Clinical trials and cases

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Disclosures

- Consulting Fees: QED therapeutics, Natera

IO therapies in GI cancers

- Emerging role in some GI malignancies.
- Ongoing need to making these treatments work in majority of GI cancers.
- Most trials include a backbone of PD1/PDL1 therapy.

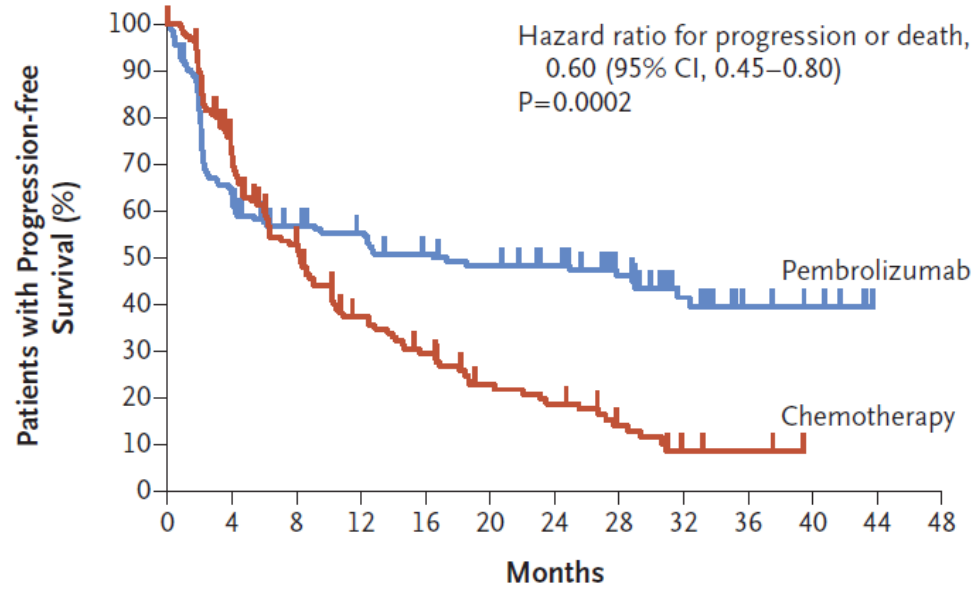
Ott, P.A., Hodi, F.S., Kaufman, H.L. *et al.* Combination immunotherapy: a road map. *j. immunotherapy cancer* **5,** 16 (2017). https://doi.org/10.1186/s40425-017-0218-5

Approved IO therapies, colorectal cancer

Only approved for use in dMMR/MSI-H cancer patients

- Pembrolizumab (first-line metastatic/unresectable).
- Nivolumab + Ipilimumab (second-line, after chemotherapy in the metastatic setting).

Keynote-177: Results



No. at Risk

Pembrolizumab	153	96	77	72	64	60	55	37	20	7	5	0	0
Chemotherapy	154	100	68	43	33	22	18	11	4	3	0	0	0

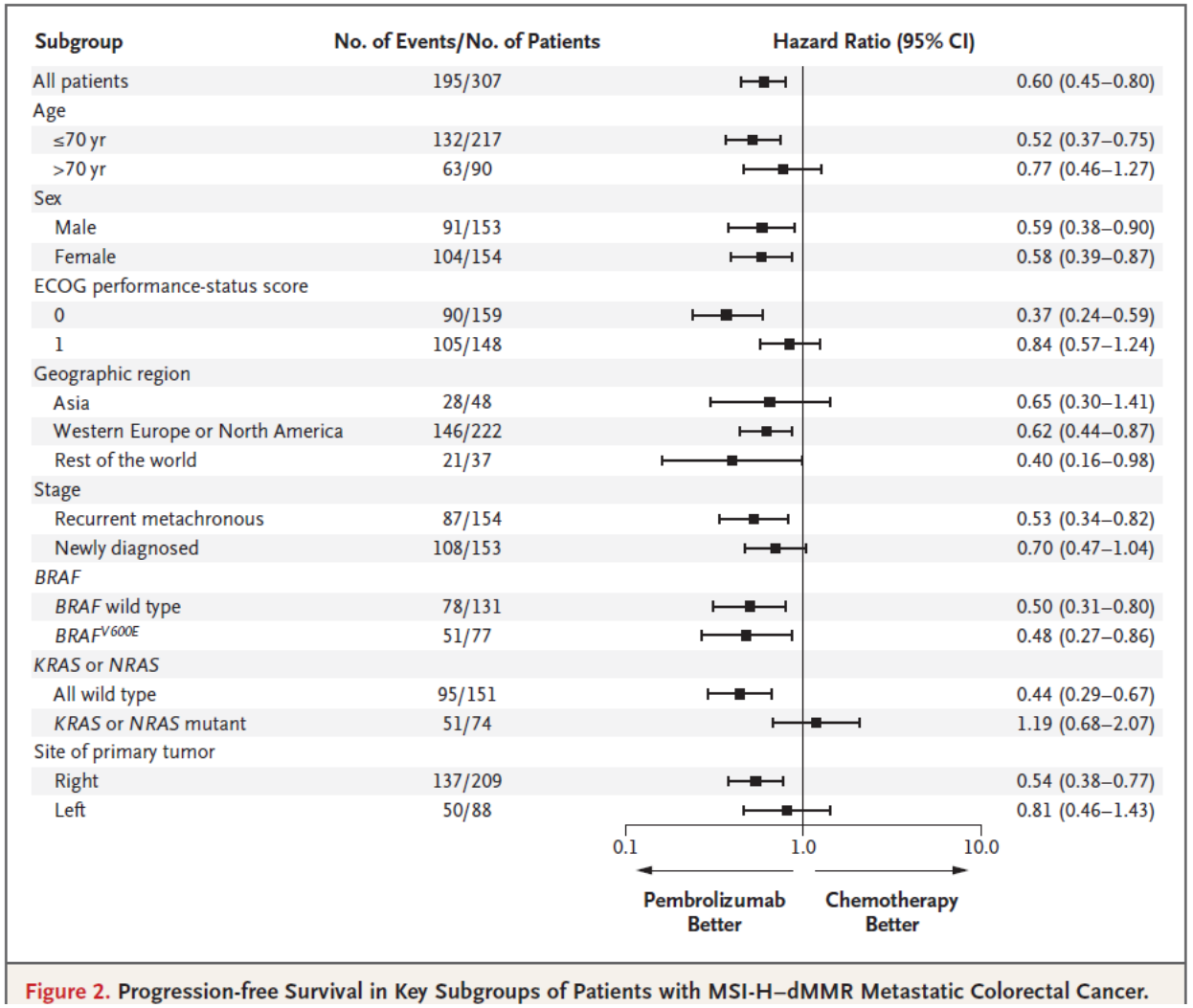
Figure 1. Progression-free Survival in Patients with MSI-H–dMMR Metastatic Colorectal Cancer.

Table 2. Antitumor Activity in the Intention-to-Treat Population.

Variable	Pembrolizumab (N=153)	Chemotherapy (N=154)
Overall response*		
No. of patients	67	51
% (95% CI)	43.8 (35.8 to 52.0)	33.1 (25.8 to 41.1)
Best response — no. (%)†		
Complete response	17 (11.1)	6 (3.9)
Partial response	50 (32.7)	45 (29.2)
Stable disease	32 (20.9)	65 (42.2)
Progressive disease	45 (29.4)	19 (12.3)
Could not be evaluated or no assessment made‡	9 (5.9)	19 (12.3)
Median time to response (range) — mo	2.2 (1.8 to 18.8)	2.1 (1.7 to 24.9)
Median duration of response (range) — mo§	NR (2.3+ to 41.4+)	10.6 (2.8 to 37.5+)
Response duration of ≥24 months — %§	82.6	35.3

Andre, T, et al. NEJM. 2020;383:2207-18.

Keynote-177: Results



Subgroup	No. of Events/No. of Patients	Hazard Ratio (95% CI)
All patients	195/307	0.60 (0.45–0.80)
Age		
≤70 yr	132/217	0.52 (0.37–0.75)
>70 yr	63/90	0.77 (0.46–1.27)
Sex		
Male	91/153	0.59 (0.38–0.90)
Female	104/154	0.58 (0.39–0.87)
ECOG performance-status score		
0	90/159	0.37 (0.24–0.59)
1	105/148	0.84 (0.57–1.24)
Geographic region		
Asia	28/48	0.65 (0.30–1.41)
Western Europe or North America	146/222	0.62 (0.44–0.87)
Rest of the world	21/37	0.40 (0.16–0.98)
Stage		
Recurrent metachronous	87/154	0.53 (0.34–0.82)
Newly diagnosed	108/153	0.70 (0.47–1.04)
BRAF		
BRAF wild type	78/131	0.50 (0.31–0.80)
$BRAF^{V600E}$	51/77	0.48 (0.27–0.86)
KRAS or *NRAS*		
All wild type	95/151	0.44 (0.29–0.67)
KRAS or *NRAS* mutant	51/74	1.19 (0.68–2.07)
Site of primary tumor		
Right	137/209	0.54 (0.38–0.77)
Left	50/88	0.81 (0.46–1.43)

Figure 2. Progression-free Survival in Key Subgroups of Patients with MSI-H–dMMR Metastatic Colorectal Cancer.

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- **Need for therapies for the 95% of MSS patients.**

Case 1: 63 yo F with appendiceal cancer

- 2016: Diagnosed with low-grade appendiceal adenocarcinoma. Completes cytoreductive surgery/HIPEC with mitomycin-C.

- Jan 2018: Develops peritoneal recurrence. KRAS G12D mutated, microsatellite stable disease, TMB-low, 5 mut/Mb.

- What systemic therapy? Is repeat surgery a consideration?

Case 1: 63 yo F with appendiceal cancer

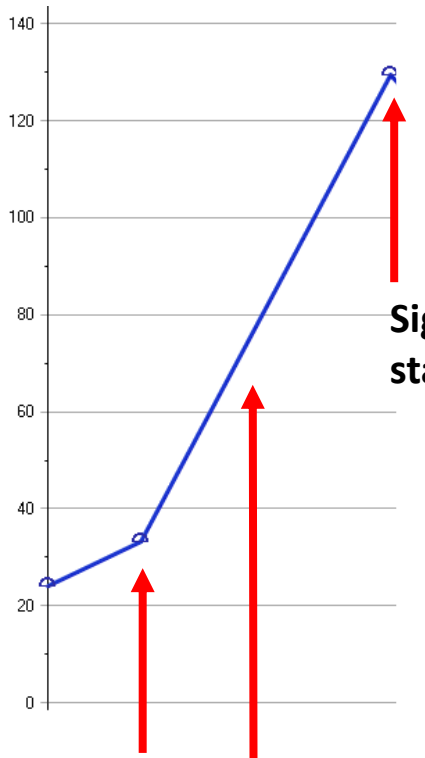
- Jan 2018: Starts capecitabine monotherapy.
- Aug 2018: CT shows mild progression of disease.
- 2019: Begins to require therapeutic paracenteses, requiring dose-reductions in capecitabine due to cytopenias.

- Fall 2019: Enrolled on NCT02963831: A Phase 1/2 Study to Investigate the Safety, Biologic and Anti-tumor Activity of ONCOS-102 in Combination With Durvalumab in Subjects With Advanced Peritoneal Malignancies.

Case 1: 63 yo F with appendiceal cancer

- November 2019: Starts intraperitoneal (IP) treatments, discontinued early due to inflammatory reaction around catheter.
- After recovery, continued on IV durvalumab (anti-PD-L1) on trial.

Case 1: CEA response on trial

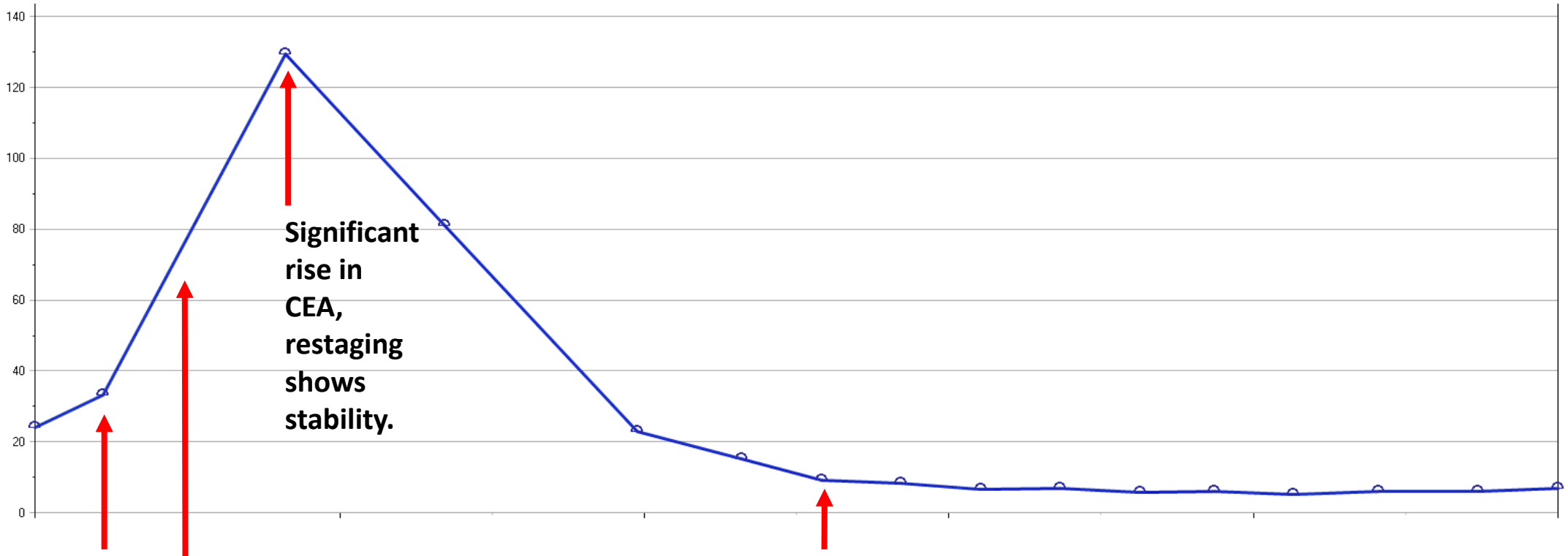


Significant rise in CEA, restaging shows stability.

1st Intra-peritoneal treatment

Intraperitoneal treatments discontinued due to toxicity

Case 1: CEA response on trial

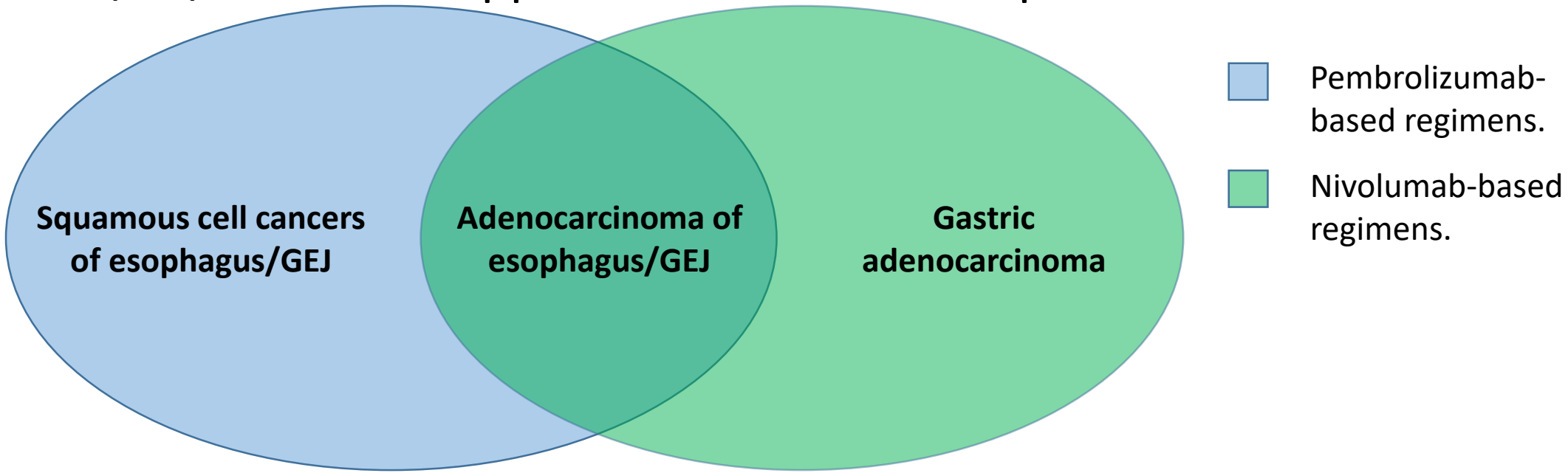


Case 1: 63 yo F with appendiceal cancer

- Remains on treatment with ongoing response.

Approved IO therapies, upper GI

- Recent FDA approvals for broader use of frontline IO therapies in esophageal, GEJ, and gastric cancers.
  - 3/22/2021: FDA approves 5FU + platinum + pembrolizumab*.
  - 4/16/2021: FDA approves mFOLFOX or CapeOx + nivolumab*.



* Approvals do not directly overlap. This Venn diagram is my attempt to show how the use these regimens.

Case 2: 41 yo F with gastric adenocarcinoma

- July 2018: Diagnosed with localized gastric cancer.
- July – Sept 2018: Completes 4 cycles of FLOT (5FU, leucovorin, oxaliplatin, docetaxel) chemotherapy. Restaging shows interval response to therapy.
- October 2018: Total gastrectomy, ypT4bN1 (2/27 LN), R0, G3 tumor.

- December 2018: Restarts post-op mFOLFOX (docetaxel held due to slow recovery post-operatively, difficulty with getting adequate nutrition). Only completes 1 cycle prior to pursuing surveillance.

Case 2: 41 yo F with gastric adenocarcinoma

- March 2019: Restaging shows ‘interval increase in ill-defined soft tissue along the common and proper hepatic arteries consistent with recurrent disease.’
- IHC testing of tumor demonstrates ‘loss of expression of MLH1 and PMS2 in tumor cells… This is consistent with a microsatellite unstable tumor.’

- What is the next treatment option?

Case 2: 41 yo F with gastric adenocarcinoma

- Treatment option(s)
  - Today, could consider chemotherapy + IO, IO monotherapy, or local therapies (radiation).

Case 2: 41 yo F with gastric adenocarcinoma

- For this patient, decided to start with local therapy (chemoradiation) followed by immunotherapy (pembrolizumab).

- April 2019: Started radiation with infusional 5FU, discontinued early due to poor tolerance. Subsequently started on pembrolizumab.

- April 2021: Most recent follow-up, remains on therapy with ‘Unchanged soft tissue along the posterior aspect of the common hepatic artery and right aspect of the celiac trunk.’

IO clincial trials at the University of Virginia

- Pancreatic cancer:
  - NCT03611556: Phase 2, randomized trial of frontline chemotherapy +/- immunotherapy in patients with metastatic disease.
  - NCT03872206: Phase 1/2a trial of a bispecific antibody to CD3/mesothelin in patients who have failed standard therapy.
  - NCT03269526: Phase 2 trial of bispecific antibody armed T-Cells.

- Colorectal cancer:
  - NCT04068610: Phase 2, randomized trial of frontline chemotherapy +/- immunotherapy in patients with metastatic disease.
  - NCT04381650: Phase 1b/2 study of TAK-981 (sumo-inhibitor) + pembrolizumab in 3/4th line.

IO clincial trials at the University of Virginia

- Cholangiocarcinoma:
  - NCT04677504: A Phase 2 frontline study of atezolizumab + gemcitabine + cisplatin +/- bevacizumab in advanced biliary tract cancer.

- Esophageal/GE junctional adenocarcinoma:
  - NCT03604991: A Phase 2/3 Study of Peri-operative Nivolumab and Ipilimumab in Patients with Locoregional Esophageal and Gastroesophageal Junction Adenocarcinoma.

Thank you

- Thank you for your attention and participation in this workshop.