Combinations of Ibrutinib and Venetoclax

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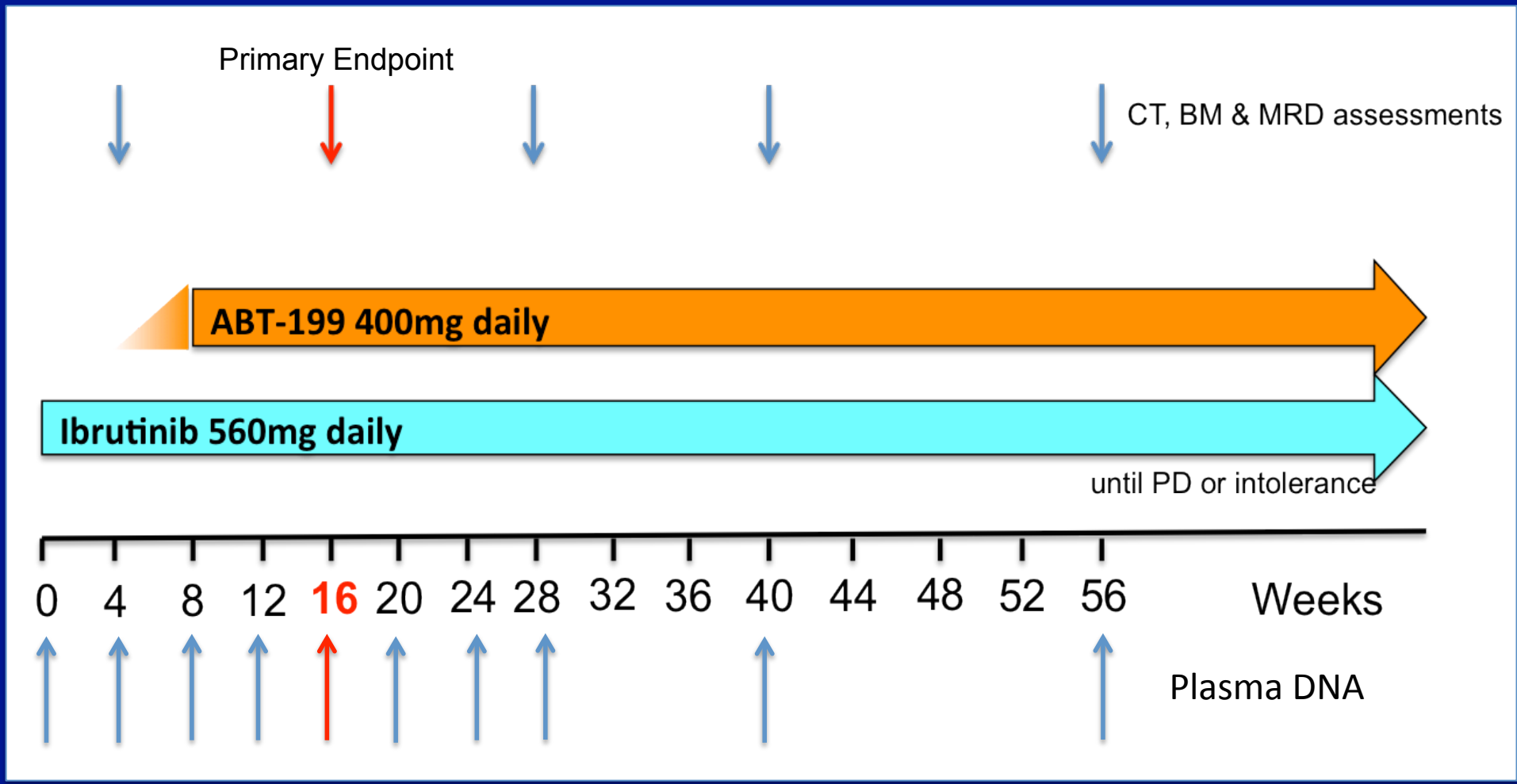
AIM (ABT-199 & Ibrutinib in MCL) Study Schema



Background

- Ibrutinib and Venetoclax active in relapsed MCL
  - IB : OR 68%, CR 21%, median PFS 13.9 months
  - VEN : OR 75%, CR 21%, median PFS 14 months
- Multiple preclinical studies indicate *in-vitro* synergism between ibrutinib and venetoclax

Wang, NEJM 2013; Davids JCO 2017; Li, Oncogene 2016; Chiron Oncotarget 2015

AIM Study Overview

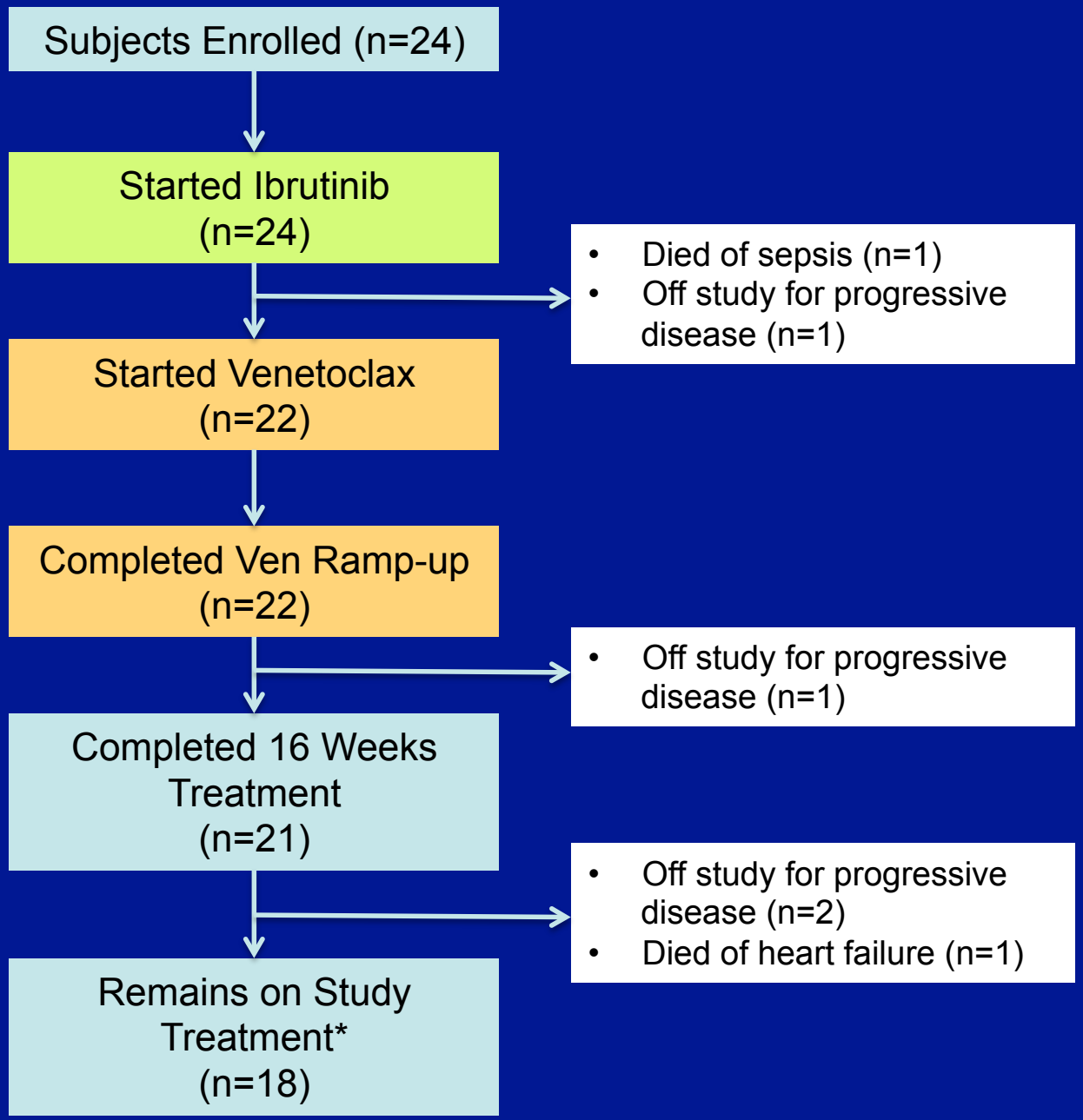
- Primary Endpoint : Complete Remission (CR) Rate at Week 16*.
- Inclusion: Relapsed / Refractory MCL**, adequate marrow and organ function, creatinine clearance ≥ 50 ml/min.
- Exclusion: Prior IB or VEN, NYHA 3 – 4 status

*CR as assessed by CT and BMAT, in order to compare against week 16 CR rate of 9% as reported in the PCYC-1104 study of ibrutinib in R/R MCL
**Protocol amendment 1 allowed one subject with first-line MCL to be enrolled

Data-Cutoff 10-Jan-2017

First pt enrolled: July 22, 2015
Last pt enrolled: Sep 15, 2016

Median Follow-up 8.3 months
(1.4 to 17.7+ months)



*2 subjects remain on study therapy after disease progression

Baseline Patient Characteristics

Baseline Characteristic (N = 24)	Value	
Age (years), median (range)	68	(47 – 81)
Male	21	88%
ECOG 0 – 1 ECOG 2	19 5	79% 21%
B-symptoms	4	17%
Largest bulk 5 to 10 cm Largest bulk > 10cm	4 7	17% 29%
MIPI Low MIPI Intermediate MIPI High	2 3 19	8% 13% 79%
No prior therapy for MCL	1	4%
Previously treated for MCL	23	96%
- Lines of prior therapy, median (range) - Prior autologous stem cell transplantation - No response (<PR) to last treatment	2 7 11	(1 – 6) 29% 48%

Tumour Lysis Risk

Category*	Baseline (n = 24)	Week 4 (n = 22**)
Low Tumour <5cm and ALC <25 x 10^9/L	11 (46%)	12 (55%)
Medium Tumour 5-10cm or ALC ≥25 x 10^9/L	6 (25%)	7 (32%)
High (a) Tumour ≥10cm or (b) Tumour 5 – 10cm & ALC ≥25 x 10^9/L	7 (29%)	3 (14%)

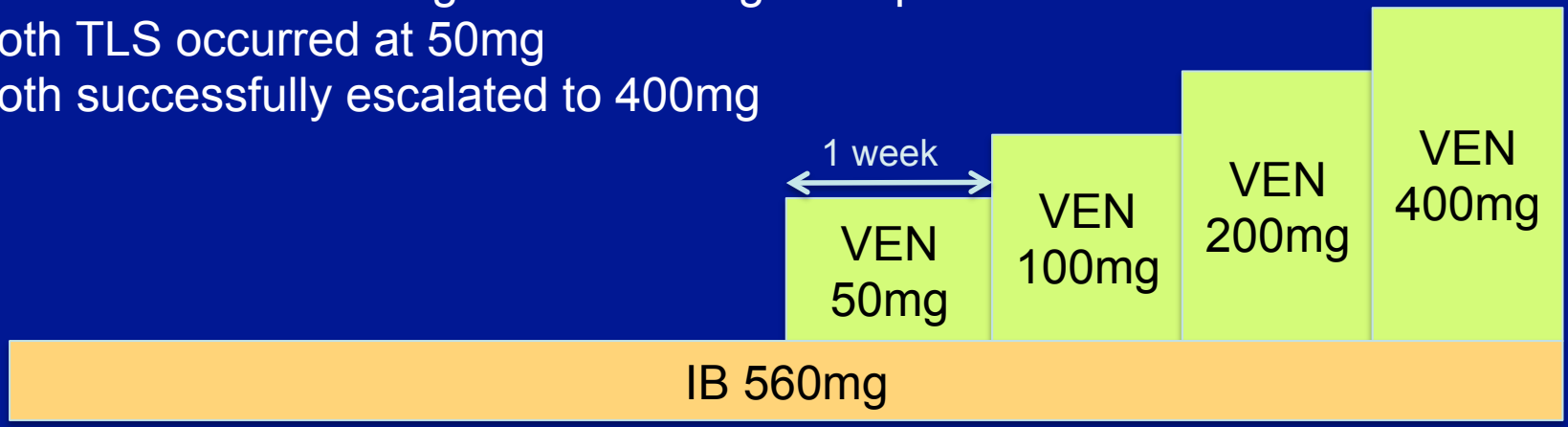
Reduction in TLS Risk after ibrutinib induction (n=4)	3 high-risk subjects improved to low-(2) and medium-(1) risk**; 1 medium-risk subject improved to low-risk.
Increase in TLS Risk after ibrutinib induction (n=1)	1 low-risk subject had tumour progression to medium-risk.

*TLS categories derived from analysis of patients with CLL receiving single-agent venetoclax

**2 subjects progressed or died during ibrutinib induction and were not restaged at week 4

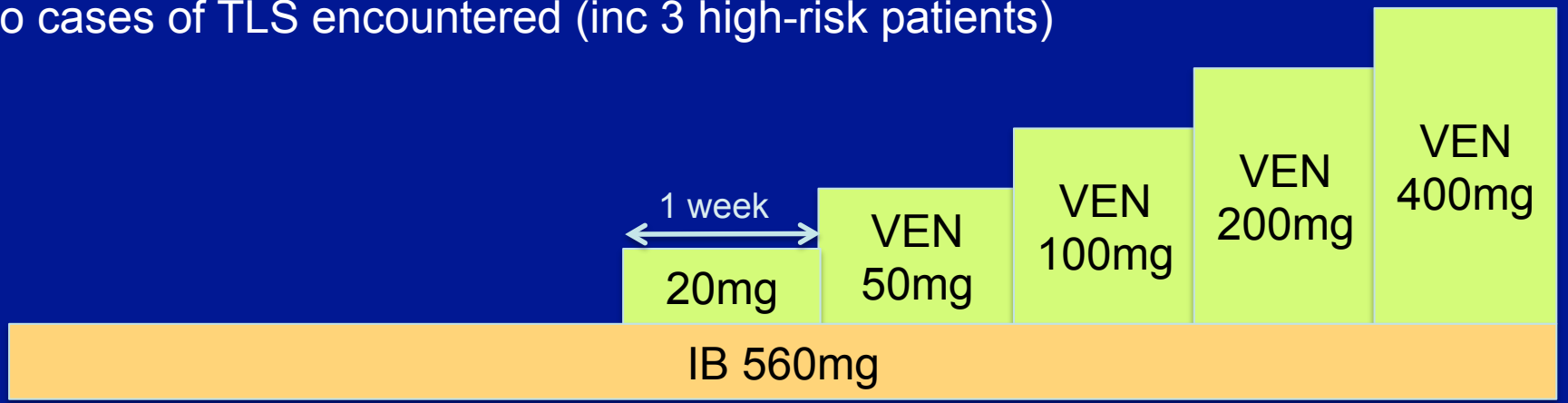
Tumour Lysis Syndrome

N = 16 treated using initial schedule
2 cases of TLS* among 4 baseline high-risk patients
Both TLS occurred at 50mg
Both successfully escalated to 400mg



*one case of grade 3 clinical TLS (acute renal impairment); one case of self-limiting fever, hyperphosphataemia and 400% elevation in LDH, regarded as grade 3 biochemical TLS in absence of alternative explanation.

N = 8 treated using revised schedule (20mg start)
No cases of TLS encountered (inc 3 high-risk patients)



Adverse Events Irrespective of Causality
(AE ≥ 20% and/or Grade 3+ listed)

Adverse Event	All Grades		Grade 3+	
Diarrhoea	20	83%	1	4%
Fatigue	18	75%	0	
Nausea and/or Vomiting	16	67%	0	
Upper Respiratory Tract Infection	10	42%	0	
Gastro-oesophageal Reflux	8	33%	0	
Neutropenia	8	33%	8	33%*
Cough	7	29%	0	
Dyspnoea	6	25%	1	4%
Anaemia	5	21%	2	8%
Bruising	5	21%	0	
Peripheral Neuropathy	5	21%	0	
Thrombocytopenia	5	21%	4	17%*
Pneumonia	3	13%	2	8%
Atrial Fibrillation	2	8%	2	8%
Tumour Lysis Syndrome	2	8%	2	8%

Other Grade 3+ AE (1 each): Heart Failure, Haematuria, Insomnia, Pleural Effusion, Amnesia, Ascites, Ischaemic Heart Disease, Colitis, Dehydration, Hyperglycaemia, Hypertension, Hypotension, Neck Pain, Otitis Externa, Thromboembolic Event, Vasovagal Reaction

*G4 neutropenia = 17%; G4 thrombocytopenia = 8%

AIM Study: Response Rates (CT)

	Week 4, CT only	Week 16, CT only
Complete Response (CR)	0	10 (42%)
CR, unconfirmed	1 (4%)	4 (17%)
Partial Response (PR)	10 (42%)	4 (17%)
Stable Disease (SD)	9 (38%)	1 (4%)
Progressive disease (PD)	2 (8%)	3 (13%)
Not Evaluable	2 (8%)	2 (8%)

Wk 16

OR = 75%

CR + CR/u = 58%

Patients were restaged at week 16 using CT, PET, double endoscopy (if baseline involvement), and BMAT with MRD studies. Two patients were not evaluable due to early death (n=1), and target lesions judged on central review to be too small and poorly FDG avid for reproducible measurement (n=1).

AIM Study: Response Rates (PET)

	Week 16, CT only	Week 16, PET/CT
Complete Response (CR)	10 (42%)	15 (63%)
CR, unconfirmed	4 (17%)	-
Partial Response (PR)	4 (17%)	2 (8%)
Stable Disease (SD)	1 (4%)	1 (4%)
Progressive disease (PD)	3 (13%)	4 (17%)
Not Evaluable	2 (8%)	2 (8%)

Wk 16

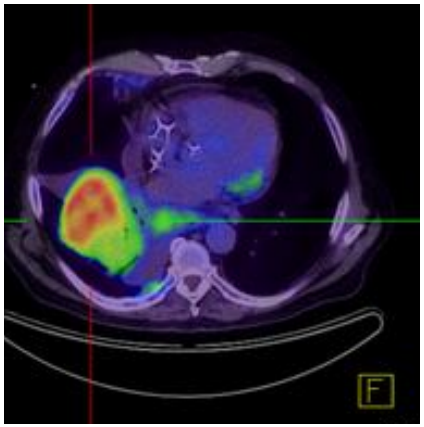
OR = 71%

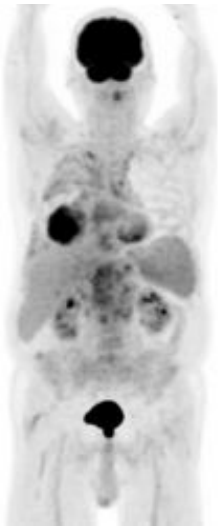
CR = 63%

Patients were restaged at week 16 using CT, PET, double endoscopy (if baseline involvement), and BMAT with MRD studies. Two patients were not evaluable due to early death (n=1), and target lesions judged on central review to be too small and poorly FDG avid for reproducible measurement (n=1).

Stage 4 MCL, failed R-CHOP, R-DHAP & Temsirolimus

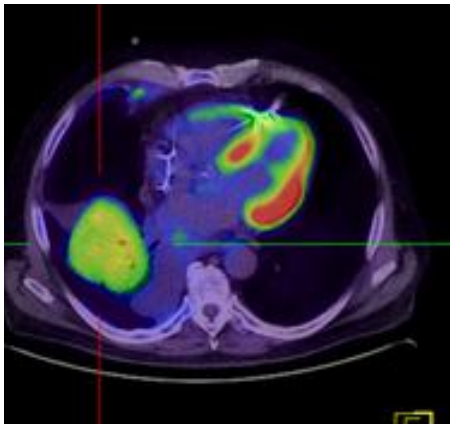
Baseline

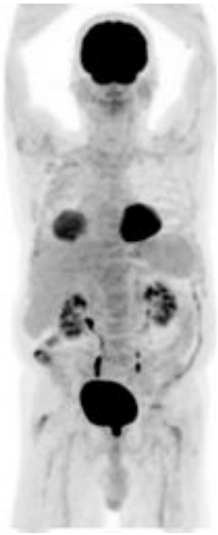




Marrow: 30% MCL

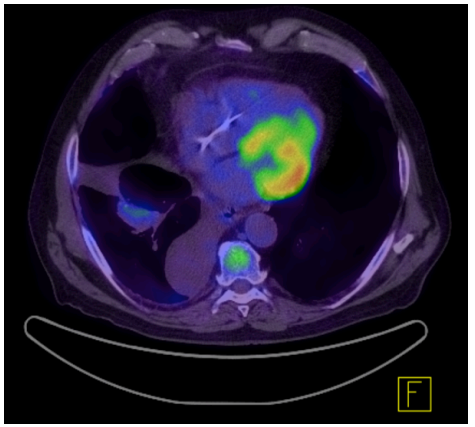
Week 4 (Ibrutinib)

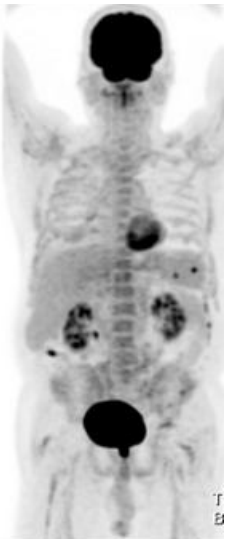




Marrow: 28% MCL

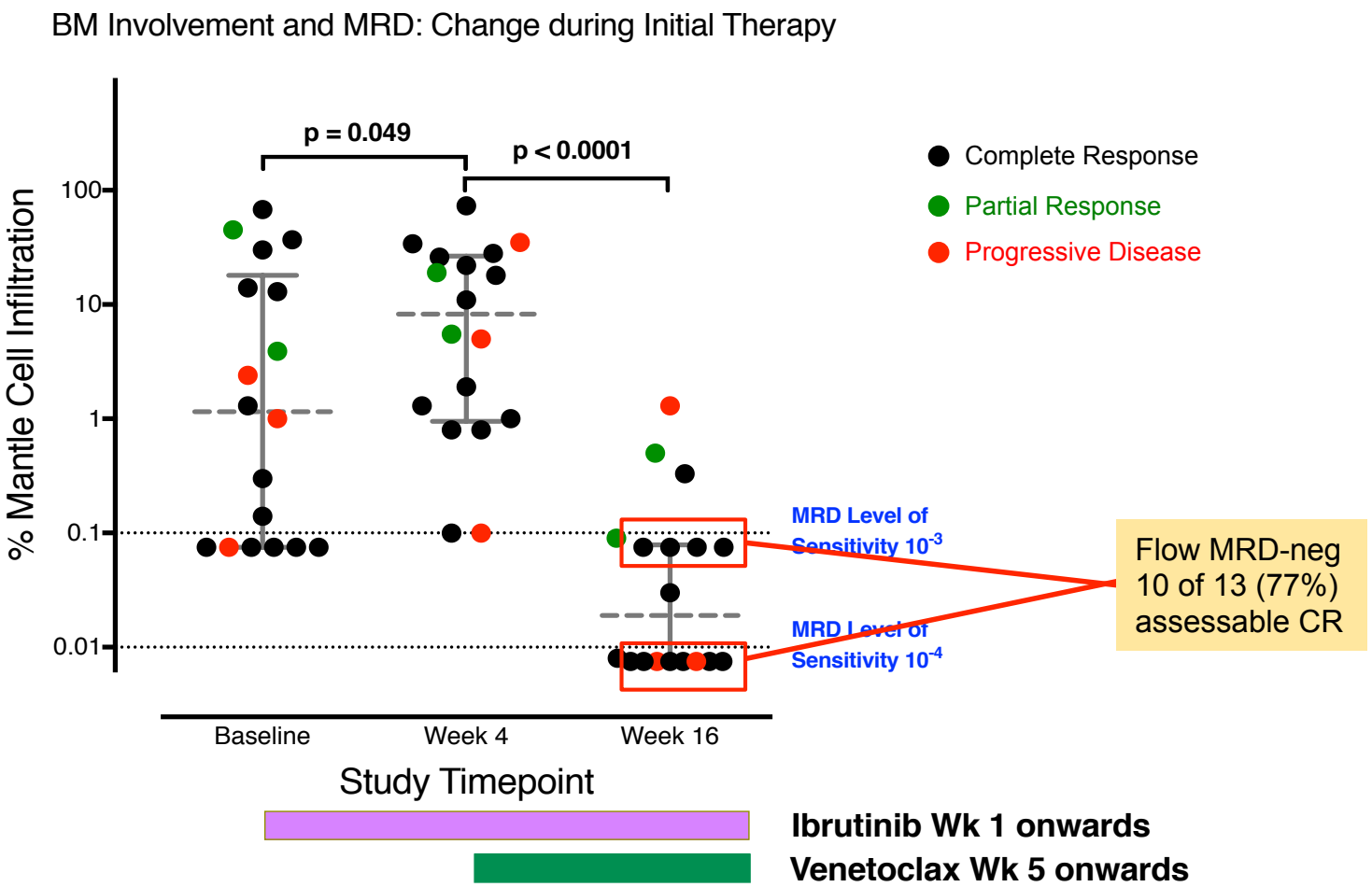
Week 16 (both drugs)





Marrow: Negative
(<10^{-4} by flow)

AIM Study : Marrow Flow MRD Kinetics*

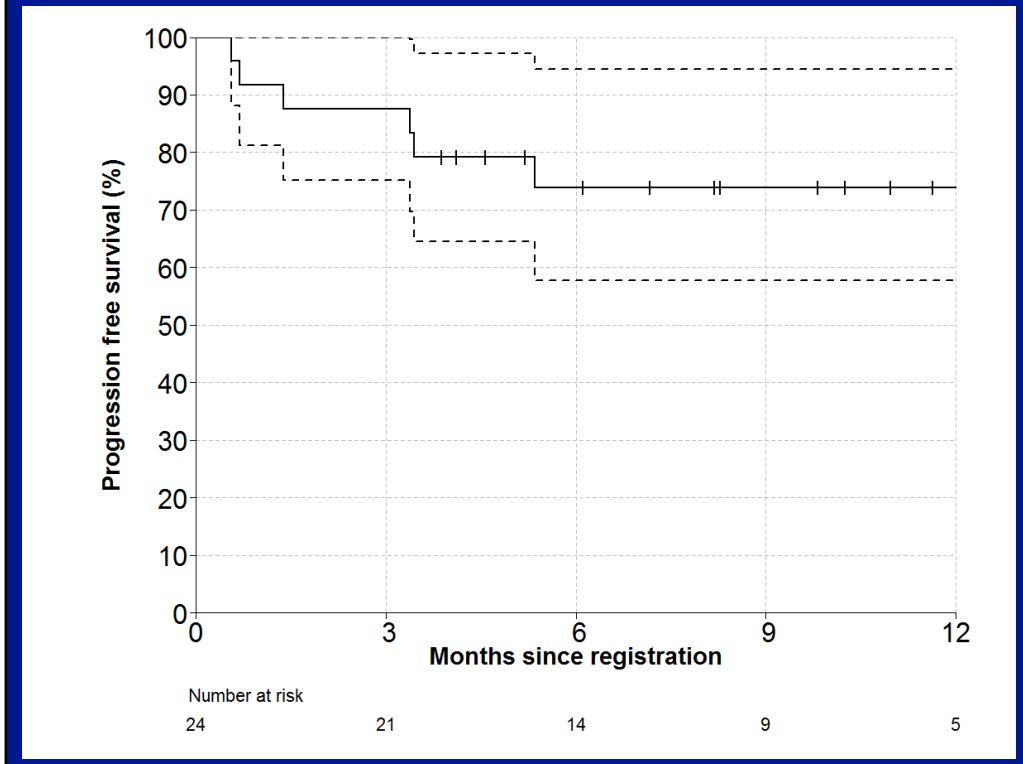


* 3 patients had no marrow involvement

AIM: Progression Free & Overall Survival

Median Follow-up 8.3 months
(1.4 to 17.7+ months)

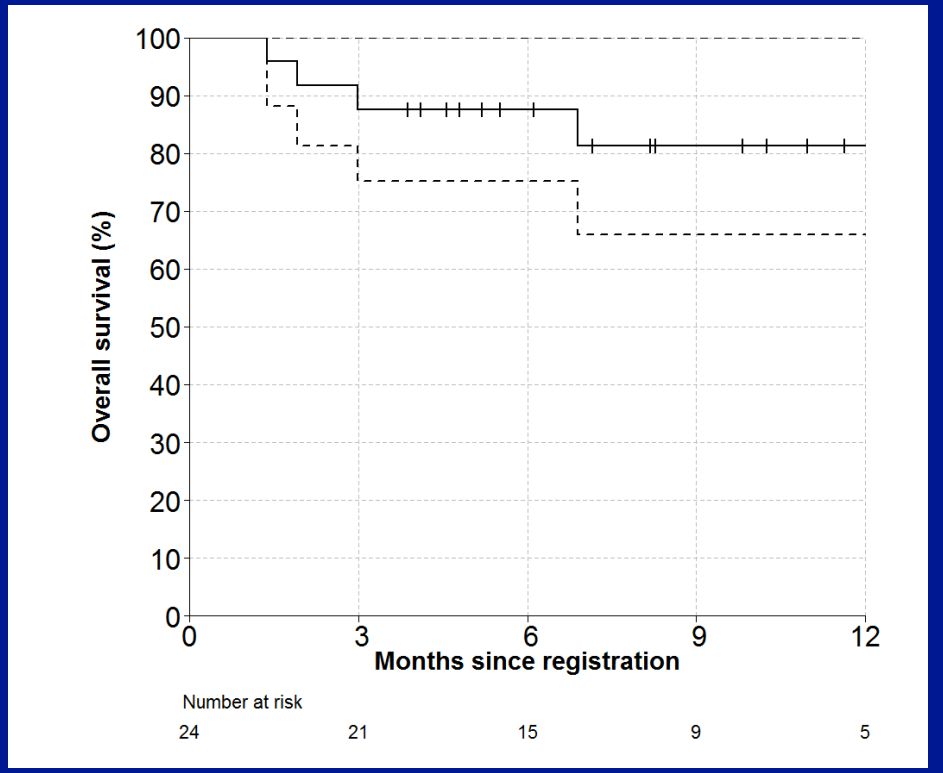
Progression Free Survival



PFS 74% at 1 year

(95%CI: 58 – 94)

Overall Survival



OS 81% at 1 year

(95%CI: 66 – 100)

Conclusions

- Combination IB + VEN tolerable and active in R/R MCL
  - TLS risk manageable
  - 63% complete response, including PET
  - Estimated PFS 74% at 1 year
- Expansion into Phase 3
- Other groups exploring GA101/IB/VEN (OASIS)