DGHO
DEUTSCHE GESELLSCHAFT FÜR HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE

onkopedia

Analkarzinom

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ASKLEPIOS TUMORZENTRUM HAMBURG

Declaration of interests: Dirk Arnold 2021-2024

- Remunerated *Advisory Boards (A)* and/or *Education Activities/ Honoraria for Presentations (H)*

  Industry:

  Amgen, Astra Zeneca, Bayer, BMS, Boston Scientific, Eli Lilly, GSK, Janssen

  Merck Serono, MSD, Roche, Sanofi, Seagen, Servier, Sirtex, Takeda, Terumo,

  CME providers:

  Aptitude Health, Art Tempi, Medscape, onkowissen.de, PriME Oncology, TRM Oncology

- Research funding to institute

  Astra Zeneca, InCyte, MSD, Roche, Sanofi

- Non-remunerated activities:

  Advisory Role and/or PI function: Oncolytics, Phanes Immunoncology

Leitlinienprogramm Onkologie

S3-Leitlinie Analkarzinom

(Diagnostik, Therapie und Nachsorge von Analkanal- und Analrandkarzinomen)

Langversion 1.2 – Dezember 2020
AWMF-Registernummer: 081/004OL

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onkopedia leitlinien

HIV-assoziiertes Analkarzinom

Leitlinie

Empfehlungen der Fachgesellschaft zur Diagnostik und Therapie hämatologischer und onkologischer Erkrankungen

DGHO Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie
ÖGHO Österreichische Gesellschaft für Hämatologie & Medizinische Onkologie
SSMO SSOM SGMO
SGH SSH

ASKLEPIOS TUMORZENTRUM HAMBURG

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Anal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up☆

S. Rao[1], M. G. Guren[2], K. Khan[3,4], G. Brown[5], A. G. Renehan[6], S. E. Steigen[7], E. Deutsch[8], E. Martinelli[9] & D. Arnold[10], on behalf of the ESMO Guidelines Committee[*]

[1]GI Unit, Royal Marsden Hospital, London, UK; [2]Department of Oncology, Oslo University Hospital, Oslo, Norway; [3]Department of GI Oncology, University College Hospital, London; [4]UCL Cancer Trials Centre, UCL Cancer Institute, London; [5]Department of Radiology, Royal Marsden NHS Foundation Trust, London; [6]Division of Cancer Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of Manchester, The Christie NHS Foundation Trust, Manchester, UK; [7]Department of Clinical Pathology, University Hospital of North Norway, Tromsø, Norway; [8]INSERM 1030, Gustave Roussy Cancer Campus, Université Paris-Saclay, Villejuif, France; [9]Department of Precision Medicine, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy; [10]Department of Hematology, Oncology, Palliative Care Medicine and Rheumatology, Asklepios Hospital Altona, Hamburg, Germany

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Epidemiologie

ICD-10 C21

	2020	
	Frauen	**Männer**
Neuerkrankungen	1.500	810
standardisierte Erkrankungsrate[1]	2,3	1,3
Sterbefälle	355	261
standardisierte Sterberate[1]	0,4	0,4
5-Jahres-Prävalenz	5.800	3.000
10-Jahres-Prävalenz	9.200	4.600
relative 5-Jahres-Überlebensrate*	72 %	63 %
relative 10-Jahres-Überlebensrate*	68 %	60 %

[1] *je 100.000 Personen, altersstandardisiert nach altem Europastandard*

** berechnet nach Periodenmethode für 2019 / 2020*

https://www.krebsdaten.de/Krebs/DE/Content/Krebsarten/Analkrebs/analkrebs_node.html

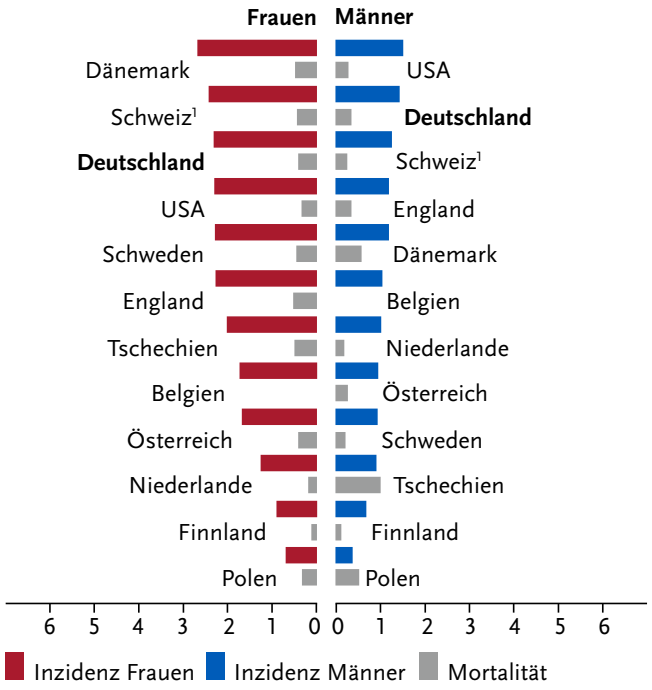
Inzidenz	2019		2020			
	Frauen	Männer	Frauen	Männer		
Neuerkrankungen	1.510	900	1.500	810		
rohe Neuerkrankungsrate [1]	3,6	2,2	3,6	2,0		
standardisierte Neuerkrankungsrate [1, 2]	2,3	1,6	2,3	1,3		
mittleres Erkrankungsalter [3]	65	64	64	65		
Mortalität	**2019**		**2020**		**2021**	
	Frauen	Männer	Frauen	Männer	Frauen	Männer
Sterbefälle	340	208	355	261	301	231
rohe Sterberate [1]	0,8	0,5	0,8	0,6	0,7	0,6
standardisierte Sterberate [1, 2]	0,4	0,3	0,4	0,4	0,3	0,4
mittleres Sterbealter [3]	75	70	75	70	77	69
Prävalenz und Überlebensraten	**5 Jahre**		**10 Jahre**		**25 Jahre**	
	Frauen	Männer	Frauen	Männer	Frauen	Männer
Prävalenz	5.800	3.000	9.200	4.600	13.300	6.800
absolute Überlebensrate (2019 – 2020) [4]	64 (60 – 72)	55	54 (51 – 62)	45		
relative Überlebensrate (2019 – 2020) [4]	72 (69 – 80)	63	68 (64 – 78)	60		

[1] je 100.000 Personen [2] altersstandardisiert nach alter Europabevölkerung [3] Median [4] in Prozent (niedrigster und höchster Wert der einbezogenen Bundesländer)

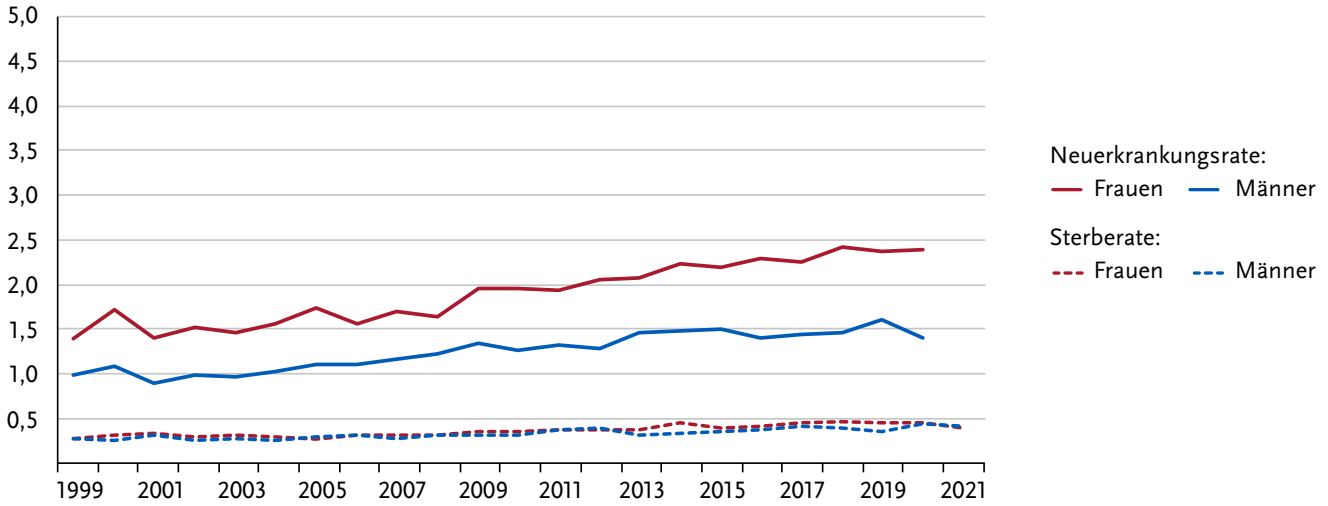
https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/kid_2023/kid_2023_c21_anus.pdf?__blob=publicationFile

Epidemiologie: Neuerkrankungs- und Sterberate

Altersstandardisierte Neuerkrankungs- und Sterberaten nach Geschlecht im internationalen Vergleich, ICD-10 C21, 2019 – 2020 oder letztes verfügbares Jahr (Einzelheiten und Datenquellen s. Anhang)
je 100.000 (alter Europastandard)



Altersstandardisierte Neuerkrankungs- und Sterberaten nach Geschlecht, ICD-10 C21, Deutschland 1999 – 2020/2021
je 100.000 (alter Europastandard)

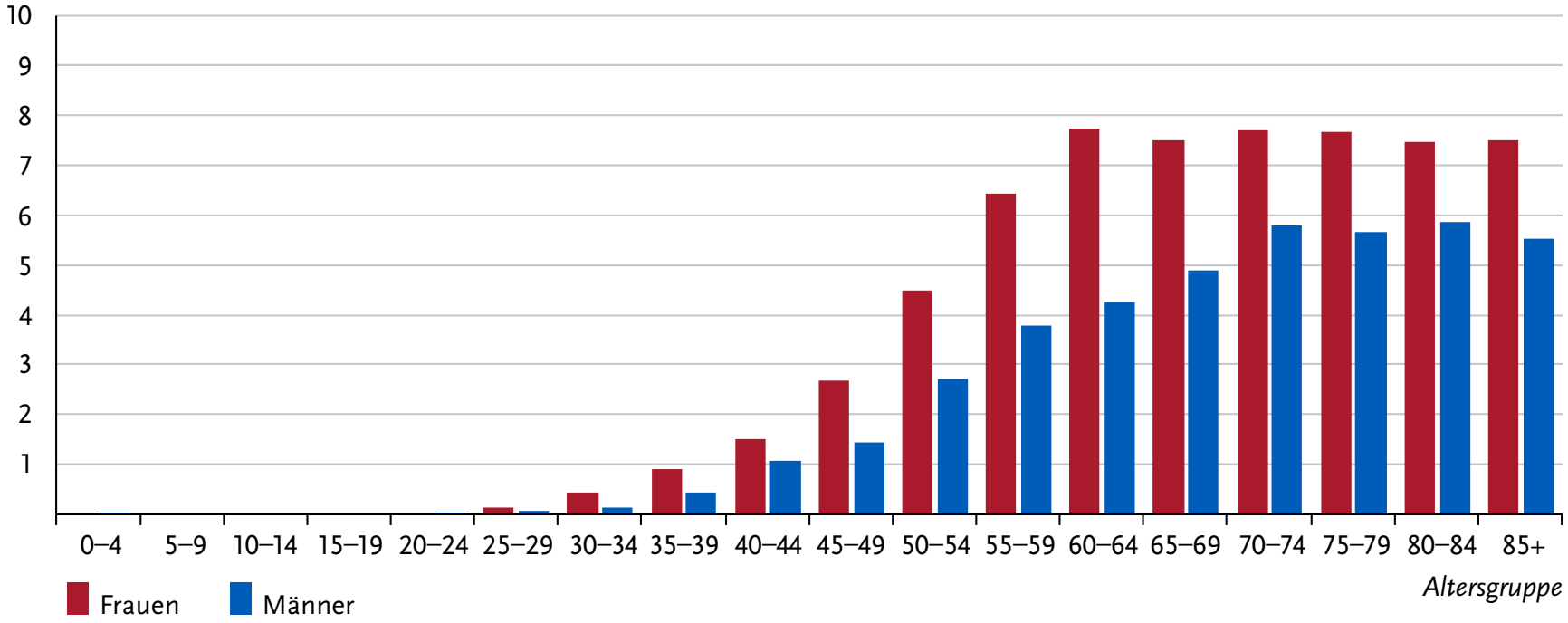


https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/kid_2023/kid_2023_c21_anus.pdf?__blob=publicationFile

Epidemiologie: Neuerkrankungs- und Sterberate

Altersspezifische Neuerkrankungsraten nach Geschlecht, ICD-10 C21, Deutschland 2019 – 2020

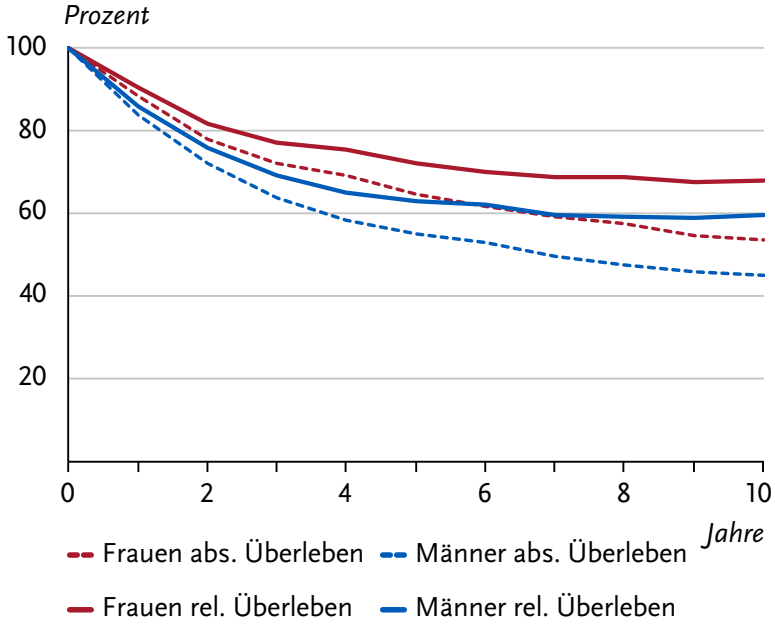
je 100.000



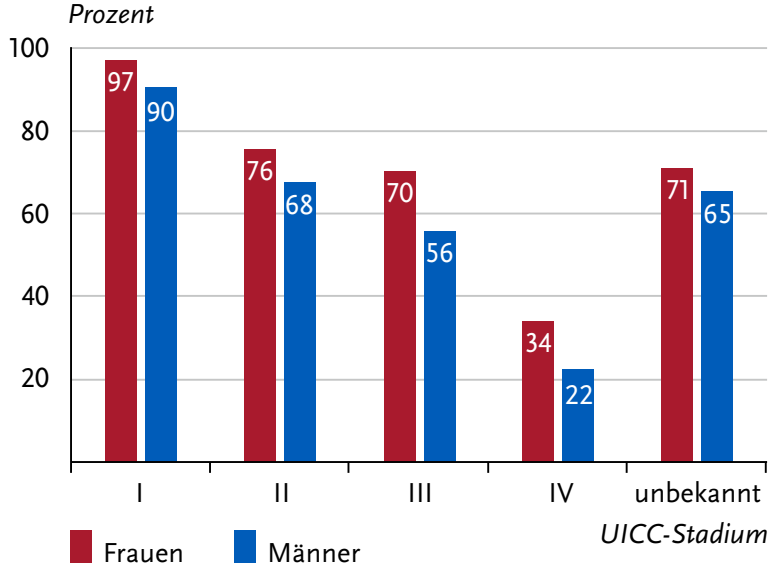
https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/kid_2023/kid_2023_c21_anus.pdf?__blob=publicationFile

Epidemiologie: Überlebensraten

Absolute und relative Überlebensraten bis 10 Jahre nach Erstdiagnose, nach Geschlecht, ICD-10 C21, Deutschland 2019 – 2020



Relatives 5-Jahres-Überleben nach UICC-Stadium (7. und 8. Auflage TNM) und Geschlecht, ICD-10 C21, Deutschland 2019 – 2020



https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/kid_2023/kid_2023_c21_anus.pdf?__blob=publicationFile

Epidemiologie: SEER Database 2022

- Lokalrezidive 22%
- 5-Jahres-Überlebensraten
  - alle Stadien 70%
  - Stadium I-IIA: >80%
  - nach Rektumexstirpation bei Resttumor: 45%
  - nach Rektumexstirpation bei Rezidiv: 51%
  - N+ bei ED (29%): 60%
  - Metastasierung bei ED (12%): 30%

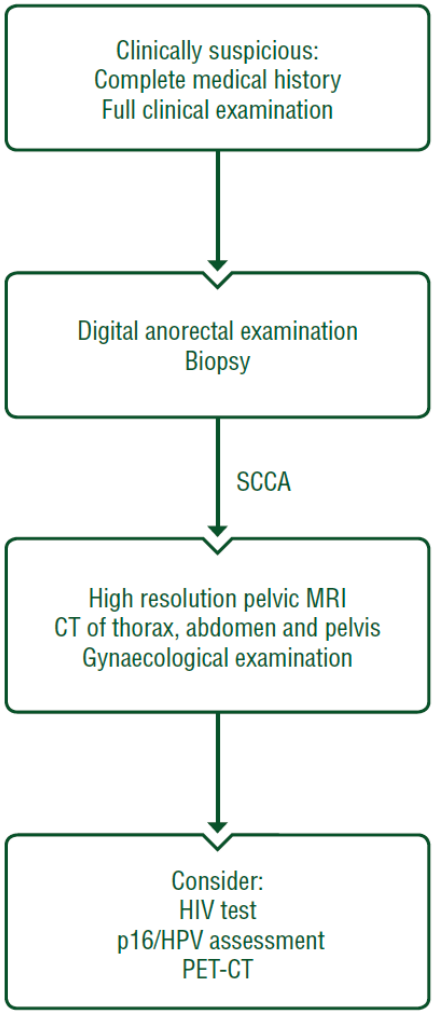
https://seer.cancer.gov/statfacts/html/2023/anus.html

Klinische Risikofaktoren

- Anzahl der Sexualpartner*innen
- Rezeptiver Analverkehr
- HPV-assoziierte anogenitale Vorerkrankungen, andere sexuell übertragbare Infektionen, anogenitale Warzen
- MSM mit HIV: Inzidenzrate von 45,9 *vs* 5,1 pro 100.000 HIV-negativen MSM
- Risiko für die Entwicklung eines Analkarzinoms bei HIV-
- positiven MSM > 100-fach erhöht im Vergleich zur „Allgemeinbevölkerung“
- Nikotinabusus = unabhängiger Risikofaktor
- M. Crohn

Diagnostik

Mandatory	Recommended	Optional
Biopsy	HIV test	Endo-anal ultrasound
DRE	PET-CT	Ultrasound-guided FNA of inguinal nodes
Complete medical history	P16/HPV assessment	Examination under anaesthesia
Full clinical examination		
High-resolution pelvic MRI		
CT of thorax, abdomen and pelvis		
Anoscopy/proctoscopy		
Gynaecological examination		



ESMO Guideline; Rao S. et al., Ann Oncol 2021

Diagnostik

Konsensbasierte Empfehlung

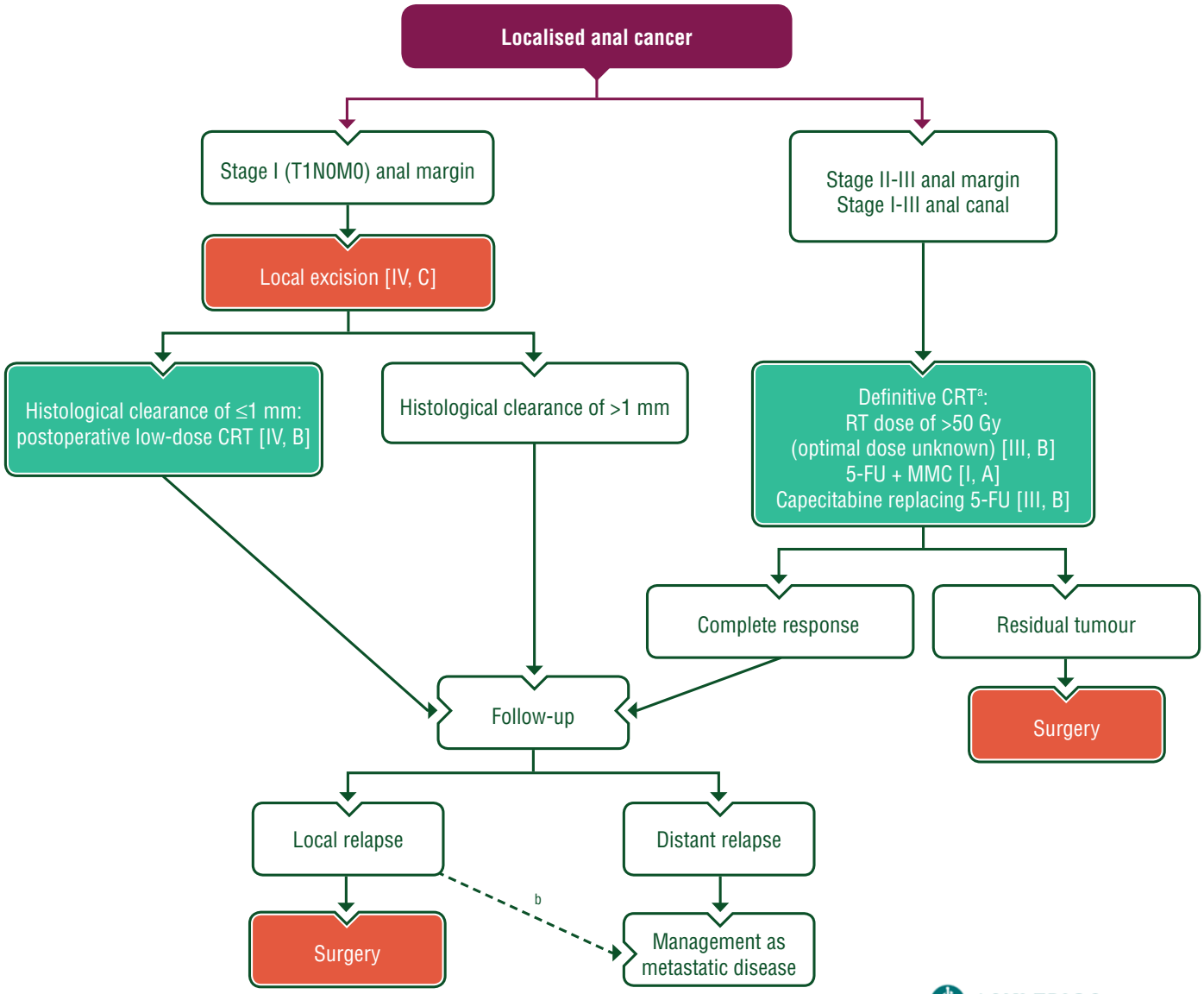
Zur Bestimmung der Tumorkategorie **soll** eine MRT-Untersuchung des Beckens erfolgen. Diese **sollte** eine multiparametrische MRT, anguliert auf den Analkanal, umfassen.

Konsensbasierte Empfehlung

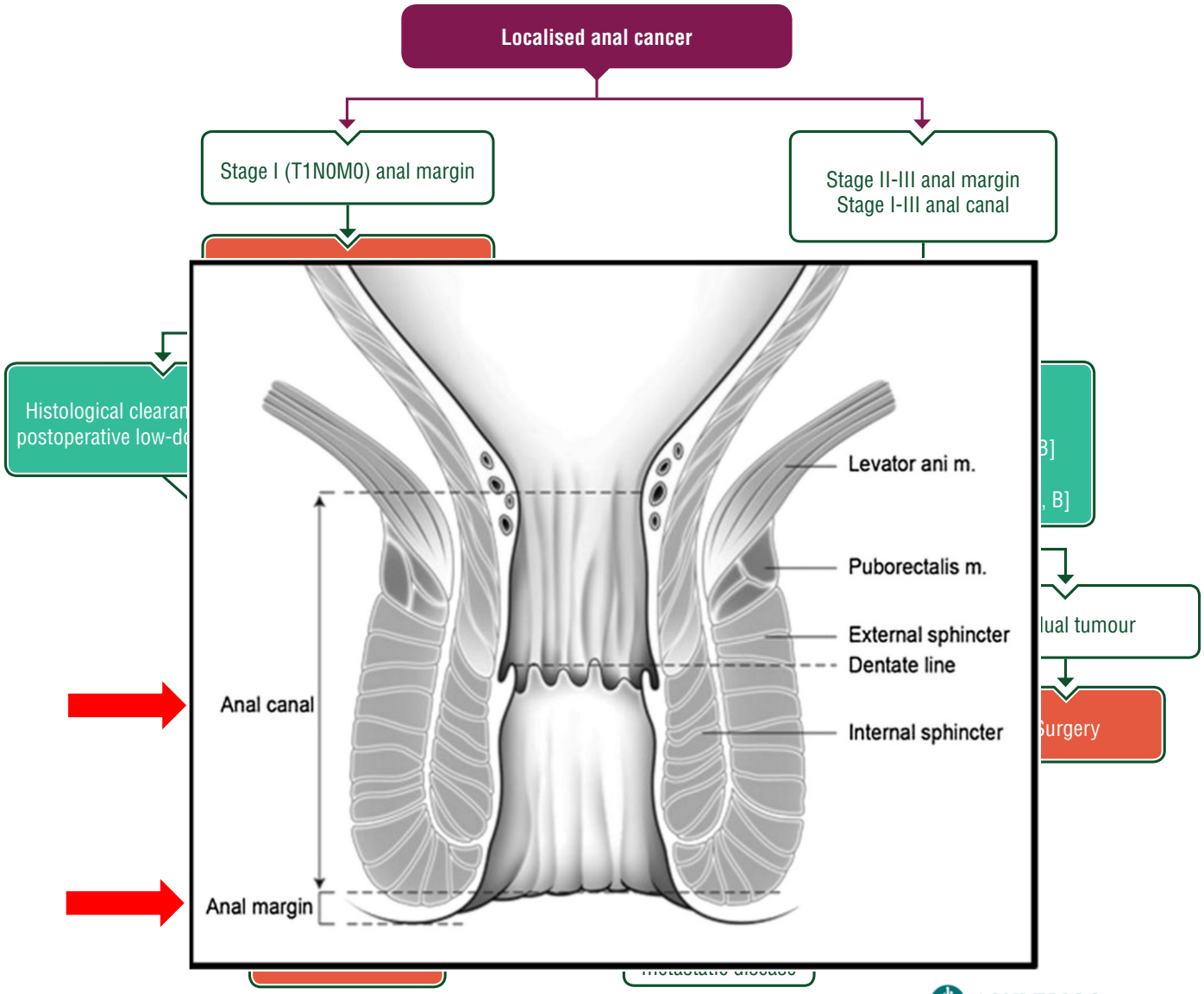
Zur Detektion lokoregionärer Lymphknotenmetastasen **soll** eine MRT des Beckens durchgeführt werden. Ergänzend **sollte** die Durchführung einer PET/CT* erfolgen. Eine CT des Beckens **kann** durchgeführt werden.

*CAVE: Die PET-Untersuchung ist im Rahmen der Diagnostik bei Analkarzinomen nicht Gegenstand des Leistungskatalogs der gesetzlichen Krankenversicherung (Kostenübernahme nicht gesichert).

https://register.awmf.org/assets/guidelines/081-004OLl_Analkarzinom_Diagnostik- Therapie-Nachsorge-Analkanalkarzinom-Analrandkarzinom_2020-12.pdfc



ESMO Guideline; Rao S et al., Ann Oncol 2021



Rao S et al., Ann Oncol 2021

Konsensbasierte Empfehlung

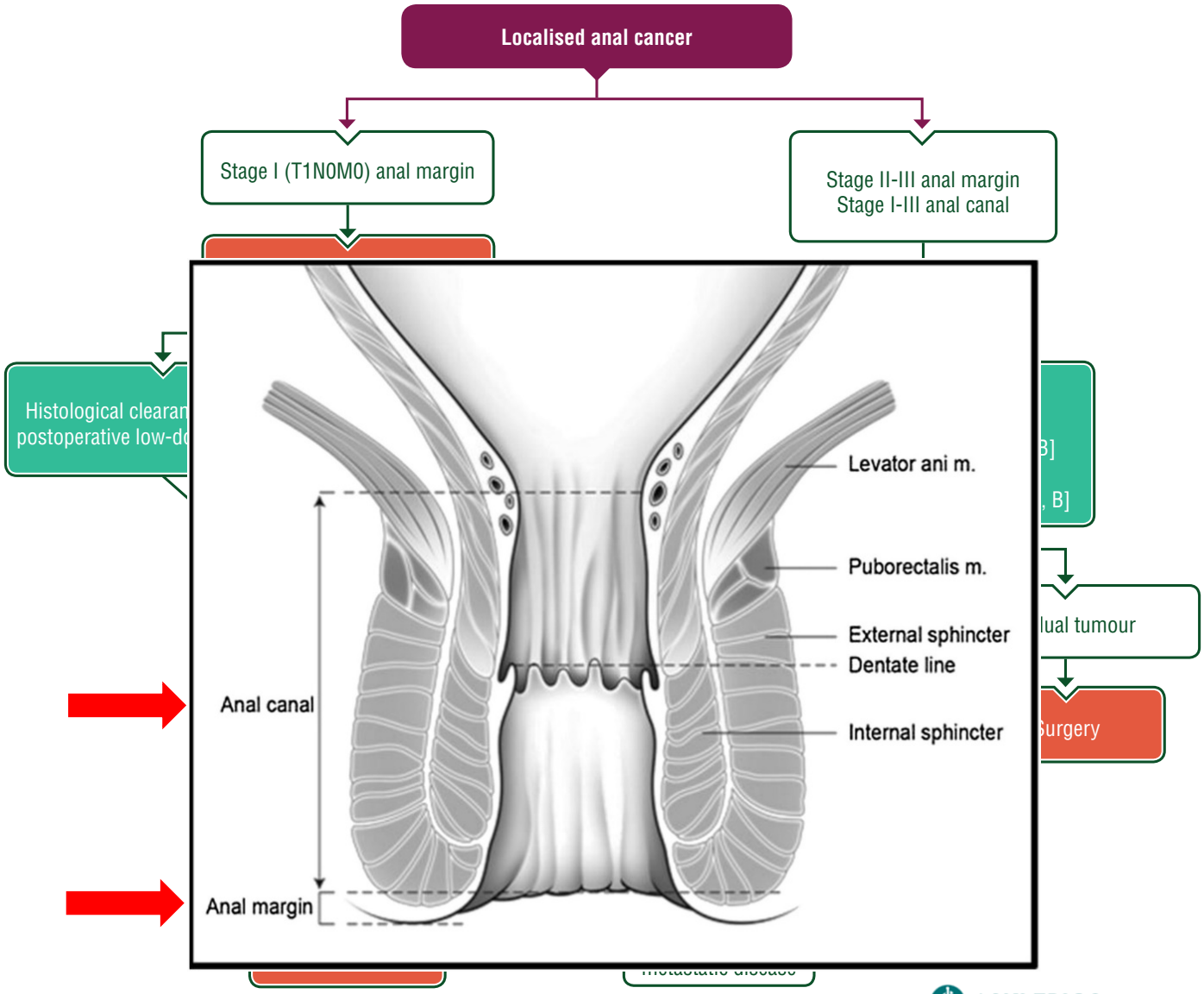
Zur Abgrenzung von Analkanal- und Analrandkarzinomen sowie zur Abgrenzung zu anderen, in dieser Leitlinie nicht behandelten plattenepithelialen Tumoren **sollen** die folgenden klinischen Kriterien angewandt werden:

1. **Analrandkarzinome**
   - sind unter Spreizung der Nates makroskopisch vollständig sichtbar
   - liegen mit ihrem überwiegenden Gewebeanteil innerhalb eines Radius von 5 cm um die Linea anocutanea
2. **Analkanalkarzinome**
   - sind mindestens teilweise so weit im Analkanal gelegen, dass eine Sichtbarkeit des makroskopischen Tumorbefundes unter Spreizung der Nates nicht oder nicht vollständig gegeben ist

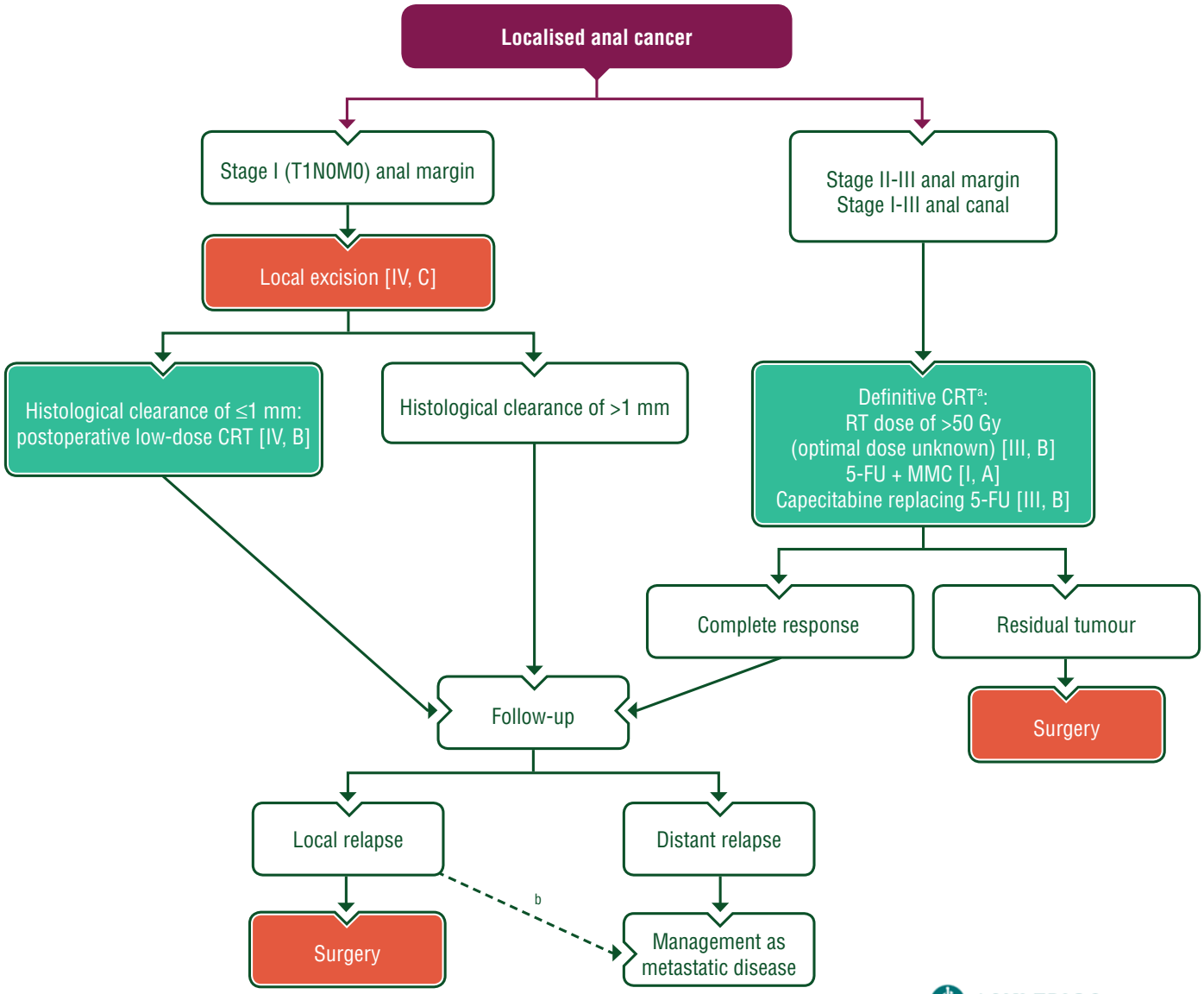
https://register.awmf.org/assets/guidelines/081-004OLl_Analkarzinom_Diagnostik- Therapie-Nachsorge-Analkanalkarzinom-Analrandkarzinom_2020-12.pdfc

Definition des Primärtumors (T)	
TX	Primärtumor nicht beurteilt
T0	Kein Anhalt für Primärtumor
Tis	Hochgradige plattenepitheliale intraepitheliale Läsion (HSIL) (zuvor bezeichnet als Carcinoma *in situ*, Morbus Bowen, anale intraepitheliale Neoplasie II-III, high-grade AIN)
T1	Tumor ≤2 cm
T2	Tumor >2 und ≤5 cm
T3	Tumor >5 cm
T4	Tumor jeglicher Größe mit Infiltration in benachbarte Organe, z.B. Vagina, Urethra oder Harnblase

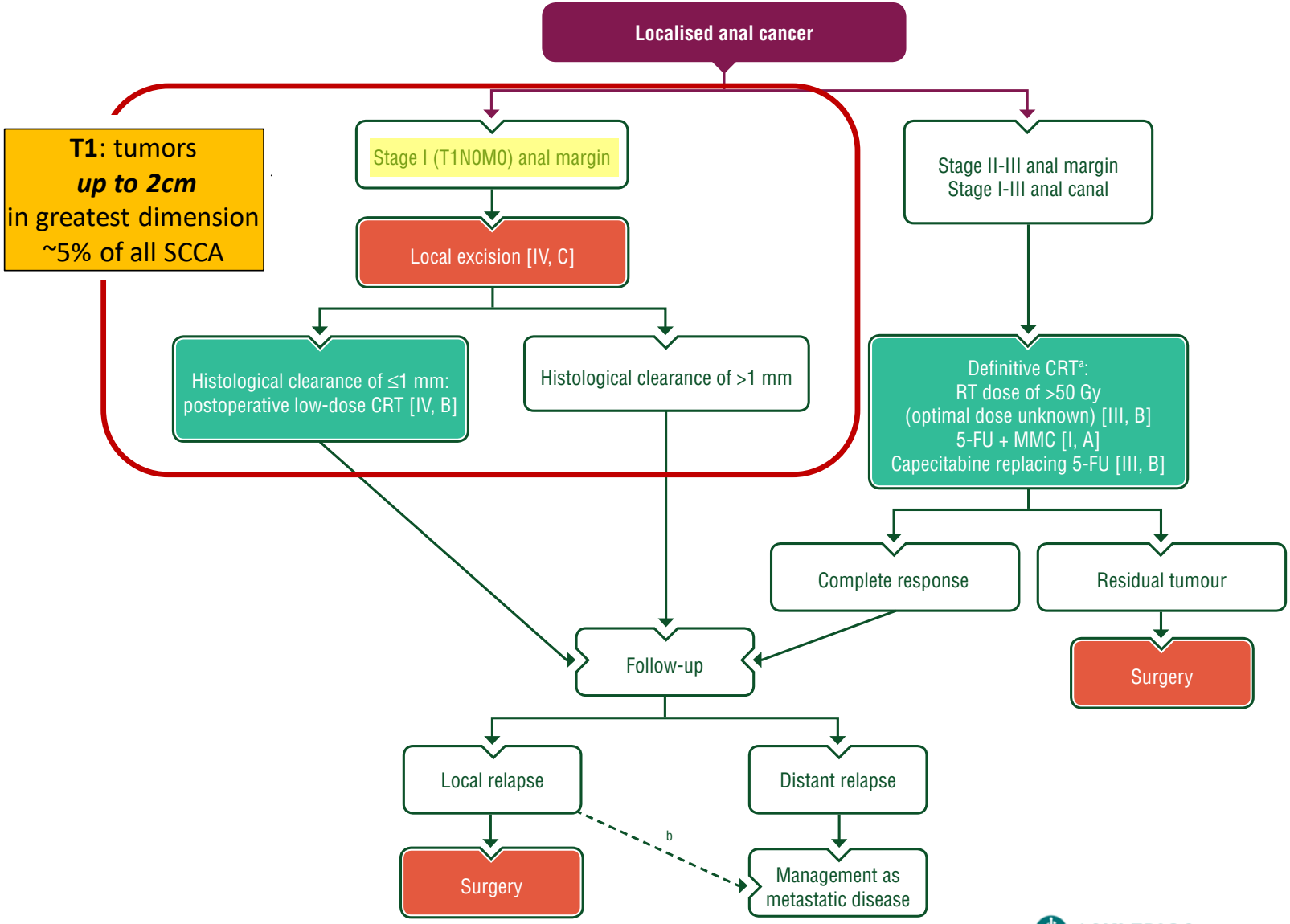
https://register.awmf.org/assets/guidelines/081-004OLl_Analkarzinom_Diagnostik- Therapie-Nachsorge-Analkanalkarzinom-Analrandkarzinom_2020-12.pdfc



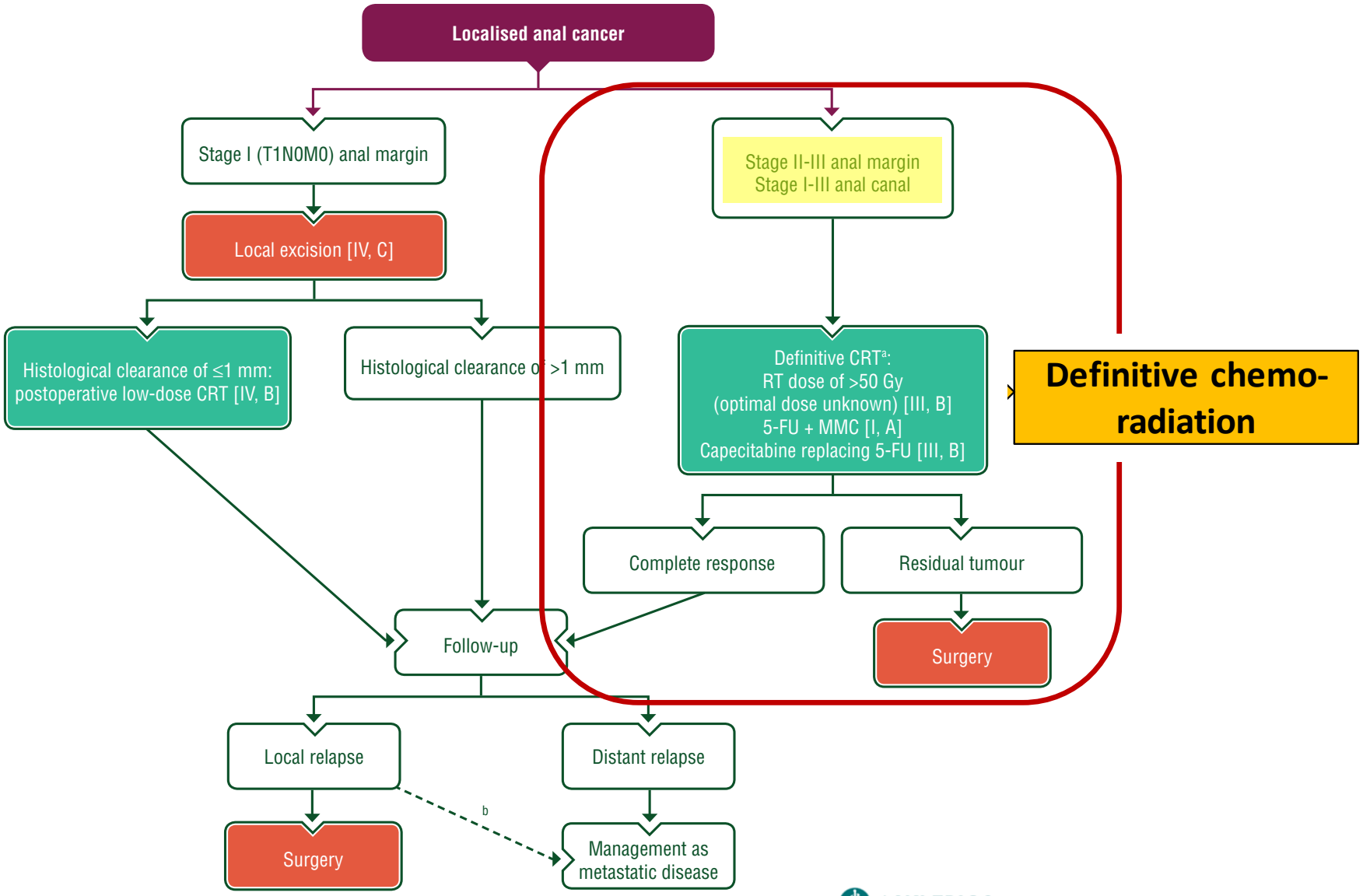
Rao S et al., Ann Oncol 2021



Rao S et al., Ann Oncol 2021



ESMO Guideline; Rao S et al., Ann Oncol 2021



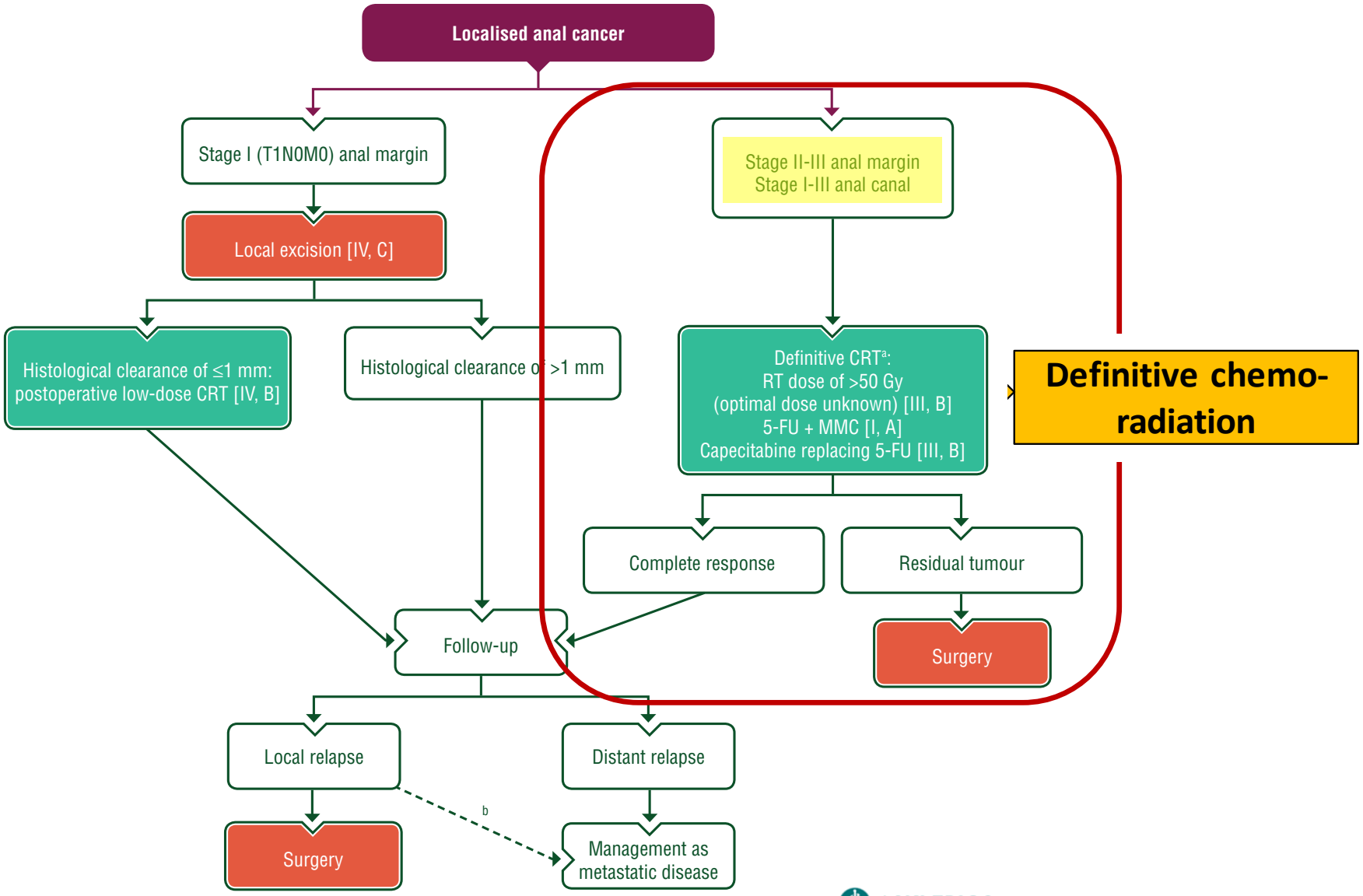
ESMO Guideline; Rao S et al., Ann Oncol 2021

AJCC 8. Auflage

Definition der regionären Lymphknoten (N)	
NX	Regionäre Lymphknoten können nicht beurteilt werden
N0	Keine regionäre Lymphknotenmetastase
N1	Metastasen in inguinalen, mesorektalen Lymphknoten, Lymphknoten der Arteria iliaca interna oder der Arteria iliaca externa
N1a	Metastasen in inguinalen, mesorektalen Lymphknoten oder Lymphknoten der Arteria iliaca interna
N1b	Metastasen in Lymphknoten der Arteria iliaca externa
N1c	Metastasen in Lymphknoten der Arteria iliaca externa sowie N1a-Lymphknoten

Stadium	Primärtumor	Regionäre Lymphknoten	Fernmetastasen
0	Tis	N0	M0
I	T1	N0	M0
IIA	T2	N0	M0
IIB	T3	N0	M0
IIIA	T1, T2	N1	M0
IIIB	T4	N0	M0
IIIC	T3, T4	N1	M0
IV	jegliches T	jegliches N	M1

https://register.awmf.org/assets/guidelines/081-004OLl_Analkarzinom_Diagnostik- Therapie-Nachsorge-Analkanalkarzinom-Analrandkarzinom_2020-12.pdfc



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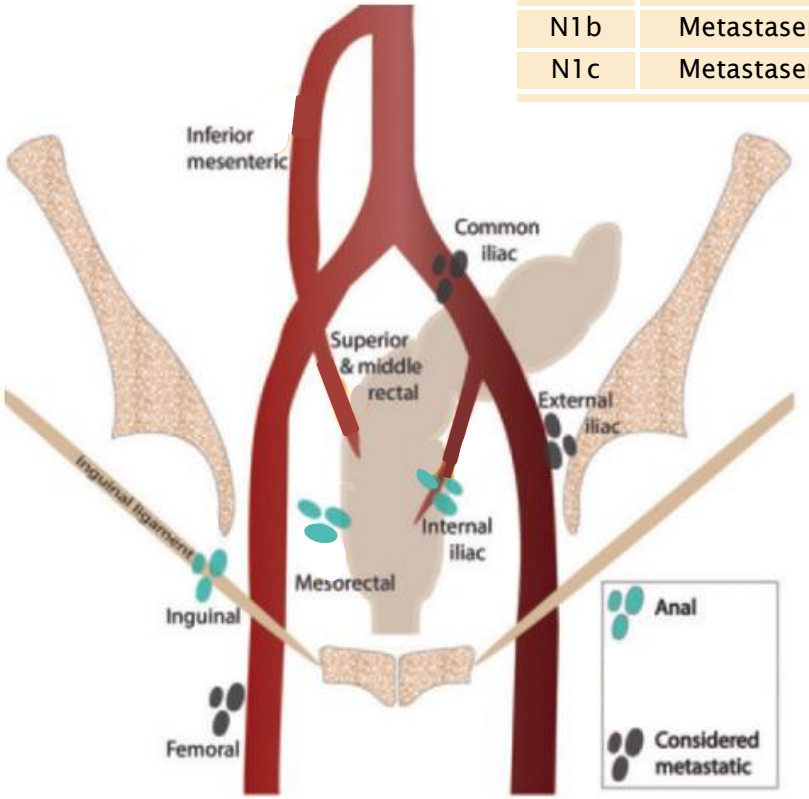
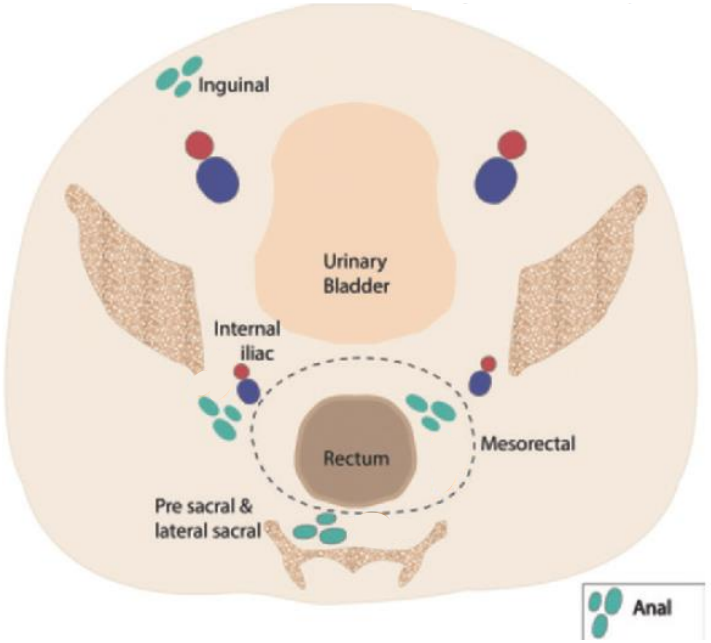


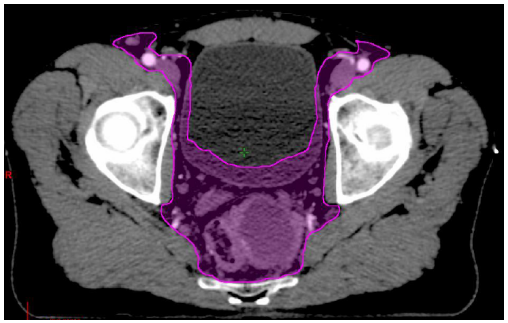
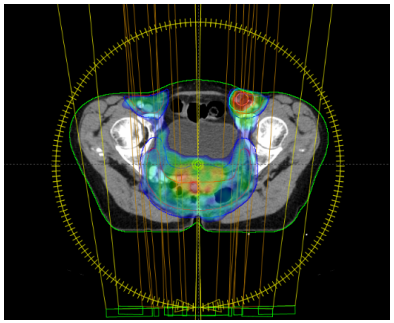


Matalon SA et al., RadioGraphics 2015; AJCC 8

Chemoradiotherapy (CRT) for anal cancer

Definitive CRT[a]:
RT dose of >50 Gy
(optimal dose unknown) [III, B]
5-FU + MMC [I, A]
Capecitabine replacing 5-FU [III, B]

- Radiotherapy >50 Gy (up to 60 Gy)
  - Modern radiotherapy techniques
- Concurrent chemotherapy
- Improving clinical outcomes
  - Tumour control and survival
  - QOL and late effects

Improved locoregional control and survival

ANCARAD Oslo

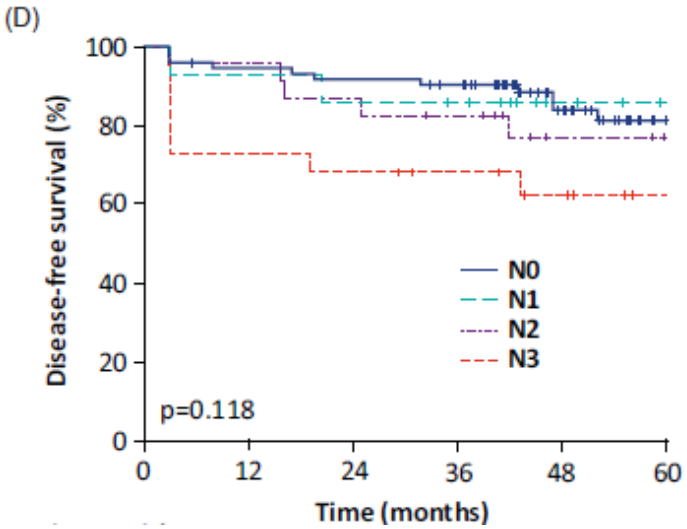
3-y DFS 85%

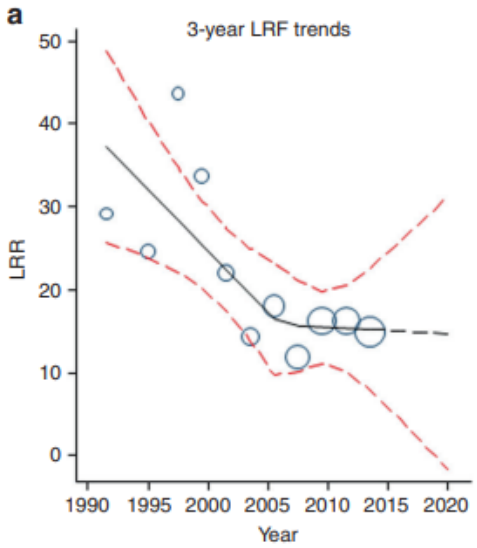
14% treatment failure

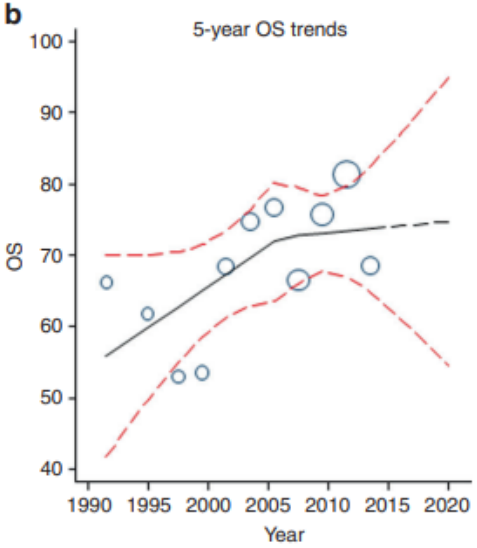
UK 1990-2014

Improved survival

3-y locoregional failure 15%







Slørdahl KS, Acta Oncol 2021; Sekhar H, Br J Cancer 2020

Support Care Cancer (2015) 23:3613–3623
DOI 10.1007/s00520-015-2879-2

REVIEW ARTICLE

Systematic review of the quality of life issues associated with anal cancer and its treatment with radiochemotherapy

Samantha C. Sodergren[1] · Vassilios Vassiliou[2] · Kristopher Dennis[3] · Krzysztof A. Tomaszewski[4] · Alexandra Gilbert[5] · Robert Glynne-Jones[6] · Karen Nugent[1] · David Sebag-Montefiore[5] · Colin D. Johnson[1] · On behalf of the EORTC Quality of Life Group

EORTC QLQ-ANL27

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had leakage of stools or mucus from your anal opening (back passage)?	1	2	3	4
32. Have you experienced frequent bowel movements?	1	2	3	4
33. Have your bowel movements been painful?	1	2	3	4
34. Have you had pain/discomfort around your anal opening (back passage)?	1	2	3	4
35. Have you had pain while sitting?	1	2	3	4

Sodergren SC, Radiother Oncol 2018; Sodergren SD, Int J Rad Oncol Biol Phys 2023

Core Outcome Research Measures Anal Cancer (CORMAC)

Disease activity

- Treatment response
- Local failure
- Regional failure
- Distant failure
- Disease progression
- Salvage surgery

Survival

- Overall survival
- Cancer-specific survival
- Disease-free survival
- Metastasis-free survival
- Progression-free survival

Toxicity

- Anal incontinence
- Faecal urgency
- Pelvic fistula
- Colostomy or ileostomy
- Skin loss

Life impact

- Physical function
- Sexual function
- Health-related quality of life

Fish R, Lancet Gastro Hep 2018

EORTC trial, 1997

Concomitant Radiotherapy and Chemotherapy Is Superior to Radiotherapy Alone in the Treatment of Locally Advanced Anal Cancer: Results of a Phase III Randomized Trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups

By H. Bartelink, F. Roelofsen, F. Eschwege, P. Rougier, J.F. Bosset, D. Gonzalez Gonzalez, D. Peiffert, M. van Glabbeke, and M. Pierart

Complete response: 54% vs. 80% (without surgery)

Complete response: 85% vs. 96% (with surgery)

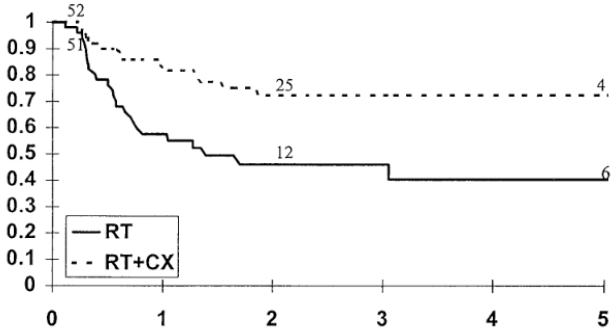


Fig 2. Colostomy-free interval. $P = .002$ (log-rank test).

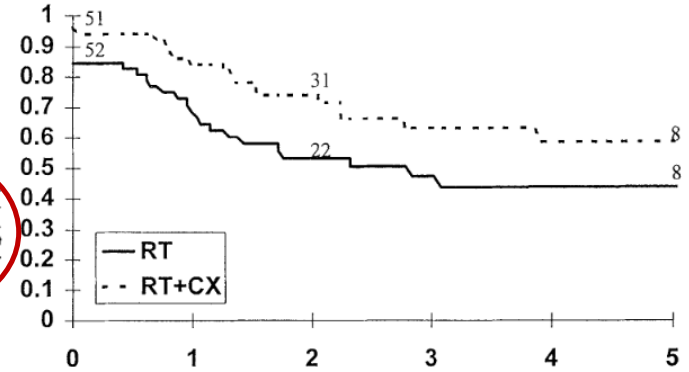


Fig 5. Progression-free survival. No change or residual tumor was considered as failure. Therefore, the curves do not start with 100% at the time of randomization. $P = .05$ (log-rank test).

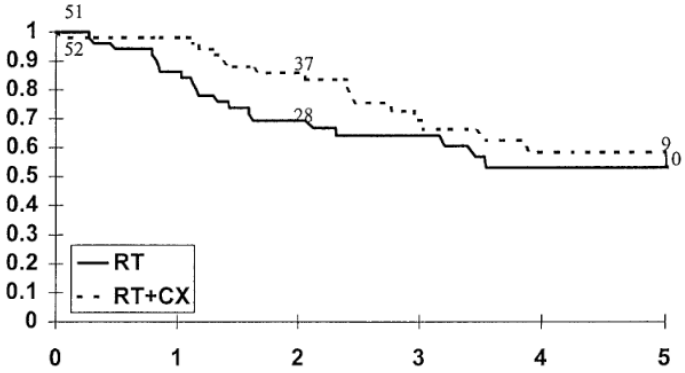


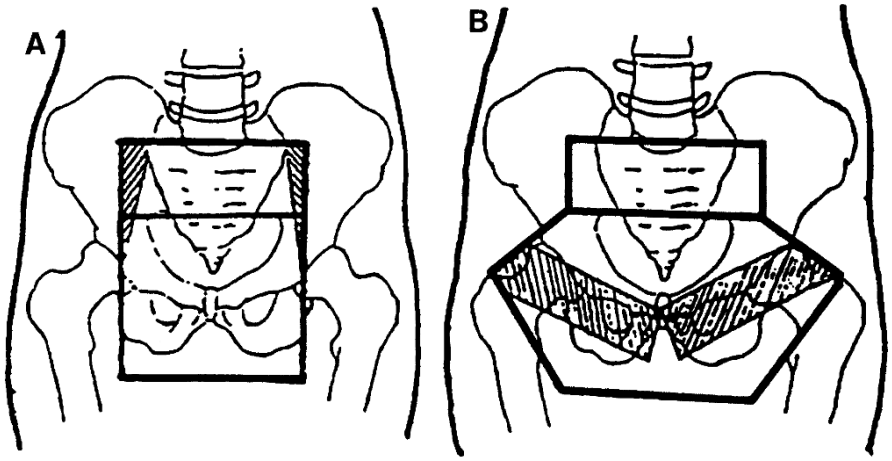
Fig 6. Overall survival for patients treated with radiotherapy only or concomitant radiotherapy and chemotherapy. $P = .17$ (log-rank test).

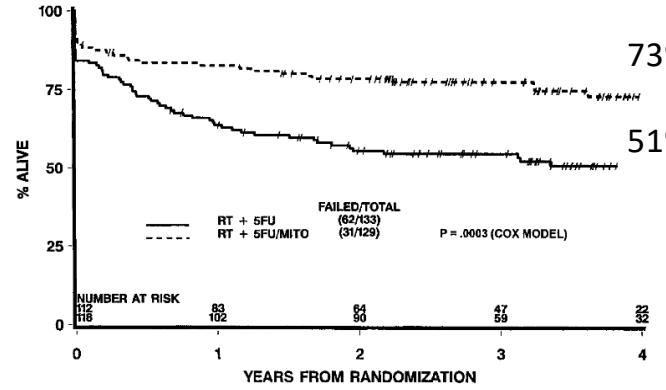
Bartelink H et al., J Clin Oncol 1997

Intergroup trial, 1996

Role of Mitomycin in Combination With Fluorouracil and Radiotherapy, and of Salvage Chemoradiation in the Definitive Nonsurgical Treatment of Epidermoid Carcinoma of the Anal Canal: Results of a Phase III Randomized Intergroup Study

By Marshall Flam, Madhu John, Thomas F. Pajak, Nicholas Petrelli, Robert Myerson, Scotte Doggett, Jeanne Quivey, Marvin Rotman, Herbert Kerman, Lawrence Coia, and Kevin Murray





73% 4yr-DFS rate

51% 4yr-DFS rate

Fig 7. Disease-free survival—RTOG 87-04/ECOG 1289.

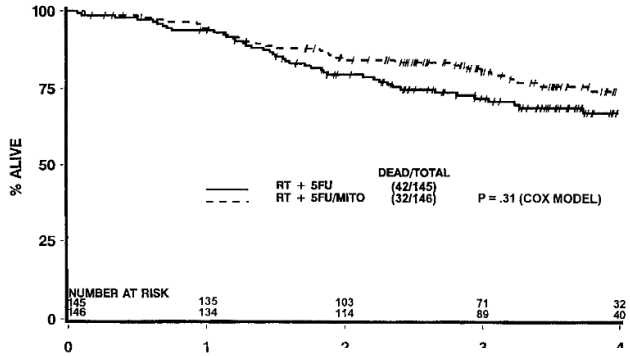


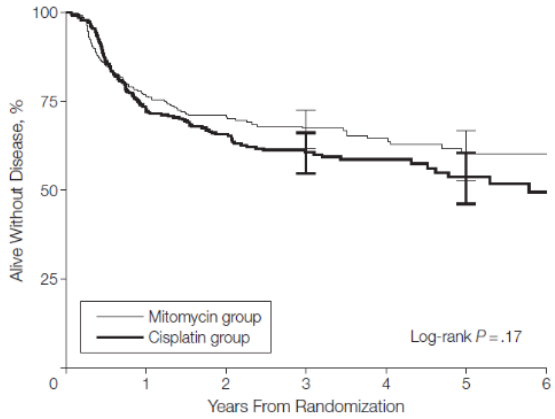
Fig 8. Overall survival—RTOG 87-04/ECOG 1289.

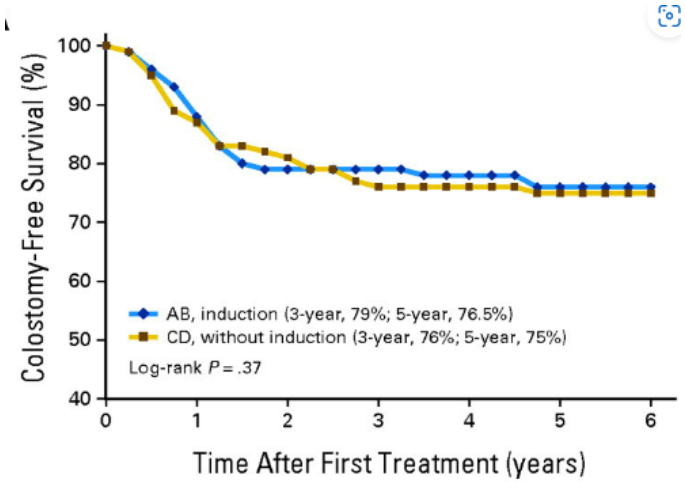
Flam M et al., J Clin Oncol 1996

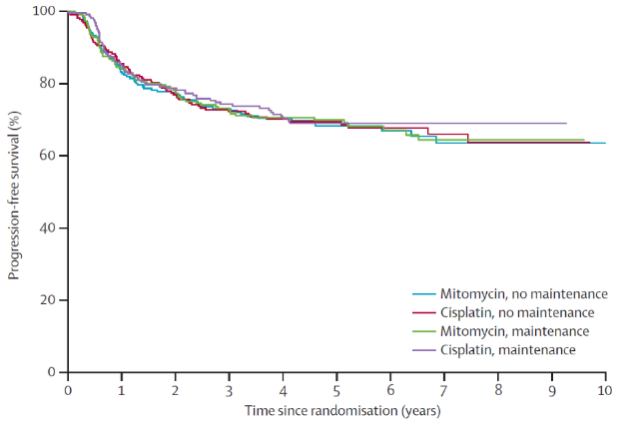
Concurrent Mitomycin and 5-FU....?

Concurrent chemotherapy, preferred regimen Mitomycin C and 5-FU

No effect of induction or maintenance chemotherapy







5-FU infusion can be substituted by oral capecitabine all days of radiotherapy

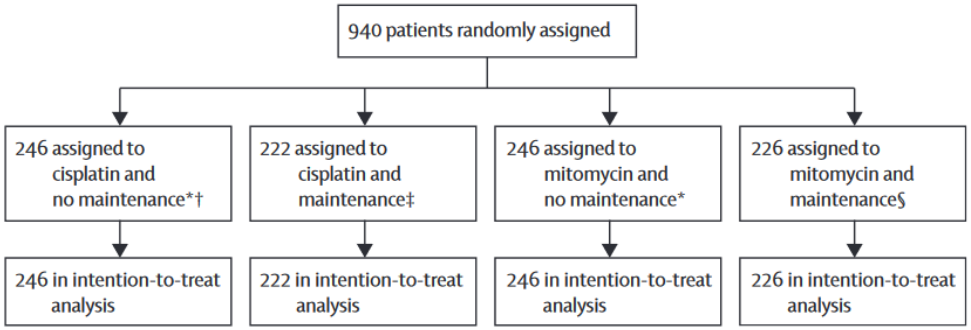
Ajani JA et al., JAMA 2008; Peiffert D et al., J Clin Oncol 2012; James RD et al., Lancet Oncol 2013

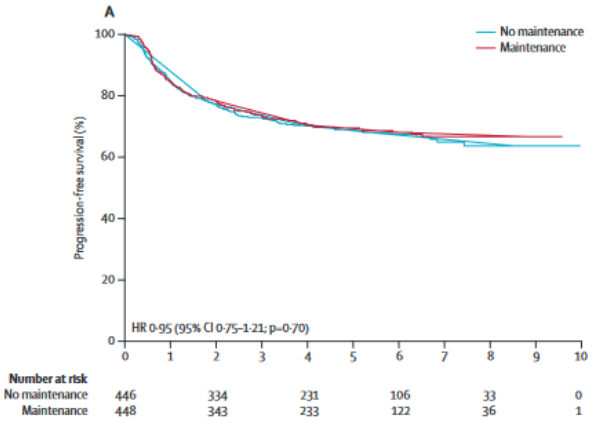
Goodman KA et al., Int J Rad Onc Biol Phys 2017; Jones CM et al., Int J Rad Onc Biol Phys 2018

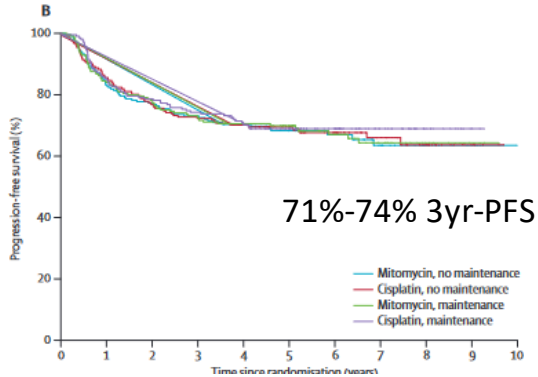
ACT II trial

Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2×2 factorial trial

Roger D James, Robert Glynne-Jones*, Helen M Meadows, David Cunningham, Arthur Sun Myint, Mark P Saunders, Timothy Maughan, Alec McDonald, Sharadah Essapen, Martin Leslie, Stephen Falk, Charles Wilson, Simon Gollins, Rubina Begum, Jonathan Ledermann, Latha Kadalayil, David Sebag-Montefiore*







Standard treatment:

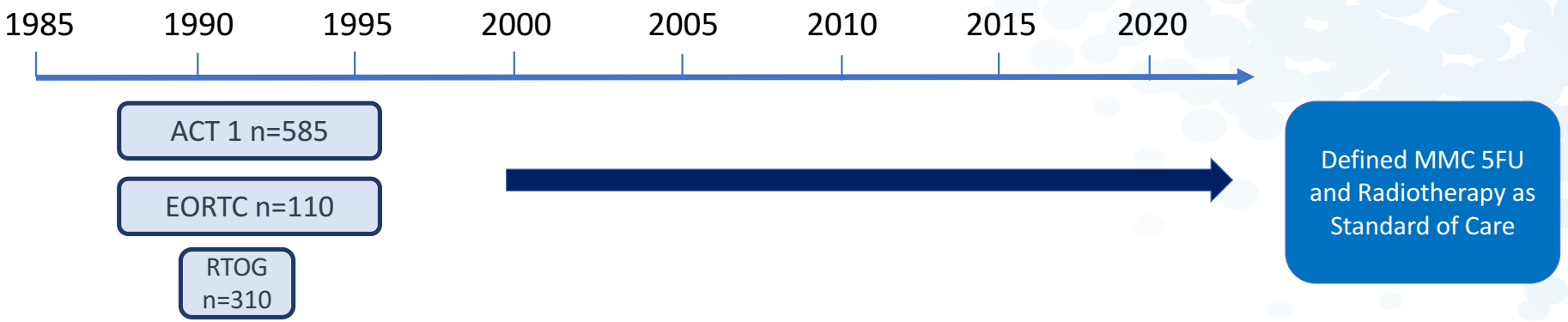
- 50.4 Gy in 28 daily fractions
- fluorouracil (1000 mg/m(2) per day on days 1-4 and 29-32
- mitomycin (12 mg/m(2) on day 1)

71%-74% 3yr-PFS rate

James RD et al., Lancet Oncol 2013

ASKLEPIOS TUMORZENTRUM HAMBURG

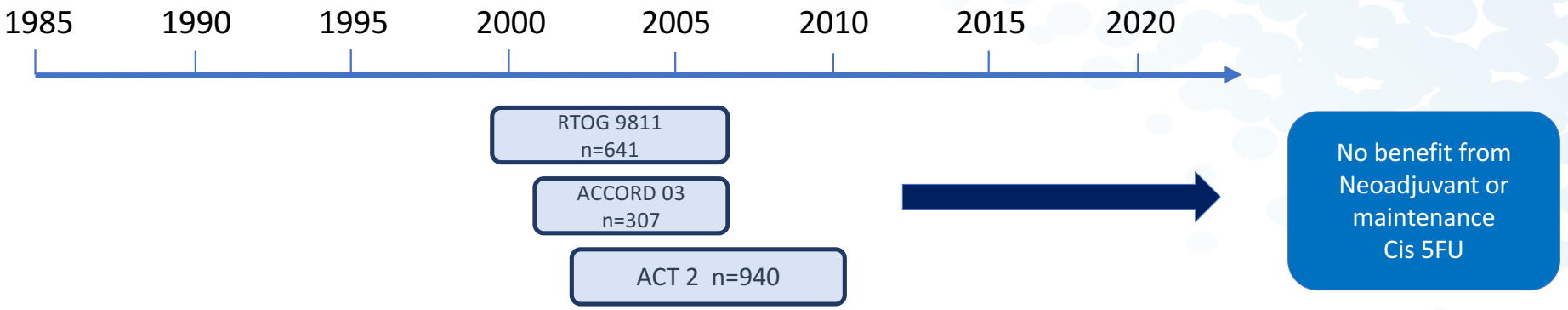
What have we learnt - 1



- UKCCR (ACT1) trial n=585
  - MMC 5FU RT superior to Radiotherapy alone – local failure
- EORTC trial n=110
  - MMC 5FU RT superior to Radiotherapy alone – local failure
- RTOG trial n=291
  - MMC 5FU RT superior to 5FU RT – colostomy free survival

Sebag Montefiore D, presented at IMACC 2023

What have we learnt - 2



- RTOG 9811 trial
  - Neoadjuvant Cis 5FU inferior DFS compared to MMC 5FU CRT
- ACCORD 03
  - No improvement in CFS using neoadjuvant Cis 5FU
  - No improvement signal in CFS for higher dose brachy boost
- ACT 2
  - No improvement in PFS for concurrent cisplatin versus Mitomycin C
  - No improvement in PFS with the addition of maintenance Cis FU

Sebag Montefiore D, presented at IMACC 2023

Improving radiation oncology: Boost?

Original Research Article

Brachytherapy boost in anal canal cancer – A GEC ESTRO PDR task force meta-analysis

Patient and tumor characteristics.

Authors, year of publication	BT modality	Country	Mono/multicentric	Median FU (years)	Patients' characteristics			Tumor characteristics	
					Number	% male	Age (median)	% T_3-T_4	% N_1-N_3
Karin Sigrid Kapp, 2001	HDR	Austria	monocentric	31	39	23.1	59	25.6	20.5
Julius Marek Doniec, 2006	HDR	Germany	monocentric	34	50	20.0	64	16.0	30.0
Christoph Oehler-Jänne, 2007	HDR	Switzerland	monocentric	60	34	11.8	60.4	29.4	26.5
Emilien Bertin, 2018	HDR	France	monocentric	61	46	19.6	65	4.3	13.0
Leonel Varela Cagetti, 2019	HDR	France	monocentric	33	50	16.0	67	6.0	6.0
Antoine Bruna, 2006	PDR	Belgium, France	multicentric	28.5	71	15.5	61.2	22.5	26.8
Thomas Gryc, 2016	PDR	Germany	monocentric	60	47	29.8	60	55.3	34.0
Alessandra Arcelli, 2019	PDR	Italy	monocentric	71	102	29.4	61	38.2	52.0
Remi Bourdais, 2021	PDR	France	monocentric	60.4	42	16.7	69	4.8	11.9

BT: brachytherapy, FU: follow-up, HDR: high dose rate, PDR: pulsed dose rate.

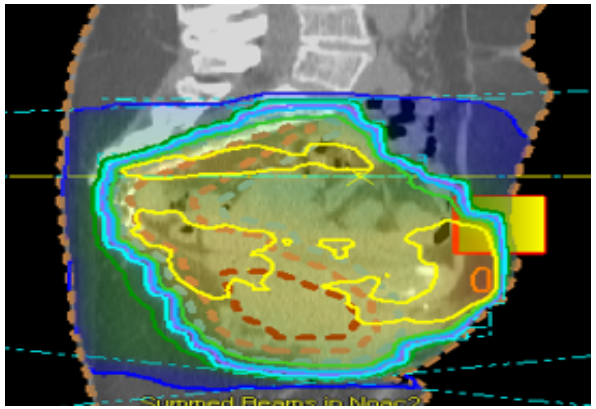
N= 481

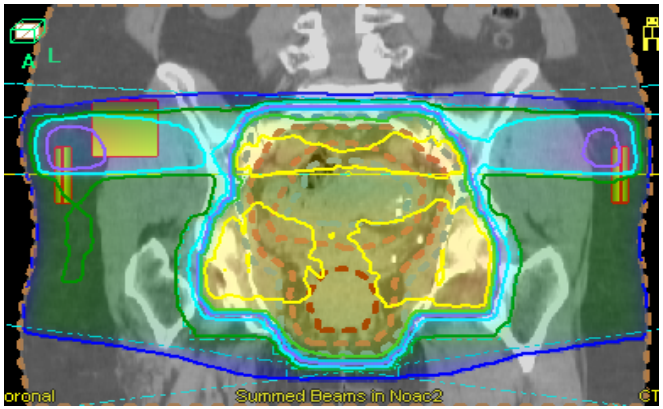
5-year RFS rate: 83-85%

Annede P et al., Clinical and Translational Radiation Oncology 2023 – from Stintzing S, ESMO Deep Dive Webinar 2023

Improving radiation oncology: Conformal techniques

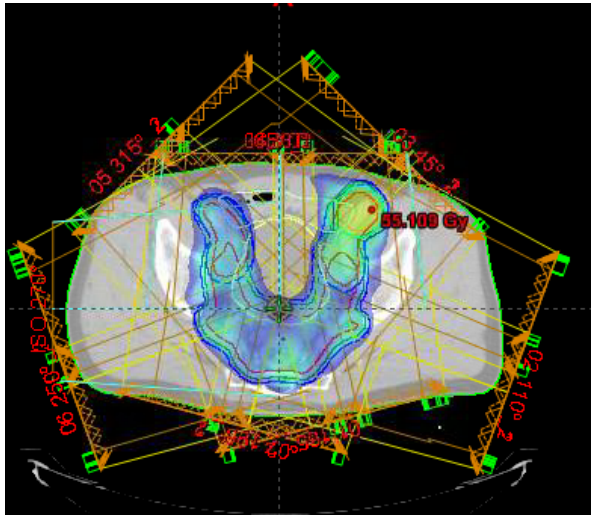
2010

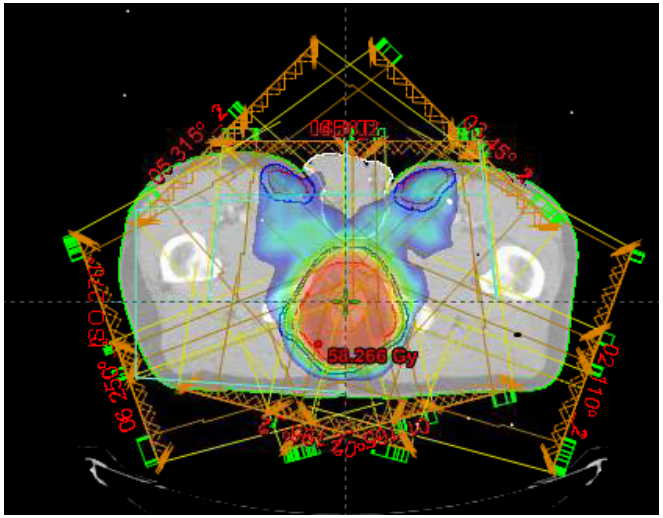




3-4 fields

2013





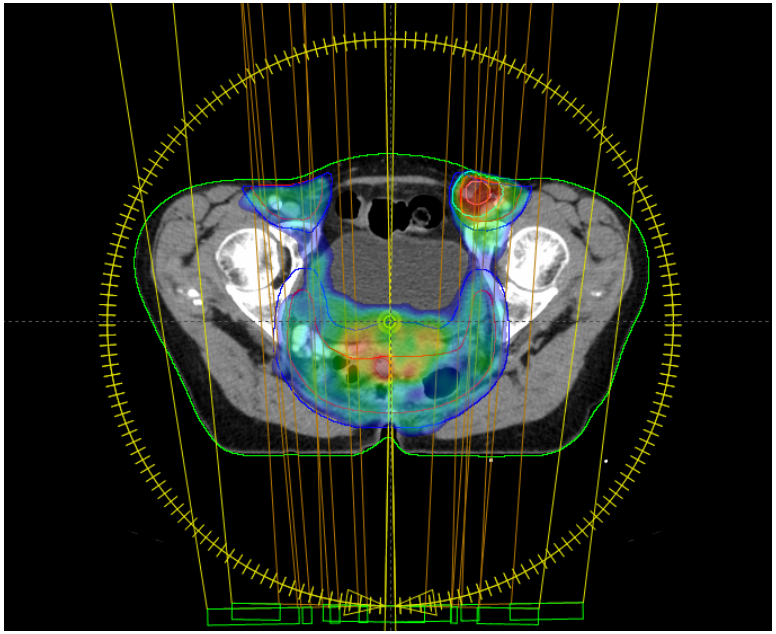
Intensity modulated RT

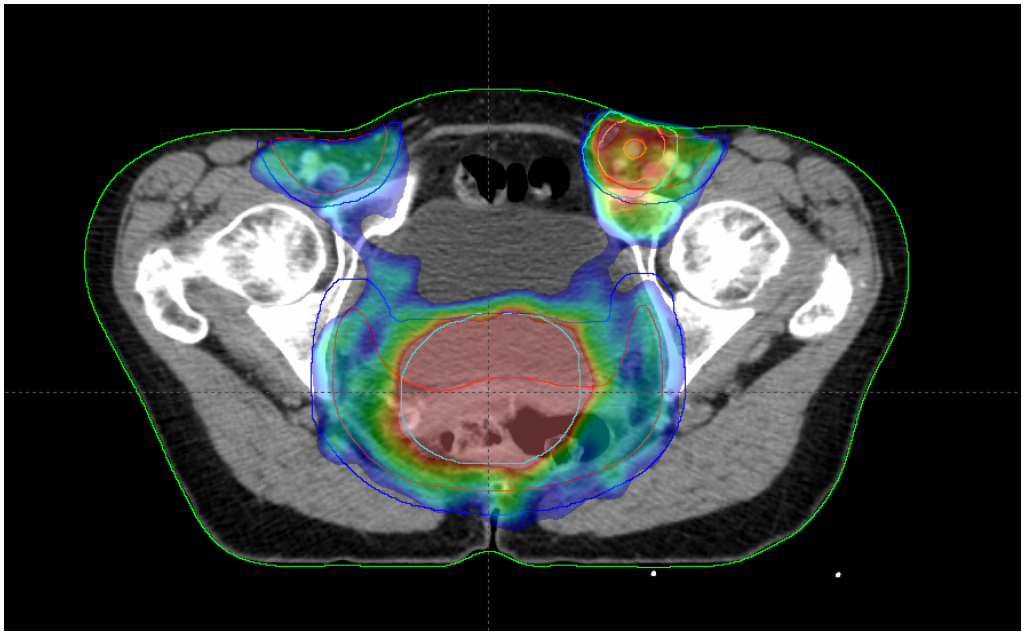
Kachnic L, Int J Rad Onc Biol Phys 2013

Courtesy of Marianne Gúren, Oslo

Improving radiation oncology: Volumetric Art Therapy (VMAT)

Different dose levels, simultaneous integrated boost





Courtesy of Marianne Gúren, Oslo

Improving radiation oncology: Volumetric Art Therapy (VMAT)

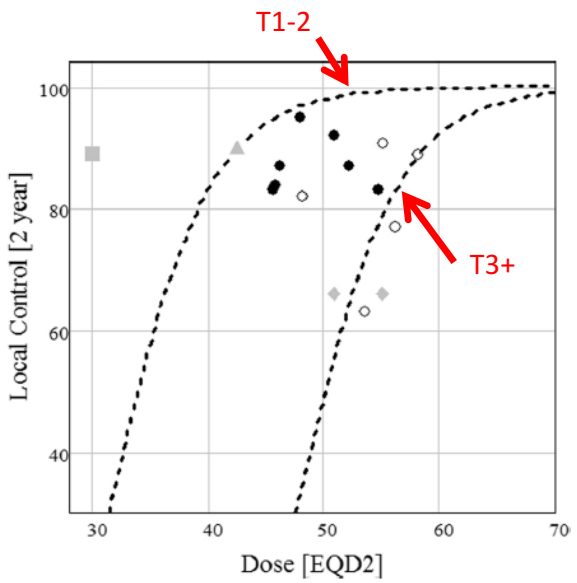
	UK	Denmark	Sweden	Norway
Primary T1-2N0	**50.4 Gy**	**54.0 Gy**	**54.0 Gy**	**54.0 Gy**
Primary T3-4 or N+	**53.2 Gy**	**60.0 Gy**	**57.5 Gy**	**57.5 Gy**
Nodal metastases (size)	40-50.4 Gy	54-60 Gy	50.5-57.5 Gy	54-57.5 Gy
Elective CTV	**40.0 Gy**	**48.0 Gy**	**41.6 Gy**	**41.6 Gy**
Fractions	28	30	27	27

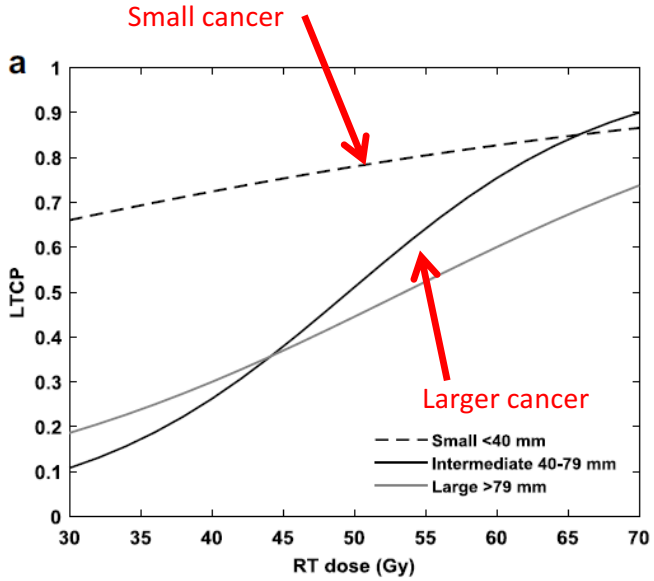
Courtesy of Marianne Gúren, Oslo

Tumour control probability – by radiation doses

Small tumours may have tumor control also at lower doses

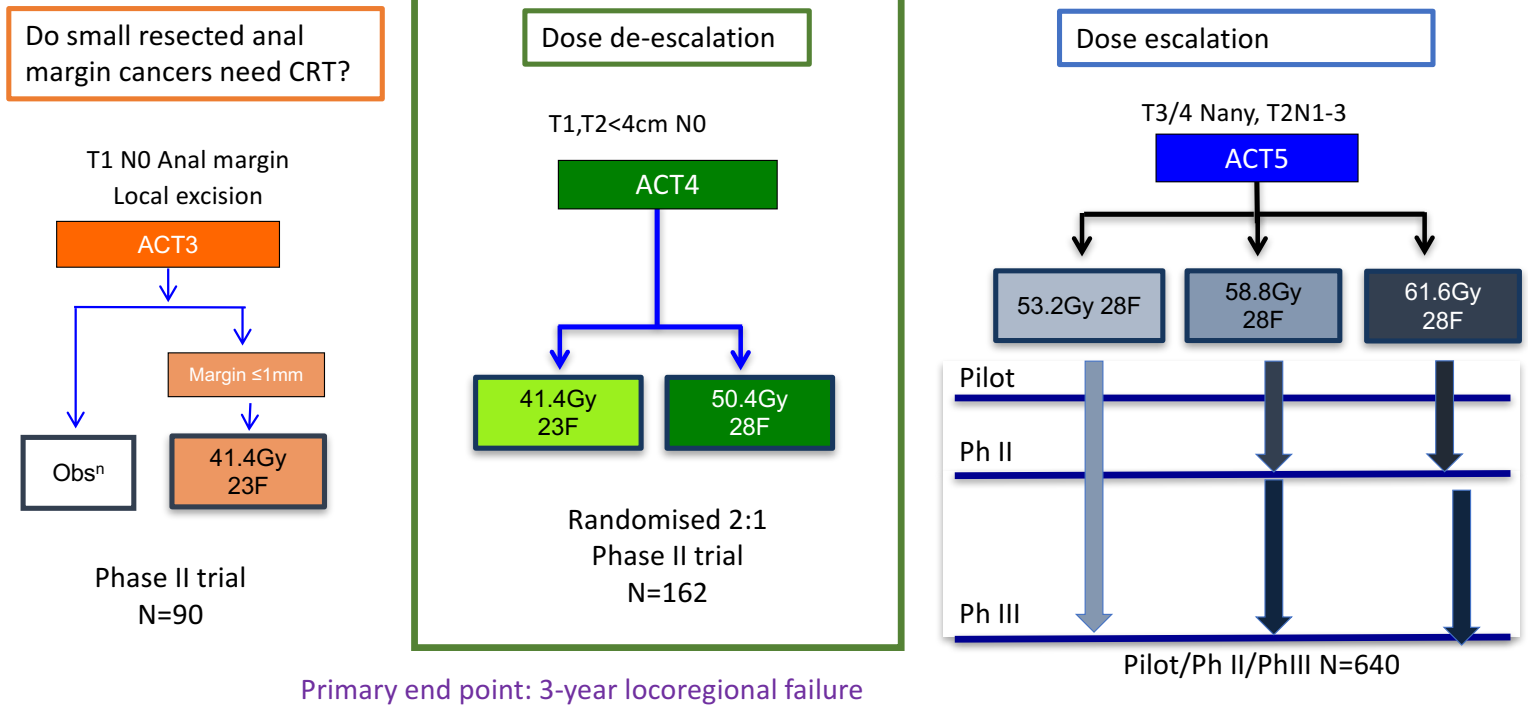
Larger tumours likely to have effect of higher radiation dose





Muirhead R et al., Radiother Oncol 2015; Johnsson A et al.,, Radiother Oncol 2018. Courtesy of Prof. Marianne Gronlie Guren, Oslo

PLATO - PersonaLising RadioTherapy dOse for Anal Cancer



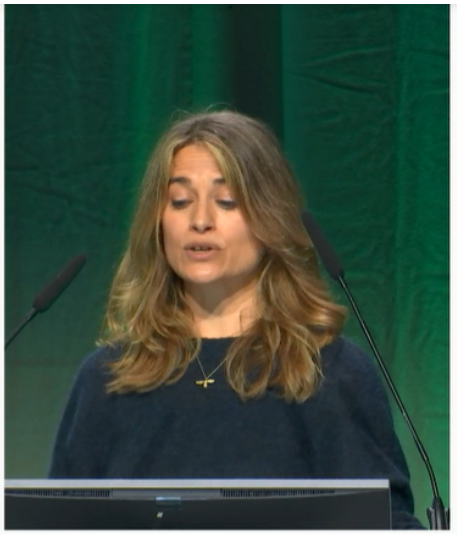
Primary end point: 3-year locoregional failure

Courtesy of Prof. Marianne Gronlie Guren, Oslo

ACT 4 Trial: Short-term results

ACT 4 TRIAL - CLINICAL RESPONSE RATE

	Standard dose IMRT (50.4Gy 28F) N (%) n=55	Reduced dose IMRT (41.4Gy 23F) N (%) N=105	Total n=160
TRG grade – 3 MONTHS			
Grade 1 (no evidence)	**25 (45.5%)**	**53 (50.5%)**	**78 (48.8%)**
Grade 2 (fibrosis only)	**24 (43.6%)**	**35 (33.3%)**	**59 (36.9%)**
Grade 3 (partial)	2 (3.6%)	7 (6.7%)	9 (5.6%)
Grade 4 (minimal response)	0 (0.0%)	1 (1.0%)	1 (0.6%)
Grade 5 (no response/progression)	1 (1.8%)	1 (1.0%)	2 (1.3%)
Missing*	3 (5.5%)	8 (7.6%)	11 (6.9%)
Total TRG1&2 excl. missing data	**49 (94.2%)+**	**88 (90.7%)++**	**137 (91.9%)**
TRG grade – 6 MONTHS			
Grade 1 (no evidence)	**26 (47.3%)**	**49 (46.7%)**	**75 (46.9%)**
Grade 2 (fibrosis only)	**19 (34.5%)**	**36 (34.3%)**	**55 (34.4%)**
Grade 3 (partial)	4 (7.3%)	5 (4.8%)	9 (5.6%)
Grade 4 (minimal response)	0 (0.0%)	1 (1.0%)	1 (0.6%)
Grade 5 (no response/progression)	1 (1.8%)	1 (1.0%)	2 (1.3%)
Missing*	5 (9.1%)	13 (12.4%)	18 (11.3%)
Total TRG1&2 excl. missing data	**45 (90.0%)^**	**85 (92.4%)^^**	**130 (91.5%)**



Alexandra Gilbert
United Kingdom

Similar high clinical complete response rates at 6 months in both arms

Gilbert A, presented at ESTRO 2023. Courtesy of Prof. Marianne Gronlie Guren, Oslo

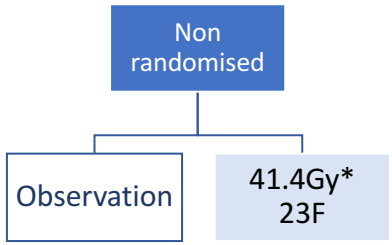
The PLATO trial platform

UNIVERSITY OF LEEDS

ACT3

Trial leads - Renehan and Muirhead

T1 N0/X Anal margin
Local excision



*Margin <=1mm

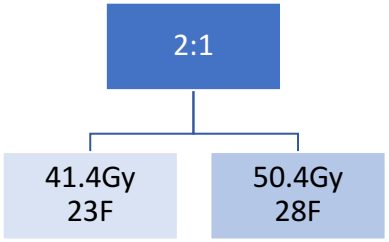
Phase II trial
N=90

83/90

ACT4

Trial Leads – Adams and Harrison

T1,T2<4cm N0/X



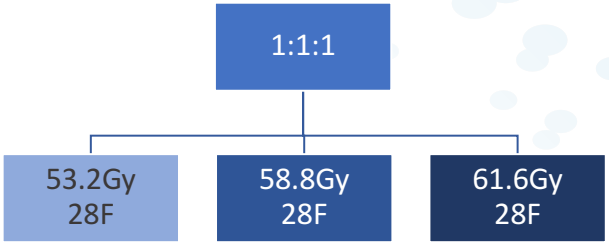
Randomised Ph 2 trial
N=162

163/162

ACT5

Leads – Hawkins and Sebag-Montefiore

T3/4 Nany,T2N1-3



Randomised Phase 3 trial n=459
(Internal pilot n=60, Phase II n=140)

463/459

CANCER RESEARCH UK | ctru LEEDS CLINICAL TRIALS UNIT | STAND UP TO CANCER | CANCER RESEARCH UK

Courtesy of Sebag-Montefiore D. Presented at IMACC 2023

Immunmodulation through radiation- a double edged sword

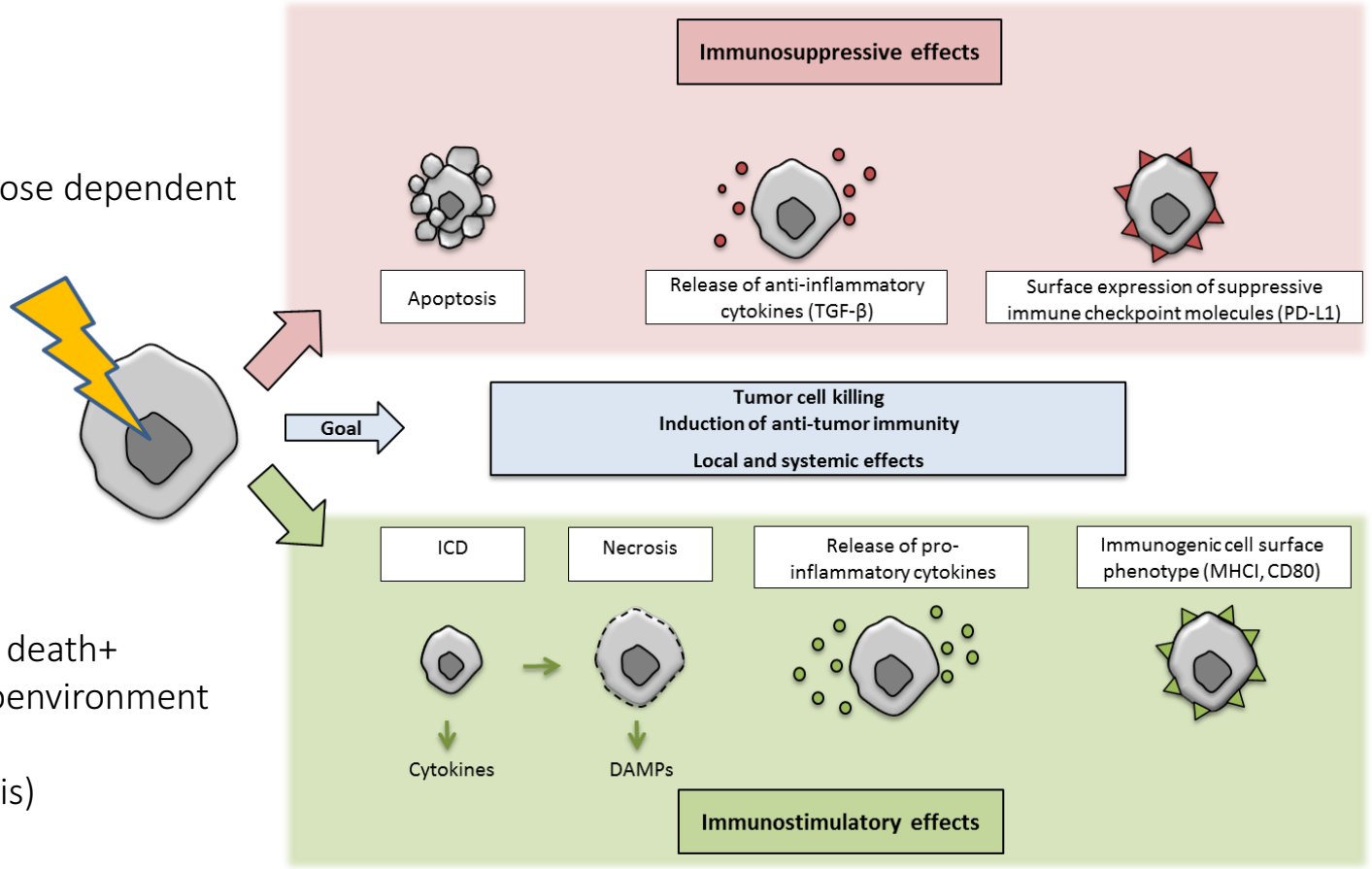
Effect probably dose dependent

Necrosis
Inflammation
T-cell-Activation

↓

Immunogenic cell death+
immunstim. microenvironment

(RT+HT = >Necrosis)



Reprogramming of macrophages+ recruitment of T-cells

↓

Apoptosis

Antiinflammatory pathway

Rückert M et al. Strahlenther Onkol 2018

Benefit of immune therapy with chemoradiation?

Tiraglolumab Atezolizumab and Chemoradiotherapy in Localized Anal Carcinoma (TIRANUS)

- proof-of-concept clinical trial of atezolizumab and tiragolumab in concomitancy with standard chemoradiotherapy (RT, 5-Fluorouracil, and Cisplatin) as first-line in localized squamous cell carcinoma of the anal canal.
- Single arm
- N= 45
- Spain

Chemoradiotherapy Combined With or Without PD-1 Blockade in Anal Canal Squamous Carcinoma Patients

- Assessing the efficacy and safety of concurrent mitomycin C/5-Fu chemotherapy and long-course IMRT combined with PD-1 antibody Sintilimab for locally advanced anal canal squamous carcinoma patients, by comparing an experiment group (traditional chemoradiotherapy with PD-1 antibody Sintilimab) with a control group (traditional treatment without Sintilimab).
- N= 102
- China

Benefit of immune therapy with chemoradiation?

Tiraglolumab Atezolizumab and Chemoradiotherapy in Localized Anal Carcinoma (TIRANUS)

- proof-of-concept clini
  tiragolumab in concor
  chemoradiotherapy (F
  first-line in localized sc
  canal.
- Single arm
- N= 45
- Spain

Chemoradiotherapy Combined With or Without PD-1 Blockade in Anal Canal Squamous Carcinoma Patients

Anti-PD-1 and mDCF Followed by Chemoradiotherapy in Patients With Stage III Squamous Cell Anal Carcinoma. (INTERACT-ION)

- proof of concept for radiotherapy combined with docetaxel, cisplatin and 5-fluorouracil and Ezabenlimab (BI 754091) in patients with stage III squamous cell anal carcinoma.
- Investigate Ezabenlimab (BI 754091) in synergy with mDCF to improve efficacy
- N= 55
- France

Radiochemotherapy +/- Durvalumab for Locally-advanced Anal Carcinoma. (RADIANCE)

- Investigate to improve the current standard treatment by incorporating durvalumab to the primary MMC/5-FU-based RCT in patients with locally-advanced ASCC (T2=>4cm Nany, stage IIB-IIIC)
- Randomized multicenter
- N=178
- Germany

Benefit of immune therapy with chemoradiation?

Tiraglolumab Atezolizumab and Chemoradiotherapy in Localized Anal Carcinoma (TIRANUS)

- proof-of-concept clini
  tiragolumab in concor
  chemoradiotherapy (F
  first-line in localized s
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- N=
- Sp

Chemoradiotherapy Combined With or Without PD-1 Blockade in Anal Canal Squamous Carcinoma Patients

Anti-PD-1 and mDCF Followed by Chemoradiotherapy in Patients With Stage III Squamous Cell Anal Carcinoma. (INTERACT-ION)

Radiochemotherapy +/- Durvalumab for Locally-advanced Anal Carcinoma. (RADIANCE)

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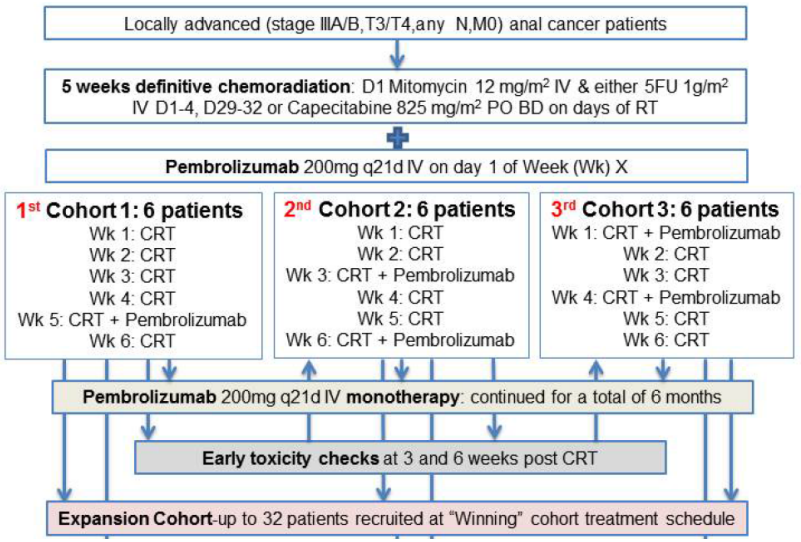
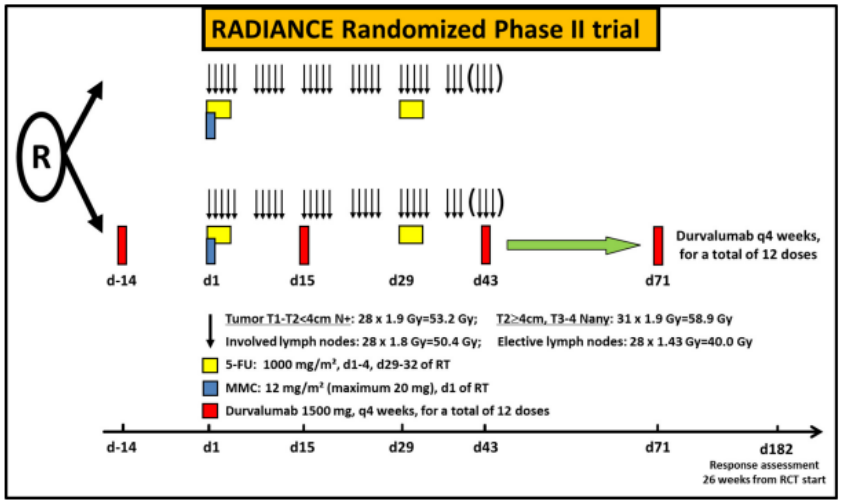


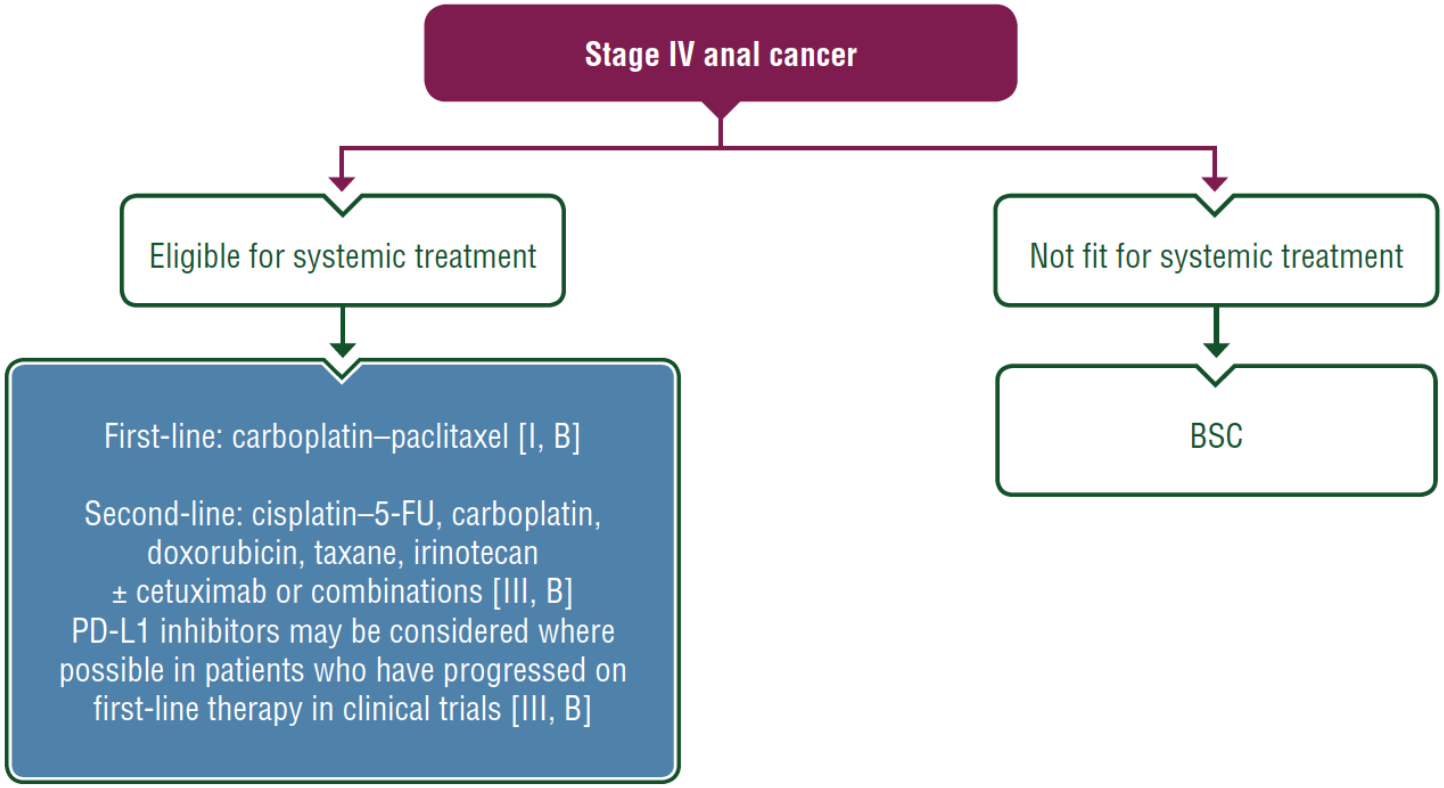


Nach der Primärtherapie: strukturierte Nachsorge

Untersuchung	Monate nach erfolgreichem Therapieabschluss													
	3	6	9	12	15	18	21	24	30	36	42	48	54	60
Anamnese	X	X	X	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	X
Klinische Untersuchung inkl. inguinaler Palpation und digital-rektaler Untersuchung	X	X	X	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	X
Proktoskopie und ggf. Rektoskopie	X	X	X	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	X
MRT-Becken		(X)		X				X		(X)		(X)		
CT-Thorax und -Abdomen mit Kontrastmittel(1)		X				(X)			(X)					
Optional PET/CT*		(X)				(X)			(X)					

https://register.awmf.org/assets/guidelines/081-004OLl_Analkarzinom_Diagnostik- Therapie-Nachsorge-Analkanalkarzinom-Analrandkarzinom_2020-12.pdfc

Metastatic disease



ESMO Guideline, Rao S et al., Ann Oncol 2021

Metastatic disease

Stage IV anal cancer

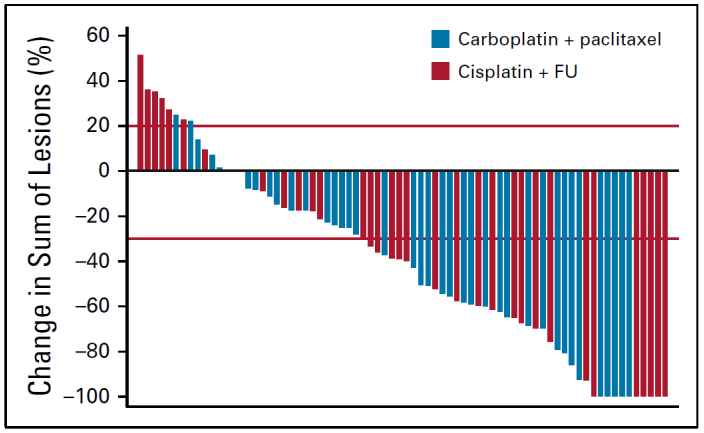
International Rare Cancers Initiative Multicenter Randomized Phase II Trial of Cisplatin and Fluorouracil Versus Carboplatin and Paclitaxel in Advanced Anal Cancer: InterAAct

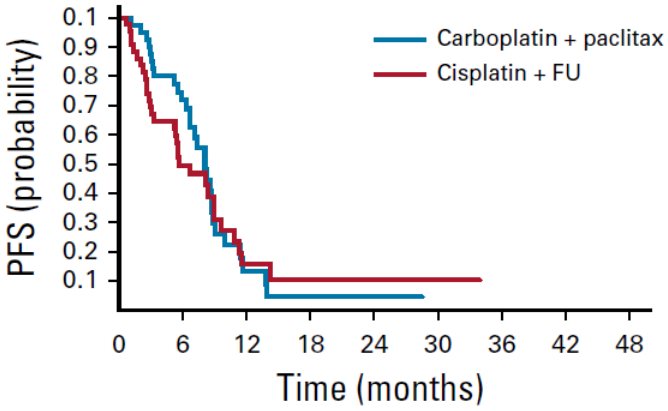
Sheela Rao, MD[1]; Francesco Sclafani, MD, PhD[1]; Cathy Eng, MD[2]; Richard A. Adams, MD[3]; Marianne G. Guren, MD, PhD[4]; David Sebag-Montefiore, MD[5]; Al Benson, MD[6]; Annette Bryant[1]; Clare Peckitt, MSc[1]; Eva Segelov, PhD[7]; Amitesh Roy, MSc, MD[8]; Matt T. Seymour, MA, MD[5]; Jack Welch, MD, PhD[9]; Mark P. Saunders, PhD[10]; Rebecca Muirhead, MD[11]; Peter O'Dwyer, MD[12]; John Bridgewater, PhD[13]; Shree Bhide, MRCP, PhD[14]; Rob Glynne-Jones, MD[15]; Dirk Arnold, MD[16]; and David Cunningham, MD FRCP[1]

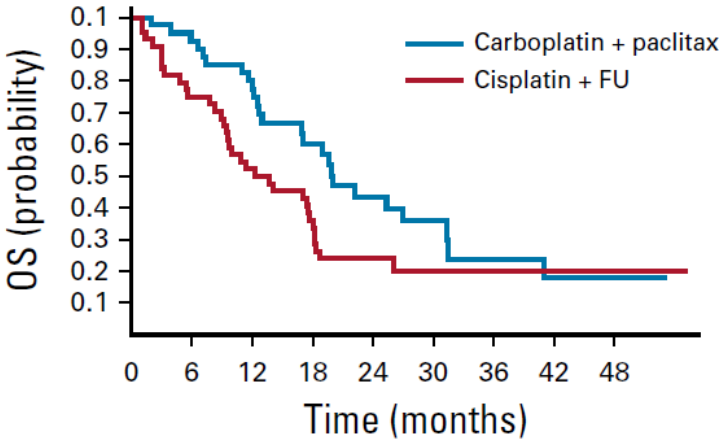
ESMO Guideline, Rao S et al., Ann Oncol 2021; Rao et al., J Clin Oncol 2020

InterAACT: Carboplatin and paclitaxel

- Randomised 1st line trial
- No difference in ORR (59%)
- Fewer SAE (36% vs 62%)



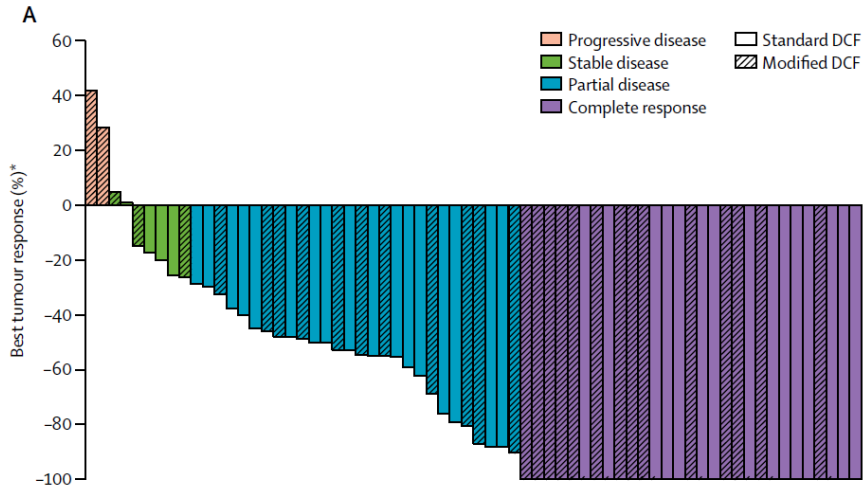


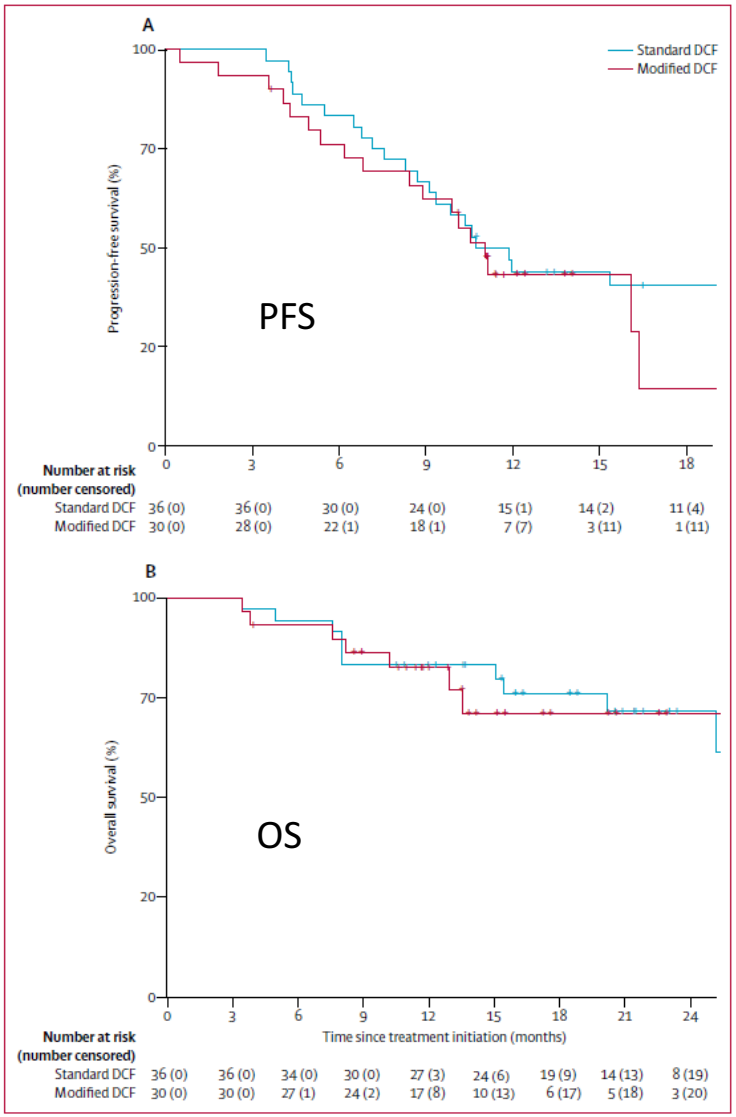


Rao S et al, J Clin Oncol 2020

Epitopes-HPV02: Modified DCF

- Single-arm phase II
- DCF (Docetaxel, Cisplatin, Fluorouracil) or modified DCF based on age / performance status
- Modified DCF similar efficacy, less toxicity





Kim S et al, Lancet Oncol 2018

A cross-trial comparison: What is SOC?

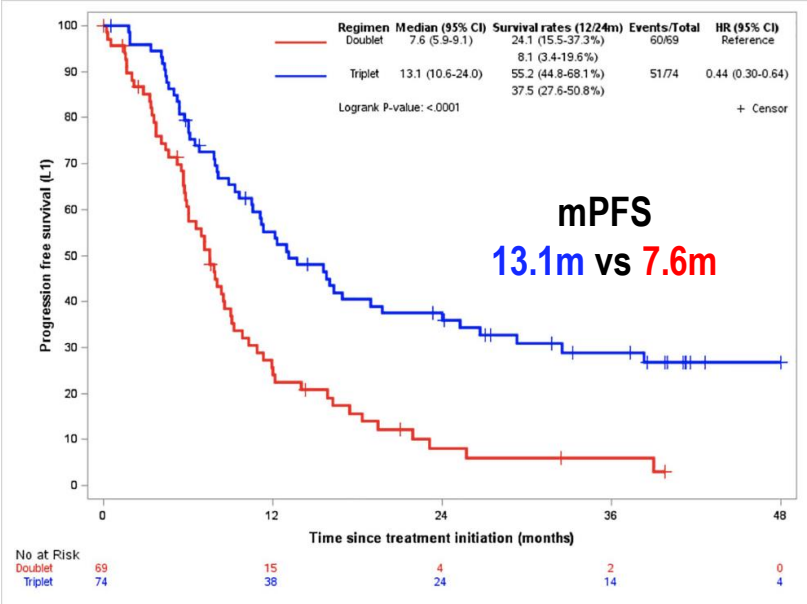
	TRIPLET	DOUBLET
	mDCF (Docetaxel, CDDP, 5FU)	**CP (Carboplatin + Paclitaxel)** CF (Cisplatin + 5FU)
Endpoints	**Epitopes-HPV02 study**	**InterAACT study**
1y PFS rate	**47%**	**~15%**
ORR	**83%**	**59%** vs 57.1%
CRR	**47%**	**12.8%** vs 17.1%
G3/4 Toxicity	**53%** (vs 83% sDCF)	**71%** vs 76%
SAE		**36%** vs 62%*
OS (months)	**50.2**[3]	**20** vs 12.3
HPV ctDNA -	**61.1%**	**17.9%**

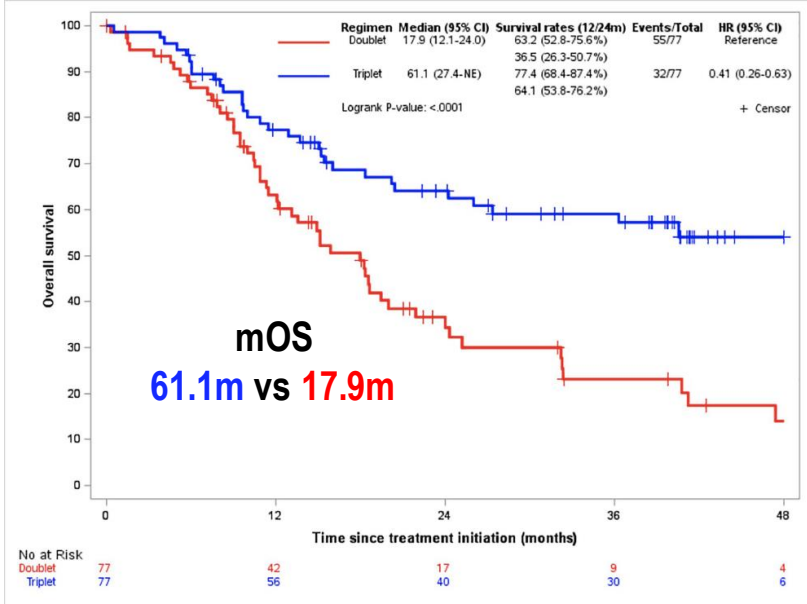
Kim S et al, ESMO Deep Dive Webinar 2023. Kim S et al., Lancet Oncol 2018; Rao S et al., J Clin Oncol 2020

A cross-trial comparison: What is SOC?

Propensity Score matching study

TRIPLET **Versus** **DOUBLET**





Kim S et al, Experimental Hematoloigy and Oncology 2023

ASKLEPIOS TUMORZENTRUM HAMBURG

Summary of Published Results of Drugs Used for Second-Line Treatment in SCAC

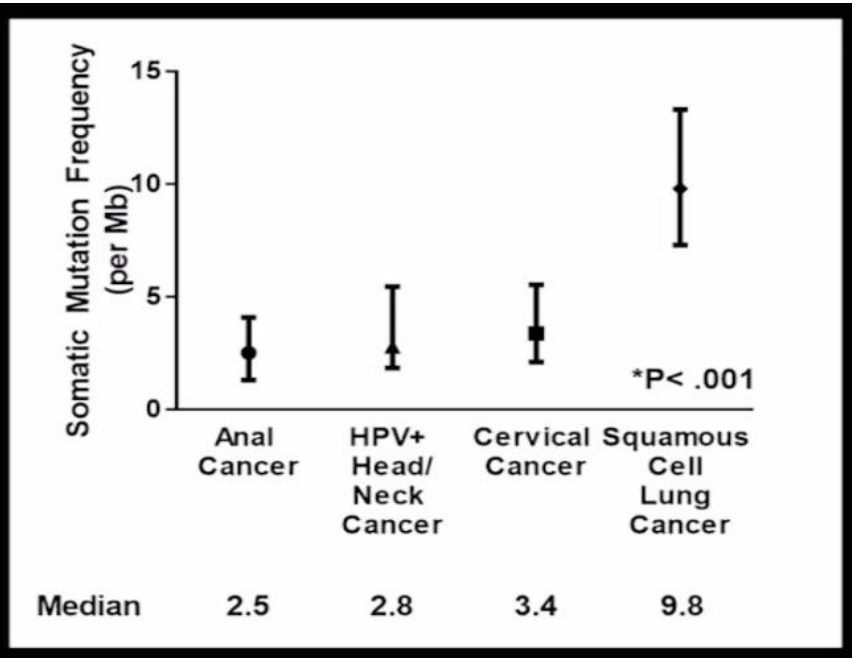
Drug (Study or Study Design)	**N**	**ORR* %** (95% CI)	**Median DOR** (months)	**Median OS** (months)	**HIV+** (n)
Mitomycin + 5-FU (Retrospective, single-institution)	**19**	**26%** (7, 46)	**4**	**7**	**1**
Chemotherapy (Retrospective, single-institution)	**21**	**33%** (NA)	**NA**	**NA**	**5****
Nivolumab[3] (NCl967310) Van Morris et al Lancet Onc 2017	**37**	**24%** (15, 33)	**5.8**	**11.5**	**2**
Pembrolizumab[5] (KEYNOTE-158) Marabelle et al Lancet Gastro and Hep 2017	**112**	**11%** (6, 18)	**NR**	**11.9**	**0**
Retifanlimab Rao et al ESMO Open 2022	**94**	**13.8%** (7.6,22.5)	**9.5**	**10.5**	**9**

Rao S, oral presentation; IMACC Congress 2023

Advanced Anal SCC: A „homerun“ for immunotherapy?

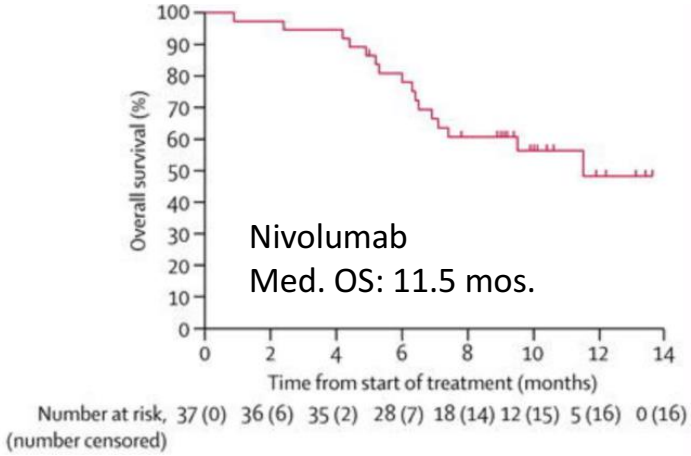
Anal canal cancer usually arises from HPV infection (integration of viral DNA with epithelial cell DNA)
Presence of viral neoantigens→possible immunotherapy activity

- 30 patients on the NCI9673 study had pretreatment cfDNA analyzed for mutation profiling on Guardant 70-gene panel.
- While TP53 (29%) and PIK3CA (23%) were the most commonly mutated genes, no associations were noted between response to therapy and the presence/absence of mutations.
- Median 1.6 mutations per patient noted in the 30 patients here.
- These results are consistent with other reports, with one recent series of SCCA patients using a 255-gene panel showed 3.6 mutations/patient.



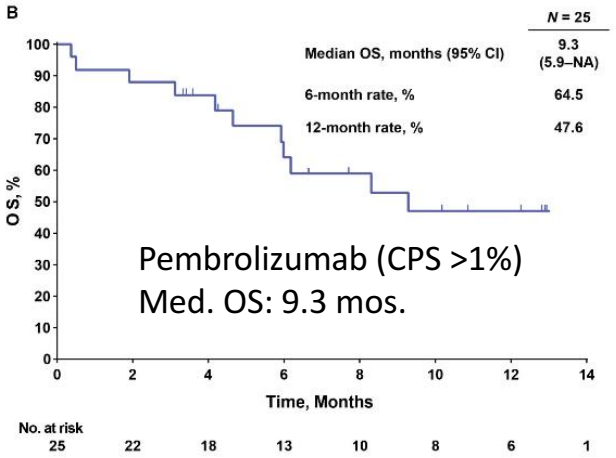
Hung et al., Ann Oncol 2016; Van Morris et al., Mol Can Res 2017

Immune checkpoint inhibitors: Single agent



Nivolumab
Med. OS: 11.5 mos.

24% ORR, 2 CR
Median DFS 4.1 mos.

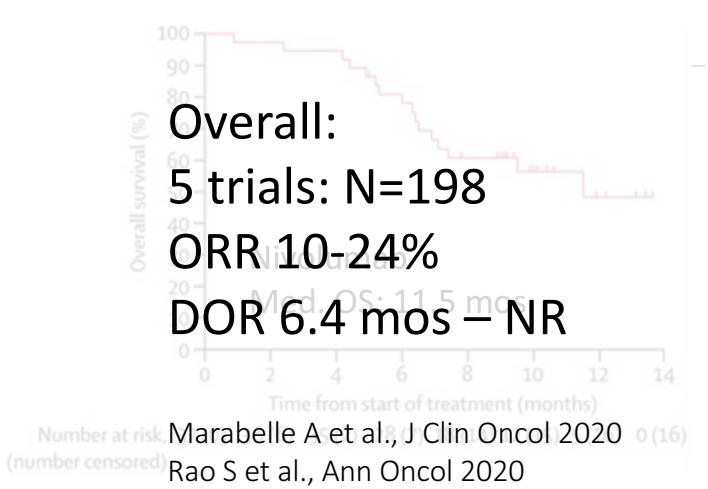


Pembrolizumab (CPS >1%)
Med. OS: 9.3 mos.

17% ORR, (no CR)
Median DFS 3.0 mos.

Van Morris K et al., Lancet Oncol 2017; Ott PA et al., Ann Oncol 2016

Immune checkpoint inhibitors: Single agent



Overall:
5 trials: N=198
ORR 10-24%
DOR 6.4 mos – NR

Marabelle A et al., J Clin Oncol 2020
Rao S et al., Ann Oncol 2020
Lonardi S et al., JIC 2021

Pembrolizumab (CPS >1%)
Med. OS: 9.3 mos.

24% ORR, 2 CR
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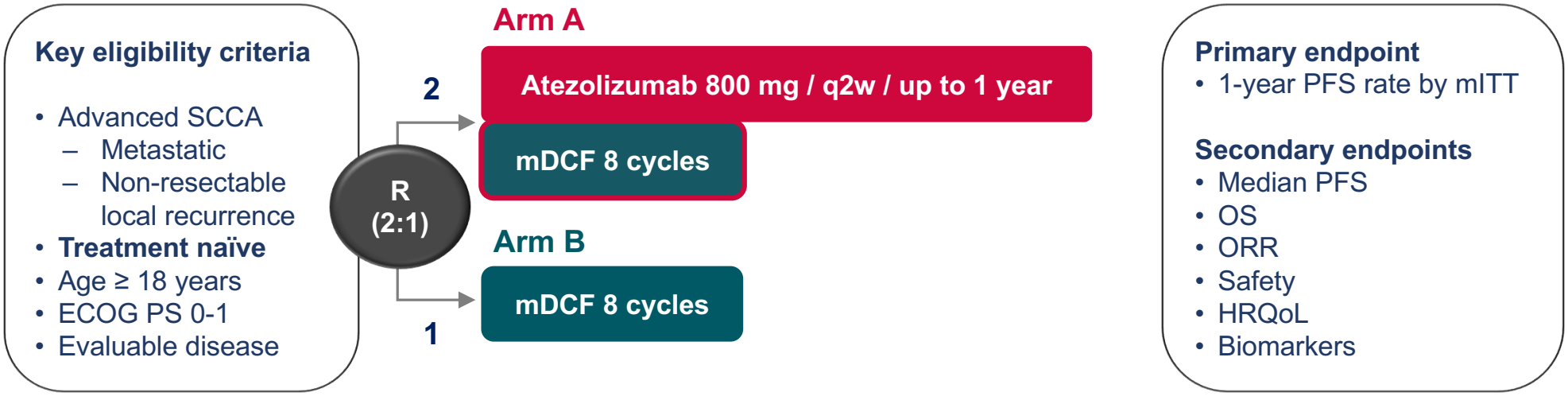
Van Morris K et al., Lancet Oncol 2017; Ott PA et al., Ann Oncol 2016

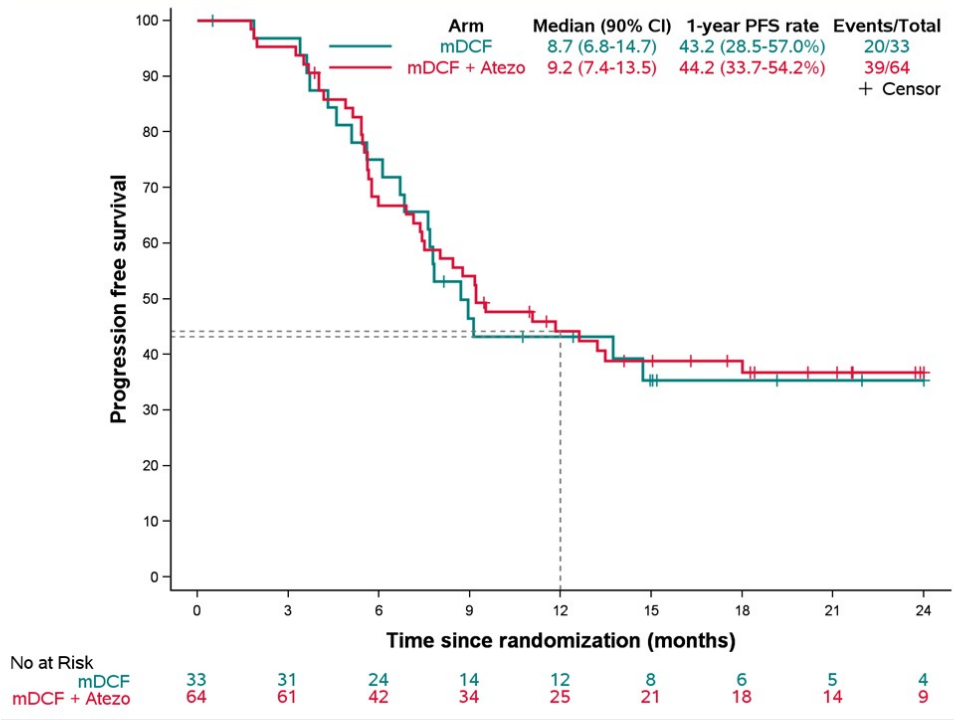
Chemo plus ICI: The first randomized trial

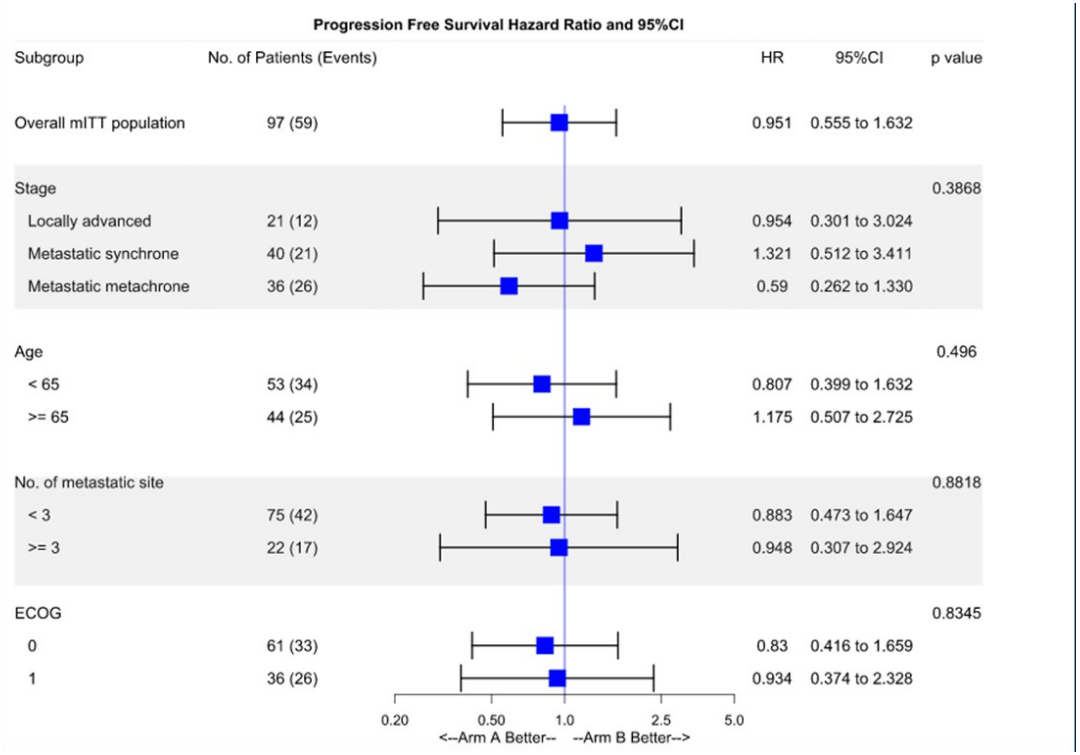


Stratification: age (<65 vs ≥65 years), stage (synchronous metastatic vs metachronous metastatic vs locally advanced unresectable disease without metastasis)

Kim S. et al., ASCO 2022

Chemo plus ICI: The first randomized trial





Kim S. et al., ASCO 2022

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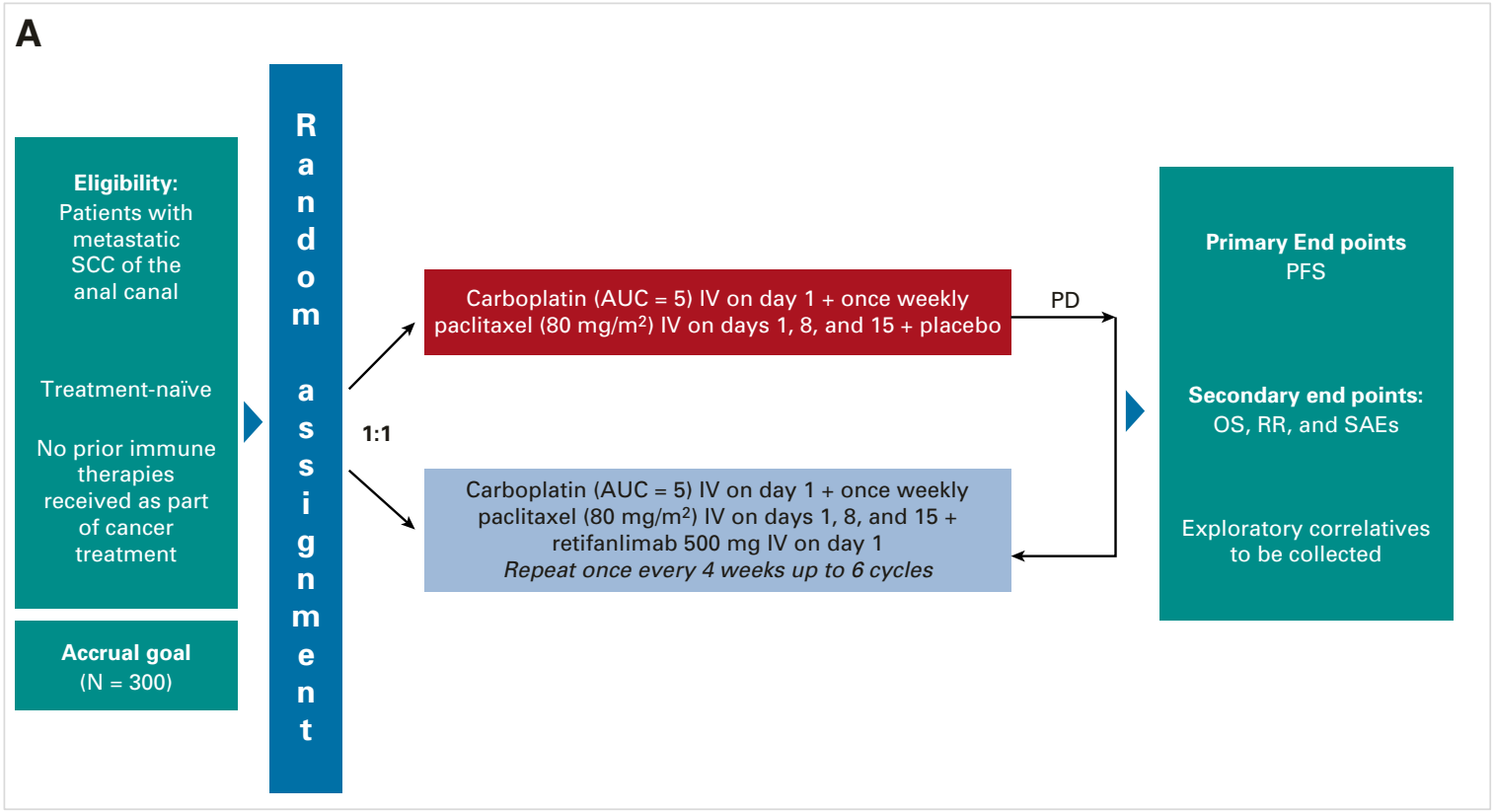
Chemo plus ICI: The first randomized trial

	All (N=97)	Arm A (N=64)	Arm B (N=33)	Epitopes-HPV (N=115)[1,2]
Objective response, n (%)	72 (**75.8**)	47 (**74.6**)	25 (**78.1**)	100 (**87.7**)
Complete response	34 (35.8)	19 (30.2)	15 (**46.9**)	46 (40.3)
Partial response	38 (40.0)	28 (44.4)	10 (31.3)	54 (47.4)
Stable disease	20 (21.1)	14 (22.2)	6 (18.8)	10 (8.8)
Progression disease	3 (3.2)	2 (3.2)	1 (3.1)	4 (3.5)
Missing	2	1	1	0

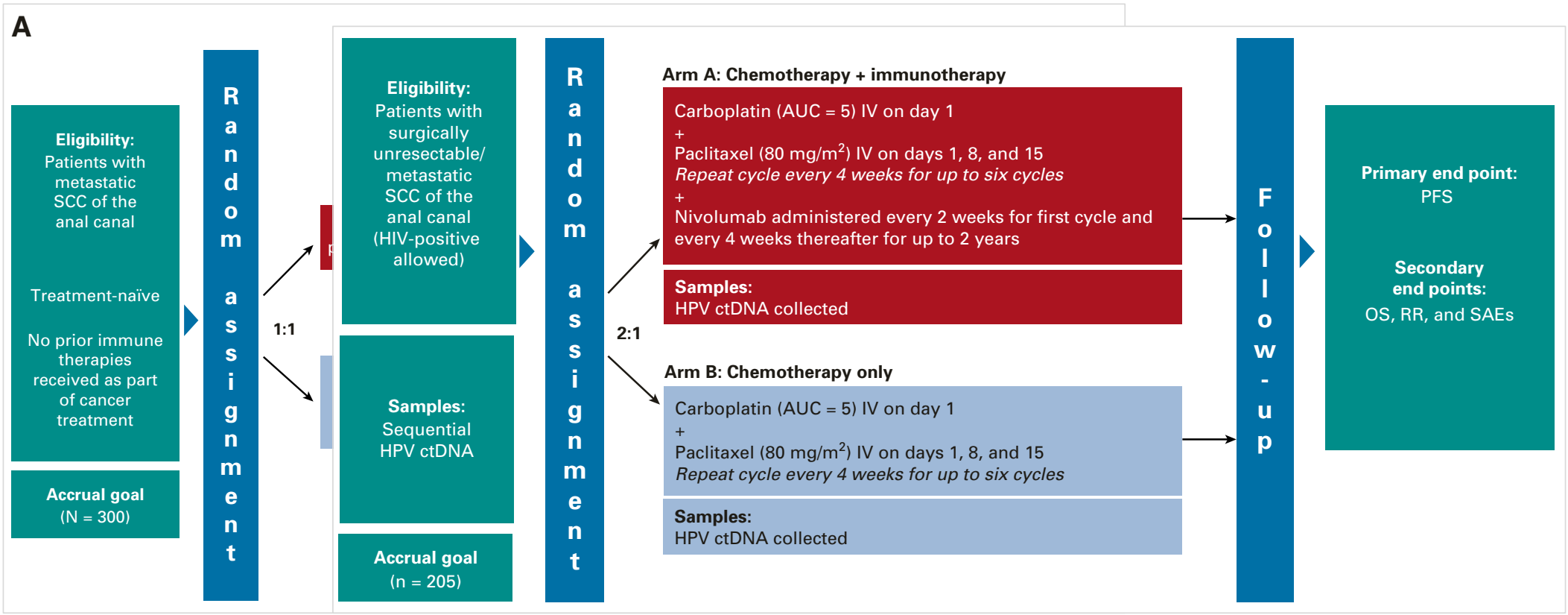
Kim S. et al., ASCO 2022

Ongoing randomized immunotherapy trials



Eng C et al., J Clin Oncol 2022

Ongoing randomized immunotherapy trials



Eng C et al., J Clin Oncol 2022

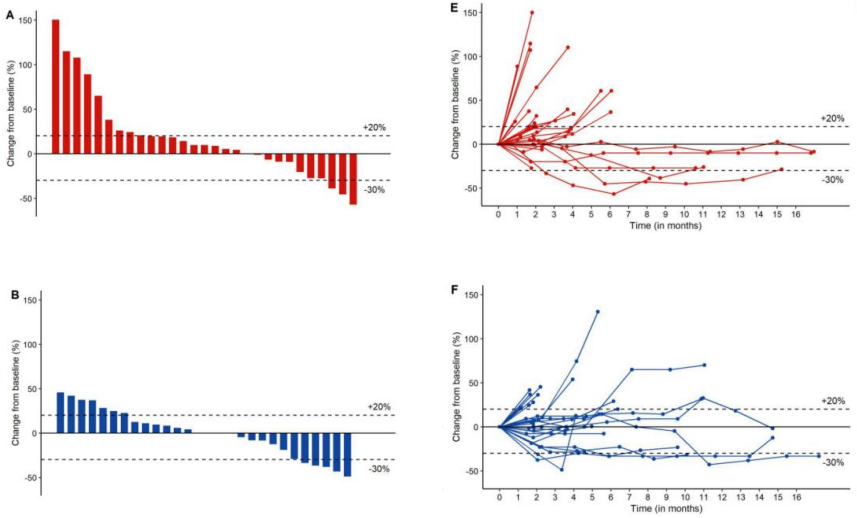
ICI plus anti-EGFR: CARACAS trial

Unresectable, advanced or metastatic SCAC after 1st line

N=60
Ratio 1:1

Arm A
N=30
Avelumab 10 mg/kg q2w

Arm B
N=30
Avelumab 10 mg/kg +
Cetuximab 500 mg/mq q2w



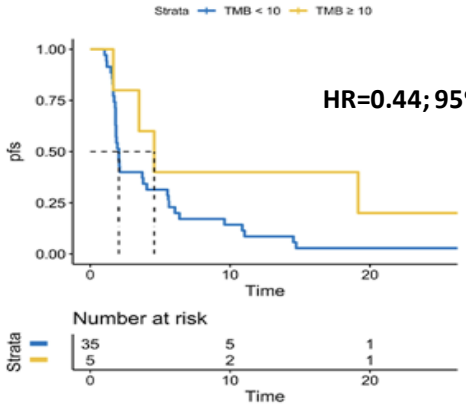
ORR 10%
DCR 50%

ORR 17%
DCR 57%

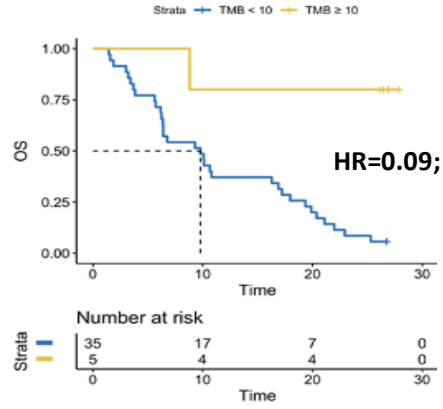
Lonardi S et al., J Immunother Cancer 2020

ICI plus anti-EGFR: Biomarkers matter

TMB

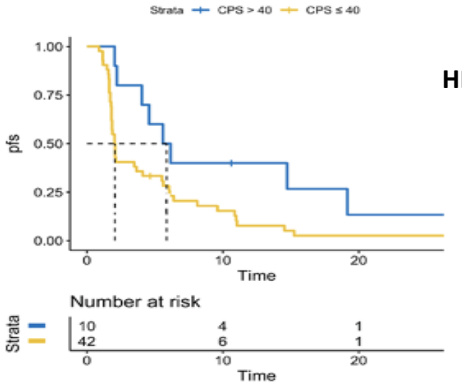


HR=0.44; 95%CI=0.15-1.27; p=0.129

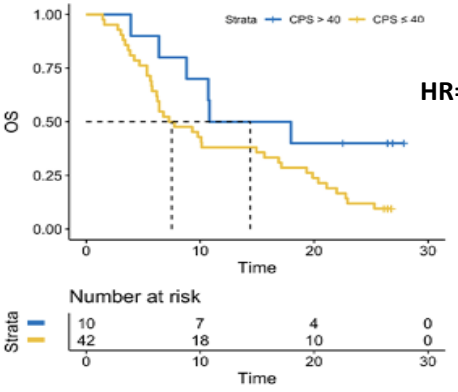


HR=0.09; 95% CI 0.01-0.68; p=0.019

PD-L1 CPS



HR=2.35; 95%CI=1.09-5.1; p=0.03



HR=2.19; 95% CI=0.92-5.19; p=0.075

Prete AA et al., Eur J Cancer 2023

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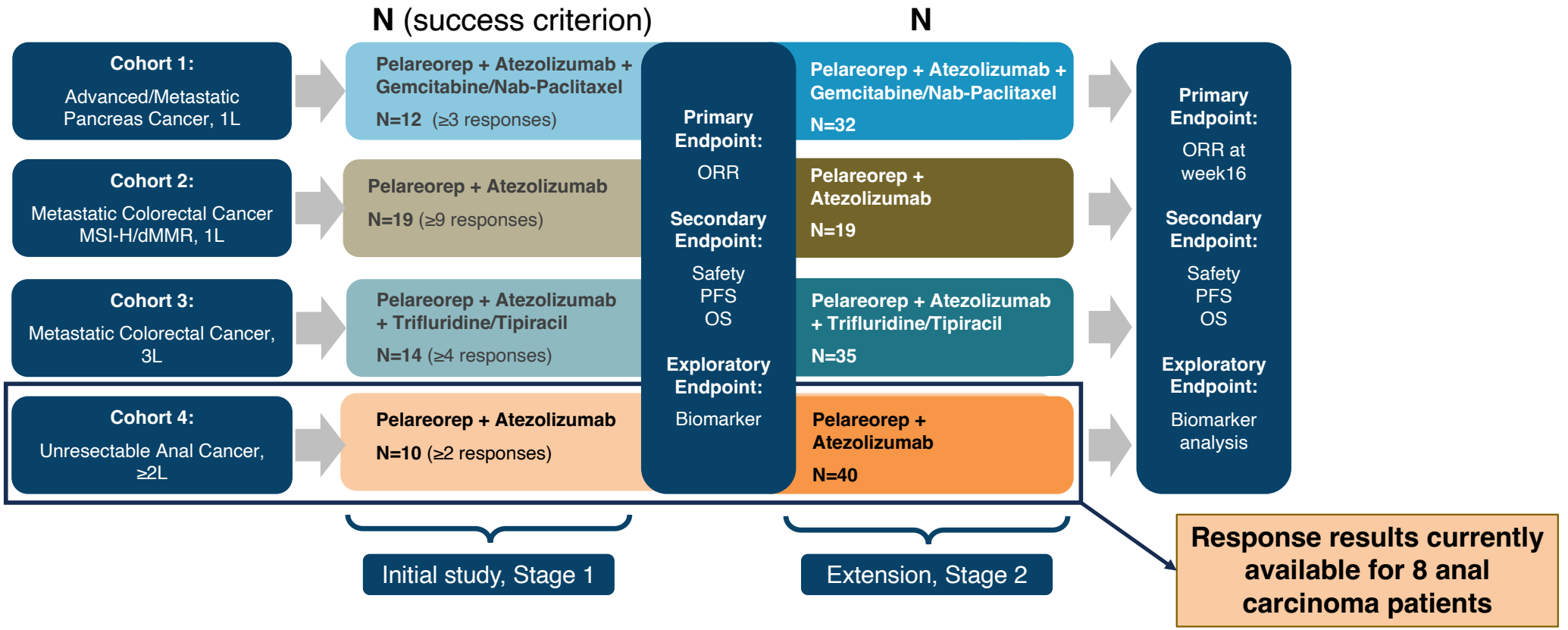
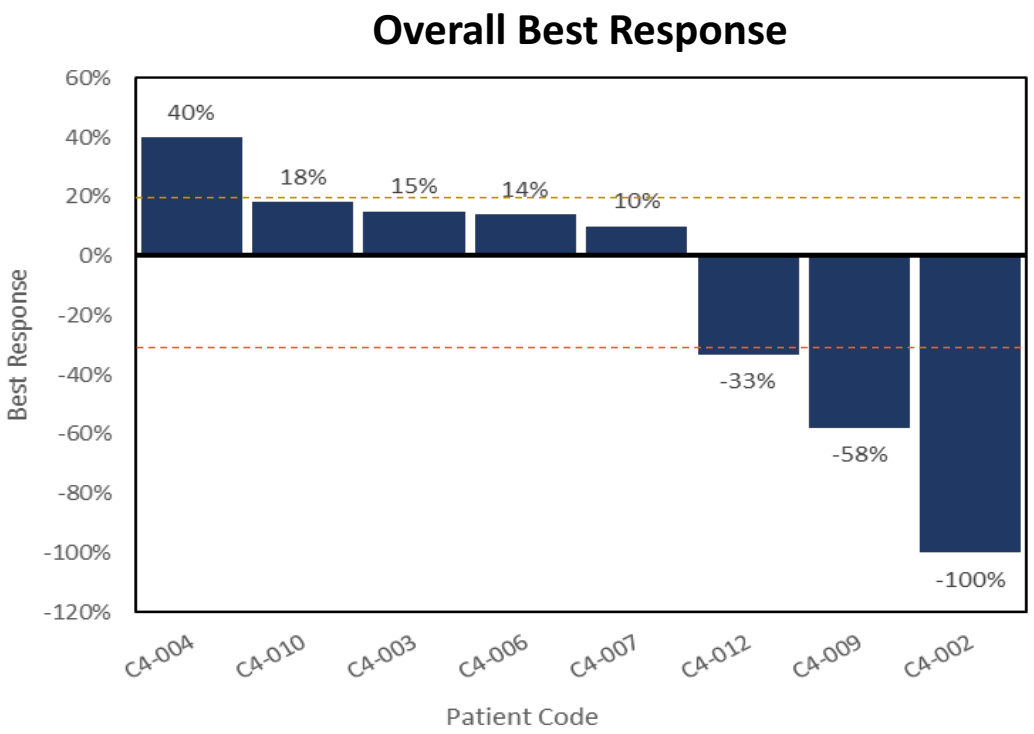
Oncoloytic virus Pelareorep plus ICI: AIO GOBLET

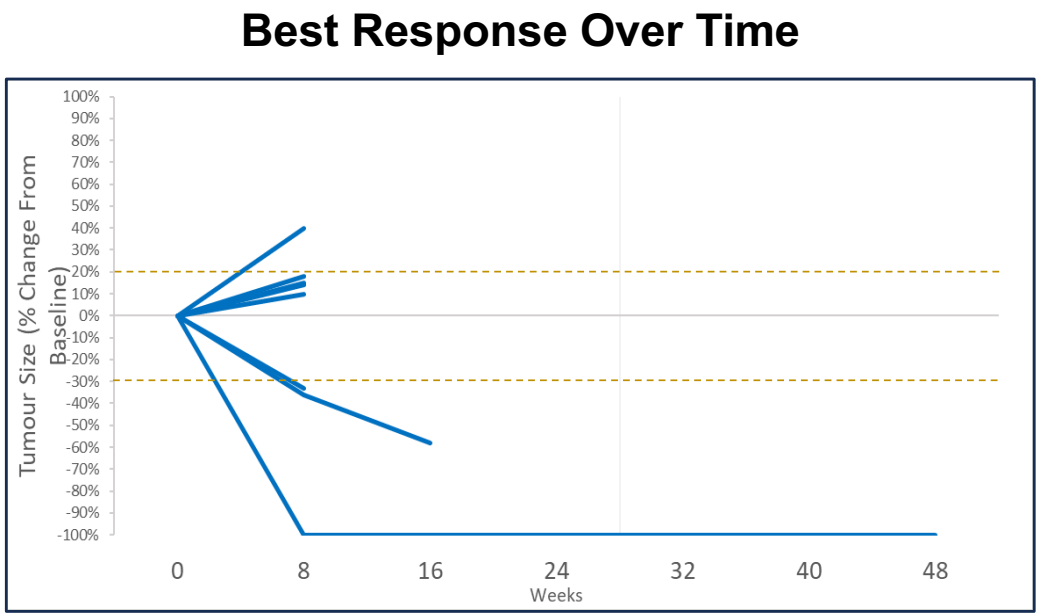


Arnold D et al., ESMO 2023; IMACC 2023

ASKLEPIOS TUMORZENTRUM HAMBURG

Oncoloytic virus Pelareorep plus ICI: AIO GOBLET





Arnold D et al., ESMO 2023; IMACC 2023

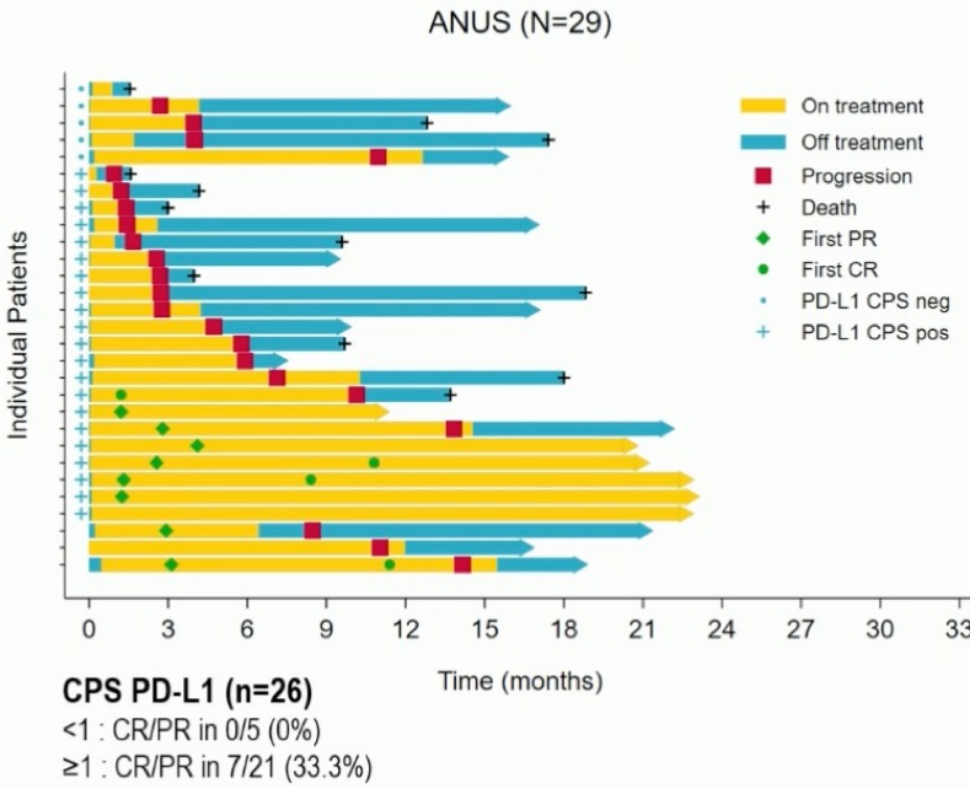
ASKLEPIOS TUMORZENTRUM HAMBURG

HDAC inhibitor Vorinostat plus ICI (Pembro): PEVOSq trial

Objective Response Rate (ORR)

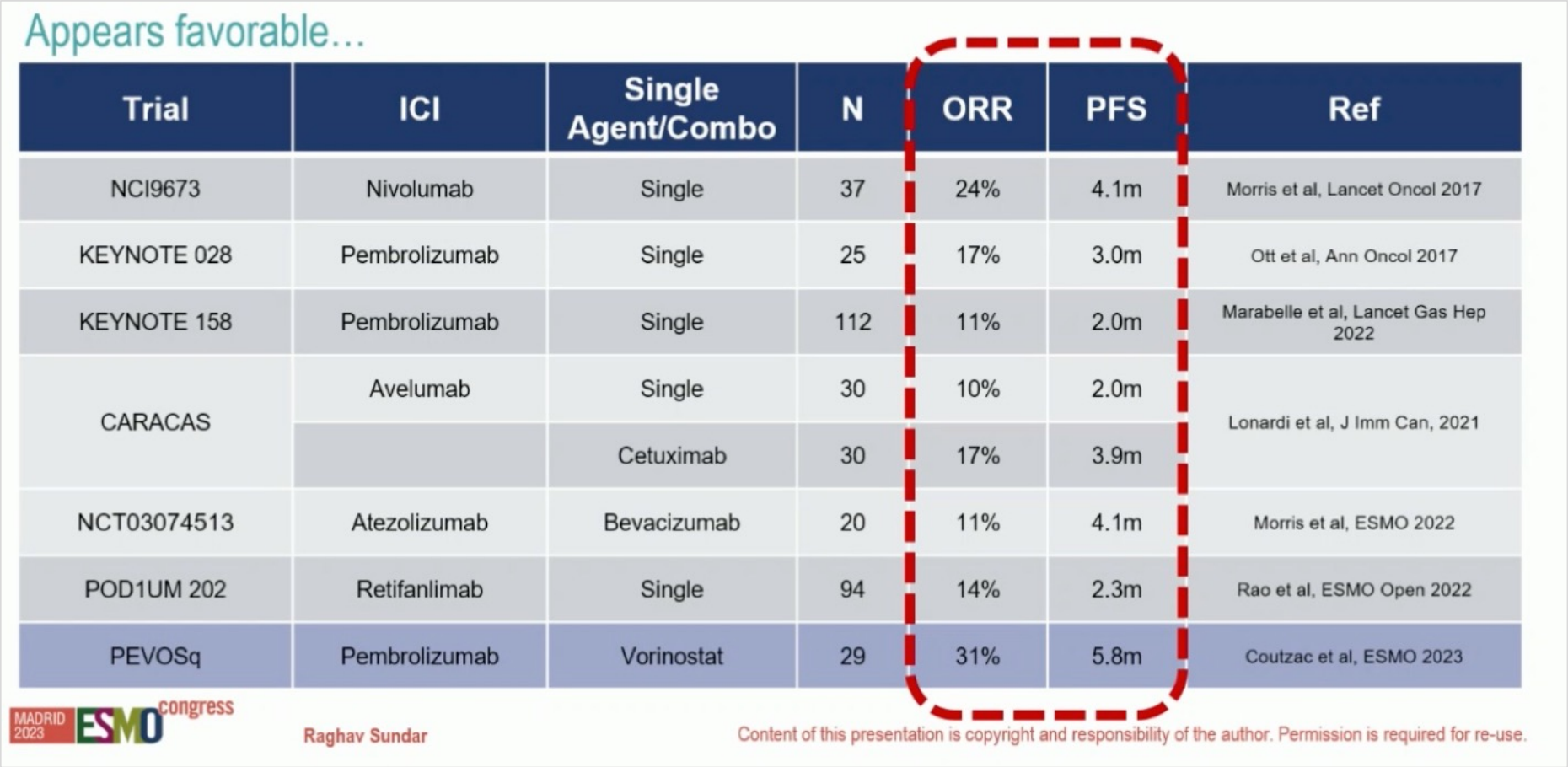
	SCAC cohort (n=29)
Best response, n (%)	
CR	4 (13.8)
PR	5 (17.2)
SD	14 (48.3)
PD	5 (17.2)
NE	1 (3.4)*
ORR, % [95% CI]	**31.0** [15.3-50.8]
Median PFS, months [95% CI]	**5.8** [2.7-11.0]
Median OS, months [95% CI]	**18.8** [12.8-NR]

* Death before the first tumor assessment



Coutzac C et al., ESMO 2023

Combinations: „Appear favourable...:“



Appears favorable...

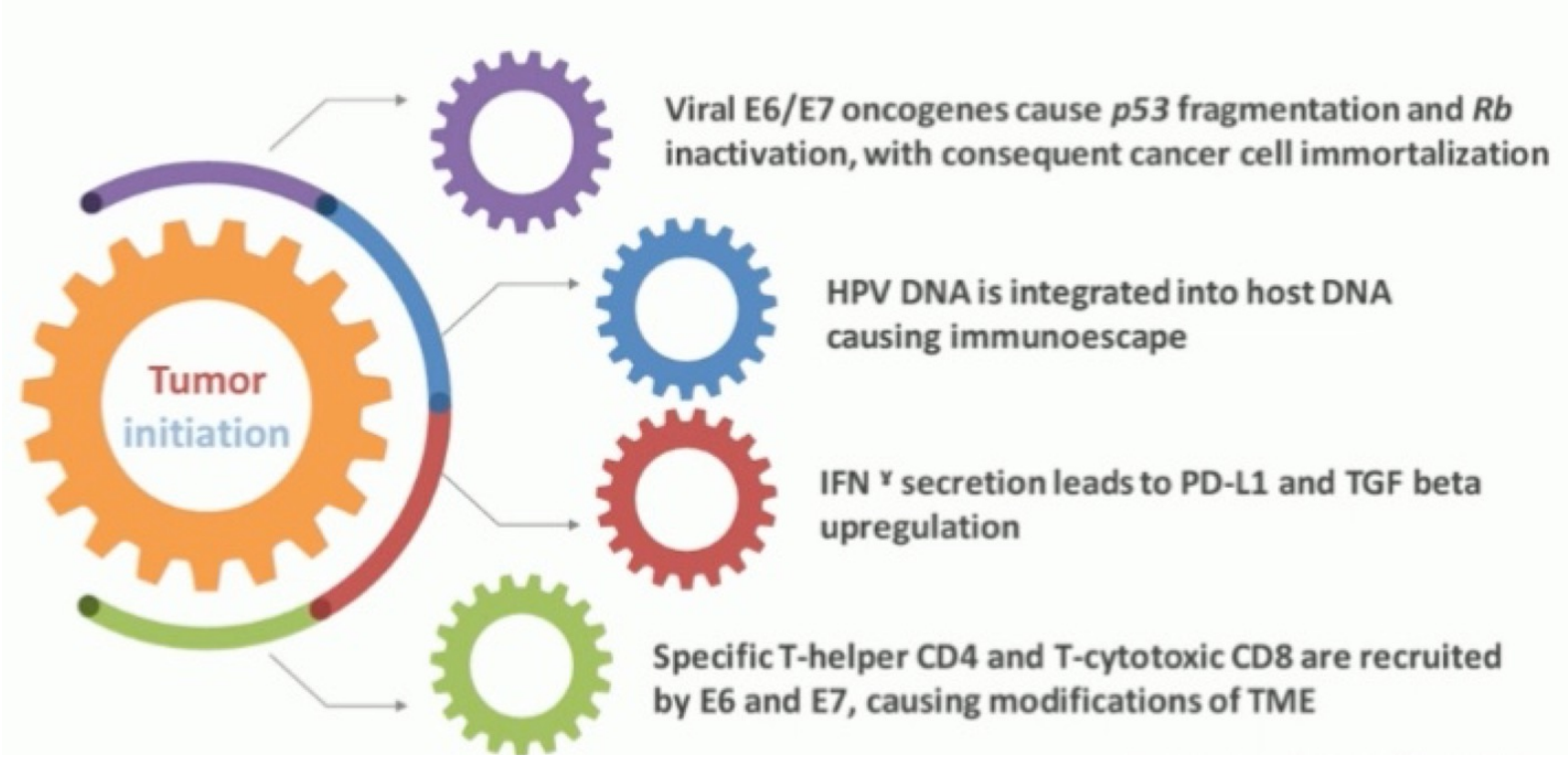
Trial	ICI	Single Agent/Combo	N	ORR	PFS	Ref
NCI9673	Nivolumab	Single	37	24%	4.1m	Morris et al, Lancet Oncol 2017
KEYNOTE 028	Pembrolizumab	Single	25	17%	3.0m	Ott et al, Ann Oncol 2017
KEYNOTE 158	Pembrolizumab	Single	112	11%	2.0m	Marabelle et al, Lancet Gas Hep 2022
CARACAS	Avelumab	Single	30	10%	2.0m	Lonardi et al, J Imm Can, 2021
		Cetuximab	30	17%	3.9m	
NCT03074513	Atezolizumab	Bevacizumab	20	11%	4.1m	Morris et al, ESMO 2022
POD1UM 202	Retifanlimab	Single	94	14%	2.3m	Rao et al, ESMO Open 2022
PEVOSq	Pembrolizumab	Vorinostat	29	31%	5.8m	Coutzac et al, ESMO 2023

MADRID 2023 ESMO congress

Raghav Sundar

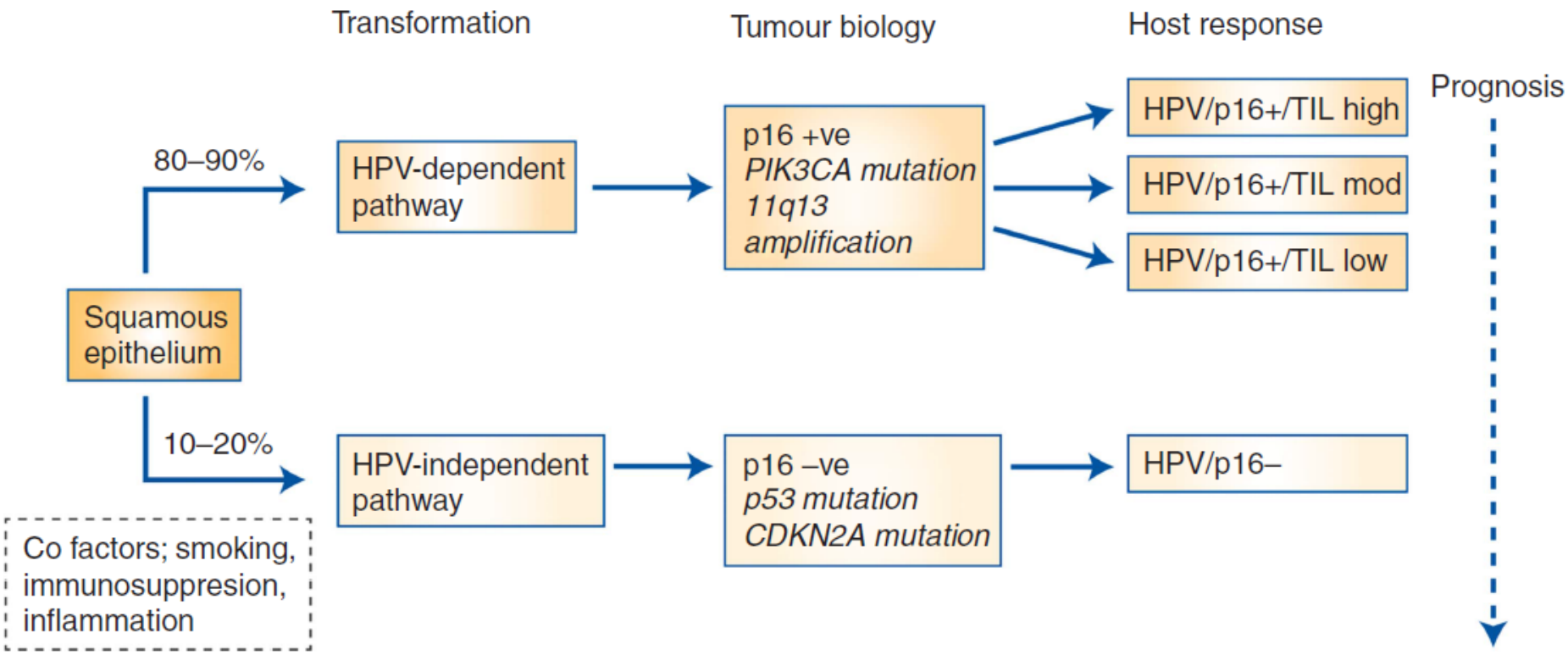
Sundar R et al., ESMO 2023; oral discussant

SCC of the anal tract: Why immunotherapy matters



Lonardi S et al., ESMO Webinar Deep Dive Series 2023

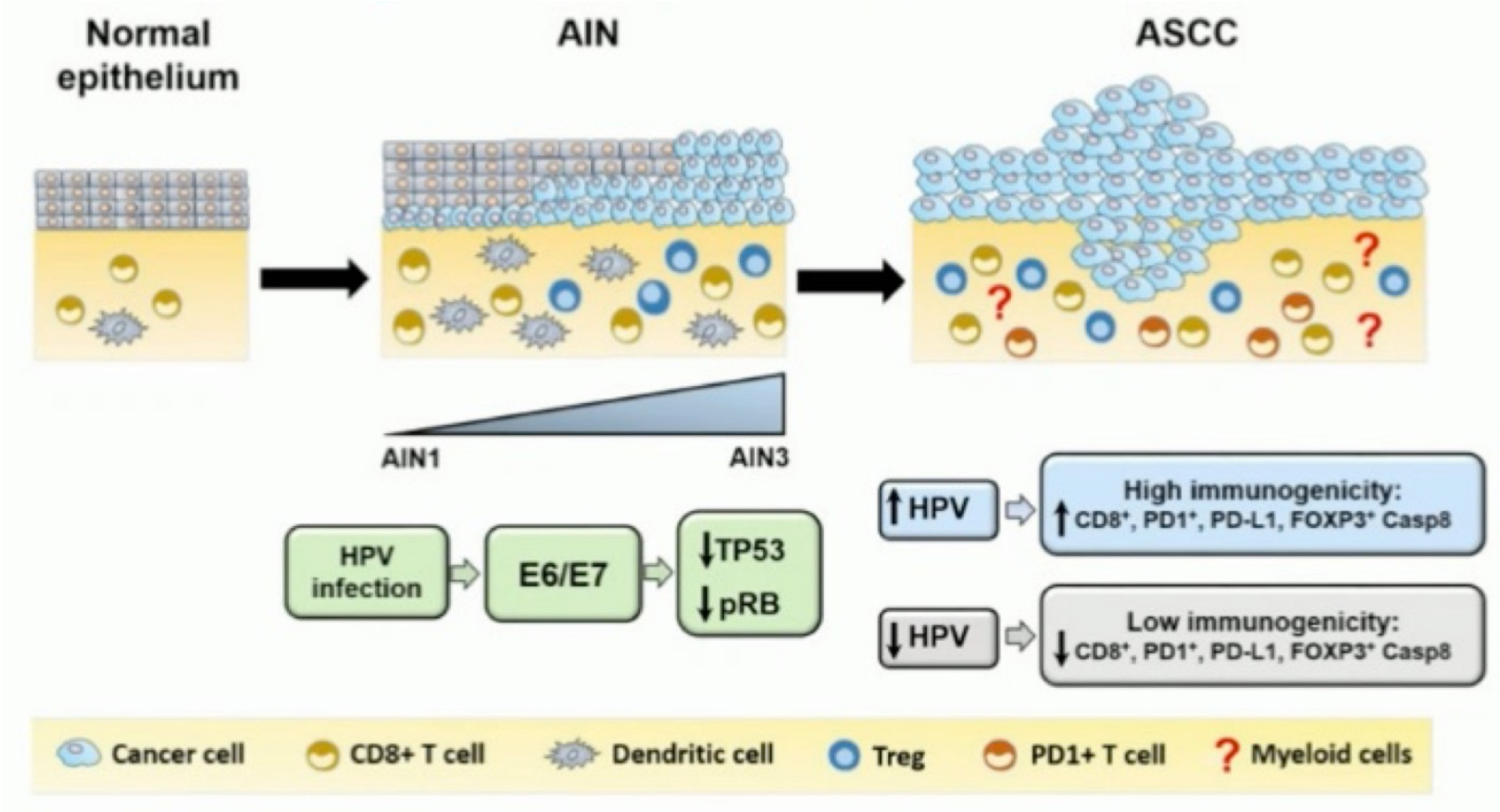
Biological model of response to CRT



Need for biology-driven studies and strategies for HPV negative tumours

Jones CM et al., Br J Cancer 2017

The route for HPV targeted approaches?

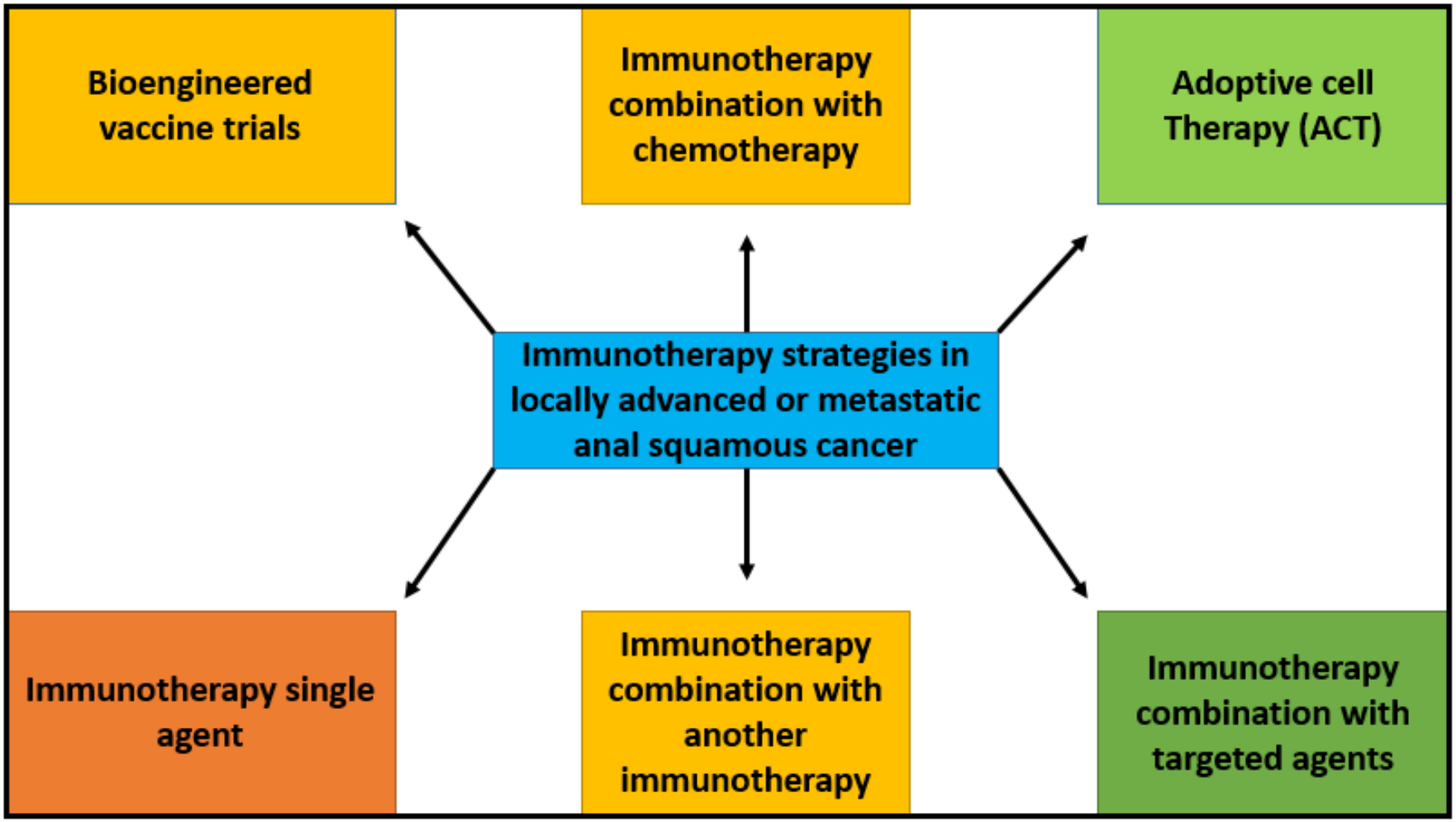


HPV targeted approaches under investigation

- HPV E6 and E7 T-cell receptor inhibitor, followed by aldesleukin
- HPV 16 E7-protein fusion protein (axalimogene filolisbasc)
- Anti-HPV vaccination
- TILs plus aldesleukin plus nivolumab

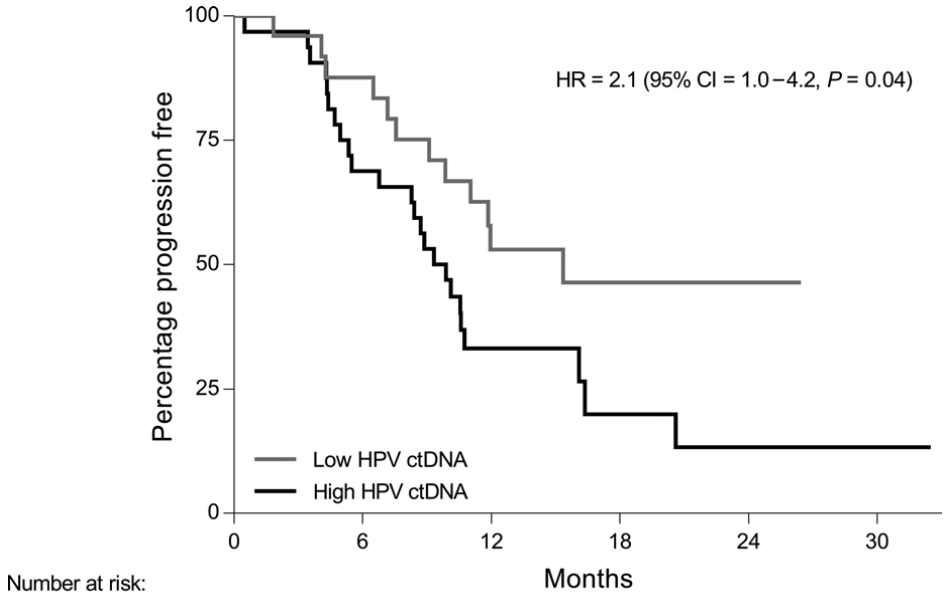
Zusammenfassung Anal-Ca.: Metastasierte Erkrankung

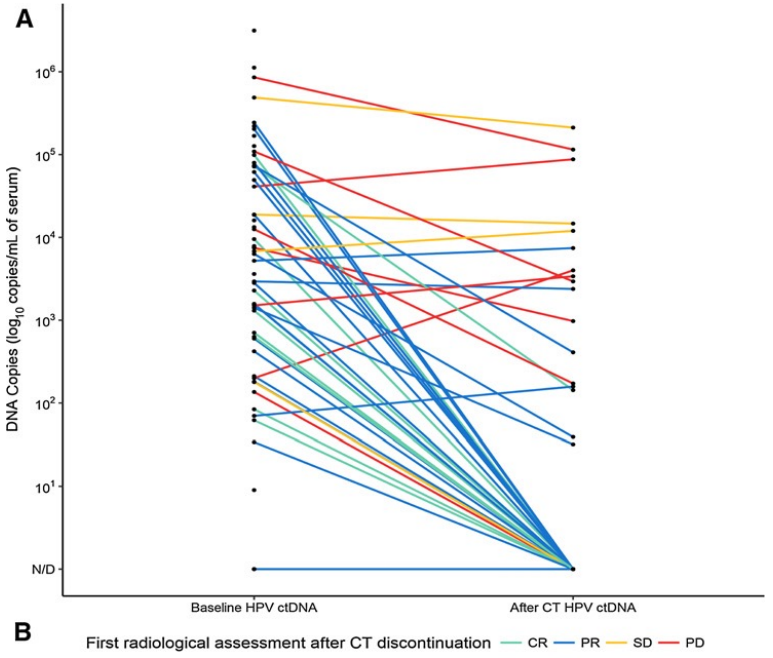
- Der „unmet need“ beim fortgeschrittenen / metastasierten Anal-Ca. ist (sehr) hoch
- SOC: Kombinationschemotherapie (Carbo/Tax DCF)
- Daten für Immuntherapie in späteren linien: Interessant, aber (noch) nicht „super exciting“
- Kombination mit Chemotherapie in früheren Linien? Kombinationen mit andeen zielgerichteten oder immunologischen Prinzipien in späteren Linien?
- Biomarker-stratifizierte Therapie: HPV? ctDNA-gesteuert?
- Neue Immunotherapien (Vakzinierungen, zelluläre Therapie, CAR-T,...) und Selektion sind die interessantesten Pfade



Dhawan N et al., Curr Oncol 2023

Clinical Validity of HPV ctDNA in using ddPCR: Epitopes Trial





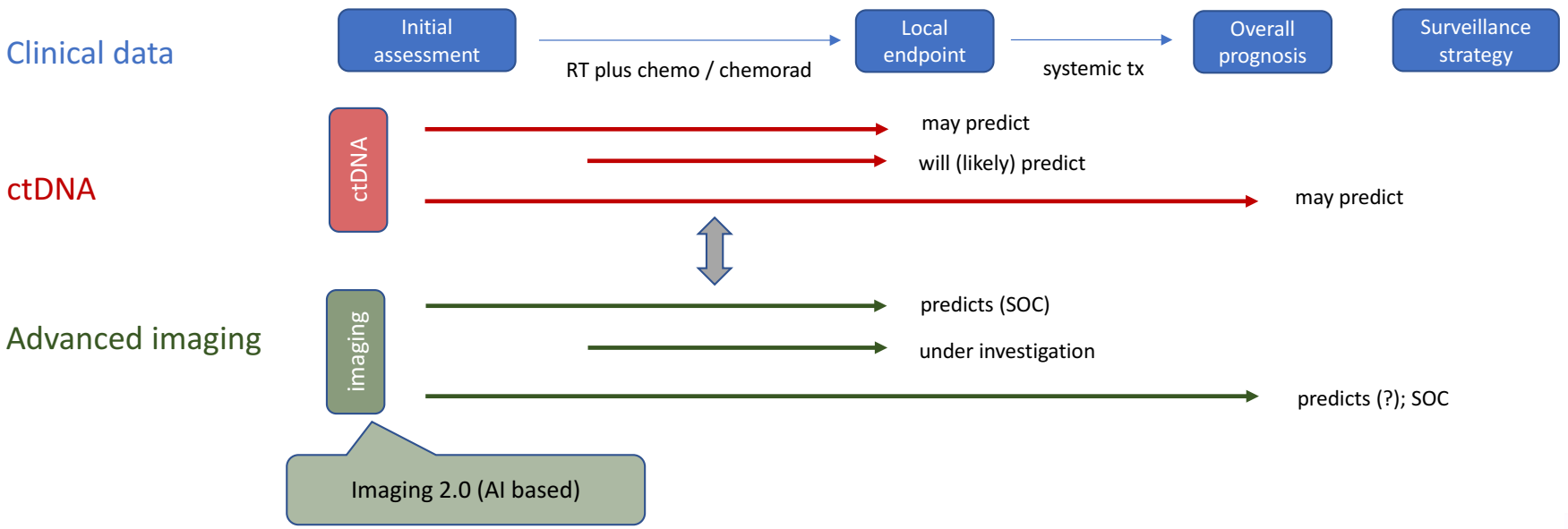
	Baseline HPV ctDNA median (range)	Median change during CT (%) (range)	*P*
CR (*n* = 8)	1792 (61; 98950)	-100% (-99.8; -100)	0.008
PR (*n* = 19)	2940 (0; 243750)	-100% (-100; 127)	0.0004
SD (*n* = 3)	6910 (178; 488700)	-57% (-100; 76)	0.75
PD (*n* = 6)	26825 (135; 865500)	-92% (-100; 124)	0.44

PFS according to baseline HPV ctDNA level by ddPCR. AUC analysis was used to classify the population into 2 relevant subgroups before chemotherapy.

Bernard-Tessier et al., Clin Cancer Res 2019

New proposal: An IRCI/EORTC registry for clinical course, ctDNA assesssment over time and advanced imaging

Presented at the meeting by Dirk Arnold



Arnold D., presented at ESMO GI 2023 and IMACC 2023

Zusammenfassung Anal-Ca.: Lokalisierte Stadien

- Stadium I-III (außer Analrand-Ca. im Stadium I):
  - Behandelt (= in 85% geheilt) mit Radiochemotherapie
- Optimale Radiochemotherapie für jeden Patienten
  - Verbesserte Lokalkontrolle bei Hochrisiko durch bessere RT, vielleicht Immuntherapie
  - Cave – (chronisch) Toxizität. Deeskalation bei frühen Stadien Decrease late effects in low-risk patients
- Rolle der Immuntherapie – Status: “kurz vor Klärung”
- Viele offene Fragen hinsichtlich Biomarkern, translational research und (wirklich) stratifizierten, zielgerichteten Strategien
- Seltene Erkrankung – kleine Patient:innengruppen; wir brauchen internationale Kollaborationene (und: Studieneinschlüsse!)

Kollaborative Studiengruppen

Mitglieder: (u.a.) Deutsche Krebsgesellschaft/AIO
(und: Cancer Research UK, US NCI, EORTC,....)

Mitglieder: gesucht ☺ (individuelle Teilnahme).
Meetings, Webinare, Fortbildungen,....

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ASKLEPIOS TUMORZENTRUM HAMBURG

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IMACC
International Multidisciplinary Anal Cancer Consortium

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Summary anal cancer: Localized stages

- Stage I-III (except rim stage I): treated (= cured in 85%) with chemoradiotherapy
- Optimal CRT for each patient
  - Improve tumour control in high-risk patients
  - Decrease late effects in low-risk patients
- Role of immune therapy is being investigated
- Need translational research and biology-guided clinical trials
- Small tumour groups benefit from international collaborations
- Include patients in international clinical trials

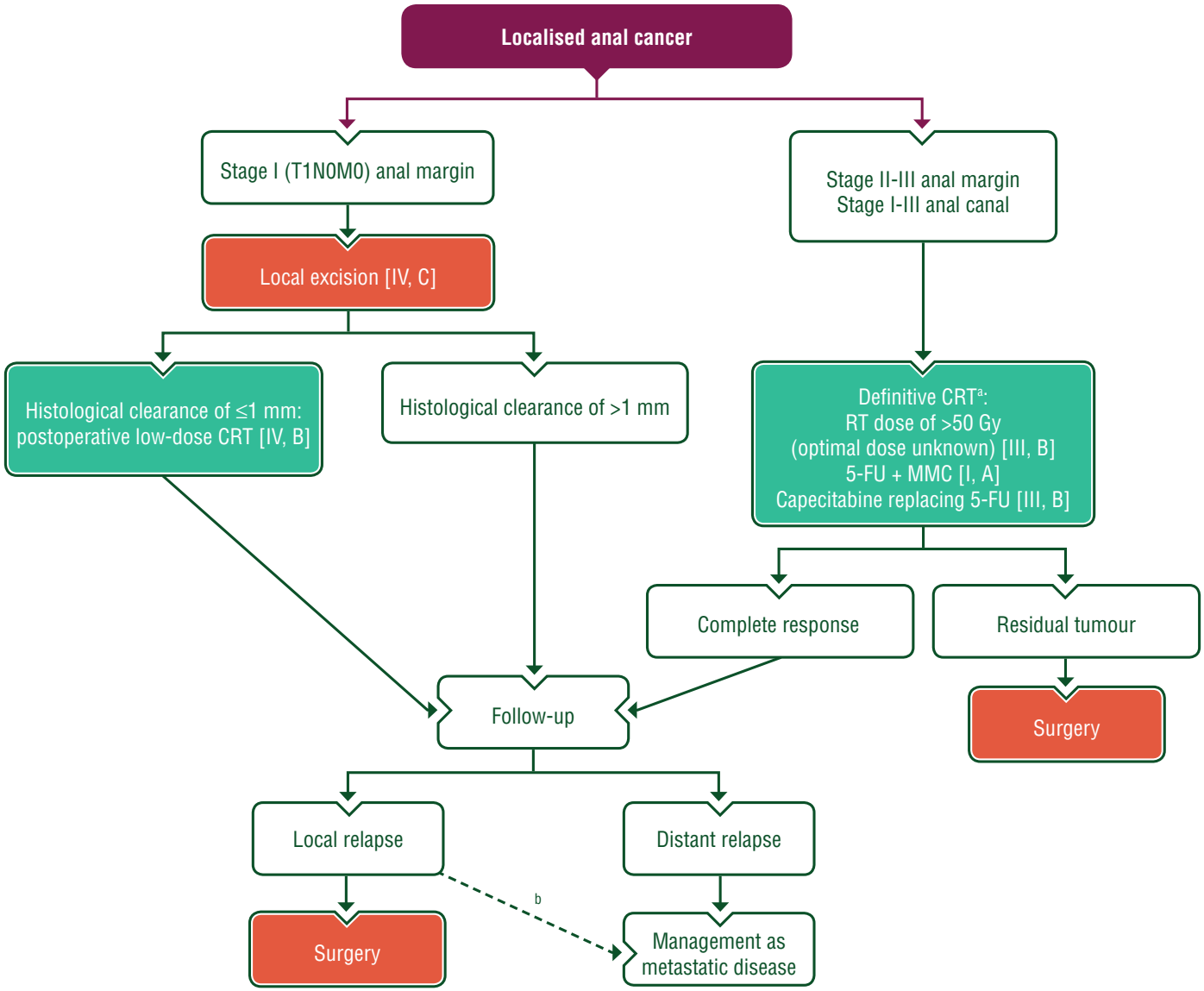
Treatment of advanced (metastatic) Anal Cancer: Summary

- The unmet need in advanced and metastatic anal cancer is high
- SOC – combination chemotherapy (Carbo/Tax DCF)
- Current data on later lines immunotherapy are encouraging - but not „super exciting“
- Combination with chemo in earlier settings might enhance the benefit
- New immunotherapy strategies (vaccines, CAR-T,...) or selection by HPV infection might be at the moment the more promising roads to follow

AJCC 8. Auflage

Definition des Primärtumors (T)	
TX	Primärtumor nicht beurteilt
T0	Kein Anhalt für Primärtumor
Tis	Hochgradige plattenepitheliale intraepitheliale Läsion (HSIL) (zuvor bezeichnet als Carcinoma *in situ*, Morbus Bowen, anale intraepitheliale Neoplasie II-III, high-grade AIN)
T1	Tumor ≤2 cm
T2	Tumor >2 und ≤5 cm
T3	Tumor >5 cm
T4	Tumor jeglicher Größe mit Infiltration in benachbarte Organe, z.B. Vagina, Urethra oder Harnblase
Definition der regionären Lymphknoten (N)	
NX	Regionäre Lymphknoten können nicht beurteilt werden
N0	Keine regionäre Lymphknotenmetastase
N1	Metastasen in inguinalen, mesorektalen Lymphknoten, Lymphknoten der Arteria iliaca interna oder der Arteria iliaca externa
N1a	Metastasen in inguinalen, mesorektalen Lymphknoten oder Lymphknoten der Arteria iliaca interna
N1b	Metastasen in Lymphknoten der Arteria iliaca externa
N1c	Metastasen in Lymphknoten der Arteria iliaca externa sowie N1a-Lymphknoten
Definition der Fernmetastasen (M)	
M0	Keine Fernmetastasen
M1	Fernmetastasen

https://register.awmf.org/assets/guidelines/081-004OLl_Analkarzinom_Diagnostik- Therapie-Nachsorge-Analkanalkarzinom-Analrandkarzinom_2020-12.pdfc



Rao S et al., Ann Oncol 2021

Benefit of immune therapy?

CORINTH