AstraZeneca
What science can do

American Society of Hematology (ASH) Annual Meeting & Exposition 2019

Conference call for investors and analysts

10 December 2019

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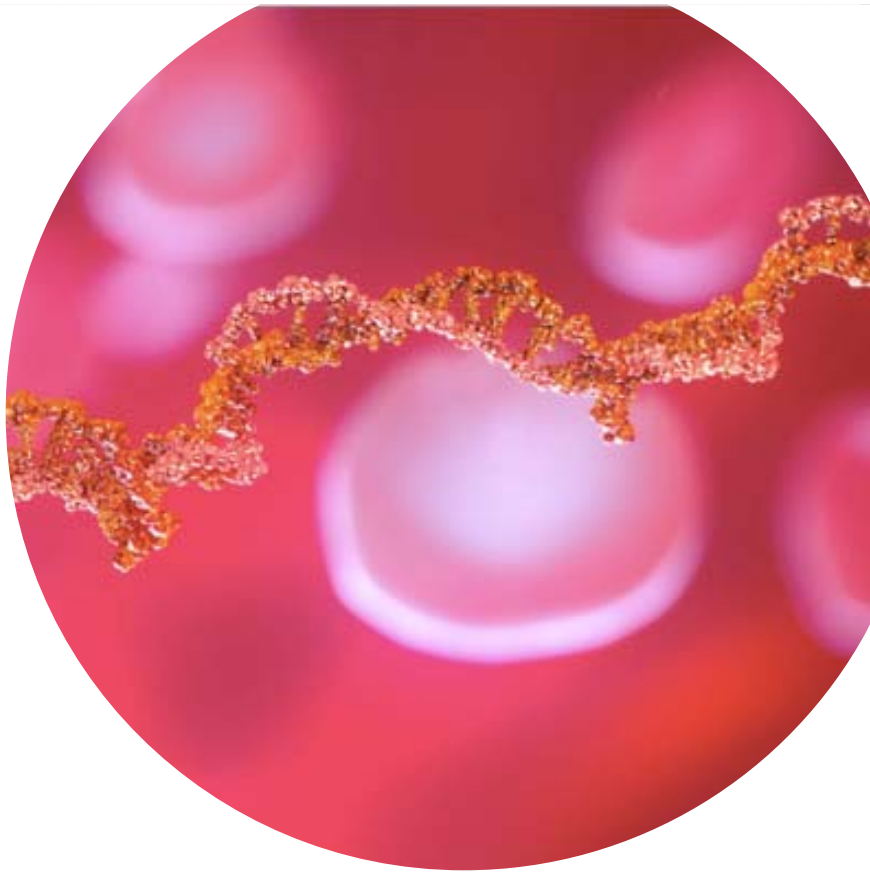
Agenda

Introduction

Calquence Phase III ELEVATE TN trial

Haematology update

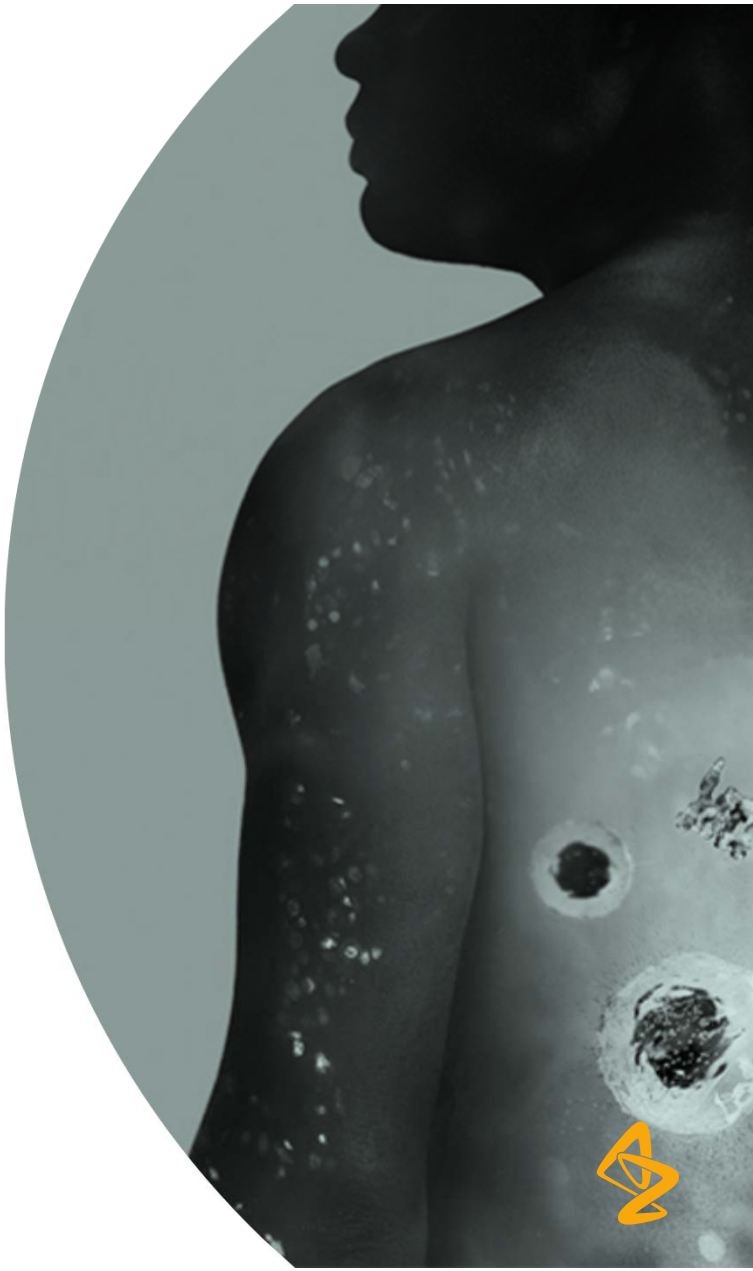
Q&A



2019: a successful year for the pipeline

Investor science events in each therapy area

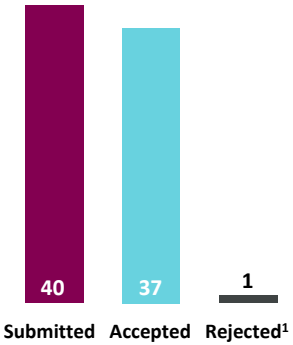
Oncology	Cardiovascular, renal and metabolism	Respiratory (and immunology)
American Society of Clinical Oncology (Jun) • Meet AZN management event(s); conference call	**European Society of Cardiology** (Sep) • Conference call	**American College of Rheumatology** (Nov) • Conference call
European Society of Medical Oncology (Sep) • Conference call	**American Society of Nephrology** (Nov) • Conference call	
American Society of Hematology (Dec) • Conference call		

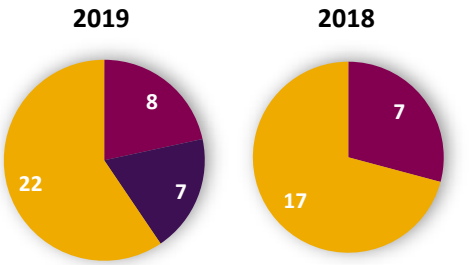


For AstraZeneca investor and analyst events, please visit https://www.astrazeneca.com/investor-relations/results-and-presentations.html.

2019 ASH: strong, increasing presence

54% increase in ASH abstracts 2018 to 2019

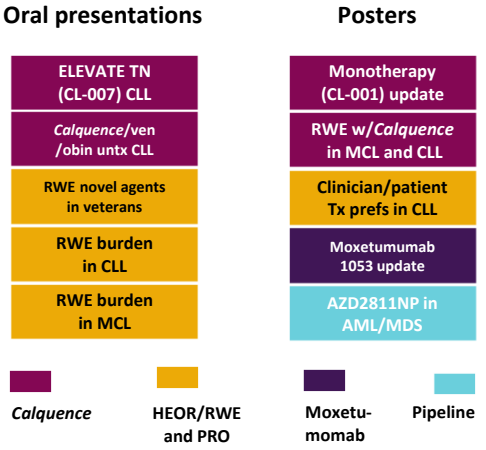




2019
- 8 oral presentations
- 22 poster presentations
- 7 published only
- 37 total accepted abstracts

2018
- 7 oral presentations
- 17 poster presentations
- 24 total accepted abstracts

Key abstracts at ASH 2019



40 abstracts submitted; 37 abstracts accepted - externally-sponsored research ~13% of total

1. Two abstracts were withdrawn.

Commonly used abbreviations in this presentation:
CLL = chronic lymphocytic leukaemia MCL = mantle cell lymphoma
SLL = small lymphocytic lymphoma PFS = progression-free survival.

Presenters

Dr. John Byrd
Primary investigator,
Phase III ELEVATE TN trial

Susan Galbraith
Senior Vice President,
Head of Early Oncology

Agenda

Introduction

Calquence **Phase III ELEVATE TN trial**

Haematology update

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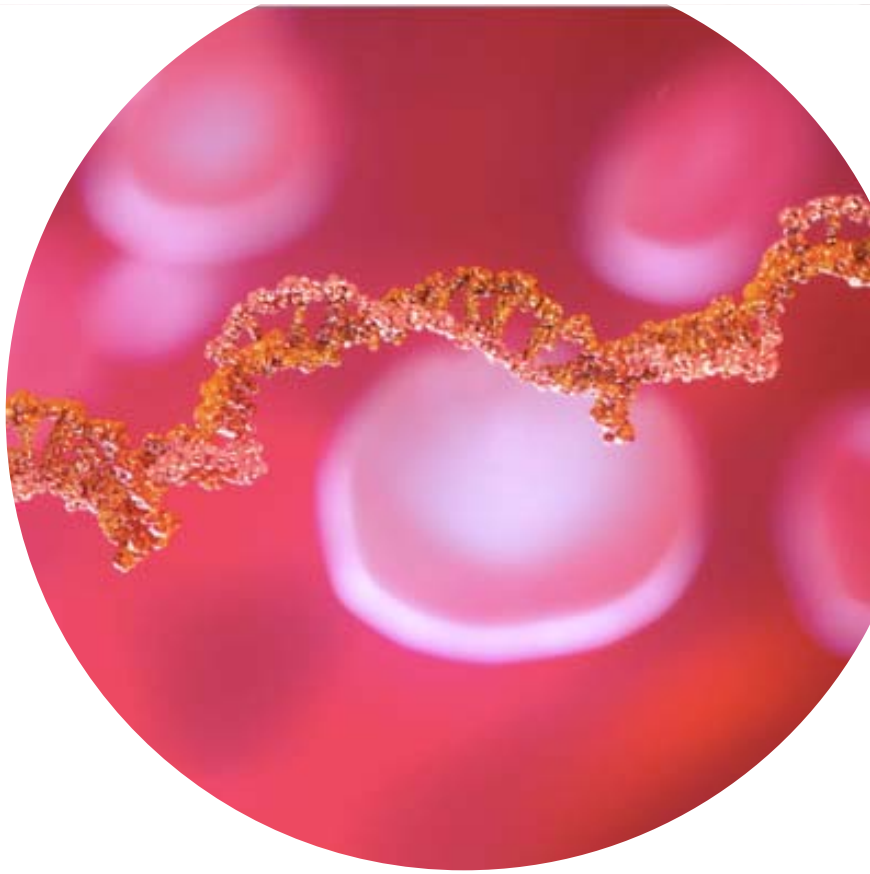

Calquence Phase III ELEVATE TN trial

Background

Sharman, ASH 2019

Background

- The treatment of symptomatic CLL has changed dramatically with the introduction of the Bruton tyrosine kinase inhibitor (BTKi) ibrutinib
- Prior to ibrutinib introduction, obinutuzumab (G) plus chlorambucil (Clb) was a standard frontline chemoimmunotherapy for CLL, with median PFS of 26.7 months and an ORR of 78%.[1] This regimen has served as a control arm for several recent phase 3 studies[2,3]
- Studies combining rituximab with ibrutinib have not shown added benefit over ibrutinib alone[4,5]
- G combined with ibrutinib has been FDA-approved;[6] however, the benefit of adding G to a BTKi vs a BTKi alone has not been evaluated
- Acalabrutinib is a more selective BTKi, with less off-target kinase inhibition in vitro compared with ibrutinib[7] and a favorable safety profile, prompting this evaluation as a frontline therapy with or without G

CLL, chronic lymphocytic leukemia; ORR, overall response rate; PFS, progression-free survival

1. Goede V, et al. *NEJM* 2014;370:1101-1110; 2. Moreno C, et al. *Lancet* 2019;20:43-45; 3. Fisher K, et al. *NEJM* 2019;380:2225-2236; 4. Woyach JA, et al. *NEJM* 2018;379:2517-2528; 5. Burger JA, et al. *Blood* 2019;133:1011-1019; 6. Janssen Global. Imbruvica press release. 2019. Available from: https://www.janssen.com/us-fda-approves-imbruvica-ibrutinib-plus-obinutuzumab-first-non-chemotherapy-combination-regimen (Accessed November 8, 2019); 7. Barf T, et al. *J Pharmacol Exp Ther* 2017;363(2):240-252

Calquence Phase III ELEVATE TN trial

Trial design

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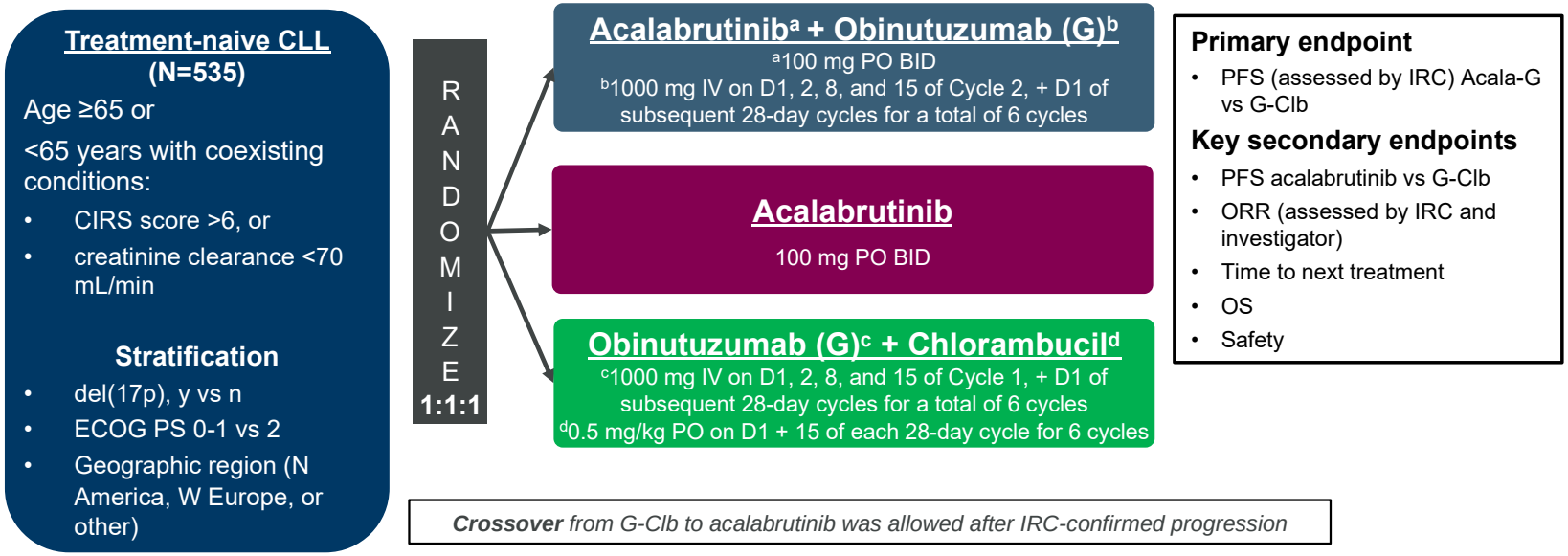
ELEVATE TN Study Design (ACE-CL-007)



- Interim analysis was planned based on events (after occurrence of ~111 IRC-assessed PFS events in the combination therapy arms) or after 24 months if the required number of events was not met by this time

Acala, acalabrutinib; CIRS, Cumulative Illness Rating Scale; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; IV, intravenously; OS, overall survival; PO, orally

Calquence Phase III ELEVATE TN trial

Patient demographics

Sharman, ASH 2019

Patient Demographics and Baseline Characteristics

Characteristic	Acala-G N=179	Acalabrutinib N=179	G-Clb N=177
Age, median (range), years	70.0 (41.0-88.0)	70.0 (44.0-87.0)	71.0 (46.0-91.0)
≥65 years, n (%)	144 (80.4)	151 (84.4)	153 (86.4)
<65 years,[a] n (%)	35 (19.6)	28 (15.6)	24 (13.6)
Creatinine clearance 30-69 mL/min	2 (1.1)	4 (2.2)	7 (4.0)
CIRS-G >6	30 (16.8)	21 (11.7)	15 (8.5)
EGOG-PS, n (%)			
0-1	169 (94.4)	165 (92.2)	167 (94.4)
2	10 (5.6)	14 (7.8)	10 (5.6)
Rai stage, n (%)			
III	48 (26.8)	50 (27.9)	40 (22.6)
IV	38 (21.2)	37 (20.7)	38 (21.5)
High-risk features, n (%)			
del(17p)	17 (9.5)	16 (8.9)	16 (9.0)
del(11q)	31 (17.3)	31 (17.3)	33 (18.6)
Unmutated IGHV	103 (57.5)	119 (66.5)	116 (65.5)
Mutated *TP53*	21 (11.7)	19 (10.6)	21 (11.9)
Complex karyotype	29 (16.2)	31 (17.3)	32 (18.1)
Time from initial diagnosis, median (range), months	30.5 (0.4-284.5)	24.4 (0.4-242.6)	30.7 (0.3-247.0)

[a]Twelve patients <65 years old did not meet eligibility criteria of having a CIRS score of >6 or creatinine clearance of 30-69 mL/min
IGHV, immunoglobulin heavy-chain variable gene; *TP53*, tumor protein 53 gene

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PFS (primary endpoint)

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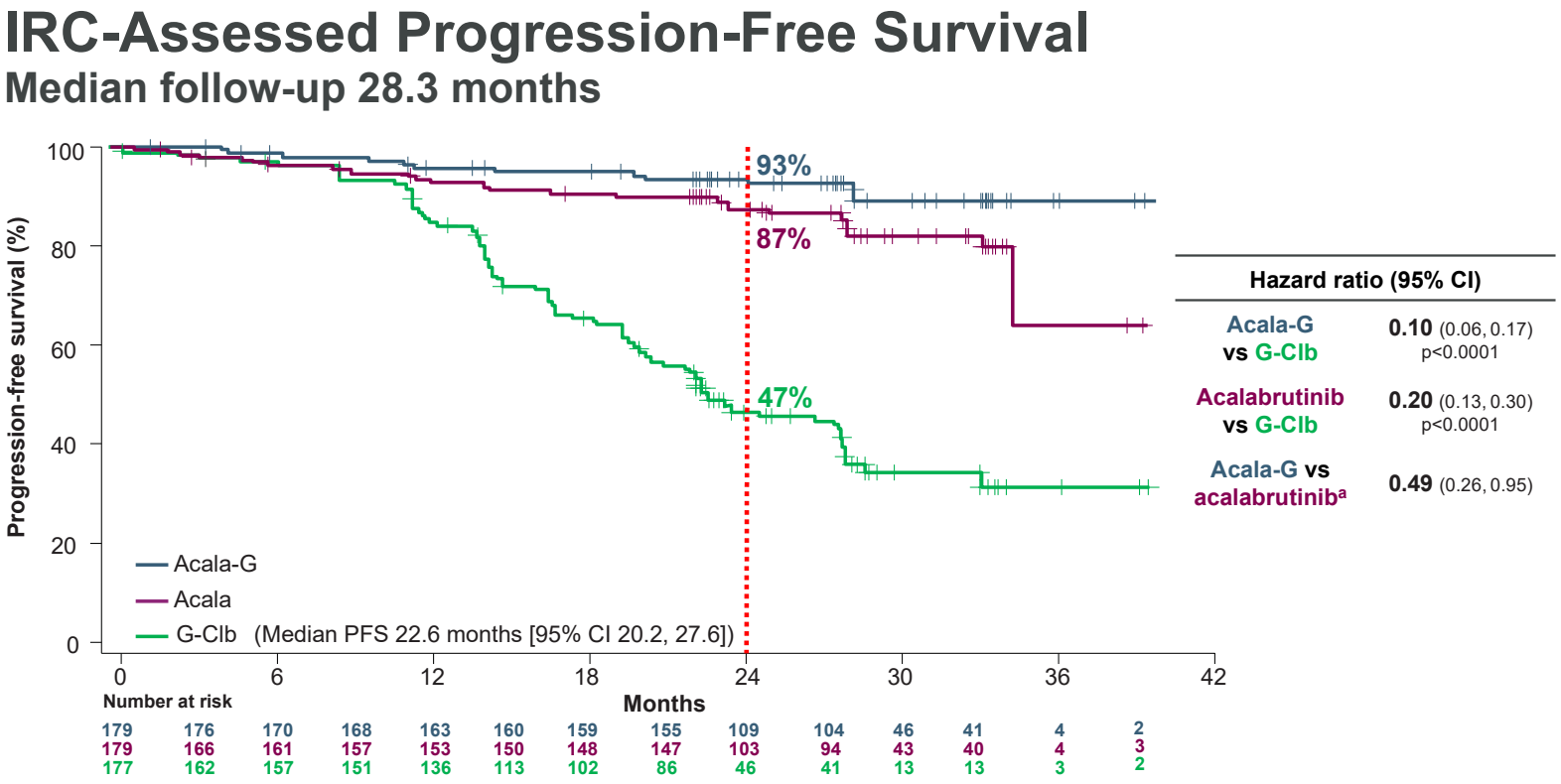


Kaplan-Meier estimates performed by IRC and all analyses for the intention-to-treat population. No. of events: Acala-G, 14 (7.8%); Acala, 26 (14.5%); G-Clb, 93 (52.5%)

[a]*Post hoc* analysis.

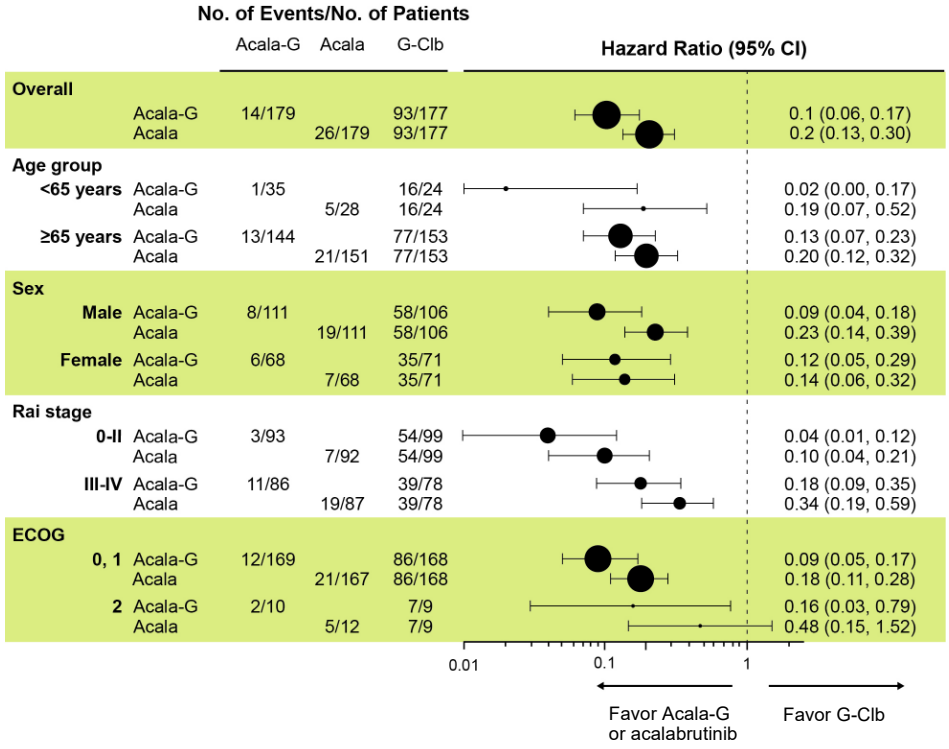
Richter's transformation occurred in: Acala-G n=1, Acala n=5, G-Clb n=1

Calquence Phase III ELEVATE TN trial

PFS by subgroup, 1

Sharman, ASH 2019

IRC-Assessed PFS Benefit Consistent Across Subgroups

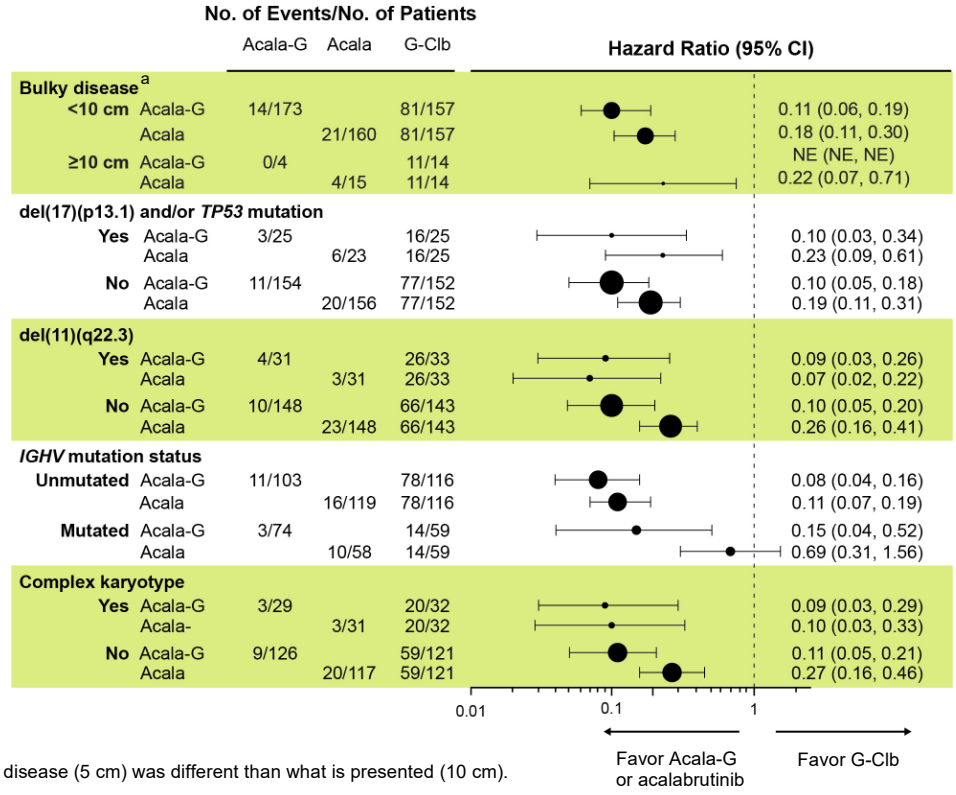


Calquence Phase III ELEVATE TN trial

PFS by subgroup, 2

Sharman, ASH 2019

IRC-Assessed PFS Benefit Consistent Across Subgroups



[a]Prespecified subgroup definition for bulky disease (5 cm) was different than what is presented (10 cm).
NE, not estimable

Calquence Phase III ELEVATE TN trial

Overall response rate

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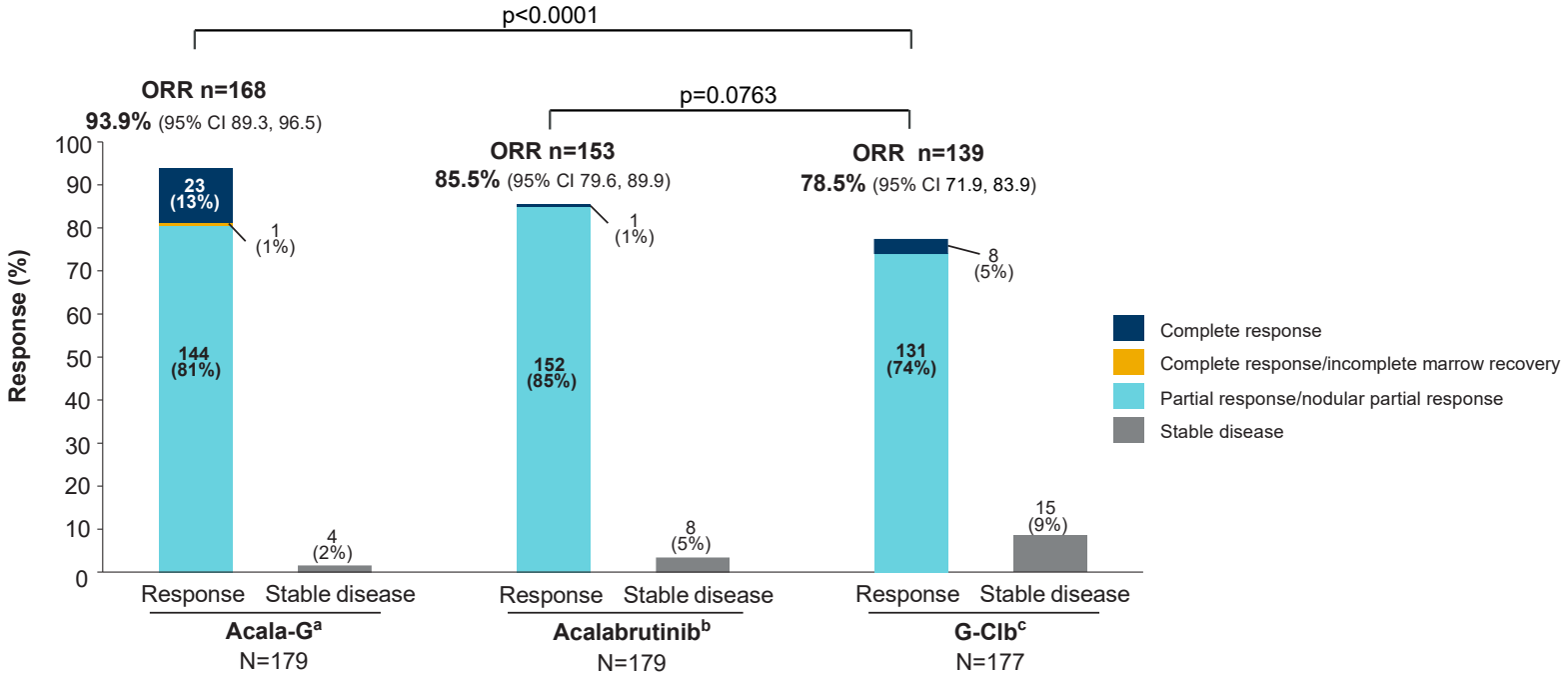
IRC-Assessed Response Rates



[a]Six patients (3%) had unknown response, and one patient (1%) had a response of non-PD, defined as not having adequate CT or MRI data and not meeting criteria for PD by physical examination. [b]Two patients (1%) had PR-L, three patients (2%) had PD, 12 patients (7%) had unknown response, and one patient's (1%) response was not evaluable. [c]Two patients (1%) had non-PD, 12 patients (7%) had an unknown response, one patient (1%) had no evaluable disease, and eight patients' (5%) responses were not evaluable

PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis

Calquence Phase III ELEVATE TN trial

Overall survival

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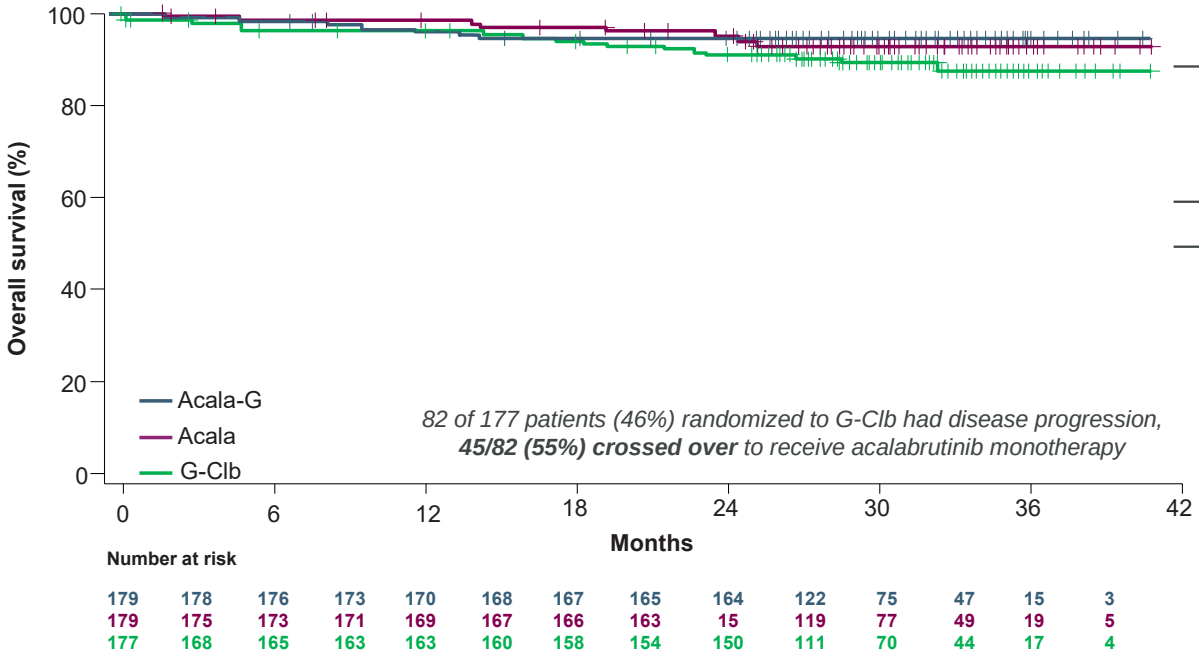
Overall Survival
(Median follow-up 28.3 months)



Deaths	N (%)
Acala-G	9 (5.0)
Acala	11 (6.1)
G-Clb	17 (9.6)
Hazard ratio (95% CI)	
Acala-G vs G-Clb	**0.47** (0.21, 1.06) p=0.0577
Acalabrutinib vs G-Clb	**0.60** (0.28, 1.27) p=0.1556

Calquence Phase III ELEVATE TN trial

Safety overview

Sharman, ASH 2019

Safety Overview

AE type, n (%)	Acala-G N=178	Acalabrutinib N=179	G-Clb N=169
Patients with ≥1 AE (all grades)	171 (96.1)	170 (95.0)	167 (98.8)
Serious AEs	69 (38.8)	57 (31.8)	37 (21.9)
Grade ≥3	125 (70.2)	89 (49.7)	118 (69.8)
Grade 5	5 (2.8)[a]	7 (3.9)[b]	12 (7.1)[c]

Safety was assessed in all patients who received ≥1 dose of treatment. Continuous acalabrutinib treatment resulted in a longer reporting period for AEs in both acalabrutinib-containing arms, with median exposure of 27.7 months (2.3-40.3) for Acala-G, 27.7 months (0.3-40.2) for Acala vs 5.6 months (0.9-7.4) for G-Clb

Grade 5 AEs are presented for randomization and cross over periods including treatment and non-treatment emergent AEs. [a]Pneumonia (n=1), metastases to bone (n=1), sepsis (n=2), gastric cancer stage IV (n=1). [b]Bronchopulmonary aspergillosis, goiter, myositis, septic shock, cardiac failure, febrile neutropenia, Parkinson's disease (all n=1). [c]Bacterial sepsis, cardiac arrest, acute myocardial infarction, acute myelomonocytic leukemia, brain neoplasm, cholangiocarcinoma, duodenal ulcer hemorrhage, lung adenocarcinoma, pneumonia pneumococcal, progressive multifocal leukoencephalopathy, sepsis, subarachnoid hemorrhage (all n=1)

Calquence Phase III ELEVATE TN trial

Adverse events, most common (≥15% patients)

Sharman, ASH 2019

Most Common AEs (≥15% Patients) in Any Treatment Arm

	Acala-G N=178		Acalabrutinb N=179		G-Clb N=169	
AEs, n (%)	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Headache	71 (39.9)	2 (1.1)	66 (36.9)	2 (1.1)	20 (11.8)	0
Diarrhea	69 (38.8)	8 (4.5)	62 (34.6)	1 (0.6)	36 (21.3)	3 (1.8)
Neutropenia	56 (31.5)	53 (29.8)	19 (10.6)	17 (9.5)	76 (45.0)	70 (41.4)
Fatigue	50 (28.1)	3 (1.7)	33 (18.4)	2 (1.1)	29 (17.2)	1 (0.6)
Contusion	42 (23.6)	0	27 (15.1)	0	7 (4.1)	7 (4.1)
Arthralgia	39 (21.9)	2 (1.1)	28 (15.6)	1 (0.6)	8 (4.7)	2 (1.2)
Cough	39 (21.9)	0	33 (18.4)	1 (0.6)	15 (8.9)	0
URTI	38 (21.3)	4 (2.2)	33 (18.4)	0	14 (8.3)	1 (0.6)
Nausea	36 (20.2)	0	40 (22.3)	0	53 (31.4)	0
Dizziness	32 (18.0)	0	21 (11.7)	0	10 (5.9)	0
IRR	24 (13.5)	4 (2.2)	0	0	67 (39.6)	9 (5.3)
Pyrexia	23 (12.9)	0	12 (6.7)	1 (0.6)	35 (20.7)	1 (0.6)

AEs reported are from the treatment-emergent period (first dose through to 30 days after the last dose of study drug or the first date starting a new CLL therapy, whichever is earliest)
IRR, infusion-related reaction; URTI, upper respiratory tract infection

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Adverse events, serious

Sharman, ASH 2019

Most Common Serious AEs

SAEs (≥2% patients), n (%)	Acala-G N=178	Acalabrutinib N=179	G-Clb N=169
Any	69 (38.8)	57 (31.8)	37 (21.9)
Pneumonia	12 (6.7)	5 (2.8)	3 (1.8)
IRR	4 (2.2)	0	2 (1.2)
Anemia	3 (1.7)	4 (2.2)	0
Febrile neutropenia	3 (1.7)	2 (1.1)	7 (4.1)
Tumor lysis syndrome	1 (0.6)	0	8 (4.7)

SAE, serious adverse event

Calquence Phase III ELEVATE TN trial

Adverse events, clinical interest

Sharman, ASH 2019

Events of Clinical Interest for Acalabrutinib

AEs, n (%)	Acala-G N=178		Acalabrutinib N=179		G-Clb N=169	
	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Atrial fibrillation	6 (3.4)	1 (0.6)	7 (3.9)	0	1 (0.6)	0
Hypertension	13 (7.3)	5 (2.8)	8 (4.5)	4 (2.2)	6 (3.6)	5 (3.0)
Bleeding	76 (42.7)	3 (1.7)	70 (39.1)	3 (1.7)	20 (11.8)	0
Major bleeding[a]	5 (2.8)[b]	3 (1.7)	3 (1.7)[c]	3 (1.7)	2 (1.2)[d]	0
Infections	123 (69.1)	37 (20.8)	117 (65.4)	25 (14.0)	74 (43.8)	14 (8.3)
Second primary malignancies, excluding NMSC	10 (5.6)[e]	6 (3.4)	5 (2.8)[f]	2 (1.1)	3 (1.8)[g]	2 (1.2)

There were no reported events of ventricular tachyarrhythmias
[a]Defined as any serious or grade ≥3 hemorrhagic event, or any grade hemorrhagic event in the central nervous system. [b]Includes gastric ulcer hemorrhage, gastrointestinal hemorrhage, hematemesis, postprocedural hemorrhage, and subdural hemorrhage. [c]Includes hemarthrosis, postprocedural hematoma, and retinal hemorrhage. [d]Includes subdural hemorrhage and hemoptysis. [e]Includes non-small cell lung cancer (n=2), squamous cell carcinoma (n=2), basosquamous carcinoma, bladder transitional cell carcinoma, breast cancer, gastric cancer stage IV, metastases to bone, prostate cancer, and renal cell carcinoma (all n=1). [f]Includes prostate cancer (n=2), glioblastoma, malignant melanoma in situ, transitional cell carcinoma (all n=1). [g]Includes prostate cancer, acute myelomonocytic leukemia, and lung adenocarcinoma (all n=1)
NMSC, nonmelanoma skin cancer

Calquence Phase III ELEVATE TN trial

Conclusions

Sharman, ASH 2019

Conclusions

- In the **ELEVATE TN** study:
  - acalabrutinib + G and acalabrutinib monotherapy both significantly improved progression-free survival vs chemoimmunotherapy (G + Clb), with a tolerable safety profile in patients with TN CLL
  - benefit of acalabrutinib with or without G was consistent across most prespecified subgroups irrespective of high-risk disease characteristics
  - despite crossover for disease progression in the G + Clb arm, fewer deaths were seen with acalabrutinib + G and acalabrutinib monotherapy, though longer follow-up is needed to detect a difference in overall survival
- Acalabrutinib has demonstrated efficacy and a consistent safety profile in TN and R/R patients (ASCEND[1]), and is now an approved treatment for patients with CLL

R/R, relapsed/refractory; TN, treatment-naive

1. Ghia P, et al. *European Hematology Association Library* 2019;273259:LB2606

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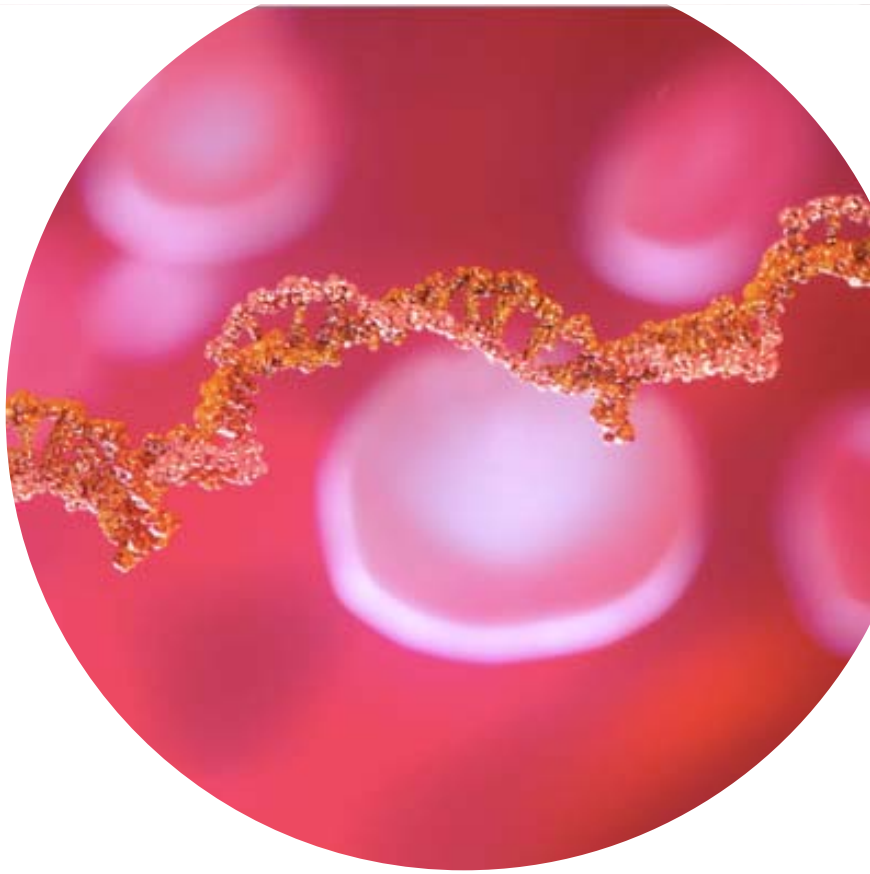


Haematology: *Calquence*

Phase III data readouts in CLL provide momentum

$173m
worldwide *Calquence* sales since launch in November 2017

17,000
patients in front-line CLL; US and EU5[1]

11,000
patients in relapsed/refractory CLL; US and EU5

Key data readouts and milestones

Trial/milestone	Phase	Status
ACE-CL-309 ASCEND in relapsed/refractory CLL	III	Approved (US)
ACE-CL-007 ELEVATE TN in previously-untreated CLL	III	Approved (US)
Calquence regulatory submissions in CLL (EU, JP)	-	H1 2020
ACE-CL-006 ELEVATE RR in relapsed/refractory high-risk CLL	III	Data 2021+
ACE CL-311 in previously-untreated CLL (w/venetoclax)	III	Data 2021+

1. France, Germany, Italy, Spain and UK.
Source: company-published sales and epidemiology data.

Haematology: *Calquence*

US prescribing information key aspects

Indication and usage

Calquence is indicated for the treatment of adult patients with:

- MCL who have received at least one prior therapy[1]
- CLL or SLL (front line and relapsed/refractory CLL)

Monotherapy (MCL, CLL or SLL) or *Calquence* in combination with obinutuzumab for front-line CLL/SLL

CALQUENCE (acalabrutinib) 100 mg capsules

Warnings and precautions

Adverse events	Rate of occurrence
Serious and opportunistic infections	Grade 3 or higher 19%
Hemorrhage	Grade 3 or higher 3.0%
Cytopenias	Grade 3/4, neutropenia (23%), anemia (8%), thrombocytopenia (7%), and lymphopenia (7%)
Second primary malignancies	12%
Atrial fibrillation and flutter	Grade 3 1.1%

No warning for hypertension, tumour lysis syndrome, embryo-fetal toxicity. No ventricular tachyarrhythmias

1. Accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
Source: FDA prescribing information.

Haematology: 'What's next?'

Building on *Calquence* foundation, as CLL emerges

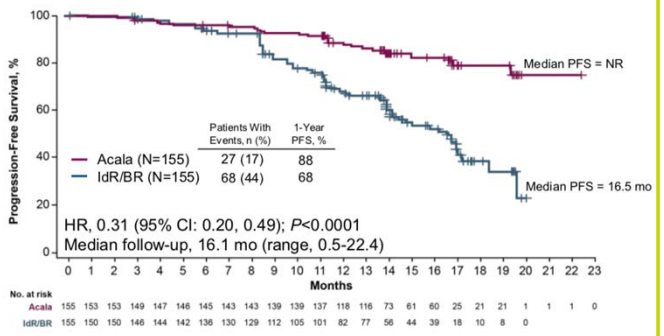
Calquence in CLL

- **ASCEND**
  Met Phase III primary endpoint in relapsed/refractory CLL
- **ELEVATE TN**
  Met Phase III primary endpoint in previously-untreated CLL
  Also met key secondary endpoint of monotherapy *Calquence* vs. chlorambucil and obinutuzumab

EU, JP regulatory submission in H1 2020

EHA presentation and front-line high-level results

ASCEND PFS hazard ratio 0.31



Favourable safety profile in CLL

IdR = idelalisib and rituximab.
BR = bendamustine and rituximab.
Source: EHA 2019.

'What's next?'

- AZD5991 (MCL1 inhibitor): novel macrocyclic chemistry
- AZD4573 (CDK9[1] inhibitor): distinct mechanism of targeting MCL1
- AZD2811 (Aurora kinase B inhibitor): targeting various tumours
- AZD0466 (Bcl2/xL programme): Phase I planning

Next wave of innovation in haematology

1. Cyclin-dependent kinase 9.

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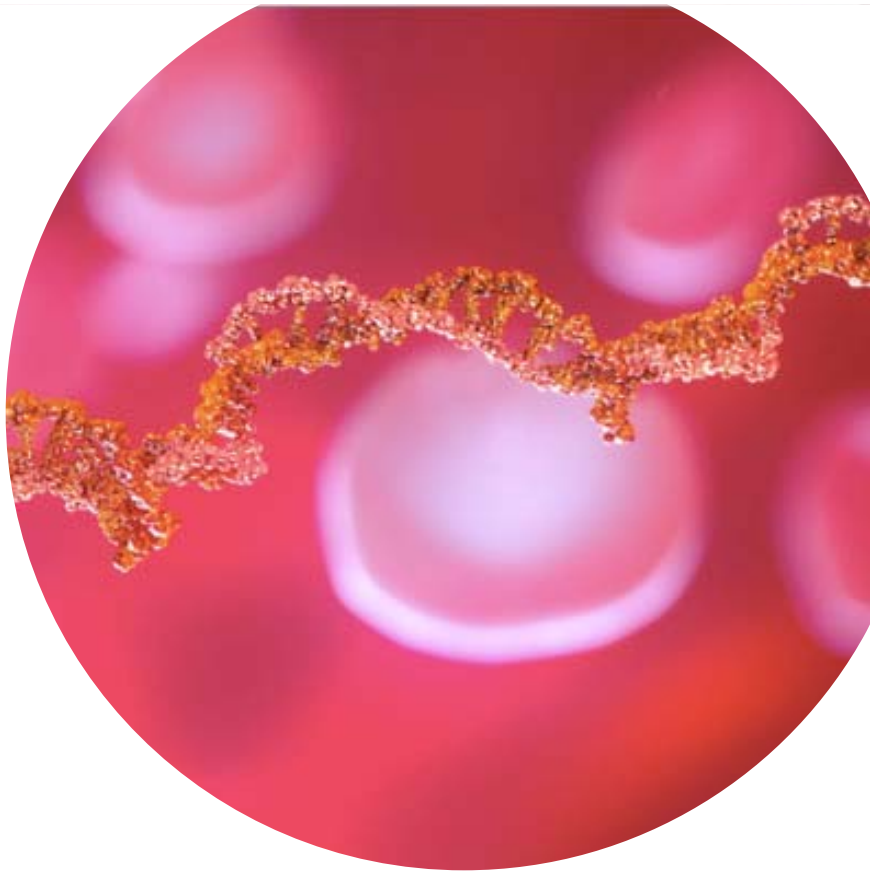
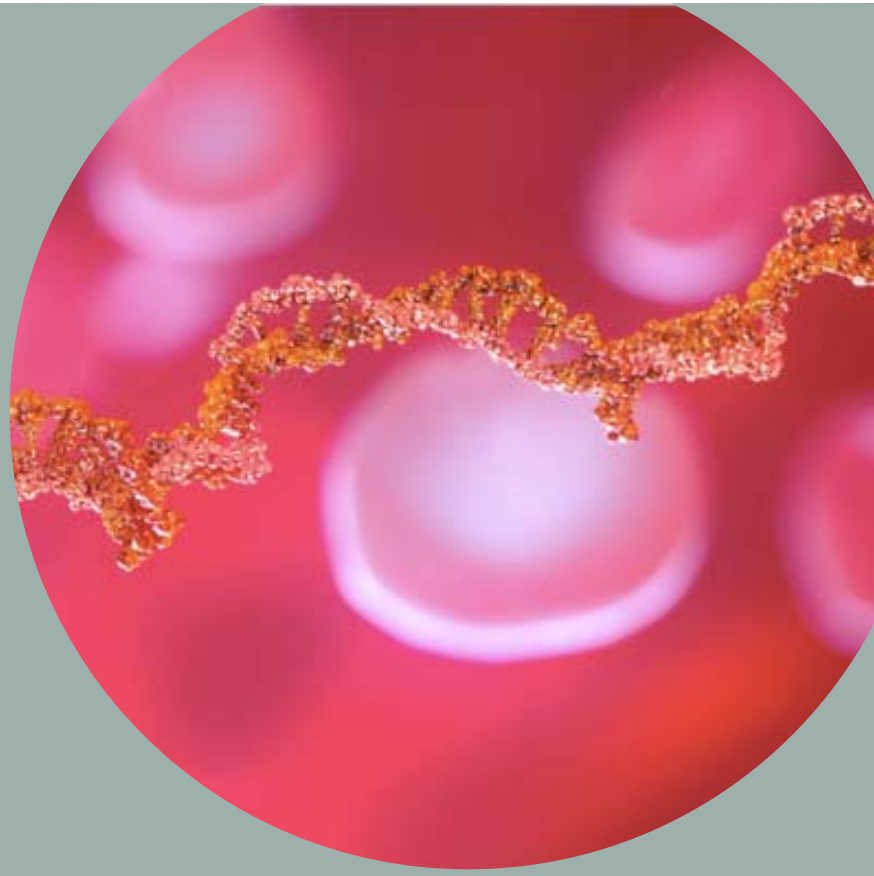


Q&A



Use of AstraZeneca conference call, webcast and presentation slides