# Promising Investigational Agents and Strategies

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# Objectives

- To discuss noncovalent BTK inhibitors as a strategy for covalent BTK inhibitor-resistant CLL
- To discuss cellular therapies including CAR-T in CLL
- To briefly discuss other promising agents and strategies under investigation in CLL

# Rationale for non-covalent BTK inhibition in CLL

- Resistance to ibrutinib, and with less certainty acalabrutinib and zanubrutinib, is driven by mutations in BTK (C481S)

- In the presence of this mutation, covalent inhibitors bind non-covalently, and binding kinetics and short half-life make these agents less effective

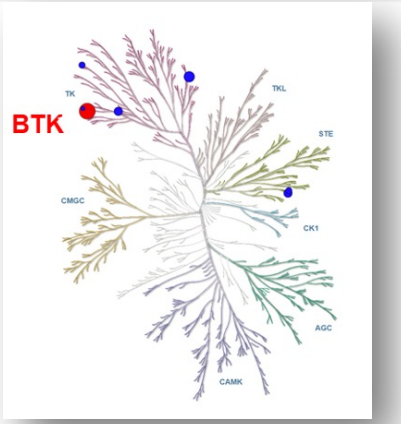
- However, the mutation does not appear to alter CLL dependence on the BCR pathway

# Reversible BTK Inhibitors

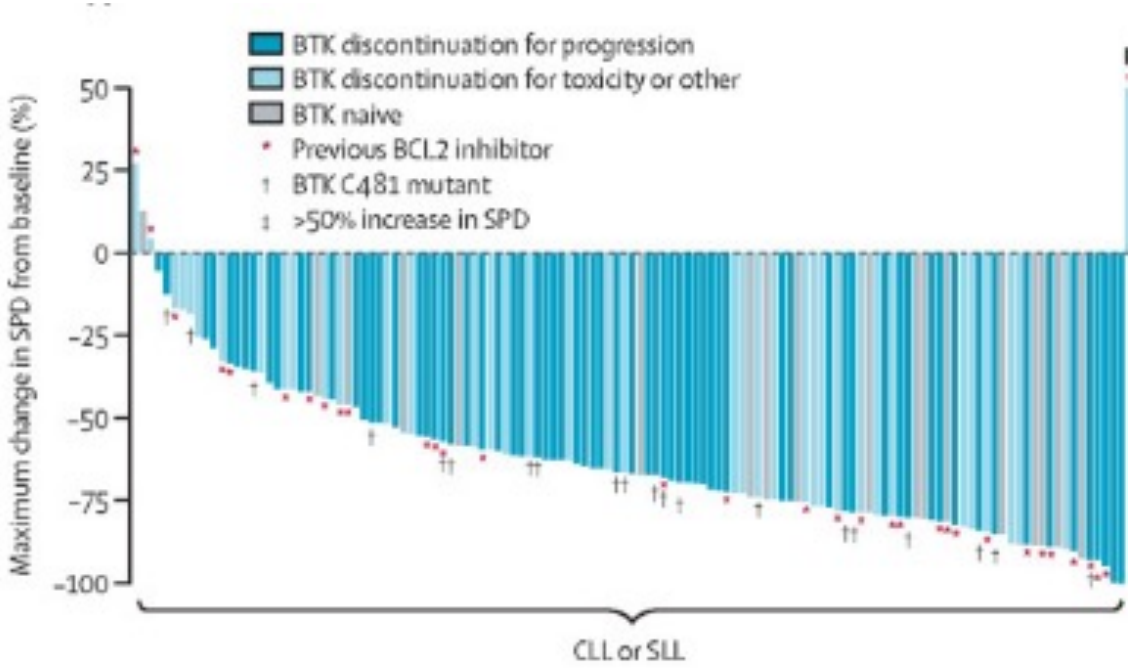
- Pirtobrutinib (Loxo 305) Abstract 391
- MK 1026 (formerly ARQ 531) Abstract 392
- Many others in earlier stages

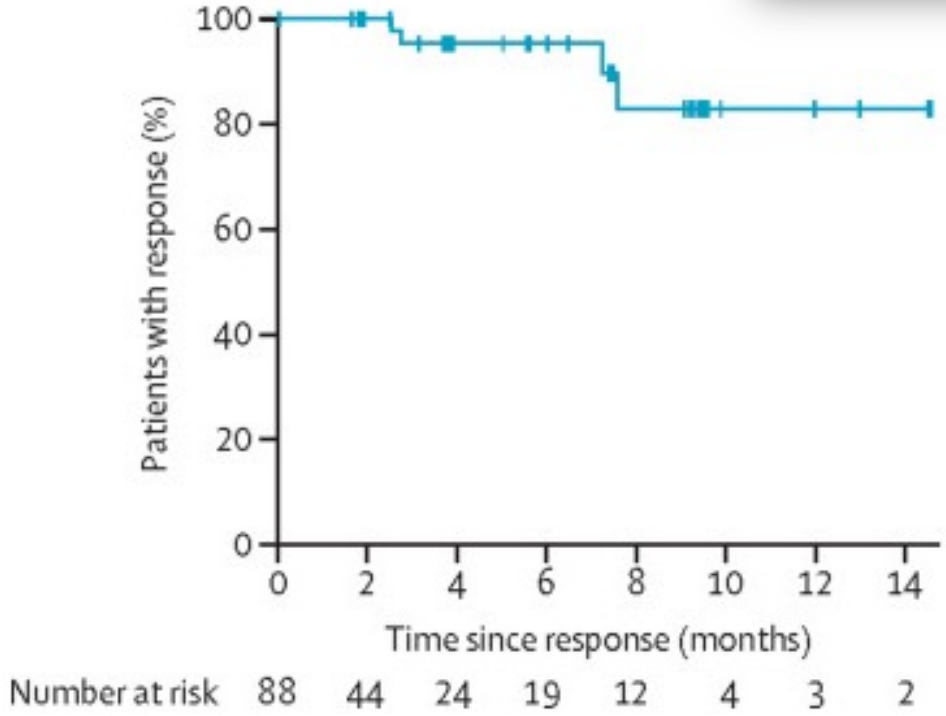
- Reversible inhibitors bind different sites on BTK than irreversible inhibitors and have PK that is favorable to reversible drug binding

# Pirtobrutinib in CLL/SLL: BRUIN Study




- 139 patients treated on phase 1/2 study
- Overall response rate 62%




Mato et al, Lancet 2021

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# Efficacy in patient subgroups

| Characteristic | Number of Patients Evaluable | Overall Response Rate |
|---|---|---|
| **All Patients** | 139 | 63% |
| **Previous tx BTK and BCL2i** | 45 | 64% |
| **Previous tx chemo,BTKi, BCL2i, PI3Ki** | 12 | 58% |
| **Previous tx CAR-T** | 10 | 90% |
| **BTK C481S Mutation** | 24 | 71% |
| **Previous progression on BTKi** | 79 | 67% |

Mato et al, Lancet 2021

# Pirtobrutinib Adverse Events

| All doses and patients (n=323) | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Treatment-emergent AEs, (≥10%), n (%) | | | | | Treatment-related AEs, n (%) | |
| Adverse Event | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Any Grade | Grades 3/4 | Any Grade |
| Fatigue | 40 (12%) | 22 (7%) | 3 (1%) | - | 65 (20%) | 2 (<1%) | 27 (8%) |
| Diarrhea | 45 (14%) | 10 (3%) | - | - | 55 (17%) | - | 28 (9%) |
| Contusion | 37 (12%) | 5 (2%) | - | - | 42 (13%) | - | 29 (9%) |
| AEs of special interest[a] | | | | | | | |
| Bruising | 48 (15%) | 5 (2%) | - | - | 53 (16%) | - | 37 (12%) |
| Rash | 30 (9%) | 5 (2%) | - | - | 35 (11%) | - | 18 (6%) |
| Arthralgia | 13 (4%) | 3 (1%) | - | - | 16 (5%) | - | 5 (2%) |
| Hemorrhage | 10 (3%) | 4 (1%) | 1 (<1%) | - | 15 (5%) | - | 5 (2%) |
| Hypertension | 2 (<1%) | 9 (3%) | 4 (1%) | - | 15 (5%) | - | 4 (1%) |
| Atrial fibrillation/flutter | - | 2 (<1%) | - | - | 2 (<1%) | - | - |

Mato et al, Lancet 2021

# Chimeric Antigen Receptor T Cells (CAR-T Cells) in CLL

| Study | Co-stimulatory molecule | Ibrutinib | n | ORR, (n) % | CR, (n) % |
|---|---|---|---|---|---|
| Brentjens et al Blood 2011 | CD28 | N/a | 8 | 87 | 50 |
| Frey et al JCO 2020 | 41BB | 28% | 32 | 44 | 28 |
| Kochenderfer et al JCO 2015 | CD28 | N/a | 4 | 100 | 75 |
| Turtle et al JCO 2017 | CD28/41BB | 100% | 24 | 74 | 21 |
| Gauthier et al Blood 2020 | CD28/41BB | Concurrent | 19 | 83 | 22 |

# BTKi and T-cell function

- Ibrutinib:
  - Increases T-cell number, reduces PD-1 and CTLA-4 expressing cells
  - Improves expansion, engraftment of CAR T-cells, and tumor clearance and survival in a mouse model
  - May improve ORR when given before CART

Long et al J Clin Investig 2017, Fraietta et al Blood 2016, Brentjens et al Blood 2016

# Phase I/II TRANSCEND CLL 004: Study Design

**Monotherapy Cohort**
Patients with R/R CLL/SLL; either standard-risk (≥3 prior tx failed) or high-risk disease (≥2 prior tx failed); ineligible for BTKi or prior BTKi failure; ECOG PS 0/1

**Combination Cohort**
Patients with R/R CLL/SLL; either progressing on ibrutinib at enrollment, with high-risk features and did not attain CR on ibrutinib for ≥6 mo, *BTK* or *PLCγ2* mutations, or prior ibrutinib without contraindications to reinitiating ibrutinib

| Lymphodepletion* | Dose Escalation | Dose Expansion (mTPI-2 Design) 28-Day DLT Period |
|---|---|---|
| **Fludarabine** 30 mg/m$^2$ + **Cytarabine** 300 mg/m$^2$ x 3 days | **Phase I Monotherapy** **Liso-cel** DL1 or DL2$^{\dagger}$ (n = 23) | **Phase II Monotherapy** **Liso-cel** DL2$^{\dagger}$ |

*Continue or reinitiate ibrutinib at enrollment through up to 90 days after liso-cel or longer if clinically beneficial.*

| | | |
|---|---|---|
| **Fludarabine** 30 mg/m$^2$ + **Cytarabine** 300 mg/m$^2$ x 3 days | **Phase I Combination** **Liso-cel** DL1 or DL2$^{\dagger}$ + **Ibrutinib** 420 mg (n = 19) | **Phase I Combination** **Liso-cel** DL2$^{\dagger}$ + **Ibrutinib** 420 mg |

*Leukapheresis at enrollment; bridging therapy permitted during liso-cel manufacturing; measurable disease reconfirmed before lymphodepletion. $^{\dagger}$DL1: 50 x 10$^6$ CAR+ T-cells. DL2: 100 x 10$^6$ CAR+ T-cells.

- **Primary endpoints (dose escalation):** safety, identify recommended dose
- **Exploratory endpoints (dose escalation):** antitumor activity per iwCLL 2018 criteria, MRD, cellular kinetics

Siddiqi. ASH 2020. Abstr 546. Wierda. ASH 2020. Abstr 544.

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# TRANSCEND-CLL-004: Patient Characteristics

## Liso-cel monotherapy

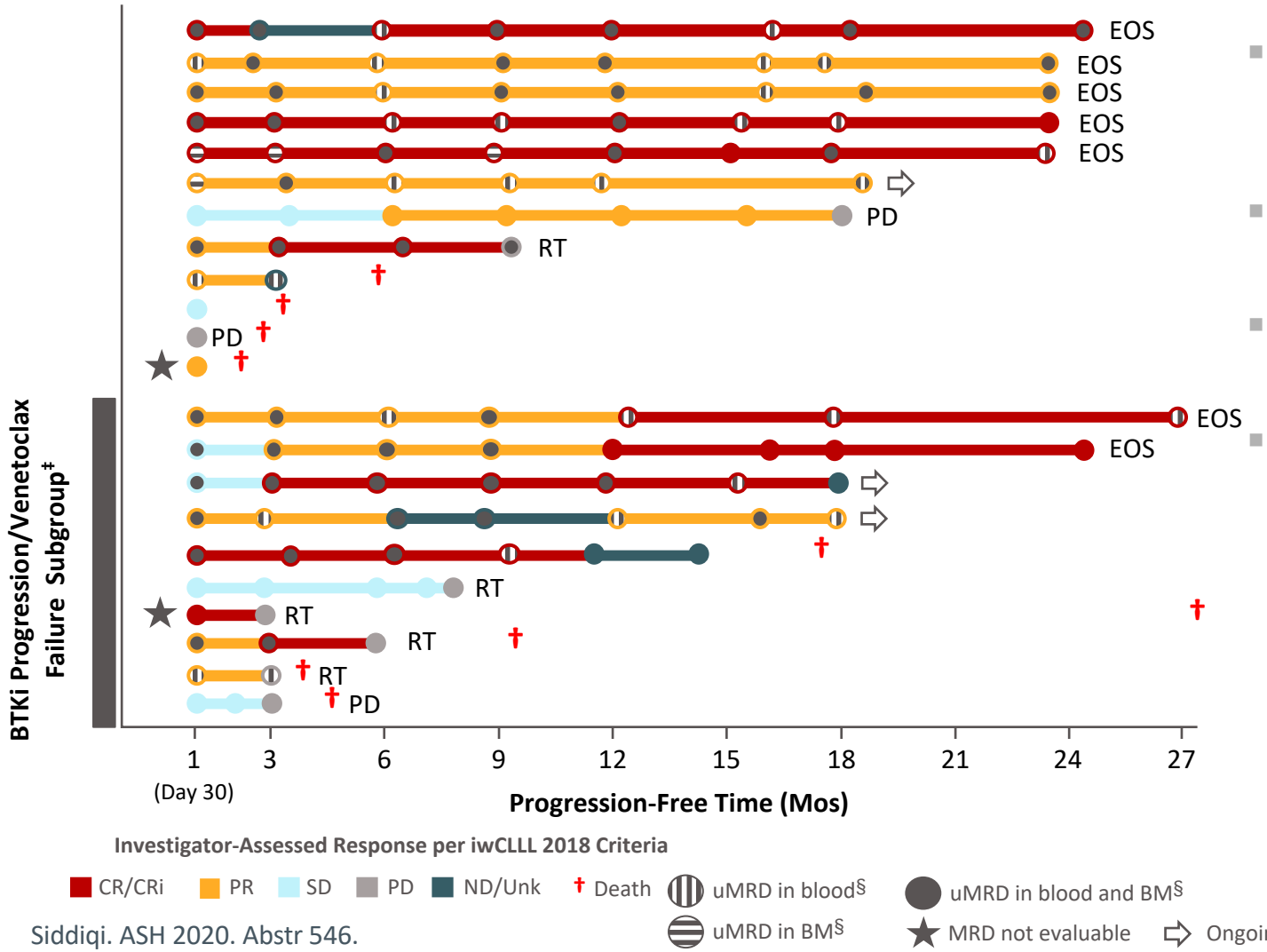
| | All Evaluable Patients (N=23) |
|---|---|
| Median Age | 66 |
| High Risk Cytogenetics | 19 (83) |
| Median # Prior TRMT | 6 (3-13) |
| Prior Ibrutinib | 23 (100) |
| Prior Ven and Ibr | 11 (48) |

## Liso-cel + Ibrutinib

| | All Evaluable Patients (N=19) |
|---|---|
| Median Age | 60 |
| High Risk Cytogenetics | 18 (95) |
| Median # Prior TRMT | 4 (2-11) |
| Prior Ibrutinib | 19 (100) |
| Prior Ven and Ibr | 11 (58) |

**Siddiqi et al Blood Supp 2020, Wierda et al Blood Supp 2020**

# TRANSCENDENT CLL 004 – Monotherapy




Siddiqi. ASH 2020. Abstr 546.

- ORR: 82% (CR/CRi, 46%; PR, 36%)
- 68% (n = 15/22* patients) achieved rapid response within 30 d, with deepening response in 27% (6/22)
- Responses were durable: at 12 mos, 50% in response; two had PD after 12 mos
- 4/15 with uMRD (blood) response have progressed (n = 3 due to RT)
- Rapid, durable responses observed in subgroup with BTKi progression/ venetoclax failure (4/6 progression events due to RT)

*Efficacy analysis excluded 1 patient who experienced RT before lymphodepleting CT. ‡Defined as those with progressive disease on BTKi and who failed venetoclax due to PD, intolerance, or failure to respond after ≥3 mos. §Evaluated in blood by FACS and/or in BM by NGS (each with sensitivity of $\leq 10^{-4}$).

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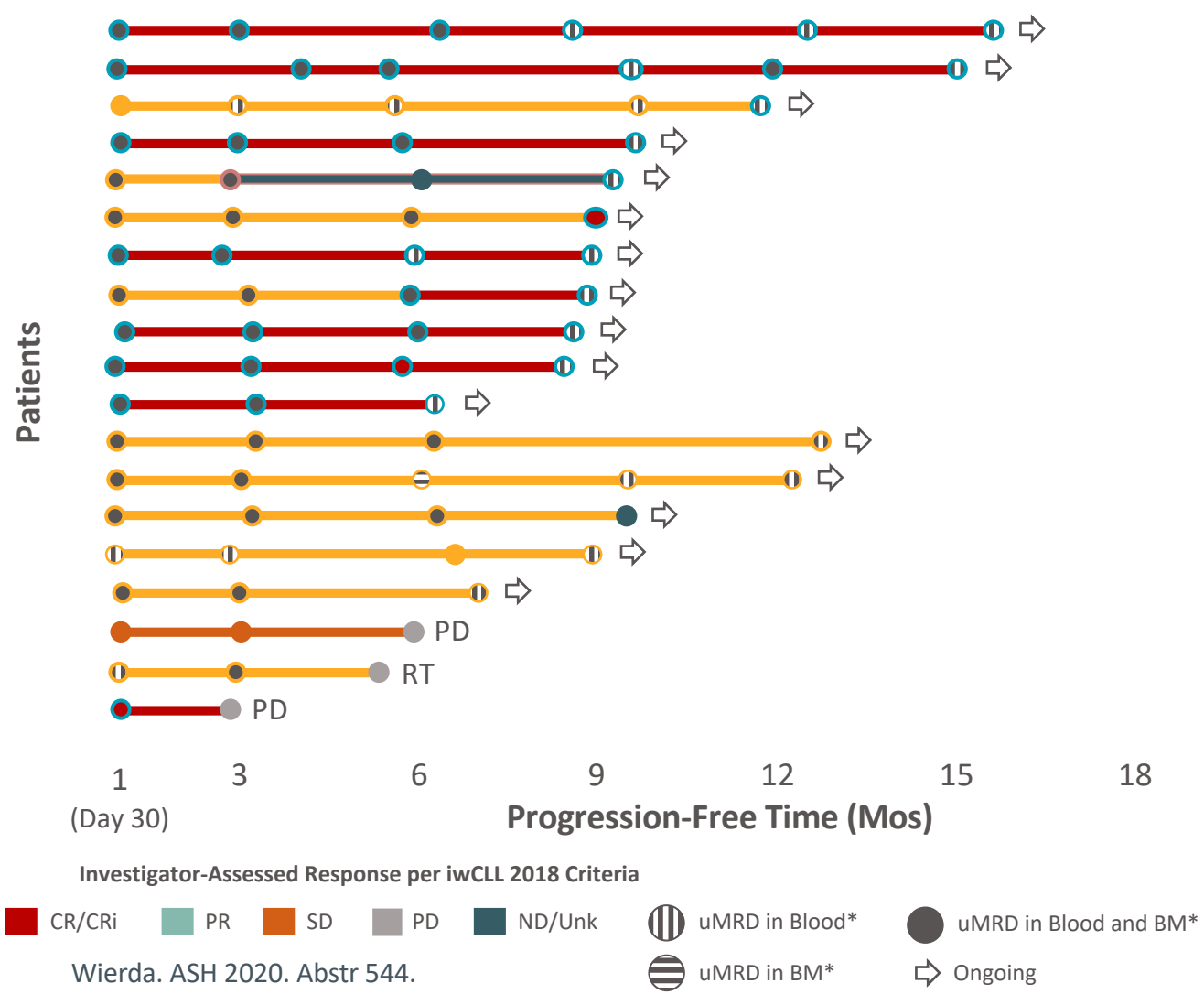
# TRANSCEND CLL 004 – Combination




Wierda. ASH 2020. Abstr 544.

- All responders (n = 18/19) achieved response by Day 30 after liso-cel
  - Among those with ≥6 mos of follow-up, 89% (n = 16/18) maintained/improved response from Day 30
- Of n = 17 achieving uMRD in blood:
  - All achieved this response by Day 30
  - One later progressed due to Richter transformation

*Evaluated in blood by FACS and/or in BM by NGS.

# TRANSCEND-CLL-004: Toxicity Both Groups

## Liso-cel monotherapy

| | Total N = 23 |
|---|---|
| Any CRS, n (%) | 17 (74) |
| Median time to onset, days (range) | 3 (1-10) |
| Grade ≥ 3 CRS , n (%) | 2 (9) |
| Any-grade neurological event, n (%) | 9 (39) |
| Median time to onset, days (range) | 4 (2-21) |
| Grade ≥ 3 neurological toxicity, n (%) | 5 (22) |

## Liso-cel + Ibrutinib

| | Total N = 19 |
|---|---|
| Any CRS, n (%) | 14 (74) |
| Median time to onset, days (range) | 6.5 (1-13) |
| Grade ≥ 3 CRS, n (%) | 1 (5) |
| Any-grade neurological event, n (%) | 6 (32) |
| Median time to onset, days (range) | 8 (5-12) |
| Grade ≥ 3 neurological toxicity, n (%) | 3 (16) |

**Siddiqi et al Blood Supp 2020, Wierda et al Blood Supp 2020**

## Promising Agents and Strategies in Development

- Alternative targeting of BTK
  - PROTAC degradation
- Alternative targeting of BCL2
- PKCβ inhibitors
- Other cellular therapies
  - Alternative CAR-T (ROR1,etc)
  - CAR-NK
  - TILs
- Alternative ways to harness immune system
  - Lenalidomide and derivatives

# Conclusions

- Reversible BTK inhibitors are a promising strategy to treat relapsed CLL. Long-term follow-up will help establish durability of remissions
- CD19 directed CAR-T represents another exciting strategy in CLL, which has significantly improved in efficacy and safety over time
- Future studies will define where in the course of treatment these strategies are best used and what is the optimal strategy for individual patients
- Many agents show promise in the laboratory for treatment of ibrutinib-resistant CLL, clinical trials are ongoing to evaluate efficacy in patients

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