LEUKEMIA2022

Rome, Hotel NH Collection - Vittorio Veneto

May 5-6, 2022

AIL President: G. Toro
Coordinators: A.M. Carella, S. Amadori

UNDER THE AUSPICES OF:

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

GITMO

SIE - Società Italiana di Ematologia

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CHRONIC LYMPHOCYTIC LEUKEMIA

Autoimmune complications

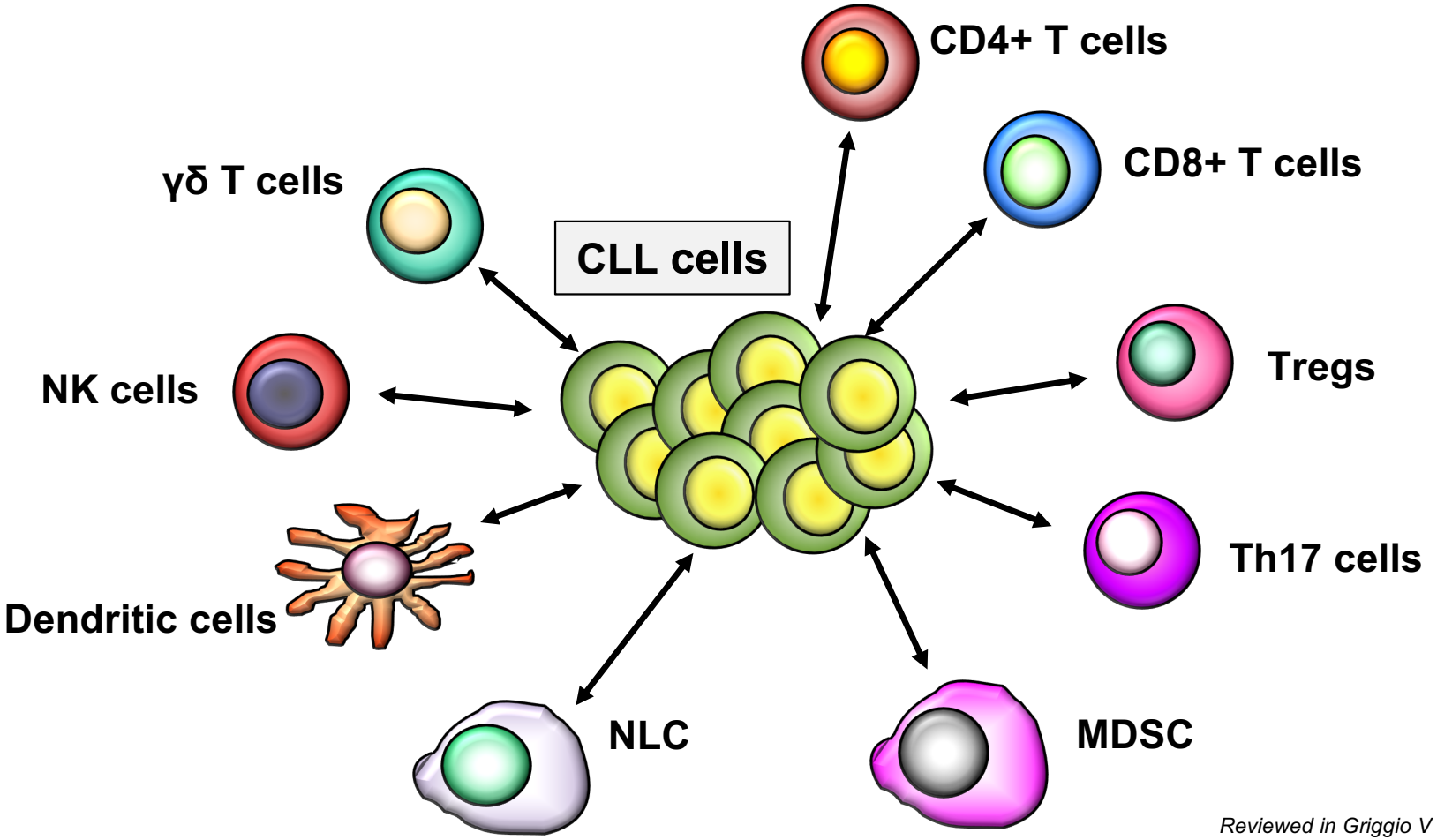
Marta Coscia

Conflict Of Interests - M arta Coscia

- Research fundings: Abbvie, Janssen, Karyopharm

- Advisory boards/honoraria: Abbvie, Janssen, Astrazeneca

CLL is characterized by a wide range of tumor-induced alterations



Reviewed in Griggio V et al, Front Immunol 2021

CLL is a model disease for secondary immune dysregulation

Modified from Niemann C, IWCLL meeting 2021

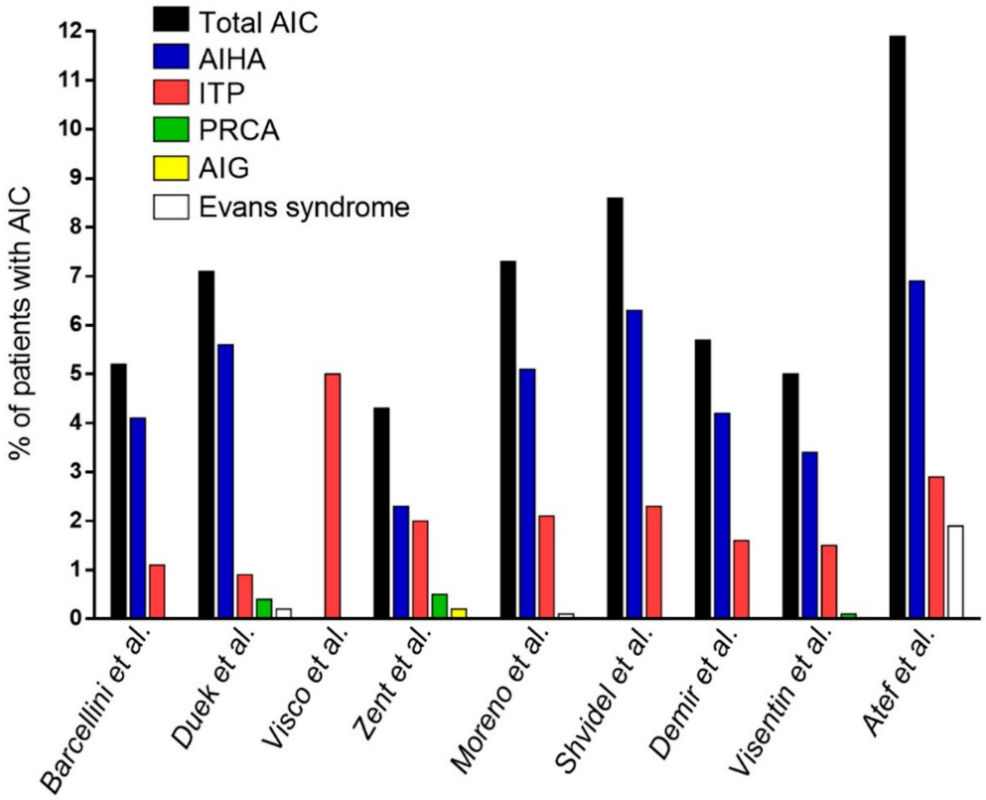
- **Infections**
- **Lower response to vaccines**
- **Second primary malignancies**
- **Autoimmune manifestations**

Autoimmune manifestations in CLL

- Reported in up to a quarter of CLL patients
- The most significant autoimmune manifestations are autoimmune cytopenias (AIC)
- Non-hematologic autoimmunity is less frequent, the most common being bullous pemphigus, Hashimoto's thyroiditis, rheumatoid arthritis, vasculitis, and acquired angioedema
- Non-hematologic autoimmunity is often observed in CLL patients with an initial stage of disease

Reviewed in Vitale C et al., Cancers 2020

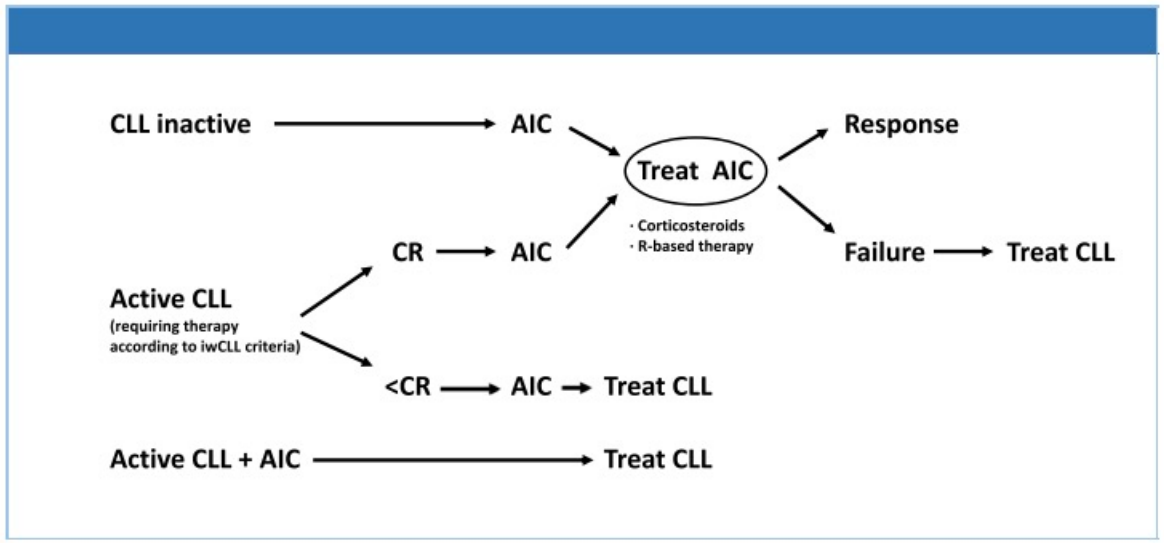
Autoimmune cytopenias in CLL



- Most frequent forms of AIC are AIHA (i.e. warm and cold AIHA) and ITP
- Several studies reported an association between AIC and CLL adverse prognostic factors
- Relapse after first line of treatmens is commom
- AIC frequently require multiple treatments
  - 43% one AIHA treatment
  - 57% multiple AIHA treatments

Reviewed in Vitale C et al., Cancers 2020

AIC treatment in patients with CLL



First-Line Treatment and its Efficacy for AIHA and ITP in CLL

Treatment and References	Recommended Dose	ORR, %
Warm AIHA		
Prednisone[17]	1 mg/kg per day for 3–4 wk (up to 2 mg/kg per day)	80–100
Dexamethasone[17]	40 mg/d for 4 d (up to 6 cycles every 2–4 wk)	
Cold AIHA		
Rituximab[116,120,121]	375 mg/m^2 weekly for 4 wk	50–80
ITP		
Prednisone[122]	1 mg/kg per day for 3–4 wk (up to 2 mg/kg per day)	70–90
Dexamethasone[122]	40 mg/d for 4 d (up to 6 cycles every 2–4 wk)	
IVIG +/– corticosteroids[122]	0.4 g/kg per day for 5 d or 1 g/kg per day for 2 d	90

d, days; IVIG, intravenous immunoglobulin; wk, weeks.

When AIC directed therapies are not sufficient to control the autoimmune cytopenia, a CLL directed treatment is recommended

Albiol N, Moreno C. Cancer J. 2021

AIC in the era of targeted drugs - Open questions

- What happens to patients with pre-existing AIC starting a targeted agent?
- Can targeted treatments improve AIC?
- How should AIC be managed?

Multicentric, retrospective study

Preexisting and treatment-emergent autoimmune cytopenias in patients with CLL treated with targeted drugs

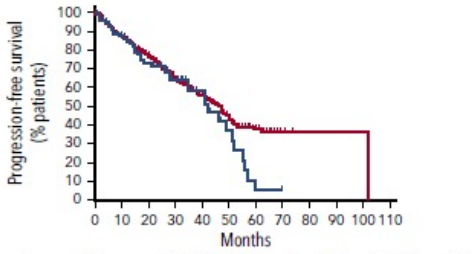
Candida Vitale,[1] Chiara Salvetti,[1] Valentina Griggio,[1] Marika Porrazzo,[2] Luana Schiattone,[3] Giulia Zamprogna,[4] Andrea Visentin,[5] Francesco Vassallo,[6] Ramona Cassin,[7] Gian Matteo Rigolin,[8] Roberta Murru,[9] Luca Laurenti,[10] Paolo Rivela,[11] Monia Marchetti,[11] Elsa Pennese,[12] Massimo Gentile,[13] Elia Boccellato,[1] Francesca Perutelli,[1] Maria Chiara Montalbano,[1] Lorenzo De Paoli,[14] Gianluigi Reda,[7] Lorella Orsucci,[6] Livio Trentin,[5] Antonio Cuneo,[8] Alessandra Tedeschi,[4] Lydia Scarfò,[3,15] Gianluca Gaidano,[14] Francesca Romana Mauro,[2] Robin Foà,[2] Mario Boccadoro,[1] and Marta Coscia[1]

blood® 24 JUNE 2021 | VOLUME 137, NUMBER 25

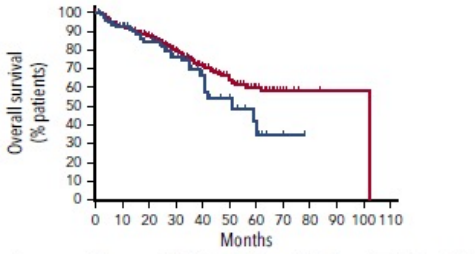
Overall	**n=815**
Ibrutinib	n=572
Idelalisib+R	n=143
Venetoclax	n=100

PFS and OS in patients with and without preexisting AICs

All patients

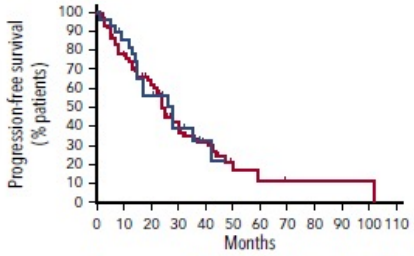


PFS	Median	12-month	24-month	36-month
Preexisting AICs	42 months	86%	72%	58%
No preexisting AICs	47 months	87%	74%	61%

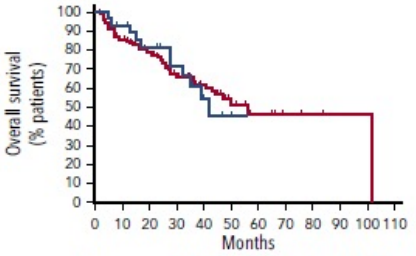


OS	Median	12-month	24-month	36-month
Preexisting AICs	51 months	93%	85%	70%
No preexisting AICs	102 months	92%	85%	75%

Idelalisib

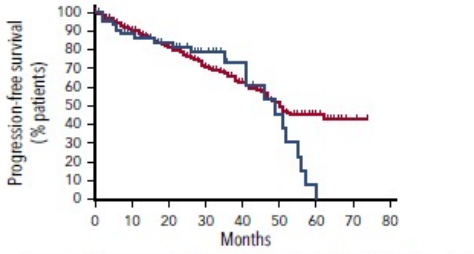


PFS	Median	12-month	24-month	36-month
Preexisting AICs	28 months	86%	56%	33%
No preexisting AICs	24 months	76%	57%	35%

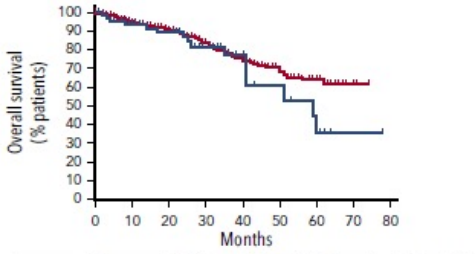


OS	Median	12-month	24-month	36-month
Preexisting AICs	42 months	93%	82%	61%
No preexisting AICs	56 months	86%	76%	66%

Ibrutinib

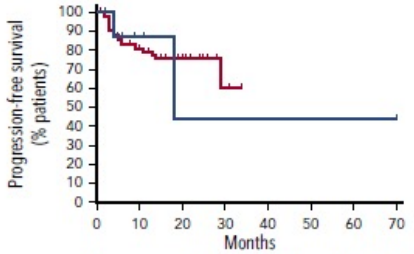


PFS	Median	12-month	24-month	36-month
Preexisting AICs	49 months	86%	82%	73%
No preexisting AICs	50 months	90%	79%	67%

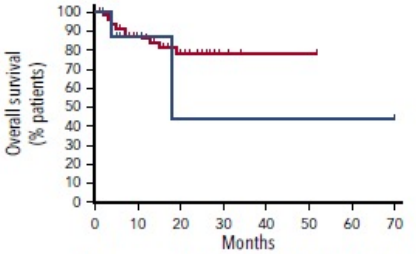


OS	Median	12-month	24-month	36-month
Preexisting AICs	59 months	93%	89%	77%
No preexisting AICs	NR	95%	88%	78%

Venetoclax



PFS	Median	12-month	24-month	36-month
Preexisting AICs	18 months	87%	44%	44%
No preexisting AICs	NR	79%	76%	60%

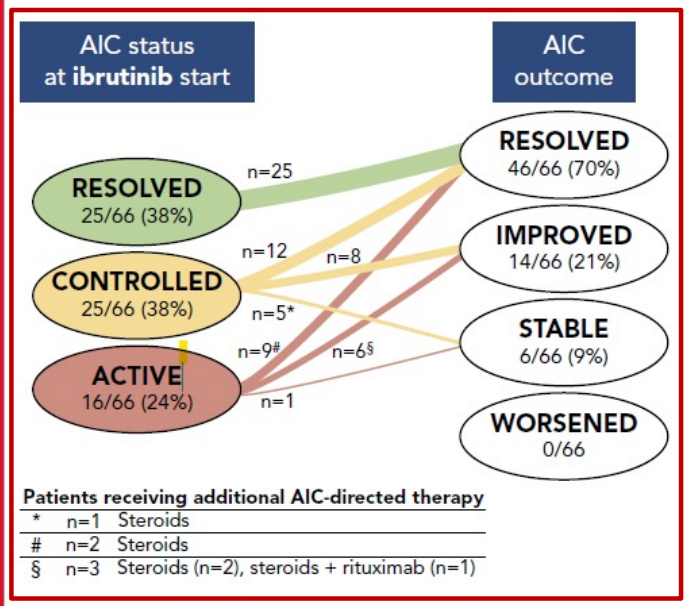


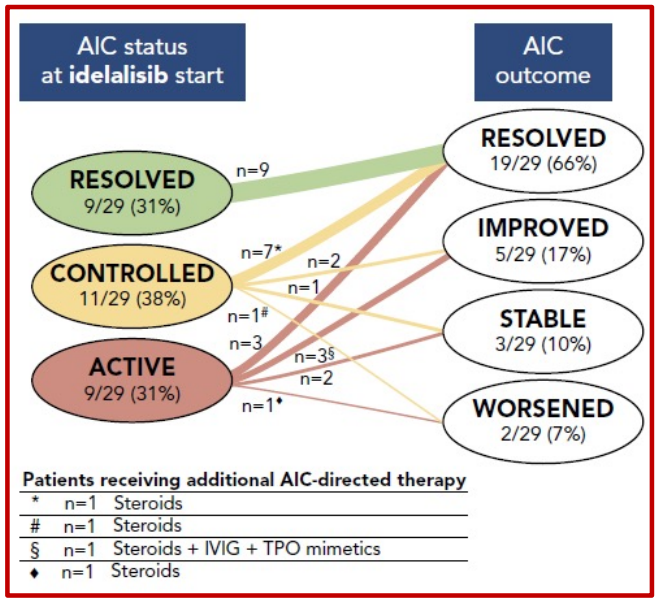
OS	Median	12-month	24-month	36-month
Preexisting AICs	18 months	87%	44%	44%
No preexisting AICs	NR	86%	78%	78%

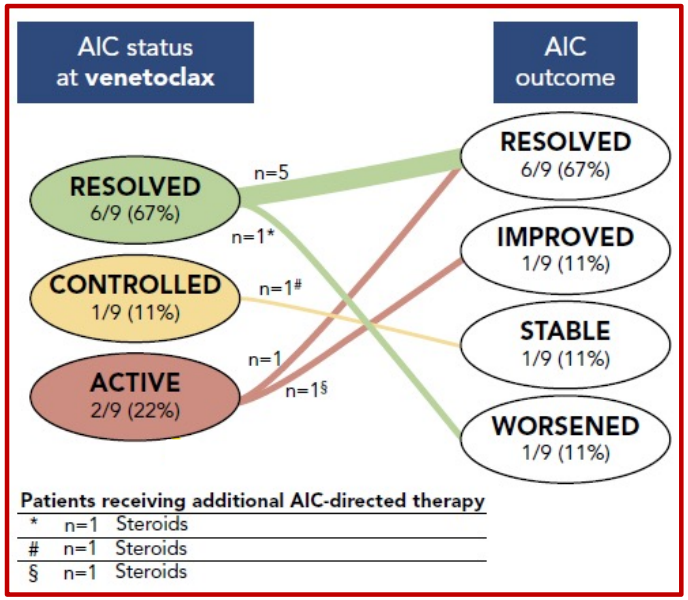
- A history of pre-existing AICs was reported in 13% of 815 patients
- Patients with or without pre-existing AICs did not significantly differ in terms of PFS and OS

Vitale C et al., Blood 2021

Preexisting AIC - outcome





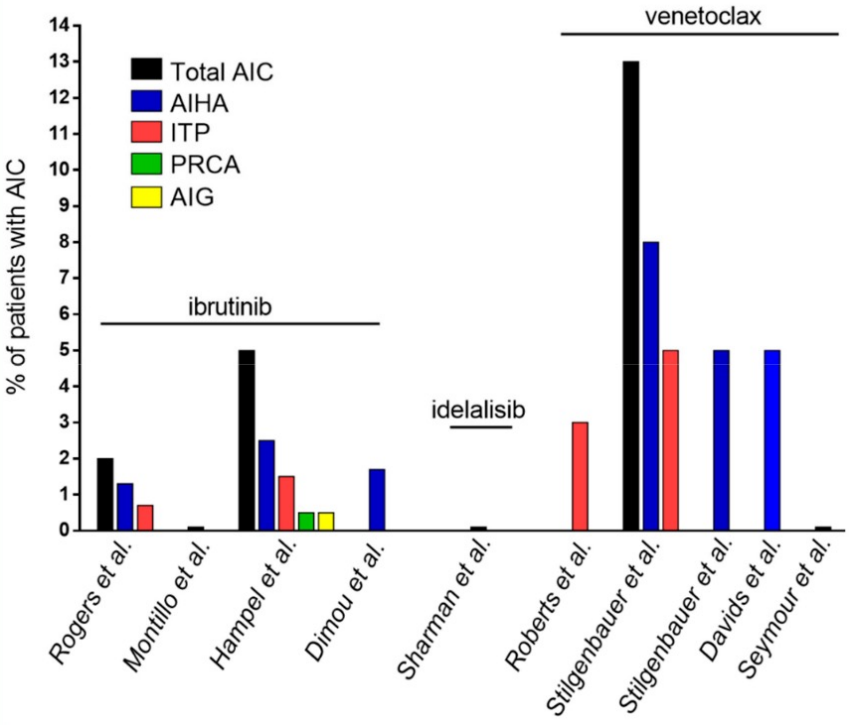


Consistent with Quinquenel et al. → Review of patients with active AIC starting CLL treatment (n=44)

- **Ibrutinib** (n=25) 72% on steroids 92% ORR
- **Idelalisib** (n=19) 63% on steroids 95% ORR

Vitale C et al., Blood 2021
Quinquenel et al, AJH 2019

Treatment-emergent AIC



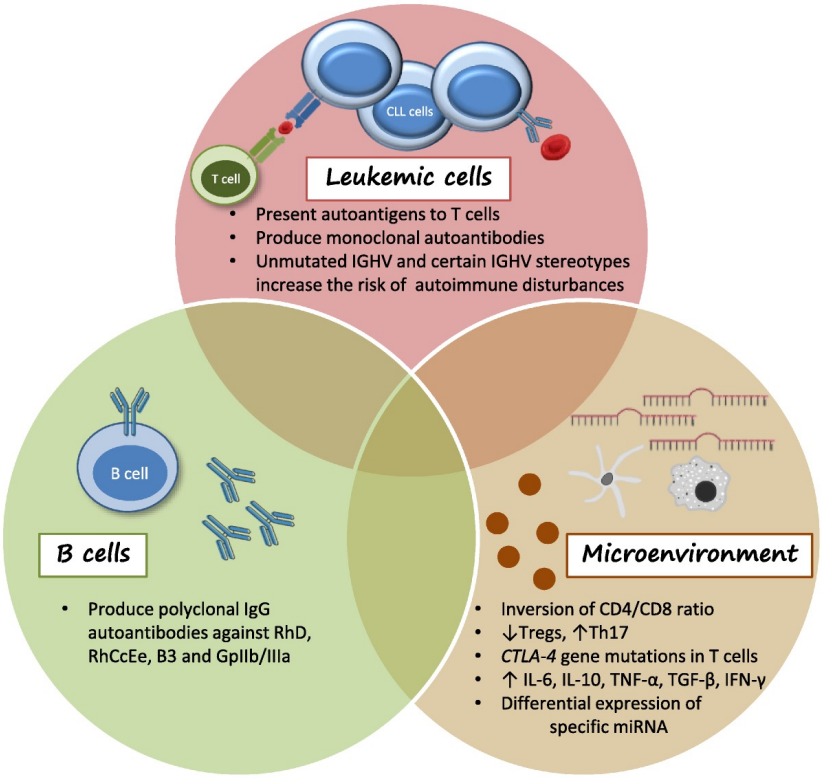
	Ibrutinib	Idelalisib	Venetoclax
N. Pts	506	114	91
AIC accurrence	5/506 (1%)	1/114 (0.9%)	6/91 (7%)
N.episodes/ 1000 pts/year	5	6	67

In 10 (83%) out of 12 patients with treatment-emergent AIC the targeted drug was continued or only temporarily held/dose-reduced

Vitale C et al., Cancers 2020
Vitale C et al. Blood 2021

AIC in the era of targeted drugs - Open questions

- What happens to patients with pre-existing AIC starting a targeted agent?
- Can targeted treatments improve AIC?
- How should AIC be managed?

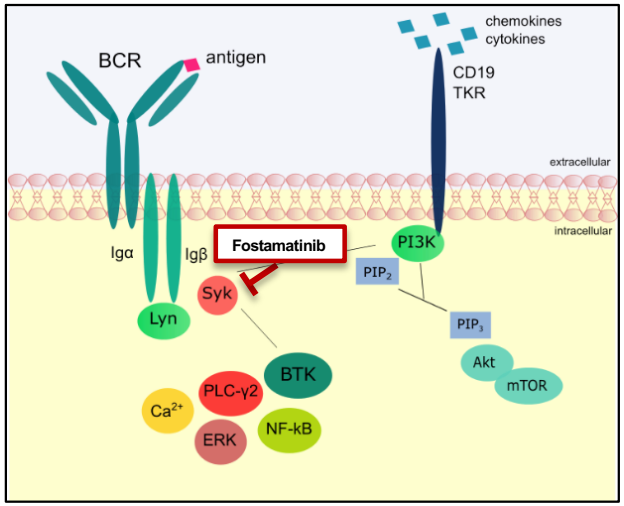


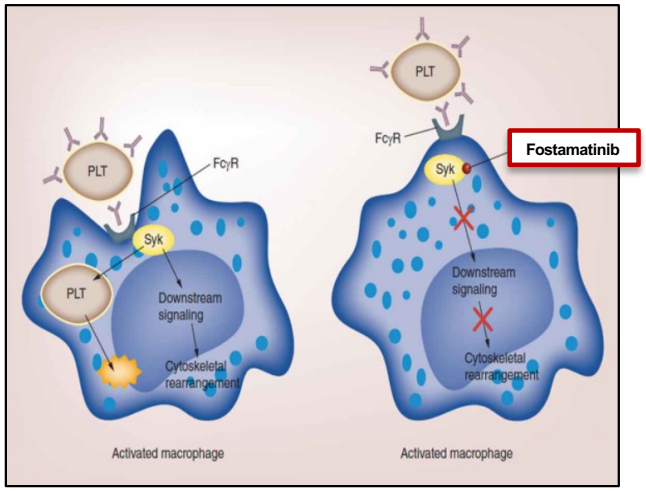
BCR signalling inhibition can be active on

- Leukemic B cells producing monoclonal autoAb
- Non-leukemic B cells producing polyclonal autoAb

Effects of BCR inhibitors on AIC

- Low rates of treatment-emergent AIC during treatment with Ibrutinib and idelalisib
- Low recurrence of pre-existing AIC
- In general, improvement of active AIC during treatment



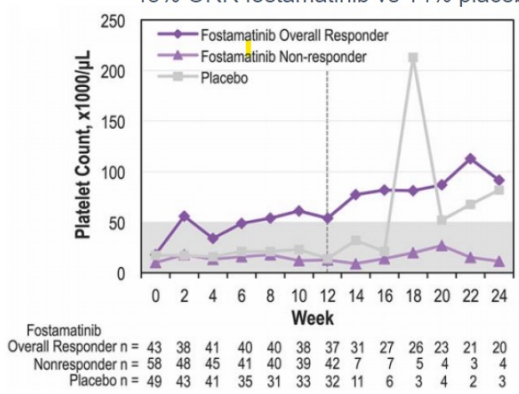


Fostamatinib → Potent oral inhibitor of spleen tyrosine kinase (SYK)

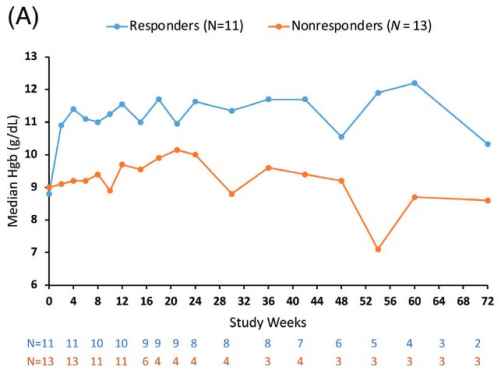
- Mechanism of action: a) reduced production of pathogenic autoantibodies; b) decreased macrophage Fcγ-R–mediated platelet destruction.
- It blocks the clearance of anti-body coated cells in mice
- FDA approved for treatment of chronic ITP in April 2018

Pooled Phase 3 Studies in Chronic ITP

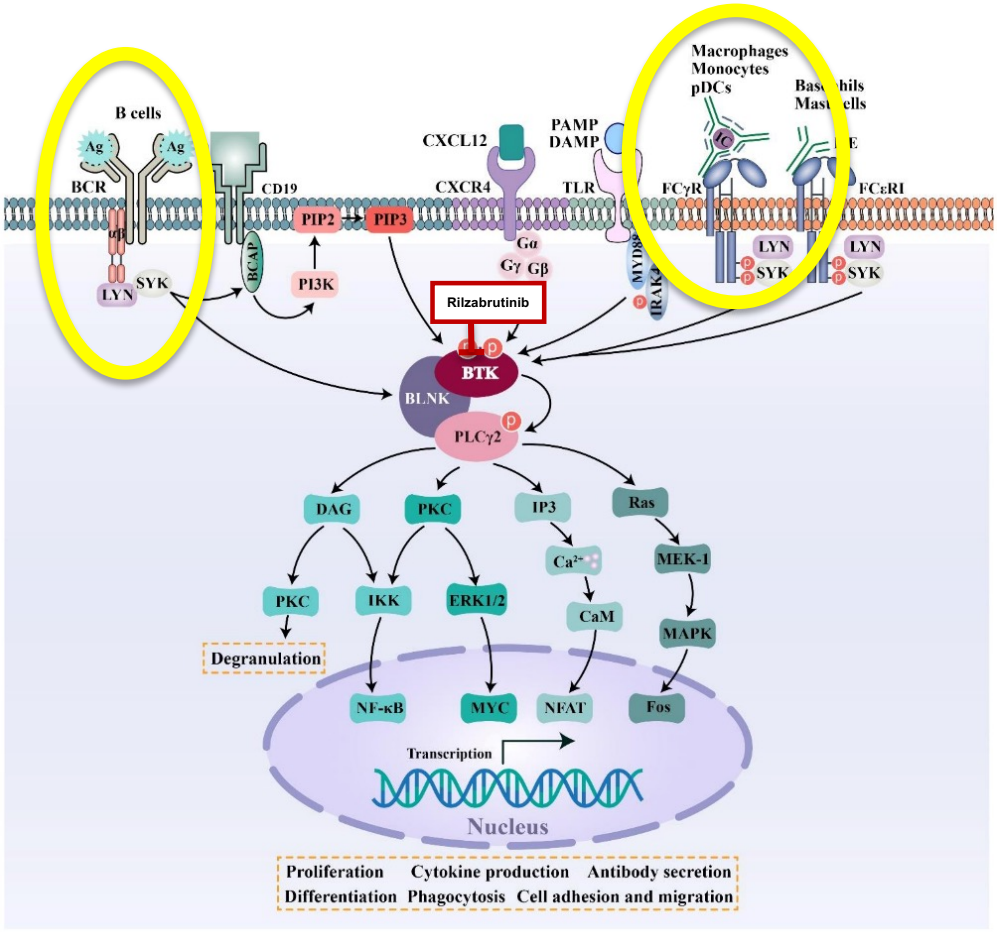
- Randomized 2:1 (n=101 fosta, n=49 placebo)
- 43% ORR fostamatinib vs 14% placebo



Phase 2 Study in Relapsed AIHA → 46% ORR



Modified from Rogers KA, IWCLL 2021; Bussel et al., AJH 2018; Rogers et al., AJH 2022



Rilzabrutinib

Selective oral reversible covalent inhibitor of BTK

- Mechanism of action: a) reduced production of pathogenic autoantibodies; b) decreased macrophage Fcγ-R–mediated platelet destruction.
- It has shown to block clearance of anti-body coated cells in mice

ORIGINAL ARTICLE

Rilzabrutinib, an Oral BTK Inhibitor, in Immune Thrombocytopenia

David J. Kuter, M.D., Merlin Efraim, M.D., Jiri Mayer, M.D., Marek Trněný, M.D., Vickie McDonald, M.D., Robert Bird, M.B., B.S., Thomas Regenbogen, M.D., Mamta Garg, M.D., Zane Kaplan, M.D., Nikolay Tzvetkov, M.D., Philip Y. Choi, M.D., A.J. Gerard Jansen, M.D., Milan Kostal, M.D., Ross Baker, M.D., Jaromir Gumulec, M.D., Eun-Ju Lee, M.D., Ilona Cunningham, M.D., Isaac Goncalves, M.D., Margaret Warner, M.D., Ralph Boccia, M.D., Terry Gernsheimer, M.D., Waleed Ghanima, M.D., Olga Bandman, M.D., Regan Burns, B.A., Ann Neale, B.S., Dolca Thomas, M.D., Puneet Arora, M.D., Beiyao Zheng, Ph.D., and Nichola Cooper, M.D.

The NEW ENGLAND JOURNAL of MEDICINE
N ENGL J MED 386;15 NEJM.ORG APRIL 14, 2022

Phase I/II study

R/R patients with ITP (n=60)

- Of the 45 patients receiving rilzabrutinib at the highest dose (i.e. 400 mg twice daily), 18 (40%) met the primary end point of platelet response
- The median time to the first platelet count of at least 50×10e3 per cubic millimeter was 11.5 days.

Kuter DJ et al. N Engl J Med 2022

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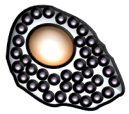
Ibrutinib has broader immunomodulatory effects (*on-target* and *off-target*)

Neutrophil development, function and recruitment

Mueller H et al., Blood. 2010
Fiedler K et al., Blood. 2011

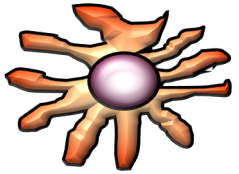


Mast cell activation, degranulation and cytokine production

Hata D et al., J Exp Med. 1998
Iwaki S et al., J Biol Chem. 2005

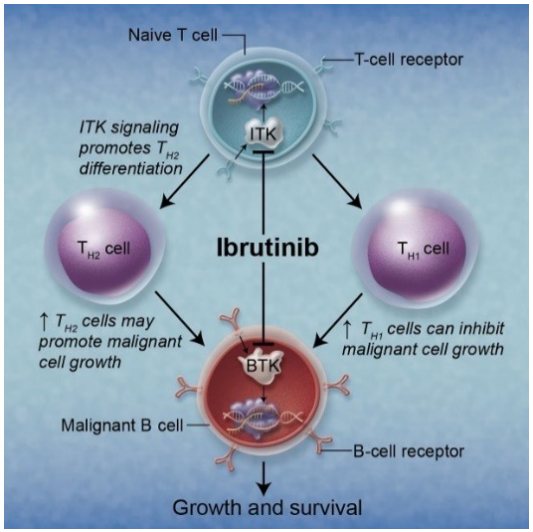
Macrophage survival and oxydative activity

Melcher M et al., J Immunol. 2008
Vijayan V et al., J Immunol. 2011



DC maturation and function

Kawakami Y et al., PNAS. 2006



Dubovsky JA et al., Blood. 2013; *Long et al., J Clin Invest. 2017*

LONG-TERM TREATMENT WITH IBRUTINIB MODULATES PHENOTYPIC AND FUNCTIONAL FEATURES OF IMMUNE CELL COMPARTMENTS IN CHRONIC LYMPHOCYTIC LEUKEMIA

F. Perutelli[1,2], R. Jones[1,2], V. Griggio[1,2], C. Vitale[1,2], F.R. Mauro[3], C. Salvetti[1,2], E. Boccellato[1,2], L. Comba[1,2] D. Pietrasanta[4], I.D. Vincelli[5], P. Ghia[6], G. Del Poeta[7], G. Gaidano[8], V. Gattei[9], R. Foà[3], M. Coscia[1,2]

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fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

Nuova proposta GIMEMA NP21-369

Tipologia Studio: Interventistico

Ibrutinib for the Treatment of Autoimmune Hemolytic Anemia in Patients With Chronic Lymphocytic Leukemia (CLL) or CLL-like monoclonal B-cell lymphocytosis

Sponsor — Fondazione GIMEMA – Franco Mandelli ONLUS
Principal Investigator — Prof.ssa Marta Coscia

Obiettivo primario dello studio: AIHA *overall response rate* (ORR) dopo 6 cicli di terapia (*28-day cycles*).

Disegno dello studio:
I pazienti riceveranno ibrutinib 420 mg/d PO per 12 cicli da 28 giorni, in assenza di progressione o tossicità inaccettabile.

Dimensione del campione: 45 pazienti ≅ 25 Centri partecipanti

CLL group - S.C. Ematologia U
A.O.U. Città della Salute e della Scienza di Torino

Candida Vitale

Elia Boccellato
Francesca Perutelli
Lorenzo Comba
Maria Chiara Montalbano

Valentina Griggio
Rebecca Jones

Our collaborators

AIC retrospective study

Marika Porrazzo
Luana Schiattone
Giulia Zamprogna
Andrea Visentin
Francesco Vassallo
Ramona Cassin
Gian M. Rigolin
Roberta Murru
Luca Laurenti
Paolo Rivela
Monia Marchetti
Chiara Salvetti
Elsa Pennese
Massimo Gentile
Lorenzo De Paoli
Gianluigi Reda
Lorella Orsucci
Livio Trentin
Antonio Cuneo
Alessandra Tedeschi
Lydia Scarfò
Gianluca Gaidano
Francesca R. Mauro
Robin Foà

Ibrutinib immune monitoring project

Francesca R. Mauro
Daniela Pietrasanta
Iolanda D. Vincelli
Lydia Scarfò
Giovanni Del Poeta
Valter Gattei
Robin Foà
Paolo Ghia
Gianluca Gaidano

DBMSS Dipartimento di Biotecnologie Molecolari e Scienze per la Salute
AZIENDA OSPEDALIERO - UNIVERSITARIA Città della Salute e della Scienza di Torino
fondazione GIMEMA onlus per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI
ASSOCIAZIONE ITALIANA CONTRO LEUCEMIE LINFOMI E MIELOMA