EUROPEAN HEMATOLOGY ASSOCIATION

EHA-ISHBT Hematology Tutorial

Clinical Case – **Session 3:**
Thrombocytopenia –
Immune Thrombocytopenia and others.

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Hyderabad, India
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Clinical history

- A 52-year-old woman with a history of hypertension returned to clinic for continued management of chronic immune thrombocytopenia (ITP).

- She was diagnosed three years previously when she presented to her primary care provider with petechiae and was found to have isolated thrombocytopenia with a platelet count of 3 x 10^9/L.

- She was referred to a hematologist and was initially treated with high-dose steroids, with an appropriate response. However, the duration of response was short, and she ultimately required multiple additional lines of therapy to maintain platelet counts above 30 x 10^9/L, including rituximab, eltrombopag, and immunosuppression.

Clinical history, con’t

- A bone marrow biopsy was performed and revealed increased megakaryocytes without evidence of dysplasia with normal cytogenetics and molecular analysis, confirming the diagnosis of ITP.

- She was administered fostamatinib and had a satisfactory response that lasted >6 months. She is still maintaining adequate platelet counts.

Which of the following is true about this medication?

1. Fostamatinib decreases platelet destruction by inhibiting Syk-dependent phagocytosis of autoantibody-coated platelets.
2. Fostamatinib increases platelet production by binding the thrombopoietin receptor on megakaryocytic precursors.
3. A potential adverse effect of fostamatinib includes congestive heart failure and study participants were required to have echocardiography prior to initiating therapy.
4. Due to severe neutropenia, patients should be started on prophylactic antibiotics concurrently with fostamatinib.
5. Fostamatinib works downstream of BTK.

Which of the following is true about this medication?

1. Fostamatinib decreases platelet destruction by inhibiting Syk-dependent phagocytosis of autoantibody-coated platelets.
2. Fostamatinib increases platelet production by binding the thrombopoietin receptor on megakaryocytic precursors.
3. A potential adverse effect of fostamatinib includes congestive heart failure and study participants were required to have echocardiography prior to initiating therapy.
4. Due to severe neutropenia, patients should be started on prophylactic antibiotics concurrently with fostamatinib.
5. Fostamatinib works downstream of BTK.

Answer

Fostamatinib decreases platelet destruction by inhibiting Syk-dependent phagocytosis of autoantibody-coated platelets.

Discussion

- Chronic ITP is defined as ITP persisting for more than 12 months.[1] Therapy options for chronic ITP include glucocorticoids, splenectomy, rituximab, immunosuppression, thrombopoietin analogues (eltrombopag and romiplostim, mechanism described in answer 2), and more recently, fostamatinib.
- Fostamatinib is an oral small-molecule spleen tyrosine kinase (Syk) inhibitor, approved for use in patients with chronic ITP after insufficient response to at least one prior line of therapy.[2] Syk signaling plays a role in all activating Fc receptors.[3] It affects cell proliferation, immune regulation, and cytoskeleton rearrangement for macrophage phagocytosis, including those involved in phagocytosis of antibody-coated platelets (answer 1).

1. Connell NT et al. Fostamatinib for the treatment of chronic immune thrombocytopenia. Blood. 2019 doi:10.1182/blood-2018-11-852491.
2. Newland A et al. Fostamatinib for persistent/chronic adult immune thrombocytopenia. Immunotherapy. 2018 10:9-25.
3. Bussel J et al. Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: Results of two phase 3, randomized, placebo-controlled trials. Am J Hematol. 2018 93:921-930.

Discussion, con't

- FIT-1 and FIT-2 studies evaluated fostamatinib in two parallel, phase III, randomized, placebo-controlled trials in patients with chronic ITP.[3] In the treatment group (n=101), patients received fostamatinib 100 mg BID for 24 weeks with dose escalation to 150 mg BID for non-responders at four weeks. Eighteen percent of patients receiving fostamatinib met the primary endpoint of stable response with platelet count higher than 50 x 10^9/L on at least four of six visits during weeks 14 to 24, compared to 2 percent on placebo (p=0.003). The median time to response was 15 days, and the most common adverse effects included diarrhea, hypertension, and nausea.[1]
- Blood pressure below 140/90 was required for study participants prior to starting therapy. Blood pressure should be monitored every two weeks in all patients receiving fostamatinib, until stable. Congestive heart failure is not a known adverse effect of fostamatinib (answer 3).

1. Connell NT et al. Fostamatinib for the treatment of chronic immune thrombocytopenia. Blood. 2019 doi:10.1182/blood-2018-11-852491.
2. Newland A et al. Fostamatinib for persistent/chronic adult immune thrombocytopenia. Immunotherapy. 2018 10:9-25.
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Discussion, con't

- Though overall infection rates were higher in the fostamatinib group (30% vs. 21% for placebo), prophylactic antibiotics are not recommended (answer 4). Absolute neutrophil count should be monitored monthly while on therapy.[1]

1. Connell NT et al. Fostamatinib for the treatment of chronic immune thrombocytopenia. Blood. 2019 doi:10.1182/blood-2018-11-852491.
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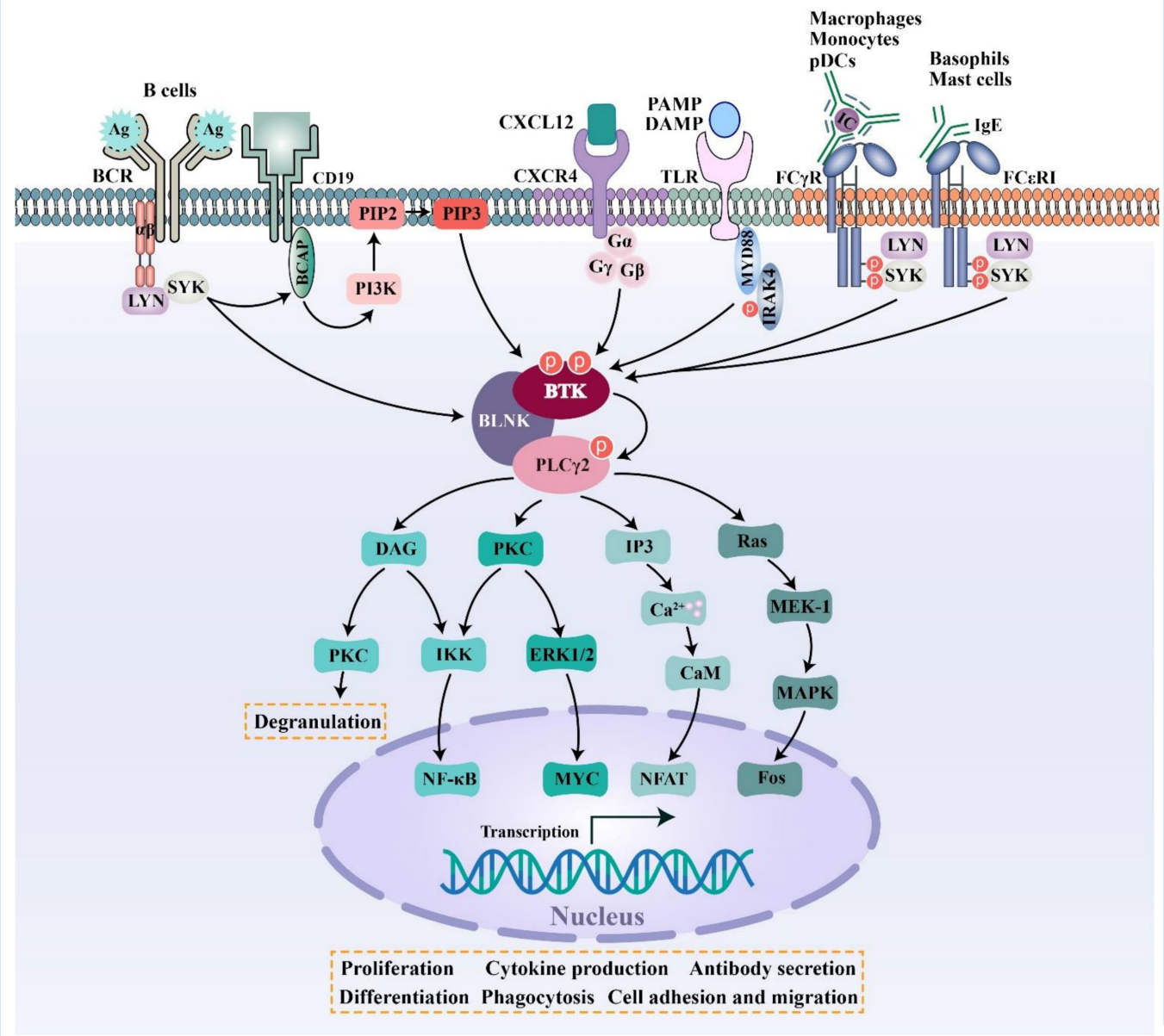
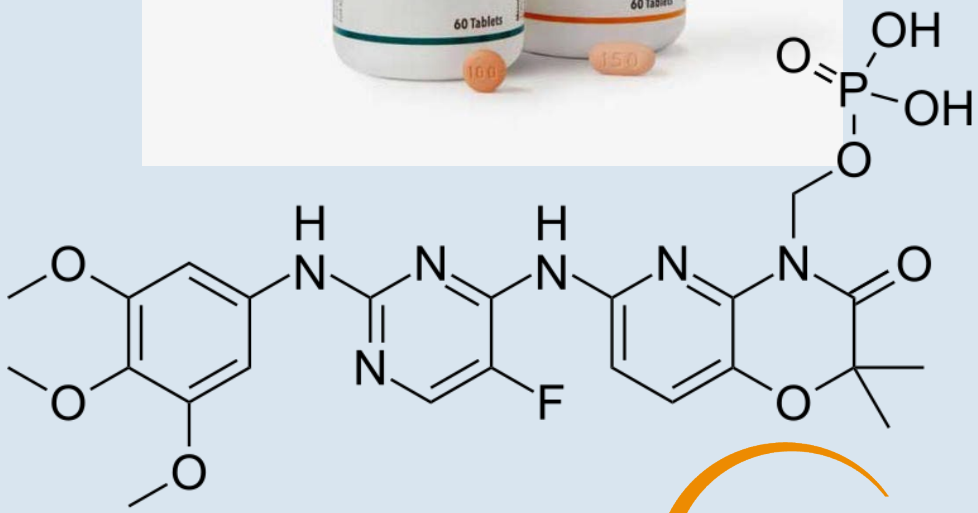
Spleen Tyrosine Kinase (Syk) Inhibitor



Fostamatinib (FDA Approved, 2018)



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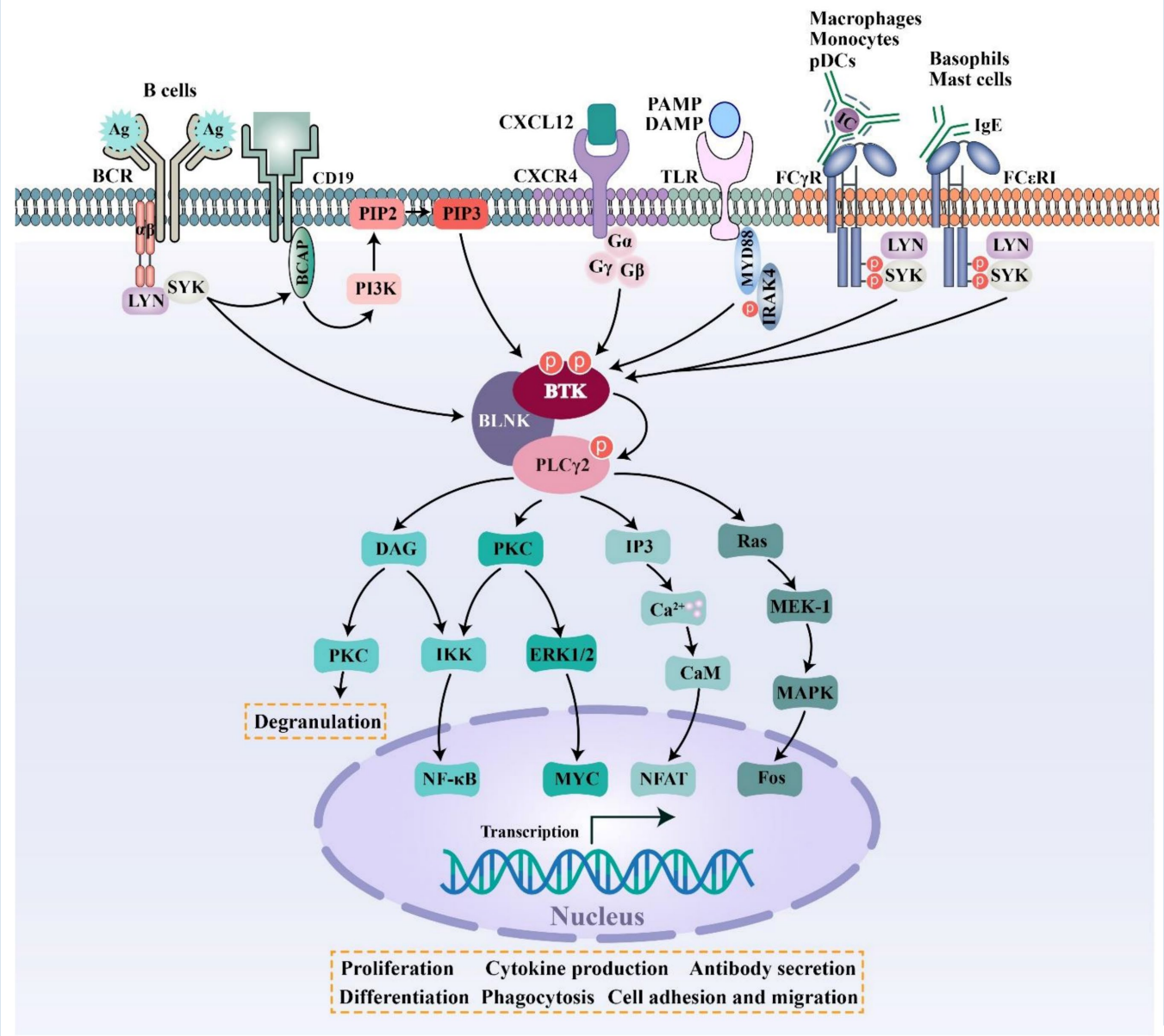
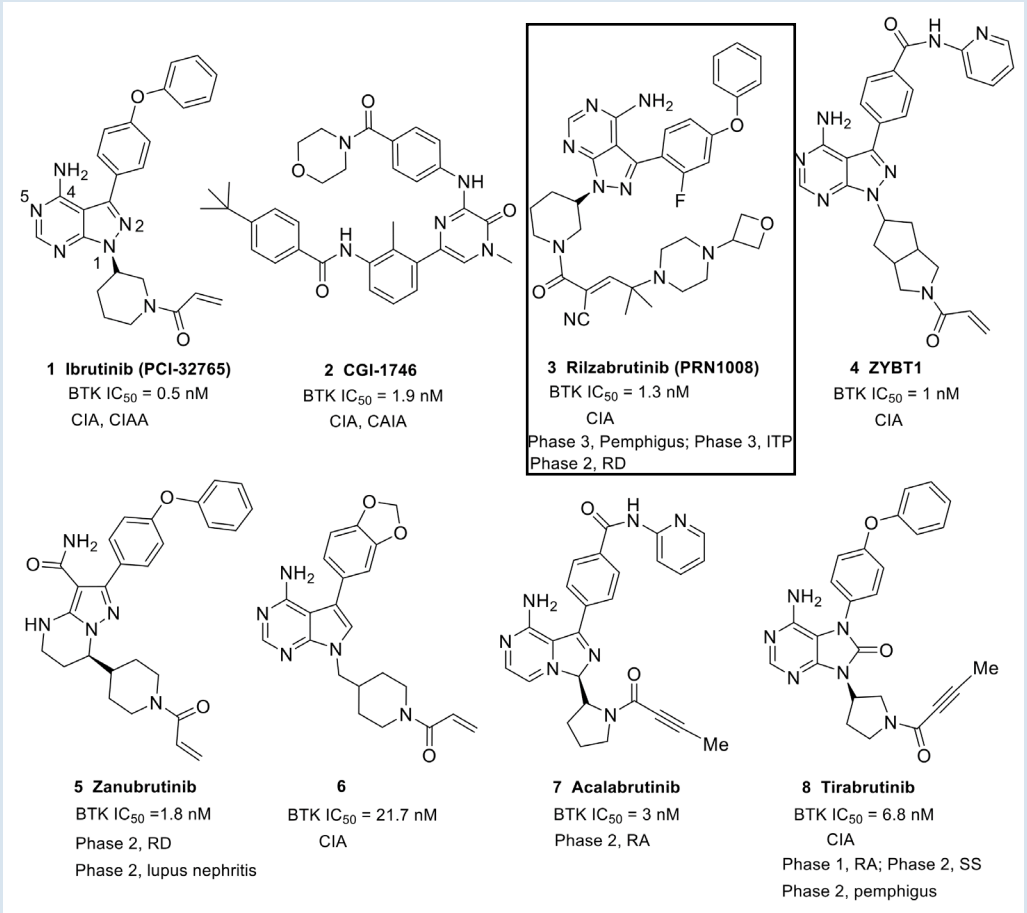
Paik J. Drugs. 2021;81,935–943

Bruton Tyrosine Kinase (BTK) Inhibitors





Zhang D et al. Molecules. 2021;26,4907.