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Retrospective cohort study of treatment with BCL-2 inhibitor venetoclax in advanced AL amyloidosis

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Venetoclax, an oral Bcl-2 inhibitor, has shown promising results in t(11;14)-positive systemic light-chain (AL) amyloidosis, a translocation found in about half of patients. In this retrospective single-center study, 44 patients with relapsed or refractory (RR) t(11;14)- positive AL amyloidosis after a median of three previous therapy lines were analyzed. Best hematologic responses (≥VGPR) occurred in 77% (34/44) of the patients. Estimated event-free survival (EFS) was 86%, 68%, 53% at 12, 24, and 36 months and overall survival (OS) 95%, 81%, and 64% respectively. Organ responses after 12 months were observed in 39% of cases with cardiac and 62% of cases with renal involvement. Stratification by typical versus atypical t(11;14) variants revealed significantly inferior responses at 3 and 6 months for atypical cases. Grade ≥2 adverse events were significantly more frequent in patients with renal impairment (eGFR ≤30 ml/min). Venetoclax proves efficacy even in advanced AL amyloidosis but atypical cytogenetic signatures and renal impairment may influence outcome and tolerability.

In AL amyloidosis misfolded light-chain deposits cause progressive organ dysfunction. Many patients relapse or become refractory and are ineligible for intensive regimens (1). Cytogenetically, t(11;14)(q13;q32.3), juxtaposing CCND1 and IGH, is the most common aberration, observed in approximately 40–60% of AL-patients by iFISH. This abnormality induces cyclin D1 overexpression and enhanced BCL-2 activity, creating a biologic rationale for Venetoclax (2, 3, 4). Overall response rates up to 90–100% in relapsed/refractory cases have been reported (5, 6), yet, no data exists on the impact of variant translocation patterns or renal impairment (7).

We analyzed 44 Venetoclax-treated patients with biopsy-proven AL amyloidosis and ≥ 1 prior therapy at the University Hospital Heidelberg (September 2020-May 2023, Table 1; written informed consent obtained; approved by Institutional Ethics Committee per Helsinki Declaration). Outcomes comprised OS, EFS, hematologic and organ responses at baseline as well as 3, 6 and 12 months after treatment initiation, and treatment toxicity (CTCAE) (8, 9). EFS was defined as time from Venetoclax start until the first event of hematologic relapse and/or progression, initiation of new anticancer therapy or death from any cause. t(11;14) was confirmed by interphase FISH; typical and atypical variants were categorized based on

CCND1:IGH fusion signal patterns (Figure 1). Venetoclax was predominantly applied as monotherapy (73%) and in 27% with Dexamethasone. Doses ranged from 50–400mg/day (initiation dose 100mg) according to tolerance and response (median 200mg; infection monitoring followed standard practice with recommended biweekly complete blood counts. No routine prophylactic antimicrobials were used. Prophylaxis was introduced based on clinical or laboratory signs of infection. In 29 patients (66%) Venetoclax dosage was permanently or temporarily reduced; toxicity-driven discontinuation occurred in 8 (18%), with two maintaining response (VGPR, CR) after cessation. 12 patients received additional weekly dexamethasone due to minor responses, impending relapse or treatment tolerability. Dexamethasone was given upfront (25%), within the first 6 months (42%) and added after 8 months in 4 cases.

Descriptive statistics and Kaplan–Meier analysis were applied, with Fisher's exact and Mann-Whitney tests used for categorical and quantitative comparisons (SPSS Version 29).

95% of patients had t(11;14); median prior therapy lines were three. 95% had been exposed to daratumumab (84% refractory), 86% to bortezomib; prior lenalidomide and alkylator treatments were frequent. Venetoclax was started for refractory (34%) / relapsed disease (23%), or for suboptimal hematologic response to prior lines (43%). Target dose was 400mg. Addition of dexamethasone improved hematologic responses in 63% of cases. Overall response rate (ORR) was 93% with ≥VGPR in 77% (39% CR). Median time to best response (CR, VGPR, PR, SD or PD) was three months; median duration of response 21 months. Median EFS and OS were not reached after a median follow up of 26 months; at cutoff 50% remained on Venetoclax, some maintaining response post-discontinuation (Supplemental Figure 1).

Most patients had multiorgan involvement (89% cardiac, 73% renal, 23% hepatic). Advanced cardiac involvement was evident, with 61% classified as stage IIIa or IIIb according to the European cardiac staging system (10). After 12 months, organ responses were achieved in 39% of evaluable cardiac, 62% renal, and 37% hepatic cases. Organ improvement paralleled hematologic responses but tended to occur later.

Adverse events included diarrhea, nausea, neutropenia, infections, and fatigue.

Grade ≥3 events occurred in 9% (2 hematologic, 2 infectious with pulmonary focus). Dose reductions were frequent,18% discontinued Venetoclax due to toxicity; Other discontinuation reasons were complete response (n=2), organ progression, new malignancies, or evolving plasma-cell clones. Eleven discontinued due to progression. 12 patients died during follow-up, 4 from AL-related organ failure, 1 suicide, 1 intestinal ischemia, and 6 after subsequent therapies. A heart transplanted patient tolerated Venetoclax well and achieved CR. Baseline characteristics, response rates and toxicities are summarized in Supplemental Tables 1 and 2.

Renal dysfunction (eGFR ≤ 30 ml/min) was present in 32%. These patients required more frequent dose reductions (71%; eGFR ≤ 30 ml/min observed in 14/44: Venetoclax range: 50-400mg, median 200mg; eGFR > 30ml/min observed in 30/44: range 100-400mg, median 300mg) and represented 75% of grade ≥3 toxicities. Hemodialysis was required in five cases at baseline and in two more during therapy, who both died due to advanced AL organ progression. Adverse events ≥grade 2 were significantly more frequent in this subgroup (p=0.048, Figure 2). Impaired renal filtration was associated with higher NT-proBNP levels, reflecting decreased clearance and advanced systemic disease.

Typical t(11;14) was present in 63% and atypical variants in 36% (42/44 cases evaluable). Atypical cases, showing deletions of either IGH signal, were more frequent among males and presented with higher baseline organ burden and poorer hematologic status. EFS was numerically longer for typical translocations (29 vs 25 months, p=0.285; Figure 3A). Median OS did not differ significantly, response depth did: non-responders occurred only in the atypical group. Early response rates (3 and 6 months) were significantly inferior in atypical variants (p=0.027 and 0.03; after 3 months: VGPR + CR 57% and no PD for typical versus VGPR + CR 75% and 17% PD for atypical variants; after 6 months: VGPR + CR 65% and no PD for typical versus VGPR + CR 70% and 20% PD for atypical variants); significance was lost by month 12 likely due to small cohort size (Figure 3B/C). ORR was 100% for typical and 79% for atypical patterns, with median DOR (duration of response) of 21 vs 19 months. Amplification of 1q21 (11%) showed heterogeneous outcomes (2 CR, 2

VGPR, 1 PD). Response and survival were not associated with hematologic status at Venetoclax start.

Venetoclax demonstrated robust activity in heavily pretreated AL amyloidosis (e.g. 86% daratumumab refractory), providing sustained hematologic control and clinically relevant organ improvement. The 93% ORR and 70% ≥VGPR align with previous reports and confirm that BCL-2 inhibition effectively targets the t(11;14)-positive clone (9, 11-15). Median EFS and OS were not reached and estimated 3-year survival above 60% suggests long-lasting benefit. The safety profile was favorable, with few grade 3-4 events despite extensive prior treatments and organ impairment (6), though mortality was non-negligible and mainly linked to underlying disease and infections, emphasizing the need for vigilant supportive care.
This analysis is, to our knowledge, the first to explicitly evaluate toxicity by kidney function. The significant association between renal impairment and higher-grade adverse events suggests altered metabolism or delayed drug clearance. Clinically, reduced renal capacity should prompt cautious dose titration and close laboratory and clinical monitoring. A lower target dose (200mg vs. 400mg) might optimize safety/efficacy balance in this subgroup.

Glucocorticoid co-medication appeared beneficial in a subset of patients suggesting possible synergism. In myeloma, Venetoclax + daratumumab or bortezomib have yielded exceptional response rates, small AL cohorts mirror these findings (5, 6). Given its strong monotherapy efficacy, combination approaches may be reserved for relapse or suboptimal responders, balancing toxicity risks.

Our study suggests that not all t(11;14) translocations are biologically equivalent. Atypical variants with single fusion signals may represent unbalanced translocations leading to altered BCL-2 dependence or expression, potentially explaining inferior early response kinetics (13). Our data support a refined cytogenetic classification of AL amyloidosis that integrates variant signal patterns. This could change Venetoclax-based therapy selection and might explain inter-individual differences in sensitivity. The role of overlapping genomic alterations such as 1q21 amplification also deserves exploration since it may modify apoptotic mechanisms.

In the evolving therapeutic landscape-including BCMA-targeted bispecifics and CAR-T products, Venetoclax retains specific importance for t(11;14) carriers. Study limitations included its retrospective character, small subgroup sizes, and reliance on clinical chart documentation for adverse event grading. Dose and combination heterogeneity preclude standardized toxicity-efficacy correlation. The study's strengths lie in detailed cytogenetic and renal stratification and longest follow-up in the largest single-center study in a real-world cohort.

Our investigation confirms that Venetoclax provides substantial and durable responses in RR t(11;14)-positive AL amyloidosis with manageable toxicity. The findings encourage integration of Venetoclax earlier in therapy algorithms and emphasize the need to individualize dosage and monitoring, particularly in patients with renal dysfunction. Differences between typical and atypical t(11;14) signatures may influence early response and outcome, advocating inclusion of variant analysis in future studies. Prospective trials are warranted to define standardized dosing strategies, explore optimal combination regimens and evaluate predictive biomarkers. Venetoclax thus represents a significant advance in AL amyloidosis therapy, offering targeted disease control and paving the way for precision-based treatment approaches.

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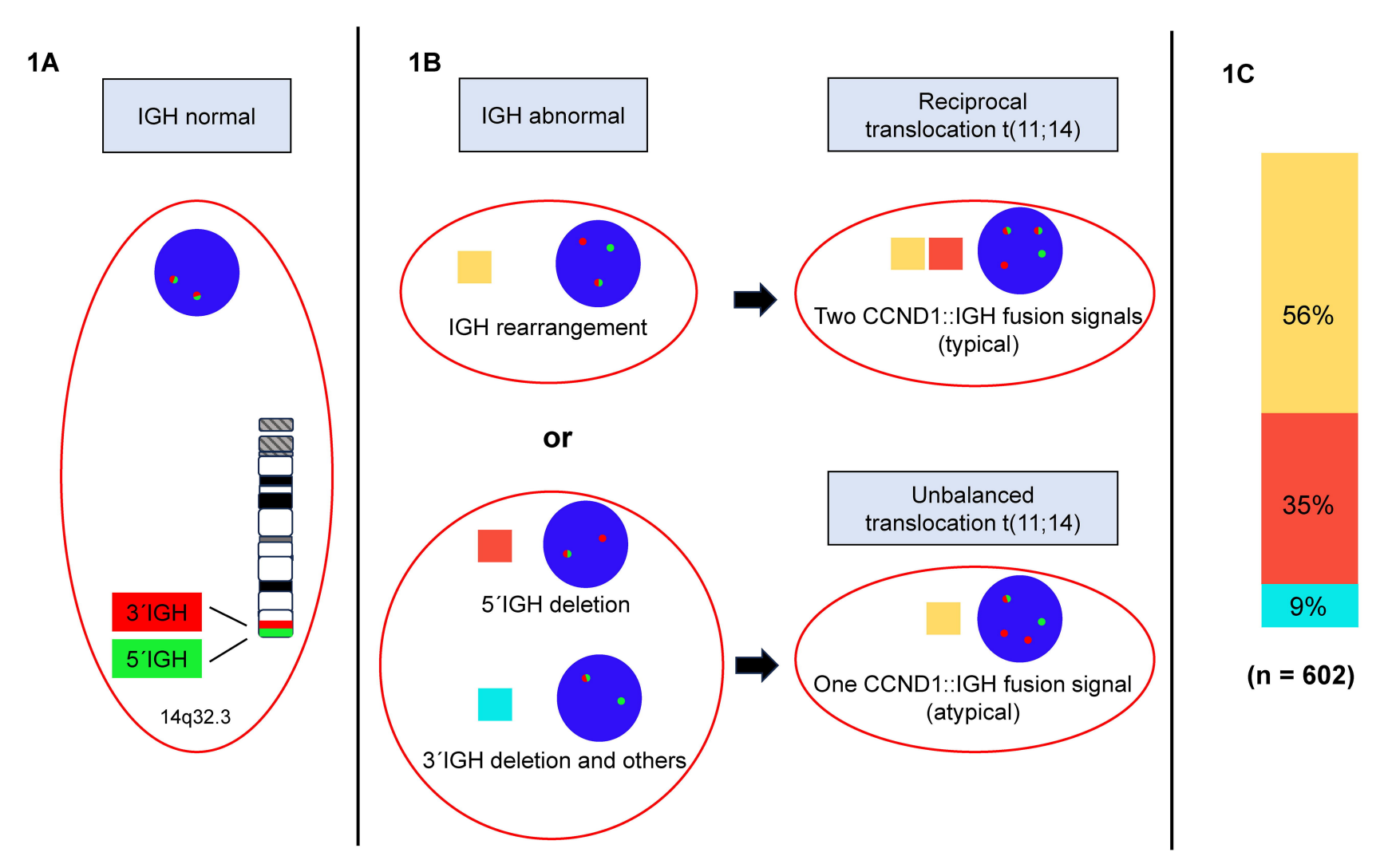
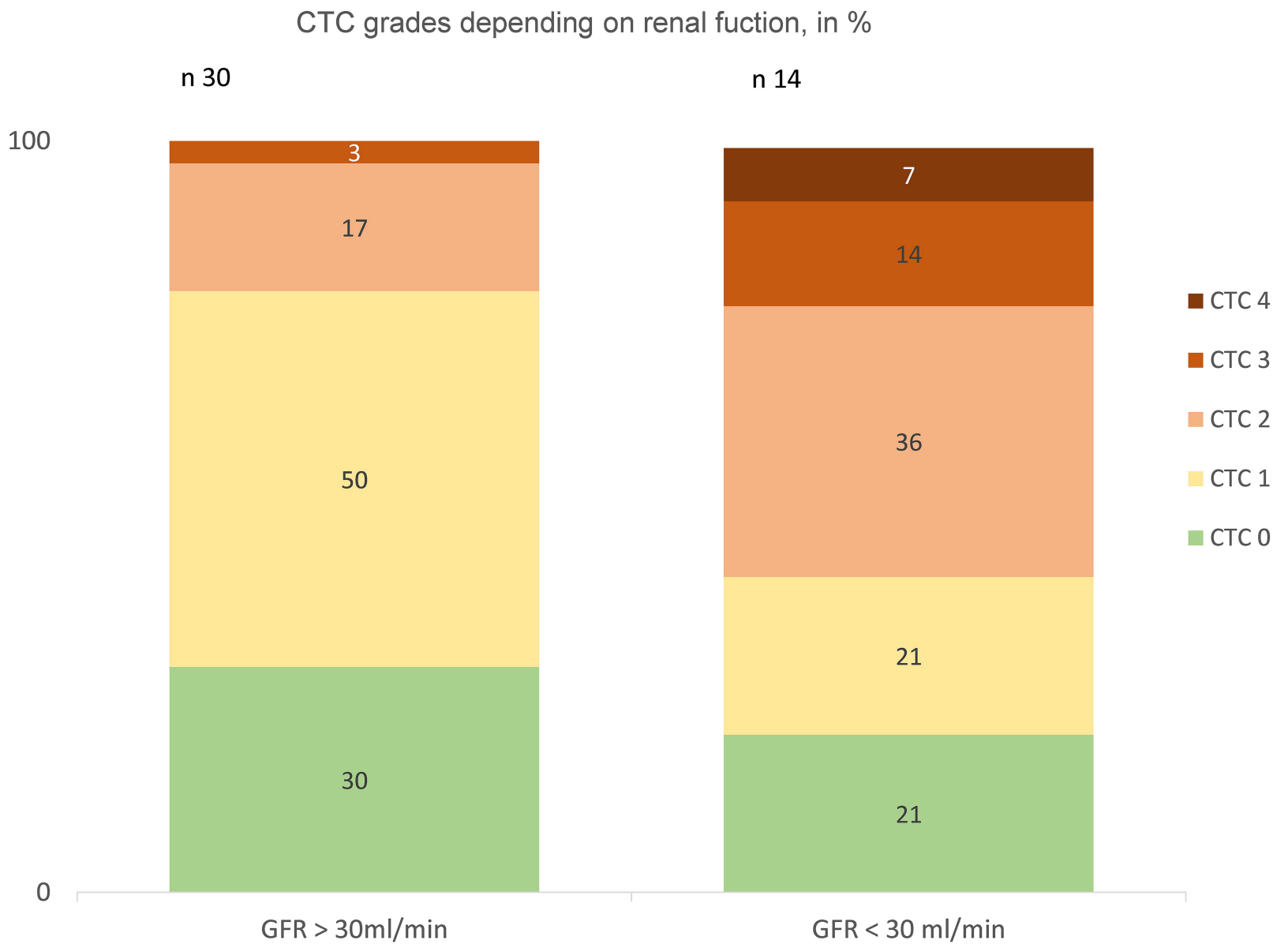
Figure Legends:

Fig. 1 Schematic representation of normal and abnormal IGH patterns and t(11;14) signals. 1A IgH break-apart probe: schematic representation of a chromosomal rearrangement involving the heavy chain locus, particularly t(11;14) and normal finding in FISH diagnostics exhibiting two co-localized signals. **1B/C** FISH results of structural abnormalities in the IGH gene: most commonly (56%) detection of 1 fusion signal, 1 red and 1 green signal. Below atypical signatures: in 35% 1 fusion and 1 R signal suggesting an IgH deletion and in 9,5% other variations are found.

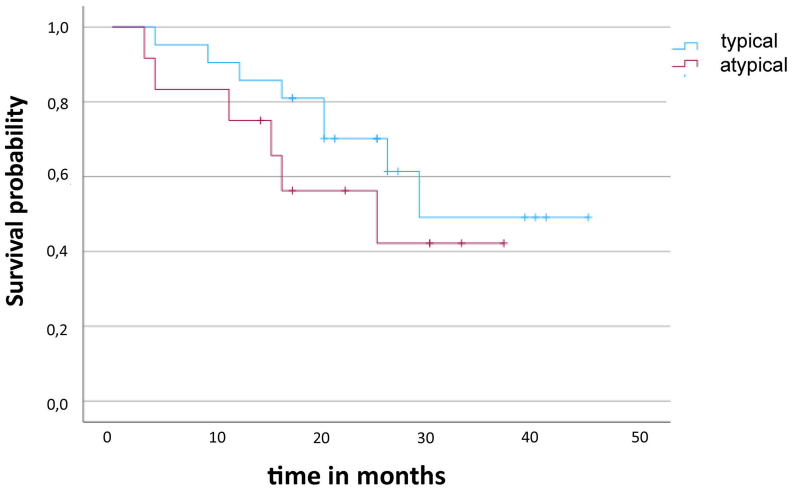
Fig. 2 Comparison of CTC grades for the segregated cohort depending on renal function: CTC grades for the subgroup of eGFR > 30 ml/min, n= 30 compared to CTC grades for the subgroup of eGFR </= 30 ml/min, n= 14; CTC grades differ significantly between groups (GFR </= 30 ml/hr vs. > 30 ml/hr)
(p value 0,048) with more higher grade CTC grades in the subgroup of eGFR < 30ml/min.

Fig. 3 Venetoclax in typical versus atypical t(11;14) positive AL Amyloidosis
3A Kaplan-Meier Curves for the segregated cohort: EFS for typical (blue) and atypical (purple) t(11;14) with the median EFS being 29 and 25 months respectively; p-value 0.285. Progression, relapse or death of any cause counted as event. **3B Best hematologic responses** for the segregated cohorts: typical t(11;14) versus atypical t(11;14). 14% of patientes in the atypical t(11;14) cohort were primarily refractory. **3C Comparison of hematologic response rates** for typical vs. atypical t(11;14) after 3, 6 and 12 months: for the assessment of hematologic response after 3 and 6 months the distribution of hematologic response rates between both groups is statistically significant indicated by the star (3 months: p-value 0,05; 6 months: p-value 0,027; 12 months: p-value 0,31).

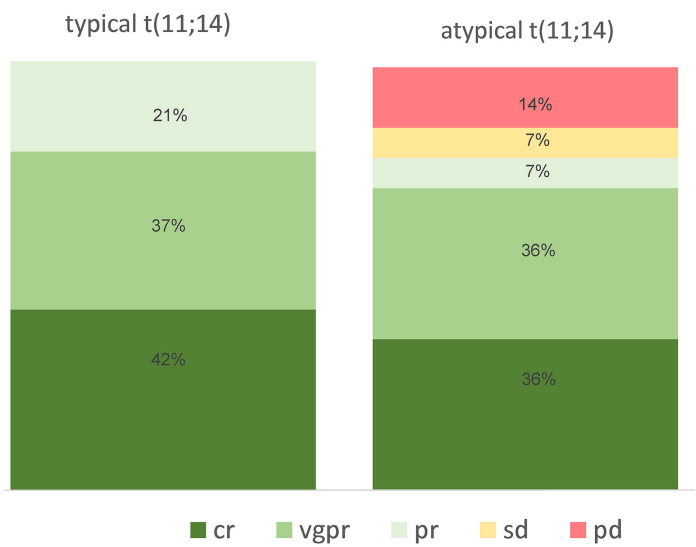

1A
IGH normal
3´IGH
5´IGH
14q32.3
1B
IGH abnormal
Reciprocal translocation t(11;14)
IGH rearrangement
Two CCND1::IGH fusion signals (typical)
or
Unbalanced translocation t(11;14)
5´IGH deletion
3´IGH deletion and others
One CCND1::IGH fusion signal (atypical)
1C
56%
35%
9%
(n = 602)


CTC grades depending on renal fuction, in %
n 30
n 14
100
0
3
17
50
30
7
14
36
21
21
CTC 4
CTC 3
CTC 2
CTC 1
CTC 0
GFR > 30ml/min
GFR < 30 ml/min

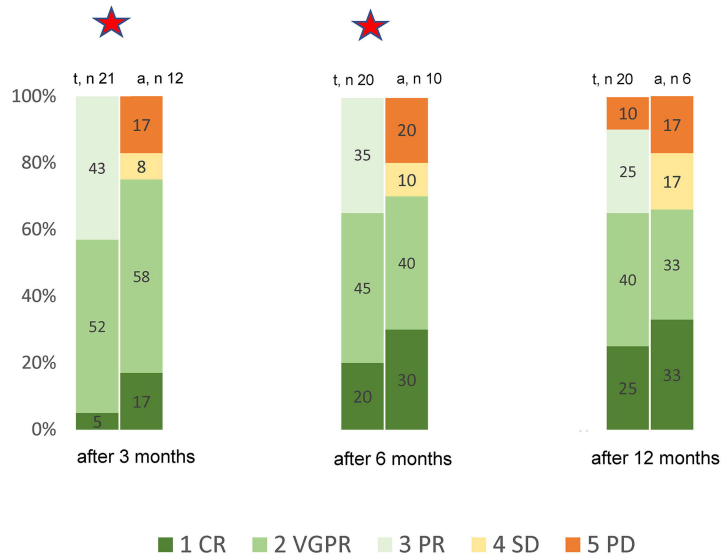
3A Event free survival



3B Best hematologic response

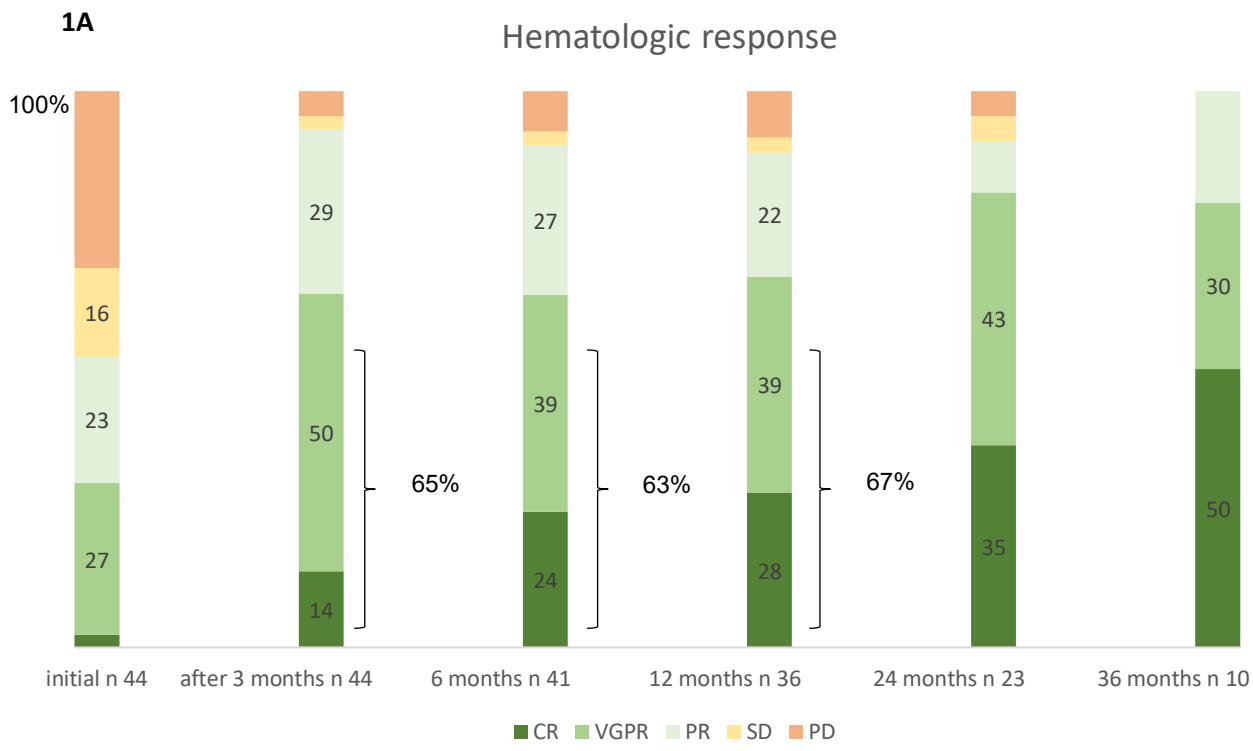


3C Hematological response depending on typical (t) vs. atypical (a) t(11;14) status

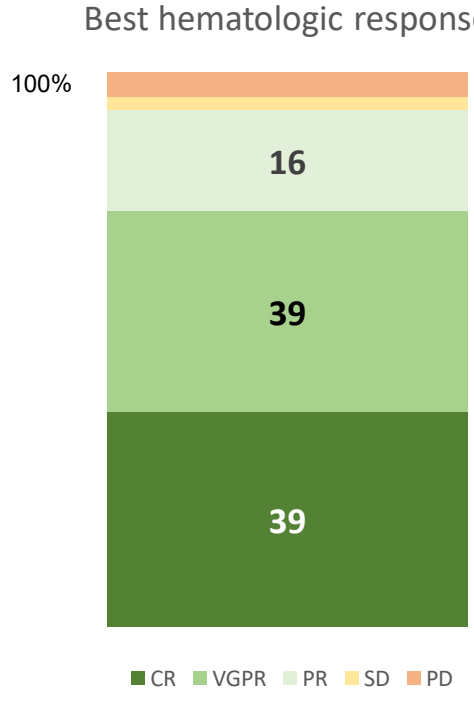


SUPPLEMENTARY DATA

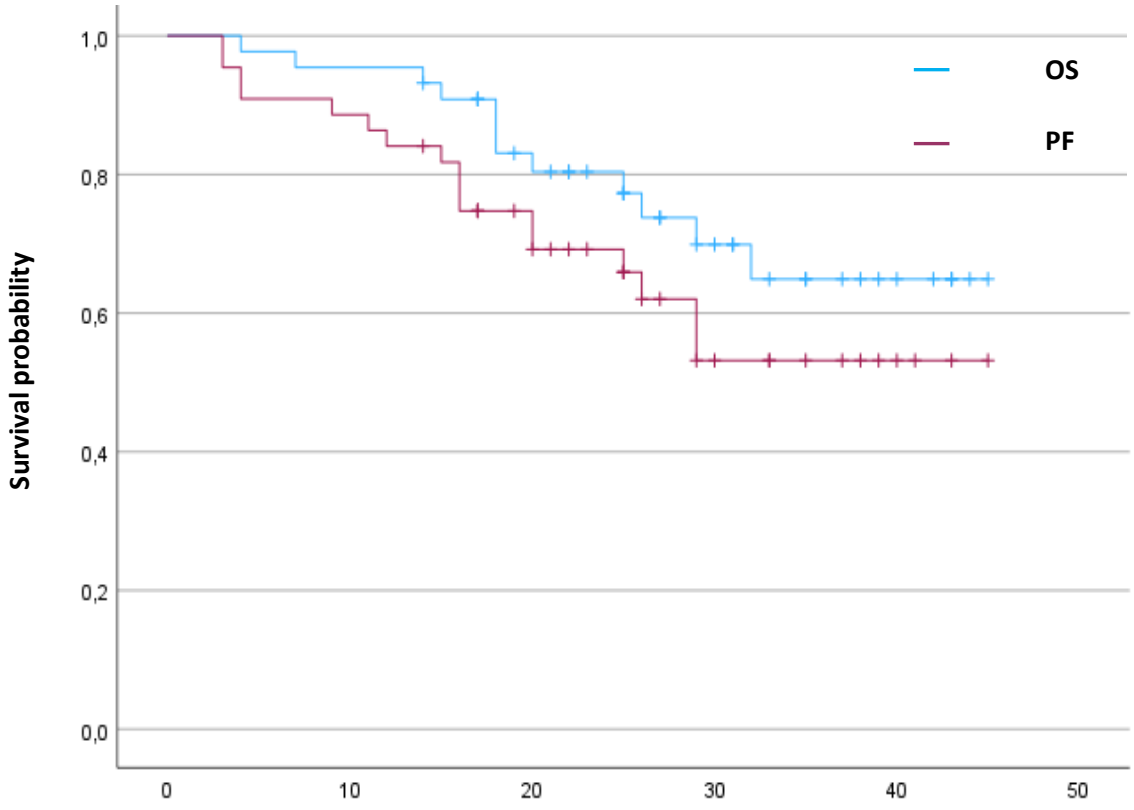
1A



1B



1C



Supplemental Figure 1 Hematologic Response Rates under Venetoclax
1A Response rates for the whole cohort at baseline and after 3, 6, 12, 24 and 36 months repectively. Time to best response was 3 months and best response (including CR and VGPR) could be maintained long-term. Corticosteroids were given in a subset off patientes to enhance treatment response or to alleviate side effects. **1B Best hematologic response** in all evaluable patients (n=44). **Fig. 1C Kaplan-Meier Curves** for event free survival (EFS, purple) and overall survival (blue), mEFS and mOS was not reached.

SUPPLEMENTAL TABLE 1:
Patient demographics and characteristics (%), n = 44

Age (Median, range)		68, 45-78
Male		24 (55)
Lambda restricted		30 (68)
Paraproteinemia	MG	11 (25)
	Smoldering M	30 (68)
	MM	2 (5)
	M. W.	1 (2)
t(11;14)		42 (95) (1 MW, 1 n.a.)
iFISH test results UKHD		33 (75)
atypical t(11;14)		12 (36)
typical t(11;14)		21 (64)
amplification of 1q21		5 (11)
dFLC at initiation in mg/l (median, range)		91 (0-1,178)
dFLC over 180 mg/dl		7 (16)
Organ involvement:	Heart	39 (89)
	Renal	32 (73)
	Liver	10 (23)
	Other	26 (59)
More >/= 2 organs involved		37 (84)
NTproBNP at baseline (pg/ml) **(median, range)**		2755 (247-57,000)
Median eGFR at baseline (ml/min) **(median, range)**		44 (6-109)
Median Proteinuria at baseline (g/d) **(median, range)**		3,0 (0.1-26)
Median AP at baseline (U/l) **(median, range)**		101 (88-1,084)
>/ one line of prior therapy		39 (89)
Median		3
Previous therapy lines including:		
	Daratumumab	42 (95)
	refractory	37 (84)
	Bortezomib	38 (86)
	Cyclophosphamide	15 (34)
	Lenalidomide	24 (55)
	Pomalidomide	11 (25)
	Melphalan	19 (43)
	ABSCT	

heart transplant	7 (15)
other:	1 (2) 3 (7)
Reasons to start Venetoclax	
Refractory disease Relapse Non-optimal hematological response	15 (34) 10 (23) 19 (43)
Hematologic response at baseline	
CR (MRD positive in bone marrow)	1 (2)
VGPR	12 (27)
PR	10 (23)
non-response	7 (16)
PD	14 (32)

Supplemental Table 1: Categorical data are shown as counts (% of respective total), continuous data are shown as medians (range). MG: monoclonal gammopathy. Smoldering M: smoldering myeloma. MM: multiple myeloma. M. W.: Morbus Waldenstrom`s disease. dFLC: difference between involved and uninvolved free light chains. NTproBNP: N-terminal Pro-B-type natriuretic peptide. eGFR: estimated glomerular filtration rate. AP: alkaline phosphatase. ASCT: autologous stem cell transplantation. CTC: common toxicity criteria. ORR: overall response rate. mDOR: median duration of response. mEFS: median event free survival.

SUPPLEMENTAL TABLE 2:
Response rates and toxicities

Dosis in mg/day	50 - 400
Best hematological response	
CR	17 (39)
VGPR	17 (39)
PR	7 (16)
SD	1 (2)
PD	2 (5)
Time to best hematological response (median in months)	3
PD	11 (25)
Median time to PD in months, range	17, 0-24
Primarily refractory	2 (4)
Ongoing response under Venetoclax	48 (21)
Ongoing response, Venetoclax off	1 (5)
Organ response after 12 months	
Cardiac **34 evaluable after 3, 6, or 12 months (92%)***	9 (39)
Renal **22 evaluable after 3, 6, or 12 months (69%)***	10 (62)
Liver **10 evaluable after 3, 6, or 12 months (100%)***	3 (37)
Addition of Dexamethason	12 (27)
Dose of dexamethason in mg	
- 12 mg	6 (50)
- 8 mg	5 (42)
- 4 mg	1 (8)
Months until Start Dex	
- Upfront	3 (25)
- Within 6 months	5 (42)
- After 12 months	2 (17)
- After 18 months	2 (17)
ORR	41 (93)
ORR (VGPR&CR)	34 (77)
Time to best response in months	7
mDOR in months	21
mEFS in months	32
mOS in month	37

mEFS in months	32
mOS in months	36
12 months EFS in %	86
12 months OS in %	95

Infections	Hematological Toxicities	GI	Dose Reduction	Treatment discontinuation	Death on therapy
5 (11) **CTC Grade 3: II (both pulmonary)**	8 (18) CTC grade 4: I (Neutropenia) CTC grade 3: I (low platelets)	8 (18)	29 (66)	19 (43) 2: toxicity, ongoing hematologic response 2: CR/VGPR, ongoing response 11: PD, 6 with dose reduction due to toxicity before 2: renal organ progress 2: new oncological diagnoses (new MM clone, newly diagnosed ovarian carcinoma)	6 (14): 1: suicide 1: intestinal ischemia 4: Organ complication of AL

SUPPELEMTAL TABLE 2: Categorical data are shown as counts (% of respective total). *For organ response rates after 12 months % is calculated for the respective organs involved. ORR: overral response rate. mDOR: median duration of repsonse. mEFS: median event free survival; mOS: median overall survival. CTC: common toxicity criteria.