



Efficacy Endpoints in Adjuvant and Neoadjuvant Oncology Trials

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AGENDA



Clinical trial classification in terms of surgery involvement



Efficacy endpoints

Surrogate endpoints for adjuvant and neoadjuvant studies



Challenges in surrogate endpoints selection and validation



Pathological response: what does it mean for different cancer types?



Analysis methods in adjuvant and neoadjuvant oncology

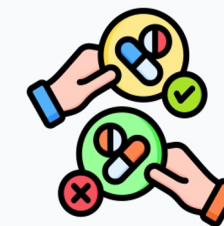
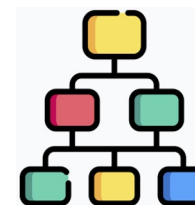


Correlation between the pathological response and overall survival

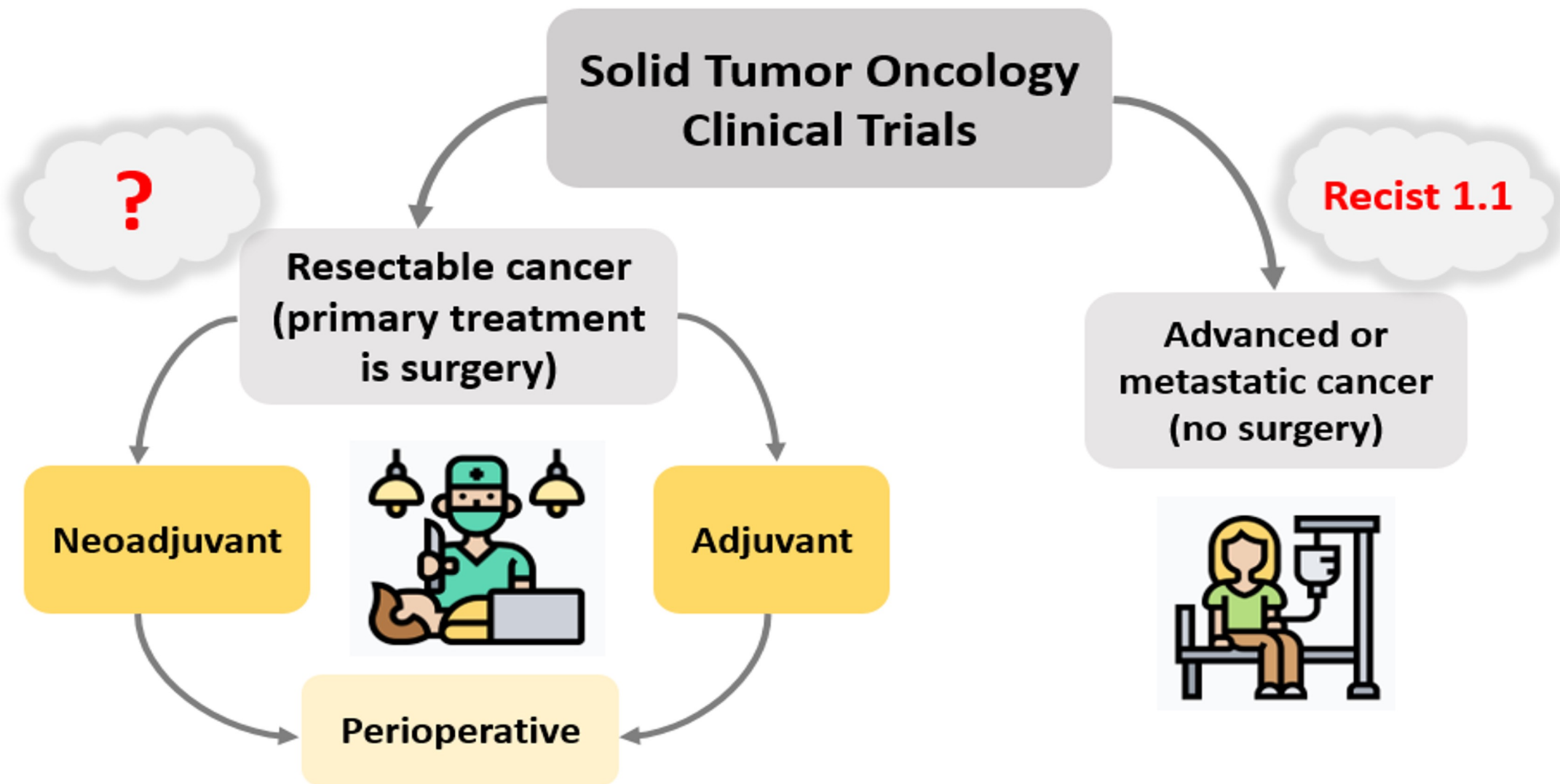


Conclusions

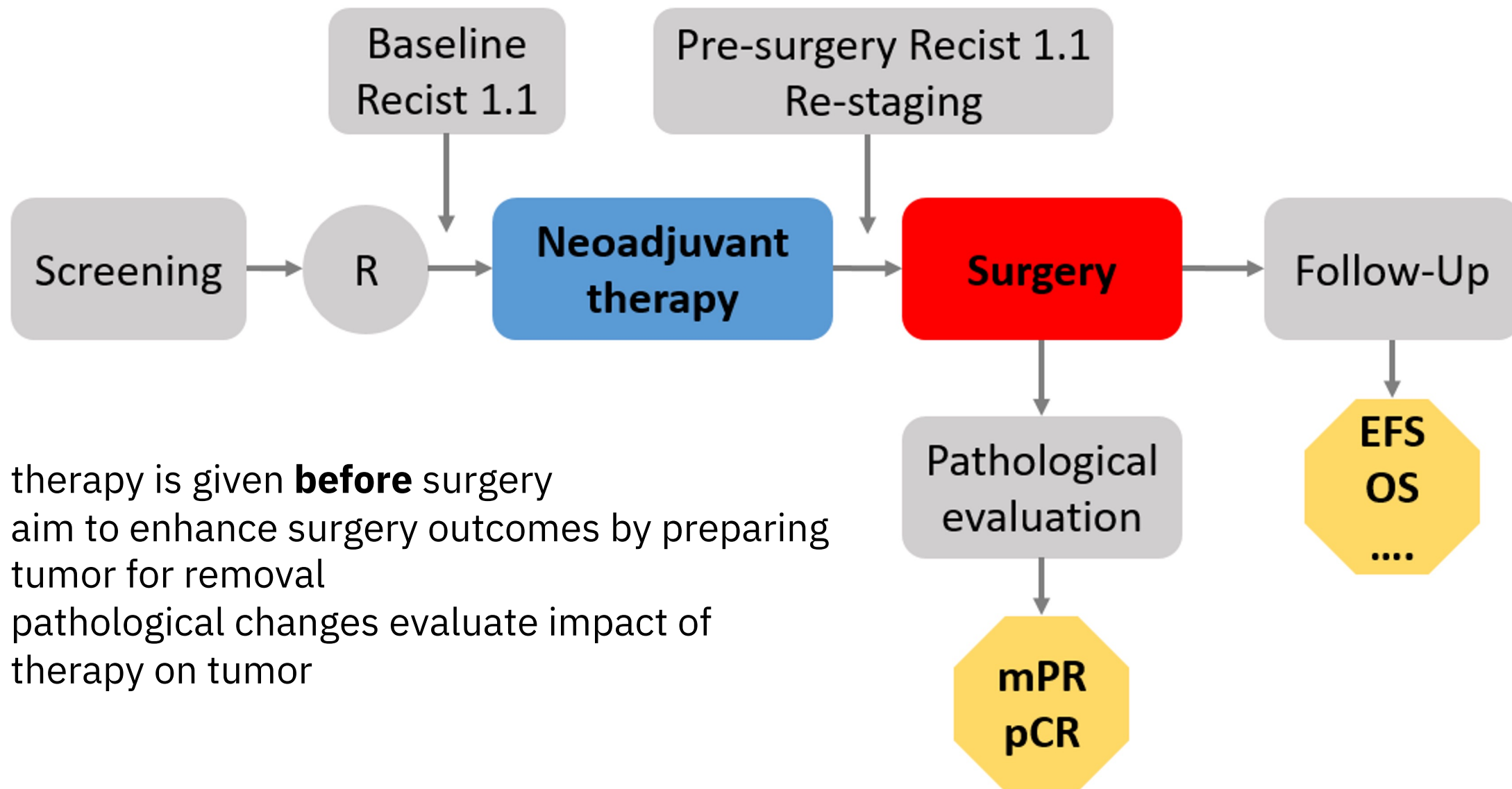
CLINICAL TRIALS CLASSIFICATION: is the surgery part of the therapy?



TYPES OF CLINICAL TRIALS: WHAT IS THE MAIN TREATMENT?

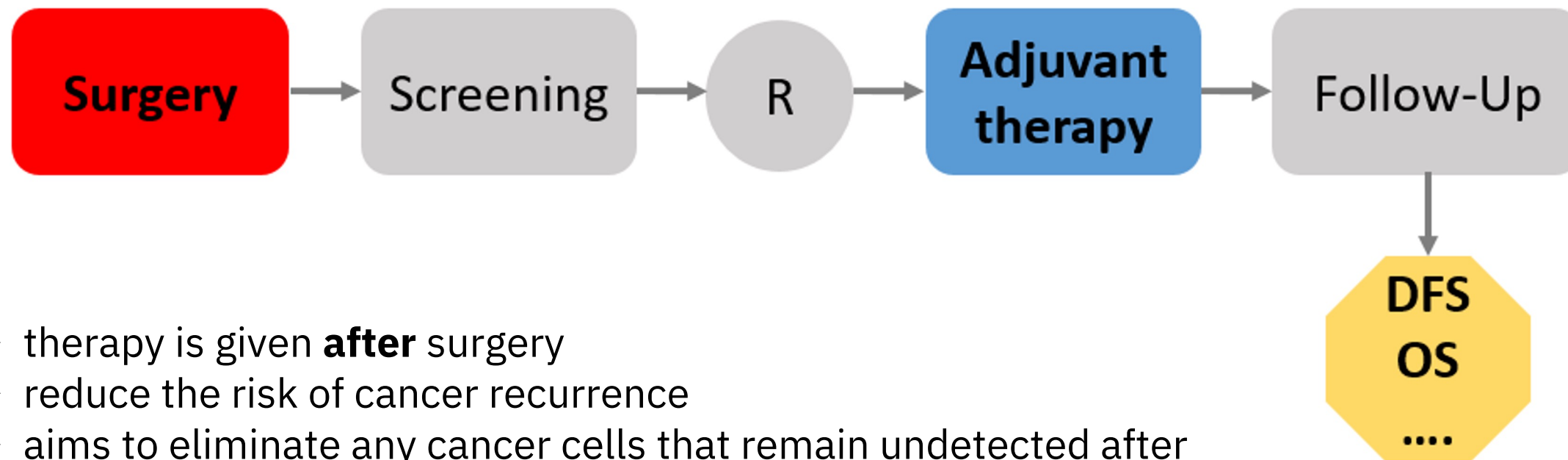


BASIC STUDY DESIGN FOR NEOADJUVANT SETTINGS



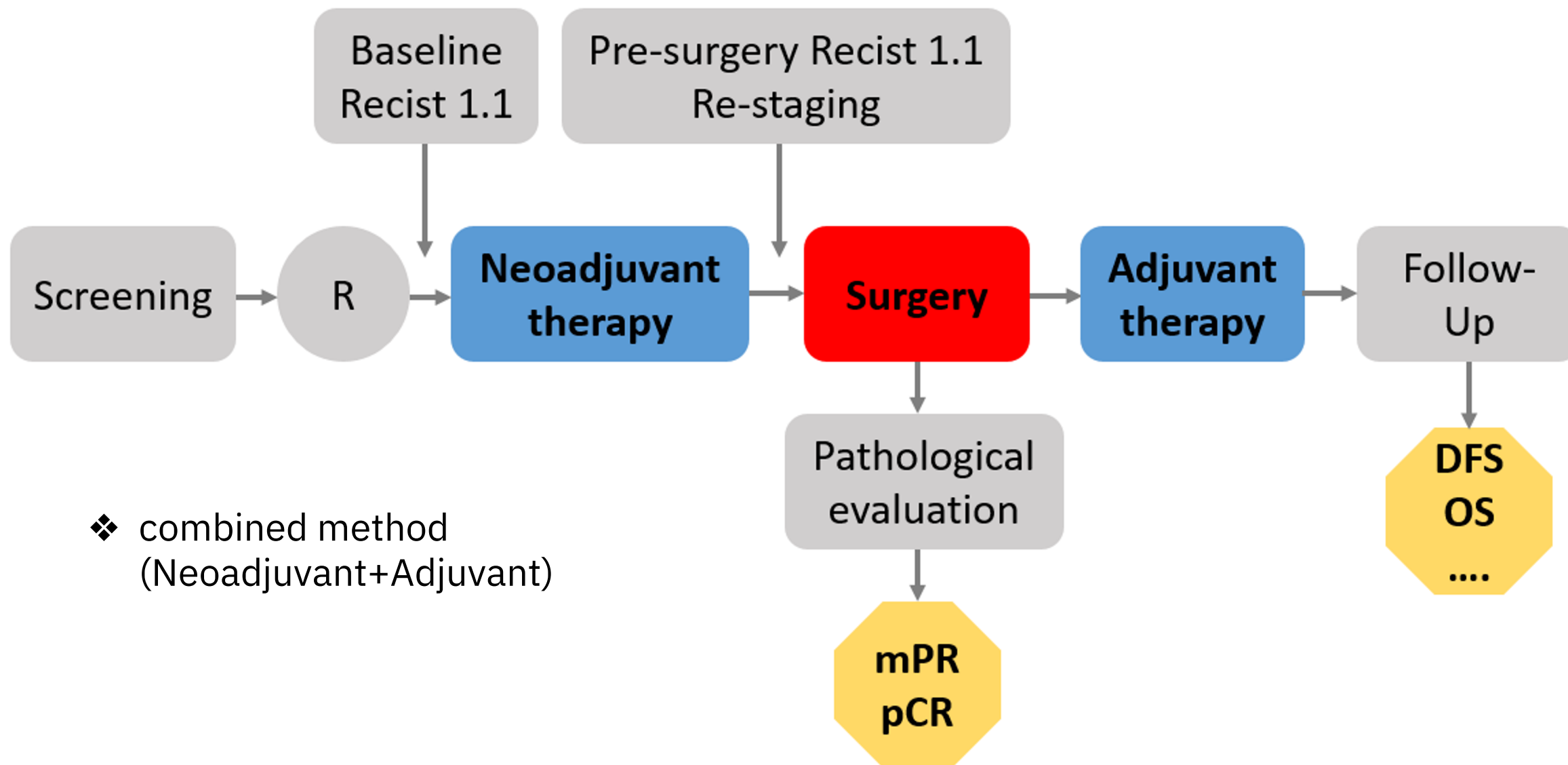
- ❖ therapy is given **before** surgery
- ❖ aim to enhance surgery outcomes by preparing tumor for removal
- ❖ pathological changes evaluate impact of therapy on tumor

BASIC STUDY DESIGN FOR ADJUVANT SETTINGS

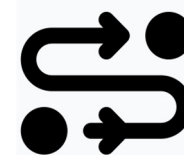


- ❖ therapy is given **after** surgery
- ❖ reduce the risk of cancer recurrence
- ❖ aims to eliminate any cancer cells that remain undetected after resection

BASIC STUDY DESIGN FOR PERIOPERATIVE SETTINGS



CLINICAL ENDPOINTS CLASSIFICATION



CLINICAL ENDPOINTS CLASSIFICATION

PATIENT-CENTERED CLINICAL ENDPOINTS:

- assess a direct patient clinical benefit
- more prolonged observation period
- increase the cost of clinical trials

overall survival (OS)

health-related quality of life (QoL)

TUMOR-CENTERED CLINICAL ENDPOINTS:

- can be assessed earlier
- do not reflect a direct patient clinical benefit
- lack of consistency in the definitions
- should be validated as surrogate endpoints for OS

disease-free
survival (DFS)

cancer-specific
survival (CSS)

progression-free
survival (PFS)

time to treatment
failure (TTF)

pathological complete response (pCR)

SURROGATE ENDPOINTS FOR ADJUVANT AND NEOADJUVANT THERAPIES

	DFS	RFS	TTR	TTF	CSS	OS
Locoregional recurrence	●	●	●	●	●	●
Distant metastases	●	●	●	●	●	●
Second primary, same cancer	●	●	●	●	●	●
Second primary, other cancer	●	●	●	●	●	●
Death from the same cancer	●	●	●	●	●	●
Death from other cancer	●	●	●	●	●	●
Non-cancer-related death	●	●	●	●	●	●
Treatment-related death	●	●	●	●	●	●
Loss to follow-up	●	●	●	●	●	●

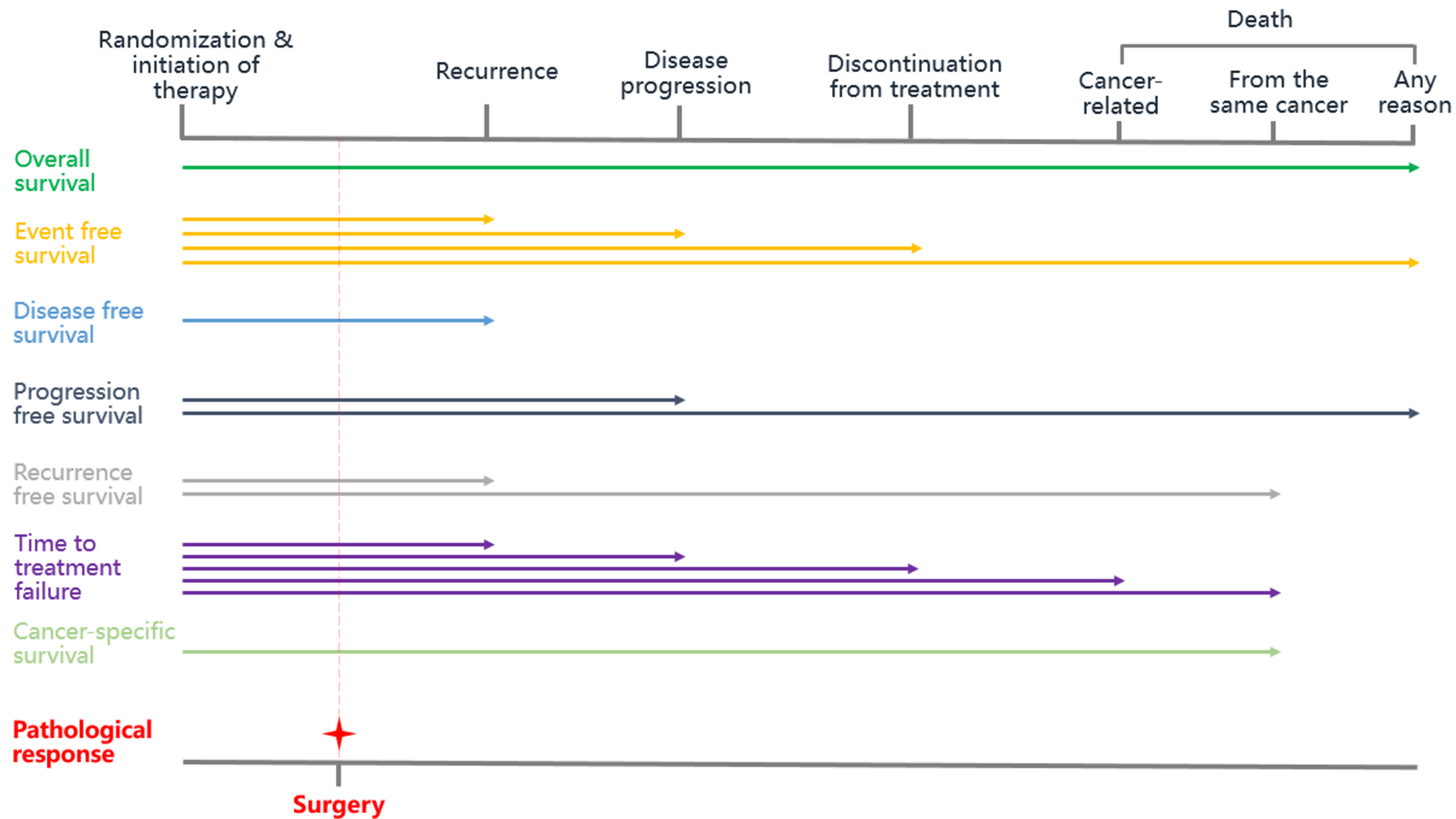
● Event
● Censor
● Ignore

DFS = Disease-free survival
RFS = Relapse-free survival

TTR = Time to recurrence
TTF = Time to treatment failure

CSS = Cancer-specific survival
OS = Overall Survival

VARIOUS ENDPOINTS ON A TIME SCALE

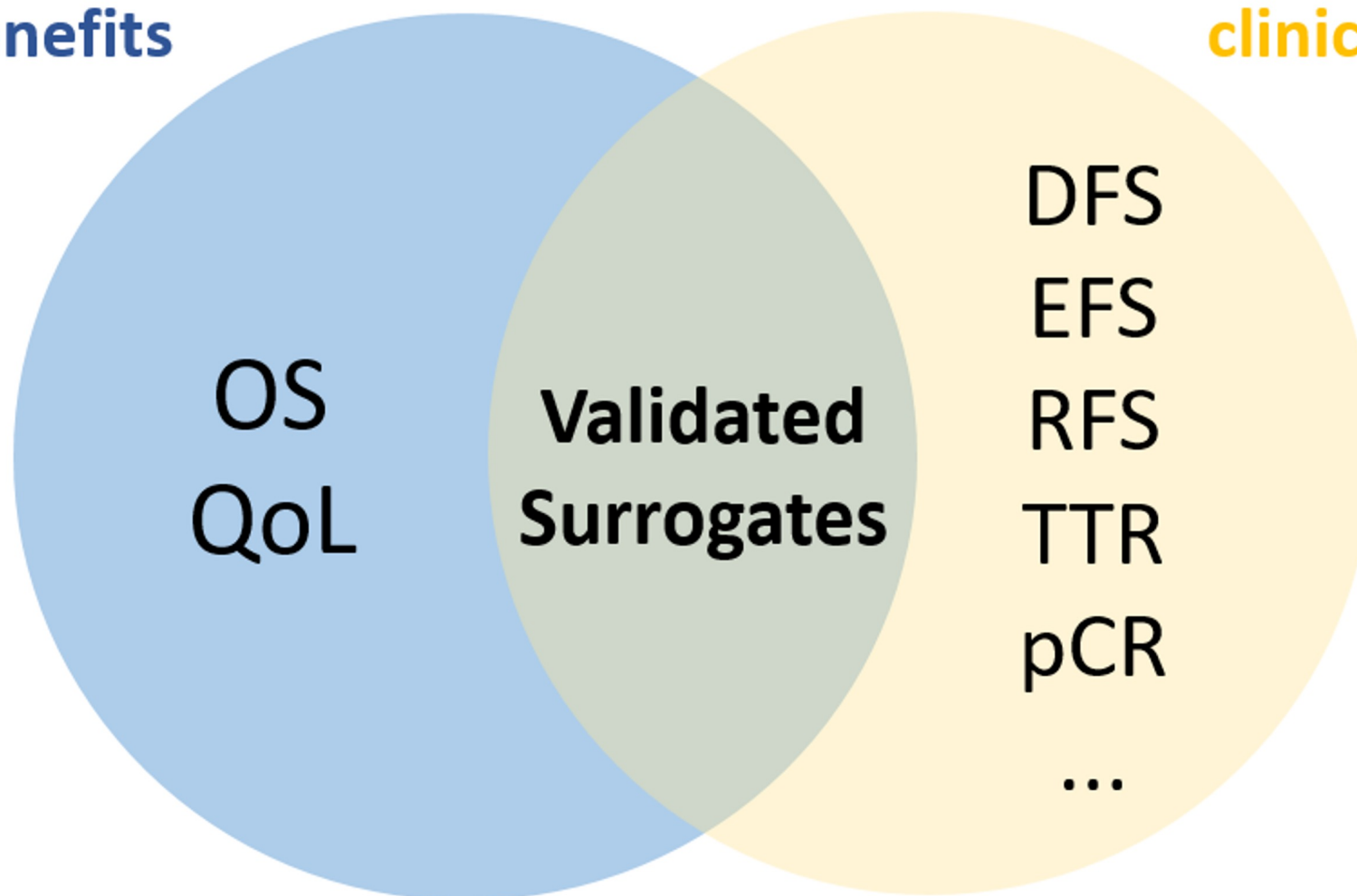


CHALLENGES IN SURROGATE ENDPOINTS SELECTION & VALIDATION



**Evaluate direct
clinical benefits**

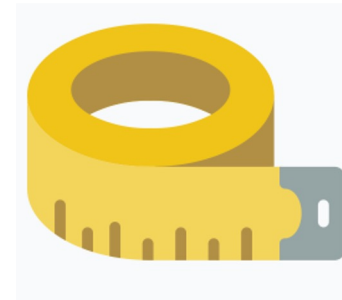
**Evaluate indirect
clinical benefits**



CHALLENGES IN SURROGATE ENDPOINTS SELECTION & VALIDATION



A specific therapeutic class/disease/stage should be considered



How will the endpoints be measured and analyzed?



Is the endpoint relevant to the disease being studied?
Is it meaningful?



Lack of clarity leads to inconsistent interpretation

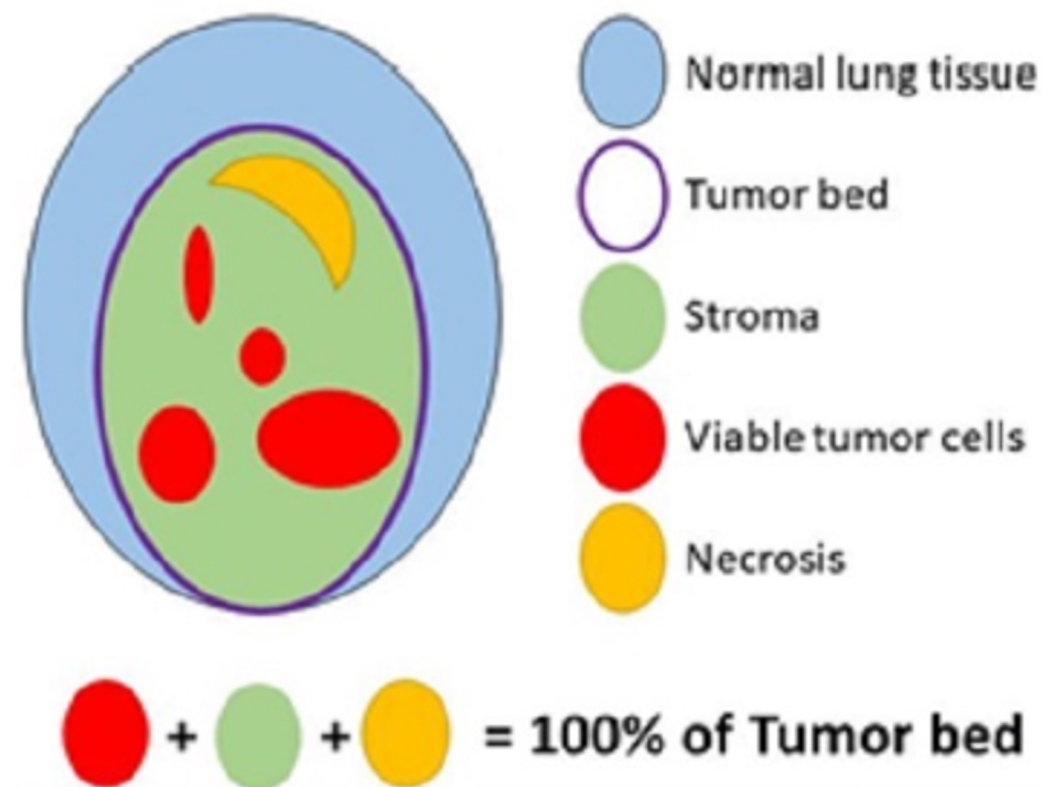
EFFICACY ENDPOINTS SPECIFIC TO NEOADJUVANT TRIALS

PATHOLOGICAL RESPONSE



PATHOLOGICAL RESPONSE IN NEOADJUVANT CLINICAL TRIALS

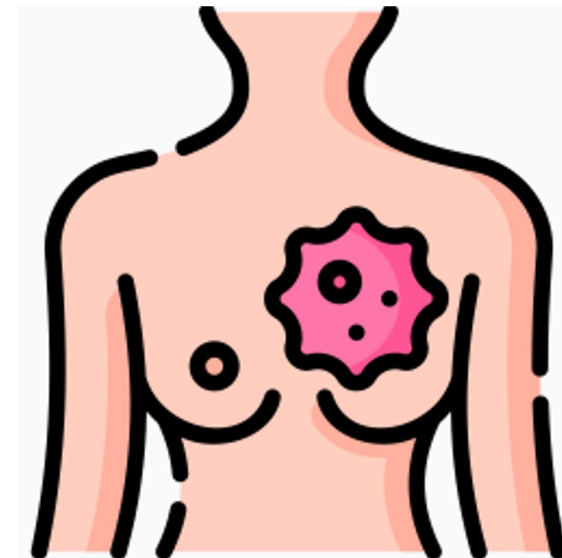
-  important prognostic factor
-  assessment of changes in tumor tissue after the pre-surgery therapies
-  determination of the extent to which the treatments have modified the tumor characteristics
-  valuable insights into the treatments' potential efficacy in achieving long-term results
-  guiding future treatment decisions



BREAST CANCER

 **pCR:** no invasive and non-invasive residual cancer in the breast and lymph nodes (**ypT0 ypN0 ***)

 **pCR:** no invasive residual cancer in the breast and lymph nodes irrespective of residual non-invasive disease (**ypT0/is ypN0***).



(*) TNM classification:

yp - staging information is determined after a patient has undergone treatment for cancer

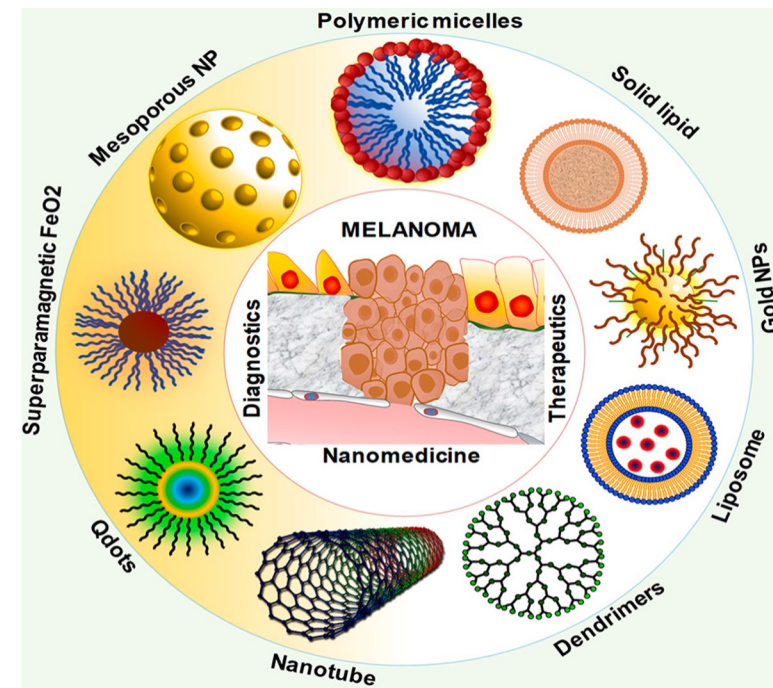
T0 - no evidence of primary tumor

N0 - no regional lymph node metastasis

is - carcinoma in situ

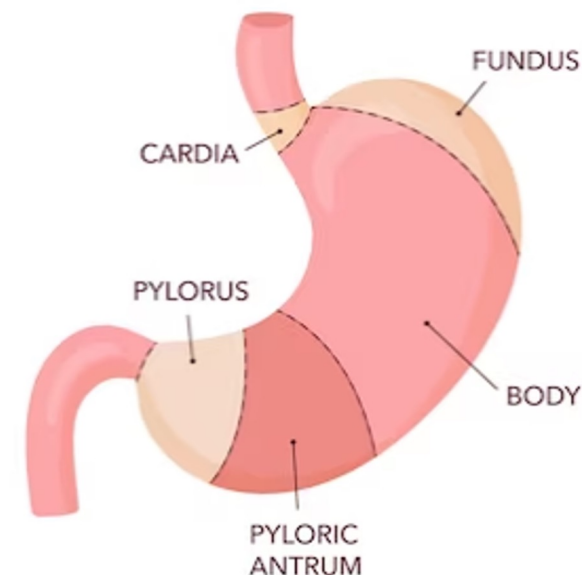
MELANOMA

-  **pCR:** defined as the complete absence of residual viable tumor
-  **MPR / near pCR:** defined as $<10\%$ of viable tumor in the treated tumor bed
-  **pPR:** empirically defined as $\leq 50\%$ of the tumor bed occupied by viable tumor cells
-  **pathologic non-response (pNR):** defined as $>50\%$ of the tumor bed occupied by viable tumor cells



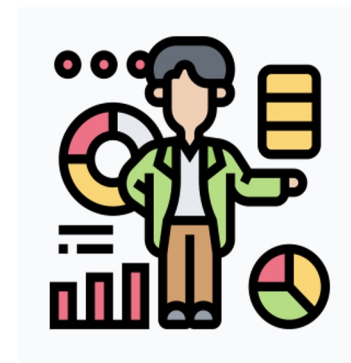
GASTRIC (*)

-  **Grade 1a (GR1a)** - Complete Response - complete disappearance of tumor cells
-  **Grade 1b (GR1b)** - Near-Complete Response - a small number of tumor cells might be present
-  **Grade 2 (GR2)** - Partial Response - both tumor cells and fibrosis or inflammation are present in the treated tumor bed
-  **Grade 3 (GR3)** - Poor Response - a significant number of viable tumor cells are present, the degree of fibrosis or inflammation is minimal



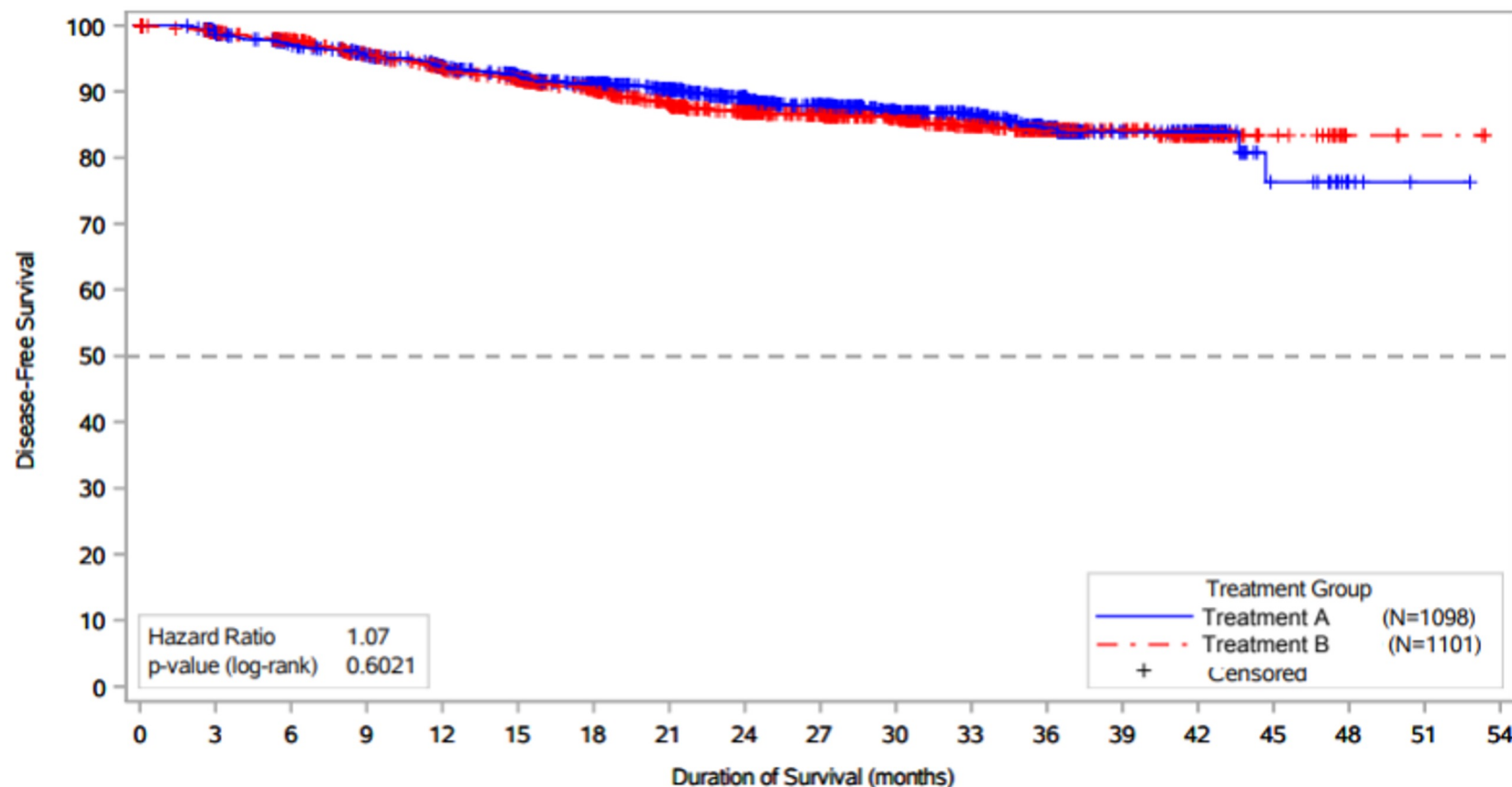
(*) Japanese Gastric Cancer Association (JGCA) Criteria

ANALYSIS METHODS FOR NEOADJUVANT AND ADJUVANT STUDIES



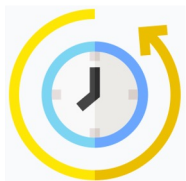
TIME-TO-EVENT ANALYSIS: STATISTICAL METHODS (example)

Kaplan-Meier Plot of Disease-Free Survival, Intent-to-Treat Patients
Protocol: AB123456.

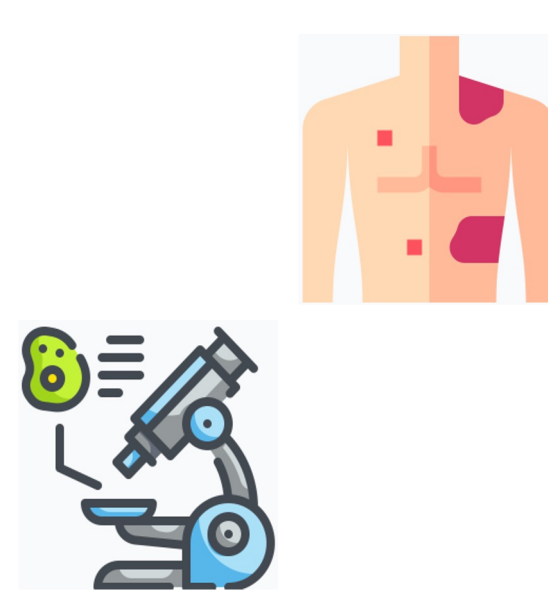


Patients remaining at risk																	
Treatment A	1098	1022	969	921	862	810	729	661	563	470	370	288	202	108	74	16	NE
Treatment B	1101	1042	995	931	867	818	733	645	561	479	389	292	200	118	64	20	NE

- Median and percentiles are Kaplan-Meier Estimates
- Hazard ratios are estimated by Cox regression
- Stratified/Unstratified Analysis



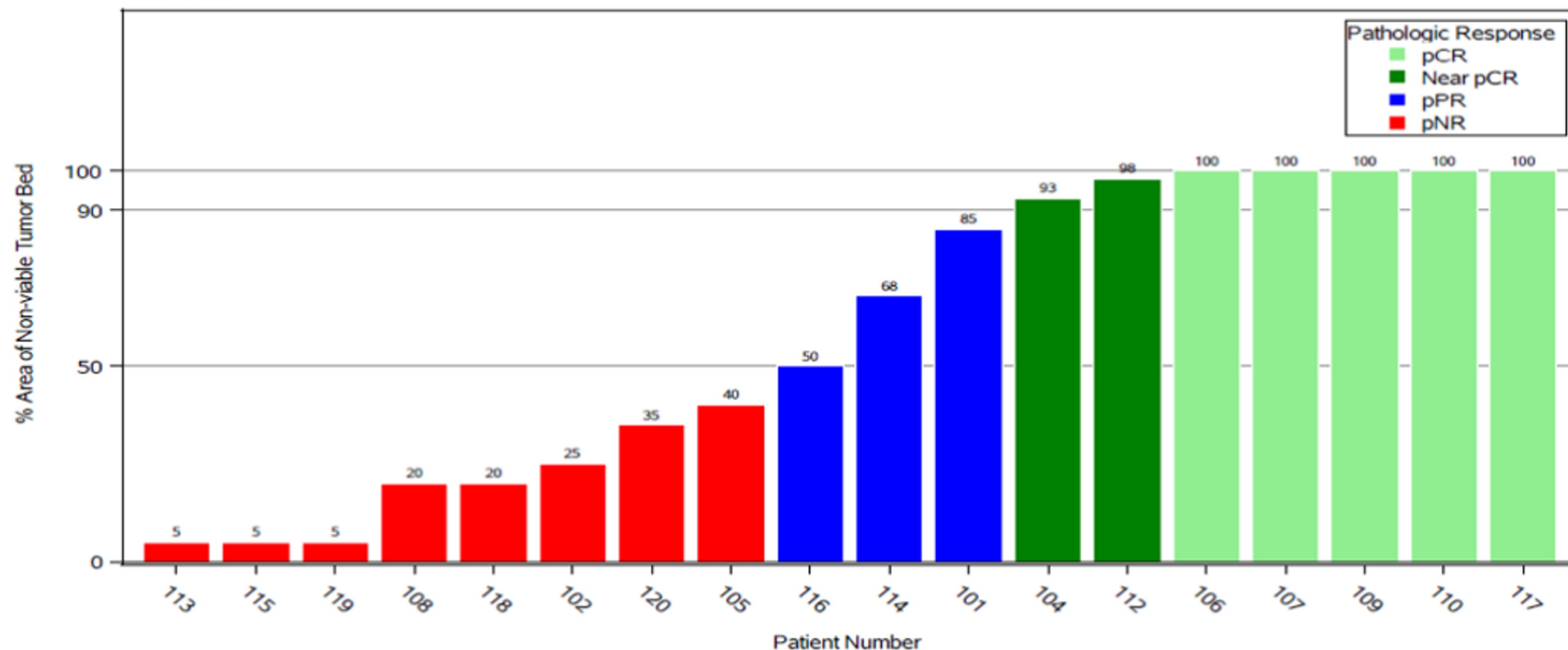
ANALYSING OF THE PATHOLOGICAL RESPONSE DATA



WATERFALL PLOT BY % AREA OF NON-VIABLE TUMOR BED BY PATHOLOGICAL RESPONSE (example)

Area of Non-viable Tumor Bed by Pathologic Response

Treatment Group: Arm A

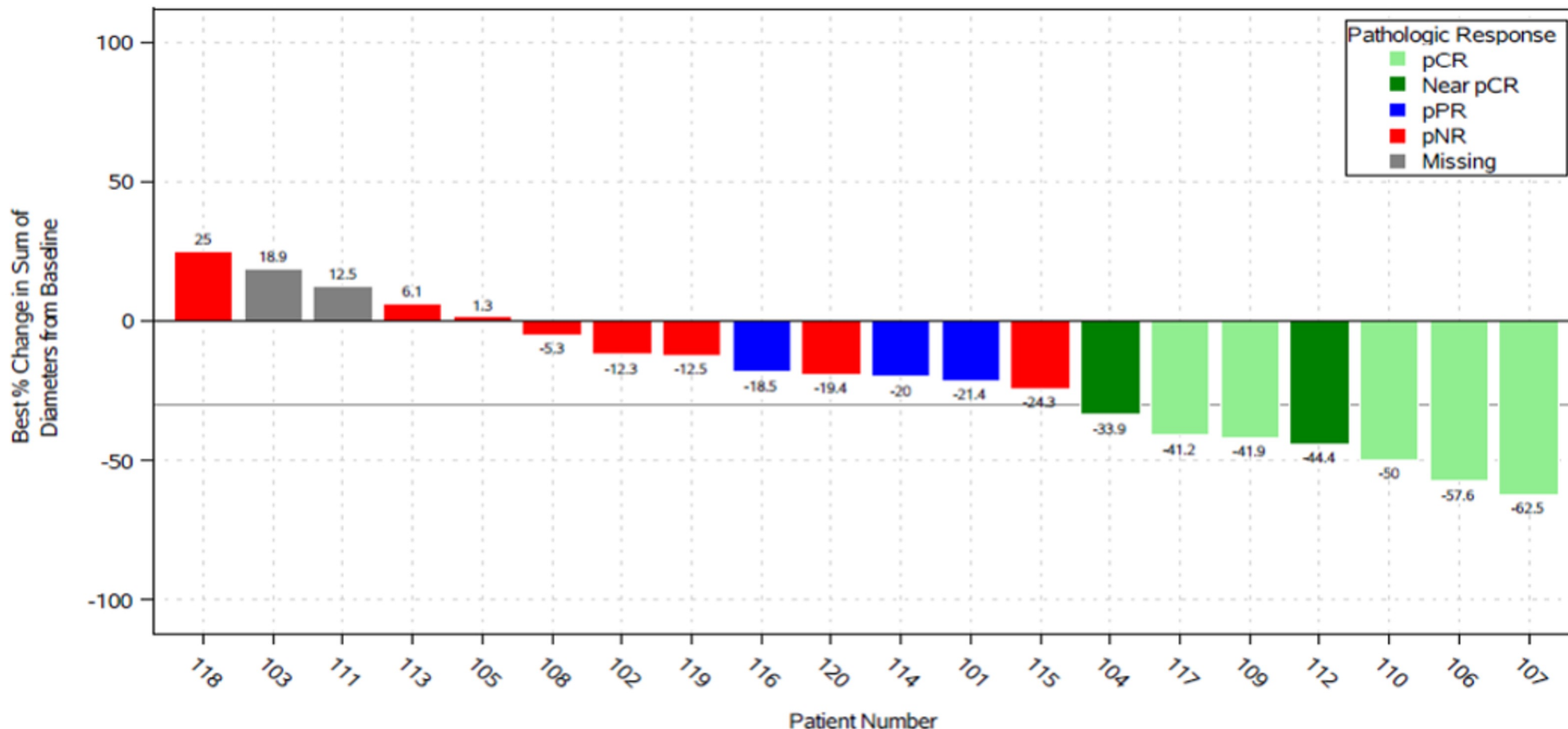


* pCR = Pathologic Complete Response (0% Viable Tumor), Near pCR = Pathologic Near Complete Response ($\leq 10\%$ Viable Tumor), pPR = Pathologic Partial Response (> 10 to $\leq 50\%$ Viable Tumor), pNR = Pathologic No Response ($> 50\%$ Viable Tumor Cells).

WATERFALL PLOT BY BEST CHANGE IN SUM OF DIAMETERS FROM BASELINE BY PATHOLOGIC RESPONSE (example)

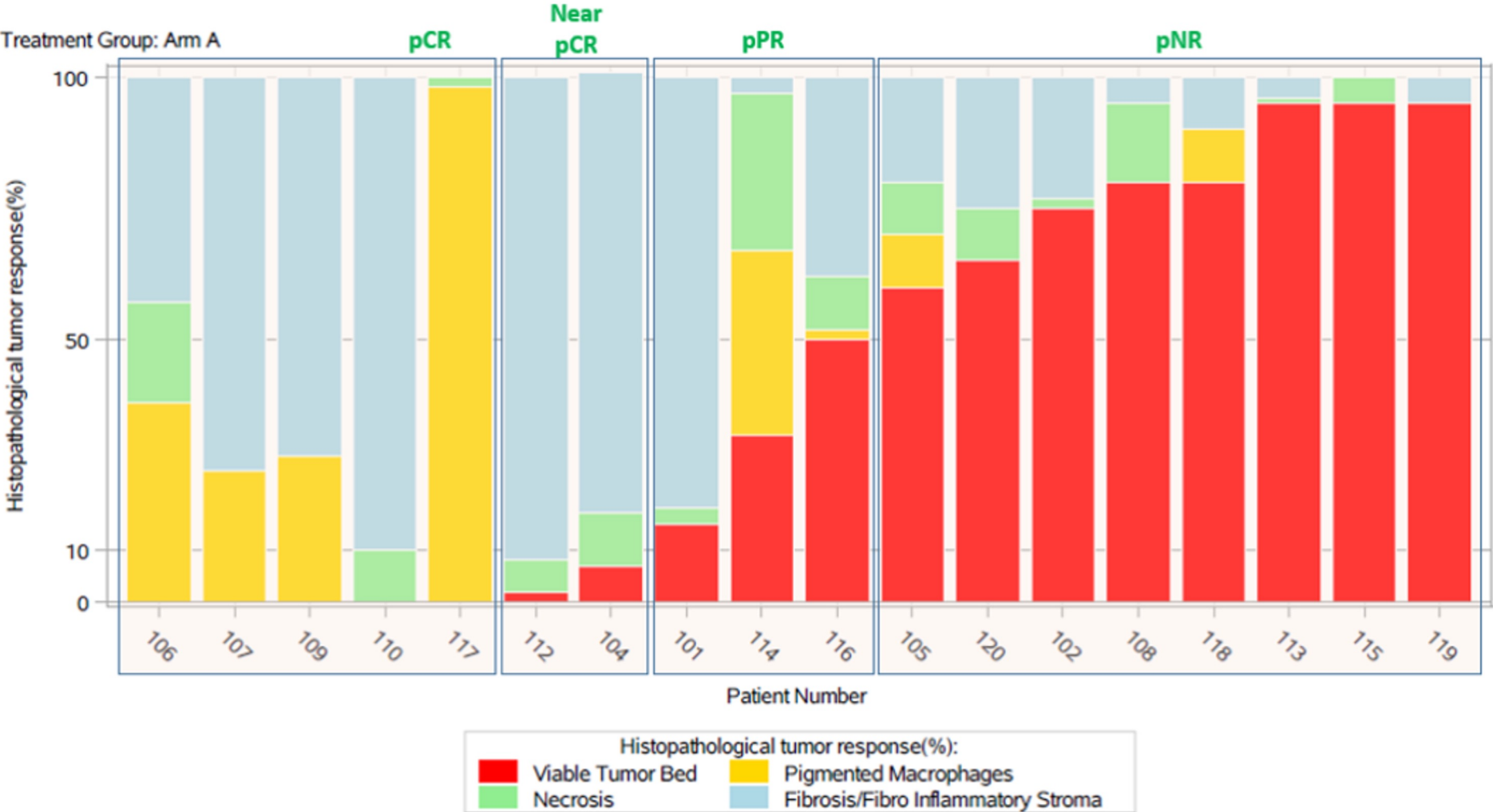
Best Change in Sum of Diameters from Baseline by Pathologic Response

Treatment Group: Arm A



* pCR = Pathologic Complete Response (0% Viable Tumor), Near pCR = Pathologic Near Complete Response ($\leq 10\%$ Viable Tumor), pPR = Pathologic Partial Response (> 10 to $\leq 50\%$ Viable Tumor), pNR = Pathologic No Response ($> 50\%$ Viable Tumor Cells).

Histopathological tumor response



* pCR = Pathologic Complete Response (0% Viable Tumor), Near pCR = Pathologic Near Complete Response (<=10% Viable Tumor), pPR = Pathologic Partial Response (> 10 to <=50% Viable Tumor), pNR = Pathologic No Response (> 50% Viable Tumor Cells).

Pathologic Response Rates, Intent-to-Treat Patients

	Arm A	Arm B
	(N=xxx)	(N=xxx)
Pathologic Responders	xx (xx.x%)	xx (xx.x%)
95% CI	(xx.xx, xx.xx)	(xx.xx, xx.xx)
Analysis		
Difference in Overall Response Rates (95% CI)	xx.xx (xx.xx, xx.xx)	
Odds Ratio for Overall Response (95% CI)	xx.xx (xx.xx, xx.xx)	
Pathologic Complete Response (pCR)	xx (xx.x%)	xx (xx.x%)
95% CI	(xx.xx, xx.xx)	(xx.xx, xx.xx)
Pathologic Near Complete Response (Near pCR)	xx (xx.x%)	xx (xx.x%)
95% CI	(xx.xx, xx.xx)	(xx.xx, xx.xx)
Pathologic Partial Response (pPR)	xx (xx.x%)	xx (xx.x%)
95% CI	(xx.xx, xx.xx)	(xx.xx, xx.xx)
Pathologic No Response (pNR)	xx (xx.x%)	xx (xx.x%)
95% CI	(xx.xx, xx.xx)	(xx.xx, xx.xx)

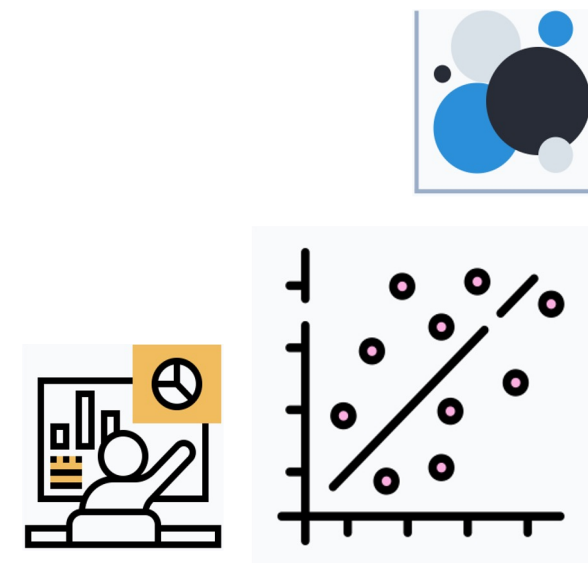
95% CI for rates were constructed using Clopper-Pearson method.

95% CI for difference in rates were constructed using the Wald method with continuity correction. 95% CI for odds ratio was constructed using the Wald method.

pCR: 0% Viable Tumor, Near pCR: <=10% Viable Tumor, pPR: >10 to <=50% Viable Tumor, pNR: > 50% Viable Tumor Cells.

- Number of subjects with the particular pathologic response
- Difference in Overall Response Rates
- Odds Ratio for Overall Response

CORRELATION BETWEEN THE PATHOLOGICAL RESPONSE AND OVERALL SURVIVAL



CORRELATION BETWEEN THE PATHOLOGICAL RESPONSE AND OVERALL SURVIVAL DEPENDS ON MANY FACTORS

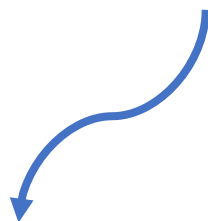
- definitions of pathological response
- assessment methods for pathological response at surgery
- subtype and prognosis of the particular type of cancer at diagnosis
- number of patients recruited
- adjuvant treatments applied
- the mechanism of action of the investigational drug
- the length of follow-up at the time of reporting
- the definitions used in longer-term outcomes analysis



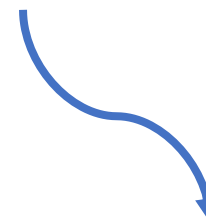
CORRELATION BETWEEN THE PATHOLOGICAL RESPONSE AND OS: NO COMMON CONCLUSION



Could pCR serve as a valid surrogate endpoint for such trials?



The clinical response to neoadjuvant chemotherapy does not always accurately reflect the pathological response



There are a number of meta- and literature-based analysis **for and against** using pCR is a valid predictor for OS

CONCLUSIONS



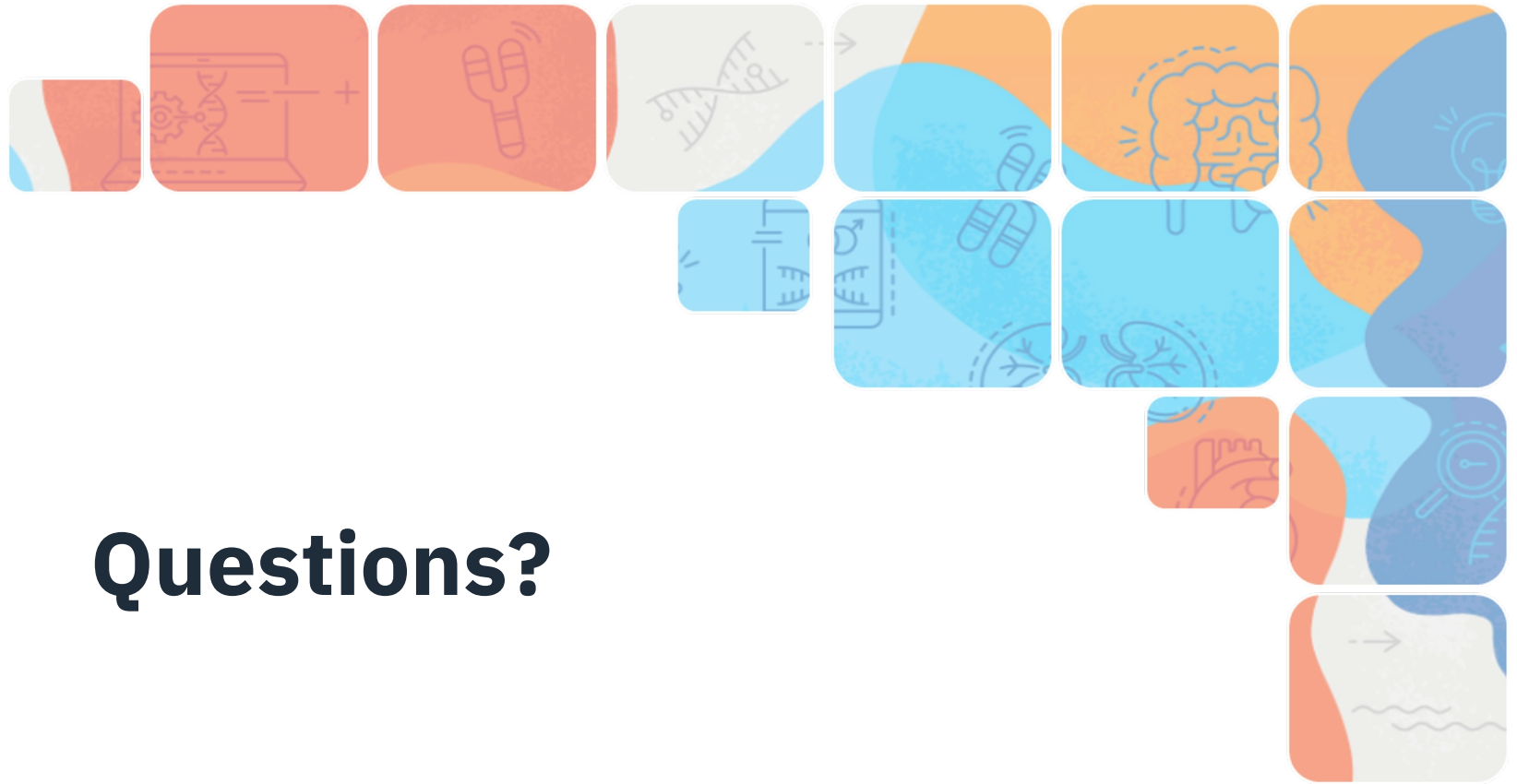
Efficacy endpoints in adjuvant and neoadjuvant oncology have their advantages and drawbacks



pCR might become a key endpoint for neoadjuvant therapies if the correlation with long-term survival is established



It is crucial to standardize pathologic assessment and reporting of tumor response after the therapy



Questions?

