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TRILACICLIB IMPROVES OVERALL SURVIVAL WHEN GIVEN WITH GEMCITABINE/CARBOPLATIN (GCb) IN PATIENTS WITH METASTATIC TRIPLE NEGATIVE BREAST CANCER (mTNBC) IN A RANDOMIZED, OPEN-LABEL, PHASE 2 TRIAL

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DISCLOSURES

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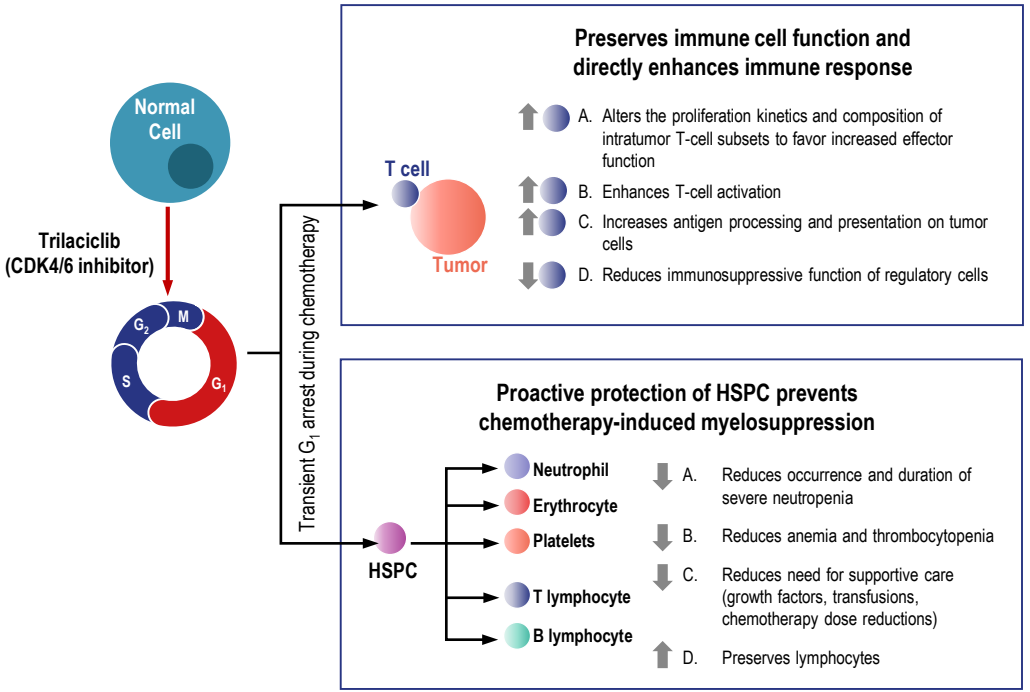
AbbVie Inc., Agendia, Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene Corporation, Eisai, G1 Therapeutics Inc., Genentech, Genomic Health, GRAIL, Immunomedics, Heron Therapeutics, Ipsen Biopharmaceuticals, Jounce Therapeutics, Lilly, Merck, Myriad, Novartis, Ondonate Therapeutics, Pfizer, Puma Biotechnology, Prime Oncology, Roche, Seattle Genetics, and Syndax Pharmaceuticals

Study sponsored by G1 Therapeutics, Inc.

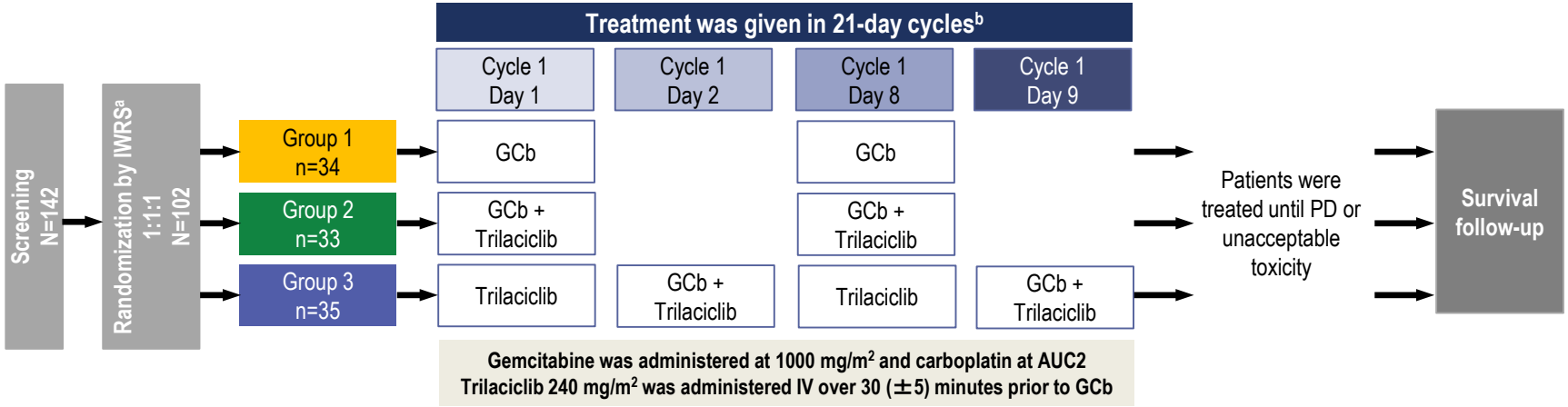
TRILACICLIB (G1T28), A HIGHLY POTENT, TRANSIENT CDK 4/6 INHIBITOR, HAS THE POTENTIAL TO DECREASE MYELOTOXICITY AND IMPROVE ANTI-TUMOR EFFICACY

- Gemcitabine + carboplatin (GCb) causes treatment-limiting cumulative myelosuppression[1] potentially compromising anti-tumor efficacy
- Chemotherapy-induced immune cell toxicity may limit host immune system's response against TNBC[2,3]
- Trilaciclib is an IV CDK4/6 inhibitor, which can induce transient G1 arrest in immune cells and HSPCs, potentially preserving T-cell function and bone marrow
  - T_{max}:~0.25–0.5 hr[4]
  - Terminal $t_{1/2}$: ~14 hr[4]
  - In kinase screen, IC_{50} for CDK4/cyclin D1 and CDK6/cyclin D3 was 1 nmol/L and 4 nmol/L, respectively[5]



1. O'Shaughnessy J, et al. J Clin Oncol. 2014;32:3840–7; 2. Lyman GH. Oncology (Williston Park). 2006;20:16–25; 3. Smith RE. J Natl Compr Canc Netw. 2006;4:649–58; 4. He S, et al. Sci Transl Med. 2017;9:pii:eaal3986; 5. Bisi JE, et al. Mol Cancer Ther. 2016;15:783–93.
CDK, cyclin-dependent kinase; GCb, gemcitabine/carboplatin; hr, hour(s); HSPC, hematopoietic stem and progenitor cell; IC50, half maximal inhibitory concentration; IV, intravenous; mTNBC, metastatic triple-negative breast cancer; t1/2, half-life; Tmax, time when maximum plasma concentration is reached.

RANDOMIZED, OPEN-LABEL, MULTICENTER, GLOBAL PHASE 2 STUDY OF TRILACICLIB PLUS GCb IN PATIENTS WITH mTNBC (G1T28-04; NCT02978716)



Eligibility criteria

- Evaluable, locally recurrent or metastatic TNBC
  - TNBC defined as ER and PR negative (local assessment of IHC; <10% nuclei staining) and HER2- per ASCO CAP
- Hemoglobin ≥9.0 g/dL; ANC ≥1·5 × 10^9/L; platelets ≥100 × 10^9/L
- 0–2 prior cytotoxic regimens for locally recurrent/metastatic disease
- ECOG PS 0—1

[a] Randomization stratified by number of prior lines of systemic therapy (0 vs 1 or 2) and presence of liver metastases (Yes or No). [b] CBCs assessed minimum of at least once per week during each chemotherapy cycle; FACT-An and FACT-B administered on Day 1 of each Cycle in the treatment phase and at the post treatment visit; prophylactic growth factors were **not** allowed in Cycle 1, otherwise, supportive care was allowed as needed.

ASCO CAP, American Society of Clinical Oncology College of American Pathologists; CBC, complete blood count; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; FACT-AN, Functional Assessment of Cancer Therapy-Anemia; FACT-B, FACT-Breast Cancer; GCb, gemcitabine/carboplatin; HER2-, human epidermal growth factor receptor 2 negative; IHC, immunohistochemistry; IV, intravenously; IWRS, interactive web-response system; mTNBC, metastatic triple-negative breast cancer; PD, progressive disease; PR, progesterone receptor.

ENDPOINTS AND STATISTICAL ANALYSES

Myelosuppression efficacy endpoints	
Primary	Duration of severe (G4) neutropenia in Cycle 1
	Occurrence of severe (G4) neutropenia during treatment period
Key secondary[a]	Occurrence of RBC transfusions
	Occurrence of G-CSF administrations
	Occurrence of platelet transfusions
Antitumor efficacy endpoints	
Secondary	ORR
	PFS
	OS
TEAEs and additional safety endpoints	
Exploratory endpoints	
	PROs

- Analyses of endpoints were prespecified to demonstrate superiority of Group 3 over Group 1 for at least one primary endpoint
- With 102 pts, the study would have 90% power to detect the treatment effect specified below at a 2-sided significance level of 0.05
  - 3-day reduction of duration of severe neutropenia (DSN) in Cycle 1, or
  - 41% absolute reduction in the proportion of patients with SN
- Group 2 vs Group 1 and Groups 2 + 3 vs Group 1 were prespecified secondary comparisons
- Timing of the PFS and OS analyses was determined by an independent DMC who viewed PFS/OS as a safety endpoint
  - PFS and OS median times and HRs calculated with 95% CIs and nominal p values
  - OS is planned to be final when ≥ 70% events have occurred
- Median follow-up for all patients: 10.5 months (range: 0.1–25.8 months)

[a] Key secondary endpoints assessed throughout treatment period; occurrence of RBC transfusions determined on/after Week 5.
DMC, data monitoring committee; DSN, duration of severe neutropenia; G4, Grade 4; G-CSF, granulocyte-colony stimulating factor; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PROs, patient-reported outcomes; RBC, red blood cell; SN, severe neutropenia; TEAEs, treatment-emergent adverse events.

BASELINE DEMOGRAPHICS AND TUMOR CHARACTERISTICS

	Group 1: GCb (Day 1/8) (n=34)	Group 2: GCb + Trilaciclib (Day 1/8) (n=33)	Group 3: GCb + Trilaciclib (Day 1/2/8/9) (n=35)	Total (n=102)
Age, n (%)				
18–<65	26 (76.5)	24 (72.7)	26 (74.3)	76 (74.5)
≥65	8 (23.5)	9 (27.3)	9 (25.7)	26 (25.5)
Hormone receptors n (%)				
ER <1%	31 (91.2)	30 (90.9)	33 (94.3)	94 (92.2)
ER 1–10%	2 (5.9)	2 (6.1)	2 (5.7)	6 (5.9)
ER negative other[a]	1 (2.9)	1 (3.0)	0	2 (2.0)
PR <1%	29 (85.3)	29 (87.9)	34 (97.1)	92 (90.2)
PR 1–10%	4 (11.8)	3 (9.1)	1 (2.9)	8 (7.8)
PR negative, other[a]	1 (2.9)	1 (3.0)	0	2 (2.0)
ECOG PS, n (%)				
0	15 (44.1)	17 (51.5)	21 (60.0)	53 (52.0)
1	19 (55.9)	16 (48.5)	14 (40.0)	49 (48.0)
Liver involvement[b], n (%)	8 (23.5)	8 (24.2)	10 (28.6)	26 (25.5)
Prior cytotoxic regimens[b], n (%)				
0	21 (61.8)	22 (66.7)	21 (60.0)	64 (62.7)
1 or 2	13 (38.2)	11 (33.3)	14 (40.0)	38 (37.3)

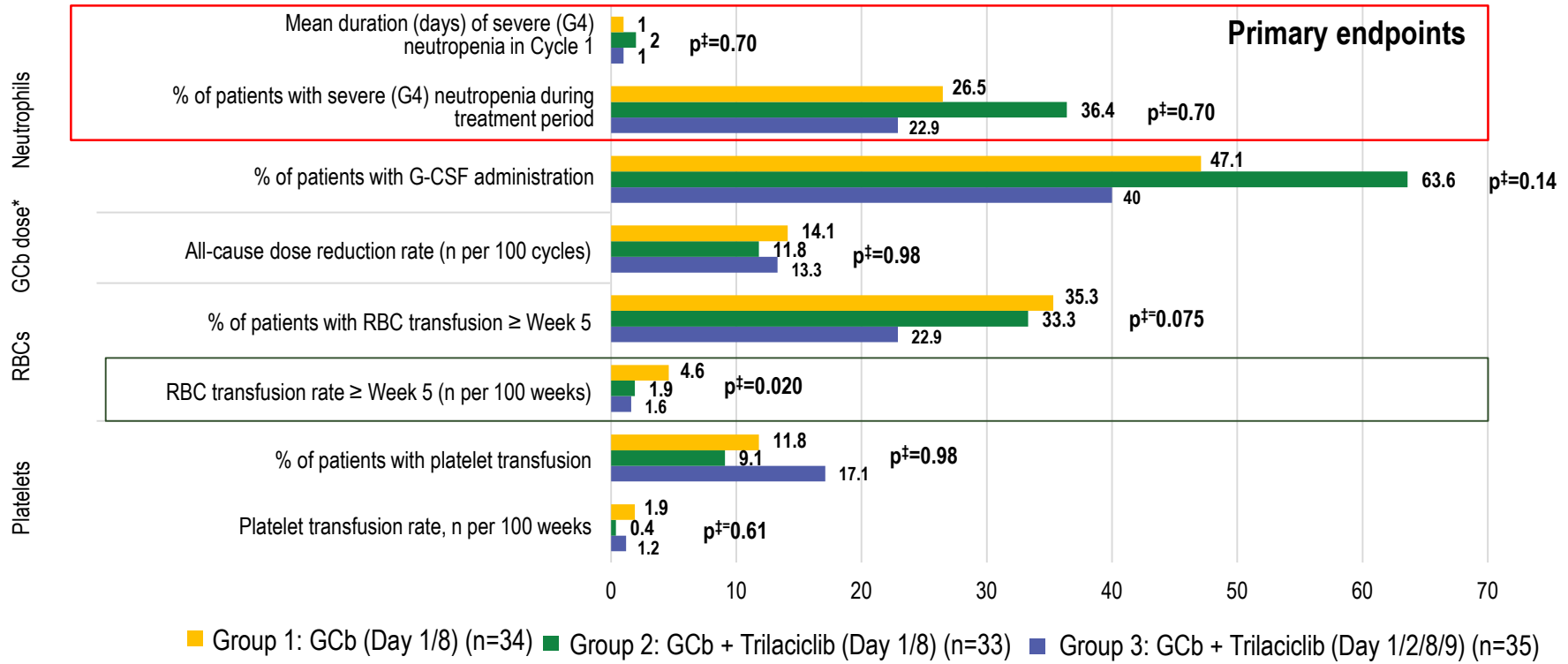
[a] Indicates patients were defined as TNBC by investigator; however, pathology reports were not available for confirmation (by Sponsor).
[b] Randomization stratified by number of prior lines of systemic therapy and presence of liver metastases.
ECOG PS, Eastern Cooperative Oncology Group performance status; GCb, gemcitabine/carboplatin; TNBC, triple-negative breast cancer.

TRILACICLIB INCREASED THE DURATION OF EXPOSURE AND CUMULATIVE DOSES OF GCb COMPARED WITH GCb ALONE

	Group 1 GCb (Day 1/8) (n=30)	Group 2 GCb + Trilaciclib (Day 1/8) (n=33)	Group 3 GCb + Trilaciclib (Day 1/2/8/9) (n=35)
Duration of exposure			
Months, median (min, max)	3.3 (0.7, 14)	5.3 (1.4, 19.6)	5.5 (0.7, 14.3)
Cycles, median (min, max)	4 (1, 18)	7 (2, 27)	8 (1, 20)
Cumulative dose			
Median gemcitabine dose, mg/m^2 (min, max)	7306.2 (1000.0, 34396.0)	12000.0 (3000.0, 43565.8)	11800.1 (2000.0, 37004.9)
Median carboplatin dose, AUC (min, max)	15.0 (2, 68.5)	24.0 (6, 89)	22.0 (4, 74)

Safety analysis set, based on data cut-off of May 17, 2019.
AUC, area under the curve; GCb, gemcitabine/carboplatin.

TRILACICLIB PLUS GCb DID NOT SIGNIFICANTLY IMPROVE PRIMARY MYELOSUPPRESSION ENDPOINTS OF DURATION AND OCCURRENCE OF SEVERE (GRADE 4) NEUTROPENIA



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Based on data as of July 30, 2018.
*No dose modifications of trilaciclib were allowed; ‡For comparison between Groups 3 and 1.
p-value reported for primary endpoints are multiplicity adjusted one-sided p value, all other p values are two-sided.
GCb, gemcitabine/carboplatin; G4, Grade 4; G-CSF, granulocyte-colony stimulating factor; RBC, red blood cell.

TRILACICLIB PLUS GCb: KEY ADVERSE EVENTS

Key TEAEs (all Grades) reported in ≥20% of patients in any treatment group, n (%)	Group 1: GCb (Day 1/8) (n=30)	Group 2: GCb + Trilaciclib (Day 1/8) (n=33)	Group 3: GCb + Trilaciclib (Day 1/2/8/9) (n=35)
Anemia	22 (73.3)	17 (51.5)	15 (42.9)
Neutropenia	21 (70.0)	27 (81.8)	23 (65.7)
Thrombocytopenia	18 (60.0)	18 (54.5)	22 (62.9)
Fatigue	11 (36.7)	14 (42.4)	15 (42.9)
Vomiting	8 (26.7)	7 (21.2)	11 (31.4)
Nausea	7 (23.3)	14 (42.4)	17 (48.6)
Headache	6 (20.0)	9 (27.3)	14 (40.0)

Hematologic AEs (Grade 3/4), n (%)	Group 1: GCb (Day 1/8) (n=30)	Group 2: GCb + Trilaciclib (Day 1/8) (n=33)	Group 3: GCb + Trilaciclib (Day 1/2/8/9) (n=35)
Neutropenia	20 (66.7)	26 (78.8)	20 (57.1)
Thrombocytopenia	15 (50.0)	9 (27.3)	15 (42.9)
Anemia	14 (46.7)	8 (24.2)	11 (31.4)

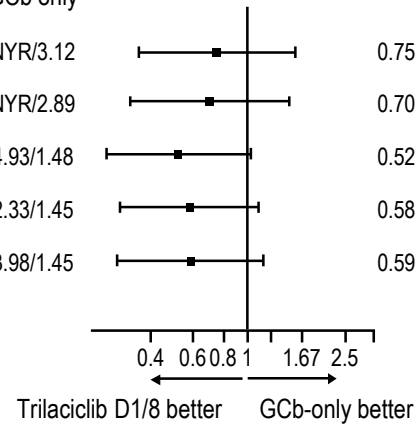
- Despite more GCb delivered in Groups 2 + 3, hematologic toxicity was similar between groups
- No serious TEAEs, or TEAEs leading to treatment discontinuation, were considered related to trilaciclib
- Trilaciclib TEAEs of special interest were primarily low grade and included headache, injection-site reactions and localized phlebitis

Safety analysis set, based on data cut-off of May 17, 2019; ordered from highest frequency to lowest frequency in Group 1.
AEs, adverse events; GCb, gemcitabine/carboplatin; TEAE, treatment-emergent adverse event.

TRILACICLIB DID NOT ADVERSELY AFFECT PATIENTS' OVERALL FUNCTION

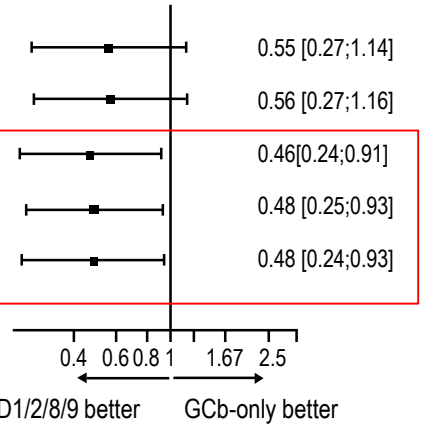
Group 2 vs Group 1

Domain	No. of Events Trilaciclib/ GCb only	Median TTD, Months Trilaciclib/ GCb only	Hazard Ratio [95% CI]
FACT-G	14/15	NYR/3.12	0.75 [0.36;1.56]
FACT-B	13/15	NYR/2.89	0.70 [0.33;1.48]
FACT-An	16/19	4.93/1.48	0.52 [0.26;1.04]
Fatigue	18/21	2.33/1.45	0.58 [0.30;1.11]
Anemia TOI	17/18	3.98/1.45	0.59 [0.30;1.17]



Group 3 vs Group 1

Domain	No. of Events Trilaciclib/ GCb only	Median TTD, Months Trilaciclib/ GCb only	Hazard Ratio [95% CI]
FACT-G	15/15	5.9/3.12	0.55 [0.27;1.14]
FACT-B	15/15	5.9/2.89	0.56 [0.27;1.16]
FACT-An	18/19	3.52/1.48	0.46[0.24;0.91]
Fatigue	19/21	3.48/1.45	0.48 [0.25;0.93]
Anemia TOI	20/18	3.52/1.45	0.48 [0.24;0.93]



No worsening of patients' overall function or QoL with the addition of trilaciclib to GCb

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Group 1: GCb (Day 1/8) (n=34); Group 2: GCb + Trilaciclib (Day 1/8) (n=33); Group 3: GCb + Trilaciclib (Day 1/2/8/9) (n=35).
Threshold=3 for Fatigue, =8 for FACT-B total, =6 for Anemia TOI, =7 for FACT-G total and FACT-An total, =1 for items.
CI, confidence interval; FACT-An, Functional Assessment of Cancer Therapy-Anemia; FACT-G, FACT-General; FACT-B, FACT-Breast; GCb, gemcitabine/carboplatin; NYR, not yet reached; QoL, quality of life; TOI, Trial Outcome Index;

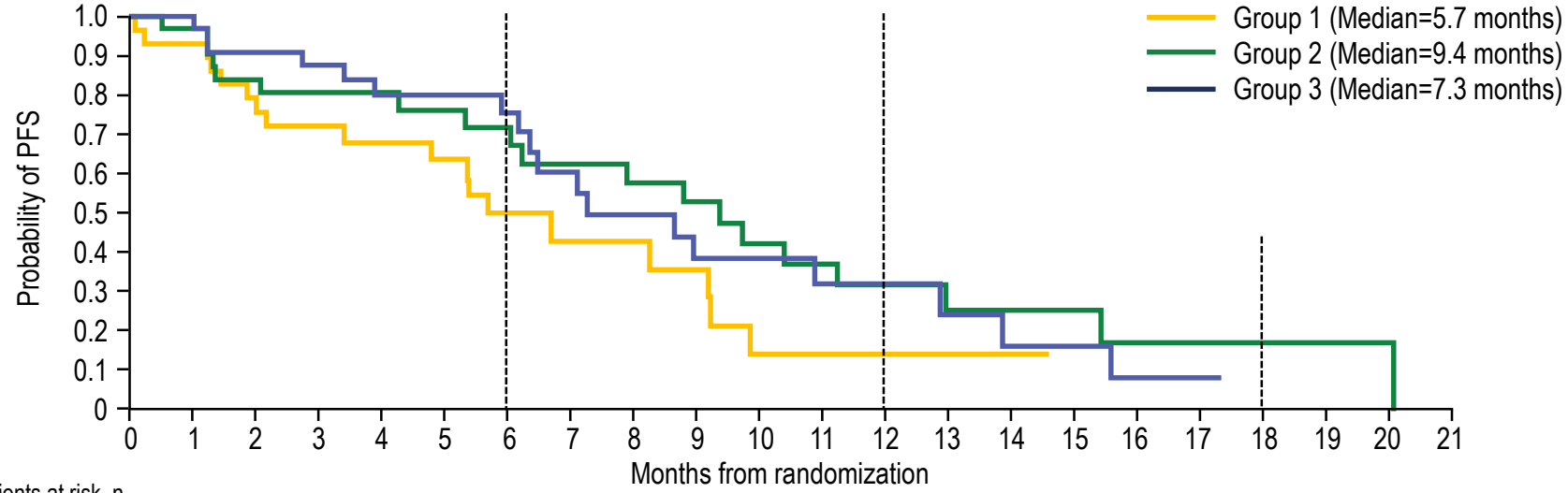
ANTITUMOR EFFICACY WITH TRILACICLIB PLUS GCb COMPARED WITH GCb ALONE

Best overall response, n (%)	Group 1: GCb (Day 1/8) (n=24)	Group 2: GCb + Trilaciclib (Day 1/8) (n=30)	Group 3: GCb + Trilaciclib (Day 1/2/8/9) (n=30)
ORR[a]	8 (33.3)	15 (50.0)	11 (36.7)
CBR for 24 weeks[a,b]	9 (37.5)	17 (56.7)	13 (43.3)
p-value[c]		0.23	0.68

- No significant differences in ORR or CBR between Group 2 vs Group 1 and Group 3 vs Group 1

[a] Patients were evaluable for response if they had measurable disease at baseline and ≥1 post baseline tumor assessment, investigator-noted clinical progression before the first post baseline tumor scan, or had died due to disease progression before the first post baseline tumor scan.
[b] Per protocol, clinical benefit was determined in response evaluable patients and included any patient who had a complete or partial response at any time post treatment or stable disease for ≥24 weeks.
[c] The two-sided p-value was calculated using stratified exact Cochran-Mantel-Haenszel method to account for the stratification factors.
CBR, clinical benefit rate; ORR, overall response rate.

PROGRESSION-FREE SURVIVAL (PFS) WITH TRILACICLIB PLUS GCb COMPARED WITH GCb ALONE



Patients at risk, n

Group 1	34	27	21	19	16	15	11	6	6	5	2	2	2	1	1	0	0	0	0	0	0
Group 2	33	30	25	22	20	17	16	13	12	11	8	7	5	4	4	3	2	1	1	1	0
Group 3	35	32	29	25	20	18	16	11	9	7	6	5	4	3	2	2	1	1	0	0	0

No differences in PFS between Group 3 vs Group 1 (HR=0.59; 95% CI 0.30-1.16; nominal p=0.12); Group 2 vs Group 1 (HR=0.60; 95% CI 0.30-1.18; nominal p=0.13); or Group 2 + 3 vs Group 1 (HR=0.59; 95% CI 0.33-1.05; nominal p=0.063)

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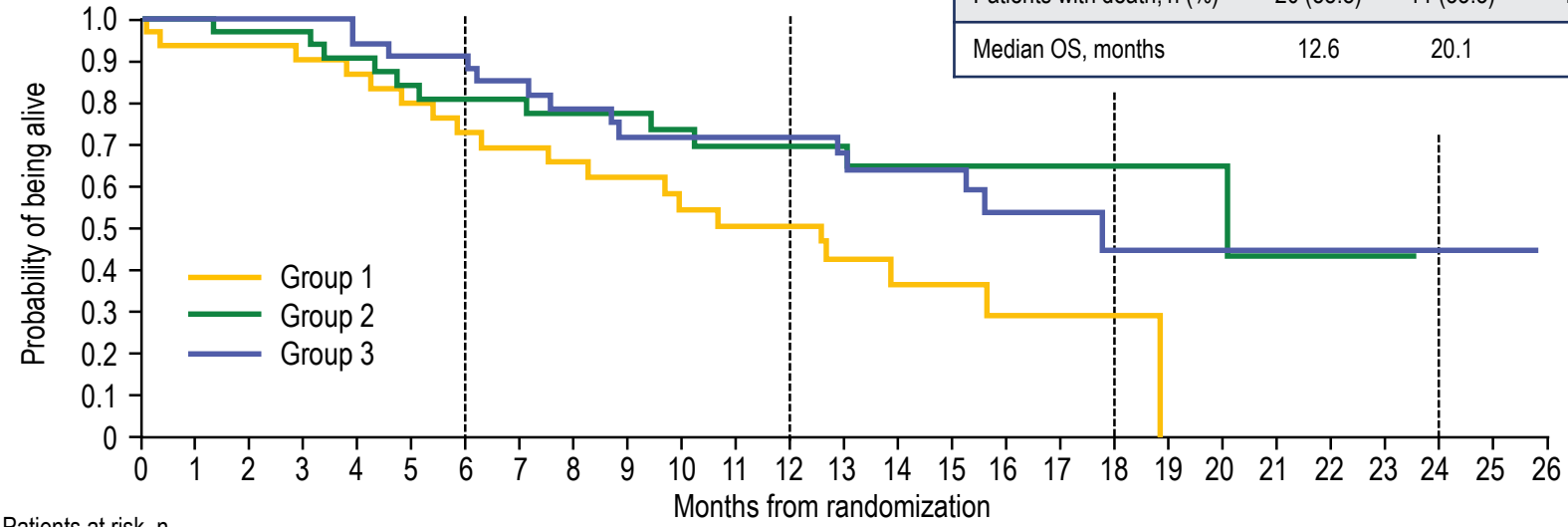
Data stable as of May 17, 2019.
Group 1: GCb (Day 1/8) (n=34); Group 2: GCb + Trilaciclib (Day 1/8) (n=33); Group 3: GCb + Trilaciclib (Day 1/2/8/9) (n=35).
GCb, gemcitabine/carboplatin; HR, hazard ratio; PFS, progression-free survival.

OVERALL SURVIVAL (OS) WITH TRILACICLIB PLUS GCb COMPARED WITH GCb ALONE

	Group 1	Group 2	Group 3
Patients with death, n (%)	20 (58.8)	11 (33.3)	14 (40.0)
Median OS, months	12.6	20.1	17.8



Patients at risk, n

Group 1	34	27	27	26	25	23	21	19	18	16	14	13	13	9	6	6	3	2	1	0	0	0	0	0	0	0
Group 2	33	33	32	31	28	26	24	22	20	20	19	17	17	15	13	13	12	10	8	5	3	2	1	1	0	0
Group 3	35	35	35	35	32	31	30	26	23	21	21	20	19	17	13	13	9	8	5	3	3	1	1	1	1	0

OS was longer for Group 3 vs Group 1 (HR=0.34; 95% CI 0.16 – 0.70; nominal p=0.0023), Group 2 vs Group 1 (HR=0.33; 95% CI 0.15-0.74; nominal p=0.028) and Group 2 + 3 vs Group 1 (HR=0.36; 95% CI 0.19-0.67; nominal p=0.0015)

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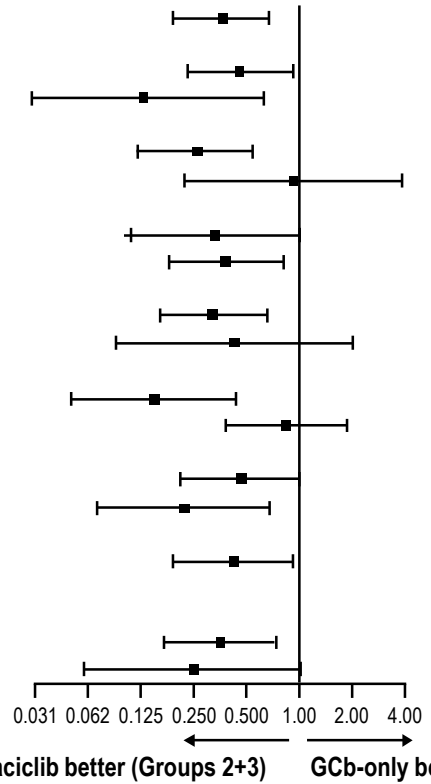
Based on data as of May 17, 2019.
Group 1: GCb (Day 1/8) (n=34); Group 2: GCb + Trilaciclib (Day 1/8) (n=33); Group 3: GCb + Trilaciclib (Day 1/2/8/9) (n=35).
HR, hazard ratio; OS, overall survival.

POOLED OVERALL SURVIVAL (OS) ANALYSIS IN PRESPECIFIED SUBGROUPS

Pre-specified subgroup analyses

Subgroup	No. of patients	No. of events	HR	95% CI
Overall (ITT)	102 (100)	45	0·36	(0·19–0·67)
Age				
<65 years	76 (74·5)	36	0·45	(0·23–0·91)
≥65 years	26 (25·5)	9	0·13	(0·03–0·63)
Race				
White	78 (76·5)	33	0·26	(0·12–0·54)
Non-white	24 (23·5)	12	0·92	(0·22–3·84)
Liver involvement				
Yes	26 (25·5)	17	0·33	(0·11–1·01)
No	76 (74·5)	28	0·38	(0·18–0·81)
Region				
USA	83 (81·4)	37	0·32	(0·16–0·65)
Ex-USA	19 (18·6)	8	0·42	(0·09–2·02)
ECOG PS				
0	53 (52)	18	0·15	(0·05–0·44)
1	49 (48)	27	0·72	(0·33–1·61)
Number of prior lines therapy				
0	64 (62·7)	28	0·46	(0·21–0·99)
1 or 2	38 (37·3)	17	0·22	(0·07–0·67)
BRCA classification				
Unknown	66 (64·7)	28	0·42	(0·19–0·92)
Positive	8 (7·8)	3	NE	(NE–NE)
Histological TNBC classification				
Always	71 (69·6)	31	0·35	(0·17–0·74)
Acquired	25 (24·5)	12	0·25	(0·06–1·02)



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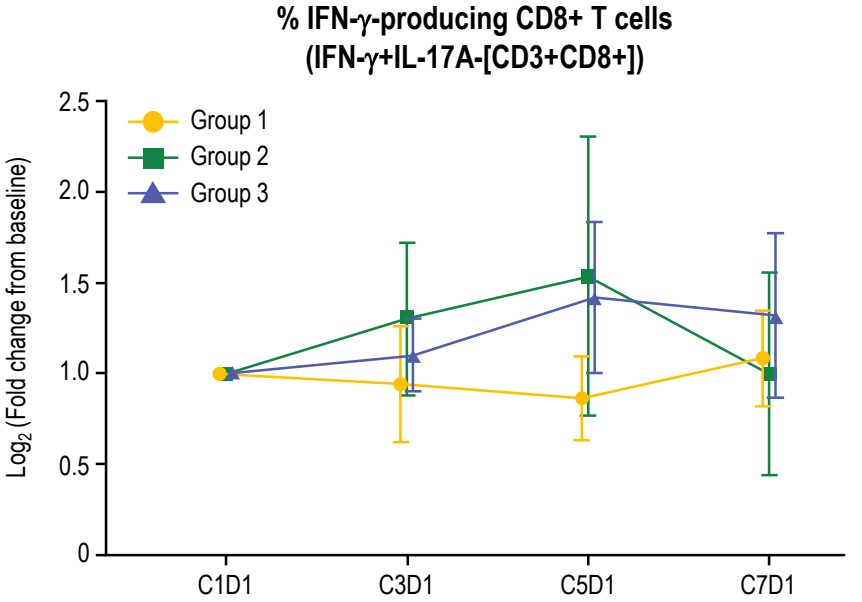
Group 1: GCb (Day 1/8) (n=34); Group 2: GCb + Trilaciclib (Day 1/8) (n=33); Group 3: GCb + Trilaciclib (Day 1/2/8/9) (n=35).
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; GCb, gemcitabine/carboplatin; HR, hazard ratio; ITT, intention-to-treat; NE, not estimable; TNBC, triple-negative breast cancer.

POSSIBLE MECHANISMS OF TRILACICLIB ANTITUMOR EFFICACY

- Increased duration of chemotherapy exposure
  - Patients on trilaciclib received ~twice as many chemotherapy cycles without increased toxicity nor worsening of overall function
- Protecting and/or enhancing immune cell function, thereby increasing immune-mediated antitumor effects
  - After *ex vivo* stimulation, there is a greater number of CD8+ T cells producing IFNγ in patients who received GCb + trilaciclib compared with GCb alone, suggesting a more functional lymphocyte population
- CDK4/6 inhibitors can increase platinum sensitivity and decrease proliferation by inhibiting FOXM1 phosphorylation (FOXM1 commonly over-expressed in TNBC)[1,2]



Patients, n	C3D1	C5D1	C7D1
Group 1	13	9	10
Group 2	11	11	8
Group 3	15	10	10

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1. Rubio C, et al. Clin Cancer Res. 2019;25:390–402. 2. Ni Y, et al. Nature Comm 2019; 10: 2860.

FOXM1, Forkhead Box M1; GCb, gemcitabine/carboplatin; IFNγ, interferon-gamma; IL, interleukin; Rb, retinoblastoma; TNBC, triple-negative breast cancer.

CONCLUSIONS

- The addition of trilaciclib to GCb in patients with mTNBC did not improve the primary myelosuppression endpoints of duration of severe neutropenia in cycle 1 and occurrence of severe neutropenia
- There were no significant differences in ORR and PFS with addition of trilaciclib to GCb
- There was a significant improvement in OS with trilaciclib added to GCb with both dosing schedules
- Trilaciclib did not increase high-grade toxicity when added to GCb, despite patients having received more cycles of therapy (median 7 or 8 cycles) compared with GCb alone (median 4 cycles)
- The addition of trilaciclib to GCb did not worsen the patients' functional status on chemotherapy
- Preliminary evidence suggests trilaciclib may enhance CD8+ T cell activation
- Additional biomarker studies, including PDL1 expression, are ongoing to evaluate potential immune effects of trilaciclib on patients' outcomes
- Final OS analyses will be performed when ≥70% events have occurred
- Further evaluation of trilaciclib with platinum-based chemotherapy in TNBC is warranted

GCb, gemcitabine/carboplatin; mTNBC, metastatic triple-negative breast cancer; ORR, overall response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; SN, severe neutropenia.

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THE LANCET Oncology

Trilaciclib plus chemotherapy versus chemotherapy alone in patients with metastatic triple-negative breast cancer: a multicentre, randomised, open-label, phase 2 trial

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Trilaciclib plus chemotherapy versus chemotherapy alone in patients with metastatic triple-negative breast cancer: a multicentre, randomised, open-label, phase 2 trial

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Summary

Background Trilaciclib is an intravenous cell-cycle inhibitor that transiently maintains immune cells and haemopoietic stem and progenitor cells in G1 arrest. By protecting the immune cells and bone marrow from chemotherapy-induced damage, trilaciclib has the potential to optimise antitumour activity while minimising myelotoxicity. We report safety and activity data for trilaciclib plus gemcitabine and carboplatin chemotherapy in patients with metastatic triple-negative breast cancer.

Methods In this randomised, open-label, multicentre, phase 2 study, adult patients (aged ≥18 years) with evaluable, biopsy-confirmed, locally recurrent or metastatic triple-negative breast cancer who had no more than two previous lines of chemotherapy were recruited from 26 sites in the USA, three in Serbia, two in North Macedonia, one in Croatia, and one in Bulgaria; sites were academic and community hospitals. Availability of diagnostic samples of tumour tissue confirming triple-negative breast cancer was a prerequisite for enrolment. Eligible patients were randomly assigned (1:1:1) by an interactive web-response system, stratified by number of previous lines of systemic therapy and the presence of liver metastases, to receive intravenous gemcitabine 1000 mg/m² and intravenous carboplatin (area under the concentration-time curve 2 μg×h/mL) on days 1 and 8 (group 1), gemcitabine and carboplatin plus intravenous trilaciclib 240 mg/m² on days 1 and 8 (group 2), or gemcitabine and carboplatin on days 2 and 9 plus trilaciclib on days 1, 2, 8, and 9 (group 3) of 21-day cycles. Patients continued treatment until disease progression, unacceptable toxicity, withdrawal of consent, or discontinuation by the investigator. The primary objective was to assess the safety and tolerability of combining trilaciclib with gemcitabine and carboplatin chemotherapy. The primary endpoints were duration of severe neutropenia during cycle 1 and the occurrence of

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