t(11;14) status is stable between diagnosis and relapse and concordant between detection methodologies based on fluorescence *in situ* hybridization and next-generation sequencing in patients with multiple myeloma

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Abstract

Multiple myeloma (MM) is associated with a wide variety of recurrent genomic alterations. The most common translocation in MM is t(11;14). In this retrospective, single-center, non-interventional study, patients' bone marrow samples were examined at diagnosis and at relapse(s) following treatment with anti-myeloma regimens to determine whether t(11;14) status was stable over time. This stability cohort consisted of 272 patients, of whom 118 were t(11;14)-positive at diagnosis and 154 were negative. All patients in the stability cohort retained the same t(11;14) status at relapse that they had at diagnosis of MM. Sixteen patients who had t(11;14)-positive MM at diagnosis had multiple longitudinal assessments by fluorescence *in situ* hybridization (FISH) at relapse events and remained t(11;14)-positive across all timepoints. Patients who had t(11;14)-positive disease at diagnosis of monoclonal gammopathy of unknown significance or smoldering MM also retained t(11;14) positivity through MM diagnosis and relapse. The t(11;14) fusion patterns also remained constant for 90% of patients. For detection of t(11;14), results from FISH and next-generation sequencing (NGS) were compared to determine the rate of concordance between these two methods. This concordance cohort contained 130 patients, of whom 66 had t(11;14)-positive disease and 64 were t(11;14)-negative. In this sample set, the concordance between FISH- and NGS-based detection of t(11;14) was 100%. These results strongly suggest that the t(11;14) rearrangement remains stable during the full disease course in patients with MM and can be detected by FISH- and NGS-based methodologies.

Introduction

Multiple myeloma (MM) is a clonal plasma cell malignancy associated with recurrent chromosomal and genetic aberrations.[1] Mutational events in the clonal evolution of MM include those considered primary and secondary genetic events, based on their immediacy during clonal development.[2,3] Primary among genetic alterations are *IGH* translocations, including t(11;14),[2] which frequently places the *IGH* enhancer in proximity to the *CCND1* gene.[4] Such primary cytogenetic abnormalities, acquired during B-cell development, facilitate transformation of normal plasma cells into pre-malignant, clonal plasma cells. Subsequent proliferation within the bone marrow results in monoclonal gammopathy of undetermined significance (MGUS), evolving to asymptomatic smoldering MM (SMM), and finally into symptomatic MM. The t(11;14) translocation is the most common and is present in approximately 15-20% of patients;[5,6] it has been associated with aberrant cyclin D1 expression and high BCL-2 expression.[7] Considered as a primary genetic abnormality in plasma cell dyscrasias, t(11;14) has been shown to be present from precursor stages (MGUS and SMM) to MM and plasma cell leukemia.[3,8,9] Previous studies demonstrated the relative inter-patient stability of t(11;14) status over time, but few evaluated intra-patient stability through multiple longitudinal bone

marrow assessments over the course of disease in MM.[10-12] One study of 195 patients found that 25% of the patients were t(11;14)-positive at diagnosis of MM; however, 4.3% of those patients had undetectable t(11;14) at relapse.[10] Conversely, 1.4% of the patients who were t(11;14)-negative at diagnosis had detectable t(11;14) at relapse.[10] Similarly, a longitudinal study by Merz *et al.* (n=128) showed no change in *IGH* translocation status, including t(11;14), between primary diagnosis and relapse.[11] Thus, additional studies employing longitudinal assessment of t(11;14) status across the disease spectrum of MM are necessary to confirm the stability of t(11;14).

Although fluorescence *in situ* hybridization (FISH) is the standard technique used to assess the presence of t(11;14), plasma cell enrichment (PCE) can be used to isolate and enrich clonal plasma cells from heterogenous bone marrow aspirate samples and enhance detection of chromosomal abnormalities by standard FISH. PCE also significantly improves the sensitivity of downstream next-generation sequencing (NGS) assays by facilitating detection of low-frequency mutations, while reducing background signal from non-clonal plasma cells.[13] A recent study suggested that PCE may be more critical to accurate detection of cytogenetic abnormalities than previously believed, as using PCE improved the detection of abnormalities by direct FISH from 38.0% to 95.5% in diagnostic MM samples.[14] This suggests that PCE has strong clinical value for improving FISH-based detection of genomic variability in MM.

Given the genomic variability commonly associated with MM, personalized therapy targeted to individual genetic aberrations may become increasingly important in the era of targeted therapies.[7] Venetoclax, a selective, orally bioavailable inhibitor of BCL-2, is the first targeted therapy for MM and, as monotherapy, has produced high response rates (40% overall response rate) in patients with detectable t(11;14).[15] t(11;14) is a key predictive biomarker of response to venetoclax in relapsed and refractory (RR) MM, as observed in the BELLINI trial.[15,16] Venetoclax is currently being studied in a phase III clinical trial, in combination with dexamethasone, for treatment of patients with t(11;14)-positive RRMM who have completed at least two prior lines of therapy.[17] Thus, the stability of t(11;14), as well as the ability to reliably detect such aberrations through various assays, are of increasing importance in the treatment of RRMM.

NGS combined with PCE has demonstrated the ability to provide equal genomic rearrangement detection as that provided by FISH,[18] and may give insights into the pre- to post-treatment stability of t(11;14) in MM patients.

In this study, we collected bone marrow aspirate samples from patients before and after treatment with anti-myeloma regimens to determine whether MM patients with detectable t(11;14) at diagnosis maintained t(11;14)-positive status after treatment. A NGS-based approach was used to detect t(11;14) status following PCE of bone marrow aspirates and to assess the concordance of PCE-NGS and PCE-FISH methods. Finally, we examined the genomic landscape (mutations and copy number variations) of key selected genetic aberrations in patients with t(11;14)-positive *versus* t(11;14)-negative MM. This study included a total of 272 patients in the stability cohort, used to determine the stability of t(11;14) status, and 130 patients in the concordance cohort, used to determine the concordance of t(11;14) detection by the NGS- and FISH-based methodologies.

Methods

Objectives

The primary objective of this retrospective, single-center, non-interventional study was to evaluate the stability of t(11;14) status at MM diagnosis and relapse using PCE-FISH on bone marrow samples collected before and after treatment with anti-myeloma regimens. The secondary objective was to assess the rate of concordance between PCE-FISH and PCE-NGS for t(11;14) detection in bone marrow samples from patients with MM.

Sample collection

All patients provided informed consent. Bone marrow samples were collected for both the stability cohort and the concordance cohort. Longitudinal paired samples from patients with MM at initial diagnosis and at relapse of disease were obtained only in the stability cohort. Inclusion criteria comprised age ≥18 years old and confirmation of newly diagnosed MM, MGUS, SMM, or RRMM. All samples must have had >80% plasma cells after PCE. Samples were stored in a biobank approved for research purposes at the Toulouse Cancer Institute Oncopole (Toulouse, France). Data were collected from samples that had been previously tested, as well as those that were thawed and tested explicitly for this study.

Plasma cell enrichment and t(11;14) testing

PCE was performed for all samples prior to FISH or NGS testing, using magnetic beads according to the manufacturer's instructions (Miltenyi Biotec, Bergisch Gladbach, Germany). FISH assays were performed using the Vysis IGH/CCND1 XT DF FISH Probe Kit (Abbott Molecular, Des Plaines, IL, USA). The FISH probes detected a 942 Kb region on chromosome 11 (68,363 ~ 69,305 Kb) spanning the *CCND1* breakpoint region, and a 1.6 Mb *IGH* region on chromosome 14 (104,736 ~ 106,339 Kb). Slides were analyzed on a Zeiss Axio fluorescence microscope. For each patient, at least 100 nuclei were scored, counting the number of cells with no translocation, and the number of cells with a translocation. For cells with a translocation, the number of fusions was reported. The cutoff for determination of t(11;14) positivity was 30% of cells/nuclei with an abnormal fusion signal.

NGS was performed as previously described[19] using an Agilent capture panel for sequencing on the Illumina NextSeq

platform. DNA was extracted only from samples with ≥80% plasma cells in the final cell pellet after PCE. For samples stored in RLT+ buffer, DNA was extracted using the AllPrep® DNA/RNA/miRNA kit (QIAGEN, Venlo, the Netherlands). For samples stored as dry pellets, the NucleoSpin Tissue kit (Macherey-Nagel, Düren, Germany) was used. The NGS structural variant detection windows on chromosome 11 (68,800 ~ 69,800 Kb) included the *CCND1* gene and upstream regulatory elements, and on chromosome 14 (105,500 ~ 106,900 Kb) included *IGH*. Samples with low numbers of supporting reads (≤5), suggesting that no t(11;14) translocation was detected (n=64), were identified as t(11;14)-negative. Samples with at least one structural variant within the detection window with >5 supporting reads confirming the presence of a t(11;14) translocation (n=66) were identified as t(11;14)-positive.

The frequency and characteristics of selected genetic alterations were analyzed by t(11;14) status: *DIS3*, *MAPK* pathway genes (*BRAF*, *KRAS*, *NRAS*, *MYC*, *TRAF3*), *ATM*, *TP53*, *ATR*, *BIRC3*, *IRF4*, and *CYLD*.[12]

For analysis of the raw data, a dedicated bioinformatics pipeline (see the *Online Supplementary Methods* for more detail), developed especially for automatic analysis, was used.

Cohorts of patients

The t(11;14) stability cohort collected paired longitudinal samples (at diagnosis and first relapse) from 272 patients; these samples were tested for t(11;14) status using FISH and the findings at diagnosis and at first relapse were compared for each patient.

The concordance cohort collected samples from 130 patients who were analyzed by both FISH and NGS. The results obtained were compared to assess concordance, sensitivity, and specificity of the testing methods.

Statistical power calculations and methods can be found in the *Online Supplementary Information*.

Results

The stability cohort consisted of 272 patients, of whom 118 were t(11;14)-positive at diagnosis and 154 were negative; this cohort had samples that were tested at diagnosis and relapse(s) for detection of t(11;14) by PCE-FISH. The concordance cohort contained 130 patients, of whom 66 were t(11;14)-positive at diagnosis and 64 were negative; this cohort had samples tested by both PCE-FISH and PCE-NGS to determine the concordance of t(11;14) detection between the two methods. Approximately 60% of all tested patients across both cohorts were male. The median age of patients included in the concordance cohort was 69 years (range, 43–91). The median age of those in the stability cohort was 60 years (range, 37-85) for t(11;14)-positive cases, and 63 years (range, 34-85) for t(11;14)-negative patients (Table 1). Patients in the concordance cohort received a variety of anti-myeloma treatment regimens; the most commonly received regimens were triplet therapy with daratumumab, lenalidomide, and dexamethasone; combination therapy with lenalidomide and dexamethasone; and triplet therapy with daratumumab, pomalidomide, and dexamethasone.

Stability of t(11;14) status

In the stability cohort, the median time between the collection of two samples for t(11;14) testing (at diagnosis and relapse) was 29.1 months (range, 1.9-149.4). In this population, stability of t(11;14) status was absolute; all patients who had detectable t(11;14) at diagnosis (n=118) retained the same status at disease relapse (Figure 1), and no t(11;14)-negative patients at diagnosis (n=154) had detectable t(11;14) at relapse. Sixteen patients with t(11;14)-positive samples at diagnosis also had samples collected at multiple relapse events (*Online Supplementary Figure S1*); these patients had a median of two (range, 2-3) post-diagnosis assessments, over a median of 43.3 months (range, 11.4-196.9). All these

Table 1. Patients' baseline demographics.

	Stability cohort		Concordance cohort N=130
	t(11;14)-positive N=118	t(11;14)-negative N=154	
Age in years, median (range)	60 (37-85)	63 (34-85)	69 (43-91)
Male, N (%)	74 (63)	89 (58)	76 (58)
Multiple myeloma stage, N (%)			
MGUS	8 (7)	10 (7)	-
SMM	7 (6)	18 (12)	-
NDMM	103 (87)	97 (63)	65 (50)
RRMM	0	28 (18)	60 (46)
PCL	0	1 (1)	-
Not specified			5 (4)
Longitudinal FISH assessments, median (range)	2 (2-4)	2 (2-5)	NA

N: number; MGUS: monoclonal gammopathy of undetermined significance; SMM: smoldering multiple myeloma; NDMM: newly diagnosed multiple myeloma; RRMM: relapsed/refractory multiple myeloma; PCL: plasma cell leukemia; FISH: fluorescence *in situ* hybridization; NA: not applicable.

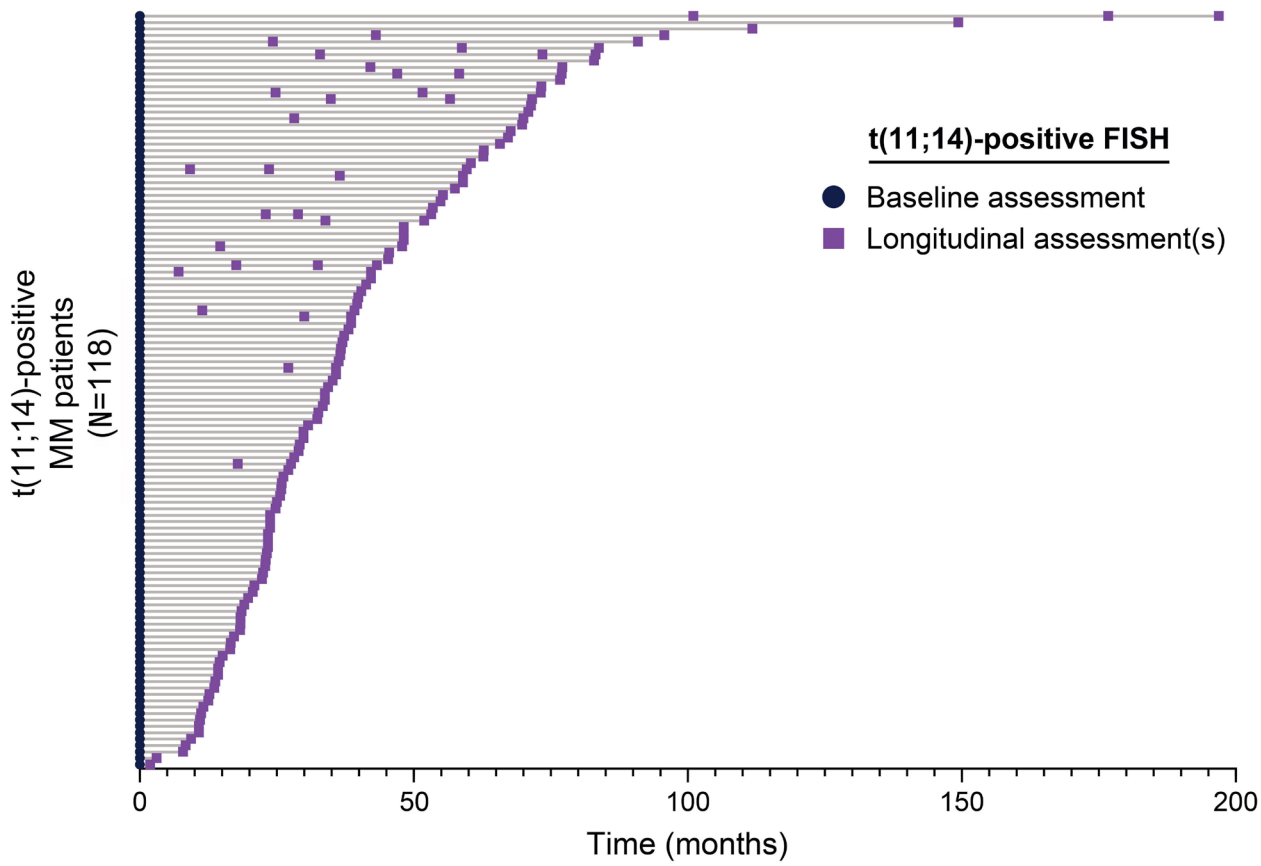

Figure 1. Timing of t(11;14) assessments, between diagnosis and at relapse, for t(11;14)-positive patients. FISH: fluorescence *in situ* hybridization; MM: multiple myeloma.

samples, across all timepoints, retained detectable t(11;14). When samples were positive at initial detection in patients with MGUS or SMM, the patients remained consistently t(11;14)-positive through MM diagnosis and into relapse, a median time span of 28.7 months (range, 7.1-83.2) (n=15) (*Online Supplementary Figure S2*). Chromosomal fusion analysis was done for t(11;14)-positive patients who transitioned from SMM/MM to RRMM on-study. The number of chromosomal fusions remained constant for 90% of patients (n=106/118), but 7% had an increase in the number of fusions from one to two, and another 3% had a decrease from two to one fusion (Figure 2).

Concordance

Among samples with at least one structural variant detection window, a total of 121 structural variants were identified. Figure 3 shows the variety of translocations found across the samples. The same 64 samples found to be t(11;14)-negative by NGS were also determined to be t(11;14)-negative by FISH. Moreover, the same 66 samples identified as t(11;14)-positive by NGS were also identified as t(11;14)-positive by FISH. This indicates 100% concordance between the two detection methods (Table 2).

Genomic profiling

Other genetic aberrations detected by NGS were highly heterogeneous and varied between t(11;14)-positive and -negative samples (Figure 4). The median total copy number aberrations was lower in t(11;14)-positive samples than in t(11;14)-negative samples (median 119 *vs*. 291; *P*<0.001). The frequency of *DIS3* alterations was higher in t(11;14)-positive samples than in negative samples (21.2% *vs*. 4.7%; *P*=0.008). *MAPK* pathway mutations (*BRAF*, *KRAS*, *NRAS*, *MYC*, *TRAF3*) were the most prevalent among all patients (n=47/130; 36%). In contrast, *BRAF* alterations were less common in t(11;14)-positive samples than in negative samples (6.1% *vs*. 18.8%; *P*=0.034) (Figure 4).

Discussion

The present study demonstrated that all patients examined for stability of t(11;14) status (i.e., the stability cohort) maintained their t(11;14) status throughout the course of the disease, from MM diagnosis to relapse, as well as during progression from MGUS/SMM to MM. Additionally, analysis of concordance for t(11;14) detection between PCE-FISH and PCE-NGS was 100%. NGS data also showed differential expression of key genetic alterations such as *DIS3*, *BRAF*, and *MAPK* pathway mutations between t(11;14)-positive and -negative samples.

In the 272 previously treated patients in the stability cohort, we found no instances of change in t(11;14) status between diagnosis and relapse. This is consistent with previous reports of t(11;14) status changes in only 1-6% of patients;[10,11] as such, the present study in a large longitudinal cohort of patients with MM (n=272) indicates that the t(11;14) rearrangement is an early genetic event that remains stable throughout MM disease evolution, including the MGUS/SMM-to-MM transition, as well as across lines of therapy to disease relapse. The 100% intra-patient stability of t(11;14) observed in this study could be attributed to the

well-controlled plasma cell input prior to FISH and NGS analysis, obtained after PCE (>80%), or due to improvements in technology and detection methods over the last 6-10 years. Recent studies have demonstrated that PCE is critical to optimize detection of genomic alterations;[14] thus, in the present study, it is possible that t(11;14) was detected in samples in which it would have previously been determined to be undetectable. However, it should be noted that no samples in our study were excluded for having <80% plasma cells after PCE, suggesting that consistent high-level PCE is readily achievable in clinical practice.

It is notable that t(11;14) stability was also observed at the genomic level with regards to the number of fusions present. The number of t(11;14) fusions remained constant for 90% of patients (n=106/118), but an increase in the number of fusions from one to two, and a decrease from two to one fusion were observed in 7% and 3% of patients, respectively. This suggests that some genomic instability

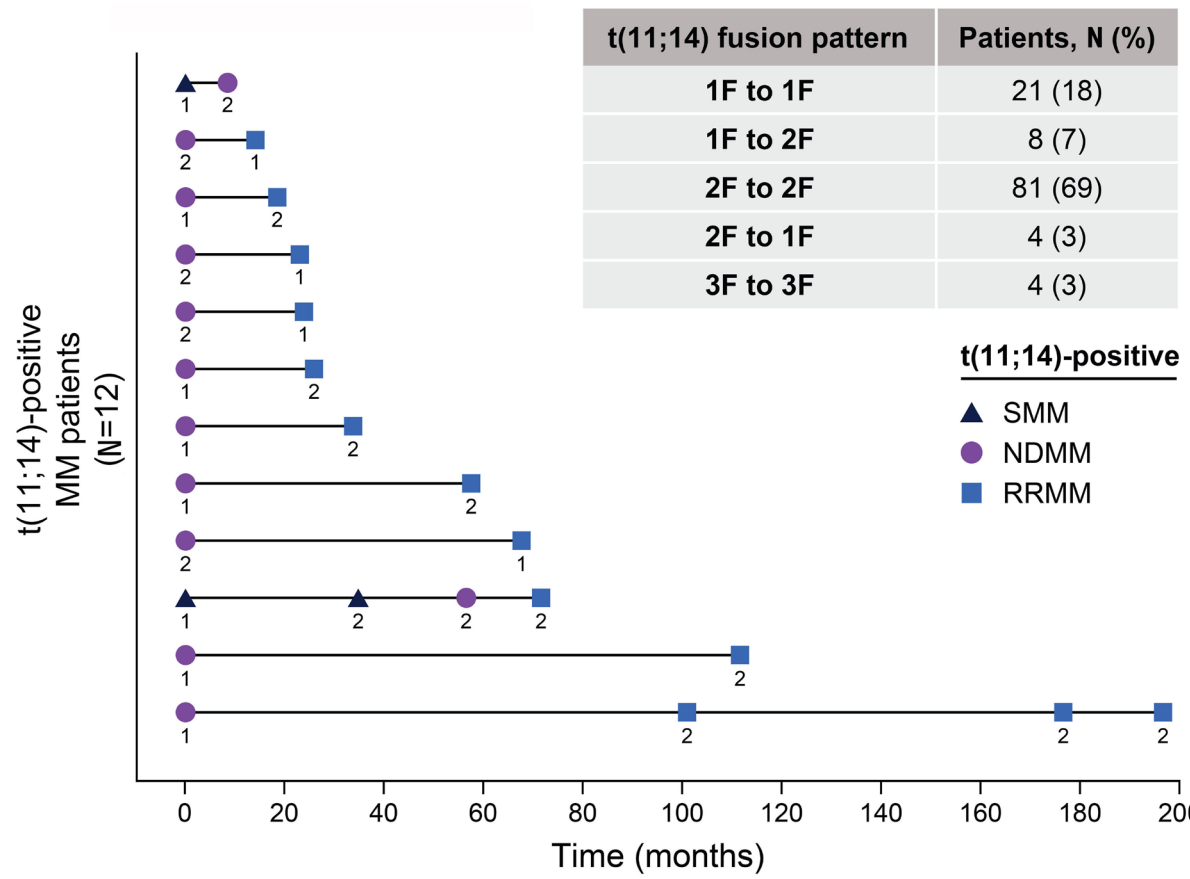

Figure 2. Disease status over time, based on chromosomal fusion analysis, for t(11;14)-positive patients who transitioned from smoldering multiple myeloma (MM) to newly diagnosed MM to relapsed/refractory MM while on-study. MM: multiple myeloma; F: fusion; SMM: smoldering multiple myeloma; NDMM: newly diagnosed multiple myeloma; RRMM: relapsed/refractory multiple myeloma.

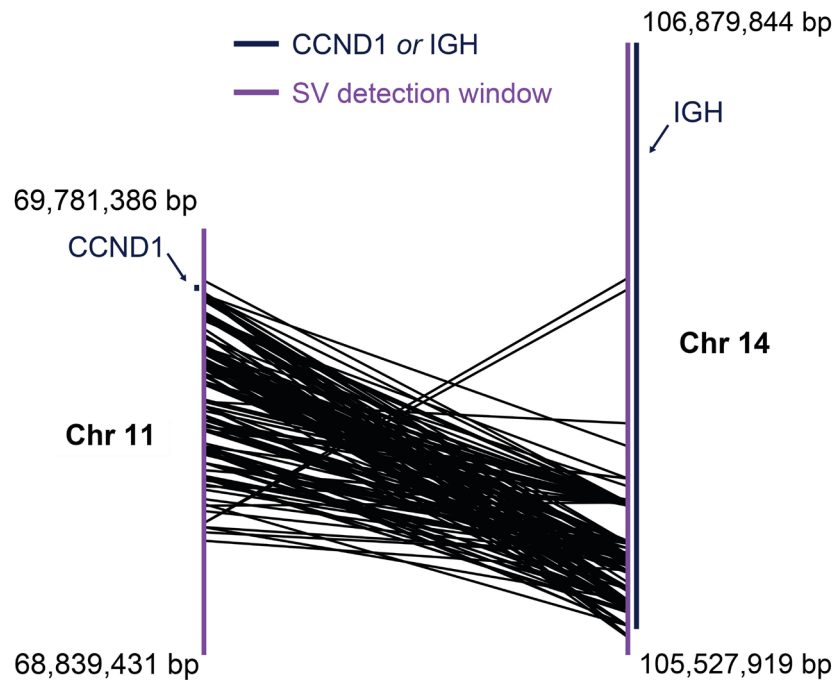

Figure 3. Genomic rearrangement (fusion) points between sites on chromosome 11 (including the location of *CCND1*) and chromosome 14 (including the location of *IGH*) in t(11;14)-positive multiple myeloma patients based on structural variant window detection. Each connecting line represents one detected rearrangement. bp: base pairs; Chr: chromosome; SV: structural variant.

is present during MM evolution, but that loss or gain of t(11;14) does not appear to be a common event that occurs outside of the primary window of transformation. The stability of t(11;14) status between diagnosis and relapse found in this study suggests that a single test for t(11;14) at diagnosis - or at any time during the patient's journey - may be sufficient when considering targeted therapeutic approaches for patients with MM. This is particularly relevant given that post-treatment bone marrow biopsies for patients with RRMM are uncommon because they are not considered clinically relevant to justify the associated risk to patients.[20] Taken together, these data indicate that targeted agents, such as venetoclax,[15,16] may not require t(11;14) retesting at disease relapse when a patient has demonstrated t(11;14) positivity at a prior timepoint. These findings may also advocate for biomarker testing at diagnosis for all patients to help inform therapeutic options during the treatment journey.

Concordance in determination of t(11;14) status with FISH and NGS was 100% across 130 patients' samples. These findings are similar to those of a recently published study of MM in which a head-to-head comparison of FISH and NGS was performed; 78 *IGH* translocations, including t(11;14), were detected by both methods with a 100% concordance.[21] Based on the results of this study, for the purpose of t(11;14) detection, NGS and FISH methods appear to be equally functional and accurate. The NGS workflow can be labor-intensive, and variant curation can be time-consuming and require specialized molecular geneticists; however, NGS provides additional information, such as the precise location of the chromosomal transformation in each sample and identification of other genomic alterations within these

Table 2. Concordance rates between fluorescence *in situ* hybridization and next-generation sequencing methods for the detection of t(11;14).

	Positive by FISH, N (%)	Negative by FISH, N (%)
Positive by NGS, N (%)	66 (100)	0
Negative by NGS, N (%)	0	64 (100)

N: number; FISH: fluorescence *in situ* hybridization; NGS: next-generation sequencing.

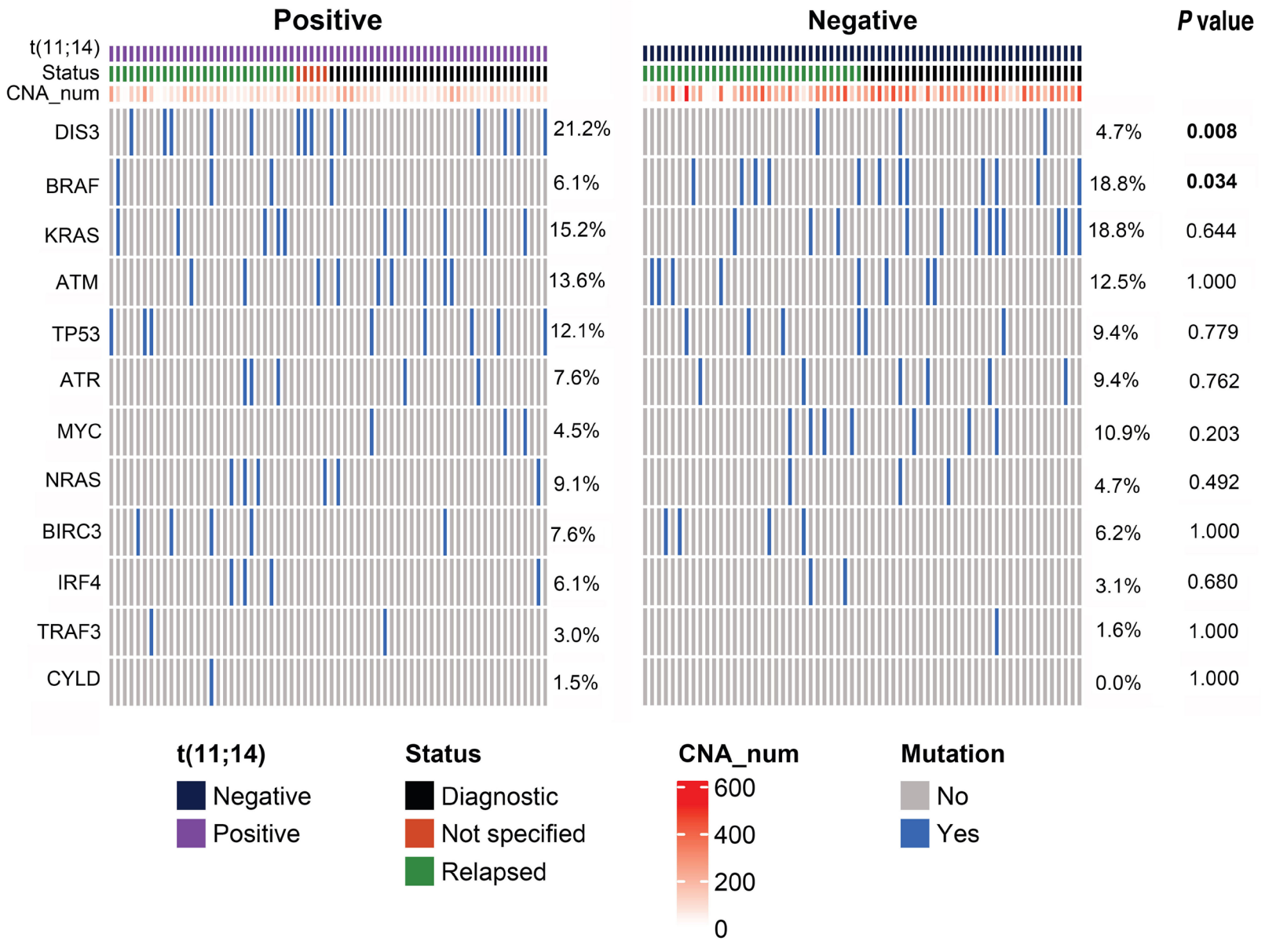

Figure 4. The frequency of recurrent genetic aberrations in patients with multiple myeloma, shown according to t(11;14) status. Patients' disease status, t(11;14) status, and whether mutations were detected in each gene are represented above. Bold *P* values are statistically significant at $P<0.05$. CNA: copy number alteration.

samples. FISH assays are readily available in the clinical setting, and reliably and accurately detected t(11;14) status in this cohort of patients.

In this study, we found that the frequency of *DIS3* alterations was significantly higher in t(11;14)-positive samples than in negative samples (*P*=0.008). This may have clinical implications for patients with t(11;14)-positive MM, because *DIS3* mutations are associated with worse event-free survival outcomes in MM; however this must be confirmed in future studies.[22] We also found that *BRAF* alterations were less common in t(11;14)-positive samples than in negative ones. It has been proposed that *BRAF* alterations may be associated with better outcomes in MM.[23] By contrast, in this study, *MAPK* pathway mutations (*BRAF*, *KRAS*, *NRAS*, *MYC*, *TRAF3*) were highly prevalent overall (36%), but most tended to be less common in t(11;14)-negative samples. Regardless of specific alterations, the practicality of FISH for routine clinical testing is invaluable, while utilizing NGS to determine the presence of additional alterations will be required to provide a comprehensive assessment of the genomic heterogeneity in MM.

In conclusion, this study has demonstrated absolute stability of t(11;14) status from diagnosis to relapse, and across multiple relapses, in patients treated with anti-myeloma therapeutic regimens. Furthermore, the results demonstrate a 100% concordance in detection and determination of t(11;14) status by FISH- and NGS-based methodologies.

Disclosures

HA-L has no conflicts of interest to disclose. RT-M, XL, JAR, and CH are employees of AbbVie, and may hold stock or options in the company.

Contributions

RT-M, JAR, and CH conceived and designed the study. RT-M, JAR, and CH collected the data. All the authors were involved in the analysis and interpretation of results and in preparation of the manuscript.

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Data-sharing statement

AbbVie is committed to responsible data-sharing regarding the clinical trials it sponsors. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (e.g., protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/

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