Carfilzomib or bortezomib in combination with cyclophosphamide and dexamethasone followed by carfilzomib maintenance for patients with multiple myeloma after one prior therapy: results from a multicenter, phase II, randomized, controlled trial (MUKfive)

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Received: January 25, 2021.
Accepted: April 14, 2021.
Pre-published: April 29, 2021.
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Supplementary Figures and Tables

Figure S1. Weighted overall survival from initial randomisation

Proportion alive

Number at Risk

|   | KCd   | VCd   |
|---|-------|-------|
| 0 | 199   | 96    |
| 6 | 188   | 81    |
| 12| 110   | 49    |
| 18| 54    | 27    |
| 24| 32    | 12    |
| 30| 16    | 6     |
| 36| 5     | 2     |
| 42| 1     | 0     |
| 48| 1     |       |
| 54| 0     |       |

Time from initial randomisation (months)

|   | 0 | 6  | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 |
|---|---|----|----|----|----|----|----|----|----|----|
| KCd| 199| 188| 110| 54 | 32 | 16 | 5  | 1  | 1  | 0  |
| VCd| 96 | 81 | 49 | 27 | 12 | 6  | 2  | 0  |    |    |
Figure S2. Dynamics of MRD status during maintenance vs observation
104 participants had evaluable samples at randomisation to maintenance; at 6 months 75 participants had an evaluable sample or had progressed. In the maintenance arm, 5/8 MRD negative patients remained MRD negative at 6 months, while only 1/10 MRD negative patients in the control arm remained MRD negative; 4 of 40 MRD positive patients who received maintenance became MRD negative at 6 months, while no MRD positive patients in the control arm became MRD negative.
Figure S3. Landmark analysis of PFS at 6 months post first randomisation
A post-hoc landmark analysis was performed at 6 months post first randomisation, to assess PFS for those patients who had not progressed at this time, comparing VCD with KCD plus maintenance, and KCD with no maintenance.
Figure S4. At least VGPR rate at end of induction by genetic risk, and treatment arm

A. ≥VGPR rate (%) according to adverse or standard risk
B. ≥VGPR rate (%) according to particular high risk lesion, numbers in bars indicate number of patients in each subgroup. None of the 8 patients with del(17p) who received VCd achieved at least VGPR.
Figure S5. PFS from maintenance randomisation according to genetic risk

Adverse risk

Standard risk
Table S1: Weighting of participants in the KCd vs. VCd comparison of PFS and OS using inverse probability of censoring weighted methodology

| Participant group                        | Weight |
|------------------------------------------|--------|
| VCd                                      | 1      |
| KCd, not undergoing maintenance          | 1 [probability of receiving maintenance is 0 as can only receive maintenance if undergo the randomisation] |
| randomisation                            |        |
| KCd, randomised to maintenance           | 0      |
| KCd, randomised to no maintenance        | 2 [probability of receiving maintenance = 0.5 due to 1:1 randomisation] |

Table S2: Response to treatment (induction treatment, best response within 12 months)

*10 and 13 participants were included with their maximum response, within 12 months and overall, respectively, taken at the time of maintenance randomisation in the main analysis and their maximum response within 12 months and overall, regardless of maintenance treatment, in the sensitivity analyses.

| Time-point                        | Outcome                  | KCd | VCd | KCd vs. VCd comparison |
|-----------------------------------|--------------------------|-----|-----|------------------------|
|                                   |                          |     |     | Difference (%)         | OR, 90% CI, p-value |
| Within 12 months of initial       | Participants with available response | 201*| 98  |                        |                      |
| randomisation                     | sCR                      | 0%  | 1%  | -1.1 (-11.4, 9.3)      | N/A                  |
|                                  | CR                       | 3.1%| 3.2%| -0.1 (-10.4, 10.2)     |                      |
|                                  | VGPR                     | 49.5%| 41.1%| 8.4 (-1.9, 18.7)      |                      |
|                                  | PR                       | 38.8%| 33.7%| 5.1 (-5.3, 15.4)     |                      |
|                                  | MR                       | 3.1%| 11.6%| -8.5 (-18.7, 1-8)     |                      |
|                                  | SD/NC                    | 1.5%| 8.4%| -6.9 (-17.1, 3.4)     |                      |
|                                   | Maximum response         |     |     |                        |                      |
|                                   | (sensitivity analysis:    |     |     |                        |                      |
|                                   | ignoring maintenance)    |     |     |                        |                      |
|                                   | sCR                      | 0%  | 1%  | -1.1 (-11.4, 9.3)      | N/A                  |
|                                   | CR                       | 5.6%| 3.2%| 2.5 (-7.9, 12.7)      |                      |
|                                   | VGPR                     | 50.0%| 41.1%| 8.9 (-1.4, 19.2)     |                      |
|                                   | PR                       | 35.7%| 33.7%| 2.0 (-8.3, 12.4)     |                      |
|                                   | MR                       | 3.1%| 11.6%| -8.5 (-18.7, 1-8)     |                      |
|                                   | SD/NC                    | 1.5%| 8.4%| -6.9 (-17.1, 3.4)     |                      |
| Within 12 months of initial       | Overall response         | 91.3%| 78.9%| 12.4, (2.0, 22.6)     | 2.95, (1.61, 5.41), p=0.0034 |
| randomisation                     |                          |     |     |                        |                      |
|                                   | Participants with available response | 201*| 98  |                        |                      |
|                                   | sCR                      | 0%  | 1%  | -1.1 (-11.4, 9.3)      | N/A                  |
|                                   | CR                       | 3.1%| 3.2%| -0.1 (-10.4, 10.2)     |                      |
|                                   | VGPR                     | 50.0%| 41.1%| 8.9 (-1.4, 19.2)     |                      |
|                                   | PR                       | 38.3%| 33.7%| 4.6 (-5.8, 14.9)     |                      |
|                                   | MR                       | 3.1%| 11.6%| -8.5 (-18.7, 1-8)     |                      |
|                                   | SD/NC                    | 1.5%| 8.4%| -6.9 (-17.1, 3.4)     |                      |
| Overall                           | Maximum response         |     |     |                        |                      |
|                                   | (main analysis: conservative) |     |     |                        |                      |
|                                   | sCR                      | 0%  | 1%  | -1.1 (-11.4, 9.3)      | N/A                  |
|                                   | CR                       | 6.1%| 3.2%| 3.0 (-7.4, 13.2)      |                      |
|                                   | VGPR                     | 50.5%| 41.1%| 9.5 (-0.9, 19.7)     |                      |
|                                   | PR                       | 34.7%| 33.7%| 1.0 (-9.3, 11.4)     |                      |
|                                   | MR                       | 3.6%| 11.6%| -8.0 (-18.2, 2.3)     |                      |
|                                   | SD/NC                    | 1.0%| 8.4%| -7.4 (-17.6, 2.9)     |                      |
Table S3. Minimal residual disease at end of induction treatment

| Sample received? | KCd (n=196) | VCd (n=96) | Total (n=292) |
|------------------|-------------|------------|---------------|
| Yes              |             |            |               |
| MRD positive     | 134 (67.9%) | 49 (51.0%) | 182 (62.3%)   |
| MRD negative     | 93 (69.9%)  | 39 (79.6%) | 132 (72.5%)   |
| Suspicious       | 22 (16.5%)  | 6 (12.2%)  | 28 (15.4%)    |
| Inadequate sample| 6 (4.5%)    | 1 (2.0%)   | 7 (3.8%)      |
| Not evaluable    | 11 (8.3%)   | 3 (6.1%)   | 14 (7.7%)     |
|                  | 63 (32.1%)  | 47 (49.0%) | 110 (37.7%)   |

Table S4 Weighted Cox’s proportional hazards modelling for progression-free survival, adjusted for minimisation factors (induction comparison)*

| Variable                                         | Hazard ratio (HR) | 80% CI lower limit for HR | 80% CI upper limit for HR | Chi-square test statistic | Degrees of freedom | p-value |
|--------------------------------------------------|-------------------|---------------------------|----------------------------|---------------------------|--------------------|---------|
| Randomisation treatment: KCd vs. VCd             | 0.95              | 0.77                      | 1.18                       | 0.1020                    | 1                  | 0.7494  |
| B2M: 3.3-5.5 vs <3.5                             | 1.71              | 1.34                      | 2.19                       | 19.0949                   | 2                  | <0.0001 |
| B2M: >5.5 vs <3.5                                | 2.27              | 1.67                      | 3.08                       |                           |                    |         |
| Previous bortezomib: Yes vs. No                  | 1.35              | 1.01                      | 1.79                       | 2.7527                    | 1                  | 0.0971  |
| Previous autograft: Yes vs. No                   | 1.56              | 1.24                      | 1.95                       | 8.9275                    | 1                  | 0.0028  |
| Relapse timing/primary refractory: 1st relapse ≥12 months vs <12 months | 0.78 | 0.56 | 1.10 | 2.6068 | 2 | 0.2716 |
| Relapse timing/primary refractory: primary refractory vs 1st relapse <12 months | 0.49 | 0.18 | 1.32 | | | |

* CIs created using sandwich variance estimate to account for weighting
### Table S5. Reasons for stopping induction treatment

| Reason(s) for stopping treatment                        | KCd (n=201) | VCd (n=99) | Total (n=300) |
|--------------------------------------------------------|-------------|------------|---------------|
| Maximum number of cycles                               | 157 (78.1%)| 52 (52.5%) | 209 (69.7%)   |
| Maximum number of cycles, Disease progression          | 1 (0.5%)    | 1 (1.0%)   | 2 (0.7%)      |
| Maximum number of cycles, Patient died                 | 1 (0.5%)    | 0 (0.0%)   | 1 (0.3%)      |
| Maximum number of cycles, Unacceptable toxicity        | 1 (0.5%)    | 0 (0.0%)   | 1 (0.3%)      |
| Maximum number of cycles, Withdrew consent             | 0 (0.0%)    | 1 (1.0%)   | 1 (0.3%)      |
| Unacceptable toxicity                                  | 11 (5.5%)   | 13 (13.1%) | 24 (8.0%)     |
| Unacceptable toxicity, Clinician decision              | 0 (0.0%)    | 4 (4.0%)   | 4 (1.3%)      |
| Unacceptable toxicity, Disease progression             | 1 (0.5%)    | 1 (1.0%)   | 2 (0.7%)      |
| Unacceptable toxicity, Patient died                    | 1 (0.5%)    | 0 (0.0%)   | 1 (0.3%)      |
| Unacceptable toxicity, Withdrew consent                | 0 (0.0%)    | 1 (1.0%)   | 1 (0.3%)      |
| Disease progression                                    | 10 (5.0%)   | 4 (4.0%)   | 14 (4.7%)     |
| Disease progression, Clinician decision                | 1 (0.5%)    | 0 (0.0%)   | 1 (0.3%)      |
| Patient died                                           | 2 (1.0%)    | 1 (1.0%)   | 3 (1.0%)      |
| Patient died, Clinician decision                       | 1 (0.5%)    | 0 (0.0%)   | 1 (0.3%)      |
| Clinician decision                                     | 6 (3.0%)    | 10 (10.1%) | 16 (5.3%)     |
| Clinician decision, Other                              | 0 (0.0%)    | 1 (1.0%)   | 1 (0.3%)      |
| Clinician decision, Withdrew consent                   | 0 (0.0%)    | 1 (1.0%)   | 1 (0.3%)      |
| Withdrew consent                                       | 5 (2.5%)    | 8 (8.1%)   | 13 (4.3%)     |
| Other                                                  | 3 (1.5%)    | 1 (1.0%)   | 4 (1.3%)      |

### Table S6. Drug modifications during induction

| Modification to any drug? | Cycle 1 only | All cycles |
|---------------------------|--------------|------------|
|                           | KCd (n=196)  | VCd (n=96) | KCd (n=196)  | VCd (n=96) |
| Yes                       |              |            |              |            |
| Bortezomib                | 55 (28.1%)   | 22 (22.9%) | 154 (78.6%)  | 82 (85.4%) |
| Carfilzomib               | N/A          | 15 (68.2%) | N/A          | 79 (96.3%) |
| Cyclophosphamide          | 44 (80.0%)   | N/A        | 136 (88.3%)  | N/A        |
| Dexamethasone             | 29 (52.7%)   | 8 (36.4%)  | 95 (61.7%)   | 48 (58.5%) |
|                           | 32 (58.2%)   | 12 (54.5%) | 116 (75.3%)  | 54 (65.9%) |
| No                        | 141 (71.9%)  | 74 (77.1%) | 42 (21.4%)   | 14 (14.6%) |
Table S7A: Neuropathy during induction: ≥grade 3 or ≥grade 2 with pain

| Neuropathy Grade 3+ or Grade 2+ with pain? | KCd (n=196) | VCd (n=96) | Total (n=292) |
|------------------------------------------|--------------|------------|---------------|
| Yes                                      | 3 (1.5%)     | 19 (19.8%) | 22 (7.5%)     |
| Grade 2 with pain                        | 2 (66.7%)    | 18 (94.7%) | 20 (90.9%)    |
| Grade 3 (without pain)                   | 1 (33.3%)    | 0 (0.0%)   | 1 (4.5%)      |
| Grade 3 with pain                        | 0 (0.0%)     | 1 (5.3%)   | 1 (4.5%)      |
| No                                       | 193 (98.5%)  | 77 (80.2%) | 270 (92.5%)   |

Table S7B. Neuropathy at baseline and worsening during induction treatment

| Did the patient have neuropathy? | Present at baseline | Starting or worsening during treatment |
|---------------------------------|---------------------|----------------------------------------|
|                                 | KCd (n=196)         | VCd (n=96)                            |
|                                 | Total (n=292)       | Total (n=292)                         |
|                                 |                     |                         |
| Yes                             | 36 (18.4%)          | 25 (26.0%)                |
| No                              | 160 (81.6%)         | 71 (74.0%)                |
| Number of events per patient    |                     |                         |
| Mean (SD)                       | 1.0 (0.17)          | 1.0 (0.00)                |
| Median (Range)                  | 1.0 (1.0, 2.0)      | 1.0 (1.0, 1.0)            |
| Total number of events          | 37 (100%)           | 25 (100%)                 |
| Reason for inclusion as starting or worsening during treatment (by # events) |                     |                         |
| Increase in CTC grade and development of associated pain | 1 (2.1%) | 10 (10.8%) |
| Development of associated pain  | 0 (0.0%)            | 2 (2.2%)                  |
| Increase in CTC grade           | 4 (8.3%)            | 2 (2.2%)                  |
| Started during induction         | 43 (89.6%)          | 79 (84.9%)                |
| Type of neuropathy               |                     |                         |
| Motor                            | 1 (2.7%)            | 1 (4.0%)                  |
| Sensory                          | 35 (94.6%)          | 24 (96.0%)                |
| Autonomic                        | 0 (0.0%)            | 0 (0.0%)                  |
| Missing                          | 1 (2.7%)            | 0 (0.0%)                  |
| Associated pain                  |                     |                         |
| Yes                              | 3 (8.1%)            | 3 (12.0%)                 |
| No                               | 34 (91.9%)          | 22 (88.0%)                |
| Missing                          | 0 (0.0%)            | 0 (0.0%)                  |
| CTCAE grade                      |                     |                         |
| 1                                | 34 (91.9%)          | 25 (100.0%)               |
| 2                                | 3 (8.1%)            | 0 (0.0%)                  |
| 3                                | 0 (0.0%)            | 0 (0.0%)                  |
Table S8A. Serious adverse events occurring during induction

|                          | KCd (n=196 participants) | VCd (n=96 participants) |
|--------------------------|---------------------------|-------------------------|
| Patients with SAEs       | 88 (44.9%)                | 45 (46.9%)              |
| SAEs: # events           | 142                       | 74                      |
| SAEs related to treatment| 88 (including 3 SUSARs)    | 39 (0 SUSARs)           |
| SAEs resulting in death  |                           |                         |
|                          | 1 x multi-organ failure    |                         |
|                          | 1 x chest infection        |                         |
|                          | 1 x H1N1 infection         |                         |
| Categorisation of all SAEs|                          |                         |
| Cardiac                  | 6 (4.2%)                  | 1 (1.4%)                |
| Renal/urinary            | 5 (3.5%)                  | 4 (5.4%)                |
| Gastrointestinal         | 11 (7.7%)                 | 4 (5.4%)                |
| Infections/Infestations  | 73 (51.4%)                | 35 (47.3%)              |
| Other categorisations    | 47 (33.0%)                | 30 (40.5%)              |
| Maximum CTCAE grade for all SAEs |            |                         |
| 1                        | 10 (7.0)                  | 3 (4.1)                 |
| 2                        | 25 (17.6)                 | 16 (21.6)               |
| 3                        | 88 (62.0)                 | 49 (66.2)               |
| 4                        | 16 (11.3)                 | 6 (8.1)                 |
| 5                        | 3 (2.1)*                  | 0 (0.0)                 |
| Outcome for all SAEs     |                          |                         |
| Recovered                | 114 (80.3)                | 63 (85.1)               |
| Recovered with sequelae  | 14 (9.9)                  | 7 (9.5)                 |
| Condition improving      | 1 (0.7)                   | 2 (2.7)                 |
| Death                    | 3 (2.1)                   | 0 (0.0)                 |
| Ongoing at time of death | 9 (6.3)                   | 2 (2.7)                 |
| Missing                  | 1 (0.7)                   | 0 (0.0)                 |

Table S8B: Adverse reactions experienced by at least 5% of participants (in either treatment arm during induction treatment) at grade 3 or above

| Adverse reaction              | KCd (n=196) | VCd (n=96) |
|-------------------------------|-------------|------------|
| Thrombocytopenia              | 23 (11.7%)  | 35 (36.5%) |
| Neutropenia                   | 22 (11.2%)  | 21 (21.9%) |
| Anaemia                       | 33 (16.8%)  | 10 (10.4%) |
| Lung infection                | 15 (7.7%)   | 8 (8.3%)   |
| Hyponatremia                  | 19 (9.7%)   | 4 (4.2%)   |
| White blood cell decreased    | 15 (7.7%)   | 4 (4.2%)   |
| Hypophosphatemia              | 15 (7.7%)   | 0 (0.0%)   |
Table S8C: Specific adverse reactions of interest (regardless of frequency): maximum grade experienced during induction treatment

|                                          | KCd (n=196) | VCd (n=96) |
|-----------------------------------------|-------------|------------|
|                                         | 1           | 2          | 3          | 4/5         | 1           | 2          | 3          | 4/5         |
| Lung infection                          | 3 (1.5%)    | 15 (7.7%)  | 15 (7.7%)  | 0           | 2 (2.1%)    | 12 (12.5%) | 8 (8.3%)   | 0           |
| Upper respiratory infection             | 9 (4.6%)    | 33 (16.8%) | 6 (3.1%)   | 0           | 3 (3.1%)    | 13 (13.5%) | 3 (3.1%)   | 0           |
| Cardiac events                         | 7 (3.6%)    | 4 (2.0%)   | 6 (3.6%)   | 0           | 3 (3.1%)    | 5 (5.2%)   | 0          | 0           |
| Hypertension                           | 2 (1.0%)    | 1 (0.5%)   | 7 (3.6%)   | 0           | 0           | 2 (2.1%)   | 0          | 0           |
| Dyspnea                                | 36 (18.4%)  | 16 (8.2%)  | 4 (2.0%)   | 0           | 13 (13.5%)  | 2 (2.1%)   | 0          | 0           |
| Bronchial infection                    | 2 (1.0%)    | 7 (3.6%)   | 0          | 0           | 0           | 4 (4.2%)   | 1 (1.0%)   | 0           |

Table S9. Safety and treatment tolerability by age and renal function, induction comparison

CrCl = Creatinine clearance

|                                          | KCd          | VCd          |
|-----------------------------------------|--------------|--------------|
| **Patients receiving intended 24 weeks of treatment** |              |              |
| Age <70                                 | 95/118 (80.5%) | 28/53 (52.8%) |
| Age ≥70                                 | 69/83 (83.1%)  | 25/46 (54.3%) |
| CrCl ≤60ml/min                          | 47/67 (70.1%)  | 15 (60.0%)    |
| CrCl >60ml/min                          | 117/133 (88.0%) | 38/74 (51.4%) |
| **Median duration of treatment (for patients starting treatment)** |              |              |
| Age <70                                 | 24 weeks     | 24 weeks     |
| Age ≥70                                 | 24 weeks     | 24 weeks     |
| CrCl ≤60ml/min                          | 24 weeks     | 24 weeks     |
| CrCl >60ml/min                          | 24 weeks     | 24 weeks     |
| **Number of patients in safety analyses** |              |              |
| Age <70                                 | 115          | 51           |
| Age ≥70                                 | 81           | 45           |
| CrCl ≤60ml/min                          | 65           | 24           |
| CrCl >60ml/min                          | 131          | 72           |
| **Number of patients with an SAE**      |              |              |
| Age <70                                 | 50 (43.5%)   | 24 (47.1%)   |
| Age ≥70                                 | 38 (46.9%)   | 21 (46.7%)   |
| CrCl ≤60ml/min                          | 32 (49.2%)   | 11 (45.8%)   |
| CrCl >60ml/min                          | 56 (42.7%)   | 34 (47.2%)   |
| **Number of SAEs reported**             |              |              |
| Age <70                                 | 84           | 40           |
| Age ≥70                                 | 58           | 34           |
| CrCl ≤60ml/min                          | 55           | 19           |
| CrCl >60ml/min                          | 87           | 55           |
### Table S10: Maintenance randomization: Cox Proportional Hazards modelling for PFS adjusting for minimization factors

| Randomisation treatment: Maintenance with carfilzomib vs. no maintenance | Hazard ratio (80% CI) | Chi-square test statistic | p-value |
|---|---|---|---|
| | 0.59 (0.46,0.77) | 6.9091 | 0.0086 |

| Response category at the end of therapy with KCD: VGPR, CR or sCR vs. PR, MR or SD | Hazard ratio (80% CI) | Chi-square test statistic | p-value |
|---|---|---|---|
| | 0.42 (0.32, 0.55) | 17.5214 | <.0001 |

| Previous autograft: Yes vs. No | Hazard ratio (80% CI) | Chi-square test statistic | p-value |
|---|---|---|---|
| | 1.32 (1.00, 1.73) | 1.7049 | 0.1916 |

### Table S11: Adverse reactions in maintenance Carfilzomib arm (n=67)

| CTCAE grade – n (%) |
|---|
| | 0 (Not experienced) | 1 | 2 | 3 | 4 | 5 |
| Neutropenia | 49 (73.1) | 10 (14.9) | 7 (10.4) | 1 (1.5) | 0 | 0 |
| Thrombocytopenia | 38 (56.7) | 25 (37.3) | 4 (6.0) | 0 | 0 |
| Anaemia | 8 (11.9) | 38 (56.7) | 18 (26.9) | 3 (4.5) | 0 | 0 |
| Nausea | 44 (65.7) | 16 (23.9) | 6 (9.0) | 1 (1.5) | 0 | 0 |
| Vomiting | 53 (79.1) | 9 (13.4) | 3 (4.5) | 2 (3.0) | 0 | 0 |
| Diarrhoea | 53 (79.1) | 11 (16.4) | 2 (3.0) | 1 (1.5) | 0 | 0 |
| Constipation | 59 (88.1) | 7 (10.4) | 1 (1.5) | 0 | 0 |
| Hypertension | 65 (97.0) | 0 | 1 (1.5) | 1 (1.5) | 0 | 0 |
| Infusion reactions | 60 (89.6) | 3 (4.5) | 4 (6.0) | 0 | 0 |
| DVT | 67 (100.0) | 0 | 0 | 0 | 0 |
| Pulmonary embolism | 67 (100.0) | 0 | 0 | 0 | 0 |
| Chest pain cardiac | 66 (98.5) | 0 | 1 (1.5) | 0 | 0 |
| Acute kidney injury | 61 (91.0) | 3 (4.5) | 2 (3.0) | 1 (1.5) | 0 | 0 |
| Hypertension | 63 (94.0) | 1 (1.5) | 1 (1.5) | 2 (3.0) | 0 | 0 |
| Upper respiratory infection | 45 (67.2) | 3 (4.5) | 18 (26.9) | 1 (1.5) | 0 | 0 |
| Bronchial infection | 64 (95.5) | 0 | 3 (4.5) | 0 | 0 |
| Lung infection | 61 (91.0) | 1 (1.5) | 2 (3.0) | 3 (4.5) | 0 | 0 |

### Table S12. Treatment cycles of induction received by genetic risk group

| | KCd | VCd |
|---|---|---|
| Patients receiving intended 24 weeks of treatment |
| Adverse risk | 54/69 (78.3%) | 21/33 (63.6%) |
| Standard risk | 51/55 (92.7%) | 13/30 (43.3%) |
| Median duration of treatment (for patients starting treatment) |
| Adverse risk | 24 weeks | 24 weeks |
| Standard risk | 24 weeks | 18 weeks |