UNIVERSITÄT LEIPZIG
MEDIZINISCHE FAKULTÄT

10. Prague ONCO
ONCOLOGY COOPERATION

ESOPHAGEAL CANCER

Standards and Novel Directions in Multimodal Treatment

Professor Florian Lordick

University Cancer Center Leipzig, Germany

Prague, 24 January 2019

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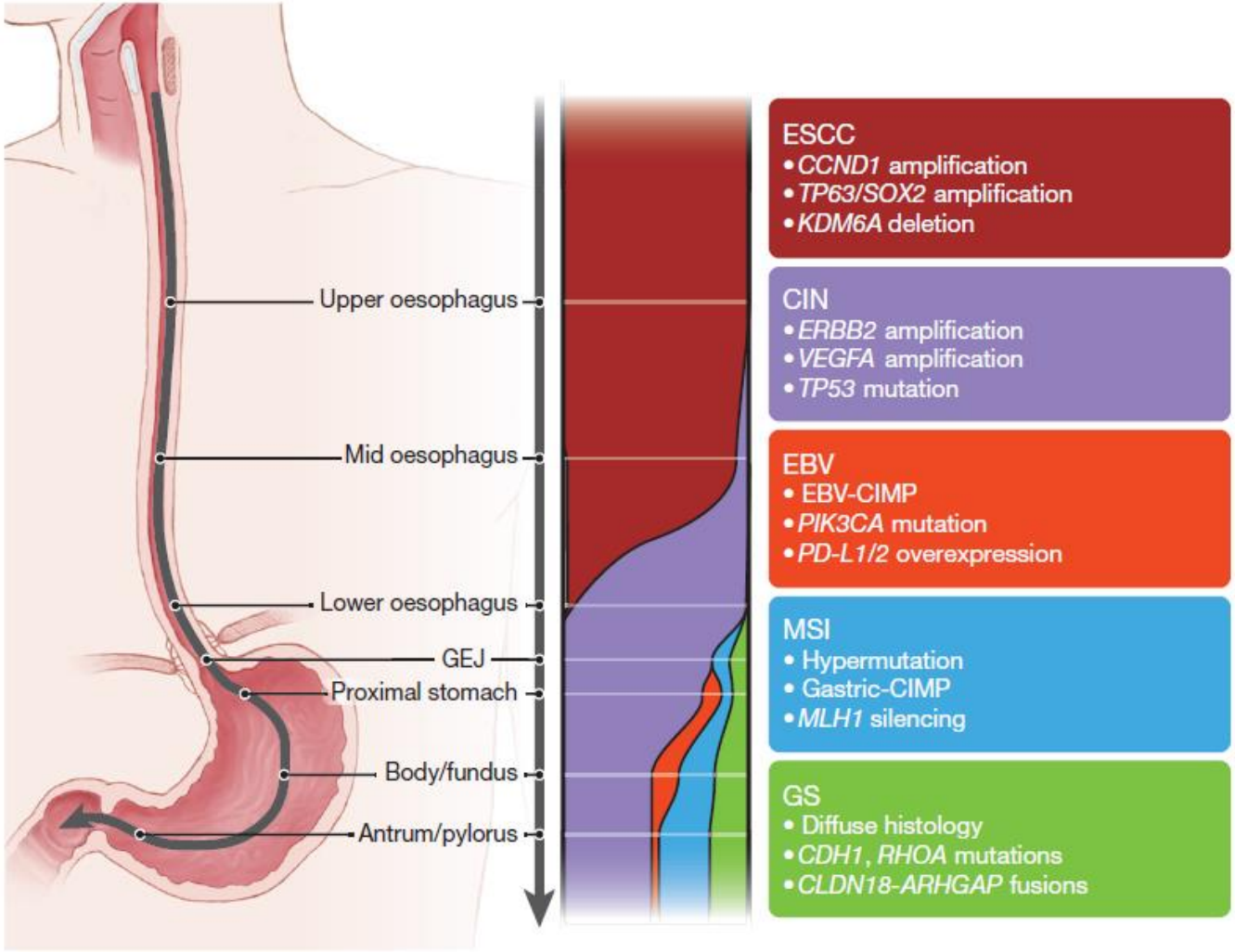
EPIDEMIOLOGY

- **Incidence** — **Seventh worldwide: 572,000 new cases / year**
- **Mortality** — **Sixth worldwide: 509,000 deaths / year**
  signifying that esophageal cancer will be responsible for an estimated 1 in every 20 cancer deaths in 2018
- **Gender** — 70% of cases occur in men
- **Histology** — **Squamous cell carcinoma**
  Adenocarcinoma
  Others <5% (small cell cancer, neuroendocrine, sarcoma,…)
- **Nota bene** — **Marked differences around the world!**
  Increasing frequency of adenocarcinoma in the West
  Squamous cell cancer still leading in Asia & Africa

Bray F, et al. *CA CANCER J CLIN* 2018; 0: 1–31

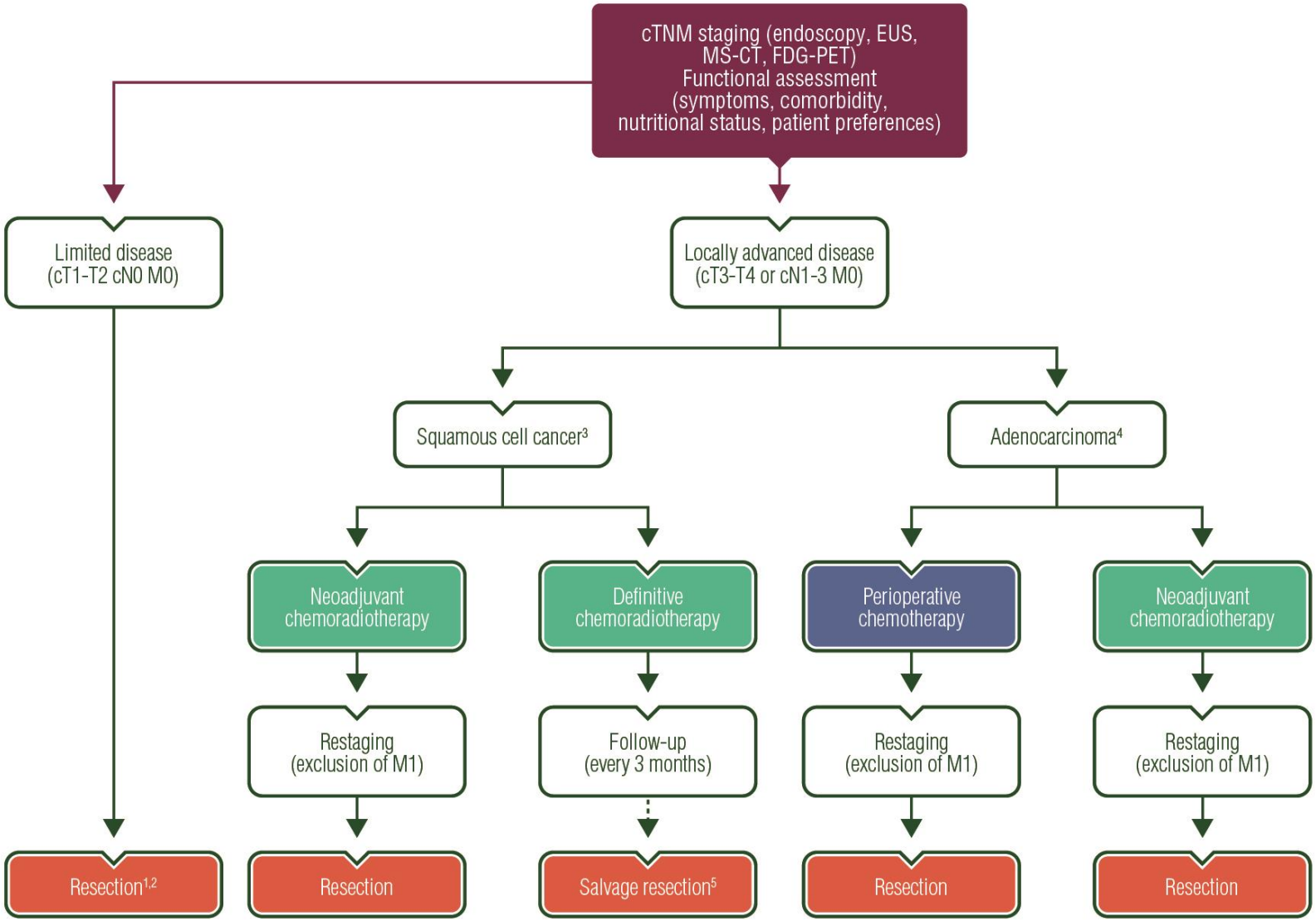
BIOLOGY



Molecular subclasses of gastroesophageal carcinoma

The Cancer Genome Atlas Research Network. *Nature.* 2017;541:169-175

ESMO TREATMENT GUIDELINES



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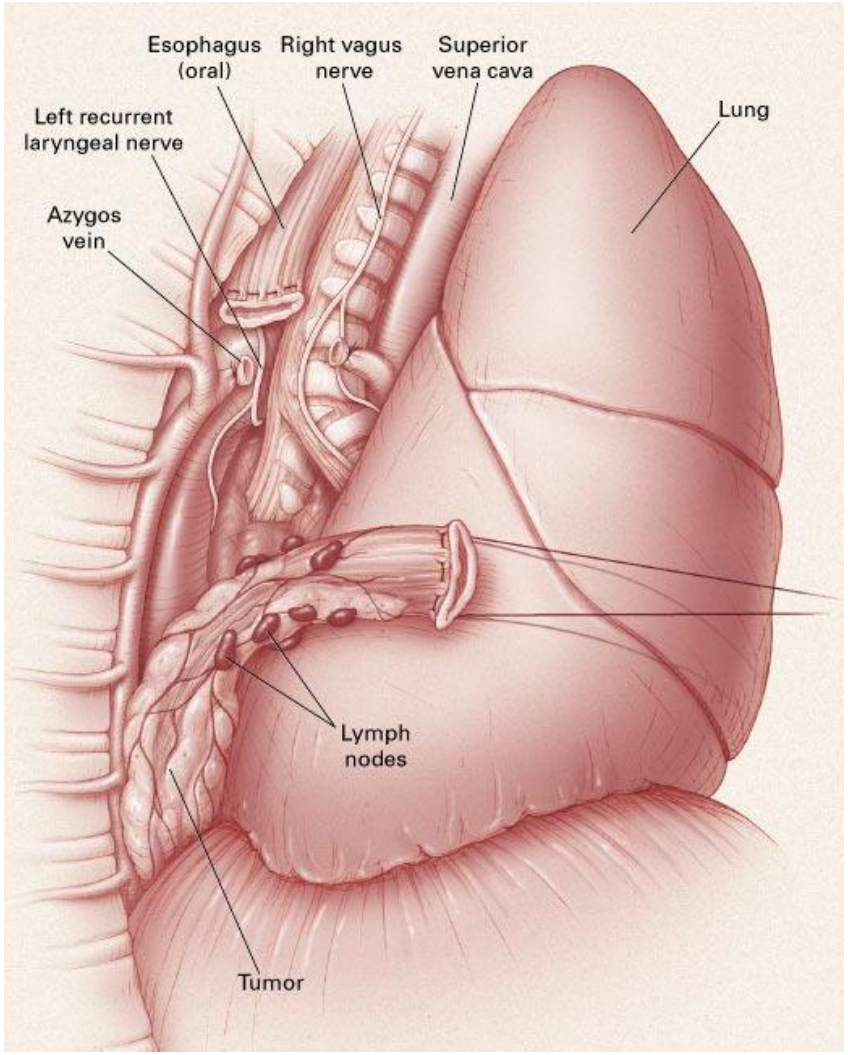
Lordick F et al. *Ann Oncol* 2016 Sep;27(suppl 5):v50-v57

SURGICAL TREATMENT



Oesophagectomy
Open transthoracic
or minimally invasive

Minimally invasive esophagectomy

Hybrid

Ivor Lewis (laparoscopy + thoracotomy)

Total

Ivor Lewis (laparoscopy + thoracoscopy)

Hulscher JBF et al. *N Engl J Med* 2002; 347:1662-9

MINIMALLY INVASIVE VS. OPEN ESOPHAGECTOMY

The NEW ENGLAND JOURNAL of MEDICINE

Hybrid Minimally Invasive Esophagectomy for Esophageal Cancer

C. Mariette,* S.R. Markar, T.S. Dabakuyo-Yonli, B. Meunier, D. Pezet, D. Collet, X.B. D'Journo, C. Brigand, T. Perniceni, N. Carrère, J.-Y. Mabrut, S. Msika, F. Peschaud, M. Prudhomme, F. Bonnetain,* and G. Piessen, for the Fédération de Recherche en Chirurgie (FRENCH) and French Eso-Gastric Tumors (FREGAT) Working Group†

End Points	Total Trial Population (N=207)	Hybrid Minimally Invasive Esophagectomy (N=103)	Open Esophagectomy (N=104)
Primary end point			
Major complication at 30 days — no. (%)	104 (50)	37 (36)	67 (64)
Secondary end points			
Postoperative death — no. (%)			
At 30 days	3 (1)	1 (1)	2 (2)
At 90 days	10 (5)	4 (4)	6 (6)
Major pulmonary complication at 30 days — no./total no. (%)†	49/205 (24)	18/102 (18)	31/103 (30)

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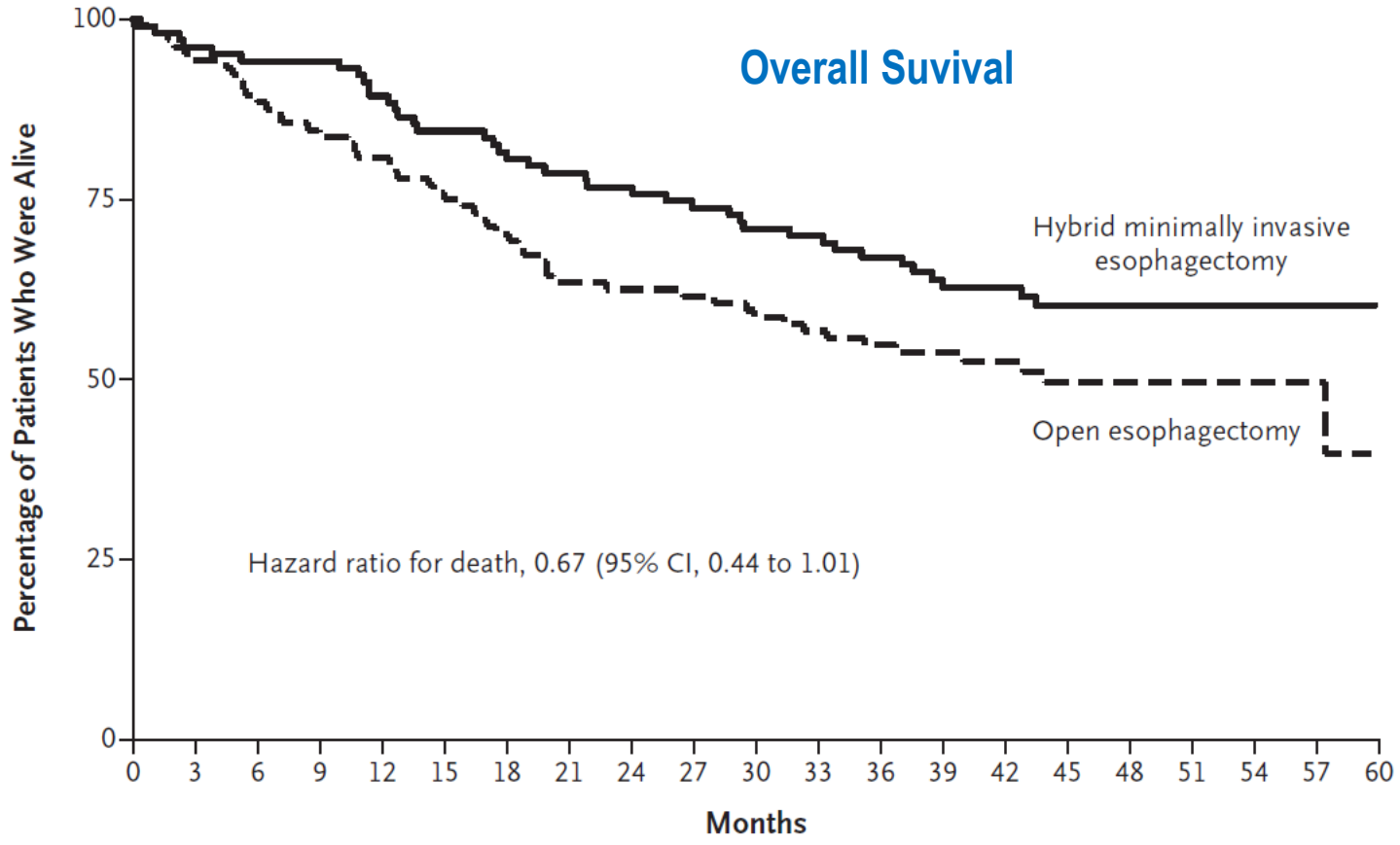
Mariette C et al. *N Engl J Med* 2019; 380:152-62

MINIMALLY INVASIVE VS. OPEN ESOPHAGECTOMY



No. at Risk

Hybrid minimally invasive esophagectomy	103	99	97	97	92	87	84	81	79	76	73	72	69	58	54	43	37	33	27	20	7
Open esophagectomy	104	98	93	87	84	79	73	66	65	64	61	59	57	48	40	33	22	17	13	5	1

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Mariette C et al. *N Engl J Med* 2019; 380:152-62

THE NEOADJUVANT PARADIGM

ADJUVANT

SURG | AC | AC

SURG: Surgery

AC: Adjuvant Chemotherapy

OR CRTX

CRTX: Chemoradiotherapy

NEOADJUVANT

Neo-C: Neoad. Chemotherapy

Neo-C | Neo-C | SURG

OR CRTX | SURG

CRTX: Chemoradiotherapy

SURG: Surgery

Arguments for neoadjuvant

- Tumor shrinkage → R0
- Treat occult met‘s early
- Better tolerability
- Response assessment
- Positive study data

NEOADJUVANT CHEMORADIOTHERAPY

CROSS - Study

N=363

T1N1M0
or
T2–3N0–1M0

AC*
SCC**

R A N D O M

Neoadjuvant R-CTX. 41,4 Gy:
Carbo AUC2 + Paclitaxel 50mg/m² weekly
RESECTION

Primary Endpoint: Overall Survival

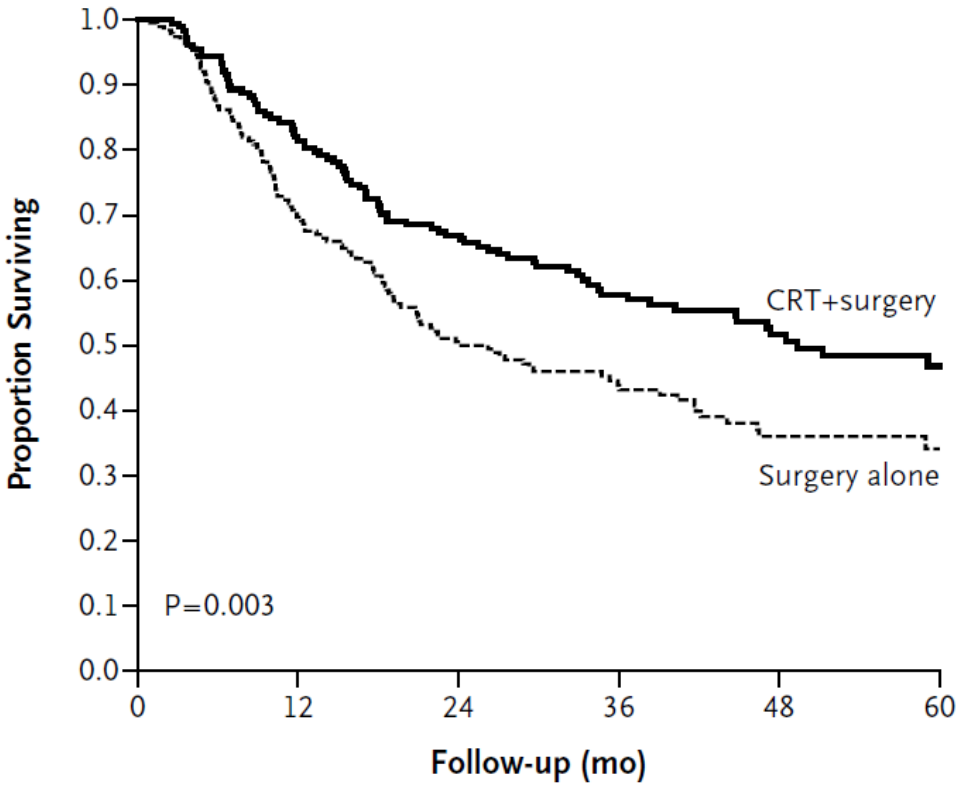
RESECTION

*AC: Adenocarcinoma
**SCC: Squamous Cell Carcinoma

Van Hagen et al. *N Engl J Med* 2012; 366: 2074-2084
Shapiro J et al., *Lancet Oncol* 2015; 16: 1090–98

NEOADJUVANT CHEMORADIOTHERAPY

CROSS Study: survival according to treatment group



No. at Risk						
CRT+surgery	178	145	119	75	49	28
Surgery alone	188	131	94	62	33	17
Total	366	276	213	137	82	45

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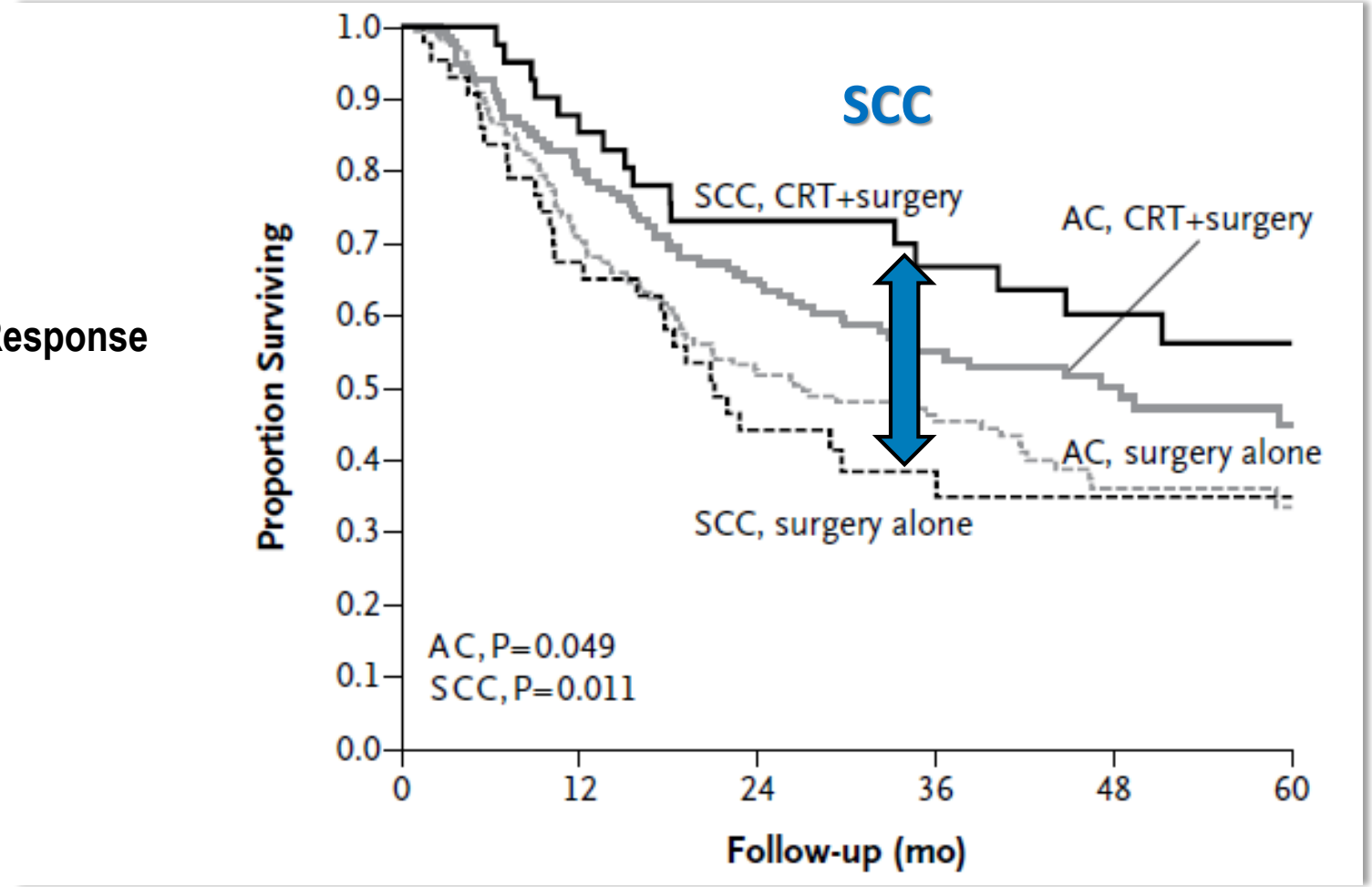
Van Hagen et al. *N Engl J Med* 2012; 366: 2074-2084
Shapiro J et al., *Lancet Oncol* 2015; 16: 1090–98

NEOADJUVANT CHEMORADIOTHERAPY

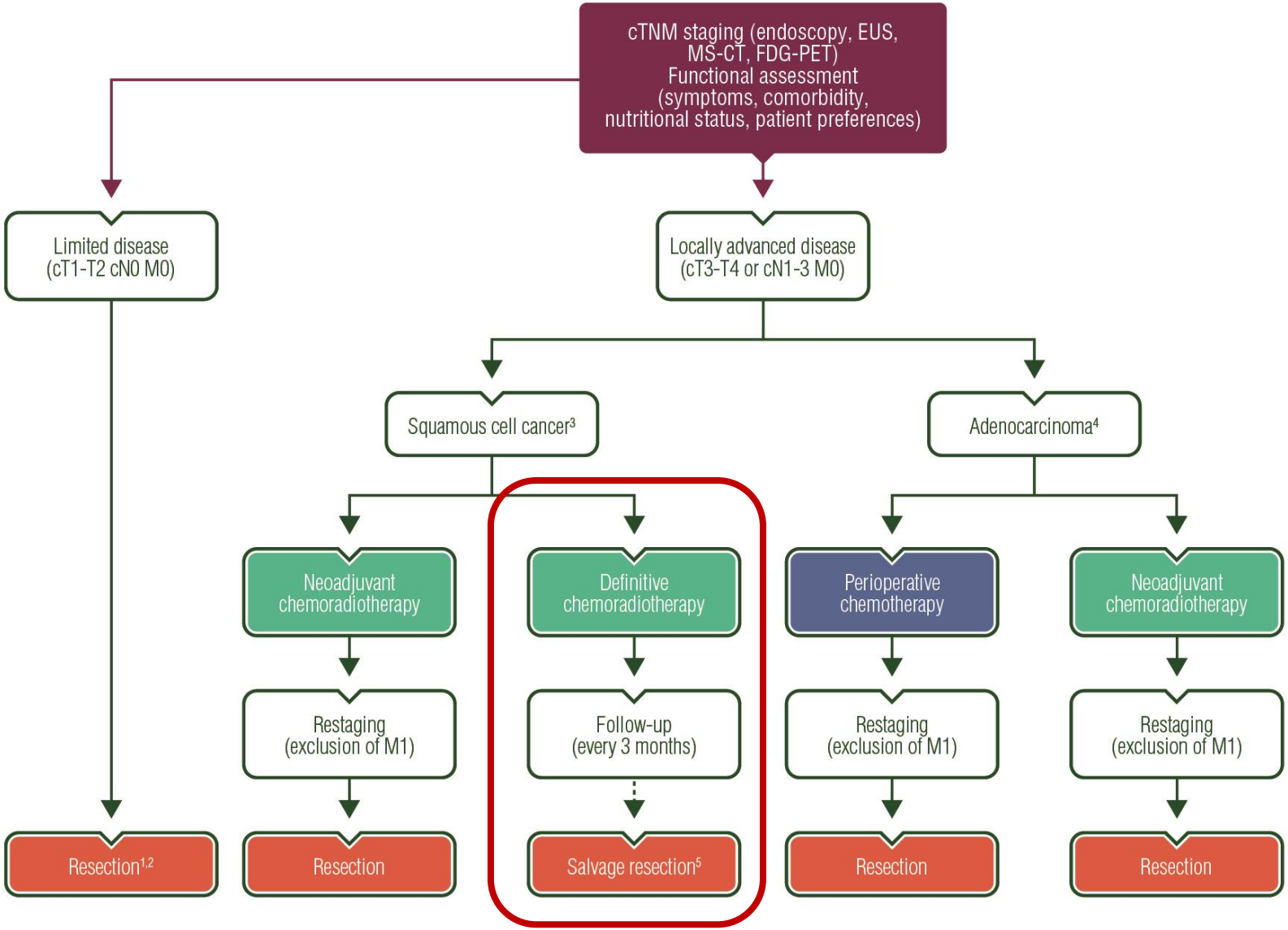
CROSS Study: big effect for Squamous Cell Cancer

Complete Response
(ypT0N0)
49%



Van Hagen et al. *N Engl J Med* 2012; 366: 2074-2084
Shapiro J et al., *Lancet Oncol* 2015; 16: 1090–98

SQUAMOUS CELL CANCER



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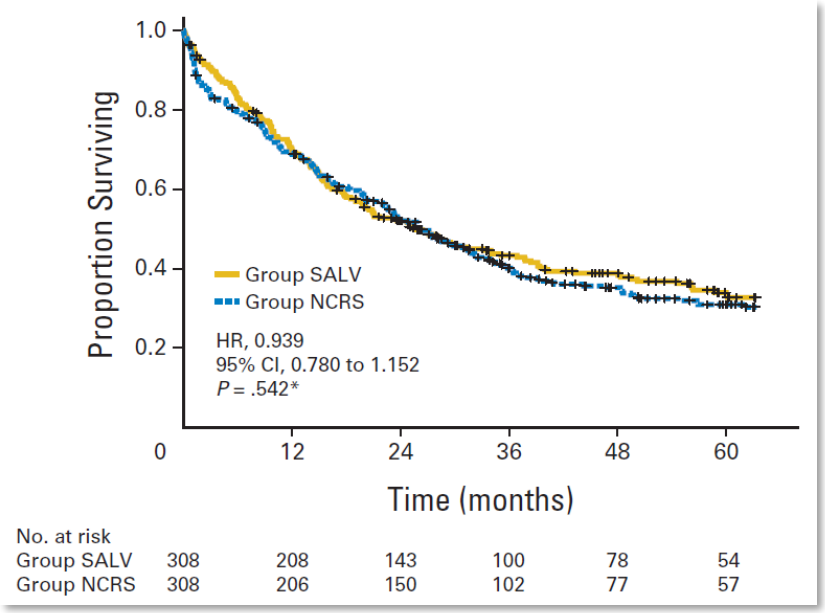
Lordick F et al. *Ann Oncol* 2016 Sep;27(suppl 5):v50-v57

SQUAMOUS CELL CANCER

Salvage Surgery compared to planned surgery (cohort registry study)



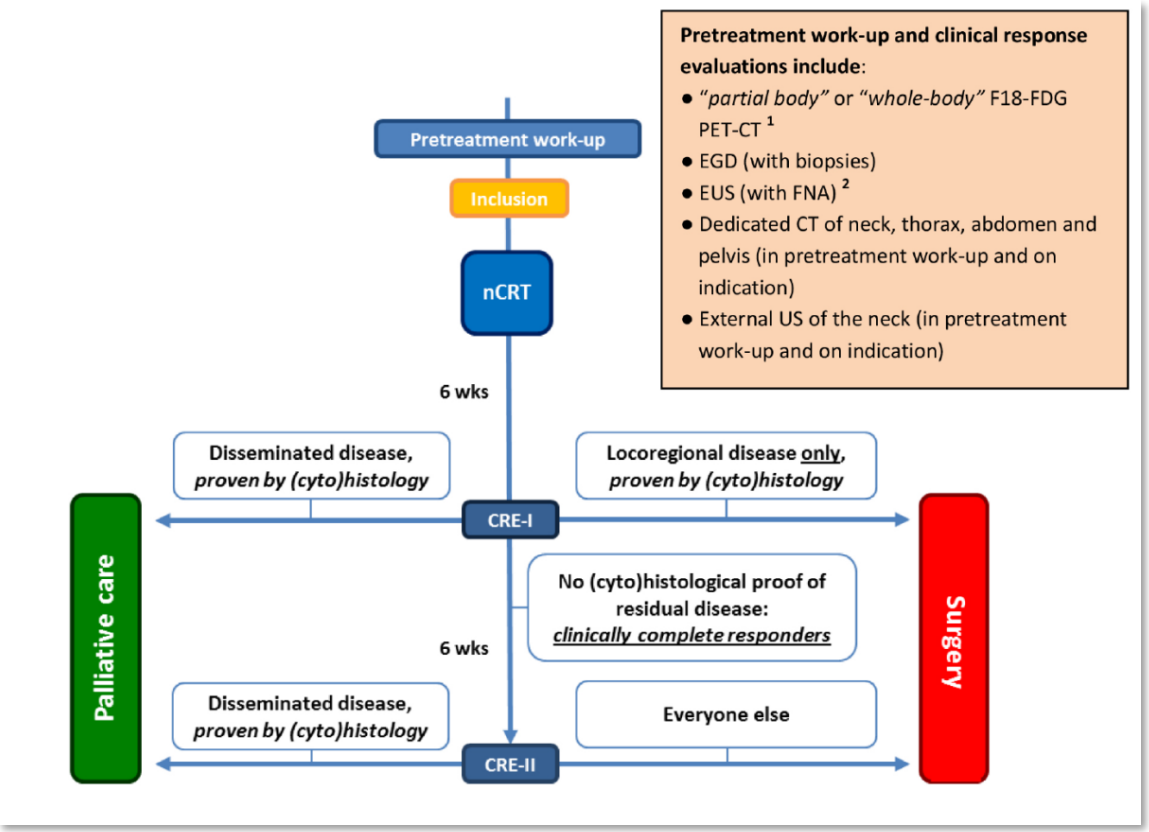
	SALV	NCRS	P-value
In-hospital mortality	8.4%	9.3%	
Anastomotic leak rate	17.2%	10.7%	0.007
3-y-OS	43.3%	40.1%	0.542
3-y-DFS	39.2%	32.8%	0.232

- High mortality (16% vs 6%) in low vs. high volume centers
- High mortality (28% vs 4%) after > 55Gy radiation dose

Markar S, et al. *J Clin Oncol* 2015; 33: 3866-3873

SALVAGE SURGERY

Pre-SANO trial



Selection of patients for a watch-and-wait strategy

- Endoscopy
- Bite-on-bite biopsy
- Endosonography
- Fine needle aspiration
- PET-CT

Clinical Response Evaluation
week 6 and week 12
to detect ypCR

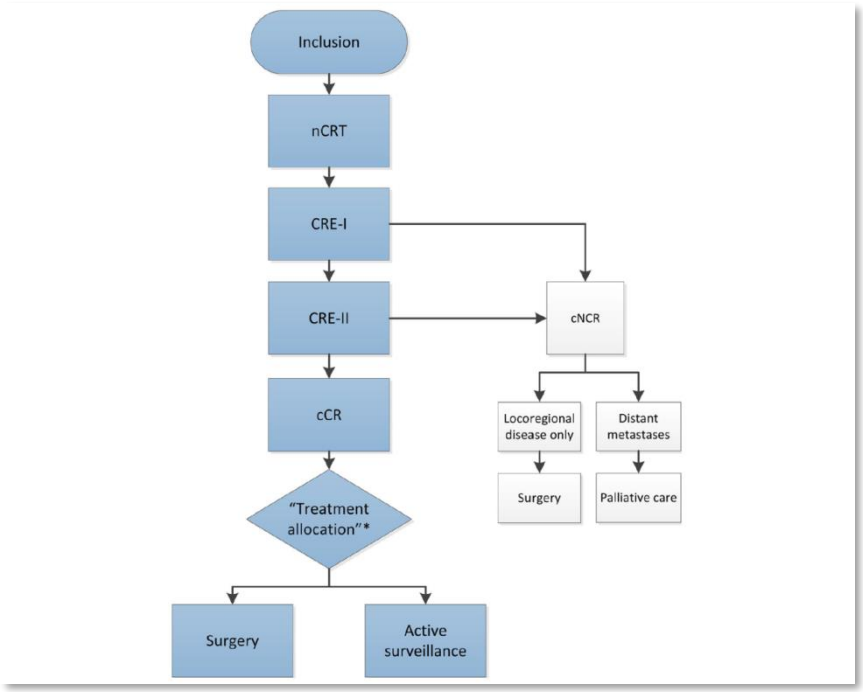
- Sensitivity 90%
- Specificity 72%

Noordman B, et al. *Lancet Oncol* 2018 Jul;19(7):965-974

SALVAGE SURGERY

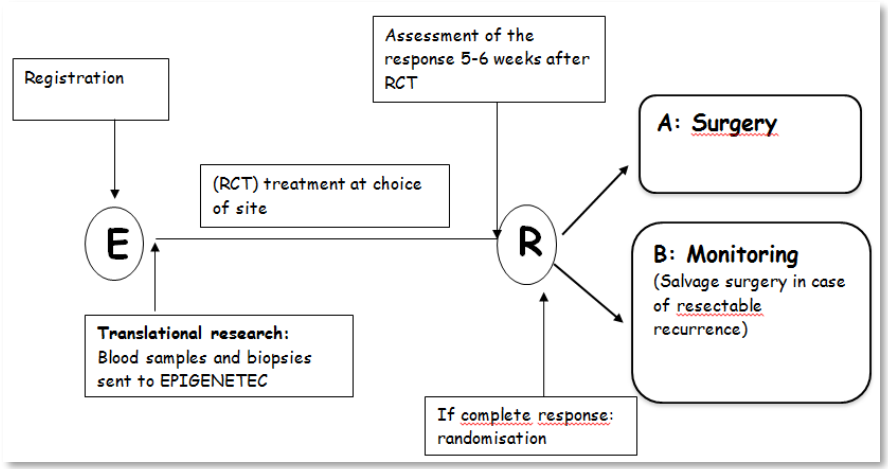
Ongoing Trials

NETHERLANDS SANO TRIAL



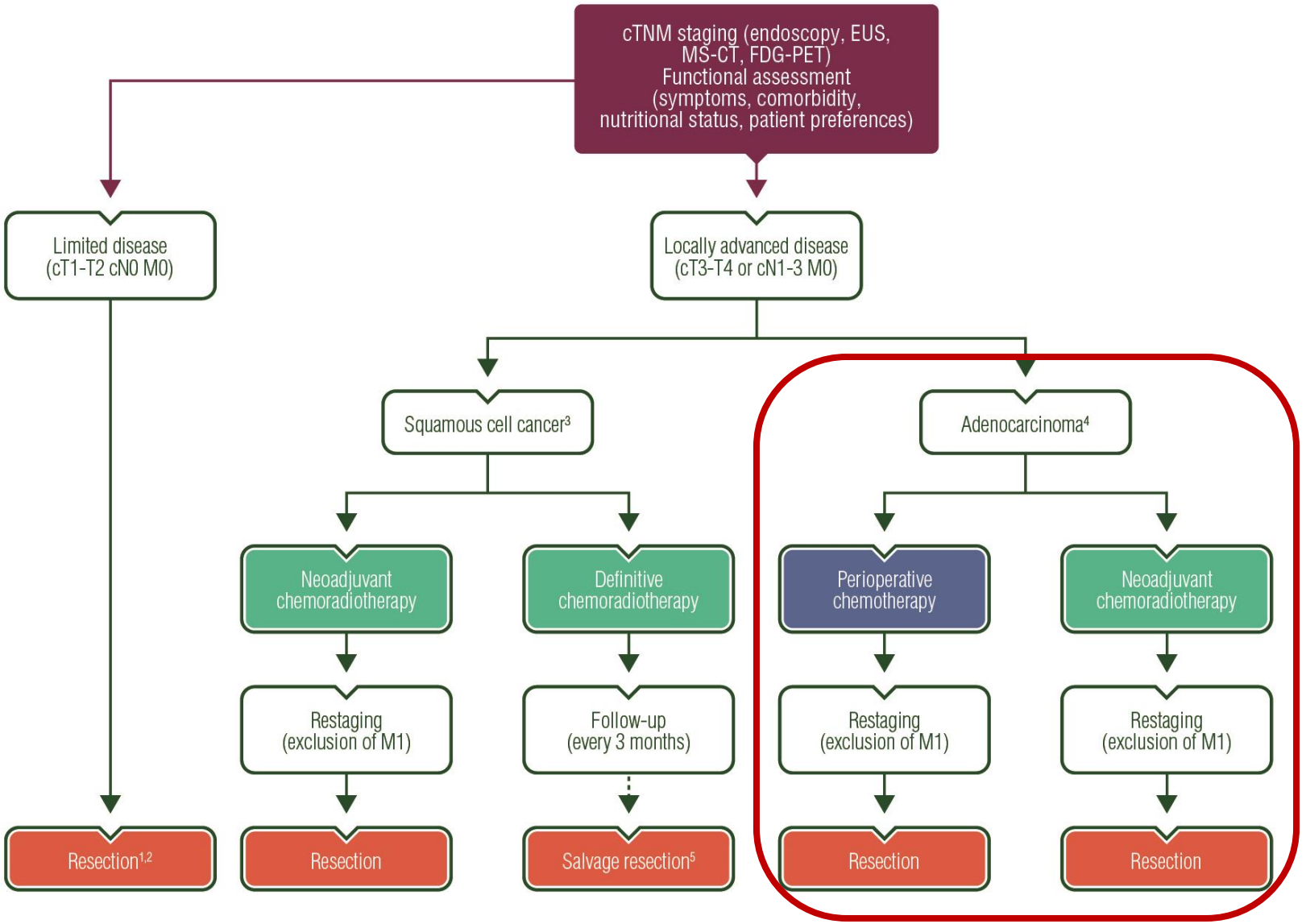
Noordman BJ, et al. *BMC Cancer.* 2018; 18:142

FRANCE ESOSTRATE



https://clinicaltrials.gov/ct2/show/NCT02551458

ESMO TREATMENT GUIDELINES



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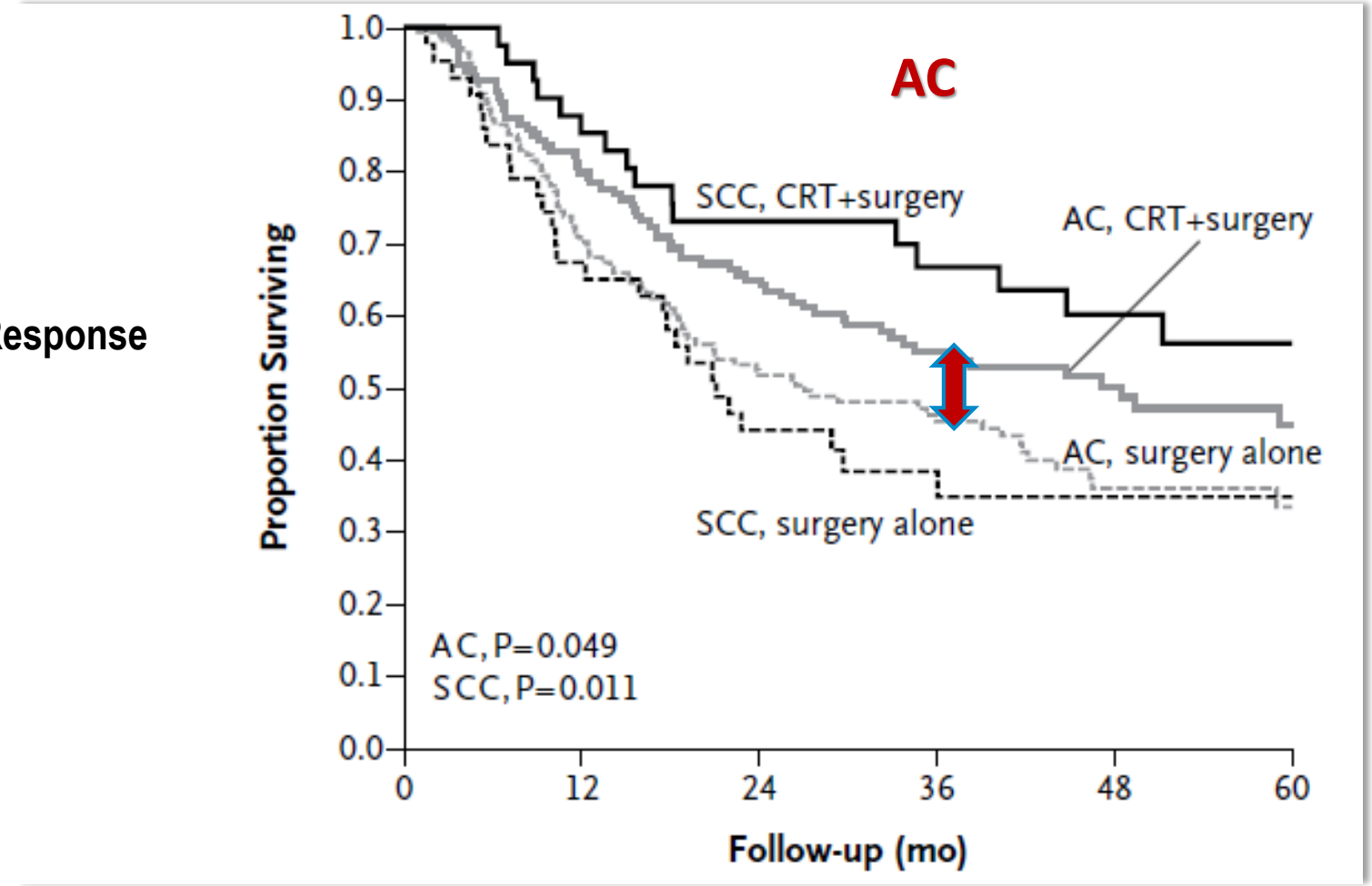
Lordick F et al. *Ann Oncol* 2016 Sep;27(suppl 5):v50-v57

ADENOCARCINOMA

Neoadjuvant Chemoradiotherapy plus Surgery: CROSS

Complete Response
(ypT0N0)
23%



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Van Hagen et al. *N Engl J Med* 2012; 366: 2074-2084
Shapiro J et al., *Lancet Oncol* 2015; 16: 1090–98

ADENOCARCINOMA

ESOPEC Study Ongoing (Germany)

N=438

T1N1M0
or
T2–4aN0–1M0

RANDOM

Perioperative CTX: FLOT* 4 x pre and post
RESECTION

Primary endpoint: survival
3-year-OS-rate
55% CROSS vs. 68% FLOT)

Neoadjuvant Radio-CTX – CROSS Regimen
RESECTION

*FLOT = 5-FU Leucovorin, Oxaliplatin, Docetaxel

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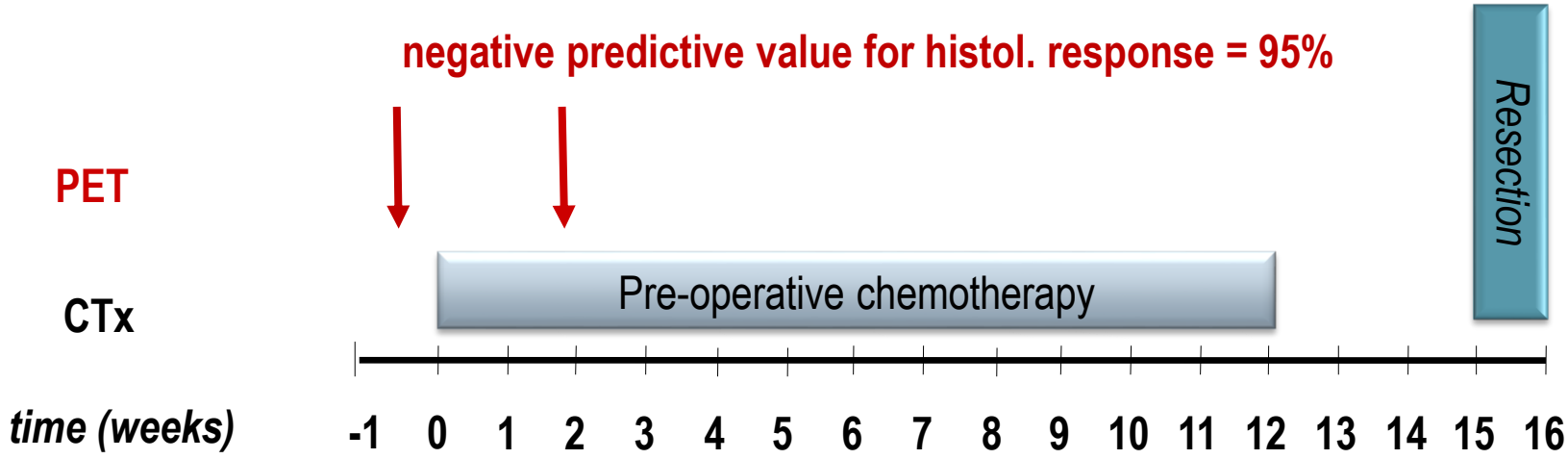
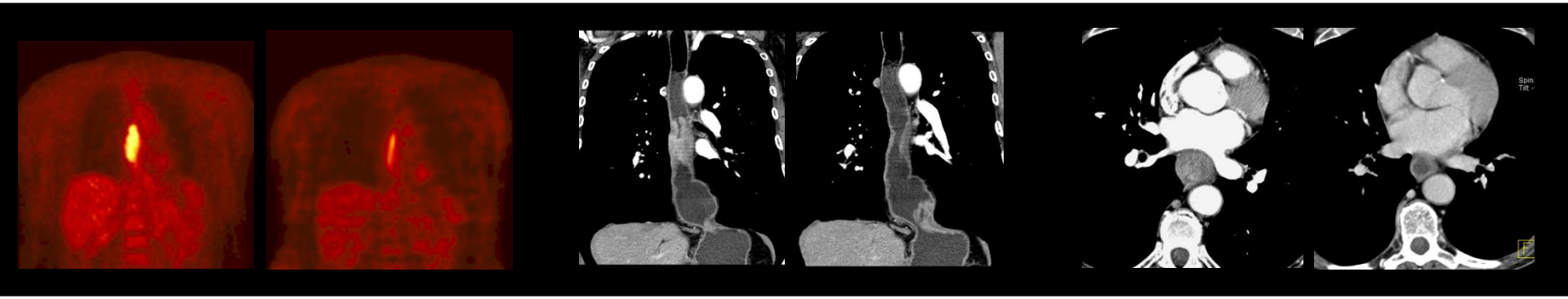
Hoeppner J, Lordick F. et al. *BMC Cancer* 2016; 16: 503

INDIVIDUALIZATION OF PERIOPERATIVE TREATMENT

Functional imaging for response prediction





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Lordick F. et al. *Eur J Cancer.* 2008 Sep;44(13):1807-19

FUNCTIONAL IMAGING FOR ESO-GASTRIC CANCER

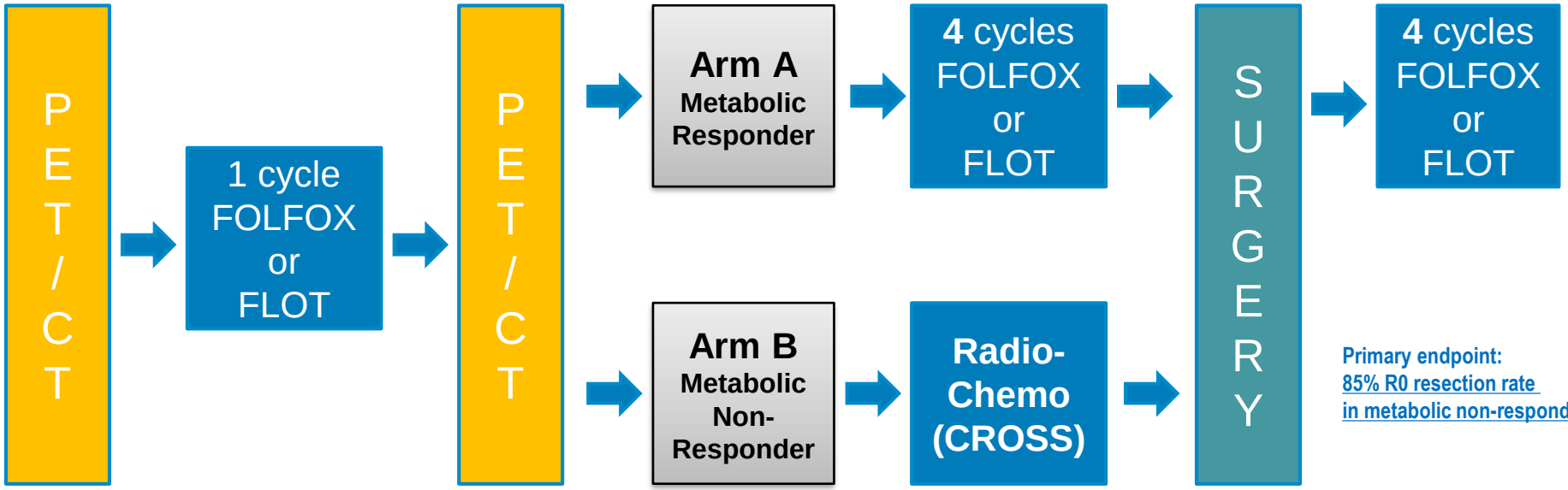
FDG-PET-studies in esophageal cancer

▪ **MUNICON**	Germany	**Lordick**, Lancet Onc 2007
▪ **CALGB 80803**	USA	**Goodman**, ASCO-GI 2017
▪ **Doctor Study**	Australia	**Barbour**, ESMO 2018
▪ **Scope-2**	UK	**Crosby**, ongoing
▪ **GastroPet**	Czech Republic	**Obermannová**, ongoing

FUNCTIONAL IMAGING FOR ESO-GASTRIC CANCER

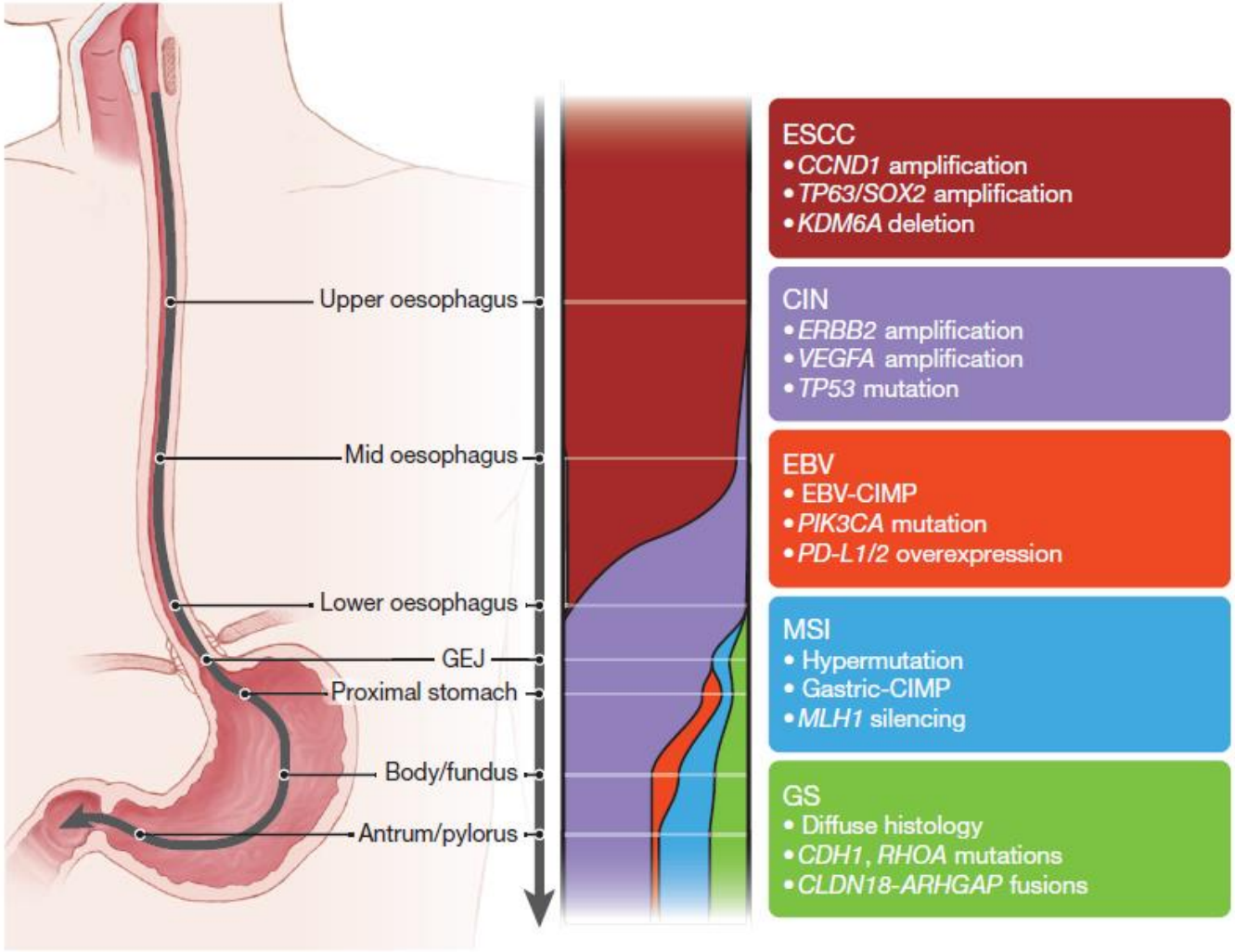
GastroPet

PI: Radka Obermannová, Brno



Response definition: Decrease of the SUVmean PETd14 / PETbaseline ≥ 35%

BIOLOGY

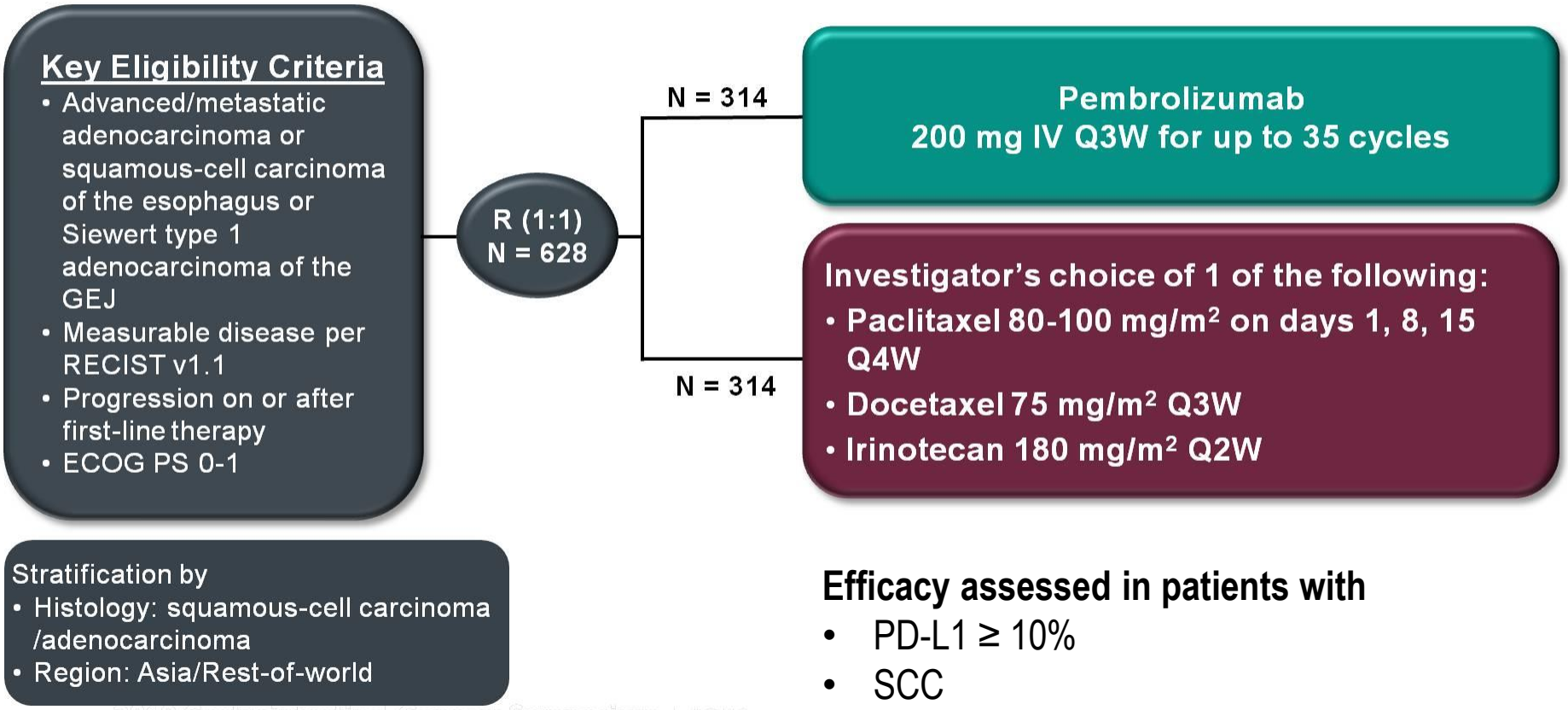


Molecular subclasses of gastroesophageal carcinoma

The Cancer Genome Atlas Research Network. *Nature.* 2017;541:169-175

IMMUNOTHERAPY – KEYNOTE-181 – PEMBRO VS CHEMO

Phase 3 KEYNOTE-181 Study (NCT02564263)



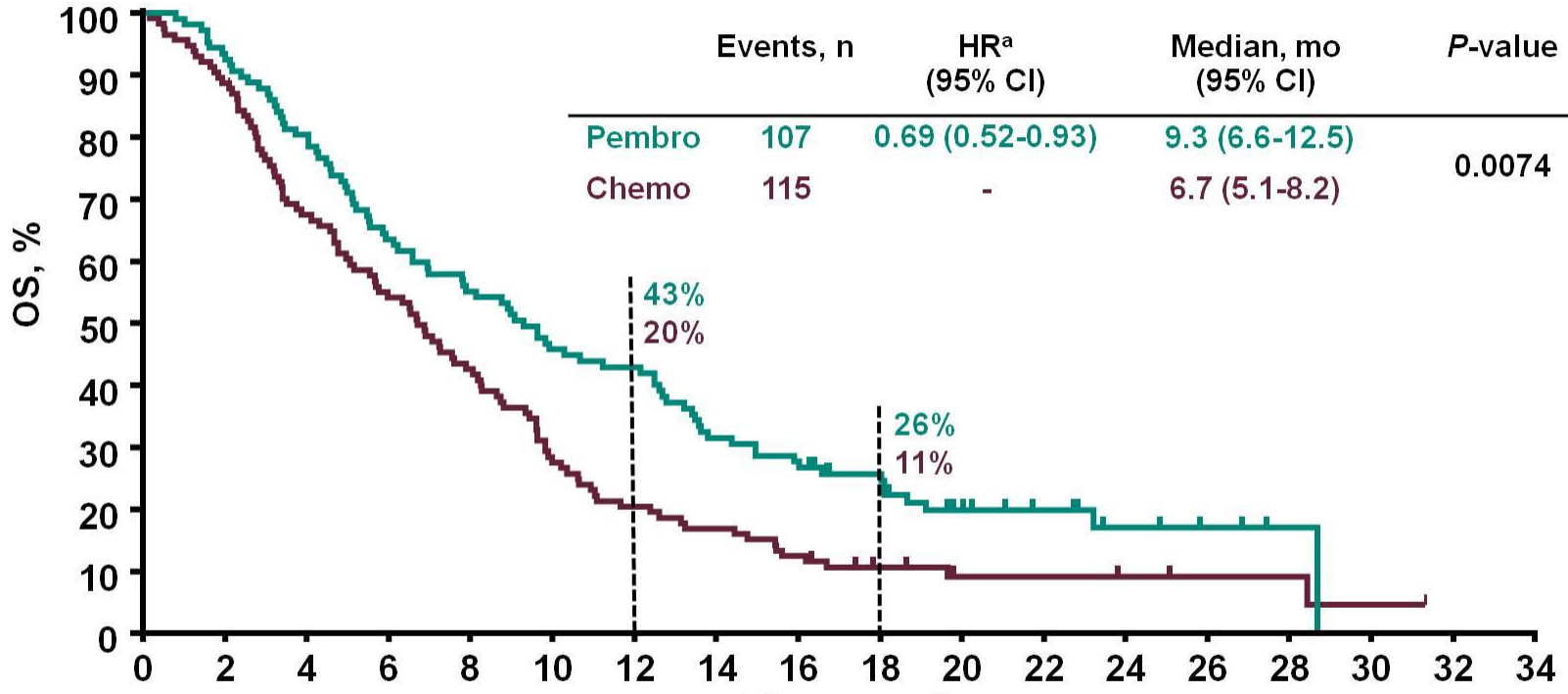
Efficacy assessed in patients with

- PD-L1 ≥ 10%
- SCC
- ITT

Kojima T et al. *ASCO-GI 2019; abstract 2*

IMMUNOTHERAPY – KEYNOTE-181 – PEMBRO VS CHEMO

Overall Survival (PD-L1 CPS ≥10)



	Events, n	HR[a] (95% CI)	Median, mo (95% CI)	*P*-value
Pembro	107	0.69 (0.52-0.93)	9.3 (6.6-12.5)	0.0074
Chemo	115	-	6.7 (5.1-8.2)	

No. at risk

Pembrolizumab	107	100	86	68	59	49	45	33	29	23	13	9	5	3	1	0	0	0
Chemotherapy	115	102	76	61	48	31	23	19	14	8	4	4	3	2	2	1	0	0

[a]Based on Cox regression model with treatment as a covariate stratified by region and histology.
Data cutoff: October 15, 2018.

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Kojima T et al. *ASCO-GI 2019; abstract 2*

ESOPHAGEAL CANCER

Summary

- Esophageal cancer is a **global health problem**
- **Minimally-invasive surgery**: standard of care for localized disease
- **Guidelines: multimodal treatment** for locally advanced disease
- **SCC:** Definitive chemorad or neoadjuvant chemorad + surgery
- **AC:** Neoadjuvant chemorad or periop. chemotherapy + surgery
- **Response imaging for personalized care** – ongoing studies
- **Immunotherapy** effective in PD-L1(+) advanced disease (2nd-line)

THANK YOU FOR YOUR KIND ATTENTION

Greetings from Leipzig, Germany

University Cancer Center Leipzig (UCCL)

INTERNATIONAL GASTRIC CANCER CONGRESS PRAGUE 2019

Prague, Czech Republic

13th INTERNATIONAL GASTRIC CANCER CONGRESS IGCC 2019

8–11 May 2019

www.igcc2019-prague.org