RAF-Independent MEK1 Mutations Drive Histiocytic Neoplasms *In Vivo* and Are Sensitive to Single-Agent ERK Inhibition

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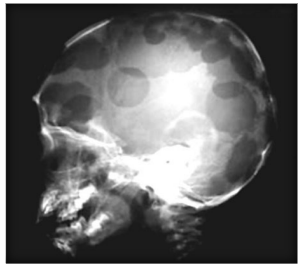
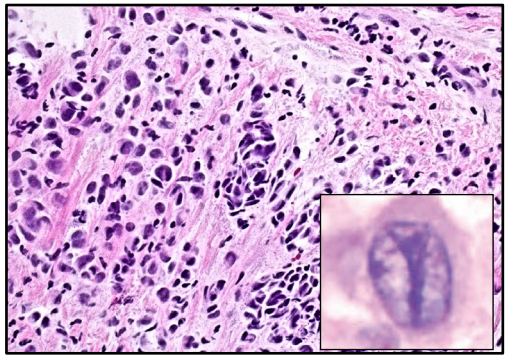
Erdheim-Chester Disease Medical Symposium
Mayo Clinic
Rochester, MN, USA
Thursday, April 27, 2023

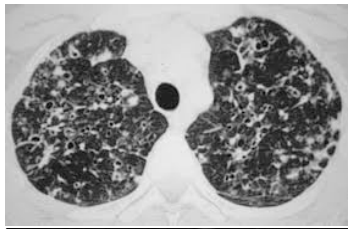
Overview of the Systemic Histiocytoses

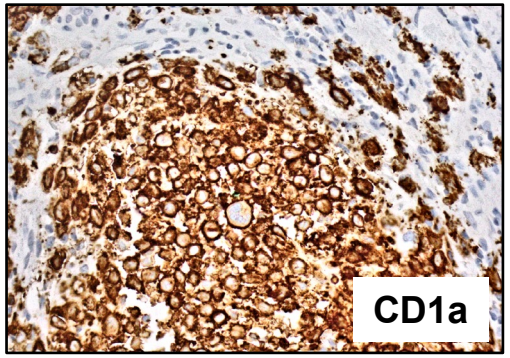
Disorders characterized by the accumulation of "histiocytes" (macrophage, dendritic cell, or monocyte-derived cells) in various tissues with a historicallypoorly characterized and obscure pathophysiology.

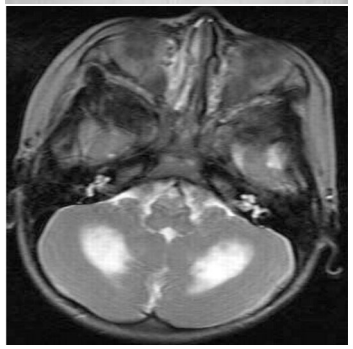
Langerhans Cell Histiocytosis (LCH)







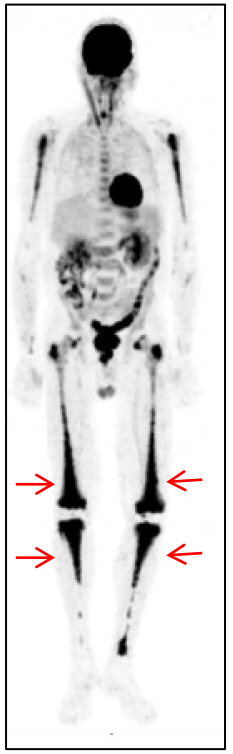


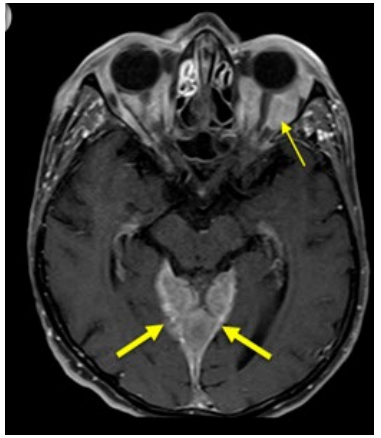


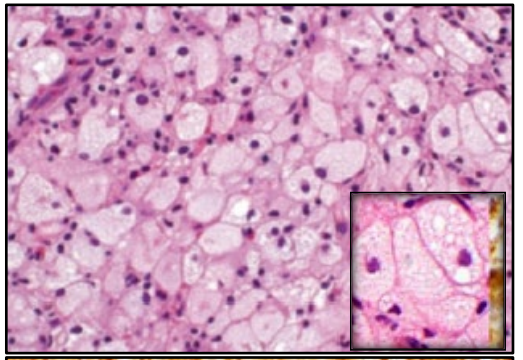
There has been extensive debate as to whether or not histiocytoses represented immunological or neoplastic conditions.

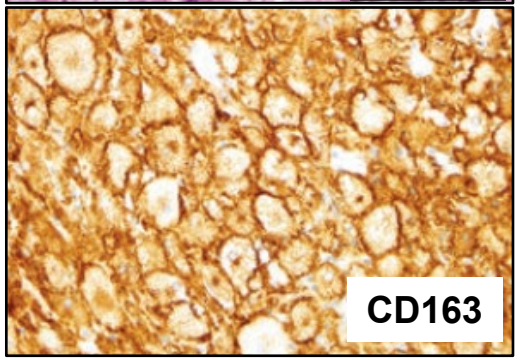
Non-Langerhans Cell Histiocytoses

- Erdheim-Chester Disease (ECD)
- Juvenile/Adult Xanthogranulomatosis (JXG/AXG)
- Rosai-Dorfman Disease (RDD)



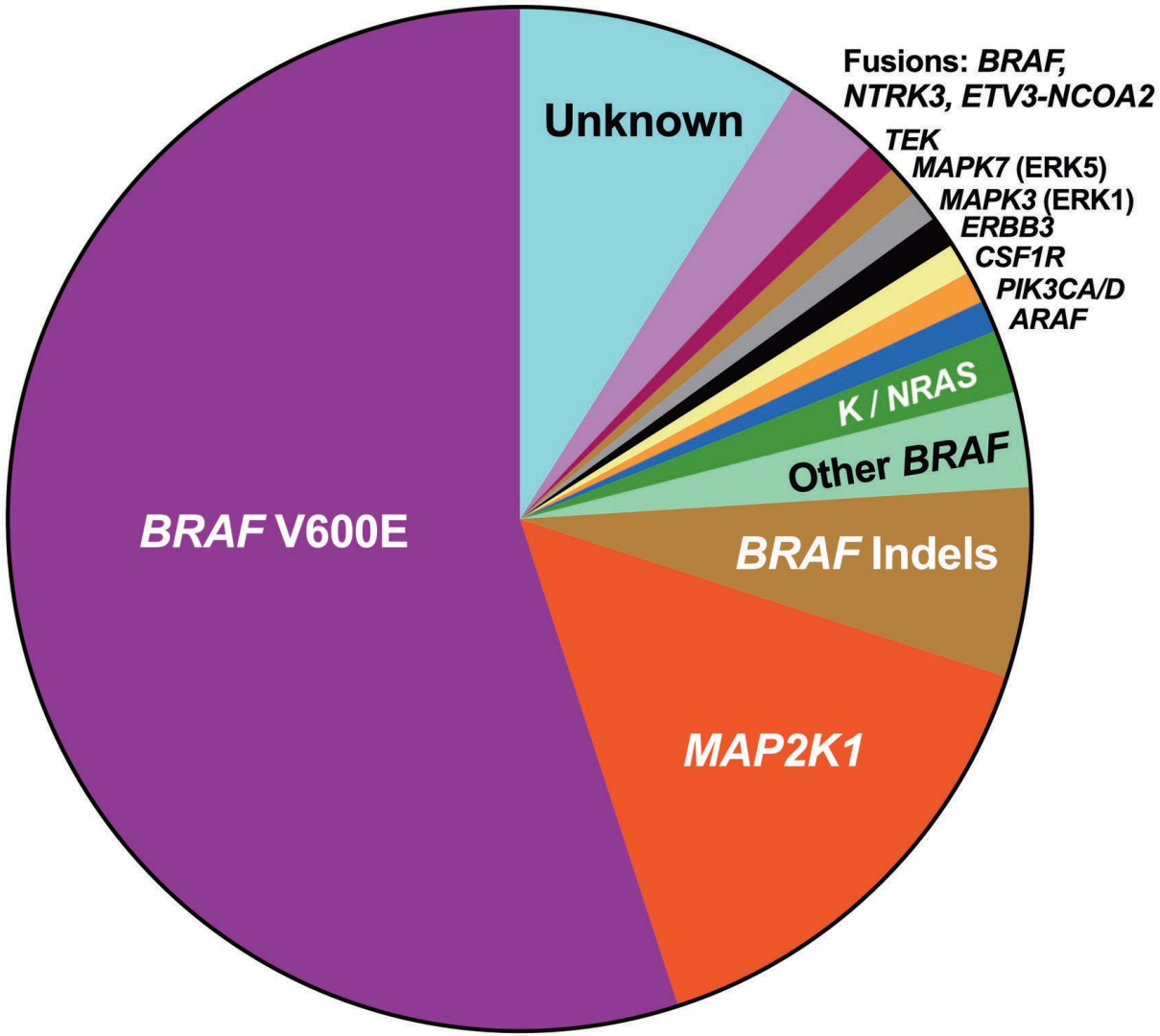




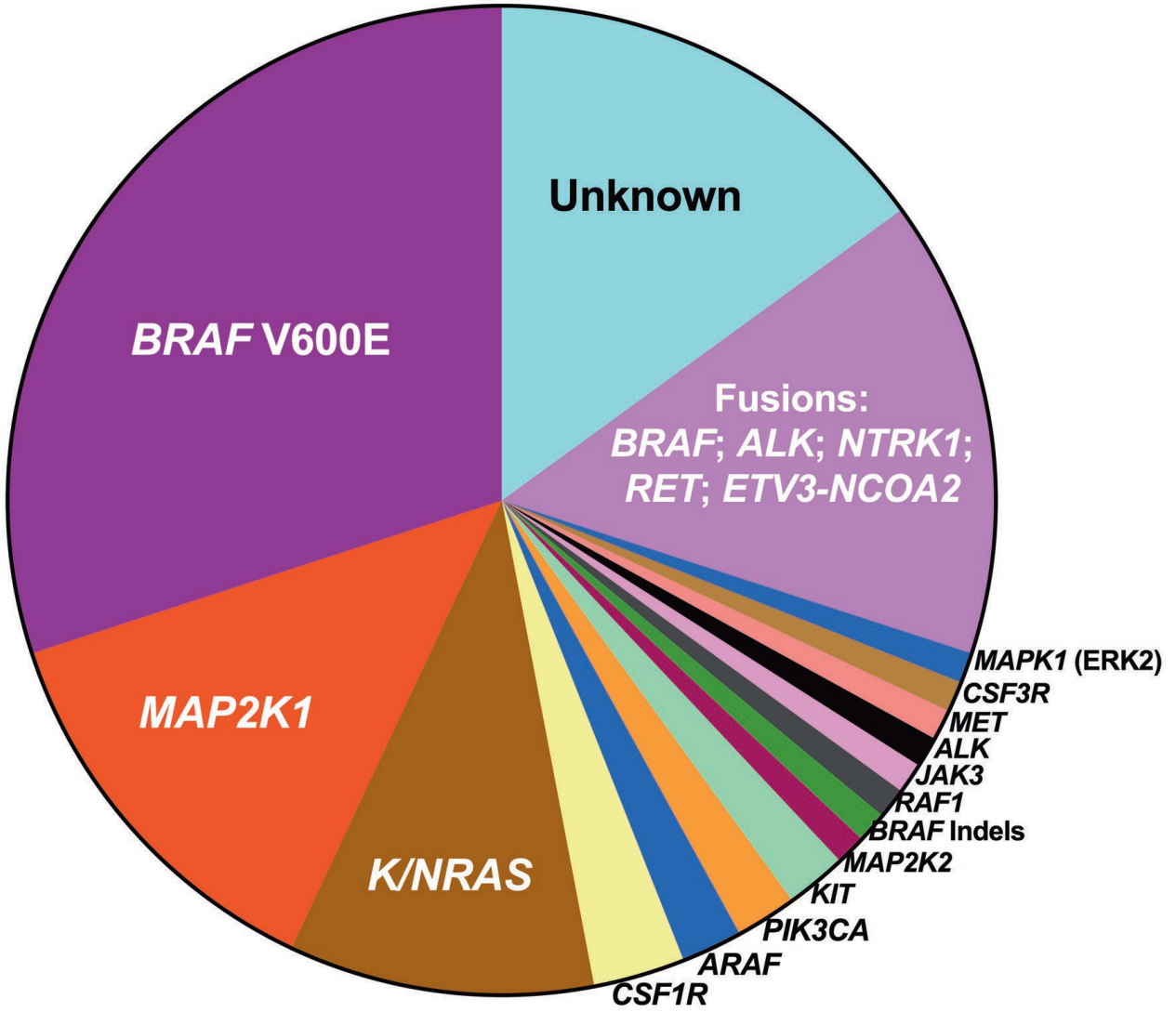


Kinase Alterations in the Histiocytoses as of 2022

Langerhans Cell HIstiocytosis



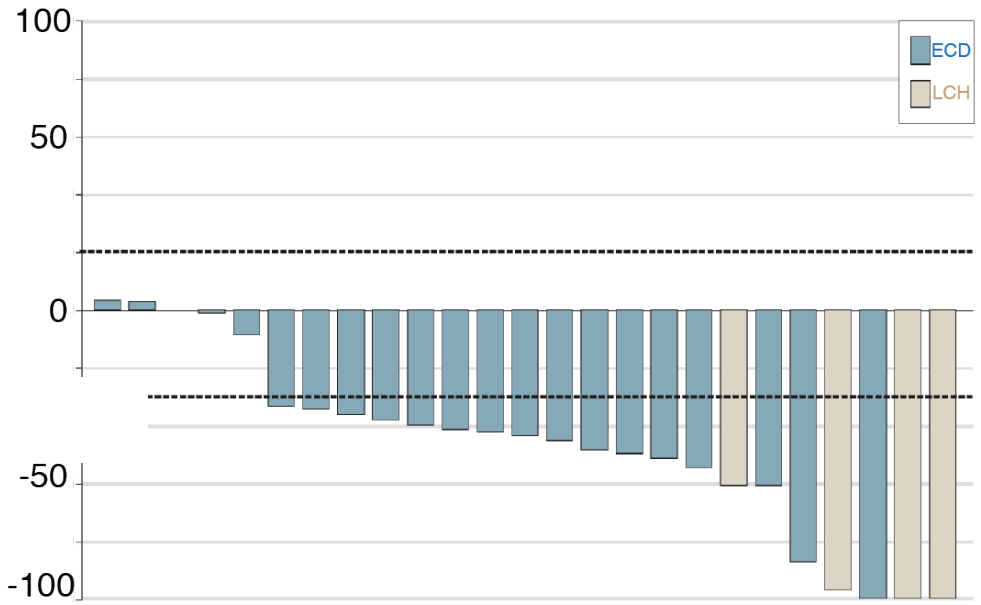
Non-Langerhans Cell HIstiocytosis



FDA-Approved Molecular Therapeutics of Histiocytic Neoplasms

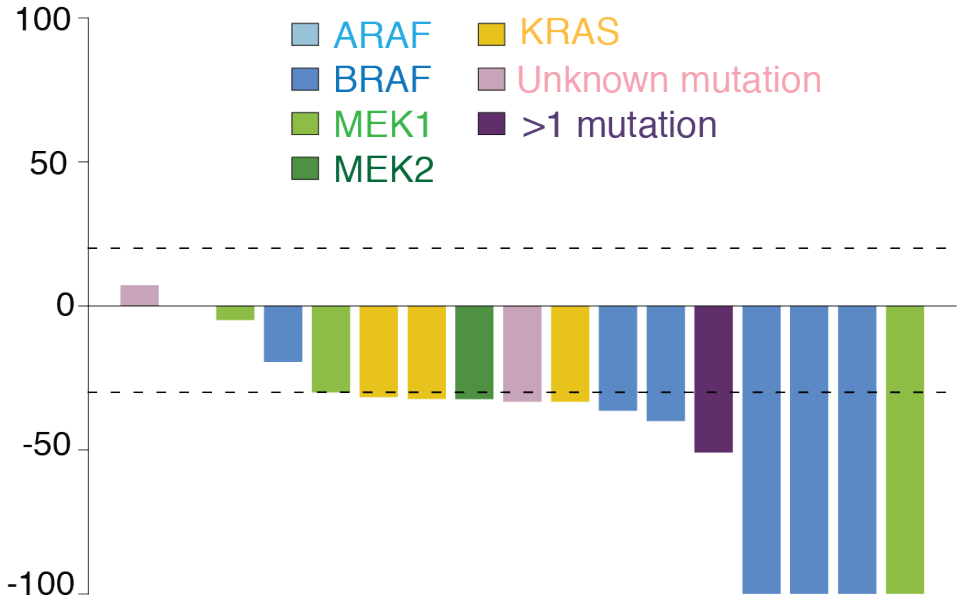
Vemurafenib for $BRAF^{V600}$-mutant histiocytosis

Best % change in sum of tumor size



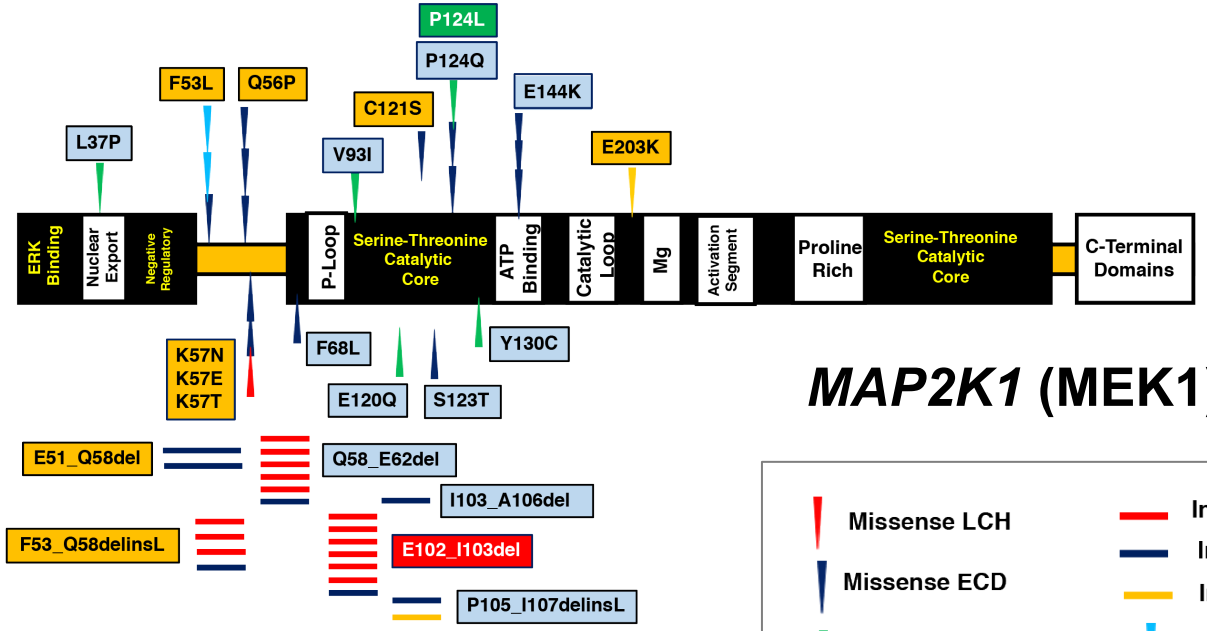
Vemurafenib was FDA approved for the treatment of BRAF V600-mutated ECD in 2017.

Cobimetinib for histiocytosis any genotype

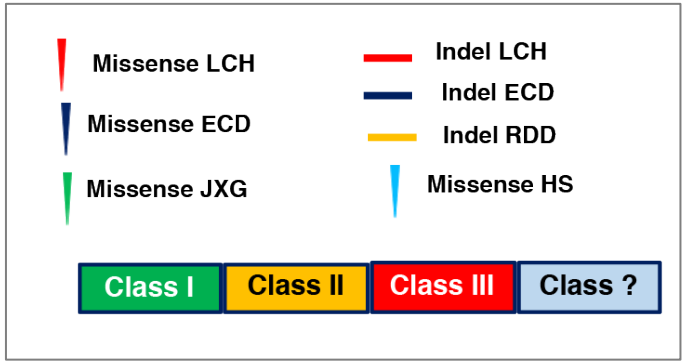


FDA approved cobimetinib in the treatment of BRAF V600-wild type histiocytic neoplasms on 11/02/2022.

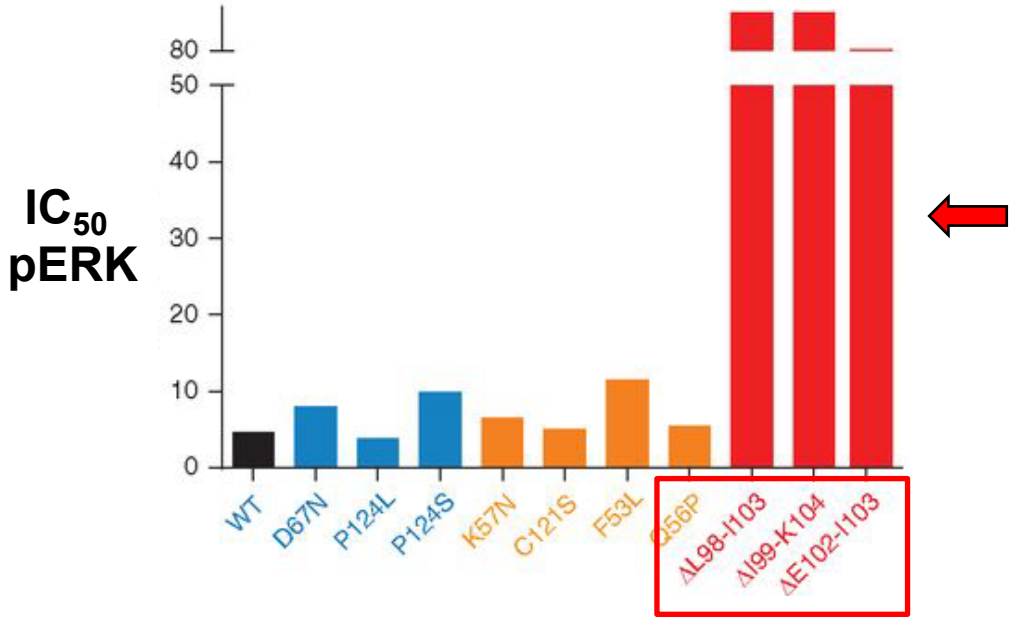
MEK1^{E102_I103del} mutations are RAF Independent & Resistant to Allosteric MEK Inhibitors (Trametinib; Cobimetinib)



***MAP2K1* (MEK1)**



Trametinib

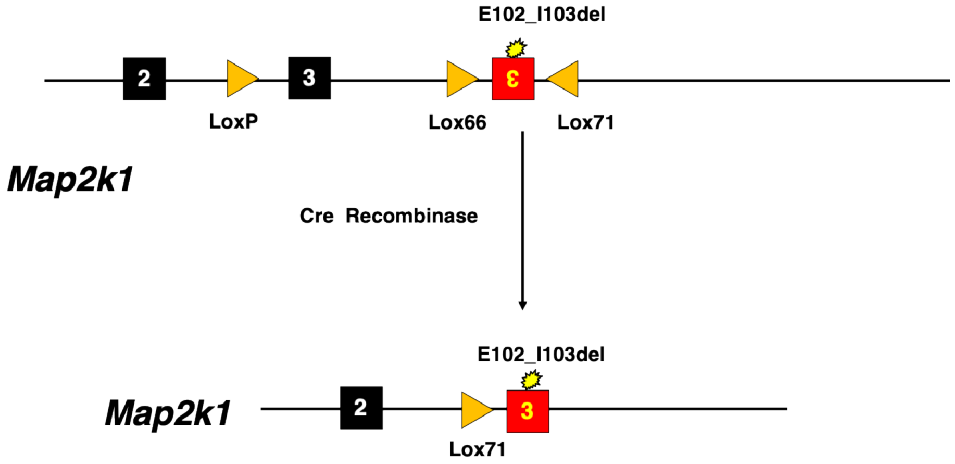


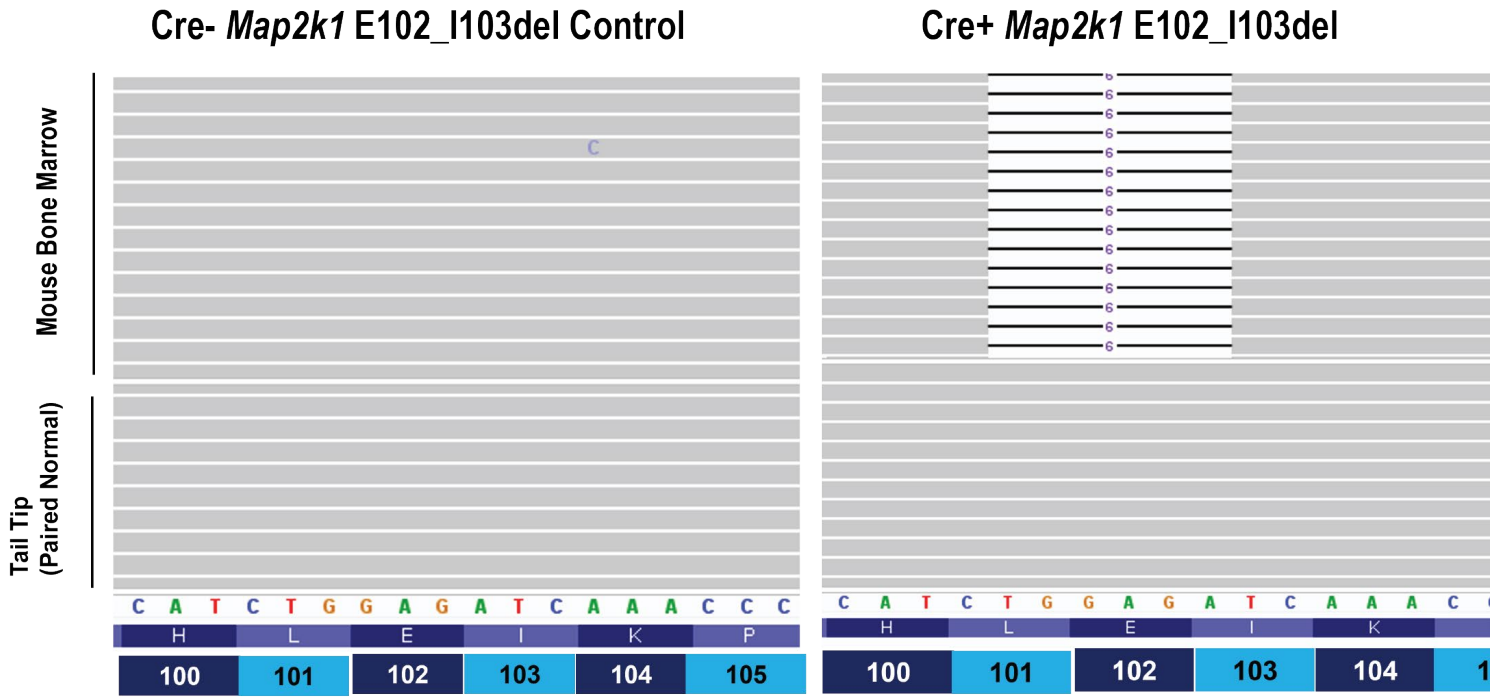
Gao, *et al. Cancer Discovery* 2018
Durham *et al.* unpublished

Research Questions

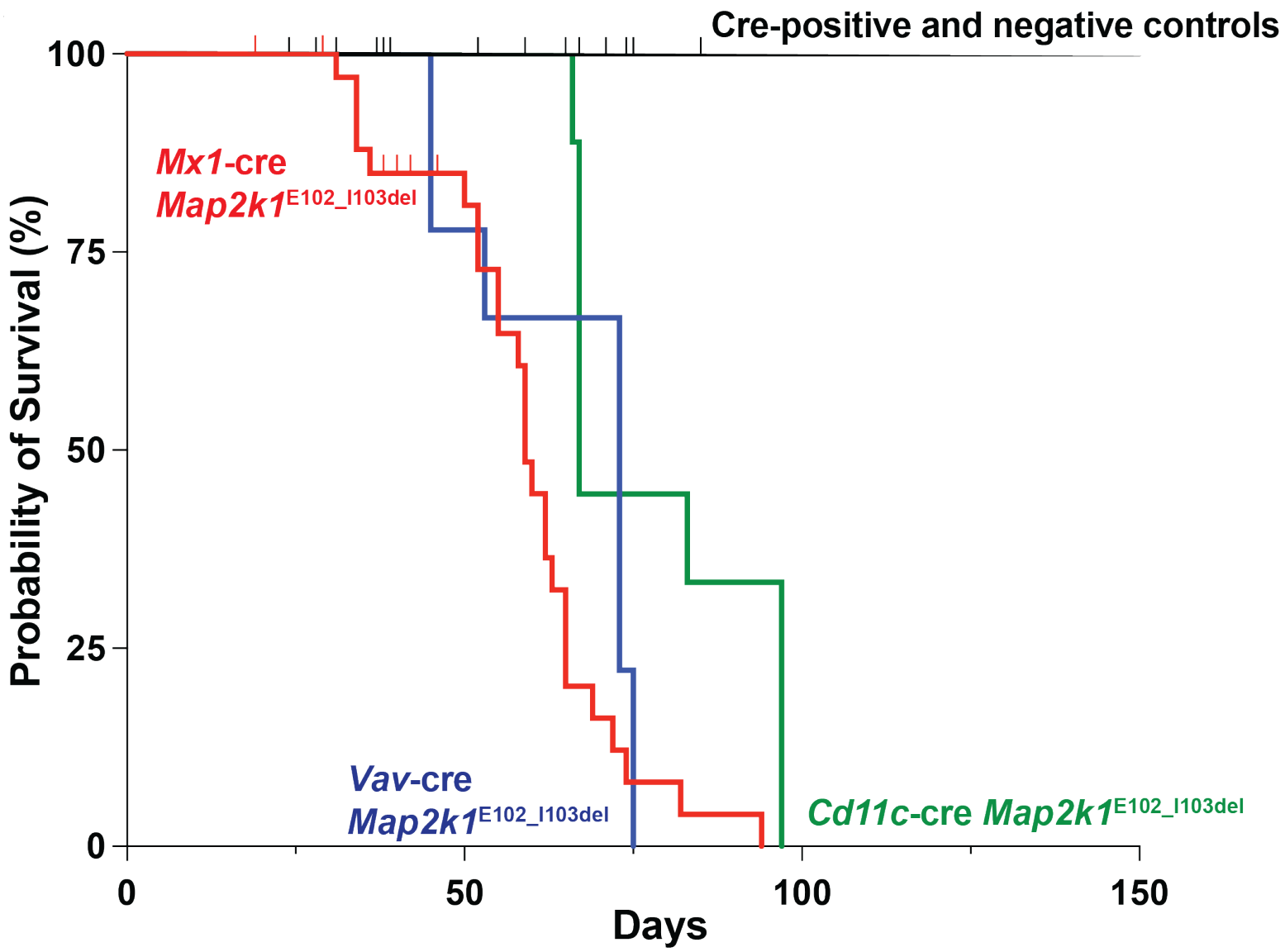
- Can MEK1 mutations drive histiocytosis development *in vivo*?
- What disease phenotypes emerge when MEK mutations are expressed at different stages of hematopoietic development (using *Mx1*-cre, *Vav1*-cre, and *CD11c*-cre promoters)?
- What is the best therapeutic approach for MEK1^{E102_I103del}-mutated histiocytoses & other class III MEK1/2 mutations?

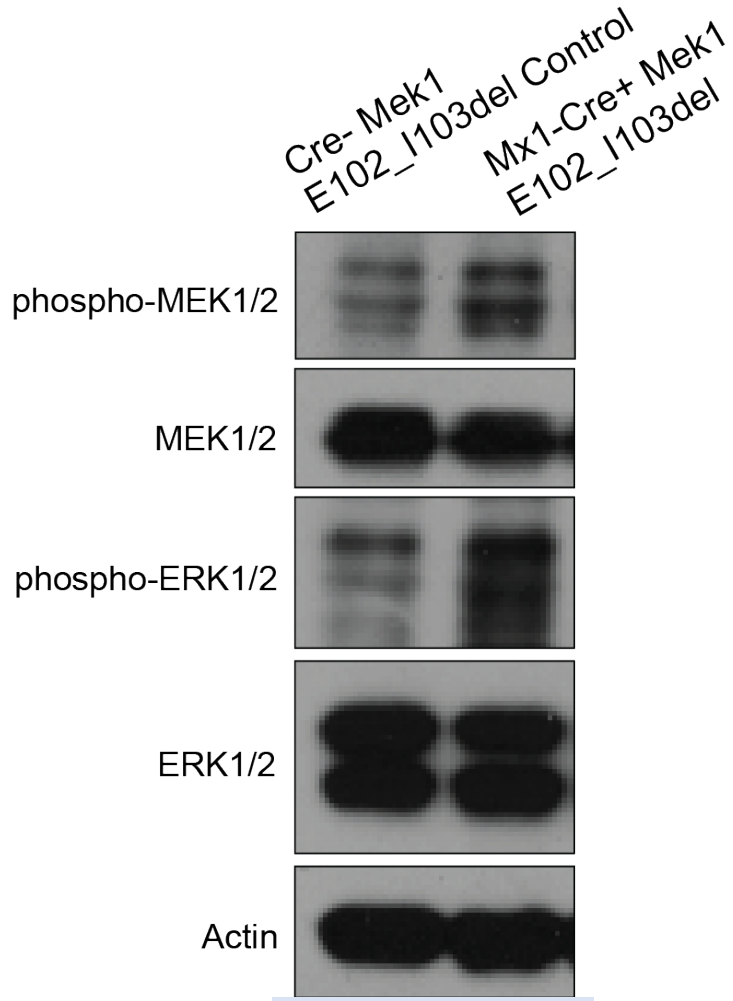
Map2k1 exon3 p.E102_I103 Present in Cre+ Conditional Knock-in Mice by Next-Generation Sequencing





MEK1 E102_I103del Model Survival Curves

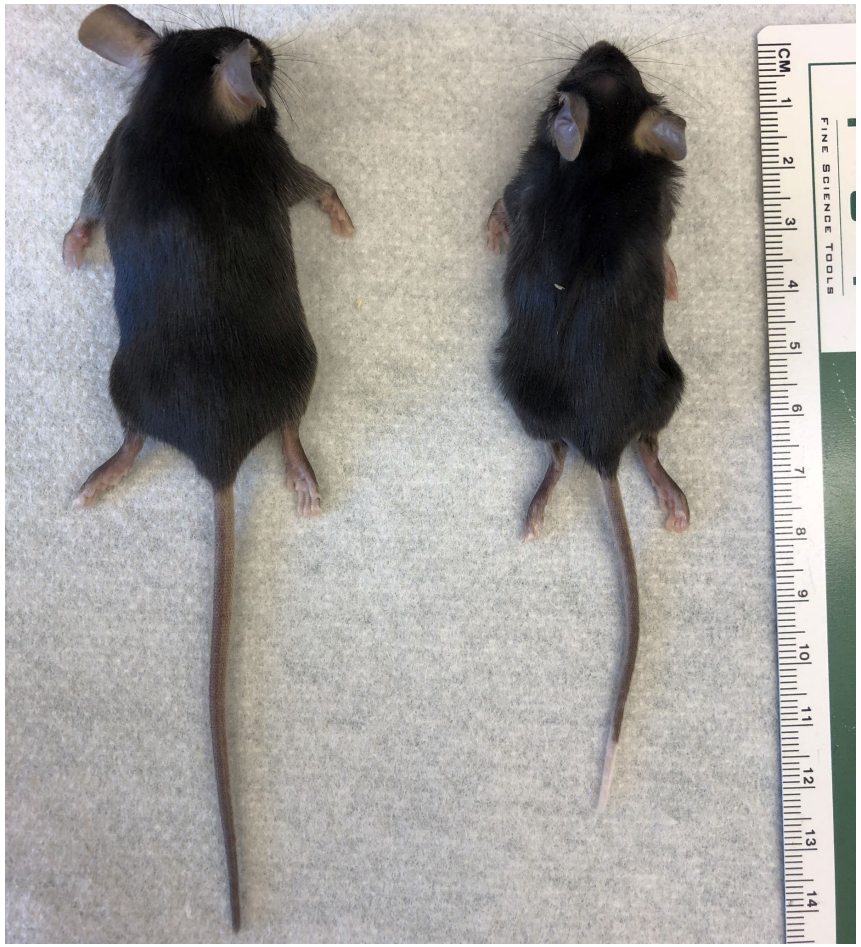




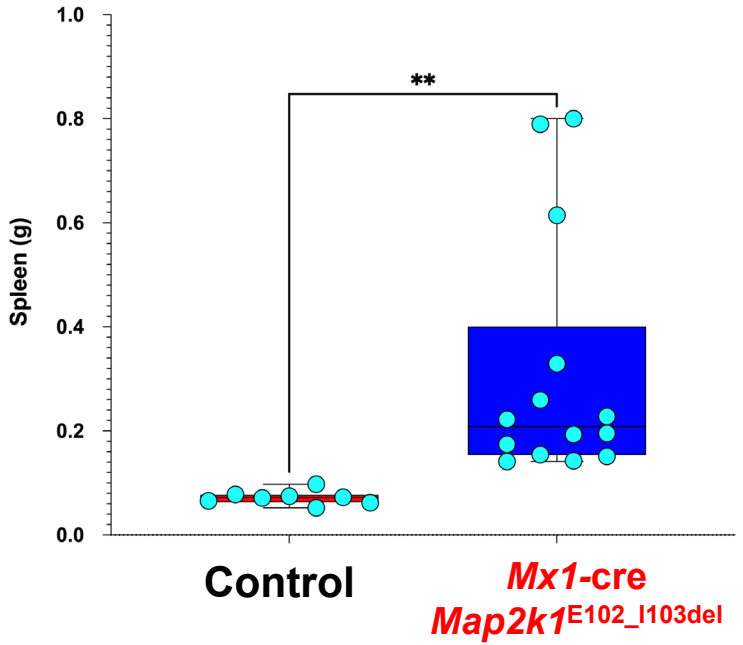
Western blot bone marrow

Primary *Mx1*-cre *Map2k1*$^{E102\_I103del}$ Mice are Smaller than Controls with Marked Splenomegaly

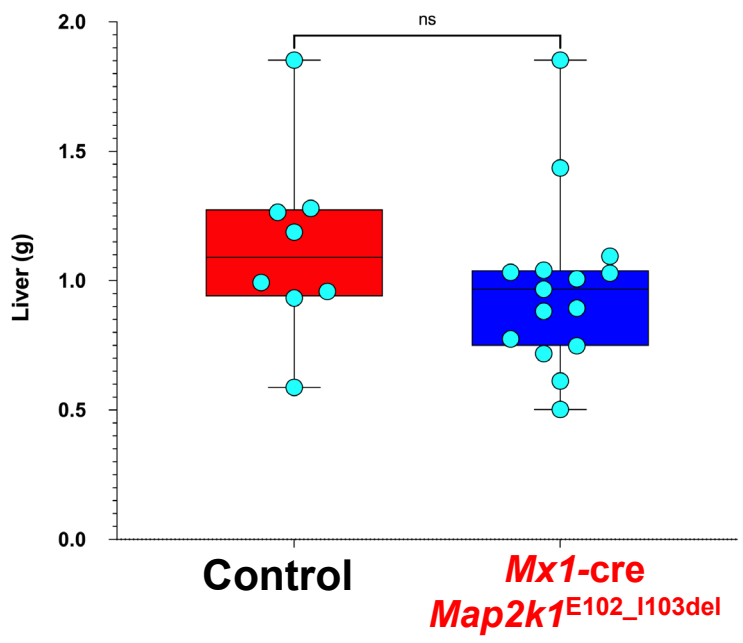
Control *Mx1*-cre *Map2k1*$^{E102\_I103del}$



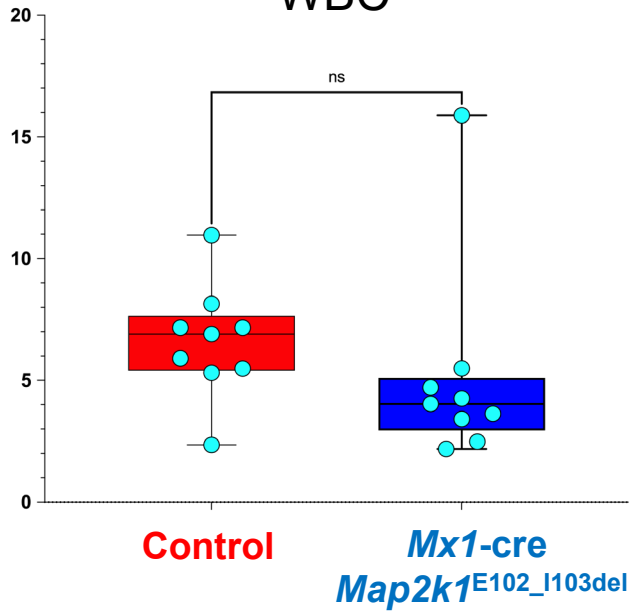
Control *Mx1*-cre *Map2k1*$^{E102\_I103del}$

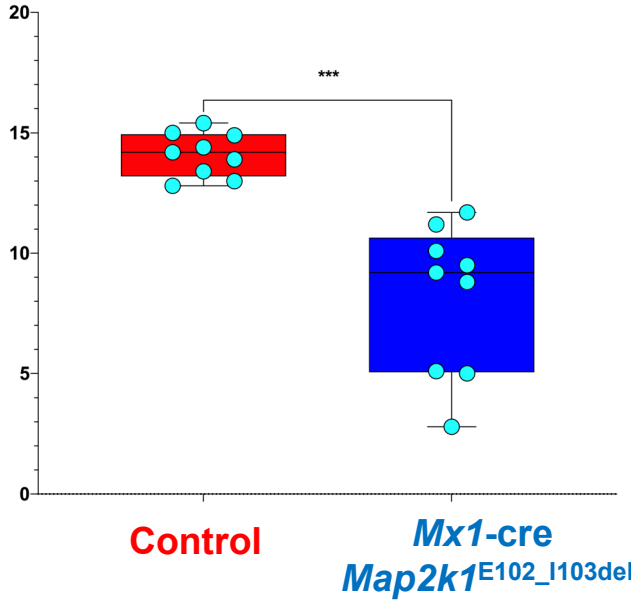


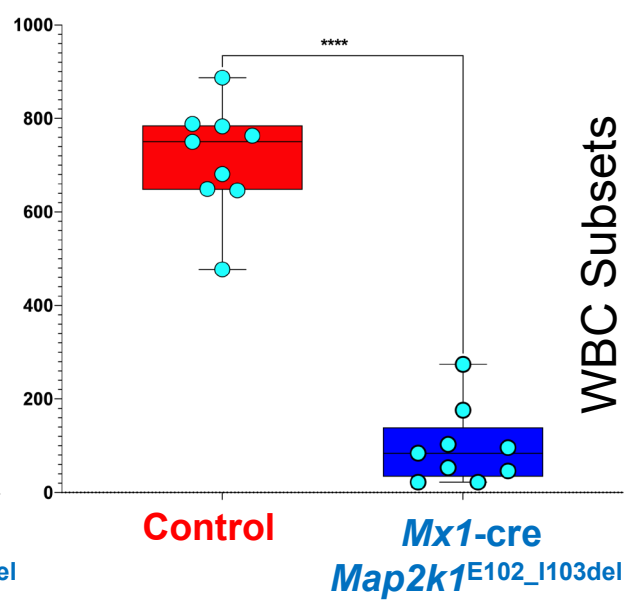
Control *Mx1*-cre *Map2k1*$^{E102\_I103del}$

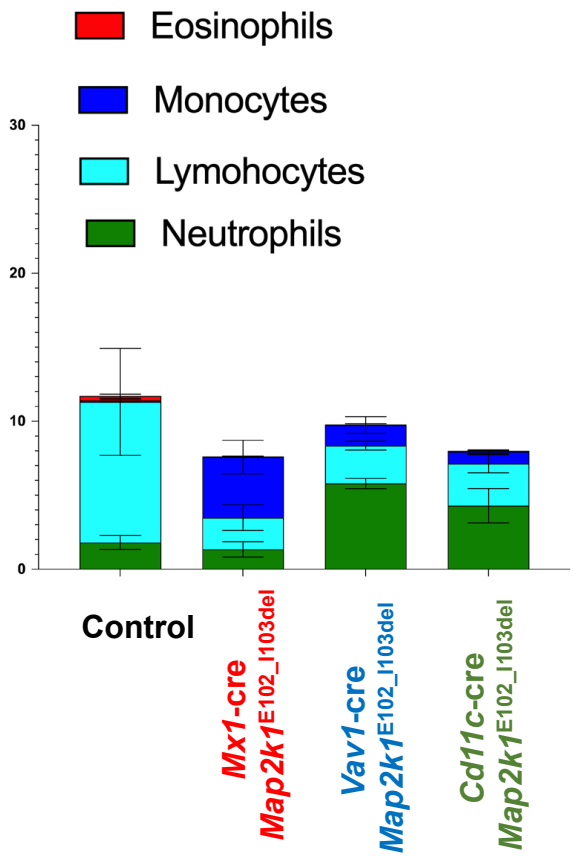


MEK1^{E102_I103del} Mice Have Anemia and Thrombocytopenia with Myelomonocytic Expansion







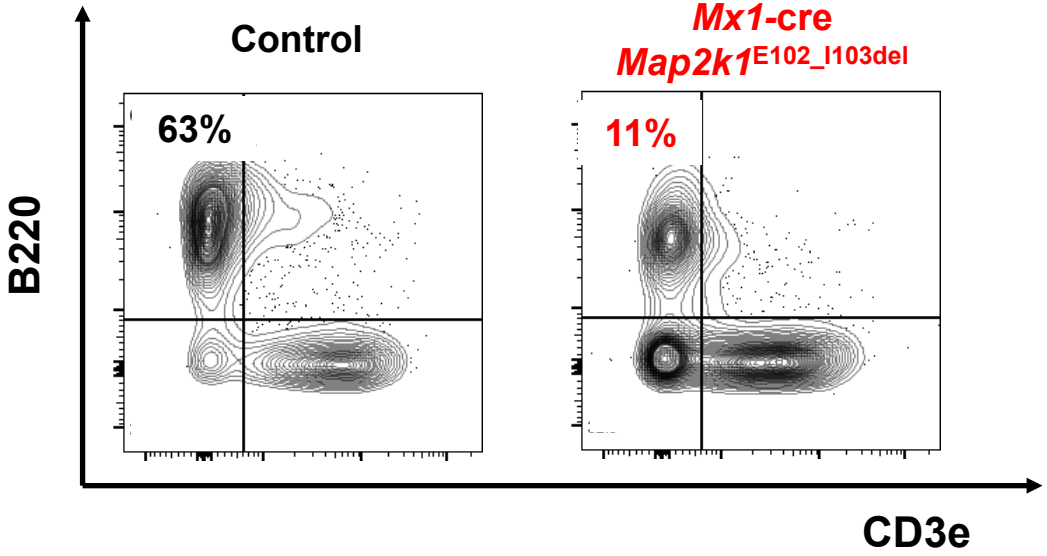


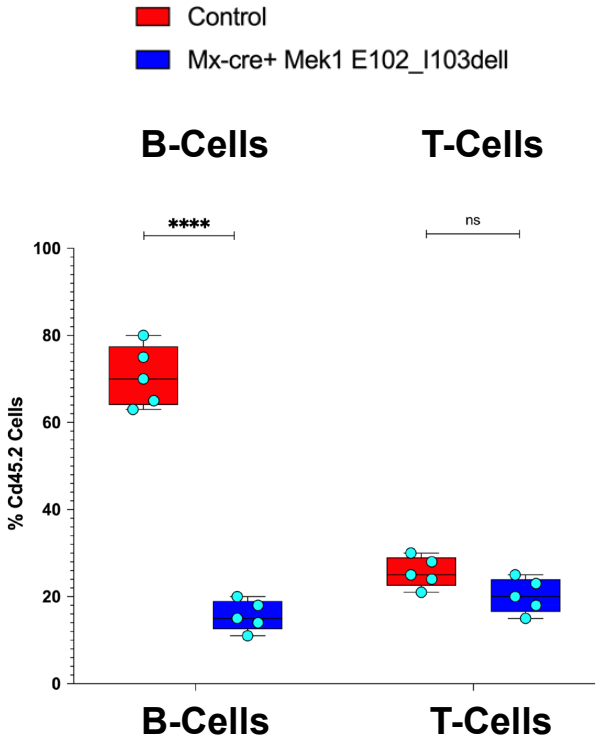
Control

Mx-cre+ Mek1 E102_I103dell

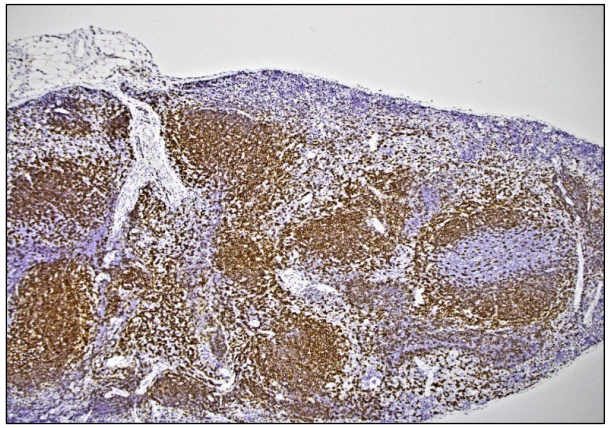
Suppression of B-Lymphopoiesis in MEK1^{E102_I103del} Mice

Gated on DAPI^{-} CD45^{+} CD11b^{-}

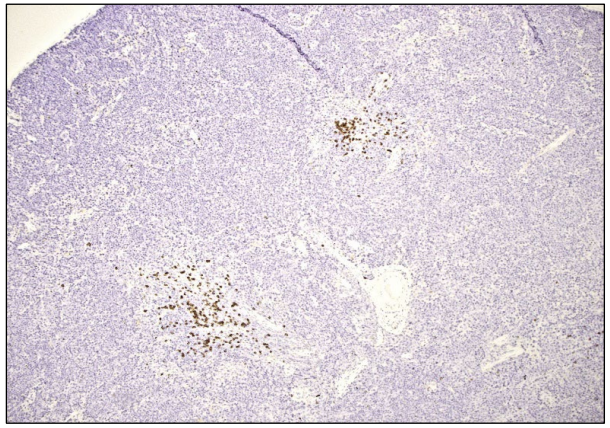




Control



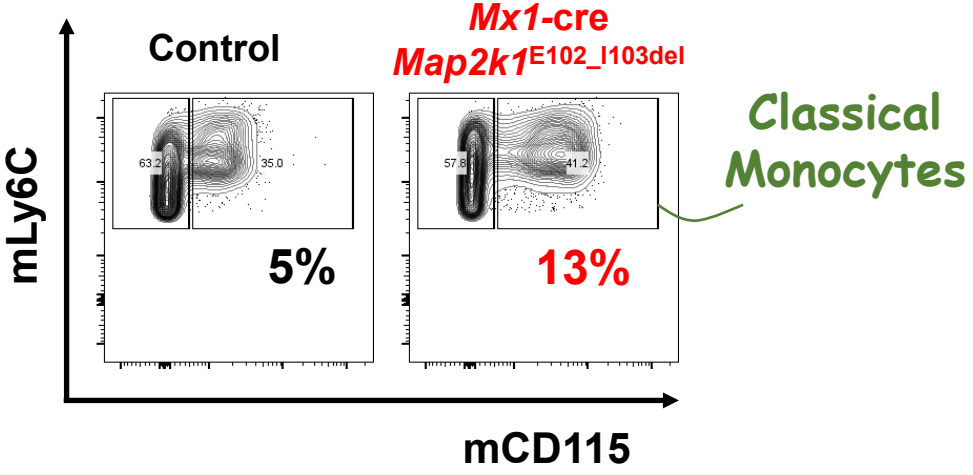
Mx1-cre *Map2k1*$^{E102\_I103del}$



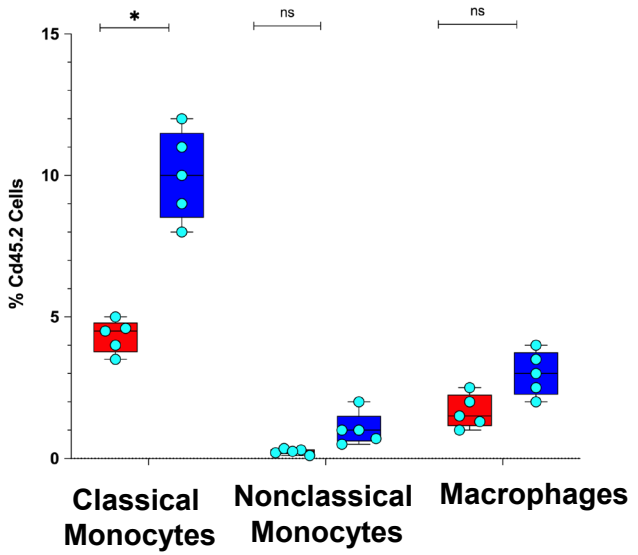
B220 IHC Spleen

Expansion of Monocyte Subsets/Macrophages in MEK1 mutant mice

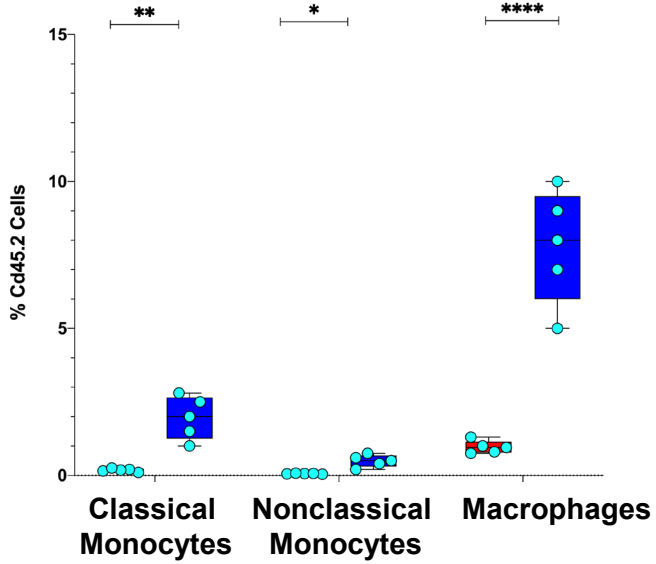
DAPI⁻ CD45⁺ CD11b⁺ Ly6C⁺⁺ Ly6g⁻



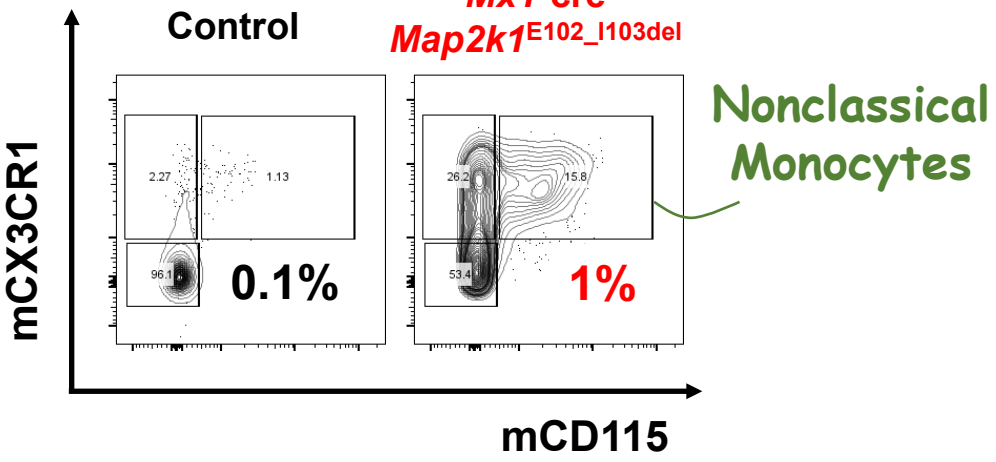
Bone Marrow

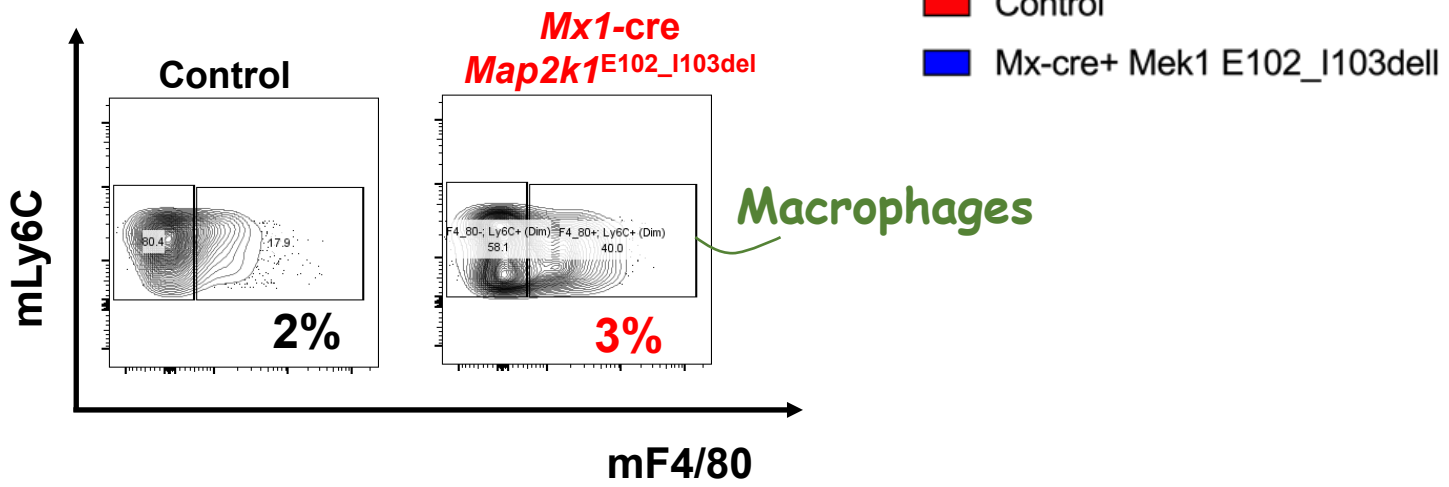


Spleen

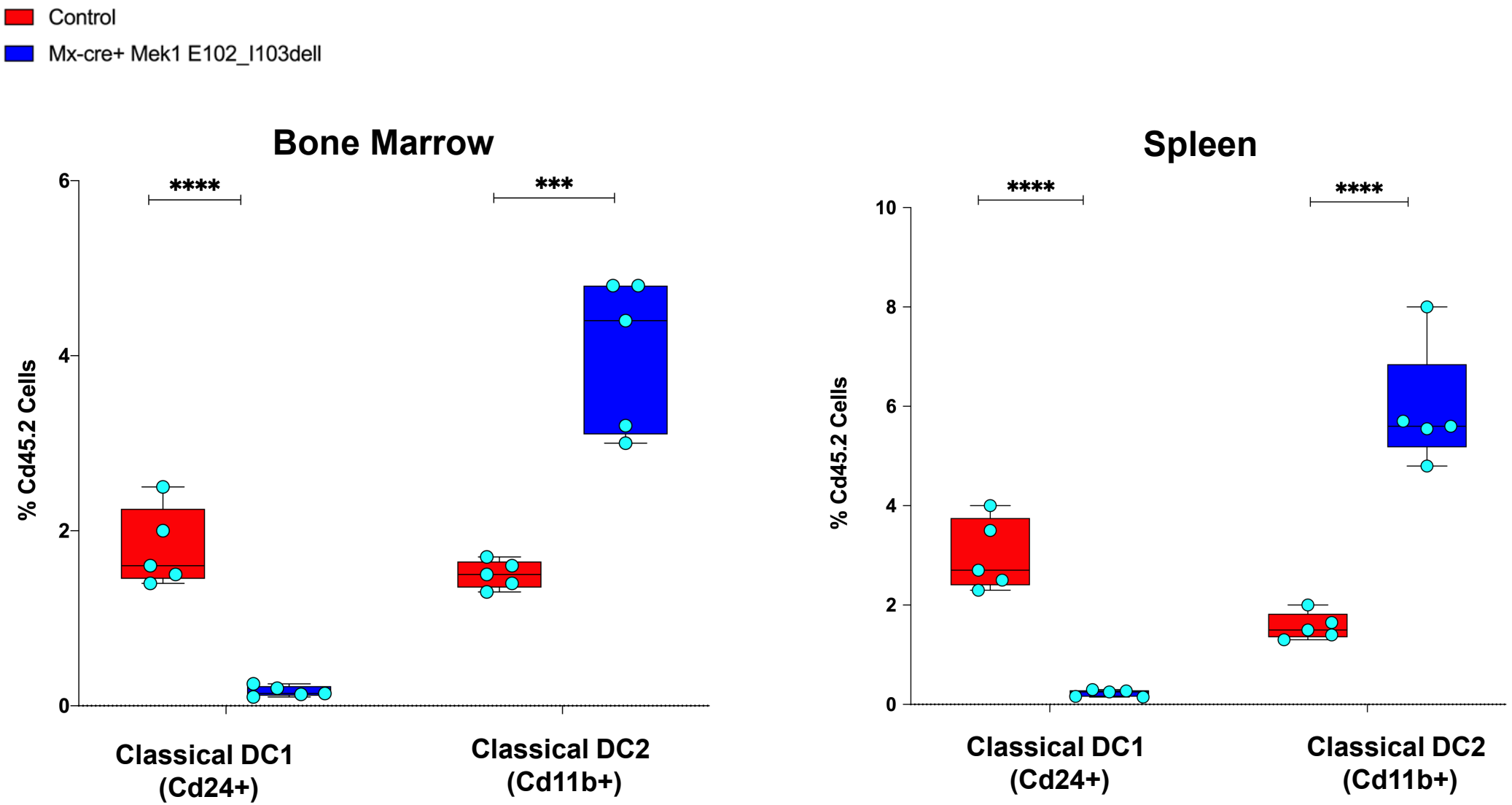


DAPI⁻ CD45⁺ CD11b⁺ Ly6C⁺/⁻ Ly6g⁻

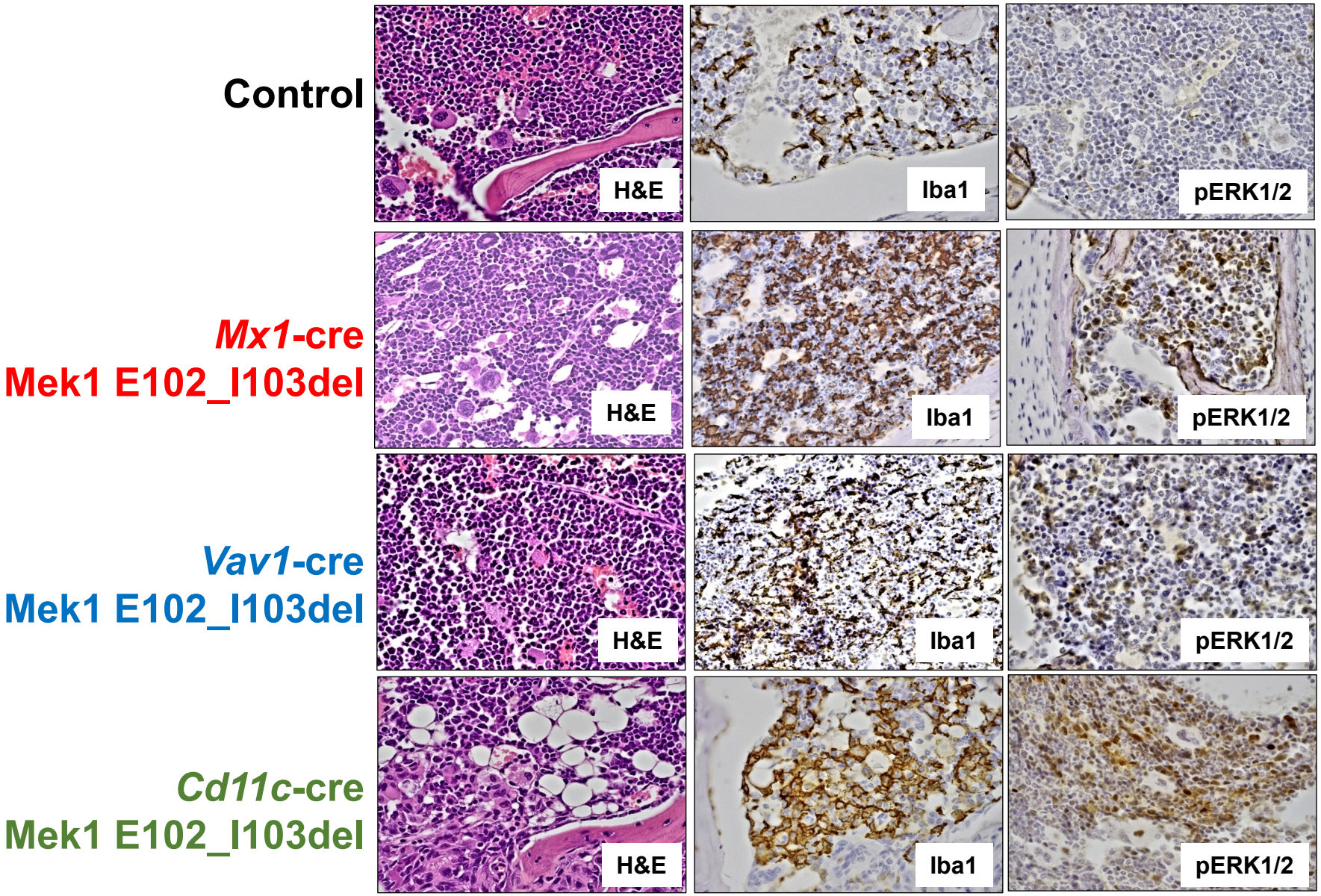




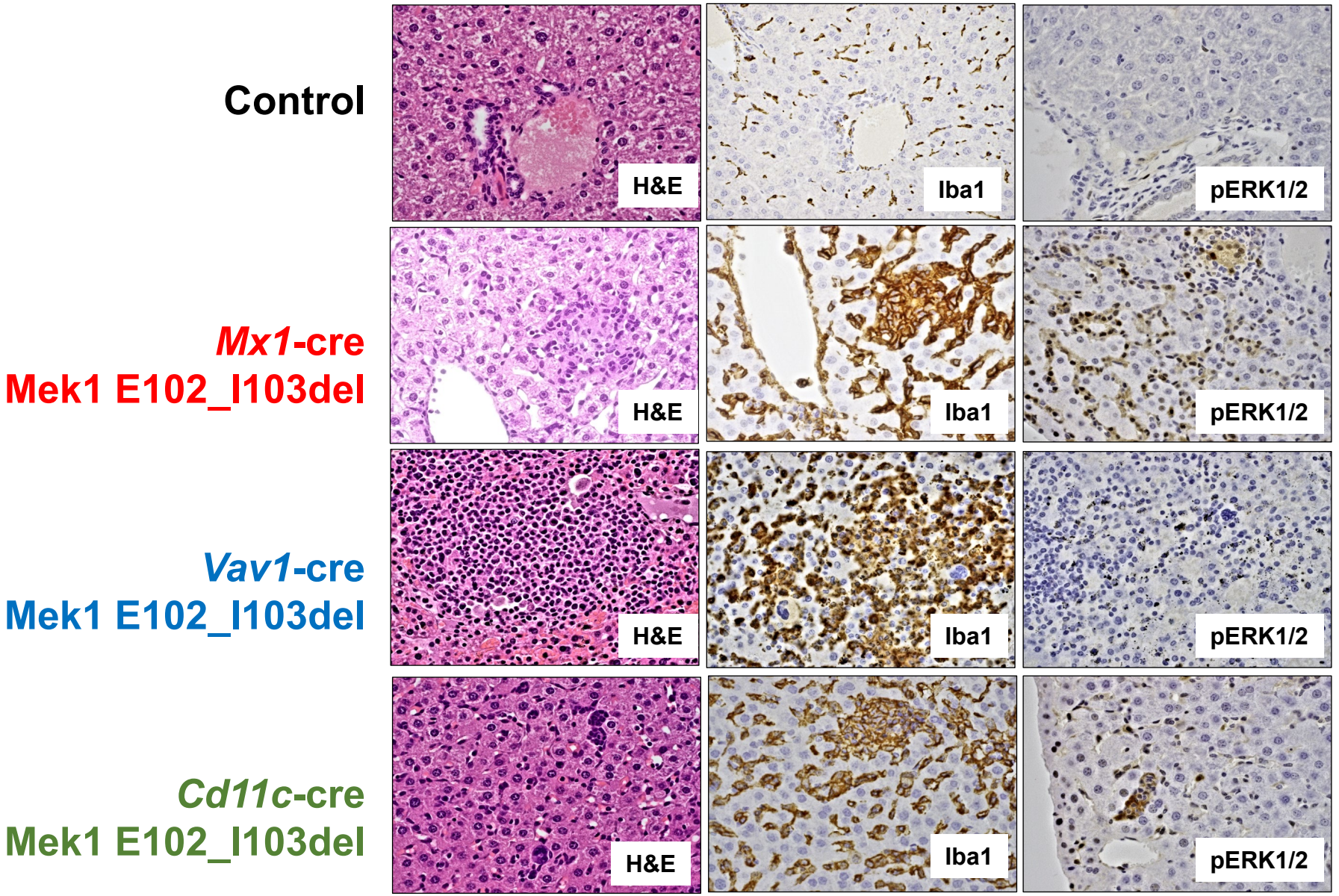
Expansion of CD11b^{+} Classical Dendritic Cells Type 2 (DC2) and Reduction of Classical Dendritic Cells Type 1 (DC1) in MEK1 mutant mice



Expansion of Iba1^{+} Monocyte/Macrophages and Cd11b^{+} Dendritic Cells in Bone Marrow of MEK1 Mutant Mice

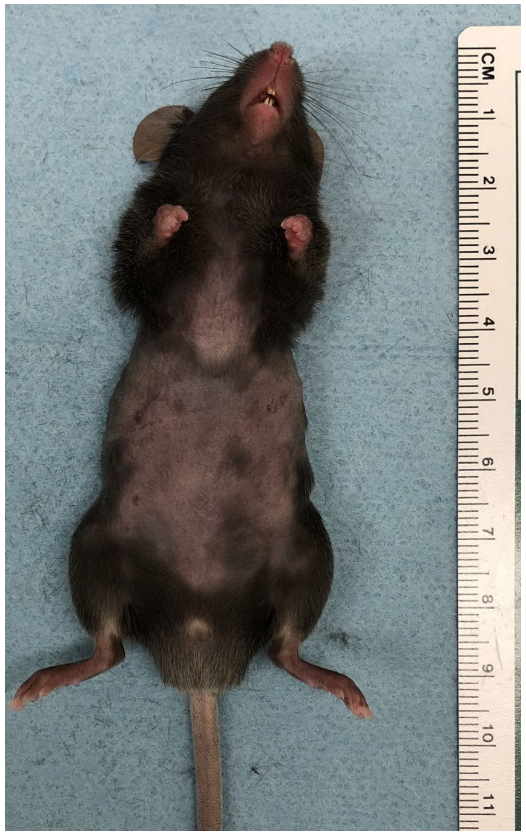


Infiltration by Iba1+ Monocyte/Macrophages and Cd11b+ Dendritic Cells in Liver of MEK1 Mutant Mice



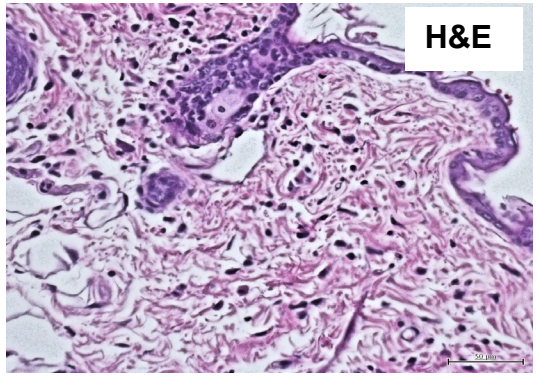
Cutaneous Histiocytosis in MEK1 Mutant Mice

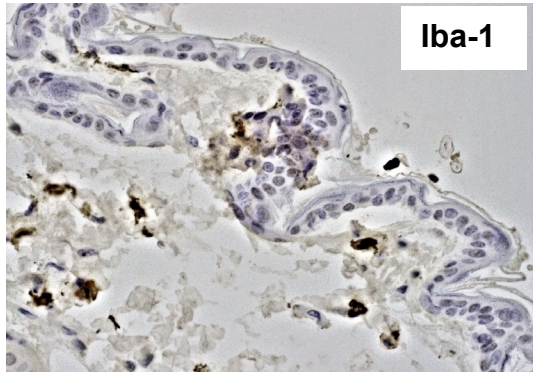
Control

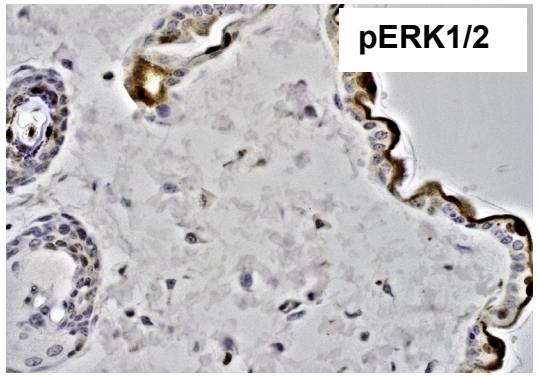


Mx1-cre
Map2k1$^{E102\_I103del}$

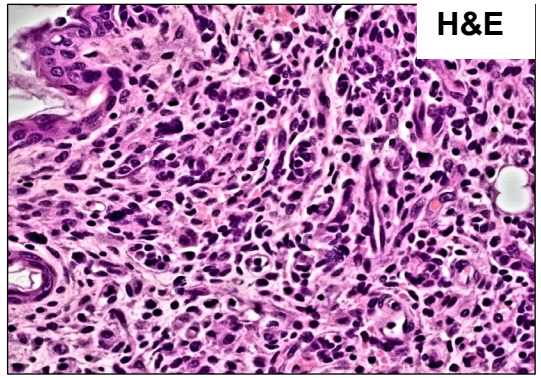
Control

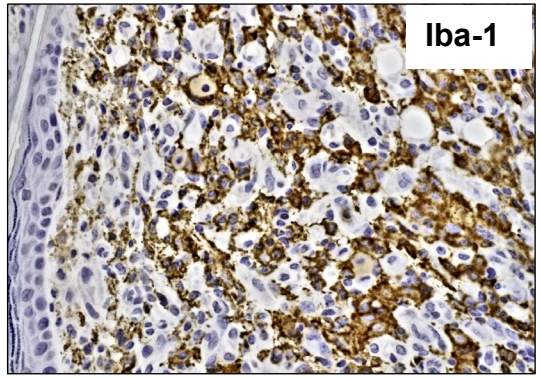


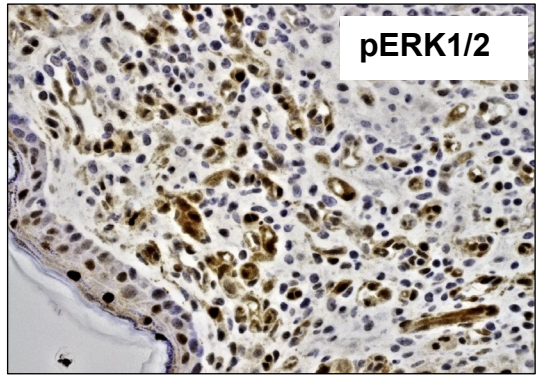




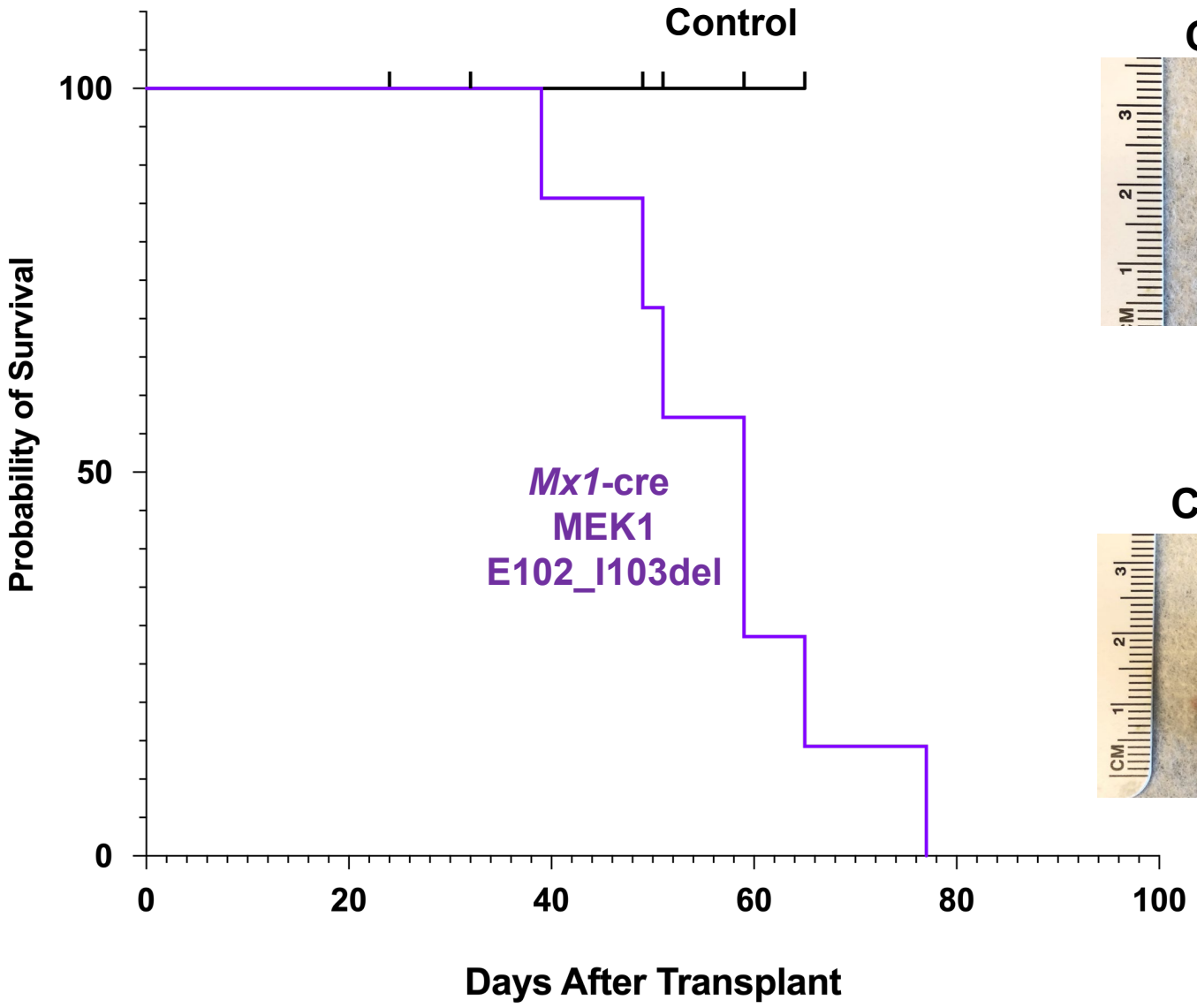
Mx1-cre
Map2k1$^{E102\_I103del}$

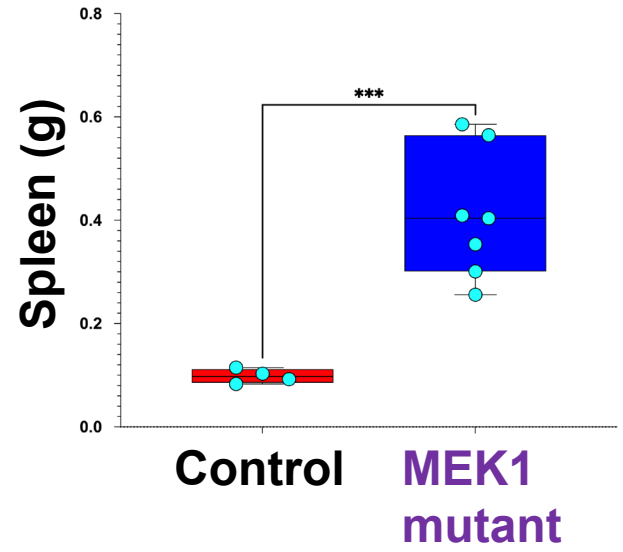


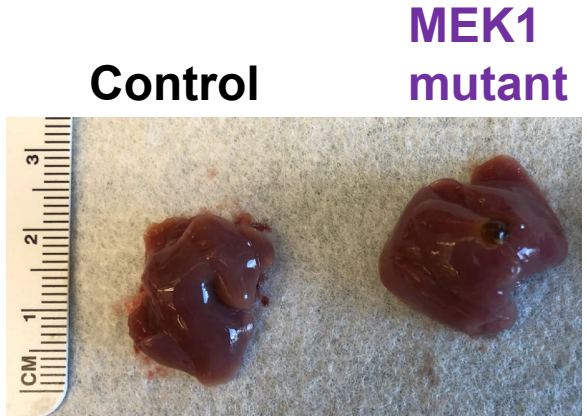


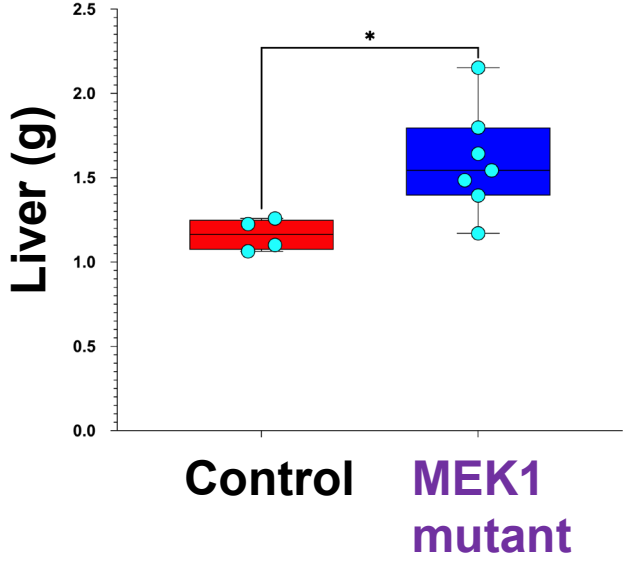


Serial Bone Marrow Transplantation of *Mx1*-cre *Map2k1* E102_I103del

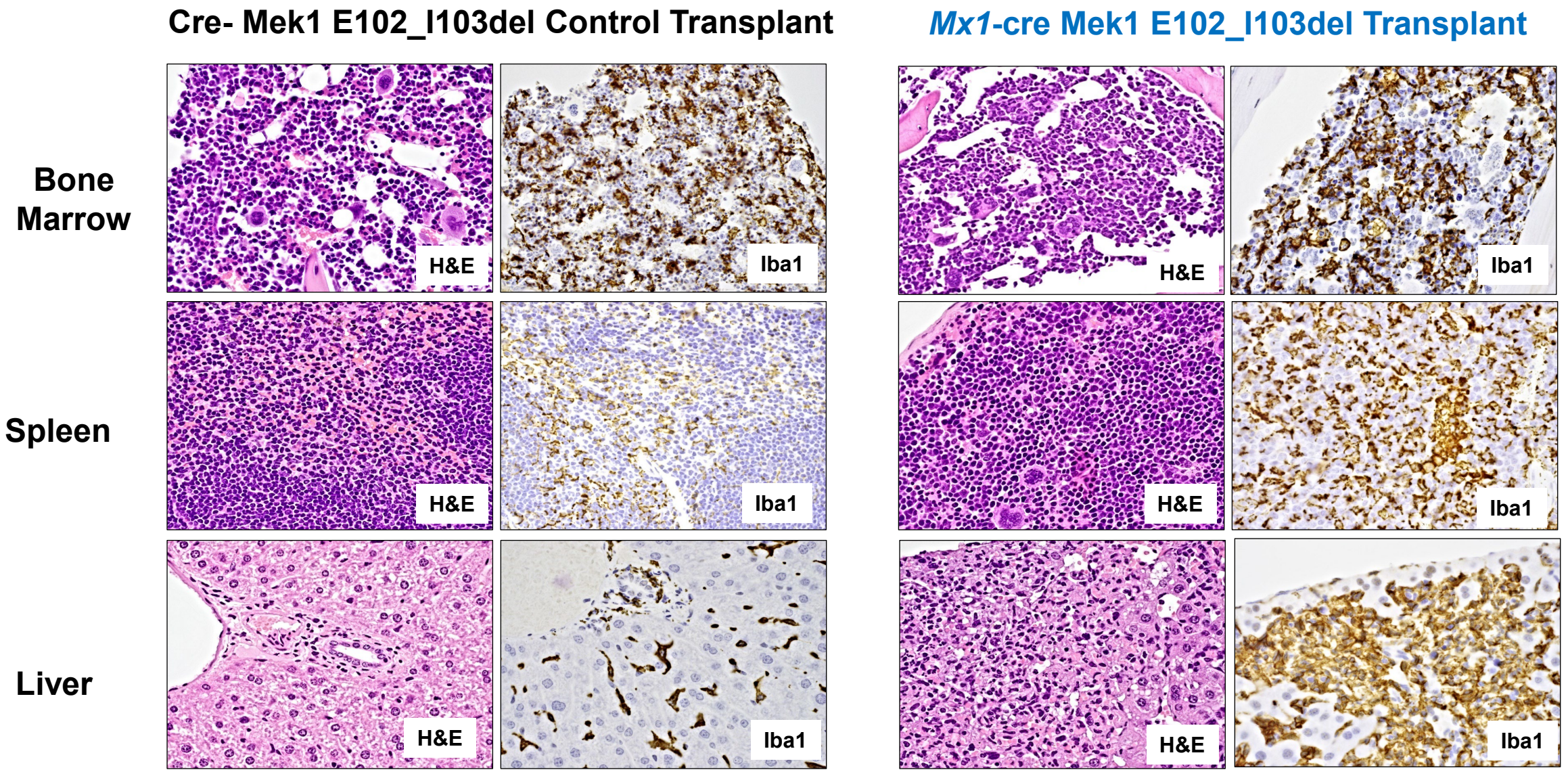








Serial Transplantation *Mx1*-cre *Map2k1*$^{E102\_I103del}$ Demonstrates Infiltration of Tissues by a Histiocytosis-like Neoplasm as in Primary *Mx1*-cre *Map2k1*$^{E102\_I103del}$



Pre-Clinical *in vivo* ERK1/2 Inhibitor Experiment – Does ERK1/2 Inhibition Provide Benefit in *Mx1*-cre *Map2k1* E102_I103del mice

Mx1-cre **Mek1 Group (Ulixertinib)**

N = 5 CD45.1 Mice

Ulixertinib = 100 mg/kg PO BID (5 days/wk)

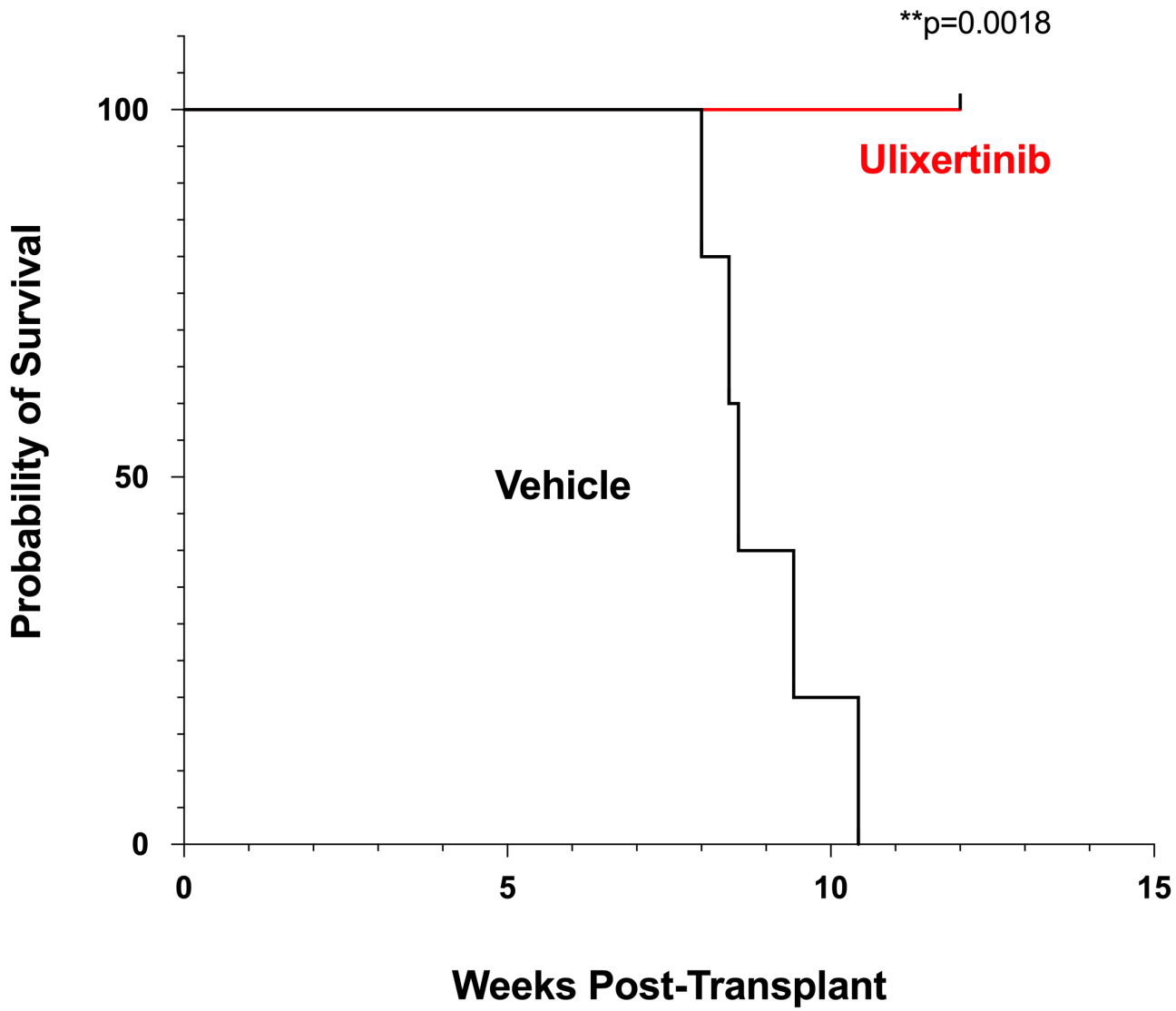
***Mx1*-cre Mek1 Group (Vehicle)**

N = 5 CD45.1 Mice

Vehicle (Carboxymethylcellulose CMC) Daily (5 days/wk)

CD45.1 BMT from Primary *Mx1*-cre *Map2k1* E102_I103del Mice

Ulixertinib (ERK1/2 Inhibitor) Provides Survival Benefit to *Mx1*-cre *Map2k1* E102_I103del Mice Based on Initial *in vivo* Ongoing Pre-clinical Studies



Conclusions

- MEK1^{E102_I103del} drives a lethal, myelomonocytic disorder reminiscent of human systemic histiocytosis *in vivo*
  - This occurs with *Mx1*-cre, *Vav1*-cre, or *CD11c*-cre promoters &
  - Is serially transplantable.
- Expressing MEK1^{I102_E103del} at the earliest stages of hematopoietic development results in a more severe disease than in committed monocyte/dendritic cells.
  - *Mx1*-cre MEK1^{I102_E103del} leads to suppression of B-lymphopoiesis and expansion of monocyte/macrophages and CD11b^{+} dendritic cells in bone marrow, spleen, liver, and skin.
- MEK1^{E102_I103del} conditional knock-in mice can serve as promising pre-clinical models to test single-agent or combinatorial agent therapeutics for histiocytic neoplasms.
- Ulixertinib (ERK1/2 inhibitor) is showing promising efficacy as a monotherapy against class III MEK1-mutant disease in ongoing pre-clinical trials in mouse models suggesting it maybe useful in histiocytosis patients with class III MEK1 mutations.

THANK YOU

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Eli Diamond

Cincinnati Children's Hospital, Cincinnati, OH

- Jennifer Picarsic

University of Colorado Anschutz, Aurora, CO

- Matthew Witkowski

St. Jude Children's Research Hospital, Memphis, TN

- Tanja Gruber, Former Member
- Patrick Campbell
- David Ellison
- John Choi, Former Member

INSERM Research Unit, Paris, France

- Julien Haroche
- Jean-Francois Emile
- Jean Donadieu

Abdel-Wahab Lab

- Michael Singer
- Salima Benbarche
- Caroline Erickson
- Jahan Rahman
- Steven Tittley
- Nina Fox
- Hana Cho (Former)
- Daniel Cui (Former)
- Young Rock Chung (Former)

Hematopathology

- Ahmet Dogan
- Mariko Yabe
- Ksenyia Petrova-Drus

Developmental Therapeutics

- David Hyman

Neal Rosen Lab

- Neal Rosen

Leukemia Service

- Raajit Rampal

Neurology

- Justin Buthorn

Center for Molecular Oncology (CMO)

- David Solit
- Mike Berger

Molecular Diagnostics

- Marc Ladanyi
- Maria Arcila

Geissmann Lab

- Estibaliz Lopez-Rodrigo
- Frederic Geissmann

Funding Sources

American Society of Hematology

Erdheim-Chester Disease Global Alliance

Geoffrey Beene Gives Back

The Society of Memorial Sloan-Kettering Cancer Center

Damon Runyon Cancer Research Foundation

NIH National Institutes of Health