Immunotherapy Integration In Thoracic Surgery: Recent Progress and Essential Perspective
-Esophageal cancer

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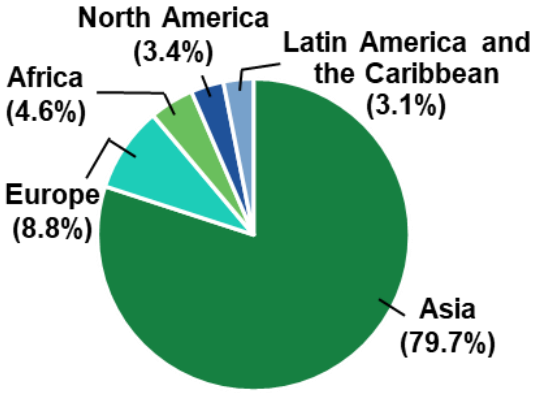
Esophageal Cancer

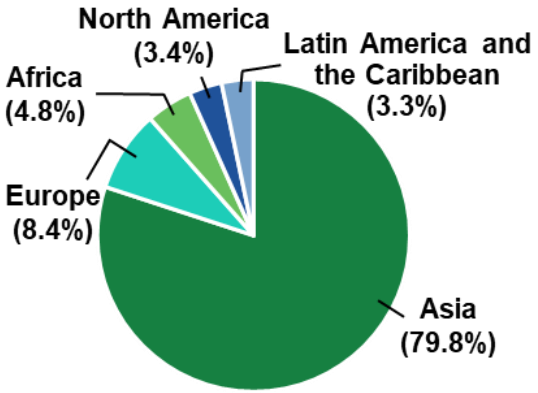
- Esophageal cancer was the 8th most common cancer and the 6th most common cause of cancer-related deaths worldwide in 2020.
  - Globally, an estimated 604,100 new cases of esophageal cancer were reported in 2020.[1]

Incidence, Both Sexes



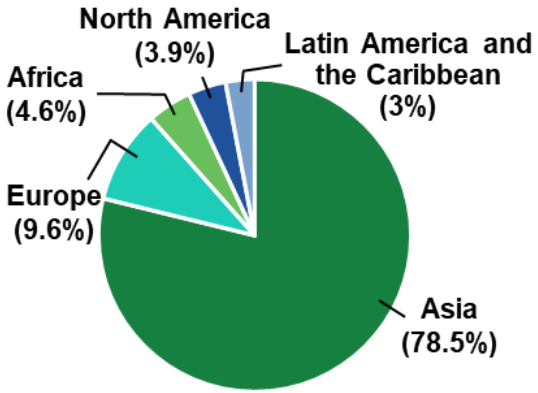
Population	Number
Asia	481,552
Europe	52,993
Africa	27,546
North America	20,806
Latin America and the Caribbean	19,011
Oceania	2,192
Total	604,100

Mortality, Both Sexes



Population	Number
Asia	434,363
Europe	45,511
Africa	26,097
North America	18,480
Latin America and the Caribbean	17,799
Oceania	1,826
Total	544,076

5-Year Prevalence, Both Sexes



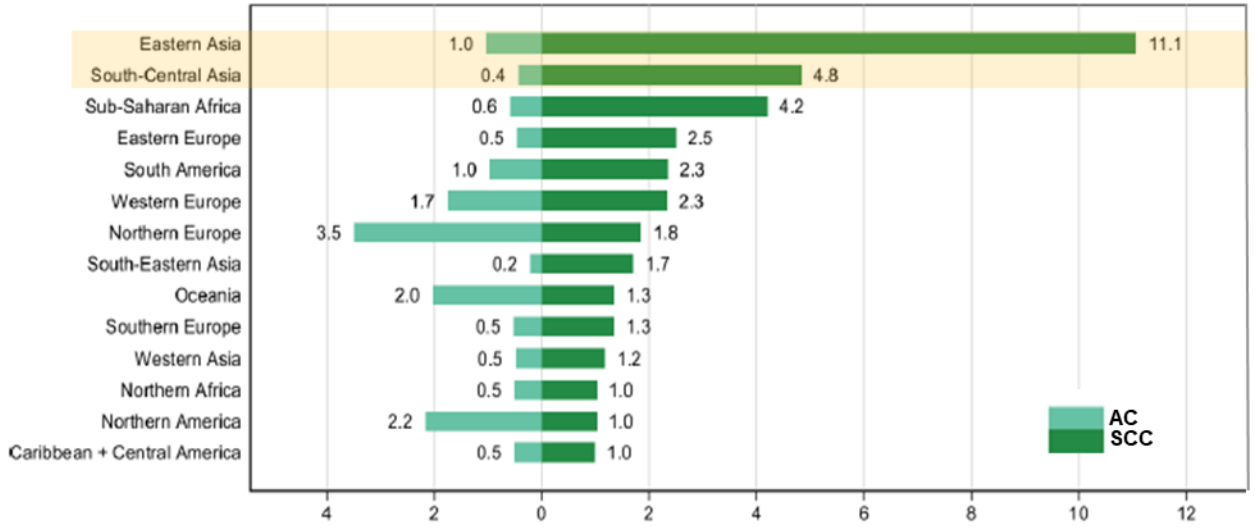
Population	Number
Asia	523,122
Europe	64,061
Africa	30,341
North America	26,160
Latin America and the Caribbean	20,058
Oceania	2,646
Total	666,388

1. Esophagus Fact Sheet. Global Cancer Observatory. December 2020. Accessed May 20, 2021. https://gco.iarc.fr/today/data/factsheets/cancers/6-Oesophagus-fact-sheet.pdf

Esophageal Cancer: Histological Subtypes

- Two main types of esophageal cancer exist, based on histology.[1]
  - **Squamous cell carcinoma (SCC)** is the most common type of esophageal cancer worldwide, with the highest incidence rates in Eastern Asia and Eastern Africa.[1]
  - **Adenocarcinoma (AC)** is more common in Northern Europe, North America, and Oceania than in other regions.[1]

Incidence Rates by Histological Subtype[1]



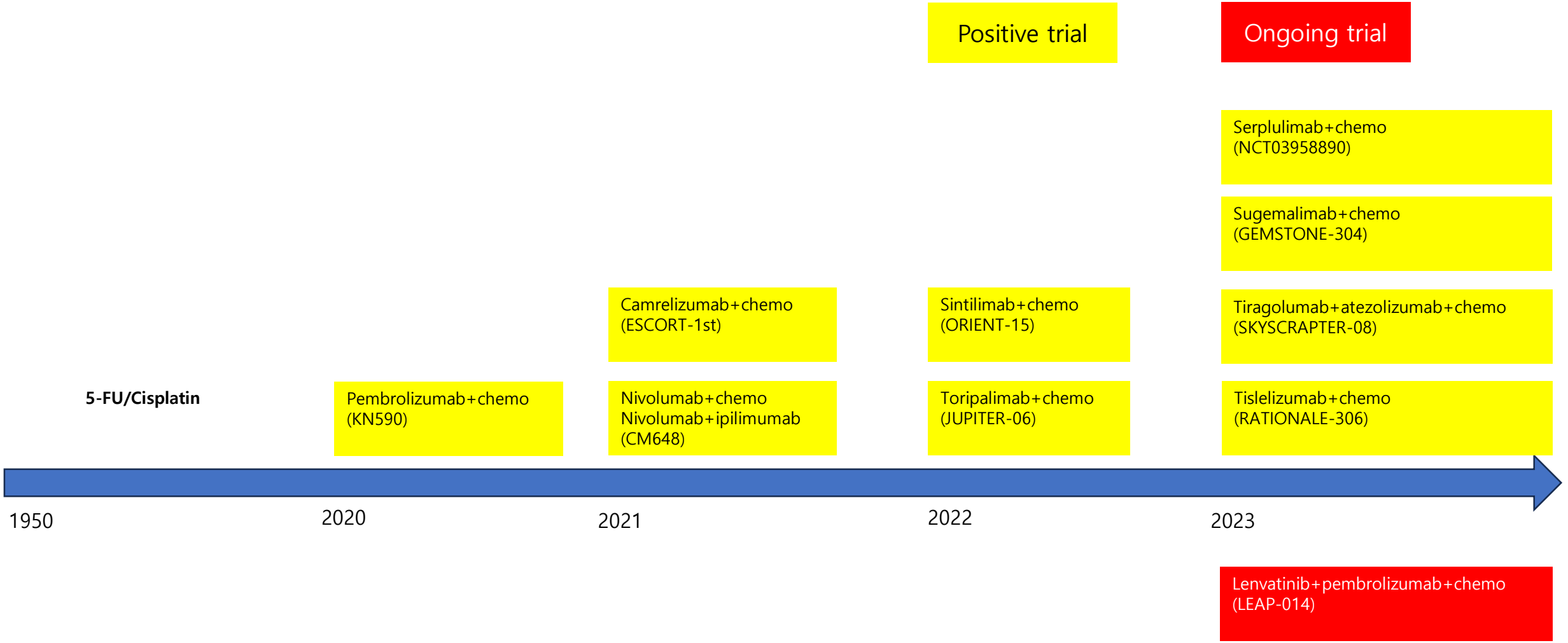
Risk Factors for Esophageal Cancer[2]

Risk Factor	Squamous Cell Carcinoma	Adenocarcinoma
Aging	✓	✓
Sex	Male > Female	Male > Female
Tobacco	✓	✓
Alcohol	✓	–
GERD/Barrett's Esophagus	–	✓
Obesity	–	✓

GERD = gastroesophageal reflux disease.

1. Arnold M et al. *Gut*. 2020;69(9):1564–1571. Reproduced from Gut, Arnold M et al, Vol. 69, 1564-1571, Copyright 2020, with permission from BMJ Publishing Group Ltd.
2. American Cancer Society. Esophageal Cancer Risk Factors. Last revised June 9, 2020. Accessed June 14, 2021. https://www.cancer.org/cancer/esophagus-cancer/causes-risks-prevention/risk-factors.html

Current 1L immunotherapy-based treatment in advanced esophageal cancer



Back to the title

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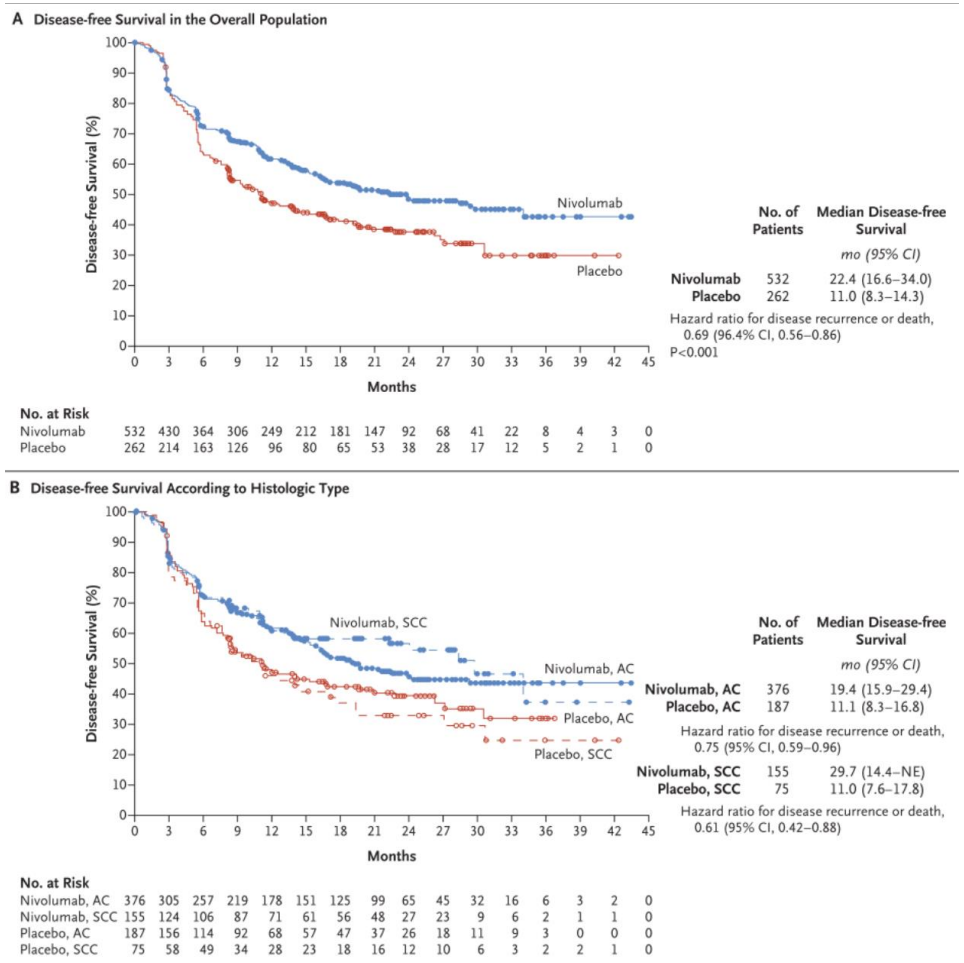
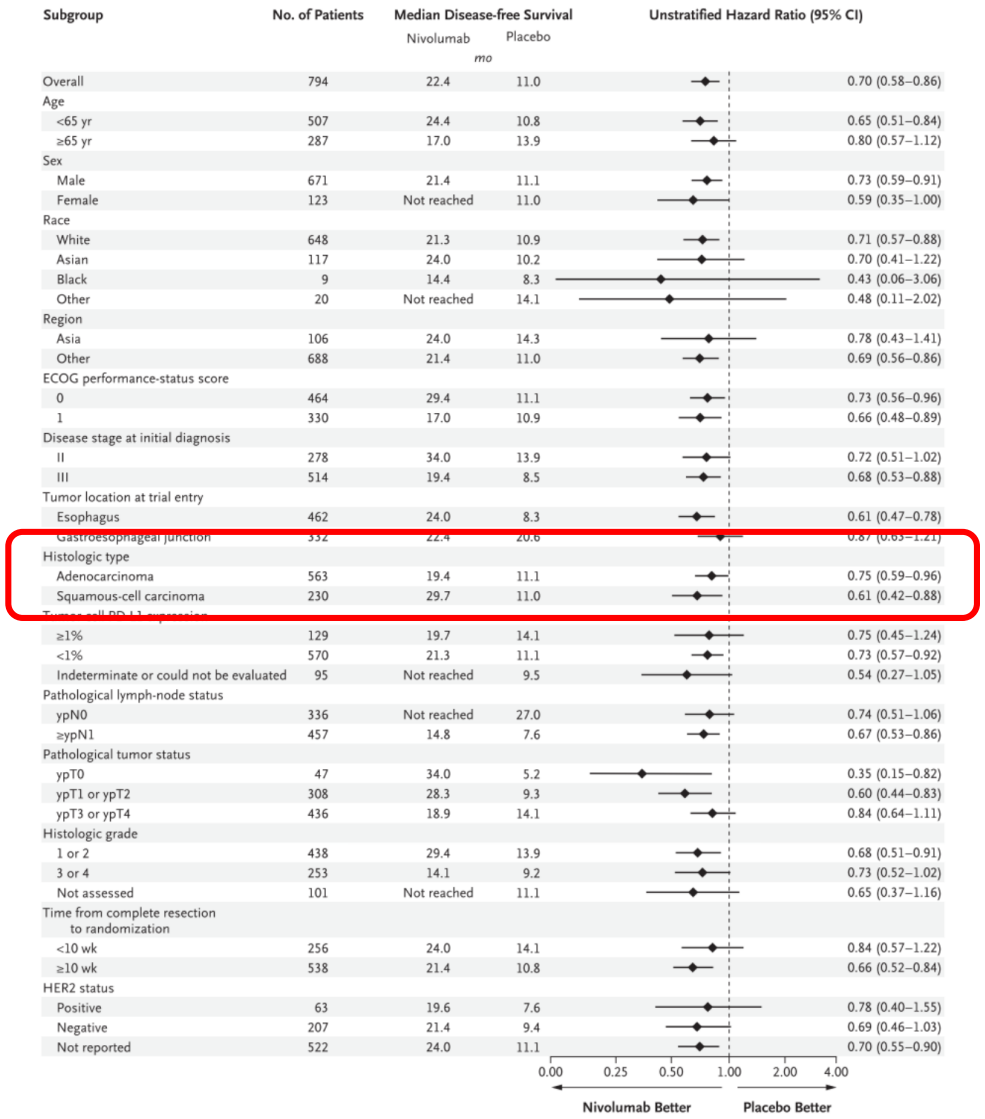
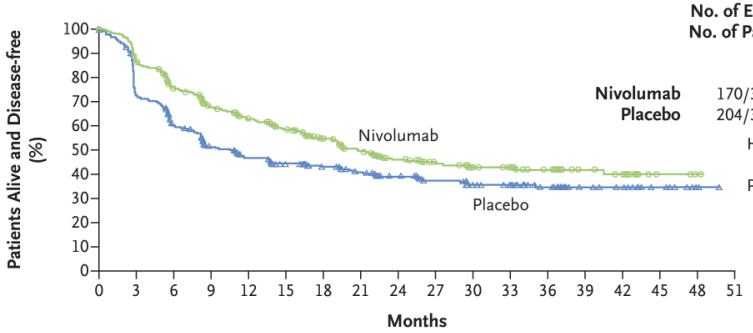




Kelly, R. J., et al. (2021). N Engl J Med 384(13): 1191-1203.

Lesson from other tumor

A Intention-to-Treat Population

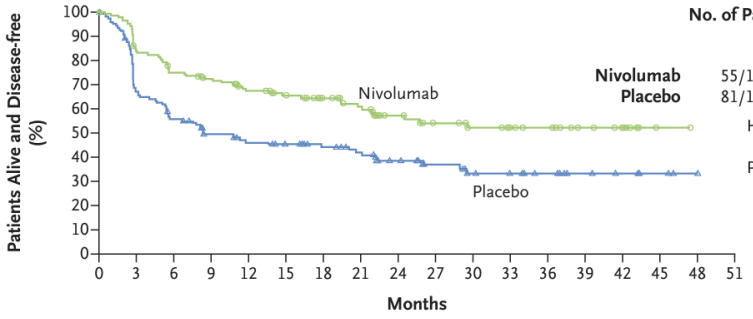


	No. of Events/ No. of Patients	Disease-free Survival at 6 Mo (95% CI)	Disease-free Survival at 12 Mo (95% CI)
		%	
Nivolumab	170/353	74.9 (69.9–79.2)	62.8 (57.3–67.8)
Placebo	204/356	60.3 (54.9–65.3)	46.6 (41.1–51.9)

Hazard ratio for disease recurrence or death, 0.70 (98.22% CI, 0.55–0.90)
P<0.001

No. at Risk																		
Nivolumab	353	296	244	212	178	154	126	106	85	68	57	51	36	23	20	3	1	0
Placebo	356	248	198	157	134	121	105	94	80	65	54	50	37	22	19	10	2	0

B Patients with a PD-L1 Expression Level of ≥1%



	No. of Events/ No. of Patients	Disease-free Survival at 6 Mo (95% CI)	Disease-free Survival at 12 Mo (95% CI)
		%	
Nivolumab	55/140	74.5 (66.2–81.1)	67.2 (58.4–74.5)
Placebo	81/142	55.7 (46.8–63.6)	45.9 (37.1–54.2)

Hazard ratio for disease recurrence or death, 0.55 (98.72% CI, 0.35–0.85)
P<0.001

No. at Risk																		
Nivolumab	140	113	98	91	76	68	58	50	38	31	27	24	21	12	10	1	0	0
Placebo	142	90	73	59	53	49	42	37	28	22	17	16	12	7	5	3	1	0

Subgroup	No. of Patients	Nivolumab	Placebo	Hazard Ratio for Disease Recurrence or Death (95% CI)
		no. of events/no. of patients		
All patients	709	170/353	204/356	0.70 (0.57–0.86)
Age				
<65 yr	291	74/155	70/136	0.77 (0.55–1.07)
≥65 yr and <75 yr	295	64/131	100/164	0.68 (0.49–0.94)
≥75 yr	123	32/67	34/56	0.63 (0.38–1.06)
Sex				
Male	540	125/265	156/275	0.68 (0.54–0.87)
Female	169	45/88	48/81	0.76 (0.50–1.16)
Race or ethnic group				
White	536	126/264	162/272	0.65 (0.52–0.83)
Black	5	1/2	3/3	NA
Asian	155	37/80	35/75	0.83 (0.51–1.35)
American Indian or Alaska Native	1	1/1	0	NA
Native Hawaiian or other Pacific Islander	0	0	0	NA
Other	11	5/6	3/5	NA
Not reported	1	0	1/1	NA
Geographic region				
United States	102	24/49	36/53	0.45 (0.26–0.80)
Europe	341	87/170	96/171	0.84 (0.63–1.13)
Asia	154	37/80	34/74	0.85 (0.52–1.39)
Rest of the world	112	22/54	38/58	0.39 (0.21–0.72)
ECOG performance-status score at baseline				
0	445	105/224	126/221	0.69 (0.53–0.90)
1	247	64/122	71/125	0.77 (0.54–1.09)
2	16	1/7	7/9	NA
Not reported	1	0	0/1	NA
Hemoglobin level at baseline				
<10 g/dl	46	8/19	17/27	0.30 (0.08–1.06)
≥10 g/dl	653	162/332	185/321	0.72 (0.58–0.88)
Not reported	10	0/2	2/8	NA
Creatinine clearance at baseline				
<60 ml/min	309	83/151	91/158	0.87 (0.64–1.18)
≥60 ml/min	388	86/199	111/189	0.58 (0.44–0.78)
Not reported	12	1/3	2/9	NA
Initial tumor origin				
Urinary bladder	560	129/279	166/281	0.62 (0.49–0.78)
Renal pelvis	96	24/44	25/52	1.23 (0.67–2.23)
Ureter	53	17/30	13/23	1.56 (0.70–3.48)
Minor histologic variants				
Yes	286	70/145	76/141	0.73 (0.53–1.02)
No	423	100/208	128/215	0.69 (0.53–0.90)
Nodal status				
N+	335	95/167	116/168	0.64 (0.48–0.85)
N0 or NX with <10 nodes removed	193	46/94	50/99	0.85 (0.57–1.28)
N0 with ≥10 nodes removed	179	29/91	37/88	0.67 (0.41–1.10)
Not reported	2	0/1	1/1	NA
Pathological tumor stage				
pT0–2	166	35/80	40/86	0.88 (0.54–1.43)
pT3	410	97/206	120/204	0.63 (0.48–0.82)
pT4a	119	36/57	40/62	0.77 (0.47–1.25)
Other	12	1/9	3/3	NA
Not reported	2	1/1	1/1	NA
Pathological tumor stage and nodal status				
pT2N–	54	6/25	10/29	0.54 (0.16–1.86)
pT3,4N–	317	68/158	78/159	0.75 (0.54–1.05)
pT0–4N1	143	39/71	45/72	0.74 (0.47–1.15)
pT0–4N2,3	192	56/96	71/96	0.57 (0.40–0.83)
pTisN–	1	0/1	0	NA
Not reported	2	1/2	0	NA
Previous neoadjuvant cisplatin therapy				
Yes	[illegible]	[illegible]	[illegible]	[illegible]
No	401	100/200	104/201	0.92 (0.69–1.21)
Any previous neoadjuvant systemic therapy				
Yes	319	75/160	104/159	0.53 (0.39–0.72)
No	390	95/193	100/197	0.91 (0.69–1.21)
Days from surgery to randomization				
0–30	5	0/2	2/3	NA
>30–60	149	43/79	40/70	0.66 (0.40–1.06)
>60–90	342	78/165	93/177	0.76 (0.55–1.03)
>90–120	198	47/103	62/95	0.67 (0.44–1.00)
>120	15	2/4	7/11	NA
Smoking status				
Current or former smoker	484	116/237	141/247	0.70 (0.55–0.90)
Never smoked	215	53/111	61/104	0.67 (0.45–0.98)
Unknown	10	1/5	2/5	NA
PD-L1 expression level at baseline				
≥1%	280	55/139	79/141	0.56 (0.40–0.80)
<1%	419	114/210	120/209	0.82 (0.63–1.06)
Indeterminate or not able to be evaluated	8	1/3	4/5	NA
Not reported	2	0/1	1/1	NA

N Engl J Med 2021;384:2102-2114

Back to the title

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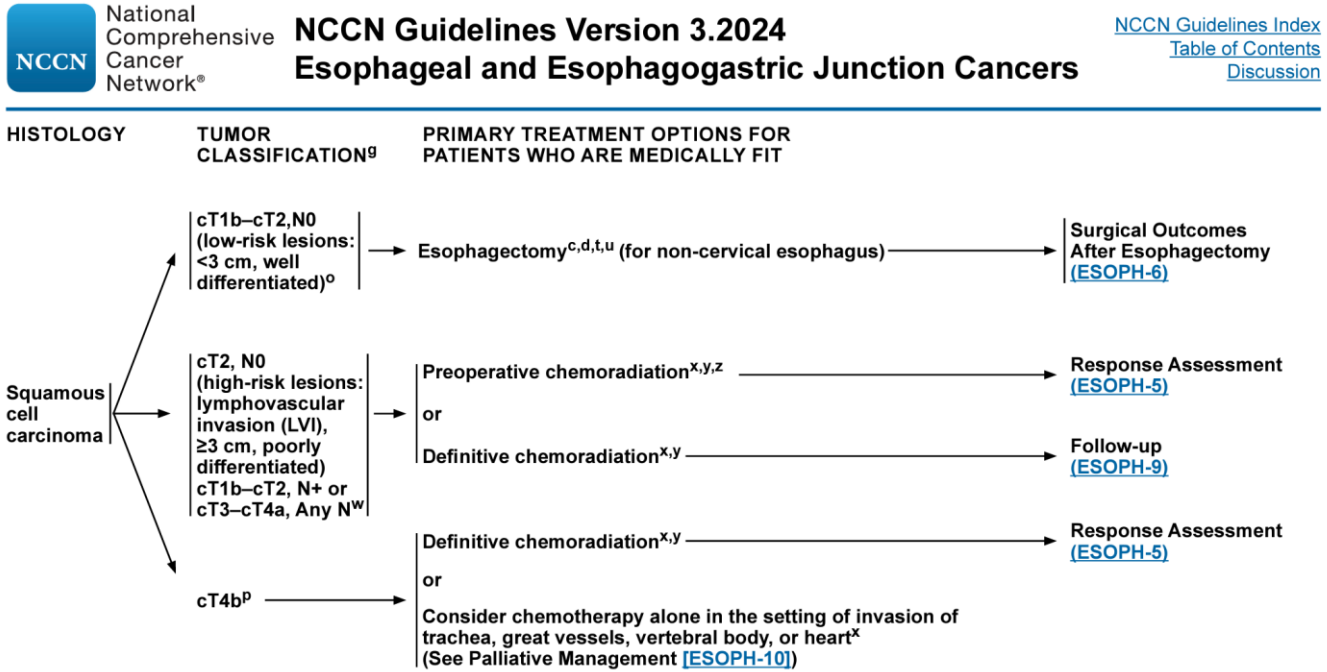
Clinical scenario

1. Preop CCRT ➔ surgery ➔ FU
2. Preop systemic therapy ➔ Surgery ➔ FU
3. Definitive CCRT ➔ FU

The role of immunotherapy

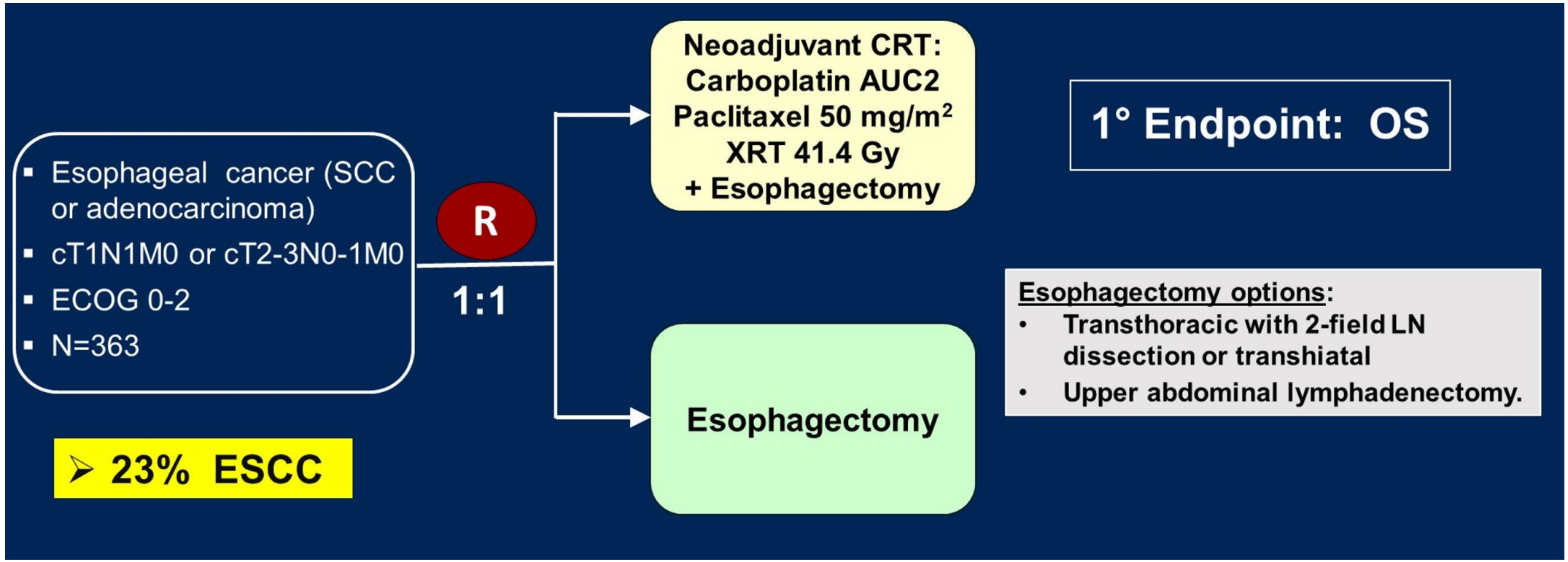


Setting the Stage: Locoregional ESCC

- Treatments are with curative intent.
- Surgical resection alone is insufficient.
- Multimodality approach is the standard of care.
- R0 resection is critical.
- Completion of planned therapies is essential.
- Systemic recurrences remain a challenge.

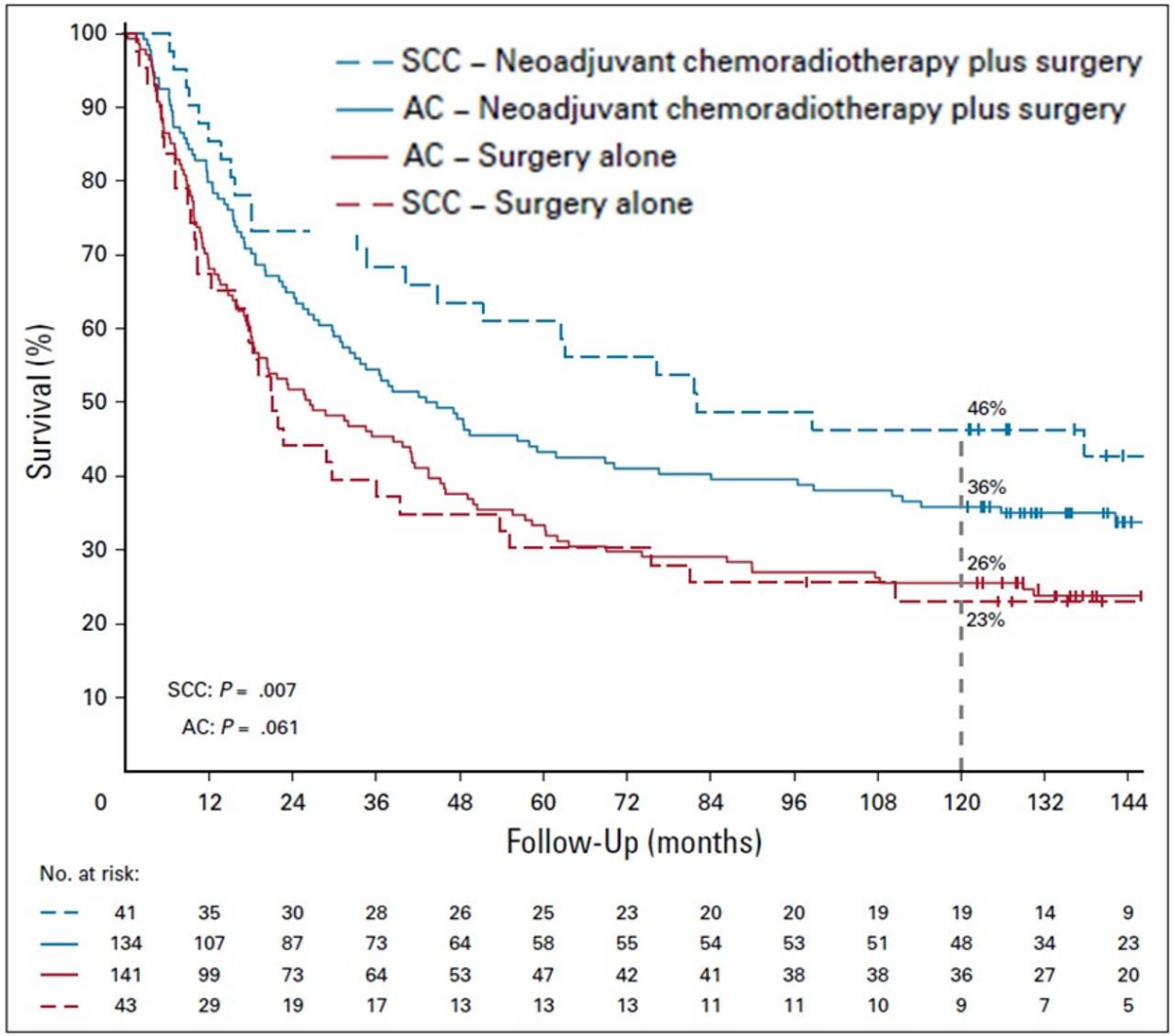
Neoadjuvant CCRT - CROSS

- CROSS trial
  - Phase III, N=366 (23% SqCC, 75% ADC, 2% Undiff.)
  - T1N1 – T2-3Nx (64% Node +ve)
  - Preop CCRT with paclitaxel/carboplatin vs. upfront surgery



van Hagen P et al. N Engl J Med 2012;366:2074-2084

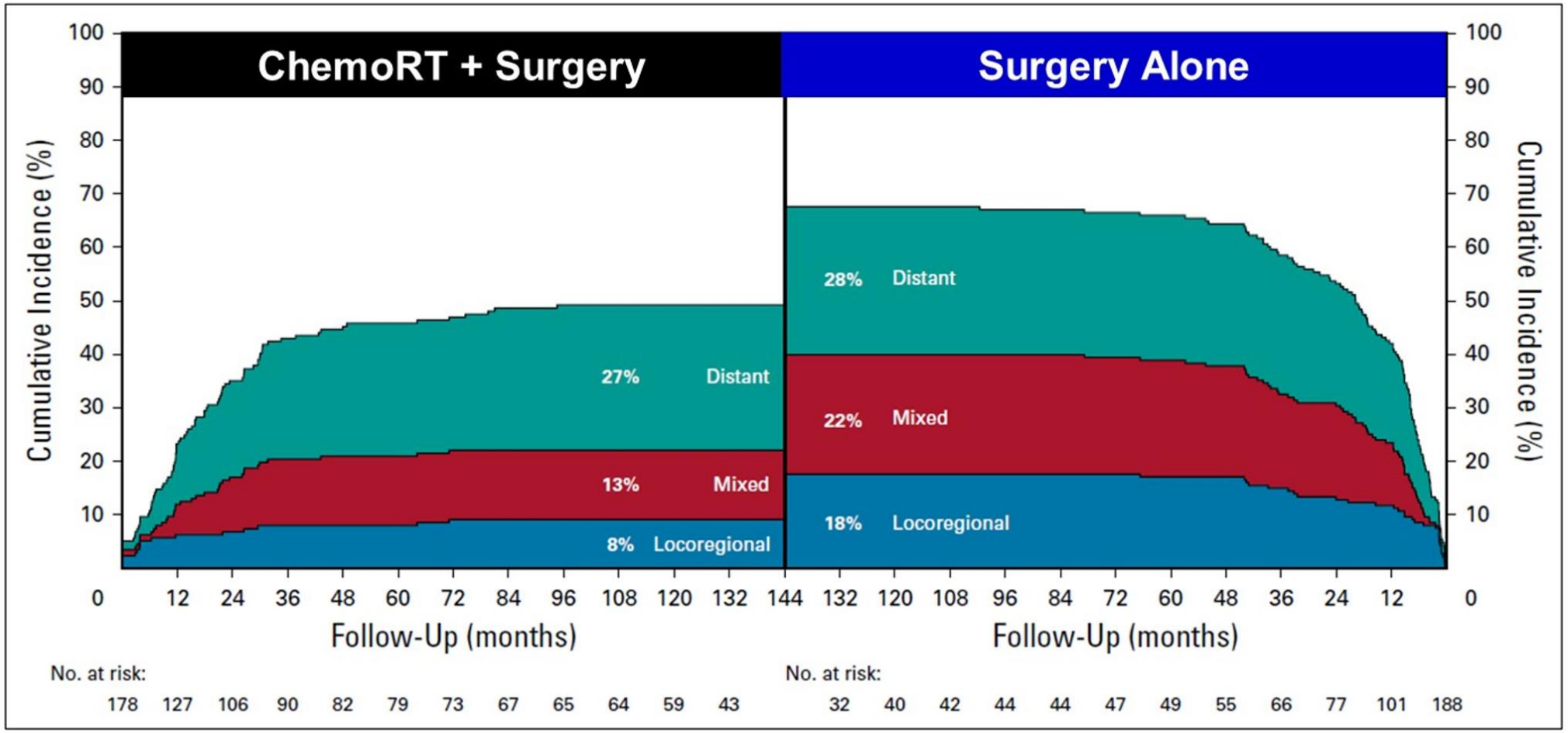
Neoadjuvant CCRT - CROSS



- Focus on ESCC
  - Median OS: 21 vs. 82 months
  - Median PFS: 11.6 vs. 74.7 months
  - pCR rate: 49%
  - 10 year OS rate: 23 vs. 46%

van Hagen P et al. N Engl J Med 2012;366:2074-2084

CROSS 10-Year Follow-Up: Significant Distant Recurrences (Both Adeno and SCC Data)

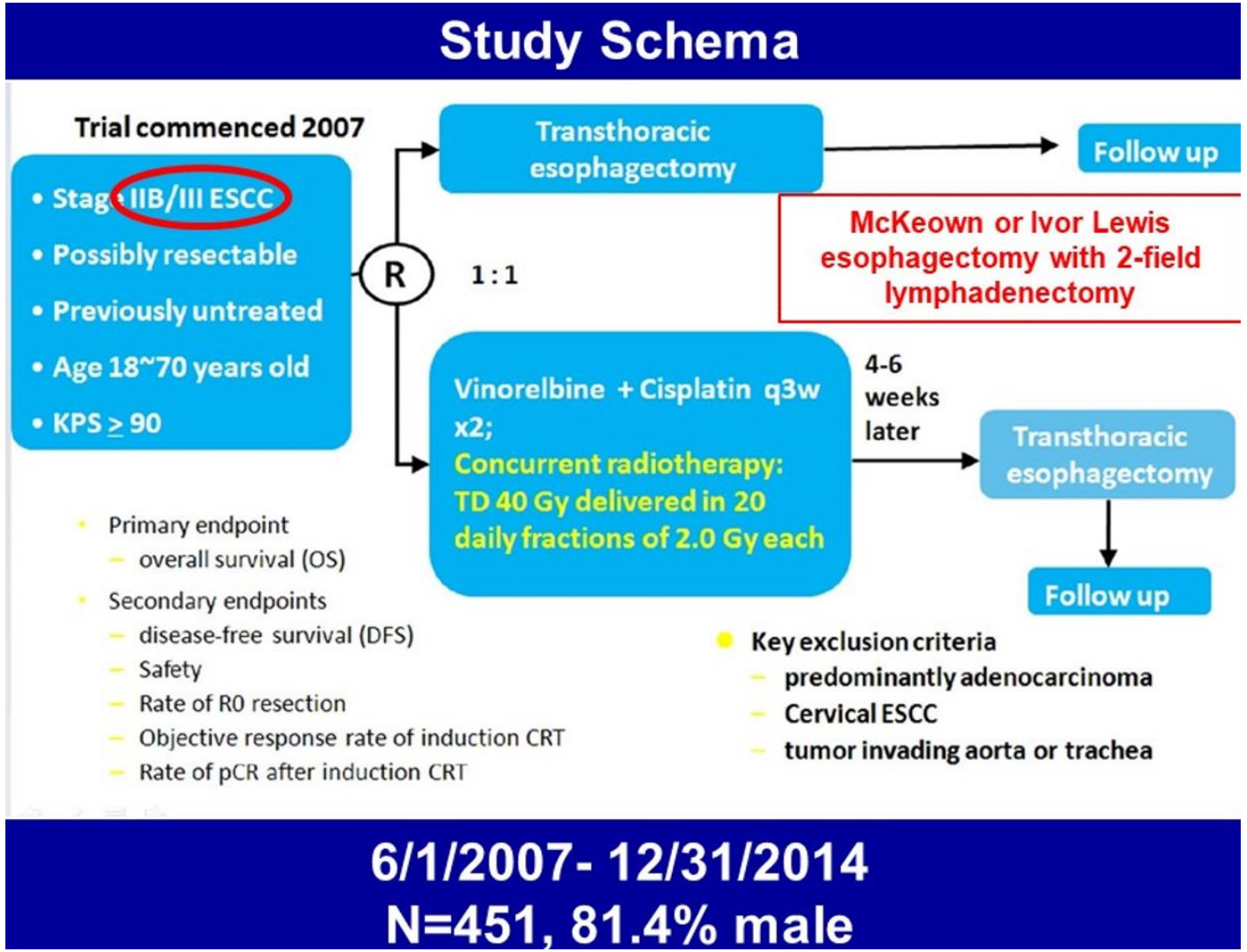


Low doses of radiosensitizing chemotherapy used limited systemic effects

Eyck BM, et al. J Clin Oncol 391995-2004, 2021

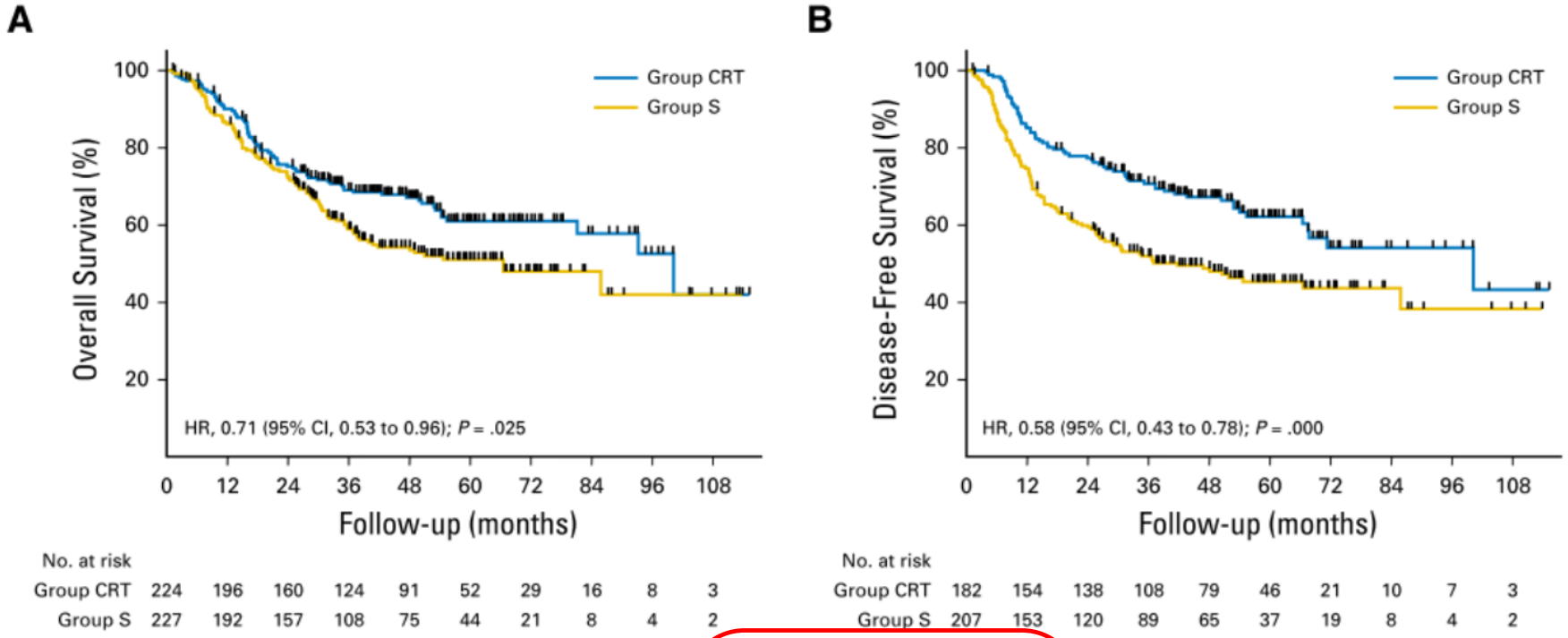
Neoadjuvant CCRT - NEOCRTEC5010
Surgery vs. ChemoRT + Surgery for ESCC in China

- Phase III, N=451 (100% SqCC), 100% Chinese
- Primary endpoint: OS
- T1-4N1M0/T4N0M0,
- Preop CCRT with vinorelbine/cisplatin vs. upfront surgery



Neoadjuvant CCRT - NEOCRTEC5010
Surgery vs. ChemoRT + Surgery for ESCC in China

- OS: 100 vs. 66.5 months, HR 0.71; P=0.025



Recurrence Rates*	ChemoRT	Surgery only
Locoregional	13.7%	21.7%
Distant	25.3%	35.7%
Overall	34.6%	49.3%

Yang, H., et al. (2018). J Clin Oncol 36(27): 2796-2803.

Impact of RT in Locoregional Esophageal Cancer

- Pros
  - Downstage the tumor including pCR
  - Increase R0 resection rates
- Cons
  - Limited systemic control

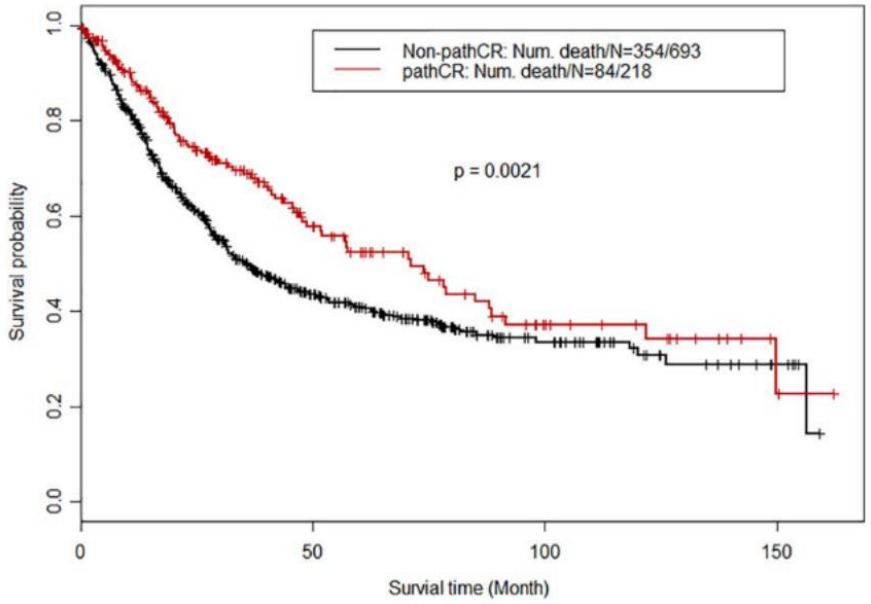
pCR rates among several neoadjuvant studies

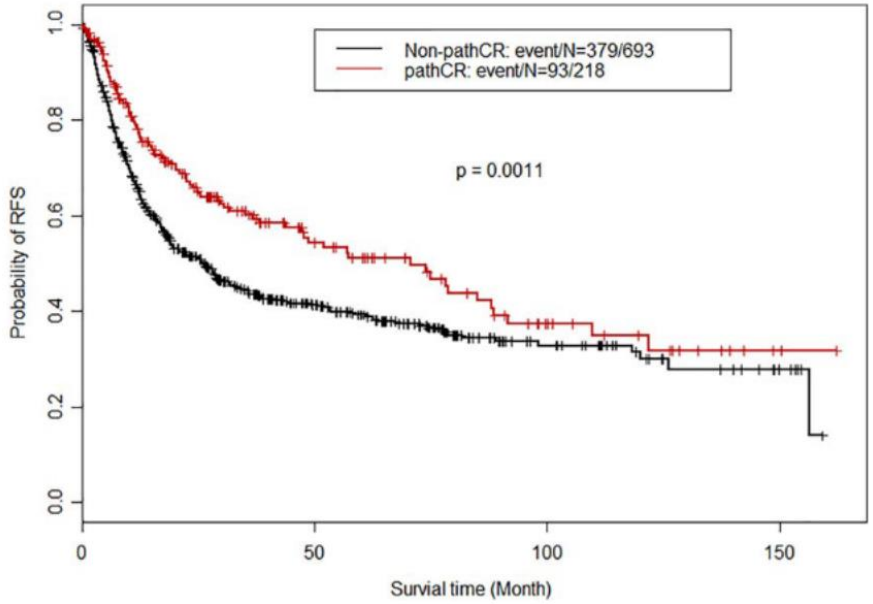
Study	Trial	Stage	Eligibility	Treatment	Patients	Pathology (%)	Chemotherapy	Radiotherapy	pCR (%)	OS (5Y, %)	R0 (%)	Postoperative mortality
Mariette et al. [10] (2014)	00-09: FFCD 9901	Stage I–II	T1-2N0-1 T3N0	S NACRT→S	97 98	Sq (70)	Cisplatin 5FU	45 Gy	33	34 41	92 94	3.4% in S 11.1% in CRT+S
Van Hagen et al. [9] (2012)	04-08: CROSS	Stage II–III	T1N1 T2-3N0-1	S NACRT→S	188 178	Sq (23)	Carboplatin Paclitaxel	41.4 Gy	29	34 47	69 92	4% in both groups
Yang et al. [11] (2018)	07-14: NEOCRTE5010	Stage IIB–III	T1-4N1 T4N0	S NACRT→S	227 224	Sq (100)	Vinorelbine Cisplatin	40 Gy	43.2	51 61	91.2 98.4	1.1% in CRT+S 0.4% in S
MRC [14] (2002)[a]	92-98: British OEO2		Resectable	S NAC→S	402 400	Sq (31)	Cisplatin 5FU	(-)	4	17 23	54 60	10% in both groups
Kelsen et al. [16] (2007)	RTOG 8911	Stage I–III	T1-3N0-N1	S NAC→S	227 213	Sq (47)	Cisplatin 5FU	(-)	2.5	19 22	59 63	6% in both groups
Ando et al. [17] (2012)	00-06: JCOG 9907	Stage II–III	T1N1 T2-3N0-1	S→AC NAC→S	166 164	Sq (100)	Cisplatin 5FU	(-)	5	43 55	91 96	Less than 1% in both groups

pCR, pathologic complete response; OS, overall survival; S, surgery; NACRT, neoadjuvant chemoradiotherapy; 5FU, 5-fluorouracil; CRT, chemotherapy; Sq, squamous cell carcinoma; NAC, neoadjuvant chemotherapy.
[a]Medical Research Council Oesophageal Cancer Working Group.

Korean J Thorac Cardiovasc Surg 2020; 53(4): 160-167.

Clincal significance of pCR from MDACC experience





Recurrence	PathCR	Non-PathCR
Distant	41/218 (18.8%)	199/693 (28.7%)
Local	4/218 (1.8%)	34/693 (4.9%)

Abbreviation: pathCR, pathological complete response.

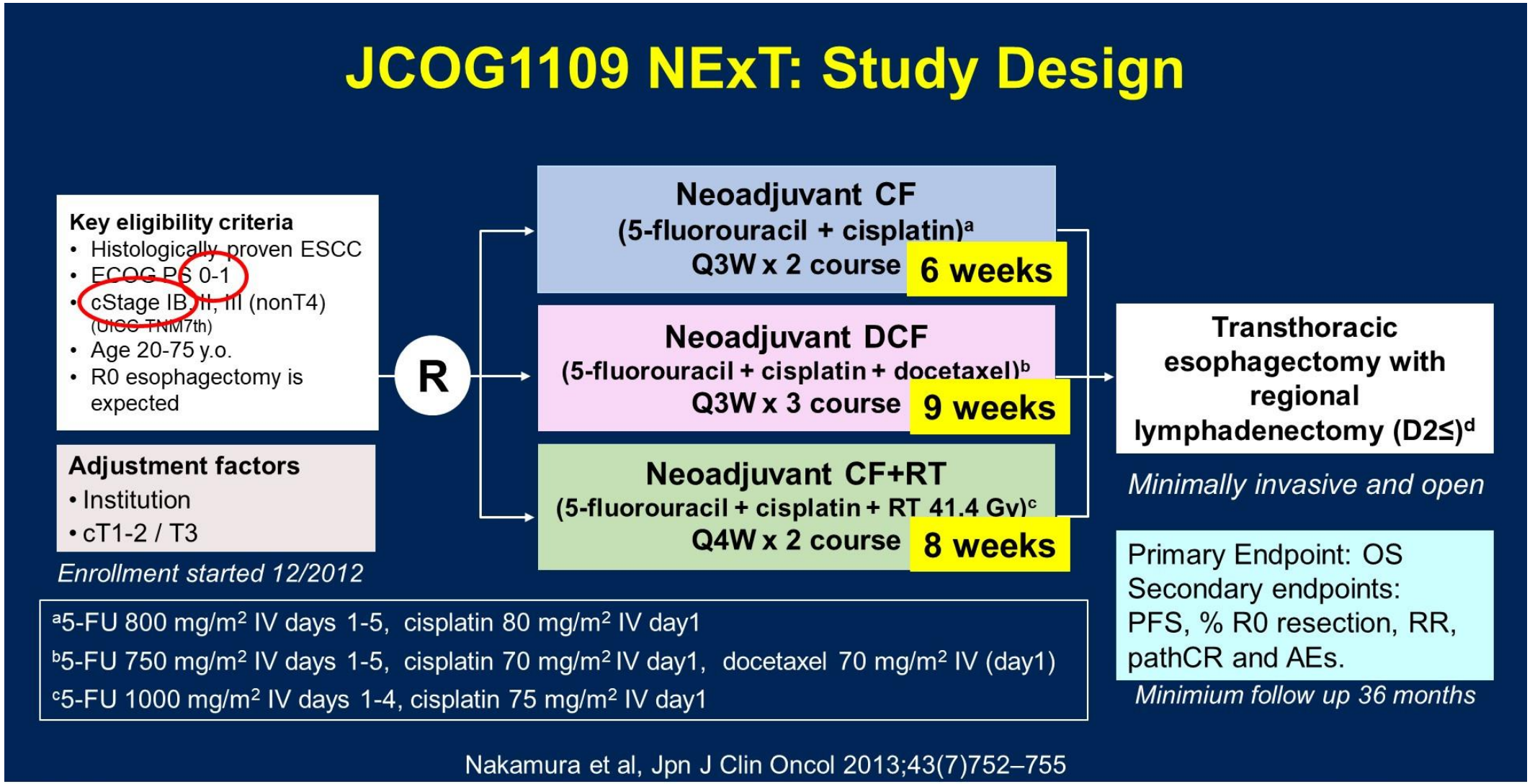
Blum Murphy, M., et al.2017 Cancer 123(21): 4106-4113.

Phase 3 Studies Defining Standard Practice in Japan

Years	Trial	Design	Results	Conclusions
1992-1997	JCOG9204	Surgery alone vs. Postop Chemo (CF*)	5 year DFS 45% vs. 55% p 0.04	**Postoperative chemotherapy is superior to surgery alone**
2000-2006	JCOG9907	Preop chemo (CF) vs. Postop chemo (CF)	5 year OS 55% vs. 43% p 0.04	**Preoperative chemotherapy is superior**

Ando et al. Jour of Clinic Onc 2003 (21): 4592-4596;
Ando et al, Ann Surg Oncol 2012 (19): 68-74

Neoadjuvant CCRT vs. chemotherapy vs. intense chemotherapy



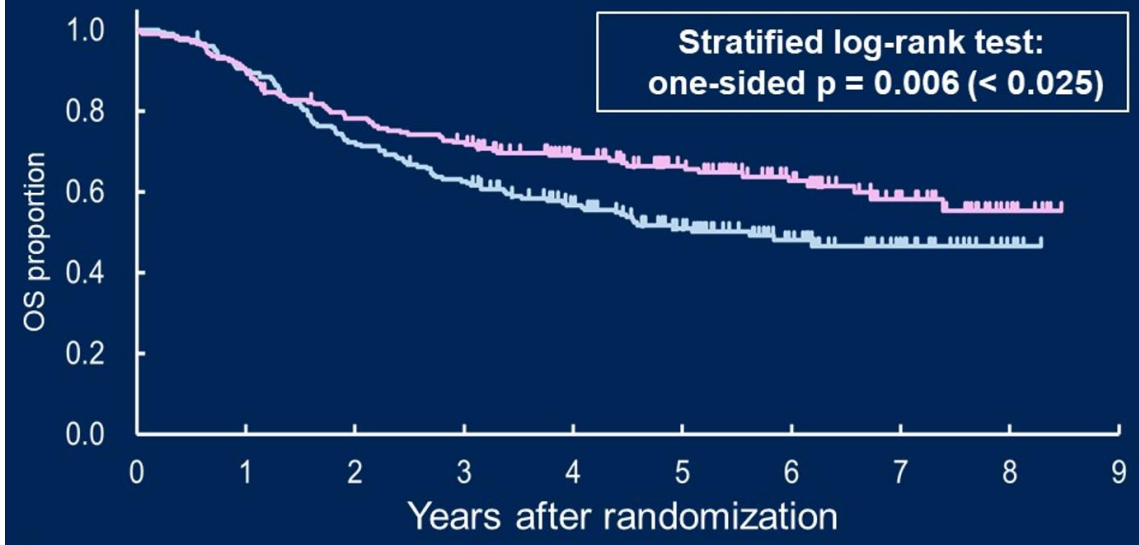
PRESENTED BY: Nataliya Uboha, MD, PhD

Intesnse chemotherapy vs. conventional chemotherapy

DCF Improves Overall Survival and Progression Free Survival

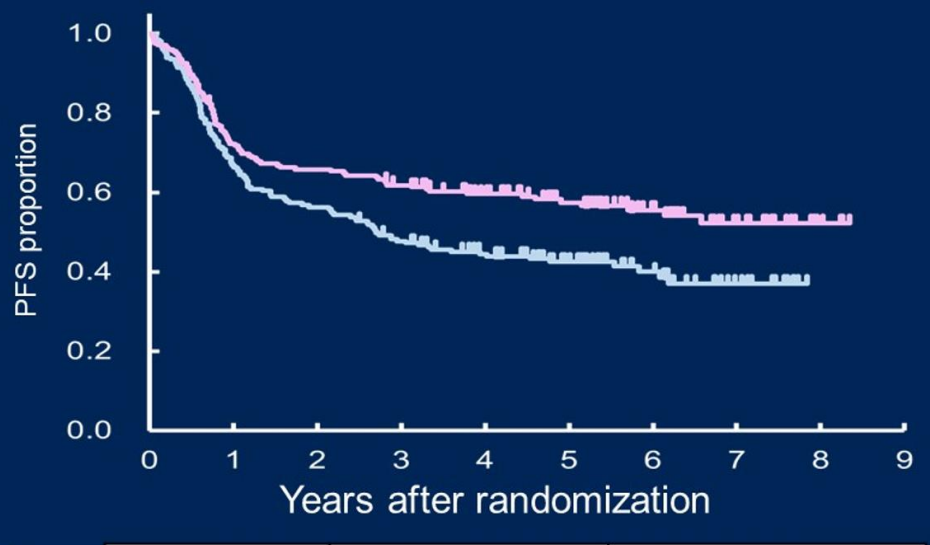
Neo DCF vs. CF

Overall Survival



	MST (95% CI)	3-y OS (95% CI)	Stratified HR (95% CI)
Neo CF	5.6y (3.9y-NE)	62.6% (55.5%-68.9%)	Ref.
Neo DCF	NR (6.7y-NE)	72.1% (65.4%-77.8%)	0.68 (0.50-0.92)

Progression Free Survival



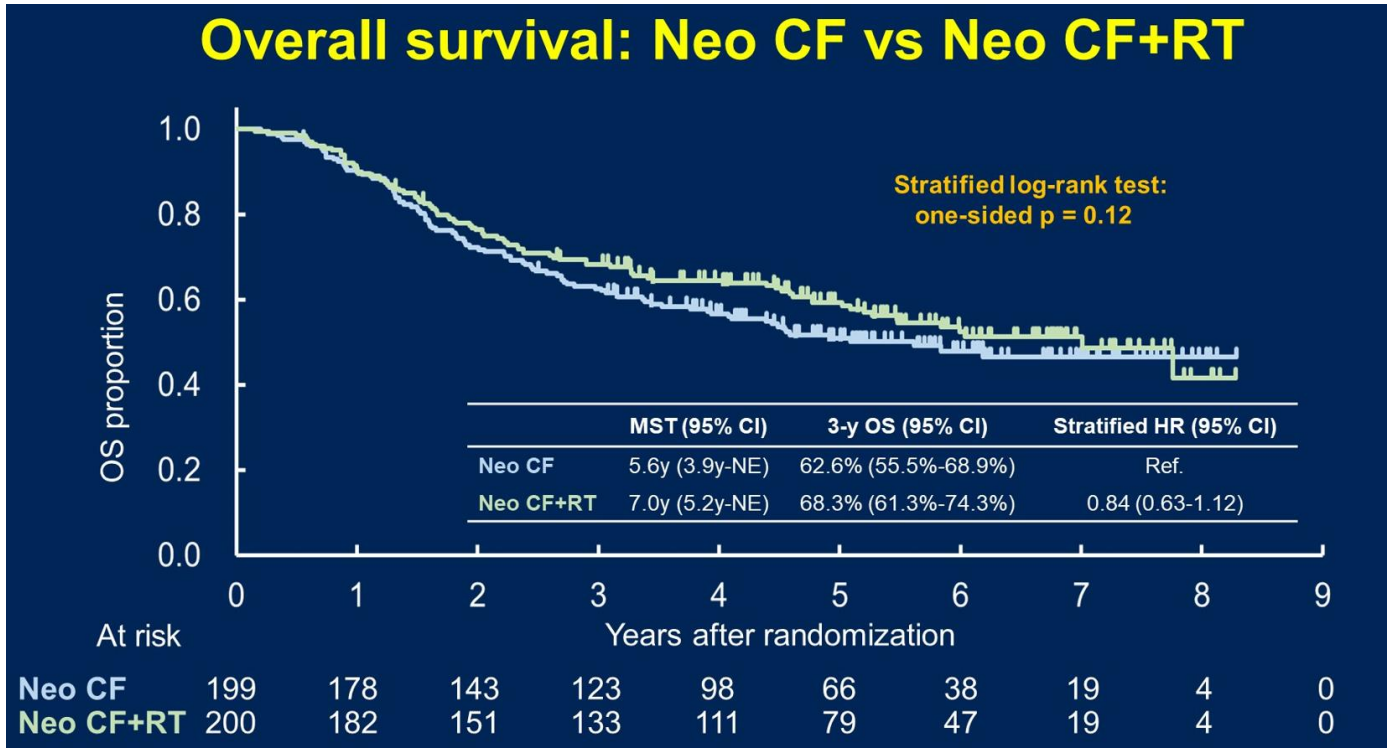
	mPFS (95% CI)	HR (95% CI)
Neo CF	2.7y (1.8y-4.8y)	Ref.
Neo DCF	NR (5.2y-NE)	0.67 (0.51-0.88)

MST: Median Survival Time

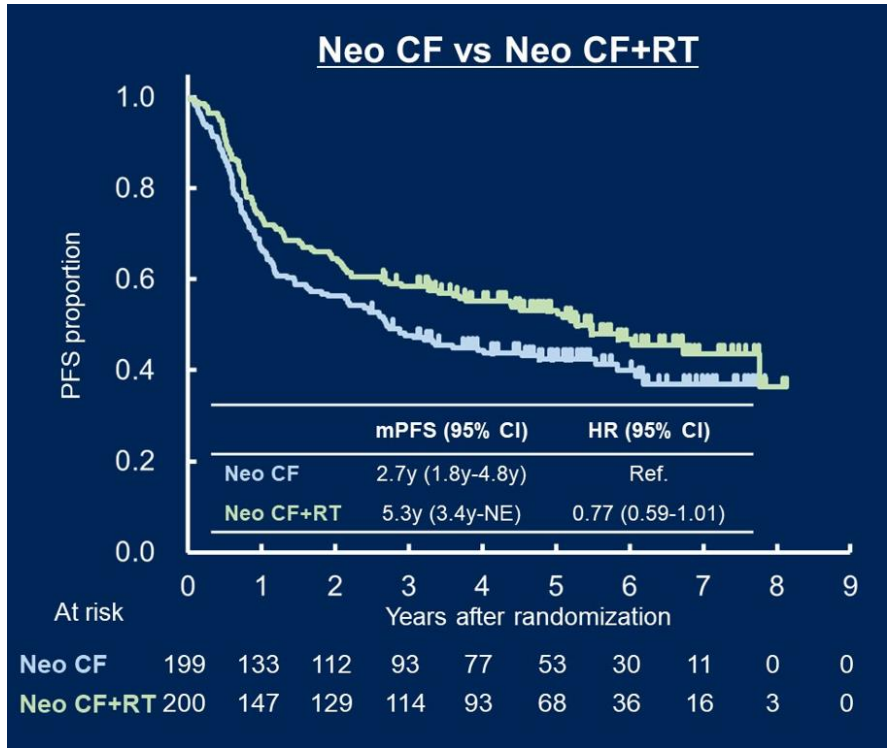
Neoadjuvant CCRT vs. conventaional chemotherapy

Neo CF+RT vs. CF

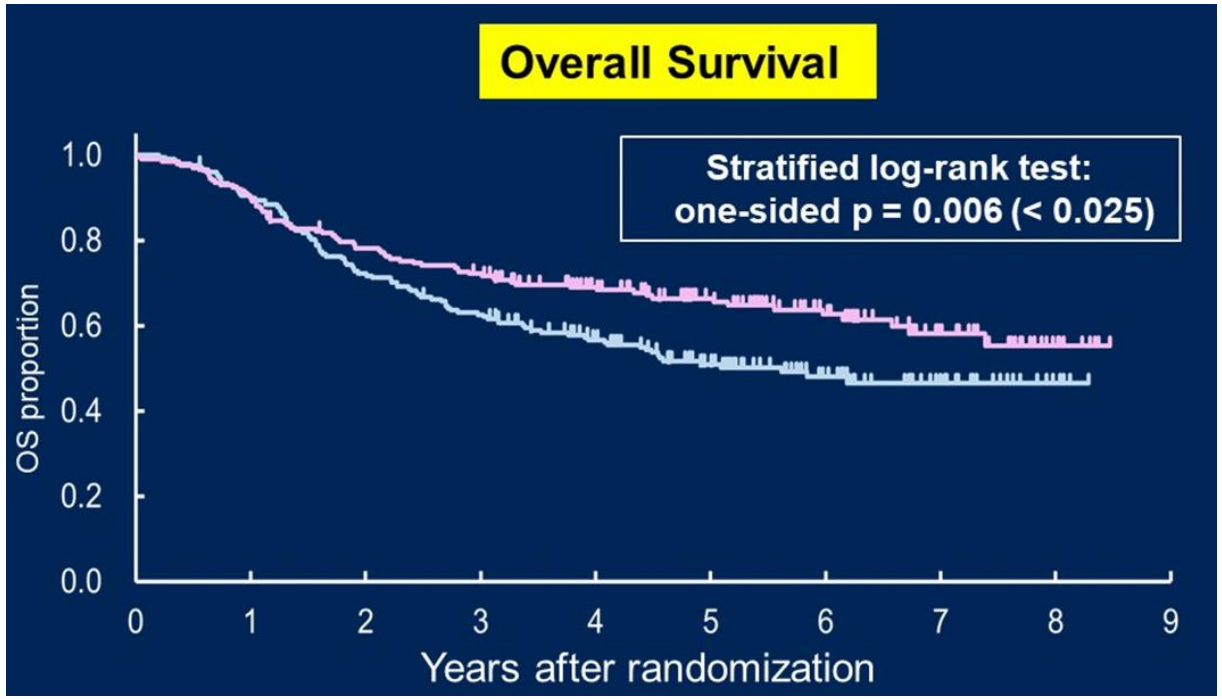
OS

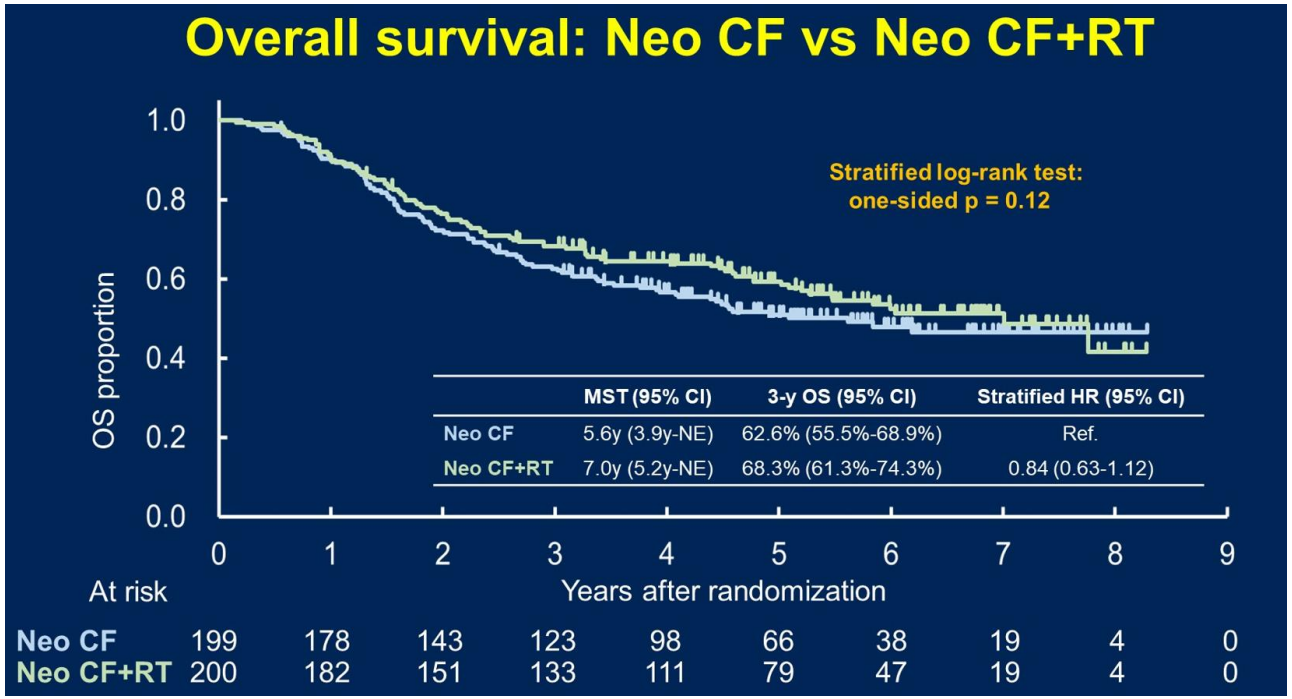


PFS



Intense chemo (DCF) vs. CCRT ?





	Median OS	3-yr OS rates
Neoadjuvant DCF	Not reached	72.1%
Neoadjuvant CF+RT	7.0yr	68.3%

JCOG-1109 (NExT study): pCR rates

Pathological outcomes

	Patients underwent surgery		
	Neo CF (n=186)	Neo DCF (n=183)	Neo CF+RT (n=177)
Histologic response of primary site*(%)			
Grade0 (ineffective)	13 (7.0)	8 (4.4)	4 (2.3)
Grade1a (slightly effective a)	113 (60.8)	63 (34.4)	15 (8.5)
Grade1b (slightly effective b)	26 (14.0)	14 (7.7)	21 (11.9)
Grade2 (moderately effective)	30 (16.1)	58 (31.7)	60 (33.9)
Grade3 (No residual tumor)	4 (2.2)	40 (21.9)	77 (43.5)
ypStage (UICC-TNM7th) (%)			
ypStage 0 (pCR)	**4 (2.2)**	**34 (18.6)**	**65 (36.7)**
ypStage I	36 (19.4)	34 (18.6)	38 (21.5)
ypStage II	46 (24.7)	50 (27.3)	36 (20.3)
ypStage III	83 (44.6)	48 (26.2)	26 (14.7)
ypStage IV	17 (9.1)	17 (9.3)	12 (6.8)

*Japanese classification of esophageal cancer 13th edition

Why didn't higher pCR rate translate into longer OS?

RO resection rates from JCOG-1109 (NExT study)

- Intense systemic treatment is Enough for R0 resection ?

	Patients underwent surgery		
	Neo CF (n=188)	Neo DCF (n=185)	Neo CF+RT (n=178)
No. of harvested LN# (median, range)	58 (24-125)	59 (19-143)	49 (11-148)
Residual tumor#			
R0 / R1-2	168 (**90.3**) / 18 (9.7)	173 (**94.5**) / 10 (5.5)	175 (**98.9**) / 2 (1.1)

	Neo DCF (Intense systemic treatment)	Neo CF+RT (Current standard)
pCR rates	18.6%	36.7%
R0 rates	94.5%	98.9%
Systemic disease control rates	?	?

Toxicities between chemotherapy and CCRT

Causes of Death	All eligible patients		
	Neo CF (n=193)	Neo DCF (n=199)	Neo CF+RT (n=197)
Alive (%)	98 (50.8)	126 (63.3)	110 (55.8)
Death (%)	95 (49.2)	73 (36.7)	87 (44.2)
Cause of death (%)			
Esophageal cancer	73 (76.8)	59 (80.8)	55 (63.2)
Other disease	11 (11.6)	6 (8.2)	23 (26.4)
Treatment related death	3 (3.2)	4 (5.5)	2 (2.3)
Others	2 (2.1)	3 (4.0)	0 (0.0)
Unknown	6 (6.3)	1 (1.3)	7 (8.1)

JCOG 1109 vs. CROSS vs. NEOCRTEC5010

	JCOG1109 Neo DCF	CROSS ChemoRT	NEOCRTEC5010 ChemoRT
EFFICACY			
OS	NR (6.7-NE)	82 months	100.1 months
OS Rate at 3 years	72.1%	51.2%	65.8%
R0 Resection Rate	94%	92% (Adeno and SCC)	99%
Path CR Rate	18.6%	49%	43.2%
TOXICITY			
Grade ≥3 Neutropenia	85.2%	2%	55.7%
Grade ≥3 Leukopenia	63.8%	6%	48.8%
Grade ≥ 3 Febrile Neutropenia	16.3%	N/A	N/A
Grade ≥3 Anorexia	21.4%	5%	2.2%

Limitation of this comparison: small # patients in CROSS trial had ESCC and midthorathic tumors.

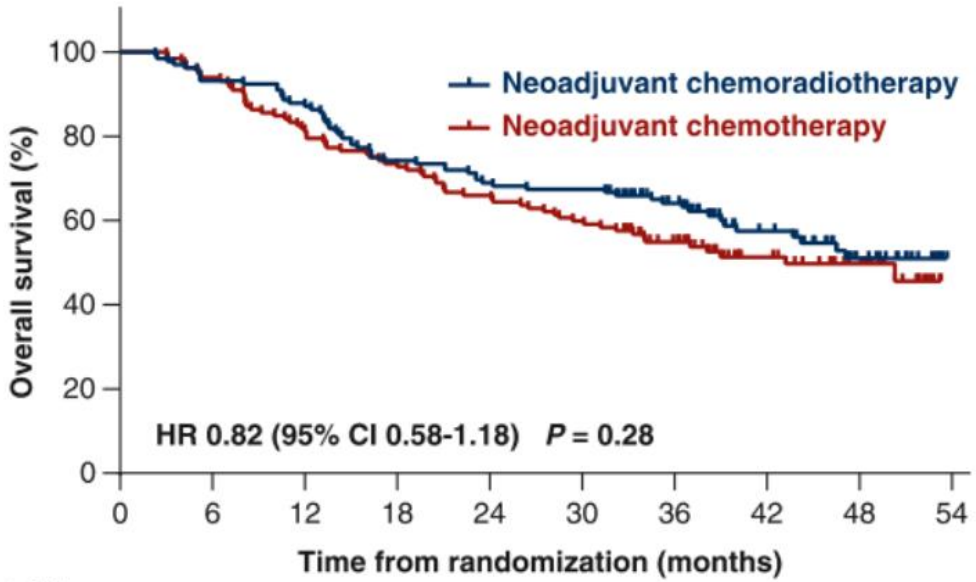
Neoadjuvant CCRT vs. chemotherapy: Chinese result

- CMISG1701 study
- Neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy followed by minimally invasive esophagectomy
- Bulky tumors: cT3-4N0-1
- Neoadjuvant CCRT (CROSS) vs. intense chemotherapy
  - Intense chemotherapy: Two cycles of paclitaxel (175 mg/ m2) and cisplatin (75 mg/m2) q3wks

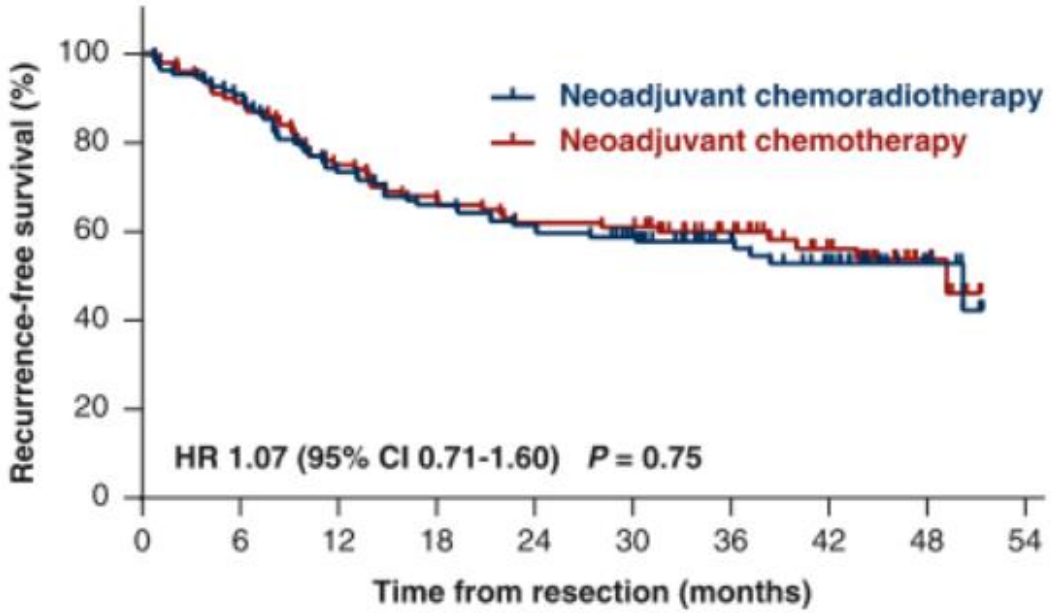
Outcome	nCRT group (n = 112), n (%)	nCT group (n = 104), n (%)	P value
R0 resection	109 (97.3)	100 (96.2)	0.921
Histological response of primary tumor			<0.001
TRG1 (residual tumor 0%)	40 (35.7)	4 (3.8)	
TRG2 (residual tumor 1%-10%)	31 (27.7)	10 (9.6)	
TRG3 (residual tumor 11%-50%)	19 (17)	17 (16.3)	
TRG4 (residual tumor >50%)	22 (19.6)	73 (70.2)	
ypT stage			<0.001
ypT0	40 (35.7)	4 (3.8)	
ypT1	17 (15.2)	15 (14.4)	
ypT2	23 (20.5)	23 (22.1)	
ypT3	22 (19.6)	48 (46.2)	
ypT4	10 (8.9)	14 (13.4)	
Lymph nodes involved			0.030
ypN0	74 (66.1)	48 (46.2)	
ypN1	26 (23.2)	36 (34.6)	
ypN2	9 (8.0)	14 (13.5)	
ypN3	3 (2.7)	6 (5.8)	
LVI + PNI			0.004
Negative	100 (89.3)	77 (74)	
Positive	12 (10.7)	27 (26)	
Lymph node harvested, median	20	24	0.001
ypStage			<0.001
ypStage I	58 (51.8)	21 (20.2)	
Including ypT0N0M0, pCR	31 (27.7)	3 (5.3)	<0.001
ypStage II	11 (9.8)	21 (20.2)	
ypStage III	34 (30.4)	49 (47.1)	
ypStage IV	9 (8.0)	13 (12.5)	
ypT0N+M0	9 (8.0)	1 (0.96)	0.013

Tang, H., et al. (2023). Annals of Oncology 34(2): 163-172.

Neoadjuvant CCRT vs. chemotherapy: Chinese result OS and PFS



Number at risk										
Neoadjuvant chemoradiotherapy	132	123	116	98	91	89	70	43	22	0
Neoadjuvant chemotherapy	132	124	107	96	87	79	56	34	20	0



Number at risk										
Neoadjuvant chemoradiotherapy	109	99	80	72	67	59	39	26	10	0
Neoadjuvant chemotherapy	100	89	75	67	62	61	40	25	9	0

Tang, H., et al. (2023). Annals of Oncology 34(2): 163-172.

Endpoint of preoperative treatment

- pCR
  - Surrogate marker for local control
  - Reflect the good systemic control ?
  - Is associated with
    - Decreased recurrence
    - Prolonged survival
    - Improved prognosis

The possible role of Immunotherapy

- Distant recurrence
  - Need systemic control

- Safety

Lesson from metastatic setting

- Response rates of ICI+chemo vs. chemo alone among the first line setting

Trial	Immunotherapy	Chemo backbone	ORR (ICI+chemo)	ORR (Chemo Alone)	CR (ICI+Chemo)	CR (Chemo Alone)
KEYNOTE-590	Pembrolizumab	5-FU+Cisplatin	45%	29%	5%	3%
CHECKMATE-648	Nivolumab	5-FU+Cisplatin	53%	20%	6%	3%
ESCORT-1st	Camrelizumab	Paclitaxel+Cisplatin	72%	62%	5%	2%
ORIENT-15	Sintilimab	Paclitaxel+Cisplatin	64%	52%	7%	3%
JUPITER-06	Toripalimab	Paclitaxel+Cisplatin	69%	52%	4.5%	2.6%
RATIONALE 306	Tislelizumab	Paclitaxel or 5-FU+Cisplatin	63%	42%	8%	2%
SKYSCRAPER-08	Tiragolumab + Atezolizumab	5-FU+Cisplatin	45%	27%	5%	3%

Chemotherapy and Immunotherapy: Friends or Foes?

- Foes with immunotherapy ?
  - Chemotherapy
    - Dose-dependent myelosuppression.
    - Immunosuppressive.
    - Sometimes, used to treat autoimmune diseases or to prevent transplant rejection.
    - Suggesting an antagonistic effect with immunotherapy.

- Friends with immunotherapy ?
  - Chemotherapy
    - The ability to debulk the BULKY tumor mass
    - Decreasing the number of tumor cells that should need to be eliminated by immune cells
    - Reducing the immunosuppressive factors produced by cancer cells

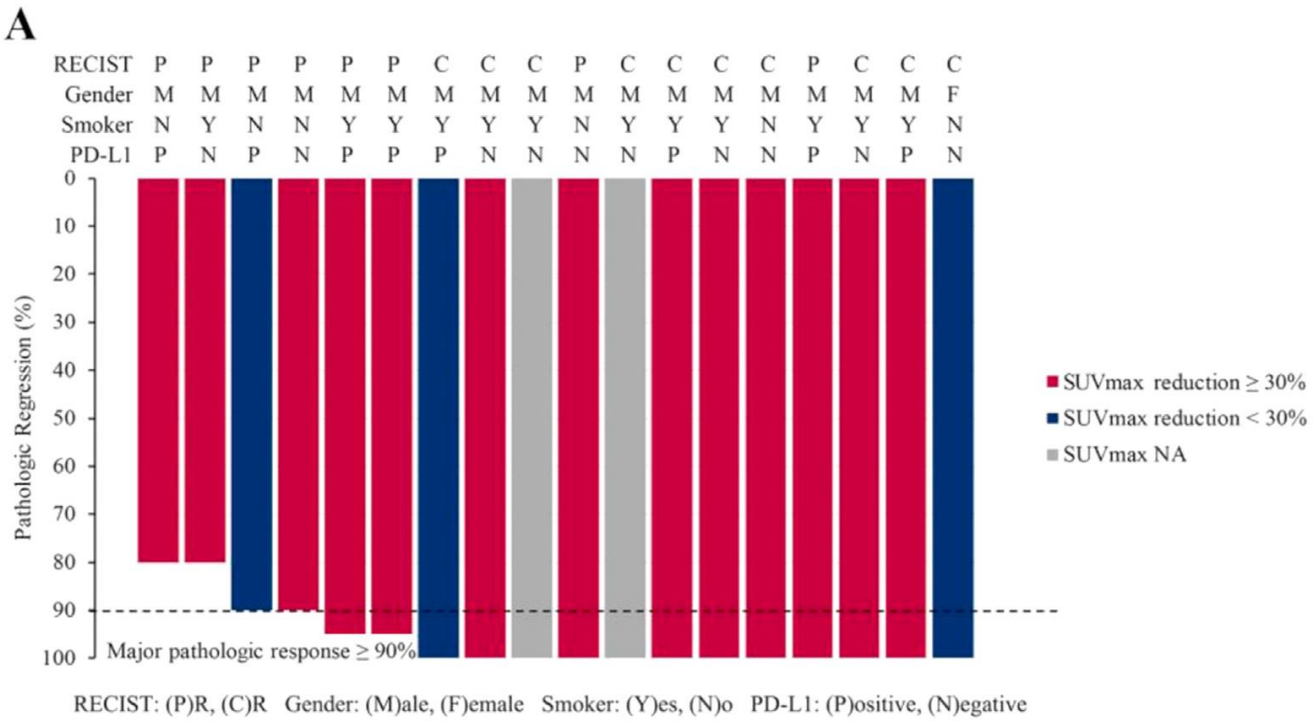
Current status of neoadjuvant immunotherapy

Neoadjuvant RT combination

Trial	Phase	# Patients	Pathology	Clinical Stage	Immune Checkpoint Inhibitor	Immune Target	Chemotherapeutic Agents	Radiotherapy	Primary Endpoint	Pathologic Complete Response (pCR)	Safety-Grade ≥ 3 AE
PALACE-1 [21]	Ib	20	ESCC	II-IVA	Pembrolizumab	PD-1	Carboplatin, Paclitaxel	23 fractions of 1.8 Gy	Safety	55.60%	65%
PERFECT [22]	II	40	EAC	II-IVA	Atezolizumab	PD-L1	Carboplatin, Paclitaxel	23 fractions of 1.8 Gy	Feasibility	40%	30%
ESONICT-1 [26]	II	30	ESCC	III-IV	Sintilimab	PD-1	Cisplatin, Albumin-bound paclitaxel	N/A	pCR, AEs	21.70%	3%
ESONICT-2 [29]	II	20	ESCC	III-IVA	Toripalimab	PD-1	Cisplatin, Docetaxel	N/A	pCR, AEs	16.70%	20%
SIN-ICE [23]	Pilot Study	23	ESCC	II-IVA	Sintilimab	PD-1	Docetaxel/ Albumin-bound paclitaxel, Nedaplatin	N/A	pCR, safety	35.30%	30.40%
PEN-ICE [27]	II	18	ESCC	II-IVA	Pembrolizumab	PD-1	Platinum-based two drug	N/A	Safety, Efficacy	46.20%	27.80%
TD-NICE [28]	II	45	ESCC	II-IVA	Tislelizumab	PD-1	Nab-paclitaxel, Carboplatin	N/A	Major Pathologic Response (MPR)	50%	42.20%
NIC-ESCC2019 [30]	II	56	ESCC	II-IVA	Camrelizumab	PD-1	Nab-paclitaxel, cisplatin	N/A	pCR	13.70%	10.70%
Shen et al. [24]	II	28	ESCC	II-IVA	Nivolumab, Pembrolizumab, Camrelizumab	PD-1	Nab-paclitaxel, Carboplatin	N/A	Safety, Feasibility	40.70%	7.10%
Yang et al. [25]	Pilot	16	ESCC	II-IVA	Camrelizumab	PD-1	Paclitaxel, Carboplatin	N/A	pCR	31.30%	N/A (only mild and tolerable AE)
Xing et al. [31]	II	30	ESCC	II-IVA	Toripalimab	PD-1	Paclitaxel, Cisplatin	N/A	pCR	36%	6.67%
Yang et al. [32]	Pilot	23	ESCC	II-III	Camrelizumab	PD-1	Nab-paclitaxel, Carboplatin	N/A	Safety, Feasibility	25%	47.80%
He et al. [20]	II	20	ESCC	III-IVA	Toripalimab	PD-1	Paclitaxel, Carboplatin	N/A	Safety, Feasibility, MPR	18.80%	20%
Liu et al. [33]	II	60	ESCC	III-IVA	Camrelizumab	PD-1	Nab-paclitaxel, Carboplatin	N/A	pCR	39.20%	56.70%
Wang et al. [34]	Ib	30	ESCC	II-III	Camrelizumab	PD-1	Nab-paclitaxel, nedaplatin, apatinib	N/A	Safety	24.10%	36.70%

PALACE-1

- Locally advanced ESCC, N=20
- Phase 1b, primary endpoint: safety
- Pembrolizumab+paclitaxel+carboplatin+RT
- Paclitaxel/carboplatin: CROSS regimen



pCR: 55%

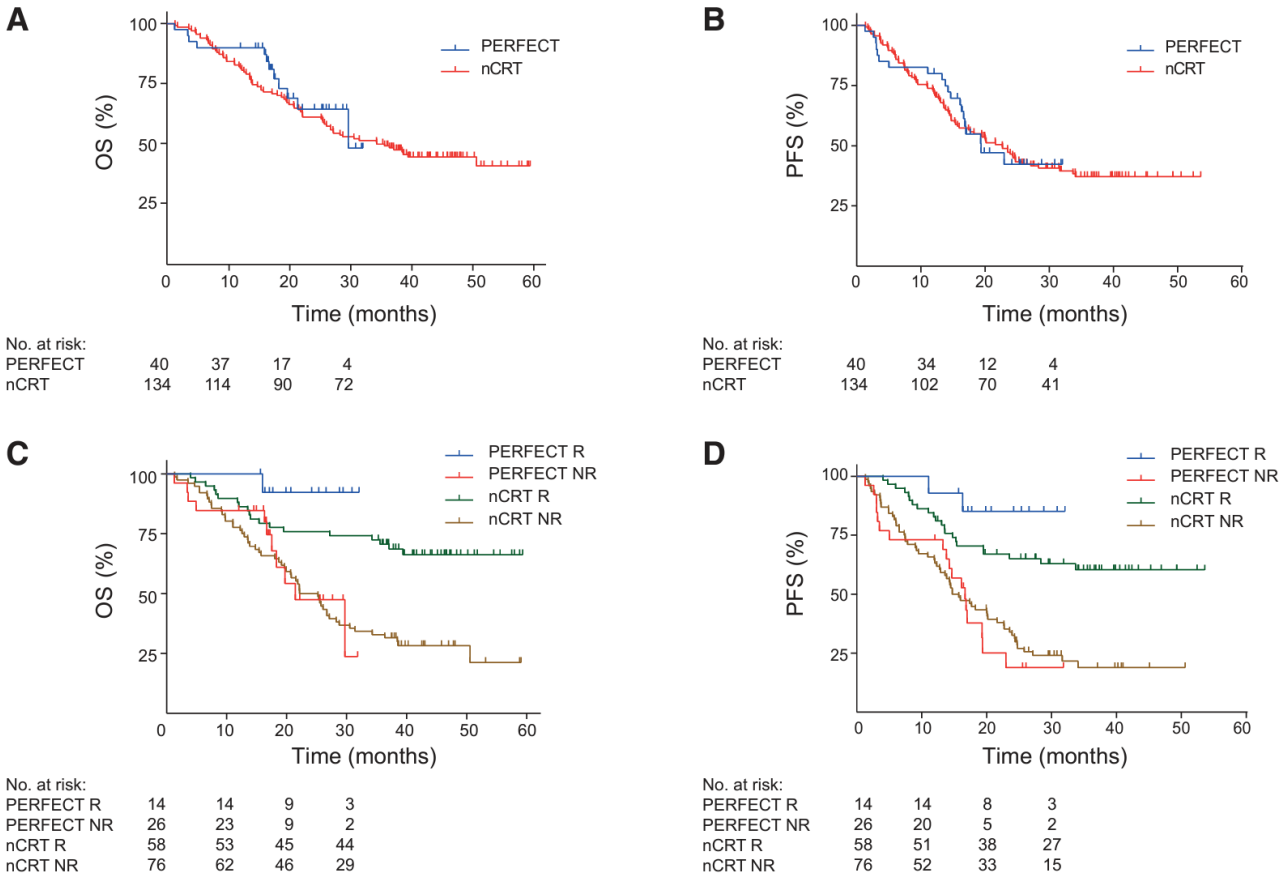
Adverse events during neoadjuvant pembrolizumab plus chemo-radiotherapy and after surgery.

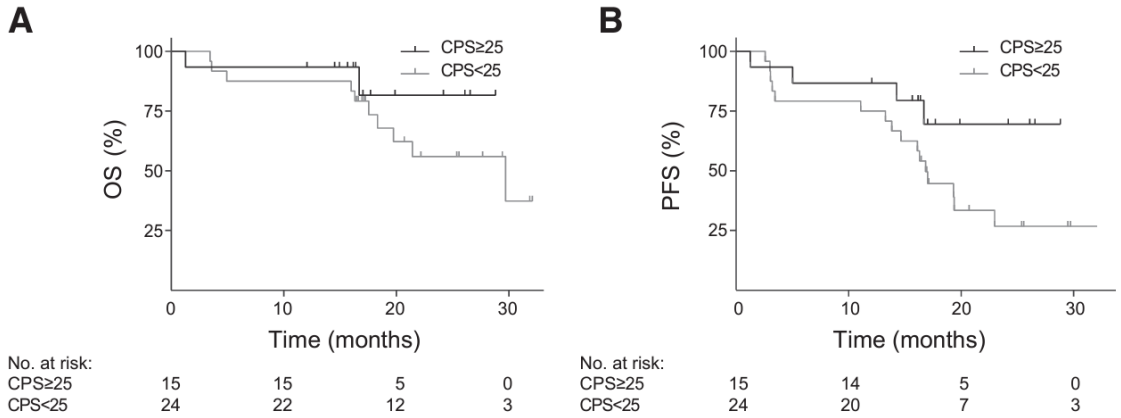
Events	No. (%)
Postoperative events (N=18)—no. of patients (%)	
Pneumonia	4 (22)
Atelectasis	4 (22)
Pleural effusion	3 (17)
Pneumothorax	1 (6)
Anastomotic leakage	1 (6)
Gastrointestinal fistula	1 (6)
Wound infection	1 (6
Hoarseness	4 (22)
Dysphagia	1 (6)
Postoperative intrathoracic haemorrhage	1 (6)
Events of any grade during neoadjuvant therapy (N=20)—no. of patients (%)	
Leukopenia	20 (100)
Decreased neutrophil count	9 (45)
Lymphopenia	20 (100)
Anaemia	16 (80)
Decreased platelet count	1 (5)
Dermatitis	1 (5)
Pneumonitis	4 (20)
Alopecia	11 (55)
Anorexia	9 (45)
Constipation	4 (20)
Diarrhoea	2 (10)
Fatigue	11 (55)
Nausea	8 (40)
Vomiting	3 (15)
Oesophageal haemorrhage	2 (10)
Esophagitis	11 (55)
Events of grade ≥3 during neoadjuvant therapy (N=20)—no. of patients (%)	
Leukopenia	2 (10)
Decreased neutrophil count	1 (5)
Lymphopenia	12 (60)
Oesophageal haemorrhage	1 (5)

Li, C., et al. (2021). European Journal of Cancer 144: 232-241.

PERFECT

- Locally advanced ESCC, N=40
- Phase 2, primary endpoint: feasibility
- Atezolizumab+paclitaxel+carboplatin+RT
- Paclitaxel/carboplatin: CROSS regimen



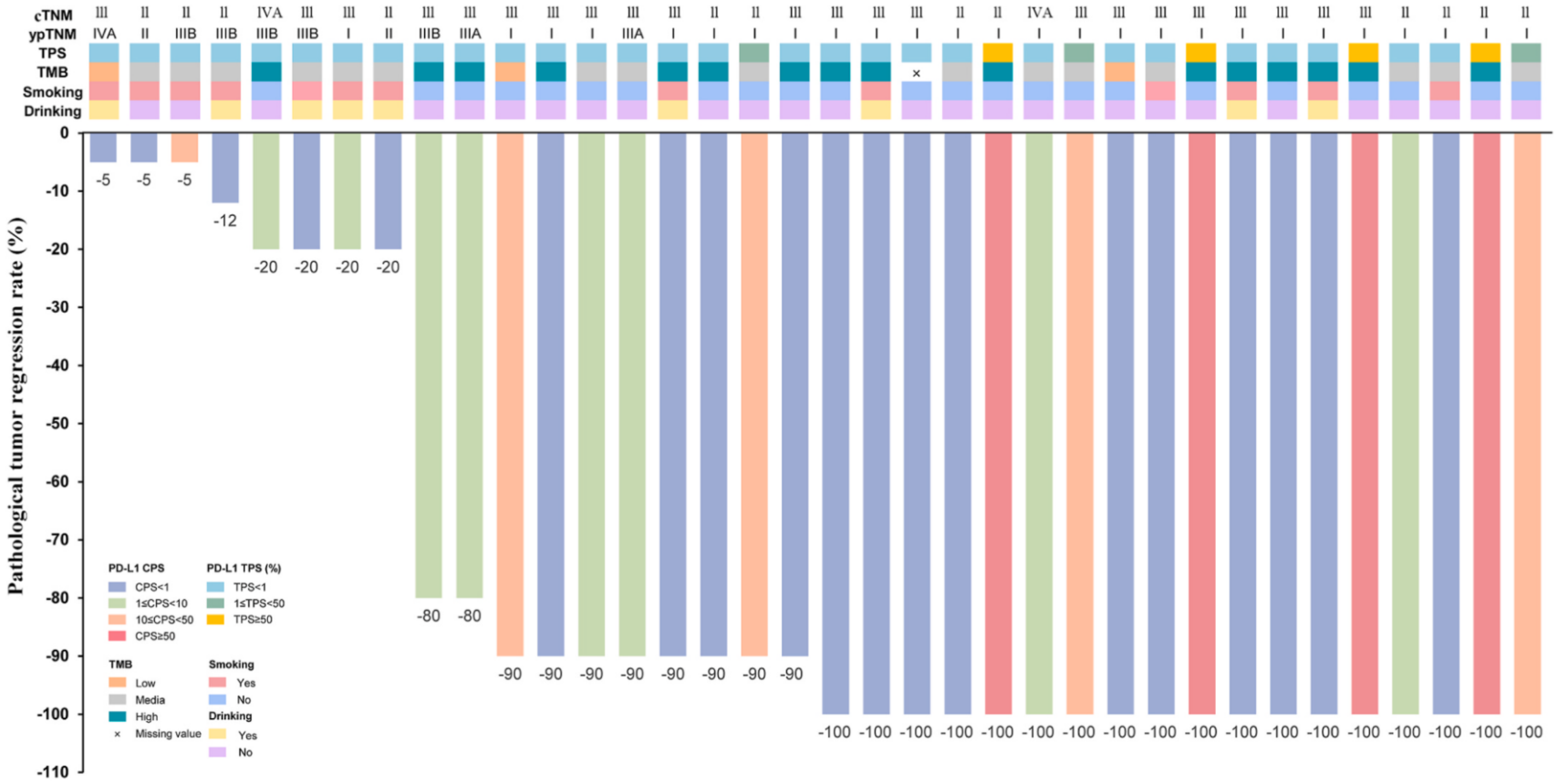


pCR: 30%

Clin Cancer Res 2021;27:3351–9

TD-NICE

- Locally advanced ESCC, N=45
- Phase 2, primary endpoint: Major pathologic response
- Tislelizumab+nab-paclitaxel+carboplatin
- Nab-Paclitaxel/carboplatin: not CROSS regimen (paclitaxel 260mg/m2. carboplatin AUC 5)



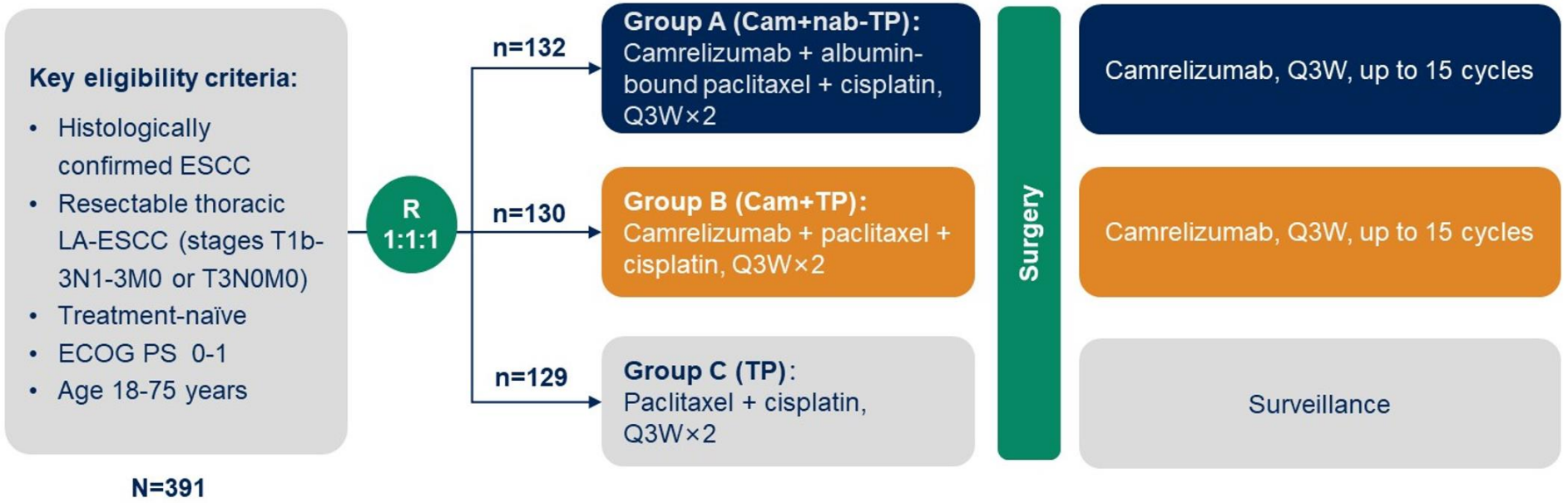
pCR: 50%

Yan, X., et al. (2022). International Journal of Surgery 103: 106680.

ESCORT-NEO/NCCESOIJ

Study design

A randomized, multi-center, open-label phase III trial (ChiCTR2000040034)



Co-primary endpoints:
- pCR assessed by BIRC
- EFS assessed by investigators

Secondary endpoints:
- MPR
- R0 resection rate
- ypTNM staging
- DFS
- OS
- Safety

Exploratory endpoints:
- Biomarker
- PRO

Stratification factors:
Stages: I-II vs III vs IVA

Regimens:
- Albumin-bound paclitaxel: 125 mg/m², IV, D1 and D8, Q3W
- Paclitaxel: 175 mg/m², IV, D1, Q3W
- Cisplatin: 75 mg/m², IV, D1, Q3W
- Camrelizumab: 200 mg, IV, D1, Q3W

Baseline characteristics in ITT population

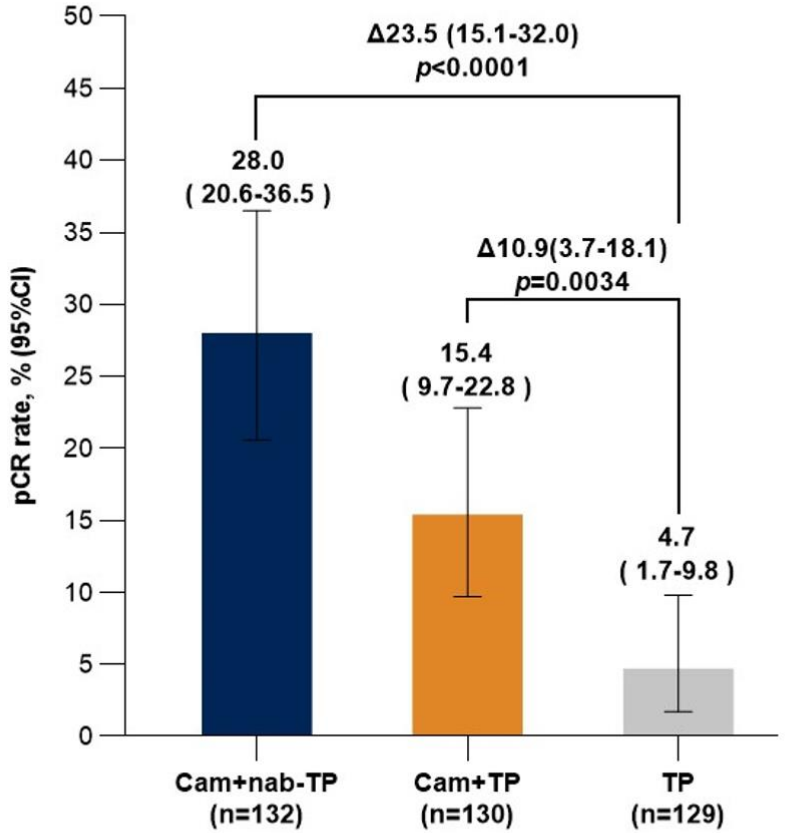
	Group A: Cam+nab-TP (n=132)	Group B: Cam+TP (n=130)	Group C: TP (n=129)
Age (years)			
<65	74 (56.1)	79 (60.8)	63 (48.8)
≥65	58 (43.9)	51 (39.2)	66 (51.2)
Median (range)	63 (45-75)	63 (44-75)	65 (44-75)
Sex, n (%)			
Male	116 (87.9)	112 (86.2)	104 (80.6)
Female	16 (12.1)	18 (13.8)	25 (19.4)
ECOG PS, n (%)			
0	105 (79.5)	106 (81.5)	104 (80.6)
1	27 (20.5)	24 (18.5)	25 (19.4)
Tumor location, n (%)			
Upper	10 (7.6)	12 (9.2)	19 (14.7)
Middle	69 (52.3)	75 (57.7)	57 (44.2)
Lower	53 (40.2)	43 (33.1)	53 (41.1)
T stage, n (%)			
T1b	3 (2.3)	1 (0.8)	2 (1.6)
T2	15 (11.4)	13 (10.0)	19 (14.7)
T3	114 (86.4)	116 (89.2)	108 (83.7)

	Group A: Cam+nab-TP (n=132)	Group B: Cam+TP (n=130)	Group C: TP (n=129)
N stage, n (%)			
N0	20 (15.2)	24 (18.5)	20 (15.5)
N1	71 (53.8)	71 (54.6)	73 (56.6)
N2	38 (28.8)	33 (25.4)	35 (27.1)
N3	3 (2.3)	2 (1.5)	1 (0.8)
Clinical stage, n (%)			
I/II	34 (25.8)	35 (26.9)	37 (28.7)
III	95 (72.0)	93 (71.5)	91 (70.5)
IVA	3 (2.3)	2 (1.5)	1 (0.8)
PD-L1 TPS, n (%)			
<1%	43 (32.6)	59 (45.4)	49 (38.0)
≥1%	78 (59.1)	61 (46.9)	62 (48.1)
<10%	99 (75.0)	98 (75.4)	97 (75.2)
≥10%	22 (16.7)	22 (16.9)	14 (10.9)
Unknown	11 (8.3)	10 (7.7)	18 (14.0)
PD-L1 CPS, n (%)			
<1	14 (10.6)	18 (13.8)	15 (11.6)
≥1	109 (82.6)	102 (78.5)	96 (74.4)
<10	68 (51.5)	80 (61.5)	72 (55.8)
≥10	55 (41.7)	40 (30.8)	39 (30.2)
Unknown	9 (6.8)	10 (7.7)	18 (14.0)

Primary endpoint: pCR rate assessed by BIRC in ITT population

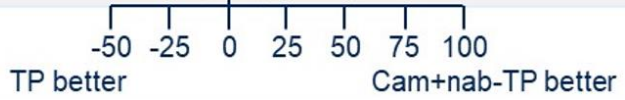
	Group A: Cam+nab-TP (n=132)	Group B: Cam+TP (n=130)	Group C: TP (n=129)
pCR rate, % (95%CI)[a]	28.0 (20.6, 36.5)	15.4 (9.7, 22.8)	4.7 (1.7, 9.8)
Difference (vs. Group C), % (95%CI)[b]	23.5 (15.1, 32.0)	10.9 (3.7, 18.1)	
OR (vs. Group C) (95%CI)[b]	8.11 (3.28, 20.06)	3.81 (1.48, 9.80)	
p value (vs. Group C)[c]	<0.0001	0.0034	

a 95%CI were calculated based on the Clopper-Pearson method.
b 95%CI for the stratification factor-adjusted rate differences were derived using the Mantel-Haenszel method.
c The CMH test, stratified by clinical staging (stage I/II vs. III/IVA), was used to compare between groups.



Subgroup analysis of pCR (Cam+nab-TP vs. TP)

Groups	Group A: Cam+nab-TP (n=132)	pCR rate, % (95% CI)	Group C: TP (n=129)	pCR rate, % (95% CI)	Unadjusted difference, % (95% CI)
Overall	37/132	28.03 (20.57, 36.51)	6/129	4.65 (1.73, 9.85)	23.38 (15.04, 32.16)
Age					
<65 years	21/74	28.38 (18.50, 40.05)	3/63	4.76 (0.99, 13.29)	23.62 (11.89, 35.58)
≥65 years	16/58	27.59 (16.66, 40.90)	3/66	4.55 (0.95, 12.71)	23.04 (10.91, 36.37)
Sex					
Male	31/116	26.72 (18.93, 35.74)	5/104	4.81 (1.58, 10.86)	21.92 (12.91, 31.29)
Female	6/16	37.50 (15.20, 64.57)	1/25	4.00 (0.10, 20.35)	33.50 (10.19, 58.48)
ECOG PS					
0	30/105	28.57 (20.18, 38.21)	6/104	5.77 (2.15, 12.13)	22.80 (13.15, 32.85)
1	7/27	25.93 (11.11, 46.28)	0/25	0.00 (0.00, 13.72)	25.93 (10.80, 44.87)
Clinical stage					
I/II	12/34	35.29 (19.75, 53.51)	2/37	5.41 (0.66, 18.19)	29.89 (12.19, 47.82)
III	23/95	24.21 (16.01, 34.08)	4/91	4.40 (1.21, 10.87)	19.81 (10.37, 29.96)
IVA	2/3	66.67 (9.43, 99.16)	0/1	0.00 (0.00, 97.50)	66.67 (-45.21, 95.04)
Tumor location					
Upper	4/10	40.00 (12.16, 73.76)	2/19	10.53 (1.30, 33.14)	29.47 (-2.02, 61.08)
Middle	17/69	24.64 (15.05, 36.49)	2/57	3.51 (0.43, 12.11)	21.13 (9.73, 33.10)
Lower	16/53	30.19 (18.34, 44.34)	2/53	3.77 (0.46, 12.98)	26.42 (13.24, 40.46)
PD-L1 TPS					
<1%	5/43	11.63 (3.89, 25.08)	1/49	2.04 (0.05, 10.85)	9.59 (-0.73, 22.83)
≥1%	30/78	38.46 (27.66, 50.17)	4/62	6.45 (1.79, 15.70)	32.01 (19.07, 44.25)
<10%	23/99	23.23 (15.33, 32.79)	4/97	4.12 (1.13, 10.22)	19.11 (10.10, 28.91)
≥10%	12/22	54.55 (32.21, 75.61)	1/14	7.14 (0.18, 33.87)	47.40 (16.67, 68.60)
Unknown	2/11	18.18 (2.28, 51.78)	1/18	5.56 (0.14, 27.29)	12.63 (-12.04, 43.80)
PD-L1 CPS					
<1	1/14	7.14 (0.18, 33.87)	0/15	0.00 (0.00, 21.80)	7.14 (-14.66, 32.01)
≥1	34/109	31.19 (22.66, 40.78)	5/96	5.21 (1.71, 11.74)	25.98 (16.17, 35.95)
<10	15/68	22.06 (12.90, 33.76)	2/72	2.78 (0.34, 9.68)	19.28 (9.25, 30.92)
≥10	20/55	36.36 (23.81, 50.44)	3/39	7.69 (1.62, 20.87)	28.67 (12.15, 43.53)
Unknown	2/9	22.22 (2.81, 60.01)	1/18	5.56 (0.14, 27.29)	16.67 (-9.45, 50.92)



MPR & pathological regression in primary tumor by BIRC

	Group A: Cam+nab-TP	Group B: Cam+TP	Group C: TP
ITT population	**n=132**	**n=130**	**n=129**
MPR rate, % (95%CI)[a]	59.1 (50.2, 67.6)	36.2 (27.9, 45.0)	20.9 (14.3, 29.0)
Difference (vs. Group C), % (95%CI)[b]	38.3 (27.4, 49.3)	15.4 (4.7, 26.2)	
OR (vs. Group C) (95%CI)[b]	5.51 (3.18, 9.56)	2.19 (1.25, 3.84)	
Tumor regression grade (Mandard criteria) in primary tumor, n (%)	**n=114**	**n=116**	**n=103**
TRG 1	47 (41.2)	23 (19.8)	7 (6.8)
TRG 2	24 (21.1)	21 (18.1)	12 (11.7)
TRG 3	30 (26.3)	36 (31.0)	32 (31.1)
TRG 4	13 (11.4)	34 (29.3)	47 (45.6)
TRG 5	0	2 (1.7)	5 (4.9)

a 95%CI were calculated based on the Clopper-Pearson method.
b 95%CI for the stratification factor-adjusted rate differences were derived using the Mantel-Haenszel method.

Surgery summary

	Group A: Cam+nab-TP (n=114)	Group B: Cam+TP (n=116)	Group C: TP (n=103)
Definitive surgery rate (%)[a]	86.4 (114/132)	89.2 (116/130)	79.8 (103/129)
Types of surgical procedures, n (%)			
McKeown	107 (93.9)	106 (91.4)	95 (92.2)
Ivor-Lewis	6 (5.3)	10 (8.6)	7 (6.8)
Sweet	1 (0.9)	0	0
Other	0	0	1 (1.0)
Lymph node dissection extent, n (%)			
Total two-field	97 (85.1)	100 (86.2)	82 (79.6)
Extended two-field	1 (0.9)	1 (0.9)	2 (1.9)
Standard two-field	1 (0.9)	0	0
Three-field	15 (13.2)	15 (12.9)	19 (18.4)

	Group A: Cam+nab-TP (n=114)	Group B: Cam+TP (n=116)	Group C: TP (n=103)
Duration of surgery (hours)			
Median (range)	4.3 (2.6-8.9)	4.2 (2.8-7.2)	4.2 (2.9-10.8)
Margin status, n (%)			
R0	113 (99.1)	111 (95.7)	95 (92.2)
R1	1 (0.9)	4 (3.4)	6 (5.8)
R2	0	1 (0.9)	2 (1.9)
Reoperations[b], n (%)	0	1 (0.9)	1 (1.0)
Mortality within 30 days[c], n (%)	1 (0.9)	2 (1.7)	1 (1.0)
Mortality within 90 days[d], n (%)	2 (1.8)	2 (1.7)	1 (1.0)

a Based on ITT population
b Two patients underwent reoperation: Group B: adhesive intestinal obstruction; Group C: anastomotic leak.
c Mortality within 30 days included: Group A: sudden postoperative death, cause unknown; Group B: both septic shock; Group C: myocardial infarction.
d Mortality within 90 days included mortality within 30 days, with one more death in Group A: severe pneumonia.

SurgicaI complications in >1 patient

Events[a], n (%)	Group A: Cam+nab-TP (n=114)		Group B: Cam+TP (n=116)		Group C: TP (n=103)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any events	**39 (34.2)**	**7 (6.1)**	**45 (38.8)**	**14 (12.1)**	**33 (32.0)**	**7 (6.8)**
Pneumonia	12 (10.5)	0	21 (18.1)	1 (0.9)	15 (14.6)	2 (1.9)
Recurrent laryngeal nerve injury	11 (9.6)	0	11 (9.5)	1 (0.9)	9 (8.7)	1 (1.0)
Dysrhythmia	7 (6.1)	0	2 (1.7)	0	3 (2.9)	0
Pleural effusion	3 (2.6)	3 (2.6)	12 (10.3)	7 (6.0)	7 (6.8)	3 (2.9)
Anastomotic leak	3 (2.6)	1 (0.9)	5 (4.3)	2 (1.7)	6 (5.8)	1 (1.0)
Conduit necrosis	2 (1.8)	0	1 (0.9)	0	1 (1.0)	0
Respiratory failure	1 (0.9)	1 (0.9)	0	0	1 (1.0)	1 (1.0)
Intrathoracic abscess	1 (0.9)	1 (0.9)	0	0	1 (1.0)	0
Delirium	1 (0.9)	0	0	0	1 (1.0)	0
Septic shock	0	0	3 (2.6)	3 (2.6)	0	0
Chylous leak	0	0	0	0	2 (1.9)	0
Atelectasis	0	0	1 (0.9)	0	1 (1.0)	1 (1.0)
Delayed conduit emptying	0	0	0	0	2 (1.9)	1 (1.0)

a Based on Clavien-Dindo classification

Summary of preoperative AEs

Events[a], n (%)	Group A: Cam+nab-TP (n=132)	Group B: Cam+TP (n=130)	Group C: TP (n=125)
TEAE	125 (94.7)	118 (90.8)	108 (86.4)
Grade ≥3 TEAE	46 (34.8)	41 (31.5)	37 (29.6)
TEAE leading to camrelizumab discontinuation	1 (0.8)	1 (0.8)	-
TEAE leading to chemotherapy discontinuation	4 (3.0)	5 (3.8)	1 (0.8)
TEAE leading to death	0	1 (0.8)	0
TRAE	124 (93.9)	108 (83.1)	104 (83.2)
Grade ≥3 TRAE	45 (34.1)	38 (29.2)	36 (28.8)
TRAE leading to camrelizumab discontinuation	1 (0.8)[b]	1 (0.8)[c]	-
TRAE leading to chemotherapy discontinuation	4 (3.0)	5 (3.8)	1 (0.8)
TRAE leading to death	0	1 (0.8)[c]	0
SAE	10 (7.6)	12 (9.2)	7 (5.6)
irAE	36 (27.3)	32 (24.6)	0
Grade ≥3 irAE	6 (4.5)	5 (3.8)	0

a Based on CTCAE version 5.0; b Preoperative acute kidney injury; c Subacute hepatic failure.

Ongoing phase III studies of perioperative immune checkpoint inhibitor therapy

Trial	ICI therapy	Histology	Patients, n	Neoadjuvant therapy	Adjuvant therapy	Primary end point
Adjuvant						
NCT05495152	Sintilimab	SCC	219	None	Sintilimab observation	DFS
Neoadjuvant						
NCT04848753	Toripalimab	SCC	632	Cisplatin + paclitaxel + toripalimab Cisplatin + paclitaxel	None	EFS
NCT05213312	Nivolumab	SCC	90	Cisplatin + paclitaxel or cisplatin + 5-fluorouracil + nivolumab Cisplatin + paclitaxel or cisplatin + 5-fluorouracil	None	pCR
NCT04973306	Tislelizumab	SCC	176	Carboplatin + paclitaxel + tislelizumab + radiotherapy Carboplatin + paclitaxel + radiotherapy	None	pCR
NCT05357846	Sintilimab	SCC	422	Cisplatin + paclitaxel + sintilimab + radiotherapy Cisplatin + paclitaxel + radiotherapy	None	OS
NCT05244798	Sintilimab	SCC	420	Carboplatin + nab-paclitaxel + sintilimab Carboplatin + nab-paclitaxel + sintilimab + radiotherapy Carboplatin + nab-paclitaxel + radiotherapy	None	pCR
Perioperative therapy						
NCT04280822	Toripalimab	SCC	400	Cisplatin + paclitaxel + tislelizumab Cisplatin + paclitaxel	Tislelizumab None	EFS
NCT04807673	Pembrolizumab	SCC	342	Cisplatin + paclitaxel + pembrolizumab Cisplatin + paclitaxel + radiotherapy	Pembrolizumab None	EFS

DFS: Disease-free survival; EFS: Event-free survival; OS: Overall survival; pCR: Pathological complete response; SCC: Squamous cell carcinoma.

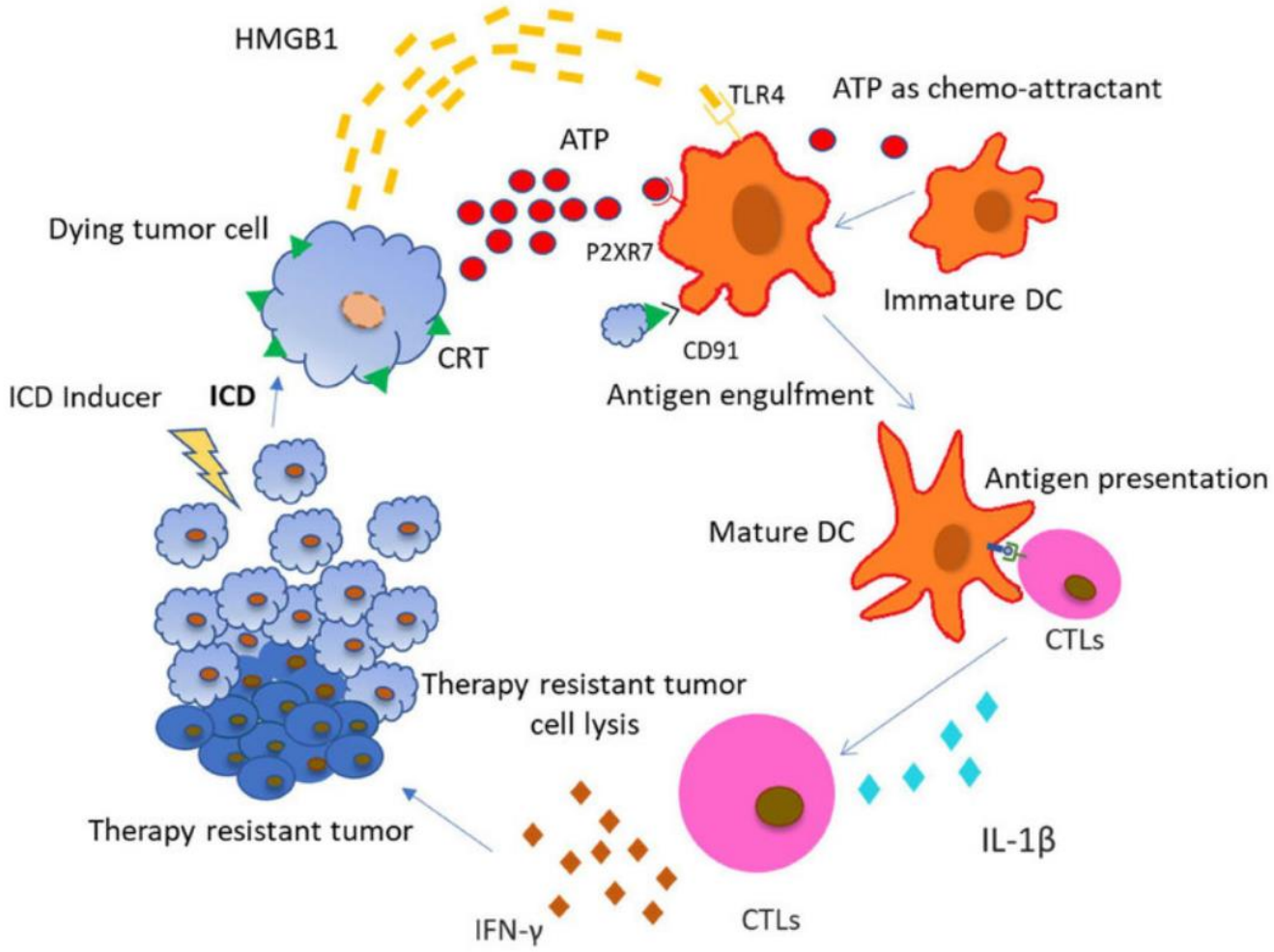
2024 Future oncology

Current challenging issue

- Proper partner of ICI (chemotherapy only vs CRT)
  - Radiotherapy induced immune-response
  - Appropriate chemotherapy ?
  - Safety
- Optimal timing, sequence ?
- Predictive biomarker

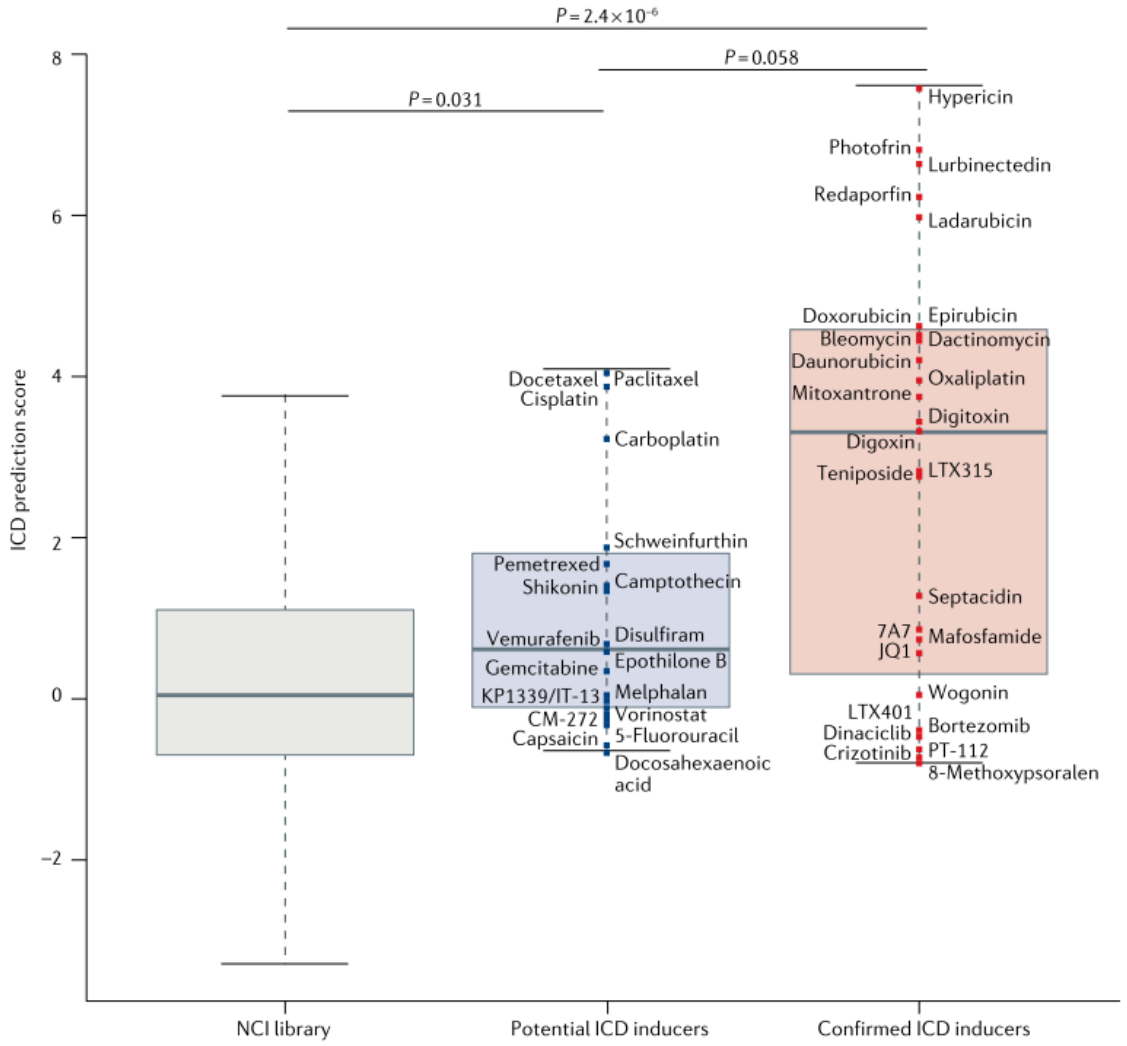
Immunogenic Cell Death: Chemotherapy Meets Immunology

- Insult of cancer cells by cytotoxic chemotherapy leads to release and relocation of damage associated molecular patterns (DAMPs) that increase the adjuvanticity of cancer cells
- Release of intracellular molecules, such as ATP, enhances the recruitment of APCs
- Cytotoxic T lymphocytes (CTLs) are activated by these mature DCs by antigen presentation and IL-1β secretion.
- CTLs produce inflammatory cytokines like IFN-γ which leads to the elimination of chemotherapy resistant tumors.



Front Oncol. 2021 Aug 23;11:728018

Immunogenic Cell Death: Chemotherapy Meets Immunology

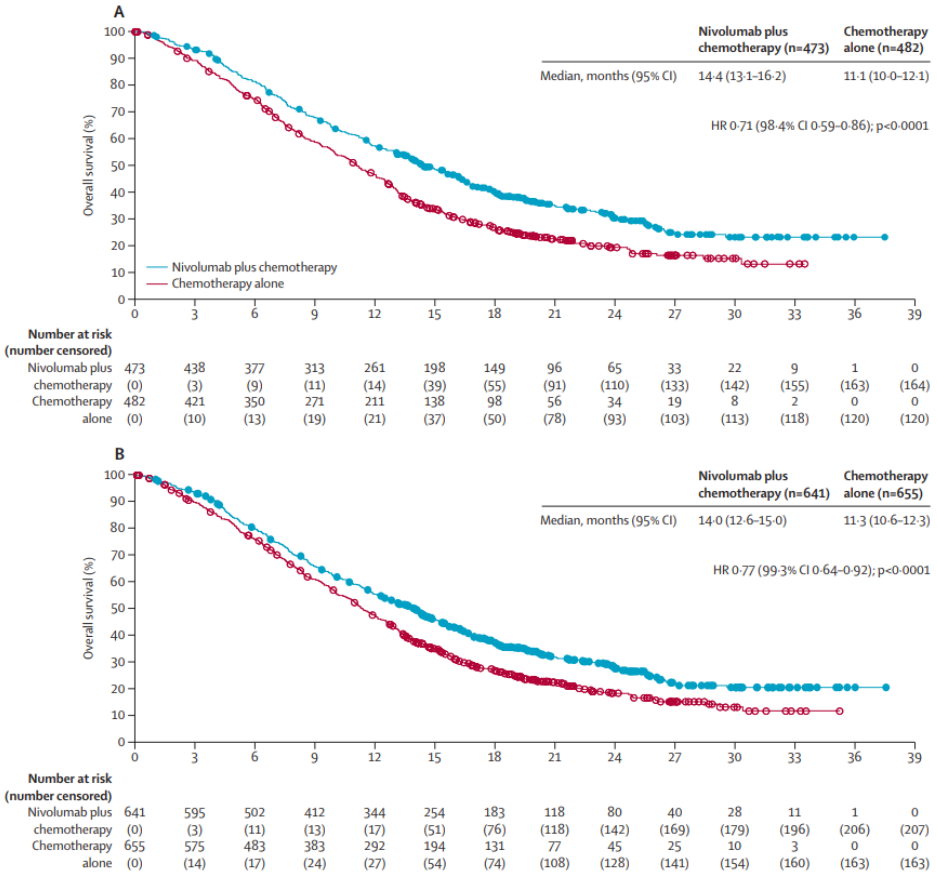


- Several studies suggested that immunogenic cell death effect according to chemotherapy.
- Conventional chemotherapy can mediate immunostimulatory effects by targeting cancer cells or immune cells as well as by altering whole-body physiology.
- Immunostimulatory chemotherapeutics stand out as promising partners for combination regimens involving immune checkpoint inhibitors, although additional research is required to identify the optimal regimens.

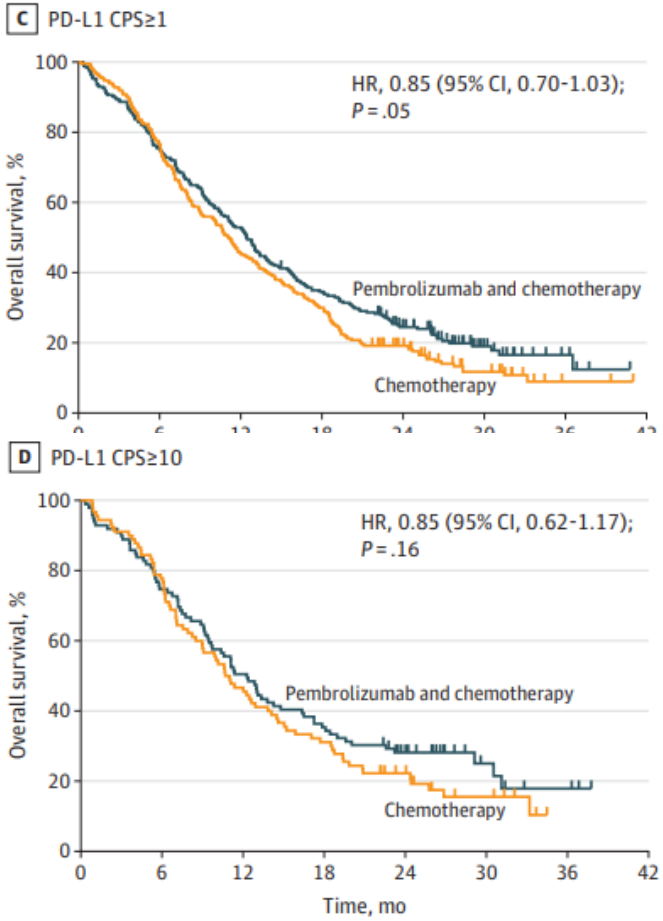
Nat Rev Clin Oncol 17(12): 725-741.

Immunogenic Cell Death: Chemotherapy Meets Immunology

CM649: Positive trial
Nivo+5-FU+**Oxaliplatin**



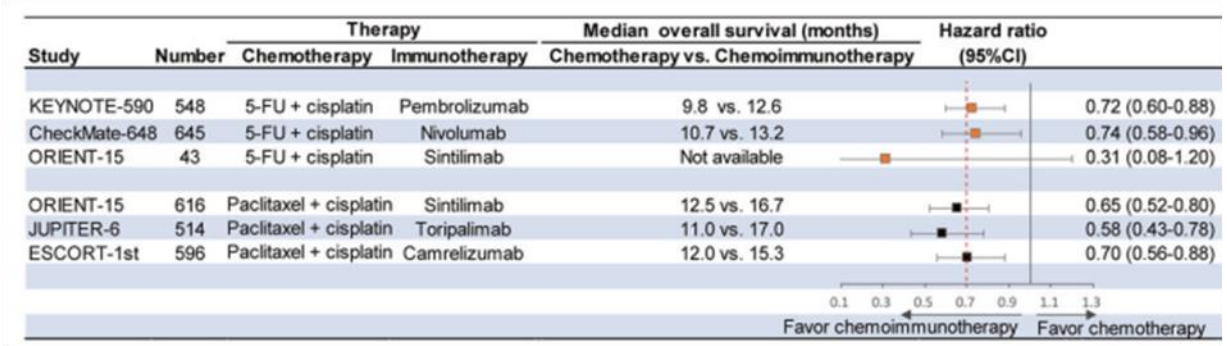
KN-062: Negative trial
Pembro+5-FU+**Cisplatin**



The Lancet 398(10294): 27-40. JAMA Oncology 6(10): 1571-1580.

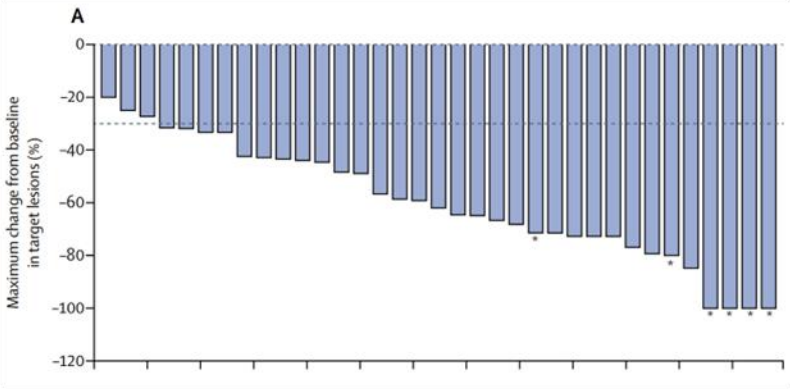
Appropriate chemotherapy regimen

- Optimizing chemo-immunotherapy regimens based on synergistic mechanism



	ICI+FP	ICI+PC
OS	13mo	15-16mo
HR	0.72-0.74	0.58-0.70

- More combination is more benefit ?
  - Trastuzumab+Pembrolizumab+chemotherapy
  - N=35
  - DCR=100%



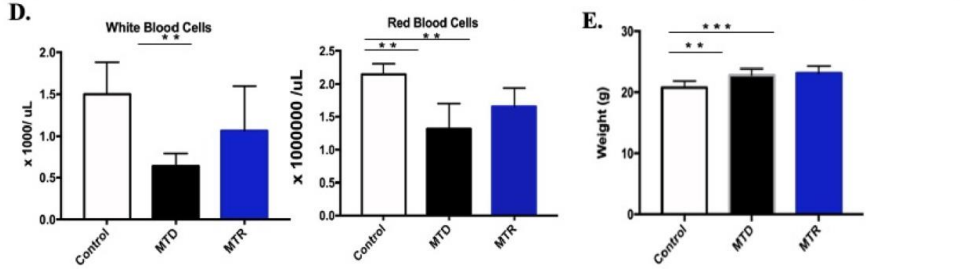
- ADCs

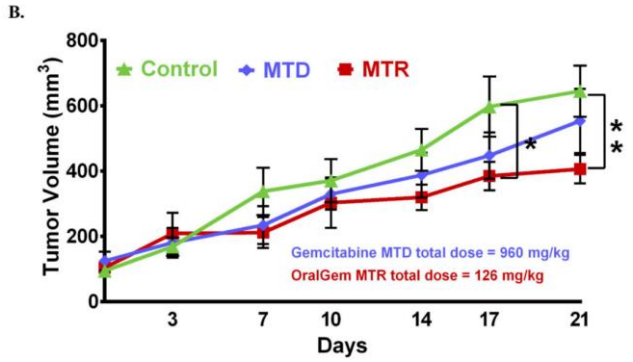
The Right Dose of Chemotherapy

- Maximum tolerated dose
  - Toxicities of combination therapy
  - Effect of killing tumor cell or tumor shrinkage
  - Dose-dependent myelosuppression
  - Depletion of effector immune cells
- Metronomic or lower dose as partners of ICI ?

C.

Compounds	Cmax (μM)	Cmax (μg/mL)	AUCs (h x μg/mL)	Tmax (h)
Gemcitabine (120 mg/kg) i.p.	285±150	75.1±33.3	66	0.25
Gemcitabine by OralGem (6 mg/kg) per os	0.37±0.12	0.097±0.018	0.31	0.5





- In clinical settings, the effect of metronomic chemotherapy has not yet been well-established.
  - The concept of metronomic or lower dose chemotherapy is only skewed to the perspective of anti-tumor immunity.

The Timing of Chemo-Immunotherapy

- TME is a key determinant of ICI responsiveness, and dynamically changes alongside tumor progression.
- Earlier metastatic stage
  - Theoretically, immunotherapy administered to patients in **earlier stages** of the disease, with less deteriorated immunity and before a myeloablative chemotherapy treatment.
  - ICI+chemo showed a promising efficacy in the first line setting.

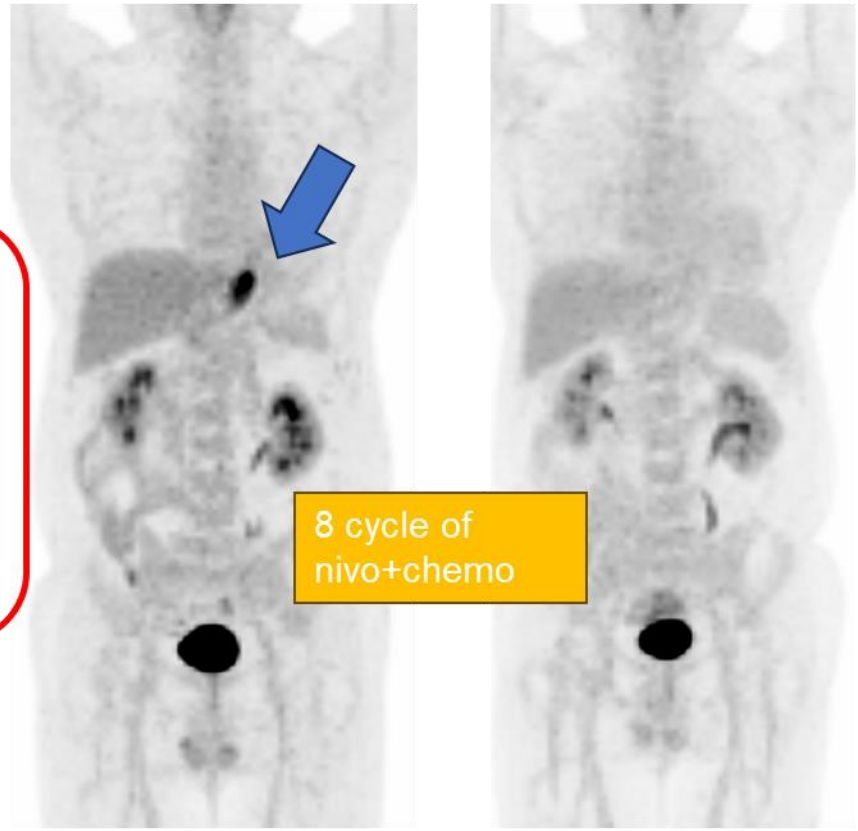
- Perioperative setting
  - Neoadjuvant
  - Adjuvant
    - No radiographic tumor
    - Micro-metastatic tumor burden: Appropriate induction of ICD from chemotherapy ?

What is appropriate biomarker of ICI and chemotherapy ?

- No answer
- Numerous pre-clinical and clinical biomarker studies.

Case: 53/M

- Metastatic gastric cancer with peritoneal seeding nodules
  - Poorly cohesive carcinoma., HER2 0/3
  - EBV neg
  - MMRp, MSS
  - PD-L1 28-8 CPS 0, PD-L1 22C3 CPS 0,
  - TMB 0.95mut/mb, no actionable alteration



[FROZEN SECTION DIAGNOSIS]

검체명	검체번호	진단명
peritoneum	001	Negative f 본 진단은 참고로 하
,peritoneum 2	002	Negative 본 진단은 참고로 하

[FROZEN SECTION PERMANENT DIAGNOSIS]
Peritoneum, excision(#1 & #2);
Chronic inflammation with fibrosis.

[MICROSCOPIC DESCRIPTION]
-Depth of invasion; unapplicable (pTx)
-Lymphatic invasion; absent
-Vascular invasion; absent
-Perineural invasion; absent
-Lymph node metastasis; absent (0/24) (pN0)
#1(0/3) #3(0/12) #4sb(0/2) #4d(0/0) #5(0/0) #6(0/1)
#7(0/3) #8a(0/0) #9(0/2) #11p(0/0) #12a(0/0) LN around hernia sac (#13)(0/1)
-Associated gastritis; lymphoid follicles

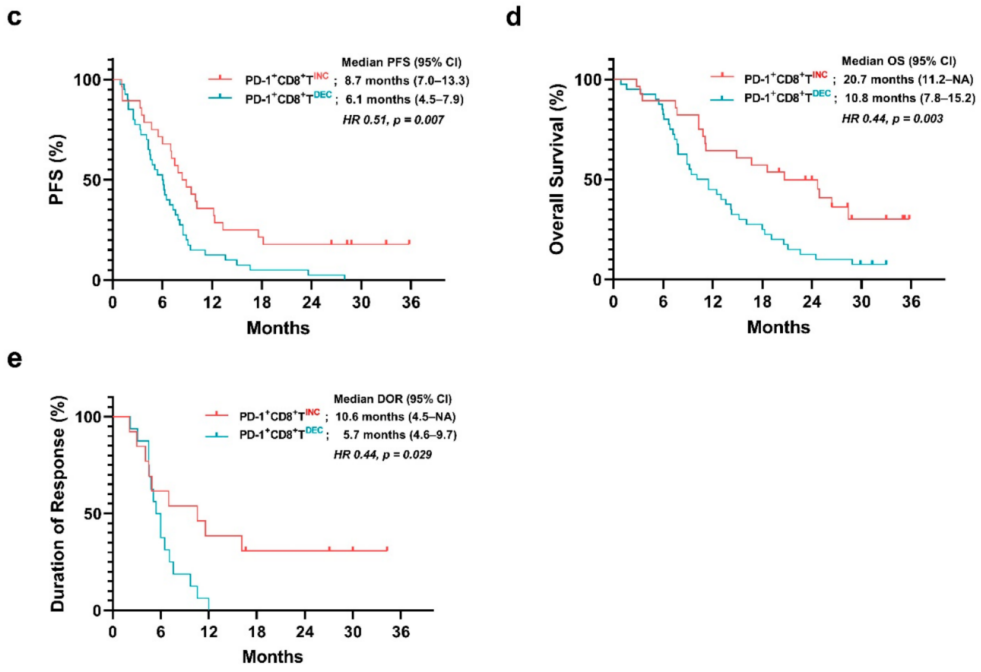
[DIAGNOSIS]
1. Stomach, subtotal gastrectomy with lymph node dissection;
1) No remaining malignancy.
2) Fibrosis with lymphoid aggregates.
2. "Hernia sac", excision(#13);
Vascular congestion.
3. Vagus nerve, excision(#14);
Unremarkable.

Effect on immune cells - Activation of Immune Effector Cells

- Several hypotheses and backgrounds.
- For examples
  - Gemcitabine restores the proliferative capacity of T effector cells
  - Paclitaxel enhances the maturation of DC precursors by the activation of TLR-4 and ultimately favors the efficient priming of CD8+ T cell.
  - Lymphotoxic chemotherapy might result in a paradoxical reshaping of the T-cell repertoire and the differentiation into tumor-attacking cytotoxic T cells.

Immune Cells	Drugs	Effect	Issues	Model
DC	PCTXL	Maturation	Experimental data	In vivo and in vitro
CD 8+ T cells	Gem	Proliferation	-	Human

Early Increase in Circulating PD-1+CD8+ T Cells Predicts Favorable Survival in Patients with Advanced Gastric Cancer Receiving Chemotherapy



Biomedicines 2022, 10, 1822.
Cancers 15(15): 3955.

Summary

- Current issue
  - pCR, down-staging, R0 resection
  - Systemic control
  - Safety
  - Neoadjuvant vs. adjuvant vs. perioperative

- Emerging issue in the immunotherapy era
  - Biomarker
  - Appropriate partner
    - Immunomodulatory properties of chemotherapeutic drugs and radiation
    - The optimal dose, timing, sequence or combination
    - Novel agents (Newer immunotherapy, ADC, bispecific antibody, etc)
  - Monitoring

Summary

Image from https://www.epmmagazine.com/pharmaceutical-industry-insights/overcoming-cultural-challenges-in-the-workplace/

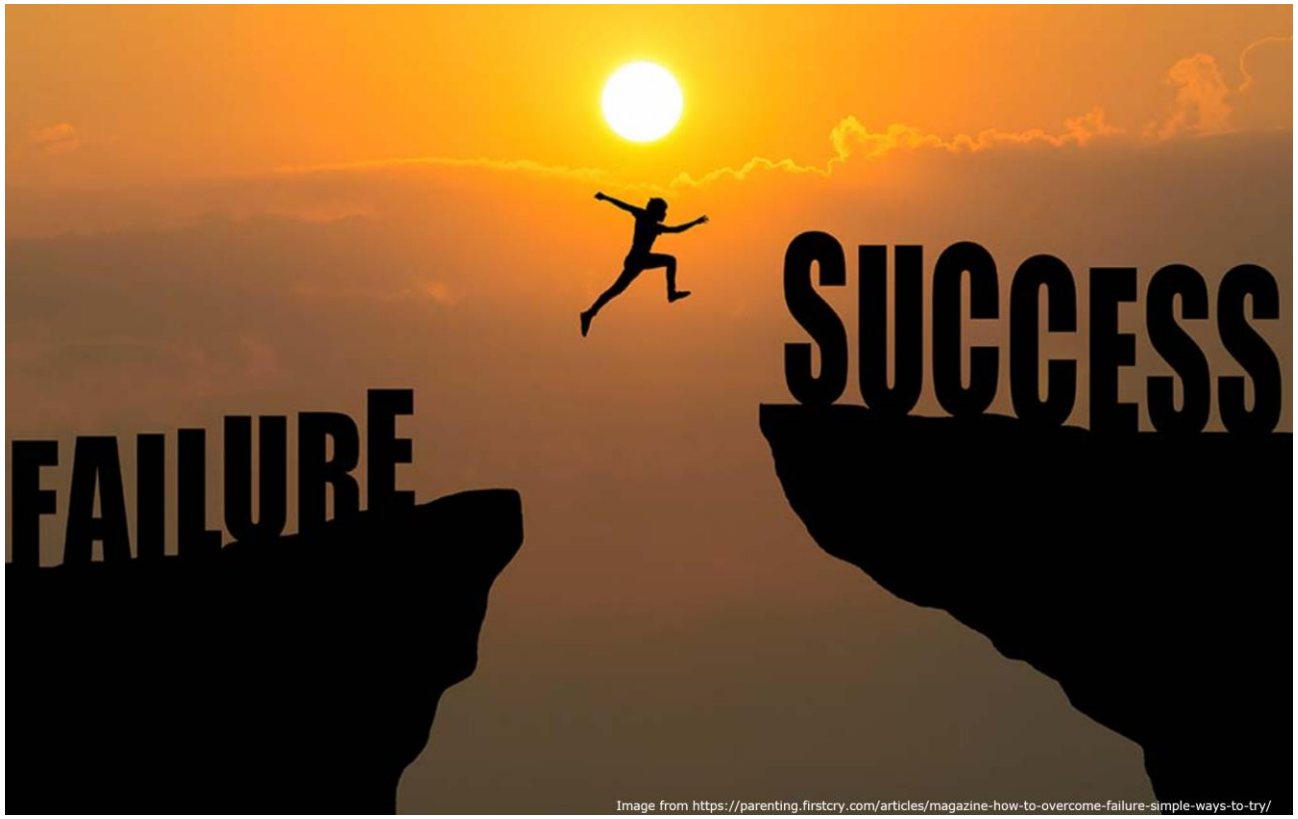


Image from https://parenting.firstcry.com/articles/magazine-how-to-overcome-failure-simple-ways-to-try/