellow). Dashed lines represent landmarks of 6 and 12 weeks.

- Individualized schedule optimization reduced the risk of Gr3 anemia by 58% in patients with baseline Hgb <11 g/dL
- Anemia management algorithm implementation likely reduced Gr3 anemia in this lower-risk group

Prospectively incorporated individualized schedule optimization reduced anemia rates, transfusions, and dose modifications

	Gr3 anemia, n (%)	Gr3 anemia, events/pt-mo	Gr3 anemia-related: RBC transfusions, n (%)	Gr3 anemia-related: Dose interruptions, n (%)	Gr3 anemia-related: Daily dose reductions[a], n (%)
Before optimization (n=35)	18 (51.4)	0.213	15 (42.9)	8 (22.9)	6 (17.1)
After optimization (n=53)	12 (22.6)	0.080	7 (13.2)	7 (13.2)	3 (5.7)

[a] Daily dose reductions were changes to the amount given each day vs. dose reductions due to schedule changes.

- In patients who started on a weekly schedule and switched to a 2/1w schedule (n=24; median DOT after switching: 9.6w; range: 3.0–57.3w), subsequent Gr3 anemia was reported in 16.7% of patients and 20.8% received an RBC transfusion

Clinical benefit is maintained after change to a less frequent schedule

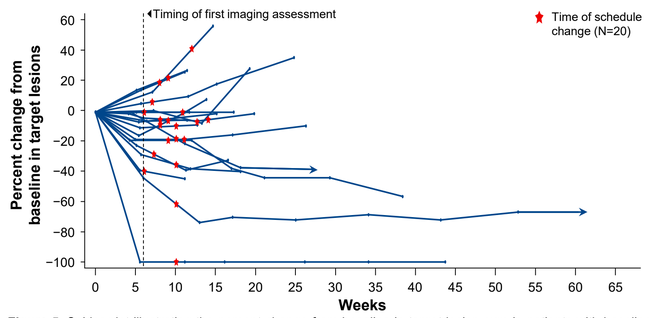

Figure 5. Spider plot illustrating the percent change from baseline in target lesion sum in patients with baseline Hgb ≥11 g/dL who switched from an initial weekly continuous to a 2/1w schedule, and who had a post-switch target lesion assessment (n=20). Patients were switched either due to Gr3 anemia or a >2 g/dL decrease in Hgb. Dashed lines represent time of first imaging assessment.

- The trajectory of tumor lesion decrease was generally maintained in patients across all tumors with baseline Hgb ≥11g/dL who switched to 2/1w after the first imaging assessment
  - After a change in schedule, deepening of target lesion regression was noted in some patients
- Less frequent schedule likely has minimal impact on efficacy

Molecular responses were maintained after schedule change

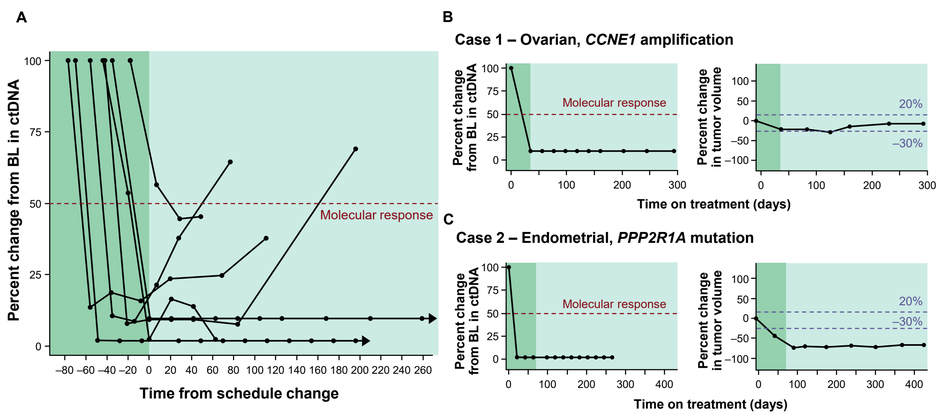

Figure 7. Five out of seven patients with ctDNA declines during weekly continuous dosing achieve and/or maintain molecular response following schedule change. (**A**) Relative ctDNA changes in patients during weekly continuous dosing (dark green) and weekly intermittent schedule (light green). Molecular responses are defined as 50% decline in mVAF compared to baseline and is denoted by a dashed line. Patients included in this analysis had no dose interruptions ≥7 consecutive days during Cycle 1. Case reports of (**B**) a patient with ovarian cancer and *CCNE1* amplification and (**C**) a patient with endometrial cancer and *PPP2R1A* deleterious mutation illustrating disease control following change in schedule, estimated by RECIST and ctDNA dynamics.

PFS after Week 9 is comparable between weekly and 2/1w schedule (either started on or switched to 2/1w)

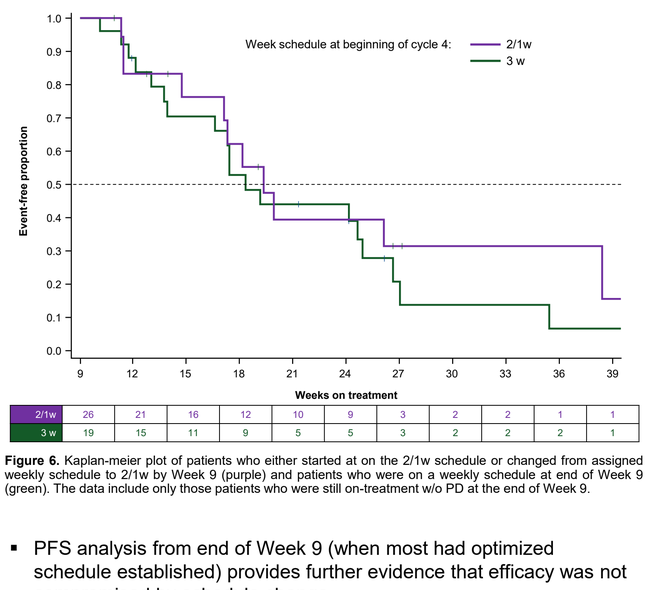

Figure 6. Kaplan-meier plot of patients who either started at on the 2/1w schedule or changed from assigned weekly schedule to 2/1w by Week 9 (purple) and patients who were on a weekly schedule at end of Week 9 (green). The data include only those patients who were still on-treatment w/o PD at the end of Week 9.

- PFS analysis from end of Week 9 (when most had optimized schedule established) provides further evidence that efficacy was not compromised by schedule change

Conclusions

- Meaningful reduction of Gr3 anemia (51% vs. 23%) in all patients by implementation of dosing optimization (individualized schedule, anemia management strategy)
  - Baseline Hgb, prior therapies, and treatment intensity (weekly vs. 2/1w) predicted Gr3 anemia frequency with combination lunre + cam
  - Anemia reduction was greatest in patients with baseline <11g/dL (Gr3 anemia at week 12: 68% vs. 34%; overall risk reduction: 58%)
  - RBC transfusions (43% vs 13%), dose interruptions (23% vs 13%) and dose reductions (17% vs. 6%) were also reduced with new schedule
  - Other Gr3 events were already uncommon (<5% incidence) and remained consistently low, regardless of schedule (data not shown)
- Overall clinical benefit was maintained after schedule change from weekly to 2/1w with generally maintained radiographic regressions and molecular responses
  - Additionally, no apparent impact on PFS in patients who started on or switched to 2/1w after Week 9
- These findings indicate a successful approach in mitigating mechanism-based anemia and support an individualized schedule based on entry Hgb to prevent anemia as an optimized dosing approach for the combination

References: 1. Gallo D, et al. *Nature*. 2022;604(7907):749–756. 2. Yap TA, et al. *Nat Med*. 2023;29(6):1400–1411. 3. Fontana E, et al. *J Natl Cancer Inst*. 2024;116(9):1439–1449. 4. Yap TA, et al. Plenary presentation at: AACR-NCI-EORTC International Conference; 2023; Boston, MA.

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Abbreviations: 2/1w, 2 weeks on/1 week off; 3w, 3 weeks continuous; ANC, absolute neutrophil count; ATRi, ataxia telangiectasia-mutated – and rad3-related inhibitor; AUC, area under the curve; BID, twice daily; cam, camonsertib; BL, baseline; BMI, body mass index; CI, confidence interval; ctDNA, circulating tumor DNA; DOT, duration of treatment; ECOG PS, Eastern Cooperative Oncology Group performance status; Gr, grade; Hgb, hemoglobin; HR, hazard ratio; hr, hour; lun, lunresertib; mo, month; mVAF, mean variant allele frequency; NGS, next generation sequencing; PD, pharmacodynamics; PK, pharmacokinetics; PKMYT1i, membrane-associated tyrosine- and threonine-specific Cdc2-inhibitory kinase inhibitor; Pts, patients; QD, once daily; PFS, progression-free survival; RBC, red blood cell; RECIST, Response evaluation criteria in solid tumors; RP2D, RP2D, recommended phase w, week.

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