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cfDNA analysis from Phase 1/2 study of lerociclib (G1T38), a continuously dosed oral CDK4/6 inhibitor, with fulvestrant in HR+/HER2- advanced breast cancer (ABC) patients

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Disclosures

Boris Krastev, MD

- Principal investigator for G1 Therapeutics, Inc. and Leutpold Pharmaceuticals
- Senior investigator for Astra Zeneca, Novartis, and Roche
- Received honoraria for public lecturing from Amgen, Angelini, Astellas, Bayer, Eli Lilly, Merck, MSD, Mundipharma, and Pfizer

Study sponsored by G1 Therapeutics, Inc.

Lerociclib is a potent and selective oral CDK4/6 inhibitor

- Lerociclib has a high potency for CDK4/6 without significantly inhibiting CDK2 or other kinases

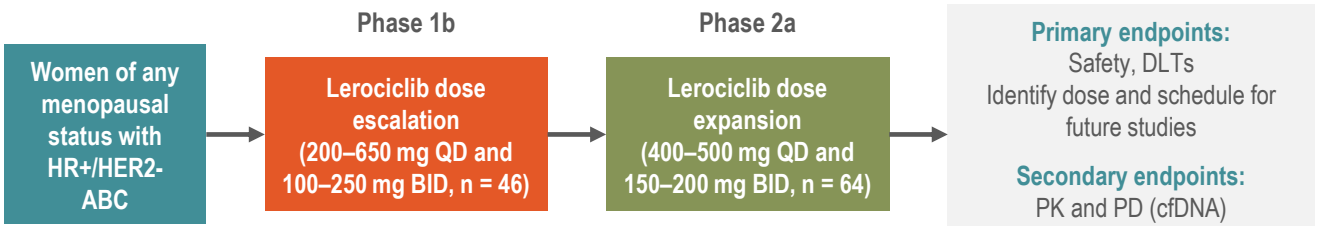
IC_{50} (μM) CDK4	**0.001**
IC_{50} (μM) CDK6	**0.002**
IC_{50} (μM) CDK2-E	3.6
IC_{50} (μM) CDK2-A	1.5
Ratio CDK2-E/CDK4	3600
Ratio CDK2-A/CDK4	1500

- Lerociclib has a differentiated safety and tolerability profile due to its target selectivity and PK/PD characteristics[1]
  - Low rates of diarrhea, nausea, vomiting, stomatitis, and alopecia
  - Low rates of Grade 3/4 neutropenia, allowing for continuous dosing
- Efficacy data are consistent with marketed oral CDK4/6 inhibitors used in combination with fulvestrant[2–4]
  - Safety and efficacy results from an ongoing study in ABC are presented in Poster #1407

ABC, advanced breast cancer; CDK, cyclin-dependent kinase; IC_{50}, half maximal inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamic.

1. Bulat I, et al. SABCS 2019 poster presentation. Abstract #P1-19-17. **2.** Cristofanilli M, et al. *Lancet Oncol.* 2016;17:425–39. **3.** Sledge GW, et al. *JAMA Oncol.* 2020;6:116–24. **4.** Slamon DJ, et al. *N Engl J Med.* 2019;382:514–24.

Phase 1b/2a, open-label, single-arm, multicenter study design: lerociclib + fulvestrant*

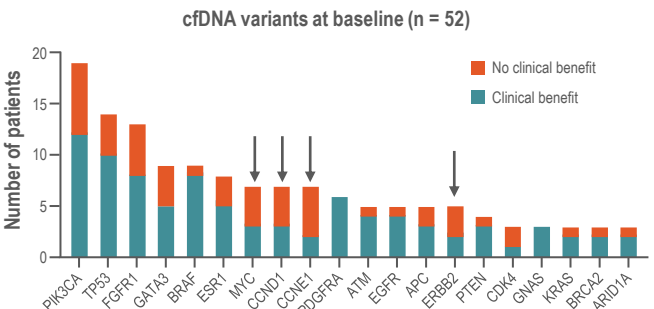


- **Here, results from an analysis of cfDNA using the Guardant 360 panel are presented**
  - **Baseline, C1D15, time of progression**
- 67/110 patients had at least one sample analyzed for cfDNA
- 63 patients were analyzed at baseline; 55 patients had detectable somatic variants and 1 patient did not have any variants detected (somatic or germline)

* Fulvestrant 500 mg on days 1, 15, and 29, then once monthly as per standard of care.

ABC, advanced breast cancer; BID, twice daily; C1D15, cycle 1 day 15; cfDNA, cell-free DNA; DLTs, dose-limiting toxicities; HR+/HER2-, hormone receptor–positive/human epidermal growth factor receptor 2–negative; ORR, objective response rate; OS, overall survival; PD, pharmacodynamic; PFS, progression-free survival; PK, pharmacokinetic; QD, once daily.

Potential baseline predictors of response

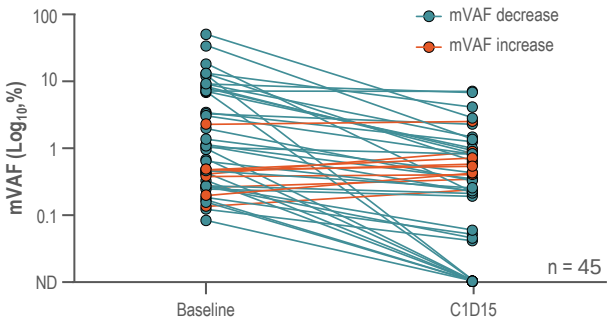


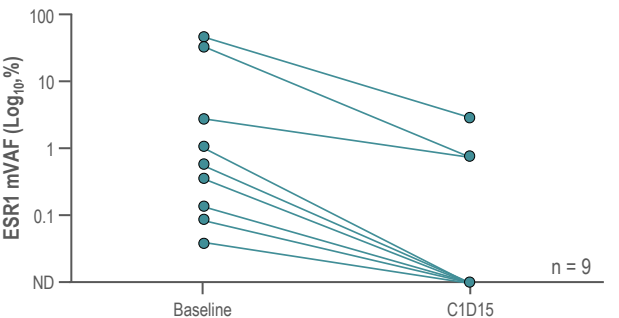
		mPFS, months	HR (95% CI)	*P* value	Censored
Total # of genes with variants	≤ 3 (n = 43)	15	0.28 (0.13; 0.58)	0.008	5 (25%)
	> 3 (n = 20)	9			28 (65%)
ERBB2	WT (n = 58)	13	0.13 (0.04; 0.4)	0.008	1 (20%)
	Variant (n = 5)	2			32 (55%)
CCNE1	WT (n = 56)	13	0.22 (0.09; 0.56)	0.011	1 (14%)
	Variant (n = 7)	4			32 (57%)
MYC	WT (n = 55)	15	0.27 (0.11; 0.64)	0.015	1 (13%)
	Variant (n = 8)	7			32 (58%)
CCND1	WT (n = 55)	13	0.26 (0.1; 0.67)	0.017	2 (25%)
	Variant (n = 8)	7			31 (56%)

- A higher number of genes with variants was significantly associated with shorter PFS
- Alterations in MYC, ERBB2, CCND1, or CCNE1 were significantly associated with shorter PFS
  - Variants included:
    - ERBB2: 2 patients (40%) had missense mutations, 1 patient (20%) had inframe mutations, 2 patients (40%) had amplifications
    - CCNE1: 4 patients (57%) had amplifications, 1 patient (14%) had missense mutations, 1 patient (14%) had truncating mutations, 1 patient (14%) had synonymous mutations
    - MYC: 8 patients (100%) had amplifications
    - CCND1: 7 patients (88%) had amplifications, 1 patient (13%) had missense mutations

Variants include amplifications and inframe, missense, promoter, and truncating mutations. Bar graph includes genes altered in ≥3 patients. Arrows highlight alleles with statistically significant differences in PFS.
HRs and 95% CI were determined using Cox proportional hazards regression models. The statistical significance of each association was evaluated using a Wald test, and corrected for multiple testing using the Benjamini-Hochberg procedure to yield an adjusted *P* value. Presented data are exploratory and warrant prospective validation in future studies.
cfDNA, cell-free DNA; CI, confidence interval; HR, hazard ratio; mPFS, median progression-free survival; WT, wild type.

Decrease in mVAF at C1D15 in majority of patients treated with lerociclib + fulvestrant





- 36/45 patients (80%) had a decrease in mVAF at C1D15
  - PFS did not correlate with change in mVAF due to low number of events in patients with a mVAF increase
- Somatic variants were non-detectable in 9/45 patients (20%) at C1D15
- All patients (n = 9) with ESR1 variants at baseline had a decrease in ESR1 mVAF, including 6 patients (67%) who cleared all ESR1 variant cfDNA by C1D15

C1D15, cycle 1 day 15; cfDNA, cell-free DNA; mVAF, mean variant allele frequency; ND, non detectable; PFS, progression-free survival.

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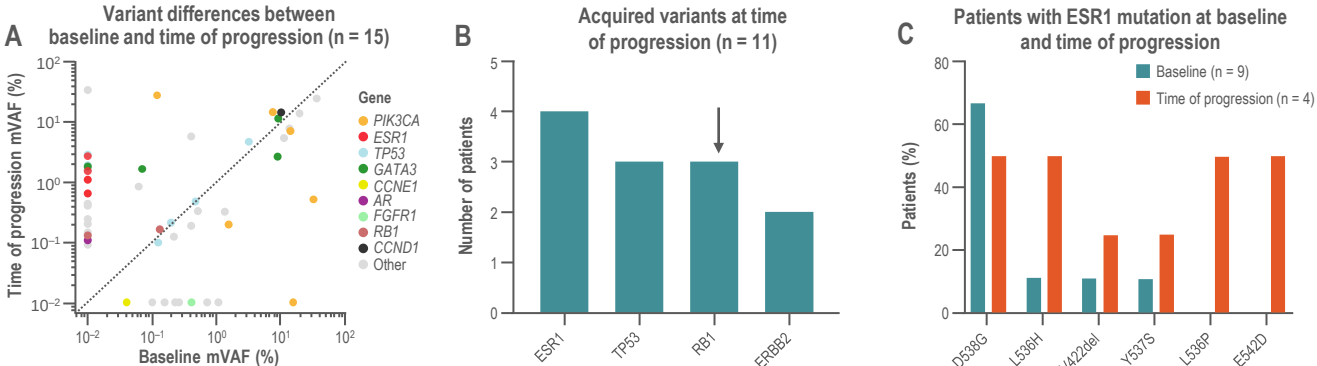
Potential mechanisms of acquired resistance



- A broad range of genes were altered at the time of progression (A), with acquired variants in ESR1, TP53, RB1, and ERBB2 being the most common (B)
- 11/15 patients acquired variants, including 3 patients (27%) who acquired mutations in RB1 at time of progression (B)
  - All 3 mutations in RB1 acquired at progression (S567L, R661W, and K574) were considered "likely" loss-of function and oncogenic[1]
- While D538G was the most common mutation in ESR1 at baseline, L536P and E542D were only found at the time of progression (C)

(A) Each point represents a gene for a single patient, the VAF is the mean VAF of variants in that gene. (B) Bar graph includes genes that were altered in at least 2 patients and excludes synonymous mutations. Presented data are exploratory and warrant prospective validation in future studies. mVAF, mean variant allele frequency.

1. Zehir A, et al. *Nat Med*. 2017;23:703–13.

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Clinical safety and efficacy updates, and additional cfDNA analysis, can be found on Poster #1407 (NCT02983071)