LEČENJE PRIMARNE MIJELOFIBROZE, GDE SMO DANAS?

PREGLEDNI RAD

REVIEW ARTICLE

TREATMENT OF PRIMARY MYELOFIBROSIS, WHERE WE STAND TODAY?

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SAŽETAK

Uvod: Primarna mijelofibroza (PMF) je klonsko oboljenje hematopoeze koje odlikuju konstitutivne tegobe, uvećanje slezine, anemija i često trombocitopenija.

Cilj rada: prikazati uporedne podatke o sprovedenim studijama i lekovima koji su nam dostupni ali i novim terapijskim opcijama.

Metode: analiza publikovanih kliničkih studija i relevantnih radova.

Rezultati: u ovom trenutku zlatni standard lečenja bolesnika sa PMF je još uvek ruksolitinib, prvi predstavnik JAK inhibitora (JAKi). Postiže smanjenje volumena slezine (SVS≥35%) kod 41,9% bolesnika u odnosu na placebo i smanjuje tegobe >50% (TSS<50%) kod 49,5% lečenih. Nije idealan lek, jer se tokom primene javlja anemija, trombocitopenija i sklonost ka infekcijama, pa određeni broj bolesnika mora da prekine lečenje. Fedratinib je drugi JAKi, koji ima dobre rezultate kao druga linija nakon neuspeha ruksolitiniba. Primenjen u prvoj liniji, fedratinib postiže SVS≥35% od 47% uz TSS<50 od 40%.

Kod bolesnika sa transfuziono zavisnom anemijom, dobre rezultate je postigao momelotinib, koji nije bio inferioran u odnosu na ruksolitinib (SVS≥35% je sličan, 26.5% u odnosu na 29% za lečene ruksilitinibom). Primena momelotiniba je smanjila transfuzionu zavisnost za 17% u odnosu na ruksolitinib (66% prema 49%). Kod bolesnika sa trombocitopenijom (Tr 50-100x10^9/L), pakritinib predstavlja najnoviju terapijsku opciju; postiže smanjenje slezine u odnosu na modifikovane doze ruksolitiniba bez daljeg pogoršanja trombocitopenije.

Kombinacije sa ruksolitinibom (navitoklaks, pelabresib) imaju za cilj da značajno poboljšaju odgovor, prvenstveno smanjenjem slezine.

Zaključak: lečenje PMF je i dalje izazov. Primena ruksolitiniba omogućava dobru kontrolu bolesti kod skoro polovine bolesnika, a novi lekovi treba da omoguće lečenje refrakternih bolesnika ili da poboljšaju odgovor.

Ključne reči: primarna mijelofibroza, JAK inhibitori, ruksolitinib, fedratinib, momelotinib, pakritinib

ABSTRACT

Introduction: Primary myelofibrosis (PMF) is a clonal hematopoietic neoplastic disease characterized by constitutive complaints, splenomegaly, anemia and very often thrombocytopenia.

Aim: To analyze and compare data from clinical trials, focusing on both current and emerging therapeutics.

Methods: The analysis of published clinical trials and relevant papers.

Results: Currently, the gold standard for treating primary myelofibrosis (PMF) is ruxolitinib, the first-in-class JAK inhibitor (JAKi). It has achieved a ≥35% reduction in spleen volume (SVR) in 41.9% of patients compared to placebo and has led to a >50% improvement in symptoms, as measured by the Total Symptom Score (TSS), in 49.5% of treated individuals. Ruxolitinib is not an ideal drug, as some patients experience worsening anemia, thrombocytopenia, and an increased susceptibility to various infections. Some patients are required to discontinue the treatment or reduce the dosage. Another approved JAK inhibitor, fedratinib, has shown promising results as a second-line treatment following ruxolitinib failure. As a first-line therapy, fedratinib achieved a spleen volume reduction (SVR) of ≥35% in 47% of patients, with a >50% improvement in TSS in 40% of cases.

In transfusion-dependent patients, momelotinib has demonstrated good results, showing non-inferiority to ruxolitinib, with similar spleen volume reduction (SVR≥35%) rates of 26.5% compared to 29% with ruxolitinib. Momelotinib treatment reduced transfusion independence by 17% compared to ruxolitinib (66% vs 49%). In thrombocytopenic patients (Plt 50-100 x10^9/L), pacritinib is the newest therapy; it reduces spleen volume compared to adjusted ruxolitinib dosing without worsening thrombocytopenia.

Drugs combined with ruxolitinib (e.g. navitoklaks, pelabresib) have the purpose to improve the outcome, especially in spleen reduction.

Conclusion: Treating PMF remains a challenge. While ruxolitinib provides effective disease control in nearly half of patients, new therapies are needed to enhance outcomes both overall and in those with refractory disease.

Keywords: primary myelofibrosis, JAK inhibitors, ruxolitinib, fedratinib, momelotinib, pacritinib

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UVOD

Primarna mijelofibroza (PMF) je klonsko oboljenje matične ćelije hematopoeze koje odlikuje specifičan niz genetskih i patofizioloških poremećaja koji dovodi do neadekvatnog sazrevanja matičnih ćelija megakariocitne i granulocitne loze u kostnoj srži [1,2].

U nastanku svih Filadelfija negativnih mijeloproliferativnih neoplazmi učesvuju mutacije koje se javljaju već na nivou matičnih ćelija hematopoeze i ćelija progenitora. Smatra se da postoje dve vrste mutacija, tzv *driver* ili mutacije pokretači bolesti i „epigenetske", odnosno dodatne mutacije. Mutacije pokretači bolesti pogađaju 3 gena bitna za nastanak i održavanje ćelijskog fenotipa PMF i to su mutacija *JAK2* V617 (*JAK2*), mutacija *Calreticulin* gena (*CALR* exon 9 indel) i mutacija c-*MPL* W515K/L (*MPL*) gena [3]. Ove mutacije se javljaju u značajnom procentu kod bolesnika sa PMF (*JAK2* mutacija je pozitivna u 50-60%, *CALR* kod oko 25% bolesnika, dok je po oko 10% *MPL* pozitivno ili potpuno negativno na ove tri bitne mutacije-trostruko negativne) [3]. Dodatne mutacije su odgovorne za molekularne interakcije i za progresiju bolesti u pravcu akutne leukemije i određuju brzinu i agresivnost pogoršanja bolesti. Te mutacije obuhvataju gene koji regulišu epigenetsku regulaciju (*ASXL1*, *TET2*), delovanje *splicing* procesa na nivou RNK (*SRSF2*, *U2AF1*), mehanizme remodulacije hromatina (*DNMT3A*, *EZH2*) kao i regulaciju tumor supresornih mehanizama i apoptoze (na prvom mestu p53 gen, ali i *BCL*-X_L I, retko, *BCL*-2) [4,5].

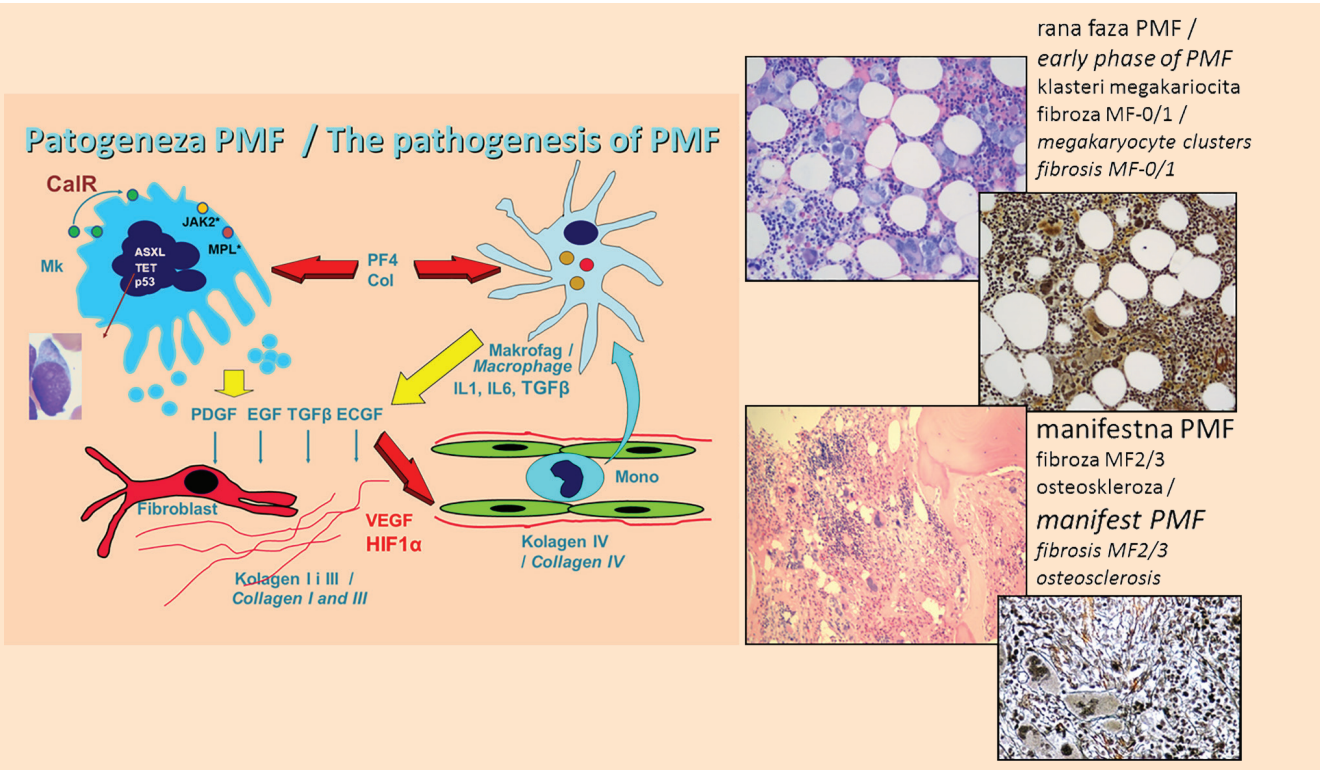
U etiopatogenezi PMF genetski izmenjene matične i progenitorne ćelije reaguju na, često genetski izmenjene, ćelije strome koštane srži, neadekvatnim mehanizmima regulacije i nastankom kontinuiranog zapaljenskog odgovora (hiperinflamacije) [6,7]. Ovakav odgovor dovodi do reakcije strome i aktivacije fibroblasta u smislu stvaranja profibrogenih i proangiogenih citokina (Shema 1) kao što su interleukin-1β (IL-1β), β-fibroblastni faktor rasta (β-FGF "fibroblastic growth factor"), transformišući faktor rasta beta (TGF-β, *transforming growth factor*-β), faktor rasta poreklom iz trombocita (PDGF, *platet derived growth factor*), vaskularni endotelijalni faktor rasta (VEGF, *vascular endothelial growth factor*) [1,6,7]. Poremećaj ove regulacije dovodi do disregulacije i drugih puteva kao što je AKT/mTOR [7,8] ili do disregulacije puteva oksidativnog stresa [8], što za posledicu ima nekontrolisanu proliferaciju ne samo megakariocitnih već i granulocitnih progenitora kao i neoangiogenezu [9-11]. Proliferacija veziva u početku se ogleda kroz retikulinsku fibrozu koštane srži da bi u kasnijim stadijumima bolesti retikulin polimerizovao u kolagen a time i omogućio formiranje novih koštanih gredica

INTRODUCTION

Primary myelofibrosis (PMF) is a clonal disorder of hematopoietic stem cells, marked by specific genetic mutations and pathophysiological changes that disrupt the normal maturation of megakaryocyte and granulocyte lineage cells in the bone marrow [1,2].

All Philadelphia-negative myeloproliferative neoplasms arise from mutations that originate at the level of hematopoietic stem cells and progenitor cells. There are thought to be two types of mutations: the so-called "driver" or disease-initiating mutations, and "epigenetic" or additional mutations. Disease-causing mutations in primary myelofibrosis (PMF) primarily involve three key genes that are crucial for the development and maintenance of the disease phenotype: the JAK2 V617F mutation, the calreticulin (CALR) gene mutation (exon 9 indel), and the c-MPL W515K/L mutation [3]. These mutations are found in a significant percentage of patients with PMF: the JAK2 mutation is present in 50-60% of cases, the CALR mutation in about 25%, and the MPL mutation in approximately 10%. A subset of patients may be triple-negative, lacking all three of these key mutations [3]. Additional mutations play a crucial role in driving molecular interactions and contribute to the progression of the disease towards acute leukemia. These mutations also influence the rate and aggressiveness of disease progression. They involve genes that regulate various critical processes, including epigenetic modification (ASXL1, TET2), RNA splicing (SRSF2, U2AF1), chromatin remodeling (DNMT3A, EZH2), and the regulation of tumor suppressor mechanisms and apoptosis (primarily the p53 gene, as well as BCL-X_L, and, less commonly, BCL-2) [4,5].

In the etiopathogenesis of PMF, genetically altered stem and progenitor cells interact with often mutated stromal cells in the bone marrow, leading to dysregulated mechanisms and the development of a persistent inflammatory response, or hyperinflammation [6,7]. This response triggers stromal reactions and activates fibroblasts, leading to the production of profibrogenic and proangiogenic cytokines (Scheme 1), including interleukin-1β (IL-1β), β-fibroblast growth factor (β-FGF), transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) [1,6,7]. Disruption of this regulation leads to the dysregulation of pathways such as AKT/mTOR [7,8] and oxidative stress pathways [8], resulting in uncontrolled proliferation of both megakaryocyte and granulocyte progenitors, as well as neoangiogenesis [9-11]. The proliferation of connective tissue initially manifests as reticulin fibrosis in the bone marrow. In the later stages of the disease, reticulin fibers polymerize into collagen, leading to the formation of new bone structures (osteogenesis) [2,6]. This progression results in the irreversible



Shema 1. Osnovni prikaz patofizioloških događaja u nastanku primarne mijelofibroze.
IL-1: interleukin-1; β-FGF: β-fibroblastni faktor rasta; TGF-β transformišući faktor rasta β; PDGF: faktor rasta poreklom iz trombocita; VEGF: vaskularni endotelijalni faktor rasta; PF4: trombocitni faktor 4; Col kolagen; EGF: epidermalni faktor rasta; NO*: azot monoksid i nitrozo-oksidativni radikali; HIF1α: hipoksija inducibilni faktor 1α. JAK2, CALR, MPL, ASXL, TET i p53 geni od značaja za patogenezu PMF.

Scheme 1. Key pathophysiological events in the development of primary myelofibrosis.
IL-1: interleukin-1; β-FGF: β-fibroblastic growth factor; TGF-β: transforming growth factor- β; PDGF: platet-derived growth factor; VEGF: vascular endothelial growth factor; PF4: platelet factor 4; Col: collagen, EGF: epidermal growth factor; NO*: nitrogen monoxyde and nitroso-oxidative radicals; HIF1α: hypoxia-inducibile factor 1-alpha. JAK2, CALR, MPL, ASXL, TET and p53 driving and bystander genes genes crucial for the pathogenesis of PMF.

(osteogeneza) [2,6], čime PMF ulazi u ireverzibilnu fazu insuficijencije koštane srži. U toku te faze tranzicije, matične ćelije i progenitori migriraju u slezinu i jetru gde nastaje mijeloidna metaplazija pa se u kasnim stadijumima bolesti hematopoeza odvija u ekstramedularnim zonama (slezina i jetra) uz sve znake insuficijencije koštane srži [1].

Otkriće JAK2 V617F mutacije 2005. godine u četiri nezavisne laboratorije u svetu (JAK2 gen je smešten na hromozomu 9), kao i otkriće mutacije c-*MPL* (receptora za trombopoetin) i kasnije mutacije na CALR genu (takođe na 9. hromozomu) [1,5] omogućilo je bolje sagledavanje potencijalnih terapijskih meta za razvoj terapije PMF koja je do tada bila više palijativna i simptomatsko-supotivna. Jedina terapijska opcija koja je tada, a i sada, mogla da ponudi mogućnost izlečenja je transplantacija matičnih ćelija hematopoeze, ali je ona rezervisana za manji broj mlađih bolesnika kod kojih postoji HLA podudarni davalac [4].

Sa druge strane, u PMF je opisan veći broj citogenetskih aberacija koje sa svoje strane dovode do genetskih poremećaja i kao takve uz nepovoljne molekularne mutacije utiču na brzinu pogoršanja bolesti kao i na nastanak leukemijske transformacije [12].

phase of bone marrow insufficiency in PMF. During this transitional phase, stem cells and progenitors migrate to the spleen and liver, where myeloid metaplasia occurs. Consequently, in the late stages of the disease, hematopoiesis shifts to these extramedullary sites, resulting in signs of bone marrow insufficiency [1].

The discovery of the JAK2 V617F mutation in 2005 by four independent laboratories (the JAK2 gene is located on chromosome 9), along with the identification of mutations in the c-MPL gene (thrombopoietin receptor) and later the CALR gene (also located on chromosome 9) [1,5], significantly advanced our understanding of potential therapeutic targets for PMF. Prior to these discoveries, treatment options were primarily palliative and focused on symptom management. The only therapeutic option that offers a potential cure is hematopoietic stem cell transplantation. However, this treatment is typically reserved for a limited number of younger patients who have an HLA-matched donor [4].

Conversely, numerous cytogenetic aberrations have been identified in PMF, leading to genetic disorders that, in conjunction with unfavorable molecular mutations, influence the rate of disease progression and the likelihood of leukemic transformation [12].

U kliničkoj praksi, bolesnici sa PMF se danas dele na bolesnike sa ranom fazom PMF, što je često čak i hipercelularna, prefibrotička, faza PMF (stepen fibroze MF-0 i MF-1) i bolesnike sa manifestnom, *overt*, PMF kod kojih postoje sve odlike bolesti kao i fibroza MF-2 i MF-3 stepena. U ranoj fazi bolesti najizraženiji klinički problemi su vezani za postojanje trombocitoze i rizik od trombotskih događaja [13,14], dok su u manifestnoj fazi odlike bolesti pojava konstitutivnih sistemskih simptoma (inflamatorni efekti), uvećanje slezine pa i jetre, često pojava anemije i trombocitopenije, što čini terapijske zahvate komplikovanijim [1].

Posebna situacija je kliničko razlikovanje esencijalne trombocitemije i rane faze primarne trombocitoze jer u drugom slučaju je vrlo bitno pažljivo pratiti bolesnika u kasnijem toku bolesti da bi se blagovremeno uvela specifična terapija i/ili planirala transplantacija matičnih ćelija [15].

Postavlja se pitanje kada treba lečiti bolesnike sa PMF [1,3,4,14]. To zavisi od faze bolesti, kliničkih manifestacija kao i bioloških pokazatelja. U kliničkoj praksi se leči trombocitoza primenom hidroksiuree ili (PEG)-interferona kod mlađih bolesnika. Primena interferona je pokazala i antiproliferativni efekat kao i delovanje na smanjenje fibroznih i inflamatornih procesa. Anemija se leči primenom transfuzije eritrocita, kao i primenom eritropoetina i sintetskih androgena sa promenljivim uspehom, a pokušani su i imunomodulatorni lekovi kao što su steroidi i talidomid. Najveći problem je lečenje uvećanja slezine, jer klasični citostatici kao hidroksiurea, busulfan, alkeran i pipobroman nose rizike za pogoršanje citopenije, naročito trombocitopenije, i time onemogućavaju lečenje.

U proceni bolesnika pri izboru terapije sagledavaju se brojni parametri, pa su poslednjih godina razvijeni specifični prognostički modeli od kojih najbolju kliničku primenu imaju DIPSS+ skor (pored kliničkih koristi i negativne citogenetske parametre) (https://qxmd.com/calculate/calculator_315/dipss-plus-score-for-prognosis-in-myelofibrosis) [16] kao i kompozitni modeli koji uključuju i citogenetiku i molekularne markere kao MIPSS70 (http://www.mipss70score.it/) [17] ili GIPSS skor (https://globalrph.com/medcalcs/prognostic-scoring-for-myelofibrosis/) [2,4]. Ovi skorovi omogućavaju da se kod bolesnika proceni dalji rizik bolesti, na prvom mestu rizik od leukemijske transformacije i smrti bolesnika od progresije i da se proceni pravi trenutak za uvođenje druge specifične terapije ili da se planira transplantacija matičnih ćelija ako je izvodljivo. Svi skorovi razvrstavaju bolesnike u tri ili, češće, četiri kategorije koje se značajno razlikuju prema preživljavanju (za DIPSS+ nizak/*low* rizik 15 godina, umereni-1/*intermediate-1* rizik 6,6 godina, dok su bole-

In clinical practice, PMF patients are currently categorized into two groups: those in the early phase, which often includes a hypercellular, prefibrotic phase (fibrosis stages MF-0 and MF-1), and those with manifest, overt PMF, where all disease features are present along with advanced fibrosis (stages MF-2 and MF-3). In the early stage of the disease, the most significant clinical issues are thrombocytosis and the associated risk of thrombotic events [13,14]. As the disease progresses to the manifest stage, patients may experience systemic symptoms (such as inflammation), splenomegaly, hepatomegaly, and complications like anemia and thrombocytopenia, which complicate therapeutic interventions [1].

A critical aspect of clinical practice is distinguishing between essential thrombocythemia and the early phase of primary myelofibrosis. In the latter case, careful monitoring is essential throughout the disease's progression to timely initiate specific therapy and/or plan for stem cell transplantation if necessary [15].

When should patients with PMF be treated [1,3,4,14]? It depends on the stage of the disease, clinical manifestations, and biological indicators. In clinical practice, thrombocytosis is typically managed with hydroxyurea or PEG-interferon, particularly in younger patients. Interferon has demonstrated both antiproliferative effects and benefits in reducing fibrotic and inflammatory processes. Anemia is managed with red blood cell transfusions, erythropoietin, and synthetic androgens, although success varies. Additionally, immunomodulatory drugs such as steroids and thalidomide have been attempted. The treatment of splenomegaly poses significant challenges because traditional cytostatics such as hydroxyurea, busulfan, alkeran, and pipobroman can exacerbate cytopenias, particularly thrombocytopenia, thereby complicating treatment options.

Several parameters are considered when selecting therapy for patients, leading to the development of specific prognostic models. Among these, the DIPSS+ score is widely used for clinical assessment, incorporating clinical benefits and negative cytogenetic parameters (https://qxmd.com/calculate/calculator_315/dipss-plus-score-for-prognosis-in-myelofibrosis) [16]. Additionally, composite models that integrate both cytogenetic and molecular markers, such as MIPSS70 (http://www.mipss70score.it/) [17] and the GIPSS score (https://globalrph.com/medcalcs/prognostic-scoring-for-myelofibrosis/) are also utilized [2,4]. These scores help assess the patient's risk of disease progression, particularly the likelihood of leukemic transformation and mortality. They also guide decisions on the timing of additional specific therapies or the potential need for stem cell transplantation if appropriate. All scores categorize patients into three or, more often, four distinct risk groups, each associated with varying survival

snici sa umerenim-2/*intermediate-2* živeli 2,9 godina i sa visokim/*high* rizkom svega 1.3 god) [16].

Nakon otkrića JAK2 mutacije, došlo je do relativno brzog razvoja većeg broja lekova koji deluju na JAK/STAT signalni put koji su označeni kao JAK inhibitori (JAKi). Sve registracione studije ovih lekova su pošle od bolesnika sa uznapredovalim fazama bolesti (manifestna PMF sa intermedijernim-2 i visokim rizikom, uz manifestnu mijelofiborzu, najčešće MF-2 i MF-3 patološkog gradusa). Tek kasnije su se izdvojili preparati specifičnijeg terapijskog profila koji imaju drugačije delovanje i mogu se primenjivati kod bolesnika sa izraženom anemijom (momelotinib) ili trombocitopenijom (pakritinib).

Danas su u Americi i Evropi registrovani sledeći JAK inhibitori:

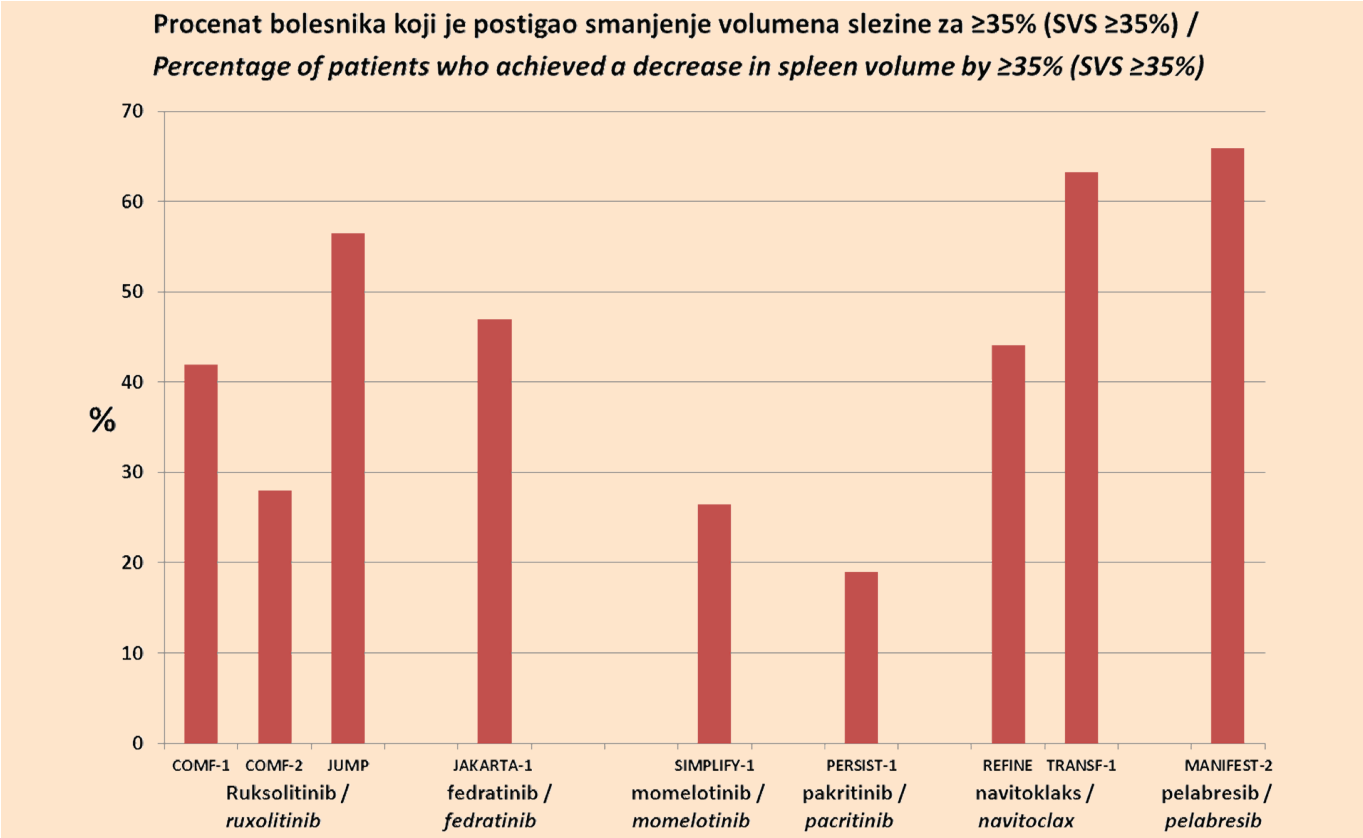
	inhibitor gena:	odobrenje u SAD	odobrenje u Evropi
ruksolitinib	JAK1 i JAK2	2011	2012
fedratinib	JAK2, FLT3, Ret, JAK3	2019	2020
momelotinib	JAK1, JAK2, ACVR1	2023	2024
pakritinib	JAK2, Flt-3, ACVR1	2022	Ne

outcomes. For example, the DIPSS+ score stratifies patients into low-risk (15 years survival), moderate-1/intermediate-1 risk (6.6 years), moderate-2/intermediate-2 risk (2.9 years), and high-risk (1.3 years) categories [16].

Following the discovery of the JAK2 mutation, a significant number of drugs targeting the JAK/STAT signaling pathway, known as JAK inhibitors (JAKi), were developed relatively quickly. All registration studies for these drugs initially focused on patients with advanced stages of the disease, including manifest PMF with intermediate-2 and high-risk profiles, and those with manifest myelofibrosis, typically at pathological grades MF-2 and MF-3. Subsequently, therapies with more specific profiles were identified, offering distinct benefits for patients with pronounced anemia (such as momelotinib) or thrombocytopenia (such as pacritinib).

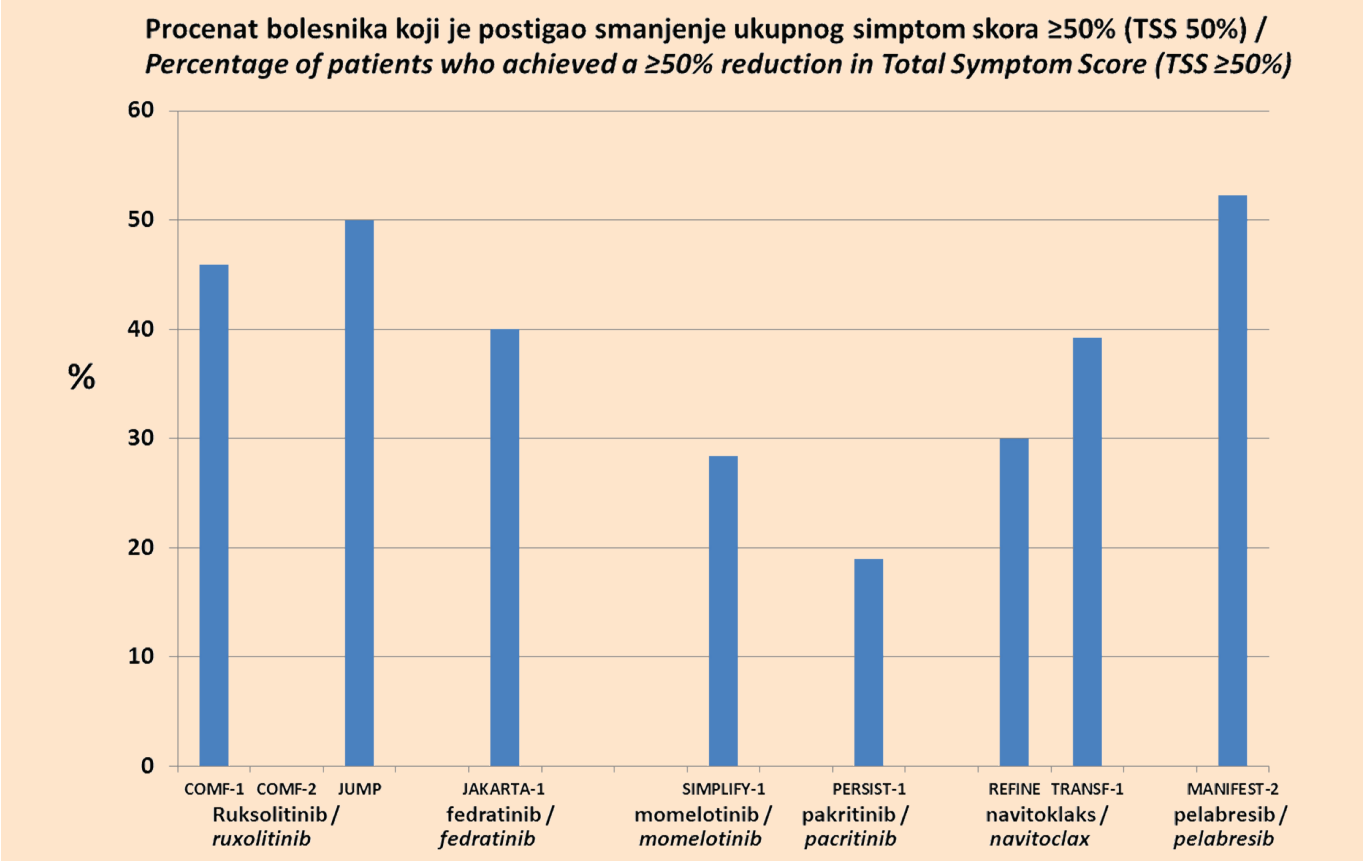
Nowadays, the following JAK inhibitors have been registered in the USA and Europe:

	gene inhibitor:	approved in the USA	approved in Europe
ruxolitinib	JAK1 and JAK2	2011	2012
fedratinib	JAK2, FLT3, Ret, JAK3	2019	2020
momelotinib	JAK1, JAK2, ACVR1	2023	2024
pacritinib	JAK2, Flt-3, ACVR1	2022	No



Grafikon 1. Uporedni rezultati i efikasnost različitih JAKi u kliničkim studijama (stepen redukcije slezine, SVS≥35%) (videti dalje tekst)

Graph 1. Comparative outcomes and efficiency of different JAK inhibitors in clinical trials (spleen volume reduction, SVR≥35%) (related to following text)



Grafikon 2. Uporedni rezultati i efikasnost različitih JAKi u kliničkim studijama (stepen redukcije ukupnog simptom skora, TSS<50%) (videti dalje tekst)

Graph 2. Comparative outcomes and efficiency of different JAK inhibitors in clinical trials (degree of symptom reduction asTotal Symptom Score reduction, TSS<50%) (related to further text)

RUKSOLITINIB (JAKAVI®)

Prvi JAKi koji je ušao u redovnu kliničku primenu je ruksolitinib koji je registrovan 2011. godine u SAD i 2012. godine u Evropi za lečenje PMF u uznapredovanoj fazi bolesti. Njegovi rezultati kroz dve kliničke studije, COMFORT-I (ruksolitinib u odnosu na placebo) [18] i COMFORT-II [19] (ruksolitinib u odnosu na najbolju dostupnu terapiju izuzev JAKi) pokazali su da ovaj lek kod značajnog broja bolesnika postiže kontrolu bolesti u smislu smanjivanja i uklanjanja simptoma koji su posledica povećane inflamacije i smanjivanja veličine odnosno volumena slezine. U COMFORT-I studiji se kod 45,9% bolesnika smanjuju simptomi za više od 50% (mereni specifičnim upitnicima, tzv. *total symptom score*, odnosno TSS<50%). Takođe, postiže se i kontrola bolesti u smislu smanjenja veličine slezine (smanjenje volumena slezine za ≥35%, SVS≥35%, mereno NMR ili CT pregledom) kod 41,9% u COMFORT-I i kod 28% u COMFORT-II studiji. Ovi rezultati su postignuti već u prvih šest meseci primene terapije i neznatno su se popravljali u daljem lečenju. Time je primena ruksolitiniba postala zlatni standard u lečenju bolesnika sa PMF omogućavajući im značajno bolji kvalitet života, a za one koji su imali povoljan odgovor i produženje

RUXOLITINIB (JAKAVI®)

Ruxolitinib, the first JAK inhibitor to enter regular clinical use, was approved in the USA in 2011 and in Europe in 2012 for the treatment of advanced-stage PMF. Results from two clinical studies, COMFORT-I (ruxolitinib vs. placebo) [18] and COMFORT-II [19] (ruxolitinib vs. best available therapy excluding JAK inhibitors), demonstrated that ruxolitinib effectively controls the disease in a significant number of patients by alleviating symptoms associated with increased inflammation and reducing spleen size or volume. In the COMFORT-I study, 45.9% of patients experienced a reduction in symptoms by more than 50%, as measured by the Total Symptom Score (TSS<50%) using specific questionnaires. Additionally, disease control in terms of spleen size reduction (spleen volume reduction of ≥35%, SVS≥35%, measured by NMR or CT) was achieved in 41.9% of patients in COMFORT-I and in 28% in COMFORT-II study. These results were achieved within the first six months of therapy and showed slight improvement with continued treatment. Therefore, ruxolitinib has become the gold standard for treating patients with PMF, significantly improving their quality of life. For those who responded favorably, it also extended

ukupnog preživljavanja (sa 3,8 godina za bolesnike na placebu ili najboljoj terapiji na 5,8 godine kod bolesnika lečenih ruksolitinibom [20]).

Nakon uspeha ove dve studije, sprovedeno je otvoreno istraživanje u realnoj kliničkoj praksi (JUMP studija) [21,22] koje je uključilo 1546 bolesnika sa primarnom mijelofibrozom nezavisno od incijalnog broja trombocita (broj Tr<100x10^9/L je bio faktor isključenja bolesnika u obe COMFORT studije). U prvih 6 meseci 56,5% bolesnika je redukovalo veličinu slezine za ≥50% palpabilne dužine a do kraja prve godine je to postignuto kod 66,5% bolesnika. Kod većine bolesnika nije određivan volumen slezine. Takođe, kod 50% bolesnika je postignuto smanjenje simptoma bolesti merenih sa nekoliko specifičnih upitnika. To je sve pokazalo da je ruksolitinib vrlo efikasan lek u pogledu smanjenja tegoba i simptoma bolesnika kao i u smanjenju veličine slezine koja predstavlja najveći terapijski problem ovim bolesnicima.

U Srbiji ruksolitinib je registrovan 2013. godine, međutim, na listu lekova je stavljen tek 2016. godine sa dosta ograničenim indikacijama preko centralne Komisije RFZO. Pre stavljanja na listu, svega nekoliko bolesnika je lečeno kroz program direktne podrške kompanije Novartis. Poslednja ukupna analiza naših rezultata urađena je 2022. godine i obuhvatila je 155 bolesnika, od toga 129 bolesnika kod kojih je lečenje trajalo najmanje 6 meseci (do prve procene) [23]. Evaluacija bolesnika je obuhvatila procenu smanjivanja opštih simptoma kao i procenu smanjivanja veličine slezine (mereno EHO ili CT pregledom, pri čemu nije bio računat volumen, već smanjenje ukupnog prečnika). Naši rezultati su pokazali da je gubitak opštih simptoma bio izražen (na 6 meseci 111/129 i na 12 meseci 84/90 bolesnika). Smanjenje slezine je uočeno u 91/125 (72,8% bolesnika) u prvih 6 meseci i u 67/90 (74,4%) bolesnika do kraja prve godine. Polovina bolesnika, 29 od 59 evaluiranih bolesnika (49%), je do kraja druge godine smanjila maksimalnu dužinu slezine za ≥25%, mereno EHO ili CT pregledom.

Ruksolitinib je lek koji se dosta dobro podnosi, i najveći deo neželjenih reakcija je posledica blokade JAK/STAT puta vezanog za hematopoezu, pa često dolazi do nastanka značajne anemije i trombocitopenije što zahteva korekciju doze leka, a što, opet, često smanjuje ukupne rezultate lečenja. Pored toga, bolesnici na ruksolitnibu takođe imaju globalno smanjen imuni odgovor, pa su kod njih češće respiratorne i druge infekcije, infekcije herpes virusima, ali su opisani i retki slučajevi aktivacije tuberkuloze [2,21].

Neuspeh terapije ruksolitinibom kao i gubitak odgovora na ruksolitinib otvorio je pitanje druge linije primene JAKi. U sklopu toga, sprovedeno je nekoliko

overall survival from 3.8 years for patients on placebo or the best available therapy to 5.8 years for those treated with ruxolitinib [20]).

Following the success of these two studies, an open-label study was conducted in real-world clinical practice (the JUMP study) [21,22] involving 1,546 patients with primary myelofibrosis, regardless of their initial platelet count. A platelet count of <100×10^9/L was an exclusion criterion in both COMFORT studies. Within the first six months, 56.5% of patients experienced a ≥50% reduction in palpable spleen length, and by the end of the first year, this was achieved in 66.5% of patients. In most patients, the spleen volume was not determined. Additionally, 50% of patients experienced a reduction in disease symptoms, as measured by several specific questionnaires. These findings demonstrate that ruxolitinib is highly effective in alleviating patient symptoms and reducing spleen size, which is one of the most challenging therapeutic issues for these patients.

In Serbia, ruxolitinib was registered in 2013 but was included on the list of reimbursed medications in 2016, with very limited indications, by the Central Commission of the Republic Health Insurance Fund. Before being listed, only a few patients were treated through Novartis' direct support program. The most recent overall analysis of our results, conducted in 2022, included 155 patients, of whom 129 had been treated for at least six months (until the first assessment) [23]. The patient evaluation included assessing the reduction of general symptoms and measuring the reduction in spleen size, using ultrasound or CT scans. While the volume was not calculated, the reduction in total spleen diameter was assessed. Our results demonstrated a significant reduction in general symptoms, with 111 out of 129 patients showing improvement at six months and 84 out of 90 patients at twelve months. Spleen reduction was observed in 91 out of 125 patients (72.8%) within the first six months and in 67 out of 90 patients (74.4%) by the end of the first year. By the end of the second year, 29 out of 59 evaluated patients (49%) had reduced the maximum length of their spleen by ≥25%, as measured by ultrasound or CT scans.

Ruxolitinib is generally well tolerated, but most adverse reactions stem from its inhibition of the JAK/STAT pathway involved in hematopoiesis. This often leads to significant anemia and thrombocytopenia, which may necessitate dose adjustments and can consequently impact overall treatment efficacy. Additionally, patients on ruxolitinib may experience a generally reduced immune response, leading to a higher frequency of respiratory and other infections, including herpesvirus infections. Although rare, cases of tuberculosis activation have also been reported [2,21].

kliničkih studija sa drugim preparatima i prvi koji je u tu arenu ušao jeste fedratinib koji se pokazao efikasnim i kod bolesnika koji su prethodno lečeni ruksolitinibom. Za njim su sprovedena klinička ispitivanja sa momelotinibom (posebno kod bolesnika sa anemijom), kao i sa pakritinibom (kod bolesnika sa trombocitopenijom).

FEDRATINIB (INREBIC®)

Fedratinib je u kliničku praksu ušao 2019. odnosno 2020. godine posle detaljnog praćenja bolesnika u dve kliničke studije, gde se kod retkih bolesnika ispoljio fenomen Vernikeove encefalopatije usled nedostatka vitamina B1, što se kod tih retkih slučajeva dovodilo u vezu sa primenom fedratiniba (*black box* upozorenje) [24]. Međutim, ono što je bitno jeste da je fedratinib u JAKARTA studiji pokazao značajnu efiksasnost u odnosu na placebo u pogledu smanjivanja sistemskih tegoba kao i veličine slezine (na kraju šestog terapijskog ciklusa, odnosno posle 6 meseci terapije, kod 47% bolesnika je značajno redukovan volumen slezine, dok je smanjenje simptoma bilo registrovano kod 40% bolesnika [25].

Kod bolesnika prethodno lečenih ruksolitinibom, postignut je takođe vrlo dobar sekundarni odgovor na terapiju jer je kod njih 55% postignuta ponovna redukcija slezine na ≥35%, mereno NMR ili CT pregledom, kao i dobra kontrola simptoma (26% bolesnika je imalo smanjenje simptoma za >50%), pri čemu je odgovor bio nešto bolji kod bolesnika koji nisu podnosili prethodnu terapiju ruksolitinibom [26].

Detaljna analiza specifične kohorte bolesnika sa incijalno niskim brojem trombocita u okviru JAKARTA studije pokazala je da se slezinski odgovor značajno ne razlikuje između bolesnika koji su incijalno imali Tr>100x10^9/L i onih sa manjim brojem Tr, od 50-100x10^9/L [27].

Na osnovu ovih rezultata fedratinib je uveden kao efiksan lek u lečenju bolesnika koji ne podnose ili nemaju/gube odgovor na prethodnu terapiju ruksolitinibom, čime se značajno poboljšavaju šanse bolesnika za dugotrajnom kontrolom bolesti.

Slično ruksolitinibu, neželjeni efekti fedratiniba su vezani za osnovni mehanizam delovanja, pa se javljaju anemija i trombocitopenija, nešto ređe infekcije, ali i već pomenut deficit vitamina B1 što se uspešno rešava primenom nadoknade [27].

MOMELOTINIB (OMJJARA®)

Momelotinib je najnoviji odobreni JAKi koji je ušao u kliničku primenu 2023. u SAD i 2024. godine u Evropi. Za razliku od ruksolitiniba, i fedratiniba, momelotinib deluje i na aktivin A receptor tipa I koji ima značajnu ulogu u modulaciji delovanja hepcidina čime se omogućava bolja dostupnost gvožđa iz rezervi za aktivnu

The failure of ruxolitinib therapy or loss of response has raised the question of using second-line JAKi. Several clinical studies were conducted to explore alternative treatments, with fedratinib being the first new option to enter the arena. Fedratinib has demonstrated effectiveness even in patients previously treated with ruxolitinib. This was followed by clinical trials of momelotinib, particularly in patients with anemia, and pacritinib, specifically for those with thrombocytopenia.

FEDRATINIB (INREBIC®)

Fedratinib entered clinical practice in 2019 and 2020 following detailed patient monitoring in two clinical studies. In rare cases, the use of fedratinib was associated with Wernicke's encephalopathy due to vitamin B1 deficiency, which has been highlighted in a black box warning [24]. Importantly, the JAKARTA study demonstrated that fedratinib was significantly more effective than placebo in reducing systemic complaints and spleen size. By the end of the sixth treatment cycle (6 months of therapy), 47% of patients had a significant reduction in spleen volume, and 40% experienced a reduction in symptoms [25].

Patients previously treated with ruxolitinib also showed a strong secondary response to fedratinib. Notably, 55% of these patients achieved a ≥35% reduction in spleen size, as measured by MRI or CT, and 26% experienced a reduction in symptoms of over 50%. The response was slightly better in patients who had not tolerated previous treatment with ruxolitinib [26].

A detailed analysis within the JAKARTA study of a cohort with initially low platelet counts revealed that the splenic response did not significantly differ between patients with an initial platelet count >100×10^9/L and those with counts between 50-100×10^9/L [27].

Based on these results, fedratinib was introduced as an effective treatment option for patients who cannot tolerate or have not responded to previous ruxolitinib therapy. It significantly enhances the likelihood of achieving long-term disease control.

Like ruxolitinib, fedratinib's side effects are linked to its mechanism of action, including anemia and thrombocytopenia. Infections occur somewhat less frequently, but there is also a risk of vitamin B1 deficiency, which can be effectively managed with supplementation [27].

MOMELOTINIB (OMJJARA®)

Momelotinib is the newest JAK inhibitor, having been approved for clinical use in the US in 2023 and in Europe in 2024. Unlike ruxolitinib and fedratinib, momelotinib also targets the activin A type I receptor, which plays a crucial role in modulating hepcidin activity. This

eritropoezu, a time i smanjuje težina anemije kod bolesnika sa PMF [28,29]. Upravo je zbog toga momelotinib preporučen za primenu kod bolesnika sa PMF koji imaju izraženu anemiju u sklopu bolesti [28]. Dve kliničke studije sa momelotinibom, SIMPLIFY-1 i 2 bile su slične po osnovnom dizajnu, sa time da je SIMPLIFY-1 [30] bila studija poređenja momelotiniba sa ruksolitinibom (po dizajnu *non-inferiority trial*) gde je pokazano da momelotinib nije inferioran u odnosu na standardnu terapiju, ruksolitinib. Ukupan odgovor u prvih 6 meseci u smislu stope značajne redukcije volumena slezine jeste (SVS≥35%) od 26,5%, što je komparabilno sa 29% u grupi bolesnika lečenih ruksolitinibom. Smanjenje simptoma kroz redukciju simptom skora (TSS<50%) takođe je bilo uporedivo, mada je procenat bolesnika lečenih ruksolitinibom sa postignutim TSS<50% bio veći, 42,2% u odnosu na broj bolesnika lečenih momelotinibom, gde je 28,4% smanjilo simptome za >50%. Međutim, ova razlika nije bila značajna, odnosno momelotinib nije bio značajno inferioran i u tom pogledu. Druga studija sa momelotinibom, SIMPLIFY-2 [29,31] je kao kontrolnu grupu koristila ne samo ruksolitinib već je dozvoljavala primenu najbolje dostupne terapije (BAT, *best available therapy*) koja je uključivala i ruksolitinib kod bolesnika koji nisu postigli optimalni odgovor na prethodno lečenje ruksolitinibom. Rezultati ove studije pokazali su da primena momelotiniba nije značajnije uticala na značajno smenjenje volumena slezine, ali je značajno uticala na smanjenje ukupnog simptom skora (43% prema 21%). Obe ove studije su takođe pokazale da značajan broj bolesnika tokom lečenja momelotinibom postaje nezavistan od transfuzija, pa se u grupi lečenih momelotinibom to dogodilo kod 66% bolesnika u odnosu na 49% lečenih ruksolitinibom (SIMPLIFY-1). U drugoj studiji, 43% bolesnika lečenih momelotinibom postiglo je transfuzionu nezavisnost, u odnosu na 21% bolesika na najboljoj dostupnoj terapiji (SIMPLIFY-2). Shodno tome, sprovedena je i studija koja je uporedila momelotinib sa primenom androgena (danazol) kod bolesnika sa PMF koji su prethodno lečeni primenom JAKi, a koji su razvili značajnu anemiju (MOMENTUM). Ta studija je pokazala da momelotinib smanjuje transfuzionu zavisnost do kraja incijalnih 6 meseci lečenja (31% prema 20% za bolesnike lečene danazolom) [2,29].

Kao i kod drugih JAKi, pri primeni momelotiniba može se javiti prolazno pogoršanje anemije kao i pojava trombocitopenije, o čemu se mora voditi računa tokom lečenja uz titraciju doze leka.

PAKRITINIB (VONJO®)

Pakritinib je poslednji odobreni JAKi. Dostupan je trenutno u SAD gde je odobren kao *orphan* lek 2022.

action enhances the availability of iron from reserves for active erythropoiesis, thereby reducing the severity of anemia in patients with PMF [28,29]. This is why momelotinib is specifically recommended for patients with PMF who have significant anemia as part of their condition [28]. The two clinical trials with momelotinib, SIMPLIFY-1 and SIMPLIFY-2, shared a similar basic design. SIMPLIFY-1 [30] was a non-inferiority trial comparing momelotinib to ruxolitinib, demonstrating that momelotinib was non-inferior to the standard therapy, ruxolitinib. Over the first six months, the overall response rate for significant reduction in spleen volume (SVR≥35%) was 26.5% with momelotinib, which is comparable to 29% in the group treated with ruxolitinib. Reduction in symptoms, as measured by a Total Symptom Score (TSS<50%), was also comparable. However, a higher percentage of patients treated with ruxolitinib achieved TSS<50% (42.2%) compared to those treated with momelotinib, where 28.4% experienced a reduction in symptoms by more than 50%. However, this difference was not significant, indicating that momelotinib was not significantly inferior in this regard either. Another study with momelotinib, SIMPLIFY-2 [29,31] compared it not only to ruxolitinib but also allowed for the use of best available therapy (BAT), which could include ruxolitinib for patients who did not achieve an optimal response to their previous treatment. The results of this study indicated that momelotinib did not significantly impact changes in spleen volume but did significantly improve the reduction of the total symptom score, with 43% of patients achieving this outcome compared to 21% in the control group. Both studies also demonstrated that a significant number of patients on momelotinib became transfusion-independent. Specifically, 66% of patients treated with momelotinib achieved this outcome, compared to 49% in the ruxolitinib group (SIMPLIFY-1). In another study, 43% of patients treated with momelotinib achieved transfusion independence, compared to 21% of patients receiving the best available therapy (SIMPLIFY-2). Consequently, a study was conducted to compare momelotinib with the use of the androgen danazol in patients with PMF who had previously been treated with JAK inhibitors and developed significant anemia (MOMENTUM). The study demonstrated that momelotinib reduced transfusion dependence by the end of the initial six months of treatment, with 31% of patients achieving this outcome compared to 20% in the danazol group [2,29].

Like other JAK inhibitors, momelotinib may cause transient worsening of anemia and thrombocytopenia, which should be considered when adjusting the drug dose during treatment.

Godine, ali za sada nije odobren u Evropi. Nekoliko kliničkih ispitivanja je trenutno u toku i ona treba da pokažu realnu vrednost ovog JAKi u kliničkoj praksi, posebno kod bolesnika sa niskim brojem trombocita kod kojih je pakritinib u prethodnim studijama pokazao dobre rezultate. U odnosu na ruksolitinib i fedratinib gde je broj trombocita limitirajući faktor za uvođenje leka i postizanje optimalnog odgovora, pakritinib je u incijalnoj studiji PERSIST-1 [32] pokazao značajan efekat u smislu smanjenja volumena slezine u odnosu na najboju dostupnu terapiju (ali bez JAKi) gde je 19% bolesnika postiglo SVS≥35% u odnosu na samo 5% u kontrolnoj grupi. Ovi rezultati su dalje ispitivani u studiji PERSIST-2 [33] u koju su uključeni bolesnici sa značajnom trombocitopenijom (<100x10^9/L) gde je kontrolna grupa obuhvatala različite terapije, a u najvećoj meri redukovane doze ruksolitiniba (45%). U ovoj studiji pakritinib je pokazao značajno smanjenje kako volumena slezine (SVS≥35% 18% prema 3%) tako i ukupnog skora simptoma (kod 25% prema 14% bolesnika).

Rezultati novih studija pokazaće pravu realnu vrednst pakritiniba kod bolesnika sa izraženom trombocitopenijom u PMF.

Kao i drugi JAKi pakritinib može da dovede do anemije, ali su takođe zbog efekta na inhbiciju AVRI receptora dugoročni efekti na bolesnike sa anemijom manji od ruksolitiniba i fedratiniba.

MOGUĆA SEKVENCA PRIMENE JAKI U LEČENJU BOLESNIKA SA PMF

U ovom trenutku u Evropi je dostupno tri a u SAD četiri JAKi koji se mogu kombinovati prema kliničkim i drugim specifičnim hematološkim odlikama, čime smo posle dužeg perioda prestali da budemo ograničeni na samo jedan lek.

Na grafikonu je prikazana orijentaciona shema redosleda primene i izbora JAK inhibitora u kliničkoj praksi [34].

Međutim, jedan od najvažnijih momenata u lečenju bolesnika sa PMF kao i sekundarnim mijelofibrozama (nastalim transformacijom iz policitemije vere ili esencijalne trombocitemije) je adekvatan tajming i pravovremeno uvođenje terapije. Analize podgrupa bolesnika unutar sprovedenih studija [35] kao i primena leka u realnom kliničkom okruženju je pokazali su da su rezultati uspešniji kada se JAKi, prvenstveno za sada ruksolitinib, uvedu ranije u toku bolesti kada bolesnik počinje da ispoljava simptome i tegobe čak i kada njegovi faktori rizika nisu previše ispoljeni (bolesnici u umerenoj/*intermediate-1* fazi). Time se omogućava uvođenje leka u situacijama sa boljim bazalnim paremtrima krvne slike a isto tako se i omogućuje bolje

PACRITINIB (VONJO®)

Pacritinib is the newest approved JAK inhibitor. It was granted orphan drug status and approved for use in the US in 2022, but it has not been approved in Europe yet. Several clinical trials are currently underway to assess the real-world value of this JAK inhibitor, particularly in patients with low platelet counts, where pacritinib has previously shown promising results. Unlike ruxolitinib and fedratinib, where platelet counts can limit drug use and response, the initial PERSIST-1 study [32] demonstrated that pacritinib had a significant effect on reducing spleen volume compared to the best available therapy (excluding JAK inhibitors). Specifically, 19% of patients treated with pacritinib achieved a spleen volume reduction of ≥35% (SVR≥35%), compared to just 5% in the control group. These results were further evaluated in the PERSIST-2 study, which included patients with significant thrombocytopenia (<100×10^9/L). The control group consisted of various therapies, with a substantial proportion receiving reduced doses of ruxolitinib (45%). In this study, pacritinib demonstrated a significant reduction in both spleen volume (SVR≥35% in 18% of patients compared to 3% in the control group) and overall symptom score (25% of patients achieved a reduction versus 14% in the control group).

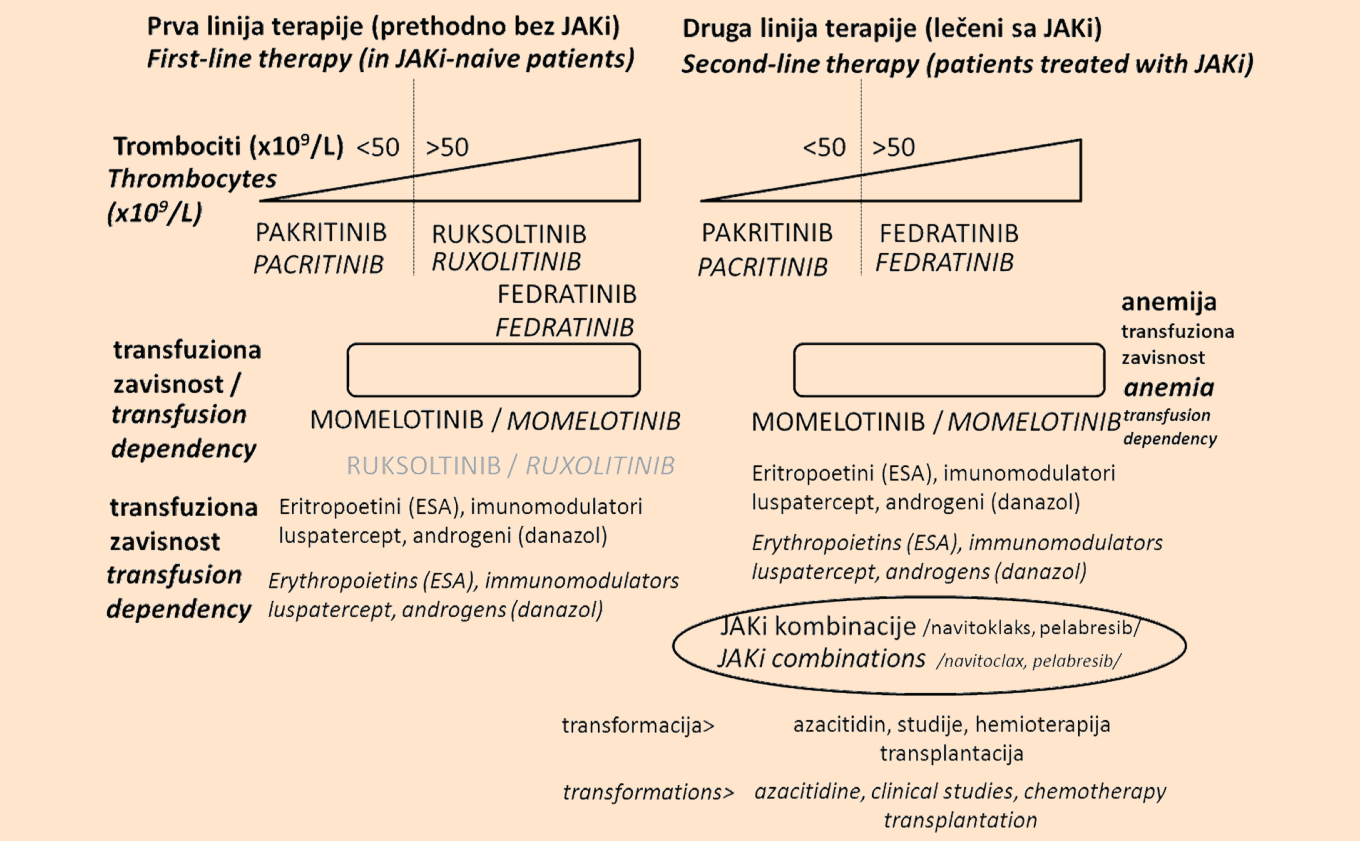
Future studies will reveal the true clinical value of pacritinib for patients with marked thrombocytopenia in PMF.

Like other JAK inhibitors, pacritinib can cause anemia. However, due to its effect on the AVRI receptor, it tends to have less severe long-term effects on anemia compared to ruxolitinib and fedratinib.

POTENTIAL SEQUENCE OF JAK INHIBITOR USE IN THE TREATMENT OF PATIENTS WITH PMF

Currently, three JAK inhibitors are available in Europe and four in the USA. This allows for tailored treatment based on clinical and specific hematological features, ending the long period of reliance on a single drug. The chart provides a guide for the sequence and selection of JAK inhibitors in clinical practic [34].

One of the most crucial aspects of treating patients with primary myelofibrosis (PMF) and secondary myelofibrosis (resulting from transformation of polycythemia vera or essential thrombocythemia) is the appropriate timing and prompt initiation of therapy. Analysis of patient subgroups from conducted studies [35], along with real-world clinical application, indicates that outcomes are more favorable when JAK inhibitors, particularly ruxolitinib, are introduced earlier in the disease course—when symptoms and complaints first appear, even if risk factors are not yet severe (patients in the moderate/intermediate-1 phase). This approach al-



Grafikon 2. Moguća primena odobrenih JAKi prema linijama terapije i kliničkim odlikama bolesnika u lečenju PMF (modifikovano prema Venugopal i sar. [34])

Graph 2. Potential therapy with approved JAK inhibitors based on lines of treatment and clinical features in PMF, modified from Venugopal et al. [34])

i efikasnije delovanje JAKi [22,35]. Za sada nije bilo kliničkih studija sa primenom JAKi u vrlo ranim fazama PMF, dok su rezultati primene ruksolitiniba kod bolesnika sa kasnom fazom policitemije vere pokazali da oni imaju dobar potencijal za kontrolu bolesti pa čak i za smanjivanje stope progresije bolesti u manifestnu fibrotičnu fazu, pa je ruksolitinib i odobren za lečenje bolesnika sa PV u fazi rezistencije na hidroksiureu, kako u SAD tako i u Evropi (EMA).

Kako je mehanizam kliničkih manifestacija u PMF vrlo kompleksan, te kako su često oni međusobno isprepletani, postoji potreba za kombinovanjem lekova koji deluju na različite molekularne sisteme unutar ćelija hematopoeze kao i na ćelije strome i njihove interakcije. Potencijal kombinovanja različitih agenasa je veoma veliki, od malih molekula kao što su signalni inhibitori drugih unutarćelijskih puteva, inhibitori apoptoze, ihibitori telomerase, do monoklonskih antitela usmerenih na neovaskularizaciju i angiogene i profibritične faktore. Imajući u vidu da je to predmet brojnih studija od kojih su mnoge u toku, osvrnućemo se samo na dva nova leka koja su do sada u kombinaciji pokazala značajne efekte na smanjenje volumena slezine kao glavnog kliničkog merila efikasnosti lekova za mijelofibrozu [36].

lows for the initiation of treatment with more favorable baseline blood parameters, which can enhance the effectiveness and efficiency of JAKi [22,35]. To date, no clinical studies have investigated the use of JAK inhibitors in the very early stages of PMF. However, results from studies of ruxolitinib in patients with late-stage polycythemia vera have demonstrated its potential for controlling the disease and slowing its progression to the manifest fibrotic phase. Consequently, ruxolitinib is approved for use in PV patients who are resistant to hydroxyurea, both in the USA and in Europe (EMA).

Given the complexity and interrelated nature of clinical manifestations in PMF, there is a need to combine therapies that target different molecular pathways within hematopoietic cells, as well as those affecting stromal cells and their interactions. The potential for combining different agents is substantial, ranging from small molecules like signaling inhibitors targeting various intracellular pathways and apoptosis inhibitors to telomerase inhibitors, as well as monoclonal antibodies that target neovascularization, angiogenic factors, and profibrotic factors. Given that this topic is the subject of numerous ongoing studies, we will focus on just two new drugs that have demonstrated significant effects in reducing spleen volume, which is the primary clinical measure of drug efficacy for myelofibrosis [36].

NAVITOKLAKS

Navitoklaks je aktivator proapototskih sistema unutar ćelije koji se zasniva na inhibiciji delovanja antiapoptoskih gena kao što su BCL-2 ali i BCL-XL koji je posebno aktivan kod bolesnika sa mijeloproliferativnim neoplazmama kao što je PMF [37]. Ovaj lek je još od 2007. godine u kliničkom razvoju i sprovedene su brojne studije čiji su dosadašnji rezultati pokazali efikasnost kako samog leka tako i leka u kombinaciji sa drugim citotoksičnim lekovima i signalnim inhibitorima. U PMF, navitoklaks se ispituje u nekoliko studija od kojih su dostupni rani rezulati REFINE i TRANSFORM-1 studije. REFINE studija je bila prva studija koja je primenjivala navitoklaks kod bolesnika koji prethodno nisu imali odgovor na ruksolitinib ili su isti izgubili, (*add on* studija) i dodavanje navitoklaksa je omogućilo da 26,5% bolesnika značajno redukuje volumen slezine kao i da se kod 30% bolesnika postigne značajno smanjenje simptoma merenih kroz specifični uputinik (TSS<50%) [37,38].

Naredna, TRANSFORM-1 studija koja je u toku pokazala je dosta impresivne rezultate koji su prikazani na sastanku Američkog udruženja (ASH) 2023. godine i Evropskog udruženja hematologa 2024. godine [39]. Ova studija je zamišljena kao dvostruko slepa, placebo kontrolisana studija u dve kohorte, pri čemu su svi bolesnici lečeni ruksolitinibom uz dodatak navitoklaksa, odnosno placeba. Preliminarni rezultati pokazali su da se u grupi bolesnika lečenih kombinacijom postiže značajno smanjene volumena slezine gde je 63,2% bolesnika postiglo cilj (SVS ≥35%) za razliku od 31,5% bolesnika u grupi koja je primala ruksolitinib sa placebom. Rezultati smanjenja TSS skora bili su manje impresivni jer je značajan broj bolesnika imao smanjenje simptoma u celini, a smanjenje TSS<50% je postugnuto u približno istoj meri u obe grupe bolesnika, 39,2% u grupi sa navitoklaksom i ruksolitinibom prema 41,7% u grupi na ruksolitinibu sa placebom, što je definitivno neposredni efekat ruksolitiniba na JAK/STAT puteve [37-39].

Jedan od najvećih problema primene navioklaksa je nastanak trombocitopenije i neophodnost precizne titracije terapije ali u dosadašnjem iskustvu kroz REFINE i TRANSFORM-1 i 2 studiju nije pokazana značajna učestalost krvarenja kao i potreba da se bolesnici isključe zbog izražene trombocitopenije [37].

PELABRESIB

Drugi lek koji obećava je pelabresib, specifični inhibitor bromodomena i ekstra-terminalnih (BET) domena proteina koji bi mogli da nishodno regulišu brojne gene uključene u onkogenezu. Pelabresib je u fazi kliničkog razvoja i u toku su različite studije sa brojnim malignim

NAVITOCLAX

Navitoclax activates pro-apoptotic pathways by inhibiting anti-apoptotic proteins such as BCL-2 and BCL-XL. This mechanism is particularly effective in patients with myeloproliferative neoplasms, such as PMF [37]. The drug has been under clinical development since 2007, with numerous studies demonstrating its effectiveness both as a standalone treatment and in combination with other cytotoxic drugs and signaling inhibitors. In PMF, navitoclax is being investigated in several studies, with early results available from the REFINE and TRANSFORM-1 trials. The REFINE study was the first to evaluate navitoclax in patients who had either not responded to ruxolitinib or had lost their response (add-on study). The addition of navitoclax led to a significant reduction in spleen volume in 26.5% of patients and a notable decrease in symptoms, as measured by a Total Symptom Score (TSS<50%) in 30% of patients [37,38].

The ongoing TRANSFORM-1 study has demonstrated promising results, which were presented at the 2023 American Society of Hematology (ASH) meeting and the 2024 European Hematology Association (EHA) meeting [39].The study was designed as a double-blind, placebo-controlled trial with two cohorts, where all patients were treated with ruxolitinib, either with the addition of navitoclax or a placebo. Preliminary results indicated that the combination therapy led to a significant reduction in spleen volume, with 63.2% of patients achieving the target (SVR ≥35%) compared to 31.5% in the ruxolitinib plus placebo group. The reduction in Total Symptom Score (TSS) was less striking. A similar proportion of patients achieved a TSS reduction to below 50% in both groups: 39.2% in the navitoclax plus ruxolitinib group and 41.7% in the ruxolitinib plus placebo group. This indicates that the observed symptom improvement is likely a direct effect of ruxolitinib on the JAK/STAT pathways [37-39].

One of the major challenges with navitoclax is the risk of thrombocytopenia, necessitating careful dose titration. However, based on experience from the REFINE, TRANSFORM-1, and TRANSFORM-2 studies, there has been no significant increase in bleeding incidents or a need to exclude patients due to severe thrombocytopenia [37].

PELABRESIB

Another promising drug is pelabresib, a specific inhibitor of bromodomain and extra-terminal (BET) proteins. By targeting these proteins, pelabresib has the potential to downregulate multiple genes involved in oncogenesis. Pelabresib is currently in clinical development, with ongoing studies across various malignancies. Specifically, two studies, MANIFEST [40] and MANIFEST-2 [40,41],

bolestima, a u mijeloproliferativnim neoplazama sprovedene su dve studije MANIFEST [40] i MANIFEST-2 [40,41], pri čemu je studija MANIFEST-2 bila dvostruko slepa, placebo kontrolisana studija kombinacije ruksolitiniba i pelabresiba, odnosno placeba. Studija MANIFEST-2 je pokazala da dodatak pelabresiba popravlja ukupni odgovor većine bolesnika na ruksolitinib, jer je SVS≥35% postignut kod 65,9% bolesnika u eksperimetalnoj grupi u odnosu na 35,2% bolesnika lečenih ruksolitnibom i placebom [41]. Takođe značajno smanjenje ukupnih simptoma je bilo znatno više u slučaju kombinacije pelabresiba i ruksolitiniba. TSS<50% je postignut kod 52,3% ispitanika na kombinaciji u odnosu na 46,3% u grupi na ruksolitinibu sa placebom. Ova studija je pokazala da je moguće postići dalju optimizaciju i poboljšanje incijalnog odgovora bolesnika na ruksolitinib čime se otvara mogućnost i za brojne druge kombinacije usmerene na poboljšanje ukupnog terapijskog ishoda bolesnika sa primarnom mijelofibrozom. Kao i drugi JAKi i pelabresib može dovesti do pogoršanja anemije kao i do pojave trombocitopenije, ali najveći broj bolesnika je vrlo dobro podneo ovu kombinovanu terapiju [40].

ZAKLJUČAK

Današnje terapijske mogućnosti u lečenju bolesnika sa mijelofibrozom obećavaju značajno poboljšanje opšteg kvaliteta života, smanjenje simptoma i smanjenje slezine i time vrlo verovatno i produženje života većine bolesnika, posebno ako se terapija uvede na vreme. Razvojem više JAKi dobili smo mogućnost boljeg terapijskog izbora u specifičnim kliničkim situacijama kao što su bolesnici sa citopeničnom mijelofibrozom ili sa izraženom transfuziono zavisnom anemijom čiji je dosadašnji kvalitet života bio neadekvatan. Pored toga, nova saznanja o biologiji bolesti, patofiziološkim i genetskim mehanizmima omogućiće u budućnosti nalaženje i drugih terapijskih ciljeva osim inhibicije JAK/STAT puta, čime će verovatno kombinovana terapija u narednim godinama postati osnova lečenja bolesnika i u prvoj terapijskoj liniji [42].

Nadamo se da će u Srbiji uskoro biti dostupan barem još jedan od registrovanih JAK inhibitora čime bi naši bolesnici imali dodatne terapijske mogućnosti pored učešća u kliničkim studijama čija je dostupnost sporadična.

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have been conducted in myeloproliferative neoplasms. MANIFEST-2 is a double-blind, placebo-controlled trial evaluating the combination of ruxolitinib and pelabresib versus ruxolitinib with placebo. The MANIFEST-2 study demonstrated that adding pelabresib to ruxolitinib significantly enhances the overall response in patients. In the experimental group, 65.9% of patients achieved a spleen volume reduction of ≥35% (SVR≥35%), compared to 35.2% in the ruxolitinib plus placebo group [41]. Additionally, the reduction in overall symptoms was significantly greater with the combination of pelabresib and ruxolitinib. TSS reduction to below 50% was achieved in 52.3% of patients receiving the combination of pelabresib and ruxolitinib, compared to 46.3% in the ruxolitinib plus placebo group. This study showed that it is possible to achieve further optimization and improvement of the patient's initial response to ruxolitinib, which opens the possibility for numerous other combinations aimed at improving the overall therapeutic outcome of patients with primary myelofibrosis. Similar to other JAK inhibitors, pelabresib can cause worsening of anemia and thrombocytopenia. However, the majority of patients tolerated the combination therapy well [40].

CONCLUSION

Current therapeutic options for myelofibrosis offer the potential for significant improvements in overall quality of life, symptom reduction, and spleen size reduction. Timely initiation of therapy is likely to enhance these benefits and potentially extend the lifespan of many patients. The development of additional JAK inhibitors has expanded our therapeutic options, allowing for more tailored treatments in specific clinical scenarios, such as patients with cytopenic myelofibrosis or severe transfusion-dependent anemia. This advancement offers the potential to significantly improve the previously inadequate quality of life for these patients. Moreover, advancing our understanding of the disease's biology, pathophysiological, and genetic mechanisms is expected to reveal new therapeutic targets beyond the JAK/STAT pathway. This progress will likely lead to the adoption of combination therapies as the standard approach for first-line treatment in the coming years [42].

We hope that at least one more of the registered JAK inhibitors will soon be available in Serbia, providing our patients with additional therapeutic options beyond the sporadic availability of clinical studies.

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