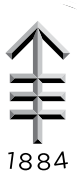

Memorial Sloan Kettering
Cancer Center

New Drugs in Hematology: IDH2 Inhibitors in Acute Myeloid Leukemia

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Disclosures of: *[enter name and surname]*

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Agios Pharmaceuticals	x					x	
Celgene Pharmaceuticals	x					x	

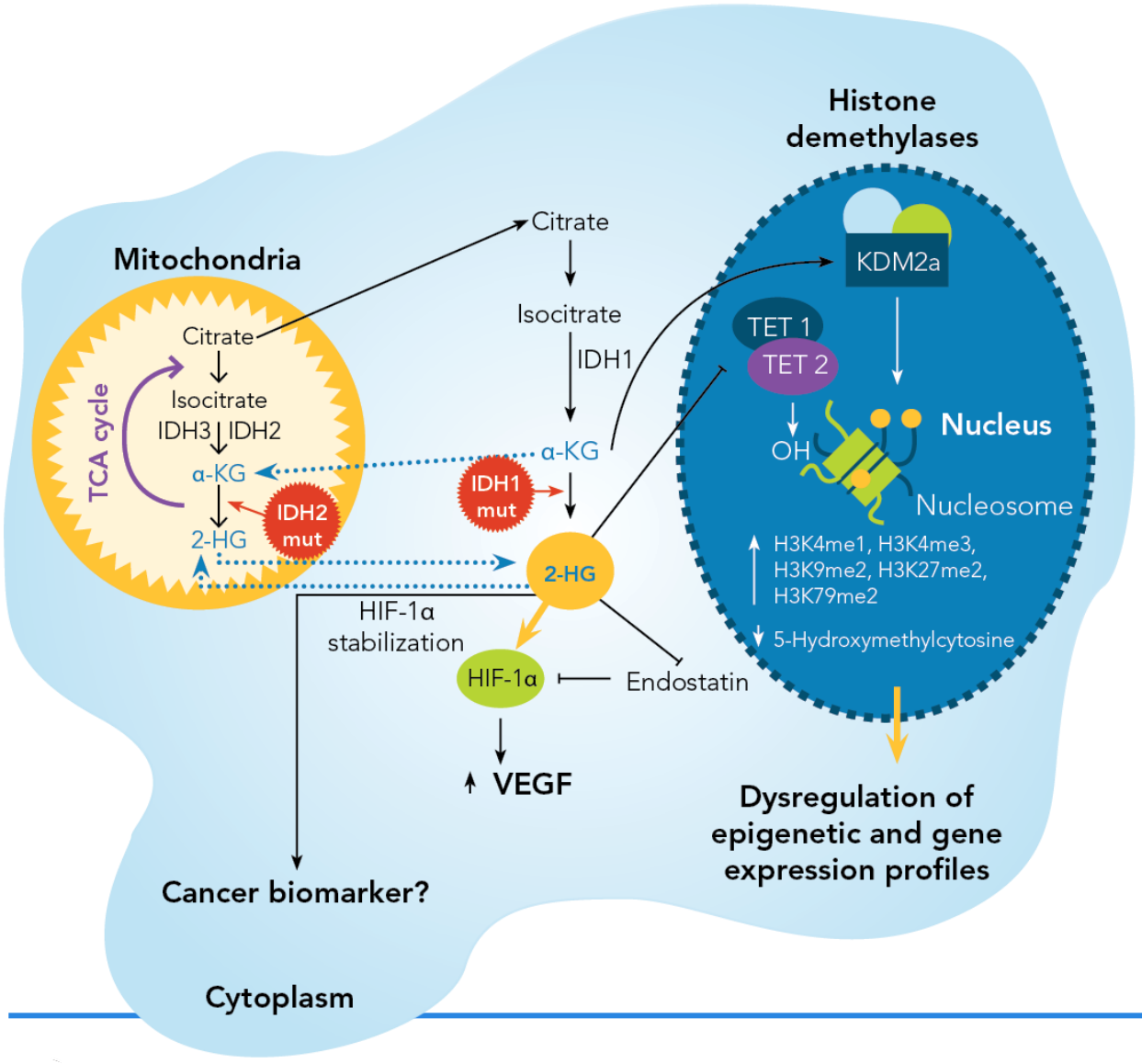
IDH1m and IDH2m: Distinct Genetically Defined Populations

IDH Mutations Seen in Multiple Cancer Types		
Target	Indication	IDHm (%)
IDH2m	AML	15%
	MDS/MPN	5%
	Angio-immunoblastic NHL	25%
	Others (melanoma, glioma, chondro)[2]	3-5%
	Type II D-2HG Aciduria (inborn error of metabolism)	100%
IDH1m	Low-grade glioma & 2^{ary} GBM[1]	70%
	Chondrosarcoma	>50%
	AML	7.5%
	MDS/MPN	5%
	Intrahepatic cholangiocarcinoma	20%
	Others (colon, melanoma, lung)[2]	1-2%

[1]Includes 8.5% of Primary GBM

[2]Includes "basket" of emerging unconfirmed indications

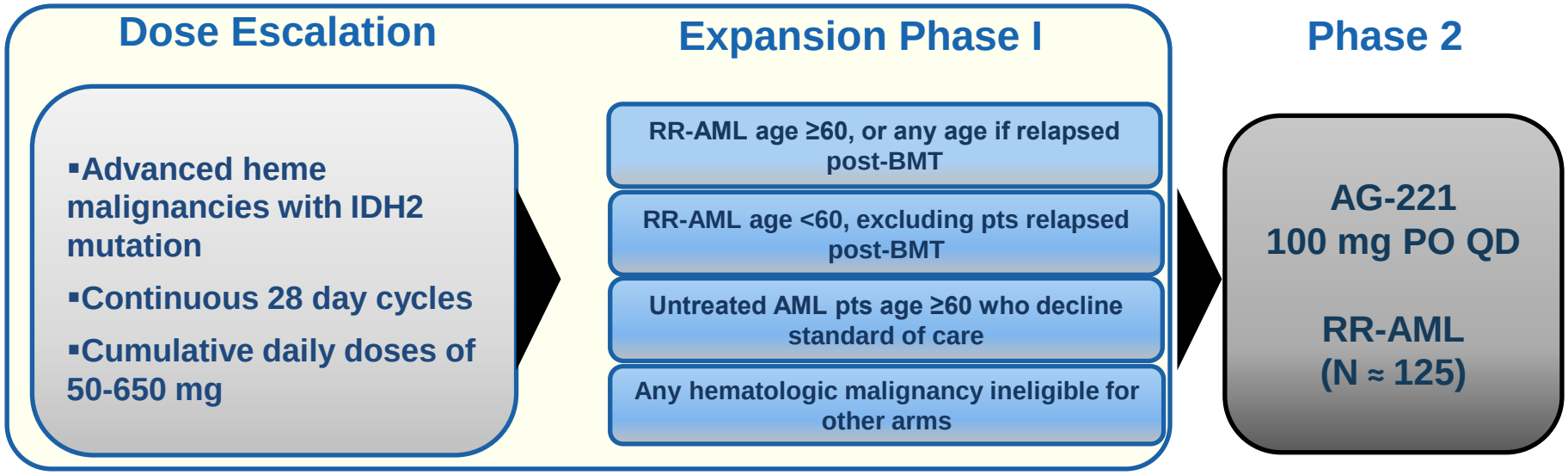
IDH in AML



- IDH is a critical metabolic enzyme in the citric acid cycle
- IDH1 in cytoplasm and IDH2 in mitochondria
- Cancer-associated IDHm produces 2-hydroxyglutarate (2-HG) and blocks normal cellular differentiation
- IDH2 R140Q more common than R172K in retrospective series

Prensner and Chinnaiyan Nature, 2011

Phase 1/2 Study Design – IDH2 inhibitor AG-221 (Celgene/Agios)

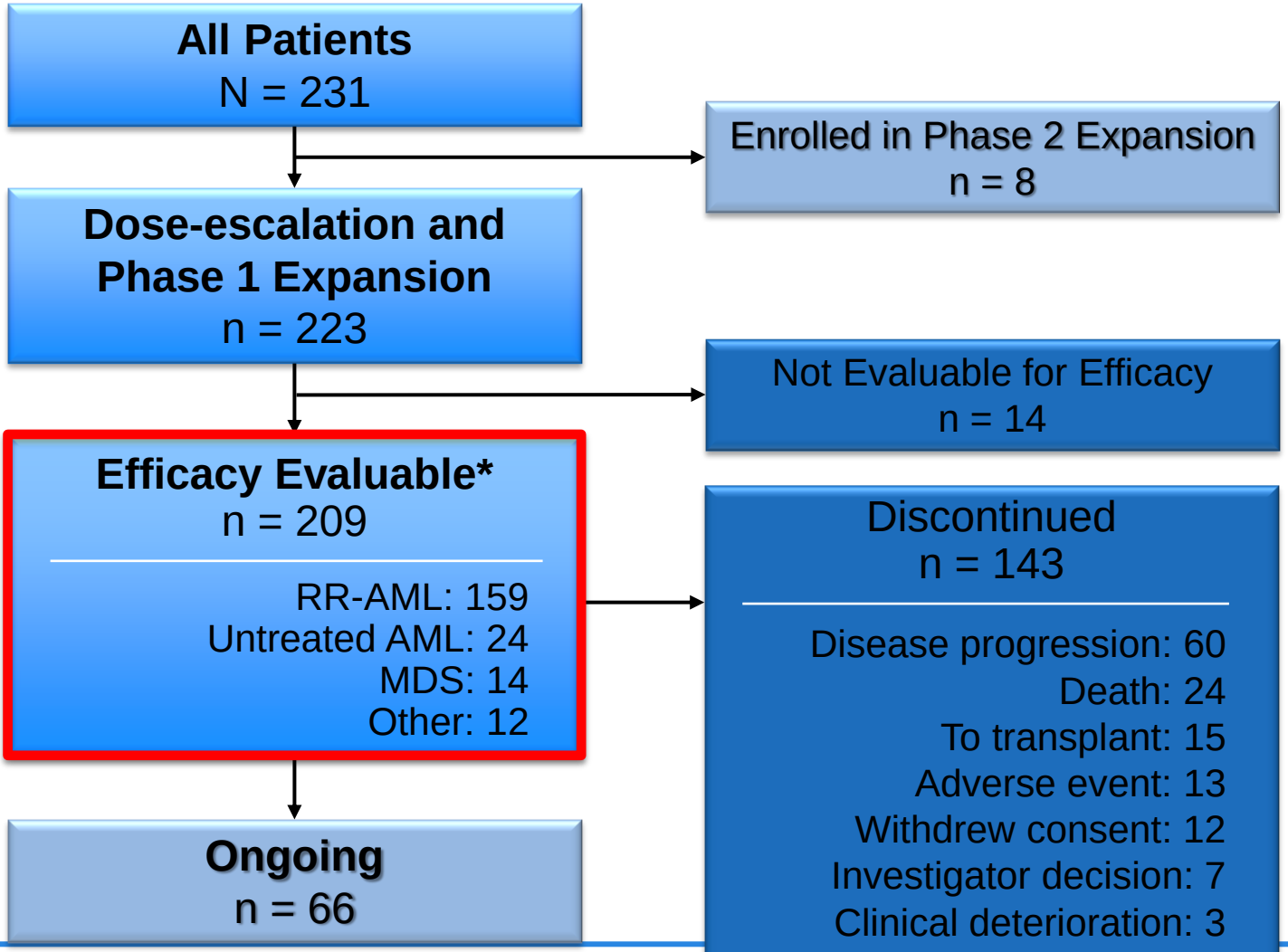


Key Endpoints:

- Safety, tolerability, MTD, DLTs
- Response rates as assessed by local investigator per IWG criteria
- Assessment of clinical activity

Stein EM, et. al. Blood 2015 126:323

Disposition (September 2015)



Baseline Characteristics

Data cut-off: 1 Sept 2015	All (N = 209)	RR-AML (n=159)
Age (years), median (range)	69 (19–100)	68 (19–100)
Gender, % M/F	56/44	50/50
IDH2 mutation, n (%)		
R140	146 (70)	109 (69)
R172	50 (24)	41 (26)
ECOG PS, n (%)		
0-1	161 (77)	120 (76)
2	41 (20)	34 (21)
Diagnosis, n (%)		
RR-AML	159 (76)	159 (100)
Untreated AML	24 (11)	-
MDS	14 (7)	-
Other	12 (6)	-
Number of prior Tx, median (range)	-	2 (1–6)

Most Frequent Treatment Emergent Adverse Events (≥15% of patients)

	Any Grade	Grade ≥3
Preferred Term	%	
Nausea	32	2
Diarrhea	28	3
Fatigue	28	6
Hyperbilirubinemia	27	10
Decreased appetite	27	3
Febrile neutropenia	27	26
Dyspnea	23	5
Pyrexia	23	4
Cough	22	0
Vomiting	20	1
Constipation	19	<1
Anemia	18	12
Peripheral edema	18	2
Thrombocytopenia	16	12

Dose-escalation and Serious Adverse Events

Dose-escalation

- **Highest daily AG-221 dose: 650 mg**
- **Dose-escalation ended; MTD not reached**

Treatment Related Serious Adverse Events

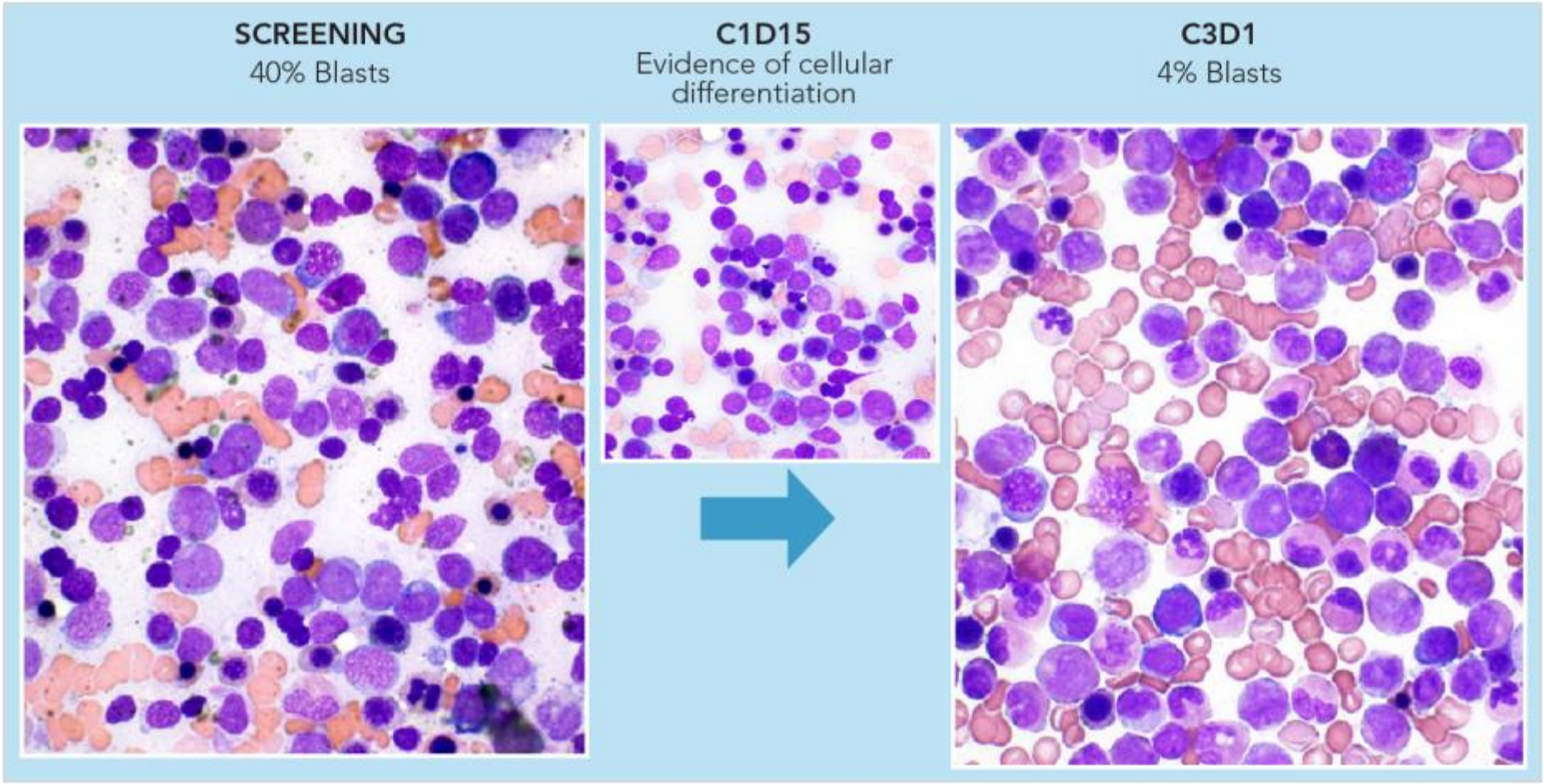
- **23% of patients had treatment-related SAEs; most frequent were differentiation syndrome (4%), leukocytosis (4%), and nausea (2%)**
- **Drug-related grade 5 SAEs:**
    - **cardiac tamponade (1)**
    - **pericardial effusion (1)**
    - **respiratory failure (1)**

Response

	RR-AML (n = 159)	Untreated AML (n = 24)	MDS (n = 14)	All (N = 209)
Overall Response (CR, CRp, CRi, mCR, PR)	59 (37%)	10 (42%)	7 (50%)	79 (38%)
CR	29 (18%)	4 (17%)	3 (21%)	37 (18%)
CRp	1 (1%)	1 (4%)	1 (7%)	3 (1%)
CRi	3 (2%)	0	0	3 (1%)
mCR	9 (6%)	1 (4%)	3 (21%)	14 (7%)
PR	17 (11%)	4 (17%)	0	22 (11%)
SD	72 (45%)	9 (38%)	6 (43%)	96 (46%)
PD	10 (6%)	1 (4%)	0	11 (5%)
Not evaluable	18 (11%)	4 (17%)	1 (7%)	23 (11%)

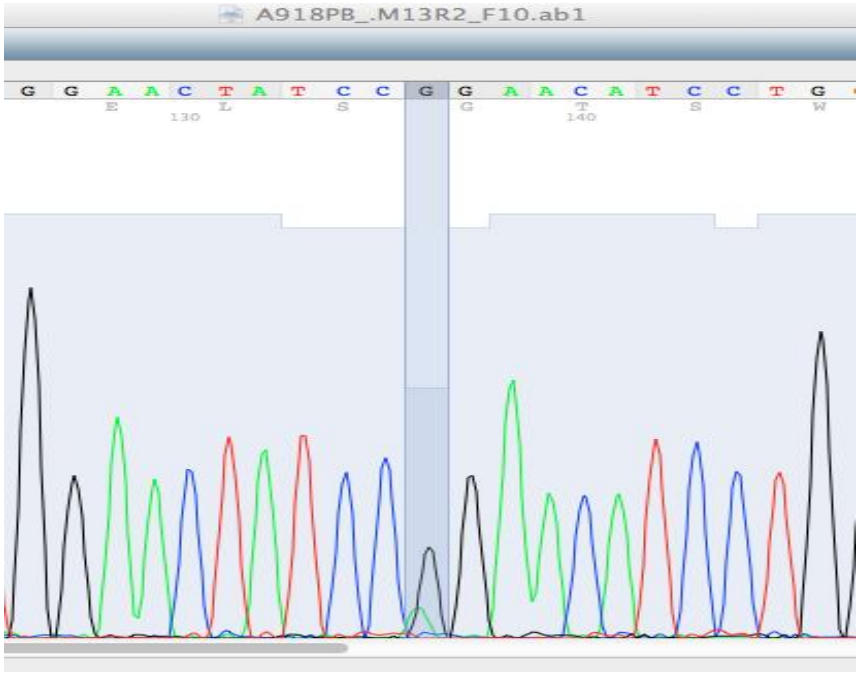
- **Overall response by IDH mutation type: R140Q 36% / R172K 42%**

Differentiation Effects in the Bone Marrow

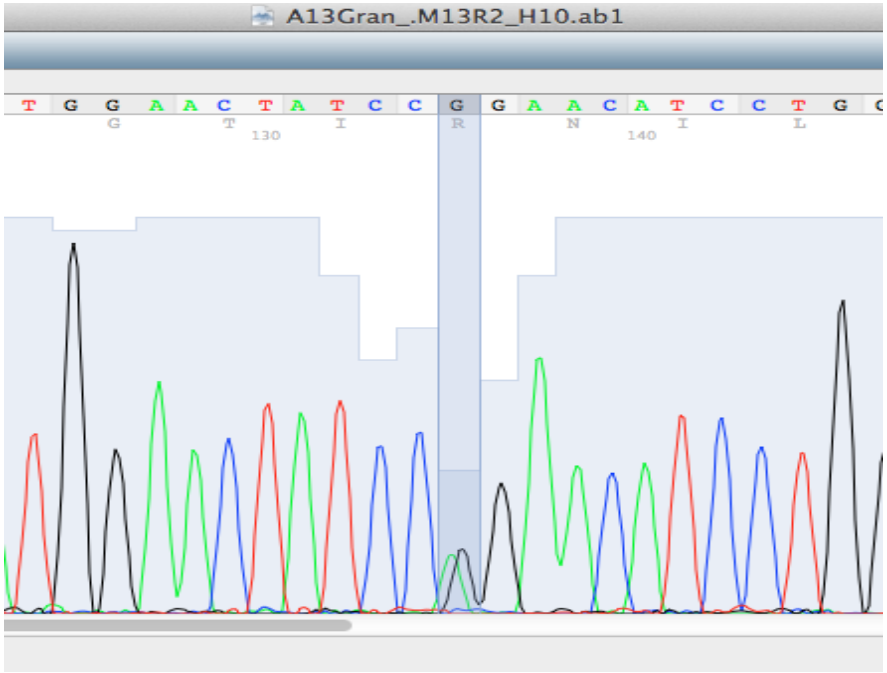


Molecular Evidence of Differentiation

Screening – PBMC



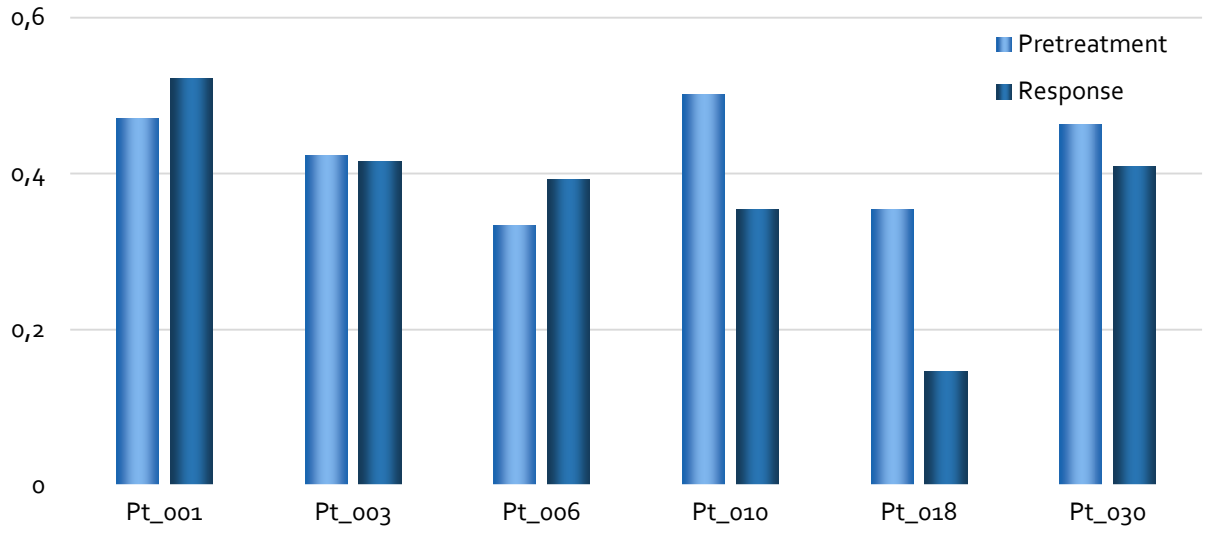
Cycle 3 day 1 – Remission - Granulocytes



Alan Shih and Ross Levine, MSKCC

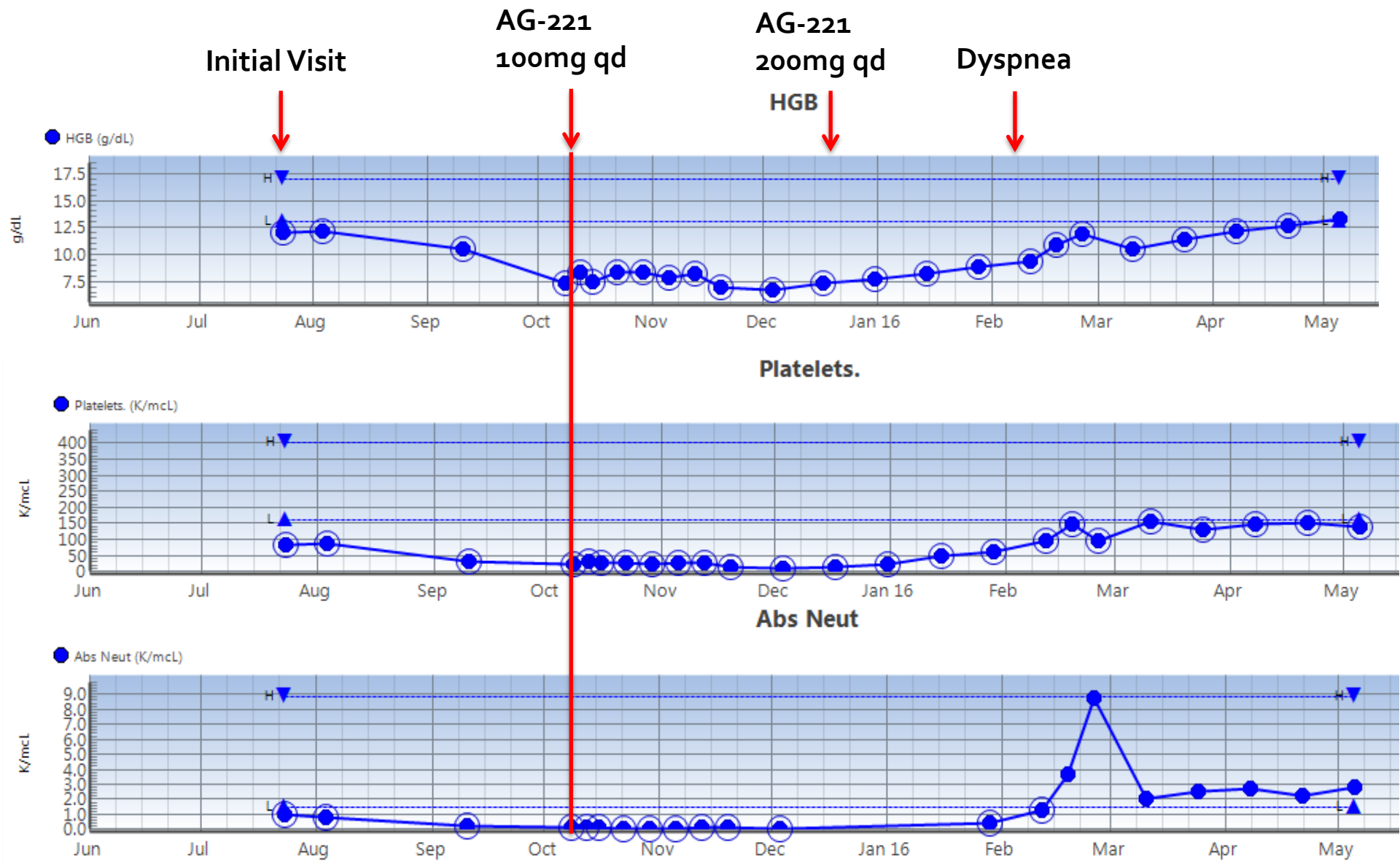
Variant Allele Frequency (VAF) During Treatment in Patients with CR

- **Majority of patients with CR treated to date at Memorial Sloan Kettering Cancer Center do not have appreciable decrease in m*IDH2* VAF**
- **Additional analyses are planned in a larger cohort of patients**



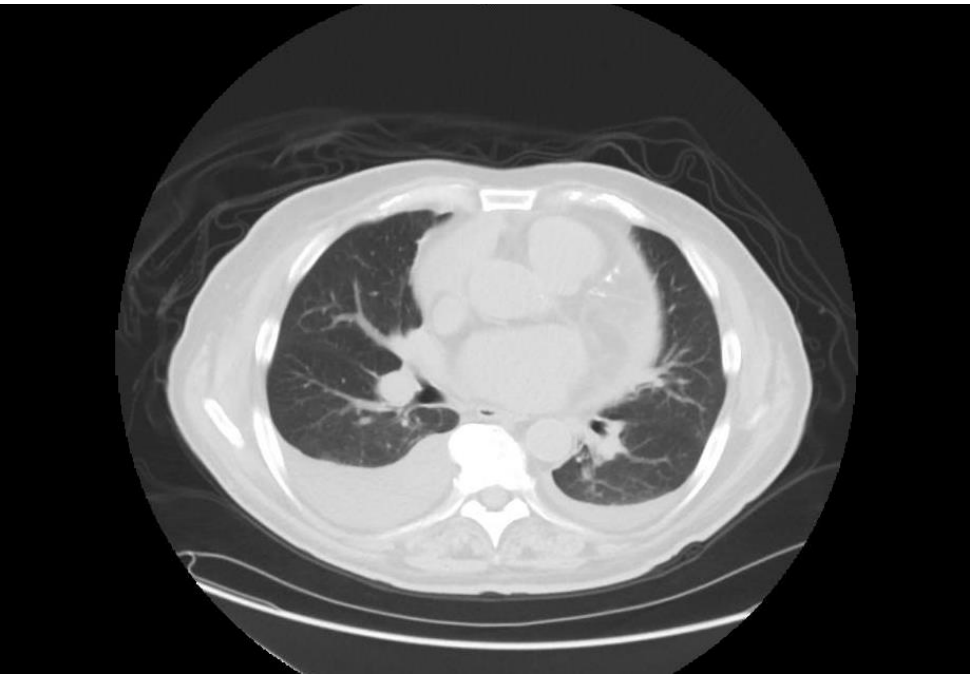
Case Study

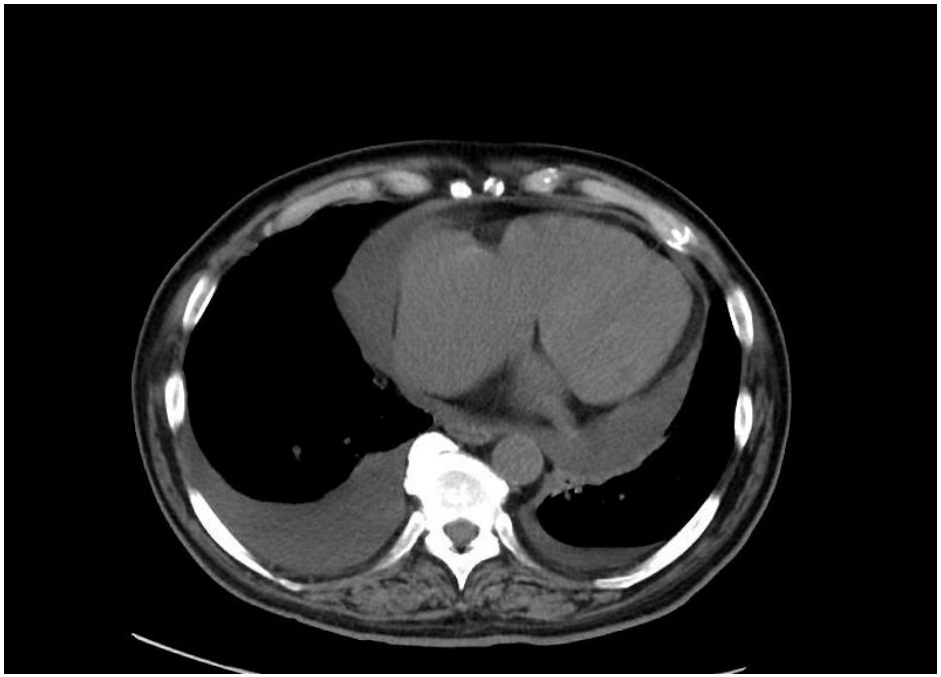
- 75yo man:
  - New AML diagnosed in 2014 – 34% myeloblasts
    - Normal karyotype, isolated IDH2 R140Q mutation
    - 7+3 → achieves a complete remission
    - 3 cycles of intermediate dose ara-c consolidation (1.5g/m2)
  - Relapses in 2015 (1 year after initial diagnosis) – 20% myeloblasts
    - Normal karyotype, isolated IDH2 R140Q mutation
    - Decitabine x 2 cycles with no remission
    - Starts on AG-221 in October 2015



Memorial Sloan Kettering Cancer Center

CT Chest – February 11, 2016





- Started Dexamethasone 10mg bid with rapid resolution of symptoms
- Rapid taper of dex without recurrence of symptoms

Dose-escalation and Serious Adverse Events

Dose-escalation

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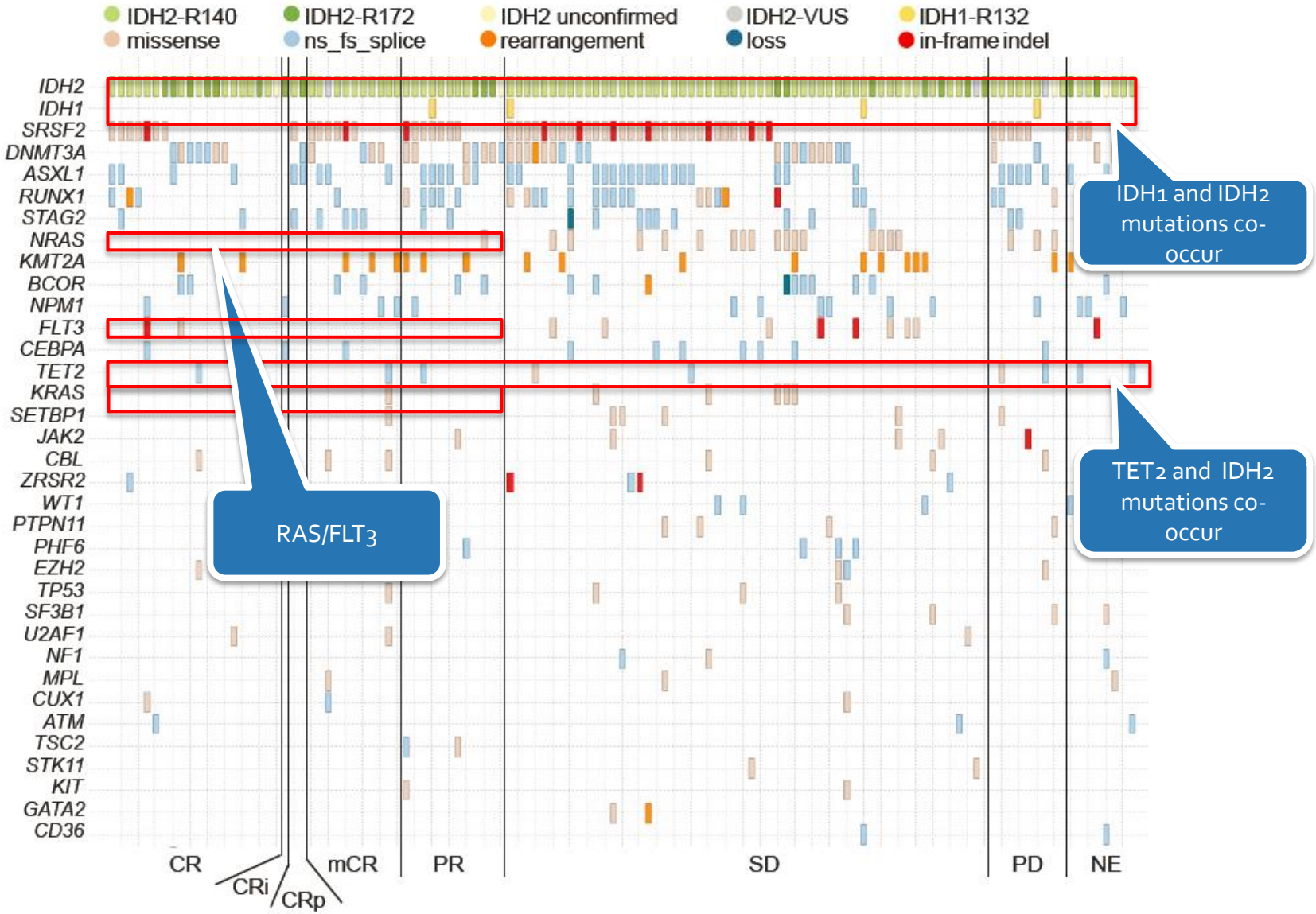
} **Differentiation Syndrome?**

Genetic (Foundation-Heme Panel)Profiling of Patients on Study at Time of Screening



Take Home Points

- IDH2 inhibition has remarkable efficacy as a single agent in relapsed/refractory AML.
  - Response may depend on co-occurring mutations and clonal evolution
- Responses may not be seen for multiple cycles
  - Biomarkers for who is destined to respond
- Beware of differentiation syndrome. Despite late onset and potentially atypical presentation.

Ongoing Questions (many)

- How "deep" are the remissions that are achieved with IDH2 inhibition?
  - At the time of morphologic CR, what proportion of patients are MRD positive (next gen sequencing and flow)

- How does the depth of remission translate into:
  - An ability to stop an IDH2 inhibitor in patients who respond
  - Outcomes post allo-transplant

Next Steps

- **Combination studies:**
  - **Induction chemotherapy (ongoing study)**
  - **Hypomethylating agents (ongoing study)**
  - **"novel-novel" (in development)**

- **Maintenance therapy**
  - **Post induction/consolidation for patients in CR (ongoing)**
  - **Post-transplant – especially in those patients who go to transplant with evidence of MRD**

Thank You!