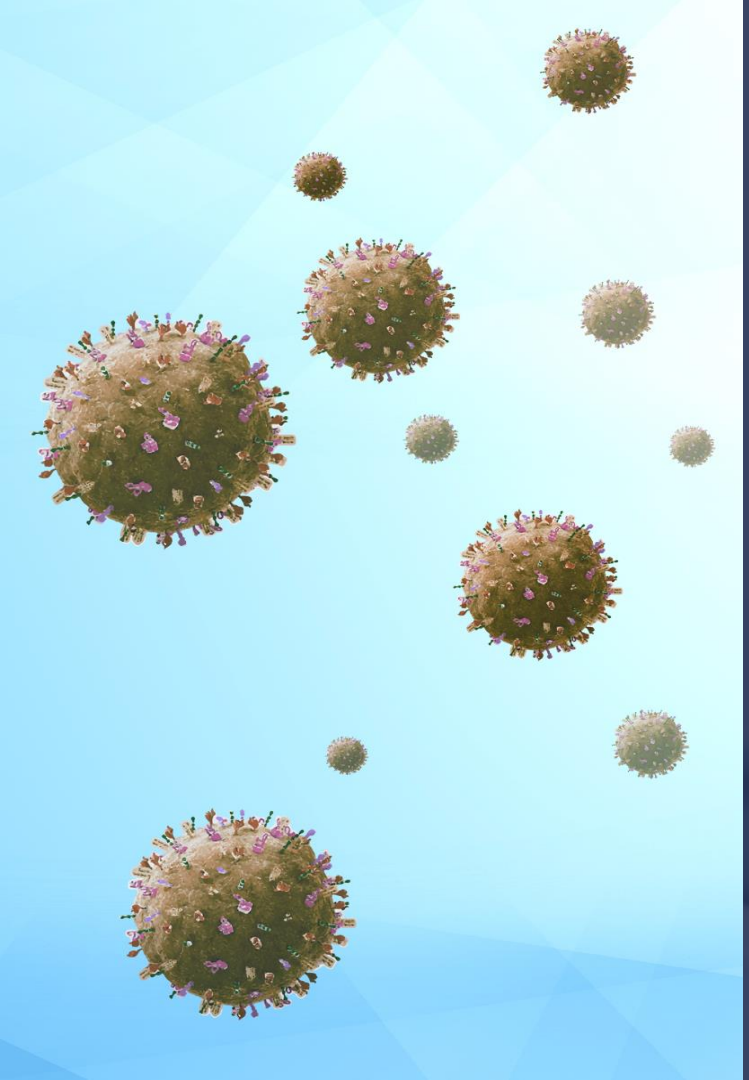


touchPANEL DISCUSSION

Have the next generation of BTK inhibitors come of age for the treatment of Waldenstrom's macroglobulinemia?

An expert panel discussion recorded in June 2020

This educational activity is supported by an educational grant from BeiGene

touch ONCOLOGY®

BTK, Bruton's tyrosine kinase.

Disclaimer

Unapproved products or unapproved uses of approved products may be discussed by the faculty; these situations may reflect the approval status in one or more jurisdictions.

The presenting faculty have been advised by touchIME to ensure that they disclose any such references made to unlabelled or unapproved use.

No endorsement by touchIME of any unapproved products or unapproved uses is either made or implied by mention of these products or uses in touchIME activities.

touchIME accepts no responsibility for errors or omissions.

touch ONCOLOGY®

Expert panel

Dr Roger Owen (Chair)
Consultant Hematologist/Hematopathologist,
St James's Institute of Oncology,
Leeds, UK

Prof. Christian Buske
Medical Director,
Comprehensive Cancer Center Ulm,
University Hospital Ulm,
Germany

Prof. Veronique Leblond
Professor in Hematology,
Department of Hematology,
Pitié Salpêtrière Hospital,
Paris, France

touch ONCOLOGY®

Agenda

What are the failings of first-generation BTK inhibitors?

Presentation: Roger Owen
Panel discussion: Christian Buske and Veronique Leblond; moderated by Roger Owen

New generation, new hope?

Presentation: Roger Owen
Panel discussion: Christian Buske and Veronique Leblond; moderated by Roger Owen

Safety's generation gap

Presentation: Roger Owen
Panel discussion: Christian Buske and Veronique Leblond; moderated by Roger Owen

BTK, Bruton's tyrosine kinase.

touch ONCOLOGY®

First-generation BTK inhibitors in WM

Ibrutinib has been approved by the EMA for patients with WM who have relapsed after primary therapy and for the first-line treatment of patients who are not eligible for chemoimmunotherapy[1]

Oral, irreversible BTK inhibitor that covalently binds to cysteine at position 481 in the kinase domain and thereby blocks kinase activity[2]

iNNOVATE phase III study[3]

- Ibrutinib with rituximab vs rituximab monotherapy in patients who had received no previous treatment or in pretreated, rituximab-sensitive patients
- PFS was 82% with ibrutinib/rituximab vs 28% with placebo/rituximab (HR, 0.2; 95% CI, 0.11–0.38)

Effectiveness of ibrutinib depends on the mutational status of the *MYD88* and *CXCR4* genes[1]

Number of off-target effects and can inhibit other tyrosine kinases[4]

Known to cause bleeding and atrial fibrillation[4]

BTK, Bruton's tyrosine kinase; CI, confidence interval; EMA, European Medicines Agency; HR, hazard ratio; PFS, progression-free survival; WM, Waldenstrom's macroglobulinemia.

1. Kastritis E, et al. *Ann Oncol* 2018;29:iv41–50; 2. Singh P, et al. *Mol Cancer* 2018;17:57; 3. Dimopoulos MA, et al. *N Engl J Med* 2018;378:2399–410; 4. Owen C, et al. *Curr Oncol* 2019;26:e233–40.

touch ONCOLOGY®

Why mutational status matters

Common mutations

- MYD88 L265P is found in over 90% of patients with WM
- Patients with wild-type *MYD88* have a higher risk of aggressive transformation to DLBCL and a worse survival rate
- Recurrent mutations in *CXCR4* have been detected in 30–40% of patients with WM
- Patients with *CXCR4* mutations tend to have higher serum IgM levels, a higher risk of developing symptomatic hyperviscosity and lower rates of extramedullary disease

Response to ibrutinib

- Patients with *MYD88* L265P tend to have deeper and more sustained responses to ibrutinib with a major response rate of 80% and a 5-year PFS rate of 75%
- Patients with WM with concurrent *MYD88* and *CXCR4* mutations had a major response rate of 60% and a median PFS of 4 years
- None of the patients with WM and wild-type *MYD88* achieved a partial response, and the median PFS was shorter at 2 years

DLBCL, diffuse large B-cell lymphoma; PFS, progression-free survival; WM, Waldenstrom's macroglobulinemia.

Castillo JJ, Treon SP. *Leukemia* 2019;33:2555–62.

ASPEN: Phase III randomized trial of zanubrutinib vs ibrutinib for patients with WM

- WM with *MYD88* mutation
- Assigned 1:1 to receive zanubrutinib (160 mg twice daily) or ibrutinib (420 mg once daily)
- Randomization was stratified by *CXCR4* mutational status and the number of lines of prior therapy (0 vs 1–3 vs >3)

CR (%)

Zanubrutinib: **0.00**
Ibrutinib: **0.00**

VGPR (%)

Zanubrutinib: **28.4**
Ibrutinib: **19.2**

Adverse events	Zanubrutinib (%)	Ibrutinib (%)
Grade ≥3	58.4	63.3
Leading to dose reduction	13.9	23.5
Leading to discontinuation	4.0	9.2
Leading to death	1.0	4.1
Atrial fibrillation or flutter	2.0	15.3
Minor haemorrhage	36.6	42.9
Major haemorrhage	5.9	9.2
Hypertension	10.9	17.3
Neutropenia	29.7	13.3

- Improvement in CR+VGPR was not statistically significant between arms
- The zanubrutinib arm reported a safer and more tolerable adverse event profile

CR, complete response; VGPR, very good partial response; WM, Waldenstrom's macroglobulinemia.

1. Dimopoulos M, et al. Presented at 25th European Hematology Association Annual Congress. June 11–21, 2020. Abstract S225.

Single-arm, Phase II study of acalabrutinib monotherapy in patients with WM

- Patients were either treatment-naive (n=14; declined or not eligible for chemoimmunotherapy) or relapsed/refractory (n=92; at least one previous therapy)
- Acalabrutinib (100 mg twice daily) in 28-day cycles until disease progression or unacceptable toxicity

Treatment -naive

OR: **93% (CI 66–100)**

Relapsed/ refractory

OR: **93% (CI 86–98)**

Adverse events	Grade 1–2 (%)	Grade ≥3 (%)
Contusion	29	0
Epistaxis	10	1
Hypertension	2	3
Atrial fibrillation	4	1
Headache	39	0
Neutropenia	1	16

- Tolerable safety profile in patients with treatment-naive or relapsed/refractory WM
- Additional trials needed to compare efficacy with other treatment options

CI, confidence interval; N/A, not applicable; OR, overall response; WM, Waldenstrom's macroglobulinemia.

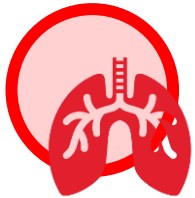
1. Owen RG, et al. *Lancet Haematol* 2020;7:e112–21.

touch ONCOLOGY®

Adverse events of grade ≥3 with ibrutinib

Anemia
Ibrutinib + rituximab: 11%
Rituximab + placebo: 17%

Atrial fibrillation
Ibrutinib + rituximab: 12%
Rituximab + placebo: 1%



Hypertension
Ibrutinib + rituximab: 13%
Rituximab + placebo: 4%

Management of adverse events for patients receiving ibrutinib therapy requires careful planning and recognition of the reported safety profile

Dimopoulos MA, et al. *N Engl J Med* 2018;378:2399–410.

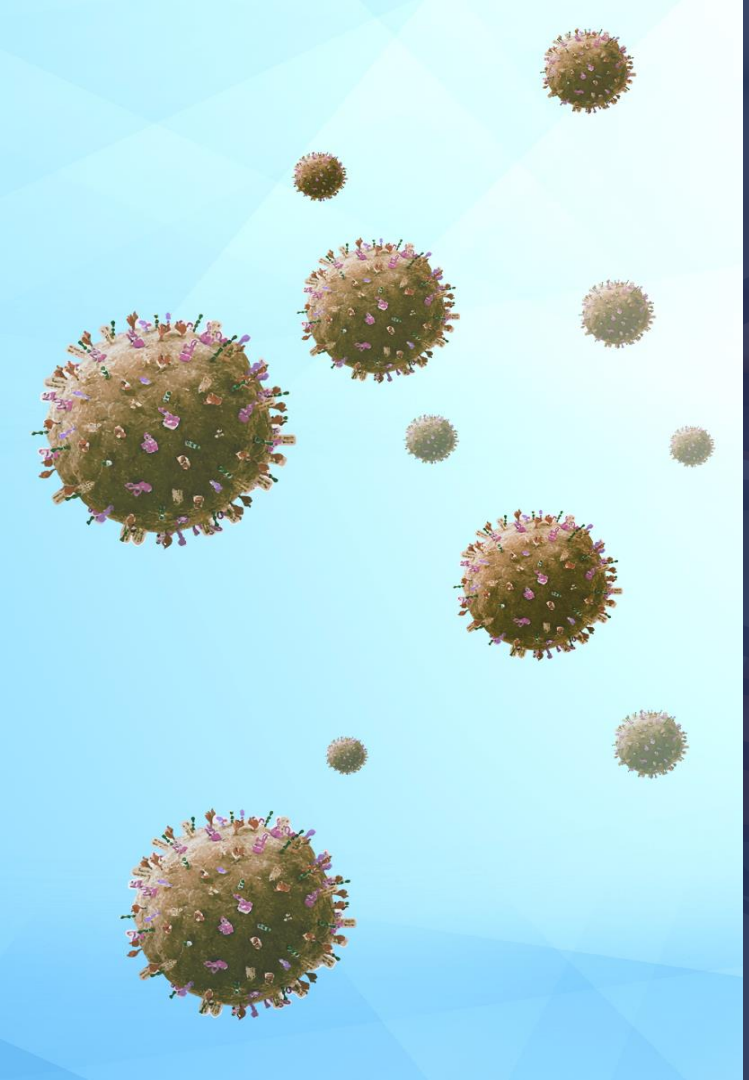
Potential mechanisms for ibrutinib-related adverse events

Atrial fibrillation: inhibition of PI3K

Bleeding: inhibition of platelet aggregation via glycoprotein VI

Infection: inhibition of ITK and/or macrophages

Stephens DM, Byrd JC. *Blood* 2019;133:1298–1307.



Thank you for watching this on-demand event

educationzone.touchoncology.com

touch ONCOLOGY®