An odyssey and a journey through digestive oncology: Immunotherapy in digestive cancers

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Disclosure information

- Participation to advisory boards for: Array, Astrazeneca, Bayer, Biocartis, Bristol-Myers Squibb, Celgene, Daiichi, Pierre-Fabre, Incyte, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, Servier, Sirtex, Taiho

- Research grants from: Bayer, Boehringer Ingelheim, Celgene, Ipsen, Lilly, Roche, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, Servier paid to the institution.

- Receives an honorarium for speaking as this symposium is supported from Bristol Myers Squibb

- New data are discussed on drugs, including data for which an approval is not yet granted

Colorectal Cancer Subtypes
Microenviroment targeting in mCRC

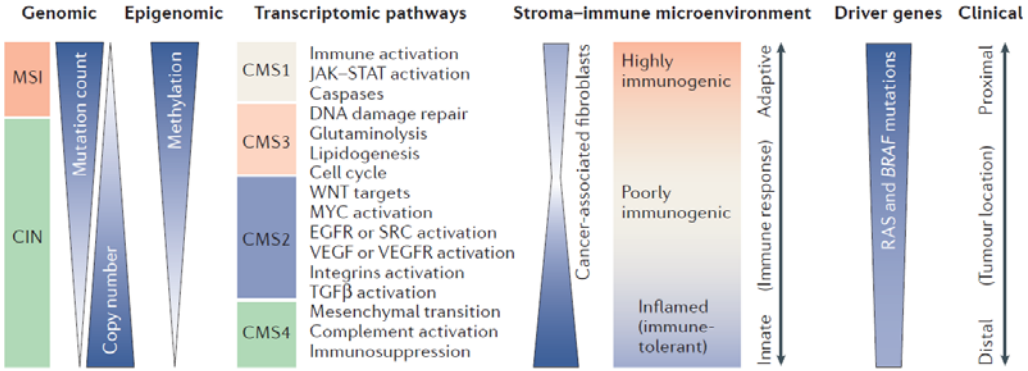
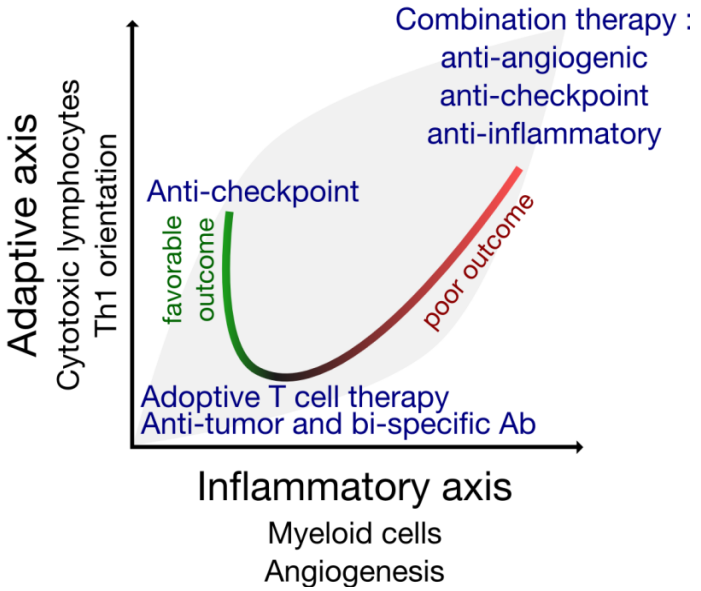


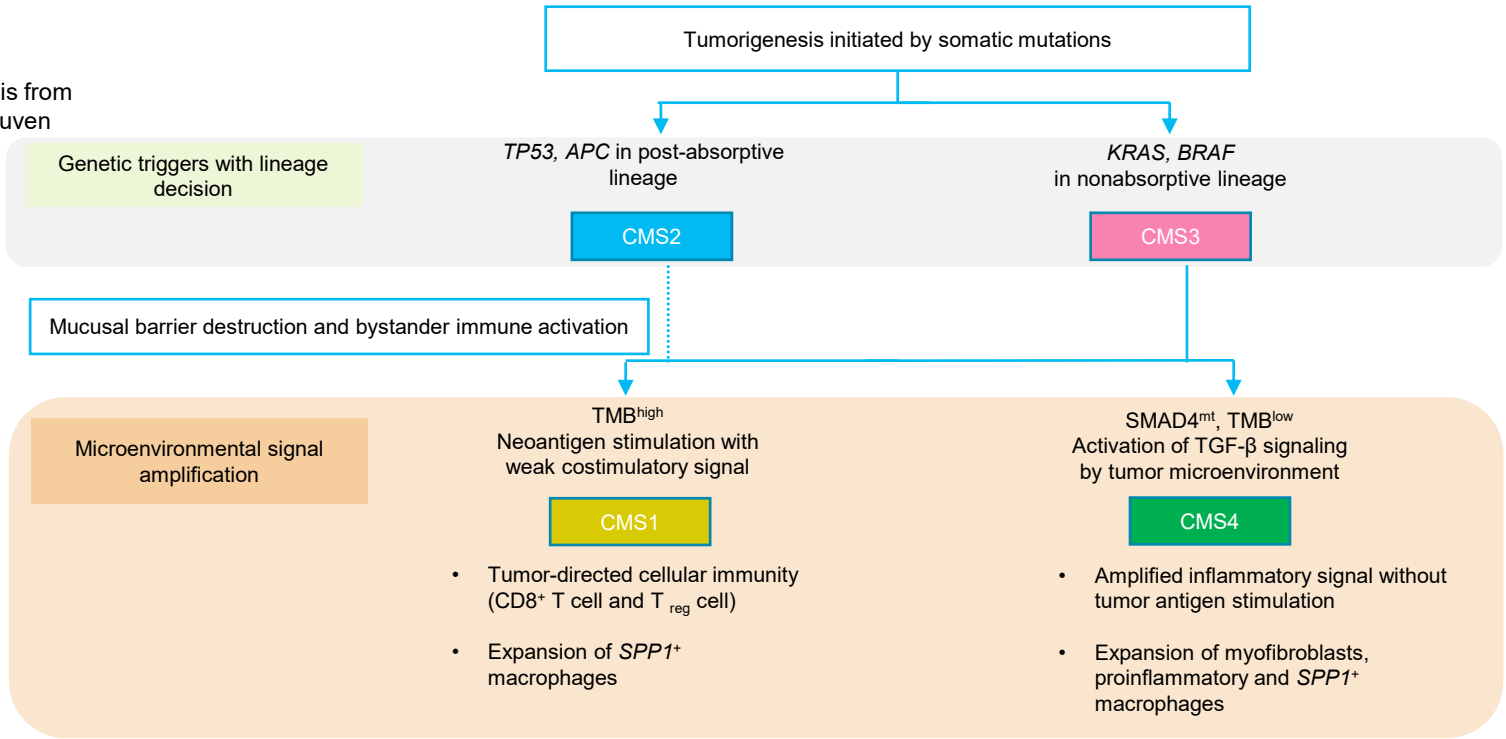
Figure 1 | **Schematic representation of CRC subtypes.** Microsatellite instability (MSI) is linked to hypermutation, hypermethylation, immune infiltration, activation of RAS, *BRAF* mutations, and locations in the proximal colon. Tumours with chromosomal instability (CIN) are more heterogeneous at the gene-expression level, showing a spectrum of pathway activation ranging from epithelial canonical (consensus molecular subtype 2 (CMS2)) to mesenchymal (CMS4). Tumours with CIN are mainly diagnosed in left colon or rectum, and their microenvironment is either poorly immunogenic or inflamed, with marked stromal infiltration. A subset of CRC tumours enriched for RAS mutations has strong metabolic adaptation (CMS3) and intermediate levels of mutation, methylation and copy number events. EGFR, epidermal growth factor receptor; JAK, Janus kinase; STAT, signal transducer and activator of transcription; TGFβ, transforming growth factor-β; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.



1. Dienstmann R et al. *Nat Rev Cancer* 2017;17(2):79-92. 2. Becht et al. *Advances Immunol* 2016;130:95-190.

Lineage-dependent gene expression programs influence the immune landscape of colorectal cancer

Transcriptome analysis from CRC in Korea and Leuven



Adapted from Lee HO et al. *Nat Genet* 2020;52(6):594-603.

Colorectal Cancer: Two Different Diseases

CIN+ (85%) Chromosomal Instability	MSI-H (15%) Genetic (Microsatellite) Instability
Aneuploidy, loss of heterozygosity/loss of genetic material	Diploidy, no loss of heterozygosity
Proficient Mismatch Repair system Microsatellite stable (MSS)	Deficient Mismatch Repair system Microsatellite instability (MSI)
Sporadic or Familial Adenomatous Polyposis (FAP)	Sporadic or Lynch syndrome
95% of metastatic colorectal cancer	5% of metastatic colorectal cancer. Prognosis and chemosensitivity of MSI seems worse vs MSS
More prevalent in distal location	More prevalent in proximal location
Frequent mutation of KRAS	Frequent mutation of $BRAF^{V600E}$
Tumor mutation burden low	Tumor mutation burden high Increased immune infiltration, higher tumour neo-antigens
No clear efficacy of immune check point inhibitor	Efficacy of immune check point inhibitor in phase I and II

MSI-H/MMRd tumors exhibit high mutational load and increased immune inflammation

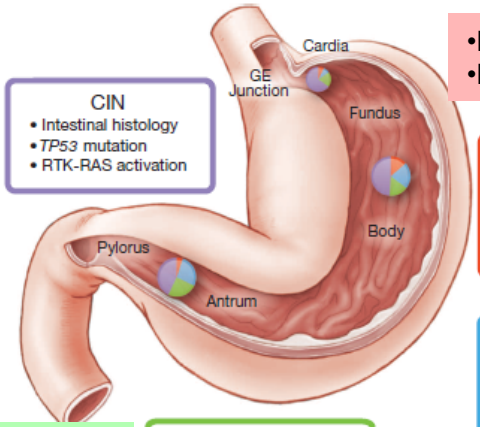
Adapted from Andre T et al. Oral presentation at ASCO 2020. Abstract LBA4.

Comprehensive Molecular Characterization in Gastric Cancer

CIN

Chromosomal instability

- Intestinal histology
- Aneuploidy
- RTK amplification
- *TP53* mutations
- HER2, EGFR, MET



EBV

- High EBV burden
- Extensive DNA hypermethylation
- Amplification of *PD-L1/2*
- *PIK3CA* mutations

MSI

Microsatellite unstable

- Older age, High MSI
- Elevated mutation rate
- Hypermethylation (*MLH1*)

GS

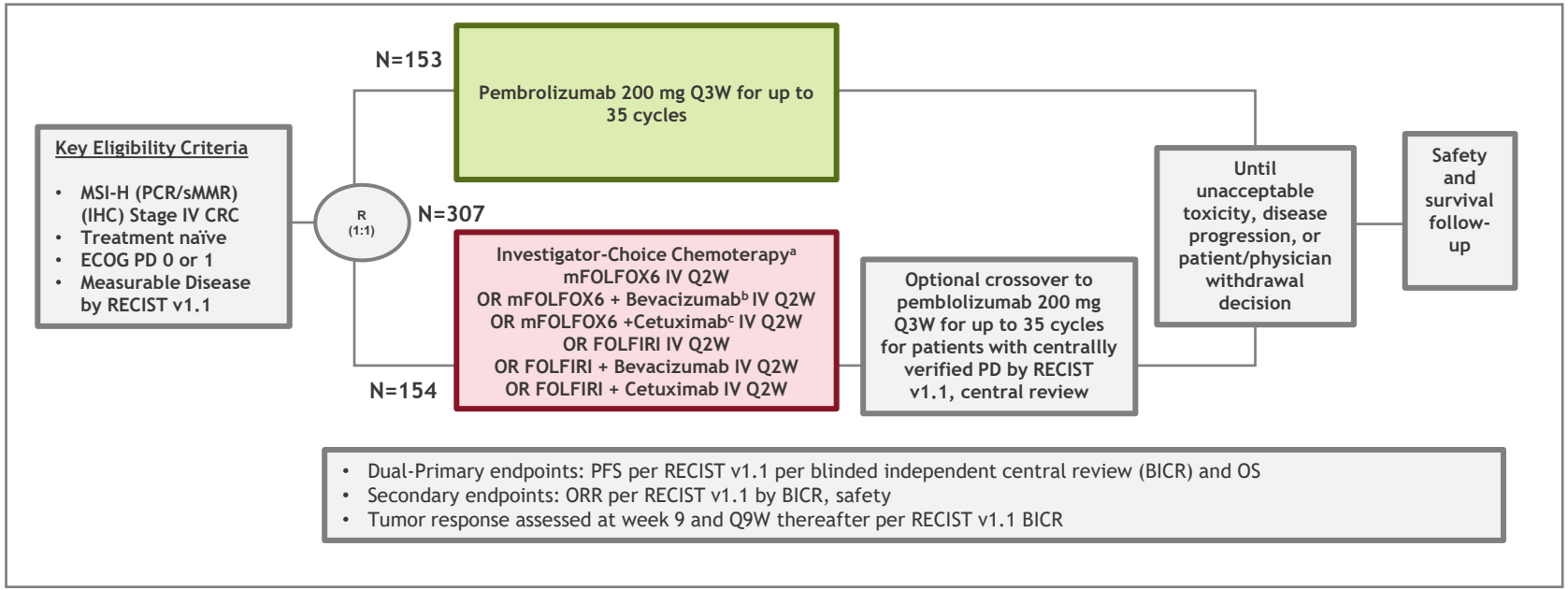
Genomically stable

- Diffuse histology, young age
- *CDH1, RHOA* mutations (mobility, adhesion)
- Sensitivity to m-TOR inhibitors in vitro

1. The cancer Genome Atlas Research Network. *Nature* 2014;513:202-9. 2. Lei et al. *Gastroenterology* 2013;145:554-565.

Keynote-177: Pembrolizumab vs chemotherapy in first line MSI-H mCRC

Study design (NCT02563002)



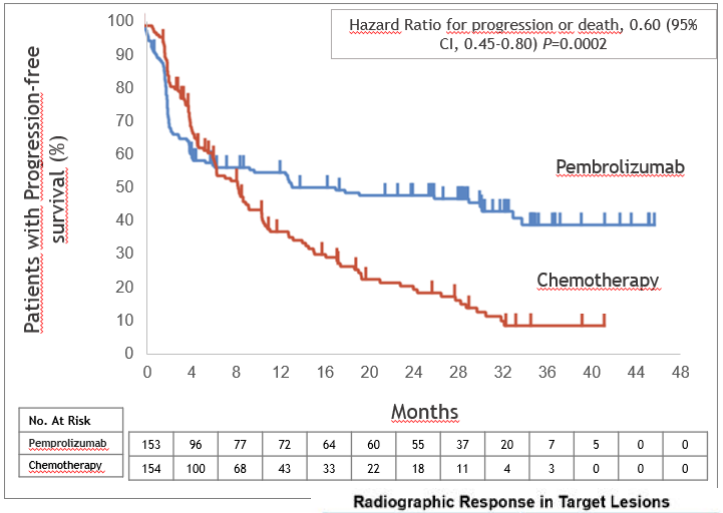
[a]Chosen before randomization; [b]Bevacizumab 5 mg/kg IV; [c]Cetuximab 400mg/m2 over 2 hours then 250 mg/m2 IV over 1 hour weekly.
IHC: immunohistochemistry with hMLH1, hMSH2, hMSH6; PCR polymerase chain reaction; PFS, progression-free survival; OS: overall survival; ORR: overall response rate; Q9W: every 9 weeks.

Adapted from Andre T, Van Cutsem E et al. *N Engl J Med* 2020;383(23):2207-2218

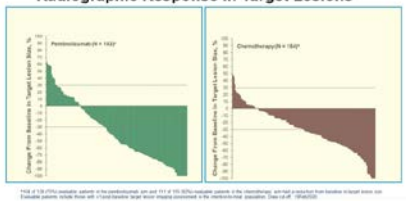
Checkpoint inhibition in first line MSI-H mCRC

Keynote 177

Figure 1. Progression-free Survival in Patients with MSI-H–dMMR Metastatic Colorectal Cancer [1]



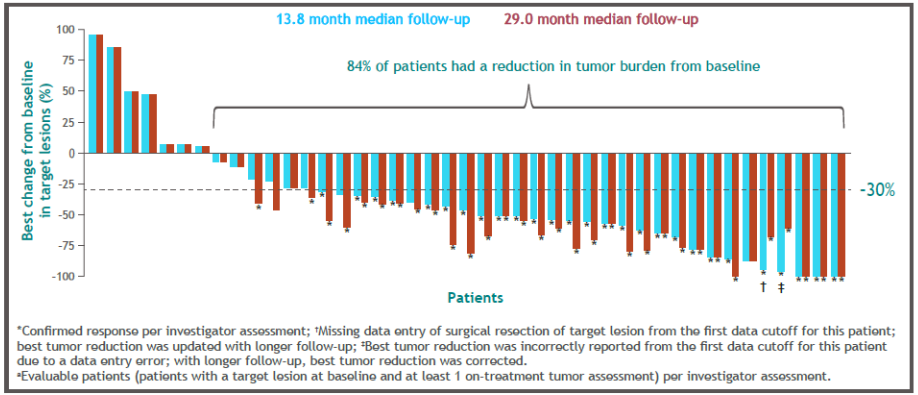
Radiographic Response in Target Lesions



Non-randomized phase 2 cohort in first line: checkmate 142 study, N=45

* CHMP positive opinion – EMA approval is not yet granted[3]

Figure 3. Best change from baseline in target lesions[2].



Median PFS and were not reached

— At 24 months, PFS and OS rates were 74% and 79%, respectively

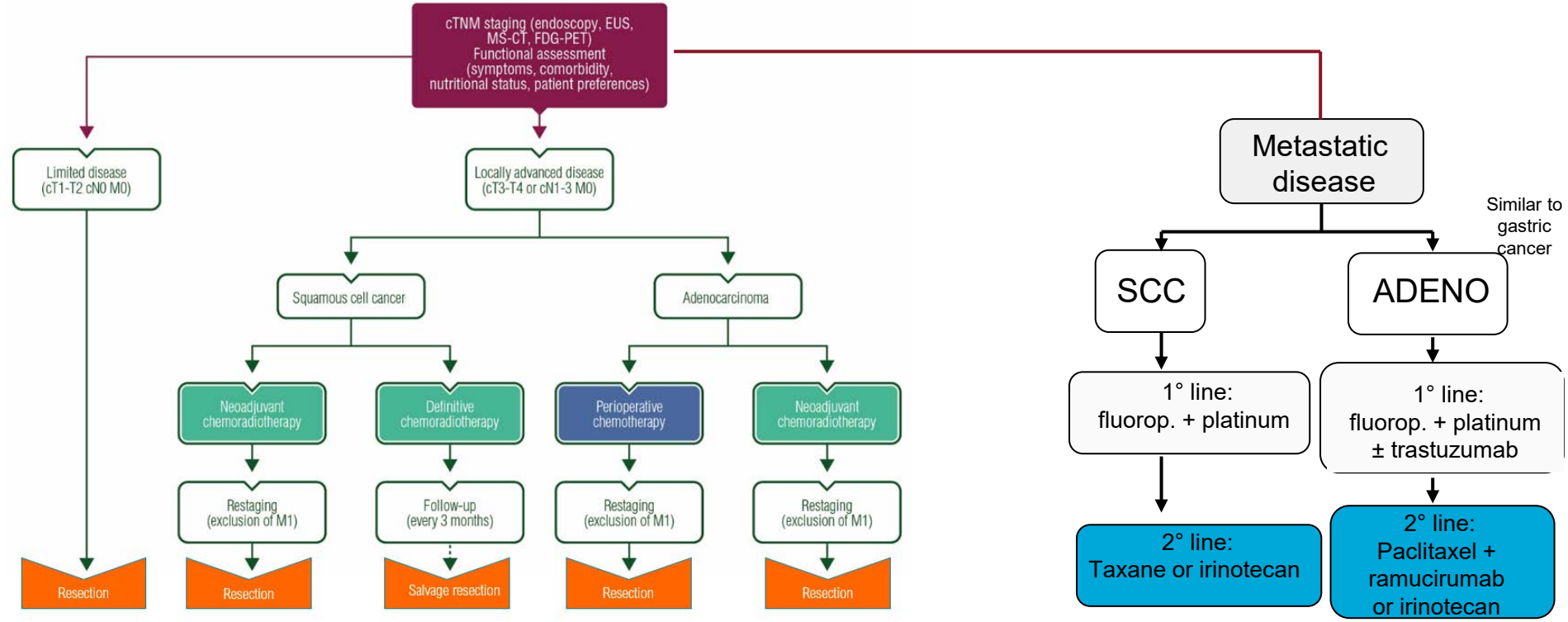
- Overal RR: 69% (53–82)
  CR: 13%
- 24-month PFS rate: 74%
- 24-month OS rate: 79%

1. Andre T, Van Cutsem E et al. *N Engl J Med* 2020;383(23):2207-2218. 2. Adapted from Lenz H, Van Cutsem E et al. *J Clin Oncol* 2020;38:15_suppl 4040.
3. https://www.ema.europa.eu/en/news/meeting-highlights-committee-medicinal-products-human-use-chmp-17-20-may-2021

Oesophageal Cancer
ESMO guidelines and JSMO/ESMO guidelines

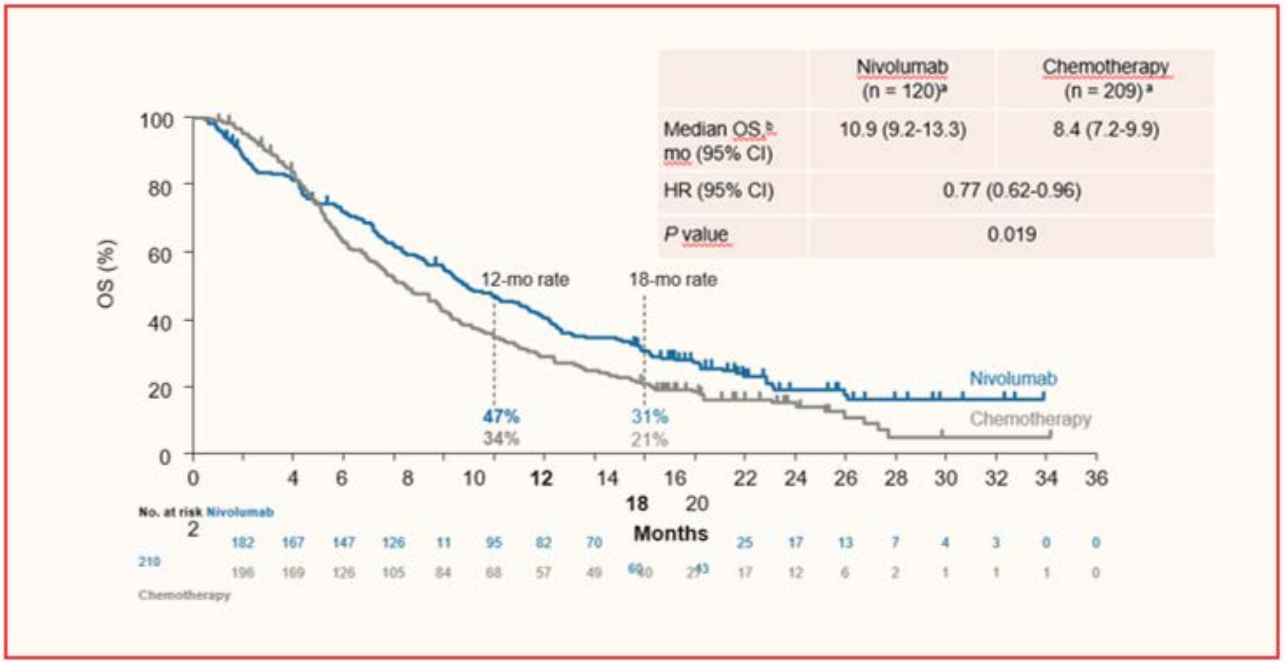
Oesophageal Cancer: ESMO Clinical Practice Guidelines[1]

Pan-Asian adapted ESMO Clinical Practice Guidelines[2]



1. Lordick F et al. *Ann Oncol* 2016;27(suppl 5):v50-v57. 2. Adapted from Muro K, Van Cutsem E et al. Published in 2018 – *Ann Oncol* 2019; 30:19–33.

First approved checkpoint inhibitor in Oesophageal Cancer nivolumab versus docetaxel or paclitaxel in patients with ESCC



ATTRACTION-3

Although the benefit in CPS<1 (OS HR = 0.84 (95% CI 0.62, 1.14)) patients was lower in magnitude than in PD-L1 CPS≥1 patients (OS HR = 0.69 (95% CI: 0.51, 0.94)), nivolumab was approved in the EU for 2L esophageal cancer.

Adapted from Kato K et al. *Lancet Oncol* 2019;20(11):1506-1517.

KN590: randomized, open-label, phase 3 study in 1st line esophageal cancer

Key eligibility criteria
- Locally advanced unresectable or metastatic EAC or ESCC or advanced/metastatic EGJ Siewert type 1 adenocarcinoma
- Treatment naive
- ECOG PS 0 or 1
- Measurable disease (RECIST v1.1)

Stratification factors
- Asia vs Non-Asia region
- ESCC vs EAC
- ECOG PS 0 vs 1

R 1:1

Pembrolizumab 200 mg IV Q3W for ≤ 35 cycles
+
Chemotherapy
5-FU 800 mg/m² IV for days 1-5 Q3W for ≤ 35 cycles
+ Cisplatin 80 mg/m² IV Q3W for ≤ 6 cycles

Placebo[a]
+
Chemotherapy
5-FU 800 mg/m² IV for days 1-5 Q3W for ≤ 35 cycles
+ Cisplatin 80 mg/m² IV Q3W for ≤ 6 cycles

- Dual primary endpoints: OS and PFS (RECIST v1.1, investigator)
- Secondary endpoint: ORR (RECIST v1.1, investigator)
- Tumor response assessed at week 9 then Q9W (RECIST v1.1, investigator)

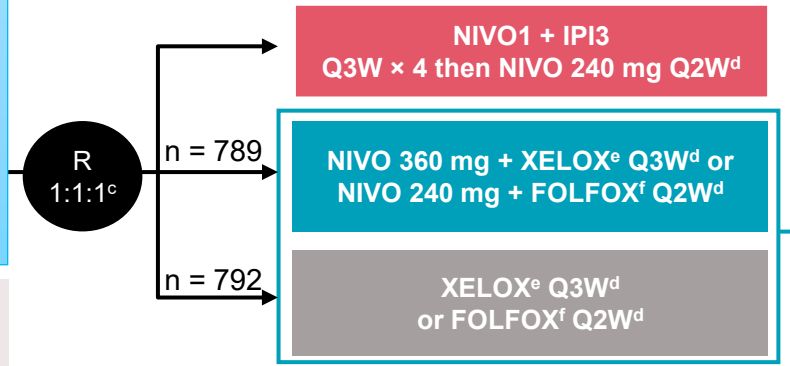
[a]Saline IV Q3W for ≤35 cycles. All treatments were continued for the specified number of cycles or until disease progression, intolerable toxicity, withdrawal of consent, or physician decision; EAC, esophageal adenocarcinoma; EGJ, esophagogastric junction, ESCC, esophageal squamous cell carcinoma.

Adapted from Kato K et al. Oral presentation at ESMO 2020. Abstract LBA8.

CheckMate 649: randomized, open-label, phase 3 study in 1st line gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma

Key eligibility criteria
- Previously untreated, unresectable, advanced or metastatic gastric/GEJ/ esophageal adenocarcinoma
- No known HER2-positive status
- ECOG PS 0–1

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (Asia vs United States/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (XELOX vs FOLFOX)



N = 1581, including 955 patients (60%) with PD-L1 CPS ≥ 5

Dual primary endpoints:
- OS and PFS[g] (PD-L1 CPS ≥ 5)

Secondary endpoints:
- OS (PD-L1 CPS ≥ 1 or all randomized)
- OS (PD-L1 CPS ≥ 10)
- PFS[g] (PD-L1 CPS ≥ 10, 1, or all randomized)
- ORR[g]

At data cutoff (May 27, 2020), the minimum follow-up was 12.1 months[h]

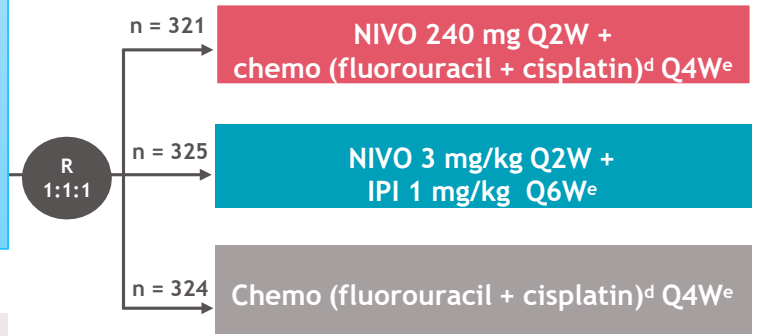
[a]ClinicalTrials.gov number, NCT02872116; [b]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c]After NIVO + chemo arm was added and before new patient enrollment in the NIVO1+IPI3 group was closed; [d]Until documented disease progression (unless consented to treatment beyond progression for NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given for a maximum of 2 years; [e]Oxaliplatin 130 mg/m^2 IV (day 1) and capecitabine 1000 mg/m^2 orally twice daily (days 1–14); [f]Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 IV (day 1) and FU 1200 mg/m^2 IV daily (days 1–2); [g]BICR assessed; [h]Time from concurrent randomization of the last patient to NIVO + chemo vs chemo to data cutoff.

Adapted from Moehler M et al. Oral presentation at ASCO 2021. Abstract 4002.

CheckMate 648: randomized, open-label, phase 3 study in 1st line for advanced esophageal squamous cell carcinoma

Key eligibility criteria
- Unresectable advanced, recurrent or metastatic ESCC
- ECOG PS 0-1
- No prior systemic treatment for advanced disease
- Measurable disease

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (East Asia[c] vs rest of Asia vs ROW)
- ECOG PS (0 vs 1)
- Number of organs with metastases (≤ 1 vs ≥ 2)



Primary endpoints:
- OS and PFS[f] (tumor cell PD-L1 ≥ 1%)

Secondary endpoints:
- OS and PFS[f] (all randomized)
- ORR[f] (tumor cell PD-L1 ≥ 1% and all randomized)

At data cutoff (January 18, 2021), the minimum follow-up was 12.9 months[g]

[a]ClinicalTrials.gov. NCT03143153; [b]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c]East Asia includes patients from Japan, Korea, and Taiwan; [d]Fluorouracil 800 mg/m^2 IV daily (days 1-5) and cisplatin 80 mg/m^2 IV (day 1); [e]Until documented disease progression (unless consented to treatment beyond progression for NIVO + IPI or NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given alone or in combination with IPI for a maximum of 2 years; [f]Per blinded independent central review (BICR); [g]Time from last patient randomized to clinical data cutoff.

Adapted from Chau I et al. Oral presentation at ASCO 2021. Abstract LBA4001.

ESMO 2020 & ASCO 2021 in Upper GI Cancer: Practice Changing Data in Unmet Need Populations

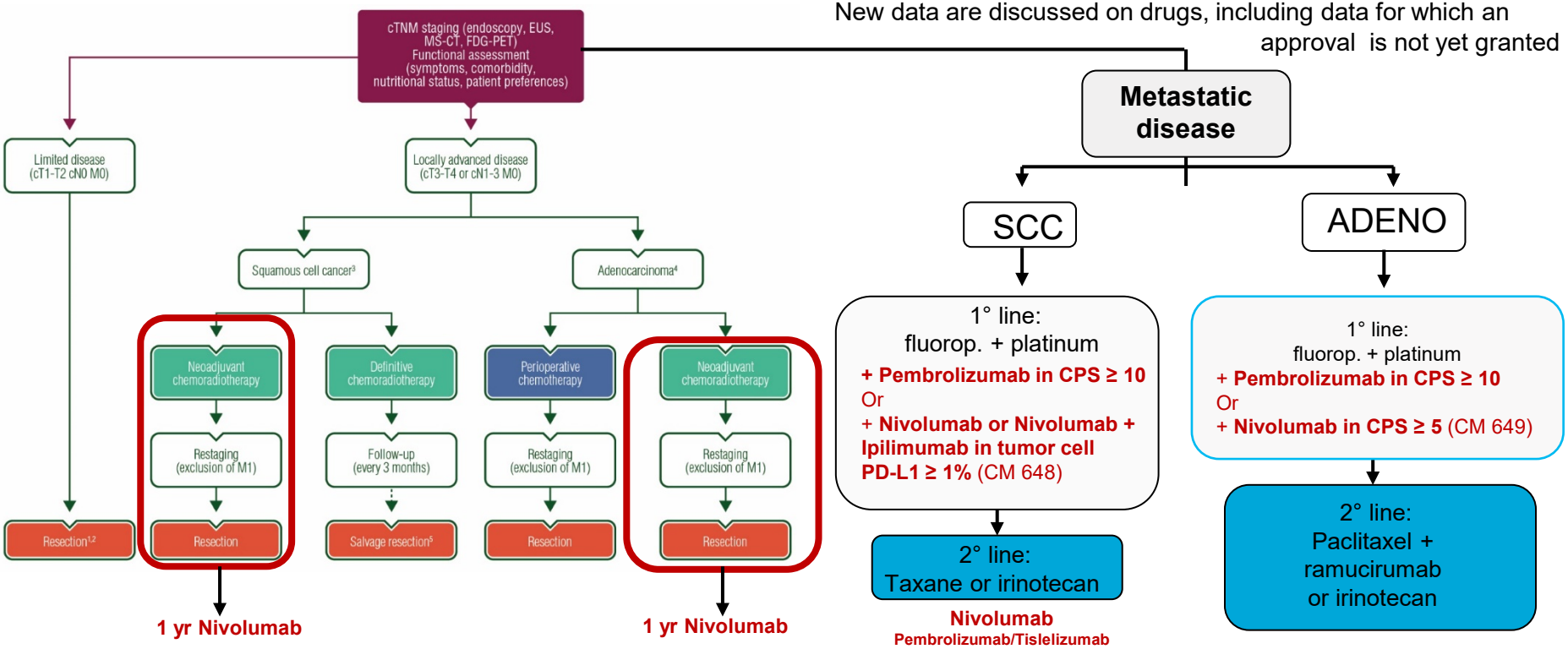
POSITIVE TRIALS

- Metastatic (1° line) oesophageal cancer (SCC & adenocarcinoma):
  - **KEYNOTE 590[1]:** Pembrolizumab + chemotherapy vs chemotherapy in PD-L1 CPS ≥ 10
- Metastatic (1° line) oesophageal cancer (SCC):
  - **CheckMate 648[2]:** Nivolumab + chemotherapy or Nivolumab + Ipililumab vs chemotherapy in PDL ≥ 1% (and all comers)
  - **ESCORT-1[3]:** Camrelizumab + chemotherapy vs chemotherapy
- Metastatic (1° line) gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma
  - **CheckMate 649[4]:** Nivolumab + chemotherapy vs chemotherapy in PD-L1 CPS ≥ 5
- Resected esophageal or gastroesophageal junction cancer (SCC & adenocarcinoma) following neoadjuvant chemoradiotherapy:
  - **CheckMate 577[5]:** nivolumab vs placebo

1. Kato et al. Oral presentation at the ESMO 2020. LBA8. 2. Chau I et al. Oral presentation at ASCO 2021. Abstract LBA4001. 3. Rui-hua X et al. Oral presentation at ASCO 2021. Abstract 4000. 4. Janjigian Y et al. *Lancet* 2021. Published Online June 5, 2021, https://doi.org/10.1016/S0140-6736(21)00797-2. 5. Kelly R, Van Cutsem E et al. *N Engl J Med* 2021;384:1191-203.

Esophageal Cancer
ESMO guidelines and JSMO/ESMO guidelines
updates in 2021 (personal opinion EVC based on evidence)

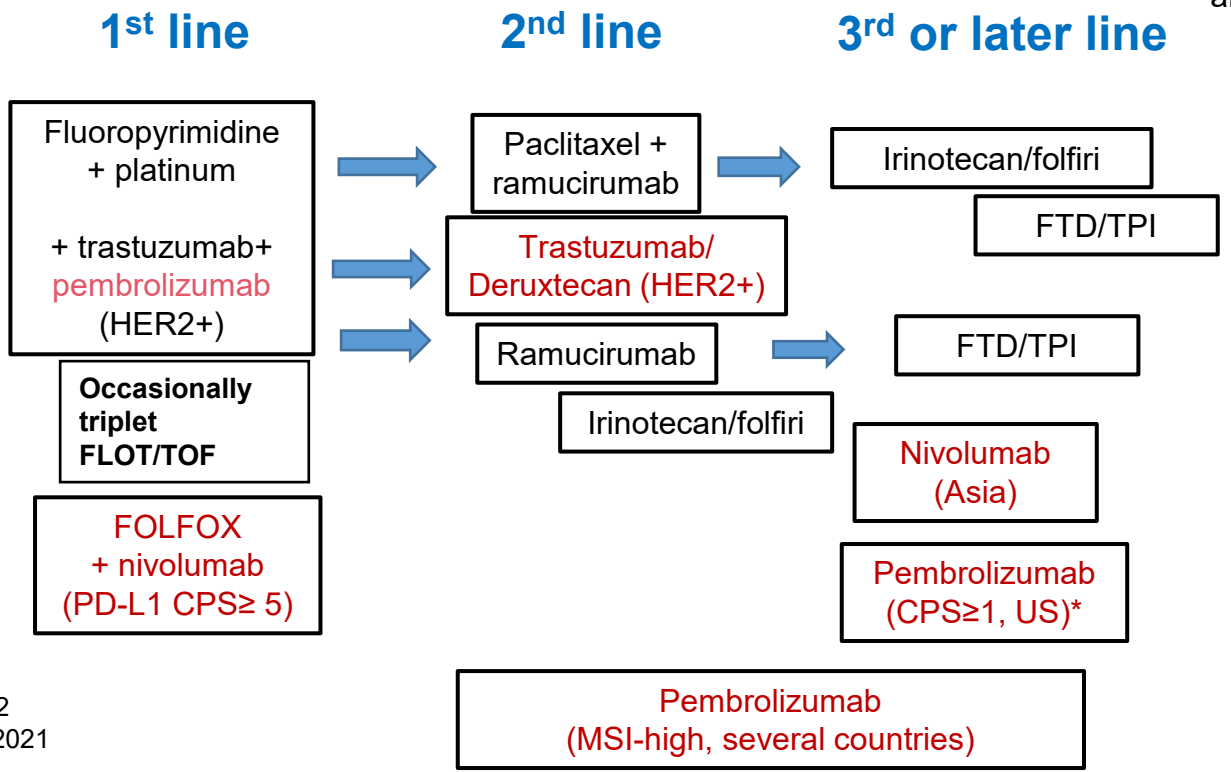
New data are discussed on drugs, including data for which an approval is not yet granted



1. Lordick F et al. *Ann Oncol* . 16;27(suppl 5):v50-v57. 2 **MODIFIED** by Eric Van Cutsem from Muro K, Van Cutsem E et al. Published in 2018 – *Ann Oncol* 2019;30:19–33.

Updated algorithm for metastatic gastric cancer in 2021
(personal opinion EVC based on evidence)

New data are discussed on drugs, including data for which an approval is not yet granted



FTD/TPI = TAS102
* Withdrawn May 2021

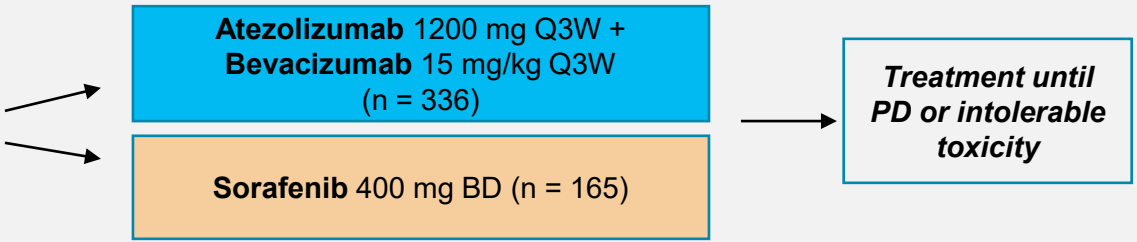
MODIFIED by Eric Van Cutsem from Muro K, Van Cutsem E et al. JSMO-ESMO guidelines. *Ann Onc* 2019;30(1):19-33.

IMbrave150: Atezolizumab + Bevacizumab vs Sorafenib for First-line Treatment of Advanced HCC

- Multicenter, randomized, open-label pase III trial
  - GO30140: randomized phase 1b study showed potential benefit of atezolizumab + bevacizumab for patients with advanced HCC (ORR 36%)

Patients with locally advanced or metastatic and/or unresectable HCC with no previous systematic therapy, Child-Pugh A, and ECOG PS ≤ 1* (N=501)

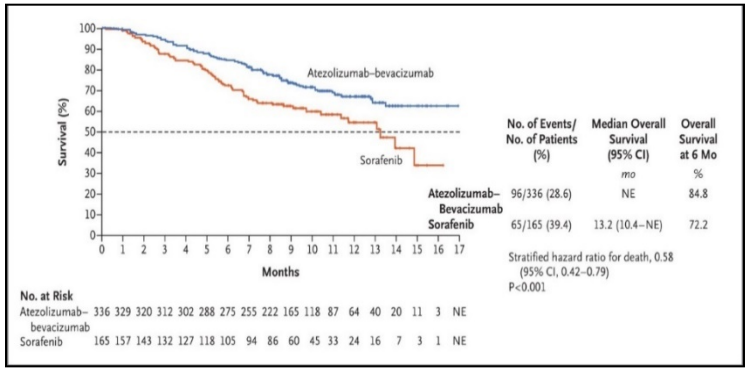
- **Coprimary endpoints: OS and PFS**

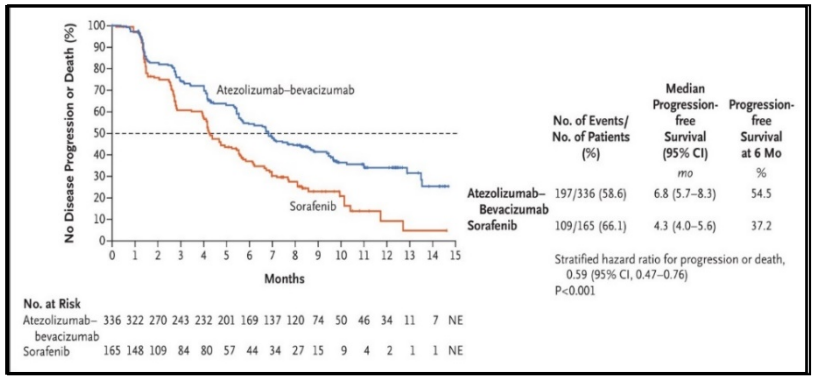


*Trial included subgroups of high-risk patients excluded from other contemporary phase III trials: ≈ 40% had macrovascular invasion; specifically included patients with 50% hepatic involvement or main portal vein invasion or invasion of the portal vein branch contralateral to the primarily involved lobe.

Adapted from Finn RS et al. *N Engl J Med* 2020;382:1894-1905.

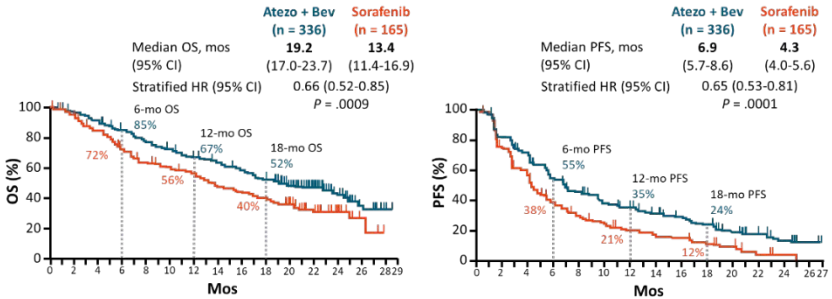
IMbrave150: Atezolizumab + Bevacizumab vs Sorafenib for First-line Treatment of Advanced HCC





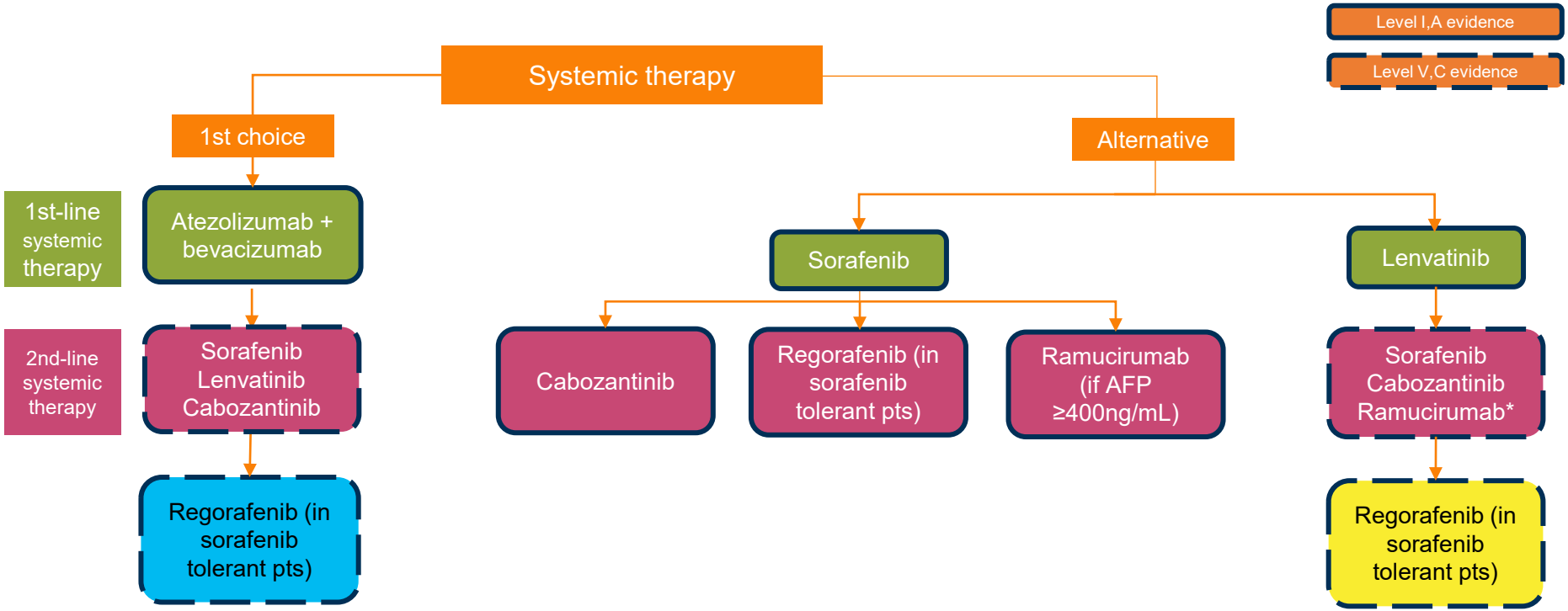
Updated analysis

- Primary analysis OS/PFS HR: 0.58/0.59 (median f/u 8.6 mos)



1. Finn RS et al. *N Engl J Med* 2020;382(20):1894-1905. 2. Finn RS et al. Abstract presented at the ASCO GI; Abstract 267.

Current HCC treatment guidelines
ILCA 2020



AFP, alpha-fetoprotein; ILCA, The International Liver Cancer Association; pts, patients.
*If AFP ≥400ng/mL

ILCA Systemic Therapy Guidance. November 2020. Available at https://ilca-online.org/wp-content/uploads/2020/06/Systemic-therapy-guidelines-V1.2.pdf. Accessed May 2021.

Summary

- Very important practice changing data in 2020/2021 with checkpoint inhibitors in:
  - Esophageal cancer
  - Gastric cancer
  - Hepatocellular cancer

  Leading to new treatment algorithms
- This is a fast-moving field with new data expected
- Optimal selection of patients is even more crucial

ImmunoScience Academy

Partnering for Education & Optimizing Treatment in ImmunoScience

Importance of biomarkers in GI tumors

P. Pauwels

(UZA, UA)

Kennis / Ervaring / Zorg

Programmed death ligand IHC scoring

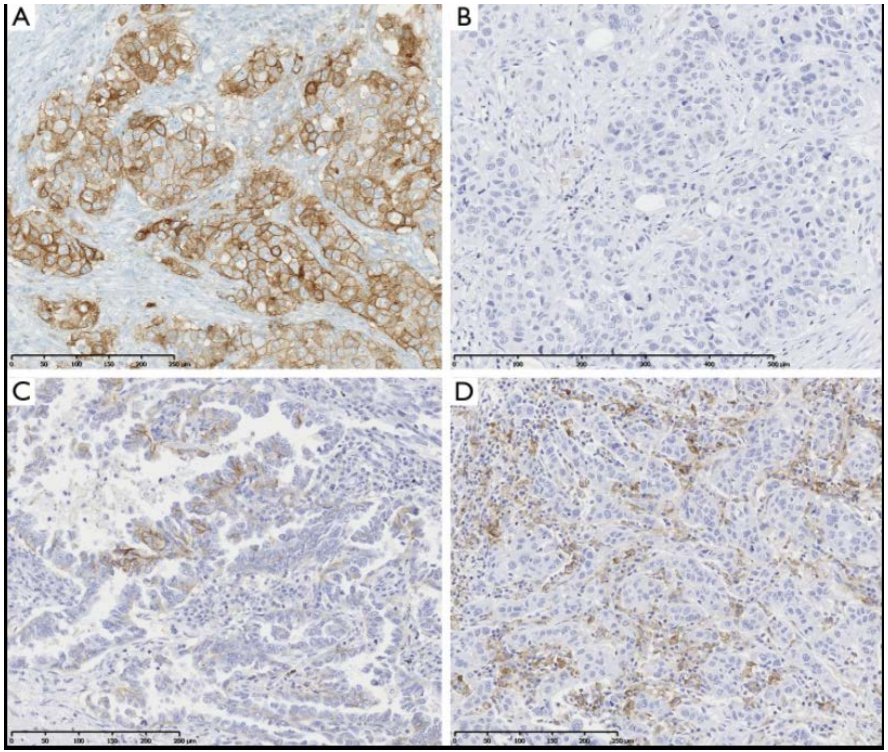
Tumor proportion score (TPS): algorithm for assessment of PD-L1 expression on tumor cells

$$\text{TPS}\ (\%) = \frac{\textit{Positive tumour cells}}{\textit{Total number of tumour cells}} \times 100$$

Combined positive score (CPS): algorithm for assessment of PD-L1 expression on both tumor and immune cells

$$\mathrm{CPS} = \frac{\begin{array}{c}\textit{Positive tumour cells}+\\ \textit{Positive intratumoural immune cells}\end{array}}{\textit{Total number of tumour cells}} \times 100$$

IHC to assess staining pattern of PD-L1 in tumor and immune cells



IHC: Immuno Histochemical Staining

Lantuejoul S et al. *J Thorac Dis* 2019;(Suppl 1):S89-S101

Key messages

- Across multiple tumor types, response to immunotherapy is seen in patients with high expression of PD-L1, especially when PD-L1 is expressed in the immune cells[1]
- PD-L1 expression varies across tumor types, and thresholds and scoring systems to determine PD-L1 positivity can vary between antibody assays[2-3]
- PD-L1 expression may be more prevalent on immune cells than tumor cells in certain cancers, such as melanoma, gastric, and colon[1]
- Clinical utility of PD-L1 have been evaluated in several GI clinical trials, PD-L1 scoring method varies between the clinical trials of different immunotherapies[4-7]

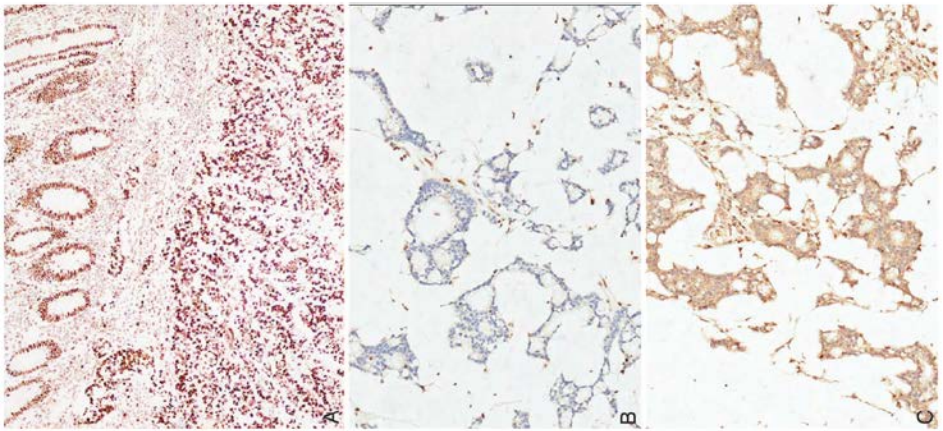
1. Herbst RS et al. *Nature* 2014;515:563–567. 2. Krigsfeld G et al. Poster presentation at the 108th American Association for Cancer Research Annual Meeting; April 1–5, 2017; Washington, DC, USA. Abstract CT143. 3. Udall M et al. *Diagn Pathol* 2018;13:12.2. 4. Moehler M et al. Oral presentation at the European Society for Medical Oncology Annual Meeting (Virtual); September 13–21, 2020. Abstract 3047; 5. Lei M et al. Oral presentation at the 110th American Association for Cancer Research Annual Meeting; March 29–April 3, 2019; Atlanta, GA, USA. Abstract 2673. 6. Kelly RJ et al. Oral presentation at the European Society for Medical Oncology Annual Meeting (Virtual); September 19–21, 2020. Abstract 2968. 7. Boku N et al. Oral presentation at the European Society for Medical Oncology Annual Meeting (Virtual); September 19–21, 2020. Abstract LBA7.

MSI/MMR testing

MSI/MMR: Microsatellite instability/mismatch repair

MMR: DNA repair pathway that identifies and corrects DNA mismatches

dMMR results from loss of expression of 1 or more of the proteins MLH1, MSH2, MSH6, or PMS2 involved in the MMR process



Presence or not of mutant markers to determine MSI-H or microsatellite stable (MSS)

The Journal of Molecular Diagnostics, Vol. 22, No. 3, March 2020

ELSEVIER

The Journal of Molecular Diagnostics

jmd.amjpathol.org

Clinical Performance of the Idylla MSI Test for a Rapid Assessment of the DNA Microsatellite Status in Human Colorectal Cancer

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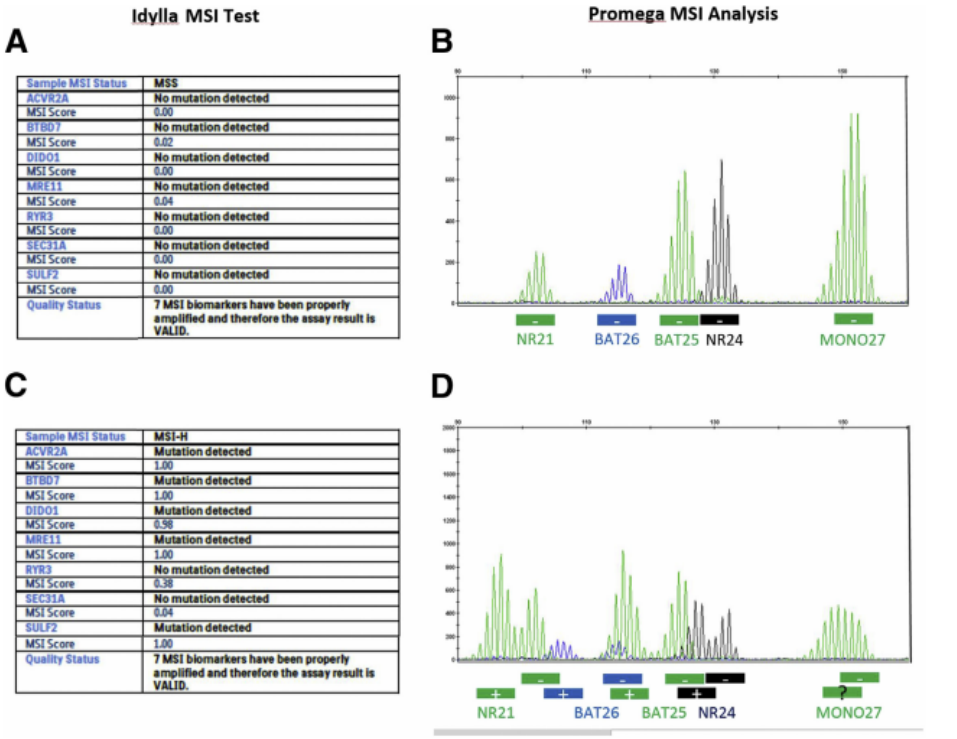


Idylla MSI Test

A

Sample MSI Status	MSS
ACVR2A	No mutation detected
MSI Score	0.00
BTBD7	No mutation detected
MSI Score	0.02
DIDO1	No mutation detected
MSI Score	0.00
MRE11	No mutation detected
MSI Score	0.04
RYR3	No mutation detected
MSI Score	0.00
SEC31A	No mutation detected
MSI Score	0.00
SULF2	No mutation detected
MSI Score	0.00
Quality Status	7 MSI biomarkers have been properly amplified and therefore the assay result is VALID.

Promega MSI Analysis

B

NR21 BAT26 BAT25 NR24 MONO27

C

Sample MSI Status	MSI-H
ACVR2A	Mutation detected
MSI Score	1.00
BTBD7	Mutation detected
MSI Score	1.00
DIDO1	Mutation detected
MSI Score	0.98
MRE11	Mutation detected
MSI Score	1.00
RYR3	No mutation detected
MSI Score	0.38
SEC31A	No mutation detected
MSI Score	0.04
SULF2	Mutation detected
MSI Score	1.00
Quality Status	7 MSI biomarkers have been properly amplified and therefore the assay result is VALID.

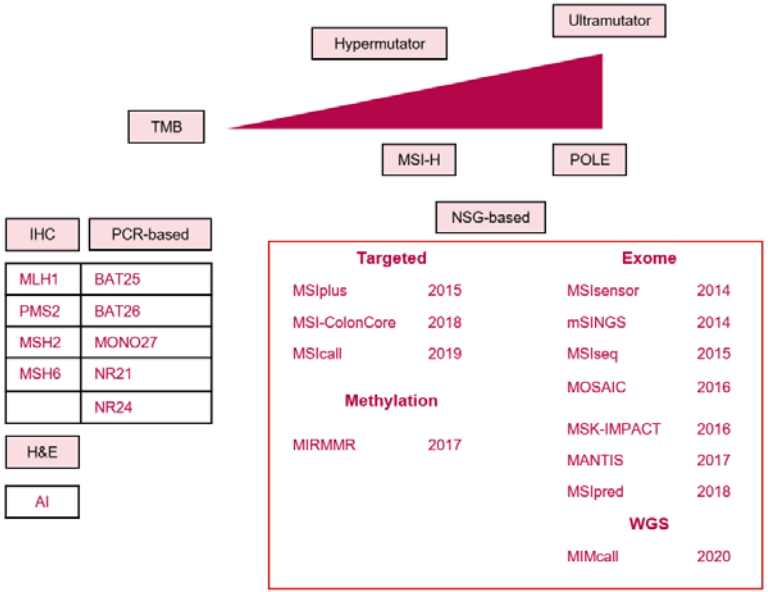
D

NR21 BAT26 BAT25 NR24 MONO27

Figure 1 Readout from the Idylla MSI test and Promega MSI analysis for a microsatellite stable (MSS) result (**A** and **B**) and a microsatellite instability—high (MSI-H) result (**C** and **D**).

Zwaenepoel K, …. Pauwels P et al. *J Mol Diagn*. 2020 Mar;22(3):386-395.

MSI status is evaluated by IHC, PCR-based assays, and NGS-based techniques



Yamamoto H eta al. *Arch Toxicol* 2020;94(10):3349-3357.

Key messages

- MMR system is a DNA repair pathway that identifies and corrects DNA mismatches dMMR results from loss of expression of 1 or more of the proteins involved in the MMR process. dMMR can cause MSI[1,2]
- MSI-H, indicative of dMMR, is found across several tumor types[3,4]
- MSI-H/dMMR tumors are highly immunogenic, which may make these tumors susceptible to immune checkpoint inhibitors[5]
- MSI-H is reported to be around 15%[6]
- Pathologic staging is a key determinant of CRC prognosis and treatment. However, stage-independent outcome variability in patients with CRC supports the implementation of robust prognostic and predictive markers, such as MSI-H and dMMR[7]
- dMMR/MSI can be asssed by IHC, PCR and NGS[8-10]
- Clinical utility of MSI-H have been evaluated in several GI clinical trials[11-14]

1. Cortes-Ciriano I et al. *Nat Commun* 2017;8:15180. 2. Buecher B et al. *Dig Liver Dis* 2013;45:441–449. 3. Cortes-Ciriano I et al. *Nat Commun* 2017;8:15180. 4. Lee V et al. *Oncologist* 2016;21:1200–1211. 5. Llosa NJ et al. *Cancer Discov* 2015;5:43–51. 6. Amonkar M et al. *J Clin Oncol* 2019;37(suppl 15):e15074. 7. Sargent DJ et al. *J Clin Oncol* 2010;28:3219–3226. 8. Kawakami H et al. *Curr Treat Options Oncol* 2015;16:30. 9. Kawakami H et al. C*urr Treat Options Oncol* 2015;16:30. 10. Luchini C et al. *Ann Oncol* 2019;30:1232–1243. 11. Overman MJ et al. *Lancet Oncol* 2017;18:1182–1191. 12. 1. Janjigian YY et al. *J Clin Oncol* 2018;36:2836–2844. 13. Andre T et al. *J Clin Oncol* 2020;38:(suppl 18). Abstract LBA4. 14. Le DT et al. *J Clin Oncol*. 2020;38:11–19.