HAL
open science

Genomics of Multiple Myeloma

Sébastien Robiou-Du-Pont, Alice Cleynen, Charlotte Fontan, Michel Attal, Nikhil C Munshi, Jill Corre, Herve Avet-Loiseau

To cite this version:

Sébastien Robiou-Du-Pont, Alice Cleynen, Charlotte Fontan, Michel Attal, Nikhil C Munshi, et al.. Genomics of Multiple Myeloma. Journal of Clinical Oncology, 2017, 35 (9), pp.963-967. 10.1200/JCO.2016.70.6705 . hal-01813387

HAL Id: hal-01813387

https://hal.science/hal-01813387v1

Submitted on 18 Jun 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Genomics of Multiple Myeloma

Sebastien Robiou du Pont, Alice Cleynen, Charlotte Fontan, Michel Attal, Nikhil Munshi, Jill Corre, and Hervé Avet-Loiseau

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on February 13, 2017.

Corresponding author: Hervé Avet-Loiseau, MD, PhD, Genomics of Myeloma Laboratory, L'Institut Universitaire du Cancer Oncopole, 1 Av Irene Joliot-Curie, 31059 Toulouse, France; e-mail: avet-loiseau.h@chu-toulouse.fr.

© 2017 by American Society of Clinical Oncology

0732-183X/17/3599-1/$20.00

A B S T R A C T

Multiple myeloma (MM) is characterized by wide variability in the chromosomal/genetic changes present in tumor plasma cells. Genetically, MM can be divided into two groups according to ploidy and hyperdiploidy versus nonhyperdiploidy. Several studies in gene expression profiling attempted to identify subentities in MM without convincing results. These studies mostly confirmed the cytogenetic data and subclassified patients according to 14q32 translocations and ploidy. More-recent data that are based on whole-exome sequencing have confirmed this heterogeneity and show many gene mutations but without a unifying mutation. These newer studies have shown the frequent alteration of the mitogen-activated protein kinase pathway. The most interesting data have demonstrated subclonality in all patients with MM, including subclonal mutations of supposed driver genes *KRAS*, *NRAS*, and *BRAF*.

J Clin Oncol 35. © 2017 by American Society of Clinical Oncology

Multiple myeloma (MM) is characterized by the accumulation (usually) of tumor plasma cells (PCs) within the bone marrow compartment. Clinically, MM is characterized by a wide heterogeneity both for clinical symptoms at diagnosis (bone fractures, anemia, renal failure, and extramedullary localizations) and for outcome (rapid fatal evolution, long-term progression-free survival, or even cure). In the early 2000s, this clinical heterogeneity was believed to be mostly driven by chromosomal abnormalities found in the tumor PCs. On the basis of conventional karyotyping (rarely informative because of the low PC proliferative index)[1-3] or interphase fluorescence in situ hybridization (FISH) experiments,[4-8] high-risk chromosomal changes have been identified, such as the translocations t(4;14) and t(14;16) and the loss of part of the chromosome 17 short arm (ie, del[17p]). With the use of more high-throughput technologies, such as gene expression profiling (GEP) on microarrays, molecular classifications have been proposed.[9-13] However, these classifications have not led to the identification of several MM entities, as described with non-Hodgkin lymphomas. With the advent of next-generation sequencing (NGS) at both the DNA and the RNA levels, the goal of this review is to summarize our current knowledge of the molecular lesions of MM.

GEP/RNA SEQUENCING

The first molecular classification of MM was proposed by Bergsagel et al[9] from GEP experiments. This first report identified eight subgroups that were mainly based on cyclin D gene expression and on the various 14q32 recurrent translocations. This molecular classification was refined in 2006 and identified seven subclasses of myelomas.[12] The first group is defined by the translocation t(4;14), which is identified by overexpression of the *MMSET* and/or *FGFR3* genes. The second group is defined by upregulation of one of the *MAF* genes related to the translocations t(14;16) or t(14;20). Cases with *CCND1* or *CCND3* upregulation (as a result of the translocations t[11;14] or t[6;14]) cluster into the third and fourth groups CD1 and CD2. The CD2 group is characterized by CD20 expression. The fifth group is characterized by hyperdiploidy. The final two groups are characterized by a low incidence of bone disease in accordance with low DKK1 expression, but the last group is characterized by a high expression of genes involved in proliferation. This molecular classification has been partially confirmed by a study by the HOVON (Haemato Oncology Foundation for Adults in the Netherlands) group.[13] The low bone disease group was not confirmed. In contrast, three other groups were identified: one enriched by myeloid genes that could be related to PC sorting problems, one characterized by overexpression of cancer testis antigen genes, and one defined by overexpression of positive regulators of the nuclear factor-κB pathway. However, these classifications failed to identify real subentities in MM. Few studies that used RNA sequencing have

DOI: 10.1200/JCO.2016.70.6705

Downloaded from ascopubs.org by Bibl Interuniv Montpellier on February 28, 2017 from 162.038.126.191
Copyright © 2017 American Society of Clinical Oncology. All rights reserved.

been reported in meetings. The role of this technology in replacing GEP in the future is still questionable, and further studies are needed.

GEP has been extensively published with the goal of identifying several groups of patients with distinct outcomes. All these studies have identified a high-risk versus standard-risk group[12-14]; however, no common gene was found through the detailing of the gene signatures. These high-risk signatures identify different groups of patients (13% to 25%). Whether each high-risk signature identifies the same patients is still an opened question. In routine practice, GEP is rarely used for assessing prognosis mainly because it requires microarray technology and bioinformatics.

DNA COPY NUMBER CHANGES

As with many cancers, MM is characterized by many chromosomal aberrations. Because karyotypes frequently are uninformative, our knowledge of the unbalanced chromosomal changes comes from single nucleotide polymorphism/comparative genomic hybridization array studies.[15,16] These molecular karyotypes usually are highly complex, with two exceptions. Approximately 10% of patients do not display a detectable abnormality at the chromosomal level.[16] The second exception is that patients with the t(11;14) translocation (approximately 15% to 20%) usually display simple karyotypes (unpublished data). In all other cases (approximately 70% of patients), numerous changes are observed. The following two groups of patients are identified: those with gains of odd chromosomes (3, 5, 7, 9, 11, 15, 19, and 21),[17] which define hyperdiploidy (observed in approximately one half of patients), and those with many structural changes (gains and losses), which define pseudo- or hypodiploidy (approximately 20% of patients). The latter group is frequently characterized by 14q32 translocations that target the *IGH* gene and several partners, mainly *FGFR3/MMSET* on chromosome 4[18,19] or, less frequently, *MAF*,[20,21] *MAFB*,[22] or *CCND3*[23] on chromosomes 16, 20, and 6, respectively. Among the recurrent unbalanced changes observed on molecular karyotypes, the most frequent changes are 1q gains and losses at 1p, 6q, 8p, 13q, 14q, 16q, and 17p.[15,16]

With regard to prognosis, many of these changes have been associated with specific outcomes. Hyperdiploidy usually is associated with longer survival, even though the situation is probably more complex than the simple number of chromosomes. Some chromosomes, such as 3 and 5, display a good outcome, whereas trisomy 21 worsens the prognosis.[24] More high-risk abnormalities have been identified, such as t(4;14),[8] t(14;16), del(17p),[8] del (1p32),[25] and 1q gains.[26] The molecular targets of these losses and gains are mostly unknown. For del(17p), the minimal deleted region includes the *TP53* gene; however, this gene is not mutated on the remaining allele in all cases,[27] and other genes in its vicinity might be important for prognosis.[28] For del(1p32), the minimal deleted region targets two genes, *FAF1* and *CDKN2C* (unpublished data). The real target gene that affects prognosis is still unknown. For 1q gains, the large majority of cases are gains of the whole long arm, which prevents the identification of specific target genes. In routine practice, these abnormalities mainly are analyzed by interphase FISH on sorted PCs by using plus or minus complete panels (Table 1). A recent meta-analysis combined FISH with the International Staging System to more precisely define prognosis (revised International Staging System).[29] Whether FISH will be supplied in the future by single nucleotide polymorphism array or NGS is unknown.

DNA SEQUENCING

Most of the DNA sequencing reports have focused on the transcribed genome (ie, whole-exome sequencing on sorted tumor PCs).[30-33] Several hundreds of primary tumors have been exome sequenced. In contrast to hematologic tumors, such as hairy cell leukemia[34] or Waldenström macroglobulinemia[35] that are characterized by a single unifying mutation (targeting *BRAF* and *MYD88*, respectively), no such unique mutation has been found in MM. The median number of mutations per transcribed genome is approximately 60.[30] Compared with other tumors, MM is in the middle of the landscape, with more mutations than other hematologic malignancies, such as leukemias, but with much fewer than carcinogen-induced tumors, such as melanoma and lung cancers.[36] A heterogeneous mutational landscape was observed in all the studies.[29-32,37] The most frequently mutated genes are *KRAS* and *NRAS* (approximately 20% each) followed by *TP53*, *DIS3*, *FAM46C*, and *BRAF*, which are all mutated in approximately 10% of patients. All other mutations were observed in $< 5\%$ of patients. Of note, some patients present two or more mutations in genes involved in the same pathway (eg, *KRAS*, *NRAS*, or *BRAF* in the MAPK pathway). This redundancy is surprising and has not been reported in other tumors, and its biologic significance is unknown. In some patients, these apparently redundant mutations are not subclonal but are observed at the clonal level.[31] Furthermore, some of these driver mutations are lowly expressed at the RNA level, which asks again about the significance of these mutations in the biology of the disease.[38]

Most of the published DNA sequencing studies addressed the issue of the mechanisms that support the mutational machinery. All the studies identified several mutational signatures, particularly deamination of methylated cytosines; kataegis; apolipoprotein B mRNA editing enzyme, catalytic polypeptide (APOBEC), signature; and somatic hypermutations driven by the activation-induced deaminase enzyme. Deamination of methylated cytosines leads to C>T transitions at CpG sites and is a rather generic mutational process observed in many cancers. The APOBEC signature is characterized by C>T, C>G, and C>A mutations at TpC sites, is driven by a family of APOBEC

Table 1. Prognostic Value of the Main Chromosomal Abnormalities of Multiple Myeloma

Abnormality	Prognostic Value
t(4;14)	Negative
Del(17p)	Negative
Del(1p32)	Negative
1q gains	Negative
t(14;16)	Negative
Hyperdiploidy	Positive (specific gains?)
t(11;14)	Neutral

Downloaded from ascopubs.org by Bibl Interuniv Montpellier on February 28, 2017 from 162.038.126.191
Copyright © 2017 American Society of Clinical Oncology. All rights reserved.

enzymes, and is mostly found in cases with *MAF/MAFB* translocations. Finally, activation-induced deaminase–driven mutations are observed in several genes involved in immunoglobulin translocations, such as *MYC* or *CCND1*, as previously described.[33]

The role of these mutations in patient outcome is still questionable. The analysis of large cohorts of homogeneously treated patients failed to relate recurrent mutations such as *KRAS*, *NRAS*, or *BRAF* to specific survival rates.[36] The only recurrent mutations that significantly affect survival are those observed in *TP53*, which is not novel. Larger cohorts might be needed, but specific mutations unlikely will affect survival given the very low frequency of these mutations. Future studies in whole-genome sequencing may provide new insights into the broad mutational landscape. Preliminary data have revealed a large set of mutations (in the 5,000 to 10,000 range) that mainly affect the nontranscribed genome; that may target microRNA, small nucleolar RNA, or long noncoding RNA; and that could modify prognosis. The large majority of these mutations probably are passenger mutations, with a few of them being drivers. With the objective of successful targeted therapy in the future, the determination of which mutations are really drivers versus passengers will be important. These studies also will detect all the translocations; some of them might be recurrent, as preliminary RNA sequencing studies of fusion genes have shown (unpublished data).

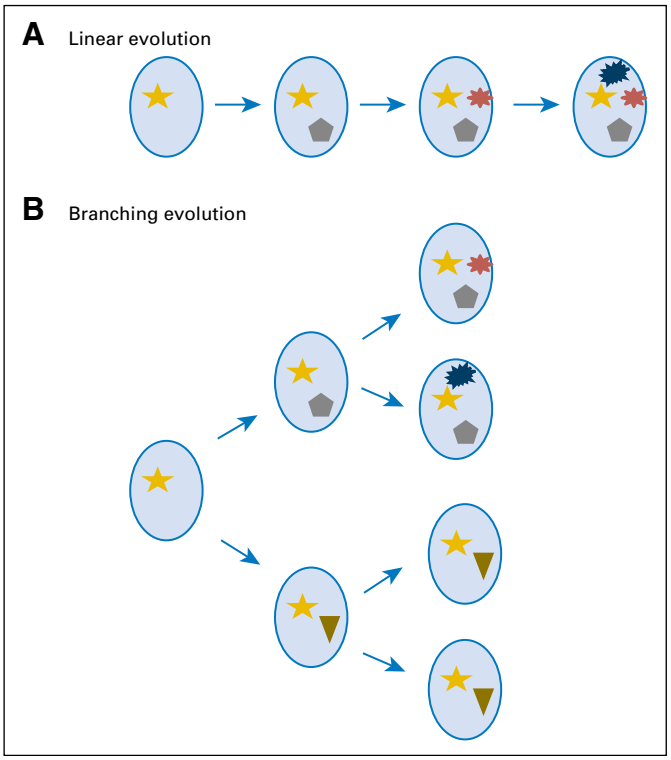

Fig 1. Myeloma is characterized by two types of subclonal evolution: (A) a linear one with acquisition of novel mutations over time in the clone and (B) a branching evolution where subclones diverge with subclonal acquisition of novel mutations.

SUBCLONALITY

One of the most striking results of the sequencing studies is the description of oligoclonality in MM. Even though the disease is characterized by the secretion of a unique monoclonal protein in the majority of patients, a degree of heterogeneity is observed at the molecular level, which suggests a Darwinian evolution of MM.[29-32,39-41] In exome sequencing studies, all the mutations were not necessarily present in all the tumor PCs. This subclonal status not only is present at the single base level but also is observed (even less frequently) at the copy number level. This heterogeneity is observed as soon as the monoclonal gammopathy of unknown significance stage (a premalignant state), meaning that immortalized PCs diverge very early in their evolution.[42] A tumor at diagnosis contains an estimated five to six subclones. This number could be much larger as a result of more-sensitive sequencing approaches. Of note, this subclonal process is not limited to supposed passenger mutations but is observed in supposed driver mutations, such *KRAS*, *NRAS*, and *BRAF*. This means that the mutational process is dynamic and that some mutations of supposed driver genes might occur late in the evolution of the disease.

This oligoclonality leads to various types of evolution of the disease over time (Fig 1). The sequencing of tumors from a same patient at different time points (eg, diagnosis, relapse) showed two types of evolution.[30] The first one is a linear evolution, which means that the major clone observed on the first time point is still present on the second one and eventually acquires novel mutations. The second one is a branching evolution, which means that the major clone observed at the second time point is different from the first one, even though this major clone was already present early but as a minor subclone. The linear evolution suggests that all the subclones observed at diagnosis, for instance, responded to therapy but repopulated the tumor at the same speed and led to relapse. In contrast, the branching evolution suggests a different kinetics of repopulation or a different sensitivity to the chosen therapy. Whether these two modes of evolution are related to the therapeutic pressure or to the natural history of each patient is still an unresolved issue.

Finally, this oligoclonality raises the question of the development of targeted therapies in MM because it is currently used in many solid tumors. Some of the mutations recurrently observed in MM are drugable. For instance, the V600E *BRAF* mutation can be targeted with BRAF inhibitors. In the same way, *RAS* mutations might be targeted by MEK inhibitors. This approach could be highly successful as shown in a case of a harbored V600E *BRAF* mutation.[43] However, this spectacular result supposes that the drugable mutation is fully clonal. It is easy to speculate that if this mutation is subclonal (eg, in 50% of the PCs), the response will be limited to the PCs that present the mutation but will be totally inefficient in the 50% of the PCs that lack the mutation. Currently, therapeutic approaches in MM are mainly based on broadly active drugs (proteasome inhibitors, immunomodulatory drugs, antibodies, HDAC inhibitors), but if physicians want to take advantage of the sequencing efforts for targeted therapeutic approaches, the detection of

© 2017 by American Society of Clinical Oncology

Downloaded from ascopubs.org by Bibl Interuniv Montpellier on February 28, 2017 from 162.038.126.191
Copyright © 2017 American Society of Clinical Oncology. All rights reserved.

mutations and the clonal or subclonal status of these mutations are important.

CONCLUSION

In the past 2 years, major studies have addressed the issue of the molecular landscape of MM by using NGS. If these studies have markedly improved our knowledge of the biology of the disease, they have failed (so far) to translate this knowledge into practical clinical application. We have no doubt that in the next 3 to 5 years, with more patients, and with more powerful technologies (whole-genome sequencing, RNA sequencing, targeted sequencing panels), sequencing will be a new tool in the routine evaluation of patients that could lead to significant improvements in patient management.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Nikhil Munshi, Jill Corre, Hervé Avet-Loiseau
Data analysis and interpretation: Sebastien Robiou du Pont, Alice Cleynen, Charlotte Fontan, Michel Attal, Nikhil Munshi, Jill Corre
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. Laï JL, Zandecki M, Mary JY, et al: Improved cytogenetics in multiple myeloma: A study of 151 patients including 117 patients at diagnosis. Blood 85:2490-2497, 1995

2. Smadja NV, Bastard C, Brigaudeau C, et al: Hypodiploidy is a major prognostic factor in multiple myeloma. Blood 98:2229-2238, 2001

3. Calasanz MJ, Cigudosa JC, Odero MD, et al: Cytogenetic analysis of 280 patients with multiple myeloma and related disorders: Primary breakpoints and clinical correlations. Genes Chromosomes Cancer 18:84-93, 1997

4. Nishida K, Tamura A, Nakazawa N, et al: The Ig heavy chain gene is frequently involved in chromosomal translocations in multiple myeloma and plasma cell leukemia as detected by in situ hybridization. Blood 90:526-534, 1997

5. Avet-Loiseau H, Li JY, Facon T, et al: High incidence of translocations t(11;14)(q13;q32) and t(4;14)(p16;q32) in patients with plasma cell malignancies. Cancer Res 58:5640-5645, 1998

6. Fonseca R, Debes-Marun CS, Picken EB, et al: The recurrent IgH translocations are highly associated with nonhyperdiploid variant multiple myeloma. Blood 102:2562-2567, 2003

7. Drach J, Ackermann J, Fritz E, et al: Presence of a p53 gene deletion in patients with multiple myeloma predicts for short survival after conventional-dose chemotherapy. Blood 92:802-809, 1998

8. Avet-Loiseau H, Attal M, Moreau P, et al: Genetic abnormalities and survival in multiple myeloma: The experience of the Intergroupe Francophone du Myélome. Blood 109:3489-3495, 2007

9. Bergsagel PL, Kuehl WM, Zhan F, et al: Cyclin D dysregulation: An early and unifying pathogenic event in multiple myeloma. Blood 106:296-303, 2005

10. Zhan F, Hardin J, Kordsmeier B, et al: Global gene expression profiling of multiple myeloma, monoclonal gammopathy of undetermined significance, and normal bone marrow plasma cells. Blood 99:1745-1757, 2002

11. Magrangeas F, Nasser V, Avet-Loiseau H, et al: Gene expression profiling of multiple myeloma reveals molecular portraits in relation to the pathogenesis of the disease. Blood 101:4998-5006, 2003

12. Zhan F, Huang Y, Colla S, et al: The molecular classification of multiple myeloma. Blood 108: 2020-2028, 2006

13. Broyl A, Hose D, Lokhorst H, et al: Gene expression profiling for molecular classification of multiple myeloma in newly diagnosed patients. Blood 116:2543-2553, 2010

14. Decaux O, Lodé L, Magrangeas F, et al: Prediction of survival in multiple myeloma based on gene expression profiles reveals cell cycle and chromosomal instability signatures in high-risk patients and hyperdiploid signatures in low-risk patients: A study of the Intergroupe Francophone du Myélome. J Clin Oncol 26:4798-4805, 2008

15. Carrasco DR, Tonon G, Huang Y, et al: High-resolution genomic profiles define distinct clinicopathogenetic subgroups of multiple myeloma patients. Cancer Cell 9:313-325, 2006

16. Avet-Loiseau H, Li C, Magrangeas F, et al: Prognostic significance of copy-number alterations in multiple myeloma. J Clin Oncol 27:4585-4590, 2009

17. Chng WJ, Kumar S, Vanwier S, et al: Molecular dissection of hyperdiploid multiple myeloma by gene expression profiling. Cancer Res 67:2982-2989, 2007

18. Chesi M, Nardini E, Brents LA, et al: Frequent translocation t(4;14)(p16.3;q32.3) in multiple myeloma is associated with increased expression and activating mutations of fibroblast growth factor receptor 3. Nat Genet 16:260-264, 1997

19. Chesi M, Nardini E, Lim RS, et al: The t(4;14) translocation in myeloma dysregulates both FGFR3 and a novel gene, MMSET, resulting in IgH/MMSET hybrid transcripts. Blood 92:3025-3034, 1998

20. Chesi M, Bergsagel PL, Shonukan OO, et al: Frequent dysregulation of the c-maf proto-oncogene at 16q23 by translocation to an Ig locus in multiple myeloma. Blood 91:4457-4463, 1998

21. Hurt EM, Wiestner A, Rosenwald A, et al: Overexpression of c-maf is a frequent oncogenic event in multiple myeloma that promotes proliferation and pathological interactions with bone marrow stroma. Cancer Cell 5:191-199, 2004

22. Hanamura I, Iida S, Akano Y, et al: Ectopic expression of MAFB gene in human myeloma cells carrying (14;20)(q32;q11) chromosomal translocations. Jpn J Cancer Res 92:638-644, 2001

23. Shaughnessy J Jr, Gabrea A, Qi Y, et al: Cyclin D3 at 6p21 is dysregulated by recurrent chromosomal translocations to immunoglobulin loci in multiple myeloma. Blood 98:217-223, 2001

24. Chretien ML, Corre J, Lauwers-Cances V, et al: Understanding the role of hyperdiploidy in myeloma prognosis: Which trisomies really matter? Blood 126:2713-2719, 2015

25. Hebraud B, Leleu X, Lauwers-Cances V, et al: Deletion of the 1p32 region is a major independent prognostic factor in young patients with myeloma: The IFM experience on 1195 patients. Blood 28: 675-679, 2014

26. Hanamura I, Stewart JP, Huang Y, et al: Frequent gain of chromosome band 1q21 in plasma-cell dyscrasias detected by fluorescence in situ hybridization: Incidence increases from MGUS to relapsed myeloma and is related to prognosis and disease progression following tandem stem-cell transplantation. Blood 108: 1724-1732, 2006

27. Lodé L, Eveillard M, Trichet V, et al: Mutations in TP53 are exclusively associated with del(17p) in multiple myeloma. Haematologica 95:1973-1976, 2010

28. Liu Y, Chen C, Xu Z, et al: Deletions linked to TP53 loss drive cancer through p53-independent mechanisms. Nature 531:471-475, 2016

29. Palumbo A, Avet-Loiseau H, Oliva S, et al: Revised International Staging System for multiple myeloma: A report from International Myeloma Working Group. J Clin Oncol 33:2863-2869, 2015

30. Chapman MA, Lawrence MS, Keats JJ, et al: Initial genome sequencing and analysis of multiple myeloma. Nature 471:467-472, 2011

31. Bolli N, Avet-Loiseau H, Wedge DC, et al: Heterogeneity of genomic evolution and mutational profiles in multiple myeloma. Nat Commun 5:2997, 2014

32. Lohr JG, Stojanov P, Carter SL, et al: Widespread genetic heterogeneity in multiple myeloma: Implications for targeted therapy. Cancer Cell 25: 91-101, 2014

33. Walker BA, Wardell CP, Murison A, et al: APOBEC family mutational signatures are associated with poor prognosis translocations in multiple myeloma. Nat Commun 6:6997, 2015

34. Tiacci E, Trifonov V, Schiavoni G, et al: BRAF mutations in hairy-cell leukemia. N Engl J Med 364: 2305-2315, 2011

35. Treon SP, Xu L, Yang G, et al: MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. N Engl J Med 367:826-833, 2012

36. Alexandrov LB, Nik-Zainal S, Wedge DC, et al: Signatures of mutational processes in human cancer. Nature 500:415-421, 2013 [Erratum: Nature 502:258, 2013]

37. Walker BA, Boyle EM, Wardell CP, et al: Mutational spectrum, copy number changes, and outcome: Results of a sequencing study of patients

Downloaded from ascopubs.org by Bibl Interuniv Montpellier on February 28, 2017 from 162.038.126.191
Copyright © 2017 American Society of Clinical Oncology. All rights reserved.

with newly diagnosed myeloma. J Clin Oncol 33: 3911-3920, 2015

38. Rashid NU, Sperling AS, Bolli N, et al: Differential and limited expression of mutant alleles in multiple myeloma. Blood 124:3110-3117, 2014

39. Magrangeas F, Avet-Loiseau H, Gouraud W, et al: Minor clone provides a reservoir for relapse in multiple myeloma. Leukemia 27:473-481, 2013

40. Walker BA, Wardell CP, Melchor L, et al: Intraclonal heterogeneity and distinct molecular mechanisms characterize the development of t(4;14) and t(11;14) myeloma. Blood 120:1077-1086, 2012

41. Morgan GJ, Walker BA, Davies FE: The genetic architecture of multiple myeloma. Nat Rev Cancer 12:335-348, 2012

42. Walker BA, Wardell CP, Melchor L, et al: Intraclonal heterogeneity is a critical early event in the development of myeloma and precedes the development of clinical symptoms. Leukemia 28:384-390, 2014

43. Andrulis M, Lehners N, Capper D, et al: Targeting the BRAF V600E mutation in multiple myeloma. Cancer Discov 3:862-869, 2013

Affiliations

Sebastien Robiou du Pont, **Charlotte Fontan**, **Michel Attal**, **Jill Corre**, and **Hervé Avet-Loiseau**, L'Institut Universitaire du Cancer Oncopole, Toulouse; **Alice Cleynen**, Centre National de la Recherche Scientifique, and Montpellier University, Montpellier, France; and **Nikhil Munshi**, Dana-Farber Cancer Institute, Boston, MA.

Support

Supported by a grant from the National Cancer Institute (CA100707-12) and the CAPTOR (Cancer Pharmacology of Toulouse-Oncopole and Region) program. Cancer Research Center of Toulouse Team 13 is labeled by Fondation ARC pour la Recherche sur le Cancer.

© 2017 by American Society of Clinical Oncology

Downloaded from ascopubs.org by Bibl Interuniv Montpellier on February 28, 2017 from 162.038.126.191
Copyright © 2017 American Society of Clinical Oncology. All rights reserved.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Genomics of Multiple Myeloma

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Sebastien Robiou du Pont
No relationship to disclose

Alice Cleynen
No relationship to disclose

Charlotte Fontan
No relationship to disclose

Michel Attal
No relationship to disclose

Nikhil Munshi
Leadership: OncoPep
Stock or Other Ownership: OncoPep
Consulting or Advisory Role: Celgene, Takeda Pharmaceuticals, Janssen Pharmaceuticals, Merck, Pfizer, OncoPep
Patents, Royalties, Other Intellectual Property: OncoPep

Jill Corre
No relationship to disclose

Hervé Avet-Loiseau
No relationship to disclose

© 2017 by American Society of Clinical Oncology

Downloaded from ascopubs.org by Bibl Interuniv Montpellier on February 28, 2017 from 162.038.126.191
Copyright © 2017 American Society of Clinical Oncology. All rights reserved.