How to Handle Myelotoxicity from Chemotherapy

From Colony-Stimulating Factors (CSF) to Agents Providing Myeloprotection to the Three Cell Lines

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Grading of Hematologic Toxicity by CTCAE v3.0

Lineage	Grade 1	Grade 2	Grade 3	Grade 4	
Neutrophils	<LLN to 1,500/mm3	1000-1,500/mm3	500-1,000/mm3	<500/mm3	+ / - Fever
Platelets	<LLN to 75,000/mm3	50,000-75,000/mm3	25,000-50,000/mm3	<25,000/mm3	
Hemoglobin	<LLN - 10 g/dL	8.0 – 10 g/dL	<8 g/dL	Life-threatening	Symptoms
Lymphocytes	<LLN – 800/mm3	500 – 800/mm3	200 – 500/mm3	<200/mm3	

Febrile neutropenia is defined as single temperature: ≥38.3 °C orally or ≥38.0 °C over 1 h; and neutropenia:
<500 neutrophils/mcL or
<1000 neutrophils/mcL and a predicted decline to ≤500 neutrophils/mcL over the next 48 h.

Management of Neutropenia in Lung Cancer

- Chemotherapy remains mainstay of therapy in 1st and 2nd line for majority of patients.
- Neutropenia is becoming less coming with advent of immunotherapy and targeted therapy (some exceptions : eg. Pralsetinib (RET inhibitor))

- Risk assessment includes
  - Age
  - Performance status
  - Endorgan function
  - Prior exposure to chemotherapy
  - Treatment intent
  - Chemotherapy regimen.

- **Caveat : Small Cell Lung Cancer has largely remained dependent on treatment with chemotherapy, risk of neutropenia is disproportionately higher for platinum/etoposide and topotecan backbones with majority of patients experiencing grade 4 neutropenia following chemotherapy exposure.**

Treatment by Risk of Neutropenic Fever

>20% Risk of Neutropenic Fever	→	Use of G-CSF is indicated (Category 1).
10-20% Risk of Neutropenic Fever	→	Consider use of G-CSF based on patient risk factors.
<10% Risk of Neutropenic Fever	→	G-CSF use not routinely recommend, may be considered based on patient risk factors.

Risk Factor Assessment of Patients with FN risk 10-20%

- Prior chemotherapy or radiation therapy (eg. 2nd line patients)
- Persistent neutropenia (prior clinical behavior)
- Bone marrow involvement by tumor (not common in lung cancer)
- Recent surgery and/or open wounds (saturation effect, risk factor)
- Liver dysfunction (bilirubin >2.0)
- Renal dysfunction (creatinine clearance <50)
- Age >65 years receiving full chemotherapy (frequent in Florida)
- Dose intensity (rare in lung cancer)

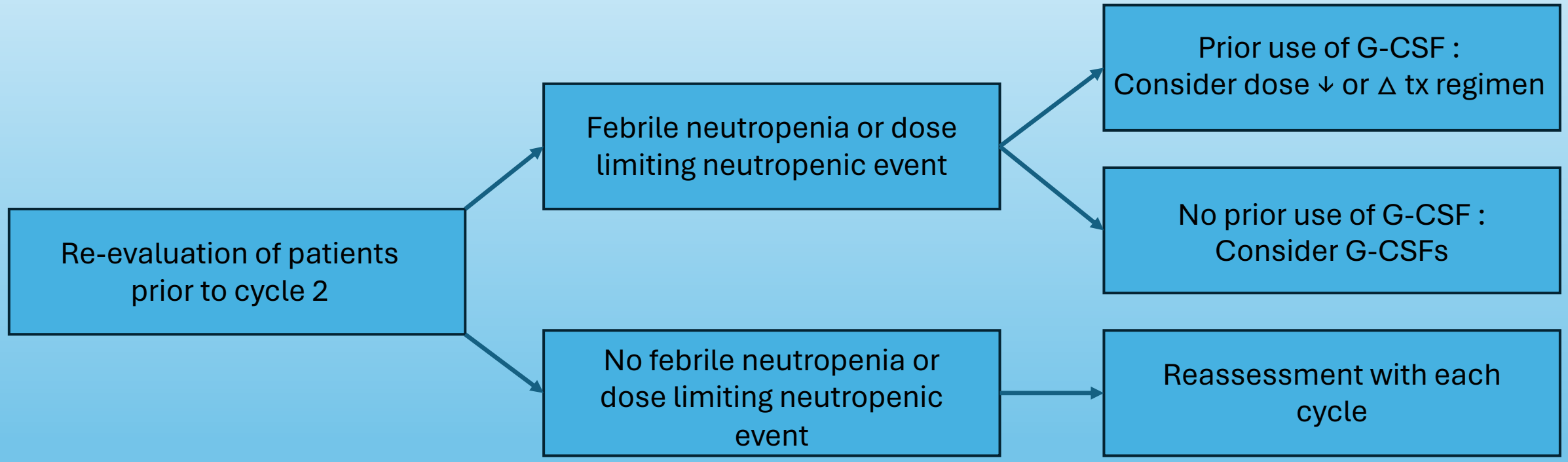
Chemotherapy Regimen and FN Risk in Lung Cancer

- High (>20%): Topotecan.

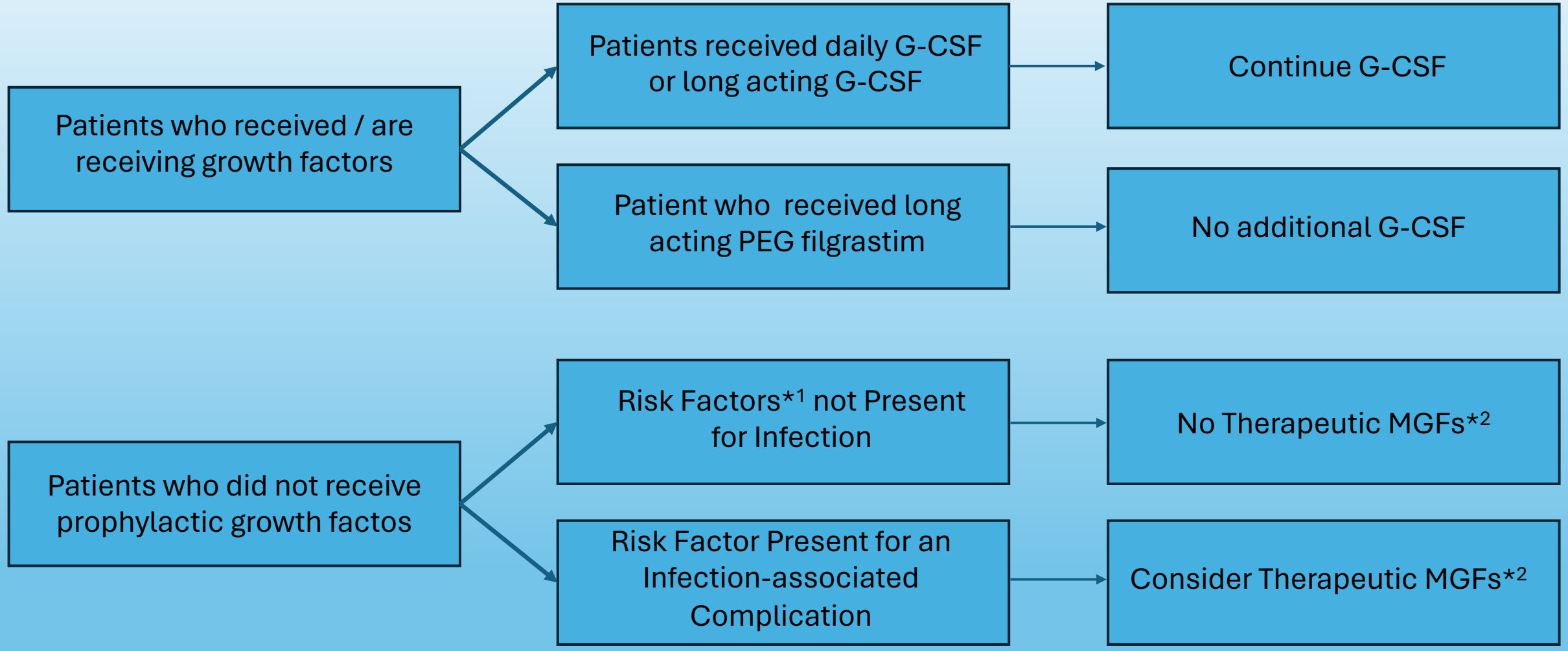
- Intermediate Risk (10-20%):
  - **Small Cell Lung cancer**
    - Carboplatin/Etoposide.
  - **Non-small cell lung cancer**
    - Cisplatin/Vinorelbine
    - Cisplatin/Paclitaxel
    - Cisplatin/Docetaxel
    - Carboplatin/Paclitaxel
    - Docetaxel

    (NOT INCLUDED : Carboplatin/Pemetrexed (0% in Keynote-021)

Monitoring for Patients while on chemotherapy



Management of Febrile Neutropenia



*1 : Sepsis syndrome, Age > 65, ANC <100/mcL, Neutropenia >10 days in duration, documented infection, invasive fungal infection, hospitalization at the time of fever, and prior episode of febrile neutropenia.

*2 : Filgrastim (or biosimilars) or tbo-filgrastim: daily dose of 5 mcg/kg; sargramostim.

Workup of CIT : Chemotherapy induced Thrombocytopenia

- Complete blood count (CBC) with differential, including evaluation for other cytopenias.
- Rule out Pseudothrombocytopenia : Blood smear morphology, including platelet clumping.
- Consider secondary etiologies:
    - Nutritional deficiencies.
    - Medications and supplements suppressing platelet production.
    - Infection (including viral reactivation).
    - Consumptive Syndromes (DIC, ITP, HIT, PNH, TTP/HUS).
    - Myelodysplasia (treatment related).Bone marrow involvement by underlying malignancy.
    - Bleeding related platelet consumption (decreased regeneration with depletion of reservoir).

Treatment of CIT : Chemotherapy induced Thrombocytopenia

- Transfusion for severe cases according to AABB guidelines.
- Chemotherapy dose reduction or change in treatment regimen.
- Clinical trial of TPO-RA.
- Romiplostim.

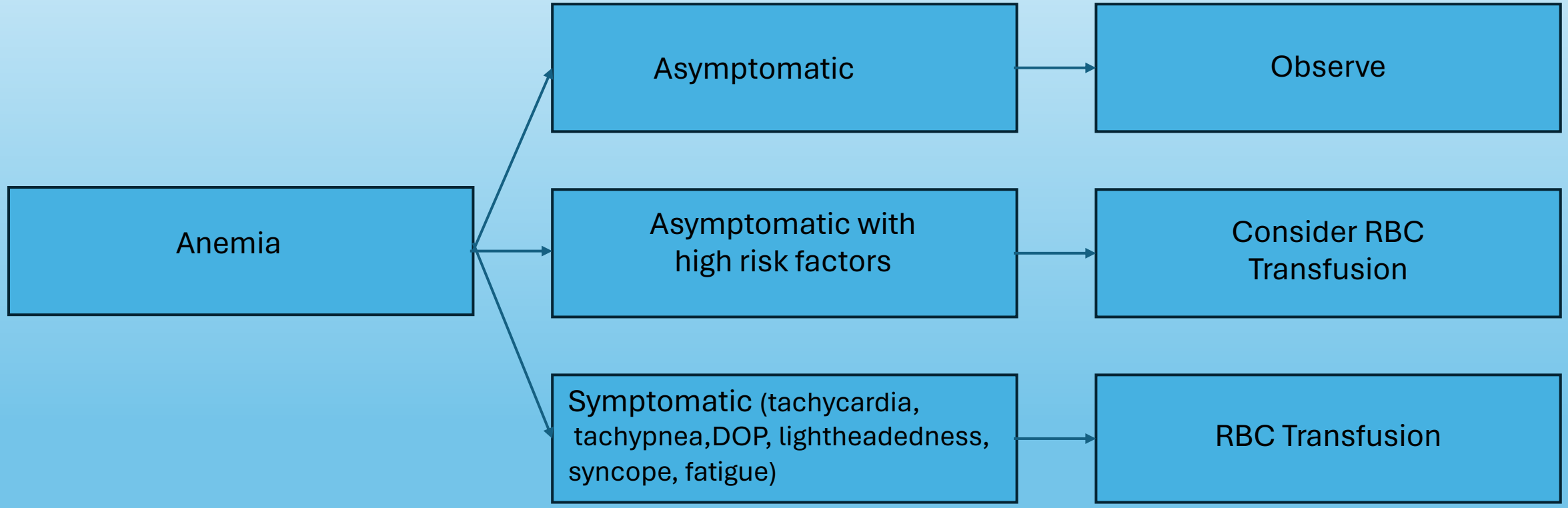
Workup of Anemia : Chemotherapy induced Anemia

Hemoglobin <11 g/dL or <2 g/dL below baseline

- Reticulocyte counte and mean corpuscular volume (MCV)
- r/o hemorrhage (consider endoscopic evaluation)
- Hemolysis (ie, direct antiglobulin test, DIC panel, haptoglobin, indirect bilirubin, lactate dehydrogenase (LDH).
- Nutritional deficiency (iron/TIBC/Ferritin, B12, Folate).
- Chronic kidney disease / Acute renal impairment (epo).
- Anemia of chronic disease (iron indices, CRP, ESR).

Consider bone marrow biopsy if primary/secondary marrow disorder (MDS, AML etc) suspected.

Management of Chemotherapy Induced Anemia (Acute)



Management of Chemotherapy Induced Anemia with ESA / growth factors

Cancer with comorbid condition of chronic kidney disease

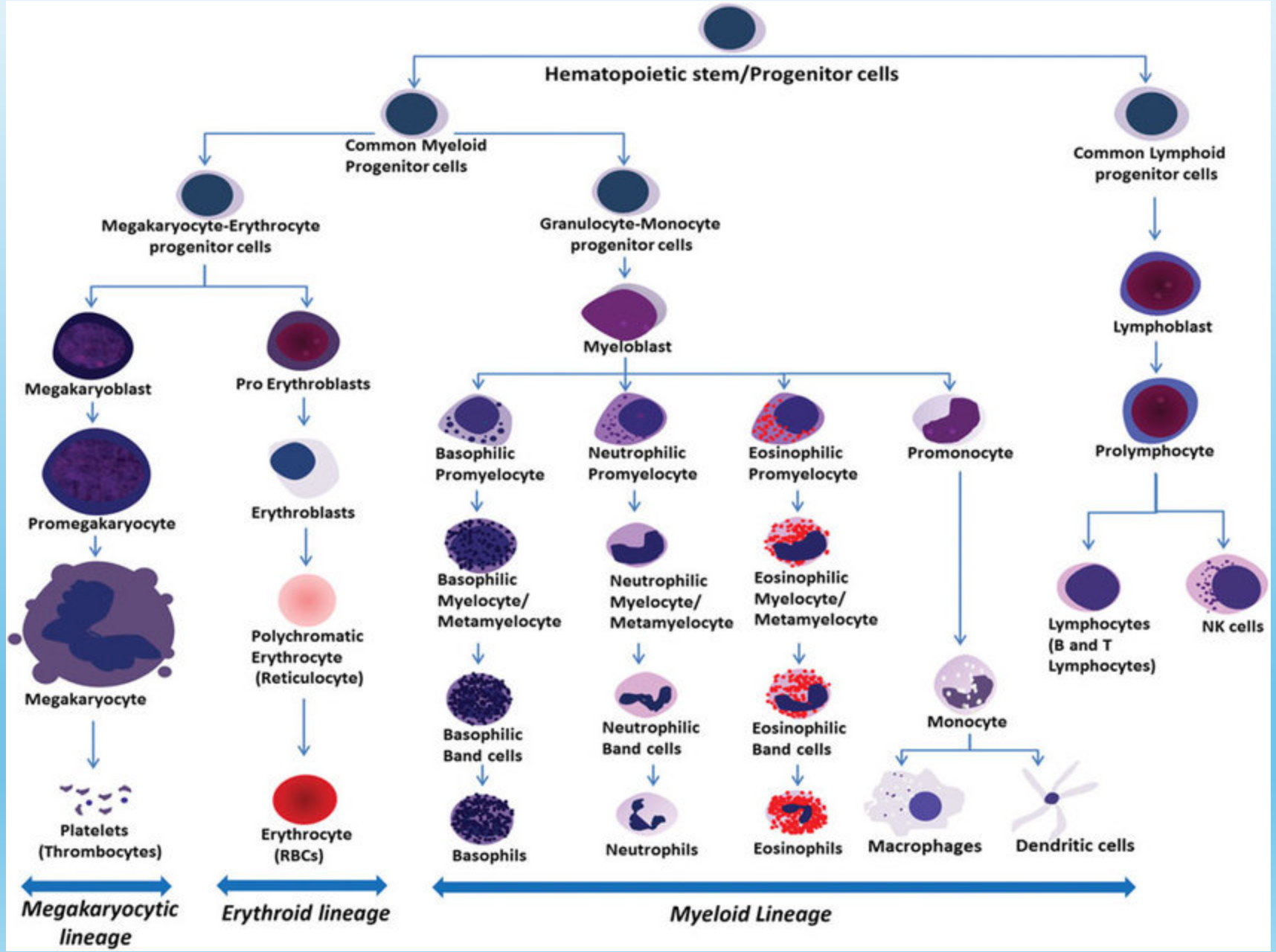
Patient undergoing palliative chemotherapy

Select patients who refuse blood transfusion

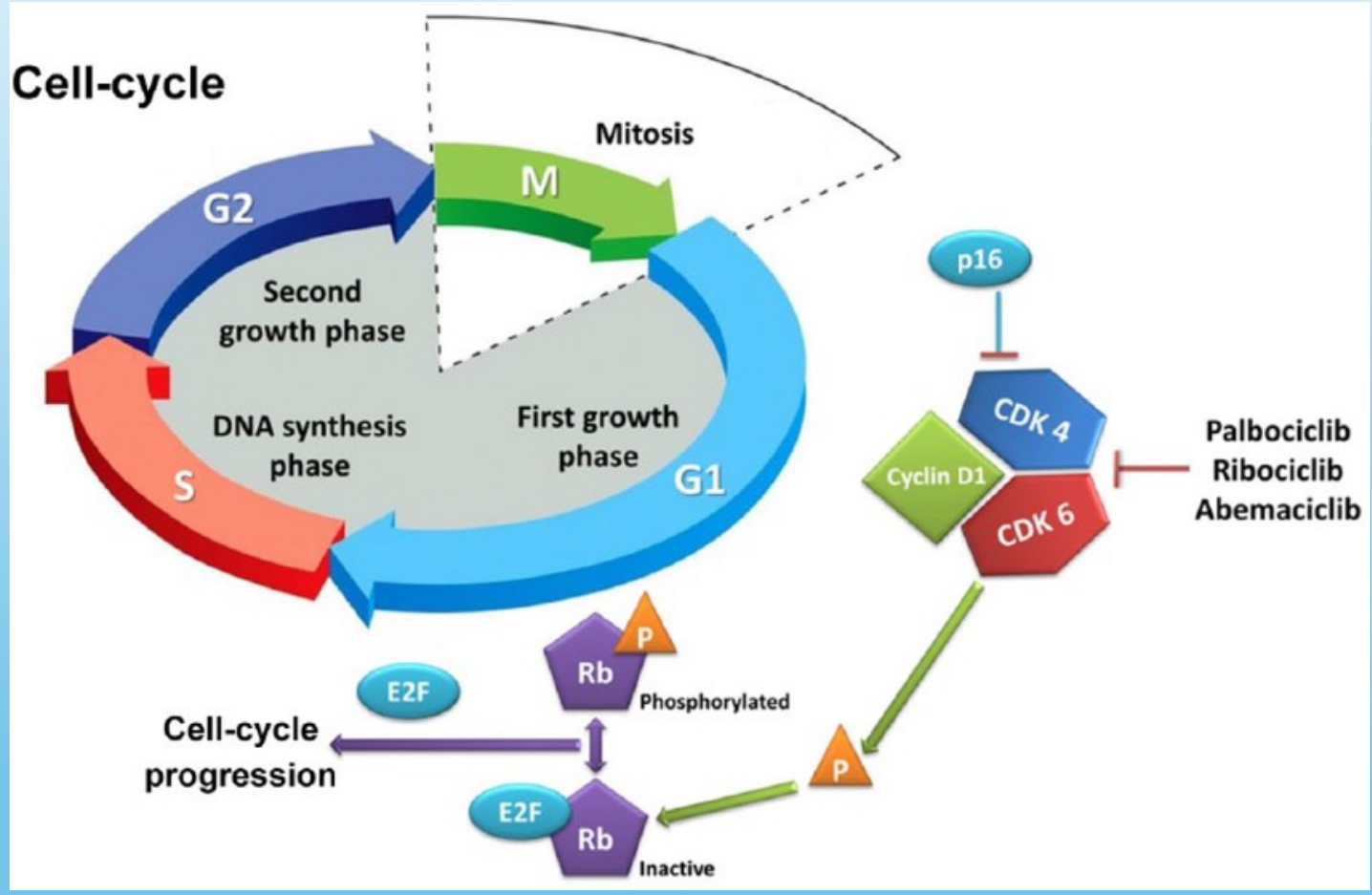
ESA are not supported by the guidelines in patients :

- Patients with cancer not receiving therapy.
- Patients receiving non-myelosuppressive therapy.
- Patients receiving myelosuppressive chemotherapy with curative intent
- (Exaples of cancers for which there is therapy with curative intent: Early-stage breast cancer, Hodgkin lymphoma, non-Hodgkin lymphomas, testicular cancer, **early-stage non-small cell lung cancer, and small cell lung cancer**)

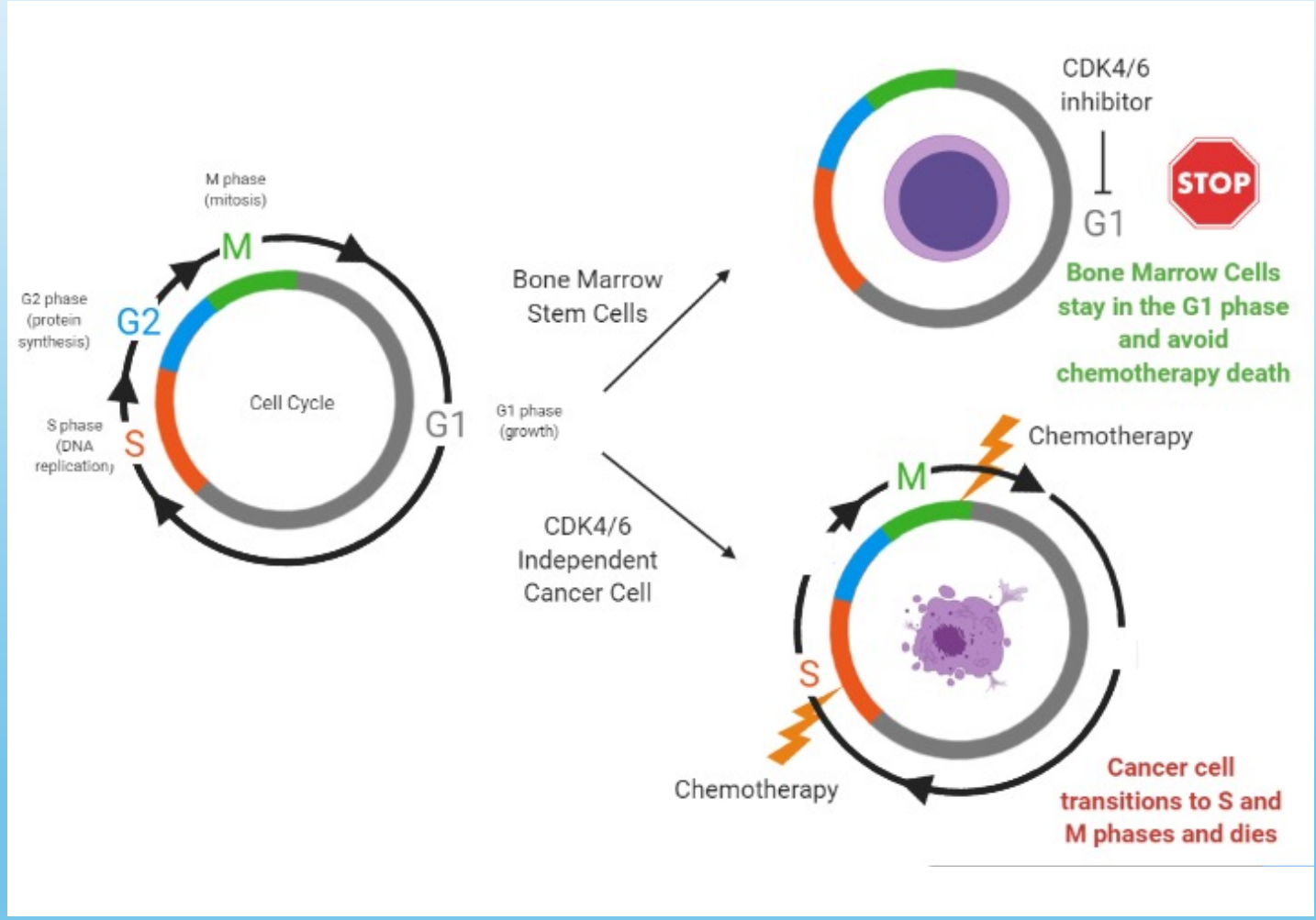
Multi-lineage Myeloprotection in SCLC



CDK4/6 in Cell Cycle Regulation in the Bone Marrow Microenvironment



Differential Effect on Growth of BM versus Cancer Cell



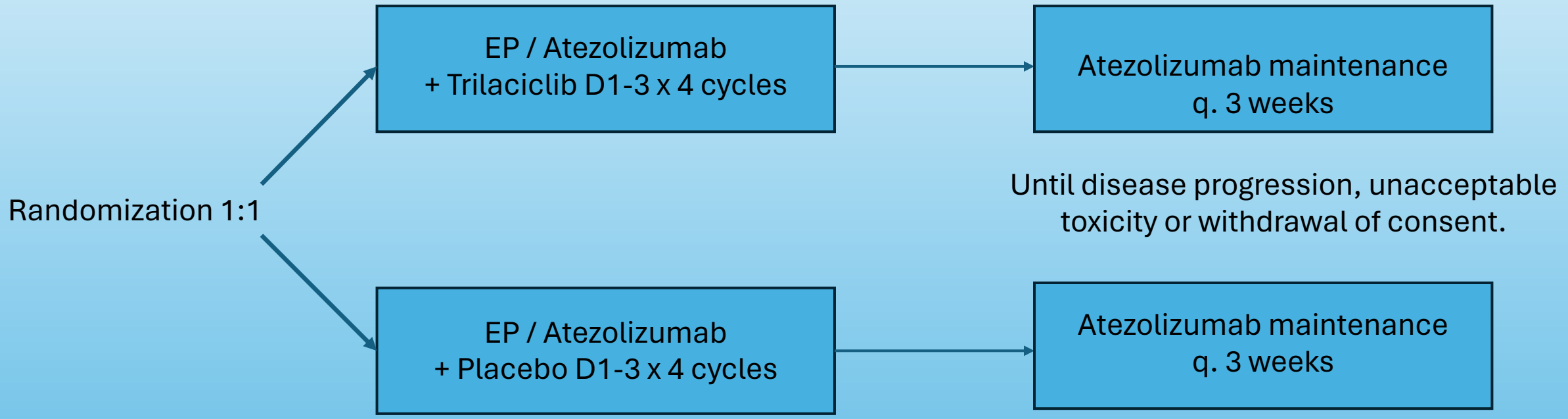
CANCER THERAPY AND PREVENTION

IJC International Journal of Cancer

Trilaciclib prior to chemotherapy and atezolizumab in patients with newly diagnosed extensive-stage small cell lung cancer: A multicentre, randomised, double-blind, placebo-controlled Phase II trial

Davey Daniel[1] | Vladimer Kuchava[2] | Igor Bondarenko[3] | Oleksandr Ivashchuk[4] | Sreekanth Reddy[5] | Jana Jaal[6] | Iveta Kudaba[7] | Lowell Hart[8] | Amiran Matitashvili[9] | Yili Pritchett[10] | Shannon R. Morris[10] | Jessica A. Sorrentino[10] | Joyce M. Antal[10] | Jerome Goldschmidt[11]

Trilaciclib prior to chemotherapy and atezolizumab in patients with newly diagnosed extensive-stage small cell lung cancer: A multicentre, randomised, double-blind, placebo-controlled Phase II trial



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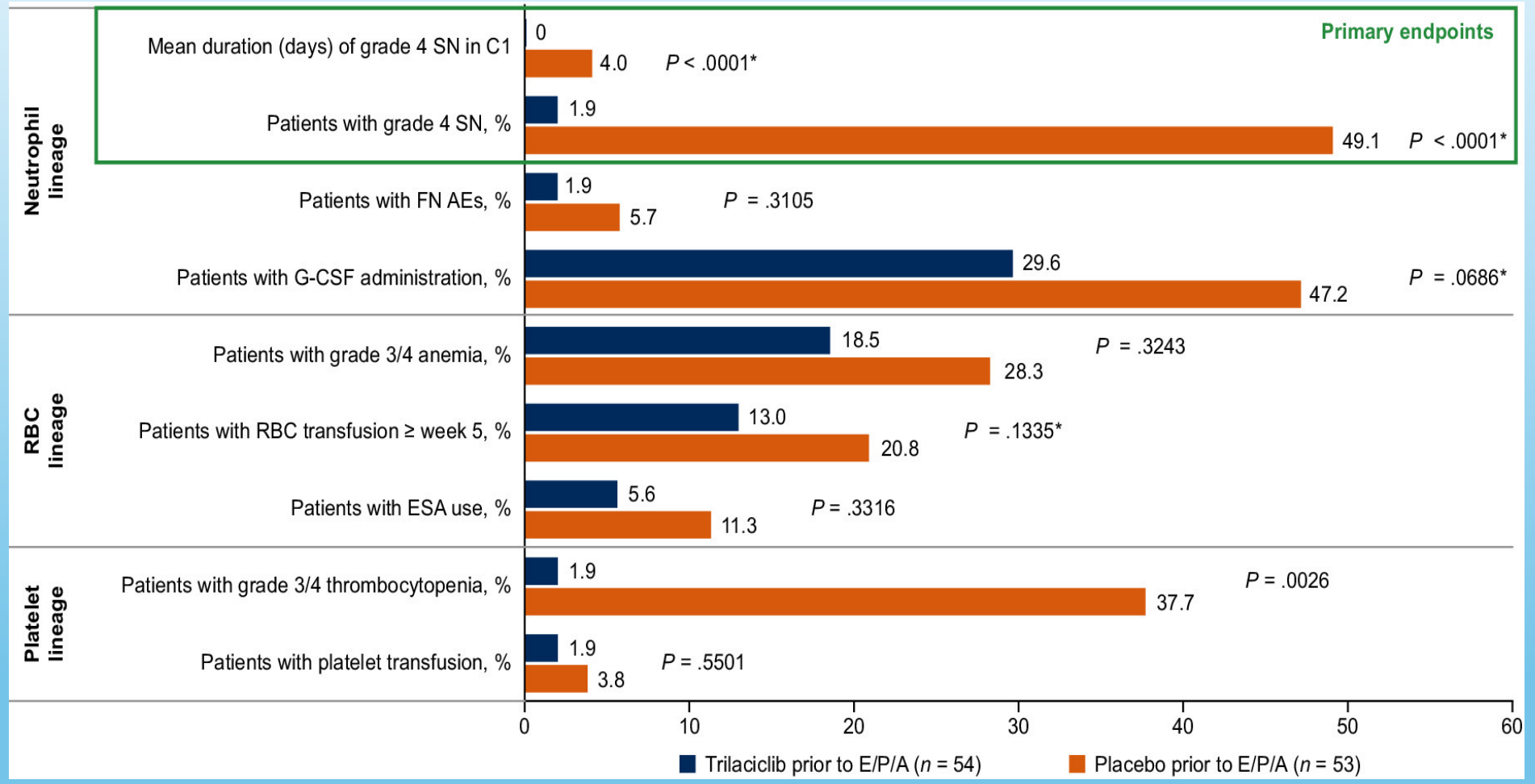
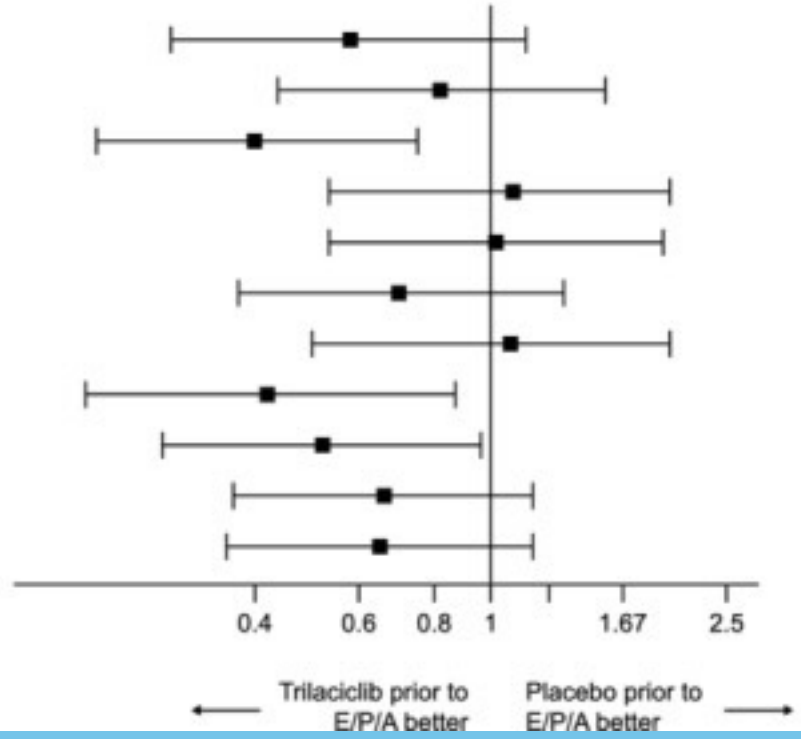
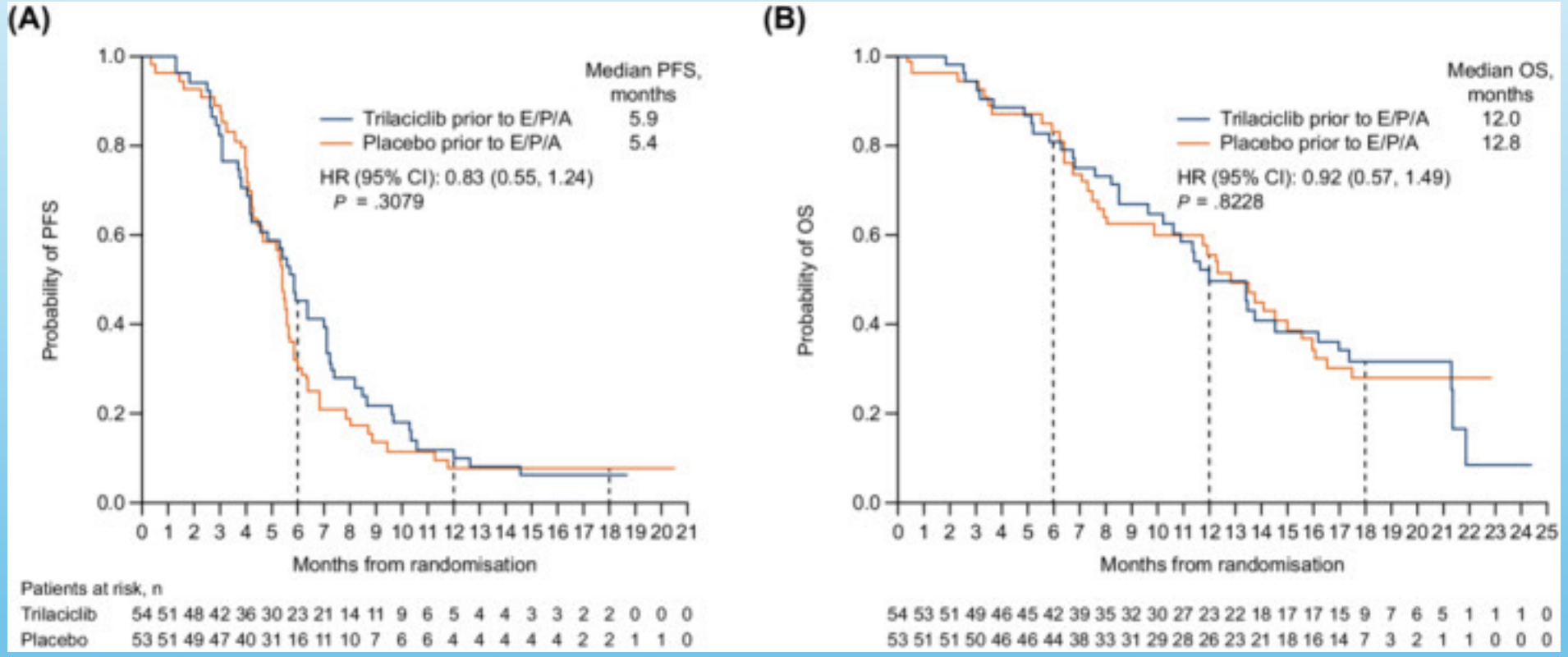


Median Time to deterioration

Domain	Events, n Trilaciclib/Placebo	Median TTD, months Trilaciclib/Placebo	Hazard ratio (95% CI)
FACT-G	13/22	NYR/NYR	0.58 (0.29, 1.15)
PWB	17/22	NYR/NYR	0.82 (0.44, 1.56)
FWB	15/30	8.57/3.53	0.40 (0.22, 0.75)
EWB	15/15	NYR/NYR	1.09 (0.53, 2.25)
SWB	19/18	NYR/NYR	1.02 (0.53, 1.95)
FACT-L	17/23	NYR/7.16	0.70 (0.38, 1.32)
LCS	13/13	NYR/NYR	1.08 (0.50, 2.33)
L-TOI	11/24	NYR/7.95	0.42 (0.21, 0.87)
FACT-An	16/28	NYR/4.17	0.52 (0.28, 0.96)
Fatigue	20/28	7.20/2.60	0.66 (0.37, 1.18)
Anemia TOI	19/27	7.20/3.84	0.65 (0.36, 1.18)



Antitumor efficacy – PFS and OS



Similar Outcomes Showing improvement in hematologic endpoints with Trilaciclib + EP alone and Trilaciclib + Topotecan

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 30: 1613–1621, 2019
doi:10.1093/annonc/mdz278
Published online 27 August 2019

ORIGINAL ARTICLE

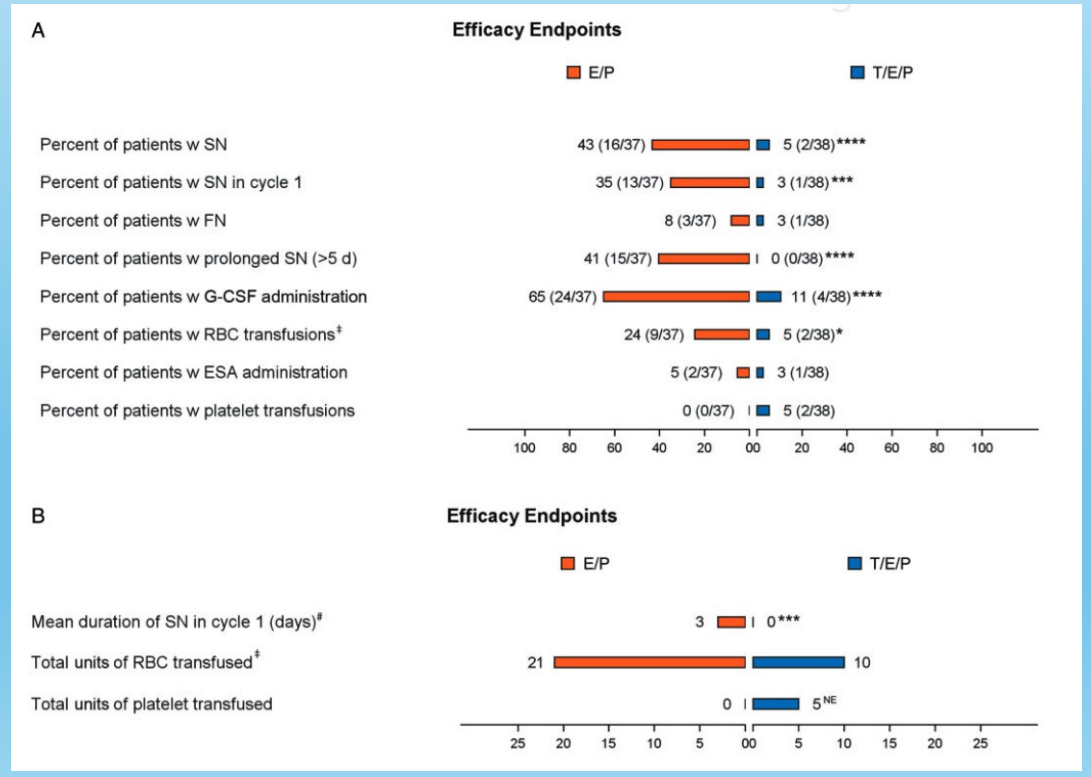
Myelopreservation with the CDK4/6 inhibitor trilaciclib in patients with small-cell lung cancer receiving first-line chemotherapy: a phase Ib/randomized phase II trial

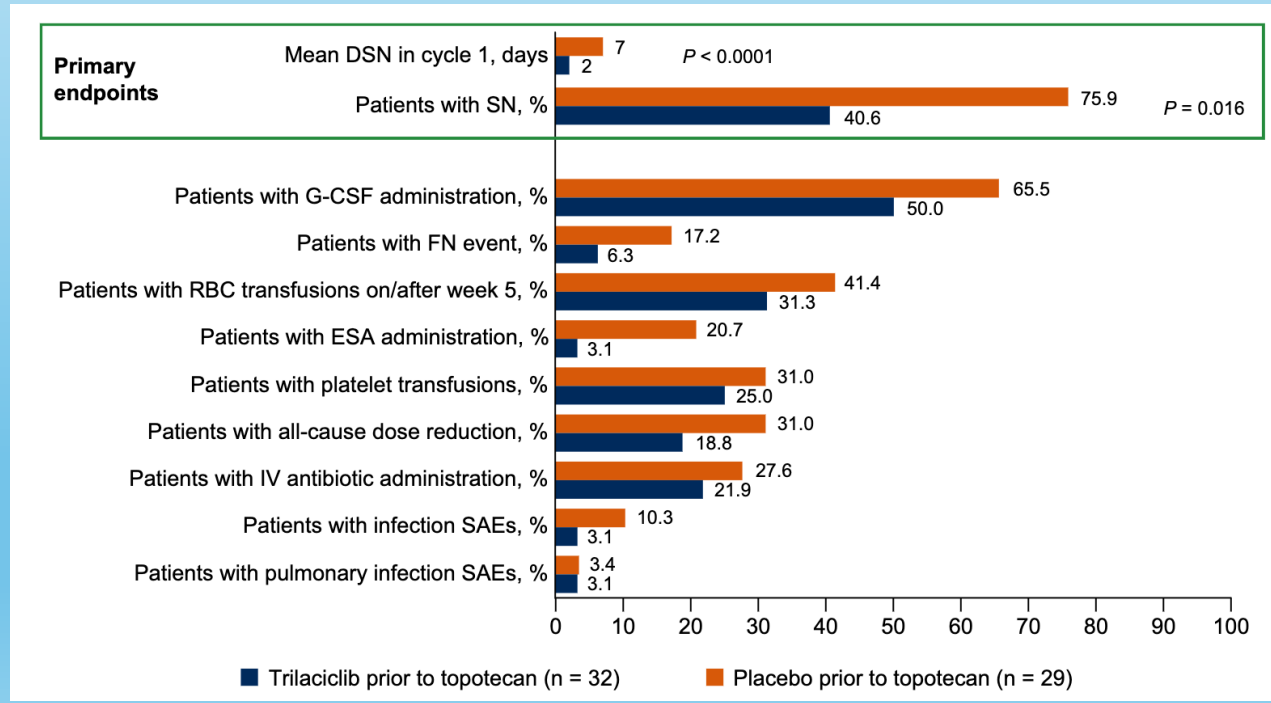
Adv Ther (2021) 38:350–365
https://doi.org/10.1007/s12325-020-01538-0

ORIGINAL RESEARCH

Myelopreservation with Trilaciclib in Patients Receiving Topotecan for Small Cell Lung Cancer: Results from a Randomized, Double-Blind, Placebo-Controlled Phase II Study

Lowell L. Hart · Renata Ferrarotto · Zoran G. Andric · J. Thaddeus Beck · Janakiraman Subramanian · Davorin Z. Radosavljevic · Bojan Zaric · Wahid T. Hanna · Raid Aljumaily · Taofeek K. Owonikoko · Didier Verhoeven · Jie Xiao · Shannon R. Morris · Joyce M. Antal · Maen A. Hussein





SUMMARY

Non-Small Cell Lung Cancer

- Myelosuppression is a frequent clinical challenge in treatment of lung cancer.
- G-CSF remains mainstay of therapy in non-small cell lung cancer with clinical risk adaptation.
- Growing role of curative intent chemotherapy with adjvent of neoadjuvant treatment approaches.
- Anemia is a frequent cause of chemotherapy-related symptoms (fatigue etc) without proper treatment opportunity. ESAs have no defined role in curative intent lung cancer, marginal role in palliative setting.
- TPOs are currently not FDA approved but some data suggests romiplostim can be used for severe cases.

Small Cell Lung Cancer

- Majority of patients experience G4 (severe) neutropenia.
- Growth Factors are given to ~80-90% of patients in real world data.
- Novel CDK4/6 inhibitor approaches allow for trilineage myeloprotection in conjunction with chemotherapy.

Thank you!

The US Oncology Network