The Research Roadmap Roundup

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Topics to be covered -

• What is unique about Waldenström macroglobulinemia?
  – What do we still need to know?

• What is the WM Roadmap?
  – Why do we need one?

• How will supporting the Roadmap help?
  – Will it improve the future?
Waldenström macroglobulinemia
“A disease with two problems”

Lymphoplasmacytic infiltrate
Monoclonal IgM protein

Gertz et al. The Oncologist 2000;5:63-67
Waldenström macroglobulinemia
Morphology and Immunophenotype

- Lymphoplasmacytic infiltrate (usually intertrabecular)
- Immunophenotype - surface IgM+, CD19+, CD20+, CD79a+ and PAX5+. CD5−, CD10−, CD23−.
- MYD88 L265P is the most common genetic abnormality seen
- del(6)(q21) and CXCR4 mutations are also seen

Waldenström macroglobulinemia
Monoclonal IgM

Symptoms related to the monoclonal IgM protein are attributable to –

– its characteristics in the circulation,

– its interaction with various body tissues when deposited,

– and its autoantibody activity.
Hyperviscosity due to Waldenström macroglobulinemia
IgM deposition due to Waldenström macroglobulinemia
Autoimmune hemolysis secondary to Waldenström macroglobulinemia
What are the Knowledge Gaps in Waldenström macroglobulinemia?
The WM Roadmap Identified 4 “Knowledge Gaps”

- Signaling
- ‘-omics’ – genomics, epigenomics, proteomics
- Immunology
- Bone marrow microenvironment
Signaling in WM and why it matters
Omics in WM and why it matters
Genomics, Epigenomics, Proteomics, Metabolomics
"According to all our tests, your immune system is 'out to lunch'!"
Getting the Immune System to target WM
Bone marrow microenvironment and why it matters

“A man is known by the company he keeps”
- Aesop
Bone Marrow supports WM growth but offers many Therapeutic Targets
How does this research and the WM Roadmap affect me?
MyD88 L265P mutations are almost universal in Waldenström macroglobulinemia

- Whole genome sequencing in 30 patients – MYD88 L265P mutation found in 27/30.
- High frequency confirmed in 49/54 additional cases (91%)
- Rarely expressed in myeloma, MZL, or IgM MGUS

CXCR4 mutations in Waldenström macroglobulinemia in 40%

A

MEGISIYTSDNYTEEMGSGDYDSMKPECFREENANFNIKFLPTLYSIIFLTGIVGNGLVILVMGYQKKLRSMTDKYRLHLSVADLLFVTLPFWAVDAVANWYFGNFLCKAVHVIYTVNLYSSVLILAFSLDRYLAIVHATNSQRPRKLLAEKVYYVGYWIPALLLTIPDFIANVS

EADDRIICDRFRPNLWVVVFQFQHHMVGLILPGIVLSCYCIIS

KLSHSGKGRKQRKALKTTVILIAFFACWLPYYIGISIDSFILLEIIEKQGCEFENTVHKWISITEALAFFHCCLNPILYAFLGAKFKIISAQHALTSMSRGSSLKLSKCKCCHSLSVSTTSESSSFHSS

LEGEND

A - Germline variant in WHIM syndrome
A - Transmembrane helix
- Somatic frame shift or nonsense WM variant

B

C

Frame shift mutation
Nonsense mutation

S338 Mutation Types

- Nonsense C/G: 21%
- Nonsense C/A: 25%
- Frame shift: 54%

Hunter et al. Blood 2014;123:1637-1646
Overall survival of 175 WM patients stratified by MYD88 and CXCR4 mutation status

Treon et al. Blood 2014;123:2791-2796
Ibrutinib in Waldenström macroglobulinemia

• 63 previously treated patients received 420 mg of oral ibrutinib daily for 2 years or until progression.
• ORR was 90.5%, with a major response rate (PR or better) of 73% and a median time to response of 4 weeks.
• 2-year progression-free and overall survival rates among all patients were 69.1% and 95.2%, respectively.
• Toxicities > grade 2 - thrombocytopenia; neutropenia; atrial fibrillation and epistaxis.
Effect of MYD88 and CXCR4 Mutation Status on Ibrutinib-Related Changes in Serum IgM and Hemoglobin Levels

Bgb-3111 (a different BTK inhibitor) has activity in WM

Tam et al. Blood 2015
Therapeutic opportunities afforded by the biology of Waldenström macroglobulinemia
Approaches to prevent immune suppression or exhaustion
Modest Responses in WM with PD-1 blockade

- ORR in WM/MZL patients – 40% (2/5 - MR)
Thank you to all of you for supporting WM research!