IDH1/2 mutations in acute myeloid leukemia patients and risk of coronary artery disease and cardiac dysfunction - a retrospective propensity score analysis

Running Title: Cardiovascular risk in IDH-mutated AML

Badder Kattiha,b,g,h, Amir Shirvani, Pirospaka, Abel Martin Garrido, Razif Gabdoullinea, Alessandro Liebiche, Maximilian Brandesa, Anuhar Chaturvedia, Timon Seegerd,f, Felicitas Thole, Gudrun Göhringe, Brigitte Schlegelberger, Robert Geffersi, David Johnh, Udo Bavendieka, Johann Bauersacha, Arnold Ganser, Joerg Heinekea, b, d, §, * and Michael Heusere, #, *

a Department of Cardiology and Angiology, Hannover Medical School, Carl-Neuberg Strasse 1, 30625 Hannover, Germany. b Department of Cardiovascular Physiology, European Center for Angioscience (ECAS), Medical Faculty Mannheim of Heidelberg University, Ludolf-Krehl-Strasse 7-11, 68167 Mannheim, Germany. c Department of Human Genetics, Hannover Medical School, Hannover, Germany. d German Center for Cardiovascular Research (DZHK), partner site Heidelberg/ Mannheim. e Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Carl-Neuberg Strasse 1, 30625 Hannover, Germany. f Department of Medicine III, University Hospital Heidelberg; Im Neuenheimer Feld 410, 69120 Heidelberg. g Institute for Cardiovascular Regeneration, Goethe University Frankfurt, Frankfurt, Germany. h German Center for Cardiovascular Research (DZHK), Frankfurt, Germany. Theodor-Stern-Kai 7, 60590 Frankfurt, Germany. i Genome Analytics, Helmholtz Center for Infection Research, Braunschweig, Germany.

§ Corresponding author: Department of Cardiovascular Physiology, European Center for Angioscience (ECAS), Medical Faculty Mannheim of Heidelberg University, Ludolf-Krehl Strasse 7-11, phone: +49 621-38371850, 68167 Mannheim, Germany. Email: Joerg.Heineke@medma.uni-heidelberg.de
*Corresponding author: Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Carl-Neuberg Strasse 1, 30625, phone no.: +49 511 532 3720 Hannover, Germany. Email: heuser.michael@mh-hannover.de

*These authors contributed equally to this work

All authors declare no relevant conflicts of interest.
Table S1. Complete remission related to IDH mutational status in patients with AML

| IDH          | Unweighted cohort | CR (without intensive induction chemotherapy), (%) | CR (with intensive induction chemotherapy), (%) |
|--------------|-------------------|-------------------------------------------------|-------------------------------------------------|
| wildtype     | CR (total n=298)  | 54.0 (161/298)                                  | 69.9 (217/313)                                  |
| IDH1 mutated | CR (total n=26)   | 53.8 (14/26)                                    | 74.2 (17/23)                                    |
| IDH2 mutated | CR (total n=39)   | 59.0 (23/39)                                    | 63.6 (14/22)                                    |
| IDH1/2 mutated | CR (total n=65)  | 56.9 (37/65)                                    | 65.7 (19/29)                                    |

NOTE. Patients with acute promyelocytic leukemia were excluded from clinical correlations. Values are expressed as % (n/total n).
Table S2. Overall survival and relapse-free survival of the AML study cohort

|                | IDH1/2 wildtype | IDH1 mutated | IDH2 mutated | IDH1/2 mutated |
|----------------|-----------------|--------------|--------------|----------------|
| 2-year OS      | 49.9%           | 64.6%        | 59.8%        | 61.7%          |
| 5-year OS      | 36.2%           | 38.3%        | 38.7%        | 38.5%          |
| 2-year RFS     | 49.4%           | 54.2%        | 44.6%        | 48.2%          |
| 5-year RFS     | 37.1%           | n/a          | 39.0%        | 44.8%          |

Abbreviation: OS = overall survival, RFS = relapse-free survival, n/a = not available.
Table S3. Baseline characteristics of the weighted AML study cohort (model1).

|                          | IDH wildtype (total n = 221) | IDH2 mutated (total n = 206) | p     | SMD   |
|--------------------------|-------------------------------|-------------------------------|-------|-------|
| Age, (years)             |                               |                               |       |       |
| median                   | 61.0                          | 64.0                          | 0.836 | 0.012 |
| range                    | 19.0-90.0                     | 29.0 – 81.0                   |       |       |
| Age ≤60 years (young), (%)|                               |                               |       |       |
|                         | 48.4                          | (107/221)                     | 47.2  | (97/206) | 0.784 | -0.019 |
| Age >60 years (old), (%)  |                               |                               |       |       |
|                         | 51.6                          | (114/221)                     | 52.8  | (109/206) | 0.019 |       |
| Male sex, (%)            |                               |                               |       |       |
|                         | 57.8                          | (128/221)                     | 61.3  | (127/206) | 0.436 |       |
| AML history, (%)         |                               |                               |       |       |
| De novo AML             | 68.3                          | (151/221)                     | 67.2  | (139/206) | 0.019 |       |
| Secondary AML            | 23.4                          | (52/221)                      | 28.0  | (58/206) | 0.086 |       |
| Therapy-related AML      | 8.4                           | (18/221)                      | 4.8   | (10/206) | 0.121 |       |
| WBC at diagnosis, (/µl) |                               |                               |       |       |
| median                   | 9.6                           | 13.9                          | 0.107 |       |
| range                    | 0.6-284.0                     | 0.9-146.3                     |       |       |
| Platelet count at diagnosis, (/µl) |             |                               |       |       |
| median                   | 51.0                          | 86.0                          | 0.006 |       |
| range                    | 2.0-523.0                     | 7.0-979.0                     |       |       |
| Hemoglobin, (g/dl)       |                               |                               |       |       |
| median                   | 9.1                           | 9.9                           | 0.004 |       |
| range                    | 4.7-16.0                      | 5.5-16.6                      |       |       |
| Blood blasts, (%)        |                               |                               |       |       |
| median                   | 28.0                          | 46.7                          | 0.003 |       |
| range                    | 0.0-97.0                      | 0.0-90.0                      |       |       |
| Bone marrow blasts, (%)  |                               |                               |       |       |
| median                   | 60.0                          | 80.0                          | 0.011 |       |
| range                    | 0.0-99.0                      | 10.0 – 92.0                   |       |       |
| Cytogenetic risk group, (%)|                               |                               | 0.026 |       |
| Favorable                | 21.1                          | (47/221)                      | 11.4  | (24/206) | -0.226 |       |
| Intermediate             | 54.4                          | (120/221)                     | 62.1  | (128/206) | 0.128 |       |
| Adverse                  | 24.5                          | (54/221)                      | 26.5  | (55/206) | 0.038 |       |
| NPM1 mutation, (%)       | 18.0                          | (40/221)                      | 19.4  | (40/206) | 0.727 | 0.028 |
| FLT3-ITD presence, (%)   | 17.6                          | (39/221)                      | 14.5  | (30/206) | 0.375 | -0.070 |
| FLT-TKD presence, (%)    | 4.6                           | (10/221)                      | 0.0   | (0/206) | 0.002 |       |
| t(8;21), (%)             | 3.5                           | (8/221)                       | 4.5   | (9/206) | 0.685 |       |
| inv(16), (%)             | 2.0                           | (4/221)                       | 4.8   | (10/206) | 0.078 |       |
| MLL-MLLT3 t(9;11), (%)   | 2.0                           | (4/221)                       | 4.8   | (10/206) | 0.078 |       |
| MLL partial tandem duplication, (%) | 4.2                           | (8/221)                      | 4.8   | (10/206) | 0.074 |       |
| ECOG performance status, (%) |                               |                               |       |       |
| ECOG 0-1                 | 63.3                          | (140/221)                     | 66.5  | (137/206) | 0.000 |       |
| ECOG 2-4                 | 35.3                          | (78/221)                      | 25.2  | (52/206) | 0.000 |       |
|   | Median | Range          |   | Median | Range          |
|---|--------|----------------|---|--------|----------------|
| M0 | 8.5    | (14/221)       | M1 | 22.1   | (35/221)       |
| M2 | 20.3   | (32/221)       | M3 | 0.0    | (0/221)        |
| M4 | 21.5   | (34/221)       | M5 | 17.7   | (28/221)       |
| M6 | 8.5    | (14/221)       | M7 | 1.5    | (2/221)        |
| CMML (%) | 1.5 | (3/221)       | Intensive induction therapy (%) | 81.2 | (180/221) |
| M0 | 10.7   | (15/206)       | M1 | 14.0   | (20/206)       |
| M2 | 30.2   | (43/206)       | M3 | 0.0    | (0/206)        |
| M4 | 40.5   | (58/206)       | M5 | 0.0    | (0/206)        |
| M6 | 4.6    | (7/206)        | M7 | 0.0    | (0/206)        |
|   | 10.7   | (15/206)       |   | 14.0   | (20/206)       |
|   | 30.2   | (43/206)       |   | 0.0    | (0/206)        |
|   | 40.5   | (58/206)       |   | 0.0    | (0/206)        |
|   | 4.6    | (7/206)        |   | 0.0    | (0/206)        |
|   | 0.0    | (0/206)        |   | 0.0    | (0/206)        |
|   | 10.7   | (15/206)       |   | 14.0   | (20/206)       |
|   | 30.2   | (43/206)       |   | 0.0    | (0/206)        |
|   | 40.5   | (58/206)       |   | 0.0    | (0/206)        |
|   | 4.6    | (7/206)        |   | 0.0    | (0/206)        |
|   | 0.0    | (0/206)        |   | 0.0    | (0/206)        |

**Cardiovascular characteristics**

|   | Median | Range          |   | Median | Range          |
|---|--------|----------------|---|--------|----------------|
| CAD (%) | 5.0 | (11/221)       | Valvular disease (%) | 1.6 | (3/221)       |
|   | 4.8    | (10/206)       |   | 1.2    | (2/206)        |
|   | (10/206)       |   | 0.625 | -0.015 |
| Heart failure (%) | 0.0 | (0/221)       | Cardiovascular Risk | 0.519 |
|   | 0.0    | (0/206)        |   | 0.0    | (0/206)        |
|   | 0.0    | (0/206)        |   | 0.0    | (0/206)        |
|   | 0.0    | (0/206)        |   | 0.0    | (0/206)        |

**Systolic blood pressure, (mmHg)**

|   | Median | Range          |   | Median | Range          |
|---|--------|----------------|---|--------|----------------|
| 130.0 | 130.0 | (88/221)       | 80.0-180.0 | 110.0 – 150.0 |
|   | 80.0-180.0 | (110/206) |
| Diastolic blood pressure, (mmHg) | 75.0 | 80.0 | 40.0-105.0 | 70.0-80.0 |
|   | 40.0-105.0 | 70.0-80.0 |
|   | 75.0 | 80.0 | 40.0-105.0 | 70.0-80.0 |
| Heart rate, (beat per min) | 88.0 | 84.0 | 60.0-152.0 | 66.0 – 108.0 |
|   | 60.0-152.0 | 66.0 – 108.0 |
| ACEI/ARB (%) | 17.6 | (39/221)       | ß-blocker (%) | 17.0 | (38/221)       |
|   | 17.0    | (35/206)       |   | 14.0    | (29/226)       |
|   | (35/206)       |   | 0.376 | -0.068 |
| MR-antagonists (%) | 0.0 | (0/221)       |   | 0.0    | (0/206)        |
|   | 0.0    | (0/206)        |   | 0.0    | (0/206)        |

Values are expressed as median and range or % (n/ total n). a.d.= available data. Abbreviation: alloHCT = allogeneic hematopoietic cell transplantation, CMML = chronic myelomonocytic leukemia, ECOG= Eastern Co-operative Oncology Group, FLT3-ITD= FMS-like tyrosine kinase 3 internal tandem duplication, NPM1= Nucleophosmin 1, SMD= standardized mean difference, SMD provided for baseline characteristics included in the propensity score model (model1).
Table S4. Baseline characteristics of the weighted AML study cohort (model2).

|                           | Weighted cohort (total n = 434) |   |   |   |
|---------------------------|----------------------------------|---|---|---|
|                           | IDH1/2 wildtype                  | pooled IDH1/2 mutated | p   | SMD |
|                           | (total n = 216)                  | (total n = 218)       |     |     |
|                           | a.d. (n/ total) n)              | a.d. (n/ total n)    |     |     |
| Age, (years)              | median                          | 58.5                    | 63.0 | 0.388 | 0.089 |
|                           | range                           | 19.0-90.0               | 29.0-82.0 |     |     |
| Age ≤60 years (young), (%)| 45.5                            | (118/216)               | 47.9 | (104/218) | 0.626 | 0.034 |
| Age >60 years (old), (%)  | 54.5                            | (98/216)                | 52.1 | (114/218) | -0.034 |     |
| Male sex, (%)             | 57.1                            | (123/216)               | 61.7 | (135/218) | 0.291 |     |
| AML history, (%)          | 71.1                            | (154/216)               | 67.6 | (147/218) | 0.030 |     |
| De novo AML               | Secondary AML                    | 19.6                    | 27.8 | (61/218) |     |     |
| Therapy-related AML       | WBC at diagnosis, (/µl)          | 9.3                     | 4.6  | (10/218) |     |     |
|                           | median                          | 9.9                     | 8.4  | (216/216) | (218/218) | 0.394 | 0.041 |
|                           | range                           | 0.6-284.0               | 0.7-206.1 |     |     |
| Platelet count at diagnosis, (/µl) | (216/216)               | (218/218)               | 0.552 | 0.059 |
| Hemoglobin, (g/dl)        | median                          | 64.0                    | 74.0 | (216/216) | (218/218) | 0.510 |     |
|                           | range                           | 2.0-523.0               | 7.0-979.0 |     |     |
| Blood blasts, (%)         | median                          | 26.0                    | 46.7 | (210/216) | (218/218) | 0.000 |     |
|                           | range                           | 0.0-95.0                | 0.0-90.0 |     |     |
| Bone marrow blasts, (%)   | median                          | 50.0                    | 80.0 | (90/232) | (90/218) | 0.029 |     |
|                           | range                           | 0.0-90.0                | 10.0-96.0 |     |     |
| Cytogenetic risk group, (%)| Favorable                       | 22.2                    | 22.6 | (39/216) | (49/218) | 0.058 | 0.058 |
|                           | Intermediate                    | 57.8                    | 49.7 | (125/216) | (108/218) | -0.125 |     |
|                           | Adverse                         | 24.0                    | 27.7 | (52/216) | (60/218) | 0.087 |     |
| NPM1 mutation, (%)        | 17.8                            | (38/216)                | 19.0 | (41/218) | 0.743 | 0.008 |
| FLT3-ITD presence, (%)    | 17.7                            | (38/216)                | 19.2 | (42/218) | 0.653 | 0.032 |
| FLT-TKD presence, (%)     | 4.7                             | (10/216)                | 0.0  | (0/218) | 0.001 |     |
| t(8;21), (%)              | 3.9                             | (8/216)                 | 1.2  | (3/218) | 0.123 |     |
| inv(16), (%)              | 2.8                             | (6/216)                 | 4.6  | (10/218) | 0.317 |     |
| MLL-MLLT3 t(9;11), (%)    | 1.5                             | (3/216)                 | 7.0  | (15/218) | 0.004 |     |
| MLL partial tandem duplication, (%) | 4.3 | (8/216) | 9.6  | (19/218) | 0.037 |     |
| ECOG performance status, (%)| Grade 0-1                       | 65.7                    | 67.0 | (142/216) | (146/218) | 0.000 |     |
|                           | Grade 2-4                       | 34.3                    | 33.0 | (74/216) | (72/218) |     |     |
## FAB subtype, (%)

|  |       |     |       |     |
|---|-------|-----|-------|-----|
| M0 | 7.7   | (12/216) | 12.2  | (17/218) |
| M1 | 25.1  | (40/216) | 17.5  | (25/218) |
| M2 | 21.1  | (34/216) | 25.0  | (35/218) |
| M3 | 0.0   | (0/232)  | 0.0   | (0/218)  |
| M4 | 20.3  | (32/216) | 33.8  | (48/218) |
| M5 | 17.8  | (28/232) | 10.7  | (15/218) |
| M6 | 6.1   | (10/232) | 0.8   | (1/218)  |
| M7 | 1.8   | (3/216)  | 0.0   | (0/218)  |

## CMML, (%)

|  |       |     |       |     |
|---|-------|-----|-------|-----|
|  | 1.8   | (4/216)  | 18.9  | (41/218) |

## Intense therapy, (%)

|  |       |     |       |     |
|---|-------|-----|-------|-----|
|  | 80.6  | (174/232) | 81.1  | (177/218) |

## Consolidation type, (%)

|  |       |     |       |     |
|---|-------|-----|-------|-----|
|  |       |     |       |     |

## Cardiovascular characteristics

### CAD, (%)

|  |       |     |       |     |
|---|-------|-----|-------|-----|
|  | 8.1   | (19/216)  | 9.5   | (21/218) |

### Valvular disease, (%)

|  |       |     |       |     |
|---|-------|-----|-------|-----|
|  | 7.7   | (17/216)  | 2.8   | (6/218)  |

### Heart failure, (%)

|  |       |     |       |     |
|---|-------|-----|-------|-----|
|  | 0.0   | (0/216)  | 0.0   | (0/218)  |

### Cardiovascular Risk, (%)

|  |       |     |       |     |
|---|-------|-----|-------|-----|
|  |       |     |       |     |

### 0-1 risk factors

|  |       |     |       |     |
|---|-------|-----|-------|-----|
|  | 90.3  | (195/216) | 92.4  | (201/218) |

### 2-4 risk factors

|  |       |     |       |     |
|---|-------|-----|-------|-----|
|  | 9.7   | (21/216)  | 7.6   | (17/218) |

### Sinusrhythm, (%)

|  |       |     |       |     |
|---|-------|-----|-------|-----|
|  | 92.9  | (201/218) | 92.0  | (200/218) |

### Systolic blood pressure, (mmHg)

|  |       |     |       |     |
|---|-------|-----|-------|-----|
| median | 130.0 | 120.0 |      |      |
| range   | 90.0-180.0 | 110.0 – 150.0 |      |      |

### Diastolic blood pressure, (mmHg)

|  |       |     |       |     |
|---|-------|-----|-------|-----|
| median | 75.0 | 80.0 |      |      |
| range   | 50.0-105.0 | 70.0-80.0 |      |      |

### Heart rate, (beats per min)

|  |       |     |       |     |
|---|-------|-----|-------|-----|
| median | 87.0 | 88.0 |      |      |
| range   | 60.0-152.0 | 66.0 – 112.0 |      |      |

### ACEi/ARB, (%)

|  |       |     |       |     |
|---|-------|-----|-------|-----|
|  | 20.0  | (43/216)  | 19.8  | (43/218) |

### β-blocker, (%)

|  |       |     |       |     |
|---|-------|-----|-------|-----|
|  | 18.1  | (39/216)  | 17.6  | (38/218) |

### MR-antagoists, (%)

|  |       |     |       |     |
|---|-------|-----|-------|-----|
|  | 0.0   | (0/216)  | 0.0   | (0/218)  |

Values are expressed as median and range or % (n/ total n). a.d.= available data. Abbreviation: alloHCT= allogeneic hematopoietic cell transplantation, CMML= chronic myelomonocytic leukemia, ECOG= Eastern Co-operative Oncology Group, FLT3-ITD= FMS-like tyrosine kinase 3 internal tandem duplication, NPM1= Nucleophosmin 1, SMD= standardized mean difference, SMD provided for baseline characteristics included in the propensity score model (model2).
Echocardiographic outcomes related to IDH mutational status in patients with AML after IPW (IDH1/2 wildtype vs. IDH2 mutated).

### Unweighted Cohort (Total n=337)

|                  | WT (n=298) | Mut (n=39) | WT vs. Mut | WT t0 vs tx | Mut t0 vs tx | Absolute Difference LVEF (95%CI) |
|------------------|------------|------------|------------|-------------|-------------|---------------------------------|
| Timepoints (t0)  |            |            |            |             |             |                                 |
| Echocardiography |            |            |            |             |             |                                 |
| Pre-AML therapy  |            |            |            |             |             |                                 |
| Ejection fraction (%) | 58.6 ±8.0 (71/298) | 57.6 ±4.5 (8/39) | 0.770       | 0.018        | 0.999       | -1.0 % (-9.58 to 7.58)          |
| Post-AML therapy |            |            |            |             |             |                                 |
| Ejection fraction (%) | 55.0 ±9.3 (74/298) | 57.6 ±4.9 (7/39) | 0.474       | 0.018        | 0.999       | 2.6 % (-6.49 to 11.69)          |
| Timepoints (t1)  |            |            |            |             |             |                                 |
| Echocardiography |            |            |            |             |             |                                 |
| Pre-AML therapy  |            |            |            |             |             |                                 |
| Ejection fraction (%) | 54.8 ±9.7 (43/298) | 51.2 ±15.5 (5/39) | 0.406       | 0.032        | 0.258       | -3.6 % (-14.47 to 7.27)         |
| Post-AML therapy |            |            |            |             |             |                                 |
| Ejection fraction (%) | 53.4 ±10.5 (22/298) | 44.6 ±12.3 (7/39) | 0.028       | 0.020        | 0.016       | -8.8 % (-18.78 to 1.18)         |

Timepoints (t0-3) are calculated as mean and median time (months) from date of diagnosis to date of echocardiography. t0 (median:0 months, range -10 to 2, mean 0, SD ±2 (52/52), t1 (median:3 months, range 0 to 53, mean 6, SD ±9 (75/75), t2 (median:9 months, range 1 to 54, mean 13, SD ±13 (34/34), t3 (median:15 months, range 2 to 161, mean 23, SD ±31 (19/19). Values are expressed as means and ±standard deviation. (n/total n) denotes available data. *comparing wildtype IDH with mutated IDH1 at the corresponding timepoint (tX), # comparing the corresponding timepoint within the same group with timepoint t0. t0 denotes the timepoint before AML therapy and t1-3 show the ejection fraction at different timepoints during AML therapy. Mut, mutated; WT, wildtype.

### Weighted Cohort (Total n=418)

|                  | WT (n=221) | Mut (n=197) | WT vs. Mut | WT t0 vs tx | Mut t0 vs tx | Absolute Difference LVEF (95%CI) |
|------------------|------------|------------|------------|-------------|-------------|---------------------------------|
| Timepoints (t0)  |            |            |            |             |             |                                 |
| Echocardiography |            |            |            |             |             |                                 |
| Pre-AML therapy  |            |            |            |             |             |                                 |
| Ejection fraction (%) | 59.0 ±8.1 (53/221) | 55.1 ±4.2 (34/197) | 0.053       | 0.025        | 0.562       | -3.9 % (-8.92 to 1.12)          |
| Post-AML therapy |            |            |            |             |             |                                 |
| Ejection fraction (%) | 54.9 ±10.2 (63/221) | 56.2 ±3.7 (42/197) | 0.475       | 0.025        | 0.562       | 1.3 % (-3.25 to 5.85)           |
| Timepoints (t1)  |            |            |            |             |             |                                 |
| Echocardiography |            |            |            |             |             |                                 |
| Pre-AML therapy  |            |            |            |             |             |                                 |
| Ejection fraction (%) | 54.8 ±10.8 (36/221) | 48.2 ±13.7 (27/197) | 0.005       | 0.046        | 0.002       | -6.6 % (-12.42 to -0.78)        |
| Post-AML therapy |            |            |            |             |             |                                 |
| Ejection fraction (%) | 54.6 ±9.8 (21/221) | 46.3 ±10.7 (16/197) | 0.005       | 0.080        | 0.001       | -8.3 % (-15.88 to -0.7159)      |

Timepoints (t0-3) are calculated as the median time (months) from date of diagnosis to date of echocardiography. t0 (median:0 months, range -10 to 1, mean 0, SD ±2 (87/87), t1 (median:3 months, range 0 to 48, mean 5, SD ±7 (105/105), t2 (median:9 months, range 1 to 53, mean 13, SD ±16 (63/63), t3 (median:11 months, range 2 to 162, mean 25, SD ±32 (37/37). Values are expressed as means and ±standard deviation. (n/total n) denotes available data. *comparing wildtype IDH with mutated IDH1 at the corresponding timepoint (tX), # comparing the corresponding timepoint within the same group with timepoint t0. t0 denotes the timepoint before AML therapy and t1-3 show the ejection fraction at different timepoints during AML therapy. Mut, mutated; WT, wildtype.
Table S6. Echocardiographic outcomes related to IDH mutational status in AML after IPW (IDH1/2 Wilcoxon vs. pooled IDH1/2 mutated).

| Mutational Status | IDH1 Mutations | IDH1/2 Mutations | p Value (IDH1 vs. IDH1/2) |
|-------------------|----------------|-----------------|--------------------------|
|                  | d1             | d2             |                           |
|                  | d1             | d2             |                           |
|                   | d1             | d2             |                           |
|                   | d1             | d2             |                           |

Echocardiographic outcomes are expressed as means and ±standard deviation. (n/total n) denotes available data. *comparing wildtype (WT) vs. mutated (Mut).

**Table Notes:**
- Echocardiographic outcomes are calculated as mean and median time (months) from date of diagnosis to date of echocardiography.
- Echocardiography outcomes related to mutational status in AML after IPW (IDH1/2 Wilcoxon vs. pooled IDH1/2 mutated).
- Echocardiography outcomes are calculated as mean and median time (months) from date of diagnosis to date of echocardiography.
Echocardiographic outcomes related to IDH mutational status in patients with AML after IPW (IDH wildtype vs. IDH1 mutated).

|                  | IDH1/2 wildtype | IDH1 mutated | *p* value | ATE (95%CI) |
|------------------|-----------------|--------------|-----------|-------------|
| Echocardiography pre-AML therapy (t₀) | 58.6 ± 8.0 | 62.1 ± 5.2 | 0.0370 | 0.018 | 0.019 3.5 % (-4.18 to 11.18) |
| Echocardiography during AML therapy (t₁) | 55.0 ± 9.3 | 56.9 ± 11.3 | 0.5780 | 0.032 | 0.004 0.349 % (-4.82 to 8.62) |
| Echocardiography during AML therapy (t₂) | 54.8 ± 9.7 | 38.0 ± 7.5 | 0.0020 | 0.020 | 0.005 -16.8 % (-27.59 to -6.01) |
| Echocardiography during AML therapy (t₃) | 53.4 ± 10.5 | 39.0 ± 15.0 | 0.0110 | 0.020 | 0.005 -14.4 % (-25.52 to -3.28) |

Timepoints (t₀-3) are calculated as mean and median time (month) from diagnosis to date of echocardiography. A (median) t₀ (median: 0 month, range -10 to 2, mean 0, SD ±2 (75/77), t₁ (median: 2 month, range 0 to 53, mean 6, SD±9 (81/82), t₂ (median: 9 month, range 1 to 54, mean 12, SD±12 (46/46), t₃ (median: 14 month, range 2 to 161, mean 24, SD±32 (25/25). Values are expressed as means and ±standard deviation. (n/total n) denotes available data. *comparing wildtype IDH with mutated IDH1 at the corresponding timepoint (tₓ), # comparing the corresponding timepoint within the same group with timepoint t₀. t₀ denotes the timepoint before AML therapy and t₁-3 show the timeframes during AML therapy. WT, wildtype; Mut, mutated.
| Timepoint (months) | IDH1/2 wildtype | IDH1 mutated | Total cohort |
|-------------------|-----------------|--------------|--------------|
| **t0**            | Mean 0 (SD ± 2) | Median 0 (range 0 to 1) | Mean 0 (SD ± 0) |
| **t1**            | Mean 6 (SD ± 9) | Median 3 (range 1 to 13) | Mean 3 (range 0 to 11) |
| **t2**            | Mean 13 (SD ± 12) | Median 6 (range 0 to 2) | Mean 6 (range 0 to 2) |
| **t3**            | Mean 23 (SD ± 33) | Median 14 (range 2 to 161) | Mean 14 (range 6 to 56) |

Table S8. Echocardiographic timing related to IDH mutational status in patients with AML
| Timepoint | Total cohort | IDH1/2 wildtype | IDH1/2 mutated |
|-----------|-------------|----------------|---------------|
| **t0**    | Mean 0 (SD ± 2) | Median 0 (range 0 to 1) | Mean 0 (SD ± 0) |
|           | Median 5 (range 2 to 16) | Mean 5 (range 2 to 16) | Median 14 (range 2 to 41) |
|           | Mean 6 (range 6 to 10) | Median 6 (range 6 to 10) | Mean 16 (range 16 to 41) |

| **t1**    | Mean 6 (SD ± 9) | Median 3 (range 0 to 53) | Mean 3 (SD ± 4) |
|           | Median 26 (range 0 to 11) | Mean 26 (range 0 to 11) | Median 12 (range 2 to 41) |
|           | Median 6 (range 6 to 10) | Mean 6 (range 6 to 10) | Mean 16 (range 16 to 41) |

| **t2**    | Mean 13 (SD ± 11) | Median 6 (range 1 to 54) | Mean 7 (SD ± 5) |
|           | Median 12 (range 6 to 11) | Mean 12 (range 6 to 11) | Median 14 (range 2 to 41) |
|           | Mean 6 (range 6 to 10) | Mean 6 (range 6 to 10) | Mean 16 (range 16 to 41) |

| **t3**    | Mean 23 (SD ± 33) | Median 15 (range 2 to 161) | Mean 25 (SD ± 27) |
|           | Median 24 (range 0 to 10) | Mean 24 (range 0 to 10) | Median 17 (range 2 to 41) |
| Timepoint (t0) | Weighted cohort | IDH1/2 Wildtype | IDH1/2 Mutated | Total cohort |
|---------------|----------------|----------------|---------------|-------------|
| **Mean** | **Median** | **Mean** | **Median** | **Mean** |
| t0 (months) | 0 (SD ±2) | 0 (range 0 to 1) | 0 (SD ±2) | 0 (range 0 to 1) | 0 (SD ±2) |
| t1 (months) | 5 (SD ±8) | 3 (range 0 to 48) | 5 (SD ±3) | 3 (range 0 to 10) | 5 (SD ±7) |
| t2 (months) | 12 (SD ±12) | 7 (range 1 to 49) | 20 (SD ±20) | 12 (range 6 to 53) | 15 (SD ±16) |
| t3 (months) | 25 (SD ±36) | 15 (range 2 to 161) | 25 (SD ±27) | 3 (range 3 to 57) | 25 (SD ±32) |

Timepoints (t0 - t3) are calculated as the mean and median time (months) from date of diagnosis to date of the study endpoint. All data is derived from patients who underwent echocardiography at each timepoint.
Supplemental Figure S1

A. Gene-ontology classifications of up-regulated genes DOX vs. control

- GO:0043065~positive regulation of apoptotic process
- GO:0010718~positive regulation of epithelial to mesenchymal transition
- GO:0006334~nucleosome assembly
- GO:0000122~negative regulation of transcription from RNA polymerase II promoter
- GO:0008285~negative regulation of cell proliferation
- GO:0045944~positive regulation of transcription from RNA polymerase II promoter

B. Gene-ontology classifications of down-regulated genes DOX vs. control

- GO:0097191~extrinsic apoptotic signaling pathway
- GO:0006281~DNA replication initiation
- GO:0006270~DNA repair
- GO:0030028~mitochondrial translational elongation
- GO:0051301~cell division
- GO:0007062~sister chromatid cohesion

P value log10 * (-1)