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Outcome of AML patients with *IDH2* mutations in real world before the era of IDH2 inhibitors

Laetitia Largeaud[a,b,c,1], Emilie Bérard[d,e,1], Sarah Bertoli[b,c,f,1], Stéphanie Dufrechou[a], Naïs Prade[a], Noémie Gadaud[f], Suzanne Tavitian[f], Pierre Bories[g], Isabelle Luquet[a], Audrey Sarry[d], Véronique De Mas[a,b,c], Françoise Huguet[f], Eric Delabesse[a,b,c,2], Christian Récher[b,c,f,*,2]

[a] Laboratoire d'Hématologie, Centre Hospitalier Universitaire de Toulouse, Institut Universitaire du Cancer de Toulouse Oncopole, Toulouse, France
[b] Université Toulouse III Paul Sabatier, Toulouse, France
[c] Cancer Research Center of Toulouse, UMR1037-INSERM, ERL5294 CNRS, Toulouse, France
[d] Service d'Epidémiologie, Centre Hospitalier Universitaire de Toulouse, Toulouse, France
[e] UMR 1027, INSERM-Université de Toulouse III, Toulouse, France
[f] Service d'Hématologie, Centre Hospitalier Universitaire de Toulouse, Institut Universitaire du Cancer de Toulouse Oncopole, Toulouse, France
[g] Réseau Onco-occitanie, Institut Universitaire du Cancer de Toulouse Oncopole, Toulouse, France

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ABSTRACT

Describing the prognosis of sub-groups of acute myeloid leukemia (AML) patients treated in real world with current therapies is becoming increasingly relevant to estimate the benefit that new targeted drugs will bring in the field. This is particularly the case when novel drugs are registered on the basis of non-randomized studies. IDH2 inhibitors have recently emerged as promising drugs in patients with *IDH2*^{R140} or *IDH2*^{R172} mutations. Enasidenib, a first-in-class IDH2 inhibitor, has been approved following promising results of a phase 1–2 clinical trial in relapsed or refractory AML patients with *IDH2* mutations. In this study, we described the characteristics, treatments and outcome of 75 *IDH2* mutated patients both at diagnosis and relapse or refractory disease. Among the 33 relapsed/refractory AML patients with either *IDH2*^{R140} or *IDH2*^{R172}, 28 (84.8%) patients received salvage therapy and 14 achieved a complete response (50%). Median duration of response was 15.2 months. Median, 1-y, 3-y and 5-y OS were 15.1 months (IQR, 4.6–37.7), 53.1% (95% CI, 33.2–69.5), 29.2% (95% CI, 12.6–48.1) and 24.4% (95% CI, 9.3–43.1), respectively. In responding patients, median OS was 37.7 months and 1-y, 3-y and 5-y OS was 85.7%, 57.1% and 47.6%, respectively. In non-responding patients, median OS was 5.0 months (IQR, 4.5–8.6) and 1-y and 3-y OS was 17.9% and 0%, respectively. Thus, a substantial number of R/R AML patients with *IDH2* mutations can be salvaged by current treatments and benefit from prolonged survival. It is expected that novel targeted agents such as enasidenib will further improve efficacy and safety in the next future.

1. Introduction

Somatic mutations of isocitrate dehydrogenase 2 gene, either *IDH2*^{R140} or *IDH2*^{R172}, occur in 5–15% and 1–4% of AML, respectively [1]. *IDH2* mutations are frequently, but not exclusively, found in cytogenetically normal AML. *IDH2*^{R140} and *IDH2*^{R172} mutations induce a neomorphic enzyme that overproduces 2-hydroxyglutarate, an oncometabolite which can inhibit many cellular processes and alter epigenetics and myeloid differentiation [2,3]. Moreover, these mutations have been described in clonal hematopoiesis, are considered as early event driving leukemogenesis, stable at relapse and thus, have emerged as promising therapeutic targets [4]. However, despite a common mechanism of action, both mutations differ regarding co-occurring mutational events and outcome. At diagnosis, *IDH2*^{R140} mutations are associated with *NPM1* and *DNMT3A* mutations whereas in the relapse/refractory setting, mutations in *SRSF2*, *DNMT3A*, *RUNX1*, *ASXL1, NRAS* and *BCOR* genes emerge as the most frequent co-mutations [1,5,6]. The prognostic impact of *IDH2*^{R140} remains unclear and may depend on

* Corresponding author at: Service d'Hématologie, Institut Universitaire du Cancer de Toulouse Oncopole, 1 avenue Irène Joliot-Curie, 31059, Toulouse cedex 9, France.
E-mail address: recher.christian@iuct-oncopole.fr (C. Récher).
[1] Contributed equally to this work.
[2] Co-senior authors.

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mutational context especially *DNMT3A* mutations [6]. Contrasting with *IDH2*^{R140}, *IDH2*^{R172} mutations are mutually exclusive with *NPM1* and other class-defining mutations whereas it is frequently co-mutated with DNMT3A. Therefore, AML with *IDH2*^{R172} has been recognized as a defined subgroup of the AML genomic classification [6].

Enasidenib, an oral, targeted, small-molecule inhibitor of mutant IDH2 has been evaluated as a single agent in a phase 1 dose-escalation and dose-expansion study in mutant *IDH2* patients refractory to standard induction chemotherapy or relapsing after complete remission (R/R AML) [7]. Compared to what is known with intensive salvage in this setting, enasidenib was well tolerated with a low frequency of treatment-related adverse events of grade 3 or higher, mainly indirect hyperbilirubinemia, differentiation syndrome and leukocytosis. The overall response rate was 40.3% including 19.3% complete remission (CR) and 6.8% CR with incomplete hematologic recovery (CRi). Median overall survival was 9.3 months and reach 19.7 months in CR patients. Based on these promising results, enasidenib has been recently approved by the Food and Drug Administration.

Regardless of the mutational context, the outcome of patients with R/R AML is very poor and no standard of care has been established in this situation [8,9]. Intermediate dose cytarabine (IDAC) has been recently settled as the control arm in large phase 3 placebo-controlled randomized trials for R/R AML [10,11]. In these trials, CR/CRi rates with IDAC monotherapy were 18.9%–22.9% and median overall survival was 6.1–6.3 months. Adding anthracyclines, purine analogs or gemtuzumab ozogamycin to cytarabine likely improves overall response rate as compared to IDAC but the gain in overall survival of these more intense salvage treatments remains uncertain [8,9]. Few studies have assessed the outcome of R/R AML patients with *IDH2* mutations with classical salvage therapies [12,13].

The aim of this study was to describe characteristics and outcome of patients with *IDH2* mutations treated in routine practice by first line intensive chemotherapy with a special focus on R/R patients to provide a reference to be compared with novel targeted therapies.

2. Methods

2.1. Patients

This study included 1,996 AML patients admitted at the Hematology department of Toulouse University Hospital-IUCT-O and/or registered in the regional oncology network from 1st January 2000 to 31st December 2016 [14]. Data are gathered in an electronic clinical research form. A written informed consent was obtained from all patients in accordance with the Declaration of Helsinki, allowing the collection of clinical and biological data in an anonymized database. Cytogenetic and molecular risk classifications were in accordance with the Medical Research Council and ELN 2010 classifications, respectively [15,16]. Details on fisrt-line chemotherapy regimen used over time have been reported elsewhere [8,14]. Salvage therapy regimen were based on single agent cytarabine (high-dose cytarabine: 3 g/m^2/12 h, d1-4; intermediate dose-cytarabine: 1 g–1.5 g/m^2/12 h, d1-4 or 1 g/m^2/d, d1-5), combination of an anthracycline plus cytarabine (daunorubicin 60 mg/m^2/d, d1-3 or idarubicin 12 mg/m^2/d, d1-3 or amsacrine 200 mg/m^2/d; d1-3 + cytarabine 1.5-3 g/m^2/12 h, d1-4) or FLAG-Ida regimen (fludarabine 30 mg/m^2/d, d1-5; cytarabine 2 g/m^2/d, d1-5; idarubicin 10 mg/m^2/d, d1-3 and G-CSF 5 µg/kg/d, d1-5).

2.2. Screening of IDH2 mutations

Molecular analyses were performed on diagnosis samples as initial screening for the recent period or retrospectively from samples stored in our tumor cell bank (INSERM, DC-2008-307-CPTP1 HIMIP). *IDH2*^{R140} or *IDH2*^{R172} mutations were screened using high resolution melting PCR (HRM-PCR). HRM-PCR was performed with 40 ng DNA, 1X LC480 HRM High Resolution Melting (Roche) and specific DNA primers encompassing the R140 (F-GAAAGATGGCGGCTGCAGT; R-TGTTTTTG CAGATGATGGGC) and R172 codon (F-GATGTGGAAAAGTCCCAAT GGA; R-CACCCTGGCCTACCTGGTC) at a final concentration of 0.2 µM. PCR program is initiated at 95 °C for 10 min followed by 50 cycles of 15 s at 95 °C, 15 s at 63 °C and 25 s at 72 °C followed by the generation of the high resolution melting curve according to the manufacturer (LC480, Roche). Positive hits were verified by Sanger sequencing to confirm and define IDH2 mutations. The sensitivity of HRM-PCR analysis is 5% whereas Sanger sequencing sensitivity is 10%. Patients positive by HRM-PCR and negative by Sanger were considerate as non-mutated for IDH2.

2.3. Statistical analysis

Resistant disease (i.e., refractory AML) was defined as failure to achieve CR or CRi after induction chemotherapy and relapse was defined as bone marrow blasts ≥5% or reappearance of blasts in the blood; or development of extramedullary disease according to ELN 2010 guidelines [16]. Endpoints, including response, event-free survival (EFS), relapse-free survival (RFS) and overall survival (OS), were assessed according to standard criteria [16].

We described patients' characteristics at diagnosis and at relapse using number and frequency for qualitative data; median (and interquartile range (IQR)) for quantitative data. For survival analyses of EFS, RFS and OS, Kaplan-Meier survival curves were drawn and described using median (IQR) and survival at 1-, 3- and 5-year. Differences in survival functions were tested using the Log-Rank test. All reported p-values were two-sided and the significance threshold was < 0.05. Statistical analyses were performed on STATA® version 14.2 (STATA Corp., College Station, TX).

3. Results

3.1. Study population

Out of the 1,996 AML patients recorded in the IUCT-O AML database, molecular screening of *IDH* mutations was performed in 674 patients. Age, white blood cell count, performance status, *de novo* status, cytogenetic risk, intensive chemotherapy and period of time were the main factors significantly associated with *IDH* screening (Supplementary Table 1). Characteristics of patients with *IDH2* mutations are depicted in Table 1.

3.2. AML with *IDH2*^{R140} mutation

IDH2^{R140} mutations were detected in 60 patients (8.9%) with *IDH* screening. Median follow-up was 75.8 months (IQR, 30.9–101.4). Nineteen patients (32.2%) had secondary AML. Cytogenetic risk was favorable, intermediate or adverse in 3.3%, 81.7% and 15.0% of *IDH2*^{R140} patients whereas 33.3%, 24.6%, 26.3% and 15.8% were classified as favorable, intermediate-1, intermediate-2 or adverse according to ELN 2010 classification. *NPM1* mutation was found in 20 out of 55 patients (36.4%). Most patients (n = 50, 83.3%) received induction chemotherapy as first line treatment whereas 5 (8.3%) and 5 (8.3%) patients were treated by hypomethylating agents or best supportive care, respectively.

Following induction chemotherapy, 40 patients (80.0%) achieved CR/CRi. Allogeneic stem cell transplantation was performed in 10 CR/CRi patients (25%). Median EFS was 17.7 months (IQR 7.9-not reached) and 1-year (y), 3-y and 5-y EFS was 62.0% (95% confidence interval [CI], 47.1–73.8), 38.8% (95% CI, 25.2–52.2) and 35.8% (95% CI, 22.3–49.5), respectively (Fig. 1A). In CR/CRi patients, median RFS was 25.9 months (IQR, 10.2-not reached) and 1-y, 3-y and 5-y RFS was 70.0% (95% CI, 53.3–81.7), 48.5% (95% CI, 32.0–63.2) and 44.8% (95% CI, 28.3–60.0), respectively. Median OS was 39.8 months (IQR, 11.0-not reached) and 1-y, 3-y and 5-y OS was 70.0% (95% CI,

Table 1
Characteristics of AML patients with *IDH2*^{R140} or *IDH2*^{R172} mutations.

Characteristics	*IDH2*^{R140}	*IDH2*^{R172}
Sex – n. (%)	N = 60	N = 15
Male	35 (58.3)	8 (53.3)
Female	25 (41.7)	7 (46.7)
Age – years	N = 60	N = 15
Median (IQR)	63.6 [56.5–72.0]	62.9 [44.9–69.3]
ECOG performance status – n. (%)	N = 52	N = 11
0–1	38 (73.1)	10 (90.9)
2–4	14 (26.9)	1 (9.1)
Extramedullary involvement – n. (%)	N = 54	N = 12
Yes	12 (22.2)	2 (16.7)
No	42 (77.8)	10 (83.3)
AML subtype – n. (%)	N = 59	N = 15
De novo AML	40 (67.8)	11 (73.3)
Secondary	19 (32.2)	4 (26.7)
FAB classification – n. (%)	N = 59	N = 15
M0	6 (10.2)	1 (6.7)
M1	12 (20.3)	7 (46.7)
M2	20 (33.9)	4 (26.7)
M4	16 (27.1)	1 (6.7)
M5	0	1 (6.7)
M6	1 (1.7)	1 (6.7)
Unclassified	4 (6.8)	–
White blood cell count – giga per liter	N = 59	N = 15
Median (IQR)	8.8 [2.8–42.0]	1.7 [1.2–5.4]
Platelet count – giga per liter	N = 59	N = 15
Median (IQR)	70.0 [39.0–130.0]	82.0 [54.0–152.0]
Bone marrow blasts – n. (%)	N = 58	N = 14
Median (IQR)	51.0 [35.0–81.0]	40.5 [35.0–71.0]
Multilineage dysplasia – n. (%)	N =55	N = 14
Yes	6 (10.9)	0
No	49 (89.1)	14 (100.0)
Cytogenetic risk – n. (%)	N = 60	N = 15
Favorable	2 (3.3)	0
Intermediate	49 (81.7)	13 (86.7)
Adverse	9 (15.0)	2 (13.3)
ELN 2010 – n. (%)	N = 57	N = 12
Favorable	19 (33.3)	2 (16.7)
Intermediate-1	14 (24.6)	2 (16.7)
Intermediate-2	15 (26.3)	6 (50.0)
Adverse	9 (15.8)	2 (16.7)
***FLT3*-ITD – n. (%)**	N = 56	N = 14
Yes	6 (10.7)	0
No	50 (89.3)	14 (100.0)
***FLT3*-TKD – n. (%)**	N = 24	N = 4
Yes	0	0
No	24 (100.0)	4 (100.0)
***NPM1* – n. (%)**	N = 55	N = 14
Yes	20 (36.4)	2 (14.3)
No	35 (63.6)	12 (85.7)
***CEBPA* – n. (%)**	N = 30	N = 9
Yes	1 (3.3)	0
No	29 (96.7)	9 (100.0)
***IDH1*^{R132}**	N = 59	N = 14
Yes	0	0
No	59 (100.0)	14 (100.0)
DNMT3A	N = 35	N = 7
Yes	8 (22.9)	2 (28.6)
No	27 (77.1)	5 (71.4)
Albumin – g/liter	N = 54	N = 14
Median (IQR)	37.5 [31.0–42.0]	38.0 [35.0–40.0]
Normal–n. (%)	36 (66.7)	11 (78.6)
Low–n. (%)	18 (33.3)	3 (21.4)
LDH – UI/l	N = 56	N = 14
Median (IQR)	579.0 [307.5–929.5]	347.0 [231.0–382.0]
Normal – n. (%)	14 (25.0)	10 (71.4)
> Normal – n. (%)	42 (75.0)	4 (28.6)
Creatinine – µmol/liter	N = 55	N = 14
Median (IQR)	86.0 [74.0–98.0]	81.5 [63.0–94.0]
Bilirubin – µmol/liter	N = 53	N = 14
Median (IQR)	8.3 [6.1–12.0]	10.9 [5.4–16.5]
Fibrinogen – g/liter	N = 51	N = 14
Median (IQR)	4.2 [3.2–5.2]	4.3 [3.7–5.1]
Serum ferritin – µg/liter	N = 37	N = 9
Median (IQR)	423.0 [283.0–916.0]	417.0 [260.0–459.0]
Period – n. (%)	N = 60	N = 15
2000–2005	9 (15.0)	5 (33.3)
2006–2011	24 (40.0)	3 (20.0)
2012–2016	27 (45.0)	7 (46.7)

IQR, interquartile range; ECOG: Eastern Cooperative Oncology Group; AML, acute myeloid leukemia; ELN, European Leukemia Net.

55.3–80.7), 50.1% (95% CI, 34.3–64.0) and 43.9% (95% CI, 28.2–58.5), respectively (Fig. 1B).

In IDH wild type (wt) patients (n = 432), median OS was 23.6 months (IQR, 8.3–155.3) and 1-y, 3-y and 5-y OS was 65.1% (95% CI, 60.4–69.3), 42.7% (95% CI, 37.9–47.4) and 37.6% (95% CI, 32.8–42.4), respectively. OS was not significantly different for *IDH2*^{R140} patients and IDH wt patients (p log $_{rank\ test}$ = 0.2559) (Supplementary Fig. 1A).

3.3. AML with *IDH2*^{R172} mutation

IDH2^{R172} mutations were detected in 15 patients (2.2%). Median follow-up was 62.3 months (IQR, 45.4–132.8). Four patients (26.7%) had secondary AML. Cytogenetic risk was intermediate (86.7%) or adverse (13.3%) whereas 16.7%, 16.7%, 50.0% and 16.7% of *IDH2*^{R172} patients were classified as favorable, intermediate-1, intermediate-2 or adverse according to ELN 2010 classification. Of note, *IDH2*^{R140} co-mutation was found in 2 patients. Most patients (n = 13, 86.7%) received induction chemotherapy as first line treatment.

Following induction chemotherapy, 13 patients (100.0%) achieved CR/CRi. Allogeneic stem cell transplantation was performed in 4 CR/CRi patients (30.8%). Median EFS was 25.9 months (IQR 17.4-not reached) and 1-y, 3-y and 5-y EFS was 92.3% (95% CI, 56.6–98.9), 42.3% (95% CI, 15.6–67.1) and 42.3% (95% CI, 15.6–67.1), respectively (Fig. 1C). In CR/CRi patients, median RFS was 23.0 months (IQR, 14.2-not reached) and 1-y, 3-y and 5-y RFS was 76.9% (95% CI, 44.2–91.9), 42.7% (95% CI, 15.9–67.5) and 42.7% (95% CI, 15.9–67.5), respectively. Median OS was 41.0 months (IQR, 21.5-not reached) and 1-y, 3-y and 5-y OS was 92.3% (95% CI, 56.6–98.9), 58.7% (95% CI, 27.4–80.4) and 49.0% (95% CI, 19.4–73.3), respectively (Fig. 1D).

OS was not significantly different for *IDH2*^{R172} patients and IDH wt patients (p log $_{rank\ test}$ = 0.1484) (Supplementary Fig. 1B).

3.4. Relapsed or refractory AML with IDH2 mutations

The characteristics of the 33 relapsed/refractory AML patients with either *IDH2*^{R140} or *IDH2*^{R172} are shown in Table 2. Among them, 28 (84.8%) patients received salvage therapy (intensive chemotherapy, n = 13; hypomethylating agent, n = 8; allogeneic stem cell transplantation as salvage treatment in refractory patients, n = 3; other, n = 4). Fourteen patients achieved CR/CRi (50%), 7, 2 and 5 following intensive chemotherapy, hypomethylating agents, or other (including 1 allogeneic SCT as salvage treatment in refractory patients). Day-60 death rates following salvage treatment was 0%. Eight patients received allogeneic stem cell transplantation following salvage treatment. Four patients relapsed and median duration of response was 15.2 months (IQR, 10.5–18.3). Median, 1-y, 3-y and 5-y OS were 8.6 months (IQR, 3.9–29.3), 48.1% (95% CI, 30.4–63.8), 24.4% (95% CI, 10.5–41.4) and 20.4% (95% CI, 7.8–37.1), respectively. For the 28 patients receiving salvage therapy, median, 1-y, 3-y and 5-y OS were 15.1 months (IQR, 4.6–37.7), 53.1% (95% CI, 33.2–69.5), 29.2% (95% CI, 12.6–48.1) and 24.4% (95% CI, 9.3–43.1), respectively (Fig. 2A).

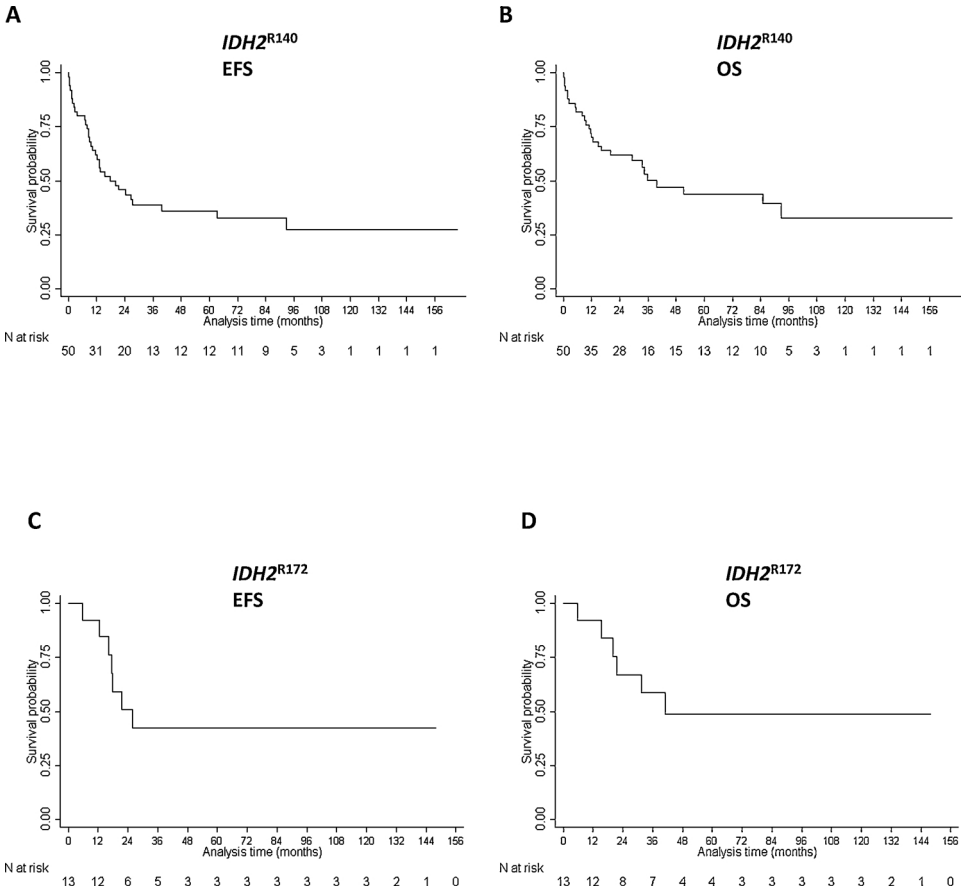

Fig. 1. (A) EFS and (B) OS from diagnosis in patients with *IDH2*^{R140} mutations treated by intensive chemotherapy; (C) EFS and (D) OS from diagnosis in patients with *IDH2*^{R172} mutations treated by intensive chemotherapy.

In CR/CRi patients (n = 14), median OS was 37.7 months (IQR, 21.5-not reached) and 1-y, 3-y and 5-y OS was 85.7% (95% CI, 53.9–96.2), 57.1% (95% CI, 24.9–79.8) and 47.6% (95% CI, 18.0–72.6), respectively. In patients without CR/CRi (n = 14), median OS was 5.0 months (IQR, 4.5–8.6) and 1-y, 3-y and 5-y OS was 17.9% (95% CI, 3.11–42.5), 0% and 0%, respectively. OS was significantly higher for CR/CRi patients (p log rank test = 0.0001) (Fig. 2B).

4. Discussion

In this study, we confirm previous findings with respect to distribution, clinical presentation and prognosis impact of *IDH2*^{R140} and *IDH2*^{R172} mutations in AML patients [6,17–20]. Because of a very low frequency, there has been controversy regarding the prognostic role of *IDH2*^{R172} with a study from the United Kingdom Medical Research Council showing a poor outcome (5-y OS of 24%) and one from the German–Austrian AML Study Group (AMLSG) showing a much better outcome [6,18]. The survival curve of *IDH2*^{R172} patients from our cohort reflects a fairly favorable prognosis though there was no statistical difference with IDHwt patients.

Soon after the discovery of IDH mutations [21,22], our strategy to detect IDH mutants was to perform HRM-PCR analysis (5% sensitivity) followed by Sanger sequencing whose sensitivity was 10% and patients found to be positive by HRM-PCR but negative by Sanger, were classified as non-mutated. Now, we perform NGS sequencing for new AML patients at diagnosis and identified only 6% of IDH2 mutated patients presenting a VAF between 5% and 10%. By extrapolating these data, we might include few patients with low VAF in non-mutated patients by using this strategy (HRM and confirmation by Sanger).

Observing the prognosis of sub-categories of patients treated in real life with available therapies is becoming increasingly important to estimate the benefit that new targeted drugs will bring in the field. This is particularly the case when drugs such as enasidenib are registered on the basis of non-randomized studies [23]. In a previous study from the M.D Anderson Cancer Center, of the 18 patients with *IDH2* mutations treated with first salvage, 50% achieved CR and their median OS was 11.1 months [12]. Here, we showed that half of the R/R AML patients with *IDH2* mutations can be salvaged by current treatments and benefited from prolonged survival. Median OS appeared similar to the enasidenib study. However, it should be noted that patients of our cohort were younger (58.9 vs. 70y) and had less often poor risk cytogenetics (12.1 vs. 33%) indicating a more favorable population of patients compared to the enasidenib study population. This could be due to the molecular testing that was performed more often in younger patients receiving intensive chemotherapy in cohort. It is known that the frequency of IDH2 mutations is higher with advanced age and the survival in a younger, intensively treated subgroup is likely to be significantly better than the entire IDH2 mutant population. Therefore, these patient populations remain hardly comparable and randomized trials are still needed to fully confirm the impact of IDH2 inhibitors in this setting.

The adverse effects of salvage treatments were not specifically addressed in this study because it is well established that high intensity regimen including high-dose cytarabine, FLAG-ida regimen or equivalents are very toxic in terms of use of healthcare resources, length of stay in hospital, transfusion support, infections and quality of life. With the growing use of IDH inhibitors in routine, we can observe now that R/R patients can obtain response with one pill a day at home which is obviously a significant advance compared to classical salvage therapies.

Table 2
Characteristics of the 33 R/R AML patients with *IDH2* mutations.

Characteristics	Relapsed or refractory N = 33
Sex – n. (%)	N = 33
Male	19 (57.6)
Female	14 (42.4)
Age at diagnosis – years	N = 33
Median (IQR)	58.9 (50.3–64.8)
***IDH2* mutations**	N = 33
R140	24 (72.7)[a]
R172	10 (30.3)[a]
Outcome of prior AML therapy	N = 33
Refractory to initial induction or re-induction	9 (27.3)
Relapse after CR	24 (72.7)
Relapsed within 1 y of initial treatment	13 (39.4)
Relapsed post-transplant	5 (15.2)
ECOG performance status – n. (%)	
At diagnosis	N = 28
0	14 (50.0)
1	8 (28.6)
2	6 (21.4)
At relapse	N = 17
0	8 (47.1)
1	7 (41.2)
2	2 (11.8)
White cell count – giga per liter	
At diagnosis	N = 33
Median (IQR)	5.4 (2.4-42.0)
At relapse	N = 18
Median (IQR)	2.8 (2.0–4.1)
AML subtype at diagnosis – n. (%)	N = 33
De novo AML	24 (72.7)
Therapy-related AML	2 (6.1)
AML with antecedent MDS	5 (15.2)
Cytogenetic risk at diagnosis – n. (%)	N = 33
Favorable	1 (3.0)
Intermediate	28 (84.8)
Adverse	4 (12.1)
Karyotype at relapse – n. (%)	N = 11/24
Similar to diagnosis	6 (54.5)
Clonal evolution	5 (45.5)
***FLT3*-ITD at diagnosis – n. (%)**	N = 31
	2 (6.5)
***NPM1* mutation at diagnosis – n. (%)**	N = 30
	6 (20.0)
Salvage treatment – n. (%)	N = 33
Yes	28 (84.8)
No	5 (15.2)
Intensive chemotherapy	13 (57.6)
IDAC/HiDAC	9 (27.3)
HiDAC + amsacrine	3 (9.1)
FLAG-Ida	1 (3.0)
Hypomethylating agents	8 (24.2)
Allogeneic stem cell transplantation (upfront)	3 (9.1)
Other[b]	4 (12.1)

[a] *IDH2*^{R140} and *IDH2*^{R72} co-mutation was found in 1 patient. IDAC/HiDAC, intermediate/high-dose cytarabine; FLAG-Ida, fludarabin, cytarabine, GCSF, idarubicin.

[b] including low dose chemotherapy (n = 2), quizartinib or panabinostat.

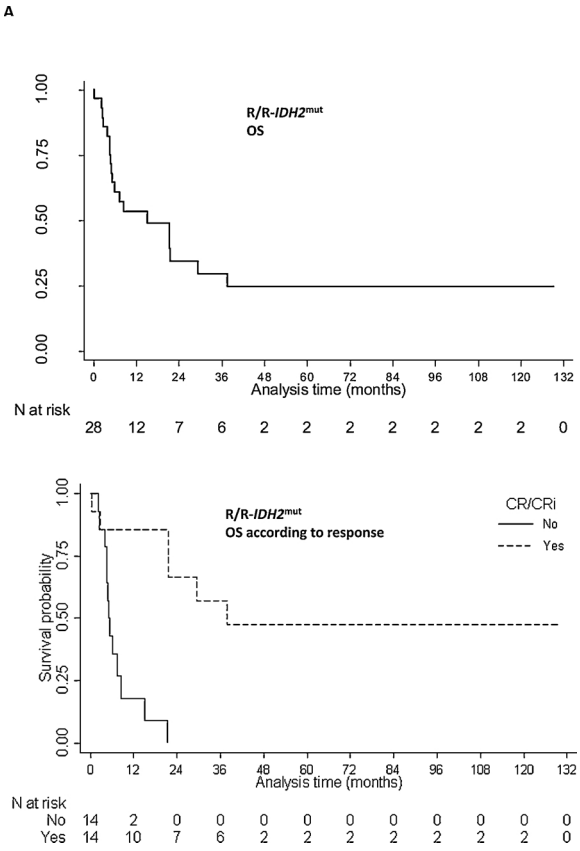

Fig. 2. (A) OS of the 28 R/R AML patients with *IDH2* mutations who received salvage therapy. (B) OS according to response to salvage treatment.

Conflict of interest

CR has received research grants from Amgen, Novartis, Celgene, Jazz Pharmaceuticals, Agios, Chugai, Sunesis, Astellas and MaatPharma and is an advisor for Abbvie, Sunesis, Janssen, Jazz, Novartis, Celgene, Astellas, Daiichi-Sankyo, Macrogenics and Pfizer. F.H is an advisor for Amgen, BMS, Celgene, Incyte, Jazz Pharma, Novartis, Pfizer. S.T and E.D are advisors for Novartis. P.B is an advisor for Sanofi and Novartis. S.B is an advisor for Sanofi and Astellas.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.leukres.2019.04.010.

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