CLL Therapy in Scotland: 2021 Update

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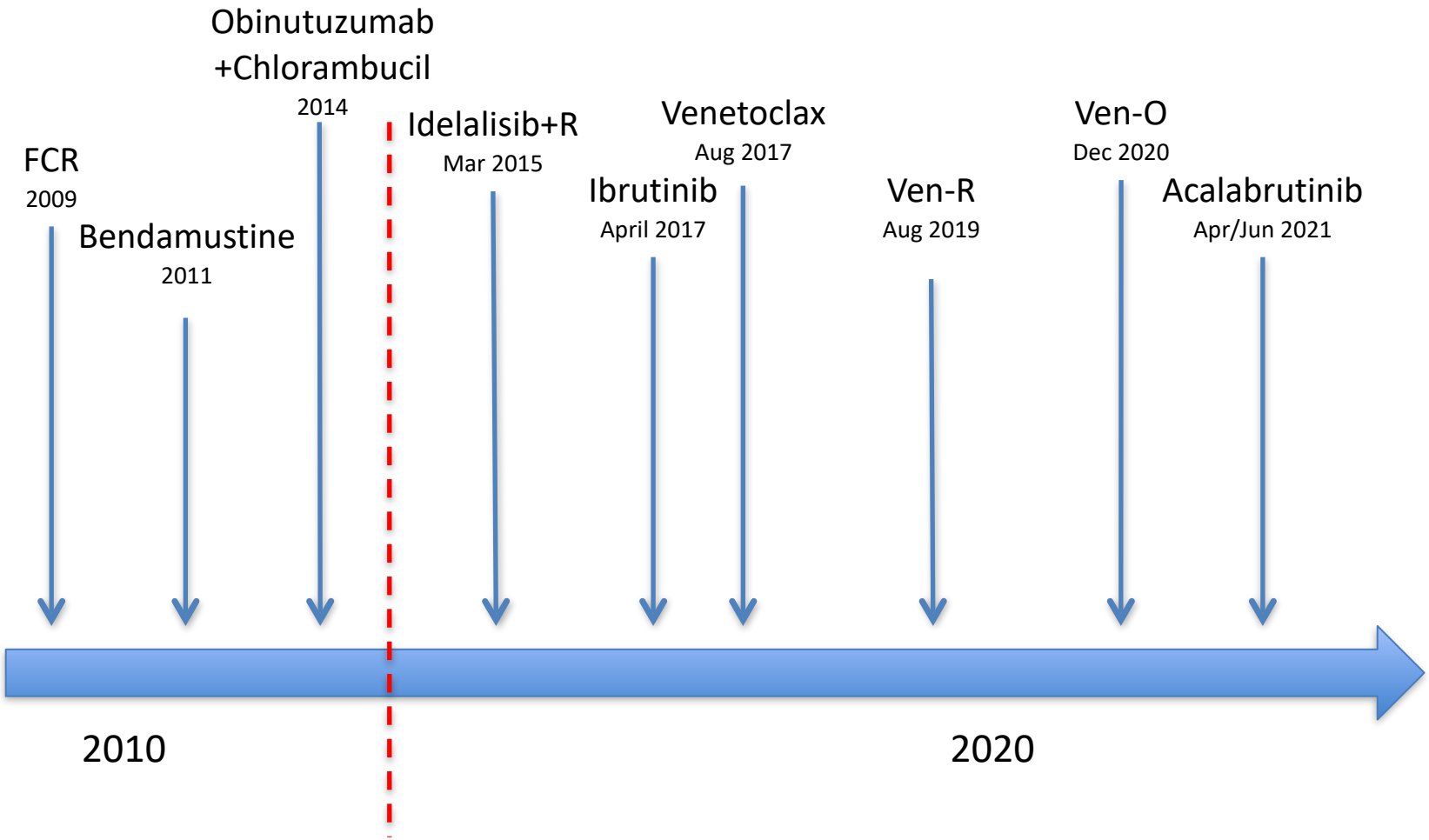
This talk will cover

- Overview of current therapies available for CLL.
- Discuss recent developments in first-line treatment.
- Discuss options available at relapse.
- Discuss key factors to consider when choosing treatment.
- Looking to the future.

Approval of New Therapies for CLL in Scotland



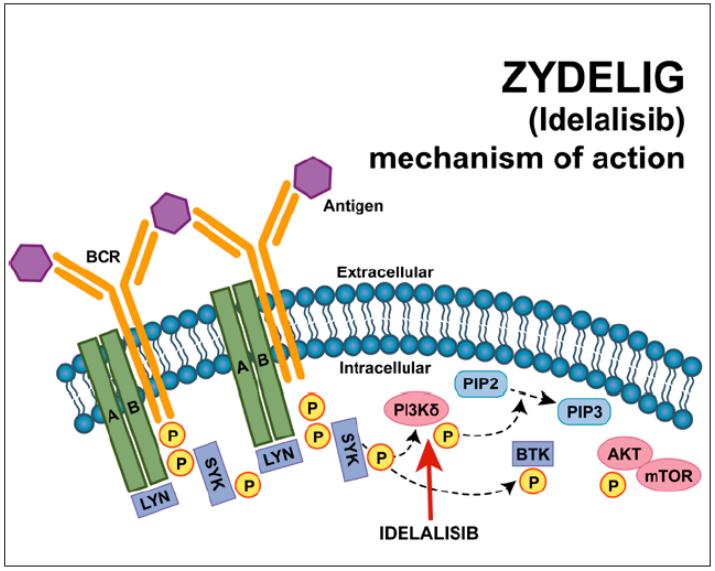
Before targeted therapies…….

- **Fludarabine, cyclophosphamide, Rituximab (FCR)**
  - IV rituximab, oral fludarabine and cyclophosphamide D1-3
  - 6 x 28 day cycles
  - Approved on basis of CLL8 trial, demonstrated significant length of 1st remission adding Rituximab to FC *(Hallek M et al., Lancet (2010) 376:1164-7).*

- **Bendamustine and Rituximab**
  - IV rituximab D1, IV bendamustine D 1+2, x six 28 day cycles.
  - Approved on data from CLL10 trial – randomised phase III trial FCR vs BR, in patients > 65 years, similar response duration to FCR, less myelosuppression/infections *(Eichhorst B et al. (2016) Lancet Oncol 17:928-42).*

- **Obinutuzumab and Chlorambucil**
  - Approved following publication of CLL11 trial – demonstrated significant improvement in response rates and remission duration with addition of obinutuzumab to oral chlorambucil (*Goede V et al. (2014) NEJM 370:1101-10).*
  - Obinutuzumab given D1, 8 and 15 cycle 1, then D1 cycles 2-6.

Idelalisib



Personalised medicine in oncology

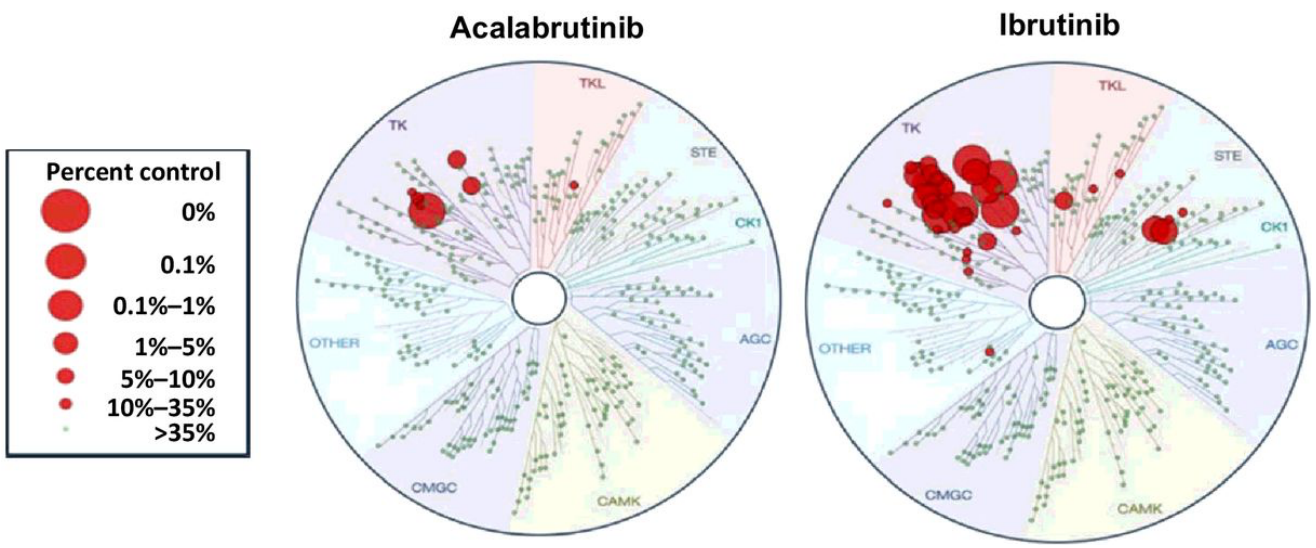
- Blocks B cell receptor signalling by binding PI-3K delta.
- Oral, twice daily continuous therapy (with rituximab 1st 6 months).
- Approved for use in Scotland on basis of 117 randomised trial showing significant improvement in response duration as compared to placebo+rituximab in relapsed CLL *(Furman RR et al, (2014) NEJM 370:997-1007).*
- Use limited by side-effect profile – frequent autoimmune colitis/diarrhoea, hepatitis, pneumonitis.
- Neutropenia common with risk of infection.
- Need prophylaxis for PCP infection and monitoring for CMV reactivation.

Ibrutinib

- 1st in class BTK inhibitor to be approved for CLL therapy.
- Once-daily oral tablet, taken continuously until progression or toxicity.
- Initial SMC approval Aug 2016 for patients with 17p deletion unsuitable for chemo-immunotherapy, then April 2017 approved for relapsed/refractory patients.

Side-effects	Incidence
Diarrhoea	50%
Fatigue	36%
Atrial Fibrillation	16%
Hypertension	26%
Major haemorrhage	11%
Arthralgia	26%
Respiratory tract infection	26%

Acalabrutinib



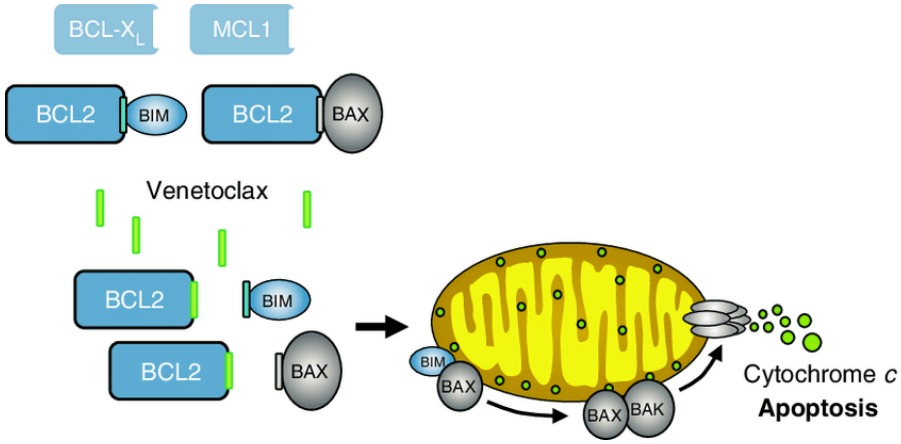
Herman S et al. (2016) Clin Cancer Research 23:2831-41.

- Acalabrutinib is a more selective BTK inhibitor than ibrutinib.
- Twice-daily oral tablet, taken continuously until progression or toxicity.
- In recently reported initial results from head-to-head study in relapsed CLL patients, acalabrutinib demonstrated comparable efficacy to ibrutinib, with significantly lower rates of atrial fibrillation, hypertension, arthralgia and diarrhoea. Bleeding complications also appear less frequent.

Byrd JC et al. (2021) https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.7500

Venetoclax

- Binds to the excess Bcl-2 protein within CLL cells, allowing activation of pro-apoptotic (cell-death triggering) proteins.
- Oral, once-daily dosing with rapid onset of action.
- In monotherapy or combination requires 5 week dose-titration phase 20, 50, 100, 200 then 400 mg daily.

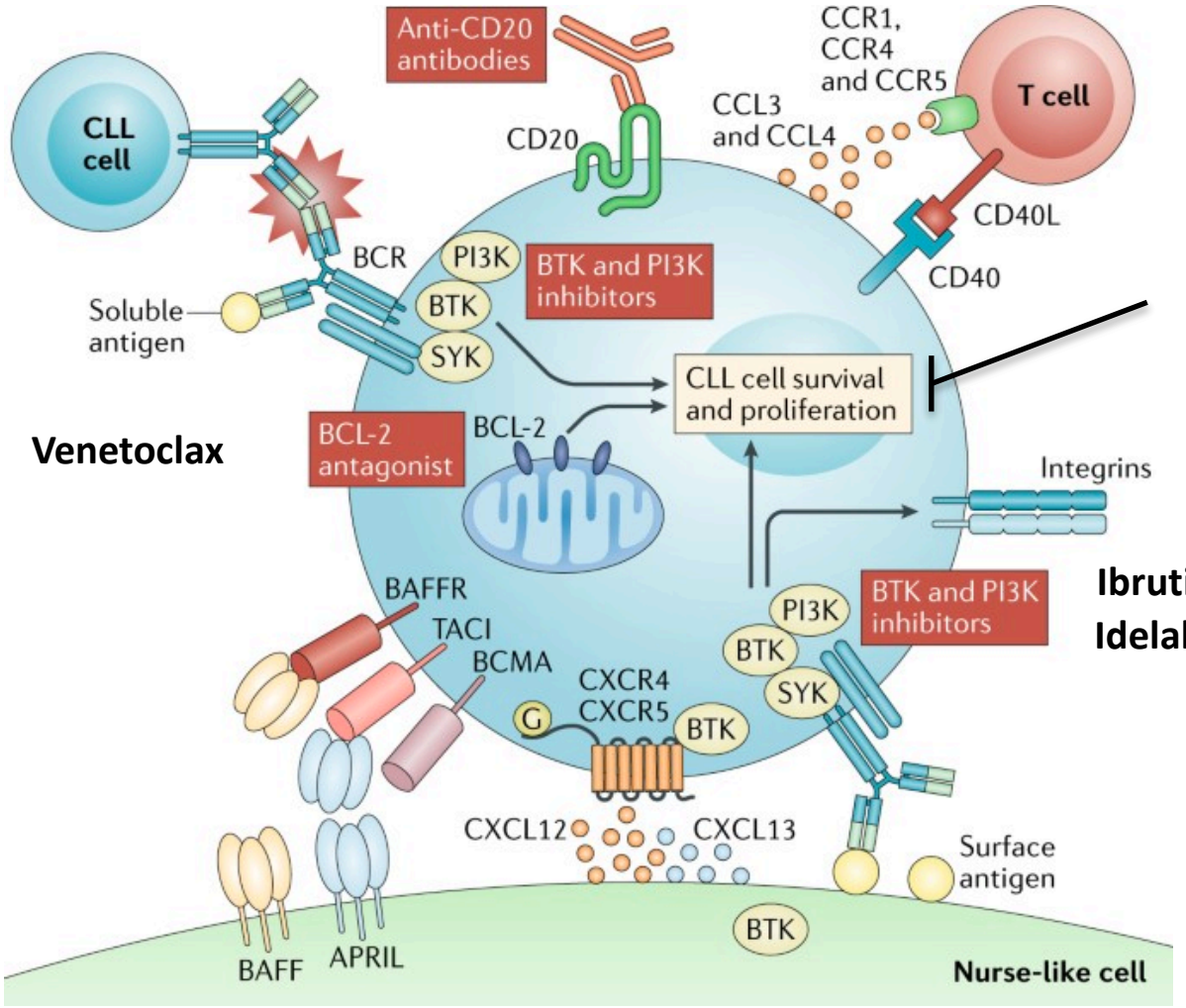


Konopleva M et al. (2016) Cancer Discov 6:1-12.

Side-effects	Incidence
Diarrhoea	52%
Respiratory tract infection	48%
Nausea	47%
Neutropenia	45%
Fatigue	40%

Roberts A et al. (2016) NEJM 374:311-22.

Rituximab
Obinutuzumab



Chemotherapy
FCR
Bendamustine
Chlorambucil

Venetoclax

Ibrutinib
Idelalisib

Adapted from Burger J & O'Brien S, Nature Reviews in Clinical Oncology (2018) 15:510-527.

1st-line treatment for patients not fit for FCR; no TP53 disruption.

Ibrutinib

- RESONATE-2 Trial: Compared continuous ibrutinib to 12 months chlorambucil in older CLL patients.
  - After 7 years, 61% ibrutinib-treated patients remain in remission, compared to < 10% of those who received chlorambucil. Just under 50% remained on treatment[1].
  - Trial also demonstrated an improvement in overall survival at 5 years.

- ALLIANCE Trial: Randomised phase III study in patients 65 and older: 1:1:1 to Rituximab-bendamustine, Ibrutinib alone or Ibrutinib+Rituximab.
  - At 2 years almost 90% of patients in Ibrutinib arms remained in remission, compared to 74% with R-Bendamustine[2].
  - This trial showed no benefit of adding Rituximab to Ibrutinib.
  - Significant infection rates similar between arms.

1 - Ghia P et al, Virtual EHA, 2021; 2 – Woyach JA et al. (2018) N Engl J Med 379:2517-2528.

1st-line treatment for patients not fit for FCR; no TP53 disruption.

Acalabrutinib

ELEVATE-TN Trial: Patients randomised to continuous acalabrutinib (+/- obinutuzumab) or 6 cycles chlorambucil and obinutuzumab.

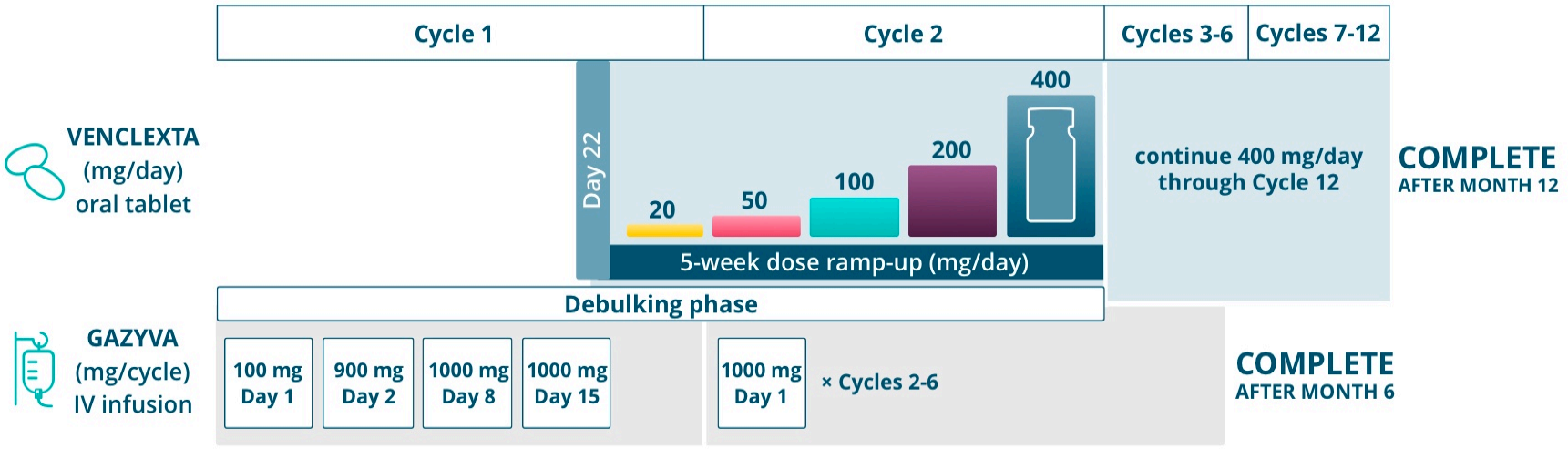
- After 4 years, 3/4 of acalabrutinib-treated patients remained in remission, compared with 1/4 of chlorambucil treated patients[1,2].
- Atrial fibrillation (4%) and significant hypertension (<3%) uncommon in acalabrutinib arms.

- During 1st wave COVID-19 pandemic Ibrutinib approved for patients who would otherwise have received chemo-immunotherapy.

- With recent SMC approval of acalabrutinib for this patient population this will be used in preference to ibrutinib.

1 – Woyach JA et al, 2018 N Engl J Med 379:2517; 2 – Sharman JP et al, J Clin Oncol 2021;39suppl:7509-

Venetoclax and Obinutuzumab



https://www.venclextahcp.com/cll/dosing/schedule.html

Graphic not to scale. Each cycle is 28 days.

CLL 14 Trial: Patients randomised to 12 month Venetoclax-Obinutuzumab schedule above or 12 months of Obinutuzumab and chlorambucil.

- At 4 year time-point of follow-up, around 3/4 patients treated with venetoclax remained in remission, as compared to just over 1/3 of patients treated with chlorambucil.
- Benefit seen across prognostic groups – 4 year PFS TP53 del/mut 53% and unmutated IgVH – PFS 68%.
- Venetoclax-Obinutuzumab now SMC approved for patients not fit for FCR.

Al-Sawaf O et al. (2021) Abstract presented at EHA Annual Meeting 2021.

1st-line Treatment options for patients fit for FCR; no TP53 disruption

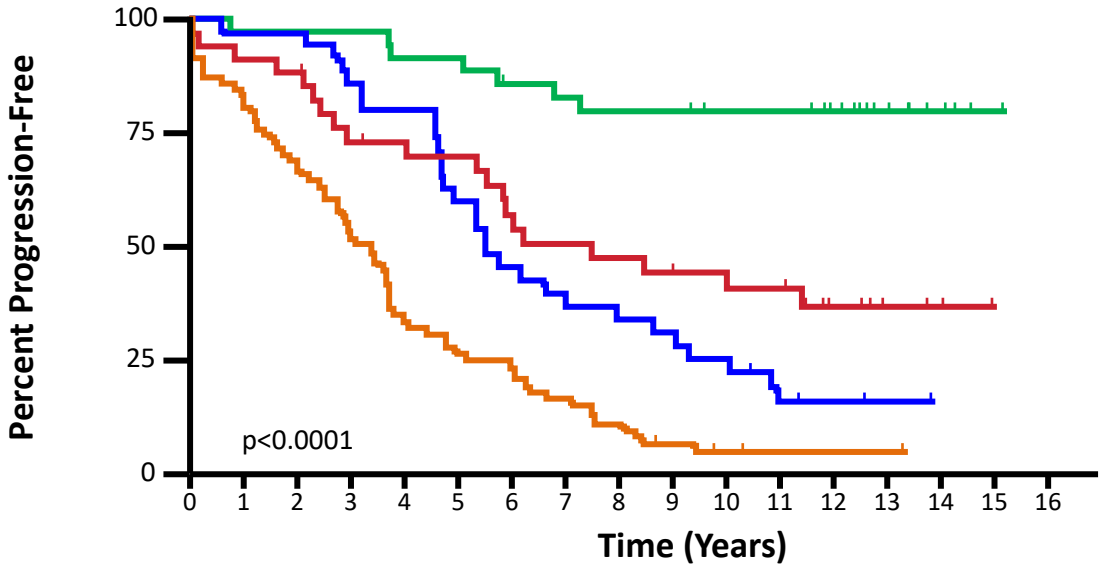
ECOG-1912 Trial: Randomised patients to receive 6 cycles of FCR or 6 cycles ibrutinib and rituximab followed by continuous ibrutinib therapy until progression.

- This study found that ibrutinib + rituximab treated patients:
  - had overall longer remission (at 3 years 89% remained in remission compared with 73% patients treated with FCR).
  - More patients still alive during follow-up (98.8% vs 91.5% FCR).
- Most benefit seen for patients with unmutated IgVH gene.
- For patients with mutated IgVH gene remission rates similar at 3 years.

Shanafelt TD et al. (2019) New Engl J Med 381:432-43.

Should we still consider FCR for anyone 1st-line?

	N
IGHV-M, MRD neg	35
IGHV-M, MRD pos	34
IGHV-UM, MRD neg	35
IGHV-UM, MRD pos	66



Thompson PA et al. (2016) Blood 127:303-309.

Some patients with mutated IgVH gene subgroup of CLL achieve very long remissions with FCR and may possibly be functionally cured.

1st-line Treatment for patients with TP53 disruption

SMC approved therapies include:

- BTK inhibitors – Ibrutinib or Acalabrutinib
- Venetoclax and obinutuzumab
- Venetoclax monotherapy (if not suitable for BTKi therapy)
- Idelalisib-rituximab.

Ibrutinib

- Six-year follow-up of non-randomised study of 34 patients with TP53 disrupted CLL treated with ibrutinib, just over 60% remained in remission and almost 80% were still alive[1].
- Pooled meta-analysis from 89 patient across 4 trials with TP53 disruption treated with 1st-line Ibrutinib confirmed 4 year remission rates of around 80%, median duration of remission not reached by 50 months[2].

1 - Ahn IE. et al. (2020) N Engl J Med 383:5, 2 – Allan J et al. (2020) Blood 136:23-24.

1st-line Treatment for patients with TP53 disruption

Venetoclax and Obinutuzumab

- In the CLL 14 trial, 212 patients were randomised to and received Venetoclax + Obinutuzumab.

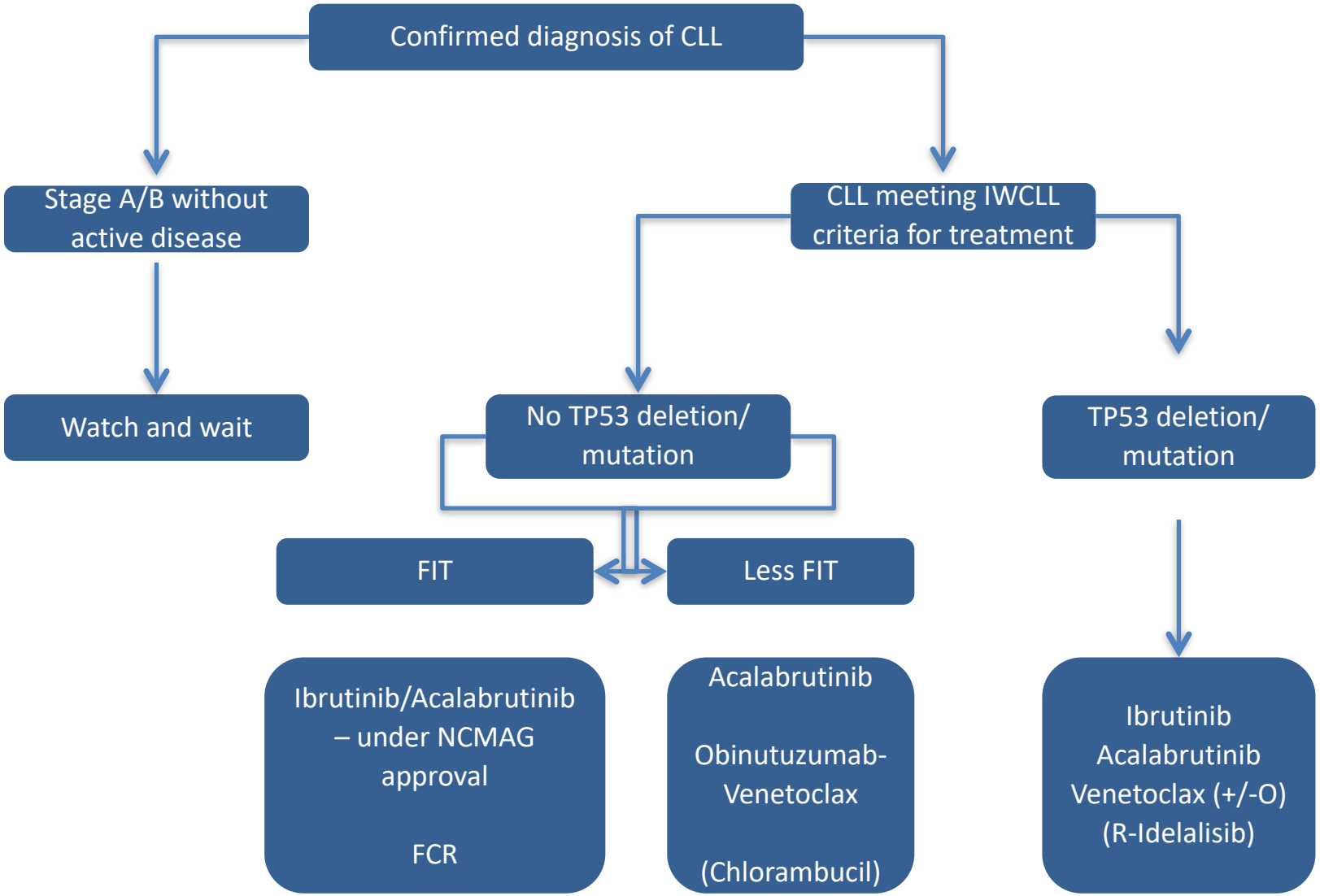
- Of these patients, 17 were known to have 17p deletion and 19 known to have mutated TP53 gene.

- Follow-up of this study has shown patients with disrupted TP53 gene to have an increased risk of earlier progression compared to other Ven-O treated patients.

- At 30 months follow-up, 85% patients with normal TP53 function remained in remission, compared to 60% of those with TP53 disruption[1].

1 – Fischer K et al. (2019) N Engl J Med 380:2225-2236.

Current Treatment Algorithm for the 1st-line Treatment of CLL in Scotland



Factors to consider when planning 1st-line treatment of CLL

- Age and overall fitness.
- Specific comorbidities – for example cardiovascular or renal disease.
- Medications – in particular need for anticoagulation/antiplatelet therapy.
- P53 status (on chromosome 17) – may be inactivated by loss or mutation within CLL cells. Patients with abnormal p53 function have poor responses to chemotherapy.
- Mutation status of the Immunoglobulin heavy chain gene (IgVH gene).
- Patient preference – time-limited or continuous therapy/frequency of hospital visits or admissions.

Considerations when choosing which targeted agent

	Pros	**Cons**
Ibrutinib	Most amount of data available. Side-effect profile well established. Once daily dosing. No need for TLS stratification. Good data on response to venetoclax post Ibrutinib. Only agent showing longer PFS and OS than FCR in a randomised trial.	Current data support indefinite therapy. Concern for use in those with cardiac disease, bleeding tendency or need for anticoagulation.
Acalabrutinib	Atrial fibrillation appears less frequent than Ibrutinib. No need for TLS risk stratification.	Twice-daily dosing. Current data support indefinite therapy. Potential for more toxicities to come to light over time.
Venetoclax	Defined duration of therapy. Does not have cardiac or bleeding side-effects. Once daily dosing.	Possible requirement for in-patient monitoring on initiation. Requires additional day case attendance for obinutuzumab. Significant neutropenia frequent.

Adapted from Brem E et al. (2021) JCO Oncology Practice

Looking to the future of 1st line therapy

UK FLAIR trial yet to report on randomisation between FCR/Ibrutinib/Ibrutinib + Venetoclax.

GLOW Trial: Randomised 211 less-fit patients at 1st line therapy to Obinutuzumab-chlorambucil (6 cycles) or Ibrutinib+Venetoclax (3 month Ibr lead-in then 12 months combination therapy. At median follow-up of 27.7 months, median PFS not reached in I+V arm, vs 21 months O-Chl arm[1].

CAPTIVATE Trial: Included 80 patients < 65 years, little comorbidity, with either TP53 disruption, 11q deletion or unmutated IgVH.

Phase II study of up to 24 cycles of Ibrutinib + Venetoclax, at 1 year – 88% complete remission, 61% MRD negative[2].

CLL13 Trial (GAIA): Phase III randomisation between FCR/BR, R-Ven, O-Ven or O+Ibr+Ven in fit patients without 17p deletion.

CLL17 Trial (German CLL study Group) currently recruiting:

1:1:1 Randomisation between Ibrutinib monotherapy, fixed-duration Ven-Obinutuzumab and fixed duration Ibrutinib-Venetoclax.

1: Kater A et al. (2021) presented at EHA congress, abstract LB1902.
2: Jain N et al. (2019) New Engl J Med 380:2095-2103.

Treatment Considerations at Relapse

Treatment often not indicated at 1st signs of relapse.

At relapse, many of the same considerations as at 1st-line therapy are important.

With numerous trials demonstrating targeted agents superiority over chemo-immunotherapy at relapse, re-treatment with CIT is now rarely the preferred option.

Current SMC approved 2nd-line therapies include:

- BTK inhibitors – Ibrutinib or Acalabrutinib
- Venetoclax and Rituximab (fixed duration 2 years)

Ibrutinib in Relapsed CLL

- Approved for use in previously treated CLL in April 2017, on basis of data from the RESONATE trial[1].
- This study compared continuous Ibrutinib to a 24 week schedule of Ofatumumab (anti-CD20 mAb).
- Responses to Ibrutinib were seen in 91% of patients, complete remissions rare.
- Significant numbers of patients stopped treatment over time, average length treatment 3-3.5 years.
- At final analysis the average length of remission in Ibrutinib-treated patients was just over 3 ½ years, as compared to just 8 months with ofatumumab[2].

1 – Byrd JC et al. (2014) N Engl J Med 371:213-23; 2- Munir T et al. (2019) Am J Hematol 94: 1353-63.

Acalabrutinib in Relapsed CLL

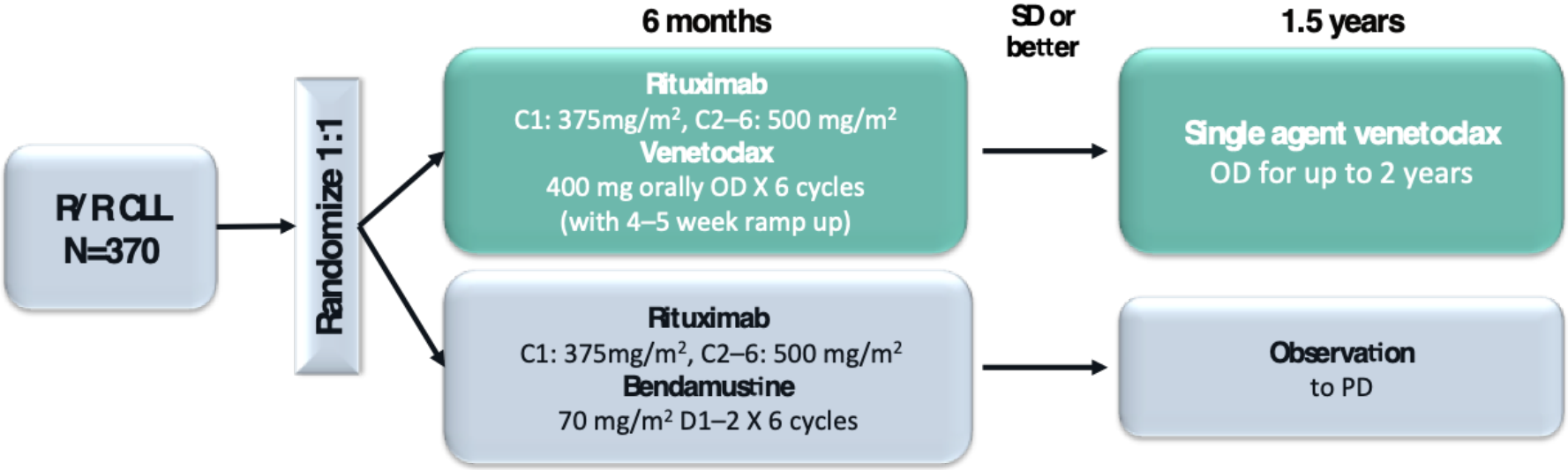
ASCEND Trial: Randomised 310 patients with relapsed CLL requiring treatment to either acalabrutinib or investigator's choice of therapy (either bendamustine-rituximab or idelalisib-rituximab).

- At 16 months of follow-up, significantly more acalabrutinib-treated patients remained in remission (88% vs 68% at 12 months).
- The improvement in remission duration was also seen in patients with unmutated IgVH and TP53 disruption.
- Just over 1 in 10 patients stopped treatment due to toxicity.

Ghia P et al., (2020) J Clin Oncol 38:2849-61.

Venetoclax and Rituximab in Relapsed CLL

2 year fixed-duration therapy, licensed and approved on basis of MURANO trial data.



- After 2 years of follow-up, around 85% Ven-R patients remained in remission as opposed to just over a third of R-bendamustine treated patients[1].

- After 4 years, over half (57%) Ven-R patients remained in remission, compared with less than 1 in 20 of the R-bendamustine patients[2].

1 – Seymour JF et al. (2018) N Engl J Med 378:1107-20;
2 - Kater A et al. (2020) J Clin Oncol. 38:4042-54

Sequencing of therapies in Relapsed CLL

Relapse after:	**Options:**
Chemo-immunotherapy	Acalabrutinib Ibrutinib R-Venetoclax
BTK inhibitor	Venetoclax (+/- Rituximab)
Fixed duration venetoclax therapy (Ven-O or Ven-R)	BTK inhibitor or retreatment with venetoclax (+/-R) if durable response to prior venetoclax.
BTK inhibitor and Venetoclax (as separate lines of therapy)	PI3Ki, clinical trial and consider allogeneic SCT.

Therapies on the horizon for relapsed CLL

Zanubrutinib: Next-generation BTK inhibitor, twice daily dosing.

ALPINE Trial: Patients with relapsed/refractory CLL randomised 1:1 to zanubrutinib or ibrutinib. Overall response rate higher with zanubrutinib (78.3% vs 62.5%) and at 18 months, 20 patients on zanubrutinib progressed compared to 42 patients on ibrutinib.

Less adverse events compared to ibrutinib, more selective BTK inhibitor.

Hillmen P et al. (2021) presented at EHA congress.

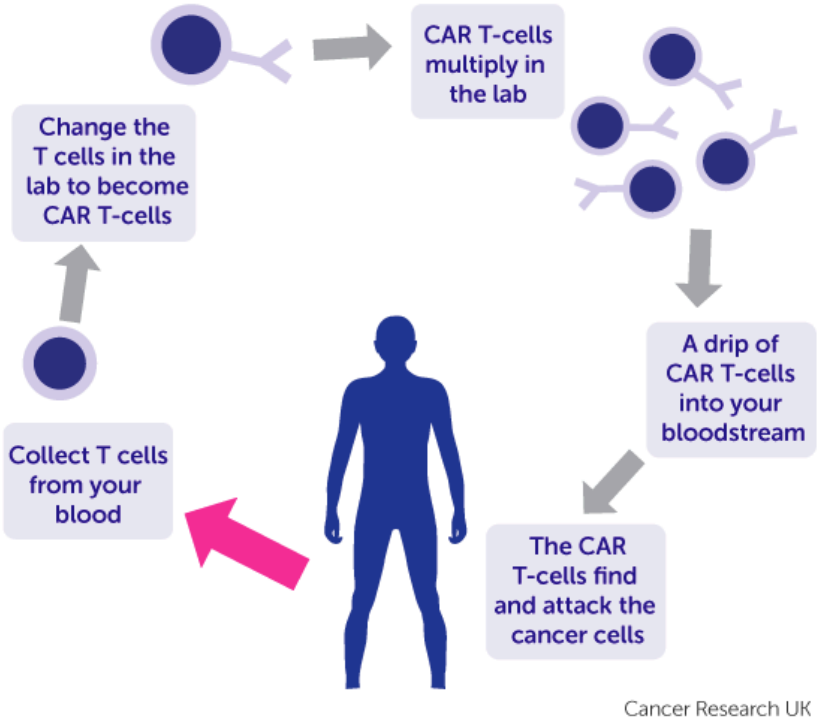
Pirtobrutinib (LOXO-305): Oral, highly-selective, reversible BTK inhibitor, designed to retain activity against BTK with acquired C481 resistance mutations.

BRUIN Trial: Phase I/II trial of pirtobrutinib in previously treated B cell malignancy. Phase II dose 200 mg daily.

In patients with median 4 lines of therapy, ORR 63%, with similar rates seen in patients refractory to prior BTK inhibitors.

Mato A et al. (2021) Lancet 397:892-901.

Chimeric antigen receptor (CAR)-T cell therapy



Numerous CAR-T cell products in early-phase study for relapsed/ refractory CLL, mainly targeting CD19.

No current licensed products for CLL currently in UK.

Ongoing clinical trials.

Supportive Care in CLL

- CLL results in impaired antibody production by normal B lymphocytes, resulting in poor responses to vaccination and recurrent infections.

- Early vaccination (at diagnosis/prior to treatment where possible) is key to maximising protection.
  - Pneumococcal vaccination – PREVNAR13 followed at least 2 months later by Pneumovax23.
  - Annual seasonal flu vaccine.
  - COVID-19 vaccination – recent recommendation for immuno-compromised patients to receive 3rd dose, with aim of improving antibody responses.
  - Need to avoid 'Live' vaccines – eg Zostavax shingles vaccination. The inactivated Shingrix varicella vaccine has very recently been licensed in the UK as an alternative for eligible patients (age 70-79 yrs) unable to receive Zostavax.

- Immunogloblin replacement therapy is advised for patients with low IgG levels who suffer repeated bacterial infections despite oral antibiotics and fail to respond to vaccination.

Conclusions

- Recent SMC approvals of targeted therapies for first-line and relapse are leading to a general move from chemo-immunotherapy to targeted treatments in CLL.

- Increasing options for CLL patients at 1st line therapy and beyond requires effective communication of benefits and risks to ensure informed and shared decision making at all stages.

- Several outstanding questions being addressed in clinical trials:
  - Optimal combination of agents.
  - Optimal sequencing of targeted therapies.
  - Optimal duration of treatment at all stages.
  - Place for MRD-directed therapy.

- New targeted agents and cellular therapies likely to increase treatment options further within coming years.