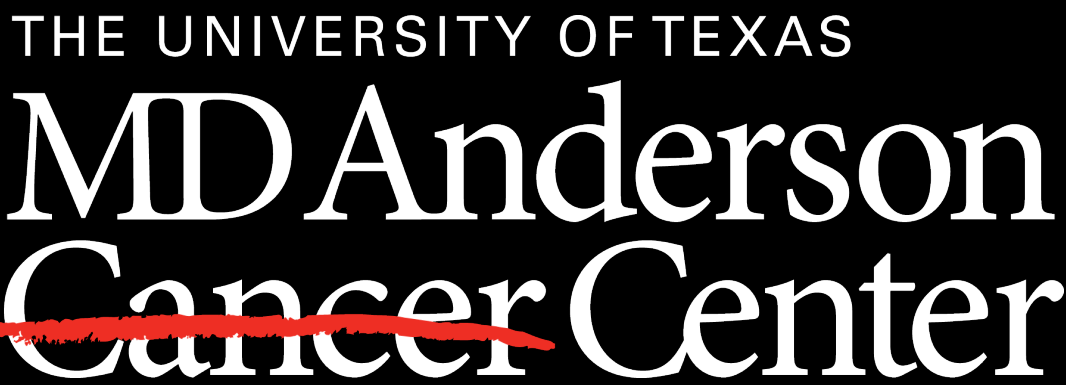


Treatment Response and Outcome in DNMT3A mutated Acute Myeloblastic Leukemia

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Introduction

- DNA methyltransferase 3A (DNMT3A) is responsible for de novo DNA methylation.
- Mutations in *DNMT3A* have been associated with clonal hematopoiesis.
- This mutations have been associated with an increased risk of developing hematological cancers including acute myeloid leukemia (AML).

Objectives

- To identify the prognostic impact of *DNMT3A* mutations and whether mutations at the codon R882 (*DNMT3A*-R882) versus mutations at codons other than R882 (non-R882) have clinically relevant differences.

Methods

- We retrospectively reviewed the clinical records of 236 patients with ND-AML with *DNMT3A* mutations who presented to our institution from 2012 to 2020.
- The study population was classified into two age groups (<65 years / >65 years).
- We analyzed the disease-related characteristics, response rates (CR/CRi), and Overall survival (OS).
- Univariate and multivariate analyses (MVA) were used to identify any association with each of the variables and OS.

Conclusions

*DNMT3A* mutations do not have an independent prognostic impact in patients diagnosed with AML across age groups. Among patients older than 65, patients with *DNMT3A*-R882 had a trend to longer OS. Additionally, therapy with Clad-LDAC-Ven and HMA-Ven provided better response rates and were associated with a survival advantage. Co-occurrence of *TP53* mutations was associated with a negative prognostic impact in all patients.

| Table 1 A: Baseline characteristics Patients <65 years of age |                      |                          |         |
|---------------------------------------------------------------|----------------------|--------------------------|---------|
| Characteristics                                               | DNMT3A R882 N=80 (%) | DNMT3A non-R882 N=29 (%) | P-value |
| Age, median (IQR)                                             | 55 (46 - 60)         | 58 (53 - 62)             | 0.04    |
| Gender: Male / Female                                         | 34 (42) / 46 (58)    | 12 (41) / 17 (59)        | 0.91    |
| AML type                                                      |                      |                          |         |
| De novo                                                       | 74 (92)              | 23 (80)                  | 0.052   |
| Secondary                                                     | 0 (0)                | 3 (10)                   | 0.004   |
| Therapy-related                                               | 6 (8)                | 3 (10)                   | 0.63    |
| Hemoglobin x g/dL, median (IQR)                               | 9.3 (8.8 – 9.8)      | 9.2 (8.3 – 9.6)          | 0.56    |
| White blood cell count x 10 <sup>3</sup> /uL, median (IQR)    | 4.6 (1.9 – 12.7)     | 5.5 (2.0 – 13.5)         | 0.74    |
| Platelet count x 10 <sup>3</sup> /uL, median (IQR)            | 37.5 (19 - 81)       | 46 (26 - 64)             | 0.71    |
| Peripheral blood blast percentage, median (IQR)               | 19 (4 - 50)          | 25 (4.5 – 69.6)          | 0.26    |
| Bone marrow blasts percentage, median (IQR)                   | 57 (42 - 76)         | 52 (32 - 65)             | 0.16    |
| Cytogenetics                                                  |                      |                          |         |
| Diploid                                                       | 53 (78)              | 17 (78)                  | 0.94    |
| Complex karyotype                                             | 7 (10)               | 3 (14)                   | 0.66    |
| +8                                                            | 5 (7)                | 1 (4)                    | 0.64    |
| -7/7q-                                                        | 2 (3)                | 1 (4)                    | 0.71    |
| -5/5q-93                                                      | 1 (2)                | 0 (0)                    | 0.56    |

| Table 1 B: Baseline characteristics Patients > 65 years of age |                      |                          |         |
|----------------------------------------------------------------|----------------------|--------------------------|---------|
| Characteristics                                                | DNMT3A R882 N=64 (%) | DNMT3A non-R882 N=63 (%) | P-value |
| Age, median (IQR)                                              | 70 (68 - 74)         | 74 (69 - 78)             | 0.01    |
| Gender: Male / Female                                          | 30 (47) / 34 (53)    | 28 (44) / 35 (56)        | 0.78    |
| AML type                                                       |                      |                          |         |
| De novo                                                        | 42 (66)              | 41 (65)                  | 0.94    |
| Secondary                                                      | 10 (16)              | 10 (16)                  | 0.96    |
| Therapy-related                                                | 12 (18)              | 12 (19)                  | 0.96    |
| Hemoglobin x g/dL, median (IQR)                                | 9.1 (8.4 – 9.8)      | 8.8 (8.0 – 9.8)          | 0.11    |
| White blood cell count x 10 <sup>3</sup> /uL, median (IQR)     | 2.9 (1.4 – 7.8)      | 3.2 (1.8 – 7.4)          | 0.92    |
| Platelet count x 10 <sup>3</sup> /uL, median (IQR)             | 50 (24 - 98)         | 35 (24 - 98)             | 0.21    |
| Peripheral blood blast percentage, median (IQR)                | 9.5 (4 - 28)         | 12 (4 - 39)              | 0.68    |
| Bone marrow blasts percentage, median (IQR)                    | 45 (27 - 67)         | 47 (26 - 76)             | 0.65    |
| Cytogenetics                                                   |                      |                          |         |
| Diploid                                                        | 37 (69)              | 30 (54)                  | 0.13    |
| Complex karyotype                                              | 6 (11)               | 18 (33)                  | 0.006   |
| +8                                                             | 4 (7)                | 3 (5)                    | 0.67    |
| -7/7q-                                                         | 6 (11)               | 2 (4)                    | 0.13    |
| -5/5q-                                                         | 1 (2)                | 2 (4)                    | 0.56    |

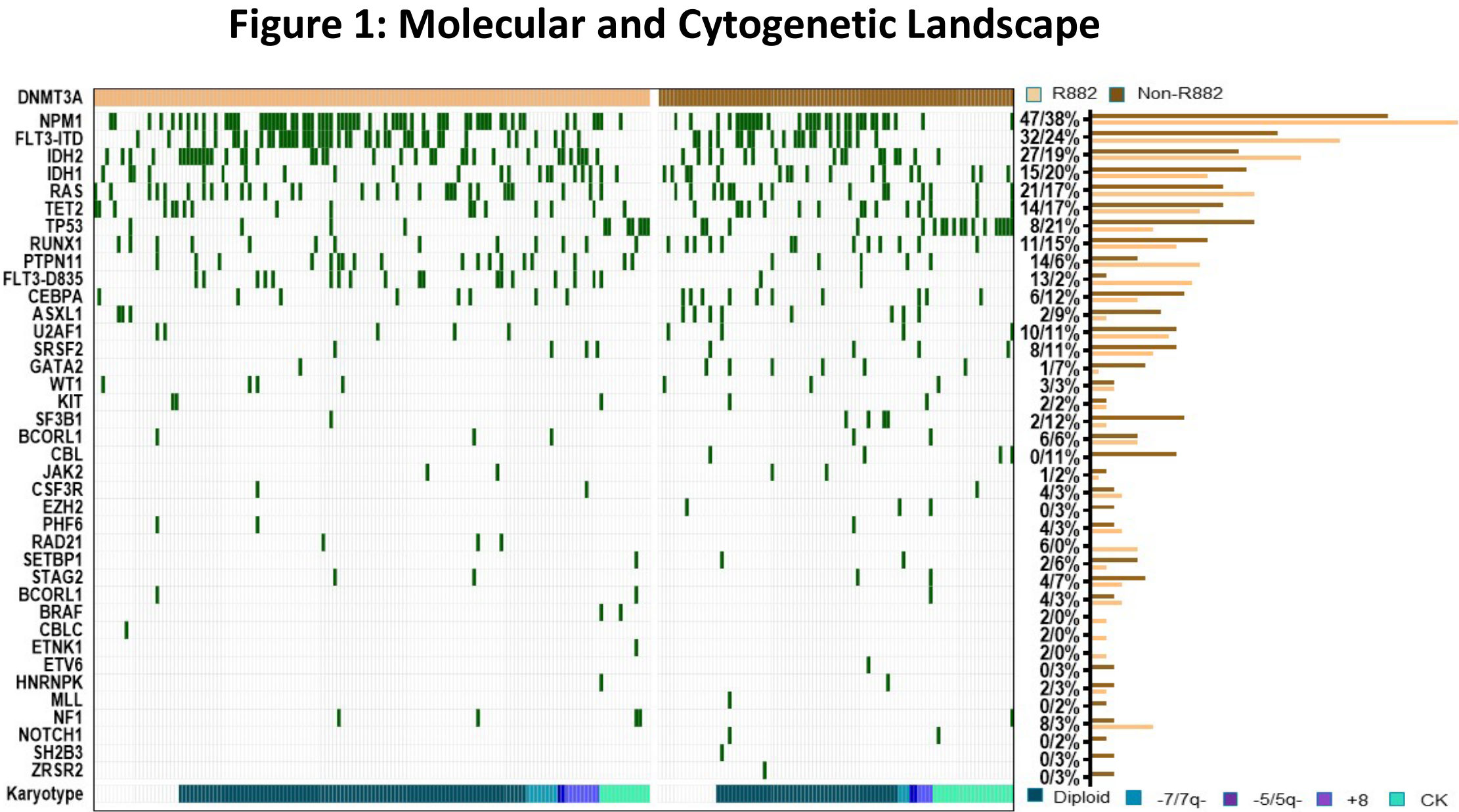
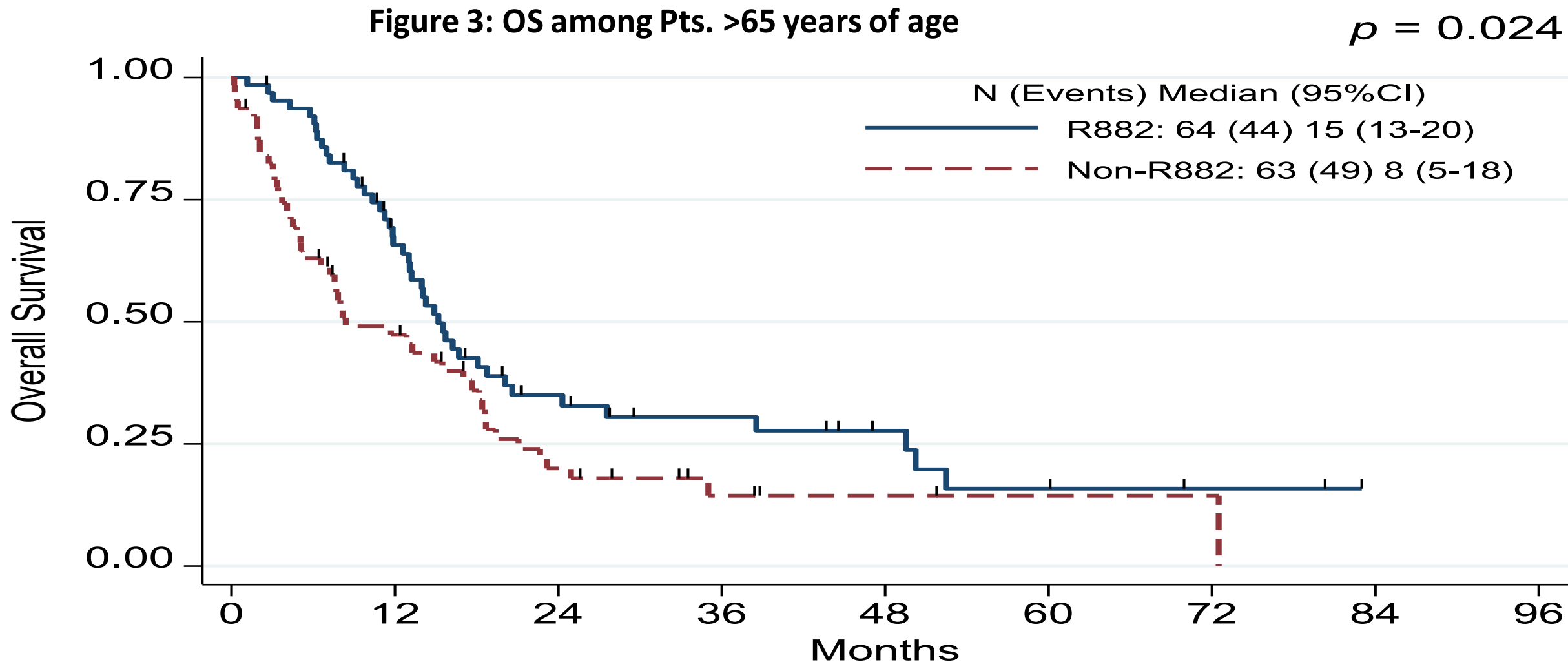
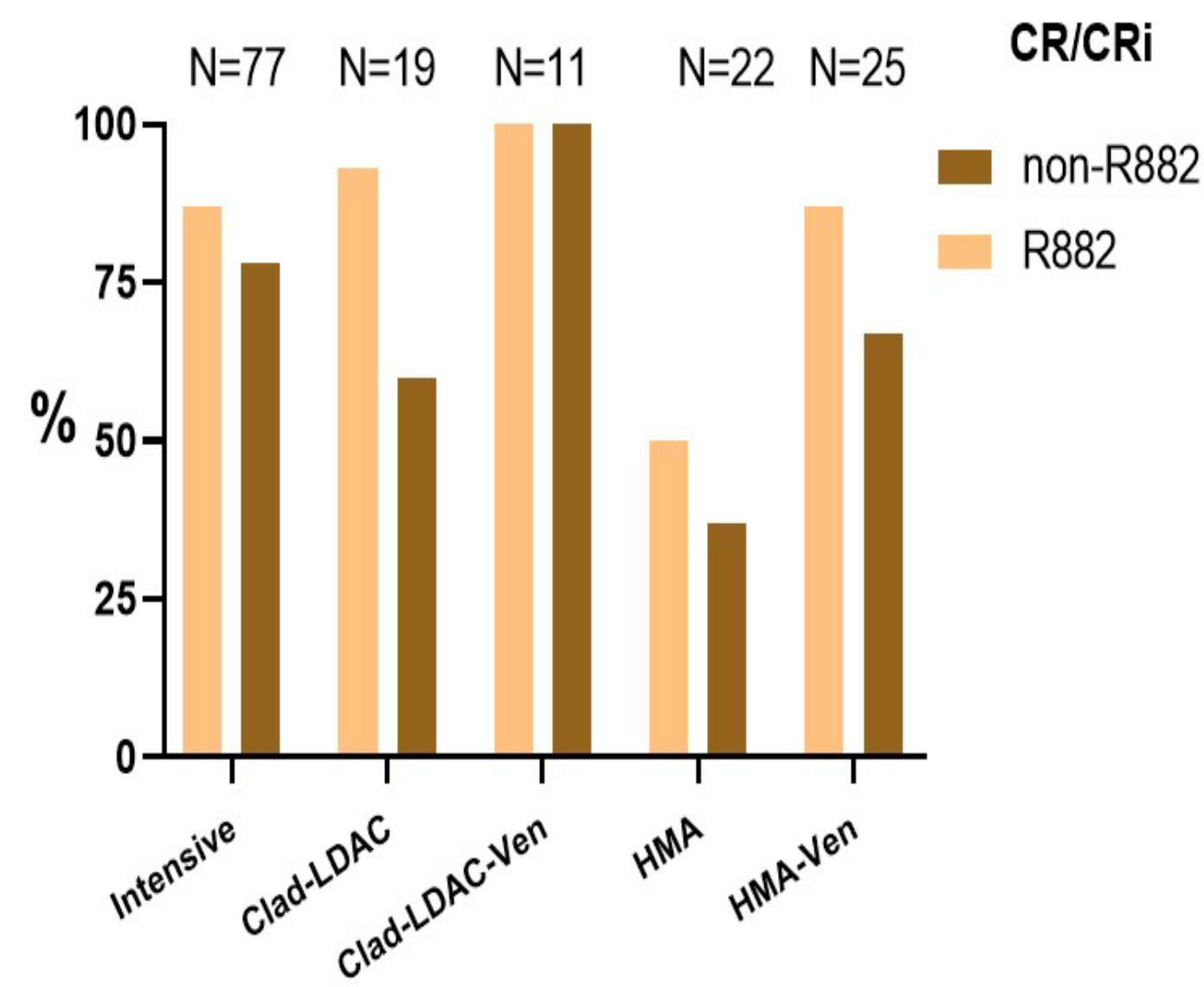
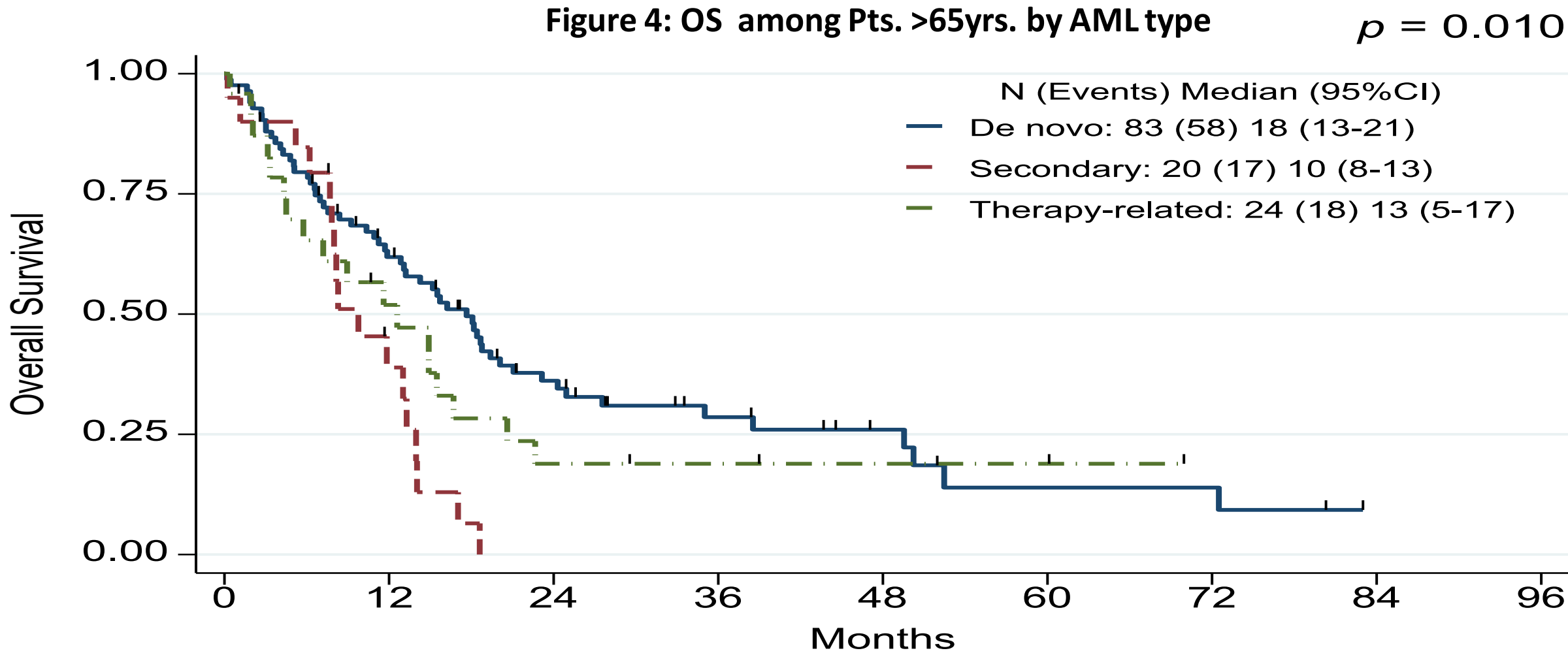


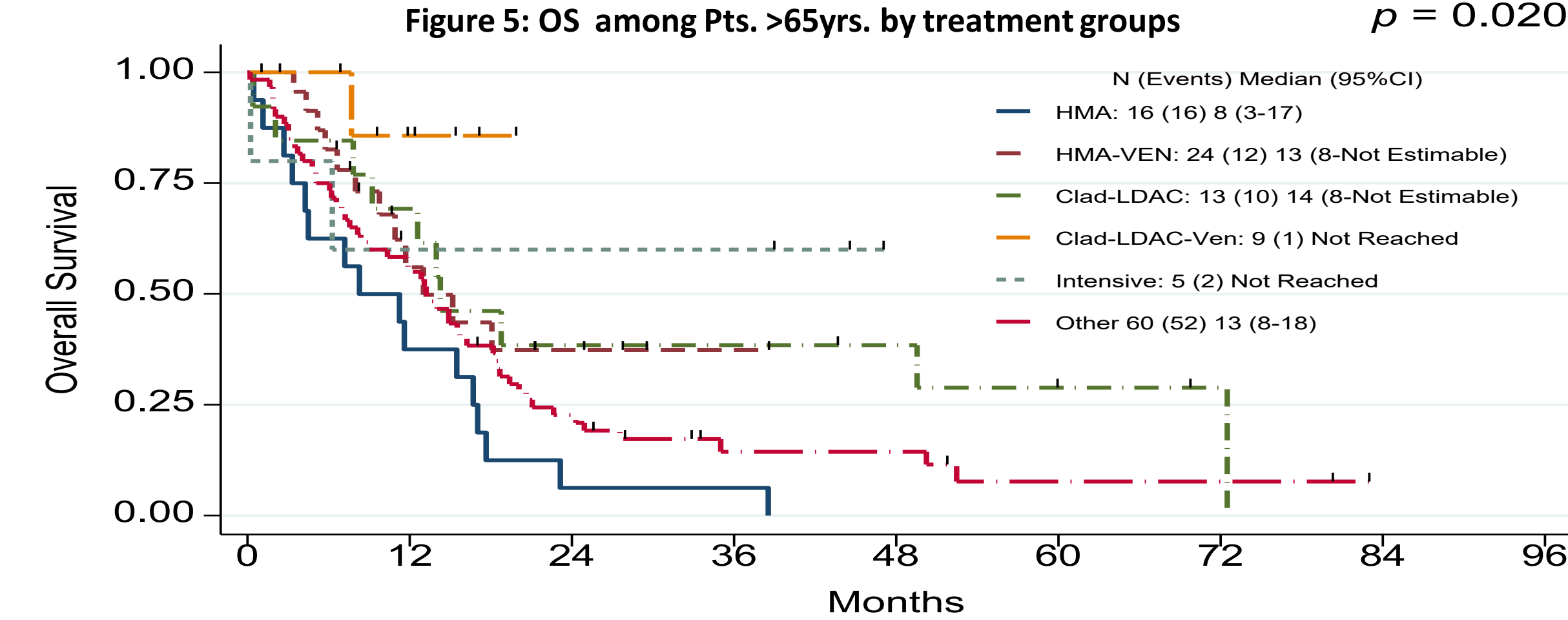
Figure 2: Response Rates by Treatment Categories



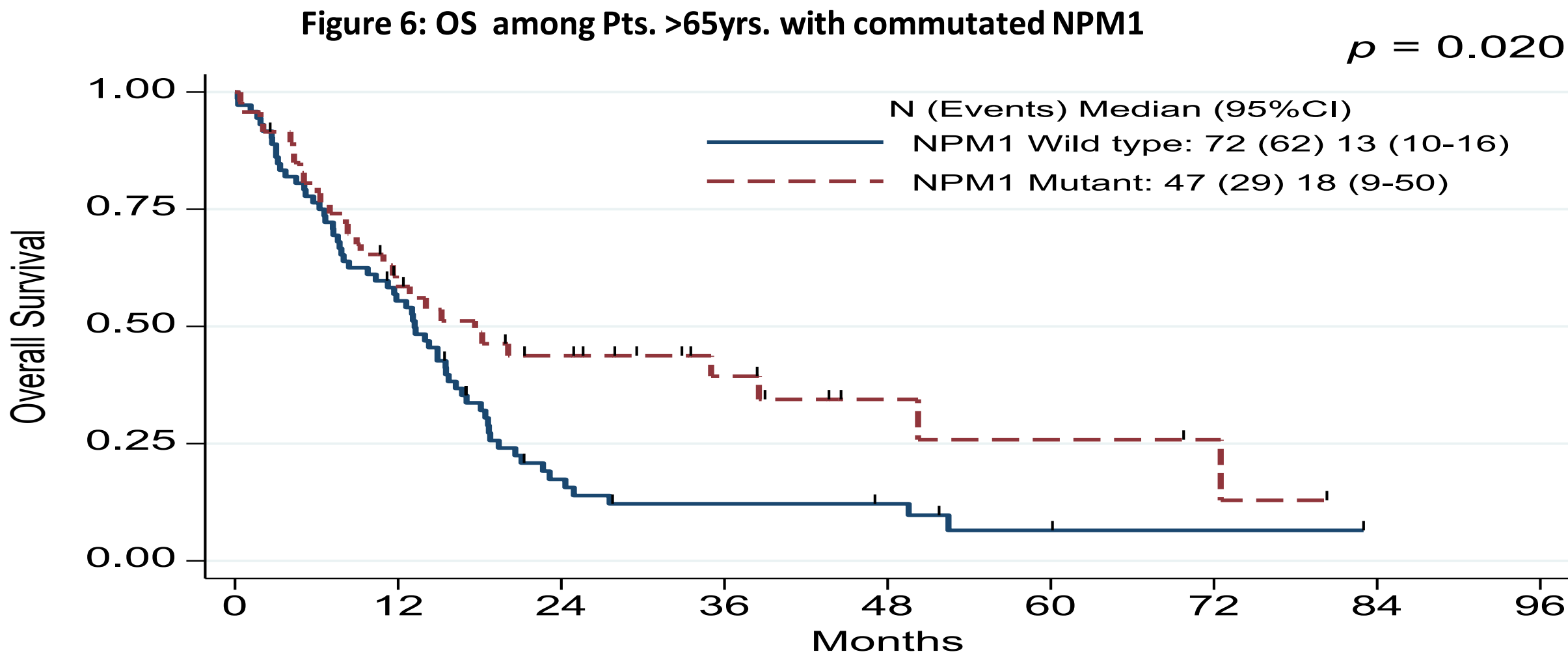
| Number at risk |    | Months |    |    |   |   |   |   |   |  |  |
|----------------|----|--------|----|----|---|---|---|---|---|--|--|
| R882           | 64 | 37     | 16 | 11 | 7 | 3 | 2 | 0 | 0 |  |  |
| Non-R882       | 63 | 27     | 10 | 4  | 2 | 1 | 1 | 0 | 0 |  |  |



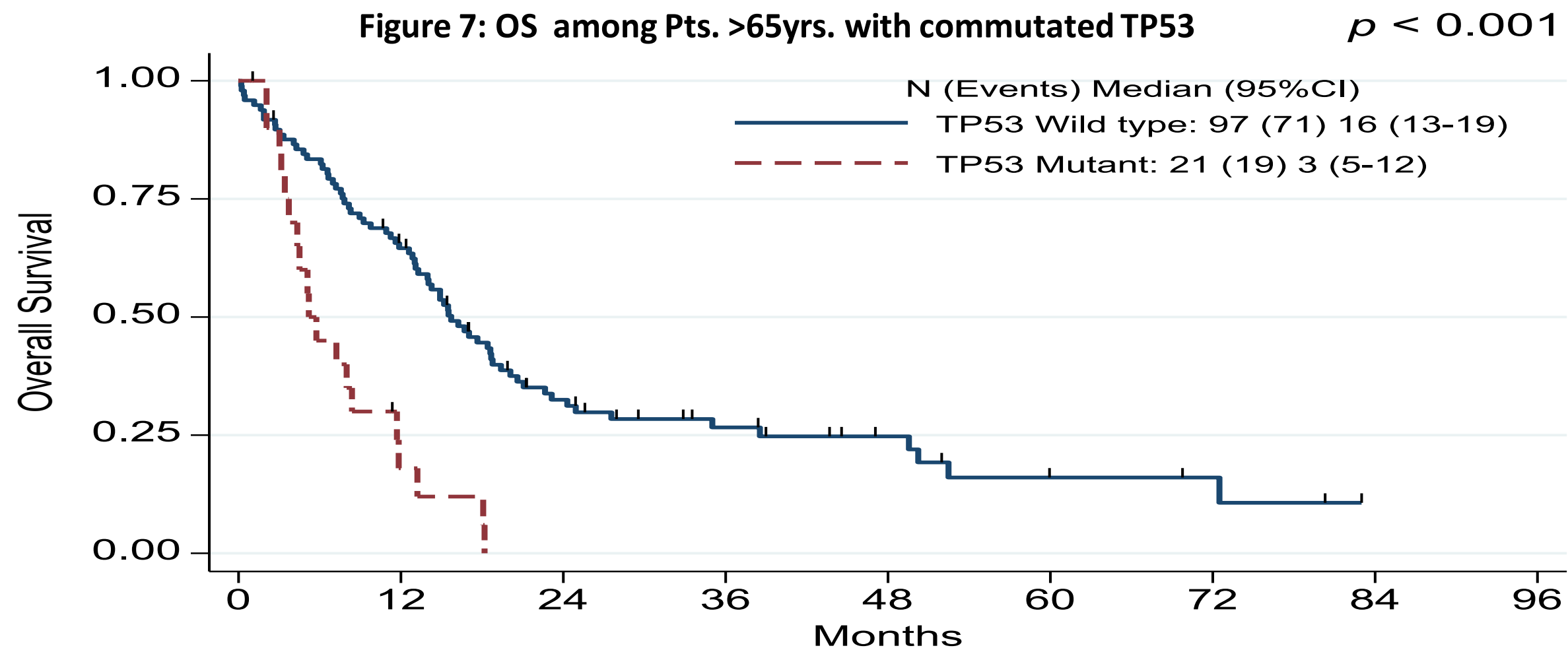
| Number at risk  |    | Months |    |    |   |   |   |   |   |  |  |
|-----------------|----|--------|----|----|---|---|---|---|---|--|--|
| De novo         | 83 | 47     | 22 | 12 | 7 | 3 | 3 | 0 | 0 |  |  |
| Secondary       | 20 | 6      | 0  | 0  | 0 | 0 | 0 | 0 | 0 |  |  |
| Therapy-related | 24 | 11     | 4  | 3  | 2 | 1 | 0 | 0 | 0 |  |  |



| Number at risk |    | Months |    |   |   |   |   |   |   |  |  |
|----------------|----|--------|----|---|---|---|---|---|---|--|--|
| HMA            | 16 | 6      | 1  | 1 | 0 | 0 | 0 | 0 | 0 |  |  |
| HMA-VEN        | 24 | 9      | 4  | 1 | 0 | 0 | 0 | 0 | 0 |  |  |
| Clad-LDAC      | 13 | 9      | 5  | 5 | 4 | 2 | 1 | 0 | 0 |  |  |
| Clad-LDAC-Ven  | 9  | 4      | 0  | 0 | 0 | 0 | 0 | 0 | 0 |  |  |
| Intensive      | 5  | 3      | 3  | 3 | 0 | 0 | 0 | 0 | 0 |  |  |
| Other          | 60 | 33     | 13 | 5 | 5 | 2 | 2 | 0 | 0 |  |  |



| Number at risk |    | Months |    |   |   |   |   |   |   |  |  |
|----------------|----|--------|----|---|---|---|---|---|---|--|--|
| NPM1 Wild type | 72 | 39     | 10 | 6 | 5 | 1 | 1 | 0 | 0 |  |  |
| NPM1 Mutant    | 47 | 25     | 16 | 9 | 4 | 3 | 2 | 0 | 0 |  |  |



| Number at risk |    | Months |    |    |   |   |   |   |   |  |  |
|----------------|----|--------|----|----|---|---|---|---|---|--|--|
| TP53 Wild type | 97 | 60     | 25 | 15 | 9 | 4 | 3 | 0 | 0 |  |  |
| TP53 Mutant    | 21 | 3      | 0  | 0  | 0 | 0 | 0 | 0 | 0 |  |  |

Figure 8: Outcome predictors among Pts. older than 65 yrs. with DMNT3A mutated AML

