



# A preliminary analysis of FLAM (Italian Non-Interventional Multi-center Study of FLT3 mutated AML patients): FLT3 receptor gene mutational analysis and FLT3 inhibitors administration in the real-life clinical practice

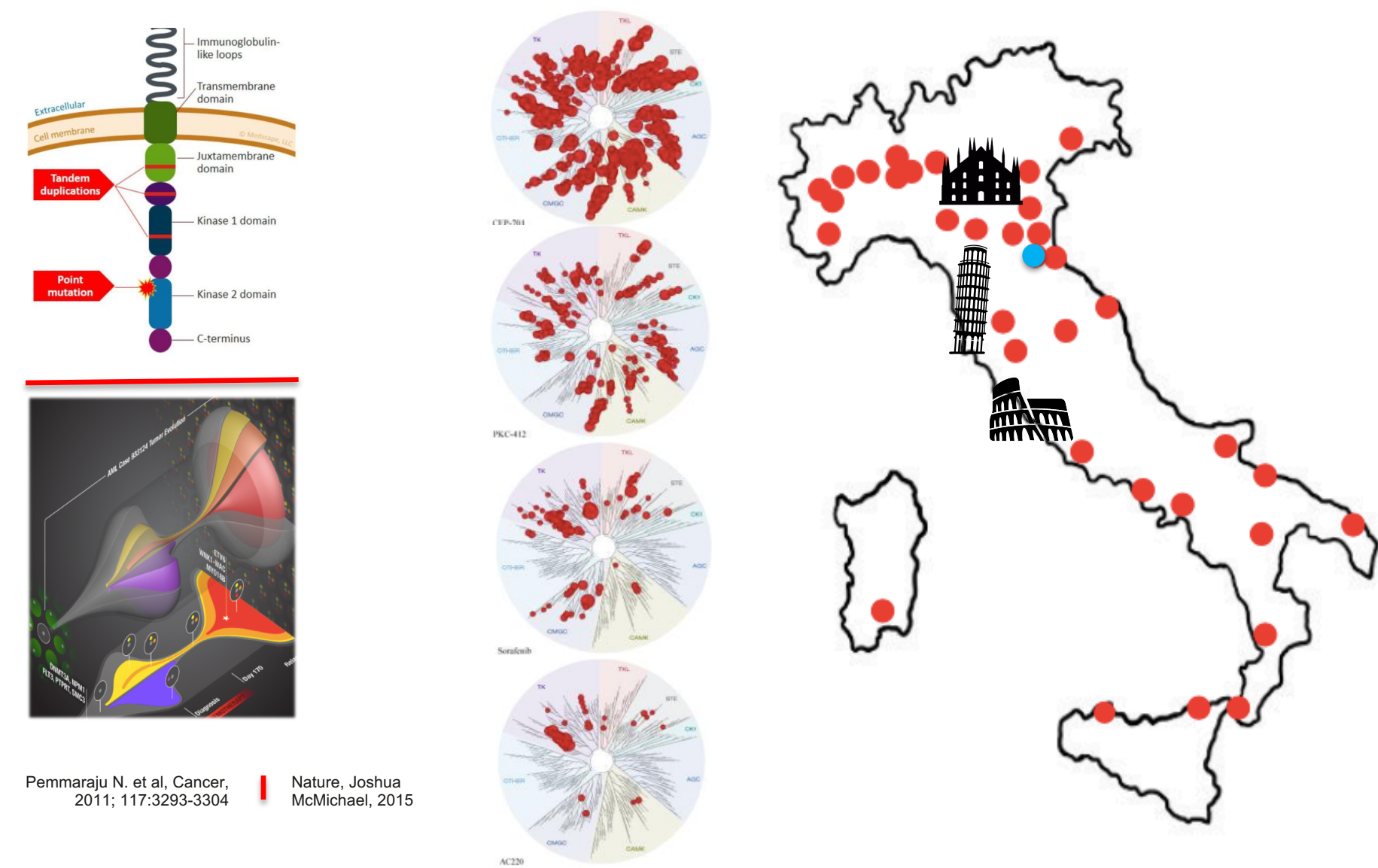
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## Background

FLT3 receptor gene has been reported to be mutated in about 30% of AML, with two different kinds of mutations identified: in-frame duplications within the juxtamembrane region (FLT3-ITD) and point mutations in the tyrosine kinase domain (FLT3-TKD). In term of prognosis, the proper role of these mutations is still debated. Moreover, FLT3 mutations are often subjected to clonal evolution, thus how to properly monitor FLT3 mutated clones, evaluate minimal residual disease, manage FLT3 inhibitors (FLT3i) are only some of the open issues. FLAM is an observational study involving FLT3 positive AMLs to gain clinical and molecular data useful to ameliorate real-life physicians' management of this disease. Here we report the results of a preliminary analysis of the retrospective phase of the study.



Pemmaraju N. et al, Cancer, 2011; 117:3293-3304

Nature, Joshua McMichael, 2015

## Objective

FLAM is an observational study involving FLT3 positive AMLs to gain clinical and molecular data useful to ameliorate real-life physicians' management of this disease. Here we report the results of a preliminary analysis of the study.

## Materials & Methods

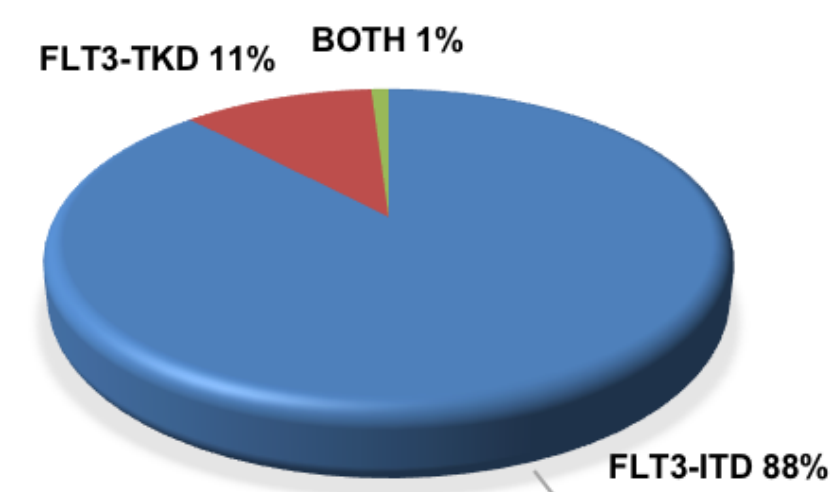
The retrospective phase of FLAM multi-center observational study enrolled each AML patient treated in 33 participating Italian centers detected to carry a FLT3 mutation since 2012.

Clinical and molecular data were collected in accordance with GCP and Helsinki declaration in electronic case report forms. Results are reported as median and minimum and maximum value for continuous variables and as frequencies and percentages for categorical ones.

**289 patients** with *FLT3* mutation at diagnosis;

- **Median age** at diagnosis: **62 years** (min-max: 18-94);
- **M:F ratio** = 141:148;
- **AML type**: *De novo* 88.2 %; Secondary 10.0 %; Therapy-related 1.8 %.

- **FLT3 mutations** detected:
  - **FLT3-ITD**: 255/289 (88 %);
  - **FLT3-TKD**: 32/289 (11 %);
  - **Both** mutations: 2/289 (1 %)



## Results

### 1 – Molecular biology

*Technical method used to assess **FLT3 status**:*

1. **Capillary electrophoresis** in 163 of 226 (72 %) patients;
2. **Sanger Sequencing** in 47 of 226 (21 %) patients;
3. **Next generation sequencing** (NGS) in 16 of 226 (7 %) patients.

❖ **FLT3-ITD allelic ratio** was available in 62 of 257 (24 %) ITD patients and was greater than or equal to 0.5 in 35/62 (56 %) .

➤ A more frequent association between **FLT3-ITD** and **normal karyotype** and between **FLT3-TKD** mutation and **other cytogenetic alterations** has been observed ( $p = 0.045$ ).

➤ 19/289 (7 %) patients affected by a **FLT3 positive AML** at diagnosis underwent a disease clonal evolution with a **FLT3 negative AML** progression or relapse.

### 2 – Treatment options and FLT3i administration

**First-line:**

- **Intensive chemotherapy** represented the induction in **73 %** (211/289) of patients.
- **FLT3i** were administered as first-line of therapy in **13 %** (36/289):
  - in 26/36 (72.2 %) with **intensive chemotherapy**;
  - in 10/36 (27,8 %) with **HMA**s.

**Rescue:**

- **FLT3i** as **rescue therapy** in **36 %** (62/171) of the cases (47/62 single-agent and 15/62 in combination).

**Re-induction therapy:**

- in **28 %** of the cases (10/22 single-agent and 12/22 in combination).

**Maintenance after-HSCT:**

- 9/289 (3 %) patients received a **FLT3i** as **maintenance**.

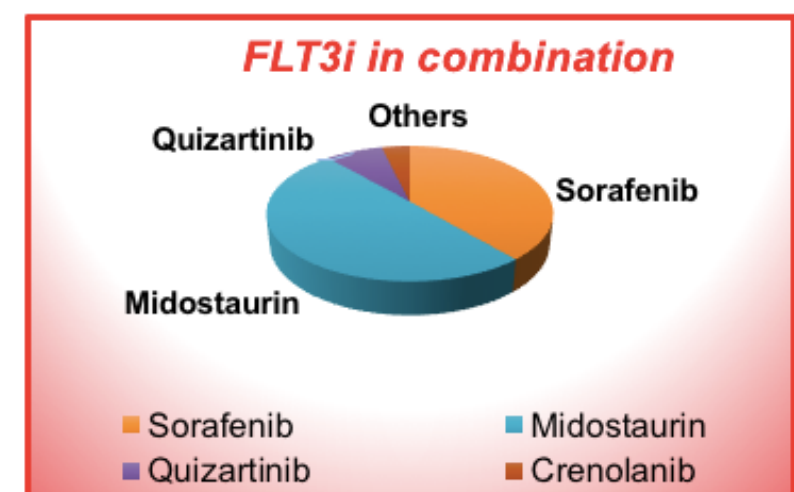
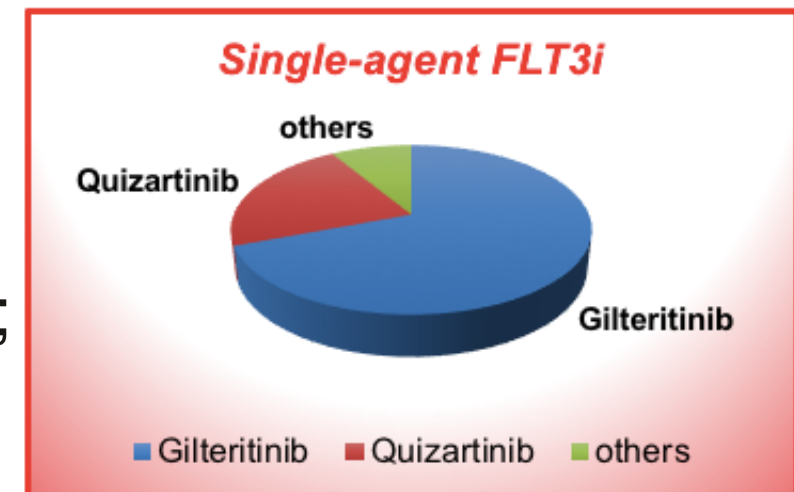
### 3 – FLT3 inhibitors choices

A **FLT3i** has been administered as **single-agent 81** times:

1. **Gilteritinib** (56/81, 69,1 %);
2. followed by **Quizartinib** (18/81, 22,2 %);
3. others (7/81, 8,6 %);

Among the **52** documented **combinations** of a FLT3i with other drugs:

1. **Midostaurin** (26/52, 50 %);
2. **Sorafenib** (20/52, 39 %);
3. **Quizartinib** (4/52, 7,7 %);
4. **others** (2/52, 3,8 %).



## Discussion

- ✓ **7 %** of FLT3+ AML underwent a **disease clonal evolution** with a FLT3- AML progression/relapse.
- ✓ **NGS technology** availability and application is still limited in routine clinical practice (7 % of patients).
- ✓ **FLT3i** administration as part of **induction** therapy was infrequent in our real-life experience.
- ✓ Its adoption **increases** as **first salvage therapy** (R/R : 28/36 %), whereas it **drops** after HSCT (3 %)
- ✓ As expected, **Midostaurin** as part of induction and **Gilteritinib** as first rescue are the most frequently used.

## References

Nature, Joshua McMichael, 2015  
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