

ΕΥΚΑΙΡΙΑΚΗ ΛΟΙΜΩΞΗ ΣΕ ΜΗ ΟΥΔΕΤΕΡΟΠΕΝΙΚΟ ΑΣΘΕΝΗ

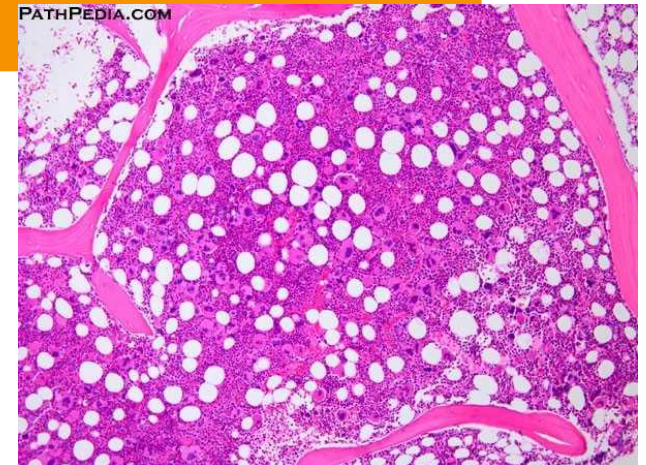
ΕΥΓΕΝΙΑ ΒΕΡΙΓΟΥ
ΕΙΔΙΚΕΥΟΜΕΝΗ
ΑΙΜΑΤΟΛΟΓΙΚΟΥ ΤΜΗΜΑΤΟΣ
ΠΓΝΠ

Η ΕΜΦΑΝΙΣΗ

Γυναίκα, ελληνικής καταγωγής, DOB: 04/08/1957, Ιx ετερόζυγη β MA

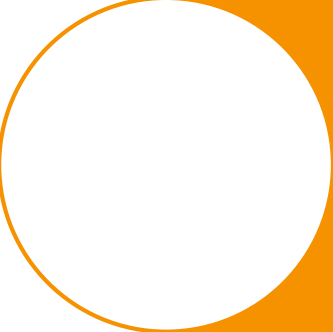
1^{ος} /2002 **Θρόμβωση πυλαίας , βιοψία ήπατος: αυτοάνοση ηπατίτιδα vs αρχόμενη απόφραξη εξωηπατικών χοληφόρων** → Τέθηκε σε αγωγή με Sintrom, Inderall

6^{ος} /2003 **Ιδιοπαθής θρομβοκυτταραιμία vs προϋνωτική μυελοσκλήρυνση(OMB), έλεγχος θρομβοφιλίας αρνητικός, έλεγχος για PNH αρνητικός** → Τέθηκε σε αγωγή με Hydroxyurea.

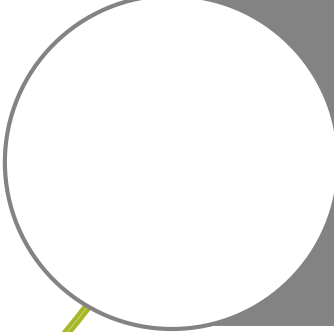




5^{ος} - 10^{ος} /2005 Επεισόδια **επιγαστραλγίας με ίκτερο** → U/S κοιλίας: μόρφωμα χοληδόχου κύστεως (πιθανώς πολύποδας), μικροοζώδης εικόνα κίρρωσης, **σπληνομεγαλία ~18cm**. MRCP (19/8/05) ηπατικοί κλάδοι και κοινός ηπατικός κφ, **συμμετρική στένωση χοληδόχου πόρου** μέχρι της εκβολής του στον 12/λο. ERCP(13/10/05) κφ.



3^{ος} /2006 **χολοκυστεκτομή** με ιστολογική εικόνα αδеноμύωσης και μέτριου βαθμού χρόνιας χολοκυστίτιδας



6^{ος}/2006 έως 9^{ος}/2009 τρία επεισόδια **χολαγγειίτιδας** για τα οποία νοσηλεύθηκε στην Π/Θ Κλινική ΠΓΝΠ.

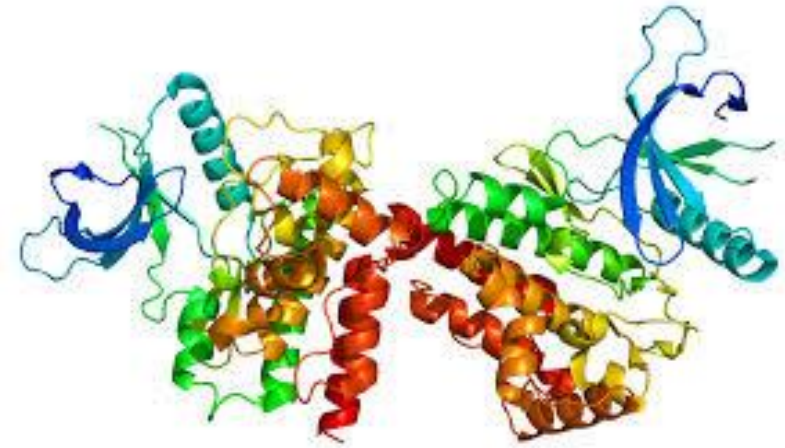
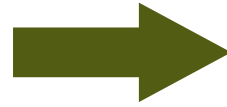
11^{ος} /2009 ΟΜΒ: ΜΥΣ με
σκλήρυνση και κατά τόπους
ίνωση του στρώματος
(Grade III).

Διακοπή Hydroxyurea έναρξη
Xagrid και ερυθροποιητίνη
30.000iu/ εβδομάδα και
Decadurabolin 50mg/
εβδομάδα.

8^{ος} /2011 CBC: WBC:8000/μl,
Ht:30-33%, PLT:300.000-
450.000/μl

8^{ος}/2011 πτώσης του Hct ~
25% έναρξη **θεραπείας με**
κορτικοστεροειδή → Hct: 30%
αλλά **εμφάνιση ασκίτη** χωρίς
επιδείνωση ηπατικής
βιοχημείας.

10^{ος}/2011 διακοπή
αναβολικών, διουρητική
αγωγή και έλεγχος μετάλλαξης
JAK2V617F(+)



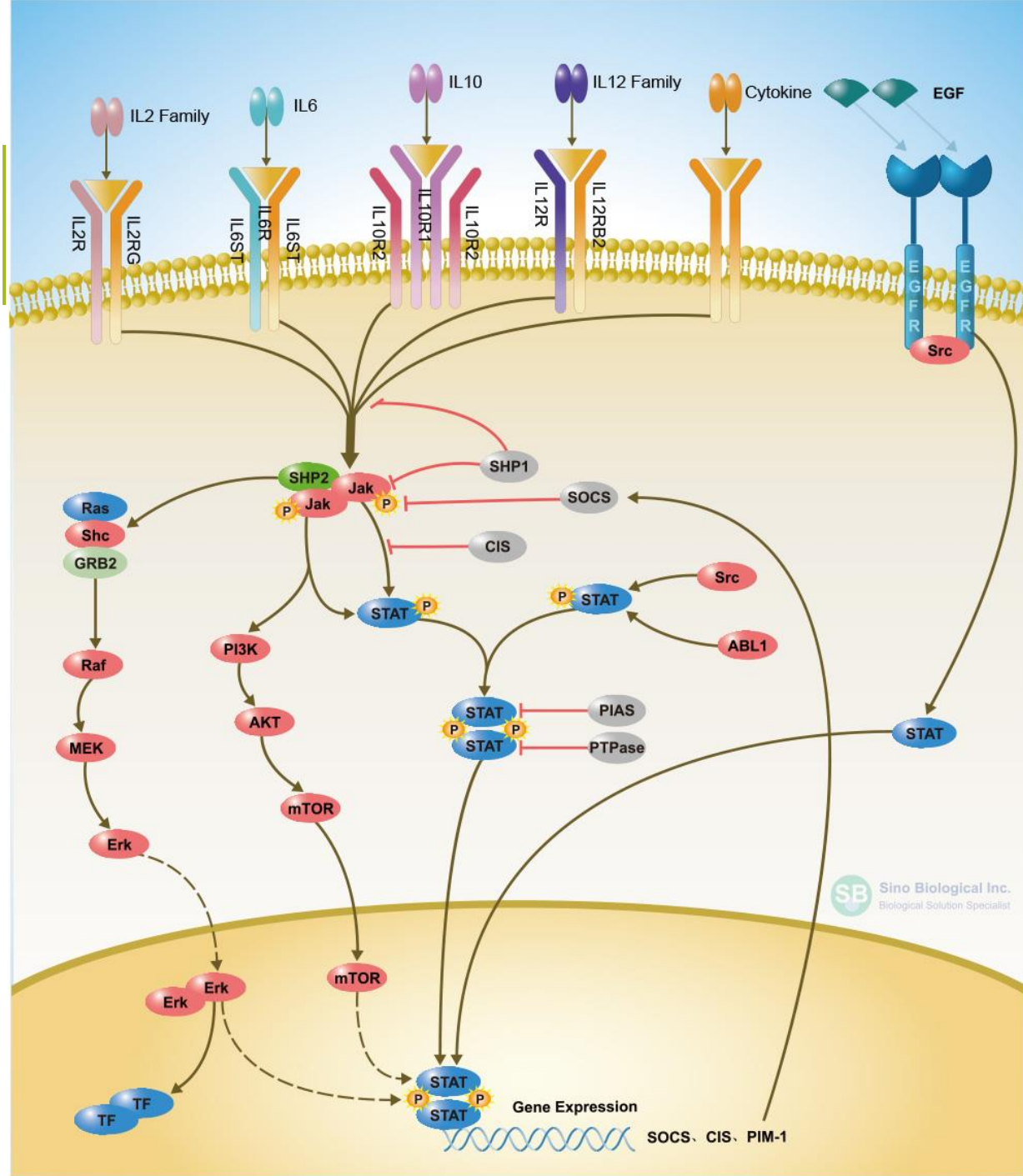
JAK2 κινάση

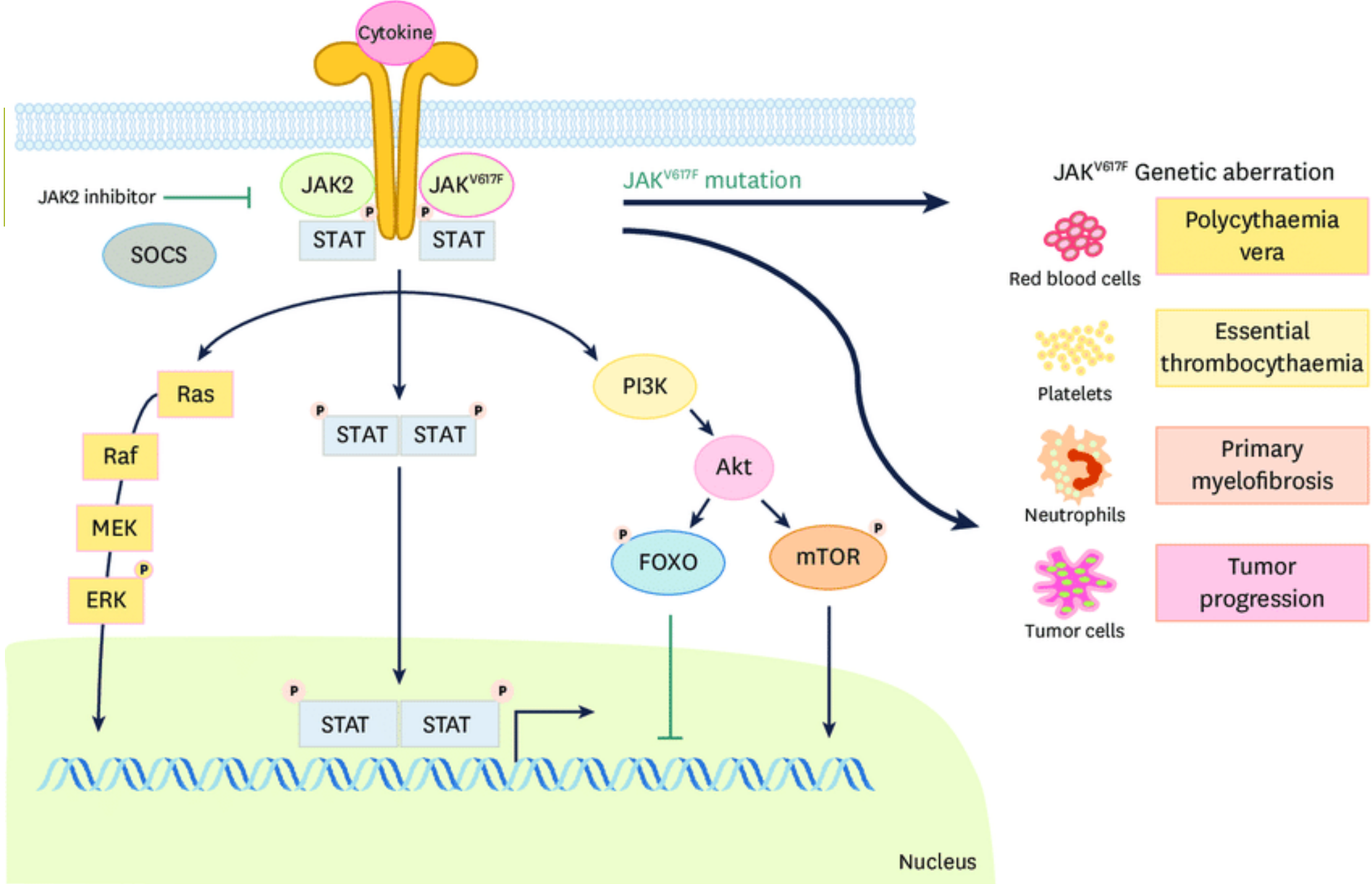


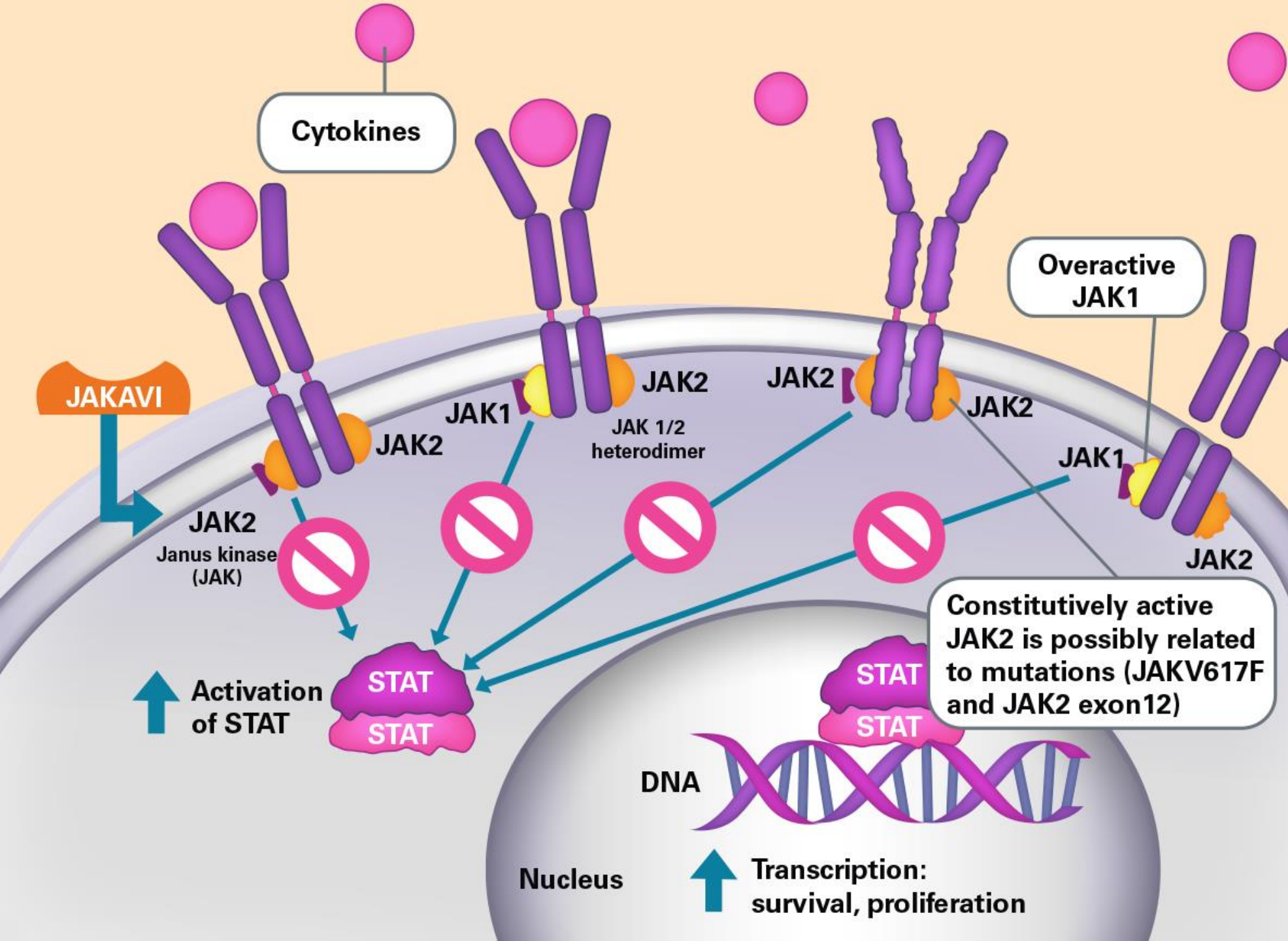
JAK – STAT



**ΑΙΜΟΠΟΙΗΣΗ
ΑΝΟΣΟΥΘΜΙΣΗ/
ΦΛΕΓΜΟΝΗ**





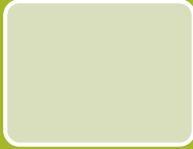


4-8/2/2012 νοσηλεία λόγω εμπυρέτου,
πλευριτικών συλλογών, επιδείνωσης
ασκιτικής συλλογής. Έλαβε levofloxacin
Πλευριτικό υγρό: εξίδρωμα με αρνητικές
καλλιέργειες για κοινά μικρόβια
(TB vs Disease)

4-7/3/2012 Νοσηλεία λόγω εμπυρέτου
έως 40°C χωρίς συνοδά. Έλαβε
levofloxacin και oseltamivir

11/4/2012
έναρξη
χορήγησης
αναστολέα JAK2
kinase –
Ruxolitinib
20mg x 2

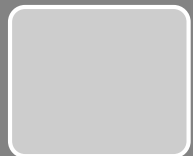
ΠΟΡΕΙΑ ΝΟΣΟΥ



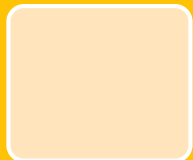
30/4 -22/6/2012 Νοσηλεία στο ΠΓΝΠ λόγω εμπυρέτου, αναιμίας (μεταγγισιοεξαρτώμενη ασθενής), λευκοπενίας → **διακοπή του φαρμάκου.**



Συνοδά: ασκитική συλλογή → πυλαία υπέρταση [ασκитικό υγρό: ΚΑ(-), κυτταρολογική (-)]. **Επιδείνωση νεφρικής λειτουργίας**
ΔΔχ: **Φαρμακευτικής αρχής ΟΝΑ vs Ηπατονεφρικό σύνδρομο**



Κατά τη νοσηλεία διακοπή και **επανάναρξη ruxolitinib** αρχικά 15mg x 2 και τις επόμενες ημέρες περαιτέρω μείωση σε 5mg x 2 (θρομβοπενία και νεφρική λειτουργία)



10/6 – 18/6/2012 απογευματινή δεκατική πυρετική κίνηση που αποδόθηκε στην υποκείμενη νόσο. (CRP:7)

. Έναρξη
terlipressin -
ηπατική νόσος
ή εξωμυελική
αιμοποίηση
;
πλάνο για
βιοψία ηπατος

16/7/2012 Εμφάνιση ανώδυνης
διόγκωσης AP υπερκλείδιας χώρας.

2/8/2012 CT θώρακος: λεμφαδένας με
κεντρική τήξη; ~2,3εκ. Χωρίς
παθολογικά ευρήματα εκ του
πνευμονικού παρεγχύματος,
ολιγάριθμοι LNs μεσοθωρακίου έως
1,1εκ.

22/8/2012 Εισαγωγή λόγω
εμπυρέτου –
Mantoux (30/8):35mm

30/8/2012: Βιοψία
μορφώματος AP υπερκλείδιας
χώρας

↓
(4/9) TBC

→ Όχι ΧΜΘ

→ Όχι ΚΣ

→ Όχι
Λευκοπενία

4/9/2012 Ασθενής απύρετη,
έναρξη αντιφυματικής αγωγής
με Dexambutol + Rifinah για 1
έτος (λόγω επιβαρυμένης
ηπατικής λειτουργίας όχι
πυραζιναμίδη)

→ Όχι «παραδοσιακό»
ανοσοκατασταλτικό
νόσημα

b. Pooled analysis of extended phase III randomized clinical trials

	Total number of patient-year	Odds Ratio (M-H, Fixed, 95% CI) (ruxolitinib vs control)
Herpes Zooster	1336	5.20 [1.27, 21.18]
Urinary tract infection	992	1.20 [0.58, 2.51]
Bronchitis	1032	1.26 [0.58, 2.71]
Pneumonia (grade 3–4)	1011	0.55 [0.28, 1.09]

10/31 case reports: φυματίωση

Received: 19 October 2017

Revised: 13 November 2017

Accepted: 14 November 2017

DOI: 10.1002/ajh.24976

RESEARCH ARTICLE

WILEY **AJH**



Ruxolitinib-associated infections: A systematic review and meta-analysis

Federico Lussana¹  | Marco Cattaneo² | Alessandro Rambaldi^{1,3} | Alessandro Squizzato⁴

Case Report

Tuberculosis and atypical mycobacterial infections in ruxolitinib-treated patients with primary or secondary myelofibrosis or polycythemia vera

Sylvain Lescuyer^{a,*}, Marie-Pierre Ledoux^a, Simon Gravier^a, Shanti Natarajan-Amé^a, Céline Duval^a, Frédéric Maloïsel^b, Laurent Mauvieux^{c,d}, Elise Toussaint^a, Luc-Matthieu Fornecker^{a,c}, Raoul Herbrecht^{a,c}

^a Department of Oncology and Haematology, Hôpitaux Universitaires de Strasbourg, Strasbourg, France

^b Clinique Sainte Anne, Strasbourg, France

^c Université de Strasbourg, Inserm UMR-S1113/IRFAC, Strasbourg, France

^d Laboratory of Haematology, Hôpitaux Universitaires de Strasbourg, Strasbourg, France



Disseminated tuberculosis associated with ruxolitinib

Leukemia (2014) **28**, 1750–1751; doi:10.1038/leu.2014.104

Infectious work-up was initially negative, but the patient continued to experience daily fevers, night sweats and anorexia.



Case Report

Tuberculosis reactivation related with ruxolitinib in a patient with primary myelofibrosis

Mehmet Sezgin Pepeler¹, Zübeyde Nur Özkurt¹, Özlem Tunçcan Güzel², Nalan Akyürek³

¹ Department of Hematology, Gazi University Faculty of Medicine, Faculty of Medicine, Gazi University, Ankara, Turkey

² Department of Infectious Diseases, Gazi University Faculty of Medicine, Faculty of Medicine, Gazi University, Ankara, Turkey

³ Department Pathology, Gazi University Faculty of Medicine, Faculty of Medicine, Gazi University, Ankara, Turkey

Hindawi Publishing Corporation
Case Reports in Infectious Diseases
Volume 2015, Article ID 284168, 3 pages
<http://dx.doi.org/10.1155/2015/284168>

Case Report

Ruxolitinib Associated Tuberculosis Presenting as a Neck Lump

Eamon Shamil, David Cunningham, Billy L. K. Wong, and Piyush Jani

ENT Department, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge CB2 0QQ, UK

Case Report

Reactivation of Pulmonary Tuberculosis following Treatment of Myelofibrosis with Ruxolitinib

Maheen Z. Abidi,¹ Javeria Haque,² Parvathi Varma,³ Horatiu Olteanu,⁴ Guru Subramanian Guru Murthy,⁵ Binod Dhakal,⁵ and Parameswaran Hari⁵

¹ Division of Infectious Diseases, Department of Medicine, University of Colorado, Denver, CO, USA

² Division of Infectious Diseases, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA

³ University of Birmingham Medical School, Edgbaston, Birmingham, UK

⁴ Pathology, Medical College of Wisconsin, Milwaukee, WI, USA

⁵ Pathology and Oncology, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA

Case Report

Ruxolitinib-associated tuberculosis – A rare complication of a novel drug!

Vinod R Patil, Chandrakala S, Nilesh P Wasekar, Farah Jijina, Aniket B Mohite

Department of Clinical Hematology, Seth GS Medical College & KEM Hospital, Mumbai, Maharashtra, India

Correspondence to: Vinod R Patil, E-mail: dr.vrp85@gmail.com

Received: August 07, 2016; Accepted: September 12, 2016

Internal Medicine
The Japanese Society of Internal Medicine

doi: 10.2169/internalmedicine.9165-17
Intern Med 57: 1297-1300, 2018
<http://internmed.jp>

[CASE REPORT]

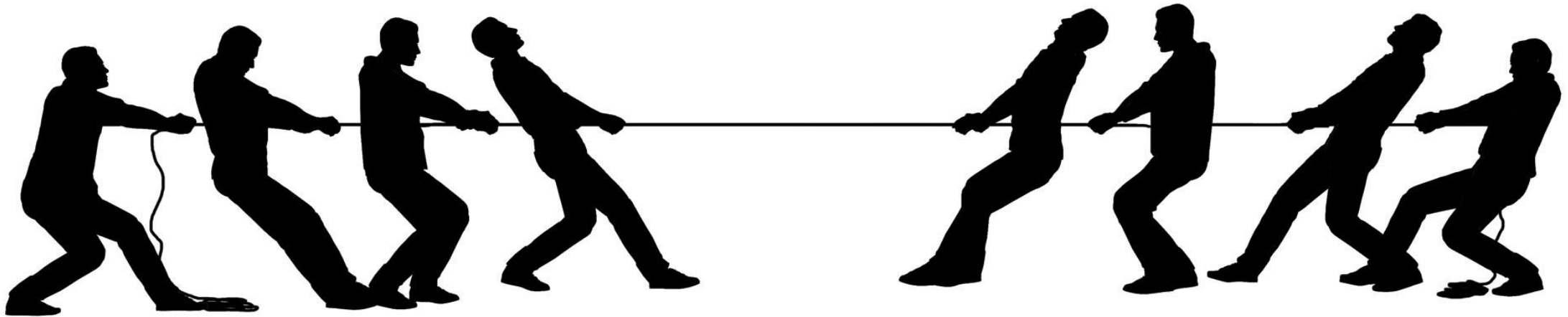
Fatal Disseminated Tuberculosis during Treatment with Ruxolitinib Plus Prednisolone in a Patient with Primary Myelofibrosis: A Case Report and Review of the Literature

Yasuhiro Tsukamoto^{1,2}, Junichi Kiyasu^{1,3}, Mariko Tsuda^{1,2}, Motohiko Ikeda¹, Motoaki Shiratsuchi², Yoshihiro Ogawa² and Yuji Yufu¹

Διαφυγή από την
ανοσοεπιτήρηση –
Κατάχρηση αμυντικών
μηχανισμών προς όφελος
του ΜΒ



Ανοσολογική
Επαγρύπνηση– Δημιουργία
κοκκιώματος/ Ιστική βλάβη
ξενιστή



“Each defense mechanism is based on a subtle balance that, if altered, can lean to one side to favor Mtb proliferation, resulting in disease progression and on the other to the host tissue damage by the immune system itself”

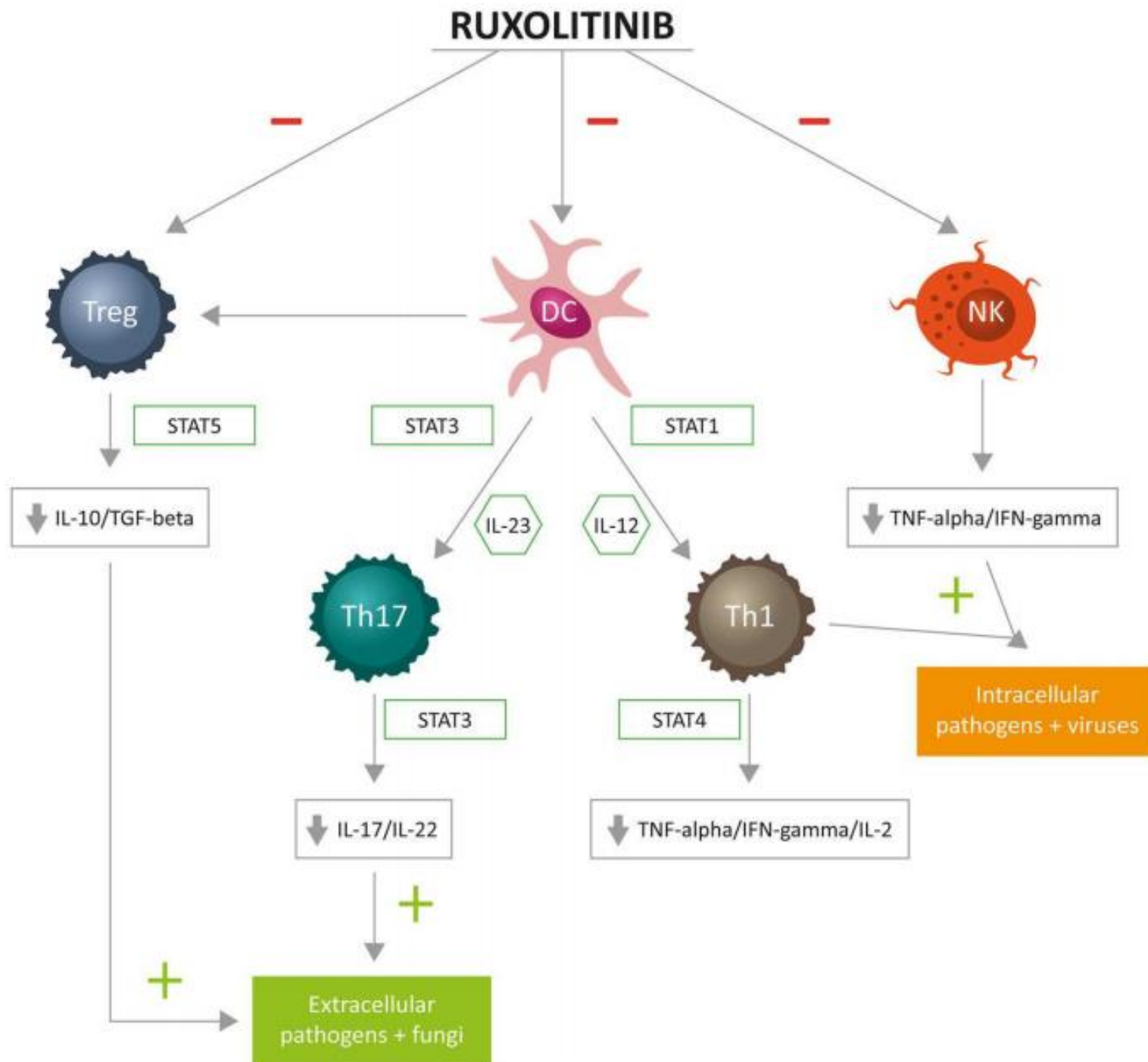
MINI REVIEW
published: 27 August 2019
doi: 10.3389/fped.2019.00350



Immune Response to *Mycobacterium tuberculosis*: A Narrative Review

Maurizio de Martino, Lorenzo Lodi, Luisa Galli and Elena Chiappini*

Department of Health Sciences, University of Florence, Florence, Italy



Mechanisms Underlying the Anti-inflammatory and Immunosuppressive Activity of Ruxolitinib

Elena Maria Elli^{1*}, Claudia Barà², Francesco Mendicino³, Francesca Palandri⁴ and Giuseppe Alberto Palumbo^{5*}

¹ Hematology Division and Bone Marrow Transplant Unit, Ospedale San Gerardo, ASST Monza, Monza, Italy, ² Department of Clinical and Experimental Medicine, Section of Hematology, University of Pisa, Pisa, Italy, ³ Hematology Unit, Department of Hemato-Oncology, Ospedale Annunziata, Cosenza, Italy, ⁴ Institute of Hematology "L. and A. Seràgnoli", Sant'Orsola-Malpighi University Hospital, Bologna, Italy, ⁵ Dipartimento di Scienze Mediche, Chirurgiche e Tecnologie Avanzate "G.F. Ingrassia", University of Catania, Catania, Italy

“Increasing evidence from pre-clinical and clinical data suggest that ruxolitinib has immunosuppressive effects : i) it interferes with the **signaling of several cytokines and growth factors** that are relevant for the immune function and lowers pro-inflammatory cytokines in MF patients; ii) it has been associated with **down-regulation of Tregs** and **impairment of the dendritic cell function** resulting in impaired CD41 and CD81 T-cell priming both in vitro and in vivo, iii) it **impairs natural killer (NK) cell function** in MPN patients. These immunosuppressive properties may play a role in the risk of infections in patients on treatment with ruxolitinib, although the exact relationship between the effects on immune function and the incidence of infections remains to be elucidated.”

Received: 19 October 2017 | Revised: 13 November 2017 | Accepted: 14 November 2017
DOI: 10.1002/ajh.24976

RESEARCH ARTICLE



Ruxolitinib-associated infections: A systematic review and meta-analysis

Federico Lussana¹ | Marco Cattaneo² | Alessandro Rambaldi^{1,3} |
Alessandro Squizzato⁴

MH ΕΙΔΙΚΗ ΑΝΟΣΙΑ

“NK cells can control mycobacterial growth indirectly via immune stimulation through macrophage activation and directly via cytotoxic mechanisms, including the production of cytoplasmic granules containing perforin, granulysin and granzyme. Additionally, NK cells [...] inhibit Mtb intracellular growth [...], promote $\gamma\delta$ T-cell proliferation [...] There are indications that NK cells may be functionally impaired during TB.”

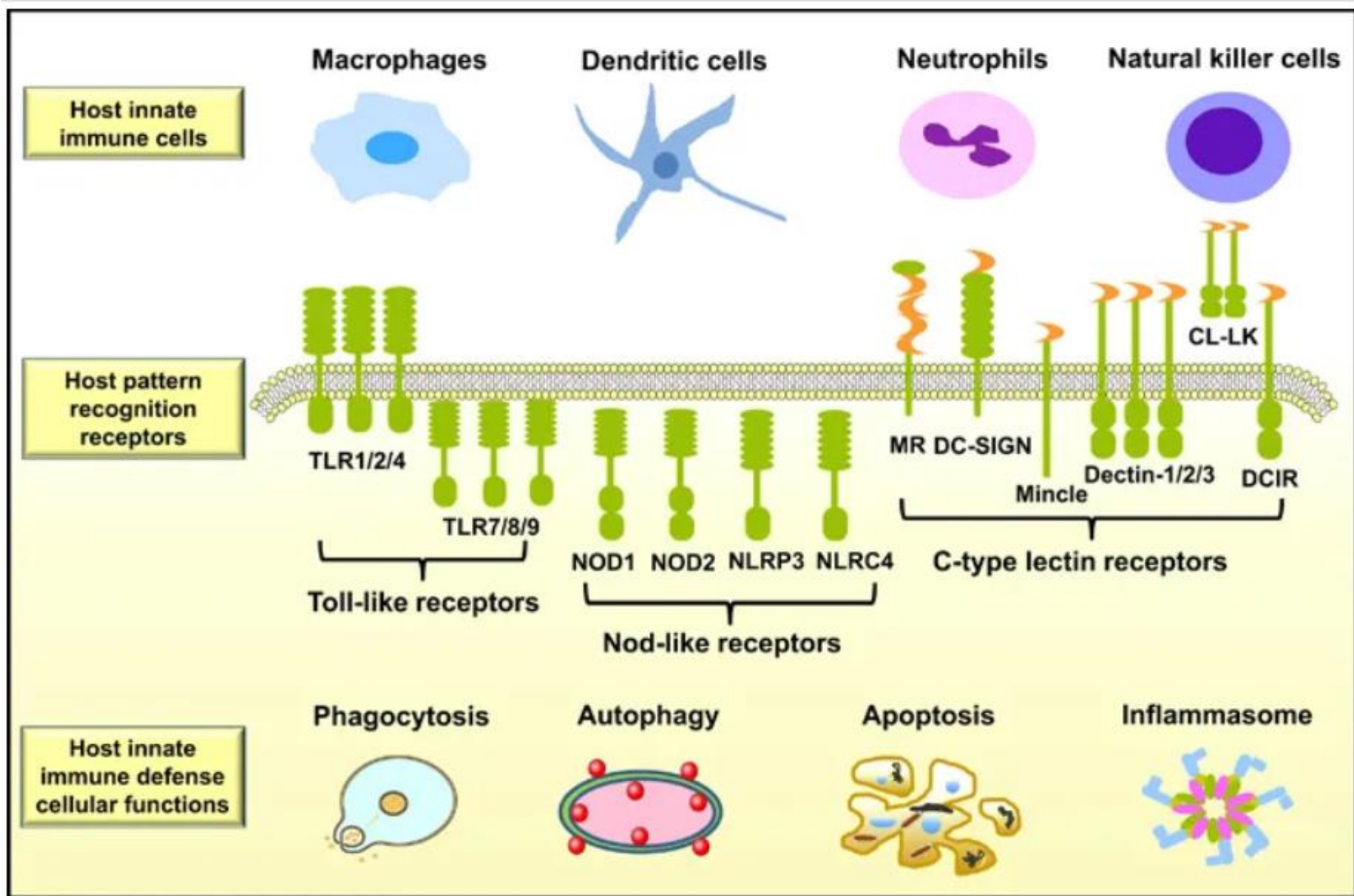
“Dendritic cells DCs play a central role in Mtb antigen presentation and are thus critical in bridging innate and adaptive immunity.”

Cellular & Molecular Immunology (2017) 14, 963–975
© 2017 CSI and USTC All rights reserved 2042-0226/17 \$32.00
www.nature.com/cmi

REVIEW

Innate immunity in tuberculosis: host defense vs pathogen evasion

Cui Hua Liu^{1,2}, Haiying Liu³ and Baoxue Ge⁴



“...human monocytes are predisposed to differentiate towards an anti-inflammatory (M2-like) macrophage activation program characterized by the **CD16⁺ CD163⁺ MerTK⁺ pSTAT3⁺ phenotype** and functional properties such as enhanced protease-dependent motility, pathogen permissivity and immunomodulation. This process is **dependent on STAT3 activation, and loss-of-function experiments point towards a detrimental role in host defense against TB.** Importantly, we provide a critical correlation between the abundance of the **CD16⁺ CD163⁺ MerTK⁺ pSTAT3⁺ cells** and the progression of the disease either at the local level in a non-human primate tuberculous granuloma context, or at the systemic level through the detection of the soluble form of CD163 in human sera.”

ORIGINAL ARTICLE

Cell Research (2015) 25:1333–1351.
© 2015 IBCB, SIBS, CAS. All rights reserved 1001-0602/15 \$ 32.00
www.nature.com/cr



Tuberculosis is associated with expansion of a motile, permissive and immunomodulatory CD16⁺ monocyte population via the IL-10/STAT3 axis

Claire Lastrucci^{1,2}, Alan Bénard^{1,2,*}, Luciana Balboa^{3,*}, Karine Pingris^{1,2}, Shanti Souriant^{1,2}, Renaud Poincloux^{1,2}, Talal Al Saati⁴, Voahangy Rasolofo⁵, Pablo González-Montaner⁶, Sandra Inwentarz⁶, Eduardo Jose Moraña⁶, Ivanela Kondova⁷, Frank AW Verreck⁷, Maria del Carmen Sasiain¹, Olivier Neyrolles^{1,2}, Isabelle Maridonneau-Parini^{1,2}, Geanncarlo Lugo-Villarino^{1,2,*}, Céline Cougoule^{1,2,*}

Invited Review

T cells and adaptive immunity to *Mycobacterium tuberculosis* in humans

Luke D. Jasenosky, Thomas J. Scriba, Willem A. Hanekom, Anne E. Goldfeld

bjh research paper

JAK1/2 inhibition impairs T cell function *in vitro* and in patients with myeloproliferative neoplasms

 **frontiers**
in Oncology

REVIEW
published: 07 November 2019
doi: 10.3389/fonc.2019.01186

Mechanisms Underlying the Anti-inflammatory and Immunosuppressive Activity of Ruxolitinib

Elena Maria Elli^{1*}, Claudia Baratè², Francesco Mendicino³, Francesca Palandri⁴ and Giuseppe Alberto Palumbo^{5*}

Sowmya Parampalli Yajnanarayana,^{1*}
Thomas Stübiger,^{2*} Isabelle Cornez,¹
Haefaa Alchalby,² Kathrin Schönberg,¹
Janna Rudolph,¹ Ioanna Trivai,²
Christine Wolschke,² Annkristin Heine,¹
Peter Brossart,¹ Nicolaus Kröger² and
Dominik Wolf¹

¹Department of Internal Medicine III, Oncology, Haematology and Rheumatology, University Hospital Bonn (UKB), Bonn, and ²Department of Stem Cell Transplantation, University Medical Centre Hamburg, Hamburg, Germany

Received 29 November 2014; accepted for publication 4 February 2015

Neurotuberculosis: Control of Steroid-Refractory Paradoxical Inflammatory Reaction With Ruxolitinib

Yingda L. Xie,^{1,*} Fanny Ita-Nagy,² Ray Y. Chen,¹ Maura M. Manion,³ Irini Sereti,³ Luxin Pei,³ and Steven M. Holland⁴

¹Tuberculosis Research Section, Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA, ²New York University Langone, New York, New York, USA, ³Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA, and ⁴Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA



The Journal of
Immunology

Ruxolitinib, a selective JAK1/2 inhibitor, for the treatment of serious diseases caused by *Staphylococcus aureus* superantigens

Henry Carnes, Brittney Mehrkens, Molly Stegman and Govindarajan Rajagopalan

J Immunol May 1, 2019, 202 (1 Supplement) 190.34;

Novel mechanisms to inhibit HIV reservoir seeding using Jak inhibitors

Christina Gavegnano , Jessica H. Brehm , Franck P. Dupuy , Aarthi Talla, Susan Pereira Ribeiro, Deanna A. Kulpa, Cheryl Cameron, Stephanie Santos, Selwyn J. Hurwitz, Vincent C. Marconi, Jean-Pierre Routy, Laurent Sabbagh, Raymond F. Schinazi , Rafick Pierre Sékaly 

Published: December 21, 2017 • <https://doi.org/10.1371/journal.ppat.1006740>

FDA approves ruxolitinib for acute graft-versus-host disease

On May 24, 2019, the Food and Drug Administration approved ruxolitinib (JAKAFI, Incyte Corporation) for steroid-refractory acute graft-versus-host disease (GVHD) in adult and pediatric patients 12 years and older.

Approval was based on Study INCB 18424-271 (NCT02953678), an open-label, single-arm, multicenter study of ruxolitinib that enrolled 49 patients with steroid-refractory acute GVHD Grades 2 to 4 (Mount Sinai Acute GVHD International Consortium criteria) occurring after allogeneic hematopoietic stem cell transplantation. Ruxolitinib was administered at 5 mg twice daily, and the dose could be increased to 10 mg twice daily after 3 days in the absence of toxicity.

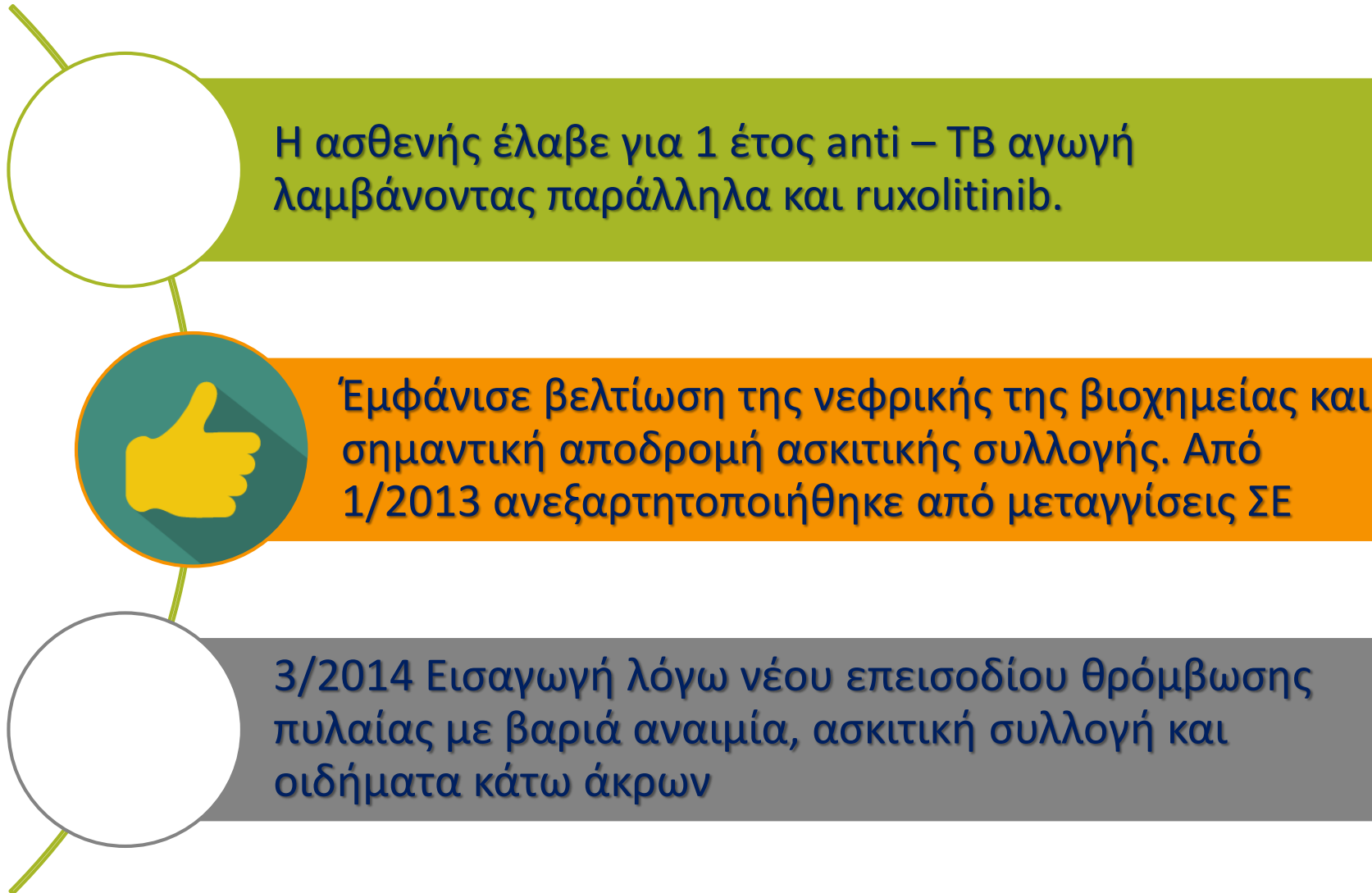
U.S. FOOD & DRUG
ADMINISTRATION


ΣΥΝΟΨΙΖΟΝΤΑΣ

Ασθενής με ιστορικό θρόμβωσης πυλαίας και
ηπατοπάθεια άγνωστης αρχής



ΠΟΡΕΙΑ ΝΟΣΟΥ



ΣΗΜΕΡΑ

Η ασθενής παραμένει σταθερή με μικρές διακυμάνσεις αιματολογικών παραμέτρων και χωρίς σημαντικά β – συμπτώματα.

Σπλήνας~17.5 εκ.

Από το 2014 έως σήμερα έχει νοσηλευτεί 2 φορές (λοίμωξη μαλακών μορίων Δε κάτω άκρου 2017, λοίμωξη αναπνευστικού 2019).

Η ασθενής διέκοψε τη θεραπεία με ruxolitinib από έτους. Πλάνο για συνέχιση με χορήγηση επόμενης γενιάς αναστολέα JAK κινάσης momelotinib

Ευχαριστώ!