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METEOR-1: A PHASE I STUDY OF GSK3326595, A FIRST-IN-CLASS PROTEIN ARGININE METHYLTRANSFERASE 5 (PRMT5) INHIBITOR, IN ADVANCED SOLID TUMORS

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DISCLOSURE

- Lillian L Siu is a consultant for Merck, Pfizer, Celgene, AstraZeneca/MedImmune, Morphosys, Roche, GeneSeeq, Loxo, Oncorus, Symphogen, and Seattle Genetics; has received grant/research support through her institution from Novartis, Bristol-Myers Squibb, Pfizer, Boehringer-Ingelheim, GlaxoSmithKline (GSK), Roche/Genentech, Karyopharm, AstraZeneca/MedImmune, Merck, Celgene, Astellas, Bayer, AbbVie, Amgen, Symphogen, Intensity Therapeutics, Mirati, and Shattucks; and her spouse is a stockholder with Agios
- Drew W Rasco has received research funding from GSK
- Sophie Postel-Vinay has received research funding from Boehringer Ingelheim, Roche, and Merck KGaA for research projects unrelated to this manuscript; has participated in advisory boards for Merck KGaA; has received nonfinancial support (travel paid and congress registration) for attending symposia from AstraZeneca; and serves as the principal or subinvestigator for several organizations
- Patricia Martin-Romano has received research grants from AstraZeneca, BMS, Boehringer Ingelheim, Janssen Cilag, Merck, Novartis, Pfizer, Roche, and Sanofi; has received nonfinancial support (drug supplied) from Bayer, BMS, Boehringer Ingelheim, Johnson & Johnson, Lilly, MedImmune, Merck, NH TherAGuiX, Pfizer, and Roche; and has participated in courses/training with AstraZeneca and Roche
- Jessica Menis has no conflicts to disclose
- Frans L Opdam has no conflicts to disclose
- Kimberley M Heinhuis has no conflicts to disclose
- Jacki L Egger is an employee of and stockholder with GSK
- Shelby Gorman is an employee of and stockholder with GSK
- Ridhi Parasrampuria is an employee of and stockholder with GSK
- Karrie Wang is an employee of and stockholder with GSK
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- Mrinal M Gounder has received research support from GSK and honoraria from Epizyme, Tracon, Amgen, Daiichi-Sankyo, Springwork Therapeutics, Bayer, and Karyopharm

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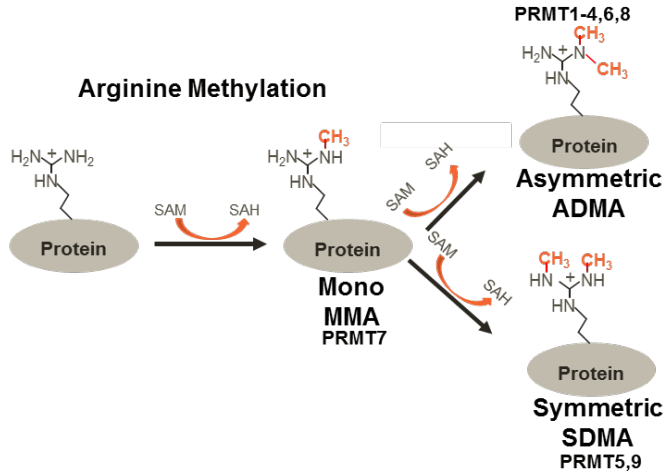
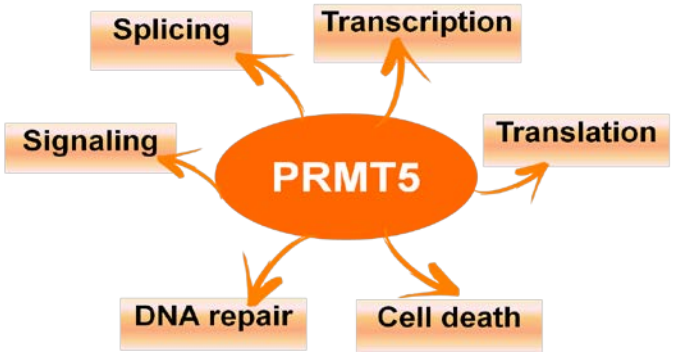
PROTEIN ARGININE METHYLTRANSFERASE 5 (PRMT5) IS A NOVEL ONCOLOGY TARGET

- PRMT5 catalyzes formation of symmetric dimethylarginine (SDMA) in many cellular proteins
- SDMA regulates cancer-relevant proteins/pathways; overexpression of PRMT5 in cancer signifies a poor prognosis
- PRMT5 is a key regulator of cellular splicing, specifically genes with weak splice sites[1]





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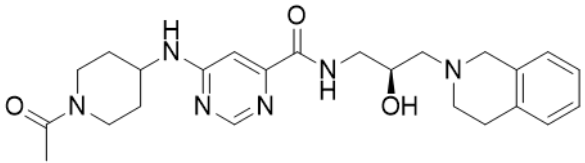
[1]Bezzi M et al. *Genes Dev* 2013.

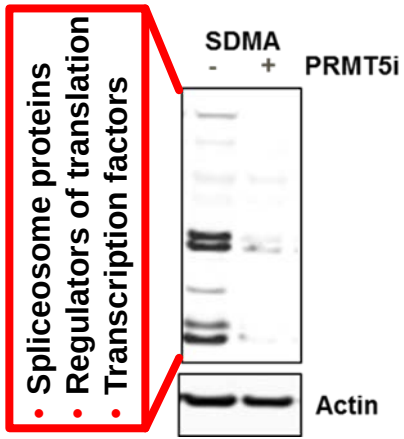
GSK3326595 IS A POTENT AND SELECTIVE INHIBITOR OF PRMT5

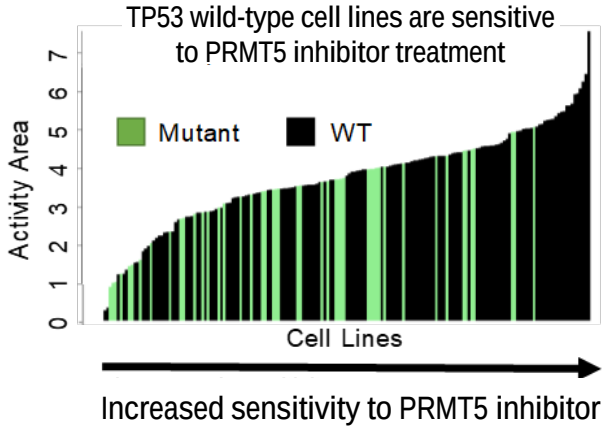
GSK3326595 has efficacy in solid and heme cancer models

- GSK3326595 is a selective inhibitor of PRMT5
- GSK3326595 inhibits global cellular SDMA, including SDMA on splicing proteins, regulators of translation, and transcription
- PRMT5 inhibition leads to alternative splicing of *MDM4* and subsequent activation of p53 pathway activity, growth arrest, and apoptosis most frequently in TP53 wild-type cancer cell lines



GSK3326595 IC_{50} = 6.2 nM

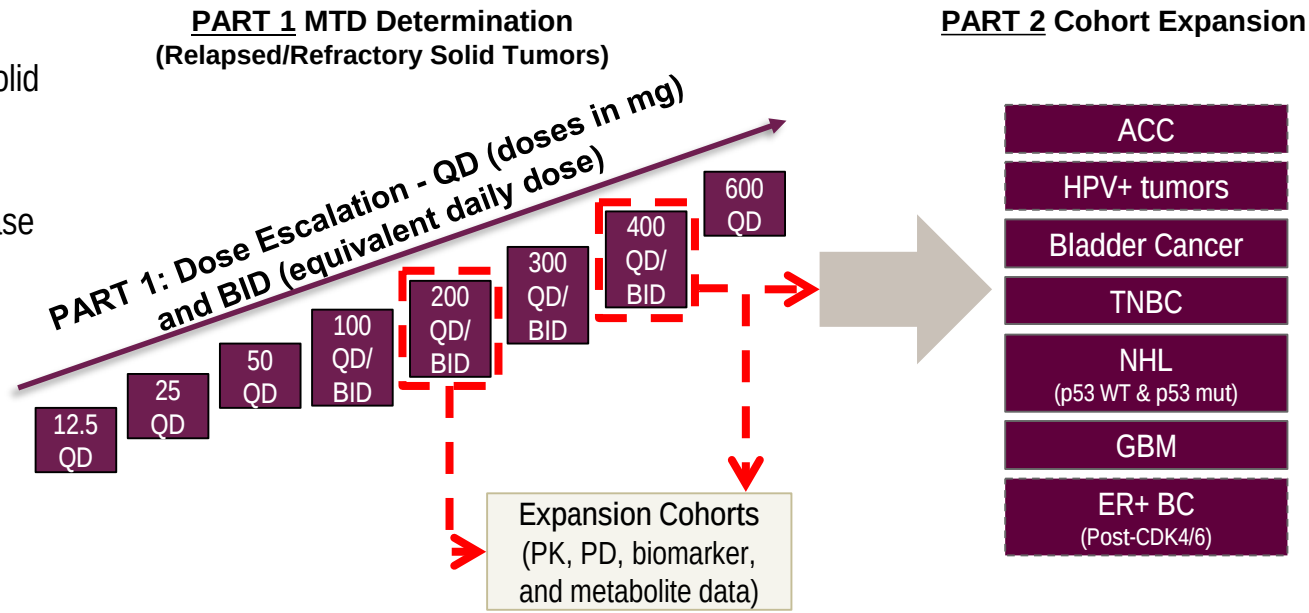




METEOR-1 (204653): STUDY DESIGN

First-in-human study of a PRMT5 inhibitor, GSK3326595, in adults with solid tumors

- Key eligibility criteria
  - Adults with advanced or metastatic solid tumors (PART 1) and selected solid tumors and NHL (PART 2)
  - Relapsed/refractory disease, or disease with no standard of care
  - Adequate organ function
  - ECOG PS 0 or 1
- Key objectives & endpoints
  - Safety, tolerability, and PART 2 dose
  - PK and PD parameters
  - Efficacy (ORR and DCR)



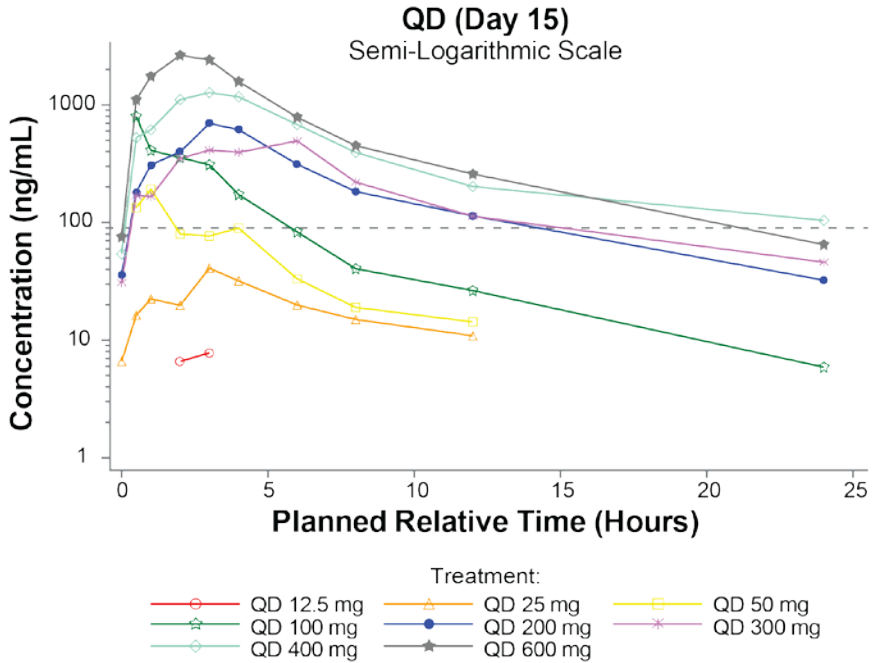
Presentation will focus on PART 1 data only

GSK3326595 PLASMA PK

GSK3326595 target plasma levels achieved in patients

- Dose-dependent increases in plasma exposures (C_{max} and AUC)
- Moderate inter-patient and intra-patient PK variability
- Modest accumulation upon repeated dosing
- Efficacious plasma exposures (C_{avg} and time above target) at clinical doses of ≥200 mg QD are attained based on multiple mouse xenograft models

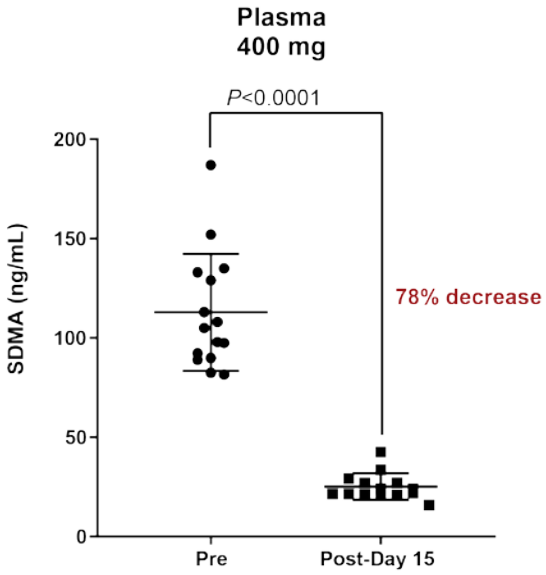
Steady State GSK3326595 PK Parameters at 400 mg QD	Geometric Mean (% CV)
t_{max}, hr (median, range)	3.08 (0.6, 6.1)
$t_{1/2}$, hr	4.94 (26.9)
C_{max}, ng/mL	1600 (63.7)
AUC, ng·hr/mL	8760 (33.9)
Mean time above target, hr	20

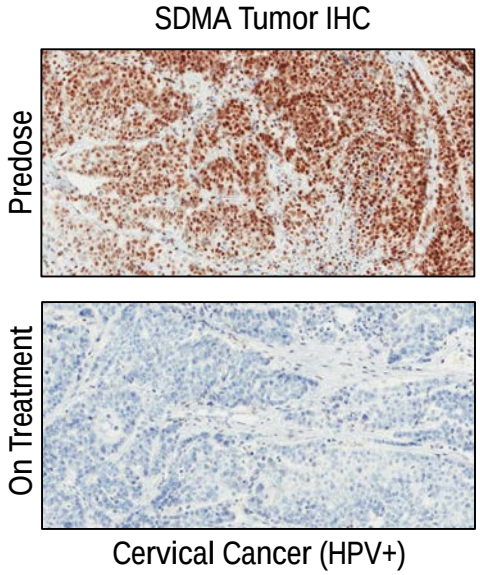


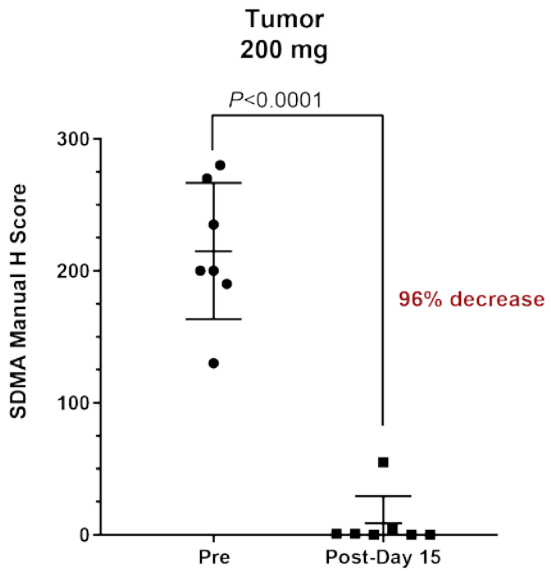
Dashed line indicates target C_{trough}.

GSK3326595 INHIBITS PRMT5 IN TUMOR AND CIRCULATION

SDMA is a biomarker of PRMT5 activity







- **Plasma:** Dose-dependent decreases in free SDMA at doses of 25–600 mg QD (independent of clinical response)
- **Tumor:** Nearly complete loss of tumor SDMA is seen at total daily doses of 200 mg (QD and BID) and higher across all tumor types assessed (independent of clinical response)

PATIENT DEMOGRAPHICS AND DISEASE HISTORY

Patients across all doses and schedules

	Total Number of Patients (N = 54)
Demographics	
Age, years, median (min, max)	60 (21–81)
Sex-Male, n (%)	29 (54)
Disease Characteristics	
Primary tumor type, n (%)	
Adenoid cystic carcinoma	14 (26)
Colorectal	9 (17)
Breast (2 HR+ BC, 1 sarcoma)	3 (6)
Cholangiocarcinoma	2 (4)
Glioblastoma multiforme	2 (4)
Liver	2 (4)
Mesothelioma	2 (4)
Prostate	2 (4)
Soft tissue sarcoma	2 (4)
Other[a]	16 (30)
Months since diagnosis, median (min, max)	29.7 (1.1, 325.7)

[a]Includes 1 of each subtype: abdomen, bile duct, bladder, corticosurrenal carcinoma, endometrium/uterus, epidermoid carcinoma, epithelioid sarcoma, esophagus, malignant peripheral nerve sheath tumor, melanoma, mouth, neuroendocrine tumor, non-small cell lung, pancreas, small cell lung, and uveal melanoma.

ADVERSE EVENTS

AEs related to GSK3326595; Dose selected for cohort expansion (400 mg QD) in bold box

n (%)	GSK3326595 Dose							Total (N = 54)
	≤200 mg QD (n = 11)	300 mg QD (n = 3)	400 mg QD (n = 19)	600 mg QD (n = 4)	≤100 mg BID (n = 8)	150 mg BID (n = 6)	200 mg BID (n = 3)	
AE (all grades)	7 (64)	2 (67)	19 (100)	3 (75)	8 (100)	6 (100)	3 (100)	48 (89)
Grade 3/4 AEs	1 (9)	1 (33)	10 (53)	1 (25)	1 (13)	2 (33)	3 (100)	19 (35)
SAEs	0	1 (33)	5 (26)	0	1 (13)	0	1 (33)	8 (15)
Dose interruption	2 (18)	1 (33)	14 (74)	2 (50)	2 (25)	5 (83)	3 (100)	29 (54)
Dose reduction(s)	0	1 (33)	12 (63)	2 (50)	0	1 (17)	1 (33)	17 (31)
Drug-related AEs of any grade occurring in >20% of patients, n (%)								
Fatigue	3 (27)	0	9 (47)[a]	2 (50)	3 (38)	3 (50)	1 (33)	21 (39)
Nausea	1 (9)	0	8 (42)	3 (75)	3 (38)	3 (50)	1 (33)	19 (35)
Anemia	0	1 (33)	10 (53)[a]	1 (25)	1 (13)	2 (33)	2 (67)	17 (31)
Alopecia	2 (18)	1 (33)	9 (47)	0	1 (13)	1 (17)	1 (33)	15 (28)
Dysgeusia	2 (18)	1 (33)	7 (37)	1 (25)	0	2 (33)	1 (33)	14 (26)

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[a]4 patients (21%) experienced grade 3 anemia; 2 patients (11%) experienced grade 3 fatigue. All other listed AEs at 400 mg were grade 1/2.

BEST OVERALL RESPONSE

Clinical activity by dose; Dose selected for cohort expansion (400 mg QD) in bold box

Best response, n (%)	GSK3326595 Dose							Total (N = 54)
	≤200 mg QD (n = 11)	300 mg QD (n = 3)	400 mg QD (n = 19)	600 mg QD (n = 4)	≤100 mg BID (n = 8)	150 mg BID (n = 6)	200 mg BID (n = 3)	
Complete response	0	0	0	0	0	0	0	0
Non-CR/Non-PD	0	0	2 (11)	0	0	0	0	2 (4)
Partial response	2 (18)	0	1 (5)	0	0	0	0	3 (6)
Stable disease	3 (27)	1 (33)	6 (32)	2 (50)	3 (38)	2 (33)	2 (67)	19 (35)
Progressive disease	5 (45)	2 (67)	7 (37)	1 (25)	5 (63)	4 (67)	0	24 (44)
Not evaluable	0	0	3 (16)	0	0	0	0	3 (6)
Not applicable	1 (9)	0	0	1 (25)	0	0	1 (33)	3 (6)

- Confirmed PRs observed in 3 patients, treated at 400 mg and below, all in ACC (grey shaded box)
- Durable stable disease was achieved in bladder cancer, ACC, and other tumors
- Non-CR/Non-PD observed in patients with non-measurable disease

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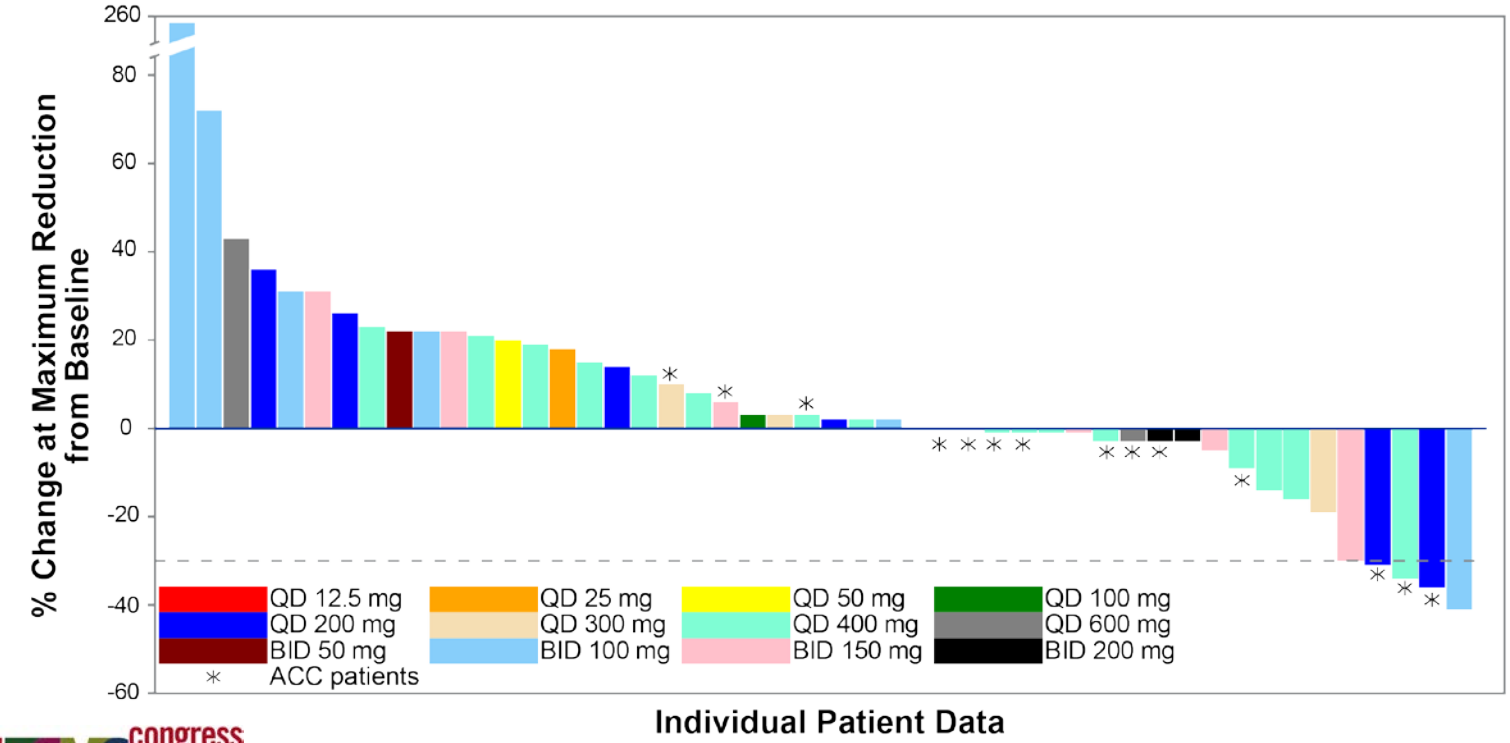
All treated patients, based on investigator assessments with confirmation by dose level.
CR, complete response; PD, progressive disease; PR, partial response.

GSK3326595 LEADS TO TUMOR REGRESSION

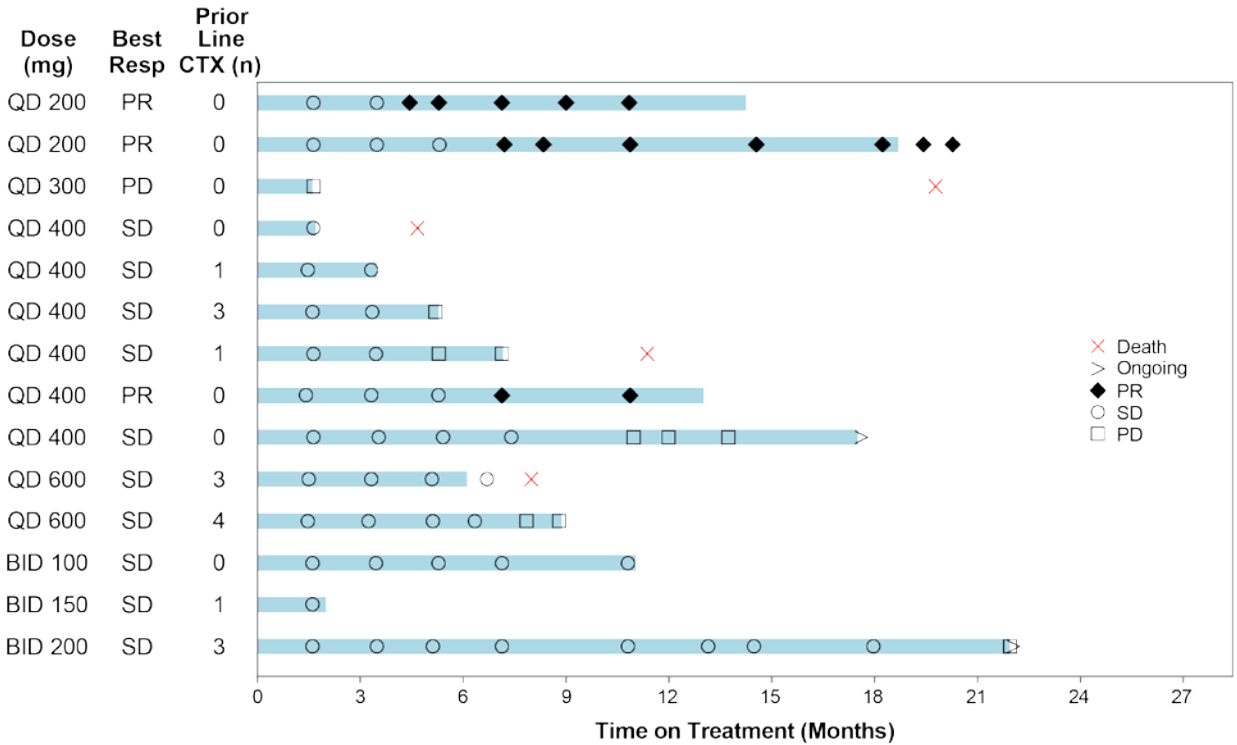
Clinical responses were observed at 200 mg and above, in patients with ACC (starred), and other tumors



Dashed line indicates cutoff for partial response (PR).

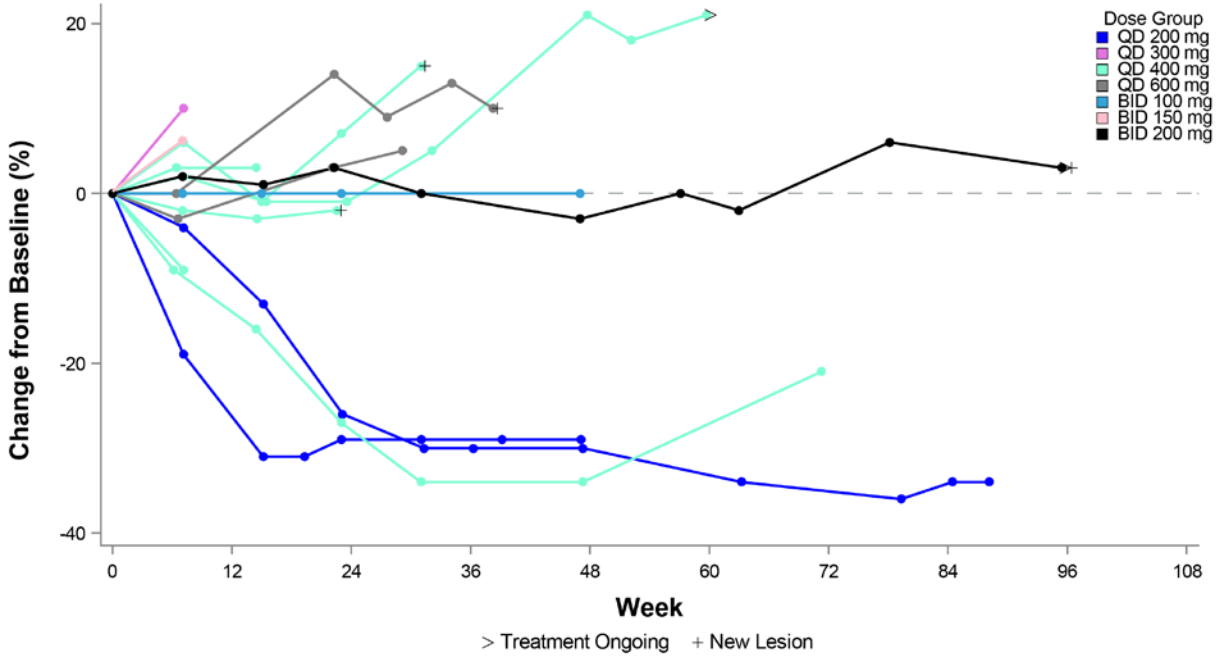
GSK3326595 RESULTS IN PRs AND PROLONGED SD IN METASTATIC/ LOCALLY ADVANCED ACC THAT REQUIRES SYSTEMIC THERAPY

	ACC Pts (N = 14)
Best response, n (%)	
Complete response (CR)	0
Non-CR/Non-PD	0
Partial response (PR)	3 (21)
Stable disease (SD)	10 (71)
Progressive disease (PD)	1 (7)
Not evaluable	0
Not applicable	0
mPFS, months (range): 11.0 (4.7, -)	
Median follow-up, months: 13.7	

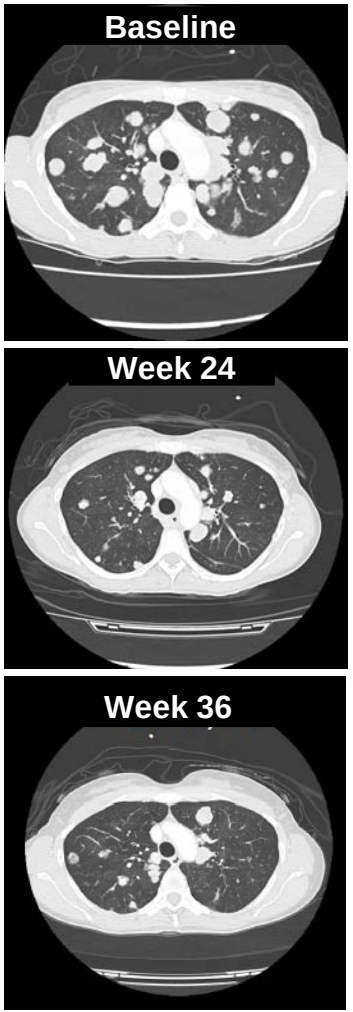


CTX, chemotherapy; mPFS, median progression-free survival.

GSK3326595 RESULTS IN DURABLE PRs AND PROLONGED SD IN METASTATIC/LOCALLY ADVANCED ACC THAT REQUIRES SYSTEMIC THERAPY



Confirmed PR



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Siu et al. METEOR-1 GSK3326595 PRMT5 Inhibitor Ph1 (Pres #438O)

CONCLUSIONS

GSK3326595 monotherapy is active in several tumor types

- This study evaluated a first-in-class PRMT5 inhibitor for treatment of advanced solid tumors
- GSK3326595 PK is dose dependent in plasma; efficacious exposures similar to preclinical *in vitro/in vivo* target levels are achieved
- GSK3326595 significantly inhibited PRMT5 (decreased SDMA levels) in plasma and tumor
- AEs were common but manageable, and were reversible with dose interruption
- GSK3326595 is active in ACC and other tumor types
- 400 mg QD was selected for dose expansion based on safety, efficacy, PK, and PD data
- Additional studies are ongoing in patients with predefined solid tumors, non-Hodgkin's lymphoma, and myeloid malignancies

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- The GSK PRMT5 team