SH2017-0299:
Acute Myeloid Leukemia with *BCR-ABL1*

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Case Presentation

- 60 yo male with no past medical history
- Fatigue x 2 weeks
- Weight loss
- No history of hematologic abnormality
- No hepatosplenomegaly

Admission Labs

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Complete Blood Count & Differential

WBC 9.2 B/L
RBC 2.69 T/L
Hemoglobin 8.1 g/dL
Hematocrit 24.2%
MCV 90 fL
MCH 30.1 pg
MCHC 33.5 g/dL
RDW 16
Platelets 11 B/L

Neutrophils 35%
Lymphocytes 23%
Monocytes 2%
Eosinophils 13%
Basophils 1%
Bands 4%
Blasts 22%

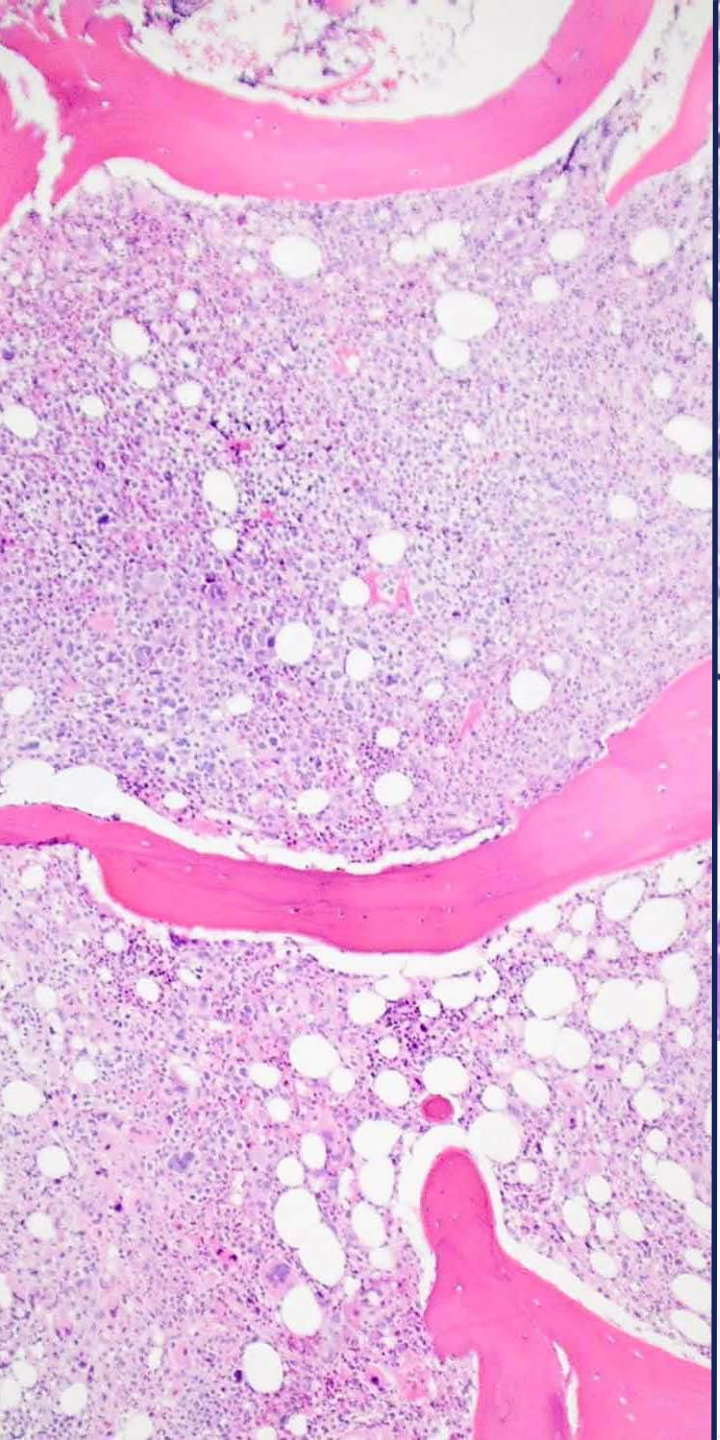
D-Dimer:
1261 ng/mL

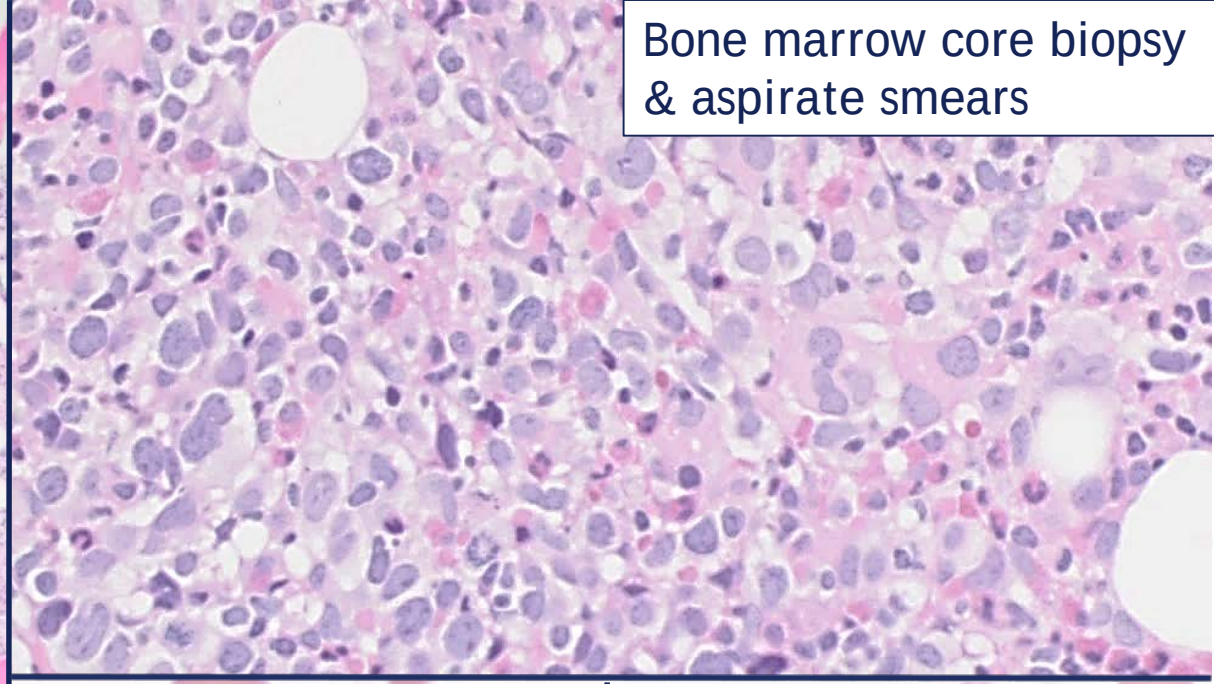
Fibrinogen:
793 mg/dL

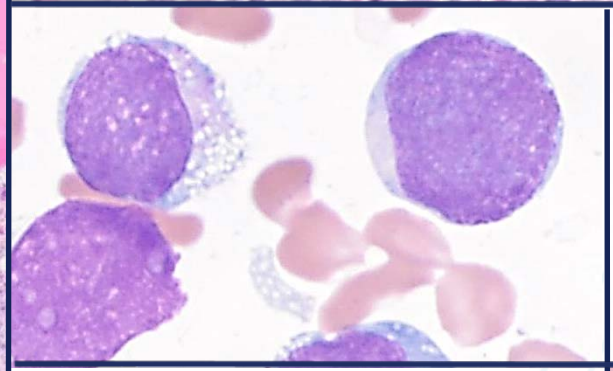
LD:
3400 IU/L

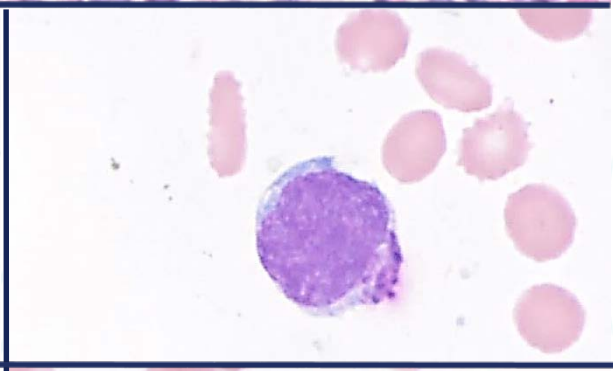
Peripheral blood smear: Many circulating blasts.

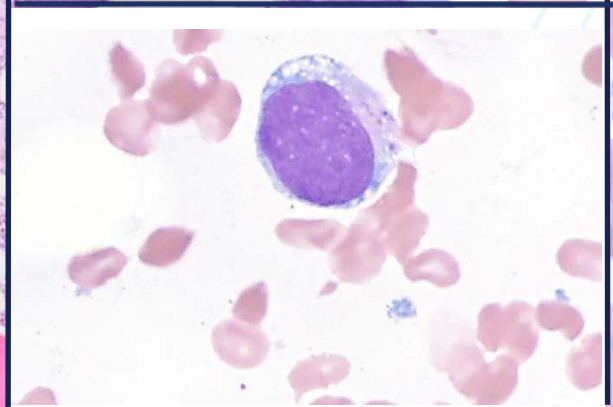
Bone marrow core biopsy & aspirate smears

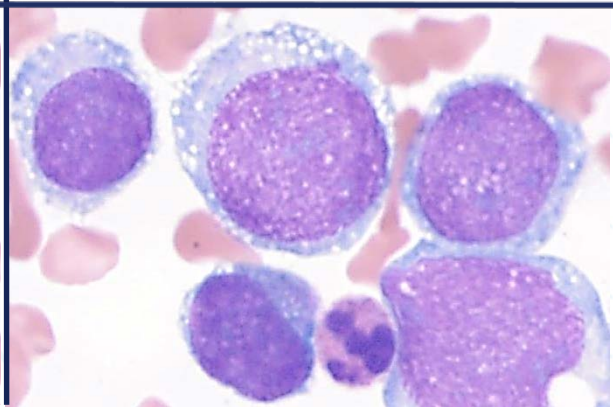




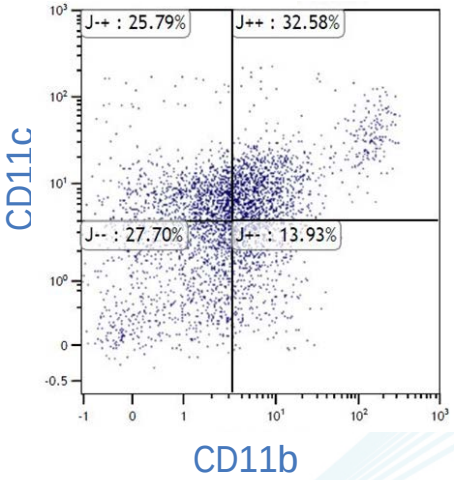


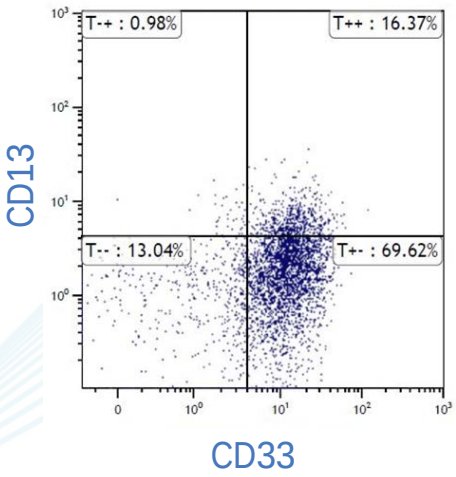


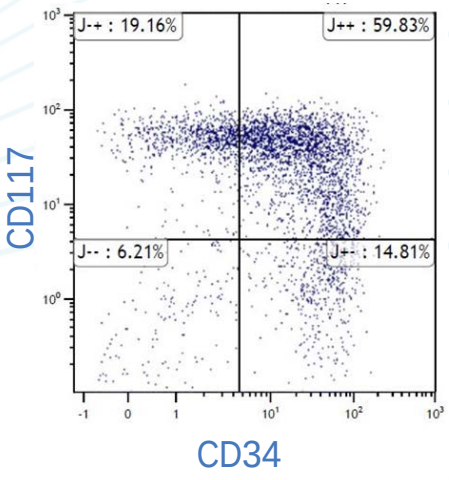


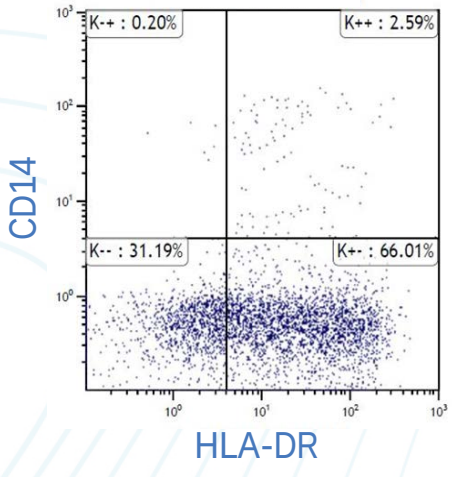


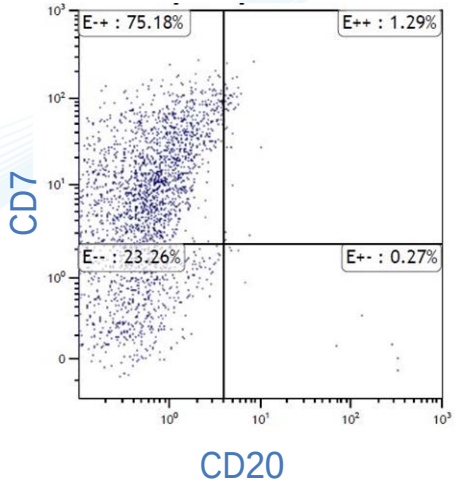
Flow Cytometry

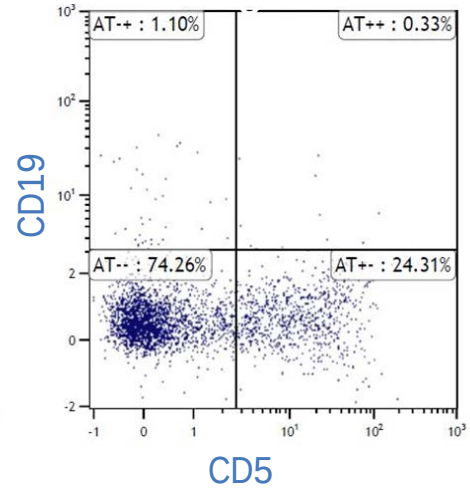


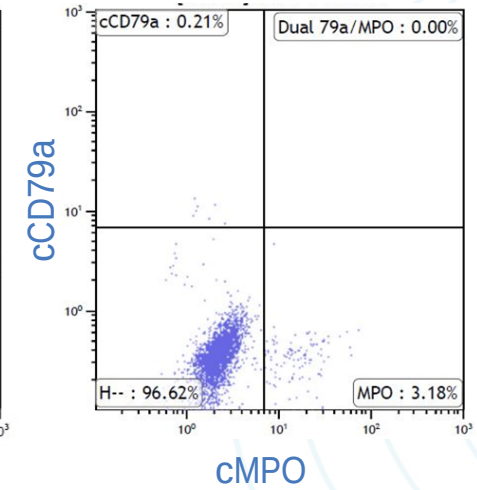


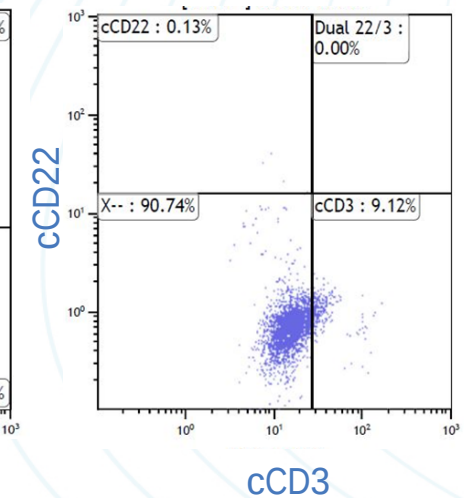




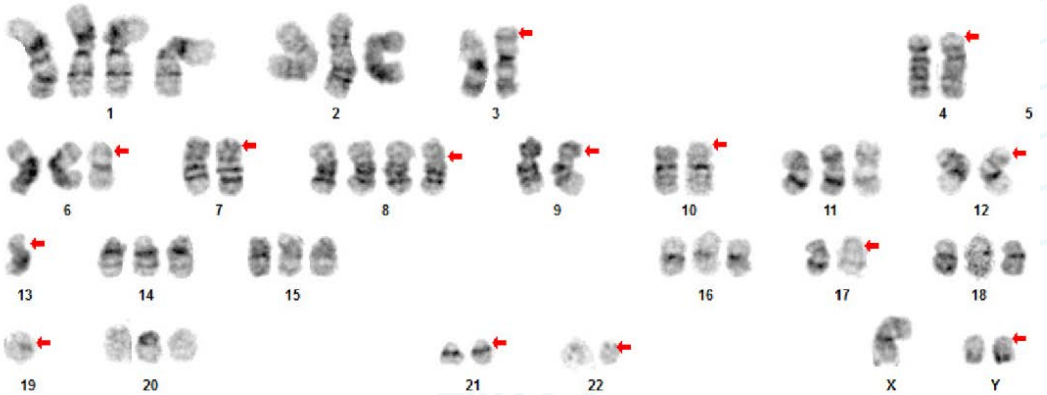




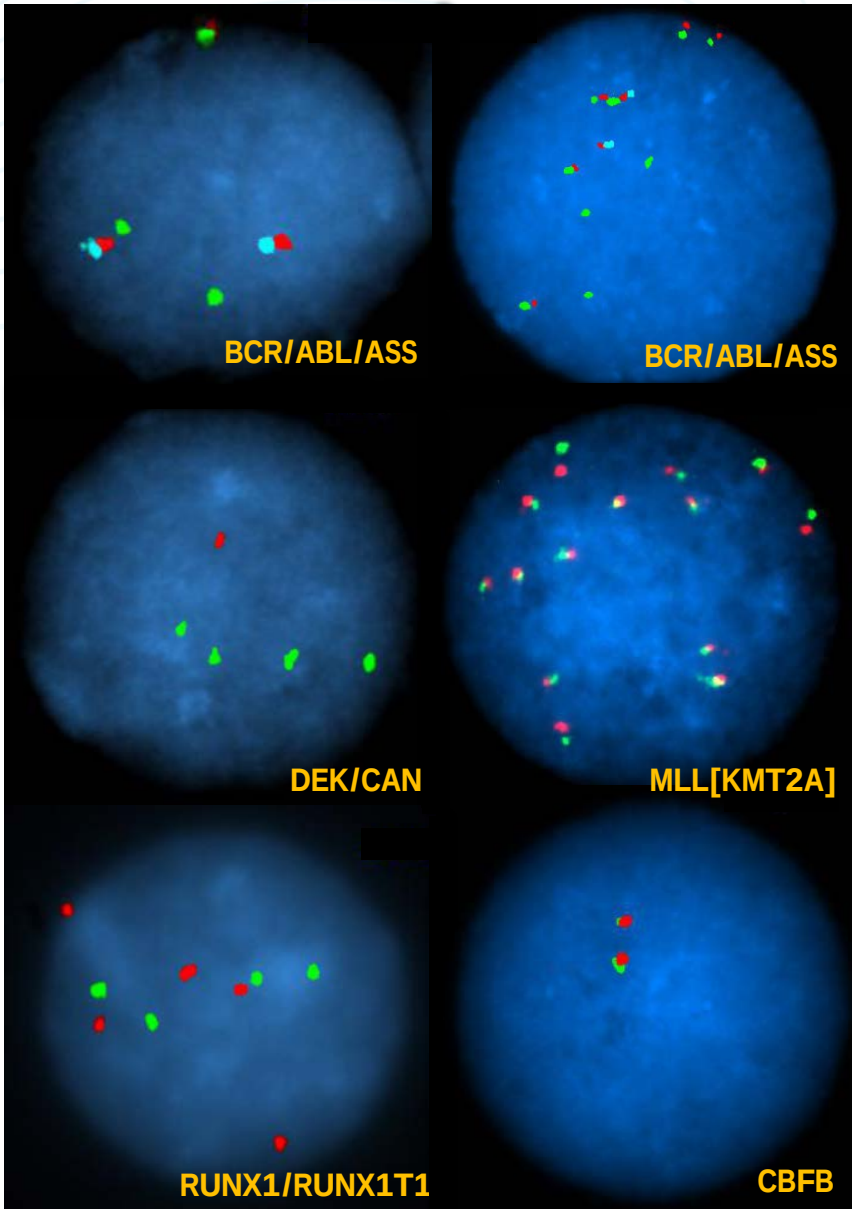




Cytogenetic Findings



51-69,XY, +Y,+1,+2,+3,+6,i(6)(p10),+8,
t(9;22)(q34;q11.2) ,+10,+11,+12,+13,
del(13)(q12q14),+14,+15,+16,+18,+19,+20,
+der(22)t(9;22) **[cp4]** /46,XY **[10]**



Molecular Genetic Findings

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RT PCR Results

- **p190 BCR-ABL1** fusion transcript detected
  - 30.103%
- p210 BCR-ABL1 fusions transcripts e13/a2 and e14/a2 not detected

NGS 48-Gene Panel

Illumina TruSight™ myeloid sequencing panel (MiSeq)

- ***TP53* mutation** detected
  - Nucleotide change: c.548C>G
  - Amino acid change: p.S183*
  - Altered allele freq: 61.6%
- Remaining 47 genes tested negative, including ABL kinase mutation

Diagnosis:
Acute myeloid leukemia with *BCR-ABL1*

- t(9;22)(q34.1;q11.2) results in the formation of the Philadelphia (Ph) chromosome and the chimeric *BCR-ABL1* fusion gene
  - CML
  - Ph+ ALL
  - **<1% of AML** cases
- *Provisional entity in the 2016 WHO classification*
  - Must be distinguished from myeloid blast crisis of CML
  - Exclude mixed phenotype acute leukemia with *BCR-ABL1*
- Poor risk group

Jaffe et al. *Hematopathology, 2e* (2016)

AML with *BCR-ABL1*: An emerging entity

- Proliferation of *BCR-ABL1*-positive blasts on presentation creates a diagnostic dilemma
- Soupir et al 2007 – 16 cases of Ph+ AML
  - Morphologic and phenotypic overlap with CML
    - Ph+ AML presented less often with splenomegaly, lacked basophilia, lower bone marrow cellularity
- Nacheva et al 2010 and 2013 – 6 cases of Ph+ AML
  - Searched for specific genomic profiles using aCGH
    - *BCR-ABL1*+ AML displays characteristics of lymphoid disease
- Neuendorff et al 2016 – 126 cases of Ph+ AML since 1975
  - Presented common clinical and molecular features
    - p190 and p210 are nearly equally distributed
    - Provided clinical algorithm

Differentiating CML in myeloid blast crisis from AML with *BCR-ABL1*

CML in MBC	AML with *BCR-ABL1*
Antecedent blood disorder, unexplained leukocytosis	No antecedent blood disorder
Splenomegaly	Absence of splenomegaly
Basophilia ≥ 2%	No basophilia
Near 100% marrow cellularity	<100% marrow cellularity; median 80%
Typical AML blast crisis phenotype	Aberrant CD19, CD7 and TdT more common
Ph+ in near 100% of cells	Ph+ in <100% of cells
p210 transcript in >99% of cases	p190 and p210 detected in nearly equal distribution
	Loss of *IKZFI* and *CDKN2A* and cryptic deletions within *IGH* and *TCR* genes

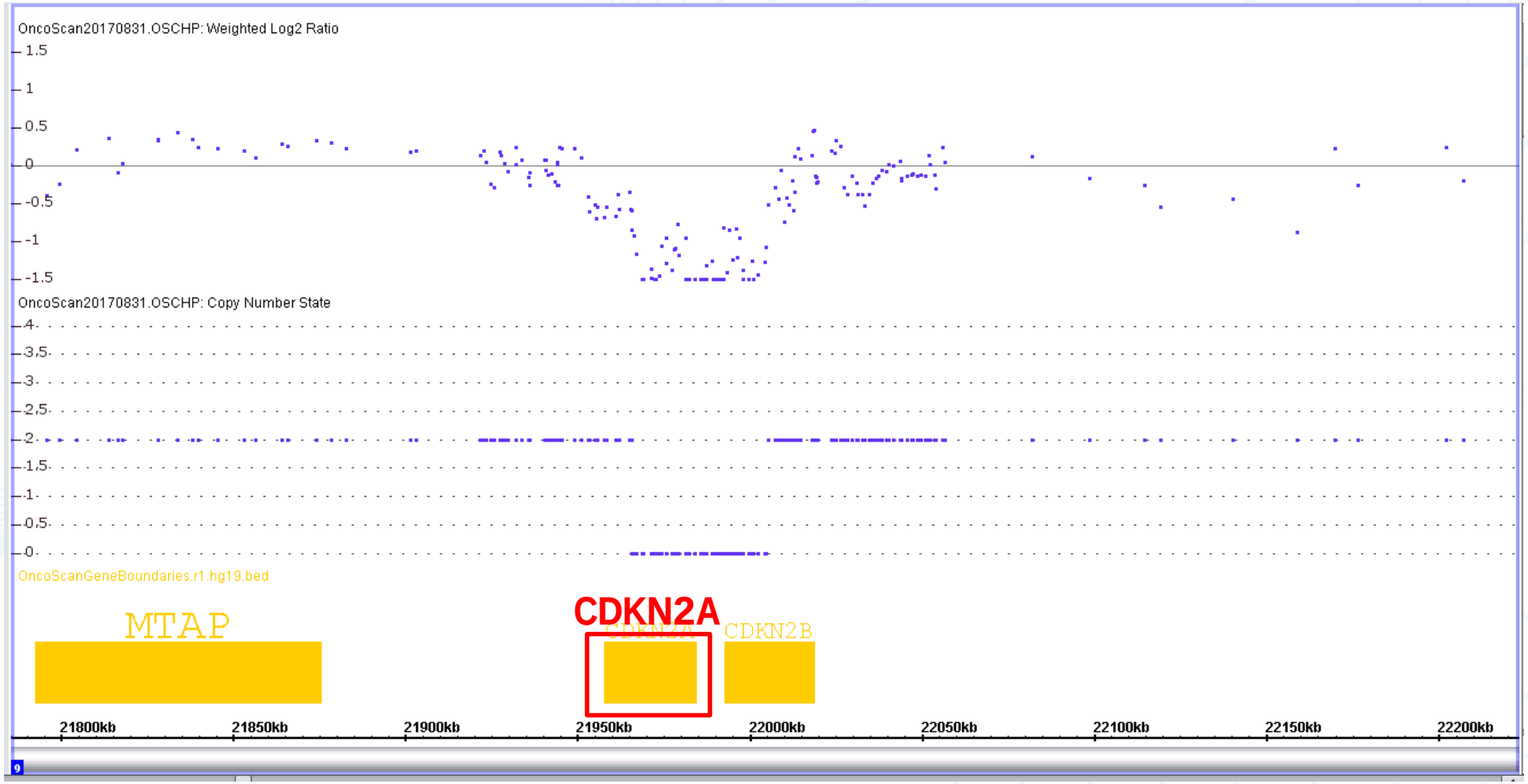
Jaffe et al. *Hematopathology*, 2e (2016)

AML with *BCR-ABL1* Carries Unique Genome Imbalances

- Nacheva et al used aCGH to perform a comparative study between several *BCR-ABL1*+ entities
  - Findings similar to Ph+ ALL and lymphoid blast crisis of CML
    - Loss of *IKZF1* and/or *CDKN2A* genes were recurrent findings in AML with *BCR-ABL1*
    - Accompanied by cryptic deletions within the *IGH* and *TRG@* genes
      - Ch14:105,405.050-105,415,455
  - Aberrations found to be absent in myeloid blast crisis of CML
- Unique loss provides a test to enable differentiation
- Further evidence for a unique biology

Nacheva et al. *Br J Haematol* (2013)

Deletion Detected at CDKN2A by OncoScan



Patient Follow-Up

- Induction chemotherapy and sirolimus plus dasatinib
- Induction failure
  - Repeat biopsy at day 30 revealed persistent AML
- Died <45 days following initial diagnosis
- Contribution of *TP53* mutation?

Neuendorff et al. *Ann Hematol* (2016)

Final Panel Diagnosis: Acute Myeloid Leukemia with *BCR-ABL1*

- Provisional entity in the 2016 WHO classification
- Diagnostic challenge with potential therapeutic implications
  - Our diagnosis is supported by:
    - Aggressive clinical course, absence of splenomegaly or basophilia, Ph+ in <100% of cells, and presence of p190 transcript
- Array CGH has identified recurrent genome features similar to Ph+ lymphoid disease
  - May allow distinction from CML in myeloid blast crisis