6.2 Event-free survival

The primary analysis of the study is the comparison of EFS between the treatment arms. This will be done using multivariate Cox proportional hazards model where the treatment arm effect will be adjusted for age group (18-60 vs 61-70 years) and WHO performance status (0-1 vs 2-3) at randomization. The likelihood ratio P-value will be reported. P-value < 0.05 will be considered statistically significant.

EFS is defined as: Time from registration to no CR(u) on protocol treatment, relapse or death from any cause, whichever comes first.

6.2.1   Descriptive statistics

EFS estimates in total and by arm, accompanied by the competing risks - `no CR(u)' (NR), relapse after CR(u)' and `death in CR(u)'.

```
****   (Event free survival [m])
    ccr: #              -> efs
    nr : #              -> NR
    rel: #              -> REL
    d  : #              -> D

Time [mnth]                                          _____12_____            _____60_____
            N ccr  nr rel   d Max Med #at efs se  NR se REL se  D se  #at efs se  NR se REL se  D se
            #   #   #   #    # [m] [m]   #   %     %      %      %       #   %     %      %      %

 Total     199  76  66  53   4  75  13   98  51  4  33  3  15  3  2  1    8  29  5  33  3  36  5  2  1

Rnr 1 rand. arm
  MBVP     100  37  34  27   2  75  11   49  49  5  34  5  15  4  2  1    3  28  8  34  5  36  8  2  1
  R-MBVP    99  39  32  26   2  67  15   49  52  5  32  5  14  4  1  1    5  29  7  32  5  36  7  2  2
```

Legend (see results for Total):

- N   : number of patients in the analysis;

- ccr : number of patients still in CR;

- nr : number of patients who did not achieve CR on protocol treatment;

- rel : number of patients with relapse after CR;

- d   : number of patients who died in CR (without previous relapse);

- Max : maximum observed efs time (in months);

- Med : median efs;

- #at : number of patients at risk at 12 months (and furtheron at 60 months);

- efs : actuarial estimate of 12-months efs;

- se : standard error of estimate of 12-months efs;

- NR : actuarial estimate of 12-months 'not-in-CR';

- REL : actuarial estimate of 12-months relapse;

- D   : actuarial estimate of 12-months death in CR.

For PFS, and OS, the tables will look very similar.

```
              Beg.                    Survivor      Std.
     Time    Total      Fail          Function     Error      [95% Conf. Int.]
-----------------------------------------------------------------------------
Total
     12        99        98           0.5057      0.0355      0.4341     0.5729
     36        37        18           0.3973      0.0361      0.3264     0.4672
     60         9         6           0.2872      0.0510      0.1923     0.3891
MBVP
     12        50        51           0.4900      0.0500      0.3890     0.5833
     36        15         9           0.3757      0.0512      0.2763     0.4748
     60         4         2           0.2775      0.0760      0.1425     0.4302
R-MBVP
     12        50        47           0.5214      0.0505      0.4183     0.6148
     36        23         9           0.4156      0.0512      0.3148     0.5133
     60         6         4           0.2893      0.0707      0.1613     0.4303
-----------------------------------------------------------------------------
Note: Survivor function is calculated over full data and evaluated at indicated times; it is
not calculated from aggregates shown at left.
```

Median EFS by arm:

```
        failure _d: efsi
  analysis time _t: efs

             |  no. of
arm1         |  subjects        50%     Std. Err.      [95% Conf. Interval]
-------------+--------------------------------------------------------------
        MBVP |     100    10.80904      5.934014       5.91376     26.3162
      R-MBVP |      99    14.88296       4.15637       6.96509     41.3963
-------------+--------------------------------------------------------------
       total |     199    13.20739      4.066125       7.35934     23.5565
```

EFS estimates at 1,3, and 5 years by arm, and stratification factors:

```
****   (Event free survival [m])

Time [mnth]                  ___12___   ___36___   ___60___
              N ccr Max Med  ef se #at  ef se #at  ef se #at
              #   # [m] [m]   %      #   %      #   %      #

 Total      199 123  75  13  51  4  98  40  4  36  29  5   8

Rnr 1 rand. arm
  MBVP      100  63  75  11  49  5  49  38  5  14  28  8   3
  R-MBVP     99  60  67  15  52  5  49  42  5  22  29  7   5

Age
  <=60       94  47  70  41  63  5  59  53  5  23  38  8   6
  >60       105  76  75   6  40  5  39  26  5  13  21  5   2

WHO stratum
  <=1       144  90  75  11  49  4  69  39  4  25  28  6   6
  >1         55  33  67  15  54  7  29  42  7  11  34  8   2
```


Event free survival
Rnr 1 rand. arm

R-MBVP

MBVP

	N	F
MBVP	100	63
R-MBVP	99	60

Cox LR P =0.99

At risk:

MBVP	100	49	32	14	7	3
R-MBVP	99	49	33	22	15	5

29 Jun 2017
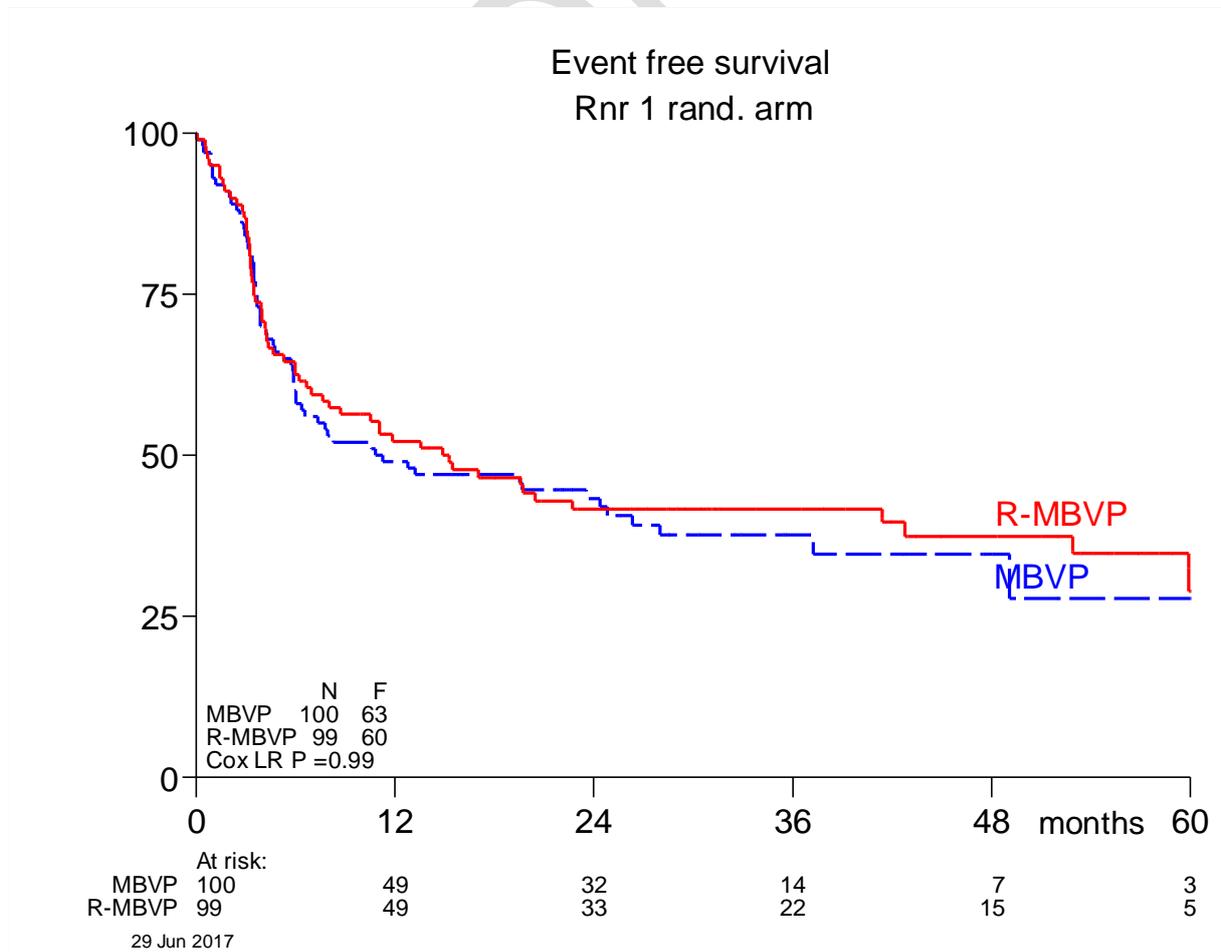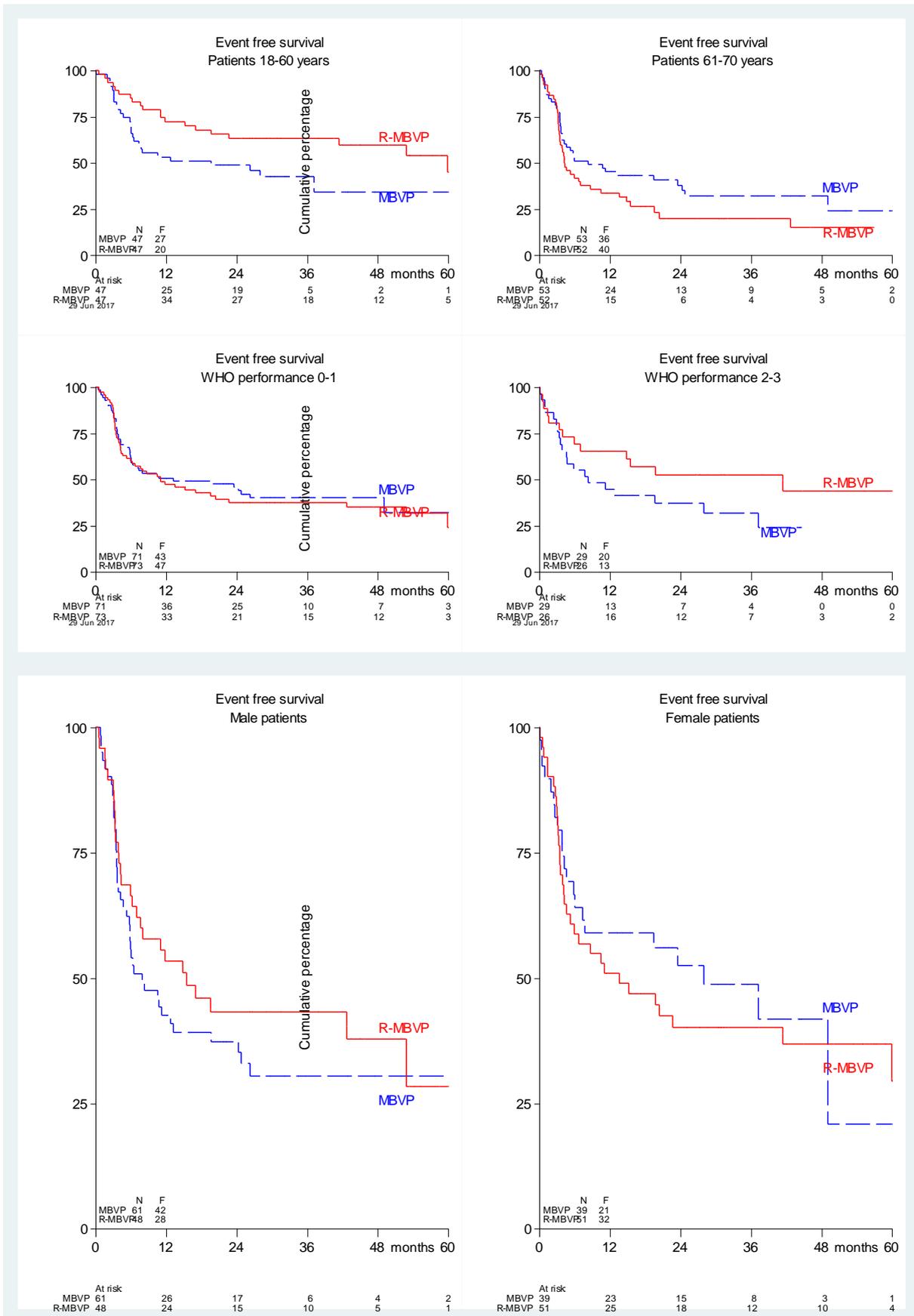
6.2.2   Formal evaluation

Univariate Cox regression analyses

```
_____
Cox regression
--------------
Time: efs      Event free survival [m]
Fail: efsi
_____
Variable  Nobs Nfail    Chi2 df   P_value    RelHR    SE   [95% Conf Limits]
-----------------------------------------------------------------------
          199   123    .257  1   6.1e-01
 :R-MBVP - arm1                  6.1e-01    0.91   0.17   0.64    1.30
          199   123    17.3  1   3.2e-05
 age60                           4.4e-05    2.15   0.40   1.49    3.11
          199   123    .0165 1   9.0e-01
 whostrat                        9.0e-01    0.97   0.20   0.65    1.45
```

(*) Legend (see the first 2 lines):
- Nobs = 199: indicates number of patients in this analysis;
- Nfail = 123: there are 123 patients for whom a failure has been reported; for this endpoints failures are no CR, relapse, or death, whichever comes first;
- P_value = 6.1e-01: indicated that P value = 0.61, i.e. there is not a statistically significant difference between the groups according to the variable on the subsequent line;
- :R-MBVP – arm1: this indicates that the variable of interest is `arm1', and that the results in this line refer to the `group' arm B; the baseline group is arm A;
- RelHR = 0.91: indicates the hazard ratio (HR) for this groups as compared to the baseline group; a value above 1 indicates a higher risk for the events, where a value below 1 indicates lower risk for the event;
- 95% Conf Limits = 0.64-1.30: indicates the 95% confidence interval for the HR. Because the value `1' is in this interval, the P value is not statistically significant .

Multivariate Cox regression analysis

```
_____
Cox regression
--------------
Time: efs      Event free survival [m]
Fail: efsi
_____
Variable  Nobs Nfail    Chi2 df   P_value    RelHR    SE   [95% Conf Limits]
-----------------------------------------------------------------------
Baseline model:
          199   123    17.3  2   1.7e-04
 age60                           4.4e-05    2.15   0.40   1.49    3.11
 whostrat                        9.6e-01    1.01   0.21   0.68    1.51
Additional factors:
          199   123   8.7e-05 1  9.9e-01
 :R-MBVP - arm1                  9.9e-01    1.00   0.18   0.70    1.43
(Above estimates and P-values adjusted for age60 whostrat except for the variable tested)
```

Multivariate Cox regression analysis - age X arm interaction

```
------------------------------------------------------------------------
       _t | Haz. Ratio  Std. Err.      z    P>|z|     [95% Conf. Interval]
----------+-------------------------------------------------------------
     arm1 |
   R-MBVP |   .5637978   .1677968   -1.93   0.054    .3146226   1.010315
          |
    age60 |
      >60 |   1.37757    .3515619    1.26   0.209    .8353788   2.271664
          |
arm1#age60|
R-MBVP#>60|   2.51808    .953008     2.44   0.015    1.199274   5.287136
------------------------------------------------------------------------
```

In the latter model the HR of the arms is so much different from the results of the previous models because here it corresponds to the arm effect in younger patients. The arm effect among elderly patients is calculated by multiplying the young-arm effect (.56) with de elderly-arm effect difference (2.52), that is HR 1.42 with 95% CI (0.90-2.23).

6.2.3   Prognostic factors

Univariate Cox regression - all prognostic factors

```
Cox regression
-------------
Time: efs      Event free survival [m]
Fail: efsi
```

Variable	Nobs	Nfail	Chi2	df	P_value	RelHR	SE	[95% Conf Limits]	
	199	123	.767	1	3.8e-01				
:F - sex					3.8e-01	0.85	0.16	0.60	1.22
	154	90	5.28	1	2.2e-02				
mmse					1.4e-02	0.96	0.01	0.94	0.99
	185	115	.0979	1	7.5e-01				
:Multifocal - focal					7.5e-01	1.06	0.20	0.73	1.53
	193	119	1.2e-04	1	9.9e-01				
:Yes - vitfluid					9.9e-01	1.00	0.39	0.46	2.14
	181	115	.0295	1	8.6e-01				
:Yes - csf					8.6e-01	0.97	0.19	0.65	1.43
	197	121	3.77	1	5.2e-02				
dexa					3.9e-02	1.02	0.01	1.00	1.05
	199	123	.0165	1	9.0e-01				
:>1 - whostrat					9.0e-01	0.97	0.20	0.65	1.45
	199	123	17.3	1	3.2e-05				
:>60 - age60					4.4e-05	2.15	0.40	1.49	3.11
	198	122	.561	1	4.5e-01				
:>ULN - ldhn					4.5e-01	1.16	0.23	0.79	1.72

Multivariate Cox regression - all prognostic factors

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval]	
arm1: R-MBVP	.8879495	.214211	-0.49	0.622	.5534042	1.424735
sex : F	.9776308	.2465035	-0.09	0.929	.5964166	1.602507
mmse	.9493112	.0221625	-2.23	0.026	.9068524	.9937579
Multifocal	1.27103	.3447035	0.88	0.377	.7469812	2.162727
vitfluid:Yes	1.027646	.5169617	0.05	0.957	.3833922	2.754508
csf : Yes	.9247149	.2307039	-0.31	0.754	.5670803	1.507895
dexa	1.059305	.0192919	3.16	0.002	1.022161	1.0978
whostrat: >1	.5460283	.1966505	-1.68	0.093	.2695612	1.106045
age60 : >60	2.744651	.6887502	4.02	0.000	1.678357	4.488384
ldhn : >ULN	.9085443	.2450239	-0.36	0.722	.5355338	1.541364

6.2.4   Conclusions
- The median EFS is 10.8 months in arm A and 14.9 months in arm B;
- EFS is not significantly improved in the R-MBVP arm (arm B):
  - In the univariate Cox regression analysis, HR = 0.91, 95% CI = [0.64,1.30], P = 0.61;
  - When adjusted for age group and WHO stratum, i.e. the primary analysis, HR = 1.00, 95% CI = [0.70,1.43], P = 0.99;
  - In the multivariate analysis, HR = 0.89, 95% CI = [0.55,1.42], P = 0.62;
- There is an indication that the impact of R-MBVP arm on EFS was different between the age groups (18-60 vs 61-70).

6.3 Progression-free survival

PFS is defined as: Time from registration to progression, relapse or death from any cause, whichever comes first.

6.3.1   Descriptive statistics

PFS estimates in total and by arm, accompanied by the competing risks - relapse and death.

```
****  (Progression free survival [m])
     cpr: #           ->  PFS
     rel: #           ->  REL
     d  : #           ->  D

Time [mnth]                              12_____            36_____             60_____
          N cpr rel  d Max Med #at PFS se REL se  D se #at PFS se REL se  D se #at PFS se REL se  D se
          #   #   #  # [m] [m]  #   %      %    %   %   #   %     %     %   %   #   %     %     %   %

 Total  199  93  89 17  75  26 119  62  3  31  3   8  2  43  48  4  44  4   8  2  10  35  5  55  5  10  3

Rnr 1 rand. arm
 MBVP   100  43  48  9  75  24  57  58  5  32  5   9  3  16  42  5  49  5   9  3   4  33  8  58  8   9  3
 R-MBVP  99  50  41  8  74  43  62  65  5  29  5   6  2  27  54  5  39  5   7  3   6  37  8  53  8  10  4


              Beg.                  Survivor       Std.
     Time     Total      Fail       Function      Error      [95% Conf. Int.]
Total
       12      120         75        0.6187       0.0347     0.5469     0.6826
       36       44         23        0.4821       0.0371     0.4077     0.5525
       60       11          7        0.3532       0.0540     0.2497     0.4582
MBVP
       12       58         41        0.5846       0.0497     0.4809     0.6747
       36       17         13        0.4225       0.0530     0.3179     0.5233
       60        5          2        0.3286       0.0762     0.1874     0.4774
R-MBVP
       12       63         34        0.6529       0.0482     0.5497     0.7380
       36       28         10        0.5390       0.0516     0.4329     0.6337
       60        7          5        0.3733       0.0788     0.2232     0.5235
--------------------------------------------------------------------------
Note: Survivor function is calculated over full data and evaluated at indicated times; it is
not calculated from aggregates shown at left.
```

Median PFS by arm:

```
           | no. of
arm1       | subjects        50%      Std. Err.     [95% Conf. Interval]
-----------+----------------------------------------------------------------
     MBVP  |     100     23.55647      5.461493       10.809      49.0842
   R-MBVP  |      99     42.77618     14.93027       15.4743            .
-----------+----------------------------------------------------------------
    total  |     199     26.31622      7.869872       15.8029      49.0842
```

PFS estimates at 1,3, and 5 years by arm, and stratification factors:

```
****  (Progression free survival [m])

Time [mnth]            _____12___  _____36___  _____60___
          N cpr Max Med PF se #at  PF se #at  PF se #at
          #   # [m] [m]  %      #   %      #   %      #

 Total  199 106  75  26  62  3 119  48  4  43  35  5  10

Rnr 1 rand. arm
 MBVP   100  57  75  24  58  5  57  42  5  16  33  8   4
 R-MBVP  99  49  74  43  65  5  62  54  5  27  37  8   6

Age
 <=60    94  42  70  53  68  5  63  58  5  24  42  9   6
 >60    105  64  75  16  56  5  56  38  5  19  30  6   4

WHO stratum
 <=1    144  79  75  24  59  4  84  47  4  30  35  6   8
 >1      55  27  67  37  68  6  35  51  7  13  42  8   2
```

Progression free survival
Rnr 1 rand. arm

	N	P
MBVP	100	57
R-MBVP	99	49
Cox LR P =0.18		

At risk:

MBVP	100	57	37	16	8	4	1
R-MBVP	99	62	43	27	17	6	1

27 Jun 2017
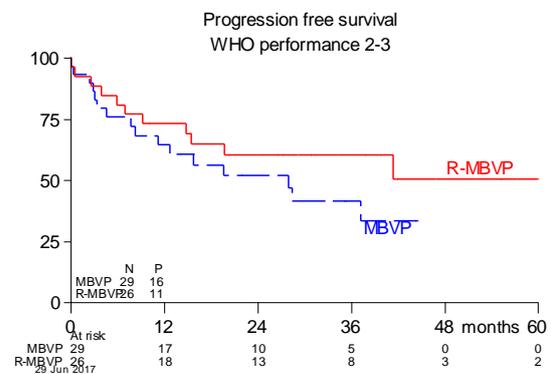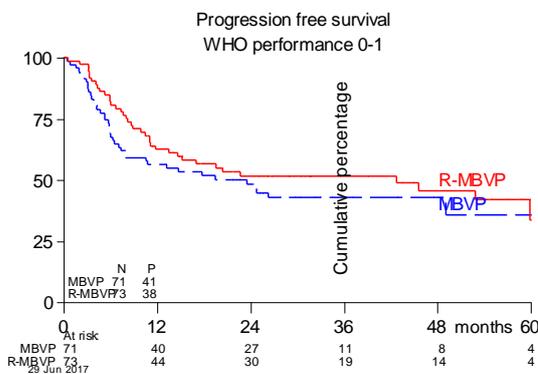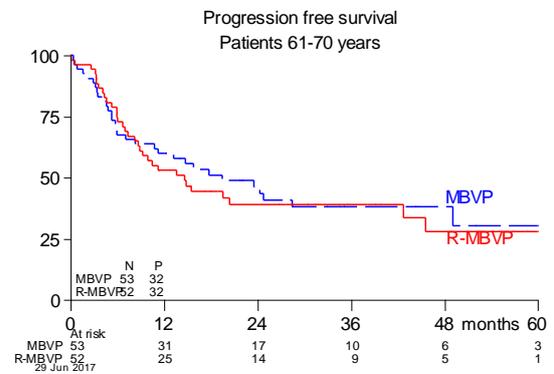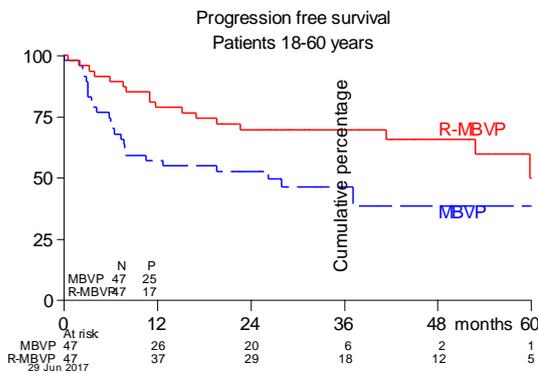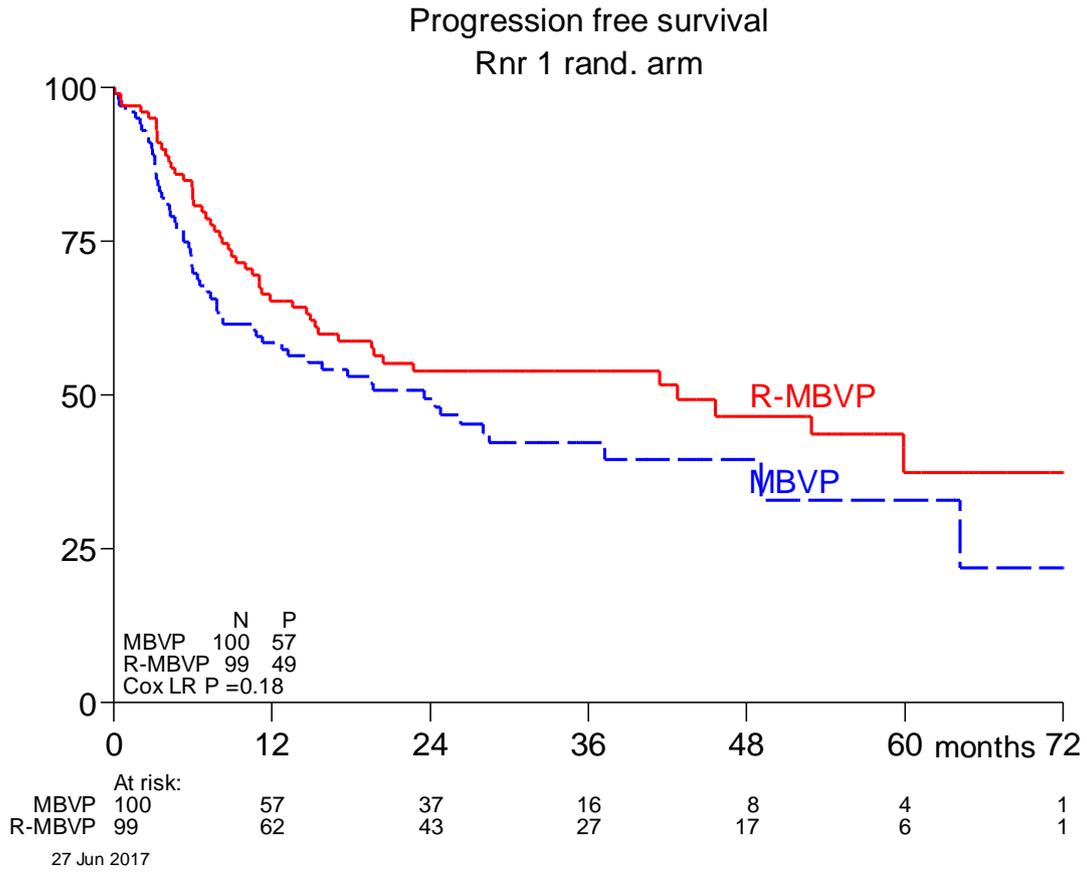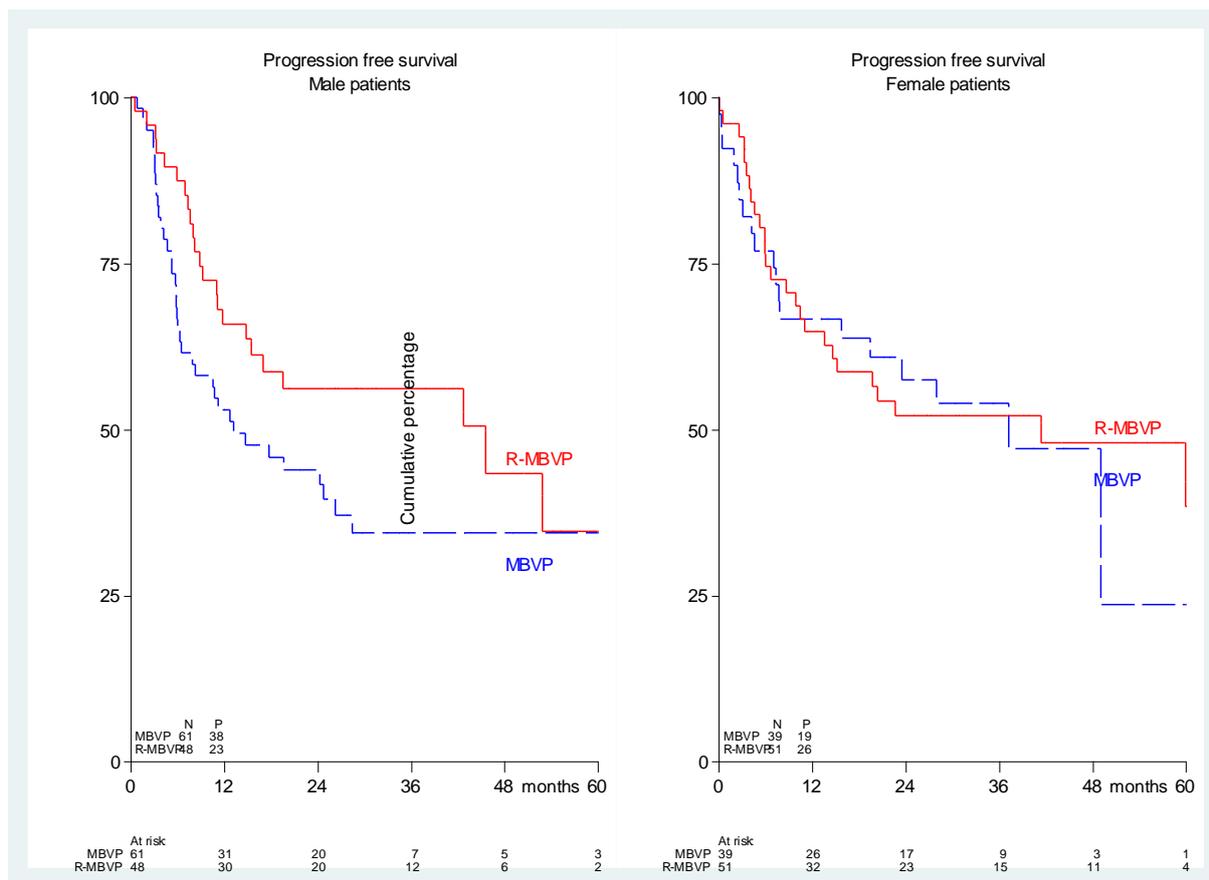
6.3.2 Formal evaluation

Univariate Cox regression analysis

```
Cox regression
--------------
Time: pfs      Progression free survival [m]
Fail: pfsi


Variable  Nobs Nfail   Chi2 df   P_value    RelHR     SE   [95% Conf Limits]
----------------------------------------------------------------------------
          199   106   2.49  1   1.1e-01
 :R-MBVP - arm1                 1.2e-01    0.73     0.14    0.50      1.08
          199   106   6.49  1   1.1e-02
 age60                          1.2e-02    1.65     0.33    1.12      2.44
          199   106   .157  1   6.9e-01
 whostrat                       6.9e-01    0.92     0.20    0.59      1.42
```

Multivariate Cox regression analysis

```
Cox regression
--------------
Time: pfs      Progression free survival [m]
Fail: pfsi


Variable  Nobs Nfail   Chi2 df   P_value    RelHR     SE   [95% Conf Limits]
----------------------------------------------------------------------------
Baseline model:
          199   106   6.54  2   3.8e-02
 age60                          1.3e-02    1.65     0.33    1.11      2.44
 whostrat                       8.3e-01    0.95     0.21    0.61      1.48
Additional factors:
          199   106   1.83  1   1.8e-01
 :R-MBVP - arm1                 1.8e-01    0.77     0.15    0.52      1.13
(Above estimates and P-values adjusted for age60 whostrat except for the variable tested)
```

Multivariate Cox regression analysis - age X arm interaction

```
------------------------------------------------------------------------
        _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-----------+------------------------------------------------------------
      arm1 |
    R-MBVP |   .4752016    .150527    -2.35   0.019    .2554156    .8841142
           |
     age60 |
       >60 |   1.117877    .2990795    0.42   0.677    .6617007    1.888542
           |
 arm1#age60 |
 R-MBVP#>60 |    2.21035    .8936036    1.96   0.050    1.000774    4.881869
------------------------------------------------------------------------
```

In the latter model the HR of the arms is so much different from the results of the previous models because here it corresponds to the arm effect in younger patients. The arm effect among elderly patients is calculated by multiplying the young-arm effect (.48) with de elderly-arm effect difference (2.21), that is HR 1.05 with 95% CI (0.64-1.72).

6.3.3   Prognostic factors

Univariate Cox regression - all prognostic factors

```
Cox regression
--------------
Time: pfs      Progression free survival [m]
Fail: pfsi
```

Variable	Nobs	Nfail	Chi2	df	P_value	RelHR	SE	[95% Conf Limits]	
	199	106	1.02	1	3.1e-01				
:F - sex					3.1e-01	0.82	0.16	0.56	1.21
	154	79	5.82	1	1.6e-02				
mmse					9.8e-03	0.96	0.02	0.93	0.99
	185	100	.862	1	3.5e-01				
:Multifocal - focal					3.6e-01	0.83	0.17	0.56	1.23
	193	102	.0078	1	9.3e-01				
:Yes - vitfluid					9.3e-01	1.04	0.44	0.45	2.37
	181	98	.0013	1	9.7e-01				
:Yes - csf					9.7e-01	1.01	0.22	0.66	1.54
	197	105	1.18	1	2.8e-01				
dexa					2.6e-01	1.01	0.01	0.99	1.04
	199	106	.157	1	6.9e-01				
:>1 - whostrat					6.9e-01	0.92	0.20	0.59	1.42
	199	106	6.49	1	1.1e-02				
:>60 - age60					1.2e-02	1.65	0.33	1.12	2.44
	198	105	1.58	1	2.1e-01				
:>ULN - ldhn					2.0e-01	1.31	0.28	0.87	1.99

Multivariate logistic regression - all prognostic factors

```
      _t | Haz. Ratio   Std. Err.      z    P>|z|      [95% Conf. Interval]
---------+--------------------------------------------------------------
arm1: R-MBVP |  .6901962   .1807754   -1.42   0.157     .413073    1.153236
    sex : F |  .7029986   .1891757   -1.31   0.190    .4148563    1.191273
       mmse |  .9409349   .0224717   -2.55   0.011     .897906    .9860258
 Multifocal |  .8092529   .2317034   -0.74   0.460     .461711    1.418398
vitfluid:Yes |  1.110888   .5722685    0.20   0.838    .4047416    3.049036
   csf : Yes |  .9851191   .2615588   -0.06   0.955    .5854453    1.657644
       dexa |  1.027519   .0220257    1.27   0.205     .985244    1.071609
 whostrat: >1 |  .6003313   .2240224   -1.37   0.171    .2889034    1.247468
  age60 : >60 |  1.663873   .4247761    1.99   0.046     1.00882    2.744268
  ldhn : >ULN |  .8820839   .2539382   -0.44   0.663    .5017209    1.550806
---------+--------------------------------------------------------------
```

6.3.4   Conclusion
- The median PFS is 23.5 months in arm A and 42.7 months in arm B;
- PFS is not significantly improved in the R-MBVP arm (arm B):
  - In the univariate Cox regression analysis, HR = 0.73, 95% CI = [0.50,1.08], P = 0.12;
  - When adjusted for age group and WHO stratum, HR = 0.77, 95% CI = [0.52,1.13], P = 0.18;
  - In the multivariate analysis, HR = 0.69, 95% CI = [0.41,1.15], P = 0.16;
- There is indication that the impact of R-MBVP arm on EFS was very different between the age groups (18-60 vs 61-70).

6.4 Overall survival

OS is defined as: Time from registration to death from any cause.

6.4.1   Descriptive statistics

OS estimates in total and by arm.

```
****  (Overall survival [m])

Time [mnth]                  _____12___  _____36___  _____60___
              N   d Max Med  OS se #at   OS se #at   OS se #at
              #   # [m] [m]  %       #   %       #   %       #

 Total       199 79  79  64  79  3 152   59  4  59   50  5  15

Rnr 1 rand. arm
 MBVP        100 41  75  57  79  4  77   61  5  28   46  8   6
 R-MBVP       99 38  79 >79  79  4  75   58  6  31   53  6   9
```

```
                Beg.                Survivor    Std.
       Time    Total     Fail       Function    Error    [95% Conf. Int.]
-----------------------------------------------------------------------------
Total
       12       153        42        0.7865     0.0292    0.7223    0.8375
       36        60        30        0.5947     0.0386    0.5149    0.6656
       60        16         6        0.5046     0.0487    0.4058    0.5954
MBVP
       12        78        21        0.7874     0.0412    0.6928    0.8559
       36        29        15        0.6147     0.0512    0.5063    0.7062
       60         7         4        0.4556     0.0848    0.2864    0.6100
R-MBVP
       12        76        21        0.7861     0.0414    0.6910    0.8549
       36        32        15        0.5776     0.0568    0.4586    0.6795
       60        10         2        0.5312     0.0610    0.4055    0.6419
-----------------------------------------------------------------------------
```

Note: Survivor function is calculated over full data and evaluated at indicated times; it is not calculated from aggregates shown at left.

Median OS by arm:

```
          failure _d: osi
   analysis time _t: os

             |   no. of
arm1         | subjects       50%     Std. Err.     [95% Conf. Interval]
-------------+---------------------------------------------------------------
        MBVP |   100     56.73922     5.90189        37.6509        .
      R-MBVP |    99        .            .           34.4312        .
-------------+---------------------------------------------------------------
       total |   199     64.3614        .           42.7433        .
```

OS estimates at 1,3, and 5 years by arm, and stratification factors:

```
Time [mnth]                  _____12___  _____36___  _____60___
              N   d Max Med  OS se #at   OS se #at   OS se #at
              #   # [m] [m]  %       #   %       #   %       #

 Total       199 79  79  64  79  3 152   59  4  59   50  5  15

Rnr 1 rand. arm
 MBVP        100 41  75  57  79  4  77   61  5  28   46  8   6
 R-MBVP       99 38  79 >79  79  4  75   58  6  31   53  6   9

Age
 <=60         94 29  70 >70  85  4  79   67  5  30   61  7   8
 >60         105 50  79  43  73  4  73   52  5  29   41  6   7

WHO stratum
 <=1         144 58  79  64  78  3 111   59  5  43   53  5  12
 >1           55 21  67  57  80  5  41   61  7  16   39 14   3
```

Overall survival
Rnr 1 rand. arm

	N	D
MBVP	100	41
R-MBVP	99	38

Cox LR P =0.74

At risk:

MBVP	100	77	51	28	17	6
R-MBVP	99	75	57	31	21	9

29 Jun 2017

Overall survival
Patients 18-60 years

	N	D
MBVP	47	17
R-MBVP	47	12

At risk

MBVP	47	37	27	11	6	1
R-MBVP	47	42	34	19	13	7

29 Jun 2017

Overall survival
Patients 61-70 years

	N	D
MBVP	53	24
R-MBVP	52	26

At risk

MBVP	53	40	24	17	11	5
R-MBVP	52	33	23	12	8	2

29 Jun 2017

Overall survival
WHO performance 0-1

	N	D
MBVP	71	29
R-MBVP	73	29

At risk

MBVP	71	56	38	20	14	6
R-MBVP	73	55	42	23	17	6

29 Jun 2017

Overall survival
WHO performance 2-3

	N	D
MBVP	29	12
R-MBVP	26	9

At risk

MBVP	29	21	13	8	3	0
R-MBVP	26	20	15	8	4	3

29 Jun 2017

6.4.2   Formal evaluation

Univariate Cox regression analysis

```
Cox regression
--------------
Time: os       Overall survival [m]
Fail: osi


Variable  Nobs Nfail    Chi2 df   P_value     RelHR     SE    [95% Conf Limits]
-------------------------------------------------------------------------------
          199   79     .282  1    6.0e-01
 :R-MBVP - arm1                  6.0e-01      0.89     0.20     0.57      1.38
          199   79    6.73   1    9.5e-03
 age60                           1.1e-02      1.81     0.42     1.15      2.87
          199   79    .0339  1    8.5e-01
 whostrat                        8.5e-01      1.05     0.27     0.64      1.73
```

Multivariate Cox regression analysis

```
Cox regression
--------------
Time: os       Overall survival [m]
Fail: osi


Variable  Nobs Nfail    Chi2 df   P_value     RelHR     SE    [95% Conf Limits]
-------------------------------------------------------------------------------
Baseline model:
          199   79    6.86   2    3.2e-02
 age60                           1.0e-02      1.82     0.43     1.15      2.89
 whostrat                        7.2e-01      1.10     0.28     0.66      1.81
Additional factors:
          199   79    .114   1    7.4e-01
 :R-MBVP - arm1                  7.4e-01      0.93     0.21     0.59      1.44
(Above estimates and P-values adjusted for age60 whostrat except for the variable tested)
```

6.4.3 Prognostic factors

Univariate Cox regression - all prognostic factors

```
Cox regression
--------------
Time: os       Overall survival [m]
Fail: osi

----------------------------------------------------------------------------
Variable   Nobs Nfail    Chi2 df   P_value     RelHR     SE   [95% Conf Limits]
----------------------------------------------------------------------------
           199   79     .512  1   4.7e-01
 :F - sex                         4.8e-01      0.85     0.19    0.54    1.33
           154   61     3.95  1   4.7e-02
 mmse                             3.4e-02      0.96     0.02    0.93    1.00
           185   74     1.22  1   2.7e-01
 :Multifocal - focal              2.7e-01      0.77     0.18    0.48    1.23
           193   78      .76  1   3.8e-01
 :Yes - vitfluid                  3.6e-01      1.48     0.63    0.64    3.41
           181   73     .349  1   5.5e-01
 :Yes - csf                       5.5e-01      1.16     0.28    0.72    1.87
           197   78     .756  1   3.8e-01
 dexa                             3.7e-01      1.01     0.02    0.98    1.04
           199   79    .0339  1   8.5e-01
 :>1 - whostrat                   8.5e-01      1.05     0.27    0.64    1.73
           199   79     6.73  1   9.5e-03
 :>60 - age60                     1.1e-02      1.81     0.42    1.15    2.87
           198   78     .297  1   5.9e-01
 :>ULN - ldhn                     5.8e-01      1.15     0.29    0.70    1.88
```

Multivariate logistic regression - all prognostic factors

```
----------------------------------------------------------------------------
        _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-----------+----------------------------------------------------------------
arm1: R-MBVP |  .801406    .239623    -0.74   0.459    .4460058    1.440007
   sex : F |  1.105538    .3347937     0.33   0.740    .6106633    2.001455
      mmse |  .9541582    .0263881    -1.70   0.090    .9038153    1.007305
 Multifocal |  .9820652     .302965    -0.06   0.953    .5364713     1.79777
vitfluid:Yes |  1.692284    .9010471     0.99   0.323    .5960127    4.804971
  csf : Yes |  1.228251    .3577443     0.71   0.480     .694006    2.173756
      dexa |  1.029689     .023951     1.26   0.208    .9837995    1.077718
whostrat: >1 |  .6327604    .2642706    -1.10   0.273    .2790855    1.434634
 age60 : >60 |  1.948139    .5725839     2.27   0.023    1.095067    3.465767
ldhn : >ULN |  .9505951     .305278    -0.16   0.875    .5065673    1.783832
----------------------------------------------------------------------------
```

6.4.4 Conclusion

- The median OS has not yet been reached after 79 months of follow up in arm B and is 56.7 months in arm A;
- OS is not significantly improved in the R-MBVP arm (arm B):
  - In the univariate Cox regression analysis, HR = 0.89, 95% CI = [0.57,1.38], P = 0.60;
  - When adjusted for age group and WHO stratum, HR = 0.93, 95% CI = [0.59,1.44], P = 0.74;
  - In the multivariate analysis, HR = 0.80, 95% CI = [0.45,1.44], P = 0.46;
- There is no indication that the impact of R-MBVP vs MBVP arm on OS was very different between subgroups (details not shown).

7.   Adverse events

AEs and infections CTCAE (version 3.0) grade 3-4 will be shown for:
- Induction cycles 1 and 2 separately;
- Consolidation with HD-Ara-C and WBRT;
- Induction cycles together (max. grade per patient);
- Complete treatment (max. grade per patient).

The tables will be shown by treatment arm for all patient together, and separately for patients age 18-60 years and for patients 61-70 years.

7.1 First course MBVP

```
                                                       1st MBVP
                                               MBVP                 R-MBVP
# Patients                                     100                    99

                                        grade 3    grade 4    grade 3    grade 4
-Any-                                   30 30%     16 16%     29 29%     15 15%
Infections and infestations             12 12%      1  1%      8  8%      5  5%
Investigations                           4  4%      9  9%      6  6%      6  6%
Metabolism and nutrition disorders      12 12%      .         10 10%      1  1%
Blood and lymphatic disorders            6  6%      2  2%     10 10%      2  2%
Gastrointestinal disorders               7  7%      1  1%      6  6%      .
Nervous system disorders                 2  2%      1  1%      8  8%      1  1%
Cardiac disorders                        1  1%      .          4  4%      1  1%
Respiratory, thoracic and mediastinal disorders   1  1%   1  1%   3  3%   1  1%
Vascular disorders                       1  1%      .          3  3%      1  1%
General disorders and administration site conditions   2  2%   1  1%   1  1%   .
Renal and urinary disorders              2  2%      .          1  1%      1  1%
Psychiatric disorders                    .          .          3  3%      .
Surgical and medical procedures          .          1  1%      2  2%      .
Hepatobiliary disorders                  .          .          1  1%      .
Injury, poisoning and procedural complications   .   .         1  1%      .
Musculoskeletal and connective tissue disorders   .   .        1  1%      .
Skin and subcutaneous tissue disorders   1  1%      .          .          .
```

In patients <= 60 years:

```
                                                       1st MBVP
                                               MBVP                 R-MBVP
# Patients                                      47                    47

                                        grade 3    grade 4    grade 3    grade 4
-Any-                                   16 34%      4  9%     12 26%      5 11%
Blood and lymphatic disorders            2  4%      1  2%      6 13%      1  2%
Investigations                           3  6%      3  6%      3  6%      1  2%
Infections and infestations              6 13%      .          1  2%      2  4%
Metabolism and nutrition disorders       4  9%      .          2  4%      .
Gastrointestinal disorders               2  4%      .          3  6%      .
Respiratory, thoracic and mediastinal disorders   1  2%   .    3  6%      .
Vascular disorders                       1  2%      .          1  2%      1  2%
Nervous system disorders                 2  4%      .          .          .
Renal and urinary disorders              1  2%      .          1  2%      .
Cardiac disorders                        .          .          1  2%      .
General disorders and administration site conditions   1  2%   .   .     .
Musculoskeletal and connective tissue disorders   .   .        1  2%      .
Psychiatric disorders                    .          .          1  2%      .
Surgical and medical procedures          .          .          1  2%      .
```

In patients >= 61 years:

```
                                                       1st MBVP
                                               MBVP                 R-MBVP
# Patients                                      53                    52

                                        grade 3    grade 4    grade 3    grade 4
-Any-                                   14 26%     12 23%     17 33%     10 19%
Infections and infestations              6 11%      1  2%      7 13%      3  6%
Metabolism and nutrition disorders       8 15%      .          8 15%      1  2%
Investigations                           1  2%      6 11%      3  6%      5 10%
Blood and lymphatic disorders            4  8%      1  2%      4  8%      1  2%
Nervous system disorders                 .          1  2%      8 15%      1  2%
Gastrointestinal disorders               5  9%      1  2%      3  6%      .
Cardiac disorders                        1  2%      .          3  6%      1  2%
```

	grade 3	grade 4	grade 3	grade 4
General disorders and administration site conditions	1 2%	1 2%	1 2%	.
Psychiatric disorders	.	.	2 4%	.
Renal and urinary disorders	1 2%	.	.	1 2%
Respiratory, thoracic and mediastinal disorders	.	1 2%	.	1 2%
Surgical and medical procedures	.	1 2%	1 2%	.
Vascular disorders	.	.	2 4%	.
Hepatobiliary disorders	.	.	1 2%	.
Injury, poisoning and procedural complications	.	.	1 2%	.
Skin and subcutaneous tissue disorders	1 2%	.	.	.

7.2 Second course MBVP

	2nd MBVP			
	MBVP		R-MBVP	
# Patients	92		88	
	grade 3	grade 4	grade 3	grade 4
-Any-	20 22%	12 13%	22 25%	8 9%
Blood and lymphatic disorders	7 8%	1 1%	6 7%	1 1%
Infections and infestations	5 5%	5 5%	4 5%	1 1%
Investigations	3 3%	4 4%	4 5%	4 5%
Metabolism and nutrition disorders	8 9%	.	3 3%	.
Vascular disorders	3 3%	3 3%	3 3%	1 1%
Nervous system disorders	6 7%	.	3 3%	.
Gastrointestinal disorders	3 3%	1 1%	3 3%	1 1%
Respiratory, thoracic and mediastinal disorders	2 2%	1 1%	4 5%	.
Renal and urinary disorders	.	.	4 5%	.
General disorders and administration site conditions	1 1%	.	1 1%	.
Immune system disorders	.	.	2 2%	.
Injury, poisoning and procedural complications	1 1%	.	.	.
Musculoskeletal and connective tissue disorders	.	.	1 1%	.
Psychiatric disorders	.	.	1 1%	.
Surgical and medical procedures	.	.	1 1%	.

In patients <= 60 years:

	2nd MBVP			
	MBVP		R-MBVP	
# Patients	46		43	
	grade 3	grade 4	grade 3	grade 4
-Any-	8 17%	5 11%	8 19%	5 12%
Infections and infestations	1 2%	2 4%	3 7%	1 2%
Investigations	1 2%	2 4%	2 5%	2 5%
Nervous system disorders	4 9%	.	2 5%	.
Blood and lymphatic disorders	1 2%	.	3 7%	1 2%
Metabolism and nutrition disorders	3 7%	.	2 5%	.
Vascular disorders	.	1 2%	2 5%	1 2%
Respiratory, thoracic and mediastinal disorders	.	.	2 5%	.
Gastrointestinal disorders	1 2%	.	.	.
Injury, poisoning and procedural complications	1 2%	.	.	.
Musculoskeletal and connective tissue disorders	.	.	1 2%	.
Renal and urinary disorders	.	.	1 2%	.

In patients >= 61 years:

	2nd MBVP			
	MBVP		R-MBVP	
# Patients	46		45	
	grade 3	grade 4	grade 3	grade 4
-Any-	12 26%	7 15%	14 31%	3 7%
Blood and lymphatic disorders	6 13%	1 2%	3 7%	.
Infections and infestations	4 9%	3 7%	1 2%	.
Investigations	2 4%	2 4%	2 4%	2 4%
Gastrointestinal disorders	2 4%	1 2%	3 7%	1 2%
Metabolism and nutrition disorders	5 11%	.	1 2%	.
Vascular disorders	3 7%	2 4%	1 2%	.
Respiratory, thoracic and mediastinal disorders	2 4%	1 2%	2 4%	.
Nervous system disorders	2 4%	.	1 2%	.
Renal and urinary disorders	.	.	3 7%	.
General disorders and administration site conditions	1 2%	.	1 2%	.
Immune system disorders	.	.	2 4%	.
Psychiatric disorders	.	.	1 2%	.
Surgical and medical procedures	.	.	1 2%	.

7.3 Max AE on induction

Adverse events - Induction cycles - - Max grade in periods 1 2 - CTC grades: 3, 4

	MBVP		R-MBVP	
# Patients	100		99	
	grade 3	grade 4	grade 3	grade 4
-Any-	32 32%	24 24%	40 40%	19 19%
Infections and infestations	15 15%	5 5%	12 12%	6 6%
Investigations	5 5%	10 10%	10 10%	7 7%
Blood and lymphatic disorders	11 11%	3 3%	14 14%	2 2%
Metabolism and nutrition disorders	16 16%	.	12 12%	1 1%
Nervous system disorders	8 8%	1 1%	11 11%	1 1%
Gastrointestinal disorders	7 7%	2 2%	7 7%	1 1%
Vascular disorders	4 4%	3 3%	6 6%	2 2%
Respiratory, thoracic and mediastinal disorders	3 3%	2 2%	7 7%	1 1%
Renal and urinary disorders	2 2%	.	5 5%	1 1%
Cardiac disorders	1 1%	.	4 4%	1 1%
General disorders and administration site conditions	3 3%	1 1%	2 2%	.
Psychiatric disorders	.	.	4 4%	.
Surgical and medical procedures	.	1 1%	3 3%	.
Immune system disorders	.	.	2 2%	.
Injury, poisoning and procedural complications	1 1%	.	1 1%	.
Musculoskeletal and connective tissue disorders	.	.	2 2%	.
Hepatobiliary disorders	.	.	1 1%	.
Skin and subcutaneous tissue disorders	1 1%	.	.	.

7.4 Consolidation with HD-Ara-C

	HD-Ara-C			
	MBVP		R-MBVP	
# Patients	83		78	
	grade 3	grade 4	grade 3	grade 4
-Any-	13 16%	5 6%	8 10%	3 4%
Infections and infestations	6 7%	.	3 4%	.
Investigations	1 1%	4 5%	2 3%	2 3%
Blood and lymphatic disorders	4 5%	1 1%	1 1%	2 3%
Nervous system disorders	3 4%	.	2 3%	.
Metabolism and nutrition disorders	3 4%	.	.	.
Congenital, familial and genetic disorders	1 1%	.	.	.
Ear and labyrinth disorders	.	.	1 1%	.
Gastrointestinal disorders	.	.	1 1%	.
Psychiatric disorders	1 1%	.	.	.
Skin and subcutaneous tissue disorders	.	.	1 1%	.
Vascular disorders	1 1%	.	.	.

In patients <= 60 years:

	HD-Ara-C			
	MBVP		R-MBVP	
# Patients	41		39	
	grade 3	grade 4	grade 3	grade 4
-Any-	7 17%	2 5%	2 5%	3 8%
Infections and infestations	5 12%	.	1 3%	.
Blood and lymphatic disorders	3 7%	.	.	2 5%
Investigations	.	2 5%	1 3%	2 5%
Nervous system disorders	2 5%	.	1 3%	.
Metabolism and nutrition disorders	2 5%	.	.	.
Psychiatric disorders	1 2%	.	.	.
Skin and subcutaneous tissue disorders	.	.	1 3%	.

In patients >= 61 years:

	HD-Ara-C			
	MBVP		R-MBVP	
# Patients	42		39	
	grade 3	grade 4	grade 3	grade 4
-Any-	6 14%	3 7%	6 15%	.
Investigations	1 2%	2 5%	1 3%	.
Blood and lymphatic disorders	1 2%	1 2%	1 3%	.
Infections and infestations	1 2%	.	2 5%	.
Nervous system disorders	1 2%	.	1 3%	.
Congenital, familial and genetic disorders	1 2%	.	.	.
Ear and labyrinth disorders	.	.	1 3%	.
Gastrointestinal disorders	.	.	1 3%	.
Metabolism and nutrition disorders	1 2%	.	.	.

```
Vascular disorders                                    1  2%     .       .       .
```

7.5 Consolidation with WBRT

```
                                                           WBRT
                                                     MBVP      R-MBVP
# Patients                                            34          36

-Any-                                                3  9%    3  8%
Eye disorders                                        1  3%     .
Gastrointestinal disorders                           1  3%     .
General disorders and administration site conditions 1  3%     .
Infections and infestations                           .       1  3%
Nervous system disorders                              .       1  3%
Skin and subcutaneous tissue disorders                .       1  3%
```

7.6 Max AE on protocol

```
Adverse events - Complete protocol treatment - - Max grade in periods 1 2 3 4 - CTC grades: 3,
4
                                                        MBVP              R-MBVP
# Patients                                               100                99

                                                   grade 3   grade 4   grade 3   grade 4
-Any-                                              35 35%    24 24%    44 44%    19 19%
Infections and infestations                        18 18%     5  5%    15 15%     6  6%
Blood and lymphatic disorders                      14 14%     3  3%    13 13%     3  3%
Investigations                                      5  5%    10 10%    10 10%     7  7%
Metabolism and nutrition disorders                 18 18%      .       12 12%     1  1%
Nervous system disorders                           10 10%     1  1%    14 14%     1  1%
Gastrointestinal disorders                          8  8%     2  2%     8  8%     1  1%
Vascular disorders                                  5  5%     3  3%     6  6%     2  2%
Respiratory, thoracic and mediastinal disorders     3  3%     2  2%     7  7%     1  1%
Renal and urinary disorders                         2  2%      .        5  5%     1  1%
General disorders and administration site conditions 4  4%    1  1%     2  2%      .
Cardiac disorders                                   1  1%      .        4  4%     1  1%
Psychiatric disorders                               1  1%      .        4  4%      .
Surgical and medical procedures                      .        1  1%     3  3%      .
Skin and subcutaneous tissue disorders              1  1%      .        2  2%      .
Immune system disorders                              .         .        2  2%      .
Injury, poisoning and procedural complications      1  1%      .        1  1%      .
Musculoskeletal and connective tissue disorders      .         .        2  2%      .
Congenital, familial and genetic disorders          1  1%      .         .         .
Ear and labyrinth disorders                          .         .        1  1%      .
Eye disorders                                       1  1%      .         .         .
Hepatobiliary disorders                              .         .        1  1%      .
```
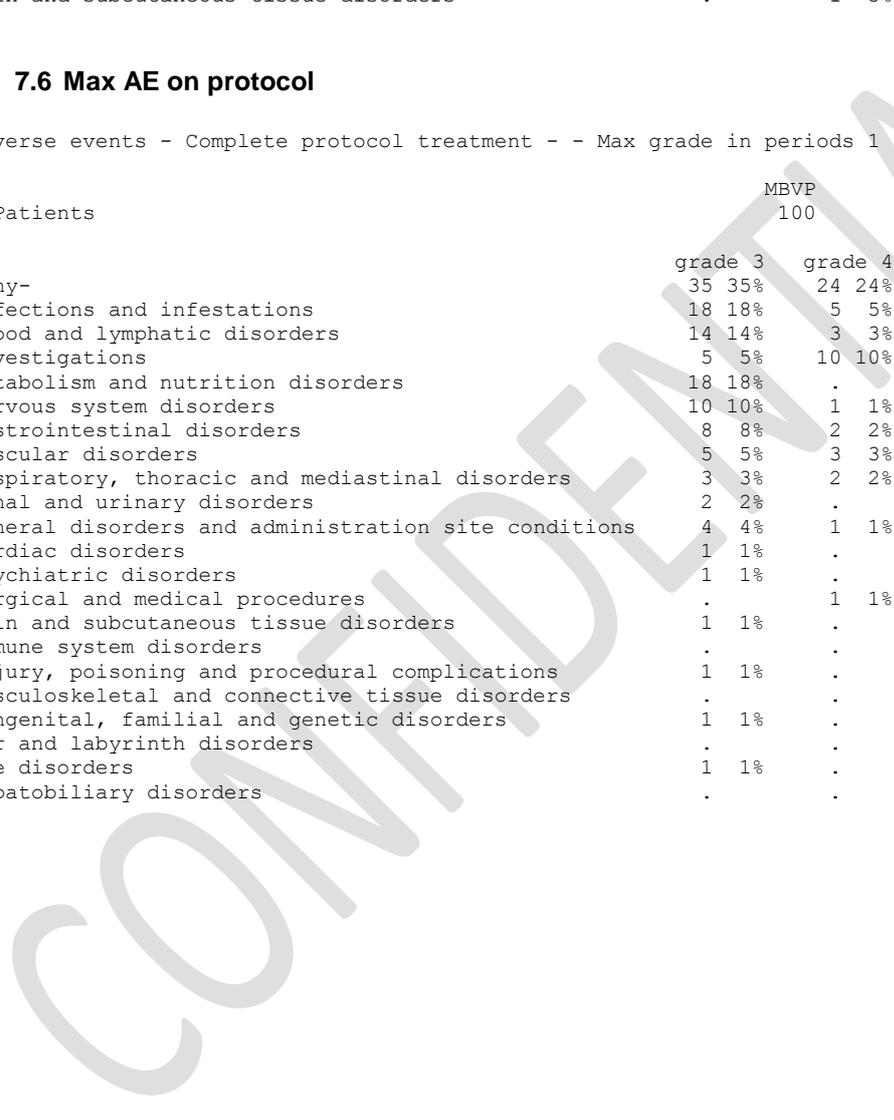
8.   Serious adverse events

	Arm 1st randomisation		Total
	mbvp	r-mbvp	
	[# and column %]		
Total	100 100%	99 100%	199 100%
SAE report(s)			
No	52 52%	46 46%	98 49%
Yes	40 40%	48 48%	88 44%
Yes,dead	8 8%	5 5%	13 7%
# SAE's			
0	52 52%	46 46%	98 49%
1	29 29%	33 33%	62 31%
2	16 16%	15 15%	31 16%
3	2 2%	4 4%	6 3%
4	1 1%	1 1%	2 1%

	Rnr 1 rand. arm		Total
	mbvp	r-mbvp	
	[# and column %]		
Total SAEs	71 100%	79 100%	150 100%
Reason AE is Serious			
death	4 6%	2 3%	6 4%
life-threatening	8 11%	8 10%	16 11%
hospitalization	55 77%	60 76%	115 77%
disability	3 4%	1 1%	4 3%
other condition	1 1%	8 10%	9 6%
Relationship to any trial medication			
unrelated	16 23%	14 18%	30 20%
unlikely	16 23%	17 22%	33 22%
possible	18 25%	18 23%	36 24%
probable	15 21%	24 30%	39 26%
definite	4 6%	6 8%	10 7%
.	2 3%	–	2 1%
Outcome of SAE			
resolved completely	48 68%	63 80%	111 74%
resolved with sequelae	5 7%	3 4%	8 5%
ongoing	4 6%	3 4%	7 5%
death	7 10%	5 6%	12 8%
ongoing at death	2 3%	3 4%	5 3%
ongoing closed	4 6%	2 3%	6 4%
.	1 1%	–	1 1%

8.1 Time to onset 1st SAE per patient

	Arm 1st randomisation		Total
	mbvp	r-mbvp	
	[# and column %]		
Total	100 100%	99 100%	199 100%
SAE indicator			
SAE	48 48%	53 54%	101 51%
No, off prot.	52 52%	46 46%	98 49%

```
****  (Time to 1st SAE or OFF, or censored at dlc [months])
    no : #           -> NO
    sae: #           -> SAE
    off: #           -> OFF

Time [mnth]              _____1_____        _____2_____
        N sae off Max Med  #at  NO se SAE se OFF se  #at  NO se SAE se OFF se
        #   #   #  [m] [m]   #   %      %      %       #   %      %      %
```

```
 Total       199 101  98   9   3  143  72  3  26   3   2   1  116  58  3  39   3   3   1

Arm 1st randomisation
  mbvp       100  48  52   9   3   75  75  4  23   4   2   1   64  64  5  34   5   2   1
  r-mbvp      99  53  46   7   3   68  69  5  29   5   2   1   52  53  5  43   5   4   2

Time [mnth]                       _____3_____    _____6_____
              N sae off Max Med  #at  NO se SAE se OFF se       #at  NO se SAE se OFF se
              #   #   #  [m] [m]   #   %      %      %            #   %      %      %

 Total       199 101  98   9   3   93  47  4  46   4   7   2    16   8  2  51   4  41   3

Arm 1st randomisation
  mbvp       100  48  52   9   3   51  51  5  43   5   6   2     9   9  3  48   5  43   5
  r-mbvp      99  53  46   7   3   42  42  5  49   5   8   3     7   7  3  54   5  39   5
```

Time to onset 1st SAE - Comp. Risk: No, off prot by treatment arm


```
            N    F
 mbvp      100   52
 r-mbvp     99   46
```
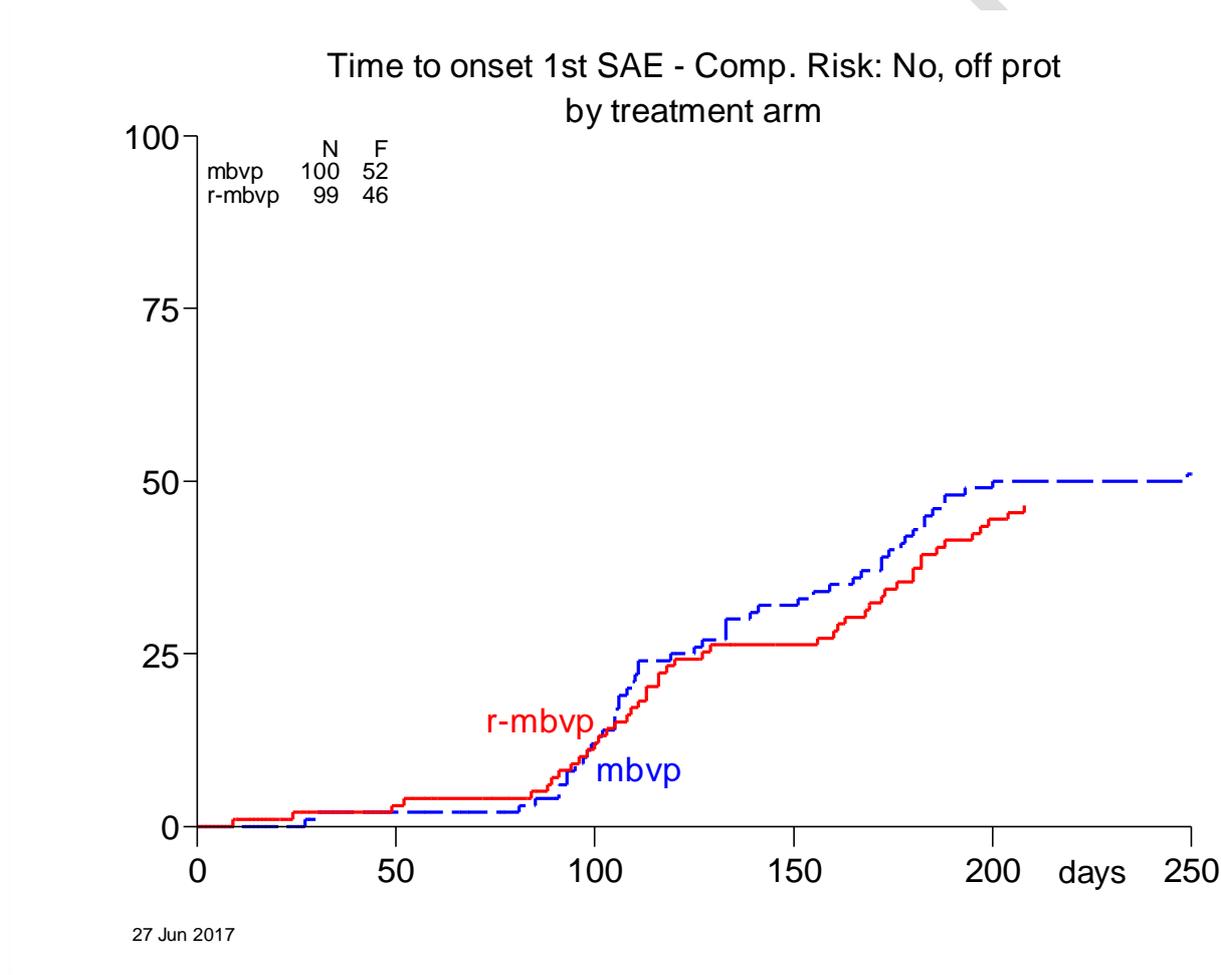
27 Jun 2017

```
Cox regression
--------------
Time: onset1   Time to 1st SAE or OFF, or censored at dlc [days]
Fail: onset1i
_____
Variable  Nobs Nfail   Chi2 df   P_value      RelHR     SE    [95% Conf Limits]
-------------------------------------------------------------------------------
          199   101    .912  1   3.4e-01
 :r-mbvp - arm1                  3.4e-01       1.21     0.24    0.82     1.79
```

8.2 Conclusions

- The proportion of patients with at least one SAE is 48% in arm A, versus 54% in arm B;
- The actuarial proportion of patients with an SAE within 1 months is 23% and 29% in arm A and arm B, respectively, and doubles at 6 months (48% vs. 54%).