A Phase IB/II Study of Duvelisib in Combination with FCR (DFCR) For Frontline Therapy for Younger CLL Patients

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Disclosure of affiliations

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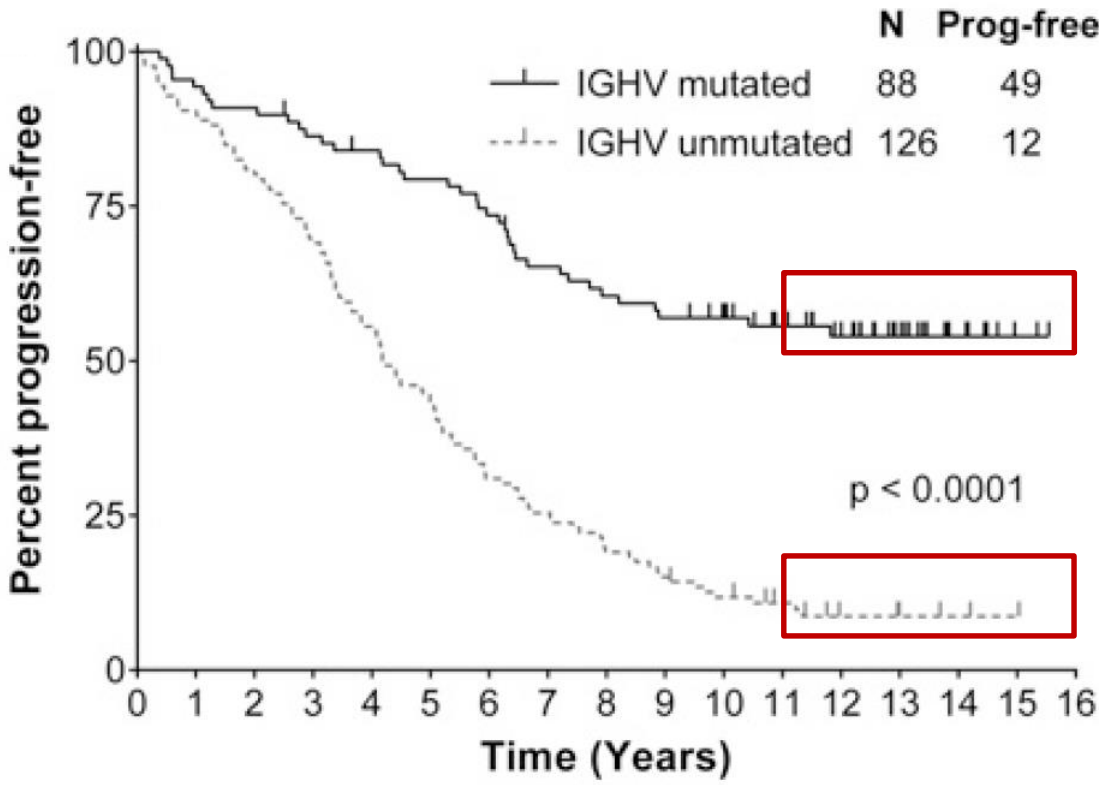
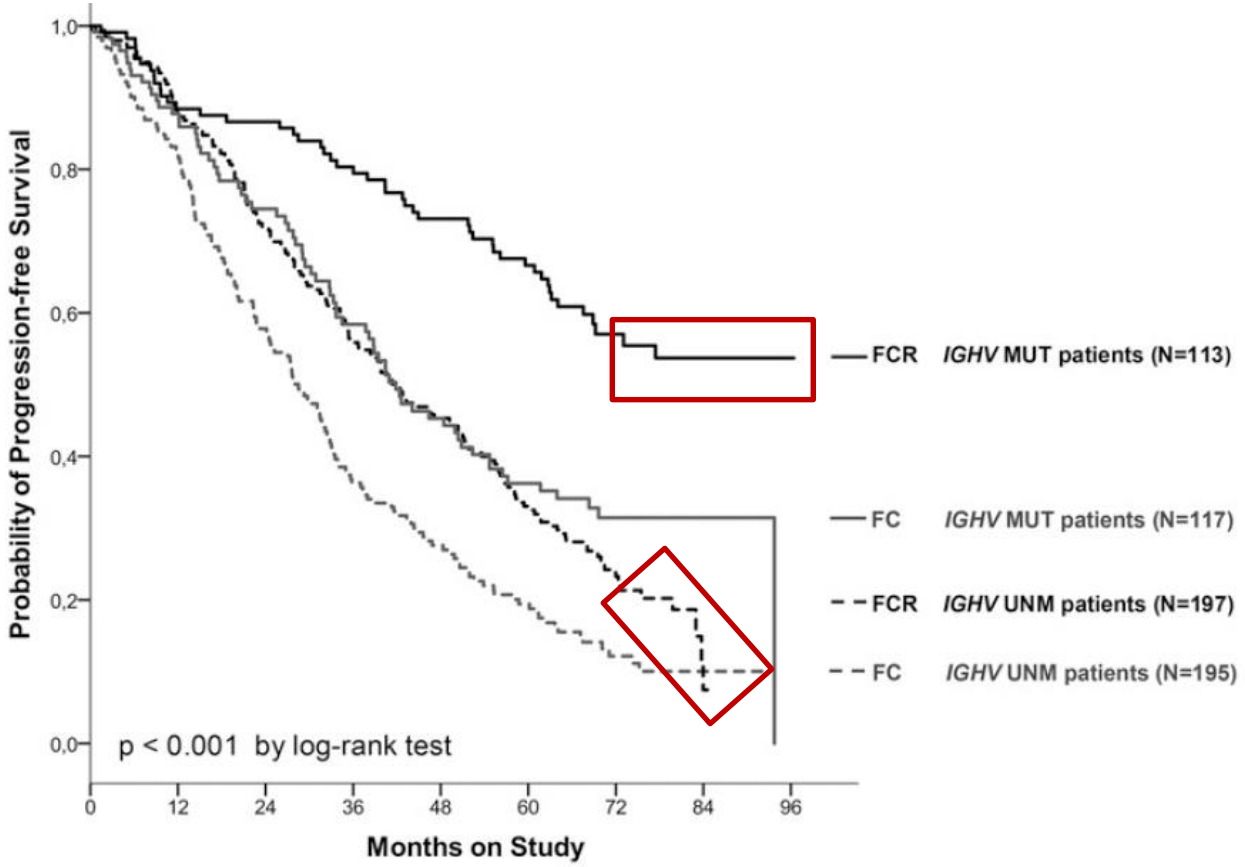
FCR has curative potential in mutated *IGHV* CLL

MDACC – FCR 300



Thompson et al., *Blood*, 2016

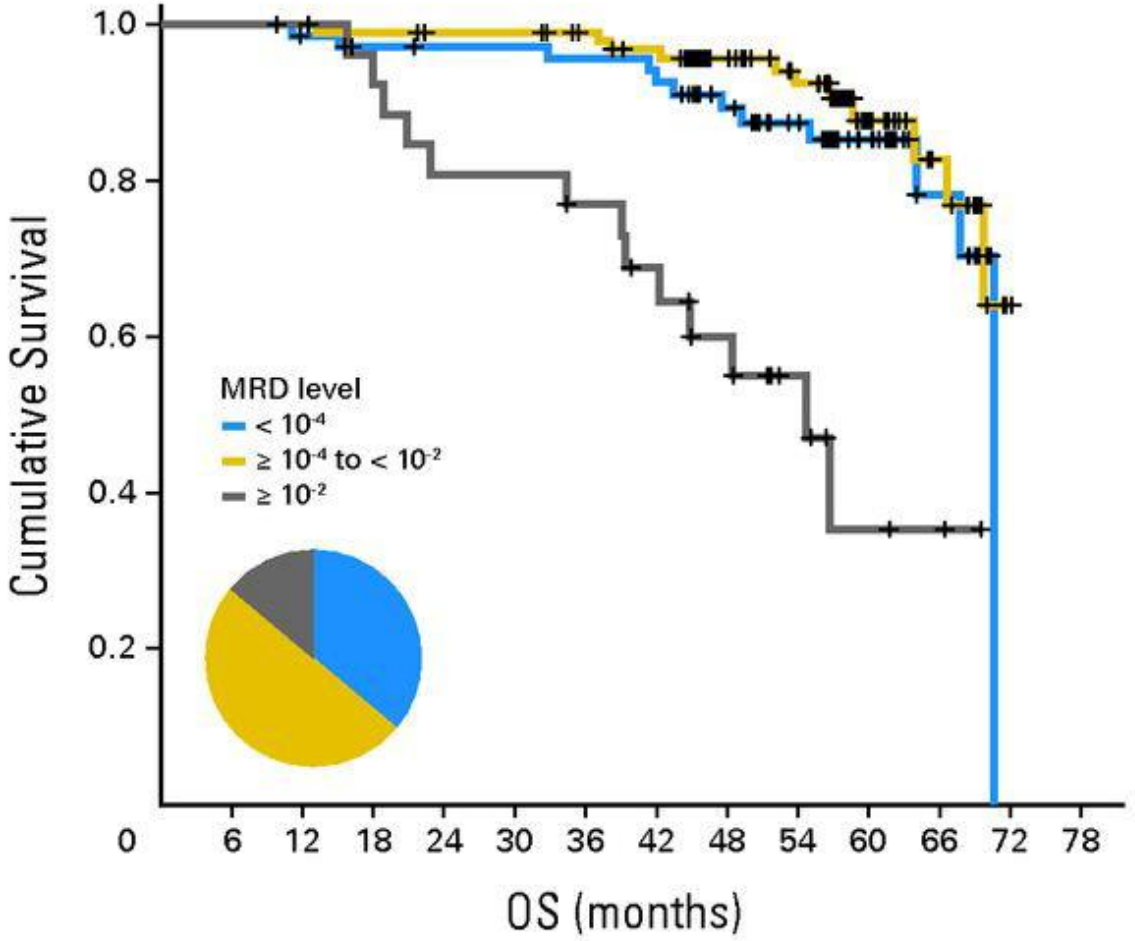
GCLLSG – CLL8



Fischer et al., *Blood*, 2016

Bone marrow MRD negativity is likely a prerequisite for cure

CLL8: OS by BM MRD Status

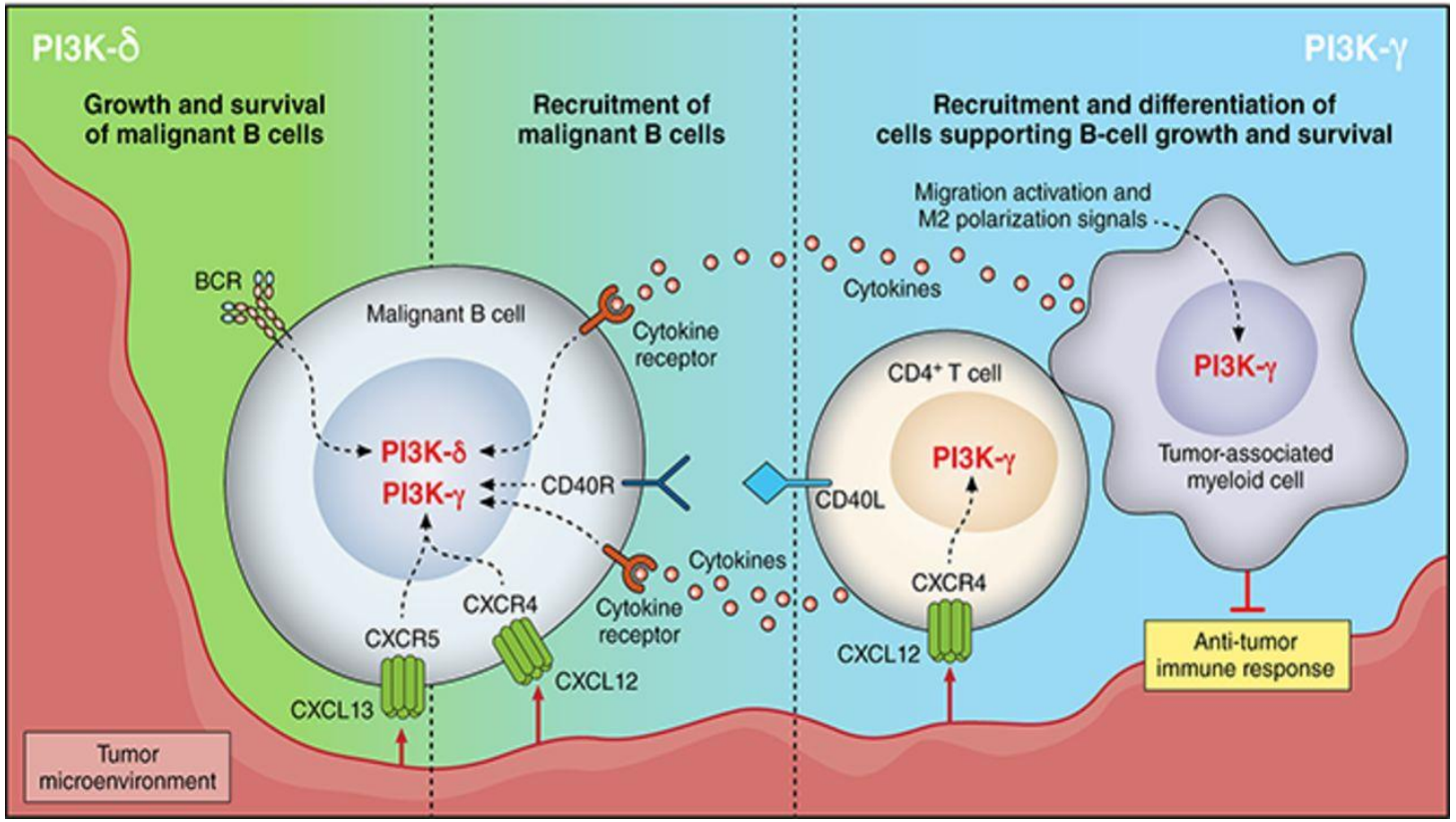


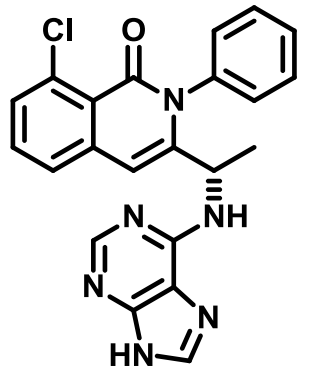
Boettcher et al, *J Clin Oncol*, 2012

Study Rationale

Our goal is to increase the curative potential of FCR for younger, fit CLL patients, including those with high risk disease markers

Duvelisib is an oral inhibitor of PI3K-δ and PI3K-γ





duvelisib

δ (delta)	duvelisib	idelalisib
Biochemical Activity (K_D)	**23 pM**	**273 pM**
Cellular Activity (IC_{50}) RAJI cells stimulated with anti-IgM	**0.36 nM**	**4.9 nM**

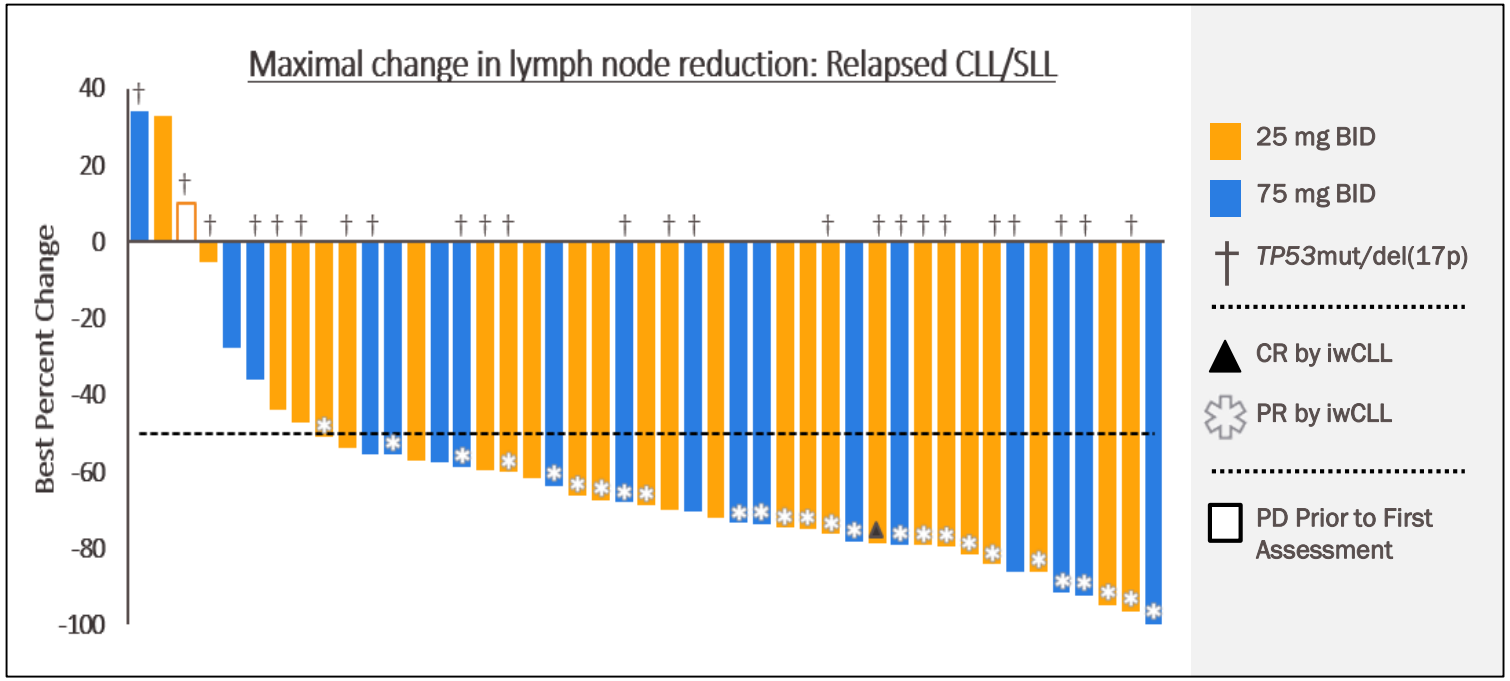
γ (gamma)	duvelisib	idelalisib
Biochemical Activity (K_D)	**243 pM**	**85,700 pM**
Cellular Activity (IC_{50}) RAW264.7 cells stimulated with C5a	**19.6 nM**	**520 nM**

Flinn et al., *Blood*, 2018
Weaver et al., Poster #PF649, *EHA Annual Meeting*, 2018

Winkler et al., *Chemistry & Biology.* 2013;20:1-11

Duvelisib is highly active across CLL risk groups

Relapsed/Refractory CLL/SLL



Relapsed CLL/SLL	25 mg BID	75 mg BID
All treated, n	**28**	**24**
ORR, %	57.1	54.2
CR, %	3.6	0
PR, %	53.6	54.2
Lesion response evaluable, n	**28**	**20**
50% lesion response, %	78.6	75.0

18 additional treatment-naïve CLL patients received duvelisib
ORR was 83%

Flinn et al., *Blood*, 2018

Hypothesis

The addition of duvelisib to FCR (DFCR) will increase the rate of CR with BM MRD (-) for frontline CLL treatment, with an acceptable safety profile

A phase Ib/II investigator-initiated study of duvelisib + FCR (DFCR) for younger, previously untreated patients with CLL

Endpoints

Primary

- Rate of CR with BM MRD negativity 2 mo. post FCR completion

Secondary

- Clinical response: ORR, CR, PR, PFS, EFS, and remission duration
- Rates of best response and best BM and PB MRD-negativity
- Safety/Tolerability
- Association of established CLL prognostic factors (e.g. FISH cytogenetics, *IGHV*, *TP53* and *NOTCH1* mutation) with clinical response

Exploratory

- Association of novel prognostic factors such as BH3 profiling with response
- Comparison of MRD assessment by 4-color flow cytometry vs. Adaptive clonoSEQ assay

A phase Ib/II investigator-initiated study of duvelisib + FCR (DFCR) for younger, previously untreated patients with CLL

Key Eligibility Criteria

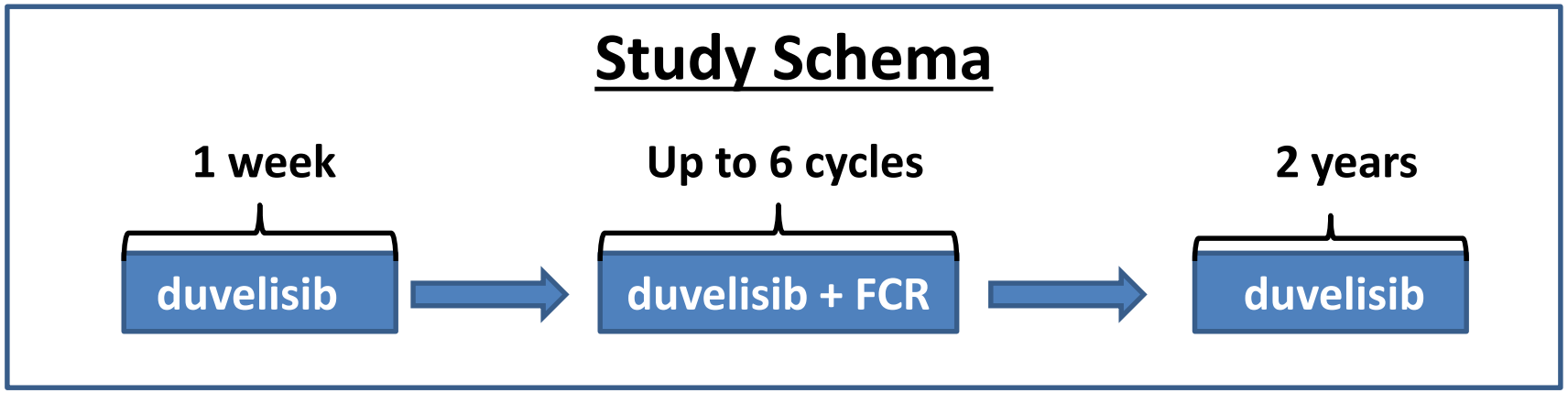
Inclusion

- Confirmed diagnosis of previously untreated CLL/SLL
- Indication for treatment per 2008 IW-CLL criteria
- Age ≥ 18 years and ≤ 65
- Adequate renal and hepatic function, ECOG performance status ≤1

Exclusion

- History of alcohol abuse, chronic hepatitis, or other chronic liver disease (other than direct CLL liver involvement)
- Unable to receive prophylactic treatment for PJP
- Known CNS involvement

A phase Ib/II investigator-initiated study of duvelisib + FCR (DFCR) for younger, previously untreated patients with CLL



G-CSF and PJP/HSV/VZV prophylaxis mandatory for all patients

- A standard 3 + 3 phase Ib design with 2 dose levels of duvelisib with monthly cycles
- 25 mg qd (starting level) and 25 mg bid, then a phase II expansion cohort
- Standard toxicity assessments by CTCAE v4.03 and 2008 IW-CLL
- Response evaluations by 2008 IW-CLL: after 3 cycles, 2 mo. after final FCR, then q6 mo.
- All CRs were confirmed with CT and bone marrow biopsy
- MRD: assessed by 4-color flow cytometry (sensitivity 10^{-4})

Baseline Patient Characteristics (fully enrolled, n=32)

- Median age at enrollment: 55 years (range 45-65)
- Male: 69%
- FISH[#]:

del (17p)*	del(11q)	Trisomy 12	del(13q)	Del(6q)	Normal
n=3 (9%)	n=8 (25%)	n=7 (22%)	n=14 (44%)	n=3 (9%)	N=6 (19%)
#some patients had >1 FISH abnormality, *all with complex karyotype					

- *IGHV*: 18/32 (56%) unmutated, ZAP-70: 19/31 (61%) pos.
- Somatic Mutations: *TP53* mut without del(17p) n=2, *NOTCH1* mut n=1
- Median β2M: 4.0 mg/L (range 2.2-8.1)
- 41% with Rai stage III/IV disease
- Median of 80% bone marrow involvement (range 0-95%)
- Baseline counts (median, range):
  - WBC: 97 K/uL (2.7-595)
  - Hgb: 11 g/dl (5.8-15.9)
  - Plts: 115 K/uL (19-377)

Safety Analysis (n=32)

- **Only 1 DLT in dose escalation (Gr 3 febrile neutropenia at 25 mg qd)**
- **RP2D of duvelisib given with FCR: 25 mg bid**

All grade hematologic toxicity:

-**neutropenia:** 59% (50% gr 3/4)

-**thrombocytopenia:** 65% (34% gr 3/4)

-**anemia:** 38% (16% gr 3/4)

All grade immune-mediated toxicities:

-transaminitis: (34%, 28% gr 3/4)

-inflammatory arthritis: (9%, all gr2)

-colitis: (6%, 1 gr2, 1 gr3)

-pericarditis and pancreatitis: (3%, gr2)

Other all grade non-heme toxicities:

- **nausea:** (72%, all gr1/2)
- **fatigue** (69%, 3% gr3)
- **fever** (53%, all gr1/2)
- **diarrhea** (47%, 3% gr3)
- **anorexia:** (34%, all gr1/2)
- **vomiting** (28%, all gr 1/2)
- **pruritus:** (16%, 3% gr3)
- **CMV reactivation** (6%, both gr2)

Safety Analysis (n=32)

Additional SAEs:

- Pneumonia (n=6 (19%), including 3 cases of PJP despite prophy.)
- Gr3 febrile neutropenia (n=6, (19%), and sinusitis, zoster, CMV infxn, rash, AIHA (n=1 each)
- Secondary malignancies:
  - Gr5 metastatic melanoma (n=1, 10 mo. after completing FCR, not on duvelisib)
  - Gr5 glioblastoma multiforme (n=1, within 3 mo. after completing duvelisib maintenance)
  - Gr4 MDS (n=1, within 3 mo. after completing duvelisib maintenance)

Additional safety information

- Rate of Gr 3 or higher infection: 9/32 (28%)
- 14/32 (44%) of pts received steroids for toxicity management
- 8 pts required dose reduction (chemo n=4 (13%), duvelisib n=6 (19%), both n=2 (6%))
- #DFCR cycles: median of 5.5 cycles (6 (n=14), 5 (n=3), 4 (n=4), 3 (n=3), 1 (n=4))

DFCR Primary Efficacy Analysis (31 patients evaluable for 1º endpoint)

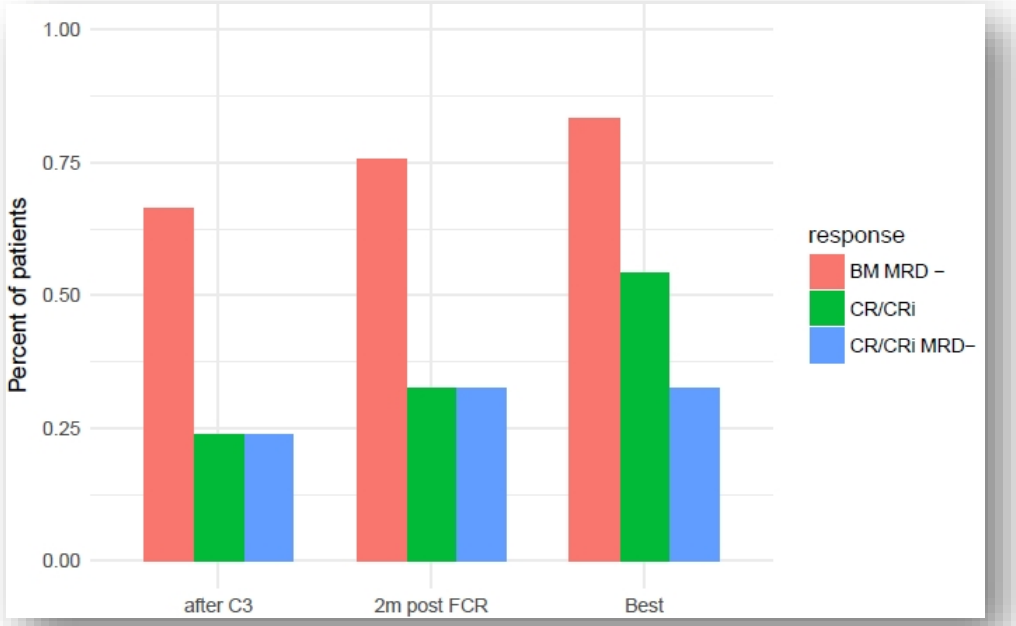
	C4D1	Primary Endpoint (2 mo. post-FCR)	Best Response
ORR	**94%** (29/31)	**94%** (29/31)	**94%** (29/31)
PR	**74%** (23/31)	**68%** (21/31)	**42%** (13/31)
CR/CRi	**19%** (6/31)	**26%** (8/31)	**52%** (16/31)
CR with BM MRD neg.	**13%** (4/31)	**26%** (8/31)*	**55%** (16/29)
BM MRD neg.	**54%** (15/28)	**67%** (18/27)	**76%** (22/29)

- All patients who achieved CR at primary endpoint also were BM MRD neg.
- 53% (10/19) of PR patients were BM MRD neg. at primary endpoint, most w/ LN <2.5 cm
- Responses deepened with duvelisib maintenance

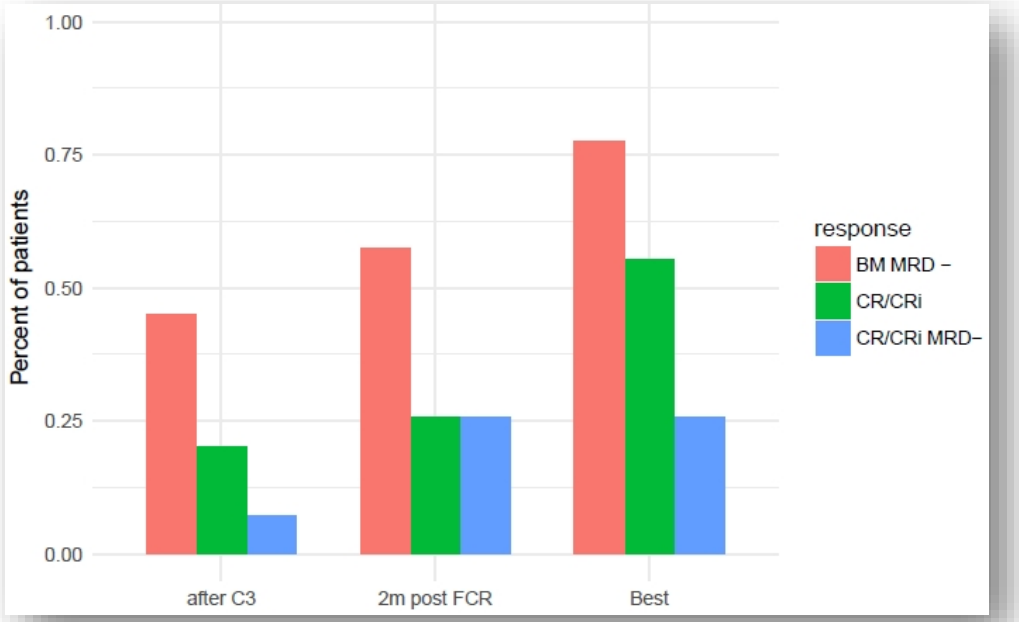
*primary endpoint

DFCR: Response deepens over time in both *IGHV* mutated and *IGHV* unmutated patients

IGHV Mutated



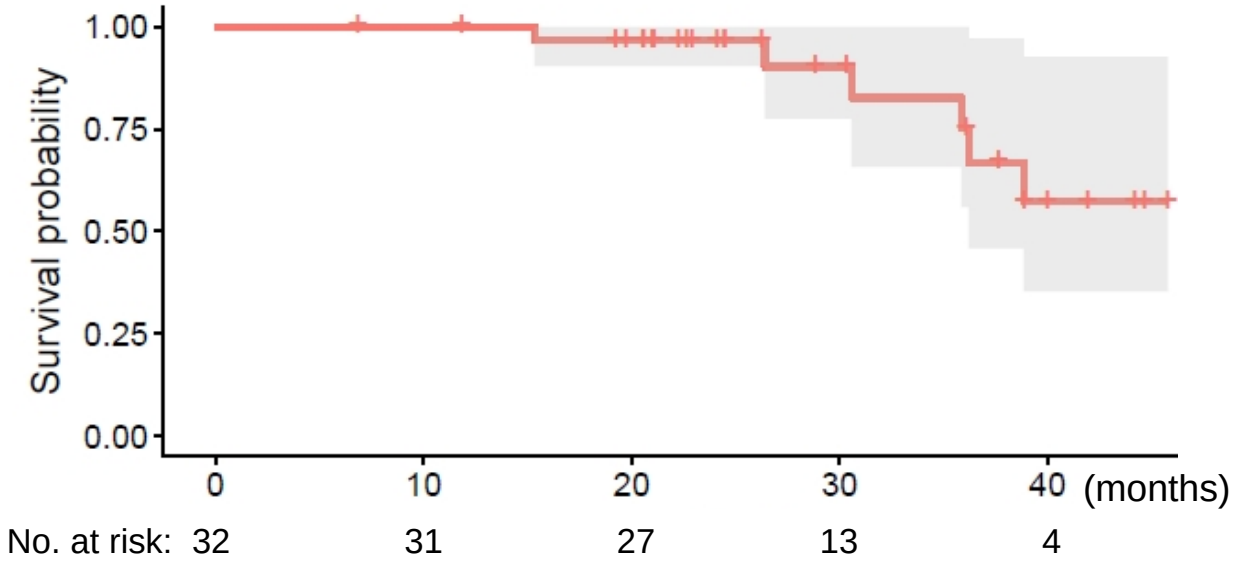
IGHV Unmutated



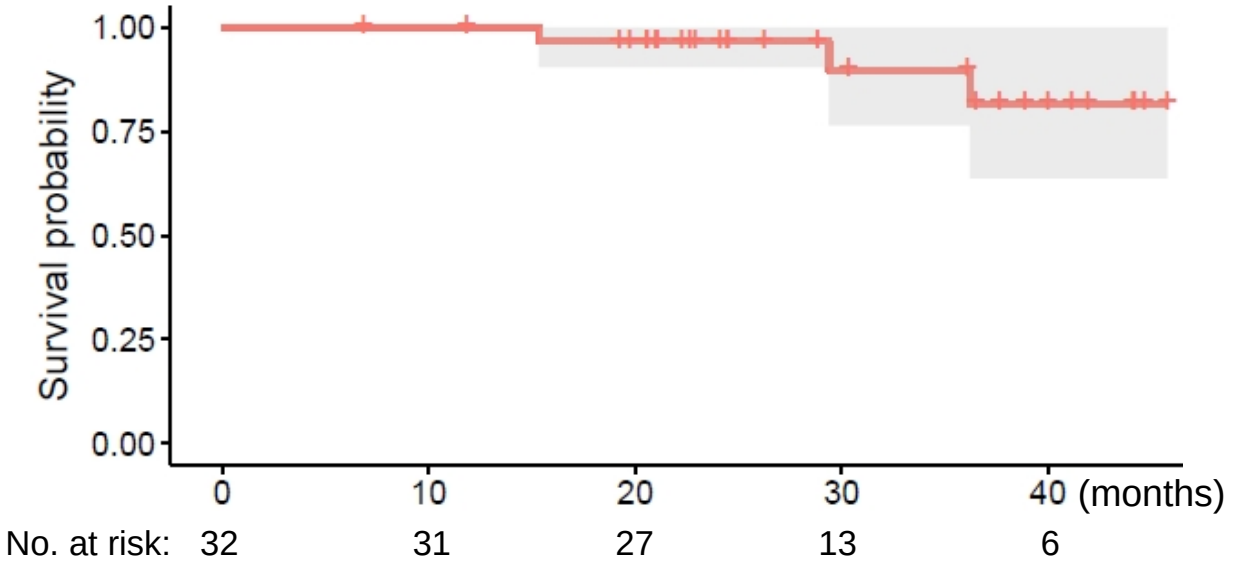
- **Best BM MRD negativity rate: 76% (22/29)**
  - ***IGHV*-M: 83% (10/12), *IGHV*-U: 71% (12/17)**

DFCR: Survival analyses

PFS



OS



- **With a median follow-up of 24.5 months (range 6.9-46):**
  - **2 year PFS and OS: 97%**

Efficacy Analysis – Additional Data

- All 3 pts with complex karyotype with del(17p) responded, including 1 with MRD neg. CR, and 2 with MRD pos. PR

- 2 patients have progressed
  - 1 with CK/del(17p) who died due to Richter's Syndrome 29 mo. after starting on study
  - 1 with del(11q)/unmut *IGHV* with asymptomatic progression 6 mo. after completing duvelisib maintenance, still not requiring therapy

- 8 patients completed a full 2 years of duvelisib maintenance, 5 of these 8 remain progression free (median follow-up since study start 44 mo.)

DFCR: Conclusions

- **Rate of best BM MRD neg. of 76% is significantly higher than historical data with FCR and similar to the ibrutinib + FCR regimen (Davids et al., ASH, 2017)**

- **High rates of BM MRD neg. were observed even in higher risk CLL such as unmutated *IGHV*, and responses deepened on duvelisib maintenance**

- **DFCR toxicities are comparable to duvelisib and FCR individually, with infectious, immune-mediated toxicities, and secondary malignancies observed**

- **DFCR is an effective regimen for the initial therapy of younger, fit CLL patients who desire a time-limited therapy with potential for long term remission**

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Infinity

Verastem

Patients and their families

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ASCO
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Workshops:
ASH CRTI
AACR/ASCO Vail Workshop

The Davids Lab
Translational CLL Research
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