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UZ LEUVEN

Duration of Immunotherapy in GI cancer:

ISA January 2024

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Disclosure information

- Participation to advisory boards/consulting of Abbvie, Agenus, ALX, Amgen, Arcus Biosciences, Astellas, Astrazeneca, Bayer, Beigene, Biontech, Boehringer Ingelheim, Bristol-Myers- Squibb, Daiichi, Debiopharma, Elmedix, Eisai, GSK, Hookipa Biotech, Incyte, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Mirati, Novartis, Nordic, Pierre Fabre, Pfizer, Roche, Seattle Genetics, Servier, Simcere, Takeda, Taiho, Terumo

Checkpoint inhibition (PD(L)-1) in GI Cancer
approved indications

- MSI-H metastatic CRC: first line PD1-AB and pretreated: PD1-AB +CTLA4-AB
  MSI-H gastric cancer, small intestine cancer, biliary tract cancer: PD1-AB
- Metastatic gastric adenocarcinoma:
  - ✓ PD1-AB + chemotherapy in PD-L1 positive tumors
- Metastatic oesophageal cancer:
  - ✓ Squamous cell cancer:
    - ➢ Second line: PD1-AB
    - ➢ First line: PD1-AB + chemotherapy or PD1-AB+ CTLA4-AB in PD-L1 positive tumors
  - ✓ Adenocarcinoma: PD1-AB + chemotherapy in PD-L1 positive tumors
- Metastatic bile duct cancer
  - ✓ PD(L)1-AB + chemotherapy
- Advanced hepatocellular carcinoma
  - ✓ PD(L)1-AB monotherapy or combo with CTLA4-AB or bevacizumab
- Adjuvant treatment of oesophageal cancer:
  - ✓ Nivolumab for 1 year

AB, antibody; CRC, colorectal cancer; CTLA4, cytotoxic T lymphocyte antigen 4; GI, gastrointestinal; MSI-H, microsatellite instability-high; PD-(L)1, programmed death-(ligand) 1

Duration in metastatic GI Cancer

- Most trials:
  - ✓ max. 2 years
    or
  - ✓ until progression/toxicity

- Challenges:
  - ✓ What about rechallenge after interruption for toxicity?
  - ✓ What about rechallenge when progression after CPI-interruption after initial CR/PR?
    Which interval? Same treatment?
  - ✓ How long to treat if complete response is reached?

CPI, checkpoint inhibitor; CR, complete response; GI, gastrointestinal; PD-(L)1, programmed death-(ligand) 1; PR, partial response.

CheckMate 577 study design in resectable oesophageal and GEJ cancer

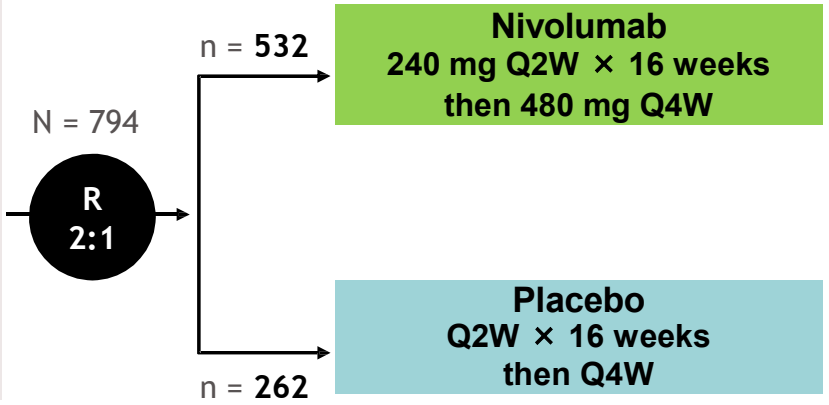
- **CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]**

Key eligibility criteria

- **Stage II/III EC/GEJC**
- **Adenocarcinoma or squamous cell carcinoma**
- **Neoadjuvant CRT + surgical resection (R0,[b] performed within 4-16 weeks prior to randomization)**
- **Residual pathologic disease**
  - **≥ ypT1 or ≥ ypN1**
- **ECOG PS 0–1**

Stratification factors

- **Histology (squamous vs adenocarcinoma)**
- **Pathologic lymph node status (≥ ypN1 vs ypN0)**
- **Tumor cell PD-L1 expression (≥ 1% vs < 1%[c])**



Total treatment duration of up to 1 year[d]

Primary endpoint:

- **DFS[e]**

Secondary endpoints:

- **OS[f]**
- **OS rate at 1, 2, and 3 years**

- **Median follow-up was 24.4 months (range, 6.2–44.9)[g]**
- **Geographical regions: Europe (38%), US and Canada (32%), Asia (13%), rest of the world (16%)**

[a]ClinicalTrials.gov number, NCT02743494; [b]Patients must have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumor present within 1 mm of the proximal, distal, or circumferential resection margins; [c]< 1% includes indeterminate/nonevaluable tumor cell PD-L1 expression; [d]Until disease recurrence, unacceptable toxicity, or withdrawal of consent; [e]Assessed by investigator, the study required at least 440 DFS events to achieve 91% power to detect an average HR of 0.72 at a 2-sided α of 0.05, accounting for a pre-specified interim analysis; [f]The study will continue as planned to allow for future analysis of OS; [g]Time from randomization date to clinical data cutoff (May 12, 2020).

CRT, chemoradiotherapy; DFS, disease-free survival; EC, oesophageal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; GEJC, GEJ cancer; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1; QW, every X weeks.

Kelly R, …Van Cutsem E et al, NEJM 2021, 381, 1191-2003

Adjuvant nivolumab after CRT + surgery for oesophageal & GEJ cancer: update of CheckMate 577

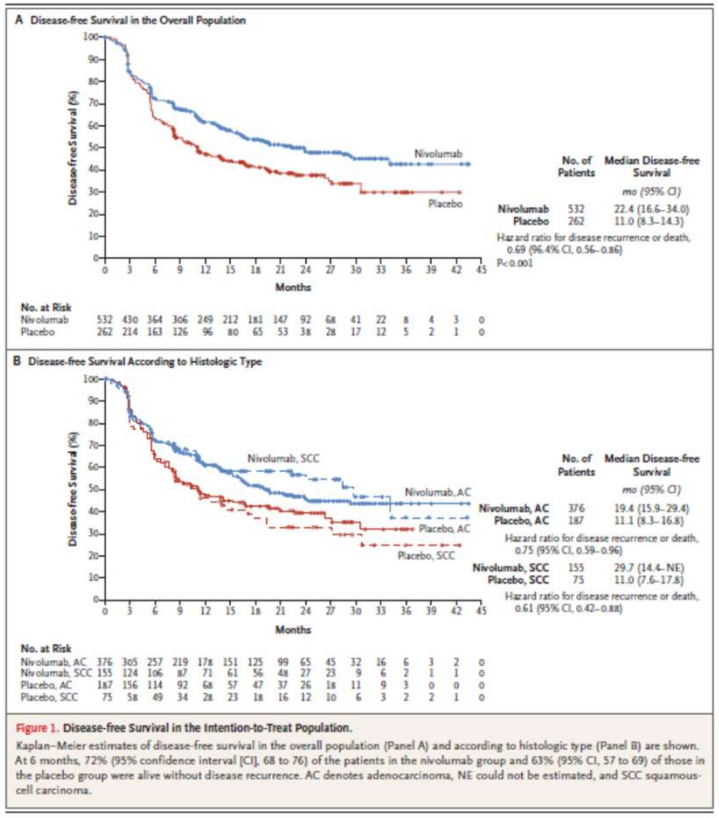
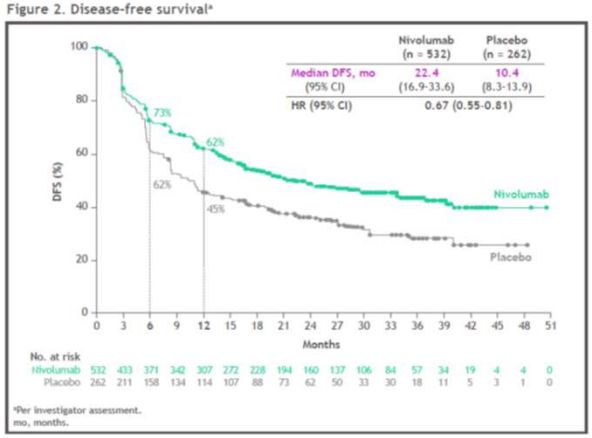


Figure 1. Disease-free Survival in the Intention-to-Treat Population.

Kaplan–Meier estimates of disease-free survival in the overall population (Panel A) and according to histologic type (Panel B) are shown. At 6 months, 72% (95% confidence interval [CI], 68 to 76) of the patients in the nivolumab group and 63% (95% CI, 57 to 69) of those in the placebo group were alive without disease recurrence. AC denotes adenocarcinoma, NE could not be estimated, and SCC squamous-cell carcinoma.

Kelly R, …Van Cutsem E et al, NEJM 2021, 381, 1191-2003

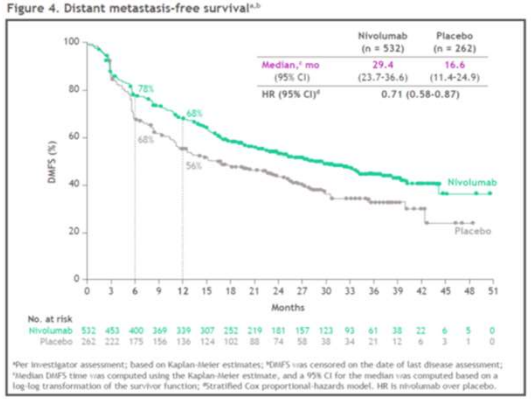
Figure 2. Disease-free survival[a]



[a]Per investigator assessment.
mo, months.

- DFS benefit was observed with nivolumab versus placebo across multiple subgroups (**Figure 3**)
  - Compared with earlier results,[a] there was a numerical reduction in HR for multiple subgroups, including GEJC (HR, 0.80 [95% CI, 0.59-1.08] from 0.87 [95% CI, 0.63-1.21]) and adenocarcinoma (HR, 0.73 [95% CI, 0.58-0.91] from 0.75 [95% CI, 0.59-0.96])

Figure 4. Distant metastasis-free survival[a,b]



[a]Per investigator assessment; based on Kaplan-Meier estimates; [b]DMFS was censored on the date of last disease assessment; [c]Median DMFS time was computed using the Kaplan-Meier estimate, and a 95% CI for the median was computed based on a log-log transformation of the survivor function; [d]Stratified Cox proportional-hazards model. HR is nivolumab over placebo.

Figure 3. Disease-free survival subgroup analysis

Subgroup	Median DFS, mo		Unstratified HR	Unstratified HR (95% CI)
	Nivolumab	Placebo		
Overall (N = 794)	22.4	10.4	0.68	
Age, years				
< 65 (n = 507)	25.1	9.3	0.63	
≥ 65 (n = 287)	19.4	13.9	0.79	
Sex				
Male (n = 671)	21.3	10.3	0.70	
Female (n = 123)	29.3	11.0	0.62	
Race				
White (n = 648)	21.3	10.8	0.69	
Asian (n = 117)	29.7	9.7	0.71	
ECOG PS				
0 (n = 464)	26.6	11.1	0.71	
1 (n = 330)	18.5	9.3	0.64	
Tumor location at initial diagnosis				
Esophagus (n = 465)	23.4	8.3	0.61	
Gastroesophageal junction (n = 329)	21.4	16.8	0.80	
Histologic type				
Adenocarcinoma (n = 563)	19.6	10.4	0.73	
Squamous cell carcinoma (n = 230)	29.7	10.6	0.60	
Tumor cell PD-L1 expression[a]				
≥ 1% (n = 129)	28.3	10.2	0.68	
< 1% (n = 567)	20.8	11.0	0.70	
Indeterminate/nonevaluable (n = 98)	26.6	9.9	0.64	
PD-L1 CPS[a,b]				
≥ 5 (n = 371)	29.3	8.5	0.60	
< 5 (n = 295)	15.3	11.1	0.85	
Indeterminate/nonevaluable/HR (n = 128)	26.6	10.8	0.64	
Pathologic lymph node status				
ypN0 (n = 337)	Not reached	27.0	0.71	
≥ ypN1 (n = 457)	14.8	7.6	0.65	
Pathological tumor status[c]				
ypT0[d] (n = 45)	34.0	5.2	0.40	
ypT1 or ypT2 (n = 311)	29.3	9.2	0.59	
ypT3 or ypT4 (n = 436)	18.5	11.5	0.80	
Time from complete resection to randomization				
< 10 weeks (n = 256)	24.0	12.7	0.85	
≥ 10 weeks (n = 538)	21.3	9.3	0.63	

0.25 0.5 1 2
Nivolumab better ← → Placebo better

[a]PD-L1 expression determined from tumor tissue specimen by the PD-L1 IHC 28-8 pharmDx assay (Dako), which, for most patients, was obtained after completion of CRT; [b]Post hoc analysis; [c]2 patients had unknown pathological tumor status in the nivolumab arm; [d]The lower bound of the 95% CI for this subgroup is 0.18.
NR, not reported.

Moehler M, … Van Cutsem E et al,
Ann Oncol, ESMO 2021 poster presentation

CRT, chemoradiotherapy; GEJ, gastroesophageal junction.

Ongoing phase 3 trials on CPI as perioperative therapy in esophagogastric cancer

Trial	N	Key eligibility criteria	Treatment: ~ 1 YEAR CPI	Primary endpoint
DANTE/FLOT8[1] **Phase 2/3** NCT03421288	295/556	≥T2 or N+ gastric and GEJ cancer, (phase3, PD-L1 >1)	Perioperative FLOT +/- **atezolizumab**	Phase 2: pCR/ pTNM Phase 3: EFS
KEYNOTE 585[2] **Phase 3** NCT03221426	1007	>T3 or N+ gastric and GEJ cancer	Perioperative FP/XP (or FLOT) +/- **pembrolizumab**	pCR, EFS, OS
MATTERHORN[3] **Phase 3** D910GC00001	900	T3–4 or N+ gastric and GEJ cancer	Perioperative FLOT +/- **durvalumab**	EFS

pCR and pTNM improved

pCR improved, EFS not

pCR improved

CPI, check-point inhibitor, EFS, event-free survival; FLOT, fluorouracil plus leucovorin, oxaliplatin, and docetaxel; FP, fluorouracil and cisplatin; GEJ, gastroesophageal junction; N, node; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; pTNM, postoperative TNM stage; T, tumor; TNM, tumor node metastases; XP, capecitabine and cisplatin.

1. Lorenzen S et al, J Clin Onc 2023. 2. Shitara K… Van Cutsem E et al, Lancet Oncol 2023. 3. Janjigian Y…. Van Cutsem E et al, Ann Oncol – ESMO 2023

PD1-blockage in mismatch repair-deficient locally advanced rectal cancer

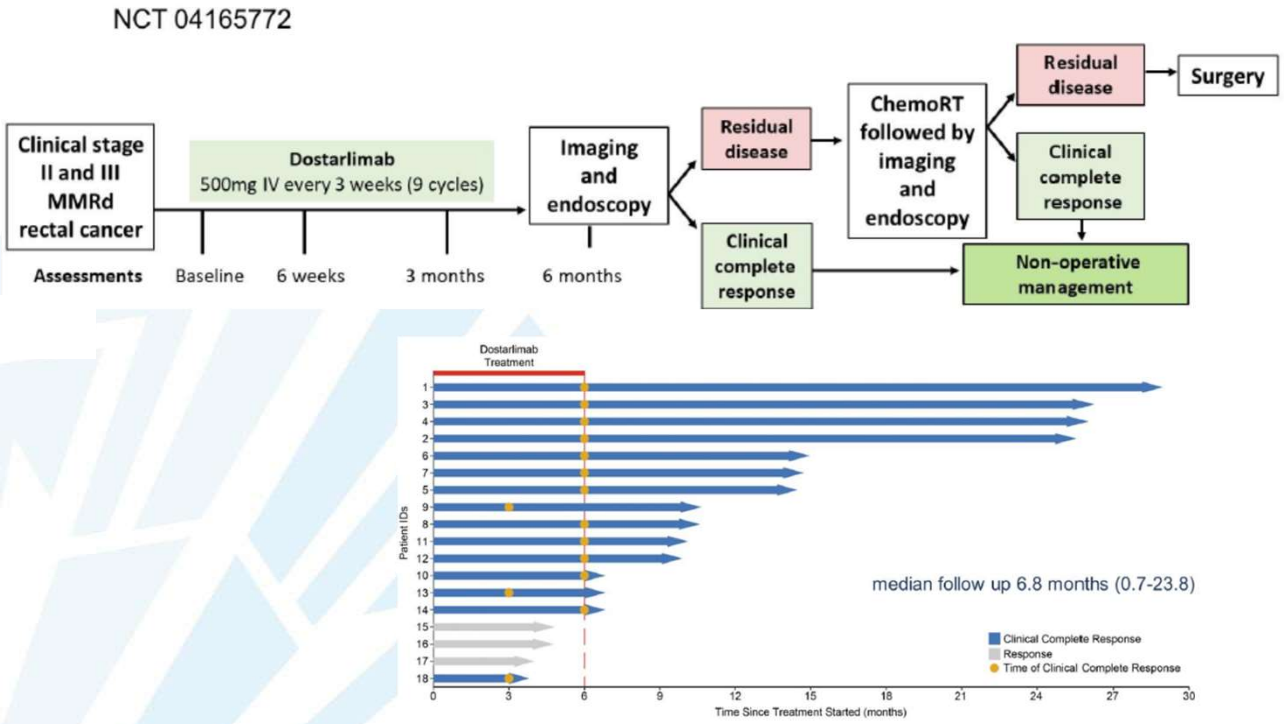


Table 2. Individual Patient Data.*

Patient No. (Sex, Age)	Tumor Stage; Nodal Status	Germline Pathogenic Variant†	Mismatch-Repair Status, Chromogenic IHC Assay	PD-L1 Level	TIL Level	*BRAF* V600E	Tumor Mutational Burden‡	Completed 6 mo of Dostarlimab Therapy	CRT or Surgery	Response on Endoscopic Visualization	Digital Examination; Endoscopic Biopsy	Response on Rectal MRI	Response on FDG-PET
1 (F, 38 yr)	T4; positive	*MSH2* (c.687delA)	MSH2 and MSH6 absent	+	+++	No	88.6	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
2 (F, 30 yr)	T3; positive	*MSH2* (c.8942+3A→T)	MSH2 and MSH6 absent	++	+	No	45.6	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
3 (F, 61 yr)	T1 to T2; positive	None	MSH2 and MSH6 absent	+++	+++	No	62.3	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
4 (F, 28 yr)	T4; positive	None	MSH2 and MSH6 absent	+	++	No	65.0	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
5 (F, 53 yr)	T1 to T2; positive	*MSH2* (c.942+3A→T)	MSH2 absent	+	+	No	103.0	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
6 (F, 77 yr)	T1 to T2; positive	*MSH6* (c.1969delC)	MSH6 absent	+++	+++	No	93.9	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
7 (F, 77 yr)	T1 to T2; positive	None	MLH1 and PMS2 absent	++	++	No	75.0	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
8 (F, 55 yr)	T3; positive	*MSH2* (c.1784T→G)	MSH2 absent	++	+	No	78.3	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
9 (M, 68 yr)	T3; positive	None	MSH2 and MSH6 absent	+++	++	No	62.6	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
10 (F, 78 yr)	T3; negative	None	MLH1 and PMS2 absent	+	+	No	37.9	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
11 (F, 55 yr)	T3; positive	*PMS2*	MSH2 and MSH6 absent	++	++	No	52.7	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
12 (M, 27 yr)	T3; positive	None	PMS2 absent	+++	+++	No	54.4	Yes	No	CR	No palpable tumor; negative for tumor	CR	CR
13 (M, 26 yr)	T3; positive	*MLH1* (c.1489dupC)	MLH1 and PMS2 absent	NA	NA	No	47.8	No; ongoing, 12 wk	No	CR	No palpable tumor; negative for tumor	CR at 3 mo	CR
14 (M, 43 yr)	T3; positive	*MSH6* (c.3476dupA)	MSH6 absent	NA	NA	No	74.1	No; ongoing, 12 wk	No	CR	No palpable tumor; negative for tumor	Near-CR at 3 mo	CR
15 (M, 59 yr)	T3; positive	NA	PMS2 absent	NA	NA	NA	NA	No; ongoing, 5 wk	No	NE	NE; NE	NE	NE
16 (M, 51 yr)	T4b; positive	NA	MSH2 absent	NA	NA	NA	NA	No; ongoing, 3 wk	No	NE	NE; NE	NE	NE

* CR denotes complete response, CRT chemoradiotherapy, FDG-PET ^{18}F-fluorodeoxyglucose–positron-emission tomography, IHC immunohistochemical, NA not available, NE not able to be evaluated, PD-L1 programmed death ligand 1, and TIL tumor-infiltrating lymphocyte.
† All alterations identified are associated with the Lynch syndrome.
‡ Units are reported in mutations per megabase.

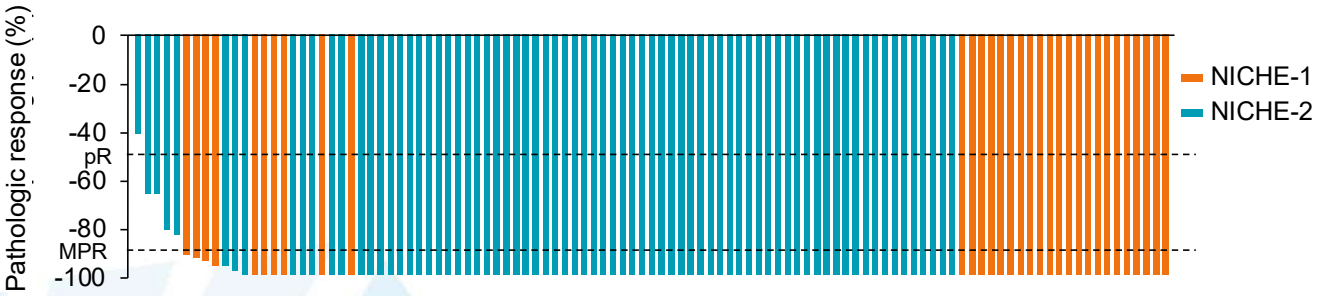
PD1, programmed death 1.

Cercek A et al, New Eng J Med 2022

PDL-1/PD-1 ± CTLA4 blockage in localized MSI-H/dMMR colon cancer

Anti-PD1± Anti-CTLA4: Pathological Complete Response (pCR) > 60% in 2 phases II

Nivolumab d1-d15 and ipilumumab d1, surgery 6 weeks after (n=112)

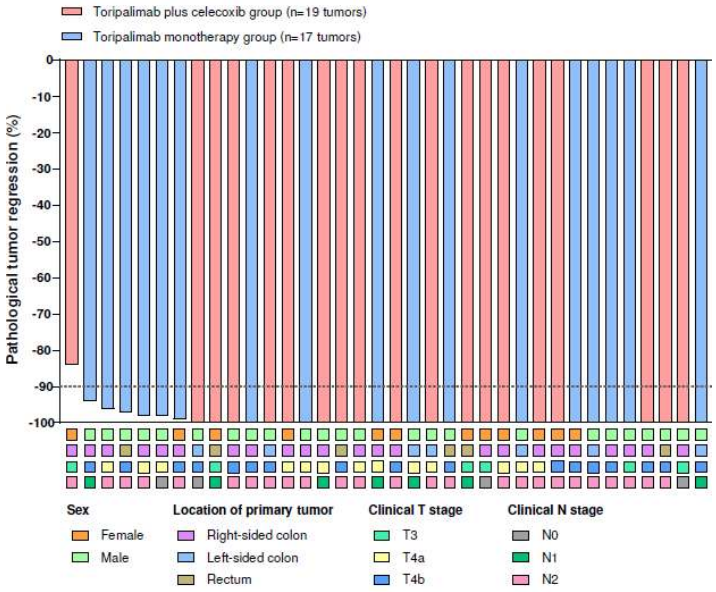


Pathologic Response Residual Viable Tumor	Patients n=107
Yes (≤ 50%)	106 (99%)
Major (≤ 10%)*	102 (95%)
Complete (0%)	72 (67%)
Partial (10%-50%)	4 (4%)
No (> 50%)	1 (1%)

- Radiologic stage
  - stage I or II: 13%
  - Low risk stage III: 13%
  - High risk stage III: 74%
- Major pathologic response: defined as 10% or less residual viable tumor

Cross trial comparisons cannot be inferred.
CTLA4, cytotoxic T lymphocyte antigen 4; d, day; dMMR, deficient mismatch repair; MPR, major pathological response; MSI-H, microsatellite instability-high; pCR, pathological complete response; PD-(L)1, programmed death-(ligand) 1; pR, pathological response.

Toripalimab ± celecoxib (n=34)
6 cycles (every 14 days) surgery 3 weeks later
6 patients had rectal cancer



26/34 pCR (76%)
Concerning 6 patients with rectal cancer:
5 pCR and one Major pR

Chalabi M et al, Nature Med 2020; Chalabi M et al, ESMO 2022 abstr LBA7;
Hu et al, Lancet Gastro&Hep 2021

Studies in MSI-H Local Rectal Cancer in Progress or Coming soon

Type of phase 2 (number of pts planned)	Primary	Name	Coordinator Group and Country	Drug	Schedule before surgery or Watch and Wait strategy	Primary end-point
Mono-arm n=32 NCT05197322 In progress	Colon & rectum	NEOPRISM-CRC	Shiu KK, UCL, UK	Pembrolizumab	1 to 3 cycles depending & stratified to TMB before surgery	**Pathological complete response rate**
Mono-arm n =120 NCT04795661 In progress[1]	All GI including rectum	IMHOTEP	de la Fouchardière C UNICANCER, France	Pembrolizumab	1 or 2 cycle before surgery	**Pathological complete response rate**
Mono-arm n =150 NCT05723562 In progress	Rectum	AZUR	Cercek A GSK study, Word	Dostarlimab	8 cycles and W&W with salvage surgery vs surgery	**Sustained complete clinical response (cCR 12 at 12 months)**
Phase 1[2] NCT04636008 In progress	Rectum	?	Li X China	Sintilimab	Sintulimab 3 injections/15 d and RT (5x5 Gy)	**Pathological complete response rate (surgery at 6 weeks of last injection)**
Randomized non comparative n=64 upcoming	Rectum	PREDIR	Karoui M FFCD, France	Dostrlimab	6 months of dostarlimab vs RT (5x5 Gy) then 6 months of dostarlimab	**residual or metastatic disease at 24 months with or without surgery**

Slide courtesy T André

cCR, complete clinical response; d, day; GI, gastrointestinal; RT, radiotherapy; TMB, tumor mutational burden; W&W, watch & wait.

1 de la Fouchardière C, ASCO 2023; 2 Li X et al, Cancer Medecine 2023

Checkpoint inhibition (PD-(L)) in GI Cancer

- Optimal duration is not known in adjuvant treatment of upper oesophagogastric cancer:
  often 1 year
  Same duration in neo-adjuvant or peri-operative treatment?

- Duration in ongoing adjuvant trials in MSI-H/dMMR colon cancer: 1 year
  also extrapolation of other cancers
  - ✓ Is this the best?

- Optimal duration in neo-adjuvant treatment of MSI-H/dMMR colon cancer, rectal cancer or upper GI cancer?

- What about rechallenge with CT + CPI after relapse on adjuvant CPI?

CPI, check-point inhibitor; CT, chemotherapy; dMMR, deficient mismatch repair; GI, gastrointestinal; MSI-H, microsatellite instability; PD-(L), programmed death-(ligand).

Chairs: Eric Van Cutsem, Michel Ducreux, Teresa Macarulla

Enjoy your break

18.05-18.20	BREAK			
18.25	18.25 => 19.05 PLENARY 2 Novel concepts in cancer Immunotherapy B ROUTY T KERRE S RAUH (Mod)			
19.10		19.10=>19.50 Patient education: Examples from academics centers T KERRE S STREEL M VANDEVELDE J VANSTEENKISTE (Mod)	19.10=>19.50 CAR T vs Bispecifics : Toxicity and sequencing P VANDENBERGHE J CAERS R SCHOTS (Mod)	19.10=>19.50 Drug Interference during Immunotherapy M ILZKOVITZ B ROUTY A AWADA (Mod)
19.50	19.50 => 20.05 CLOSING P LACANTE & P COULIE			
20.00 - 22.00	WALKING DINNER			