Caso clinico 1

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LEUCEMIA LINFATICA CRONICA:
L'INNOVATIVITÀ TERAPEUTICA ED OLTRE...

28-29 MARZO 2023 BOLOGNA ROYAL HOTEL CARLTON

Clinical case (1)

Clinical History

- ♂ 1964
- G2 HPT
- Conc med: ACEi; omeprazole

<u>Jan 2016 CLL diagnosis</u>

Prognostic markers: **Unmutated** IgHV; TP53 WT; negative FISH; PB karyotype 46 XY[20]

→ **March – Oct 2016 first line treatment with FCR (6 cycles) for bulky adenopathies**

Partial remission → follow up

Clinical case (2)

- **March 2021 (+53 mo from 1° line EOT)**

CBC: **Hb 8.9 g/dl**; Ly 158000/mmc; **Plts 72000/mmc**
CT scan: **spleen 21 cm**; upper/below diaphragm adenopathies max 6 cm
PET tb: SUVmax 8
BM biopsy: massive CLL infiltration
Echo: EF 60%, no significant alteration

PB prognostic factors:
Karyotype: 46XY [20]
FISH: **17p-**
TP53: del c604_610 exon 6. mutation=p- (Arg202Serfs]43)[p.(R202Sfs]43)

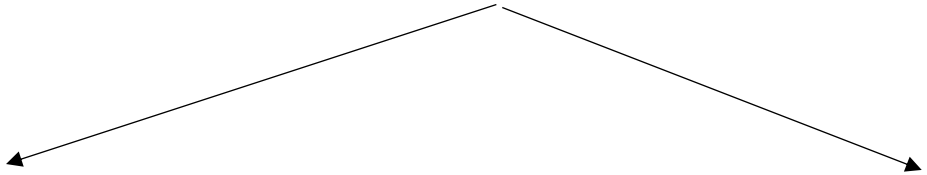
Clinical case (3)

March 2021 (+53 mo from 1° line EOT)

- 57 yrs
- Active working life, often abroad, no significant comorbidities

→ 1° line FCR → remission >3 yrs in UNM IGHV
→ Current Tx criteria: anemia, splenomegaly

→ 17p-, TP53 mutated



- **Continous BTKi**
- **Continous venetoclax monotharapy**

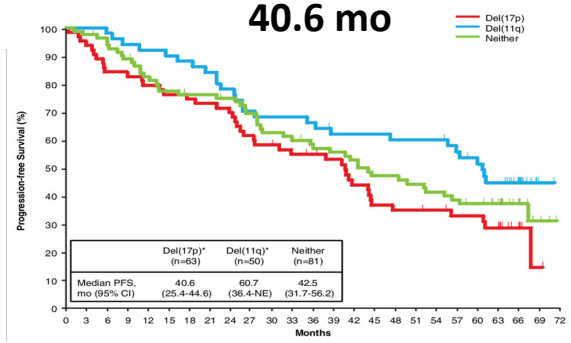
FD with venetoclax + rituximab

Clinical case (4)

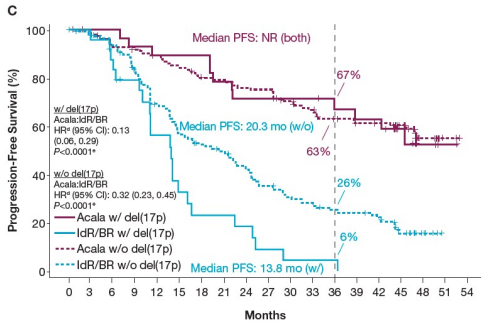
- Continous BTKi
- Continous venetoclax monotharapy

- FD with venetoclax + rituximab

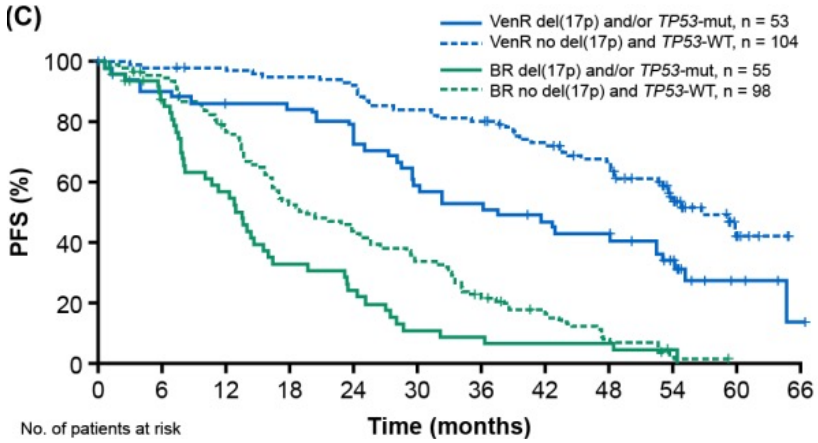
[1]RESONATE PFS in *TP53*
40.6 mo



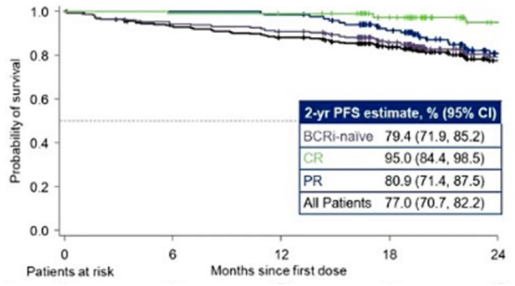
[2]ASCEND 3 yrs PFS in *TP53*
67%



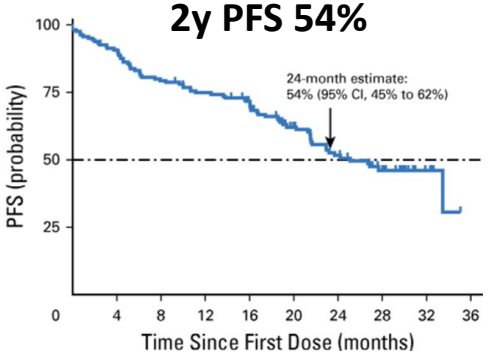
[6]MURANO m PFS in *17p-/TP53*: 37.4 mo



[3]Ven single agent in BTKi naive (16% TP53), 2y PFS 79%



[4]Ven single agent in 17p-
2y PFS 54%



[1]*Munir et al. AJH 2019*
[2]*Jurkzak et al. ASCO 2022*
[3]*Kater EHA 2020*
[4]*Stingelbauer JCO 2018*

Clinical case (5)

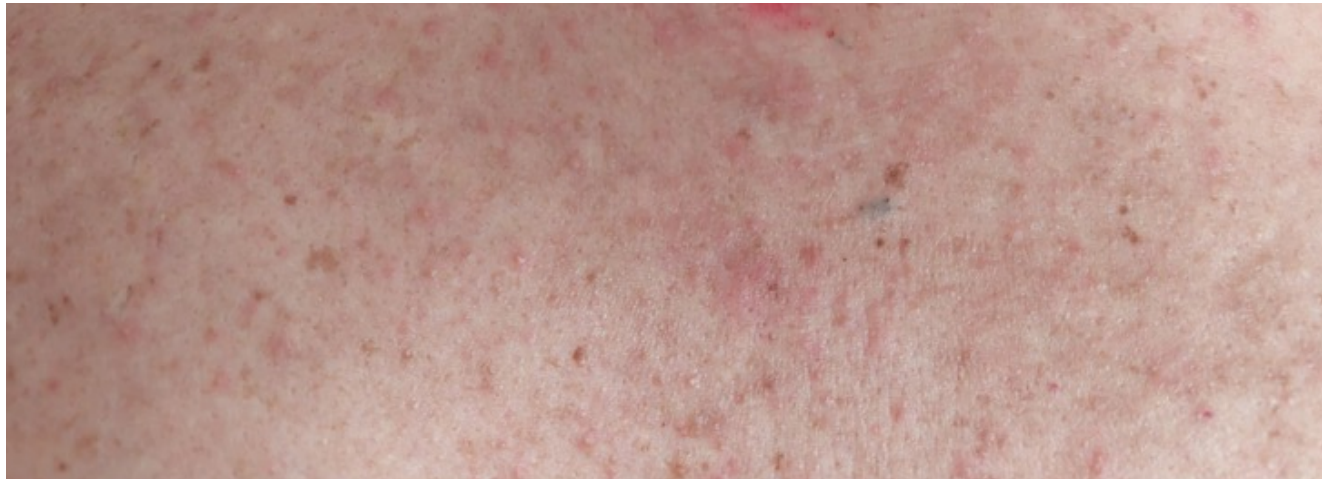
April 2021: start with ibrutinib 420 mg/d

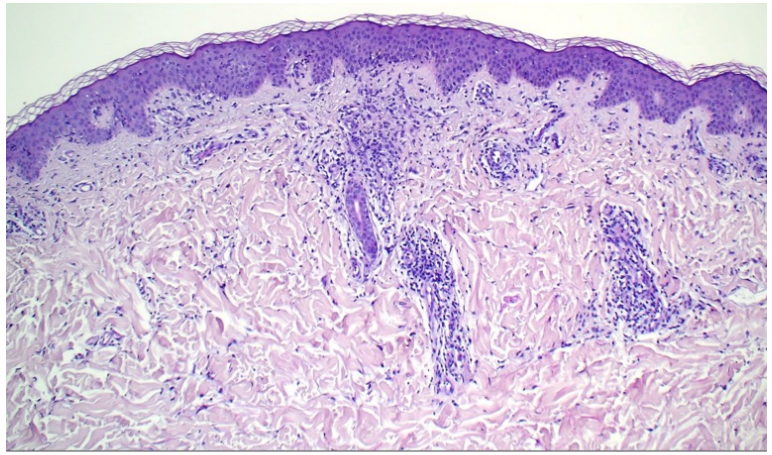
→ Oct 2021 (+ 6 months): Hb 12.1 g/dl; Plts 121.000/mmc
Abdominal US: spleen 16 cm

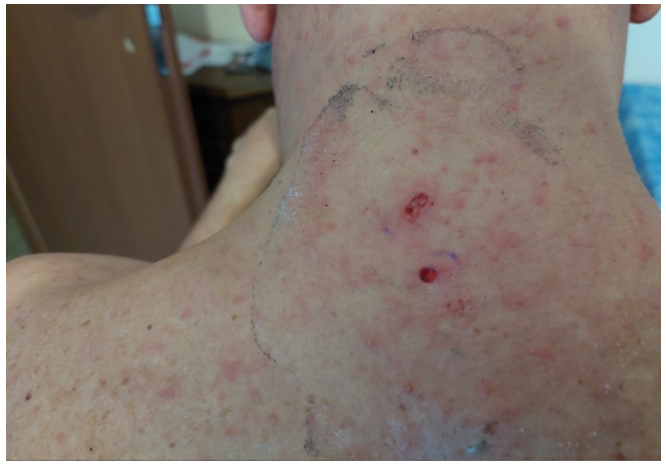
Dec 2021 (+8 mo from ibru start):

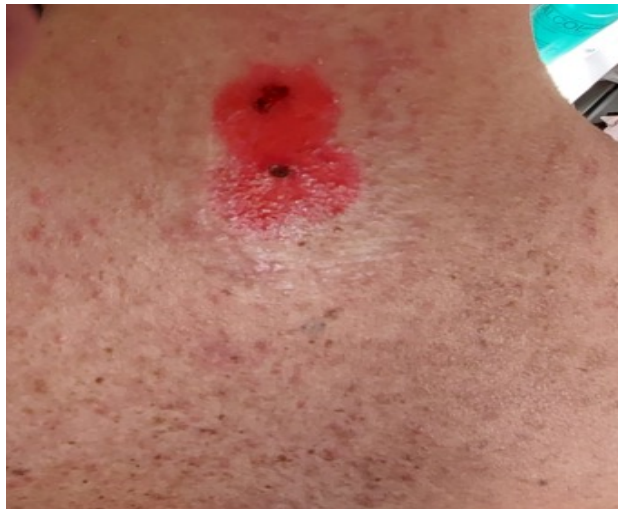
rapidly evolving, itchy, maculopapular rash of neck, arms and trunk

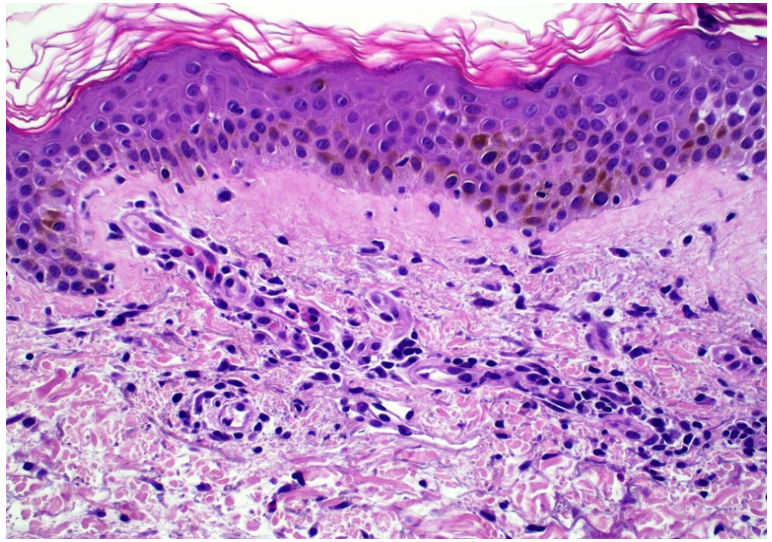
Clinical case (6)



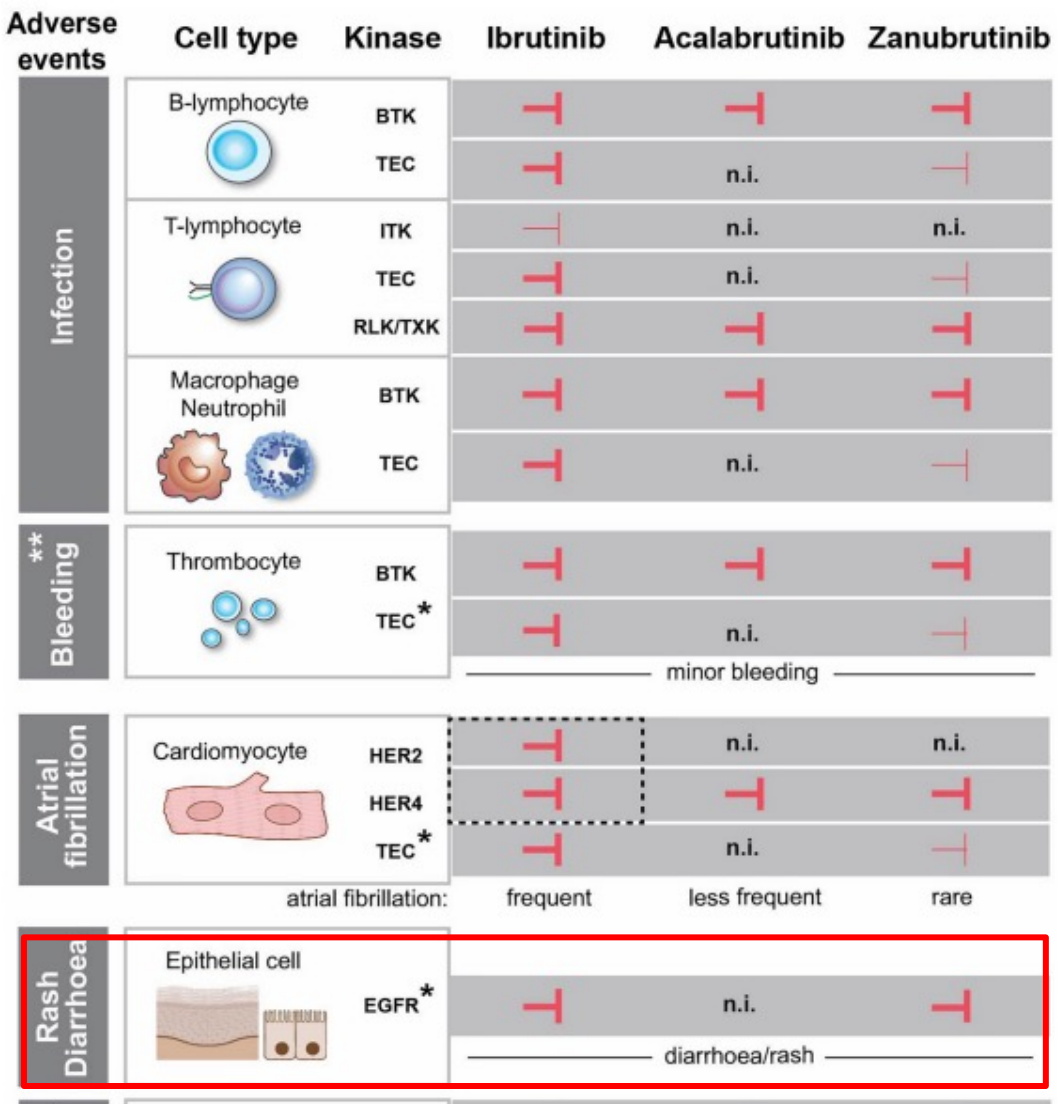






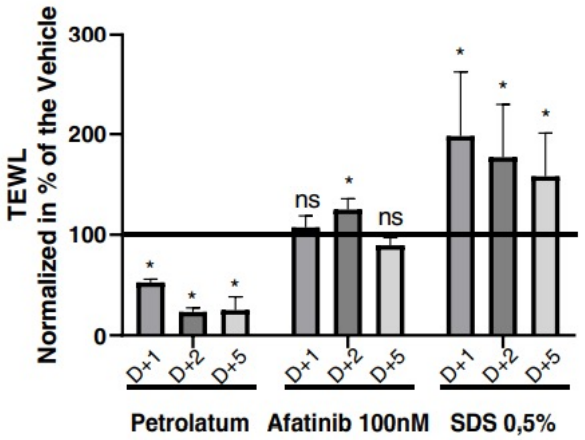


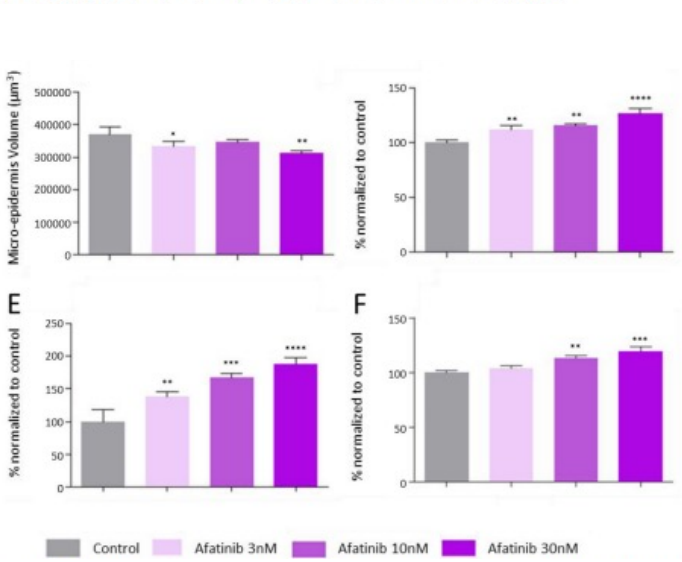
EGFR inhibition and rash



Estupinan HY, et al Front Cell Dev Biol 2021

EGFR inhibition on trans-epidermal water loss





Li, Front in Oncol 2022

Ibrutinib-associated cutaneous toxicity

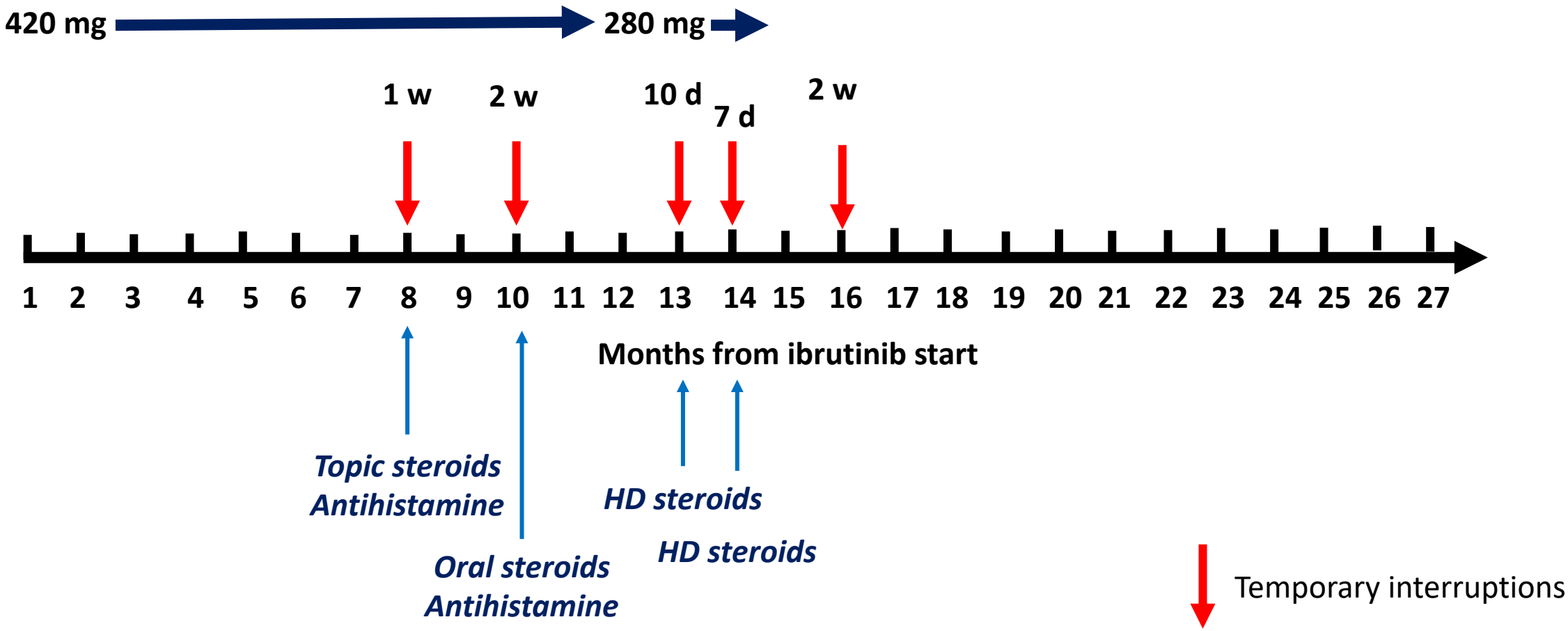
- ❑ 3-47% of patients treated for CLL (vs 2-15% in WM and MCL)
- ❑ Possible association with PB lymphocytosis (exp in early manifestations)
- ❑ Mostly case reports
- ❑ Dose-dependent
- ❑ Mostly G1-2
- ❑ Less reports with next generation BTKi

AE	Incidence all-grade AE (%)	Incidence high-grade AE (%)
Cutaneous bleeding	24.8	-
Cutaneous infections		
Rash		
Mucositis		
Edema		
Pruritus		
Xerosis	9.2	-
Nail changes	17.8	-
Hair changes	7.9	-

1) **Asympt. non-palpable petechial rash**
2) **Pruritic palpable purpura**
3) **Pityriasis rosea-like rash**
4) **Papulopustular (acneiform) rash**
5) **Painless non-pruritic edematous papules**

Nocco, Crit Rev in Oncol/Hematol 2022
Sibaud, Am J Clin Dermatol 2020

Clinical case (7)

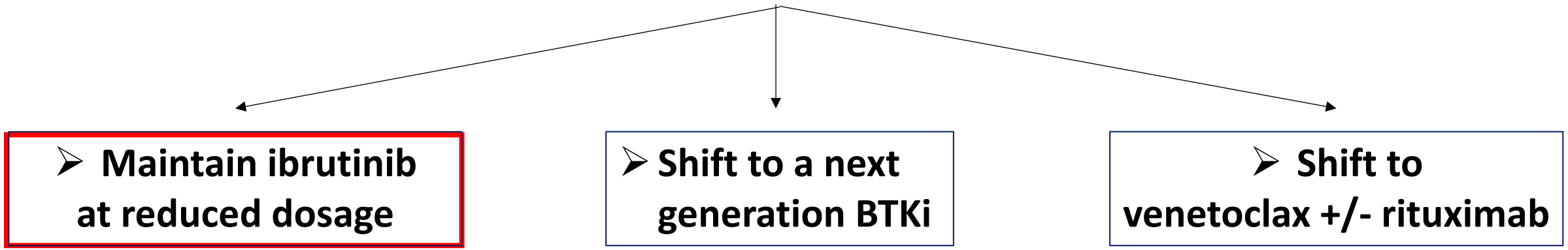


Clinical case (8)

June 2022 (+14 mo from ibrutinib start)

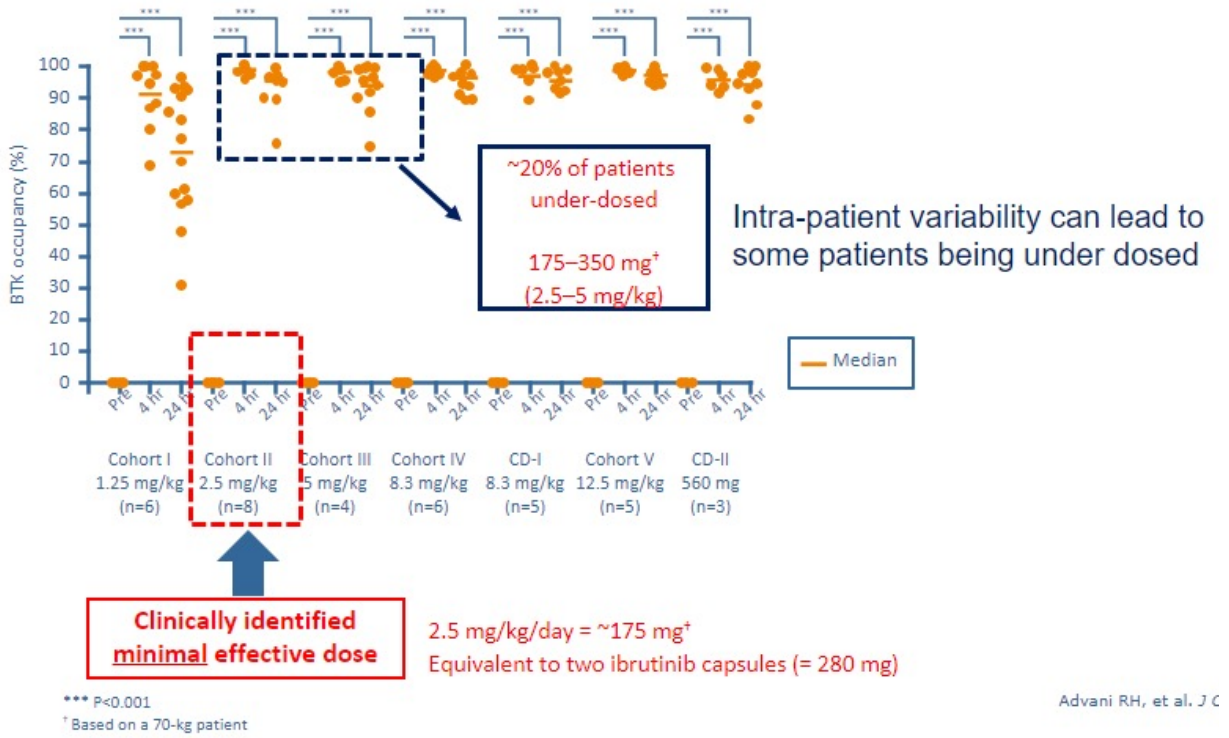
- 58 yrs
- **Active working life**, often abroad, no significant comorbidities

→ UNM IGHV; **17p-, TP53** mutated
→ Not life-treating, but significant **worsening in QoL**
→ Need of **multiple** ibrutinib **temporary interruption**
→ Mild **benefit from dose reduction**



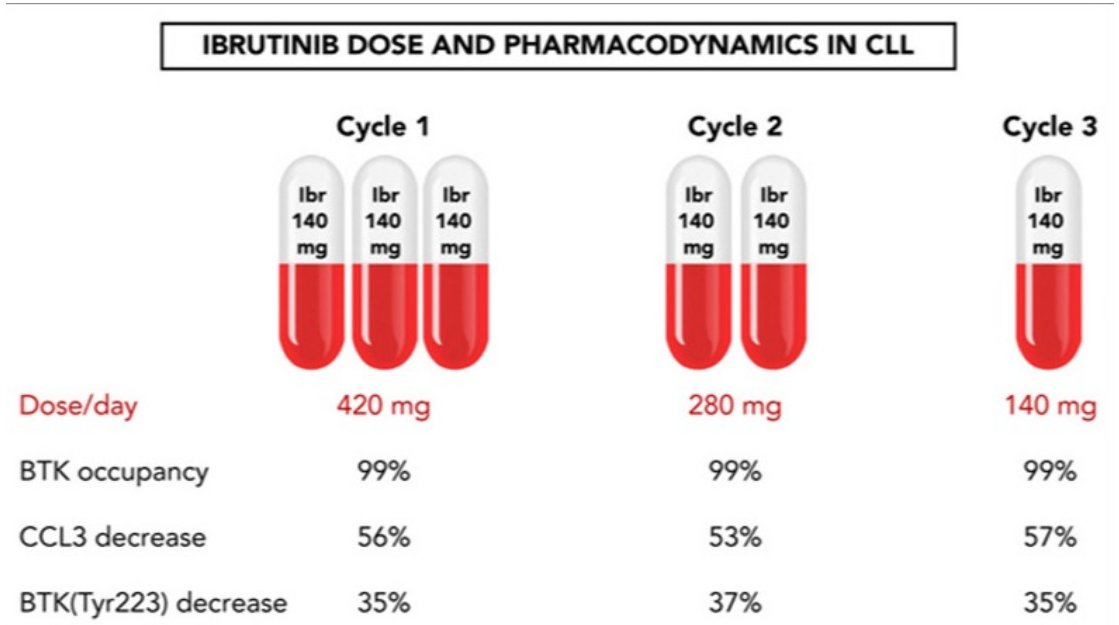
Rationale for ibrutinib dose reduction in CLL

Phase I trial:
2.5 mg/Kg identified as the minimal effective dose



Advani JCO 2013

In vitro studies suggest similar activity on CLL with dose reduction after at least 4 w on full dose



Chen Blood 2018

Impact of ibrutinib dose reduction/temp discontinuations

	Dose reduction	Temporary discontinuations
Parikh, Cancer Med 2020	No impact on EFS and OS (> 2.5 mg/kg vs < 2.5 mg/kg)	Negative impact on EFS and OS
Williams, Clin Myel Lymph Leuk, 2018	Negative impact on PFS and OS	-
Forum UK CLL, Haematologica 2016	No impact on DFS and OS	Negative impact (cut off 14 days) on DFS and OS
Condoluci, Hematol Oncol. 2021	No impact on PFS	No impact on PFS
Akhtar, Leukemia & Lymphoma 2019	No impact on PFS and OS	No impact on PFS and OS
Mato, Br J Hematol 2018	No impact on ORR, PFS, OS	-
Tedeschi, Blood Adv 2020	No impact on EFS, PFS, OS	-

Data on clinical impact of dose reduction are not univocal!

Clinical case (8)

June 2022 (+14 mo from ibrutinib start)

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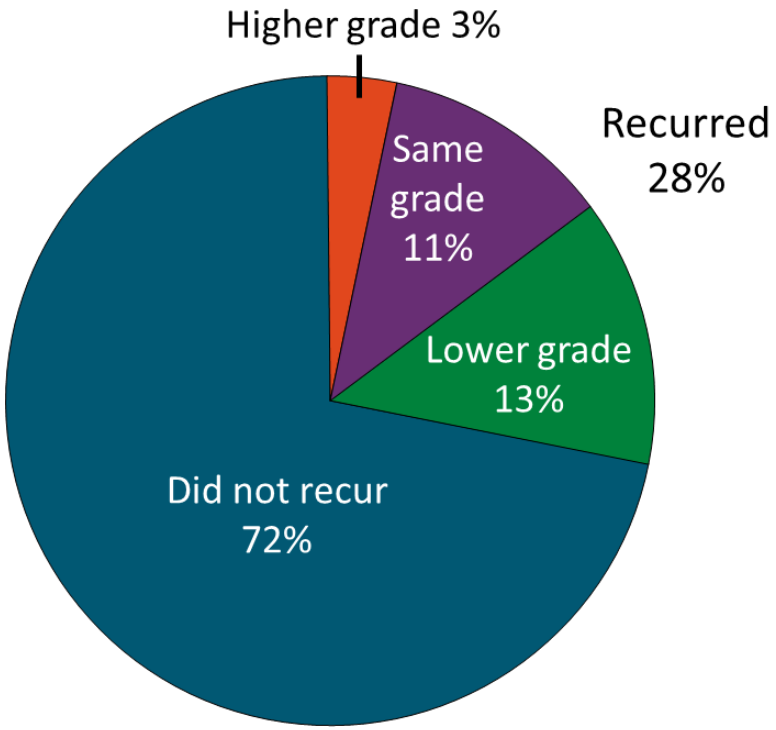
➢ **Maintain ibrutinib reduced dosage**

➢ **Shift to a next generation BTKi**

➢ **Shift to venetoclax +/- rituximab**

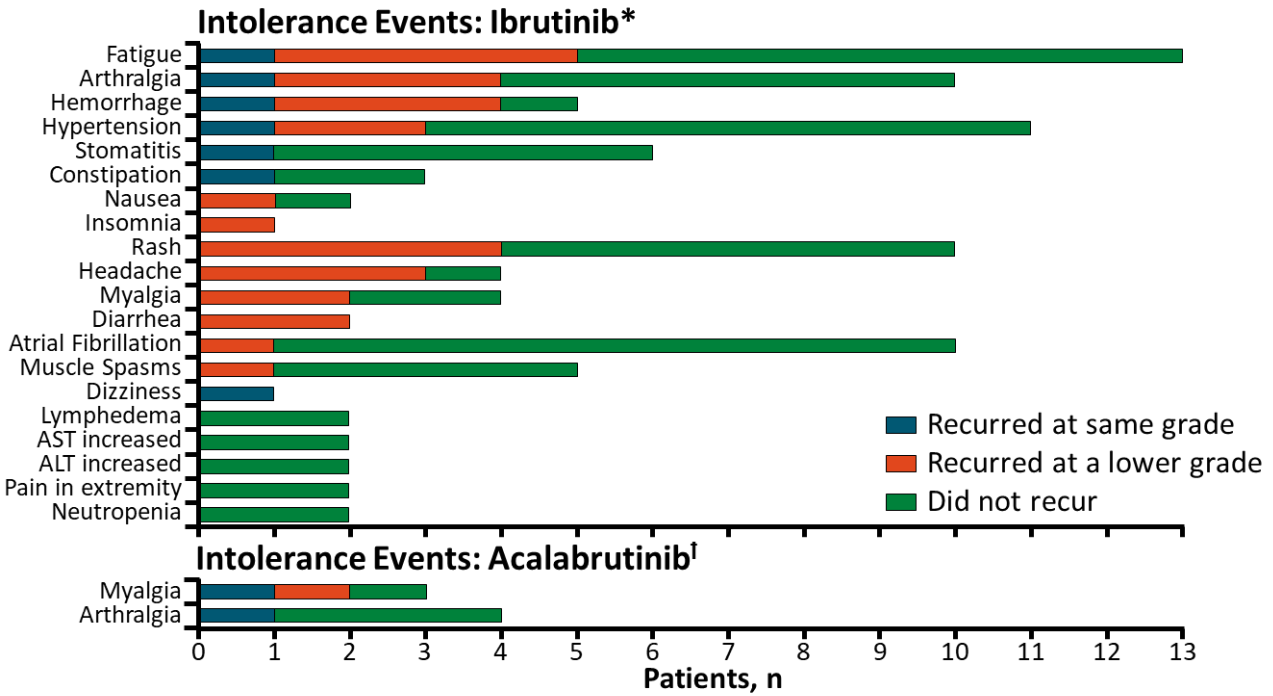
Next generation BTKi in intolerant pts

Acalabrutinib in ibrutinib intolerant



Awan. Blood Adv. 2019

Zanubrutinib in acalabrutinib or ibrutinib intolerant



Shadman. Lancet Haematol. 2022;S2352.

Clinical case (8)

June 2022 (+14 mo from ibrutinib start)

- 58 yrs
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→ UNM IGHV; **17p-, TP53** mutated
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Pro	Cons
❑ **Well-known efficacy in BTKi-pretreated**	❑ **Very limited treatment options in BTKi+Bcl2i pretreated pts**
❑ **Minimal toxicity**	❑ **Allogenic transplant is an option in this young, 17p deleted patient**

➢ **Shift to venetoclax +/- rituximab**

Clinical case (9)

June 2022 (+11 mo from ibrutinib start)

- 58 yrs
- **Active working life**, often abroad, no significant comorbidities

→ UNM IGHV; **17p-, TP53** mutated
→ Significant **worsening in QoL**
→ Need of **multiple** ibrutinib **temporary interruption**
→ Mild **benefit from dose reduction**

- **Maintain ibrutinib reduced dosage**
- **Shift to a next generation BTKi**
- **Shift to venetoclax +/- rituximab**

- **Young**
- **Eligible to allogenic SCT**
- **Intolerant, not progressive while on 1st generation BTKi**

July 2022,
shift to zanubrutinib (CUP)

Immediate recurrence of G2 rash

Acalabruitnib and Zanubrutinib: Kinase Selectivity Relative to Ibrutinib

Kinase	ACP-196	ibrutinib
Btk	5.1	1.5
Tec	93	7.0
BMX	46	0.8
Txk	368	2.0
ERBB2	~1000	6.4
EGFR	>1000	5.3
Itk	>1000	4.9
Jak3	>1000	32
Blk	>1000	0.1

Covey AACR 2015. Abstract 2596.

Targets	Assays	Ibrutinib IC_{50} (nM)	Zanubrutinib IC_{50} (nM)	Ratio (Zanubrutinib:Ibrutinib)
BTK	BTK-pY223 Cellular Assay	3.5	1.8	0.5
	Rec-1 Proliferation	0.34	0.36	1.1
	BTK Occupation Cellular Assay	2.3	2.2	1.0
	BTK Biochemical Assay	0.20	0.22	1.1
EGFR	p-EGFR HTRF Cellular Assay	101	606	6.0
	A431 Proliferation	323	3,210	9.9
ITK	ITK Occupancy Cellular Assay	189	3,265	17
	p-$PLC_{\gamma 1}$ Cellular Assay	77	3,433	45
	IL-2 Production Cellular Assay	260	2,536	9.8
	ITK Biochemical Assay	0.9	30	33
JAK3	JAK3 Biochemical Assay	3.9	200	51
HER2	HER2 Biochemical Assay	9.4	661	70
TEC	TEC Biochemical Assay	0.8	1.9	2.4

Acalabruitinib and Zanubrutinib: data on clinical trials

Elevate RR: Acalabrutinib vs Ibrutinib

	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
Event	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Diarrhea[a,b]	92 (34.6)	3 (1.1)	**121 (46.0)**	**13 (4.9)**
Headache[a,b]	**92 (34.6)**	**4 (1.5)**	53 (20.2)	0
Cough[a]	**77 (28.9)**	2 (0.8)	56 (21.3)	1 (0.4)
Upper respiratory tract infection	71 (26.7)	5 (1.9)	65 (24.7)	1 (0.4)
Pyrexia	62 (23.3)	8 (3.0)	50 (19.0)	2 (0.8)
Anemia	58 (21.8)	31 (11.7)	49 (18.6)	34 (12.9)
Neutropenia	56 (21.1)	52 (19.5)	65 (24.7)	60 (22.8)
Fatigue[b]	54 (20.3)	**9 (3.4)**	44 (16.7)	0
Arthralgia[a]	42 (15.8)	0	**60 (22.8)**	2 (0.8)
Hypertension[a,b]	23 (8.6)	11 (4.1)	**60 (22.8)**	**23 (8.7)**
Nausea	47 (17.7)	0	49 (18.6)	1 (0.4)
Pneumonia	47 (17.7)	28 (10.5)	43 (16.3)	23 (8.7)
Thrombocytopenia	40 (15.0)	26 (9.8)	35 (13.3)	18 (6.8)
Dyspnea	37 (13.9)	6 (2.3)	23 (8.7)	1 (0.4)
Bronchitis	34 (12.8)	3 (1.1)	23 (8.7)	2 (0.8)
Constipation	31 (11.7)	0	37 (14.1)	2 (0.8)
Contusion[a]	31 (11.7)	0	**48 (18.3)**	1 (0.4)
Nasopharyngitis	29 (10.9)	0	27 (10.3)	0
Dizziness	28 (10.5)	0	26 (9.9)	0
Vomiting	28 (10.5)	1 (0.4)	36 (13.7)	3 (1.1)
Peripheral edema	26 (9.8)	0	38 (14.4)	1 (0.4)
Rash	26 (9.8)	2 (0.8)	33 (12.5)	0
Myalgia	25 (9.4)	2 (0.8)	27 (10.3)	1 (0.4)
Atrial fibrillation[a]	24 (9.0)	12 (4.5)	**41 (15.6)**	9 (3.4)
Urinary tract infection[a]	22 (8.3)	3 (1.1)	**36 (13.7)**	6 (2.3)
Back pain[a]	20 (7.5)	0	**34 (12.9)**	2 (0.8)
Epistaxis	19 (7.1)	1 (0.4)	28 (10.6)	1 (0.4)
Muscle spasms[a]	16 (6.0)	0	**35 (13.3)**	2 (0.8)
Dyspepsia[a]	10 (3.8)	0	**32 (12.2)**	0

Byrd et al, 2021

Alpine: Zanubruitib vs Ibruitnib

TEAE by Preferred Term, n (%)	Zanubrutinib (n=324)	Ibrutinib (n=324)
≥1 TEAE	**318 (98.1)**	**321 (99.1)**
COVID-19	75 (23.1)	58 (17.9)
Neutropenia	74 (22.8)	59 (18.2)
Hypertension	71 (21.9)	64 (19.8)
Upper respiratory tract infection	68 (21.0)	46 (14.2)
Diarrhea	52 (16.0)	78 (24.1)
Anemia	49 (15.1)	51 (15.7)
Arthralgia	47 (14.5)	53 (16.4)
Contusion	44 (13.6)	34 (10.5)
Cough	38 (11.7)	34 (10.5)
Pneumonia	34 (10.5)	40 (12.3)
Rash	33 (10.2)	40 (12.3)
Fatigue	31 (9.6)	43 (13.3)
Pyrexia	27 (8.3)	33 (10.2)
Atrial fibrillation	15 (4.6)	40 (12.3)
Muscle spasms	10 (3.1)	41 (12.7)

TEAE, treatment-emergent adverse event.

Brown et al, 2022

Clinical case (10)

- Sep 2022 STOP zanubrutinib
- As of March 2023 patient is still in PR after 13 months of BTKi
- Continous venetoclax treatment will be started in case of clinical progression

Thanks for your attention!

ACKNOLEDGMENT

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