# Safety and Activity of the Chemotherapy-free Triplet of Ublituximab, TGR-1202, and Ibrutinib in Relapsed B-cell Malignancies

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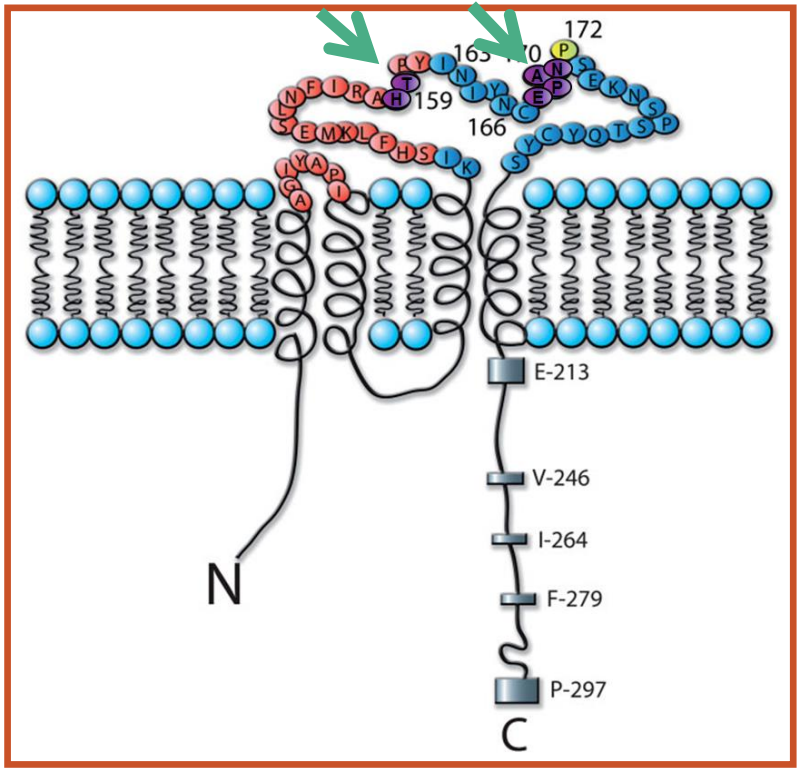
# Ublituximab: Glycoengineered Anti-CD20 mAb

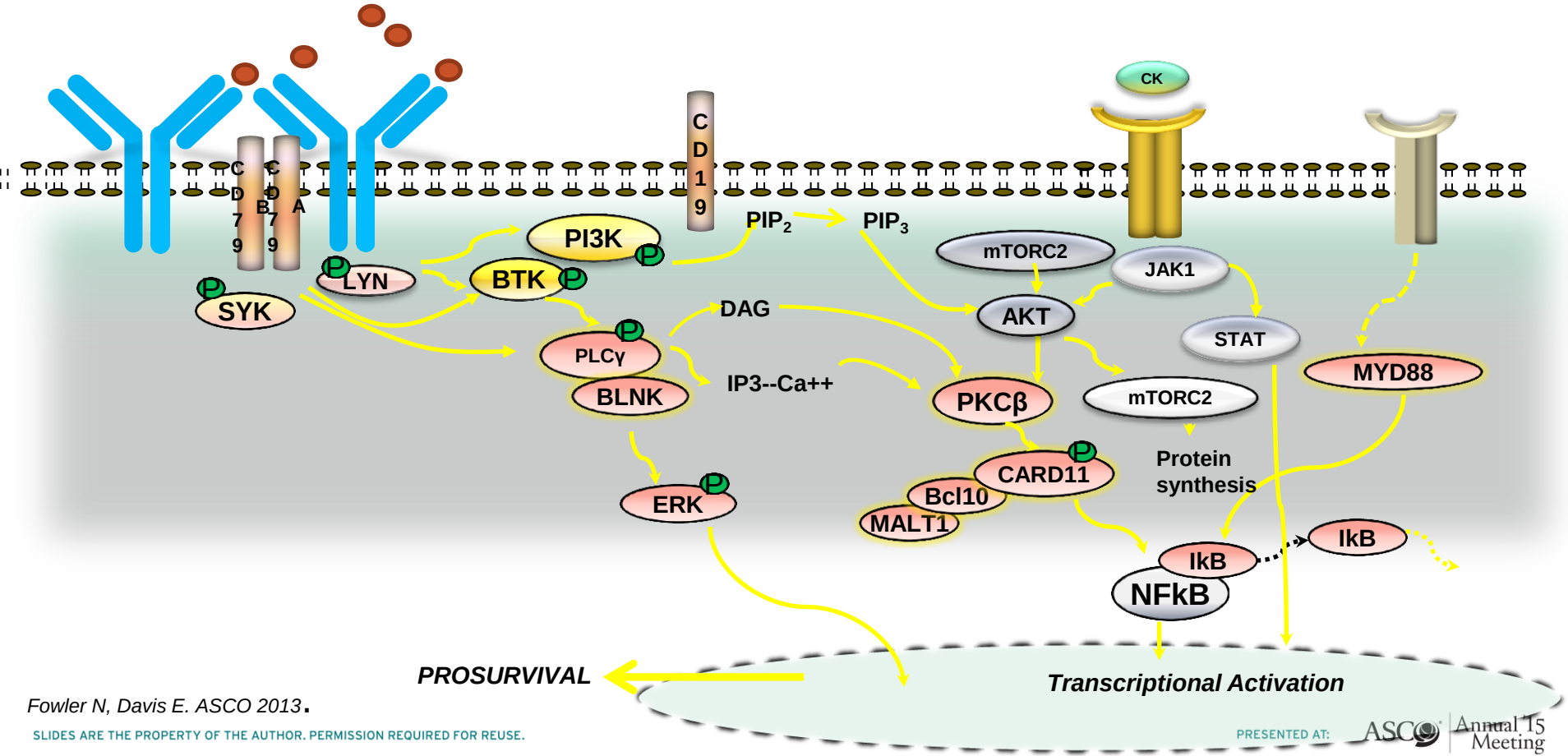
- Type 1 chimeric IgG1 mAb
- Unique binding sequence on CD20 (**Green** arrows in figure)
- Potential advantages over current standards of care:
  - Glycoengineered for enhanced ADCC
  - Activity in “low” CD20 expressing cell lines
- Single agent responses observed in rituximab refractory patients[1]




Source: Adapted from Ruuls et al 2008

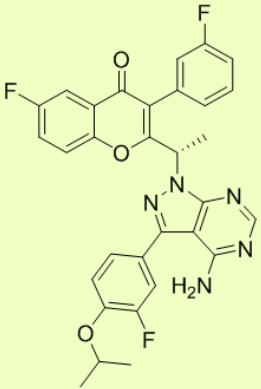
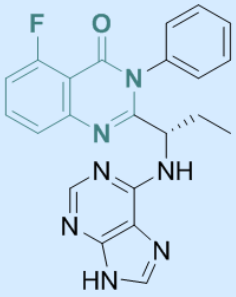
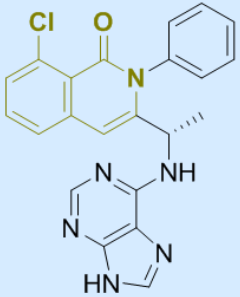
(1) O’Connor et al, ASCO 2014

# B-Cell Receptor Signaling in Lymphoma




*Fowler N, Davis E. ASCO 2013*.

# TGR-1202: Novel PI3K delta Inhibitor

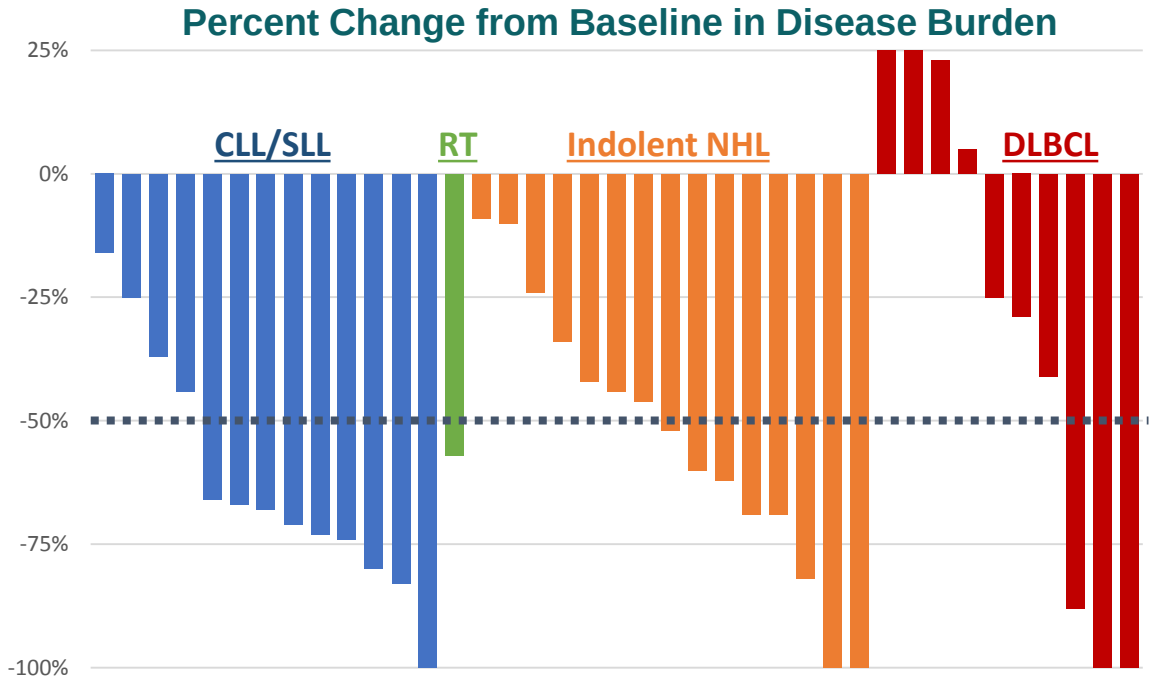
| TGR-1202 | Idelalisib (GS-1101) | Duvelisib (IPI-145) |
|---|---|---|
|  |  |  |
| Delta | Delta | Delta/Gamma |
| QD | BID | BID |

- PK profile that allows once-daily oral dosing
- 93% nodal PR rate in patients with rel/ref CLL[1]

[1]Burris et al, ASCO 2015, Abstract # 7069

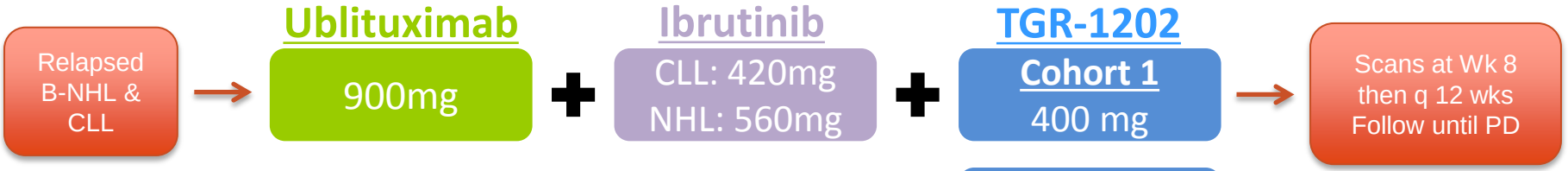
# TGR-1202 + Ublituximab Doublet

- 55 patients treated to date
  - 60% ≥3 prior therapies
  - 51% refractory to prior therapy
- Combination well tolerated
  - Minimal Gr. 3/4 AE's
- Clinical activity demonstrated in CLL, indolent NHL, and aggressive NHL




Lunning et al, ASCO 2015

# Trial Design: TGR-1202 + Ublituximab + Ibrutinib




- 3 + 3 dose escalation design (CLL and NHL)
- No limit on prior # of therapies
- ECOG Performance Status ≤ 2
- ANC > 500 / Plts > 30,000
- Patients with Richter's Transformation, or refractory to prior PI3Kδ inhibitors or prior BTK inhibitors are eligible
- All 3 agents started on Day 1

**Endpoints**:

- Primary: Safety
- Secondary: ORR, DOR, PFS

# Demographics: TGR-1202 + Ublituximab + Ibrutinib

| | | |
|---|---|---|
| **Evaluable for Safety (n)** | | 16 |
| **Evaluable for Efficacy† (n)** | | 13 |
| **Median Age, years (range)** | | 63 (51 – 85) |
| **Male/Female** | | 12/4 |
| **ECOG, 0/1/2** | | 5/8/3 |
| **Prior Treatment Regimens, median (range)** | | 4 (1 – 5) |
| **Histologies** | 4 CLL | 1 SLL |
| | 4 Follicular | 1 MZL |
| | 3 DLBCL | 2 MCL |
| | 1 Richter's Transformation | |
| **≥ 2 Prior R–Chemo Regimens, n** | | 13 (81%) |
| **Refractory to Prior Therapy, n** | | 8 (50%) |

**†1 removed per investigator discretion and 2 too early to evaluate**

- 100% of CLL had 17p and/or 11q del
- 4/5 FL/MZL pts had ≥ 4 prior lines of treatment
  - 1 ibrutinib refractory
  - 1 duvelisib refractory
- 2/3 DLBCL were ABC subtype and had ≥ 4 prior lines of treatment

# Safety: TGR-1202 + Ublituximab + Ibrutinib

Cohort Summary

- CLL and NHL cohorts evaluated separately

| | | | | | NHL Pts | # DLT | CLL Pts | # DLT |
|---|---|---|---|---|---|---|---|---|
| 1: | Ublituximab 900mg | Ibrutinib 420/560mg | + | TGR-1202 400 mg | 3 | 0 | 5 | 1* |
| 2: | Ublituximab 900mg | Ibrutinib 420/560mg | + | TGR-1202 600 mg | 4 | 0 | 0 | 0 |
| 3: | Ublituximab 900mg | Ibrutinib 420/560mg | + | TGR-1202 800 mg | 4 | 0 | 0 | 0 |

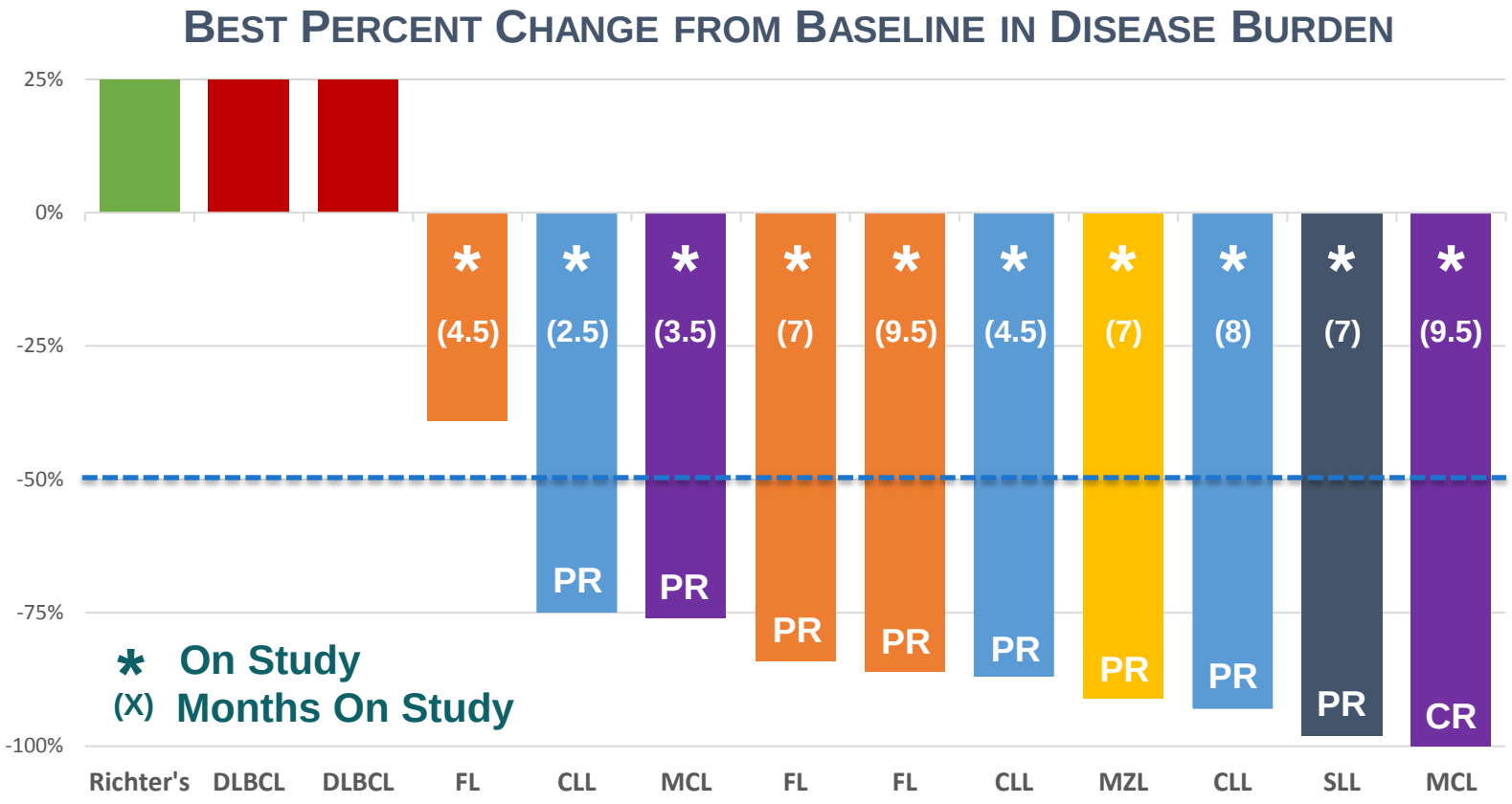
**DLT of reactivated varicella zoster – no additional DLT's to date in CLL cohort*

- Median time on study = 4 mos (range 1 – 9 mos)
- DLT in CLL 400 mg cohort
- 800 mg TGR-1202 cohort cleared in NHL

# Safety: TGR-1202 + Ublituximab + Ibrutinib

| AE's (at least possibly related) in > 1 Patient N=16 | | |
|---|---|---|
| **Adverse Event** | **All Grades** n (%) | **Grade 3/4** n (%) |
| **Infusion reaction** | 4 (25%) | - |
| **Diarrhea** | 3 (19%) | - |
| **Nausea** | 3 (19%) | - |
| **Fatigue** | 3 (19%) | - |
| **Rash** | 3 (19%) | - |
| **Anemia** | 2 (13%) | - |
| **Neutropenia** | 2 (13%) | 1 (6%) |
| **Leukopenia** | 2 (13%) | 1 (6%) |
| **Insomnia** | 2 (13%) | - |

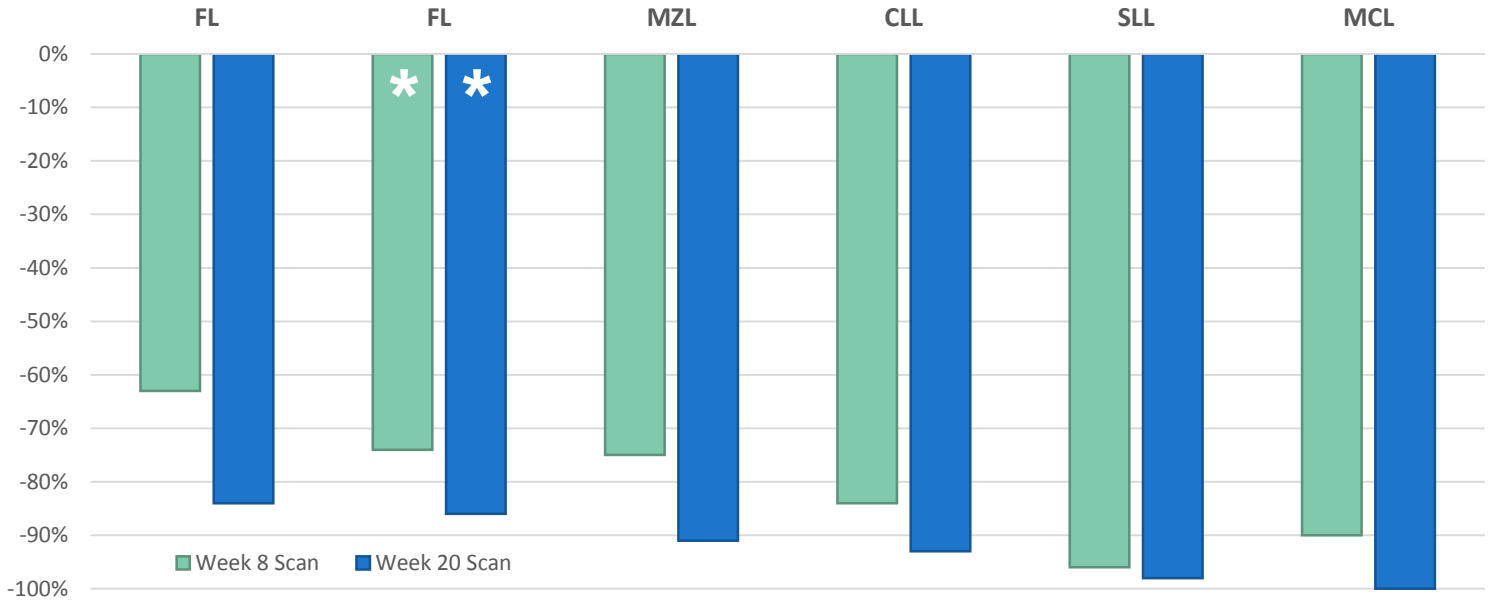
# Activity in NHL: TGR-1202 + Ublituximab + Ibrutinib



# “Triplet”: TGR-1202 + Ublituximab + Ibrutinib

**Clinical Response at First (8 week) and Second (20 week) Assessment**

(All patients who had second assessment shown)




* Durable PR (9+ months) in an ibrutinib refractory Follicular patient

# Conclusions

- The biologic combination of Ublituximab, TGR-1202 + Ibrutinib is safe in patients with relapsed B cell malignancies.
  - 800 mg cohort of TGR-1202 in NHL enrolled
  - 400mg cohort of TGR-1202 in CLL continues to enroll
    - One DLT was observed in a CLL for re-activated varicella
      - patient resumed treatment
  - The majority of patients remain on study

- The combination appears highly active in B-cell malignancies
  - CLL/SLL: ORR 100% in all patients with high risk features (n=4)
  - Responses were rapid in the majority of patients
    - 76% reduction in nodal disease noted at first assessment in responders.

- Triplet combination continues to accrue, with dose expansion planned at 800mg.
  - Clinicaltrials.gov: NCT02006485

- Phase II studies are planned in multiple histologies.

# Acknowledgements


- **Thank you to the patients and families for their participation.**

- **Participating Centers**

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