

Dossier zur Nutzenbewertung gemäß § 35a SGB V

Nusinersen (Spinraza®)

Biogen GmbH

Anhang 4-G zu Modul 4 A.3

*Präsymptomatisch behandelte 5q-assoziierte spinale
Muskelatrophie (SMA)*

Stand: 01.12.2020

Anhang 4-G zu Modul 4 A.3

Primäranalyse NURTURE vs. ENDEAR

Stand: 01.12.2020

NURTURE vs untreated ENDEAR
 Results for patients with 2 copies and
 start of therapy in ENDEAR max 12 weeks after symptom onset

[[1]]

[1] "Descriptive 2 copies"

[[2]]

	NURTURE	ENDEAR BSC
N	"15"	"18"
Age at study entry (months), mean (sd)	"0.57 (0.32)"	"4.39 (1.79)"
Gender (Female), n (%)	"7 (46.67%)"	"7 (38.89%)"
Age at Diagnosis (months), mean (sd)	"-"	"3.21 (1.93)"
Age at Symptom onset (months), mean (sd)	"-"	"2.56 (1.51)"
Age at Therapy onset (months), mean (sd)	"0.64 (0.31)"	"4.82 (1.78)"
Age at last dose (months), mean (sd)	"25.59 (6.33)"	"9.66 (3.92)"
Number of doses, mean (sd)	"9.8 (1.61)"	"4.56 (1.1)"
Age at last follow-up (months), mean (sd)	"25.21 (5.58)"	"12.2 (4.23)"
Discontinuation for patients not dead, n (%)	"0 (0%)"	"6 (33.33%)"

\#####

[[1]]

[1] "Survival rate for Patients with 2 copies at age 1 year"

\$ntab

	ENDEAR BSC	NURTURE
n_all	18	15
n_event	14	15
n_event_pct	78	100

\$stats

	estimate	se	lo95ci	hi95ci	pvalue
RR_TRTvsCTRL	"1.27"	"0.14"	"0.973"	"1.655"	"0.0782"
OR_TRTvsCTRL	"9.62"	"1.53"	"0.475"	"194.830"	"0.1402"
ARR_TRTvsCTRL	"0.22"	"0.10"	"0.030"	"0.414"	"0.0233"

\#####

[[1]]

[1] "Survival rate for Patients with 2 copies at latest common age"

\$ntab

	ENDEAR BSC	NURTURE
n_all	18	15
n_event	16	15
n_event_pct	89	100

\$stats

	estimate	se	lo95ci	hi95ci	pvalue
RR_TRTvsCTRL	"1.12"	"0.10"	"0.917"	"1.357"	"0.2740"
OR_TRTvsCTRL	"4.70"	"1.59"	"0.209"	"105.787"	"0.3303"
ARR_TRTvsCTRL	"0.11"	"0.07"	"-0.034"	"0.256"	"0.1336"

```

\#####
[[1]]
[1] "Time to death for Patients with 2 copies at age 1 year"

```

```

$stats_num
              NURTURE ENDEAR BSC
n_all          15      18
n_event         0       4
n_event_pct     0      22
time-to-event-wk-10th  NA    10
time-to-event-wk-25th  NA    NA
time-to-event-wk-50th  NA    NA
time-to-event-wk-75th  NA    NA
time-to-event-wk-90th  NA    NA
time-to-event-wk-50th-loci  NA    NA
time-to-event-wk-50th-hici  NA    NA

```

```

$stats_HR_TRTVsCTRL
      HR  SE_logHR HR.lo95ci HR.hi95ci  p.value
      NA      NA      NA      NA      NA

```

```

\#####
[[1]]
[1] "Time to death for Patients with 2 copies at latest common age"

```

```

$stats_num
              NURTURE ENDEAR BSC
n_all          15      18.0
n_event         0       2.0
n_event_pct     0      11.0
time-to-event-wk-10th  NA     8.8
time-to-event-wk-25th  NA    13.1
time-to-event-wk-50th  NA     NA
time-to-event-wk-75th  NA     NA
time-to-event-wk-90th  NA     NA
time-to-event-wk-50th-loci  NA     4.4
time-to-event-wk-50th-hici  NA     NA

```

```

$stats_HR_TRTVsCTRL
      HR  SE_logHR HR.lo95ci HR.hi95ci  p.value
      NA      NA      NA      NA      NA

```

```

\#####
[[1]]
[1] "Time to permanent ventilation for Patients with 2 copies at age 1 year"

```

```

$stats_num
              NURTURE ENDEAR BSC
n_all          15      18.0
n_event         0       5.0
n_event_pct     0      28.0
time-to-event-wk-10th  NA     7.6

```

time-to-event-wk-25th	NA	15.0
time-to-event-wk-50th	NA	NA
time-to-event-wk-75th	NA	NA
time-to-event-wk-90th	NA	NA
time-to-event-wk-50th-loci	NA	15.0
time-to-event-wk-50th-hici	NA	NA

```
$stats_HR_TRTvsCTRL
      HR   SE_logHR HR.lo95ci HR.hi95ci  p.value
      NA         NA         NA         NA      NA
```

```
\#####
[[1]]
[1] "Time to permanent ventilation for Patients with 2 copies at latest common
age"
```

```
$stats_num
                                NURTURE ENDEAR BSC
n_all                          15      18.0
n_event                        0       2.0
n_event_pct                    0      11.0
time-to-event-wk-10th          NA       6.0
time-to-event-wk-25th          NA      13.6
time-to-event-wk-50th          NA      13.6
time-to-event-wk-75th          NA       NA
time-to-event-wk-90th          NA       NA
time-to-event-wk-50th-loci      NA       6.0
time-to-event-wk-50th-hici      NA       NA
```

```
$stats_HR_TRTvsCTRL
      HR   SE_logHR HR.lo95ci HR.hi95ci  p.value
      NA         NA         NA         NA      NA
```

```
\#####
[[1]]
[1] "Patients not requiring permanent ventilation for Patients with 2 copies at
age 1 year"
```

```
$ntab
      ENDEAR BSC NURTURE
n_all      18    15
n_event    13    15
n_event_pct 72   100
```

```
$stats
      estimate se      lo95ci hi95ci  pvalue
RR_TRTvsCTRL "1.36"  "0.15" "1.010" "1.841"  "0.0430"
OR_TRTvsCTRL "12.63" "1.52" "0.638" "250.044" "0.0959"
ARR_TRTvsCTRL "0.28"  "0.11" "0.071" "0.485"  "0.0085"
```

```
\#####
```

```
[[1]]
[1] "Patients not requiring permanent ventilation for Patients with 2 copies at latest common age"
```

```
$ntab
```

	ENDEAR	BSC	NURTURE
n_all	18	15	
n_event	16	15	
n_event_pct	89	100	

```
$stats
```

	estimate	se	lo95ci	hi95ci	pvalue
RR_TRTVsCTRL	"1.12"	"0.10"	"0.917"	"1.357"	"0.2740"
OR_TRTVsCTRL	"4.70"	"1.59"	"0.209"	"105.787"	"0.3303"
ARR_TRTVsCTRL	"0.11"	"0.07"	"-0.034"	"0.256"	"0.1336"

```
\#####
```

```
[[1]]
```

```
[1] "Patients with at least 1 SAE for Patients with 2 copies at age 1 year"
```

```
$ntab
```

	ENDEAR	BSC	NURTURE
n_all	18	15	
n_event	16	6	
n_event_pct	89	40	

```
$stats
```

	estimate	se	lo95ci	hi95ci	pvalue
RR_TRTVsCTRL	"0.45"	"0.33"	"0.237"	"0.854"	"0.0146"
OR_TRTVsCTRL	"0.08"	"0.92"	"0.014"	"0.502"	"0.0067"
ARR_TRTVsCTRL	"-0.49"	"0.15"	"-0.776"	"-0.202"	"0.0009"

```
\#####
```

```
[[1]]
```

```
[1] "Patients with at least 1 SAE for Patients with 2 copies at latest common age"
```

```
$ntab
```

	ENDEAR	BSC	NURTURE
n_all	18	15	
n_event	7	6	
n_event_pct	39	40	

```
$stats
```

	estimate	se	lo95ci	hi95ci	pvalue
RR_TRTVsCTRL	"1.03"	"0.43"	"0.440"	"2.402"	"0.9481"
OR_TRTVsCTRL	"1.05"	"0.72"	"0.258"	"4.256"	"0.9481"
ARR_TRTVsCTRL	"0.01"	"0.17"	"-0.324"	"0.346"	"0.9482"

```
\#####
```

```
[[1]]
```

[1] "Patients with at least 1 severe AE for Patients with 2 copies at age 1 year"

\$ntab

	ENDEAR	BSC	NURTURE
n_all	18	15	
n_event	15	1	
n_event_pct	83	7	

\$stats

	estimate	se	lo95ci	hi95ci	pvalue
RR_TRTvsCTRL	"0.08"	"0.97"	"0.012"	"0.537"	"0.0094"
OR_TRTvsCTRL	"0.01"	"1.21"	"0.001"	"0.154"	"0.0005"
ARR_TRTvsCTRL	"-0.77"	"0.11"	"-0.980"	"-0.553"	"0.0000"

\#####

[[1]]

[1] "Patients with at least 1 severe AE for Patients with 2 copies at latest common age"

\$ntab

	ENDEAR	BSC	NURTURE
n_all	18	15	
n_event	7	0	
n_event_pct	39	0	

\$stats

	estimate	se	lo95ci	hi95ci	pvalue
RR_TRTvsCTRL	"0.08"	"1.42"	"0.005"	"1.282"	"0.0742"
OR_TRTvsCTRL	"0.05"	"1.51"	"0.003"	"0.957"	"0.0467"
ARR_TRTvsCTRL	"-0.39"	"0.11"	"-0.614"	"-0.164"	"0.0007"

\#####

[[1]]

[1] "Patients with AE leading to discontinuation for Patients with 2 copies at age 1 year"

\$ntab

	ENDEAR	BSC	NURTURE
n_all	18	15	
n_event	4	0	
n_event_pct	22	0	

\$stats

	estimate	se	lo95ci	hi95ci	pvalue
RR_TRTvsCTRL	"0.13"	"1.45"	"0.008"	"2.270"	"0.1629"
OR_TRTvsCTRL	"0.10"	"1.53"	"0.005"	"2.105"	"0.1402"
ARR_TRTvsCTRL	"-0.22"	"0.10"	"-0.414"	"-0.030"	"0.0233"

\#####

[[1]]

[1] "Patients with AE leading to discontinuation for Patients with 2 copies at latest common age"

\$ntab

	ENDEAR	BSC	NURTURE
n_all	18	15	
n_event	3	0	
n_event_pct	17	0	

\$stats

	estimate	se	lo95ci	hi95ci	pvalue
RR_TRTvsCTRL	"0.17"	"1.47"	"0.009"	"3.045"	"0.2285"
OR_TRTvsCTRL	"0.14"	"1.55"	"0.007"	"3.003"	"0.2105"
ARR_TRTvsCTRL	"-0.17"	"0.09"	"-0.339"	"0.005"	"0.0578"

\#####

[[1]]

[1] "Patients with back pain for Patients with 2 copies at age 1 year"

\$ntab

	ENDEAR	BSC	NURTURE
n_all	18	15	
n_event	0	0	
n_event_pct	0	0	

\$stats

	estimate	se	lo95ci	hi95ci	pvalue
RR_TRTvsCTRL	"NA"	"NA"	"NA"	"NA"	"NA"
OR_TRTvsCTRL	"NA"	"NA"	"NA"	"NA"	"NA"
ARR_TRTvsCTRL	"NA"	"NA"	"NA"	"NA"	"NA"

\#####

[[1]]

[1] "Patients with back pain for Patients with 2 copies at latest common age"

\$ntab

	ENDEAR	BSC	NURTURE
n_all	18	15	
n_event	0	0	
n_event_pct	0	0	

\$stats

	estimate	se	lo95ci	hi95ci	pvalue
RR_TRTvsCTRL	"NA"	"NA"	"NA"	"NA"	"NA"
OR_TRTvsCTRL	"NA"	"NA"	"NA"	"NA"	"NA"
ARR_TRTvsCTRL	"NA"	"NA"	"NA"	"NA"	"NA"

\#####

[[1]]

[1] "Patients with back pain (SAE) for Patients with 2 copies at age 1 year"

\$ntab

	ENDEAR	BSC	NURTURE
n_all		18	15
n_event		0	0
n_event_pct		0	0

\$stats

	estimate	se	lo95ci	hi95ci	pvalue
RR_TRTvsCTRL	"NA"	"NA"	"NA"	"NA"	"NA"
OR_TRTvsCTRL	"NA"	"NA"	"NA"	"NA"	"NA"
ARR_TRTvsCTRL	"NA"	"NA"	"NA"	"NA"	"NA"

\#####

[[1]]

[1] "Patients with back pain (SAE) for Patients with 2 copies at latest common age"

\$ntab

	ENDEAR	BSC	NURTURE
n_all		18	15
n_event		0	0
n_event_pct		0	0

\$stats

	estimate	se	lo95ci	hi95ci	pvalue
RR_TRTvsCTRL	"NA"	"NA"	"NA"	"NA"	"NA"
OR_TRTvsCTRL	"NA"	"NA"	"NA"	"NA"	"NA"
ARR_TRTvsCTRL	"NA"	"NA"	"NA"	"NA"	"NA"

\#####

[[1]]

[1] "Patients with back pain (severe AE) for Patients with 2 copies at age 1 year"

\$ntab

	ENDEAR	BSC	NURTURE
n_all		18	15
n_event		0	0
n_event_pct		0	0

\$stats

	estimate	se	lo95ci	hi95ci	pvalue
RR_TRTvsCTRL	"NA"	"NA"	"NA"	"NA"	"NA"
OR_TRTvsCTRL	"NA"	"NA"	"NA"	"NA"	"NA"
ARR_TRTvsCTRL	"NA"	"NA"	"NA"	"NA"	"NA"

\#####

[[1]]

[1] "Patients with back pain (severe AE) for Patients with 2 copies at latest common age"

\$ntab

	ENDEAR	BSC	NURTURE
n_all		18	15
n_event		0	0
n_event_pct		0	0

\$stats

	estimate	se	lo95ci	hi95ci	pvalue
RR_TRTvSCTRL	"NA"	"NA"	"NA"	"NA"	"NA"
OR_TRTvSCTRL	"NA"	"NA"	"NA"	"NA"	"NA"
ARR_TRTvSCTRL	"NA"	"NA"	"NA"	"NA"	"NA"

\#####

[[1]]

[1] "Baseline Value in HINE-2 for Patients with 2 copies"

[[2]]

	NURTURE	ENDEAR	BSC
N	15.000	18.0000	
MW	2.670	1.4400	
SD	1.590	1.2000	
MD	0.000	1.2200	
CI	0.198	2.2470	
pvalue	0.000	0.0213	

\#####

[[1]]

[1] "Value in HINE-2 for Patients with 2 copies at age 1 year"

[[2]]

	NURTURE	ENDEAR	BSC
N	15.000	8.00	
MW	19.670	1.50	
SD	4.150	1.51	
MD	0.000	18.17	
CI	15.663	20.67	
pvalue	0.000	0.00	

\#####

[[1]]

[1] "Value in HINE-2 for Patients with 2 copies at latest common age"

[[2]]

	NURTURE	ENDEAR	BSC
N	2.000	7.000	
MW	15.000	2.000	
SD	1.410	1.150	
MD	0.000	13.000	
CI	5.805	20.195	
pvalue	0.000	0.022	

\#####

[[1]]

[1] "Change from Baseline in HINE-2 for Patients with 2 copies at age 1 year"

\$numbers_eachgrp

	NURTURE	ENDEAR	BSC
N	15.000000	8.000000	
n	15.000000	8.000000	
mean	17.000000	-0.125000	
sd	3.909695	1.457738	
se	1.009479	0.515388	
median	17.000000	0.000000	
min	11.000000	-3.000000	
max	23.000000	2.000000	
sum	255.000000	-1.000000	

\$Hedgesg_TRTvsCTRL

est	lo95ci	hi95ci	pv
"5.00"	"3.196"	"6.804"	"0.0000"

\#####

[[1]]

[1] "Change from Baseline in HINE-2 for Patients with 2 copies at latest common age"

\$numbers_eachgrp

	NURTURE	ENDEAR	BSC
N	2.000000	7.000000	
n	2.000000	3.000000	
mean	12.000000	1.000000	
sd	2.828427	1.000000	
se	2.000000	0.577350	
median	12.000000	1.000000	
min	10.000000	0.000000	
max	14.000000	2.000000	
sum	24.000000	3.000000	

\$Hedgesg_TRTvsCTRL

est	lo95ci	hi95ci	pv
"4.38"	"-1.782"	"10.546"	"0.1635"

\#####

[[1]]

[1] "Baseline Value in CHOP-Intend for Patients with 2 copies"

[[2]]

	NURTURE	ENDEAR	BSC
N	15.000	18.000	
MW	47.000	26.560	
SD	10.040	6.750	
MD	0.000	20.440	

CI	14.166	26.723
pvalue	0.000	0.000

\#####

[[1]]

[1] "Value in CHOP-Intend for Patients with 2 copies at age 1 year"

[[2]]

	NURTURE	ENDEAR	BSC
N	15.000	7.00	
MW	57.330	11.86	
SD	6.330	9.65	
MD	0.000	45.48	
CI	36.353	54.60	
pvalue	0.000	0.00	

\#####

[[1]]

[1] "Value in CHOP-Intend for Patients with 2 copies at latest common age"

[[2]]

	NURTURE	ENDEAR	BSC
N	2.000	6.0000	
MW	62.000	29.0000	
SD	2.830	3.5200	
MD	0.000	33.0000	
CI	23.212	42.7880	
pvalue	0.000	0.0039	

\#####

[[1]]

[1] "Change from Baseline in CHOP-Intend for Patients with 2 copies at age 1 year"

\$numbers_eachgrp

	NURTURE	ENDEAR	BSC
N	15.000000	7.000000	
n	15.000000	7.000000	
mean	10.333333	-14.642857	
sd	10.847427	6.859994	
se	2.800794	2.592834	
median	8.000000	-17.000000	
min	-8.000000	-23.000000	
max	29.000000	-3.500000	
sum	155.000000	-102.500000	

\$Hedgesg_TRTVsCTRL

est	lo95ci	hi95ci	pv
"2.45"	"1.246"	"3.647"	"0.0001"

```
\#####  
[[1]]  
[1] "Change from Baseline in CHOP-Intend for Patients with 2 copies at latest  
common age"
```

```
$numbers_eachgrp  
      NURTURE ENDEAR BSC  
N      2.000000 6.000000  
n      2.000000 3.000000  
mean   13.000000 0.166667  
sd      8.485281 1.892969  
se      6.000000 1.092906  
median 13.000000 1.000000  
min     7.000000 -2.000000  
max    19.000000 1.500000  
sum    26.000000 0.500000
```

```
$Hedgesg_TRTvSCTRL  
      est   lo95ci   hi95ci      pv  
"1.82" "-1.213"  "4.847" "0.2399"
```

```
\#####
```

Anhang 4-G zu Modul 4 A.3

Sensitivitätsanalyse NURTURE vs. ENDEAR

Stand: 01.12.2020

NURTURE vs untreated ENDEAR
 Results for whole population and
 patients with two copies and start of therapy in ENDEAR max 12 weeks after
 symptom onset

Sensitivity Analysis

[[1]]

[1] "Descriptive for whole Population"

[[2]]

	NURTURE	ENDEAR BSC
N	"25"	"41"
Age at study entry (months), mean (sd)	"0.61 (0.38)"	"5.41 (1.6)"
Gender (Female), n (%)	"13 (52%)"	"24 (58.54%)"
Age at Diagnosis (months), mean (sd)	"-"	"4.37 (1.87)"
Age at Symptom onset (months), mean (sd)	"-"	"2.4 (1.17)"
Age at Therapy onset (months), mean (sd)	"0.68 (0.35)"	"5.93 (1.67)"
Age at last dose (months), mean (sd)	"24.61 (6.23)"	"11.14 (4.6)"
Number of doses, mean (sd)	"9.56 (1.56)"	"4.51 (1.38)"
Age at last follow-up (months), mean (sd)	"24.44 (5.74)"	"13.37 (5.12)"
Discontinuation for patients not dead, n (%)	"0 (0%)"	"10 (24.39%)"

\#####

[[1]]

[1] "Descriptive for Patients with 2 copies"

[[2]]

	NURTURE	ENDEAR BSC
N	"15"	"18"
Age at study entry (months), mean (sd)	"0.57 (0.32)"	"4.39 (1.79)"
Gender (Female), n (%)	"7 (46.67%)"	"7 (38.89%)"
Age at Diagnosis (months), mean (sd)	"-"	"3.21 (1.93)"
Age at Symptom onset (months), mean (sd)	"-"	"2.56 (1.51)"
Age at Therapy onset (months), mean (sd)	"0.64 (0.31)"	"4.82 (1.78)"
Age at last dose (months), mean (sd)	"25.59 (6.33)"	"9.66 (3.92)"
Number of doses, mean (sd)	"9.8 (1.61)"	"4.56 (1.1)"
Age at last follow-up (months), mean (sd)	"25.21 (5.58)"	"12.2 (4.23)"
Discontinuation for patients not dead, n (%)	"0 (0%)"	"6 (33.33%)"

\#####

[[1]]

[1] "Mortality"

\$ntab

	ENDEAR BSC	NURTURE
n_all	41	25
n_event	16	0
n_event_pct	39	0

\$stats

	estimate	se	lo95ci	hi95ci	pvalue
RR	"20.43"	"1.41"	"1.279"	"326.225"	"0.0328"
OR	"33.00"	"1.46"	"1.878"	"580.009"	"0.0168"

ARR "0.39" "0.08" "0.241" "0.540" "0.0000"

\#####

[[1]]

[1] "Mortality for Patients with 2 copies at age 1 year"

\$ntab

	ENDEAR	BSC	NURTURE
n_all	18	15	
n_event	4	0	
n_event_pct	22	0	

\$stats

	estimate	se	lo95ci	hi95ci	pvalue
RR	"7.58"	"1.45"	"0.441"	"130.376"	"0.1629"
OR	"9.62"	"1.53"	"0.475"	"194.830"	"0.1402"
ARR	"0.22"	"0.10"	"0.030"	"0.414"	"0.0233"

\#####

[[1]]

[1] "Mortality for Patients with 2 copies at latest common age"

\$ntab

	ENDEAR	BSC	NURTURE
n_all	18	15	
n_event	2	0	
n_event_pct	11	0	

\$stats

	estimate	se	lo95ci	hi95ci	pvalue
RR	"4.21"	"1.51"	"0.218"	"81.469"	"0.3416"
OR	"4.70"	"1.59"	"0.209"	"105.787"	"0.3303"
ARR	"0.11"	"0.07"	"-0.034"	"0.256"	"0.1336"

\#####

[[1]]

[1] "Time to death"

\$stats_num

	NURTURE	ENDEAR	BSC
n_all	25	41.0	
n_event	0	16.0	
n_event_pct	0	39.0	
time-to-event-wk-10th	NA	5.4	
time-to-event-wk-25th	NA	14.3	
time-to-event-wk-50th	NA	NA	
time-to-event-wk-75th	NA	NA	
time-to-event-wk-90th	NA	NA	
time-to-event-wk-50th-loci	NA	23.1	
time-to-event-wk-50th-hici	NA	NA	


```
$stats_HR_TRTVsCTRL
      HR   SE_logHR HR.lo95ci HR.hi95ci   p.value
      NA         NA         NA         NA         NA
```

```
\#####
[[1]]
[1] "Time to death for Patients with 2 copies at age 1 year"
```

```
$stats_num
              NURTURE ENDEAR BSC
n_all              15      18
n_event            0       4
n_event_pct        0      22
time-to-event-wk-10th  NA     10
time-to-event-wk-25th  NA     NA
time-to-event-wk-50th  NA     NA
time-to-event-wk-75th  NA     NA
time-to-event-wk-90th  NA     NA
time-to-event-wk-50th-loci  NA     NA
time-to-event-wk-50th-hici  NA     NA
```

```
$stats_HR_TRTVsCTRL
      HR   SE_logHR HR.lo95ci HR.hi95ci   p.value
      NA         NA         NA         NA         NA
```

```
\#####
[[1]]
[1] "Time to death for Patients with 2 copies at latest common age"
```

```
$stats_num
              NURTURE ENDEAR BSC
n_all              15      18.0
n_event            0       2.0
n_event_pct        0      11.0
time-to-event-wk-10th  NA     8.8
time-to-event-wk-25th  NA    13.1
time-to-event-wk-50th  NA     NA
time-to-event-wk-75th  NA     NA
time-to-event-wk-90th  NA     NA
time-to-event-wk-50th-loci  NA     4.4
time-to-event-wk-50th-hici  NA     NA
```

```
$stats_HR_TRTVsCTRL
      HR   SE_logHR HR.lo95ci HR.hi95ci   p.value
      NA         NA         NA         NA         NA
```

```
\#####
[[1]]
[1] "Time to permanent ventilation"
```

```
$stats_num
```

	NURTURE	ENDEAR	BSC
n_all	25		41.0
n_event	0		13.0
n_event_pct	0		32.0
time-to-event-wk-10th	NA		13.6
time-to-event-wk-25th	NA		20.4
time-to-event-wk-50th	NA		NA
time-to-event-wk-75th	NA		NA
time-to-event-wk-90th	NA		NA
time-to-event-wk-50th-loci	NA		22.6
time-to-event-wk-50th-hici	NA		NA

```
$stats_HR_TRTVsCTRL
      HR   SE_logHR HR.lo95ci HR.hi95ci  p.value
      NA         NA         NA         NA      NA
```

\#####

```
[[1]]
```

```
[1] "Time to permanent ventilation for Patients with 2 copies at age 1 year"
```

	NURTURE	ENDEAR	BSC
n_all	15		18.0
n_event	0		5.0
n_event_pct	0		28.0
time-to-event-wk-10th	NA		7.6
time-to-event-wk-25th	NA		15.0
time-to-event-wk-50th	NA		NA
time-to-event-wk-75th	NA		NA
time-to-event-wk-90th	NA		NA
time-to-event-wk-50th-loci	NA		15.0
time-to-event-wk-50th-hici	NA		NA

```
$stats_HR_TRTVsCTRL
      HR   SE_logHR HR.lo95ci HR.hi95ci  p.value
      NA         NA         NA         NA      NA
```

\#####

```
[[1]]
```

```
[1] "Time to permanent ventilation for Patients with 2 copies at latest common age"
```

	NURTURE	ENDEAR	BSC
n_all	15		18.0
n_event	0		2.0
n_event_pct	0		11.0
time-to-event-wk-10th	NA		6.0
time-to-event-wk-25th	NA		13.6
time-to-event-wk-50th	NA		13.6
time-to-event-wk-75th	NA		NA
time-to-event-wk-90th	NA		NA

```
time-to-event-wk-50th-loci      NA      6.0
time-to-event-wk-50th-hici      NA      NA
```

```
$stats_HR_TRTVsCTRL
```

```
HR      SE_logHR HR.lo95ci HR.hi95ci  p.value
NA      NA      NA      NA      NA      NA
```

```
\#####
[[1]]
[1] "Patients requiring permanent ventilation "
```

```
$ntab
```

```
          ENDEAR BSC NURTURE
n_all          41    25
n_event         13     0
n_event_pct     32     0
```

```
$stats
```

```
      estimate se      lo95ci hi95ci  pvalue
RR  "16.71"  "1.42" "1.037" "269.411" "0.0471"
OR   "24.16"  "1.47" "1.366" "427.262" "0.0298"
ARR  "0.32"   "0.07" "0.175" "0.460"  "0.0000"
```

```
\#####
[[1]]
[1] "Patients requiring permanent ventilation for Patients with 2 copies at age
1 year"
```

```
$ntab
```

```
          ENDEAR BSC NURTURE
n_all          18    15
n_event         5     0
n_event_pct     28     0
```

```
$stats
```

```
      estimate se      lo95ci hi95ci  pvalue
RR   "9.26"  "1.44" "0.553" "155.040" "0.1215"
OR   "12.63"  "1.52" "0.638" "250.044" "0.0959"
ARR  "0.28"   "0.11" "0.071" "0.485"  "0.0085"
```

```
\#####
[[1]]
[1] "Patients requiring permanent ventilation for Patients with 2 copies at
latest common age"
```

```
$ntab
```

```
          ENDEAR BSC NURTURE
n_all          18    15
n_event         2     0
n_event_pct     11     0
```

```
$stats
      estimate se      lo95ci   hi95ci   pvalue
RR   "4.21"   "1.51" "0.218"   "81.469" "0.3416"
OR   "4.70"   "1.59" "0.209"   "105.787" "0.3303"
ARR  "0.11"   "0.07" "-0.034" "0.256"   "0.1336"
```

```
\#####
[[1]]
[1] "Patients without at least 1 SAE"
```

```
$ntab
      ENDEAR BSC NURTURE
n_all      41     25
n_event     2     16
n_event_pct 5     64
```

```
$stats
      estimate se      lo95ci   hi95ci   pvalue
RR   "0.08"   "0.71" "0.019"   "0.304" "0.0003"
OR   "0.03"   "0.84" "0.006"   "0.149" "0.0000"
ARR  "-0.59"   "0.10" "-0.791" "-0.392" "0.0000"
```

```
\#####
[[1]]
[1] "Patients without at least 1 SAE for Patients with 2 copies at age 1 year"
```

```
$ntab
      ENDEAR BSC NURTURE
n_all      18     15
n_event     2      9
n_event_pct 11    60
```

```
$stats
      estimate se      lo95ci   hi95ci   pvalue
RR   "0.19"   "0.70" "0.047"   "0.729" "0.0159"
OR   "0.08"   "0.92" "0.014"   "0.502" "0.0067"
ARR  "-0.49"   "0.15" "-0.776" "-0.202" "0.0009"
```

```
\#####
[[1]]
[1] "Patients without at least 1 SAE for Patients with 2 copies at latest common age"
```

```
$ntab
      ENDEAR BSC NURTURE
n_all      18     15
n_event    11      9
n_event_pct 61    60
```

```
$stats
      estimate se      lo95ci   hi95ci   pvalue
```

```
RR "1.02" "0.28" "0.585" "1.772" "0.9482"
OR "1.05" "0.72" "0.258" "4.256" "0.9481"
ARR "0.01" "0.17" "-0.324" "0.346" "0.9482"
```

```
\#####
```

```
[[1]]
[1] "Patients without at least 1 severe AE"
```

```
$ntab
```

	ENDEAR	BSC	NURTURE
n_all	41	25	
n_event	8	20	
n_event_pct	20	80	

```
$stats
```

	estimate	se	lo95ci	hi95ci	pvalue
RR	"0.24"	"0.33"	"0.127"	"0.468"	"0.0000"
OR	"0.06"	"0.64"	"0.017"	"0.211"	"0.0000"
ARR	"-0.60"	"0.10"	"-0.803"	"-0.407"	"0.0000"

```
\#####
```

```
[[1]]
[1] "Patients without at least 1 severe AE for Patients with 2 copies at age 1
year"
```

```
$ntab
```

	ENDEAR	BSC	NURTURE
n_all	18	15	
n_event	3	14	
n_event_pct	17	93	

```
$stats
```

	estimate	se	lo95ci	hi95ci	pvalue
RR	"0.18"	"0.53"	"0.063"	"0.506"	"0.0012"
OR	"0.01"	"1.21"	"0.001"	"0.154"	"0.0005"
ARR	"-0.77"	"0.11"	"-0.980"	"-0.553"	"0.0000"

```
\#####
```

```
[[1]]
[1] "Patients without at least 1 severe AE for Patients with 2 copies at latest
common age"
```

```
$ntab
```

	ENDEAR	BSC	NURTURE
n_all	18	15	
n_event	11	15	
n_event_pct	61	100	

```
$stats
```

	estimate	se	lo95ci	hi95ci	pvalue
RR	"0.62"	"0.19"	"0.430"	"0.908"	"0.0136"

```
OR "0.05" "1.51" "0.003" "0.957" "0.0467"
ARR "-0.39" "0.11" "-0.614" "-0.164" "0.0007"
```

```
\#####
```

```
[[1]]
```

```
[1] "Patients without AE leading to discontinuation"
```

```
$ntab
```

	ENDEAR	BSC	NURTURE
n_all	41	25	
n_event	25	25	
n_event_pct	61	100	

```
$stats
```

	estimate	se	lo95ci	hi95ci	pvalue
RR	"0.62"	"0.13"	"0.483"	"0.794"	"0.0002"
OR	"0.03"	"1.46"	"0.002"	"0.533"	"0.0168"
ARR	"-0.39"	"0.08"	"-0.540"	"-0.241"	"0.0000"

```
\#####
```

```
[[1]]
```

```
[1] "Patients without AE leading to discontinuation for Patients with 2 copies  
at age 1 year"
```

```
$ntab
```

	ENDEAR	BSC	NURTURE
n_all	18	15	
n_event	14	15	
n_event_pct	78	100	

```
$stats
```

	estimate	se	lo95ci	hi95ci	pvalue
RR	"0.79"	"0.14"	"0.604"	"1.027"	"0.0782"
OR	"0.10"	"1.53"	"0.005"	"2.105"	"0.1402"
ARR	"-0.22"	"0.10"	"-0.414"	"-0.030"	"0.0233"

```
\#####
```

```
[[1]]
```

```
[1] "Patients without AE leading to discontinuation for Patients with 2 copies  
at latest common age"
```

```
$ntab
```

	ENDEAR	BSC	NURTURE
n_all	18	15	
n_event	15	15	
n_event_pct	83	100	

```
$stats
```

	estimate	se	lo95ci	hi95ci	pvalue
RR	"0.84"	"0.12"	"0.668"	"1.061"	"0.1450"
OR	"0.14"	"1.55"	"0.007"	"3.003"	"0.2105"

ARR "-0.17" "0.09" "-0.339" "0.005" "0.0578"

\#####

[[1]]

[1] "Patients without back pain"

\$ntab

	ENDEAR	BSC	NURTURE
n_all	41	25	
n_event	41	25	
n_event_pct	100	100	

\$stats

	estimate	se	lo95ci	hi95ci	pvalue
RR	"1.01"	"0.03"	"0.946"	"1.073"	"0.8176"
OR	"1.63"	"2.02"	"0.031"	"84.592"	"0.8091"
ARR	"0.00"	"0.00"	"0.000"	"0.000"	" NaN"

\#####

[[1]]

[1] "Patients without back pain for Patients with 2 copies at age 1 year"

\$ntab

	ENDEAR	BSC	NURTURE
n_all	18	15	
n_event	18	15	
n_event_pct	100	100	

\$stats

	estimate	se	lo95ci	hi95ci	pvalue
RR	"1.01"	"0.06"	"0.896"	"1.128"	"0.9310"
OR	"1.19"	"2.03"	"0.022"	"63.722"	"0.9305"
ARR	"0.00"	"0.00"	"0.000"	"0.000"	" NaN"

\#####

[[1]]

[1] "Patients without back pain for Patients with 2 copies at latest common age"

\$ntab

	ENDEAR	BSC	NURTURE
n_all	18	15	
n_event	18	15	
n_event_pct	100	100	

\$stats

	estimate	se	lo95ci	hi95ci	pvalue
RR	"1.01"	"0.06"	"0.896"	"1.128"	"0.9310"
OR	"1.19"	"2.03"	"0.022"	"63.722"	"0.9305"
ARR	"0.00"	"0.00"	"0.000"	"0.000"	" NaN"

```

\#####
[[1]]
[1] "Patients without back pain (SAE)"

$ntab
      ENDEAR BSC NURTURE
n_all      41    25
n_event    41    25
n_event_pct 100   100

$stats
      estimate se      lo95ci hi95ci  pvalue
RR  "1.01"    "0.03" "0.946" "1.073" "0.8176"
OR   "1.63"    "2.02" "0.031" "84.592" "0.8091"
ARR  "0.00"    "0.00" "0.000" "0.000"  "  NaN"

\#####
[[1]]
[1] "Patients without back pain (SAE) for Patients with 2 copies at age 1 year"

$ntab
      ENDEAR BSC NURTURE
n_all      18    15
n_event    18    15
n_event_pct 100   100

$stats
      estimate se      lo95ci hi95ci  pvalue
RR  "1.01"    "0.06" "0.896" "1.128" "0.9310"
OR   "1.19"    "2.03" "0.022" "63.722" "0.9305"
ARR  "0.00"    "0.00" "0.000" "0.000"  "  NaN"

\#####
[[1]]
[1] "Patients without back pain (SAE) for Patients with 2 copies at latest
common age"

$ntab
      ENDEAR BSC NURTURE
n_all      18    15
n_event    18    15
n_event_pct 100   100

$stats
      estimate se      lo95ci hi95ci  pvalue
RR  "1.01"    "0.06" "0.896" "1.128" "0.9310"
OR   "1.19"    "2.03" "0.022" "63.722" "0.9305"
ARR  "0.00"    "0.00" "0.000" "0.000"  "  NaN"

\#####
[[1]]

```



```
[1] "Patients without back pain (severe AE)"
```

```
$ntab
```

	ENDEAR	BSC	NURTURE
n_all	41	25	
n_event	41	25	
n_event_pct	100	100	

```
$stats
```

	estimate	se	lo95ci	hi95ci	pvalue
RR	"1.01"	"0.03"	"0.946"	"1.073"	"0.8176"
OR	"1.63"	"2.02"	"0.031"	"84.592"	"0.8091"
ARR	"0.00"	"0.00"	"0.000"	"0.000"	" NaN"

```
\#####
```

```
[[1]]
```

```
[1] "Patients without back pain (severe AE) for Patients with 2 copies at age 1 year"
```

```
$ntab
```

	ENDEAR	BSC	NURTURE
n_all	18	15	
n_event	18	15	
n_event_pct	100	100	

```
$stats
```

	estimate	se	lo95ci	hi95ci	pvalue
RR	"1.01"	"0.06"	"0.896"	"1.128"	"0.9310"
OR	"1.19"	"2.03"	"0.022"	"63.722"	"0.9305"
ARR	"0.00"	"0.00"	"0.000"	"0.000"	" NaN"

```
\#####
```

```
[[1]]
```

```
[1] "Patients without back pain (severe AE) for Patients with 2 copies at latest common age"
```

```
$ntab
```

	ENDEAR	BSC	NURTURE
n_all	18	15	
n_event	18	15	
n_event_pct	100	100	

```
$stats
```

	estimate	se	lo95ci	hi95ci	pvalue
RR	"1.01"	"0.06"	"0.896"	"1.128"	"0.9310"
OR	"1.19"	"2.03"	"0.022"	"63.722"	"0.9305"
ARR	"0.00"	"0.00"	"0.000"	"0.000"	" NaN"

```
\#####
```

```
[[1]]
```

```
[1] "Baseline Value in HINE-2 for Patients with 2 copies"
```

```
[[2]]
```

	NURTURE	ENDEAR	BSC
N	15.000	18.0000	
MW	2.670	1.4400	
SD	1.590	1.2000	
MD	0.000	1.2200	
CI	0.198	2.2470	
pvalue	0.000	0.0213	

```
\#####
```

```
[[1]]
```

```
[1] "Value in HINE-2 for Patients with 2 copies at age 1 year"
```

```
[[2]]
```

	NURTURE	ENDEAR	BSC
N	15.000	8.00	
MW	19.670	1.50	
SD	4.150	1.51	
MD	0.000	18.17	
CI	15.663	20.67	
pvalue	0.000	0.00	

```
\#####
```

```
[[1]]
```

```
[1] "Value in HINE-2 for Patients with 2 copies at latest common age"
```

```
[[2]]
```

	NURTURE	ENDEAR	BSC
N	2.000	7.000	
MW	15.000	2.000	
SD	1.410	1.150	
MD	0.000	13.000	
CI	5.805	20.195	
pvalue	0.000	0.022	

```
\#####
```

```
[[1]]
```

```
[1] "Change from Baseline in HINE-2 for all Patients"
```

```
$numbers_eachgrp
```

	NURTURE	ENDEAR	BSC
N	25.00000	41.0000000	
n	25.00000	34.0000000	
mean	21.56000	-0.2058824	
sd	2.45085	1.3878130	
se	0.49017	0.2380080	
median	23.00000	0.0000000	
min	15.00000	-4.0000000	
max	24.00000	2.0000000	
sum	539.00000	-7.0000000	

```
$Hedgesg_TRTVsCTRL
      est   lo95ci   hi95ci       pv
"11.25"  "9.087"  "13.415"  "0.0000"
```

```
\#####
[[1]]
[1] "Change from Baseline in HINE-2 for all Patients at age 1 year"
```

```
$numbers_eachgrp
      NURTURE ENDEAR BSC
N      25.0000000 13.0000000
n      25.0000000 13.0000000
mean   18.5200000 -0.1538462
sd      3.8201222  1.5730095
se      0.7640244  0.4362743
median  19.0000000  0.0000000
min     11.0000000 -3.0000000
max     24.0000000  2.0000000
sum     463.0000000 -2.0000000
```

```
$Hedgesg_TRTVsCTRL
      est   lo95ci   hi95ci       pv
"5.63"  "4.133"  "7.123"  "0.0000"
```

```
\#####
[[1]]
[1] "Change from Baseline in HINE-2 for all Patients at latest common age"
```

```
$numbers_eachgrp
      NURTURE ENDEAR BSC
N      4 10.0000000
n      4  3.0000000
mean   11  1.0000000
sd      2  1.0000000
se      1  0.5773503
median  10  1.0000000
min     10  0.0000000
max     14  2.0000000
sum     44  3.0000000
```

```
$Hedgesg_TRTVsCTRL
      est   lo95ci   hi95ci       pv
"5.03"  "0.774"  "9.291"  "0.0206"
```

```
\#####
[[1]]
[1] "Change from Baseline in HINE-2 for Patients with 2 copies at age 1 year"
```

```
$numbers_eachgrp
      NURTURE ENDEAR BSC
```

N	15.000000	8.0000000
n	15.000000	8.0000000
mean	17.000000	-0.1250000
sd	3.909695	1.4577380
se	1.009479	0.5153882
median	17.000000	0.0000000
min	11.000000	-3.0000000
max	23.000000	2.0000000
sum	255.000000	-1.0000000

```
$Hedgesg_TRTVsCTRL
      est   lo95ci   hi95ci      pv
"5.00"  "3.196"  "6.804" "0.0000"
```

```
\#####
[[1]]
[1] "Change from Baseline in HINE-2 for Patients with 2 copies at latest common
age"
```

```
$numbers_eachgrp
      NURTURE ENDEAR BSC
N      2.000000  7.0000000
n      2.000000  3.0000000
mean   12.000000  1.0000000
sd      2.828427  1.0000000
se      2.000000  0.5773503
median  12.000000  1.0000000
min     10.000000  0.0000000
max     14.000000  2.0000000
sum     24.000000  3.0000000
```

```
$Hedgesg_TRTVsCTRL
      est   lo95ci   hi95ci      pv
"4.38"  "-1.782"  "10.546" "0.1635"
```

```
\#####
[[1]]
[1] "Baseline Value in CHOP-Intend for Patients with 2 copies"
```

```
[[2]]
      NURTURE ENDEAR BSC
N      15.000    18.000
MW      47.000    26.560
SD      10.040     6.750
MD       0.000    20.440
CI      14.166    26.723
pvalue   0.000     0.000
```

```
\#####
[[1]]
[1] "Value in CHOP-Intend for Patients with 2 copies at age 1 year"
```

[[2]]

	NURTURE	ENDEAR	BSC
N	15.000		7.00
MW	57.330		11.86
SD	6.330		9.65
MD	0.000		45.48
CI	36.353		54.60
pvalue	0.000		0.00

\#####

[[1]]

[1] "Value in CHOP-Intend for Patients with 2 copies at latest common age"

[[2]]

	NURTURE	ENDEAR	BSC
N	2.000		6.0000
MW	62.000		29.0000
SD	2.830		3.5200
MD	0.000		33.0000
CI	23.212		42.7880
pvalue	0.000		0.0039

\#####

[[1]]

[1] "Change from Baseline in CHOP-Intend for Patients with 2 copies at age 1 year"

\$numbers_eachgrp

	NURTURE	ENDEAR	BSC
N	15.000000		7.000000
n	15.000000		7.000000
mean	10.333333	-14.642857	
sd	10.847427	6.859994	
se	2.800794	2.592834	
median	8.000000	-17.000000	
min	-8.000000	-23.000000	
max	29.000000	-3.500000	
sum	155.000000	-102.500000	

\$Hedgesg_TRTVsCTRL

est	lo95ci	hi95ci	pv
"2.45"	"1.246"	"3.647"	"0.0001"

\#####

[[1]]

[1] "Change from Baseline in CHOP-Intend for Patients with 2 copies at latest common age"

\$numbers_eachgrp

	NURTURE	ENDEAR	BSC
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N	2.000000	6.000000
n	2.000000	3.000000
mean	13.000000	0.166667
sd	8.485281	1.892969
se	6.000000	1.092906
median	13.000000	1.000000
min	7.000000	-2.000000
max	19.000000	1.500000
sum	26.000000	0.500000

\$Hedgesg_TRTVsCTRL			
est	lo95ci	hi95ci	pv
"1.82"	"-1.213"	"4.847"	"0.2399"

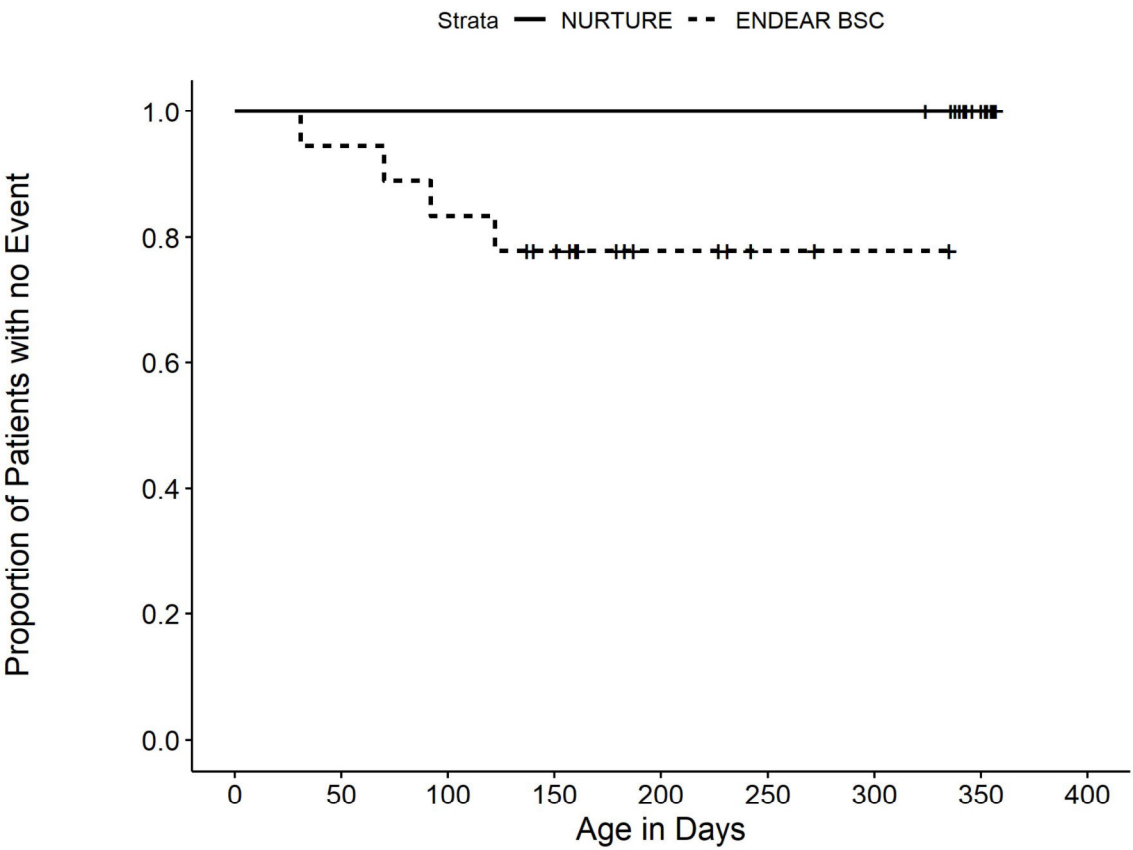
\#####

Anhang 4-G zu Modul 4 A.3

Abbildungen NURTURE vs. ENDEAR

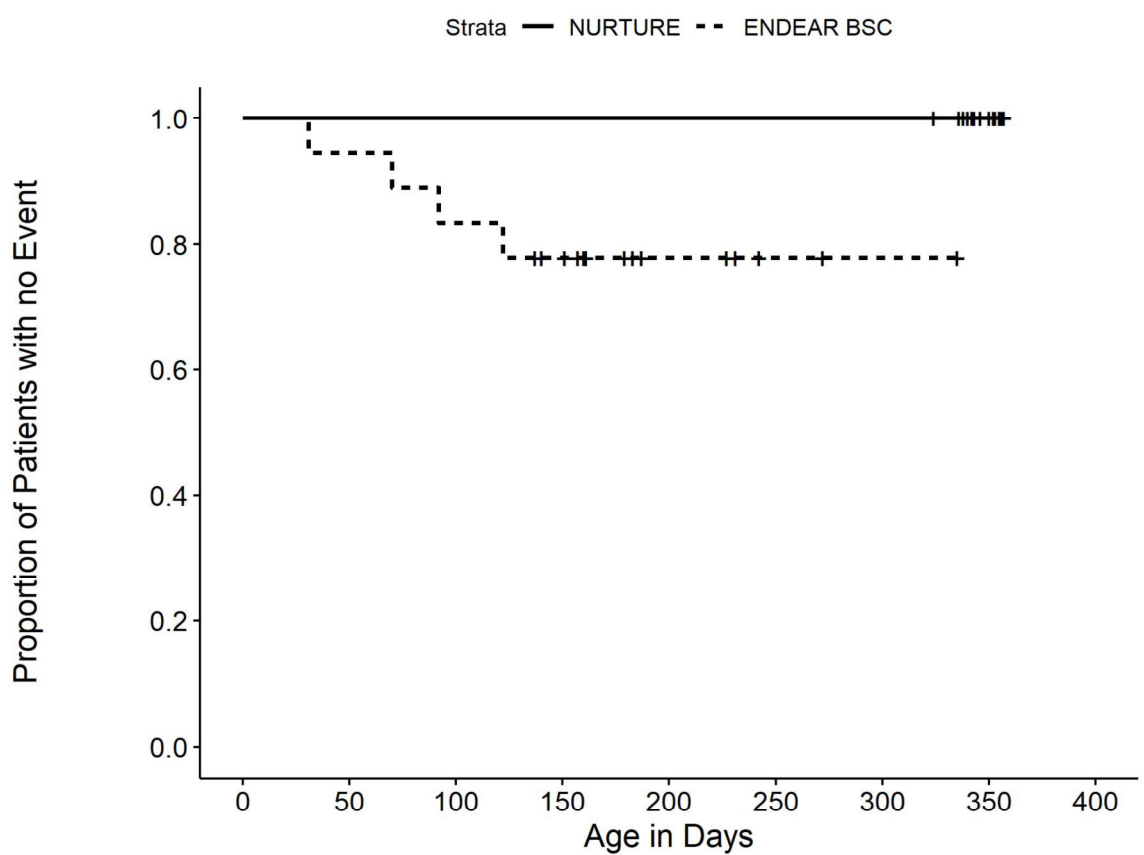
Stand: 01.12.2020

Kaplan Meier Plot for Time to death at age 1 year, Sensitivity Analysis



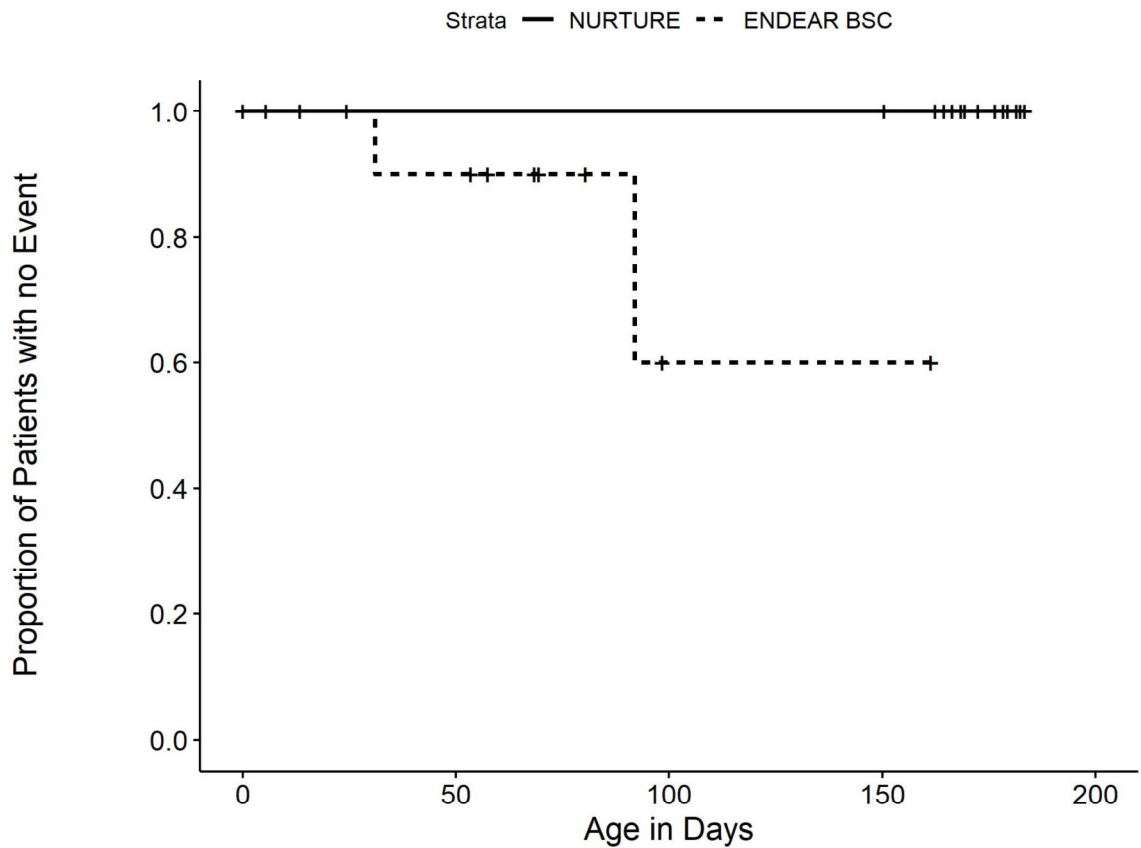
Number at risk									
NURTURE	15	15	15	15	15	15	15	7	0
ENDEAR BSC	18	17	15	12	5	2	1	0	0

Kaplan Meier Plot for Time to death at age 1 year



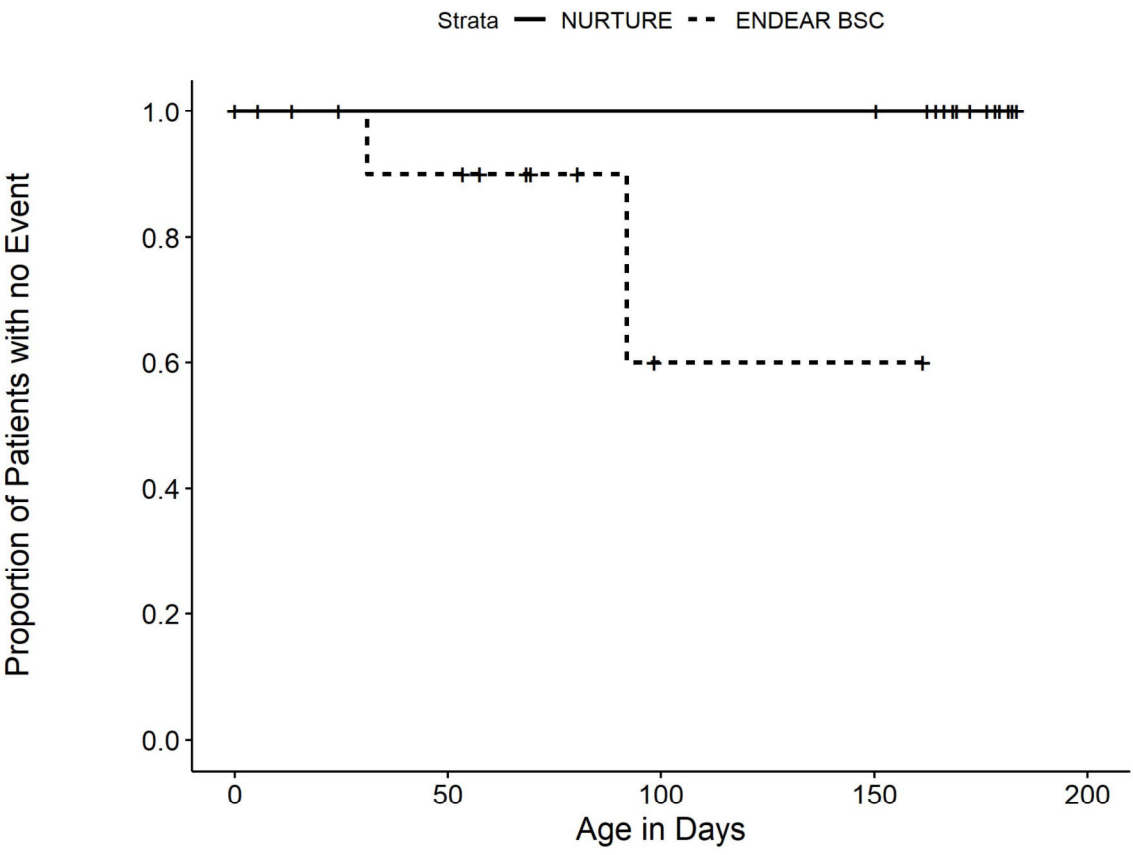
Number at risk									
NURTURE	15	15	15	15	15	15	15	7	0
ENDEAR BSC	18	17	15	12	5	2	1	0	0

Kaplan Meier Plot for Time to death at latest common age, Sensitivity Analysis



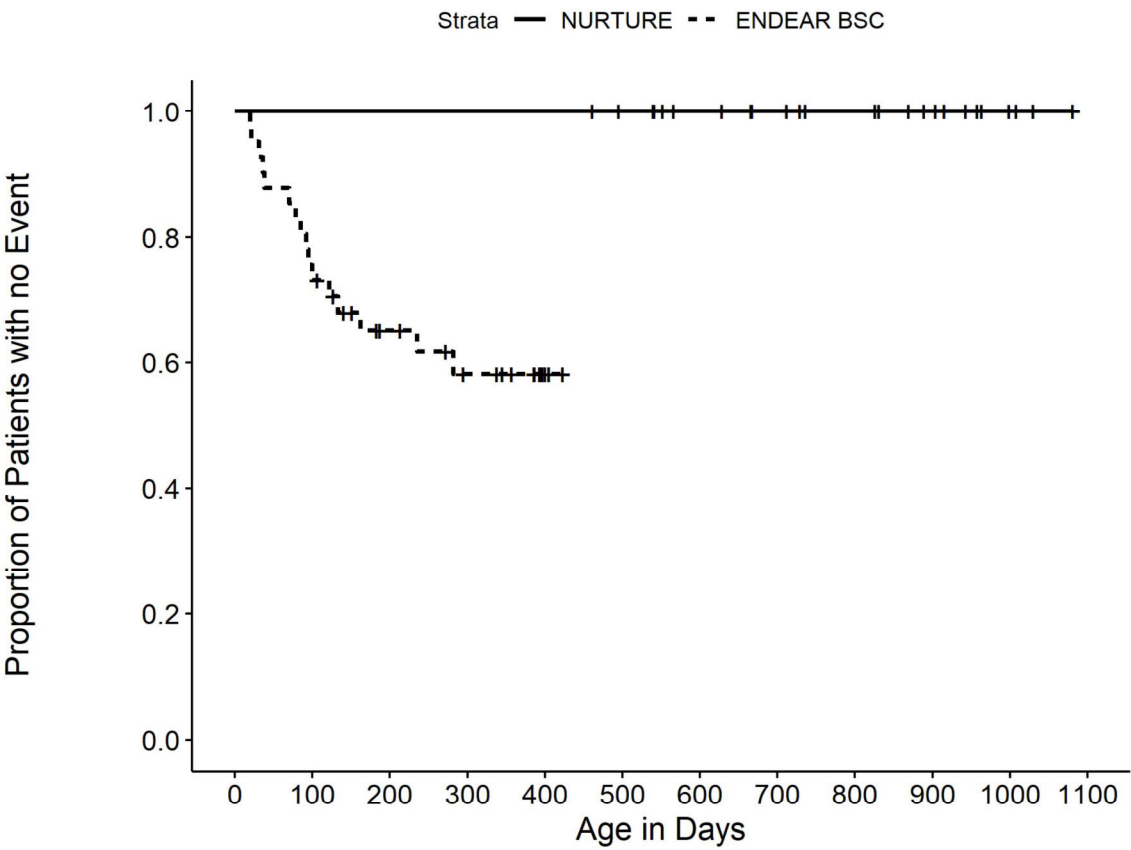
Number at risk					
NURTURE	15	15	15	15	0
ENDEAR BSC	18	9	1	1	0

Kaplan Meier Plot for Time to death at latest common age



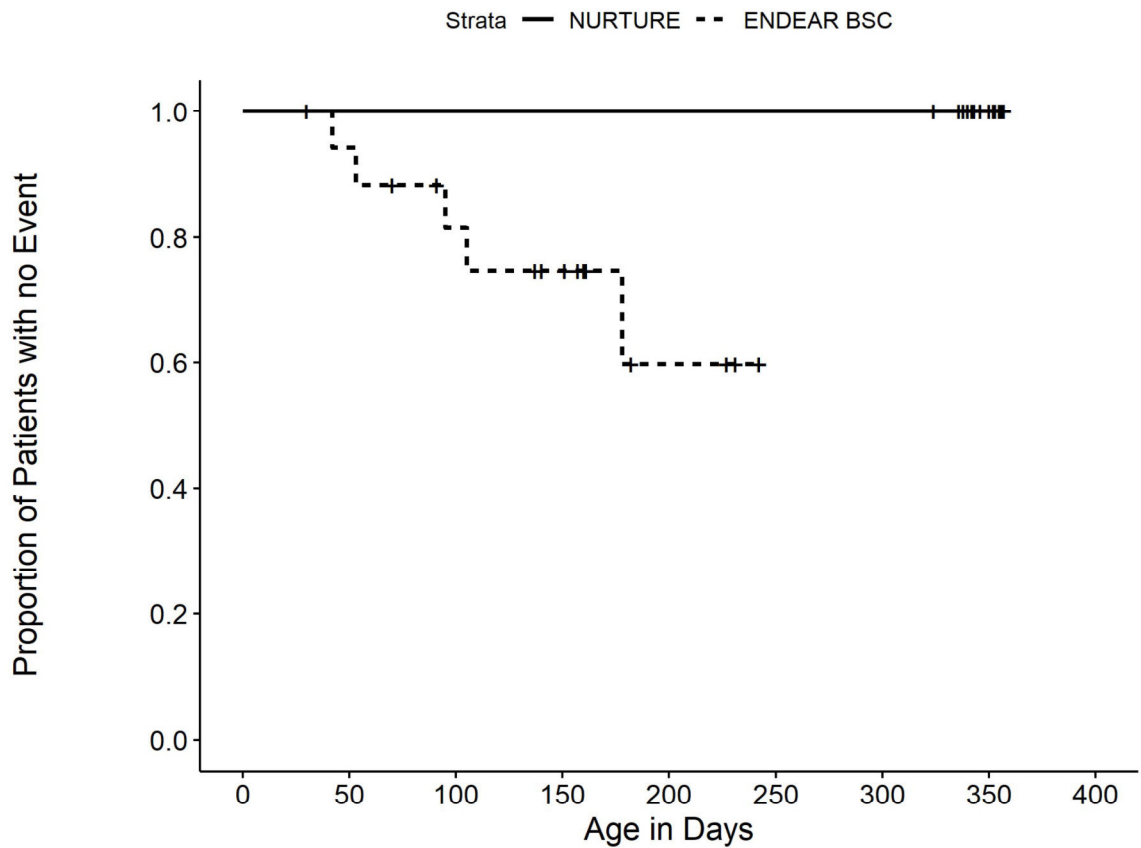
Number at risk					
NURTURE	15	15	15	15	0
ENDEAR BSC	18	9	1	1	0

Kaplan Meier Plot for Time to death, whole population



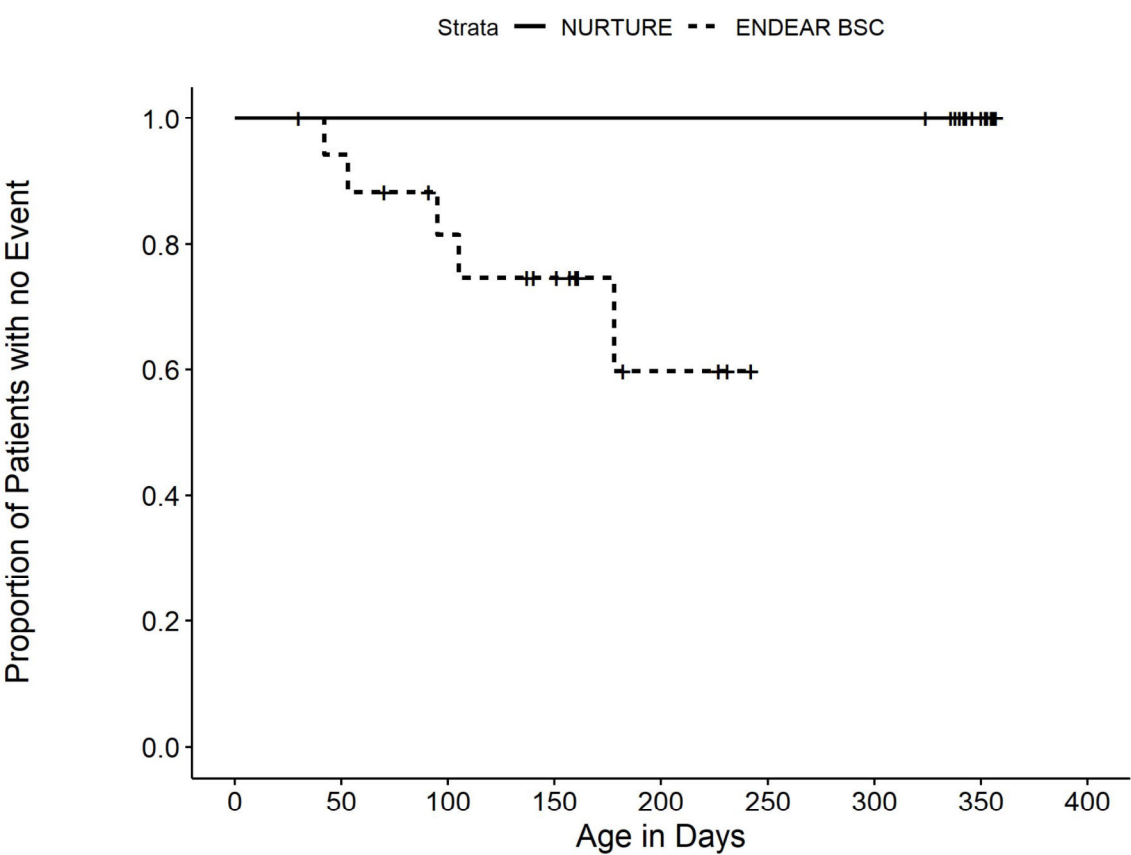
Number at risk												
NURTURE	25	25	25	25	25	23	19	16	13	9	3	0
ENDEAR BSC	41	31	20	15	4	0	0	0	0	0	0	0

Kaplan Meier Plot for Time to permanent ventilation at age 1 year, Sensitivity Analysis



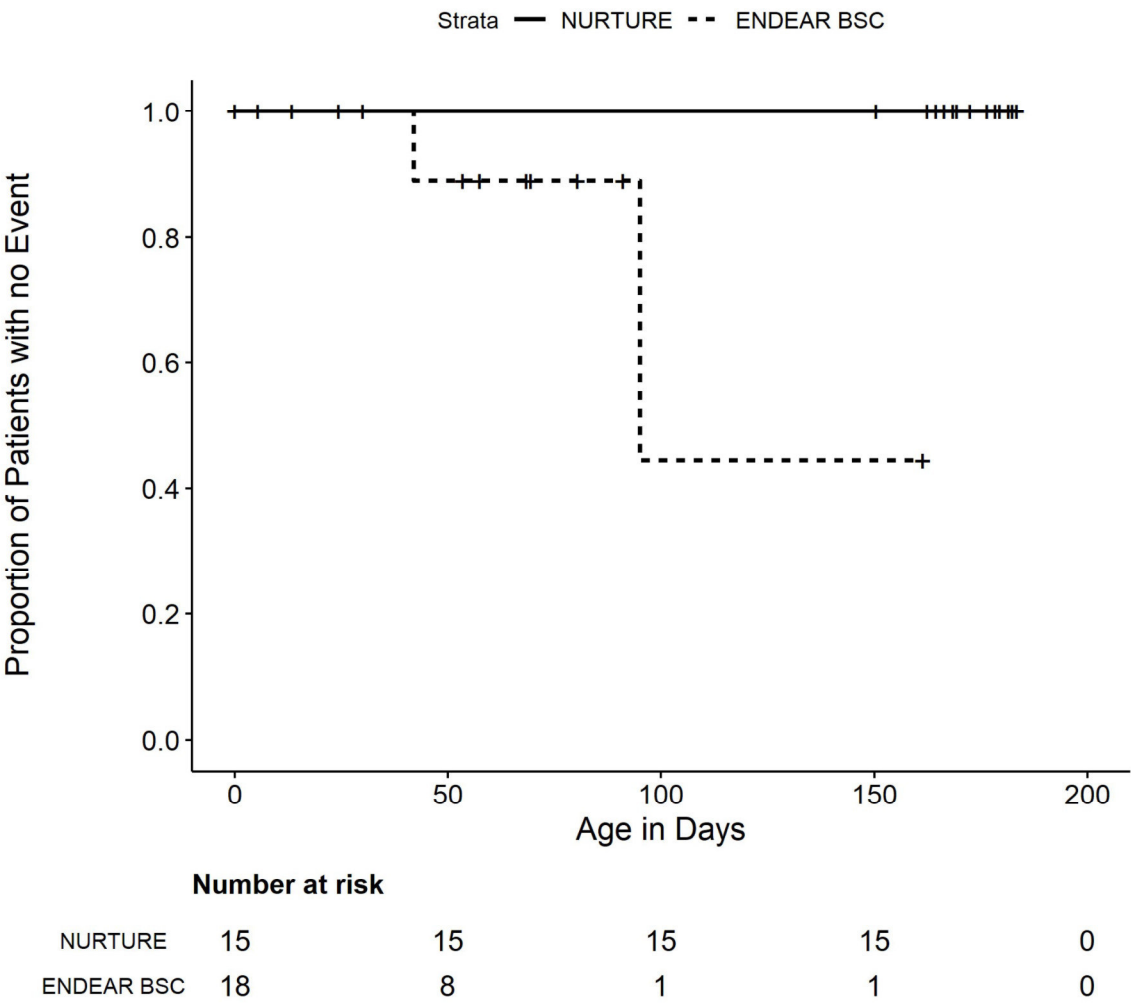
	Number at risk								
NURTURE	15	15	15	15	15	15	15	7	0
ENDEAR BSC	18	16	12	9	3	0	0	0	0

Kaplan Meier Plot for Time to permanent ventilation at age 1 year

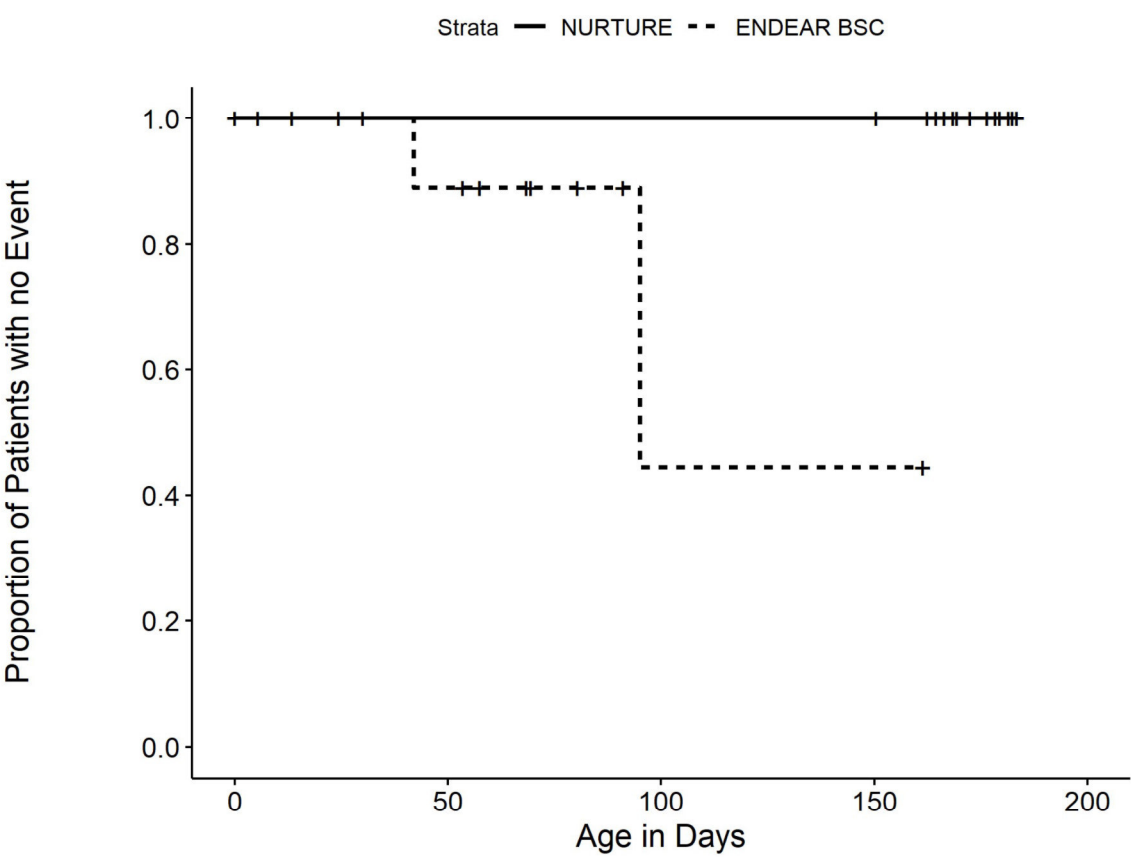


Number at risk									
NURTURE	15	15	15	15	15	15	15	7	0
ENDEAR BSC	18	16	12	9	3	0	0	0	0

Kaplan Meier Plot for Time to permanent ventilation at latest common age,Sensitivity Analysis

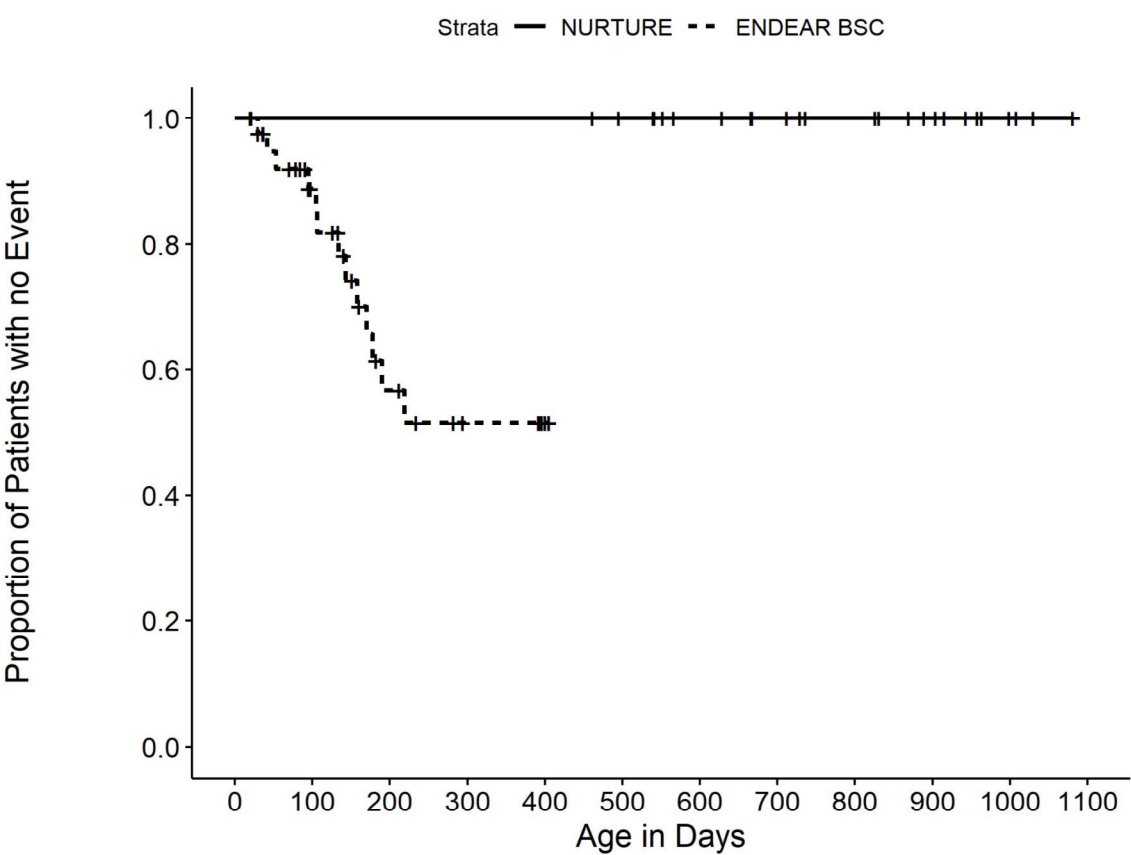


Kaplan Meier Plot for Time to permanent ventilation at latest common age



Number at risk					
NURTURE	15	15	15	15	0
ENDEAR BSC	18	8	1	1	0

Kaplan Meier Plot for Time to permanent ventilation, whole population



Number at risk												
NURTURE	25	25	25	25	25	23	19	16	13	9	3	0
ENDEAR BSC	41	26	12	7	2	0	0	0	0	0	0	0