Trilaciclib in Chemotherapy-Induced Myelosuppression

Katelyn Kennedy, PharmD
PGY-1 Pharmacy Resident
VA St. Louis Health Care System
December 15, 2022

Learning Objectives

- Describe the mechanism of action by which trilaciclib prevents chemotherapy-induced myelosuppression in patients with small-cell lung cancer.
- Describe the conclusions of the three hallmark studies leading to the Food and Drug Administration's approval of trilaciclib.
- Identify the patient characteristics that would constitute trilaciclib as a favorable chemotherapy-induced myelosuppression treatment option.

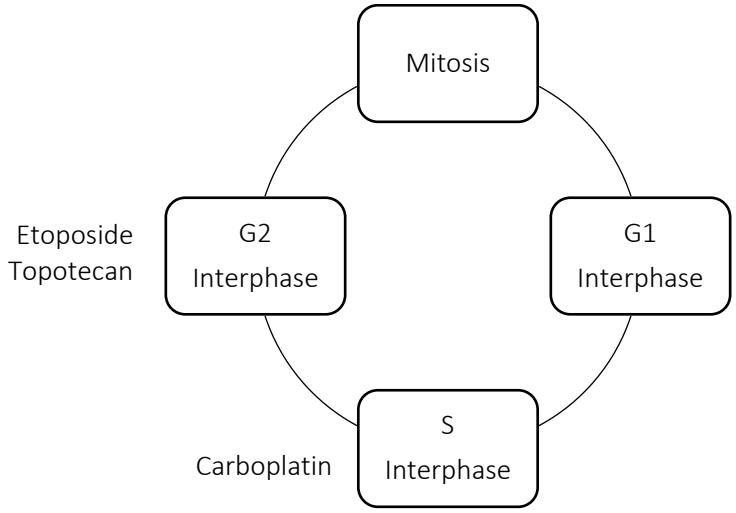
ABBREVIATIONS

Terms	Abbreviations
Small-cell lung cancer	SCLC
Extensive-stage small-cell lung cancer	ES-SCLC
Febrile neutropenia	FN
Growth colony stimulating factors	G-CSF
Red blood cell	RBC
White blood cell	WBC
Erythropoietin stimulating agents	ESA
Chemotherapy-induced myelosuppression	CIM
Hemopoietic stem and progenitor cells	HSPC
Eastern cooperative oncology group	ECOG
Response evaluation criteria in solid tumors	RECIST
Overall response rate	ORR
Progression free survival	PFS
Duration of response	DUR

Small-Cell Lung Cancer[1,2]

- SCLC accounts for roughly 15% of bronchogenic cancers
- Stages of SCLC:
  - Limited-Stage Disease: Disease confined to a specific area of the lung
  - Extensive-Stage Disease: Disease that has spread to additional parts of the body
    - Metastases are present
- Treatment

<table>
<tr><th colspan="5">First-Line Therapy</th></tr>
<tr><td colspan="2">Risk of Grade 3/4 Neutropenia: ~23%</td><td colspan="2">Risk of Grade 3/4 Anemia: ~14%</td><td>Risk of Grade 3/4 Thrombocytopenia: ~10%</td></tr>
<tr><td colspan="5">- Carboplatin
- Etoposide
- +/- Atezolizumab (if extensive-stage disease)</td></tr>
<tr><th colspan="5">Second-Line Therapy</th></tr>
<tr><td colspan="2">Risk of Grade 3/4 Neutropenia: ~54%</td><td colspan="2">Risk of Grade 3/4 Anemia: ~31%</td><td>Risk of Grade 3/4 Thrombocytopenia: ~54%</td></tr>
<tr><td>Topotecan</td><td>Lurbinectedin</td><td>Docetaxel</td><td>PO Etoposide</td><td rowspan="3">Cyclophosphamide/ doxorubicin/docetaxel</td></tr>
<tr><td>Gemcitabine</td><td>Irinotecan</td><td>Nivolumab</td><td>Paclitaxel</td></tr>
<tr><td>Pembrolizumab</td><td>Temozolomide</td><td>Vinorelbine</td><td>Bendamustine</td></tr>
</table>



Complications of Myelosuppression[3]

- Bone marrow activity is decreased due to myelosuppression; the decreased production of WBC, RBC, and platelets can lead to:
  - Neutropenia → FN, increased risk of infections and/or hospitalizations, chemotherapy dose delays and reductions
  - Thrombocytopenia → bleeding and/or excessive bruising
  - Anemia → fatigue, dyspnea, dizziness, tachycardia

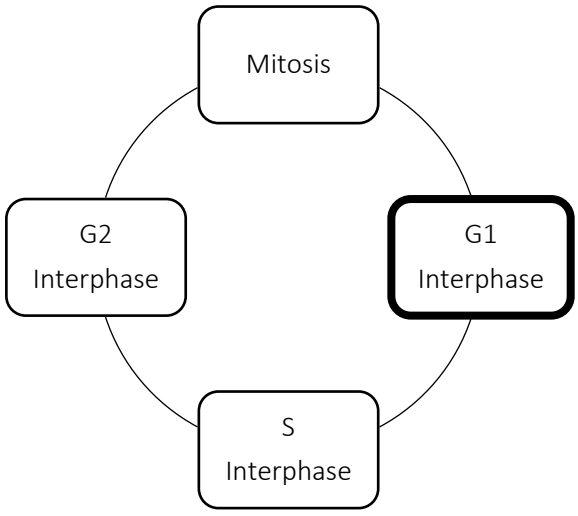
- Neutropenia, anemia, and thrombocytopenia can result in chemotherapy dose delays and reduction as well as increased morbidity, mortality, and overall healthcare costs.

Supportive Care Treatment Guidelines[3,4]

Complication	Treatment
Neutropenia	• Evaluate patient for risk of neutropenia following chemotherapy ▪ Disease, type of chemotherapy, risk factors, and intent of treatment • High Risk: administration of G-CSF recommended • Intermediate Risk: administration of G-CSF considered • Low Risk: administration of G-CSF not recommended
Anemia:	• Evaluate patient for other causes of anemia and treat as indicated • If high risk and symptomatic, patient is indicated for RBC transfusion • Therapies can also include iron supplementation and ESA
Thrombocytopenia	• Evaluate patient for other causes of thrombocytopenia and treat as indicated • If related to chemotherapy, consider platelet transfusion, chemotherapy dose reductions, or change in chemotherapy regimen

Trilaciclib (Cosela™)[5,10]

- FDA approved in February 2021 for use in patients with SCLC prior to receiving chemotherapy (platinum/etoposide or topotecan-regimens)
- Trilaciclib is administered as 240mg/m^2 infusion over 30 minutes within four hours prior to chemotherapy to decrease the risk of CIM
- Trilaciclib is indicated in patients with SCLC because:
    - SCLC treatment regimens are associated with high risk of chemotherapy related toxicities
    - SCLC replicates independently of trilaciclib, thus suggesting that the use of trilaciclib will not affect the tumor
    - SCLC is chemosensitive, so trilaciclib should not affect chemotherapy's effects on tumor burden



MYELOPRESERVATION WITH THE CDK4/6 INHIBITOR TRILACICLIB IN PATIENTS WITH SMALL-CELL LUNG CANCER RECEIVING FIRST-LINE CHEMOTHERAPY: A PHASE IB/RANDOMIZED PHASE II TRIAL[5]

- **Study Design:** phase Ib/II multicenter, randomized, placebo-controlled trial that took place in North America and Europe
- **Objective:** assess ability of trilaciclib to reduce CIM and to improve safety of toxic chemotherapy
- **Key endpoints:**
  - Primary:
    - Part 1: Define the recommended phase 2 dose of trilaciclib
    - Part 2: Severe neutropenia and growth factor administration
  - Secondary
    - Number of chemotherapy cycles completed
    - Chemotherapy dose intensities
    - Major hematological adverse events
- **Inclusion criteria:**
  - ES-SCLC
  - Measurable disease by RECIST
  - ECOG performance status 0-2
  - Adequate organ function
- Baseline characteristics

Category	Etoposide/carboplatin + Placebo (n = 38)	Etoposide/carboplatin + trilaciclib (n = 39)	*P* value
Mean Age	65	65	(not reported)
Age Group			
< 65	17	20	0.642
≥ 65	21	19	0.1573
Male	27	27	0.3394
Female	11	12	0.2909
ECOG Score			
0-1	35	35	0.1185
2	3	4	0.7062
Brain metastasis	8	5	0.5781
Prior Radiation Therapy	4	3	(not reported)
Smoking Status			
Former	25	25	(not reported)
Current	12	14	(not reported)

- Part 1 results

Part I: Carboplatin on day 3 + etoposide on days 1-3 + trilaciclib 200mg/m^2; or carboplatin on day 3 + etoposide on days 1-3 + trilaciclib 240mg/m^2		
	Cohort 1 (n = 12) (200mg/m^2 trilaciclib)	Cohort 2 (n = 8) (240mg/m^2 trilaciclib)
≥ Grade 3 hematologic adverse events	50.0%	25.0%
G-CSF administration	50.0%	33.3%
ESA administration	20.0%	0%
RBC transfusion	11.1%	40.0%
Platelet transfusion	10.0%	0%
Infection serious adverse events	20.0%	11.1%
IV antibiotic use	40.0%	11.1%

- Part 2: Carboplatin on day 3 + etoposide on days 1-3 + trilaciclib 240mg/m^2; or carboplatin on day 3 + etoposide on days 1-3 + placebo
  - Myelosuppression Results

Category	Placebo Group (n = 37)	Trilaciclib Group (n = 38)	*P* value
Severe neutropenia (% of patients)	43.2%	5.3%	0.0001
G-CSF Administration (% of patients)	64.9%	10.5%	<0.0001
RBC Transfusion (% of patients)	24.3%	5.3%	0.0338
Platelet Transfusion (% of patients)	0	5.3%	0.1542
ESA Administration (% of patients)	5.4%	2.6%	0.5578
ORR	66.7%	56.8%	0.3831
Median DUR (months)	5.7	5.4	
PFS (months)	6.2	5	0.1695

  - Chemotherapy Results

Category	Placebo Group (n = 37)	Trilaciclib Group (n = 38)
Number of cycles completed (mean)	5	5
Relative Dose Intensities		
Trilaciclib/placebo (mean)	92.8%	92.6%
Etoposide (mean)	89.3%	91.8%
Carboplatin (mean)	90.4%	95%
Cycle Delays (number of patients, %)	25	15
Dose Reductions		
Etoposide (number of patients)	13	3
Carboplatin (number of patients)	13	3

- Safety Results

Category	Placebo Group (n = 37)		Trilaciclib Group (n = 38)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Hematologic (% of patients)				
Neutropenia	62.2%	56.8%	23.7%	7.9%
Thrombocytopenia	27.0%	8.1%	26.3%	7.9%
Anemia	40.5%	16.2%	26.3%	5.3%
Nonhematologic (% of patients)				
Nausea	21.6%	2.7%	34.2%	5.3%
Diarrhea	18.9%	2.7%	15.8%	0
Dyspnea	13.5%	2.7%	21.1%	0
Fatigue	16.2%	0	42.1%	2.6%
Headache	5.4%	0	18.4%	0

- **Strengths**:
  - External validity
  - Trilaciclib used in addition to first-line chemotherapy
  - Increased strength in rationale for use
  - In line with standard guidelines
- **Weaknesses**: small sample size → difficulty observing major trends
- **Conclusions:** Trilaciclib appeared to improve safety and efficacy of toxic chemotherapy by:
  - Improving myelosuppression endpoints
  - Not impacting chemotherapy's effects on tumor burden

TRILACICLIB PRIOR TO CHEMOTHERAPY AND ATEZOLIZUMAB IN PATIENTS WITH NEWLY DIAGNOSED EXTENSIVE-STAGE SMALL CELL LUNG CANCER: A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II TRIAL[11]

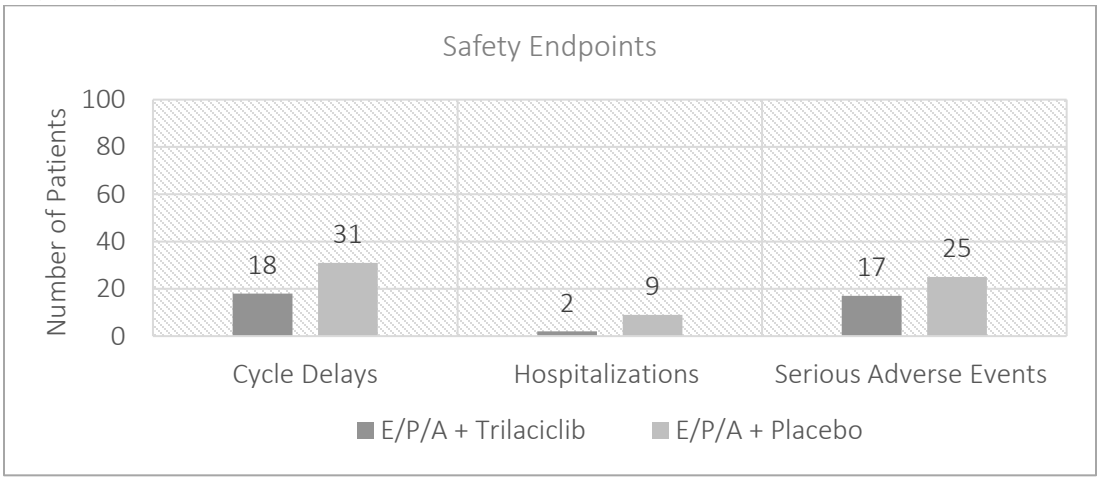
- **Study Design**: multicenter, randomized, double-blind, placebo-controlled phase II trial
- **Objectives**:
  - Confirm effects of trilaciclib when given with etoposide, carboplatin, and atezolizumab
  - Determine if trilaciclib would improve antitumor efficacy of atezolizumab
- **Primary endpoints**: duration of severe neutropenia in cycle 1, percent of patients with severe neutropenia during treatment
- **Additional endpoints:**
  - Occurrence of RBC transfusion
  - Occurrence of G-CSF administration
  - Occurrence of chemotherapy dose reductions
- **Inclusion criteria:**
  - ES-SCLC
  - ECOG performance score 0-2
  - Measure disease by RECIST Version 1.1
- **Exclusion criteria:**
  - Brain metastases present
  - Prior systemic therapy for limited-stage or ES-SCLC
- **Interventions:** Trilaciclib 240mg/m^2 or placebo
  - In addition to etoposide/carboplatin/atezolizumab chemotherapy
- Baseline characteristics

Category	Trilaciclib Group (n = 54)	Placebo Group (n = 53)
Median Age	65	64
Sex		
Male	41	34
Female	13	19
Age Group		
≥ 65	27	26
ECOG		
0-1	45	46
2	8	7
Smoking History		
Former	26	29
Current	23	18

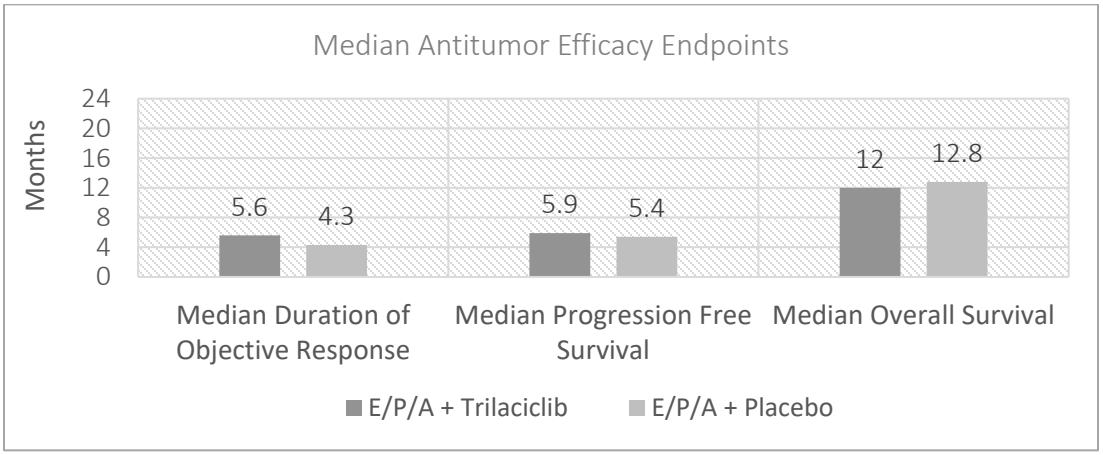
- Results
  - Regarding primary endpoints

Category	Trilaciclib Group (n = 54)	Placebo Group (n = 53)	*P* value
Mean Duration of Severe Neutropenia (days)	0	4	<0.0001
Occurrence of Severe Neutropenia	1.9%	41.9%	< 0.0001

  - Regarding safety



  - Regarding antitumor efficacy
    - Objective response rate: 56% in trilaciclib group versus 63.5% in placebo group



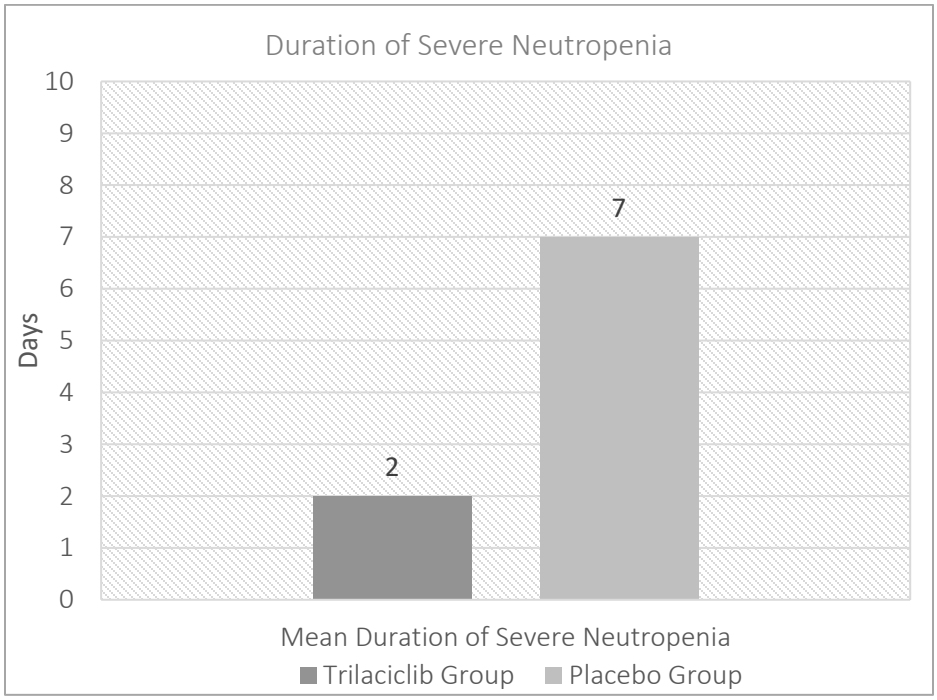
- **Strengths:** Internal validity
  - Atezolizumab included mirroring guideline recommendations
- **Weaknesses:** Small sample size → only large differences would be able to be detected
- **Conclusions:**
  - Trilaciclib appeared to improve safety and efficacy of toxic chemotherapy by:
    - Reducing the incidence of myelosuppression
    - Reducing the use of growth factor therapy

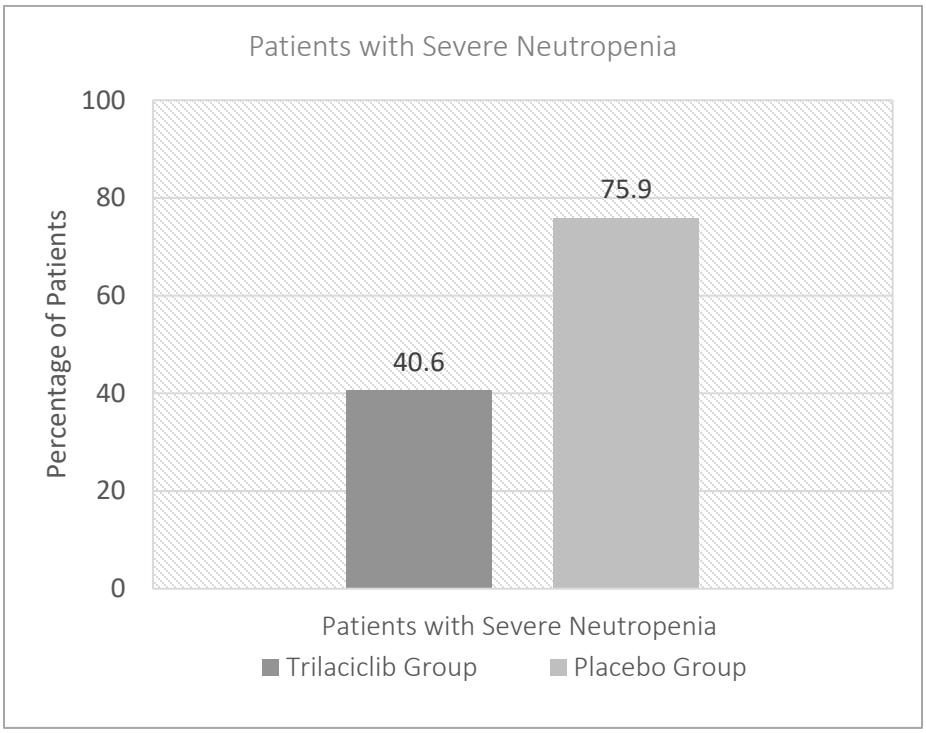
MYELOPRESERVATION WITH TRILACICLIB IN PATIENTS RECEIVING TOPOTECAN FOR SMALL-CELL LUNG CANCER: RESULTS FROM A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II STUDY[12]

- **Study Design:** randomized, double-blind, placebo-controlled, phase II trial
- **Objective:** Assess the safety and tolerability of trilaciclib given before topotecan
- **Primary endpoints:** Duration of severe neutropenia in cycle 1, occurrence of severe neutropenia
- **Additional endpoints:**
  - Occurrence of RBC transfusion
  - Occurrence of platelet transfusion
  - Number of dose reductions
- **Inclusion criteria:**
  - ES-SCLC
  - Disease progression
  - Eligible to receive topotecan
  - ≥ 1 measurable target lesion
  - Adequate organ function
  - ECOG performance status 0-2
- **Exclusion criteria:** History of topotecan treatment for SCLC, brain metastases requiring immediate treatment
- **Intervention:** topotecan 1.5mg/m^2 + trilaciclib; or topotecan 1.5mg/m^2 + placebo
- Baseline characteristics

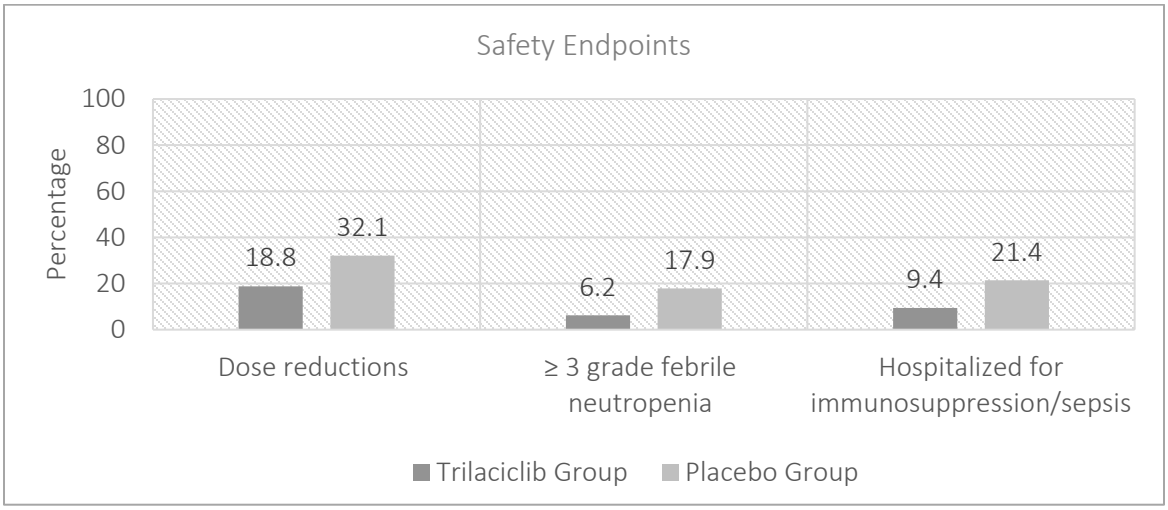
Category	Topotecan + trilaciclib (n = 32)	Topotecan + placebo (n = 29)
Median Age	62	64
Age ≥ 65	12	11
ECOG		
0-1	29	27
2	3	2
Smoking History		
Former	16	20
Current	13	7
Treatment Line		
Second	26	24
Third	6	5
Brain Metastases	8	5

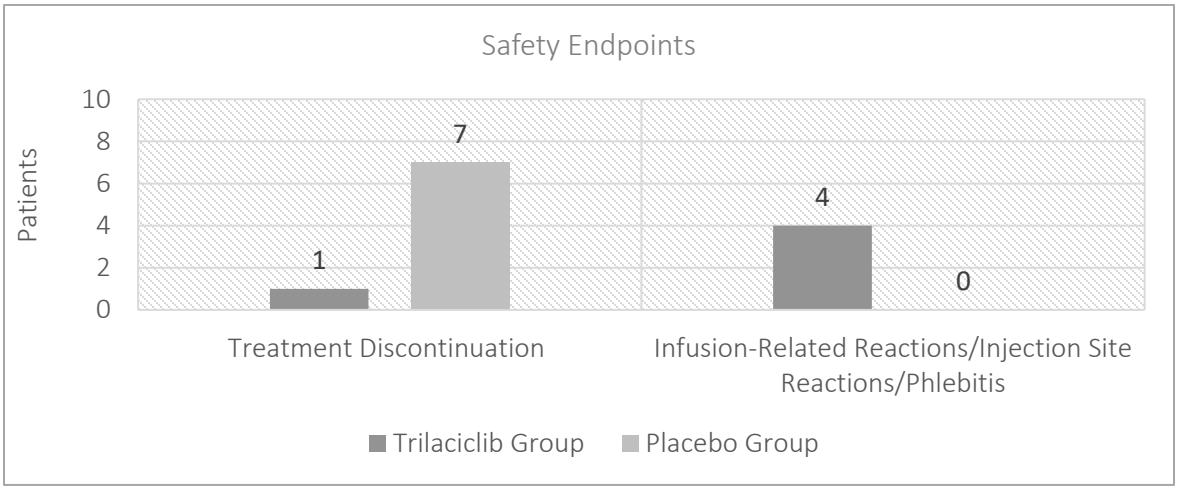
- Results
  - Regarding myelopreservation





- Regarding safety





- Regarding antitumor efficacy

Antitumor Efficacy			
Category	Trilaciclib group (n = 30)	Placebo group (n = 26)	*P* value
ORR	16.7%	23.1%	0.5494
PFS	4.2 months	4.2 months	0.5886
Overall Survival	6.2 months	6.5 months	0.3377

- **Strengths:** Different chemotherapy regimen including topotecan, standard supportive care guidelines were followed
- **Weaknesses:** Small sample size → difficulty observing large differences
  - Only large differences in overall survival could be observed
- **Conclusion:**
  - Trilaciclib appeared to reduce the risk of CIM in patients with HSPC damage by previous cycles of chemotherapy and are now being treated with chemotherapy

TRILACICLIB AND THE ECONOMIC VALUE OF MULTILINEAGE MYELOPROTECTION FROM CHEMOTHERAPY-INDUCED MYELOSUPPRESSION AMONG PATIENTS WITH EXTENSIVE-STAGE SMALL-CELL LUNG CANCER TREATED WITH FIRST-LINE CHEMOTHERAPY[13]

- Background:
  - Trilaciclib costs ~$1,500 dollars per 300mg vial or ~$3,000 per dose
  - 2021 National Inpatient Database: 5.2% of all cancer-related hospitalizations and 8.3% of all cancer-related hospitalization costs are due to cancer-related neutropenia
  - Neutropenia:
    - Data from 2006: 94% of FN ER visits resulted in hospitalization
    - ~$2,500 dollars spent per outpatient neutropenia episode and $50,000 spent per FN episode
    - Estimated total annual cost for cancer-related neutropenia $2.3 billion dollars
  - Anemia/Thrombocytopenia
    - Estimated cost of the management of anemia was $23,000 - $95,000 dollars
    - Management of thrombocytopenia: per cycle cost were ~$1,500 dollars
- Results

Parameter	Trilaciclib Group	Placebo Group
Total number of adverse events per patient	0.6	2.7
Neutropenia	0.3	1.5
Anemia	0.3	0.5
Thrombocytopenia	0.03	0.7
Adverse event management per case-base (2021 USD)	13,833	64,139
Neutropenia	5,961	32,403
Anemia	6,649	11,755
Thrombocytopenia	794	18,266

- Conclusion:
  - Trilaciclib administered prior to chemotherapy for prevention of CIM suggests a cost-savings approach when compared to chemotherapy administration alone
  - Administration of trilaciclib could provide cost savings benefit in patients with ES-SCLC being treated with chemotherapy

On Going Clinical Trials

- Metastatic Colorectal Cancer[14]
    - **Study Design:** randomized, double-blind, placebo-controlled, global, multicenter phase 3 trial
    - **Objective:** Assess effects of trilaciclib when given prior to folinic acid, fluorouracil, oxaliplatin, and irinotecan chemotherapy regimen
    - **Endpoints:**
        - Primary: rates of myelosuppression
        - Secondary: quality of life effects on fatigue, antitumor efficacy, PFS, overall survival

- Triple-Negative Breast Cancer[15]
    - **Study Design:** multinational, randomized, double-blind, placebo-controlled, phase III trial
    - **Objective:** Assess effects of trilaciclib when given prior to gemcitabine and carboplatin chemotherapy
    - **Endpoints:**
        - Primary: Overall survival
        - Secondary: time to confirmed deterioration in fatigue, PFS, objective response rate, clinical benefit rate, duration of objective response

Final Conclusions

- In conclusion, trilaciclib may be considered prior to first and second line topotecan chemotherapy in patients with SCLC
- It is important to be aware that trilaciclib has not been directly compared to other immunosuppressive treatments, such as G-CSF
- May not be enough concrete data to support the use of trilaciclib in patients with other cancer types at this time

REFERENCES

1. Small cell lung cancer treatment. *NIH.* 2022.
2. Ganti AKP, Loo BW, Bassetti M, et. al. Small cell lung cancer guidelines. *NCCN.* 2022;Version 2.2023.
3. The burden of chemotherapy-induced myelosuppression in patients with small cell lung cancer: What's new? AMCP.org. https://www.amcp.org/Resource-Center/managed-care-practice-issues/burden-chemotherapy-induced-myelosuppressoin-patients.
4. Griffiths EA, Roy V, Alwan L. Hematopoietic growth factors guidelines. *NCCN.* 2021;Version 1.2022.
5. Weiss JM, Csoszi T, Maglakelidze M, et. al. Myelospreservation with the CDK4/6 inhibitor trilaciclib in patients with small-cell lung cancer receiving first-line chemotherapy: a phase Ib/randomized phase II trial. *Annals of Oncology.* 2019;30: 1613-1621.
6. 10.2 the cell cycle-biology. OpenStax. https://openstax.org/books/biology/pages/10-2-the-cell-cycle.
7. FDA package insert. Etoposide. May 2017.
8. FDA package insert. Topotecan. February 2014.
9. FDA package insert. Carboplatin. October 2011.
10. FDA package insert. Trilaciclib. February 2021.
11. Daniel D, Kuchava V, Bondarenko I, et. al. Trilaciclib prior to chemotherapy and atezolizumab in patients with newly diagnosed extensive-stage small cell lung cancer: a multicenter, randomized, double-blind, placebo-controlled phase II trial. *Int J Cancer.* 2021;148: 2557-2570.
12. Hart LL, Ferrarotto R, Andric AG, et. al. Myelopreservation with trilaciclib in patients receiving topotecan for small cell lung cancer: results from a randomized, double-blind, placebo-controlled phase II study. *Adv Therapy.* 2021;38: 350-365.
13. Abraham I, Onyekwere U, Deniz B, et. al. Trilaciclib and the Economic Value of Multilineage Myeloprotection from Chemotherapy-Induced Myelosuppression Among Patients with Extensive-Stage Small Cell Lung Cancer Treated with First-Line Chemotherapy. *Journal of Medical Economics.* 2021;24:71-83.
14. J Sava. Enrollment Complete for PRESERVE I trial of trilaciclib in metastatic colorectal cancer. *Targeted Oncology.* 2022.
15. Goel S, Tan AR, Rugo HS, et. al. Trilaciclib prior to gemcitabine plus carboplatin for metastatic triple-negative breast cancer: phase III PRESERVE 2. *Future Oncol.* 2022.