Changing AML Outcomes via Personalized Medicine: Transforming Cancer Management with Genetic Insight

Co-Moderators:

- Rick Winneker, PhD, Senior Vice President, Research, Leukemia & Lymphoma Society
- Mike Rice, Senior Consultant, Defined Health

Panelists:

- Brian J. Druker, MD, Director, OHSU Knight Cancer Institute, JELD-WEN Chair of Leukemia Research, Oregon Health & Science University, Investigator, Howard Hughes Medical Institute
- Eric Hedrick, MD, Chief Medical Officer, Epizyme, Inc.
- Omar Abdel-Wahab, MD, Assistant Member, Memorial Sloan Kettering Cancer Center
- Nicholas J. Sarlis, MD, PhD, Vice President & Head, Medical Affairs, Incyte Corporation
- Scott Biller, PhD, Chief Scientific Officer, Agios Pharmaceuticals

CANCER PROGRESS by Defined Health

Challenges in Developing Treatment Paradigms in Molecularly-Profiled Patient Populations

Possible 'Lessons Learned' from Targeting the JAK-STAT Pathway in Myelofibrosis

Nicholas J. Sarlis, MD, PhD

Disclaimer:

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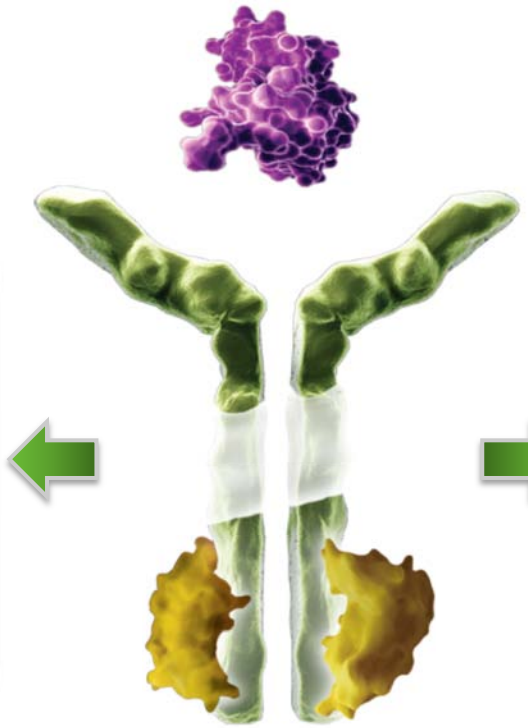
Key Functional Role of the JAK-STAT Pathway



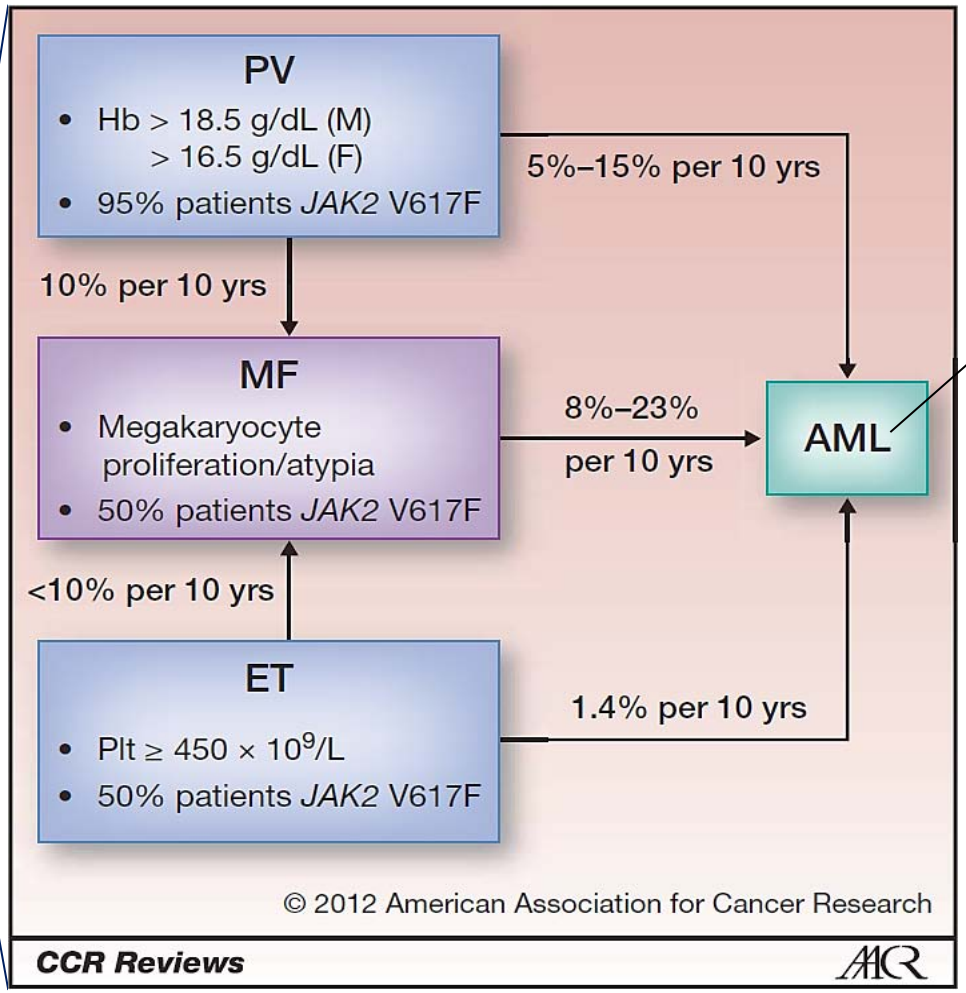
Immune Function (incl. mediation of cellular actions of assorted cytokines)

Hematopoiesis (incl. myeloid proliferation)

Based on data from: Quintás-Cardama A, et al. *Blood.* 2010;115:3109-3117

The Clinical Evolution of MPNs Toward AML: Clonal Progression Underlies Progressive Disease

Antecedent Hematologic Diseases (AHDs) associated with JAK-STAT pathway dysregulation



Secondary (s) AML (also defined as MPN-blast phase, MPN-BP)

Very poor prognosis

PV: polycythemia vera; MF: Myelofibrosis (including primary, as well as post-PV and post-ET myelofibrosis; ET: Essential thrombocythemia; AML: Acute myeloid leukemia (in this case, secondary to an antecedent hematologic disorder [AHD]); AMKL: Acute megakaryoblastic leukemia

Reprinted from Clinical Cancer Research, 2013, 19/2, 327-335, Lee HJ et al, The role of JAK pathway dysregulation in the pathogenesis and treatment of acute myeloid leukemia, with permission from AACR.

Ruxolitinib for Intermediate or High-Risk Myelofibrosis (MF)

- Ruxolitinib is an oral JAK1/JAK2 inhibitor and the only currently FDA-approved treatment for MF[1,2*]
  - Significant improvements in spleen volume
  - Significant relief from core disease-specific symptoms, as measured by a validated patient-reported outcome (PRO) symptom burden scale
  - Benefits seen with and without the *JAK2*V617F mutation
    - Inhibition of a pathway, not a mutated protein, is the principle of pharmacologic action
  - Anticipated and dose-dependent decrements in platelet counts and hemoglobin; non-hematologic side effects: bruising, dizziness and headache (mostly grades 1 & 2)
  - Individualizing ruxolitinib dosing can help achievement and maintenance of clinical benefit
- Phase III trials are on-going in polycythemia vera (PV)[3**]
- Independent, investigator-sponsored research has recently focused on JAK inhibition in other hematologic malignancies, including AML[4**]

Based on data from: 1. Deisseroth A, et al. Clin Cancer Res. 2012;18/12: 3212-2317; 2. JAKAFI ® (ruxolitinib) prescribing information. Incyte Corporation. Nov. 2011; 3. www.clinicaltrials.gov: RESPONSE Trial: NCT01243944 & RELIEF Trial: NCT01632904; 4. Daver N, Cortes J. Hematology. 2012;17 Suppl 1:S59-S62.

*Intermediate or high-risk MF, including primary MF, post–PV MF and post–ET MF

**Ruxolitinib is an investigational compound for the treatment of patients with PV or AML. Its efficacy and safety have not been established in these patient populations. There is no guarantee that this compound will become commercially available for use in either PV or AML patients.

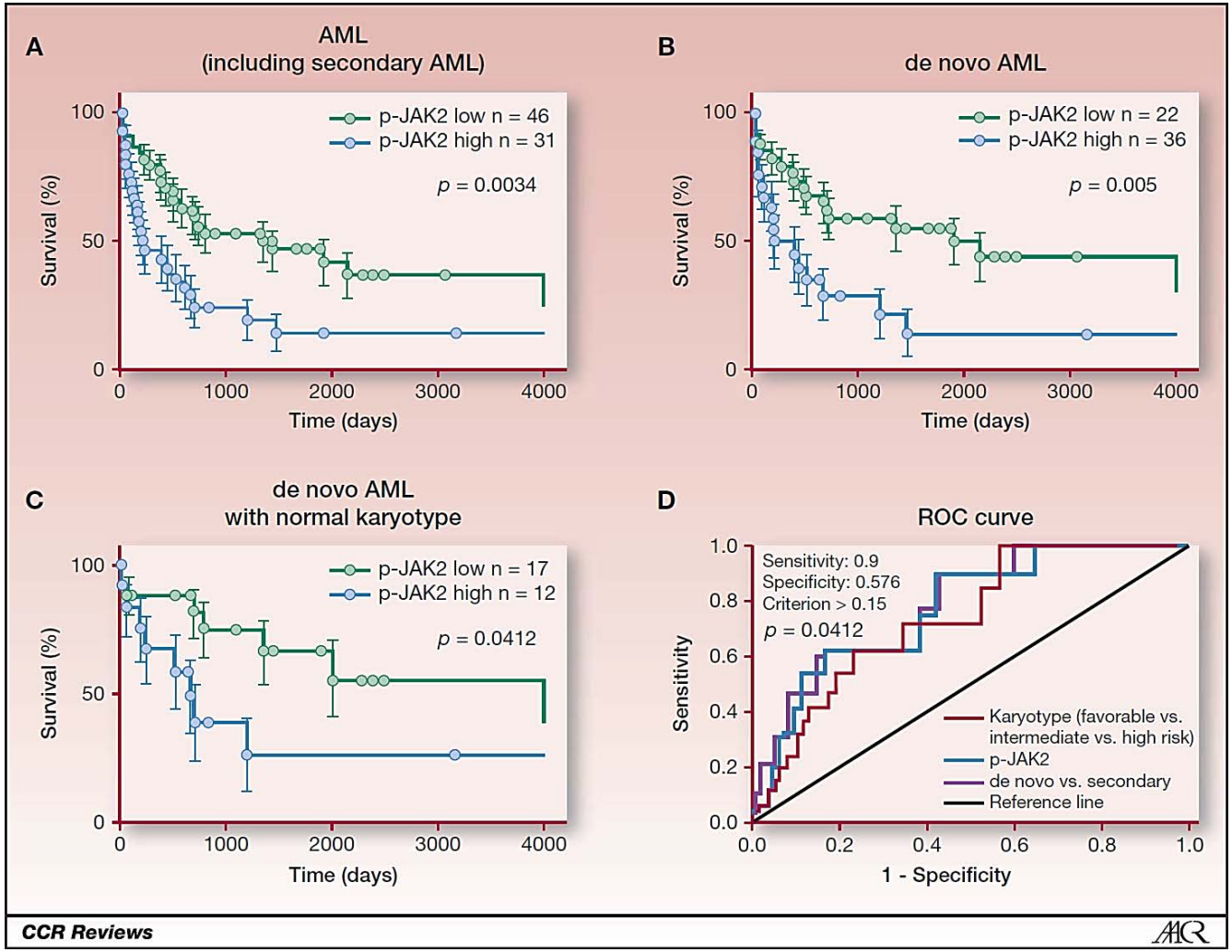
Clinically Observed JAK Mutations in AML

JAK Family Member	Specific GOF Mutation	Disease Subtype
JAK1	T478S	AML
	V623A	AML
JAK2	V617F	AML
	K607N	AML
	T875N	AMKL
	PCM1-JAK2	AML
JAK3	V722I	AMKL
	A572V	AMKL
	P132T	AMKL

AML: Acute myeloid leukemia; AMKL: Acute megakaryoblastic leukemia;
GOF: Gain of function

Reprinted from Clinical Cancer Research, 2013, 19/2, 327-335, Lee HJ et al, The role of JAK pathway dysregulation in the pathogenesis and treatment of acute myeloid leukemia, with permission from AACR.

Association of elevated levels of phosphorylated JAK2 (p-JAK2) and survival in pts with *de novo* or secondary AML



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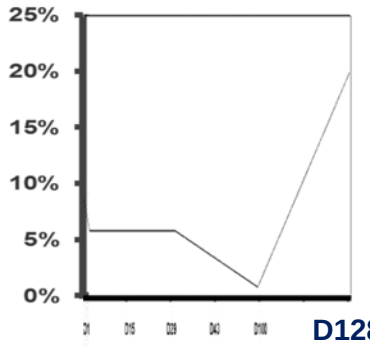
M.D. Anderson Cancer Center – Pilot Study of Ruxolitinib in Patients with Assorted Relapsed Leukemias

- 12 out of 28 pts (43%) with clinical benefit
  - CR: 2, CRi: 1; SD: 9
  - CR/CRi rate: 11% (all seen in sAML; no CRs in *de novo* AML)
  - Responses were short-lived in most cases
    - Median number of Rx cycles (range): 2 (1-22)

- 3 of 18 pts (17%) with sAML had significant decline in BM blasts
  - with resolution of splenomegaly
  - with improvement in clinical symptoms

Time Kinetics of Myeloblast Response

Pt1; CRi



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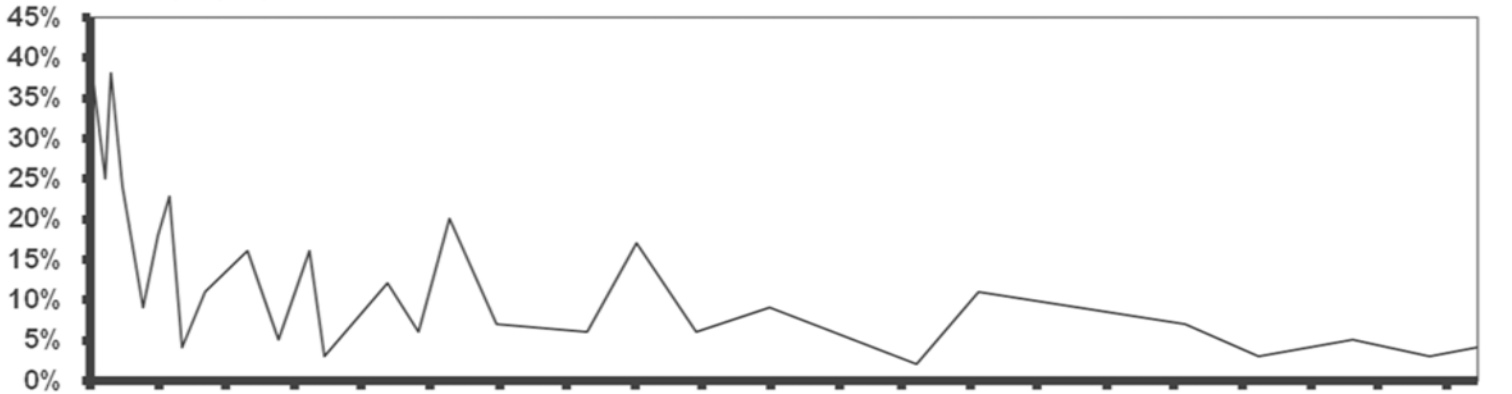
Pt2; CR



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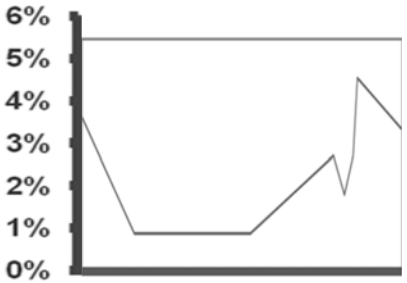
Pt3; CR



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Concluding Remarks

- Ruxolitinib was approved for the treatment of myelofibrosis (MF) based on reduction in spleen size and improvement in the symptoms of MF
- Post-approval data indicate prolonged survival in MF
- The approach taken in MF does not seem germane to clinical study designs in AML, where expeditious remission and survival benefit are critical
- JAK inhibitors may have some utility in secondary AML (MPN-BP), but have not shown activity in *de novo* AML
- Given that survival in AML will be very short if remission is not achieved, the use of symptom-based endpoints is not appropriate in this disease. Nonetheless, such endpoints are highly relevant to malignancies with heavy symptomatic burden, longer survival and high probability of application of chronic pharmacologic therapy

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