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Supported by an Independent Educational Grant from BAYER

CANCER OF THE LIVER, SMALL INTESTINE AND PANCREAS TRACT

BY DR. THOMAS WINDER, ZURICH, SWITZERLAND

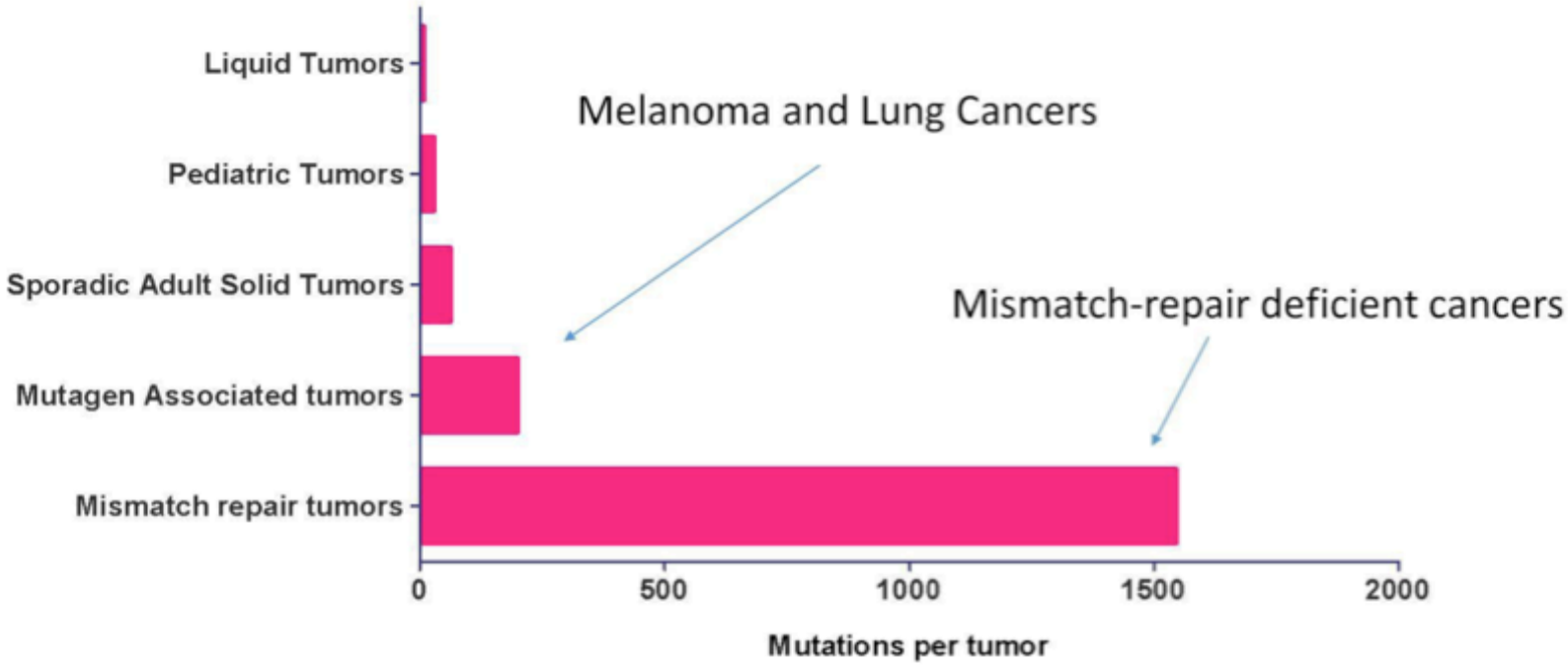
ASCO GI 2016, JANUARY 21ST -23RD 2016

Meeting summary

PD-1 blockade in mismatch repair deficient non-colorectal gastrointestinal cancers

Dung T. Le et al.

MUTATIONS PER TUMOR



PD-1 blockade in mismatch repair deficient non-colorectal gastrointestinal cancers.
Dung T. Le et al.

STUDY DESIGN

Colorectal Cancers		Non-Colorectal Cancers
Cohort A **Deficient in Mismatch Repair (n=25)**	Cohort B **Proficient in Mismatch Repair (n=25)**	Cohort C **Deficient in Mismatch Repair (n=21)**

- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks
- Mismatch repair testing was performed locally using standard IHC for MMR deficiency or PCR-based test for microsatellite instability

OBJECTIVE RESPONSES

Type of Response-no (%)	MMR-deficient GI non-CRC n=17
Completed response	4 (24)
Partial Response	4 (24)
Stable Disease (Week 12)	5 (29)
Progressive Disease	3 (18)
Not Evaluable*	1 (6)
Objective Response Rate (%) 95% CI	47 23-72
Disease Controle Rate (%) 95% CI	76 50-93
Median Follow Up (mos)	5.3

* Patients were considered not evaluable if they did not undergo a 12 week scan due to clinical progression

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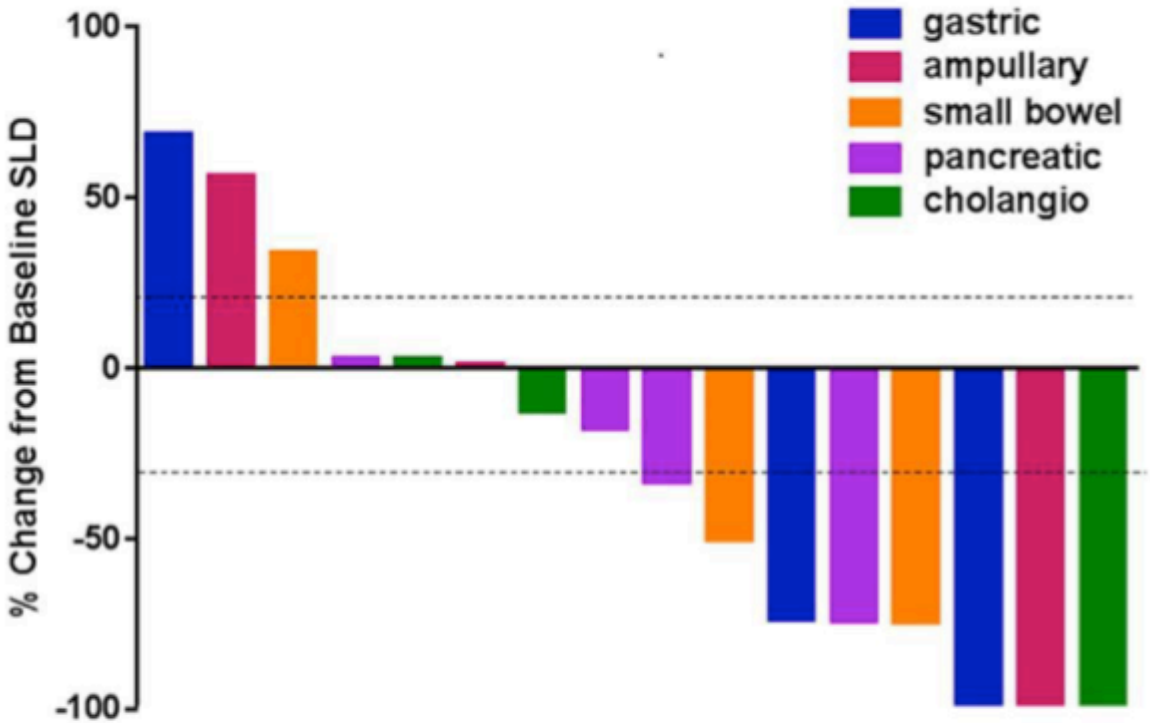
TARGET LESION MEASUREMENTS



PD-1 blockade in mismatch repair deficient non-colorectal gastrointestinal cancers.
Dung T. Le et al.

CONCLUSIONS

- Mismatch repair deficiency is easily determined using existing commercially available tests
- Early responses within 12 weeks
- High ORR (47%) and DCR (76%) in pre-treated patients (median 2 prior treatments)
- Small number, heterogeneous patients no control group
- Therefore so far no impact for routine clinical practice
  - Prospective studies are ongoing

NETTER-1 Phase III: PFS, Radiographic Response and Preliminary Overall Survival Results in Patients with Midgut Neuroendocrine Tumors Treated with ^{177}Lu-Dotatate

Jonathan R. Strosberg et al.

NETTER-1 STUDY OBJECTIVES AND DESIGN

Aim	Evaluate the efficacy and safety of ^{177}Lu-Dotatate + SSAs (symptoms control) compared to Octreotide LAR 60mg (off-label use)[1] in patients with inoperable, somatostatin receptor positive, midgut NET, progressive under Octreotide LAR 30mg (label use)
Design	International, multicenter, randomized, comparator-controlled, parallel-group

Treatment and Assessments

Progression free survival (RECIST criteria) every 12 weeks

Dose 1 Dose 2 Dose 3 Dose 4

Baseline and Randomization

n = 115 — 4 administrations of 7.4 GBq of ^{177}Lu-Dotatate every 8 weeks + SSAs (symptoms control)

n = 115 — Octreotide LAR (high dose - 60mg every 4 weeks[1])

5 Years follow up

[1] FDA and EMA recommendation

PROGRESSION-FREE SURVIVAL

N= 229 (ITT)

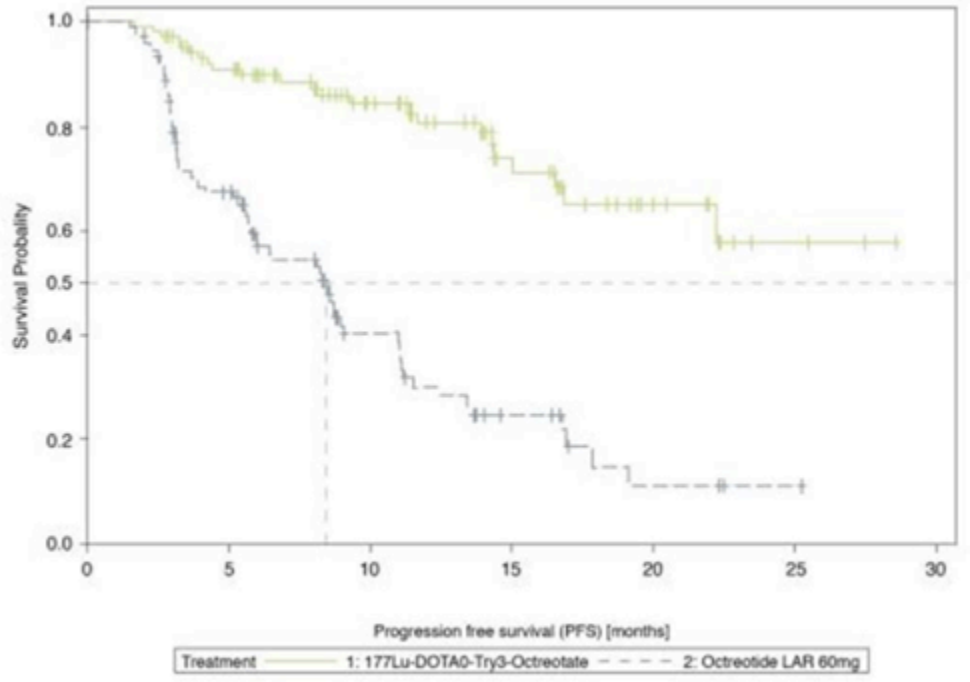
Number of events: 90

- ^{177}Lu-Dotatate: 23
- Oct 60 mg LAR: 67

Hazard ratio: **0.21**
[0.129 – 0.338] **p < 0.0001**

79% reduction in the risk of disease progression/death

Estimated Median PFS in the Lu-DOTATE arm
≈ **40 months**



All progressions centrally confirmed and independently reviewed for eligibility (SAP)

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NETTER-1 Phase III: PFS, Radiographic Response and Preliminary Overall Survival Results in Patients with Midgut Neuroendocrine Tumors Treated with ^{177}Lu-Dotatate. Jonathan R. Strosberg et al.

OBJECTIVE RESPONSES
CURRENTLY EVALUABLE PATIENTS

	177-Lu-Dotatate (n=101)*	Sandostatin LAR 60 mg (n=100)*
Completed response (n)	1	0
Partial Response (n)	17	3
Objective Response Rate (*)	18%	3%
Confidence interval (95%)	10% - 25%	0% - 6%
Statistical Significance	**P = 0.0008**	
All patients	**(n=116)**	**(n=113)**
Progressive Disease	6 (5%)	27 (24%)
Stable Disease	77 (66%)	70 (62%)

(*) Exclude patients with no post-baseline scans of central response available

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NETTER-1 Phase III: PFS, Radiographic Response and Preliminary Overall Survival Results in Patients with Midgut Neuroendocrine Tumors Treated with ^{177}Lu-Dotatate. Jonathan R. Strosberg et al.

CONCLUSIONS

- First prospective randomized study in patients with progressive metastatic midgut NET with significant benefit in PFS (HR 0.21) and ORR (18% versus 3%)
- Favourable safety profile with no clinical relevant findings
- Sequencing of treatment needs to be addressed in further clinical trials
- Clear impact for clinical practice

NETTER-1 Phase III: PFS, Radiographic Response and Preliminary Overall Survival Results in Patients with Midgut Neuroendocrine Tumors Treated with ^{177}Lu-Dotatate. Jonathan R. Strosberg et al.

Tumor and Circulating Biomarker Analysis from the Randomized Controlled Phase 2 Trial of Tivantinib in Second-line Hepatocellular Carcinoma

Lorenza Rimassa et al.

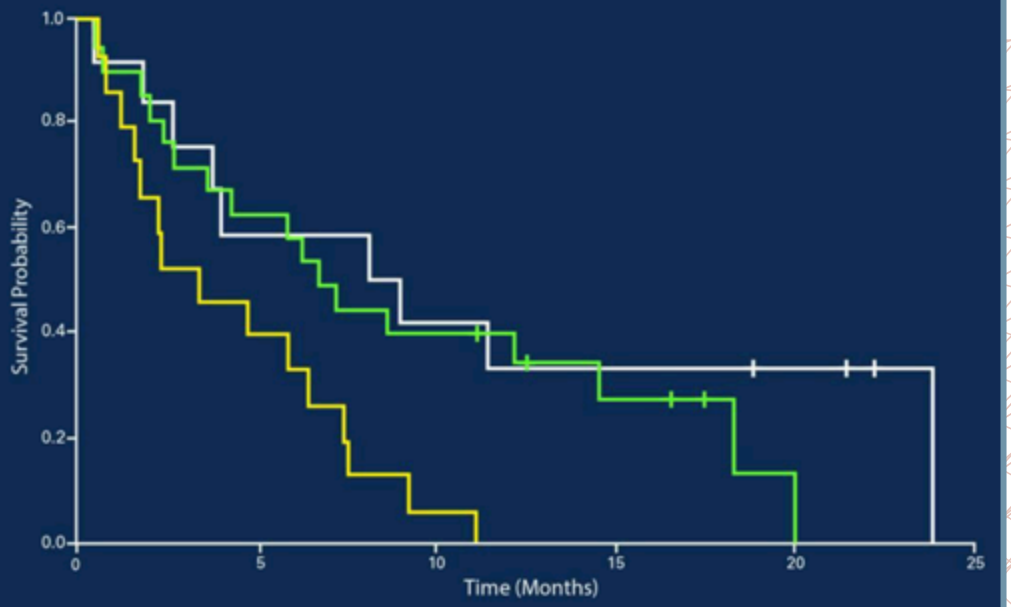
TUMOR MET AS A PROGNOSTIC AND PREDICTIVE FACTOR

	Median OS	Patients	Events
— Placebo MET-Low	9.0 mos	13	9
— Placebo MET-High	3.8 mos	15	15

HR: 0.34 (95% CI: 0.13-0.86) p=0.02

	Median OS	Patients	Events
— Placebo MET-Low	9.0 mos	13	9
— Tivantinib MET-High	7.2 mos	22	17

HR: 0.72 (95% CI: 0.30-1.70) p=0.45



Tivantinib vs placebo in 40 MET-Low patients: HR: 1.33 (95% CI: 0.58-3.04), p=0.50

Significant interaction test for tivantinib and tumor MET status in terms of OS (p=0.04)

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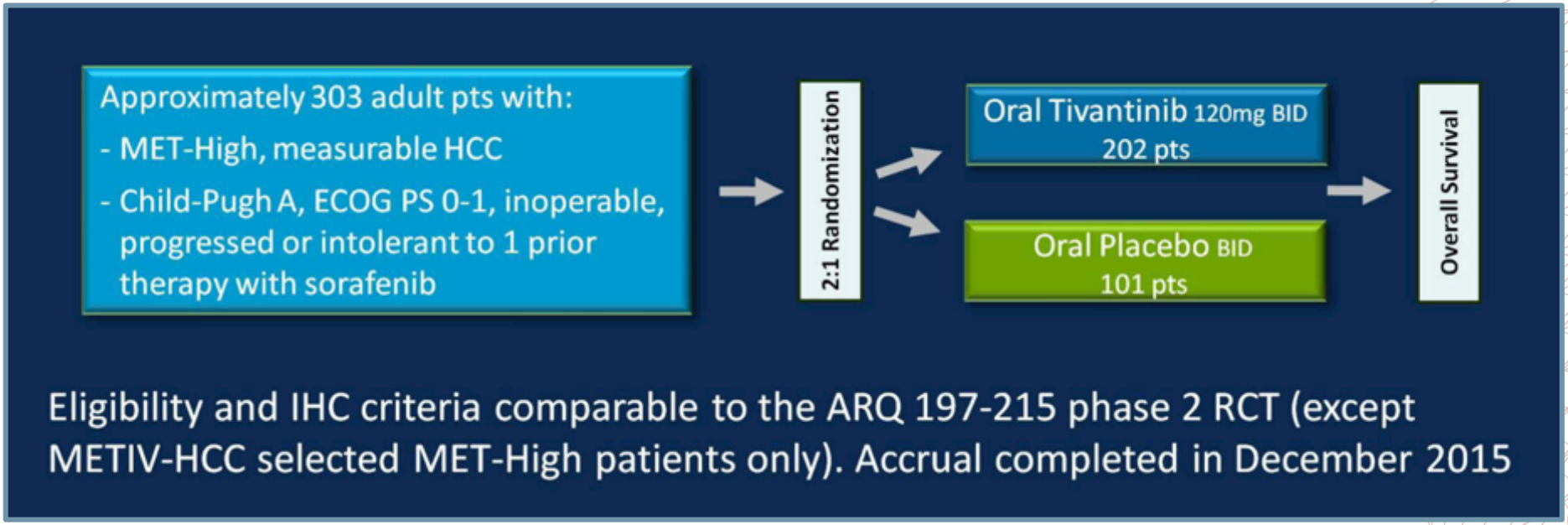
Tumor and plasma Biomarker Analysis from the Randomized Controlled Phase 2 Trial of Tivantinib in Second-line Hepatocellular Carcinoma. Lorenza Rimassa et al.

METIV-HCC (ARQ 197-A-U303)*

Phase 3 clinical trial in the Americas, Australia, Europe, New Zealand



* Data are preliminary, from non-cleaned database, from biopsied patients regardless of their enrolment status

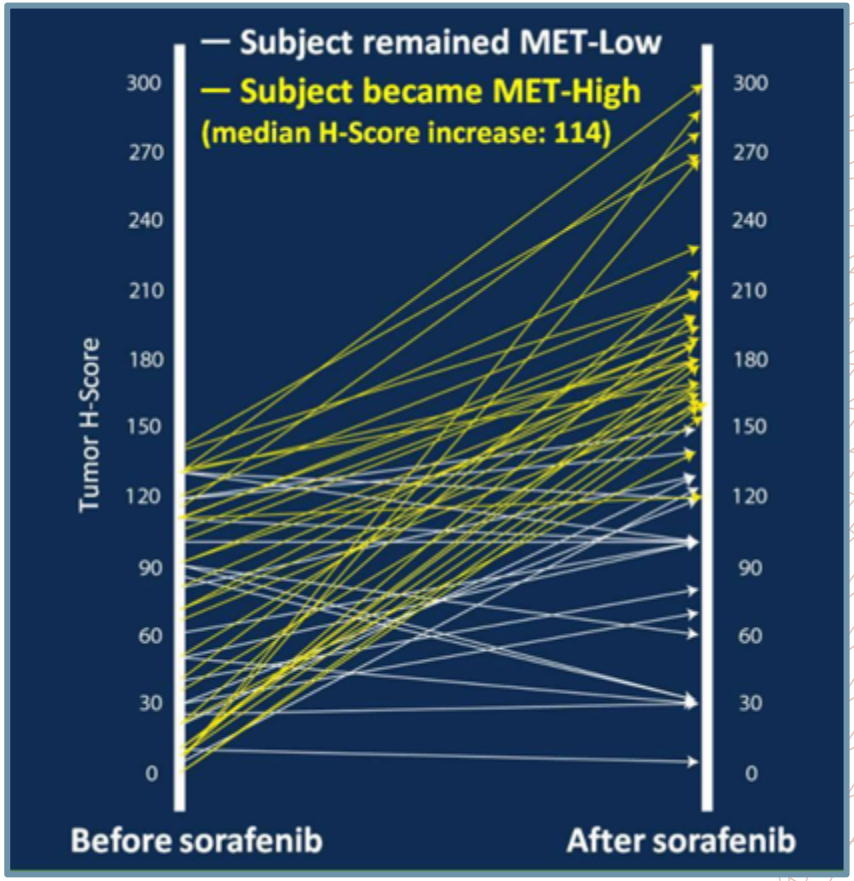
NCT01755767

METIV-HCC: BASELINE TUMOR MET STATUS*

MET-Low to MET-High Conversion:

71 patients were MET-Low at biopsy taken before sorafenib and were re-biopsied after sorafenib

50 out of 71 (70%) converted to MET-High at the biopsy taken after sorafenib



* Data are preliminary, from non-cleaned database, from biopsied patients regardless of their enrolment status

CONCLUSIONS

- Tumor MET results are comparable in both ARQ 197-215 and METIC-HCC studies with tivantinib in second-line
- Tumor MET is the only prognostic and predictive biomarker, and is more frequently “high” after sorafenib treatment
- Tumor MET expression can change within a lesion and over time – so far not clear if it is an effect of sorafenib or independent

Evofosfamide (TH-302) in combination with gemcitabine in previously untreated patients with metastatic or locally advanced unresectable pancreatic ductal adenocarcinoma: primary analysis of the randomized, double-blind phase III MAESTRO study

Eric van Cutsem et al.

CONCLUSIONS

- The phase III MAESTRO trial did not meet its primary endpoint of overall survival
- This will not have impact on daily clinical practice

Evofosfamide (TH-302) in combination with gemcitabine in previously untreated patients with metastatic or locally advanced unresectable pancreatic ductal adenocarcinoma: primary analysis of the randomized, double-blind phase III MAESTRO study. Eric van Cutsem et al.

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