Effect of Trilaciclib, a CDK 4/6 Inhibitor, on Myelosuppression in Patients with Previously Treated Extensive-Stage Small Cell Lung Cancer

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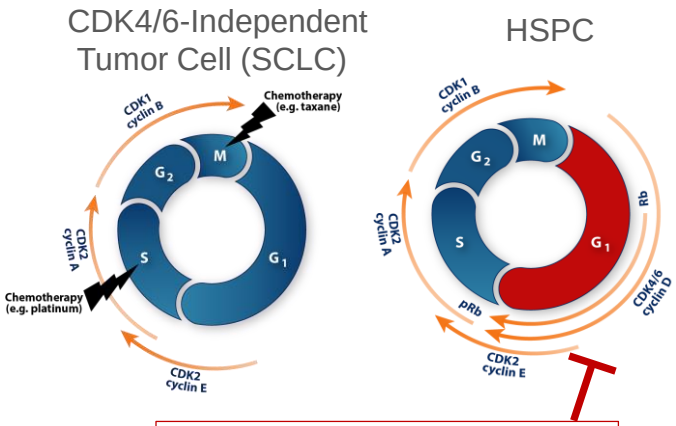
Despite the Availability of Rescue Interventions (e.g. GCSF, ESAs, and Transfusions) There is Still Significant Unmet Medical Need for SCLC Patients Treated with Topotecan

- **With current SOC, a significant percentage of patients treated with topotecan still experience severe myelosuppression and the associated consequences**

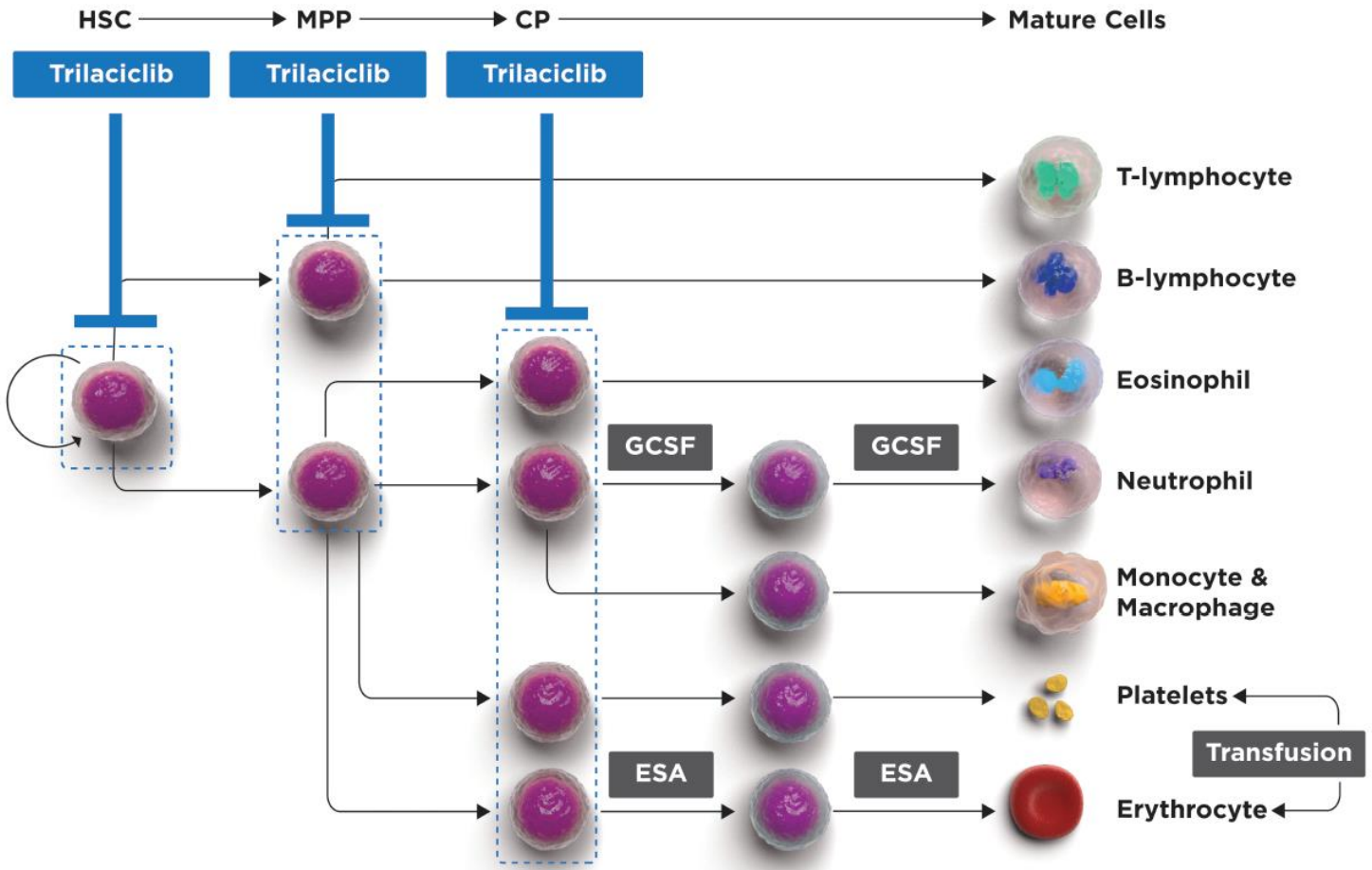
	Topotecan Grade 3/4 AEs[1]	Current Treatments	Current Treatment Unmet Needs
Neutropenia 	54% (3% FN)	GCSF rescue	~70% bone pain (~25% severe[2]) induced by GCSFs (severe pain treated with NSAIDs, antihistamines, and opioids)
Anemia 	31%	ESA rescue, Transfusion rescue	Box warning for shortened overall survival and increased risk of tumor progression
Thrombocytopenia 	54%	Transfusion rescue	No options other than transfusions

1. von Pawel J, et al. J Clin. Oncol. 2014;32:4012-4019
2. Kirshner JJ, et al. J Clin Oncol. 2012;30:1974-1979.

Trilaciclib, a First-in-Class Myelopreservation Agent, Proactively Reduces Risks Associated with Myelosuppressive Chemotherapy



Trilaciclib transiently blocks progression through the cell cycle, thereby protecting HSPCs from damage by chemotherapy



- Protection before HSPC damage occurs
- Multi-lineage protection
- Reduces need for supportive care measures

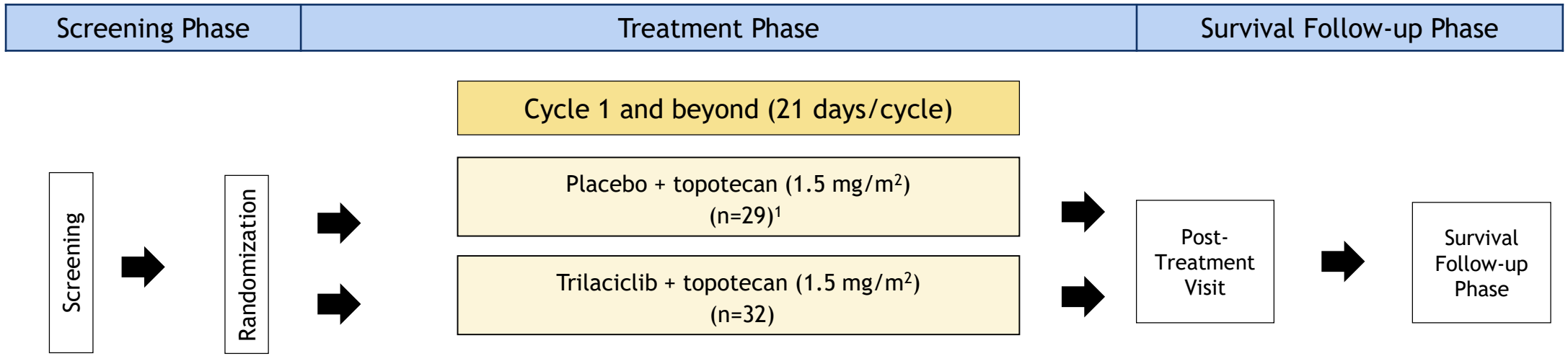
G1T28-03 Primary and Key Secondary Endpoints

PRIMARY ENDPOINTS
Duration of severe neutropenia in Cycle 1
Occurrence of severe neutropenia

KEY SECONDARY ENDPOINTS
All-cause dose reductions
Occurrence of RBC transfusion on/after 5 weeks on study
Occurrence of GCSF administration
Occurrence of platelet transfusions

- **Pre-specified endpoints included:**
  - Myelosuppression efficacy endpoints (primary, key secondary)
  - Anti-tumor efficacy endpoints (secondary)
  - Patient reported outcomes (exploratory)
  - Adverse events (AEs) and additional safety endpoints

G1T28-03 Study Design: Extensive-Stage SCLC (2L/3L)



- Randomized, double-blind, placebo-controlled, Phase 2 study stratified by ECOG status (0 to 1 versus 2) and sensitivity to 1L treatment (sensitive versus resistant)
- Trilaciclib administered IV on Days 1-5 prior to topotecan
- Patients treated until disease progression, unacceptable toxicity or withdrawal of consent
- Use of primary prophylactic colony stimulating factors in Cycle 1 was not allowed; supportive care measures per institution were permitted throughout the study
- A trilaciclib + 0.75 mg/m^2 topotecan arm was also enrolled (n=30); data not shown

ES-SCLC, Extensive-Stage Small cell lung cancer; L, Line

[1] One patient randomized to placebo was not treated

Demographics and Key Baseline Characteristics

Category	Placebo + topotecan 1.5 mg/m² (N=29)	Trilaciclib + topotecan 1.5 mg/m² (N=32)
Age (years)		
Median	64	62
Min, Max	47, 82	47, 77
Age group, n (%)		
18 - < 65 years	18 (62.1)	20 (62.5)
≥ 65 years	11 (37.9)	12 (37.5)
Gender, n (%)		
Male	12 (41.4)	22 (68.8)
Female	17 (58.6)	10 (31.3)
Region, n (%)		
US	18 (62.1)	14 (43.8)
Ex-US	11 (37.9)	18 (56.3)
ECOG Status, n (%)		
0 – 1	27 (93.1)	29 (90.6)
2	2 (6.9)	3 (9.4)
Brain metastases at baseline, n (%)		
Present	5 (17.2)	8 (25.0)
Not present	24 (82.8)	23 (71.9)
Not evaluable	0	1 (3.1)
Baseline LDH, n (%)		
≤ ULN	15 (51.7)	15 (46.9)
> ULN	13 (44.8)	16 (50.0)
Missing	1 (3.4)	1 (3.1)
Weight loss ≥6 months prior to randomization, n (%)		
No	21 (72.4)	22 (68.8)
Yes	8 (27.6)	10 (31.3)
• Weight loss >5%	6 (75.0)	9 (90.0)
• Weight loss ≤5%	2 (25.0)	1 (10.0)

While the trilaciclib and placebo arms were generally comparable, there were more male patients and more ex-US patients enrolled in the trilaciclib arm

Summary of Drug Exposure

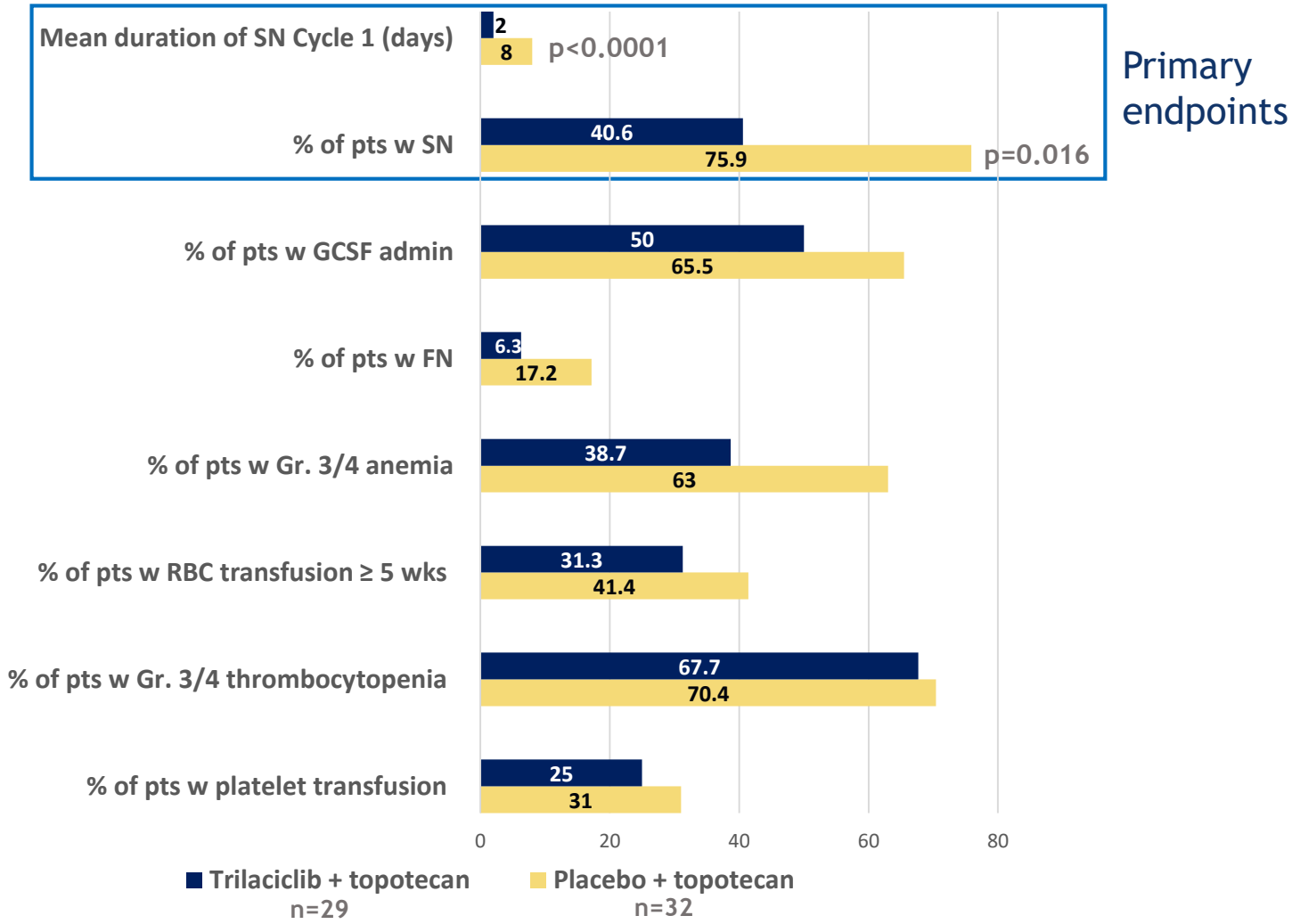
Category	Placebo + 1.5 mg/m^2 topotecan [N=28][1]	Trilaciclib + 1.5 mg/m^2 topotecan [N=32]
Duration of Exposure (days)		
Mean (SD)	94 (75.9)	107 (92.2)
Median (Min, Max)	77 (21, 294)	67 (21, 336)
Number of Cycles Completed		
Mean (SD)	4 (3.4)	5 (4.1)
Median (Min, Max)	3 (1, 14)	3 (1, 16)
Topotecan Dose Reductions		
Number of patients with any dose reductions (%)	9 (32.1)	6 (18.8)
All-cause Dose Reductions		
Event rate (per 100 cycles)	11.6	5.1

- Patients on trilaciclib completed more cycles and had fewer dose reductions compared to those on placebo
- Relative dose intensity of topotecan for the G1T28-03 study was not available due to the blinded design of the study and two doses of topotecan being utilized

[1] Based on Intent-to-treat analysis data set

Trilaciclib Demonstrates Myelopreservation Benefit Across Multiple Lineages

- Duration of severe neutropenia is a surrogate for an increased risk of febrile neutropenia, infection, IV antibiotic use and hospitalizations
- Chemotherapy-induced anemia in cancer patients correlates with fatigue and a compromised quality of life



SN, Severe neutropenia, FN, febrile neutropenia, Gr, grade, RBC, red blood cell, %, percent, pts, patients
Data are based on laboratory values

p-values are 1-sided with multiplicity adjustment

Trilaciclib Makes Chemotherapy Safer

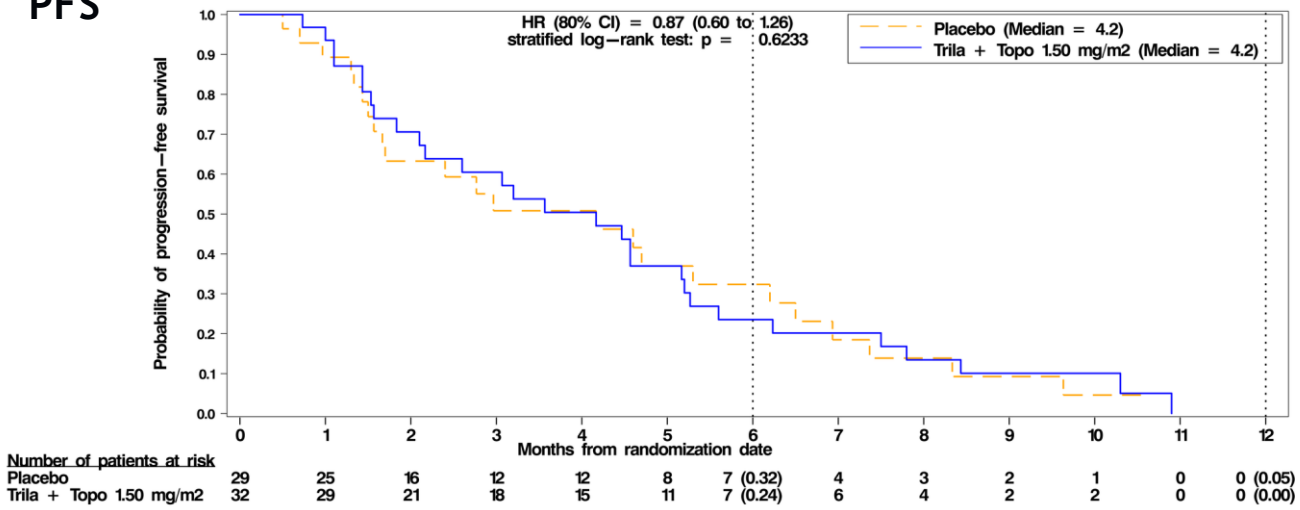
	Placebo + 1.5 mg/m^2 topotecan [N=28]		Trilaciclib + 1.5 mg/m^2 topotecan [N=32]	
Preferred Term	**AEs regardless of Grade***	**Grade ≥3**	**AEs regardless of Grade***	**Grade ≥3**
All AEs	27 (96.4)	27 (96.4)	32 (100.0)	28 (87.5)
Neutropenia	24 (85.7)	24 (85.7)	24 (75.0)	22 (68.8)
Thrombocytopenia	19 (67.9)	16 (57.1)	20 (62.5)	17 (53.1)
Anemia	24 (85.7)	17 (60.7)	17 (53.1)	9 (28.1)
Fatigue	10 (35.7)	2 (7.1)	13 (40.6)	3 (9.4)
Nausea	14 (50.0)	1 (3.6)	9 (28.1)	0 (0)

- The trilaciclib arm had fewer high grade hematologic toxicities, particularly neutropenia and anemia
- Fatal AEs were reported in 4 patients. None were assessed as related to trilaciclib
- One serious AE assessed as related to trilaciclib in combination with topotecan was reported (infusion-related grade 3 thrombophlebitis)
- AEs of special interest were primarily low grade and include:
  - headache
  - Infusion-related reaction
  - phlebitis

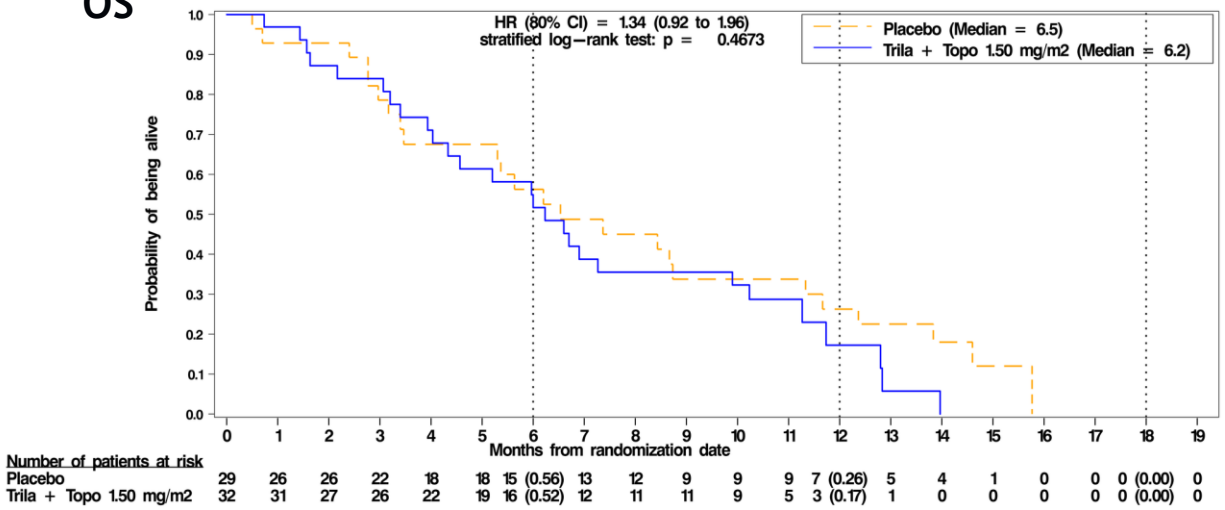
AEs percentage based on frequency of ≥20% based on total patients treated in the Phase 2 portion of the study

Trilaciclib Does Not Impair Chemotherapy Efficacy

PFS

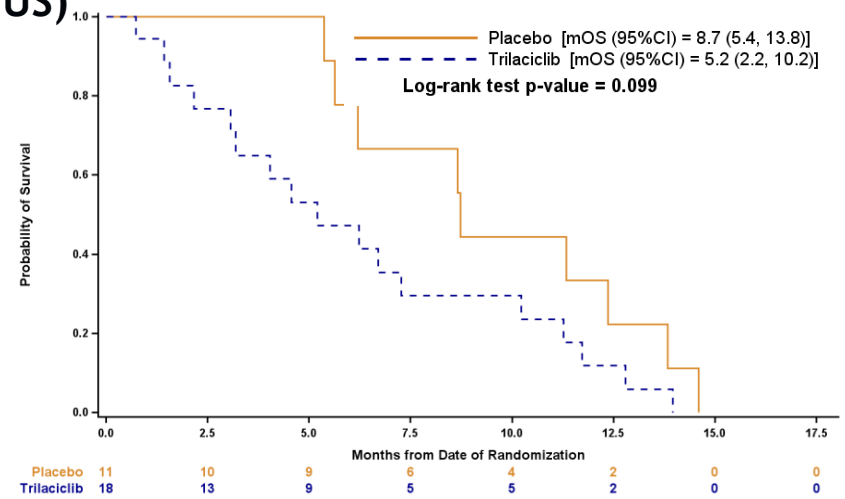


OS

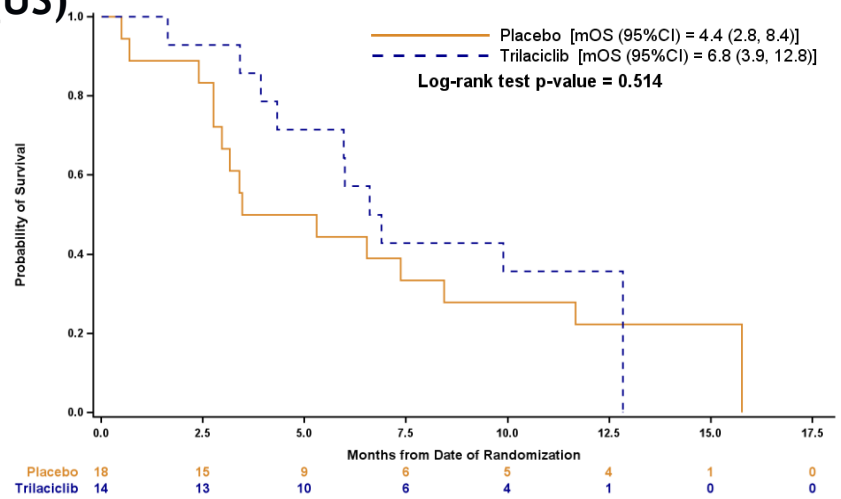


- ORR was comparable in placebo and trilaciclib arms: 6/26 (23.1%) for placebo and 5/30 (16.7%) for trilaciclib
- PFS was comparable in placebo and trilaciclib arms
- OS was comparable in the placebo and trilaciclib arms
  - OS was impacted by regional differences (ex-US placebo OS was longer than historical data)

OS (Ex-US)



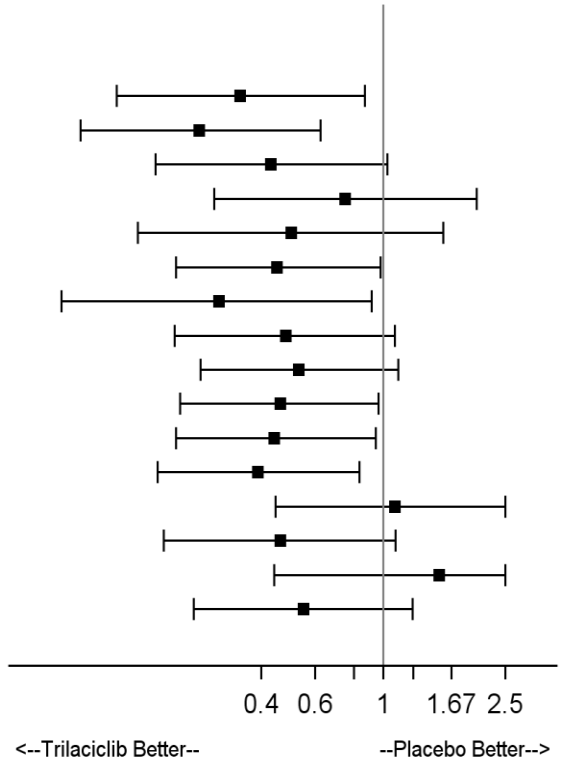
OS (US)



Trilaciclib Improves Patient Experience on Chemotherapy

G1T28-03: 2L/3L SCLC, topotecan +/- trilaciclib

Domain	No. of Events Trilaciclib/Placebo	Median TTD, Months Trilaciclib/Placebo	Hazard Ratio [95% CI]
FACT-G	7/13	NYR/2.86	0.34 [0.14;0.87]
PWB	7/16	NYR/1.64	0.25 [0.10;0.62]
FWB	10/13	8.84/2.23	0.43 [0.18;1.03]
EWB	8/8	NYR/NYR	0.75 [0.28;2.02]
SWB	6/8	6.70/NYR	0.50 [0.16;1.57]
FACT-L	12/16	4.40/2.10	0.45 [0.21;0.98]
LCS	4/11	NYR/10.02	0.29 [0.09;0.92]
Lung TOI	10/14	NYR/2.10	0.48 [0.21;1.09]
FACT-An	14/16	3.75/1.02	0.53 [0.25;1.12]
Fatigue	14/17	3.09/0.95	0.46 [0.22;0.96]
Anemia TOI	13/17	3.09/1.02	0.44 [0.21;0.94]
GP1: Energy	12/17	3.75/1.41	0.39 [0.18;0.83]
GP4: Pain	11/9	NYR/NYR	1.09 [0.45;2.66]
GP5: Side effects	9/13	NYR/2.53	0.46 [0.19;1.09]
B5: Hair loss	7/4	NYR/NYR	1.52 [0.44;5.23]
An: Tired	11/13	NYR/1.48	0.55 [0.24;1.24]



Threshold=3 for PWB,SWB,EWB,FWB,LCS and Fatigue, =6 for FACT-L total, L-TOI and An-TOI, =7 for FACT-G total and FACT-An total, =1 for items
NYR=Not yet reached

- Enrolled patients had a moderate level of functioning and were moderately symptomatic at baseline as measured by FACT-L and FACT-An instruments
- Trilaciclib improves the patient experience by decreasing the risk of deterioration (statistically significant in some instances) as compared to placebo. Overall, the benefit of trilaciclib was seen with:
  - General and physical wellbeing
  - QOL measures specific for lung cancer patients
  - Symptoms and impact of fatigue
  - Symptoms and effects on physical and functional well being due to anemia

Conclusions

- Trilaciclib makes topotecan treatment safer and more tolerable by protecting patients from chemotherapy-induced bone marrow damage. These benefits are measured by:
  - **Neutrophils: (1) shorter duration of severe neutropenia (surrogate for increased risk of FN, infections, etc.), (2) fewer episodes of severe neutropenia, and (3) less GCSF use**
  - **RBCs: (1) lower rates of Grade 3/4 anemia, and (2) fewer RBC transfusions and ESA use**
  - **Platelets: (1) lower rates of Grade 3/4 thrombocytopenia and (2) fewer platelet transfusions**
- Improved overall safety profile is evidenced by a reduction in high grade hematologic AEs
- Validated PRO instruments demonstrate that the addition of trilaciclib to topotecan improves the patient experience with chemotherapy relative to topotecan alone
- PFS and OS data demonstrate that trilaciclib does not impair chemotherapy efficacy
- These data extend the evidence[1] for the clinical benefits of trilaciclib in SCLC as a first-in-class myelopreservation agent for patients being treated with topotecan in the 2nd/3rd line setting

1 K H Dragnev, T K Owonikoko, T Csoszi, M Maglakelidze, J T Beck, M Domine Gomez, A Lowczak, A Fulop, R J Hoyer, W Hanna, P Lowry, R Aljumaily, V K Chiu, I Bulat, Z Yang, P J Roberts, J M Antal, R K Malik, S R Morris, J M Weiss, 1666PD
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