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MEETING SUMMARY

ESMO 2016 – COPENHAGEN, DENMARK
OCTOBER 7TH TO 11TH 2016

BY DR. DOMINIK – LUDWIG MAXIMILIANS UNIVERSITY OF MUNICH, MUNICH, GERMANY

CANCERS OF THE UPPER GI TRACT

IS CENTRALIZATION NEEDED FOR ESOPHAGEAL AND GASTRIC CANCER PATIENTS WITH LOW OPERATIVE RISK?

A NATIONWIDE STUDY

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FREGAT

STUDY AIM

Aim

- To evaluate the impact of center volume on POM after EC and GC surgery according to patient's condition

Hypothesis

- Low operative risk patients have similar POM rate independently of center's volume

STUDY OBJECTIVES

Primary objective

- 30-day POM according to center volume
  - Stratified according to Charlson score (0, 1-2, ⩾3)

Secondary objectives

- POM subgroup analysis: Esophagus vs. Stomach
- Variations between 30-day & 90-day POM
- Predictors of POM

Volume	Low	Intermediate	High	Very high
N per year	< 20	20 – 39	40 – 59	⩾ 60

RESULTS - OBJECTIVES

Variables	Overall population	Low volume	Intermediate volume	High volume	Very high volume	*P* value
	n (%)	n (%)	n (%)	n (%)	n (%)	
All patients	11196 (100)	7184 (64.2)	1901 (17.0)	1587 (14.2)	524 (4.7)	
30-day POM	548 (4.9)	406 (5.7)	81 (4.3)	52 (3.3)	9 (1.7)	<0.001
90-day POM	1006 (9.0)	731 (10.2)	150 (7.9)	106 (6.7)	19 (3.6)	<0.001
Charlson 0	7306 (65.3)	4640 (64.6)	1267 (66.6)	1019 (64.2)	380 (72.5)	
30-day POM	248 (3.4)	186 (4.0)	32 (2.5)	26 (2.6)	4 (1.1)	<0.001
90-day POM	460 (6.3)	344 (7.4)	64 (5.1)	43 (4.2)	9 (2.4)	<0.001
Charlson 1-2	3202 (28.6)	2129 (29.6)	517 (27.2)	439 (27.7)	117 (22.3)	
30-day POM	214 (6.7)	159 (7.5)	30 (5.8)	21 (4.8)	4 (3.4)	<0.001
90-day POM	397 (12.4)	289 (13.6)	57 (11.0)	44 (10.0)	7 (5.9)	<0.001
Charlson ⩾ 3	688 (6.1)	415 (5.8)	117 (6.2)	129 (8.1)	27 (5.2)	
30-day POM	86 (12.5)	61 (14.7)	19 (16.3)	5 (3.9)	1 (3.7)	0.003
90-day POM	149 (21.6)	98 (30.9)	29 (24.8)	19 (12.4)	3 (11.1)	0.071

A 70% [55-75] relative risk reduction for 30-day POM was systematically observed independently of Charlon's score

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RESULTS - EC SUBGROUP

Variables	Overall population	Low volume	Intermediate volume	High volume	Very high volume	*P value*
	n (%)	n (%)	n (%)	n (%)	n (%)	
All patients	3286 (29.3)	1398 (19.5)	849 (44.7)	691 (43.5)	348 (66.4)	
30-day POM	183 (5.6)	106 (7.6)	41 (4.8)	32 (4.6)	4 (1.1)	<0.001
90-day POM	321 (9.7)	167 (11.9)	83 (9.8)	60 (8.7)	11 (3.2)	<0.001
Charlson 0	2065 (62.8)	875 (62.5)	544 (64.0)	394 (57.0)	252 (72.4)	
30-day POM	83 (4)	45 (5.1)	19 (3.5)	17 (4.3)	2 (0.8)	0.017
90-day POM	150 (7.2)	79 (9.0)	41 (7.5)	24 (6.1)	6 (2.4)	0.003
Charlson 1-2	1013 (30.8)	452 (32.3)	245 (28.9)	238 (34.4)	78 (22.4)	
30-day POM	73 (7.2)	47 (10.4)	12 (4.9)	12 (5.0)	2 (0.8)	0.005
90-day POM	125 (12.3)	69 (15.3)	24 (9.8)	28 (11.8)	4 (5.1)	0.031
Charlson ⩾ 3	208 (6.4)	71 (5.2)	60 (7.1)	59 (8.6)	18 (5.2)	
30-day POM	27 (12.9)	14 (19.7)	10 (16.7)	3 (4.6)	0 (0)	0.023
90-day POM	46 (22.1)	19 (26.8)	18 (30.0)	8 (13.6)	1 (5.6)	0.038

A 86% [84-100] relative risk reduction for 30-day POM was systematically observed independently of Charlon's score

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RESULTS – GC SUBGROUP

Variables	Overall population	Low volume	Intermediate volume	High volume	Very high volume	*P value*
	n (%)	n (%)	n (%)	n (%)	n (%)	
All patients	7910 (70.7)	5786 (80.5)	1052 (55.3)	896 (56.5)	176 (33.6)	
30-day POM	365 (4.6)	300 (5.2)	40 (3.8)	20 (2.2)	5 (2.8)	<0.001
90-day POM	685 (8.6)	564 (9.7)	67 (6.4)	46 (5.1)	8 (4.5)	<0.001
Charlson 0	5241	3765	723	625	128	
30-day POM	165 (3.1)	141 (3.7)	13 (1.8)	9 (1.4)	2 (1.5)	<0.001
90-day POM	310 (5.9)	265 (7.0)	23 (3.2)	19 (3.0)	3 (2.3)	<0.001
Charlson 1-2	2189	1677	272	201	39	
30-day POM	141 (6.4)	112 (6.7)	18 (6.6)	9 (4.5)	2 (5.1)	0.667
90-day POM	272 (12.4)	220 (13.1)	33 (12.1)	16 (8.0)	3 (7.7)	0.155
Charlson ⩾ 3	480	344	57	70	9	
30-day POM	59 (12.3)	47 (13.6)	9 (15.8)	2 (4.2)	1 (11.1)	0.071
90-day POM	103 (21.4)	79 (23.0)	11 (19.3)	11 (15.7)	2 (22.2)	0.574

A 46% [18-59] relative risk reduction for 30-day POM was systematically observed independently of Charlon's score
→ similar results for partial and total gastrectomy

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CONCLUSION

First study, linear decrease in POM with increasing center volume, whatever

- Tumor location (gastric vs esophagus)
- Patients' condition (Charlson score)
- 30-day, 90-day, in-hospital (additional data) POM

46% of postoperative deaths occurred after 30 days

- 90-day POM should be given in surgical audits

EC and GC surgery should be centralized regardless of the patient's condition to significantly and markedly improve POM

A PHASE III CLINICAL TRIAL OF NEOADJUVANT CHEMO RADIOTHERAPY FOLLOWED BY SURGERY VERSUS SURGERY ALONE FOR LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE ESOPHAGUS

(NEOCRTEC5010)

Hong Yang, Jianhua Fu, Mengzhong Liu, Yuping Chen, Zhijian Chen, Chengchu Zhu, Haihua Yang, Wentao Fang, Jiaming Wang, Zhentao Yu, Qingsong Pang, Weimin Mao, Xiao Zheng, Jiaqing Xiang, Huanjun Yang, Yongtao Han

COPENHAGEN 2016 ESMO congress

SYSUCC SINCE 1964

BACKGROUND

- Surgery is the main treatment of esophageal squamous cell carcinoma (ESCC), but the prognosis of patients with locally advanced ESCC is rather poor.

- Preoperative chemo radiotherapy followed by surgery seems to hopefully improve the survival of ESCC. Nevertheless, the results of different studies were inconsistent.

- Phase III clinical trial to investigate the effect of this multidisciplinary therapy on the overall survival of patients with locally advanced ESCC.

ELIGIBILITY CRITERIA

- Stage IIB-III ESCC, according to Sixth Edition AJCC Cancer Staging
- Judged to be resectable
- Previously untreated
- Age range from 18 to 70 years
- Karnofsky performance status (KPS) of 90 or more
- Medical fitness for surgery

Key exclusion criteria

- Predominantly adenocarcinoma
- Cervical ESCC
- Tumor invading aorta or trachea

STUDY DESIGN

Trial commenced 2007

- **Stage IIB/III ESCC**
- **Possibly resectable**
- **Previously untreated**
- **Age 18~70** years **old**

R

1 : 1

Transthoracic esophagectomy → **Follow up**

Vinorelbine + Cisplatin q3w x2;
Concurrent radiotherapy:
TD 40 Gy delivered in 20 daily fractions of 2.0 Gy each

4-6 weeks later

Transthoracic esophagectomy → **Follow up**

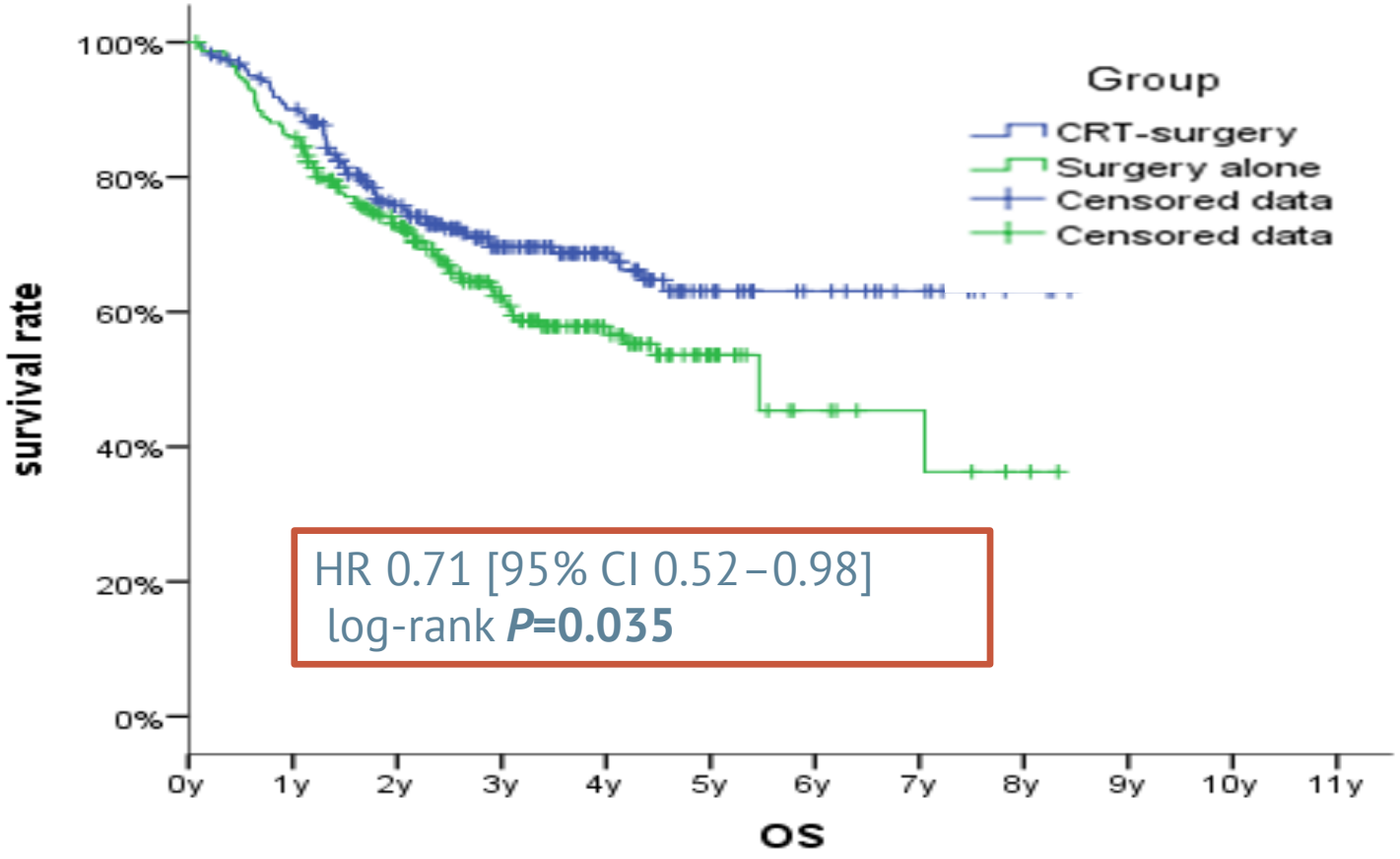
Primary endpoint:

- overall survival (OS)

Secondary endpoints:

- Disease-free survival (DFS)
- Safety
- Rate of R0 resection
- Rate of pCR after induction CRT

OVERALL SURVIVAL



HR 0.71 [95% CI 0.52–0.98]
log-rank ***P*=0.035**

	1 year	2 years	3 years
CRT-Surgery	90.0%	75.7%	69.6%
Surgery alone	85.8%	72.6%	62.4%

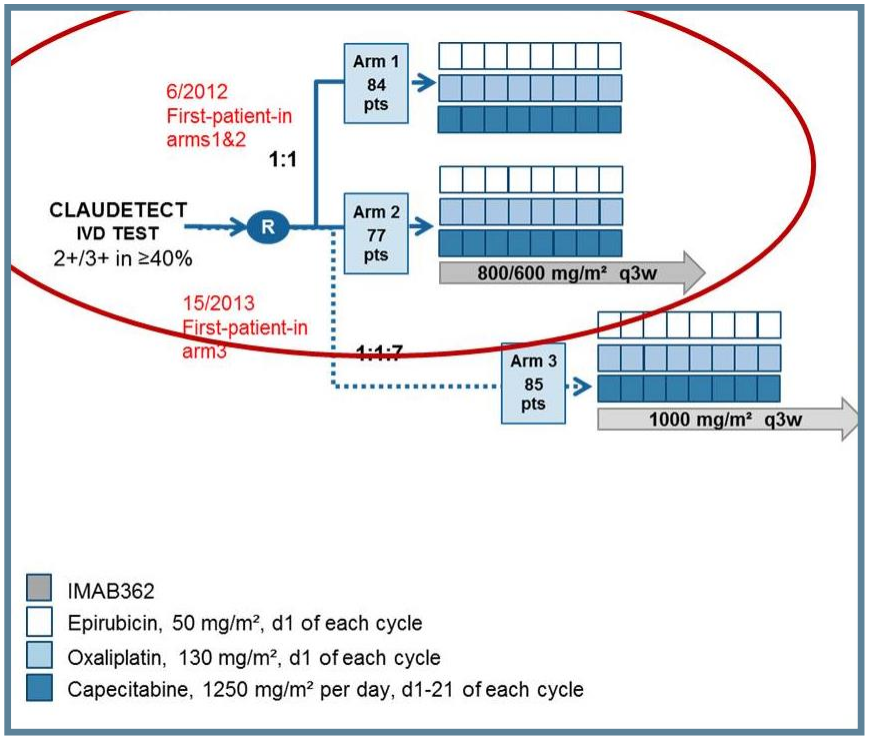
ACHIEVING HIGHER R0 RESECTION RATE THROUGH PREOPERATIVE CRT

	CRT-surgery	Surgery alone	*P Value*
Underwent surgery	185	227	
R0 resection	182 (98.4%)	207 (91.2%)	0.002
No surgery	39	0	

CONCLUSION

- CRT followed by surgery could increase R0 resection rate of patients with stage IIB-III ESCC
- Downstage ESCC significantly
- Achieve a high pCR rate
- Be satisfactorily safe
- Significantly prolong overall survival

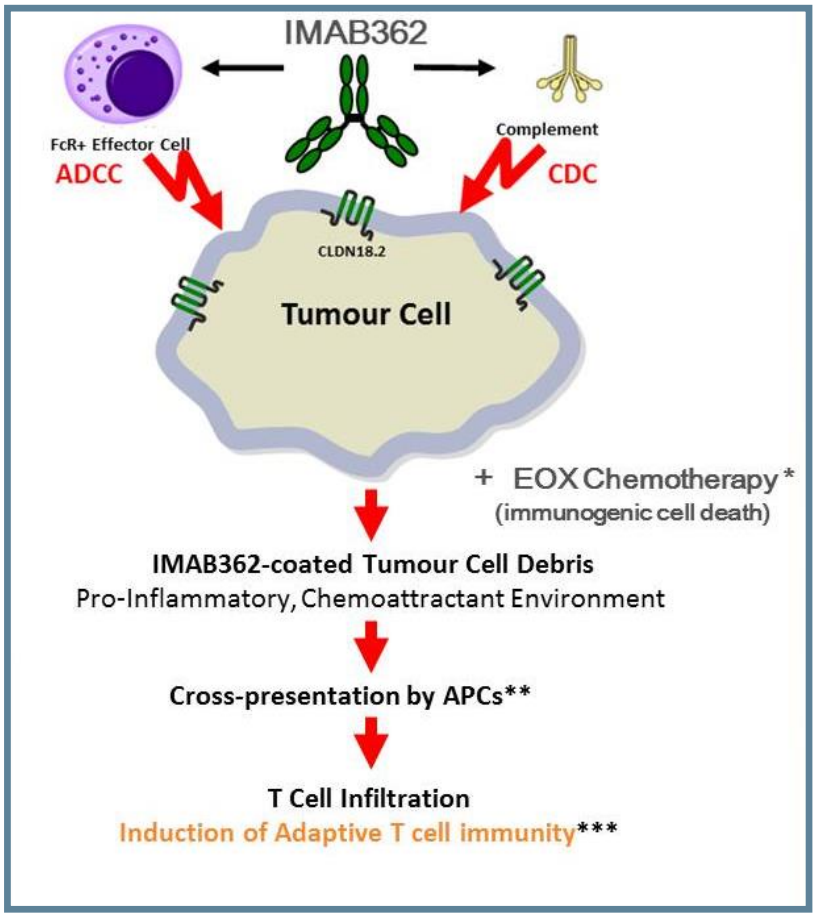
PALLIATIVE THERAPY – FAST STUDY
STUDY DESIGN



- Randomised phase II trial
- Arm 1, Arm 2 randomised 1:1
- Added exploratory Arm 3, 1:1:7 randomised for catch up
- At randomisation; Stratification according to (i) CLDN18.2 positivity, (ii) measurability of disease

Al-Batran SE, et al. ASCO 2016 (LBA4001)

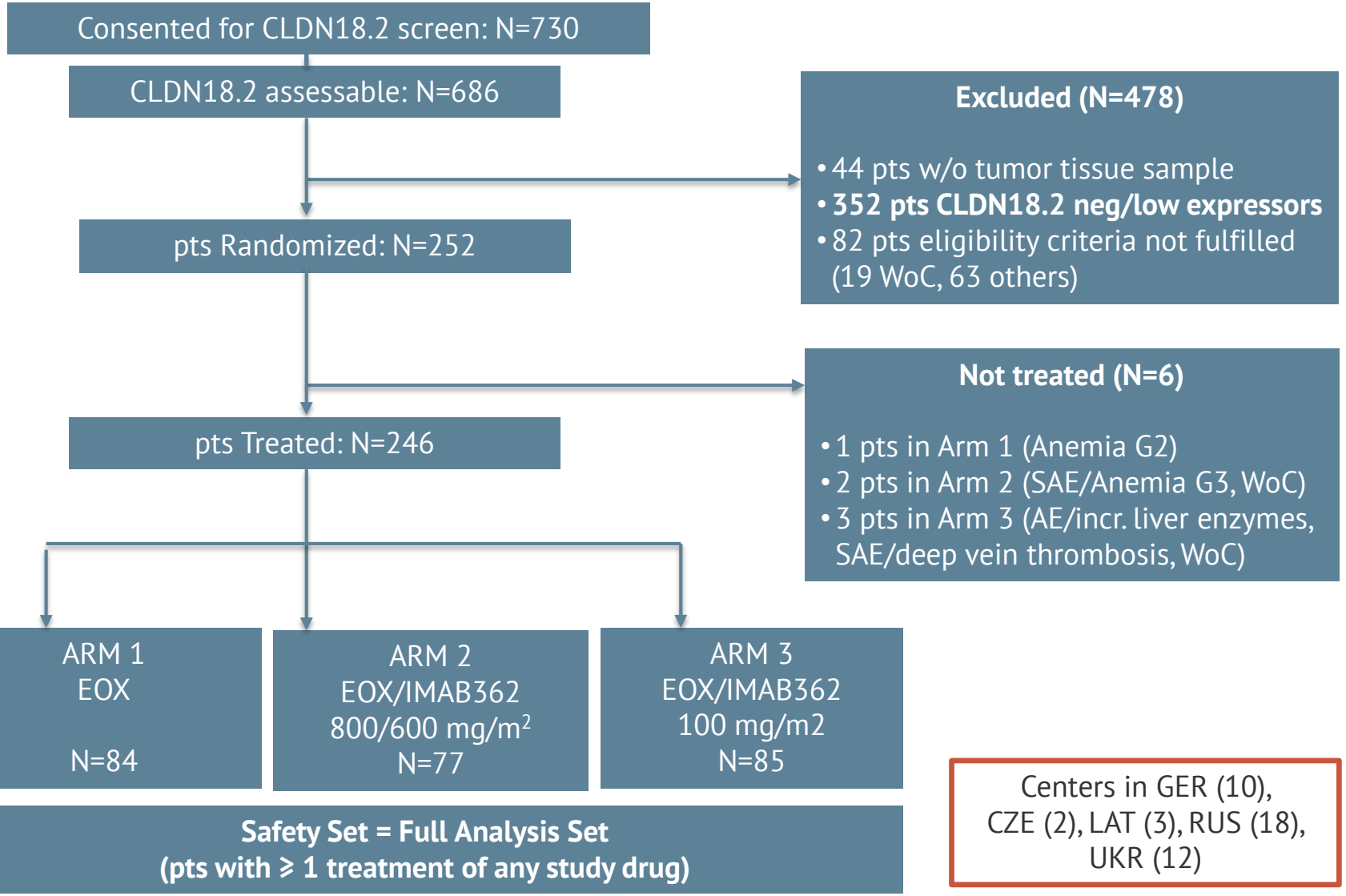
THE IMAB362 ANTIBODY



- Chimeric IgG1 backbone antibody
- Highly specific for CLDN18.2
- Modes of action:
  - Antibody-dependent cellular cytotoxicity (ADCC)
  - Complement-dependent cytotoxicity (CDC)
  - In combination with chemotherapy:
    - Enhances T-cell infiltration
    - Induces pro-inflammatory cytokines

*Kroemer et al, 2013, **Rogers, Veeramani and Weiner, 2014, ***Bianchi and Gianni 2014
EOX: Epirubicin, Oxaliplatin, Capecitabine

FAST – PATIENT DISTRIBUTION



Centers in GER (10), CZE (2), LAT (3), RUS (18), UKR (12)

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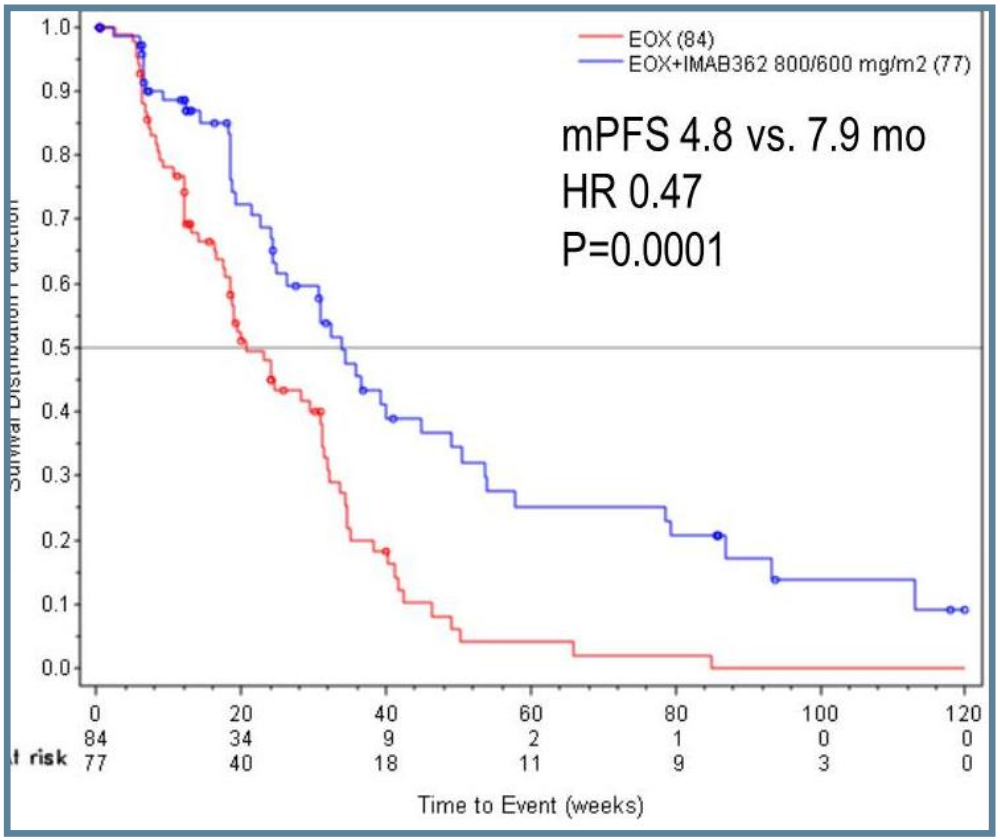
PROGRESSION-FREE SURVIVAL* (PRIMARY ENDPOINT)



Patient disposition	Arm 1 EOX (N=84)	Arm 2 EOX + IMAB362 (N=77)
Patient with event N (%)	66 (78.6)	45 (58.4)
PFS [median (95CI), months]	4.8 (4.1; 7.2)	7.9 (5.7;10.4)
Hazard ratio (95% CI)		0.47 (0.31; 0.70)
P-value (1-sided, stratified Cox model)		0.0001

*based on central imaging assessment in patients with 2+/3+ CLDN18.2 staining in ⩾40% of tumor cells (total population) Updated data!

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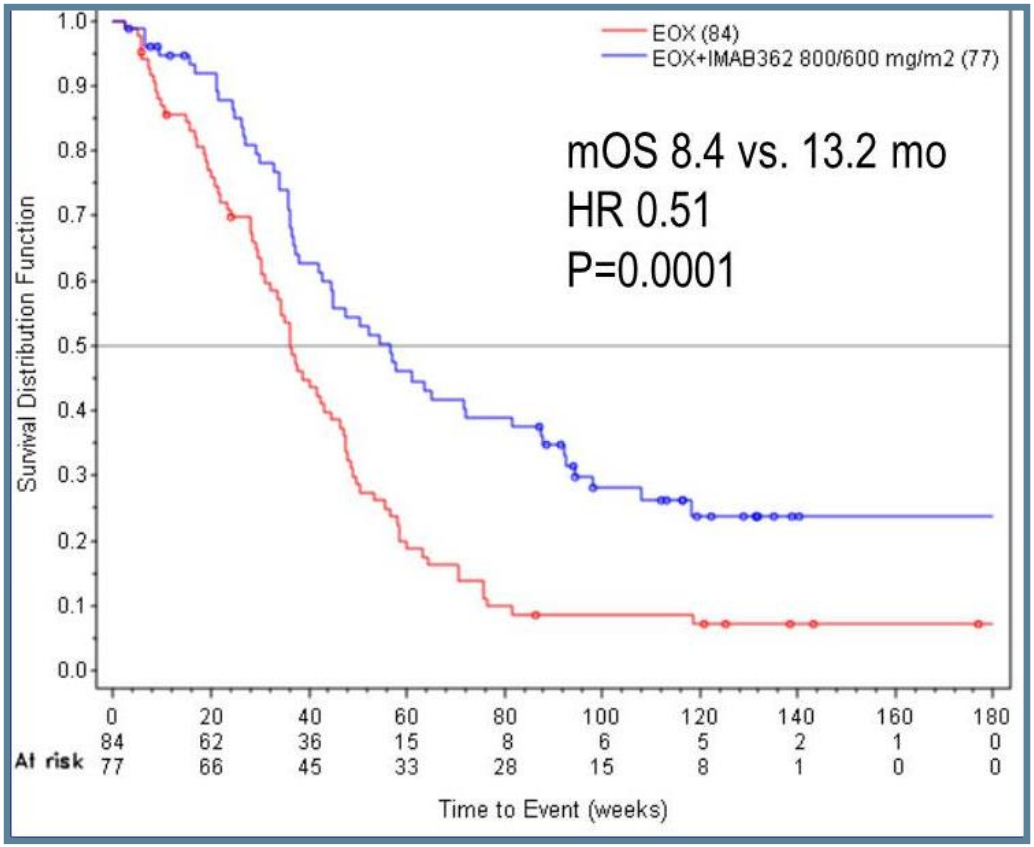
OVERALL SURVIVAL*



Patient disposition	Arm 1 EOX (N=84)	Arm 2 EOX + IMAB362 (N=77)
Patient with event N (%)	75 (89.3)	53 (68.8)
PFS [median (95CI), months]	8.4 (7.0; 10.3)	13.2 (9.7; 18.9)
Hazard ratio (95% CI)		0.51 (0.36; 0.73)
P-value (1-sided, stratified Cox model)		0.0001

* In patients with 2+/3+ CLDN18.2 staining in ⩾40% of tumor cells Total population) Updated data!

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SELECTED ADVERSE EVENTS (NCI-CTC CRITERIA)

Adverse Event/ treatment arm	EOX		EOX + IMAB362	
	G1/2	G3/4	G1/2	G3/4
Anaemia	24 (28.6)	6 (7.1)	29 (37.7)	9 (11.7)
Leukopenia	10 (11.9)	5 (6)	8 (10.4)	6 (7.8)
Neutropenia	18 (21.4)	18 (21.4)	18 (23.4)	25 (32.5)
Thrombocytopenia	7 (8.3)	3 (3.6)	12 (15.6)	0
Diarrhea	29 (34.5)	3 (3.6)	12 (15.6)	3 (3.9)
Nausea	52 (61.9)	3 (3.6)	56 (72.7)	5 (6.5)
Vomiting	29 (34.5)	3 (3.6)	43 (55.8)	8 (10.4)
Asthenia	17 (20.2)	2 (2.4)	11 (14.3)	2 (2.69)
Fatigue	14 (16.7)	3 (3.6)	20 (26)	5 (6.5)
Infections	9 (10.7)	2 (2.4)	11 (14.3)	0

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