Klinische Studien

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Es soll die Wirksamkeit und Effizient von einer neuen Therapie untersucht werden.

Was

- Neues Arzneimittel
- Neues Schema, Dosierung u.ä.
- Neue Anwendung (z.B. andere Tumorart)

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Warum

Zulassung = bessere Therapie = $$

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Klinische Phasen

- präklinische Phase
- Phase I
- Phase II
- Phase III => Zulassung
- Phase IV

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präklinische Studien

- ca. 10 Jahre
- Labor
- Tierversuche
- Toxikologie

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Phase I

- ca 20 - 80 Personen (gesunde Probanden)
- Pharmakokinetik
- Pharmakodynamik
- Verträglichkeit und Sicherheit

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Phase II

- 50 -200 Patienten
- Überprüfung des Therapiekonzepts
  (Proof of Concept, Phase IIa)
- Findung der geeigneten Therapiedosis
  (Dose Finding, Phase IIb)
- positive Effekte der Therapie sollten zu beobachten sein

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Phase III

- 200–10.000 Patienten
- Signifikanter Wirkungsnachweis (Pivotal Study)
- Marktzulassung der Therapie
- nach Marktzulassung werden laufende Studien dann zu IIIb-Studien

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Studiendesign

- Studienregistrierung
- Schreiben des Protokolls
- Auswahl der Probanden/Patienten
- Festlegung der zu messenden Parameter
- Art der Dosierung
- Art der Kontrollgruppe
- Methode zur Datenauswertung

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Studiendesign

- **Therapiegruppe**
  - zu untersuchende Therapie
- **Kontrollgruppe**
  - Nicht-behandelte Gruppe
  - Placebo-“behandelte“ Gruppe
  - andere aktive Therapie
    (z.B. bisherige Standardtherapie bzw. Standardmethode)

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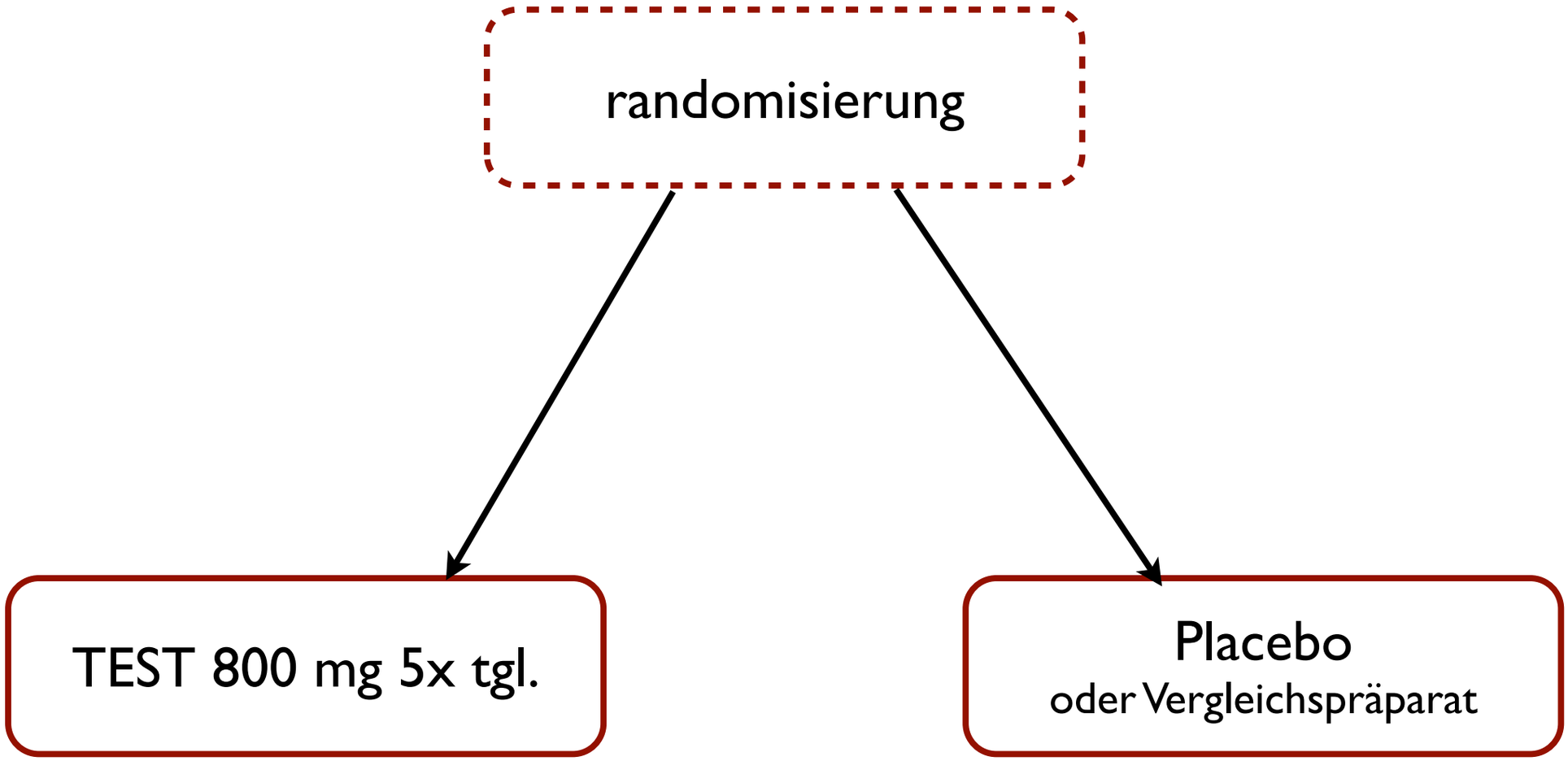
Studiendesign



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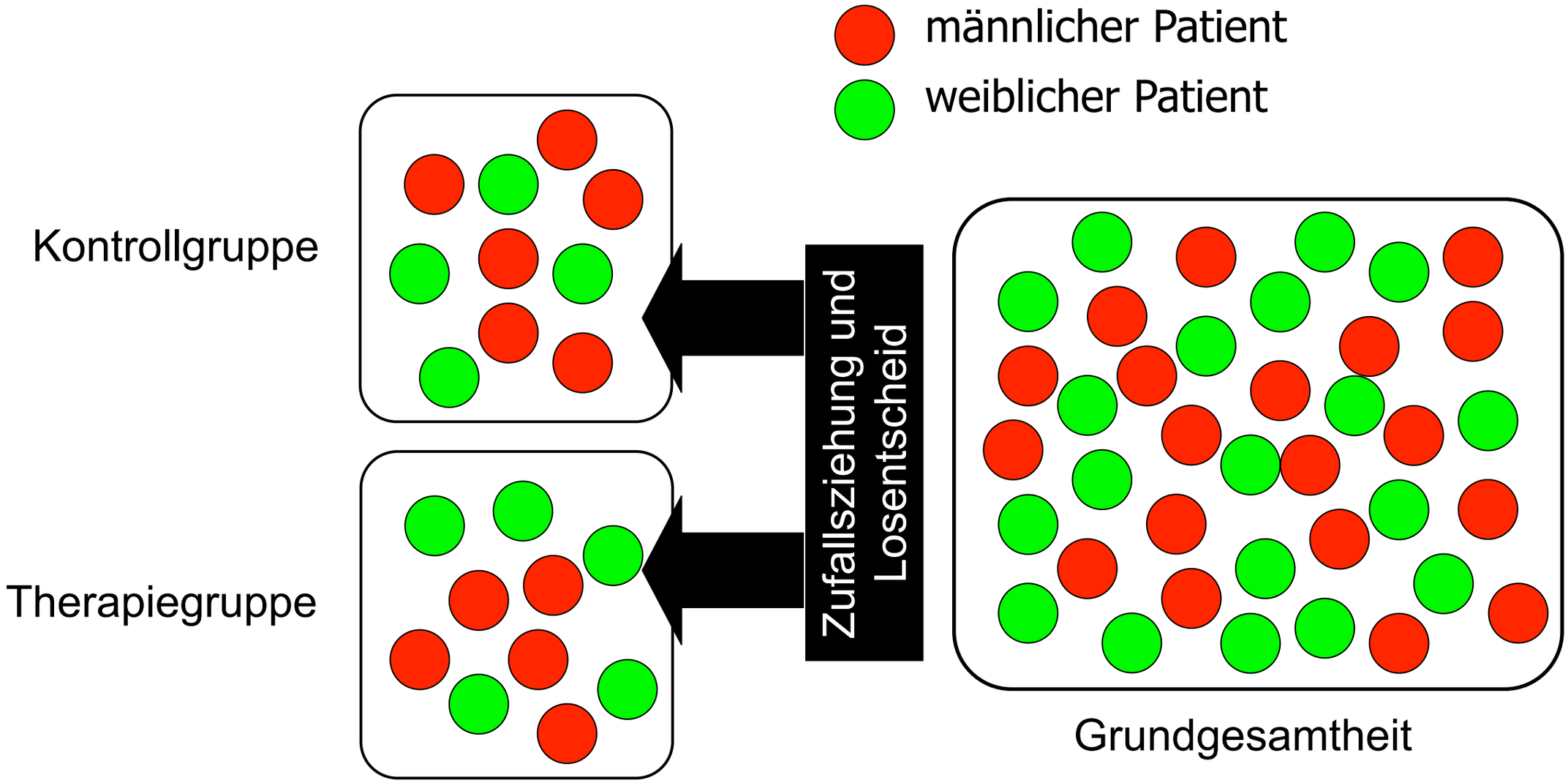
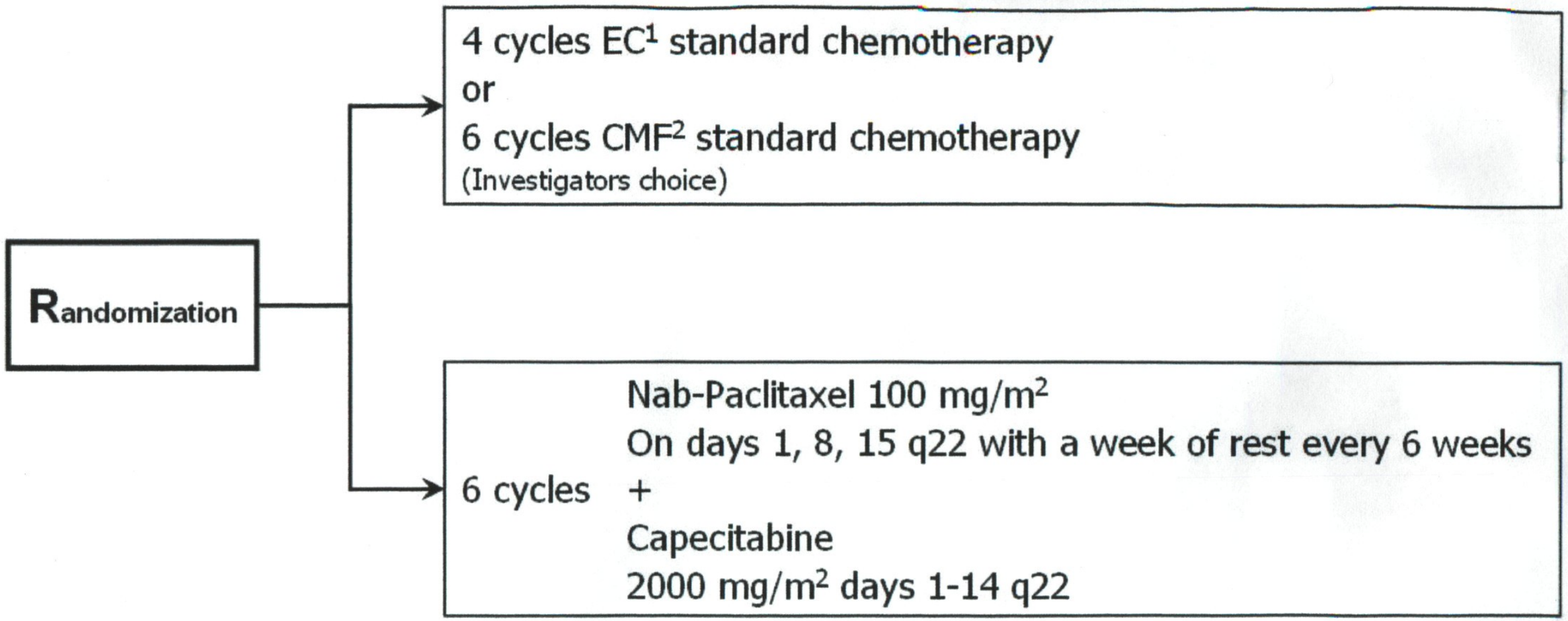
Randomisierung





Ein- & Ausschlusskriterien

Patienten mit lokal fortgeschrittenem und/oder metastasiertem Nierenzellkarzinom

Nicht vorbehandelt

oder nach Zytokinversagen

Überwiegend klarzellige Histologie

ECOG Performance Status 0/1

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Endpunkte

- Primärer Endpunkt:

  Progressionsfreies Überleben (PFS)

- Sekundäre Endpunkte:

  Gesamtüberleben (OS)

  Gesamtansprechrate (ORR)

  Ansprechdauer

  Sicherheit

  gesundheitsbezogene Lebensqualität (HRQoL)

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Isch habe fertisch

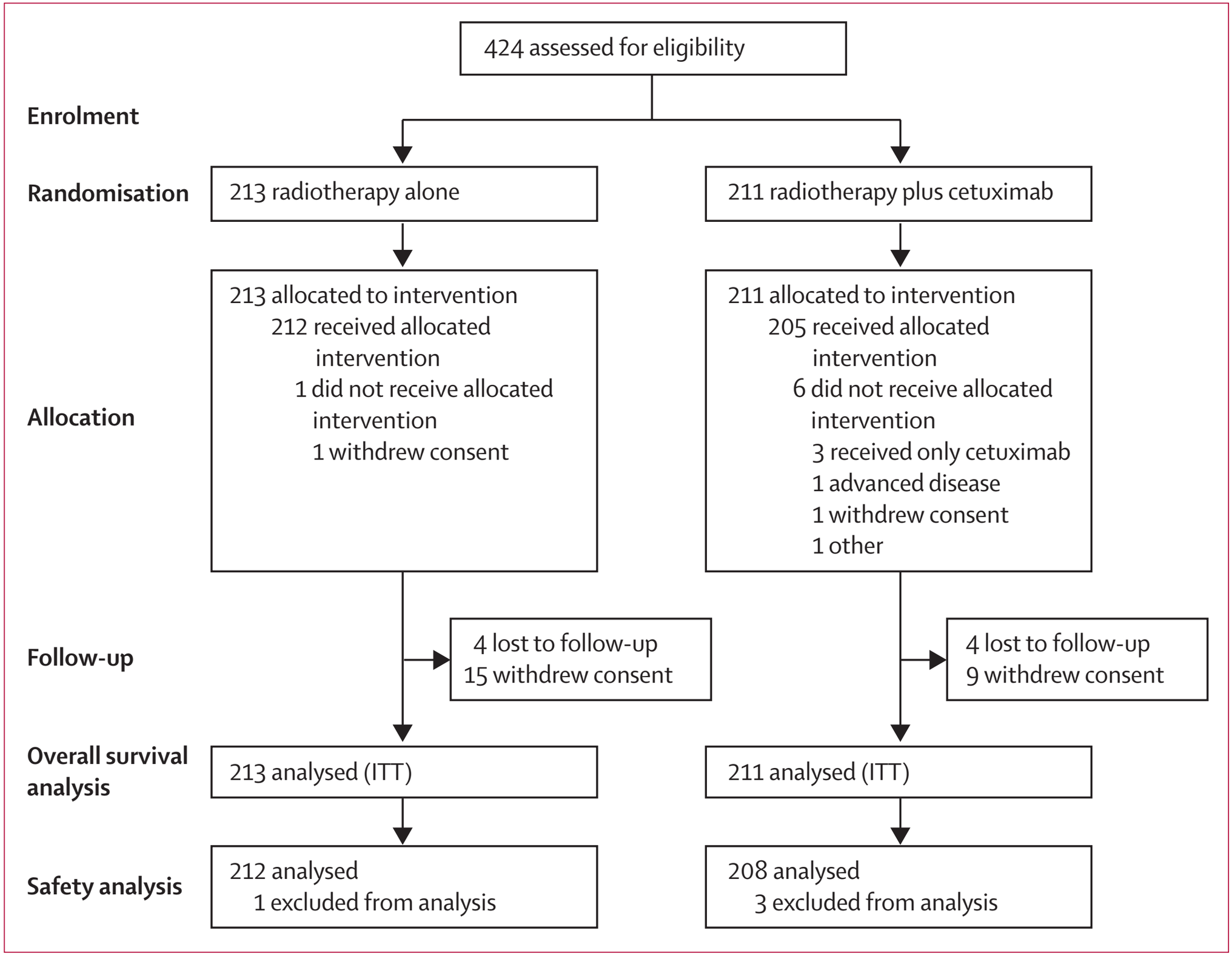

Figure 1: **Trial profile**

	Radiotherapy (N=213)	Radiotherapy plus cetuximab (N=211)
Age (years; median [range])	58 (35–83)	56 (34–81)
Sex (male/female)	169 (79)/44 (21)	171 (81)/40 (19)
KPS (90–100/60–80/unknown)	141/71/1 (66/33/1)	147/63/1 (69/30/1)
N stage (N0/N+)	41/172 (19/81)	43/168 (20/80)
T stage (T1–3/T4)	153/60 (72/28)	152/59 (72/28)
Radiotherapy fractionation		
Concomitant boost	119 (56)	118 (56)
Once a day	57 (27)	54 (26)
Twice a day	37 (17)	39 (18)
Primary tumour site		
Oropharynx	135 (63)	118 (56)
Hypopharynx	27 (13)	36 (17)
Larynx	51 (24)	57 (27)
AJCC (stage III/IV)	51/161 (24/76)	55/156 (26/74)
EGFR status		
Detectable	170 (80)	166 (79)
Non-detectable	3 (1)	0
Unknown	40 (19)	45 (21)
Neck dissection	53 (25)	51 (25)
Salvage surgery	25 (12)	29 (14)
Secondary radiation	12 (6)	13 (6)
Secondary chemotherapy	44 (21)	37 (18)

Data are n (%). KPS=Karnofsky performance score. AJCC=American Joint Committee on Cancer. EGFR=epidermal growth factor receptor.

Table 1: **Patient and tumour characteristics**

Ergebnis ?

CR, PR, RR ...

The median TTP was 4.9 months (95% CI: 3.9-5.9 months). Objective responses (RECIST) were:

CR - 1 (2.0%)
PR - 16 (32.7%)
RR - 17 (34.7%)
SD - 25 (51.0%)
PD - 7 (14.3%)

The median OS was 8.1 months (95% CI: 7.2-9.0 months).

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Ergebnis ?

CR, PR, RR ...

The median TTP was 4.9 months (95% CI: 3.9-5.9 months). Objective responses (RECIST) were:

CR - 1 (2.0%) *complete response*
PR - 16 (32.7%) *partial response*
RR - 17 (34.7%) *response rate (CR + PR)*
SD - 25 (51.0%) *stable disease*
PD - 7 (14.3%) *progressive disease*

The median OS was 8.1 months (95% CI: 7.2-9.0 months).

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teuer ?

	Radiotherapy (N=212)			Radiotherapy plus cetuximab (N=208)		
	All grades	Grade 3/4	Grade 4	All grades	Grade 3/4	Grade 4
Skin reaction*	200 (94·3%)	45 (21·2%)	3 (1·4%)	204 (98·1%)	73 (35·1%)‖	4 (1·9%)
Mucositis/stomatitis†	199 (93·9%)	110 (51·9%)	9 (4·2%)	194 (93·3%)	116 (55·8%)	13 (6·3%)
Dysphagia	134 (63·2%)	63 (29·7%)	3 (1·4%)	136 (65·4%)	54 (26·0%)	1 (0·5%)
Xerostomia‡	150 (70·8%)	6 (2·8%)	0 (0%)	150 (72·1%)	10 (4·8%)	0 (0%)
Acneiform rash§	21 (9·9%)	3 (1·4%)	0 (0%)	174 (83·7%)‖	35(16·8%)‖	1 (0·5%)
Infusion reaction¶	4 (1·9%)	0 (0%)	0 (0%)	32 (15·4%)‖	6 (2·9%)‖	2 (1·0%)

*Skin reaction includes all Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) terms in the Skin and Appendages body system. †Mucositis/stomatitis includes COSTART terms aphthous stomatitis; gingivitis; glossitis; mouth ulceration; mucous membrane disorder; stomatitis; and ulcerative stomatitis. ‡Xerostomia is COSTART term dry mouth. §Acneiform rash includes COSTART terms acne; rash; maculopapular rash; exfoliative dermatitis. ¶Infusion reaction includes COSTART terms allergic reaction; anaphylactoid reaction; and/or fever; chills; or dyspnoea on the first day of treatment. ‖Statistically significant ($p<0·05$) difference between the treatment groups; Fisher's exact test.

Table 2: **Most common adverse events**

Hazard-Ratio

	Radiotherapy alone		Radiotherapy plus cetuximab	
	N	Events	N	Events
Site of primary tumour				
Oropharynx	135	76	118	50
Larynx	51	32	57	31
Hypopharynx	27	22	36	29
Tumour stage				
AJCC T4	65	47	62	47
AJCC T1–3	148	83	149	63
Region				
USA	122	66	136	53
Other	91	64	75	57
Radiotherapy fractionation				
Twice daily	37	20	38	16
Once daily	55	35	50	37
Concomitant boost	120	75	117	53
Overall stage				
AJCC IV	161	101	156	84
AJCC II–III	52	29	55	26
Nodal stage				
AJCC N1–3	175	109	169	86
AJCC N0	38	21	42	24
KPS				
90–100	141	76	148	58
60–80	72	54	63	52
Sex				
Male	169	106	171	87
Female	44	34	40	23
EGFR-positive cells				
>50%	81	50	75	45
≤50%	92	57	91	45
Unknown	40	23	45	20
Age (years)				
≥65	65	43	45	35
<65	148	87	166	75

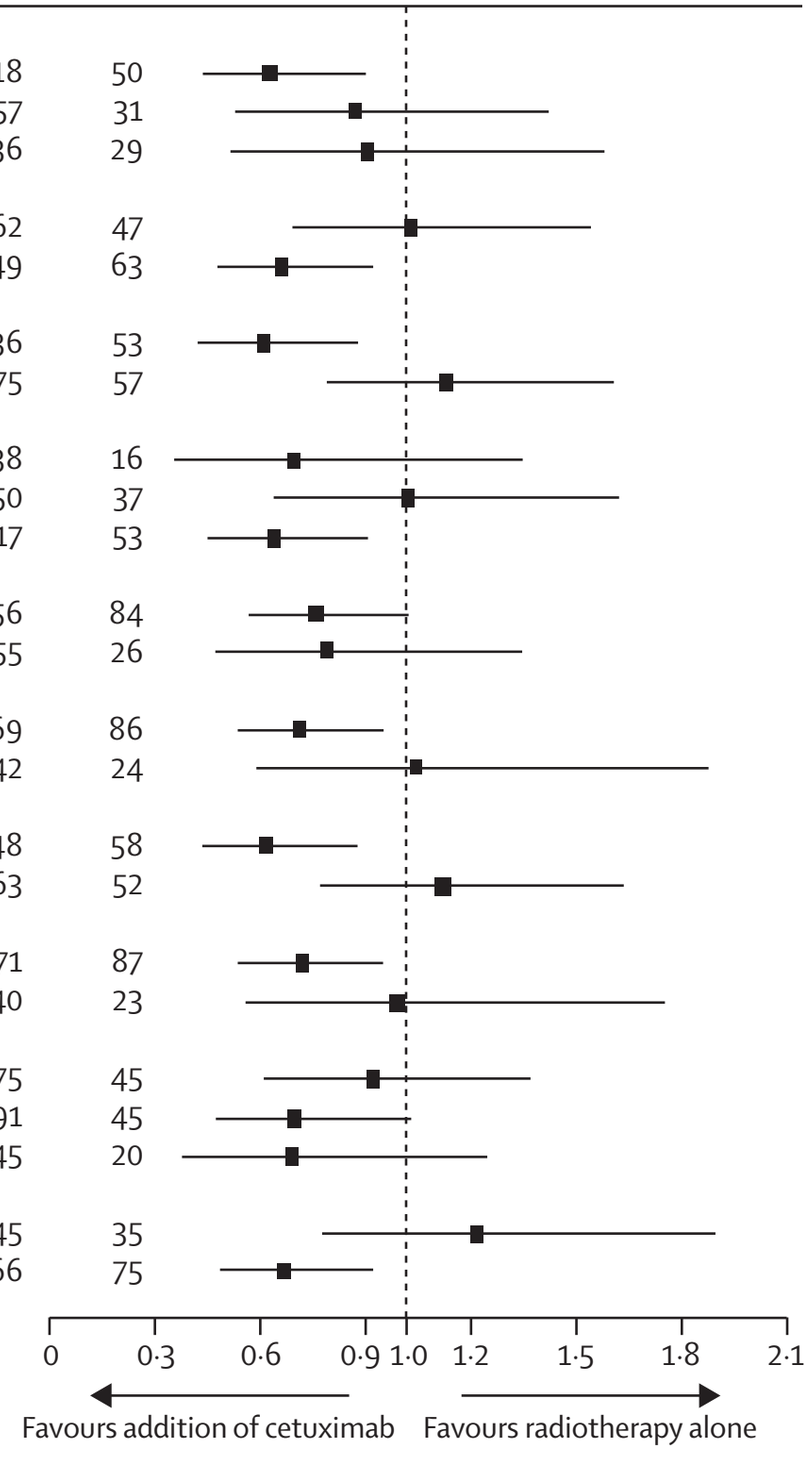


Figure 3: **Overall survival by pre-treatment characteristics: 5-year update**
AJCC=American Joint Committee on Cancer. KPS=Karnofsky performance score. EGFR=epidermal growth factor receptor.

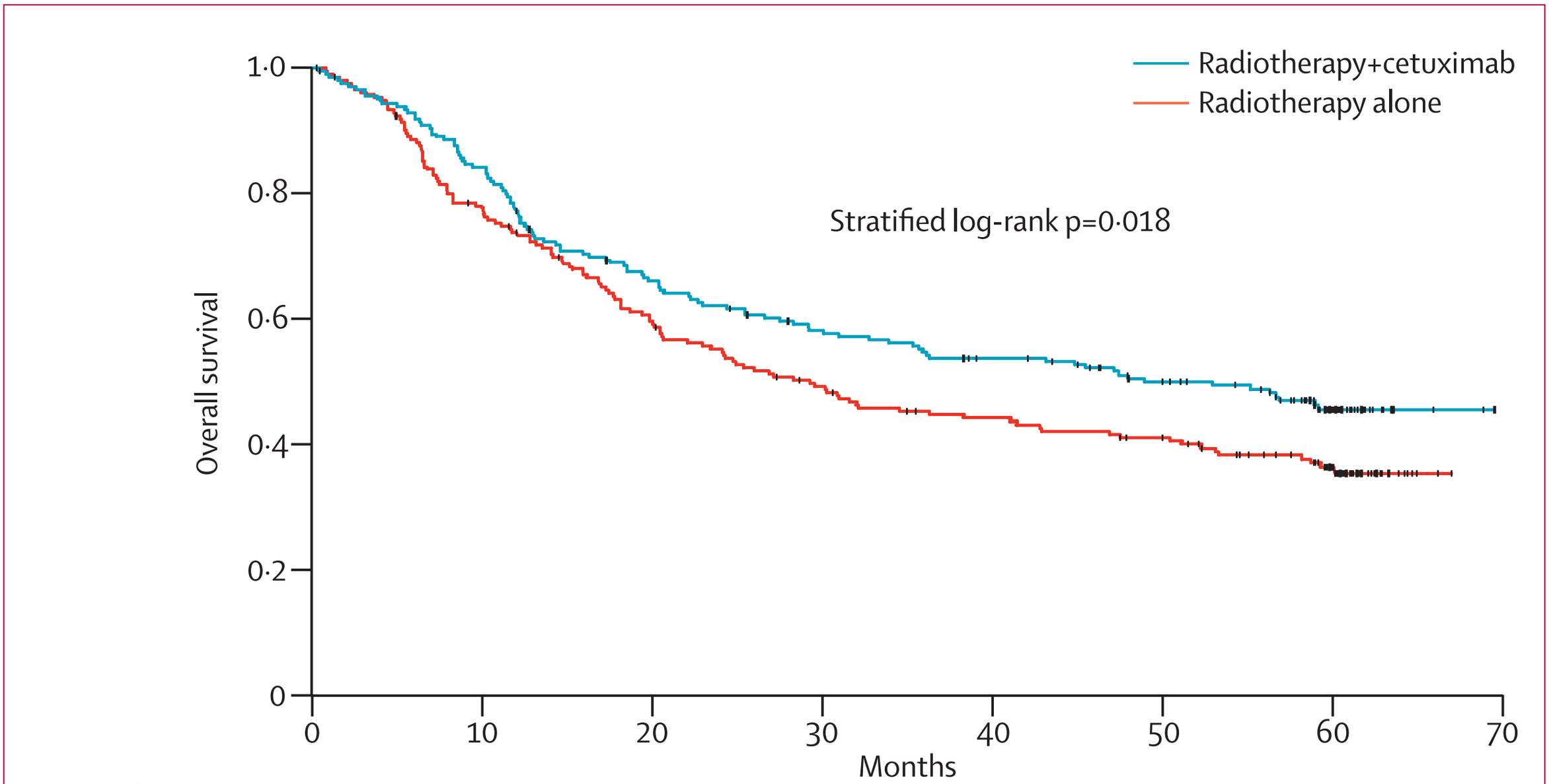
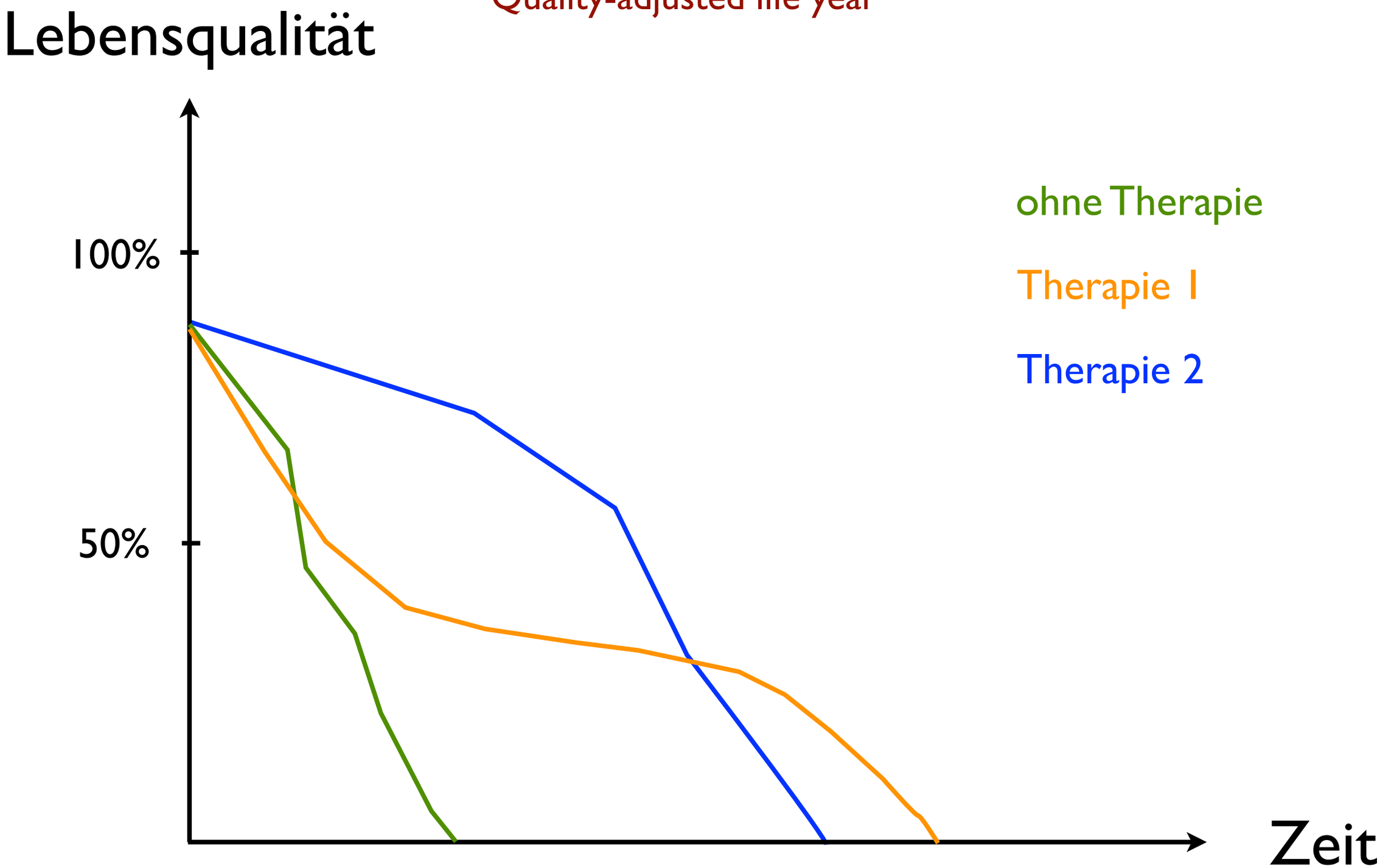


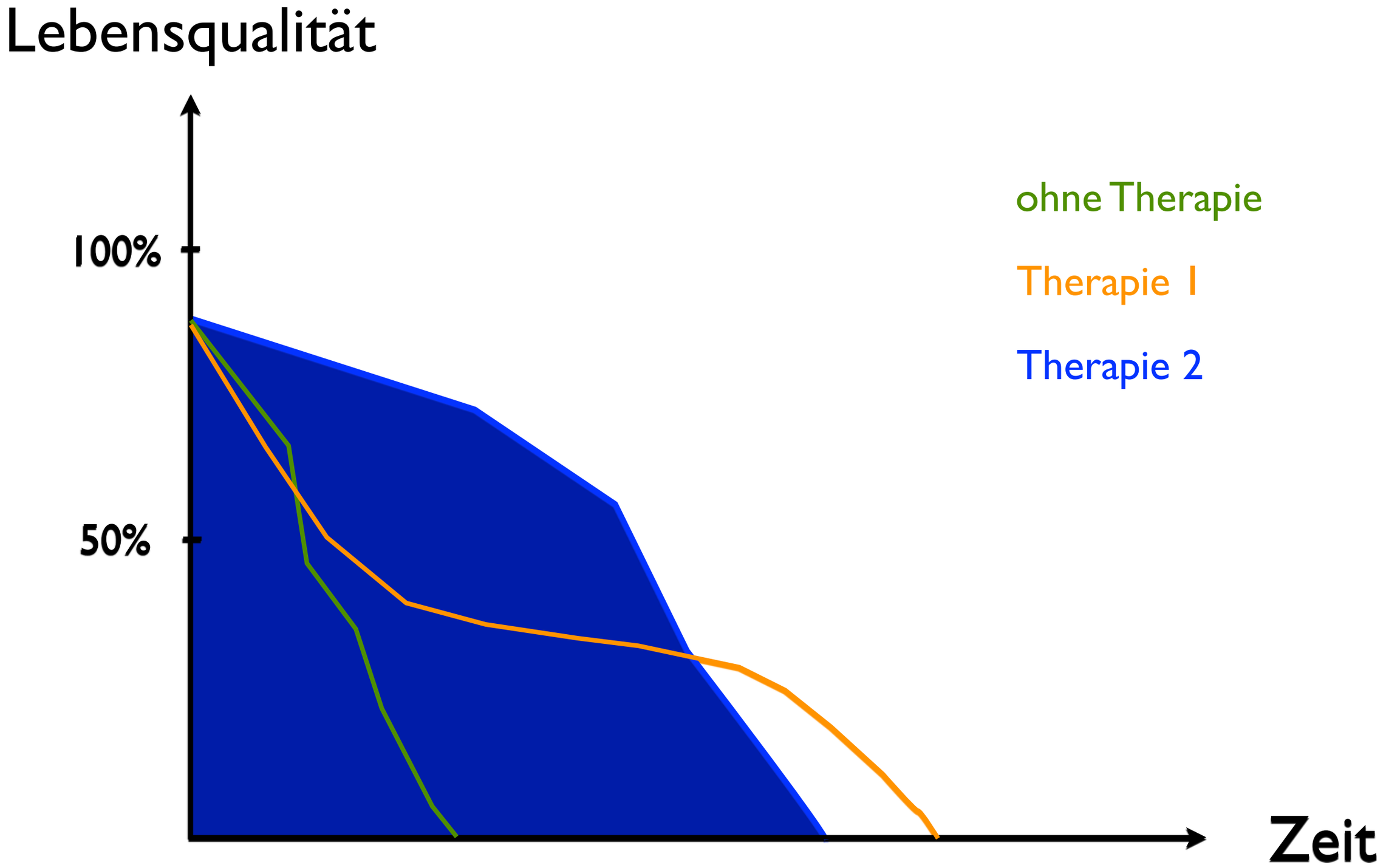
Figure 2: **Overall survival by treatment: 5-year update (median follow-up 60 months)**

QALY

Qualitätskorrigiertes Lebensjahr
Quality-adjusted life year



QALY


Lebensqualität
100%
50%
Zeit
ohne Therapie
Therapie 1
Therapie 2

QALY

Lebensqualität

Phase IV

- 1000 bis Millionen Patienten
- Erfolgen mit bereits zugelassenen Medikamenten in der zugelassenen Indikation.
- Zulassungsbehörden verlangen oftmals derartige Studien, z. B. zur Feststellung sehr seltener Nebenwirkungen, die erst in großen Patientenkollektiven erkennbar sind.

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Phase IV

- Anwendungsbeobachtung (AWB)
- Nicht-Interventionelle Studie (NIS)
- Registerstudien

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Niedergelassene Onkologen

- Anwendungsbeobachtung (AWB)
- Nicht-Interventionelle Studie (NIS)
- Registerstudien
- **Phase III - Studien**
- **Phase II - Studien**

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besten dank &

Prüfung

- Randomisierung
- P-Value
- PFS
- OS
- RR
- Hazard Ratio
- QALY

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