ESMO TAT

Targeted Anticancer Therapies

COMPREHENSIVE DOSE-FINDING STRATEGY FOR SINGLE-AGENT RP-3500, A HIGHLY SELECTIVE INHIBITOR OF ATAXIA TELANGIECTASIA AND RAD3-RELATED (ATR) KINASE

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DECLARATION OF INTERESTS

I have the following financial relationships to disclose:

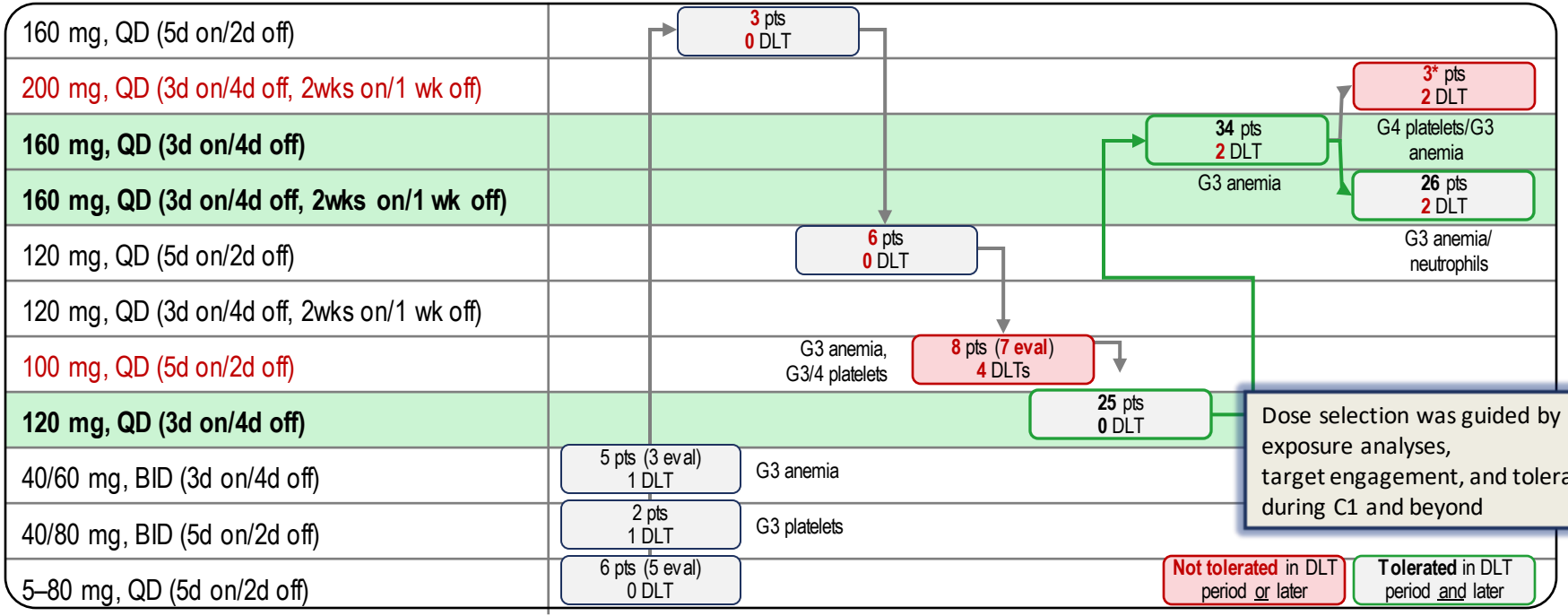
- Employment - Hospital Corporation of America (HCA) International

BACKGROUND/INTRODUCTION

- The phase 1/2a TRESR study (NCT04497116) evaluated RP-3500, a potent and highly selective ATR inhibitor (ATRi), in patients with advanced solid tumors harboring ATRi-sensitizing mutations
  - TRESR phase 1 study of RP-3500 monotherapy enrolled 120 patients between July 2020 and October 2021; enrollment into phase 2 is ongoing
- Interim data on safety and efficacy were presented at the ANE meeting in Boston (Oct. 2021)[1]
- A comprehensive approach to dose and schedule selection included pharmacokinetic/pharmacodynamic and safety analyses from three dosing cohorts at therapeutic doses (N=85)
  - 120mg once daily, 3 days on/4 days off, (n=25)
  - 160mg once daily, 3 days on/4 days off, (n=34)
  - 160mg once daily, 3 days on/4 days off, 2 weeks on/1 week off (n=26)
- A dosing nomogram was developed based on data to predict toxicity responses

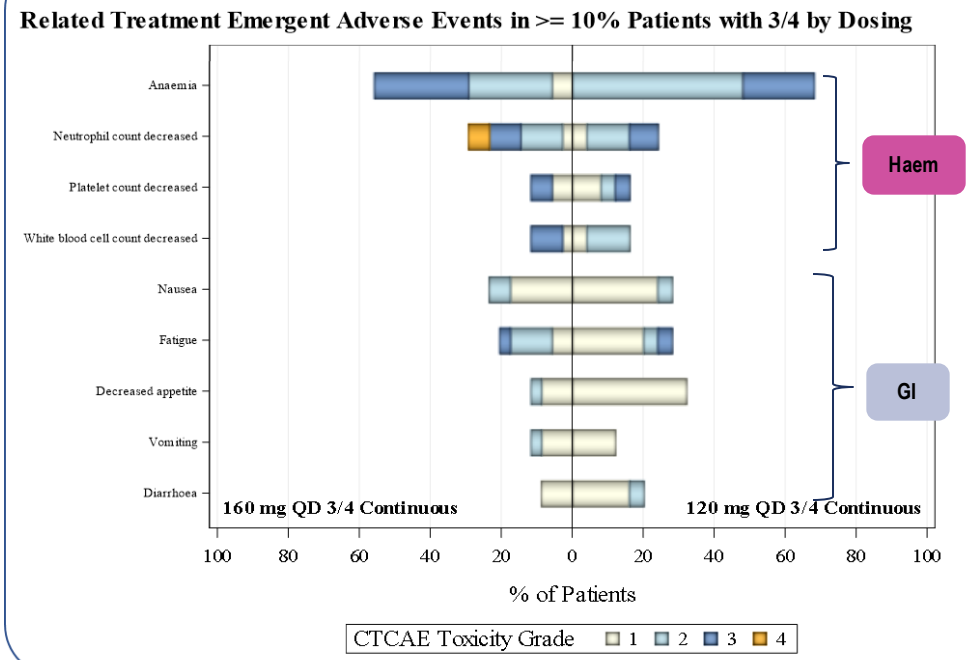
1. Yap T et al. Presented at: AACR-NCI-EORTC 2021. Abstract CC04-01.

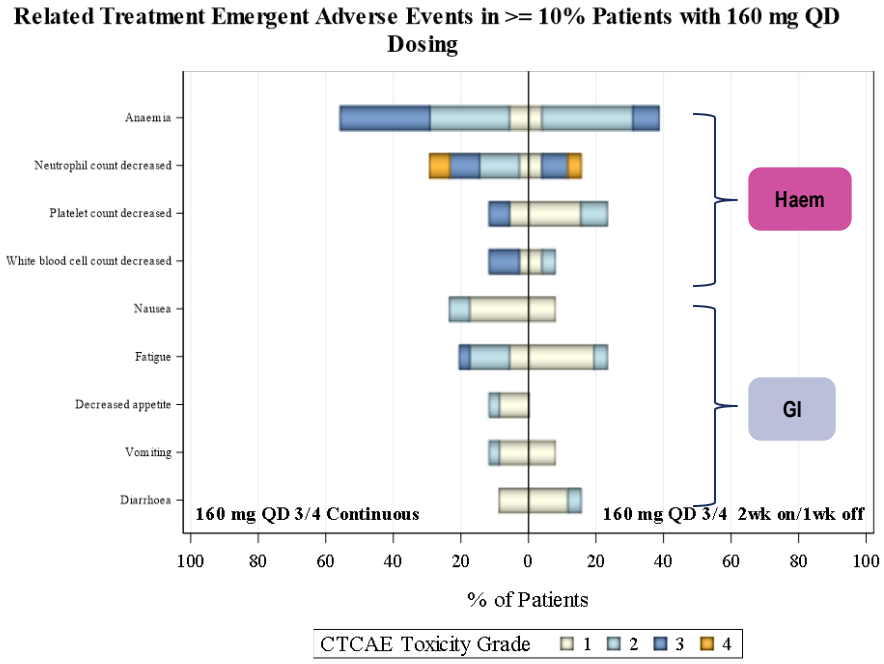
COMPREHENSIVE DOSE FINDING STRATEGY IN THE PHASE 1 TRESR STUDY



BID, twice daily; d, day; DLT, dose-limiting toxicity; eval, evaluated; Gr3, grade 3; pts, patients; QD, once daily; wks, weeks.
*2 addtnl patients enrolled at the 200 QD dose level were not evaluated at this dose level as they were switched to 160 QD early in Cycle 1, following the DLTs in the other 2 subjects

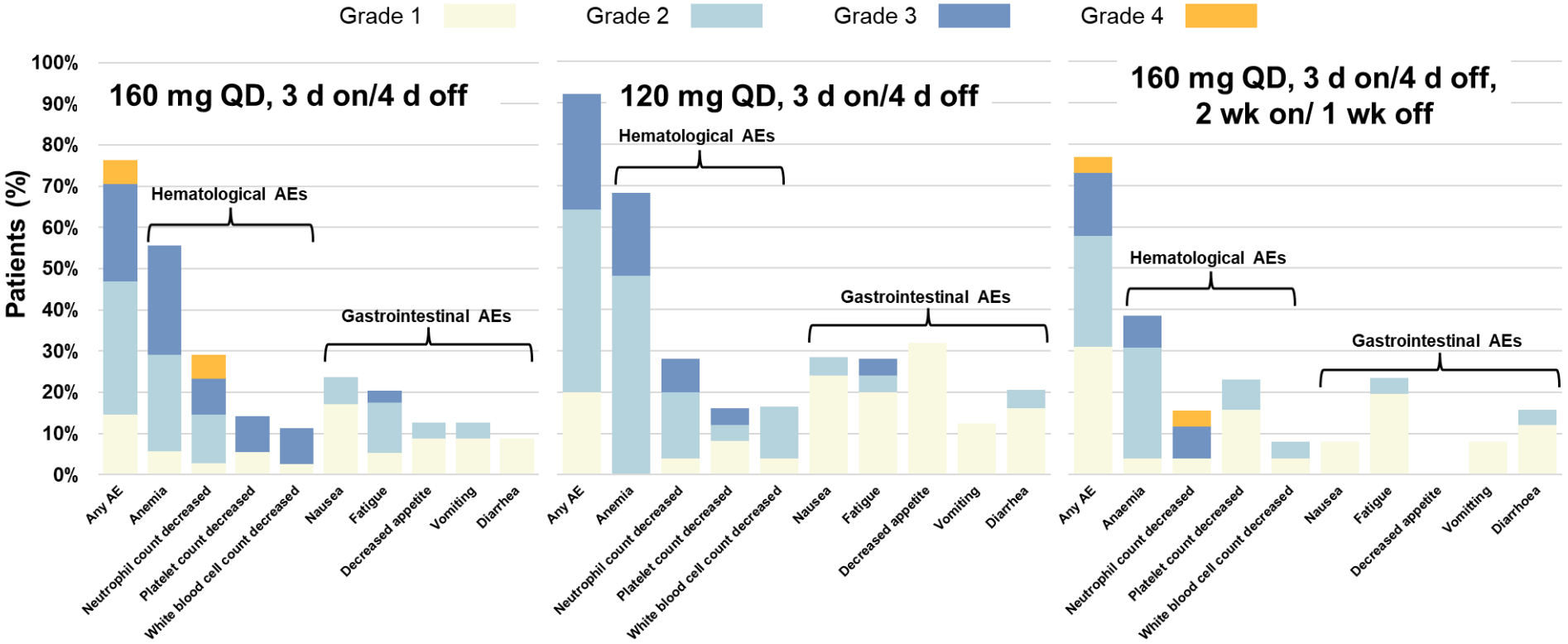
TREATMENT-RELATED AEs BY DOSE LEVEL AND GRADE (≥10% IN ANY ARM)





AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; GI, gastrointestinal; Haem, haematological; QD, once daily; wks, weeks.

TREATMENT-RELATED AEs ≥10% BY GRADE ARE SIMILAR BY DOSE LEVEL



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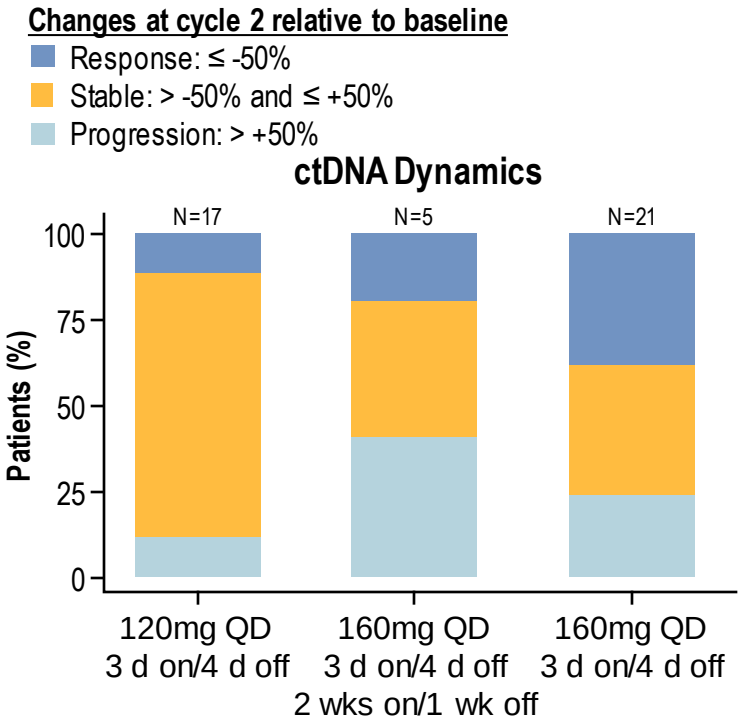
AE, adverse event; QD, once daily; wks, weeks.

DOSE MODIFICATIONS AND TRANSFUSIONS

	120 mg: 3 d on/4 d off (N=25)	160 mg: 3 d on/4 d off (N=34)	160 mg: 3 d on/4 d off 2 wk on, 1 wk off (N=26)
Cycles completed: median (range)	3 (1-9)	2 (0-12)	2 (0-8)
Patients exposed to RP-3500 n (%)			
≥1 cycle	25 (100)	31 (91.2)	23 (88.5)
≥2 cycle	19 (76.0)	21 (61.8)	17 (65.4)
Interruptions (related to AE) n (%)			
1	6 (24.0)	4 (11.8)	4 (15.4)
2	3 (12.0)	4 (11.8)	1 (3.8)
≥3	3 (12.0)	0	1 (3.8)
Dose reductions (related to AE), n (%)			
1	3 (12.0)	6 (17.6)	1 (3.8)
2	1 (4.0)	0	1 (3.8)
RBC transfusions, n (%)			
Cycle 1	2 (8.0)	2 (5.9)	1 (3.8)
Cycles 1-2	3 (12.0)	6 (17.6)	1 (3.8)
Cycles 1-3+	4 (16.0)	11 (32.4)	2 (7.7)

AE, adverse event; d, day; RBC, red blood cell; wk, week.

ctDNA DEMONSTRATES DRUG ACTIVITY ACROSS DOSING COHORTS

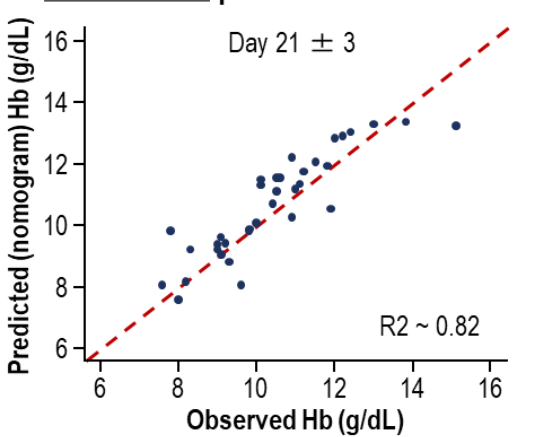


ANEMIA NOMOGRAM: A TOOL TO PREDICT EARLY DOSE MODIFICATIONS

$$Predicted\ Hb(Day) \sim HB_{Baseline} - Decay\ Rate * Day$$

Known Parameter

Predicted Parameter based on ~D7 hematology



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ctDNA, circulating tumor DNA; d, day; Hb, hemoglobin; QD, once daily; wk, week;

SUMMARY AND CONCLUSIONS

- This comprehensive safety analysis of 3 dosing schedules of RP-3500 monotherapy confirmed the acceptable tolerability of the recommended phase 2 dose (160mg 3 days/4 days off)
- Anemia was the most common reported toxicity
- A dose modification plan that includes 2 alternative dosing schedules was established to mitigate the on-target toxicity of anemia and maintain patients on an efficacious RP-3500 dosing schedule
- Based on surrogate efficacy estimation by on-treatment ctDNA decline the doses expected to be comparable in terms of efficacy
- A nomogram based on changes in monocytes and hemoglobin levels in cycle 1 is being prospectively evaluated to identify patients at increased risk of hemoglobin decrease at the initial dose/schedule and help reduce the need for dose holds or transfusions

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Thank You!

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