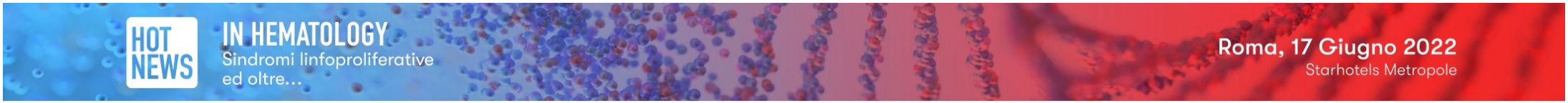
Caso Clinico 1: CLL

Fondazione Policlinico Universitario A. Gemelli –IRCCS, Roma

Innocenti Idanna

ROMA

17 Giugno 2022
Starhotels Metropole



La sottoscritta **Innocenti Idanna**

In qualità di relatore ai sensi dell'art. 76 sul Conflitto di Interessi, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

dichiara

che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

ABBVIE, Astrazeneca, Janssen, Beigene

Uomo di 52 aa: **Maggio 2009 diagnosi di LLC-B stadio A/0**

- ✓ **GB 25700/mmc** (**L 21500**) Hb 13 g/dl, MCV 87 fl, Plt 240000/ mmc, LDH 230 UI (N)
- ✓ Funzionalità epatica e renale nella norma; EP: 9 % (11-18) ipogammaglobulinemia
- ✓ **EOG:** lfn superficiali max 1,5 cm (laterocervicali, ascellari e inguinali), milza e fegato nella norma. *No* Sintomi B
- ✓ **Eco addome e linfonodi:** milza 12 cm, *lfn max 1.5 cm (laterocervicali, ascellari, inguinali)*
- ✓ **FISH:** *del 13q e del 11q positivo*, del 17p, tris 12 negativo; **IgVH** *non mutato 3-33*

→ Follow up osservazionale semestrale

- ❖ APR: IA → triatec; FAP in trattamento con $\mathcal{B}$ bloccanti; insufficienza venosa arti inferiori e pregressa TVP arto inferiore sinistro, obesita. A.Fisiologica: Nega allergie. Ex fumatore di 10 sigarette/die.
- ❖ A.Familiare: Coniugato, 2 figli in abs (maschio di 20 aa, femmina di 17 aa). 3 Fratelli: 1 sorella 55 aa aploidentica; 1 fratello 51 ex tossicodipendente; 1 sorella 53aa K tiroide

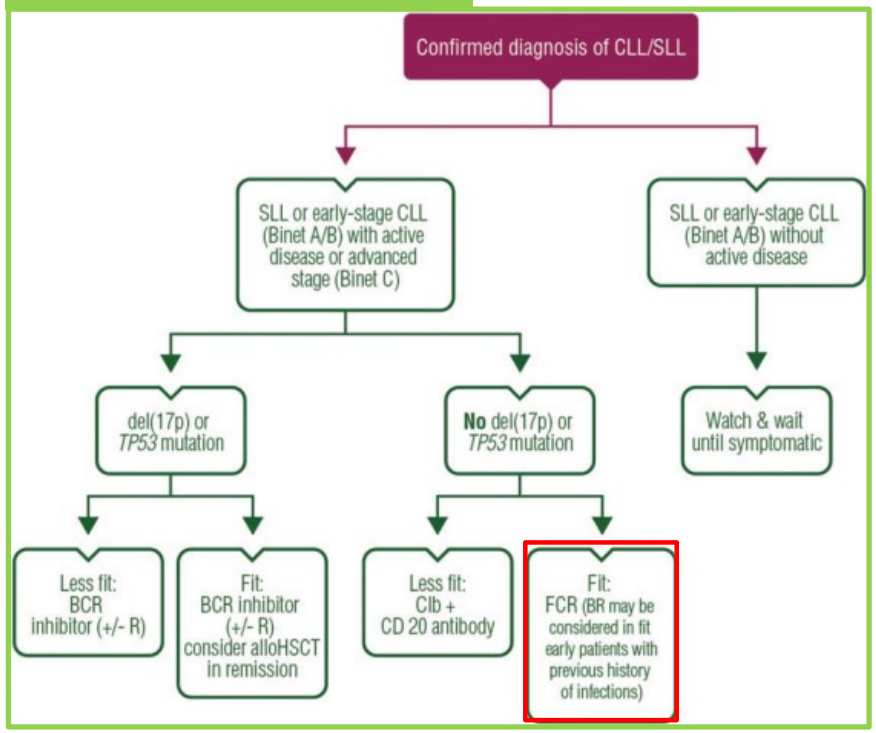
2009-2014: Stadio A/0 watch & wait

2014: Stadio BII p (GB 820000 (L 78000) T ½ < 6 mesi, Milza di 16 cm, linfoadenomegalie addominali max 5 cm e superficiali max 3 cm) (57aa; CIRS 5; **Young/Fit; FISH positiva per del 13q, del11q; IgVH non Mutato**)

Dicembre 2014: Cosa fare ?

Dicembre 2014: uomo Young/Fit; (57aa, CIRS 5, ECOG 0)
Stadio BII p (T ½ < 6 mesi, Milza di 16 cm, linfoadenomegalie addominali max 5 cm e superficiali max 3 cm)
FISH: positiva del 13q, del11q; negativa del 17p; IgVH non mutato 3-33

ESMO Guidelines, Eichhrost B et al Annals of Oncology 2015



6 FCR → CR

Dicembre 2014 →Maggio 2015
- Fludara 25 mg/m² D1,D2,D3 dal 1→6 ciclo;
- Endoxan 250 mg/m² D1,D2,D3 dal 1→6 ciclo;
- RTX 375 mg/m² D1C1; 500 mg/m² D1 dal 2→6 ciclo

Tossicità: neutropenia III° dopo il 2° ciclo→ G-CSF
Riduzione del 25% dosaggio FC
Profilassi: Bactrim forte, Aciclovir; **Follow up** semestrale

Eichhrost B et al; Lancet Oncol 2016; 17: 928–42

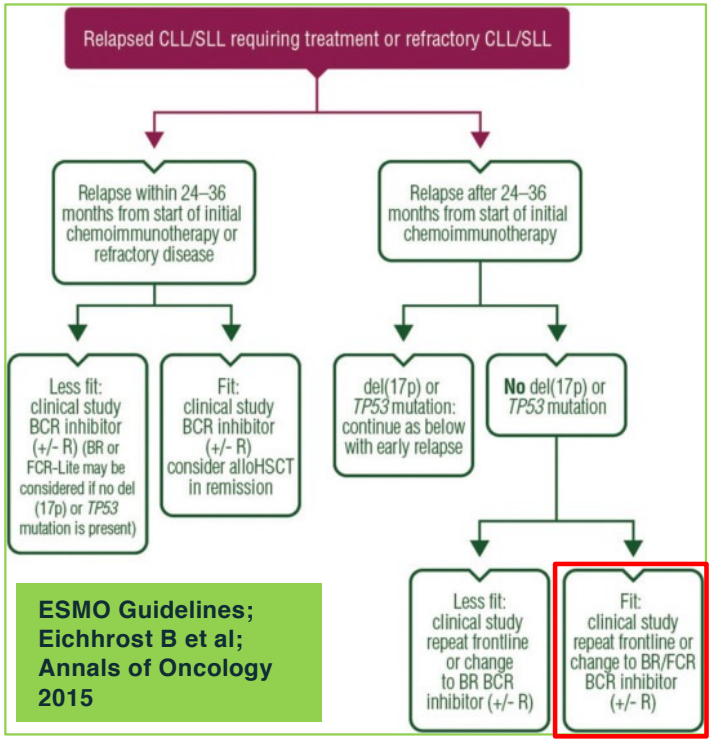
First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial

Barbara Eichhorst, Anna-Maria Fink, Jasmin Bahlo, Raymonde Busch, Gabor Kovacs, Christian Maurer, Elisabeth Lange, Hubert Köppler, Michael Kiehl, Martin Sökler, Rudolf Schlag, Ursula Vehling-Kaiser, Georg Köchling, Christoph Plöger, Michael Gregor, Torben Plesner, Marek Trneny, Kirsten Fischer, Harmut Döhner, Michael Kneba, Clemens-Martin Wendtner, Wolfram Klapper, Karl-Anton Kreuzer, Stephan Stilgenbauer, Sebastian Böttcher, Michael Hallek, on behalf of an international group of investigators and the German CLL Study Group (GCLLSG)

Luglio 2018: Relapse 37 mesi post I° linea FCR

- ✓ **Uomo 61 aa, young/ Fit (ECOG 0, CIRS 5); FISH:** *del 13q e del 11q positivo*; **IgVH** *non mutato 3-33;* **TP 53 negativa**
- ✓ **Stadio C/IV** (Milza di 17 cm, linfoadenomegalie addominale max 7 cm, ascellari e inguinali max 4 cm)

- ✓ **APR**: IA → triatec; FAP in trattamento con $\mathcal{B}$ bloccanti; insufficienza venosa arti inferiori e pregressa TVP arto inferiore sinistro.
- **GB 78900/mmc** (N 5300, **L 71500**) **Hb 9.2 gr/dl**, MCV 82 fl, **Plt 86000/ mmc**, **LDH 390 UI** (<250); Funzionalità renale ed epatica nella norma;
- **EOG:** lfn superficiali max 3 cm (laterocervicali, ascellari e inguinali), milza 2 cm dall'arco **Sintomi B**: astenia, sudorazioni notturne
- **TAC total body:** lfn laterocervicali max 2 cm, lfn ascellari e inguinali max 4 cm, lfn ilo epatico, paraortici e paracavali max 7 cm, milza 17 cm



ESMO Guidelines; Eichhrost B et al; Annals of Oncology 2015

Ibrutinib 420 mg/die

Luglio 2018: Relapse 37 mesi post I° linea FCR

- ✓ **Uomo 61 aa, Elderly/ Fit (ECOG 0, CIRS 5); FISH:** *del 13q e del 11q positivo*; **IgVH** *non mutato 3-33;* **TP 53 negativa**
- ✓ **Stadio C/IV** (Milza di 17 cm, linfoadenomegalie addominale max 7 cm, ascellari e inguinali max 4 cm)

- ✓ **APR**: IA → triatec; FAP in trattamento con $\mathcal{B}$ bloccanti; insufficienza venosa arti inferiori e pregressa TVP arto inferiore sinistro.
- **GB 78900/mmc** (N 5300, **L 71500**) **Hb 9.2 gr/dl**, MCV 82 fl, **Plt 86000/ mmc**, **LDH 390 UI** (<250); Funzionalità renale ed epatica nella norma;
- **EOG:** lfn superficiali max 3 cm (laterocervicali, ascellari e inguinali), milza 2 cm dall'arco **Sintomi B**: astenia, sudorazioni notturne
- **TAC total body:** lfn laterocervicali max 2 cm, lfn ascellari e inguinali max 4 cm, lfn ilo epatico, paraortici e paracavali max 7 cm, milza 17 cm

- **Dopo 1 mese (Aprile 2018):** GB 98000/mmc (N 5800, L 89800), Hb 11 g/dl, MCV 81 fl, PLT 104000/mmc; LDH 300 UI
- *EOG:* ***riduzione delle linfoadenomegalie*** superficiali laterocervicali, ascellari e inguinali (1.5 vs 3 cm), milza 1 cm dall'arco

- **Dopo 3 mese (Giugno 2018):** GB 131000/mmc (N 4900, L 124700), Hb 12,6 g/dl, MCV 81 fl, PLT 147000/mmc; LDH 200 UI
- *EOG:* ***linfoadenomegalie*** *laterocervicali, ascellari e inguinali (****max 1 cm****), milza e fegato nella norma.*

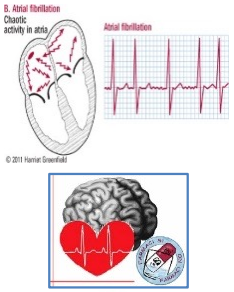
- **Dopo 6 mese (Settembre 2018):** GB 48000/mmc (N 3600, L 43200), Hb 13 g/dl, MCV 81 fl, PLT 186000/mmc; LDH 147 UI
- **Ecografia addome e linfonodi:** lfn ascellari e inguinali max 1.5 cm, lfn ilo epatico, paraortici e paracavali max 2 cm, milza 13 cm

Gennaio 2019 → PR post VI° mese IBR
- *IBR 420 mg/die x os*

Tossicità: *ematomi spontanei e provocati I°-II° nel primo semestre*
Profilassi: *Bactrim forte*
Follow up: *semestrale* e consegna trimestrale del piano terapeutico!!!

Marzo 2019: 8° mese di IBR: Da circa 4 giorni: cardiopalmo, astenia, fiato corto, febbre (TCmax 38°C)
Pz inviato in PS!

- GB 11520/mmc (N 6000, L 4600), Hb 16 g/dl, MCV 82 fl, PLT 302.000/mmc,
- ***Creatinina 1.5 mg/dl, K 2.5 mEq/l*** *, Funzionalità epatica ed LDH nella norma*
- ***Elettroforesi proteica*** *γ 11%, ipogammaglobulinemia;*
- *PCR 23 mg/l; Procalcitonina 2.5;* Enzimi cardiaci nella norma
- **ECG «fibrillo-flutter ad alta risposta. FC 150 AR » in corso di 8° mese Ibrutinib**



Terapia medica:

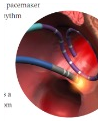
beta bloccanti/

calcio antagonisti/

Anticoagulanti(TAO/NOAC)

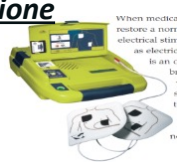
Ablazione transcatetere

o chirurgica



Pacemaker

Cardioversione elettrica



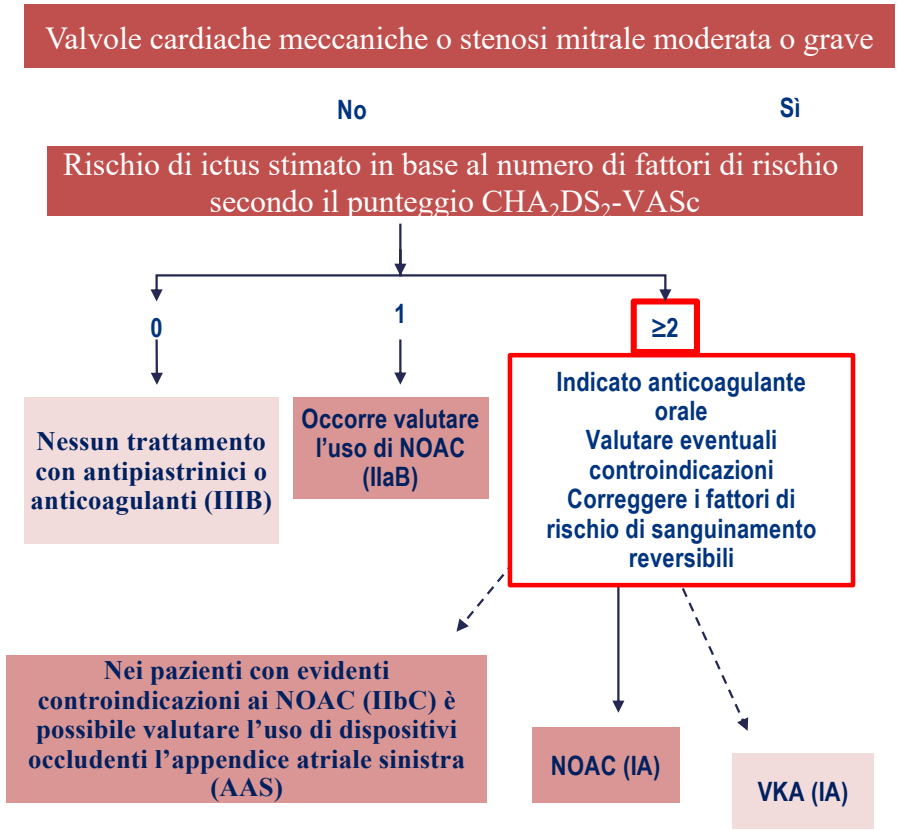
FA e Ibrutinib: rischio Ictus/Emorragico

Tipi di FA*	Definizione*
La diagnosi richiede ECG che mostri aritmia per > 30s	
FA di prima diagnosi	Prima manifestazione di FA, indipendentemente dalla durata o dalla presenza e gravità di sintomi correlati
Parossisitica	Si risolve generalmente da sola entro 48 ore. In alcuni casi si estende fino a 7 giorni. Se si risolve a seguito di cardioversione entro i 7 giorni la FA è comunque parossistica
Persistente	Dura più di 7 giorni, indipendentemente da trattamento
Persistente di Lunga Durata	FA continua che persiste per oltre 1 anno
Permanente	FA presente continuamente. Il controllo dei sintomi tramite controllo del battito e della FC non è più ricercato.

CTCAE Cardiac disorders, Version 4., Published: May 28, 2009 (v4.03: June 14, 2010).
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Cardiac disorders					
	Grade				
Adverse Event	1	2	3	4	5
Atrial fibrillation	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia without discernible P waves and an irregular ventricular response due to multiple reentry circuits. The rhythm disturbance originates above the ventricles.					
Atrial flutter	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with organized rhythmic atrial contractions with a rate of 200-300 beats per minute. The rhythm disturbance originates in the atria.					

Linee guida della Società europea di cardiologia (ESC) per la prevenzione dell'ictus nella fibrillazione atriale[1]



1. Kirchhof P, et al. Eur Heart J 2016;37(38):2893–2962;
2. 2. Imbruvica®. Riassunto delle caratteristiche del prodotto, 2017.

Points	CHA2DS2-VASc Parameters
1	C- Congestive Heart Failure
1	H- Hypertension Resting blood pressure >140/90 mmHg on at least two occasions or current antihypertensive treatment
2	A- Age 75 years or older
1	D- Diabetes mellitus Fasting glucose >125 mg/dL (7 mmol/L) or treatment with oral hypoglycaemic agent and/or insulin
2	S- Previous stroke, transient ischaemic attack, or thromboembolism
1	V- Vascular disease Previous myocardial infarction, peripheral artery disease, or aortic plaque
1	A- Age 65–74 years
1	Sc- Sex category (female)

Points	HAS-BLED Parameters	Definition
1	H- Hypertension	Sys BP > 160
1 or 2	A- Abnormal renal/ Abnormal liver function	Dialysis/transplant / Cirrhosis / T. Bili 2x or AST/ALT 3x normal
1	S- Stroke	
1	B- Bleeding	Previous bleed / predisposition Antiplatelets, NSAIDs
1	L- Labile INR	< 60% in therapeutic range
1	E- Elderly (>65 years)	
1 or 2	D- Drugs or alcohol excess	> 8 drinks per week

Clinicians' recommendations for managing AF

RECOMMENDATION

Patients on ibrutinib with CHA_2DS_2VASc score of:[1]

0: Continue ibrutinib without anticoagulant or antiplatelet agent

1: Continue ibrutinib (with optional addition of aspirin per physician preference and consideration of individual risk)

≥2: Use a NOAC (rather than VKA) without any antiplatelet agent

Shatzel et al. 2017

RECOMMENDATION

Patients with specific heart conditions who develop AF:[2]

Concomitant antiplatelet agents can be considered

Patients using aspirin for cardioprotection, who develop AF with CHA_2DS_2VASc of ≥2:[1]

Treat with NOAC plus ibrutinib alone and stop other antiplatelet agents

Shatzel et al. 2017
Chai et al. 2017

RECOMMENDATION

Patients requiring dual antiplatelet therapy (DAPT) who develop AF and have high stroke risk:[1]

Discontinue ibrutinib due to bleeding risk and switch to alternative agent

Shatzel et al. 2017

Currently there is no definitive clinical data to confirm which is the preferred NOAC to be used for the management of AF in patients treated with ibrutinib.[1–5]

Consultation with a cardiologist may inform the choice of NOAC and the decision should take into consideration polypharmacy.[1–5]

Physicians should calculate risk : benefit for each patient and make treatment decisions accordingly.

NOAC superiori rispetto al Warfarin in*:

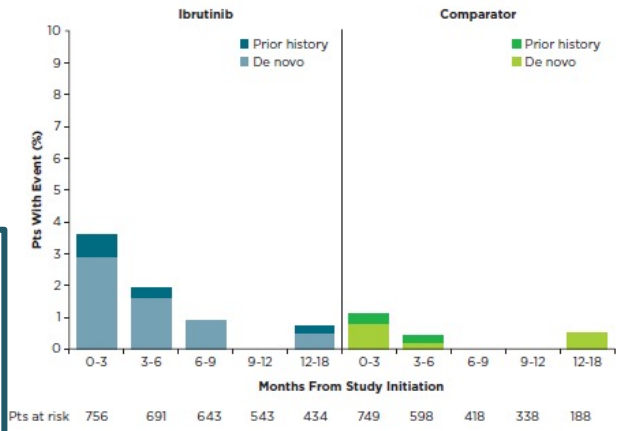
- riduzione stroke (soprattutto ictus emorragico) e eventi embolici sistemici
- riduzione mortalità
- riduzione emorragie intracraniche
- NOAC raccomandati rispetto a VKAs e Aspirina in pz con FA e precedente ictus
- Dabigatran superiore a warfarin per riduzione ictus e superiore tutti altri per riduzione mortalità, infarto miocardio e eventi emorragici**

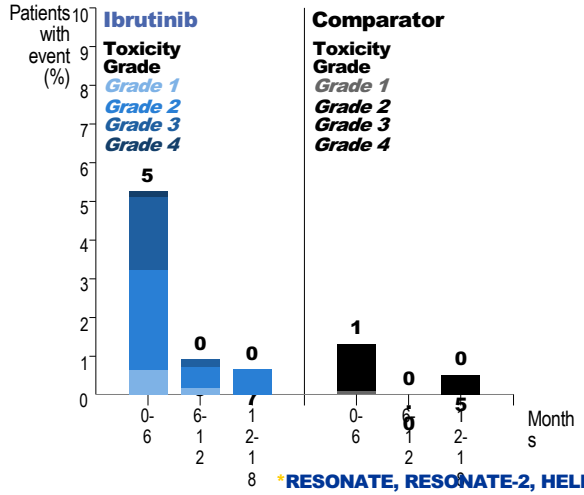
Some authors state they may temporarily reduce dose to 280 mg and re-escalate back to 420 mg; however, they acknowledge there is no clinical data to endorse this practical strategy. Please note this does not align to the Ibrutinib SmPC dosing recommendations.

1. Shatzel JJ, et al. J Thromb Haemost 2017;15(5):835–847; 2. Chai KL, et al. Leuk Lymphoma 2017;58(12):2811–2814; 3. Thorp BC, Badoux X. Leuk Lymphoma 2017; Epub ahead of print;
4. de Weerdt I, et al Haematologica 2017; Epub ahead of print; 5. Kirchhof P, et al. Eur Heart J 2016;37(38):2893–962.

The incidence of AF was highest in the first 6 months, and then continued at a low rate[1]

Figure 1. Comparison of Time to Onset of First AF Event by Treatment





*RESONATE, RESONATE-2, HELIOS, RAY (MCL study) based on 16.6 months follow-up

AE e Guida alla modifica della dose

- **La terapia con IBRUTINIB deve essere sospesa in caso di**:
  - ✓ tossicità non ematologica di grado ≥ 3,
  - ✓ neutropenia di grado 3 o superiore con infezione o febbre,
  - ✓ tossicità ematologiche di grado 4.
- Una volta che le **tossicità sono regredite a grado 1 o al basale , la terapia con IBRUTINIB può essere ripresa alla dose iniziale.**
- **Se la tossicità si ripresenta**, la **dose** giornaliera deve essere **ridotta di una capsula** (140 mg). **Una seconda riduzione** della dose, di 140 mg, può essere considerata **se** necessario. **Se le tossicità persistono o si ripresentano dopo due riduzioni di dose, interrompere la somministrazione del farmaci**

Comparsa della tossicità	CLL/WM: modifiche della dose dopo risoluzione
Prima	riprendere con 420 mg al giorno
Seconda	riprendere con 280 mg al giorno
Terza	riprendere con 140 mg al giorno
Quarta	interrompere IMBRUVICA

1. Brown JR, et al. Haematologica 2017; Epub ahead of print; 2. Thorp BC, Badoux X. Leuk Lymphoma 2017; Epub ahead of print.

How I manage ibrutinib intolerance and complications in patients with chronic lymphocytic leukemia

Deborah M. Stephens[1] and John C. Byrd[2-4]

[1]Division of Hematology and Hematologic Malignancies, Department of Internal Medicine, University of Utah, Salt Lake City, UT; and [2]Division of Hematology, Department of Internal Medicine, [3]Department of Medicinal Chemistry, and [4]Department of Veterinary Biosciences, The Ohio State University, Columbus, OH

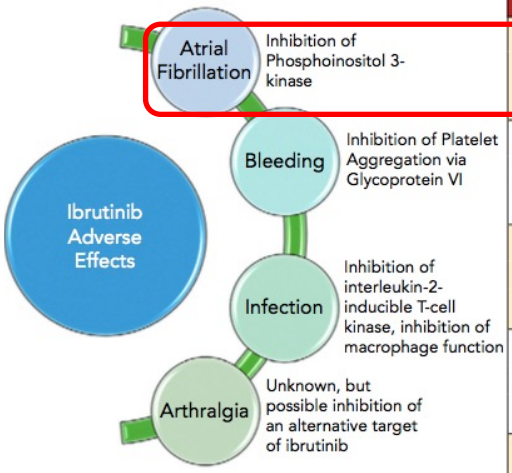


Table 1. Frequency of highlighted adverse events on selected landmark ibrutinib studies

Adverse event	Phase 2, follow-up 21 mo[6] (n = 85)	Phase 3 RESONATE		Phase 3 RESONATE2	
		Follow-up 9 mo[4] (n = 195)	Follow-up 19 mo[16,17] (n = 195)	Follow-up 18 mo[5] (n = 135)	Follow-up 21 mo[18] (n = 135)
Atrial fibrillation					
All grades	3 (4)	10 (5)	13 (7)	8 (6)	14 (10)
Grade ≥3	0	6 (3)	7 (4)	2 (1)	6 (4)
Bleeding					
All grades	14 (16)	86 (44)	NR	NR	9 (7)
Grade ≥3	4 (5)	2 (1)	4 (2)	6 (4)	8 (6)
Infection					
All grades	NR	137 (70)	NR	NR	NR
Grade ≥3	NR	47 (24)	59 (30)	NR	31 (23)
Arthralgia					
All grades	23 (27)	34 (17)	44 (23)	22(16)	27 (20)
Grade ≥3	0	2 (1)	NR	2 (1)	3 (2)
Myalgia					
All grades	16 (19)	19 (10)	NR	NR	NR
Grade ≥3	1 (1)	1 (1)	NR	NR	NR

Blood. 2019;133(12):1298-1307

Marzo 2019: Risoluzione episodio infettivo con ATB e normalizzazione dell'ipokaliemia

❖ **Cardiologo:** ROC: toni validi e pause libere. **ECG** Ritmo sinusale. FC 60 bpm. PA 140/80 mmHg,

EcoCG: Ventricolo sin ipertrofico, volumi e funzionalità normale. Atrio sin nella norma. **FE 68%. Lieve disfunzione diastolica**

Trascurabile rigurgito mitralico e tricuspidale.

Pregressi episodi di FAP. Rischio **CHA2DS2-VASc 2.**

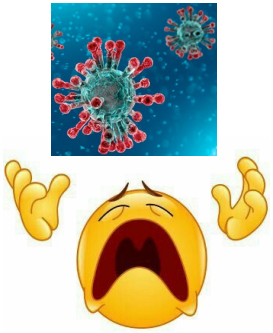
Indicazione ad proseguire beta bloccante e Iniziare Eliquis 5 mg x 2/die

❖ GB 8720/mmc (N 3200, L 4900), Hb 16 g/dl, MCV 82 fl, PLT 302.000/mmc, LDH 150 UI

❖ **Tac Total body**: milza 12,5 cm, linfoadenomegalie addominali max 4 cm e superficiali max 1,5 cm

❖ **8° mese IBR: PR & inizia terapia con Eliquis**

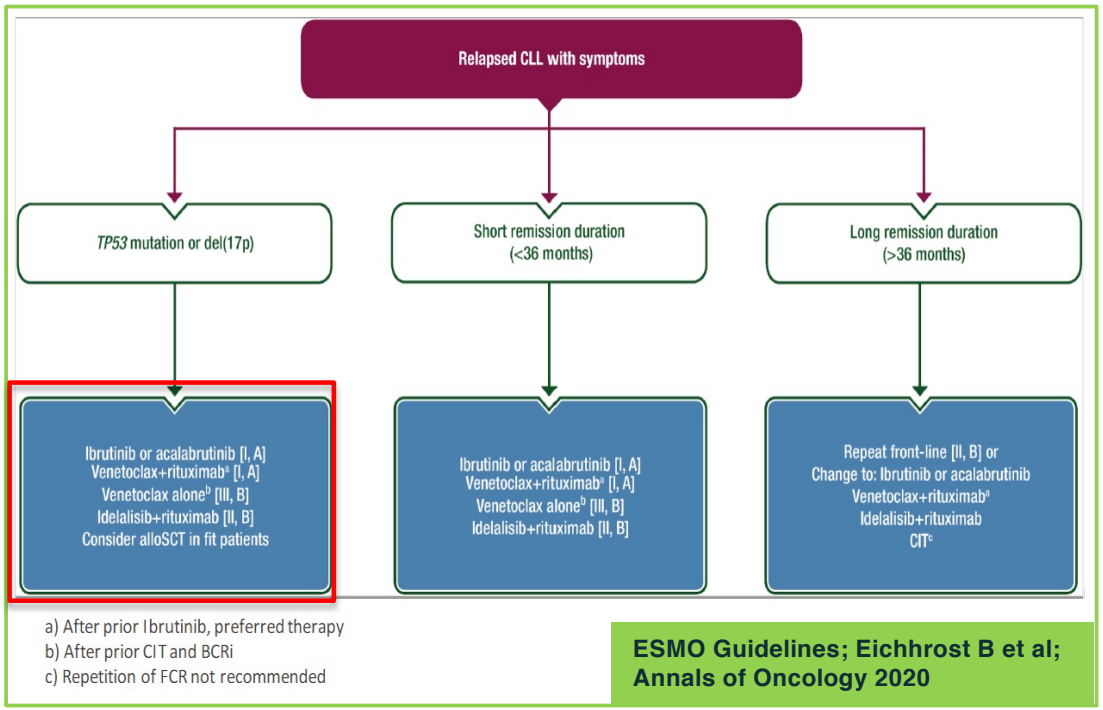
- **Marzo 2021: Dopo 32 mesi IBR …** in piena epoca Covid-19 (II° ondata)
- GB 7200/mmc (L 6800), **Hb 11.5 g/dl, MCV 73 fl,** PLT 201000/mmc; LDH 300 UI
- *EOG:* ***linfoadenomegalie*** superficiali laterocervicali, ascellari e inguinali (max 1.5), milza 1 cm dall'arco
- **Ferritina 7, sideremia 11, SOF +/+/+**
- *Stillicidio cronico intestinale ed emorroidi sanguinanti*
- Sospende Ibrutinib ed Eliquis e inizia terapia con Clexane proseguendo beta bloccante
- **Colonscopia:** *emorroidi congeste e asportazione di polipi benigni intestinali*
- ***Riprende terapia con Eliquis*** e in considerazione della PR **non riprende Ibrutinib (non Vaccinato!!!)**



Ottobre 21: Relapse 7 mesi post sospensione IBR (32 mesi)

- ✓ **Uomo 64 aa, Young/ Fit (ECOG 0, CIRS 5); FISH:** *del 13q e del 11q positivo*; **IgVH** *non mutato 3-33;* **TP 53 positivo**
- ✓ **Stadio C/IV** (Milza di 17 cm, linfoadenomegalie addominale max 7 cm, ascellari e inguinali max 4 cm)

- ✓ **APR**: IA → triatec; FAP in trattamento con $\mathcal{B}$ bloccanti; insufficienza venosa arti inferiori e pregressa TVP arto inferiore sinistro.
- • **GB 54000/mmc** (N 4300, **L 49000**) **Hb 11 gr/dl**, MCV 82 fl, **Plt 86000/ mmc**, **LDH 390 UI** (<250); Funzionalità renale ed epatica nella norma;
- • **EOG:** lfn superficiali max 3 cm (laterocervicali, ascellari e inguinali), milza 2 cm dall'arco **Sintomi B**: astenia, sudorazioni notturne
- • **TAC total body:** lfn laterocervicali max 2 cm, lfn ascellari e inguinali max 4 cm, lfn ilo epatico, paraortici e paracavali max 7 cm, milza 17 cm



ESMO Guidelines; Eichhrost B et al; Annals of Oncology 2020

III° linea terapia: Venetoclax in monoterapia

- ❖ **II ondata Covid-19**
- ❖ **Vaccinato per SARS-COV-2 con 2 dosi, sierologie negative**
- ❖ **Ricovero in Reparto per idratazione e iniziare terapia con Venetoclax 20 mg (7 gg)**
- ❖ **Titolazione Ven settimanale ben tollerata**
- ❖ ***Tossicità:*** *neutropenia III° grado in corso di Venetoclax 200 mg(GCSF)*
- ❖ ***Profilassi:*** *Bactrim forte*
- ❖ ***C*onsegna a domicilio** del Venetoclax !!!
- ❖ **6 mese in PR**

Giugno 22: Relapse 8 mesi post Venetoclax (III° linea)

- ✓ **Uomo 65 aa, Young/ Fit (ECOG 0, CIRS 5); FISH:** *del 13q e del 11q positivo*; **IgVH** *non mutato 3-33;* **TP 53 positivo**
- ✓ **Stadio C/IV** (Milza di 17 cm, linfoadenomegalie addominale max 7 cm, ascellari e inguinali max 4 cm)
- • **GB 62000/mmc** (N 3100, **L 57200**) **Hb 11 gr/dl**, MCV 82 fl, **Plt 80000/ mmc**, **LDH 320 UI** (<250); Funzionalità renale ed epatica nella norma;
- • **EOG:** lfn superficiali max 4 cm (laterocervicali, ascellari e inguinali), milza 2 cm dall'arco **Sintomi B**: astenia, sudorazioni notturne
- • **TAC total body:** lfn laterocervicali max 2 cm, lfn ascellari e inguinali max 4 cm, lfn ilo epatico, paraortici e paracavali max 7 cm, milza 17 cm

- ✓ **APR**: IA → triatec; FAP in trattamento con $\mathcal{B}$ bloccanti+ Eliquis; insufficienza venosa arti inferiori e pregressa TVP arto inferiore sinistro.

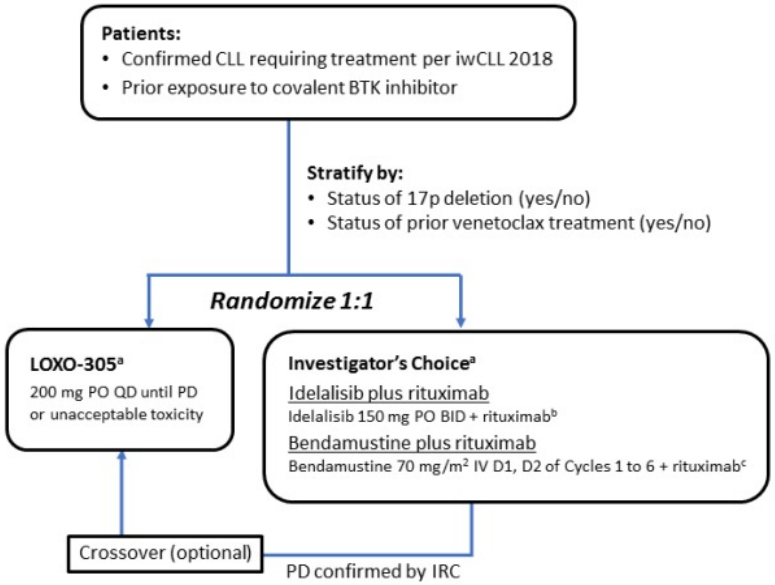
1) Quale terapia di IV° linea proporeste al paziente Young/Fit TP 53 mutato, FISH positiva per del 11q positiva e IgVH non mutato?

a) Acalabrutinib
b) Venetoclax- AbMo anti CD-20
c) Zanobrutinib off label
d) Trials (Loxo mono o in associazione VenR vsBR o Idela R)
e) Allotrapianto CSE

LOXO-20020

Studio di fase 3, in aperto, randomizzato, con LOXO-305 rispetto alla scelta dello sperimentatore di idelalisib più rituximab o bendamustina più rituximab nella leucemia linfocitica cronica/nel linfoma linfocitico a piccole cellule pretrattati con inibitore della BTK (BRUIN CLL-321)

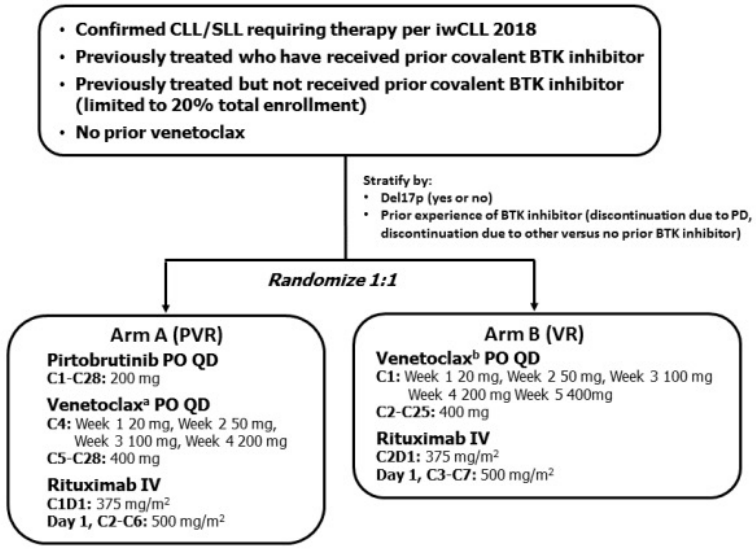
1.2.1. Study Design Schema



LOXO-20022

Studio di fase 3, randomizzato, in aperto, con LOXO-305 a durata fissa più Venetoclax e Rituximab versus Venetoclax e Rituximab nella leucemia linfatica cronica/linfoma linfocitico a piccole cellule pretrattata con un inibitore di BTK (BRUIN CLL-322).

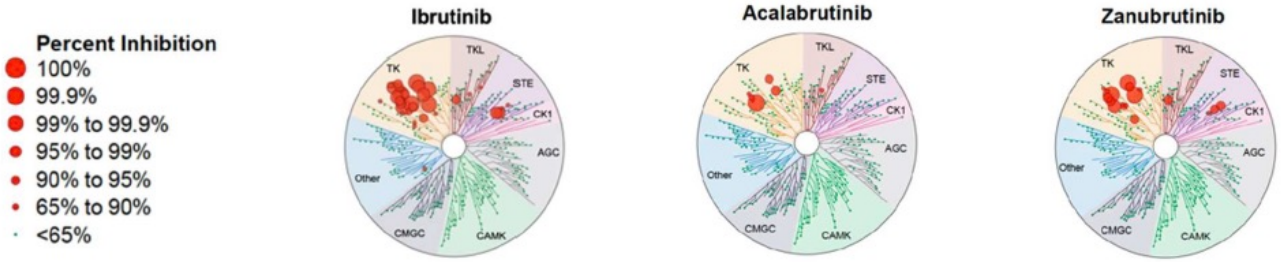
1.2.1 Study Design Schema



- Accesso al portale che gestisce richieste e spedizione del farmaco Zanobrutinib come uso compassionevole
  - **Zanubrutinib CU** (Compassionate Use) per pz con CLL

BTK inhibitors: next generation

Selectivity of different BTK inhibitors shown with average IC_{50} nmol/l

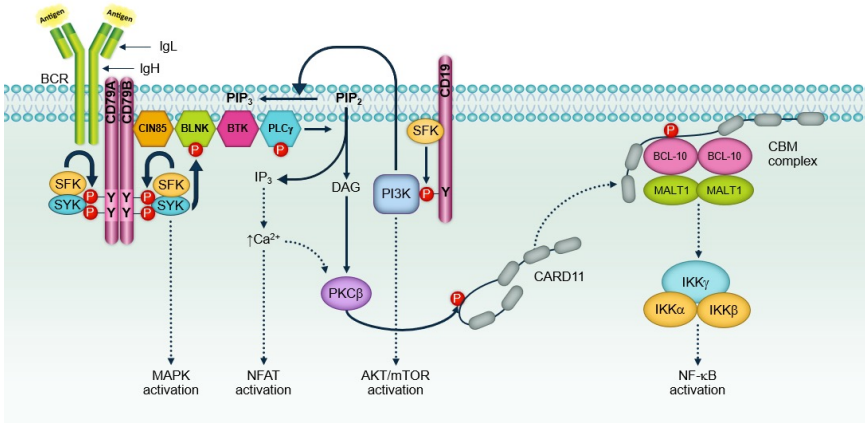


TEC Kinases	Ibrutinib	Acalabrutinib	Zanubrutinib
BTK	1.5	5.1	0.5
TEC	10	126	44
BMX	0.8	46	1.4
TXK	2.0	368	2.2
ERBB2/HER2	6.4	~1000	88
EGFR	5.3	> 1000	21
ITK	4.9	> 1000	50
JAK3	32	> 1000	1377
BLK	0.1	> 1000	2.5

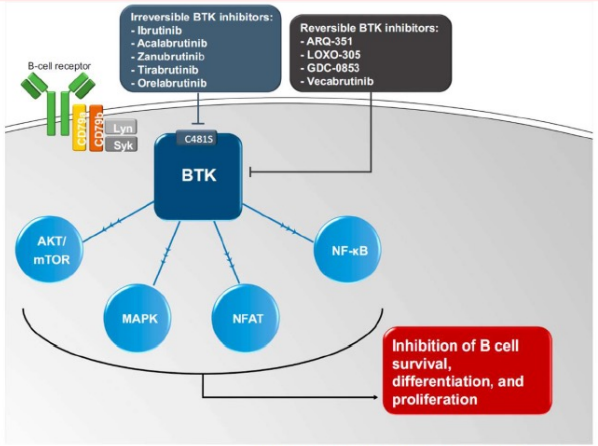
BLK, B lymphocyte kinase; BMX, bone marrow tyrosine kinase gene in chromosome X, ERBB2, erb-b2 receptor tyrosine kinase; ITK, interleukin-2-inducible T-cell kinase; JAK3, Janus kinase 3; TEC, tyrosine kinase expressed in hepatocellular carcinoma; TXK, T and X cell expressed kinase.

Kaptein A et al. Blood, 2018;132(Suppl 1):1871.

Role of BTK in the BCR Signaling Pathway



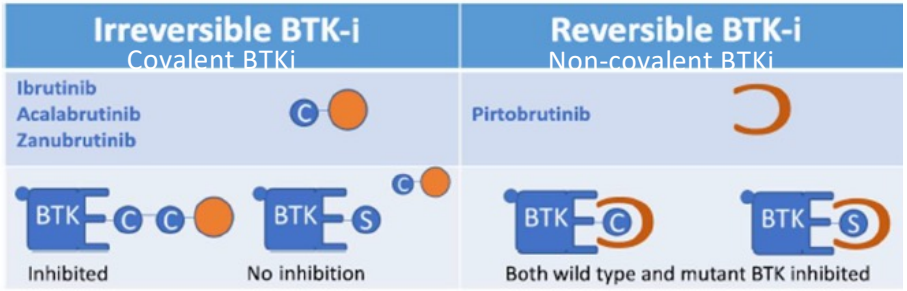
Mechanism of Action of BTK-Inhibitors on B-Cell



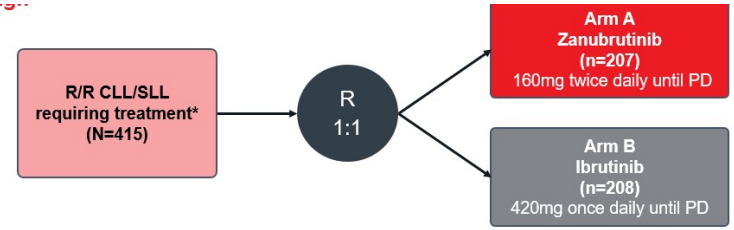
Sawalha Y et al. Onco Targets Ther, 2020 Jul 6;13: 6573-6581.

In the absence of a direct comparison between BTK inhibitors, this presentation reviews data from peer-reviewed publications. Data derived from peer-reviewed scientific publications of each individual BTK inhibitor and not from head-to-head comparative studies. Results should be interpreted with caution because of differences in study designs, populations, and standards of care; conclusions cannot be drawn about comparative efficacy and safety.

- BTK inhibitors of 1st and next generation show similar efficacy with respect to PFS, but differ in adverse event incidences
- Non-covalent BTK inhibitors show efficacy in covalent-BTKi pre-exposed and refractory patients



Zanubrutinib for CLL-SLL - ALPINE trial



*Patients had relapsed/refractory disease following ≥1 prior line of systemic therapy and measurable lymphadenopathy by CT or MRI. Patients with Richter syndrome, prior BTK inhibitor use, and treatment with warfarin or other vitamin K antagonists were excluded.

Primary endpoint:

- Investigator-assessed ORR (PR+CR) noninferiority and superiority

Key Secondary endpoints:

- Atrial fibrillation of any grade
- ORR by IRC
- Duration of response
- PFS
- OS
- Safety

Table 2: Investigator-Assessed Efficacy Outcomes in ALPINE[1]

Response, n (%)	Zanubrutinib (n=207)	Ibrutinib (n=208)
Overall response rate	162 (78.3; 95% CI, 72-83.7)	130 (62.5; 95% CI, 55.5-69.1)
CR/CRi	4 (1.9)	3 (1.4)
Nodular partial response	1 (0.5)	0
Partial response	157 (75.8)	127 (61.1)
Partial response with lymphocytosis	21 (10.1)	39 (18.8)
Stable disease	17 (8.2)	28 (13.5)
Progressive disease	1 (0.5)	2 (1.0)

Table 4: Safety Summary of Patients in ALPINE[1]

Adverse Event, n (%)	Zanubrutinib (n=204)	Ibrutinib (n=207)
Any adverse event	195 (95.6)	205 (99)
Any grade ≥3 adverse events	114 (55.9)	106 (51.2)
Serious adverse events	56 (27.5)	67 (32.4)
Grade 5 adverse events	8 (3.9)	12 (5.8)
Leading to dose reduction	23 (11.3)	25 (12.1)
Leading to dose interruption	81 (39.7)	84 (40.6)
Leading to treatment discontinuation*	16 (7.8)	27 (13)
All-Grade Adverse Events in ≥10% of patients		
Diarrhea	34 (16.7)	40 (19.3)
Neutropenia	40 (19.6)	32 (15.5)
Anemia	27 (13.2)	31 (15)
Upper respiratory tract infection	44 (21.6)	29 (14)
Arthralgia	19 (9.3)	29 (14)
Hypertension	32 (15.7)	27 (13)
Muscle spasms	6 (2.9)	23 (11.1)
Contusion	21 (10.3)	18 (8.7)
Urinary tract infection	22 (10.8)	17 (8.2)
Cough	26 (12.7)	13 (6.3)

* Includes cardiac disorders for zanubrutinib (n=0) patients and ibrutinib (n=7, 3.4%) patients.

Table 5: Adverse Events of Special Interest in ALPINE[1]

Adverse Event, n (%)	Zanubrutinib (n=204)		Ibrutinib (n=207)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Infections	122 (59.8)	26 (12.7)	131 (63.3)	37 (17.9)
Hemorrhage	73 (35.8)	6 (2.9)	75 (36.2)	6 (2.9)
Major hemorrhage*	6 (2.9)	6 (2.9)	8 (3.9)	6 (2.9)
Neutropenia†	58 (28.4)	38 (18.6)	45 (21.7)	31 (15)
Hypertension	34 (16.7)	22 (10.8)	34 (16.4)	22 (10.6)
Cardiac disorders	28 (13.7)	5 (2.5)	52 (25.1)	14 (6.8)
Thrombocytopenia§	19 (9.3)	7 (3.4)	26 (12.6)	7 (3.4)
Secondary primary malignancies	17 (8.3)	10 (4.9)	13 (6.3)	4 (1.9)
Skin cancers	7 (3.4)	3 (1.5)	10 (4.8)	2 (1)
Atrial fibrillation and flutter‖	5 (2.5)	2 (1)	21 (10.1)	4 (1.9)

* Includes Grade ≥3 hemorrhage and CNS bleeding of all grades.
† Pooled terms including neutropenia, neutrophil count decreased, and febrile neutropenia.
§ Pooled terms including thrombocytopenia and platelet count decreased.
‖ Key secondary endpoint, p=0.0014.

Adverse Events Reported with Ibrutinib, Acalabrutinib, and Zanubrutinib in Pivotal Studies

Sawalha Y et al. Onco Targets Ther, 2020 Jul 6;13: 6573-6581.

Adverse Events (AEs)	Ibrutinib (n=370)[41–43]	Acalabrutinib* (n=610)[48]	Zanubrutinib* (n=671)[52]
Headache, any grade (grade ≥3)	37% (0%)	42% (2%)	4% (not reported)**
Diarrhea, any grade (grade ≥3)	40% (4%)	38% (2%)	18% (1%)
Hypertension, grade ≥3	5%	<3%	3%
Atrial fibrillation, any grade (grade ≥3)	11% (6%)	2% (1%)	2% (1%)
Bleeding, serious or grade ≥3	5%	3%	3%
Neutropenia, grade ≥3	17%	9%	14%
Thrombocytopenia, grade ≥3	12%	4%	4%
Anemia, grade ≥3	10%	7%	8%
Treatment discontinuation due to AEs	10%	6%	10%

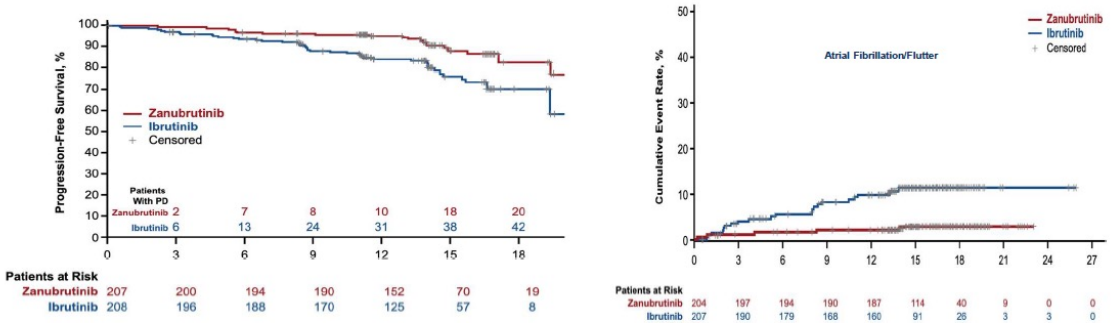
Notes: *Studies included patients with MCL and other B-cell malignancies. **From zanubrutinib's package insert.

next generation BTKi in R/R CLL

In the absence of a direct comparison between BTK inhibitors, this presentation reviews data from peer-reviewed publications. Data derived from peer-reviewed scientific publications of each individual BTK inhibitor and not from head-to-head comparative studies. Results should be interpreted with caution because of differences in study designs, populations, and standards of care; conclusions cannot be drawn about comparative efficacy and safety.

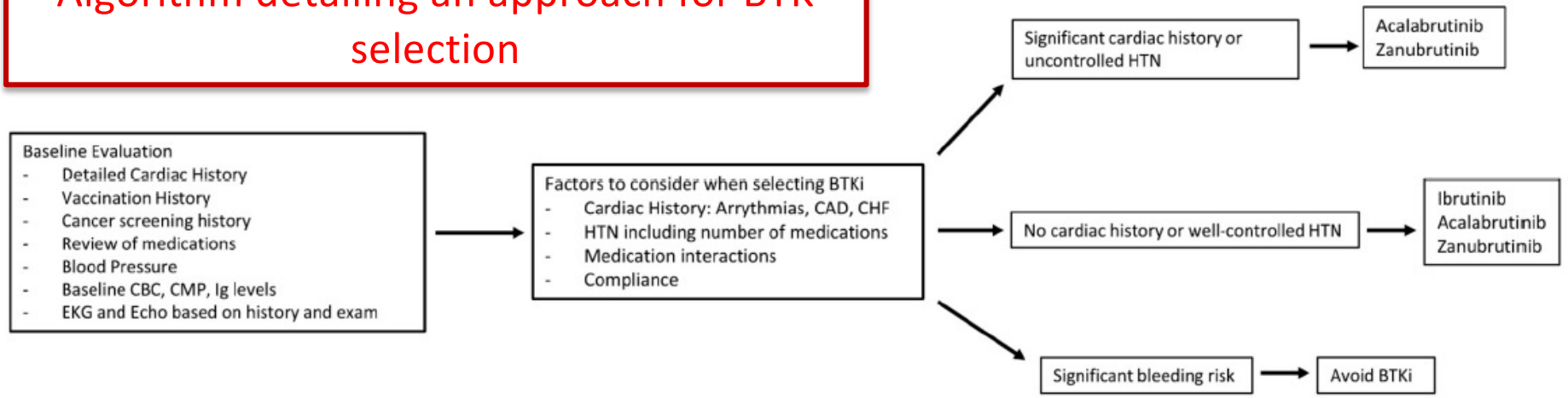
ALPINE study: zanubrutinib versus ibrutinib

12-month landmark event free rate after 15 months median observation time:
Zanubrutinib 94.9%, Ibrutinib 84.0%; HR 0.40 (95% CI 0.23-0.69) 2-sided *P*=0.0007



Hillmen P et al. Oral presentation. EHA 2021. LB Abstract 1900.

Algorithm detailing an approach for BTK selection



BTKi, Bruton Tyrosine Kinase inhibitor; CAD, coronary artery disease; CBC, complete blood count; CHF, congestive heart failure; CMP, comprehensive metabolic panel; HTN, hypertension; Ig, immunoglobulin

*Desikan SP et al. Expert Rev Hematol. 2022 May 11:1-7.

In the absence of a direct comparison between BTK inhibitors, this presentation reviews data from peer-reviewed publications. Data derived from peer-reviewed scientific publications of each individual BTK inhibitor and not from head-to-head comparative studies. Results should be interpreted with caution because of differences in study designs, populations, and standards of care; conclusions cannot be drawn about comparative efficacy and safety.

Grazie per l'attenzione !!!

- ***FA: 5-7.7 %** pz trattati con Ibrutinib (CLL, MCL, MW)*
- ***Fattori di rischio:** età avanzata; precedente episodio da FA; sesso maschile*
- ***Comorbidità:** fattori di rischio cardiovascolare (ipertensione, storia di FAP, disfunzione valvolare, insufficienza cardiaca congestizia, angina);infezioni acute; disturbi elettrolitici,*
- ***Maggior incidenza** degli eventi di FA nei pz trattati con Ibrutinib **potrebbe anche esser correlata** alla **durata del trattamento** fino a PD o tossicità*

***FA in corso di Ibrutinib**:*

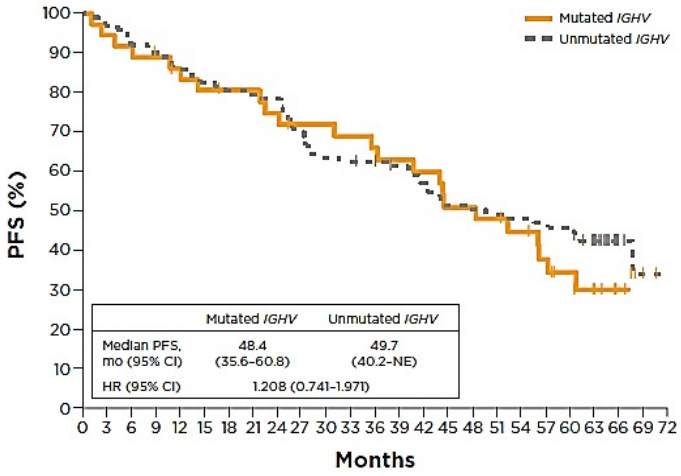
- *facilmente gestibili e non limitano la terapia;*
- *insorgono **più frequentemente entro i primi 6 mesi;***
- *di **breve durata, 1-2 giorni (range 1-11);***
- *la **maggior parte dei pz non ha bisogno di interrompere, sospendere o ridurre il dosaggio***
- ***Diversi gradi di FA, valutazione del rischio ischemico /emorragico (CHAD-VASC/HAS-BLED)***

Problematiche da gestire

- NOACs (Dabigadtran> Apixaban e Rivaroxaban) sono da preferirsi alla TAO (CHAD-VASC>2).
- Gli **antiaggreganti** possono essere somministrate con un **attento monitoraggio, non aiutano a prevenire lo stroke**!!!
- **Attenzione alle interazioni con CYP3A4** (diltiazem, verapamil, amiodarone, apixaban, rivaroxaban), **glicoproteina P** (digossina, dabigadran),…
- Attenzione al **rischio emorragico/rischio tromboembolico**
- **Equipe multidisciplinare (ematologi, oncologi, cardiologi, farmacologi)**

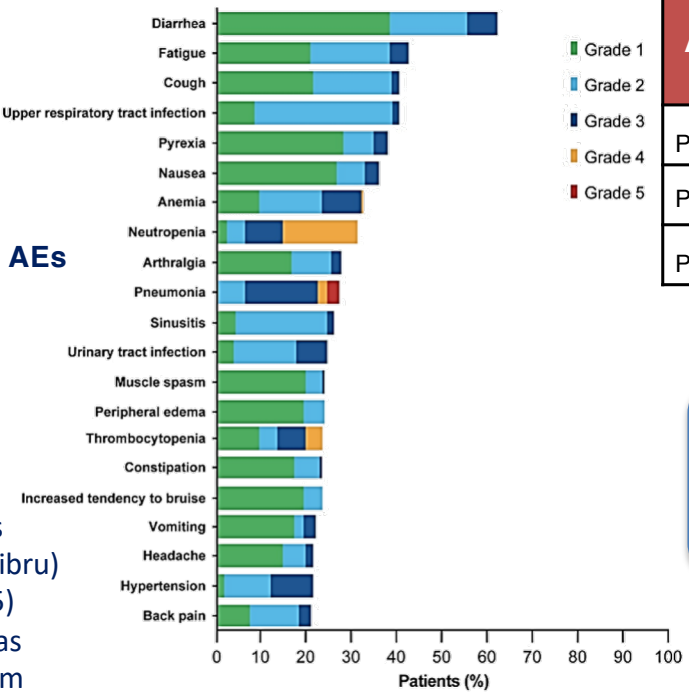
Final analysis RESONATE: 6-year F-up in R/R CLL ibrutinib

Median follow-up on study: 65.3 (range, 0.3-71.6) mo



- 60-months PFS rate in ITT: 40% (ibru) vs 3% (ofa)
- PFS benefit consistent across baseline subgroups
  - mPFS in genomic high-risk population: 44.1 (ibru) vs 8.0 ofa months (HR 0.11; 95% CI 0.08-0.15)
  - Among patients with del(17p), median OS was 61.8 months (95% CI: 38.7–NE) in the ibru arm

AEs



Duration of treatment 41.0 mo

Aes of interest	Ibrutinib (n=195)
Patients with atrial fibrillation, n (%)	24/195 (12)
Patients with hypertension, n (%)	41/195 (21)
Patients with Major hemorrhage n (%)	19/195 (10)

Dose reductions & Discontinuations

- **In ibru arm 17% of pts with dose reductions and 65% of pts with dose holds to manage AEs**
- **Reasons for ibr discontinuation: PD (37%) and AEs (16%)**

"This update confirms that ibrutinib is well tolerated, and the prevalence of most grade ≥3 AEs of clinical interest decreased with each subsequent year of treatment"

Talha Munir et al. – AJH 2019 - http://dx.doi.org/10.1002/ajh.25638

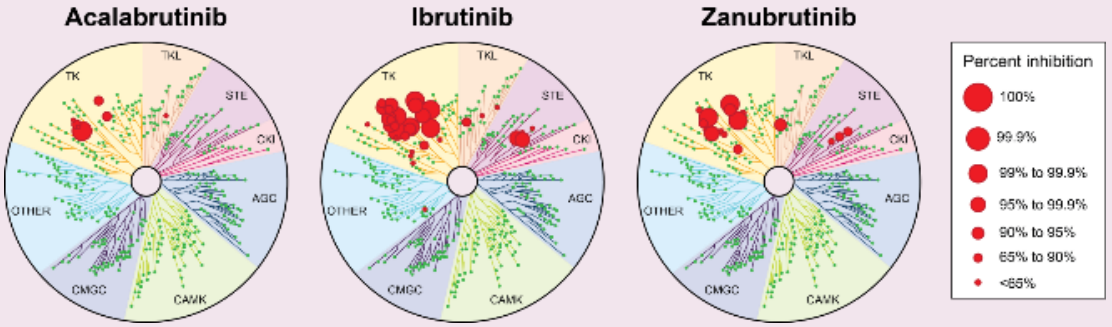
Incidenza della FA:

- ✓ Popolazione generale 1-2%
- ✓ Aumenta con l'età fino al 12% (>65aa)
- ✓ Pz con tumori 4%
- ✓ **Pz con LLC in trattamento con IBR:…. 5-7.7%**

Autori	Popolazione	N. pz in IBR	N. dei pz che presenta un episodio di FA
Byrd, NEJM 2014 (Fase III, RESONATE) Fup mediano 9,4 mesi	LLC/SLL R/R 195 IBR vs 196 Ofatumumab Del 17p in 63 pz vs 64pz	195 vs 196 67aa (30-86)vs 67aa (37-88)	3% vs 0% di Grado ≥ 3 2% vs 0,5% di Grado 1-2 1 pz ha sospeso l'IBR
O'Brien 2014 (Fase II naive)	LLC TN	31	2 (6.5%)
Brown, ASH 2014 (Fase III – RESONATE)	LLC R/R	195	13 (7%) 1 pz ha interrotto l'IBR
O'Brien, Lancet Oncol 2016 (RESONATE 17) Fup mediano 27 mesi	LLC R/R del17p	144 64 aa (57-72)	7.6 % (5% di Grado 3; 2% di Grado 4) 5 pz … storia di FA Nessuno ha interrotto l'IBR;
Burger, 2014	LLC TN & R/R	40	2 (5%)
Chanan-Khan, Lancet Oncol 2015 (Fase III, HELIOS) Fup mediano 17 mesi	LLC/SLL R/R 289 IBR-BR vs 289 PBO-BR No del 17p	287 vs 289 64 aa (31-86) vs 63 aa(36-83)	7.7 % di tutti i gradi vs 2.4% PRO-BR 2.8% di Grado 3/4 vs 0.7% BR 28% dei pz con storia di FA vs 9.1% 0% ha ridotto il dosaggio dell'IBR;1.4% ha interrotto l'IBR
Burger, NEJM 2015 RESONATE-2 Fup mediano 18,4 mesi	LLC/SLLC TN 136 IBR Vs 133 CHL No del 17p	136 vs 133 73 aa (65-89)vs 72 (65-90)	8 pz (6%) di cui 7 con fattori di rischio CV vs 1 pz 6 (4,4%) pz – grado 2 2 (1,5%) pz – grado 3 1% (2pz) ha interrotto l'IBR

Selectivity of BTKis

Differences in overall kinase selectivity have been observed among BTKis[1–3]



*Profiling of BTKi interactions with kinases having Cys in same position as Cys481 of BTK**

Kinase	Acalabrutinib	Ibrutinib	Zanubrutinib
	IC_{50} (nM) (N≥3)		
BTK[a]	5.1 ± 1.0	1.5 ± 0.2	0.5 ± 0.0
TEC[b]	126 ± 11	10 ± 12	44 ± 19
ITK[c]	>1000	4.9 ± 1.2	50 ± 5
TXK[c]	368 ± 141	2.0 ± 0.3	2.2 ± 0.6
BMX[c]	46 ± 12	0.8 ± 0.1	1.4 ± 0.4
EGFR[c]	>1000	5.3 ± 1.3	21 ± 1
ERBB2[c]	~1000	6.4 ± 1.8	88 ± 26
ERBB4[c]	16 ± 5	3.4 ± 1.4	6.9 ± 0.6
BLK[c]	>1000	0.1 ± 0.0	2.5 ± 0.4
JAK3[c]	>1000	32 ± 15	>1000

<10-fold selectivity versus BTK

>10- to <100-fold selectivity versus BTK

>100-fold selectivity versus BTK

Acalalabrutinb non inibisce ITK nè EGFR. Minimo effetto inibitorio su TEC, TXK

Profiling of BTKis on Src family kinases†

Kinase	Acalabrutinib	Ibrutinib	Zanubrutinib
	IC_{50} (nM) (N=2)		
BLK	>1000	0.1 ± 0.0	2.5 ± 0.4
FGR	>1000	3.3 ± 1.1	101 ± 20
FYN	>1000	29 ± 0	755 ± 15
HCK	>1000	29 ± 0	>1000
LCK	>1000	6.3 ± 1.3	147 ± 13
LYN	>1000	20 ± 1	668 ± 127
SRC	>1000	19 ± 1	504 ± 37
YES1	>1000	4.1 ± 0.2	420 ± 143

Acalabrutinib non inibisce le SRC family kinasi

Figures from Kaptein et al. Blood. 2018;132(Suppl 1):1871. *Values are mean ± SD, and are from: aIMAP assay, bLanthaScreen assay, cZ'-LYTE assay
†Values are mean ± SD and are from Z'-LYTE assay. 1. Kaptein et al. Blood 2018;132(Suppl 1):1871; 2. Barf et al. J Pharmacol Exp Ther 2017;363(2):240–252; 3. Estupiñán et al. Front Cell Dev Biol 2021;9:630942 AE, adverse event; BTK, Bruton tyrosine kinase; BTKi, BTK inhibitor; CV, cardiovascular; Cys, cysteine; HTN, hypertension; VF, ventricular fibrillation

Review

Management of adverse effects/toxicity of ibrutinib

Semra Paydas

Critical Reviews in Oncology / Hematology 136 (2019) 56–63

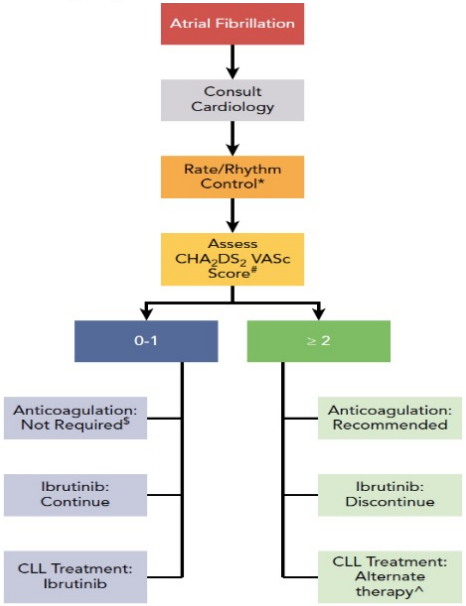
Key points in cases using ibrutinib associated atrial fibrillation.
Adapted from de Weerdt I, 2017 Figure 2.

- Rate and rythm must be controlled strictly
  - The use of The use of P-glycoprotein substrates and CYP3A inhibitors must be avoided
  - There is no need for anti-coagulation in cases CHA2DS2-VASc ≤ HAS BLED score
  - Anti-coagulation is necessary in cases CHA2DS2-VASc > HAS BLED score.
  - Direct anti-coagulants are preferred over vitamin K antagonists or alternative anti-neoplastic strategy must be considered

How I manage ibrutinib intolerance and complications in patients with chronic lymphocytic leukemia

Deborah M. Stephens[1] and John C. Byrc

Blood. 2019;133(12):129

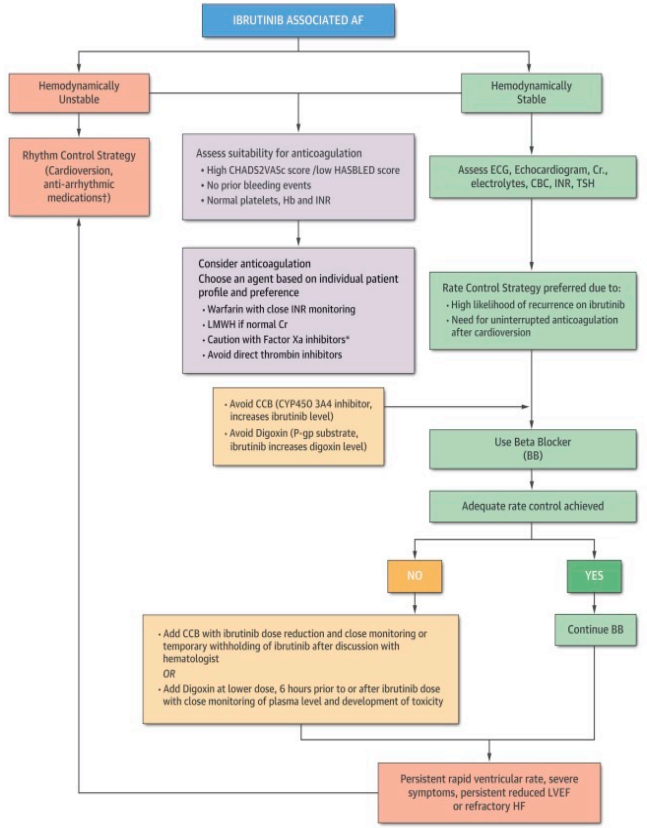


JACC Clin Electrophysiol. 2018 Dec;4(12):1491-1500. doi: 10.1016/j.jacep.2018.06.004. Epub 2018 Aug 29.

Ibrutinib-Associated Atrial Fibrillation.

Ganatra S[1], Sharma A[2], Shah S[2], Chaudhry GM[2], Martin DT[2], Neilan TG[3], Mahmood SS[4], Barac A[5], Groarke JD[6], Hayek SS[7], Dani S[8], Venesy D[2], Patten R[2], Nohria A[8].

CENTRAL ILLUSTRATION: Proposed Algorithm for Ibrutinib-Associated AF Management



Ganatra, S. et al. J Am Coll Cardiol EP. 2018;4(12):1491-500.