Myeloid/Lymphoid Neoplasms With *FGFR1* Rearrangement

Disease State Overview

MI-DIS-US-0081 09/25

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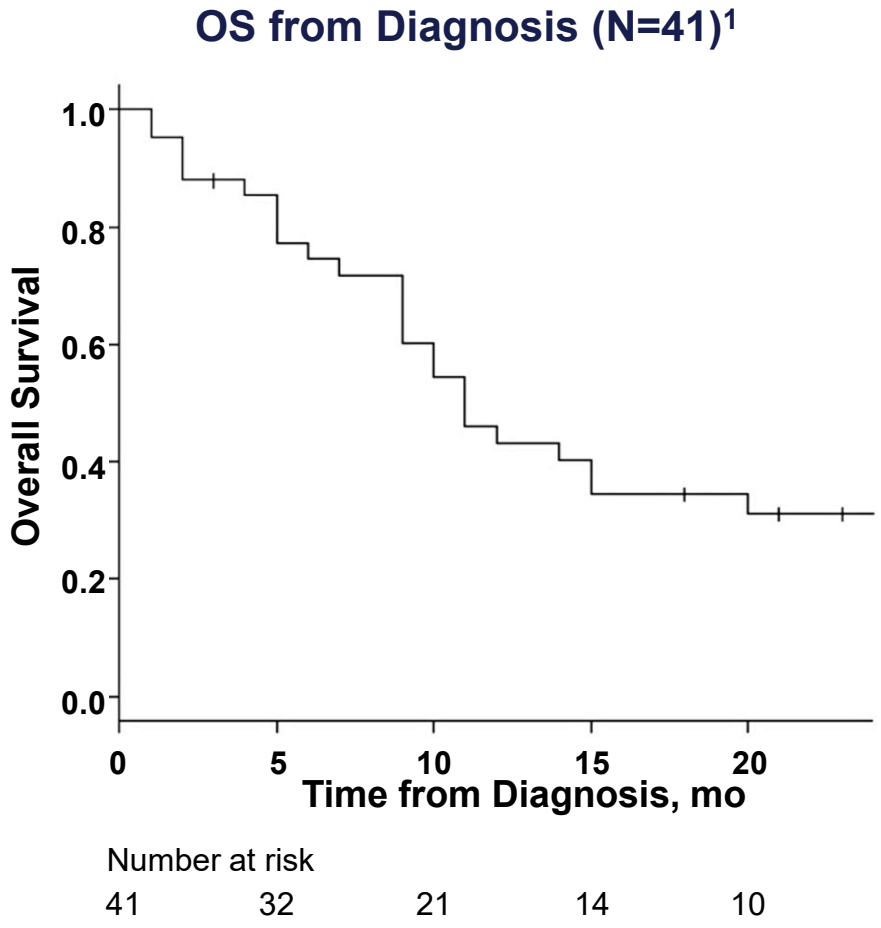
MLN With *FGFR1* Rearrangement Is an Extremely Rare and Aggressive Hematologic Malignancy[1]

Epidemiology

- No published estimates of incidence or prevalence
- Median age at onset is 46 years (range, 0-87 years)[1]
- Slight male predominance (sex ratio, 1.2:1)[1,2]

Clinical Course

- Aggressive natural course with poor prognosis[1-4]
- May present as, or progress within 1 to 2 years to, blast phase/secondary acute leukemia[1,3-5]
- 1-year OS after diagnosis is 43.1%[1]



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Mo, months; OS, overall survival.

1. Umino K, et al. *Hematol*. 2018;23:470-477. 2. Jackson CC, et al. *Human Pathol*. 2010;41:461-476. 3. Vega F, et al. *Am J Clin Pathol*. 2015;144:377-392. 4. Reiter A, Gotlib J. *Blood*. 2017;129:704-714. 5. Strati P, et al. *Leuk Lymphoma*. 2018;59:1672-1676.

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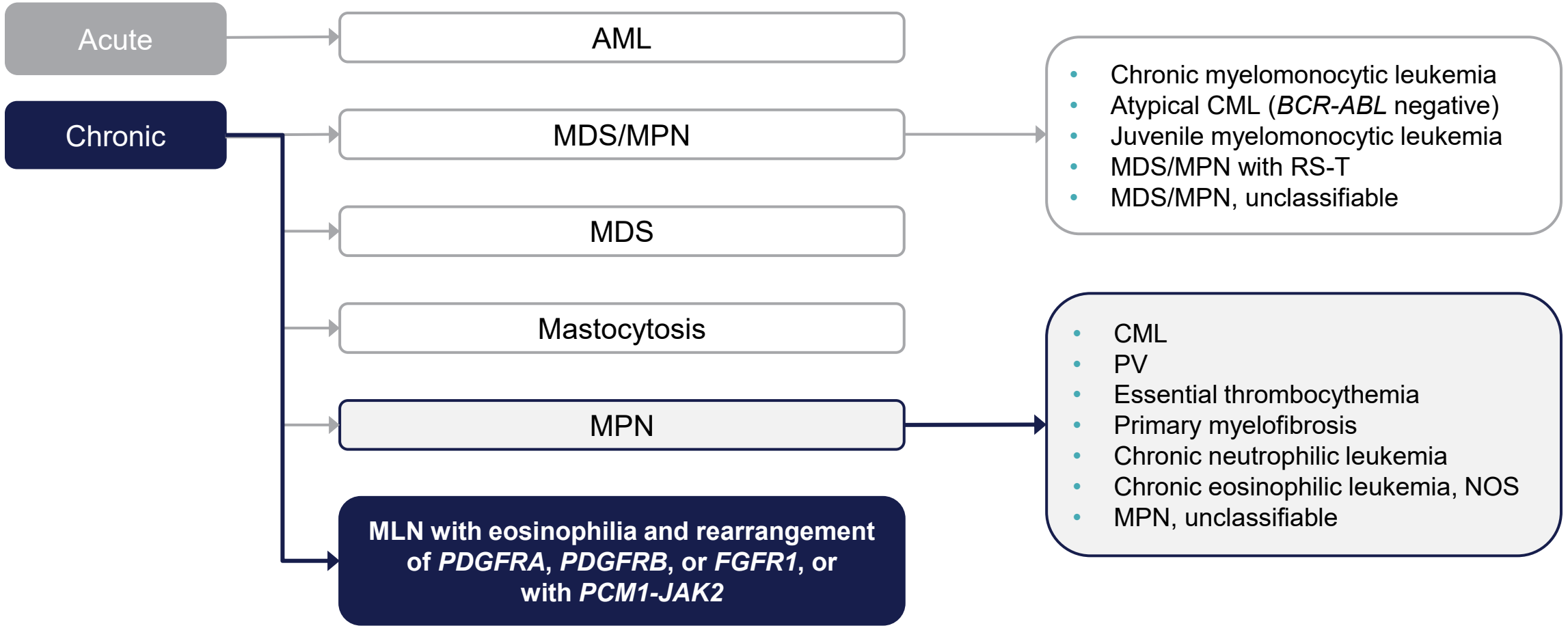
MLN With *FGFR1* Rearrangement Is Included in the 2016 WHO Classification of Myeloid Neoplasms and Acute Leukemia



ABL, Abelson murine leukemia; AML, acute myeloid leukemia; BCR, breakpoint cluster region; CML, chronic myeloid leukemia; JAK2, Janus Kinase 2; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; NOS, not otherwise specified; PCM1, pericentriolar material 1; PDGFRA, platelet-derived growth factor receptor α; PDGFRB, platelet-derived growth factor receptor β; PV, polycythemia vera; RS-T, ring sideroblasts and thrombocytosis; WHO, World Health Organization.

Arber D, et al. *Blood*. 2016;127:2391-2405.

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Identification of MLN With *FGFR1* Rearrangement Requires High Levels of Clinical Suspicion

- Clinical phenotypes are highly heterogeneous; as such, patients may present with chronic phase or acute (blast phase) disease[1-3]
- Patients may present asymptomatically with an incidental finding of abnormal blood counts[4]
- Eosinophilia has been noted in up to 85% of cases reported in the literature[4]

Frequencies of Reported Signs and Symptoms at Presentation[4]

Organomegaly	Systemic Symptoms (n=40)	Lymphadenopathy (n=46)
• 58% splenomegaly (23/40) • 32% hepatomegaly (12/37) • 28% hepatosplenomegaly[a]	• 35% fatigue • 28% night sweats • 18% weight loss • 13% fever	• 48% generalized • 15% localized

[a] Number of patients assessed for hepatosplenomegaly not defined.

NCCN, National Comprehensive Cancer Network.

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes. V.2.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed September 2023. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 2. Bain BJ. *Haematologica*. 2010;95:696-698. 3. Strati P, et al. *Leuk Lymphoma*. 2018;59:1672-1676. 4. Jackson CC, et al. *Human Pathol*. 2010;41:461-476.

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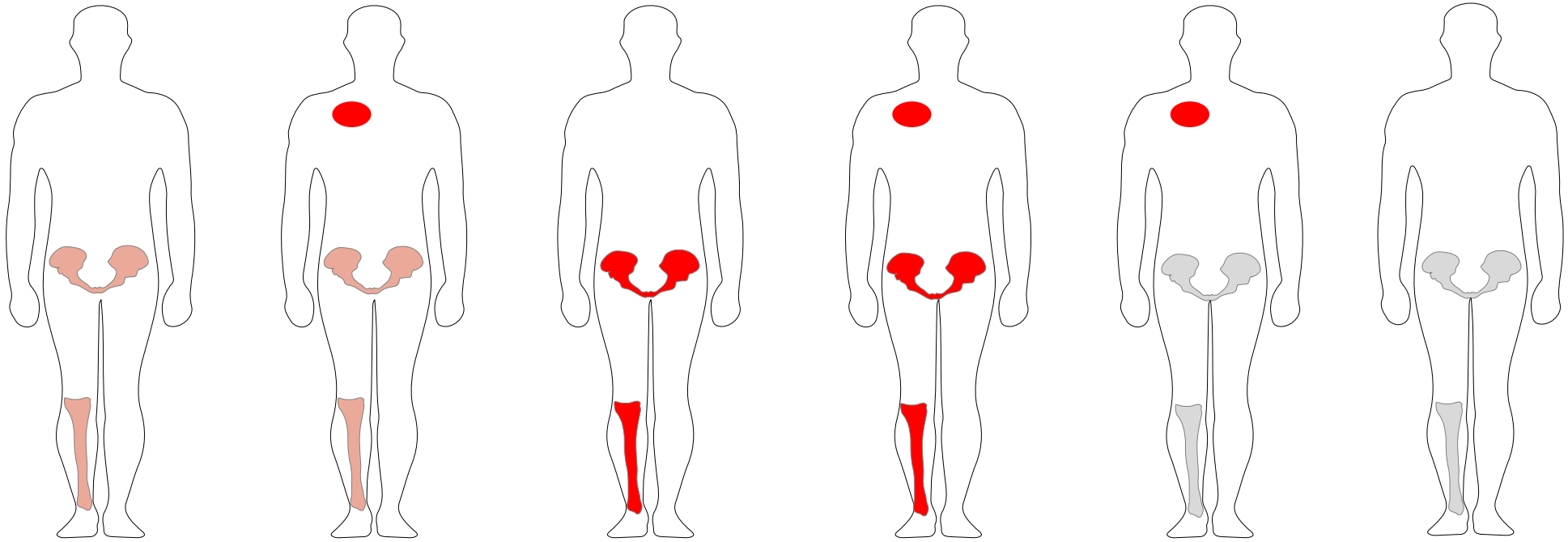
Categories of Presentation of MLN With *FGFR1* Rearrangement[1]



BM/PB: **Chronic phase** without EMD

BM/PB: **Chronic phase** with **EMD**

BM/PB: **Blast phase** without EMD

BM/PB: **Blast phase** with **EMD**

EMD only

No morphologic or radiologic evidence of disease but with cytogenetic/FISH or molecular evidence of *FGFR1* rearrangement

Patients may present with BM involvement only, EMD only, or BM plus EMD[2-4]

BM, bone marrow; BP, blast phase; EMD, extramedullary disease; FISH, fluorescence in situ hybridization; MPAL, mixed-phenotype acute leukemia; PB, peripheral blood.

1. Gotlib J, et al. ASH 2021. Oral presentation 385. 2. Macdonald D, et al. *Leukemia.* 1995;9:1628–30. 3. Reiter A and Gotlib J. *Blood.* 2017;129:704–14. 4. Arber DA, et al. *Blood.* 2016;127:2391–405.

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Role of *FGFR1* Rearrangements in Pathogenesis

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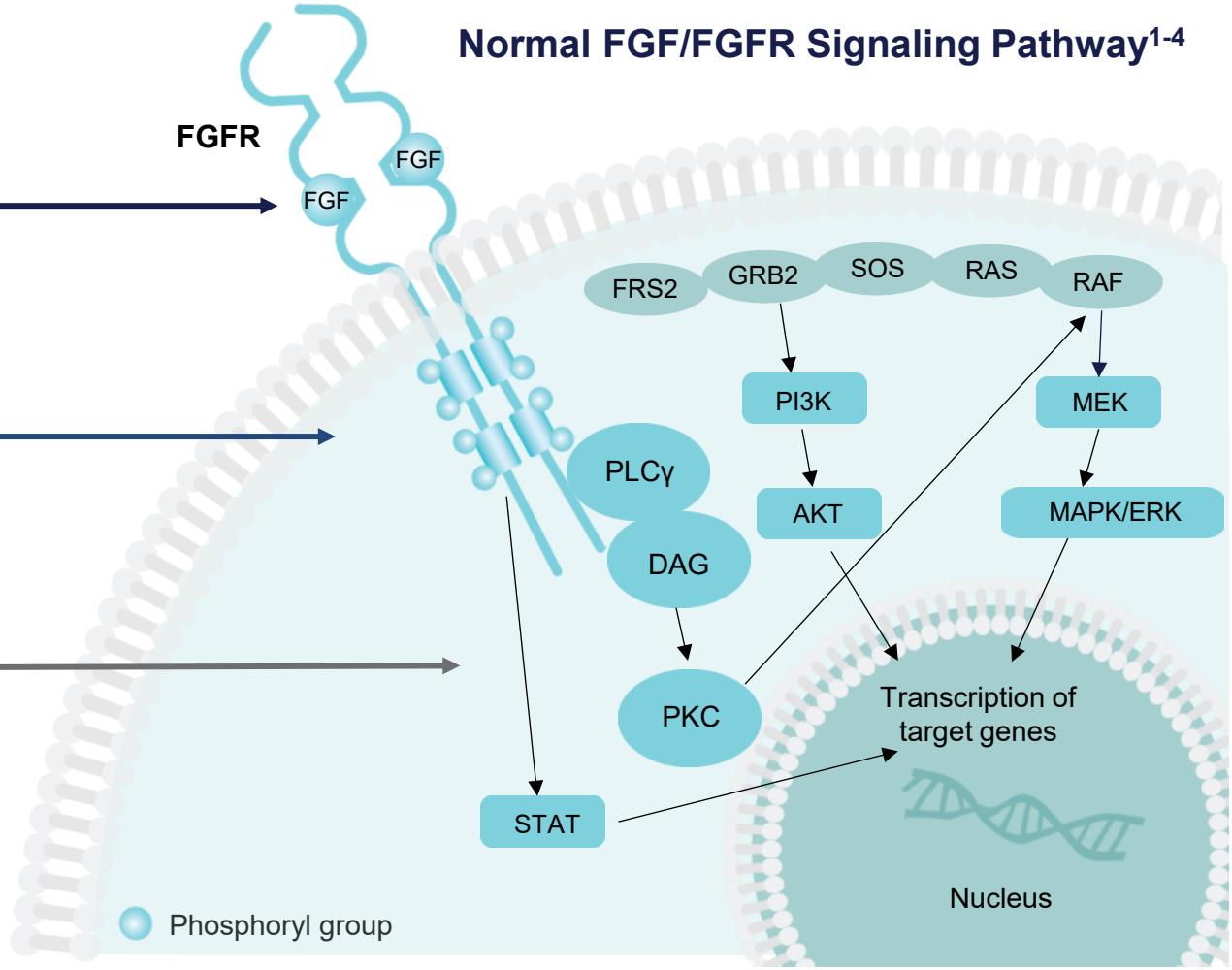
The FGF/FGFR Signaling Pathway Plays a Central Role in Multiple Cellular Processes[1-3]

Binding of FGF ligands (FGF1 to FGF23) to their cognate FGF receptors (FGFR1 to FGFR4) leads to receptor dimerization[1,2]

Receptor dimerization induces cross-phosphorylation and activation of the FGFR kinases[1-3]

FGFR kinases activate downstream signaling pathways implicated in cellular processes such as proliferation, survival, migration, and angiogenesis[1,2]

Normal FGF/FGFR Signaling Pathway[1-4]



AKT, protein kinase B; DAG, diacylglycerol; ERK, extracellular signal-regulated kinase; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; FGFR4, fibroblast growth factor receptor 4; FRS2, fibroblast growth factor receptor substrate 2; GRB2, growth factor receptor-bound protein 2; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PLCγ, phospholipase C-gamma; RAF, rapidly accelerated fibrosarcoma kinase; RAS, rat sarcoma GTPase; SOS, son of sevenless; STAT, signal transducer and activator of transcription.

1. Babina IS, Turner NC. *Nat Rev Cancer*. 2017;17:318-332. 2. Turner N, Grose R. *Nat Rev Cancer*. 2010;10:116-129. 3. Sarabipour S, Hristova K. *Nat Commun*. 2016;7:10262. 4. Touat M, et al. *Clin Cancer Res*. 2015;21:2684-2694.

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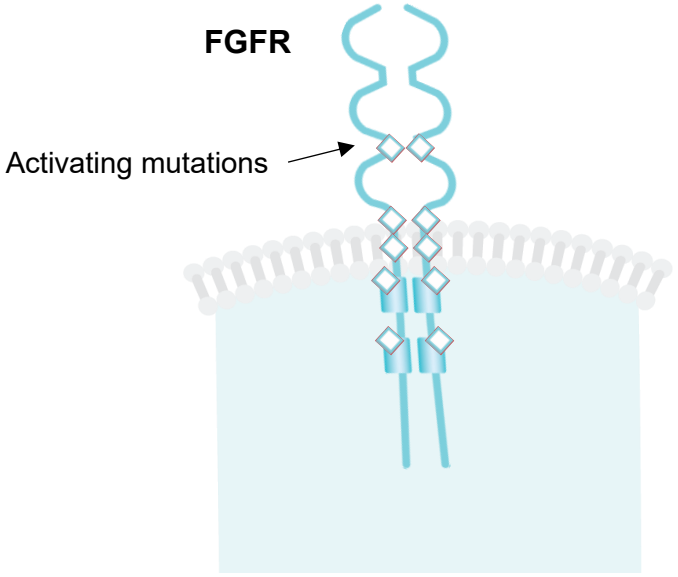
Dysregulation of FGFR Signaling Is Implicated in Tumorigenesis

- Aberrant FGFR signaling mediates tumorigenesis by enhancing cellular proliferation, migration, survival, invasion, and angiogenesis[1,2]

Different genomic alterations may result in tumorigenic FGFR signaling[1]:

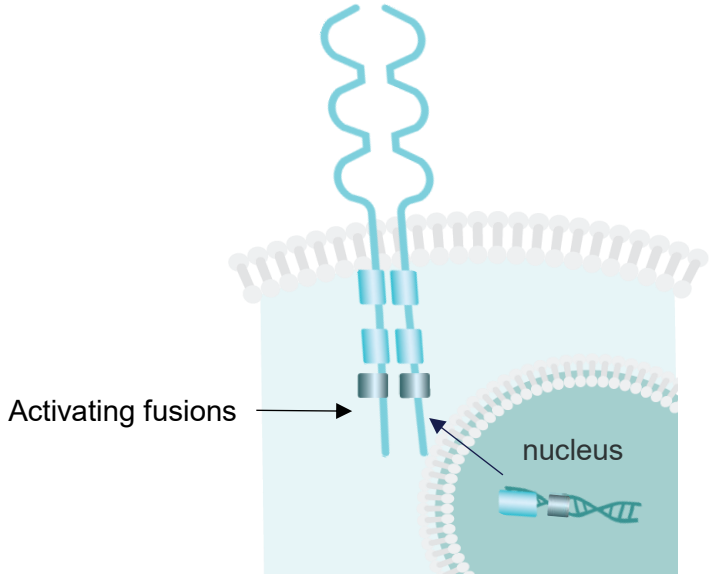
Activating Mutations

Leading to constitutive activation of the kinase domain or ligand-independent receptor dimerization



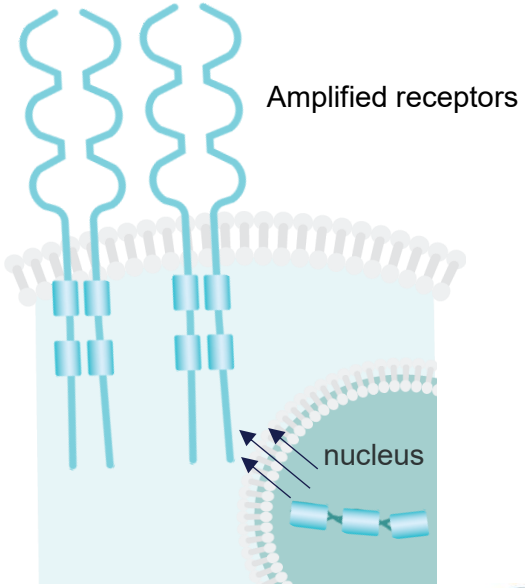
Chromosomal Rearrangements

Translocations resulting in gene fusions that allow ligand-independent receptor dimerization



Gene Amplification

Inducing protein overexpression, receptor accumulation and activation of downstream signaling pathways



1. Babina IS, Turner NC. *Nat Rev Cancer*. 2017;17:318-332. 2. Turner N, Grose R. *Nat Rev Cancer*. 2010;10:116-129.

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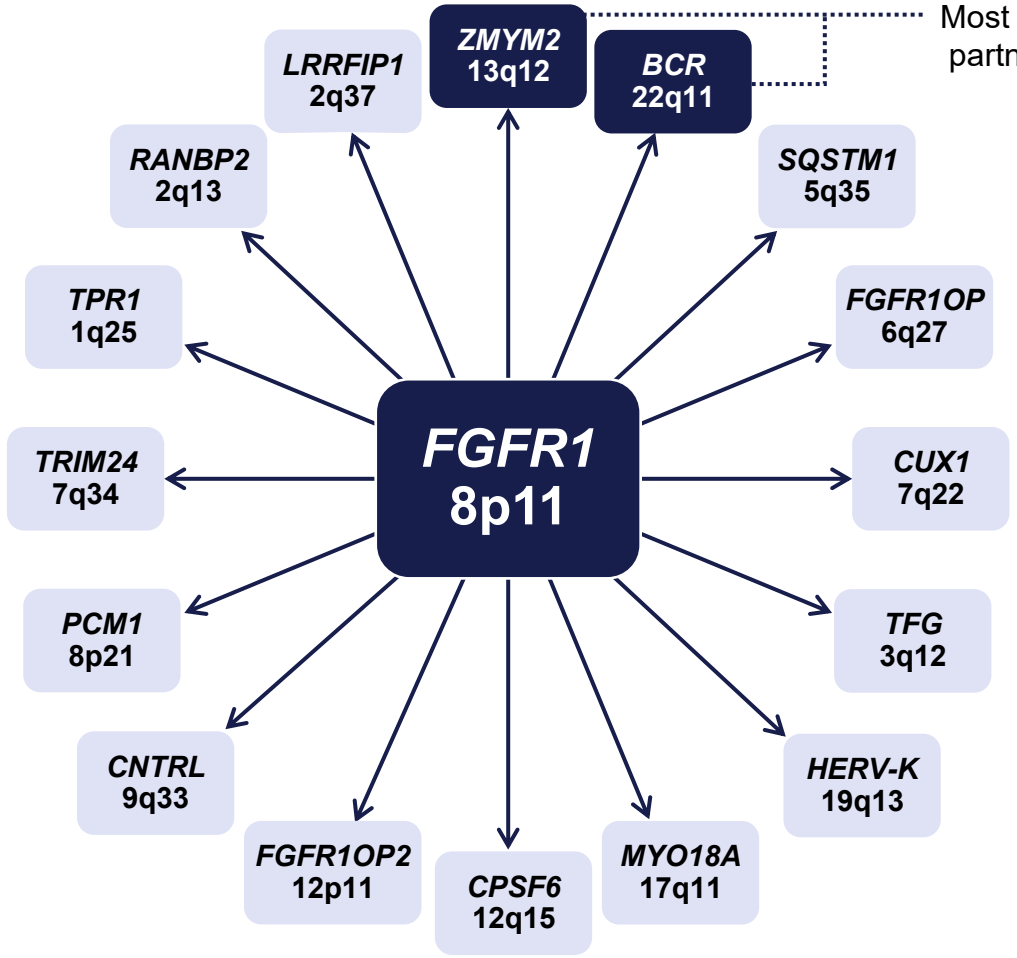
MLN With *FGFR1* Rearrangement: Cytogenetics and Molecular Genetics

- *FGFR1* rearrangements lead to the expression of aberrant tyrosine kinases[1]
- Translocations at chromosome band 8p11 result in constitutive activation of *FGFR1* with the most common translocations sites including:[2]
  - t(8;13)(p11;q12)
  - t(8;22)(p11;q11)
- Translocations are usually identified with conventional cytogenetic analysis and can be confirmed with break-apart FISH[a]

16 Currently Known Fusion Partners of *FGFR1*[3]



CP, chronic phase; ZMYM2, zinc finger MYM-type containing 2.

[a] ***FGFR1* is NOT part of standard testing panels and must be specifically ordered.**

1. Babina IS, Turner N. *Nat Rev Cancer.* 2017;17:318-332. 2. Jackson CC, et al. *Hum Pathol*. 2010;41:461-476. 3. Reiter A, Gotlib J. *Blood.* 2017;129:704-714

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Summary

- MLN with *FGFR1* rearrangement is an aggressive hematologic malignancy with poor prognosis[1]
  - 1-year OS after diagnosis is 43.1%[1]

- Diagnosis is challenging, with highly heterogeneous clinical phenotypes[2,3,4]
  - Patients may present with chronic phase disease, acute (blast phase) disease, or asymptomatically[2,3,4]
  - Evaluation of hypereosinophilia, often associated with myeloid and/or lymphoid neoplasms, can help facilitate a diagnosis[5]

- *FGFR1* rearrangements can lead to fusions with 16 known genes, leading to aberrant expression of tyrosine kinases[2,6]
  - *ZMYM2* and *BCR* are the most common fusion partners[2]

1. Umino K, et al. *Hematol*. 2018;23:470-477. 2. Jackson CC, et al. *Human Pathol*. 2010;41:461-476. 3. Bain BJ. *Haematologica*. 2010;95:696-698. 4. Strati P, et al. *Leuk Lymphoma*. 2018;59:1672-1676. 5. Reiter A, Gotlib J. *Blood.* 2017;129:704-714. 6. Babina IS, Turner N. *Nat Rev Cancer.* 2017;17:318-332.

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