G1T38, AN ORAL CDK4/6 INHIBITOR, DOSED CONTINUOUSLY IN COMBINATION WITH FULVESTRANT FOR HR+ BREAST CANCER: PRELIMINARY PHASE 1b RESULTS

IURIE BULAT[1], MARINA MAGLAKELIDZE[2], CARMEN MURIAS[3], GALINA KURTEVA[4], REBECCA ROYLANCE[5], RICHARD BAIRD[6], MAIA GOGILADZE[2], ADRIAN CRIJANOVSCHI[1], AMY MCCULLOUGH[7], JESSICA SORRENTINO[7], CHRISTINA SIPES[7], ZHAO YANG[7], YAPING CAI[8], RAJESH K. MALIK[7], ELIZABETH SHEARIN[7], ANDREW P. BEELEN[7]

[1]ARENSIA EXPLORATORY MEDICINE RESEARCH UNIT, INSTITUTE OF ONCOLOGY, CHISINAU, MOLDOVA; [2]LLC ARENSIA EXPLORATORY MEDICINE, TBLISI, GEORGIA; [3]SARAH CANNON RESEARCH INSTITUTE, LONDON, UNITED KINGDOM; [4]SPECIALIZED HOSPITAL FOR ACTIVE TREATMENT OF ONCOLOGY, SOFIA, BULGARIA; [5]NIHR UNIVERSITY COLLEGE LONDON HOSPITALS BIOMEDICAL RESEARCH CENTRE, LONDON, UNITED KINGDOM; [6]CAMBRIDGE CANCER CENTRE, CAMBRIDGE, UNITED KINGDOM; [7]G1 THERAPEUTICS, INC., RESEARCH TRIANGLE PARK, USA; [8]ICON CLINICAL RESEARCH, CHAPEL HILL, USA

BACKGROUND

- HR-positive breast cancers represent the vast majority of breast cancers[1]
- CDK4/6 inhibitors, in combination with fulvestrant, represent an established treatment for HR-positive, HER2-negative advanced or metastatic breast cancer[2]
  - Two of three approved CDK4/6 inhibitors have dose-limiting neutropenia requiring a drug holiday, potentially limiting efficacy
  - There is a significant clinical need for a well-tolerated, continuously dosed oral CDK4/6 inhibitor
- G1T38 is a potent and selective CDK4/6 inhibitor that effectively inhibits the growth of HR-positive breast cancer in preclinical models
- 28-day repeat-dose toxicity study of G1T38 in dogs led to a dose-dependent decline and subsequent plateau of neutrophil counts
- First-in-human study (G1T38-01) in healthy volunteers (3 mg – 600 mg) demonstrated that G1T38 is generally well tolerated and has a differentiated PK profile (shorter half-life and larger apparent volume of distribution (Vd/F) than palbociclib and ribociclib)

STUDY OBJECTIVES

PRIMARY OBJECTIVES

- Evaluate the safety, tolerability, and dose limiting toxicities (DLTs) of G1T38 administered continuously with fulvestrant
- Determine the recommended Phase 2 dose of G1T38 administered continuously with fulvestrant

SECONDARY OBJECTIVES

- Determine the PK parameters of G1T38
- Assess fulvestrant and goserelin Day 15 plasma concentrations when administered with G1T38
- Assess response rate, clinical benefit rate (CBR), progression free survival (PFS) and overall survival (OS)

KEY EXPLORATORY OBJECTIVES

- Assess archival tumor tissue for predictors of response/resistance to G1T38 (e.g., Ki67, phospho-Rb, etc.)
- Assess the correlation between cell-free DNA and efficacy measures
- Assess the relationship between PK parameters and efficacy measures

METHODS

STUDY DESIGN (NCT02499770)

- Multicenter Phase 1b/2a study
- Part 1: open-label, 3+3 dose escalation (ongoing; data cut-off date 01May2018)
- Part 2: open-label expansion (n=30) at the recommended Phase 2 dose (RP2D)
- G1T38 QD or BID with food at total daily doses ranging from 200-850 mg administered continuously
- Fulvestrant 500 mg administered per standard of care
- No G1T38 dose interruption or reduction required for Grade 3 neutropenia

KEY INCLUSION CRITERIA

- Histologically or cytologically confirmed locally advanced or metastatic HR+/HER2- breast cancer, not amenable to treatment with curative intent
- Any menopausal status; pre- or perimenopausal patients must have initiated treatment with LHRH agonist ≥ 28 days prior to first dose of study drug
- Progressed during or within 12 months after adjuvant therapy with an aromatase inhibitor or tamoxifen OR progressed during or within 2 months after endocrine therapy for advanced or metastatic disease
- ECOG 0-1

KEY EXCLUSION CRITERIA

- Part 1 & 2: prior treatment with fulvestrant
- Part 2: prior treatment with a CDK4/6 inhibitor
- Known active uncontrolled or symptomatic CNS metastases
- Part 1: > 2 chemotherapy regimens in the advanced/metastatic setting
- Part 2: > 1 chemotherapy regimen in the advanced/metastatic setting

RESULTS

TABLE 1. BASELINE CHARACTERISTICS AND PATIENT DISPOSITION

Dose (mg)	200 QD n=6	300 QD n=3	400 QD n=3	500 QD n=3	650 QD n=6	100 BID n=6	150 BID n=3	200 BID n=3	TOTAL N=33 n (%)
Age, years median (min,max)	58 (44,69)	46 (45,72)	55 (50,59)	54 (25,63)	63 (56,65)	61 (47,67)	55 (40,59)	53 (47,63)	59 (25,72)
ECOG PS, n									
0	4	1	3	3	5	5	2	3	26 (79)
1	2	2	0	0	1	1	1	0	7 (21)
Menopausal status, n									
pre/perimenopausal	1	0	1	1	0	1	1	1	6 (18)
postmenopausal	5	3	2	2	6	5	2	2	27 (82)
Visceral metastasis, n	4	3	3	3	6	5	2	2	25 (76)
Prior lines of therapy*, median (min,max)	2 (2,4)	3 (1,3)	3 (3,4)	3 (2,3)	3.5 (3,8)	2 (1,3)	5 (5,6)	5.5 (3,8)	3 (1,8)
endocrine	2 (1,2)	1 (1,3)	2 (1,3)	2 (1,2)	2 (1,5)	1 (1,2)	3 (3,3)	3.5 (2,5)	2 (1,5)
chemotherapy	0.5 (0,2)	2 (0,2)	1 (1,2)	1 (1,1)	2 (1,3)	1 (1,3)	2 (2,3)	1.5 (1,2)	1 (1,3)
Prior therapy*, n									
aromatase inhibitor	5	1	3	2	3	2	3	1	20 (67)
Disposition, n									
ongoing treatment	3	2	2	2	6	3	1	3	22 (67)
discontinued	3	1	1	1	0	3	2	0	11 (33)
adverse event	0	0	0	0	0	0	0	0	0
disease progression	2	1	1	1	0	3	2	0	10
patient decision	1	0	0	0	0	0	0	0	1

PS=performance status; *prior lines of therapy include adjuvant and metastatic settings (n=30)
32/33 (97%) patients are white; 32/33 (97%) patients have measurable disease

SAFETY AND TOLERABILITY

TABLE 2. SUMMARY OF G1T38-RELATED ADVERSE EVENTS (AES) BY CTCAE GRADE AND FREQUENCY

Dose (mg) (N=33)	200 QD n=6	300 QD n=3	400 QD n=3	500 QD n=3	650 QD n=6	100 BID n=6	150 BID n=3	200 BID n=3	Total, n (%)				
									Grade 1	Grade 2	Grade 3	Grade 4	All
Neutropenia	4	3	3	3	2	4	3	2	6 (18)	7 (21)	9 (27)	2 (6)	24 (73)
Leukopenia	4	2	0	1	2	3	3	1	4 (12)	9 (27)	3 (9)	0	16 (49)
Nausea	0	2	3	3	3	2	1	1	8 (24)	7 (21)	0	0	15 (46)
Diarrhea	1	2	2	1	4	1	2	1	6 (18)	8 (24)	0	0	14 (42)
Vomiting	0	2	3	1	5	0	1	0	9 (27)	3 (9)	0	0	12 (36)
Anemia	3	1	2	2	0	2	1	0	8 (24)	2 (6)	1 (3)	0	11 (33)
Fatigue	0	1	2	1	1	1	1	1	5 (15)	3 (9)	0	0	8 (24)
Thrombocytopenia	0	1	1	3	0	1	1	0	5 (15)	2 (6)	0	0	7 (21)
Hematuria**	1	1	1	0	0	1	1	0	5 (15)	0	0	0	5 (15)
ALT increased	0	0	1	1*	0	0	0	0	1 (3)*	1 (3)	0	0	2 (6)
SCr increased	0	0	0	1	0	1	0	0	2 (6)	0	0	0	2 (6)
BUN increased	1	1	0	0	0	0	0	0	2 (6)	0	0	0	2 (6)
AST increased	0	0	1	0	0	0	0	0	0	1 (3)	0	0	1 (3)
Febrile neutropenia	0	0	0	0	0	0	1	0	0	0	1 (3)	0	1 (3)
GGT increased	0	0	1	0	0	0	0	0	0	1 (3)	0	0	1 (3)
Lymphopenia	1	0	0	0	0	0	0	0	0	1 (3)	0	0	1 (3)
Metrorrhagia	0	0	0	0	0	0	1	0	0	1 (3)	0	0	1 (3)
Stomatitis	0	0	0	0	0	0	1	0	0	1 (3)	0	0	1 (3)

* patient had known liver metastases prior to enrolling in the study
** microscopic hematuria only; 3 of 5 patients with 1-4 red cells in urine at baseline
SCr = serum creatinine
Data shown for AEs experienced by >1 patient or worst grade > Grade 1

TABLE 3. PATIENTS REQUIRING G1T38 DOSE REDUCTION ANYTIME DURING STUDY

Dose (mg)	n	Event	Day of event	Duration of interruption (days)	Tolerated lower dose?
200 QD	1/6	Grade 4 neutropenia	29, 420	20, 28	Y*
400 QD	1/3	Grade 2 diarrhea	34	0	Y
650 QD	1/6	Grade 3 neutropenia and bronchitis	29	7	Y
150 BID	1/3	Grade 3 febrile neutropenia	78	7	Y
200 BID	1/3	Grade 2 fatigue	2	13	Y

* patient required a second dose reduction >1 year later
One patient (500 mg QD) had therapy interrupted due to grade 4 neutropenia and was found to have PD prior to restarting G1T38
No dose reductions at 300mg QD, 500mg QD, or 100mg BID

NEUTROPHIL EFFECTS

- Neutropenia is a class effect of CDK4/6 inhibitors
- Neutrophil counts decrease approximately 50-60% for the 3 approved CDK4/6 inhibitors[3,4,5]

FIGURE 1. NEUTROPHILS: MEAN % CHANGE FROM BASELINE BY DOSE

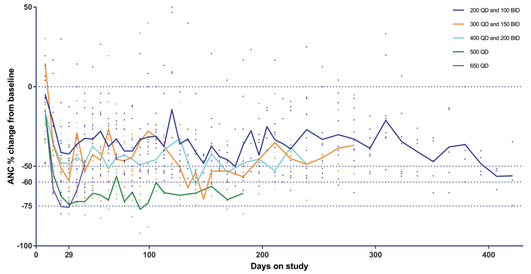
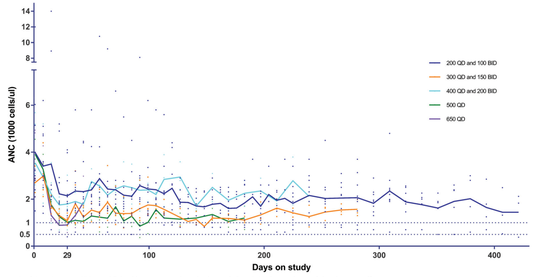


FIGURE 2. NEUTROPHILS: ABSOLUTE COUNTS BY DOSE



3 of 6 patients at 650 mg QD had been on study only through Day 8 ANC sample as of the data cutoff
Day 29 = end of DLT period

SUMMARY: SAFETY AND TOLERABILITY

- The MTD has not been reached and dose escalation is ongoing
- Continuous G1T38 dosing results in a dose-dependent decline and subsequent plateau of neutrophils after 4-5 weeks
- Only 2 patients (6%) experienced G1T38-related Grade 4 neutropenia despite dosing through Grade 3 neutropenia
- No G1T38-related SAEs were reported and no patients discontinued G1T38 due to an AE
- The majority of AEs were Grade 1 or 2
- No drug-induced liver injury (DILI) , QTc prolongation, or venous thromboembolism (VTE) reported

DOSE LIMITING TOXICITIES; DLT PERIOD = DAY 1-29

- Three patients experienced DLTs and continued therapy at a reduced dose following a dose interruption
  - Grade 4 neutropenia on Day 29 (200mg QD; 44kg female with baseline ANC=1500 cells/mm^3)
  - Grade 2 fatigue (200mg BID)
  - Grade 3 neutropenia with bronchitis (650mg QD)

GASTROINTESTINAL TOLERABILITY

- GI AEs were typically transient, appeared early in therapy, and most resolved within 1-2 days with no impact on compliance
- Median duration of diarrhea was 2 days and 57% (8/14) of patients with diarrhea required no treatment; no prophylactic loperamide was used and 1-2 doses readily managed symptoms if required
- Nausea and vomiting were managed with short-term supportive care; dosing at bedtime relieved nausea in some patients
- All GI AEs were ≤ Grade 2 and no patient discontinued G1T38 due to a GI AE; one patient (400mg QD) required a dose reduction

ANTITUMOR ACTIVITY AND DURATION OF TREATMENT

FIGURE 3. SPIDER PLOT

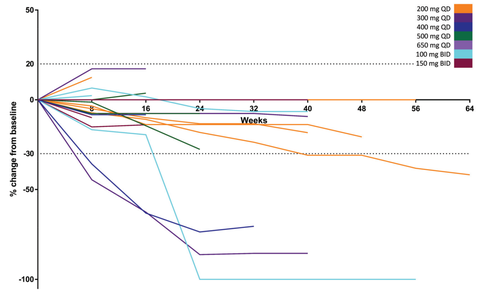
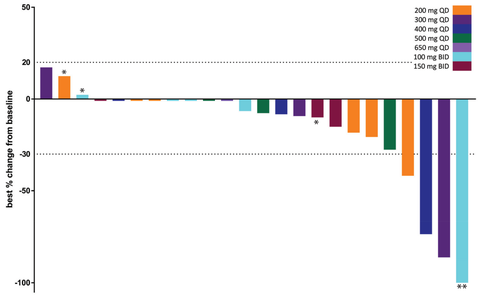


FIGURE 4. WATERFALL PLOT



n=24 response evaluable patients
* PD due to new lesions; ** PR, NTL present

TABLE 4. BEST OVERALL RESPONSE

Best response* (n=24)**	n (%)
Partial response (PR)	4 (16.7)
Stable disease (SD) ≥ 24 weeks	12 (50)
Stable disease	17 (70.8)
Progressive disease (PD)	3 (12.5)
Clinical benefit rate (CBR)#	16 (66.7)

* using RECIST version 1.1
** n=24 response evaluable patients with measurable disease and ≥ 1 post-treatment scan (n=20 in abstract)
# CBR = CR + PR + SD ≥ 24 weeks

TABLE 5. DURATION OF TREATMENT

Duration of treatment (N=33)	n (%)
0 to 3 months	14 (42.4)
>3 to 6 months	5 (15.2)
>6 to 12 months	10 (30.3)
>12 months	4 (12.1)

PHARMACOKINETICS

TABLE 6. PHARMACOKINETICS IN HEALTHY VOLUNTEERS, SINGLE-DOSE (STUDY G1T38-01)

Dose (mg)	n	T_{max}, h (min, max)	c_{max}, ng/mL (CV%)	$AUC_{0\text{-}inf}$ ng*h/mL (CV%)	$T_{1/2}$, h (CV%)	CL/F, L/h (CV%)	Vz/F, L (CV%)
48	3	2.0 (2.0,3.0)	3.65 (64.6)	20.4 (116.1)	3.07 (57.5)	2354 (116.1)	10427 (40.6)
100	3	2.0 (2.0,4.0)	9.23 (51.0)	60.2 (18.8)	4.71 (10.8)	1660 (18.8)	11277 (27.8)
200	6	3.0 (2.0,3.0)	29.3 (21.6)	275 (19.7)	13.8 (17.5)	727 (19.7)	14514 (23.1)
300	6	3.5 (3.0,6.0)	27.0 (38.6)	349 (51.2)	15.4 (24.3)	861 (51.2)	19130 (47.0)
400	6	5.0 (1.5,6.0)	26.3 (70.6)	432 (92.0)	14.9 (36.3)	926 (92.0)	19915 (63.8)
600	4	6.0 (6.0,8.0)	59.0 (49.5)	886 (43.4)	17.2 (27.2)	677 (43.4)	16822 (45.1)

AUC = Area under concentration time curve; c_{max} = maximum concentration; T_{max} = time to c_{max}; $T_{1/2}$ = terminal half life; CL/F = apparent clearance; Vz/F = apparent volume of distribution; CV% = coefficient of variation
All data geometric mean (CV%), except T_{max} is median (min, max); Blood samples for G1T38 analysis were collected pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, and 96 hours post-dose

TABLE 7. PHARMACOKINETICS IN PATIENTS, CONTINUOUS DAILY DOSING

Dose (mg)	N=25 n	DAY 1			DAY 29			Racc mean AUC D29/D1
		T_{max}, h (min, max)	C_{max} ng/mL (CV%)	$AUC_{0\text{-}24}$ ng*h/mL (CV%)	T_{max}, h (min, max)	C_{max} ng/mL (CV%)	$AUC_{0\text{-}24}$ ng*h/mL (CV%)	
200 QD	5	4.0 (3.0, 6.0)	25.5 (42.5)	187 (36.0)	4.0 (3.0,6.0)	20.4 (46.6)	229 (55.0)	1.22
300 QD	3*	4.0 (4.0, 6.0)	40.2 (70.0)	413 (64.4)	4.0 (4.0,10.0)	47.0 (49.9)	592 (34.2)	1.43
400 QD	3*	6.0 (6.0, 6.0)	20.1 (25.6)	202 (19.4)	6.0 (4.0,6.0)	19.0 (55.7)	278 (50.9)	1.38
500 QD	3*	6.0 (3.0, 8.0)	48.9 (41.9)	566 (25.8)	6.0 (4.0,6.0)	43.2 (14.1)	607 (7.8)	1.07
650 QD	3	8.0 (8.0, 8.0)	62.2 (35.0)	800 (35.3)	—	—	—	—
100 BID	5	3.0 (2.0, 4.0)	10.2 (30.8)	106 (25.0)	3.0 (1.0,12)	12.3 (49.0)	202 (51.5)	1.90
150 BID	3*	4.0 (3.0, 4.0)	21.7 (38.9)	260 (18.2)	4.0 (4.0,4.0)	50.2 (57.3)	910 (65.7)	3.50

*includes one patient who vomited shortly after dosing; Racc = accumulation ratio
All data arithmetic mean (CV%), except T_{max} is median (min, max); $AUC_{0\text{-}12}$ multiplied by 2 to approximate $AUC_{0\text{-}24}$ for BID cohorts; Blood samples for G1T38 analysis were collected pre-dose and 1, 2, 3, 4, 6, 8, 10, 12, & 24 hours post-dose.

PHARMACOKINETIC CONCLUSIONS

- Pharmacokinetics are comparable in healthy volunteers and patients
- AUC increases approximately proportionally to dose for both patients and healthy volunteers
- Median T_{max} increases with dose
- Mean $T_{1/2}$ ranges from 14 to 17 hours
- No drug accumulation with QD dosing

CONCLUSIONS

- G1T38 is a potential best in class CDK4/6 inhibitor that is generally well tolerated when dosed continuously
- Neutrophil decline plateaus following 4-5 weeks of therapy, thus supporting continuous dosing without a drug holiday
- Grade 3 neutropenia was observed in 9 (27%) patients, with only 2 (6%) patients progressing to Grade 4 despite continuous G1T38 dosing
- There were no ≥ Grade 3 non-hematologic AEs
- GI AEs, when present, were transient, appeared early in therapy with a short duration, and when required, were readily managed with standard supportive therapies
- No G1T38-related SAEs were reported and no patient discontinued G1T38 secondary to an AE
- No drug-induced liver injury (DILI), QTc prolongation, or venous thromboembolism (VTE) reported
- PK profile with no drug accumulation supports continuous once-daily dosing
- Encouraging early evidence of antitumor activity

REFERENCES

1. Esserman LJ. Burstein H, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com (Accessed on 18May2018).
2. Cristofanilli M, Turner N, Bondarenko I, et al. *The Lancet Oncology* 2016; 17(4):425-439.
3. Flaherty KT, Lorusso PM, Demichele A, et al. *Clinical Cancer Research* 2012; 18(2):568-576.
4. Goetz MP, Toi M, Campone M, et al. *Journal of Clinical Oncology* 2017; 35(32):3638-3646.
5. Infante JR, Cassier PA, Gerecitano JF, et al. *Clinical Cancer Research* 2016; 22(23):5696-5705.

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Corresponding author: abeelen@g1therapeutics.com