Zanubrutinib Versus Acalabrutinib in B-cell Malignancies: An Adverse Event-Based Economic Analysis

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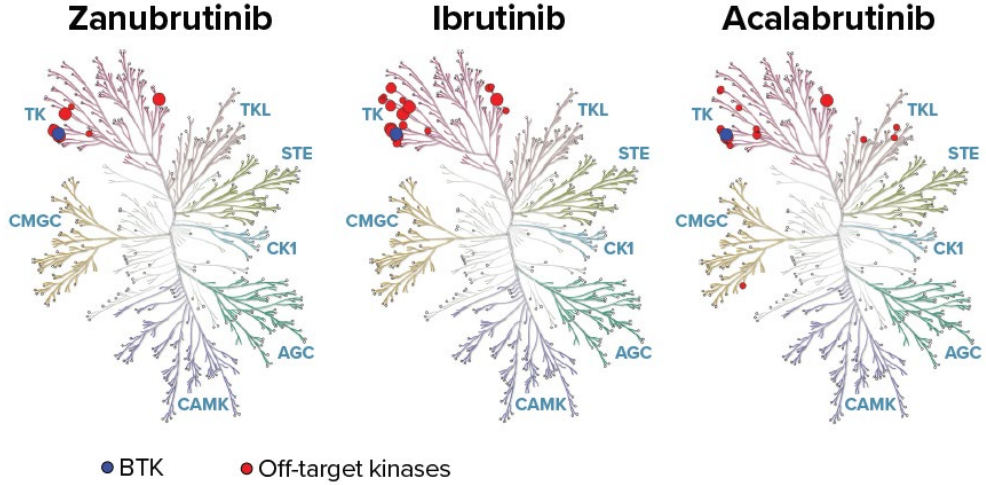
Introduction

- Ibrutinib, a first-generation BTKi, is often associated with treatment-emergent side effects due to off-target binding
- Next-generation BTKis have been designed to improve selectivity and reduce toxicity[1]
- Zanubrutinib (next-generation BTKi) and acalabrutinib (second-generation BTKi), have shown efficacy in clinical trials with better safety profiles than ibrutinib in B-cell malignancies[2,3]
- While direct comparison of zanubrutinib with acalabrutinib is lacking in the literature, a recent meta-analysis of clinical trials by Hwang et al[4] provided a comprehensive comparison of AE profiles of zanubrutinib with acalabrutinib in B-cell malignancies



Adapted from Shadman M, et al. *Lancet Haematol.* 2023;10(1):e35-e45.[5]

Objective: To evaluate the costs and quality of life (QoL) outcomes associated with the usage of zanubrutinib vs acalabrutinib based on their AE profiles as reported by Hwang et al.

AE, adverse event; BTKi; Bruton tyrosine kinase inhibitor; QoL, quality of life.

1. Estupiñán HY, et al. *Front Cell Dev Biol.* 2021;9:630942; 2. Brown JR, et al. *N Engl J Med.* 2023;388:319-332; 3. Byrd JC, et al. *J Clin Oncol.* 2021;39(31):3441-3452;
4. Hwang S, et al. Poster session presented at EHA June 8 - 15, 2023, Frankfurt, Germany; 5. Shadman M, et al. *Lancet Haematol.* 2023;10(1):e35-e45.

Meta-analysis of clinical trials by Hwang et al[1]

- AEs of clinical interest reported by clinical trials of BTKis ibrutinib, acalabrutinib, and zanubrutinib in B-cell malignancies (selected by PubMed hematology/oncology congress abstract searches) were analyzed in this meta-analysis
- Specific AEs seen more commonly with acalabrutinib than zanubrutinib included: infections, atrial fibrillation, diarrhea, nausea/vomiting, headaches, cough, fatigue, and pyrexia
- Specific AEs seen more commonly with zanubrutinib than acalabrutinib included: hematuria, neutropenia, and hypertension

All Grade AEs	Acalabrutinib		Zanubrutinib	
	Incidence (%)	95% CI	Incidence (%)	95% CI
Infection*	64.08	53.93-75.58	32.22	26.81-38.38
URI	18.24	14.46-23.13	18.97	15.09-23.81
Cellulitis*,[a]	5.34	2.66-8.89	36.82	28.99-47.44
Pneumonia	9.72	7.51-12.71	9.29	7.10-12.12
Hemorrhage	35.81	29.59-43.22	40.44	33.65-48.39
Contusion	14.13	10.85-18.37	14.77	11.53-18.97
Hematuria*	4.33	2.52-7.09	10.55	7.91-14.07
Neutropenia*	16.55	13.15-20.73	27.88	22.54-34.51
Anemia	15.13	11.82-19.22	12.81	10.02-16.35
Thrombocytopenia	10.62	8.15-13.85	13.20	10.42-16.71
Neutropenic Fever	1.58	0.88-2.93	1.33	0.73-2.16
Hypertension*	6.56	4.81-8.82	8.96	6.90-11.60
Atrial Fibrillation*	4.93	3.45-7.00	2.38	1.58-3.38
Diarrhea*	32.98	27.69-39.11	15.85	12.98-19.67
Nausea*	17.35	13.74-21.74	10.21	7.88-13.13
Vomiting*	9.95	7.60-12.92	6.84	4.78-9.51
Headache*	30.96	24.63-38.87	9.51	7.18-12.54
Cough*	19.29	15.44-24.21	13.04	10.27-16.53
Fatigue*	19.20	15.49-23.74	10.83	8.47-13.76
Pyrexia*	14.68	11.60-18.65	8.27	6.17-10.96
Arthralgia	12.72	9.77-16.72	11.23	8.72-14.41

Grade ≥3 AEs	Acalabrutinib		Zanubrutinib	
	Incidence (%)	95% CI	Incidence (%)	95% CI
Infection*	18.01	12.91-25.75	12.43	8.89-17.88
URI	0.91	0.53-1.55	1.82	1.00-3.19
Cellulitis*,[a]	2.21	0.63-5.03	13.15	8.96-19.83
Pneumonia	5.24	3.59-7.93	4.46	3.05-6.70
Hemorrhage	1.96	1.23-3.14	3.28	1.98-5.45
Contusion	0.09	0.00-0.27	0.07	0.00-0.26
Hematuria	0.21	0.05-0.77	0.13	0.00-0.47
Neutropenia*	13.56	9.97-17.66	18.37	13.43-25.05
Anemia*	7.45	5.08-11.19	4.11	2.67-6.39
Thrombocytopenia	5.22	3.63-7.75	4.80	3.28-7.14
Neutropenic Fever	1.35	0.75-2.24	1.24	0.66-1.99
Hypertension*	2.55	1.56-4.14	4.83	3.25-7.28
Atrial Fibrillation	1.63	0.86-2.97	0.93	0.45-1.75
Diarrhea	1.81	1.07-3.03	1.19	0.53-2.43
Nausea	0.48	0.26-0.85	0.38	0.06-0.80
Vomiting	0.29	0.14-0.59	0.19	0.00-0.50
Headache	0.65	0.38-1.18	0.57	0.23-1.12
Cough	0.24	0.11-0.51	0.19	0.04-0.45
Fatigue	1.97	1.25-3.09	1.15	0.44-2.36
Pyrexia	0.94	0.57-1.73	0.74	0.34-1.33
Arthralgia	0.72	0.39-1.32	0.76	0.40-1.51

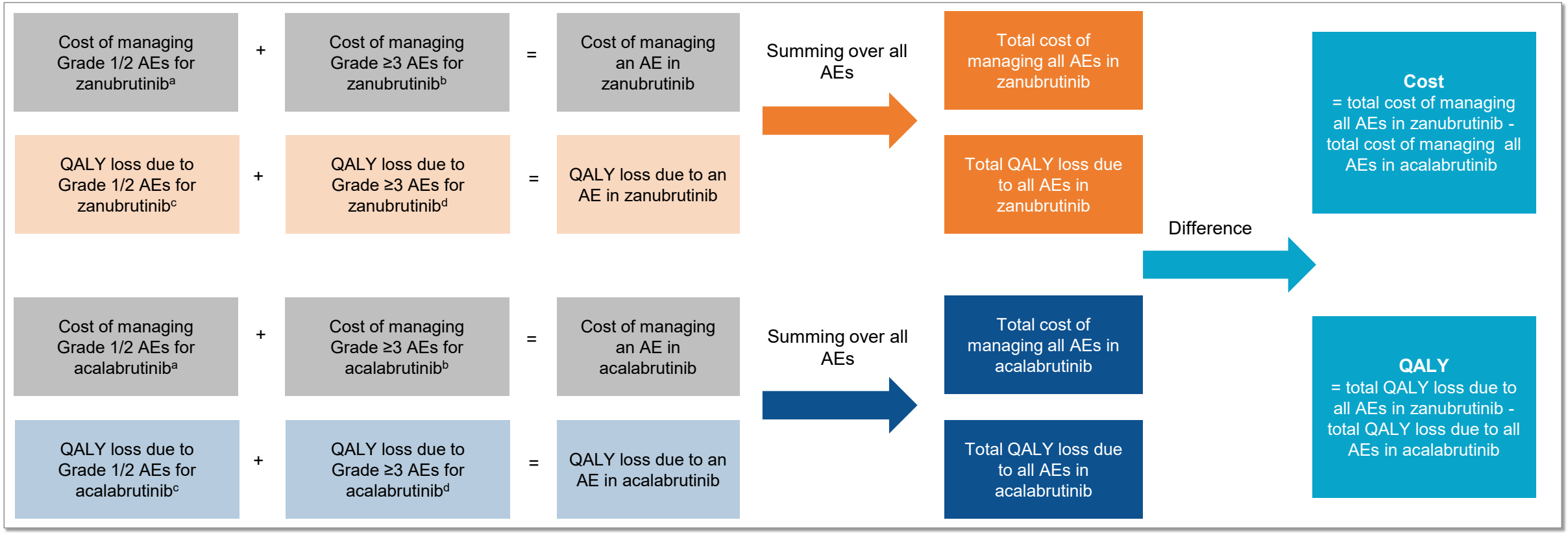
**Statistically significant difference by relative risk. [a]Reported as more common with zanubrutinib but excluded from the current economic analysis due to a data error as reported by the authors in Hwang et al. Cells in blue are AEs significantly higher for acalabrutinib. Cells in red are AEs significantly higher for zanubrutinib.*

AE, adverse event; BTKi; Bruton tyrosine kinase inhibitor; CI, confidence interval; URI, upper respiratory infection.

1. Hwang S, et al. Poster session presented at EHA June 8 - 15, 2023, Frankfurt, Germany.

Methods

- Total cost of managing AEs was estimated by summing the costs of Grade ≥3 and Grade 1/2 AEs
- The QALY loss for each AE was calculated by multiplying the incidence rates with the disutility weights assigned to them and their duration



[a]Incidence of Grade 1/2 AEs × unit cost of managing Grade 1/2 AEs. [b]Incidence of Grade ≥3 AEs × unit cost of managing Grade ≥3 AEs. [c]Incidence of Grade 1/2 AEs × disutility of Grade 1/2 AEs × duration of Grade 1/2 AEs. [d]Incidence of Grade ≥3 AEs × disutility of Grade ≥3 AEs × duration of Grade ≥3 AEs.
AE, adverse event; QALY, quality-adjusted life year.

Inputs and assumptions

Input item	Description
Incidence rates (IRs) for All Grade and Grade ≥3 AEs of interest	• Encompassed 20 different conditions including bleeding events, hypertension, atrial fibrillation, cytopenias, infections, headache, arthralgia, diarrhea • Sourced from Hwang et al[1]
Cellulitis data from Hwang et al[1]	• Excluded from this analysis due to a data error, as reported by the authors • At their request, incorrect data concerning cellulitis has been removed, ensuring its incidence will be accurately reported in the final publication

Disutility and average duration of AEs	• Sourced from the published literature and previous NICE single technology appraisals (STAs)
	• Due to lack of evidence reporting disutility for Grade 1/2 AEs:
	  ○ Disutility and average duration for Grade ≥3 AEs sourced from published literature or the NICE STAs
	  ○ Disutility for Grade 1/2 AEs assumed to be 30% less than that corresponding to severe AEs; assumption validated by clinical experts

Unit cost of each AE	• Derived from National Schedule of NHS costs database[2] (FY 2021-2022) using AE-specific Healthcare Resource Group (HRG) codes, in consultation with clinical experts; all unit costs inflated to 2023 GBP
Model inputs for a few AEs*	• Could not be obtained from literature; a substitute value of another closely related AE was assumed in consultation with clinical experts

*Hematuria, contusion, and neutropenic fever.
AE, adverse event; FY, fiscal year; GBP, British pound sterling; IR, incidence rate; NHS, National Health Service; NICE, National Institute for Health and Care Excellence.
1. Hwang S, et al. Poster session presented at EHA June 8 - 15, 2023, Frankfurt, Germany; 2. National Health Service (NHS). National Schedule of NHS Costs 2021/22. Available at: https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/

Analyses

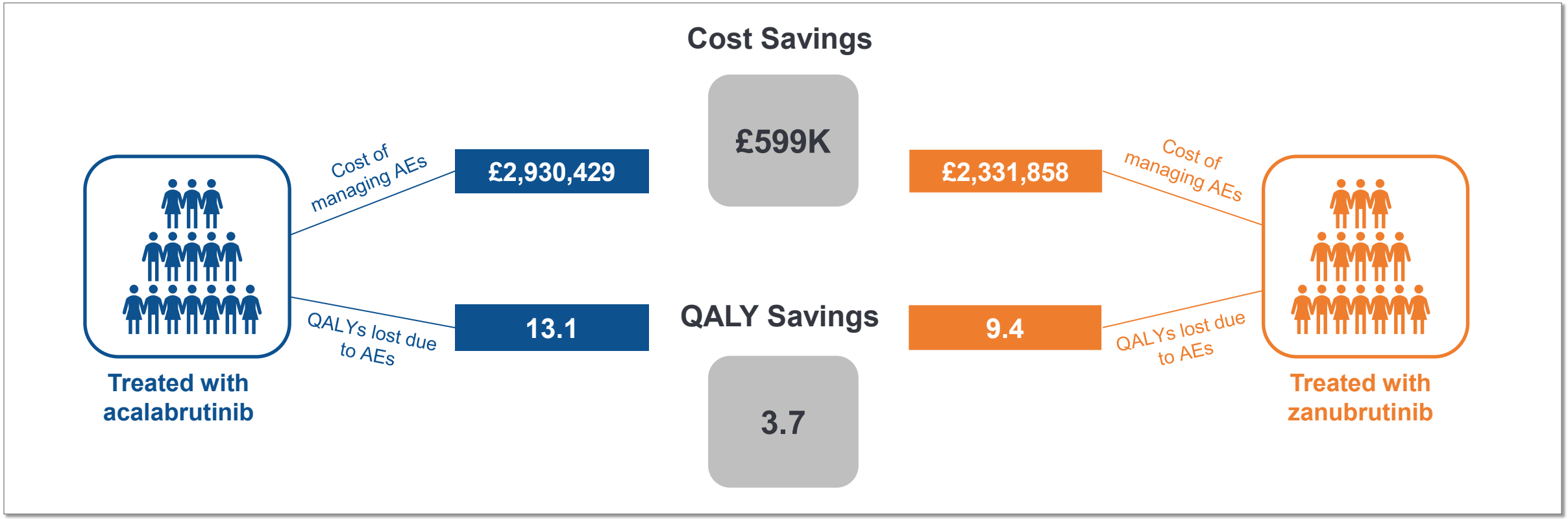
Analysis type	Description
Base case	• All AEs for a hypothetical cohort of 1,000 patients treated in clinical practice with zanubrutinib and acalabrutinib
Scenario	• Grade ≥3 AEs, Grade 1/2 AEs, and AEs that were statistically significantly different in zanubrutinib and acalabrutinib arms (n=13)[1]
Sensitivity	• Uncertainty around model parameters estimated in one-way sensitivity analysis (OWSA) • Consistency of results checked by probabilistic sensitivity analysis (PSA) with 1,000 iterations, assuming the appropriate statistical distributions for parameters

AE, adverse event.

1. Hwang S, et al. Poster session presented at EHA June 8 - 15, 2023, Frankfurt, Germany.

Results: Base case analysis

- In the base case, considering all AEs, treatment of a hypothetical cohort of 1,000 patients with zanubrutinib instead of acalabrutinib was associated with cost savings of £599K and 3.7 QALY savings



AE, adverse event; QALY, quality-adjusted life year.

Results: Scenario analyses

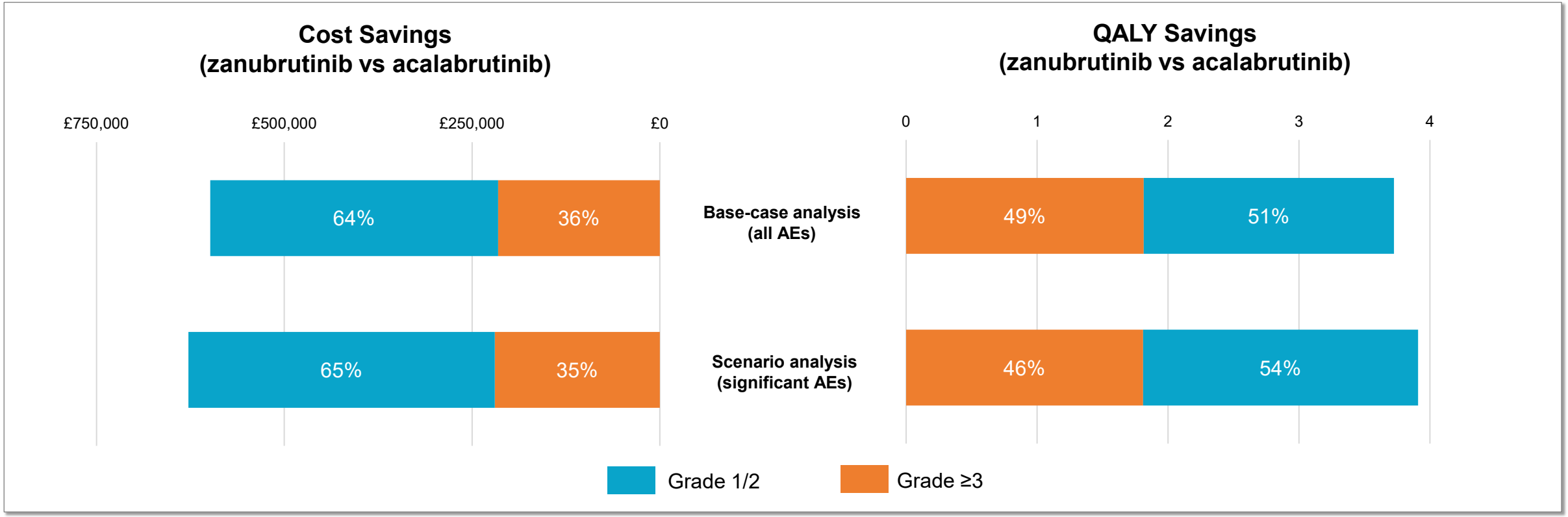
- Scenario analysis for Grade ≥3 AEs and Grade 1/2 AEs showed similar trends for cost savings and QALY savings
- Scenario analysis limited to AEs significantly different between zanubrutinib and acalabrutinib yielded consistent results

Population	AE Grade	Cost Savings (zanubrutinib vs acalabrutinib)	QALY Savings (zanubrutinib vs acalabrutinib)
Hypothetical cohort (n=1,000) | Specific-grade AEs	Grade ≥3	£215,331	1.8
	Grade 1/2	£383,240	1.9
Hypothetical cohort (n=1,000) | Significantly different AEs	All grades	£627,638	3.9
	Grade ≥3	£219,749	1.8
	Grade 1/2	£407,889	2.1

AE, adverse event; QALY, quality-adjusted life year.

Results: Disaggregated by AE severity

- In the base case and scenario analyses, the relative contribution of Grade 1/2 AEs in cost savings was higher than Grade ≥3 AEs
- In the base case and scenario analyses, QALY savings were similar among Grade ≥3 and Grade 1/2 AEs

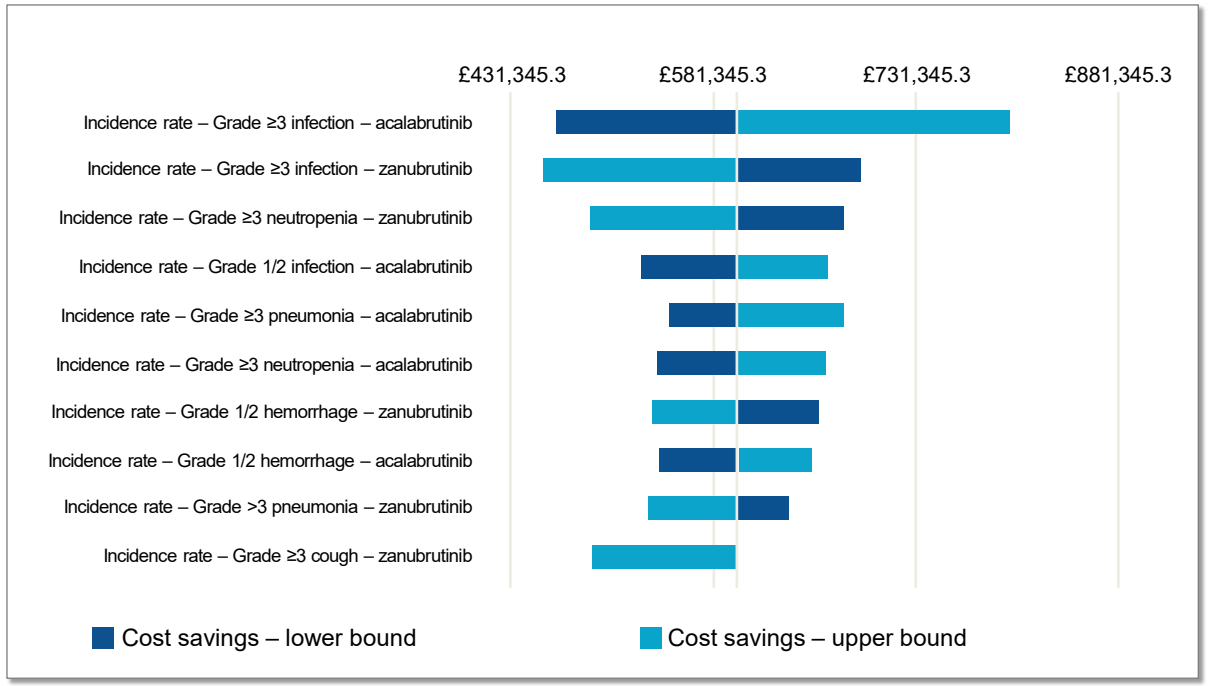


AE, adverse event; QALY, quality-adjusted life year.

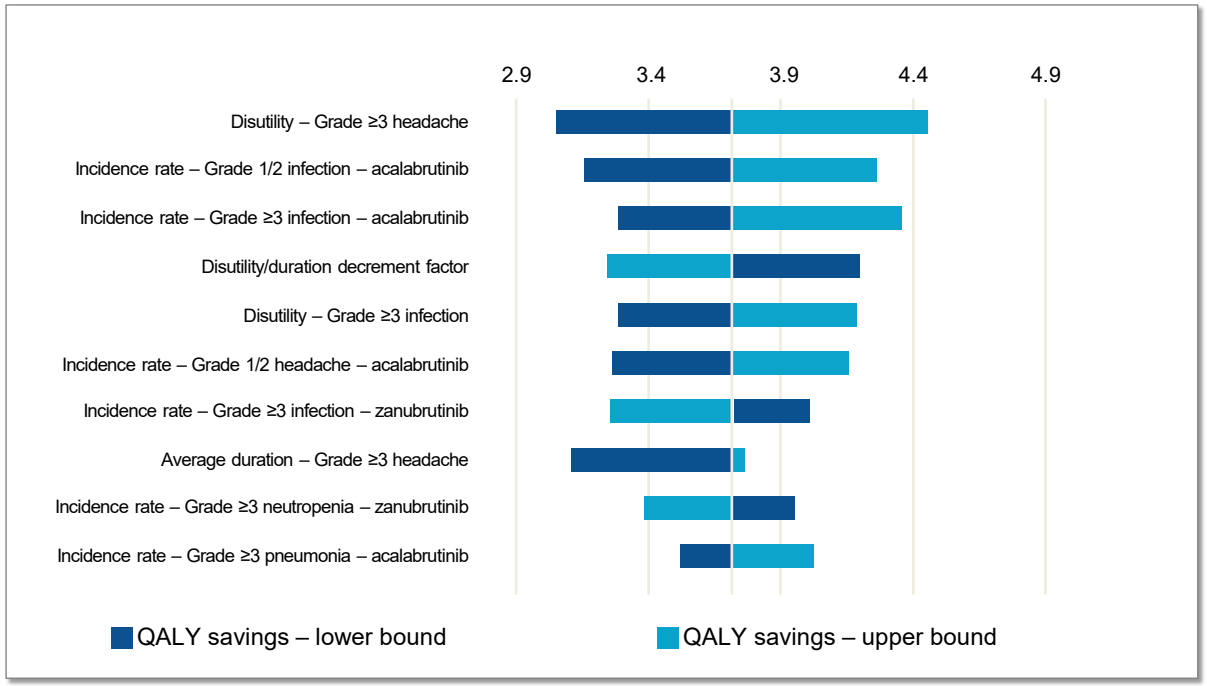
Results: Sensitivity analyses

- OWSA results indicate:
  - Infection IRs as most influential parameter affecting the cost savings
  - Disutility associated with headache and infection IRs in acalabrutinib as most influential parameters affecting QALYs
- PSA results were consistent with the base case results, thus supporting the robustness of the analysis

OWSA: Results on Cost Savings for Zanubrutinib



OWSA: Results on QALY Savings for Zanubrutinib



IR, incidence rate; OWSA, one-way sensitivity analysis; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Limitations

- Direct data such as disutility and duration of disutility of particular AEs* were not available
  - To mitigate this limitation, these assumptions were carefully considered, and the input of clinical experts was sought to validate the assumptions and ensure they were reasonable within the context of current clinical practice
- Economic and QoL benefits for zanubrutinib vs acalabrutinib demonstrated in this analysis were restricted to the impact of AEs
  - Efficacy gains demonstrated for zanubrutinib vs acalabrutinib through indirect comparisons (eg, see Shadman et al. 2024[1]) were not considered

*Hematuria, contusion, and neutropenic fever.
AE, adverse event; QoL, quality of life.
1. Shadman MS, et al. Poster session presented at ICHM Feb 29 - Mar 3, 2024; Miami, FL, USA.

Conclusions

- If results derived from meta-analysis of clinical trial data (Hwang et al[1]) are assumed to be generalizable to real-world patients, benefits to patients and payors would be substantial
- A major strength of the study is the rigorous and robust analysis undertaken to evaluate the safety profiles of zanubrutinib compared to acalabrutinib
  - This comprehensive economic analysis is grounded on an independent meta-analysis by Hwang et al[1], ensuring that our findings are based on a solid foundation of existing scientific evidence
- This economic analysis demonstrated that zanubrutinib is cost-saving and associated with QoL benefits compared to acalabrutinib in terms of AE management in patients with B-cell malignancies

AE, adverse event; QoL, quality of life.

1. Hwang S, et al. Poster session presented at EHA June 8 - 15, 2023; Frankfurt, Germany.

Acknowledgments

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