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PRECISION ONCOLOGY CONNECT

MEETING HIGHLIGHTS FROM ESMO 2023

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CLINICAL TAKEAWAYS

Cancer of unknown primary

- **CUPISCO:** In patients with newly diagnosed, unfavourable, non-squamous CUP that responded to induction CTX, CGP with MGT improved PFS, thereby supporting a precision oncology approach in these patients
- **CUP-ONE:** CTID molecular-expression classifier demonstrated similar performance overall to specialist C-IHC
- **Fudan CUP-001:** Site-specific treatment guided by the approved 90-gene expression assay resulted in more therapy options, and significantly improved PFS with favourable OS vs empirical chemotherapy in patients with *de novo* CUP

Diagnostic

- **ARCAGEN:** Molecular profiling of rare cancers identified many targetable alterations, and should be more routinely performed

Treatment

- **DESTINY-PanTumor01 (DPT-01):** In heavily pretreated patients with limited treatment options, T-DXd demonstrated encouraging anticancer activity and long DoR across multiple tumour types with HER2m and a range of HER2 expression levels
- **LIBRETTO-531:** First-line selpercatinib prolonged PFS, improved ORR, and achieved a better OS vs MKIs, and should now be considered the preferred first-line standard of care for patients with advanced *RET*-mutant MTC

C-IHC, centralised immunohistochemistry; CGP, comprehensive genomic profiling; CTID, CancerTYPE ID; CTX, chemotherapy; CUP, cancer of unknown primary; DoR, duration of response; HER2(m), human epidermal growth factor receptor 2 (mutations); MGT, molecularly guided therapy; MKI, multikinase inhibitor; MTC, medullary thyroid carcinoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan

EDUCATIONAL OBJECTIVES

- Help physicians translate the latest Precision Oncology data from ESMO 2023 into clinical practice

CANCER OF UNKNOWN PRIMARY

BACKGROUND

- CUP is a carcinoma or undifferentiated neoplasm for which a standardised diagnostic work-up fails to identify the primary tumour responsible for metastatic seeding.[1]
- CUP accounts for <5% of cancers but, because of its high mortality rate, its relative contribution to cancer deaths is higher[1]
- ESMO Clinical Practice Guidelines highlight the need for new data to support techniques such as NGS to identify potential therapeutic targets[1]
- Ongoing trials in CUP that include tissue and blood profiling may enable new therapeutic strategies, including targeted and immunotherapies, to help further improve outcomes
- Encouraging data from studies relating to precision medicine for CUPs were presented at the ESMO Congress 2023 (Madrid, 20-24 October)

CUP, cancer of unknown primary; ESMO, European Society for Medical Oncology; NGS, next-generation sequencing

1. Krämer A, et al. Ann Oncol. 2023;34:228-46

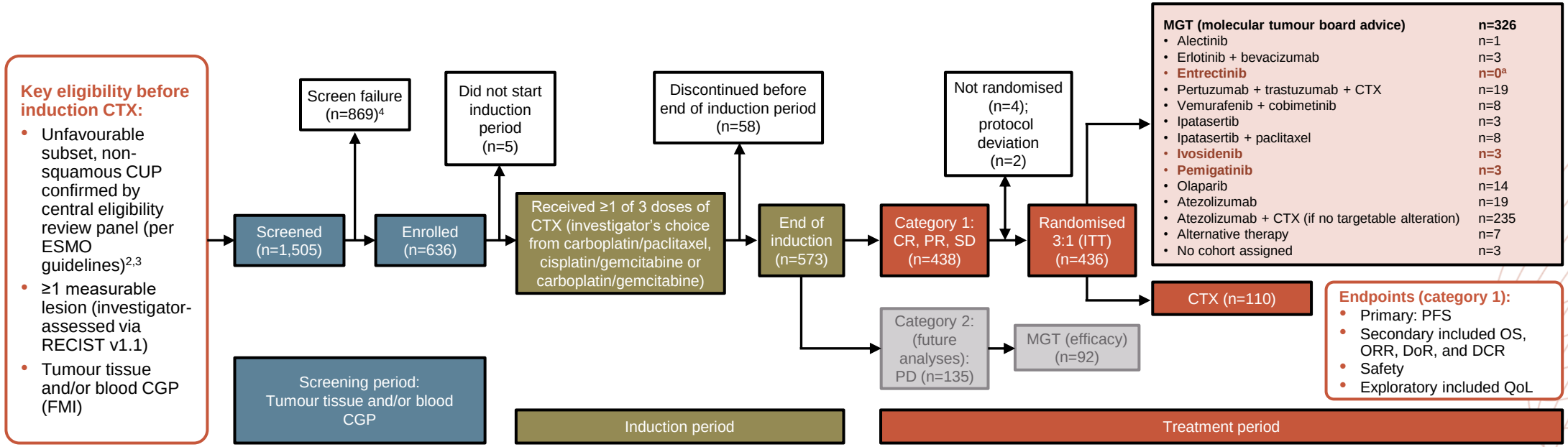
PRIMARY ANALYSIS OF EFFICACY AND SAFETY IN THE CUPISCO TRIAL: A RANDOMISED, GLOBAL STUDY OF TARGETED THERAPY OR CANCER IMMUNOTHERAPY GUIDED BY CGP VS PLATINUM-BASED CHEMOTHERAPY IN NEWLY DIAGNOSED, UNFAVOURABLE CUP

Mileshkin L, et al. ESMO 2023. Abstract #LBA16

CGP, comprehensive genomic profiling; CUP, cancer of unknown primary

CUPISCO: BACKGROUND AND STUDY DESIGN

- With platinum-based CTX, prognosis of patients with unfavourable CUP is poor; however, CGP may inform treatment strategies based on cancer genomics[1]
- The CUPISCO trial (NCT03498521) compared the efficacy and safety of MGT vs standard platinum-based CTX in patients with newly diagnosed, unfavourable, non-squamous CUP[1]



Of the 626 patients enrolled between 10 July 2018 and 9 December 2022, 94 (14.8%) had a tissue biopsy only, 55 (8.6%) had a liquid biopsy only and 483 (75.9%) had both

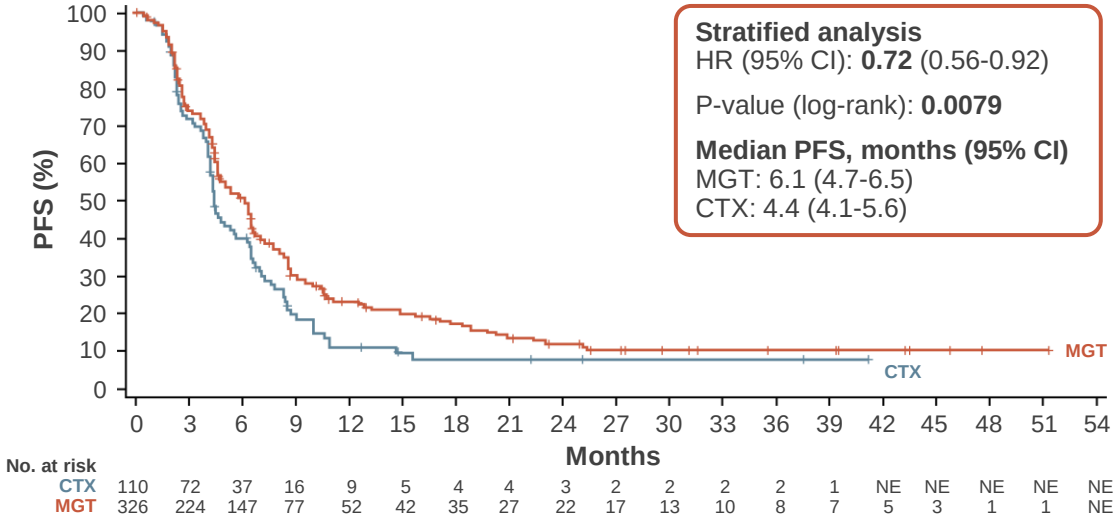
[a] No patients received entrectinib in category 1, only in category 2

CGP, comprehensive genomic profiling; CR, complete response; CTX, chemotherapy; CUP, cancer of unknown primary; DCR, disease control rate; DoR, duration of response; ESMO, European Society for Medical Oncology; FMI, Foundation Medicine Inc.; ITT, intent-to-treat; MGT, molecularly guided therapy; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease

1. Mileshkin L, et al. Ann Oncol. 2023;34 suppl 2:S1254-5 (ESMO 2023 oral presentation); 2. Fizazi K, et al. Ann Oncol. 2015;26 suppl 5:v133-8; 3. Krämer A, et al. Ann Oncol. 2023;34:228-46; 4. Pauli C, et al. Oncologist. 2021;26;e769-9

CUPISCO: RESULTS

- CGP with MGT significantly improved PFS vs CTX in the ITT population



Stratified analysis
HR (95% CI): **0.72** (0.56-0.92)

P-value (log-rank): **0.0079**

Median PFS, months (95% CI)
MGT: 6.1 (4.7-6.5)
CTX: 4.4 (4.1-5.6)

	MGT (N=326)	CTX (N=110)
Best confirmed ORR, n (%)[a]	17.8 (13.8-22.4)	8.2 (3.8-15.0)
Difference, % (95% CI)	9.6 (2.4-16.8)	
Median DoR, months (range)	16.4 (8.1-NE)	NE (4.1-NE)
HR (95% CI)	0.95 (0.33-2.72)	
DCR, n (%)	64.7 (59.3-69.9)	60.0 (50.2-69.2)
Difference, % (95% CI)	4.7 (−6.4-15.9)	
QoL Median time to deterioration in EQ-5D-5L VAS scores, months (range)	5.9 (3.9-8.8)	6.6 (4.6-31.0)
HR (95% CI)	1.14 (0.78-1.65)	
Median time to deterioration in FACT-G total scores, months (range)	10.0 (7.4-12.9)	14.7 (5.8-NE)
HR (95% CI)	1.09 (0.73-1.63)	

- Median OS (95% CI):[b]
  - 14.7 months (13.3-17.3) vs 11.0 months (9.7-15.4) with MGT vs CTX
  - HR [95% CI] 0.82 [0.62-1.09]; p=0.1779
- AE rates were generally similar with MGT vs CTX; no difference in QoL was observed

Median follow-up in the treatment period was 24.1 months (interquartile range: 11.6-35.6)

[a] All randomised patients, whether or not the assigned study treatment was received; [b] OS data were immature at cut off

AE, adverse event; CGP, comprehensive genomic profiling; CI, confidence interval; CTX, chemotherapy; DCR, disease control rate; DoR, duration of response; EQ-5D-5L, EuroQoL 5-level EQ-5D visual analogue scale; FACT-G, Functional Assessment of Cancer Therapy - General; HR, hazard ratio; ITT, intent-to-treat; MGT, molecularly guided therapy; NE, not evaluable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life

Mileshkin L, et al. Ann Oncol. 2023;34 suppl 2:S1254-5 (ESMO 2023 oral presentation)

CUPISCO: SUMMARY

- In patients with newly diagnosed, unfavourable, non-squamous CUP who responded to induction CTX, CGP with MGT improved PFS
- Early CGP and MGT should be considered the new standard of care for these patients

Clinical perspective

- **CUPISCO supports a precision oncology approach for CUP patients who have an unsatisfactory standard of care**
- **The extent to which genomic profiling is used varies by centre and it is not always widely available**

CGP, comprehensive genomic profiling; CTX, chemotherapy; CUP, cancer of unknown primary; MGT, molecularly guided therapy; NE, not evaluable; ORR, overall response rate; PFS, progression-free survival

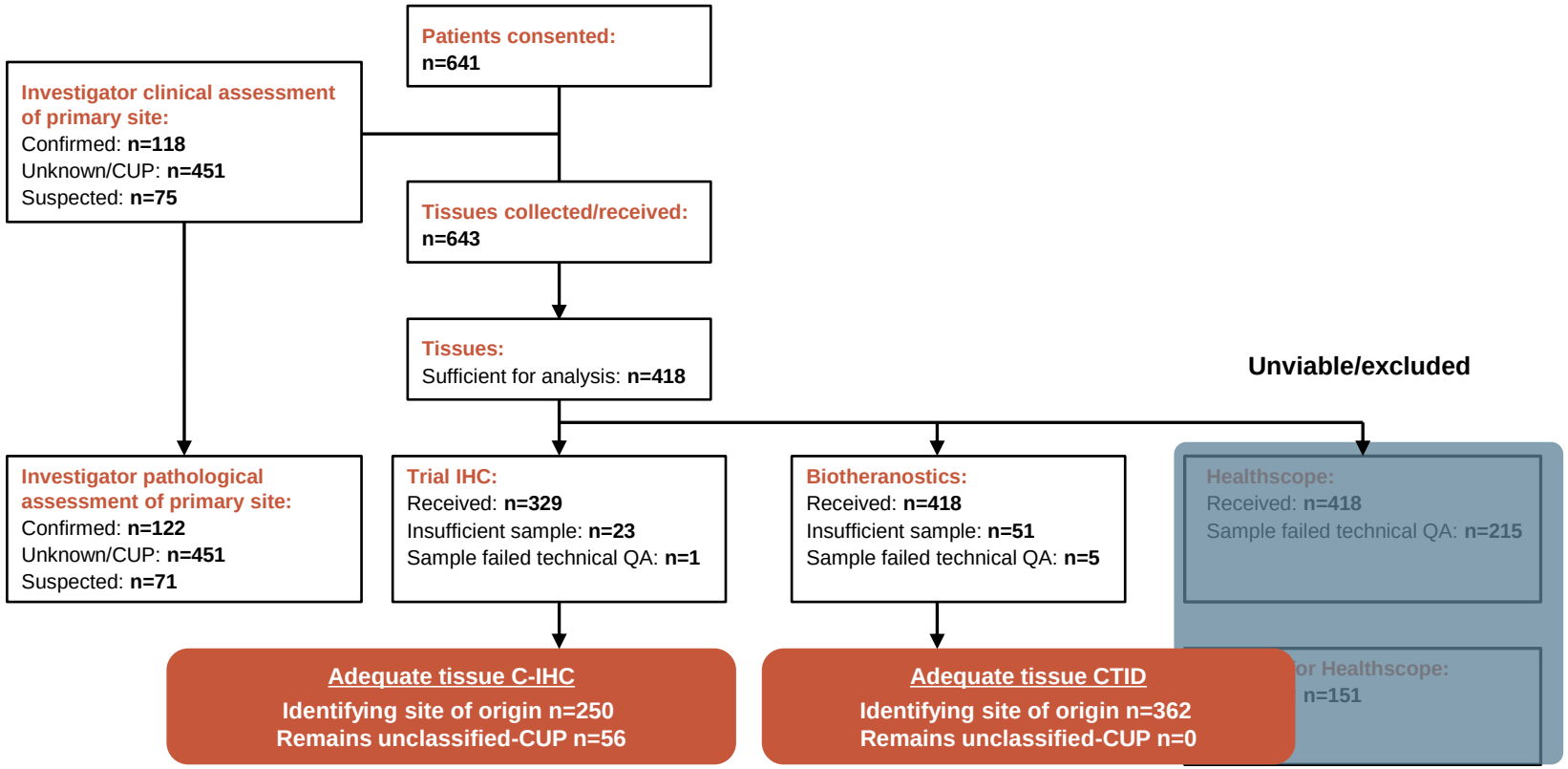
Mileshkin L, et al. Ann Oncol. 2023;34 suppl 2:S1254-5 (ESMO 2023 oral presentation)

CUP-ONE TRIAL: A PROSPECTIVE DOUBLE-BLIND VALIDATION OF MOLECULAR CLASSIFIERS IN THE DIAGNOSIS OF CANCER OF UNKNOWN PRIMARY AND CLINICAL OUTCOMES

Wasan H, et al. ESMO 2023. Abstract #LBA100

CUP ONE: BACKGROUND AND STUDY DESIGN

- GEPs show promise as molecular cancer classifiers for CUP, but their utility in diagnosis and prognosis warrants study
- CUP-ONE prospectively compared a 92-gene assay GEP vs centralised IHC (C-IHC; 11 markers) in the diagnosis of metastatic cancers initially presenting as CUPs



Primary endpoint:

Percentage match of each classifier to the RD site of origin

- Derived as the ratio of the total number of matches over the total number of samples
- Based on the ITD dataset with a C/S RD

Secondary endpoints:

- Overall classifier accuracy in evaluables with a C/S site of origin
- Concordance of classifiers test results:
  - Assessing percentage agreement between pairs of classifiers
  - A pre-specified diagnostic score

(C-)IHC, (centralised) immunohistochemistry; C/S, confirmed/suspected CTID, CancerTYPE ID; CUP, cancer of unknown origin; GEP, gene expression signature; ITD, intention to diagnose; QA, quality assurance; RD, reference diagnosis

Wasan H, et al. Ann Oncol. 2023;34 suppl 2:S1339 (ESMO 2023 oral presentation)

CUP ONE: RESULTS

- Investigators final classifications (N) were CUP (451), 'Suspected' (72), and revised 118 to 'known' sites
- In the ITD set: median 67 years, 50% male, 92% stage IV; 418 (65%) samples were sufficient for 1 classifier output
- Sample inadequacy (C-IHC: 7.3%; CTID: 13.4%) lead to 306 C-IHC and 362 CTID classifications
- In Pair-wise comparisons CTID correctly classified 17.24% (95% CI 1.9-29.6; p=0.02431) more than C-IHC; agreement of 2 classifiers was 97%
- Both CTID and C-IHC classified lung, colorectal, breast and ovary well; CTID did particularly well with cholangiocarcinoma/gall bladder (60% accuracy) but not in pancreas (9.1%) vs C-IHC (27.2%).
- Median OS (months) was poor across all 3 groups CUP: 5.3 (4.6-6.4); 'Suspected': 9.0 (8.3-11.9); 'Confirmed': 7.8 (5-13)

SUMMARY: PRIMARY ENDPOINT

Classifier	N (of which, confirmed)[a]	Individual classifier percentage age match, % (95% CI)	Δ percentage age match vs IHC, %[b] (p value [95% CI])
CTID	122 (81)	50.6 (40.2-60.9)	17.24 (0.02431 [1.9-29.6])
C-IHC	104 (65)	33.3 (24.1-43.7)	

OS BY PRIMARY SITE STATUS AND TREATMENT STATUS

	N	Events	Median survival (months, 90% CI)
Unknown, treated	248	212	6.3 (5.2-7.0)
Suspected, treated	86	69	8.9 (8.0-12.9)
Confirmed, treated	40	32	8.9 (6.8-13.1)
Unknown, untreated	195	156	3.9 (2.9-5.9)
Suspected, untreated	38	27	9.4 (3.1-12.0)
Confirmed, untreated	29	26	6.7 (1.7-15.6)

[a] Number in the ITD dataset with an RD site of origin; [b] Percentage correct IHC classifications taken from the percentage of correct CancerTYPE ID classifications

(C-)IHC, (centralised) immunohistochemistry; CI, confidence interval; CTID, CancerTYPE ID; CUP, cancer of unknown origin; ITD, intention to diagnose; OS, overall survival; RD, reference diagnosis

Wasan H, et al. Ann Oncol. 2023;34 suppl 2:S1339 (ESMO 2023 oral presentation)

CUP ONE: SUMMARY

- CTID molecular expression classifier demonstrated similar performance overall to specialist C-IHC
- CTID showed a greater accuracy for classifying cholangiocarcinoma/gall bladder cancer
- Survival was better in the confirmed/suspected subset but remains poor overall
- Overall survival for CUP remains poor and tools need to be developed to improve the accuracy of diagnosis and impact overall survival outcomes

Clinical perspective

- **CTID appears similar to C-IHC in terms of accuracy**
- **Additional tools need to be developed to improve accuracy of diagnosis**

C-IHC, centralised immunohistochemistry; CTID, CancerTYPE ID; CUP, cancer of unknown origin

Wasan H, et al. Ann Oncol. 2023;34 suppl 2:S1339 (ESMO 2023 oral presentation)

A RANDOMISED PHASE 3 TRIAL OF SITE-SPECIFIC THERAPY GUIDED BY THE 90-GENE EXPRESSION ASSAY VERSUS EMPIRIC CHEMOTHERAPY IN PATIENTS WITH CANCER OF UNKNOWN PRIMARY (Fudan CUP-001)

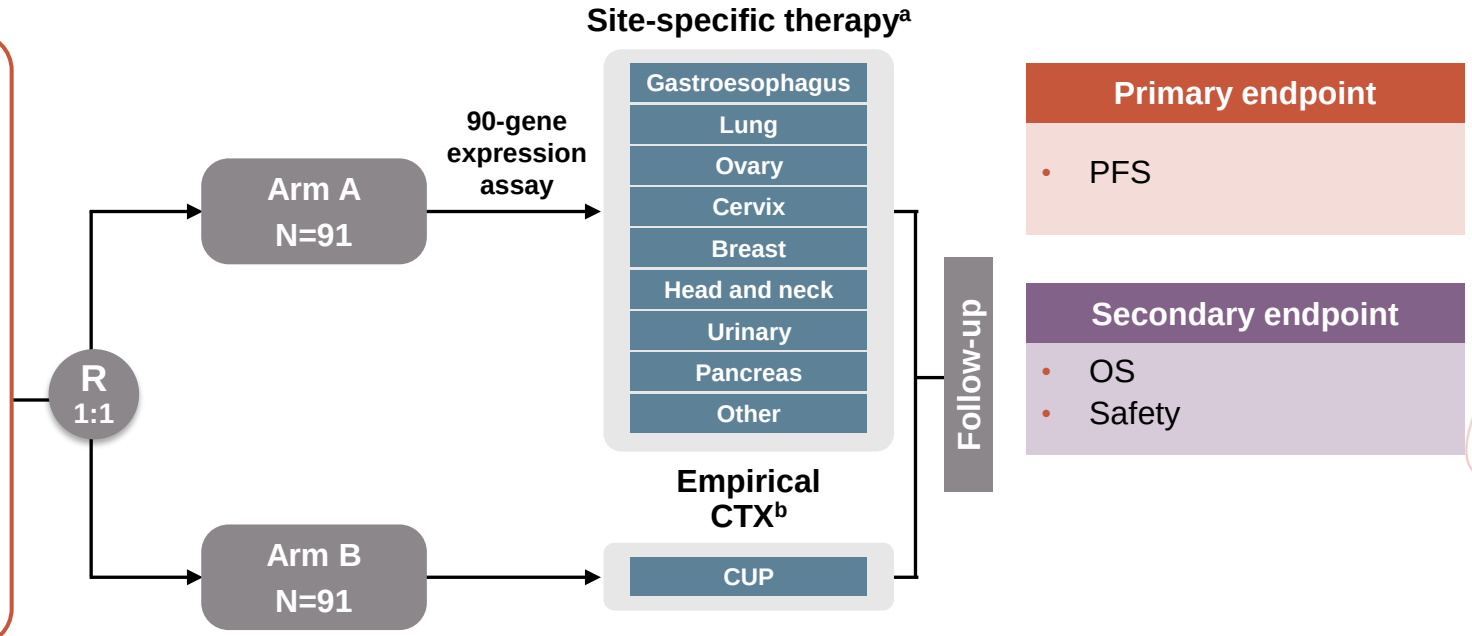
Luo Z, et al. ESMO 2023. Abstract #1208MO

Fudan CUP-001: BACKGROUND AND STUDY DESIGN

- Empirical CTX remains the standard of care in patients with CUP
- Evidence on site-specific therapy based on multi-gene tissue of origin assay is limited
- Fudan CUP-001 is a randomised phase 3 trial to evaluate the efficacy of site-specific therapy directed by an approved 90-gene expression assay compared with the empirical CTX in CUP patients (NCT03278600)

Key eligibility criteria:

1. Clinicopathologically confirmed CUP after standard evaluation (medical history, physical examination, blood counts, chemistry profile, chest-abdomen CT, PET-CT, and direct evaluation of all symptomatic areas)
2. Evaluable disease
3. Age: 18-75 years
4. ECOG PS: 0-2
5. No prior systemic therapy
6. Sufficient FFPE tissue for 90-gene expression assay



Stratification: ECOG PS (0/1 vs 2), extent of disease (lymph nodes only vs extranodal involved)

Objective: Evaluate the efficacy of site-specific therapy directed by the 90-gene expression assay compared with the empirical CTX in patients with CUP

[a] Site-specific therapy: standard treatments for predicted tumour types on the basis of the guidelines for each tumour type; [b] Empirical CTX: taxane plus platinum or gemcitabine plus platinum

CT, computed tomography; CTX, chemotherapy; CUP, cancer of unknown primary; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FFPE, formalin-fixed, paraffin-embedded; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; R, randomisation

Luo Z, et al. 2023;34 suppl 2:S712 (ESMO 2023 oral presentation)

Fudan CUP-001: RESULTS

- Site-specific therapy guided by molecular assay resulted in more treatment options than the control arm, and standard CTX regimens for CUP were administered in 26.4% vs. 92.3% (p<0.001) of the population, respectively

EFFICACY RESULTS	Site-specific therapy (N=91)	Empirical CTX (N=91)
PFS (ITT)[a]		
Median PFS, months	9.6	6.6
HR (95% CI) p value	0.68 (0.49-0.93) 0.017	
OS (ITT)		
Median OS, months	28.2	19.0
HR (95% CI) p value	0.74 (0.52-1.06) 0.098	
2-year survival rate, %	57.1	41.8

- AEs of grade ≥3 were similar between the two groups (p=0.61)

[a] Median follow-up time was 42.9 months (95% CI 40.0-49.6)

AE, adverse event; CI, confidence interval; CTX, chemotherapy; CUP, cancer of unknown primary; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; OS, overall survival

Luo Z, et al. 2023;34 suppl 2:S712 (ESMO 2023 oral presentation)

Fudan CUP-001: SUMMARY

- Site-specific treatment guided by the approved 90-gene expression assay resulted in more therapy options, and significantly improved PFS with favourable OS compared with empirical CTX in patients with *de novo* CUP
- AEs of grade ≥3 with site-specific therapy were similar to those with empirical chemotherapy

Clinical perspective

- **Fudan CUP-001 demonstrates the importance of identifying the primary tumour site to allow the use of organ-specific CTX regimens**
- **The low survival rates show there is still an unmet need in this area**

AE, adverse event; CTX, chemotherapy; CUP, cancer of unknown primary; OS, overall survival; PFS, progression-free survival

Luo Z, et al. 2023;34 suppl 2:S712 (ESMO 2023 oral presentation)

DIAGNOSTIC

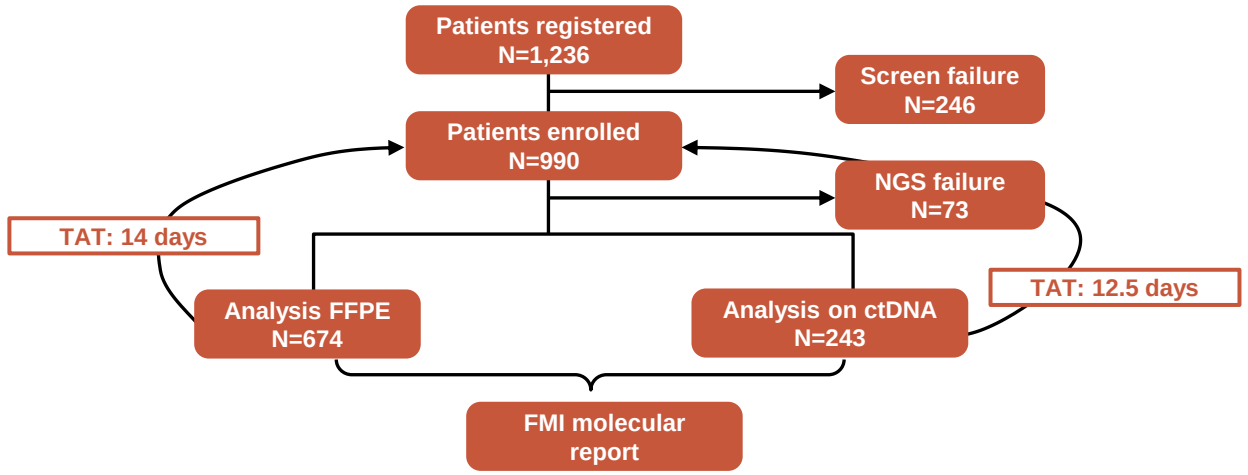
MOLECULAR PROFILING OF 991 PROSPECTIVELY RECRUITED RARE CANCERS PATIENTS IN EUROPE: FIRST RESULTS OF ARCAGEN – AN EORTC-SPECTA AND EURACAN STUDY

Morfouace M, et al. ESMO 2023. Abstract #132MO

EORTC, European Organisation for Research and Treatment of Cancer; EURACAN, European Reference Network on Rare Adult Solid Cancers

ARCAGEN: BACKGROUND AND STUDY DESIGN

- Within the EORTC-SPECTA platform, the ARCAGEN collaborative study between EORTC and EURACAN was initiated in June 2019 and aimed to assess the prevalence of genomic alterations, high TMB and MSI, as well as actionability in patients diagnosed with advanced rare cancers (defined with an incidence <6/10^5/year)
- Patients diagnosed with a recurrent or metastatic rare cancer were recruited into the ARACAGEN study via the EORTC-SPECTA platform



Molecular profiling was preferentially performed on FFPE material (FoundationOne® CDx: 73.5%); if not feasible, liquid biopsy was used as a rescue (FoundationOne ® CDx Liquid: 26.5%)

ctDNA, circulating tumour DNA; EORTC, European Organisation for Research and Treatment of Cancer; EURACAN, European Reference Network on Rare Adult Solid Cancers; FFPE, formalin-fixed, paraffin-embedded; FMI, Foundation Medicine Inc.; MSI, microsatellite instability; NGS, next-generation sequencing; TAT, turnaround time; TMB, tumour mutational burden

Morfouace M, et al. Ann Oncol. 2023;34 suppl 2:S233-4 (ESMO 2023 oral presentation)

ARCAGEN: RESULTS

- The 3 most common histotypes were:
  - CUP (103 [11.2%])
  - Mesothelioma (80 [8.7%])
  - Cholangiocarcinoma (72 [7.8%])
- Clinically relevant molecular alterations were identified in 606 patients (66%), with top alterations seen in:
  - TP53 (28.5%),
  - CDKN2A/B (16.8%)
  - KRAS (9.2%)
- The TMB was above 10 for 53 patients (5.3%); 9 MSI-high patients were identified
- 456 patients (46%) received a therapy recommendation based on the molecular analysis:
  - 63 (6.8%) patients for an already approved treatment (ESCAT 1A)
  - 232 (25.3%) for an off-label use of an approved treatment in another indication with similar molecular alteration (ESCAT IC, II, or III)
  - 161 (17.5%) for a clinical trial

CUP, cancer of unknown primary; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; ESMO, European Society for Medical Oncology; FFPE, formalin-fixed, paraffin-embedded; FMI, Foundation Medicine Inc.; NGS, next-generation sequencing; TMB, tumour mutational burden

Morfouace M, et al. Ann Oncol. 2023;34 suppl 2:S233-4 (ESMO 2023 oral presentation)

ARCAGEN: SUMMARY

- Close to 50% of patients with rare cancers received a therapeutic recommendation based on molecular characterisation, a majority within clinical trials
- ctDNA could replace FFPE for molecular profiling
- Molecular characterisation should be recommended routinely for rare cancers in advanced phase

Clinical perspective

- **Molecular profiling for rare cancer identified many targetable alterations and should be more routinely performed**

ctDNA, circulating tumour DNA; FFPE, formalin-fixed, paraffin-embedded

Morfouace M, et al. Ann Oncol. 2023;34 suppl 2:S233-4 (ESMO 2023 oral presentation)

TARGETED THERAPY

EFFICACY AND SAFETY OF TRASTUZUMAB DERUXTECAN IN PATIENTS WITH HER2-EXPRESSING SOLID TUMOURS: PRIMARY RESULTS FROM PHASE 2 DESTINY-PanTumor01 (DPT-01)

Li B, et al. ESMO 2023. Abstract #654O

HER2, human epidermal growth factor receptor 2

DPT-01: BACKGROUND AND STUDY DESIGN

- T-DXd is an antibody–drug conjugate targeting HER2, and is approved in the US in HER2-expressing breast, gastric, and NSCLC[1]
- HER2 expression is prevalent in other solid tumours; the efficacy of current treatments in these populations, including studies with HER2-directed treatment, is modest, revealing a significant unmet medical need[2]
- DESTINY-PanTumor01 is an open-label, multicentre, phase 2 study (NCT04639219) in patients with advanced solid tumours harbouring prespecified HER2m (excluding HER2-overexpressing breast and gastric cancers, and HER2m NSCLC), and who failed previous systemic treatment received T-DXd 5.4 mg/kg Q3W[3]

Key eligibility criteria:

- Patients with unresectable and/or metastatic solid tumours with locally determined prespecified HER2m
- Progression after prior treatment or with no satisfactory alternative treatment options
- Prior HER2-targeting therapy allowed

Key exclusion criteria:

- HER2^{+} (IHC 3^{+} or IHC 2^{+}/ISH^{+}) breast, gastric, or gastroesophageal junction cancer or HER2m NSCLC
- History of non-infectious ILD/pneumonitis, current ILD, or suspected ILD that cannot be ruled out by imaging at screening

T-DXd
5.4 mg/kg
Q3W

Approx 100 participants
(max. 20 per tumour type)

Primary endpoint:

- Confirmed ORR (ICR)

Secondary endpoint:

- DoR
- DCR
- Confirmed ORR (investigator assessed)
- PFS
- OS
- Safety and tolerability

Prespecified HER2m: S310F/Y, G660D, R678Q, L755S, D769H/Y, Y772_A775dup, A775_G776insYVMA, V777L, G778_P780dup, P780_Y781insGSP, V8421, T862A

DCR, disease control rate; DoR, duration of response; HER2(m), human epidermal growth factor receptor 2 (mutations/mutated); ICR, independent central review; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in-situ hybridisation; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan

1. Trastuzumab deruxtecan prescribing information; 2. Yan M, et al. Cancer Metastasis Rev. 2015; 34:157-64; 3. Li B, et al. Annals of Oncology 2023; 34: Suppl 2: S459–S460 (ESMO 2023 oral presentation)

DPT-01: RESULTS

EFFICACY RESULTS

	T-DXd N=102
PFS by ICR – 60% maturity	
Median PFS, months (95% CI)	5.4 (2.7-7.1)
Objective response rate (BICR)	
ORR %, (95% CI)	29.4 (20.8-39.3)
Overall survival – 57% maturity	
No. of events	
Median OS (95% CI)	10.9 (8.3-14.9)
DoR by ICR, %	NR 54.2% of responders remained in response at 18 months

ORR BY TUMOUR TYPE AND HER2m DOMAIN

	N	ORR by ICR	%
All patients	102	30	29.4
Tumour type			
Breast	20	10	50.0
Colorectal	20	4	20.0
Biliary tract	19	2	10.5
Oesophageal/oesophago-gastric	11	1	9.1
Urothelial	7	2	28.6
Salivary gland/head and neck AC	6	4	66.7
Small intestinal AC	5	0	-
Cervical	3	2	66.7
Endometrial	2	2	100
Other neuroendocrine	2	1	50.0
Pancreatic	2	0	-
AC of unknown primary	1	1	100
Extramammary Paget's disease	1	1	100
Melanoma	1	0	0
Ovarian	1	0	0
Urachal	1	0	0
HER2m domain[a]			
Tyrosine kinase[b]	52	19	36.5
Extracellular[c]	34	10	29.4
Transmembrane/juxtamembrane[d]	17	1	5.9

- Grade ≥3 AEs occurred in 51.0% of patients; 9.8% discontinued treatment due to AEs
- Adjudicated drug-related ILD/pneumonitis occurred in 11 patients (10.8% [grade 3, n=1; grade 5, n=2])

[a] By local testing; [b] L755S, D769H, Y772_A775dup/A775_G776insYVMA, V777L, G778_P780dup/P780_Y781insGSP, V842I, T862A; [c] S310F, S310Y; d R678Q

AC, adenocarcinoma; AE, adverse event; BICR, blinded independent central review; CI, confidence interval; DoR, duration of response; HER2(m), human epidermal growth factor receptor 2 (mutations); ICR, independent central review; ILD, interstitial lung disease; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan

Li B, et al. Annals of Oncology 2023; 34: Suppl 2: S459–S460 (ESMO 2023 oral presentation)

DPT-01: SUMMARY

- DPT-01 is the first tumour-agnostic global study of T-DXd in a range of solid tumours with prespecified HER2m
- In heavily pretreated patients with limited treatment options, T-DXd demonstrated encouraging anticancer activity and long DoR across multiple tumour types with HER2m and a range of HER2 expression levels
- No new safety signals were observed and the safety of T-DXd in was consistent with the known safety profile
- Translational research will help characterise patients who may derive greatest benefit from T-DXd

Clinical perspective

- **The study shows T-DXd to be a potential new treatment option for heavily pretreated patients with HER2-expressing solid tumours**

DoR, duration of response; HER2(m), human epidermal growth factor receptor 2 (mutations); T-DXd, trastuzumab deruxtecan

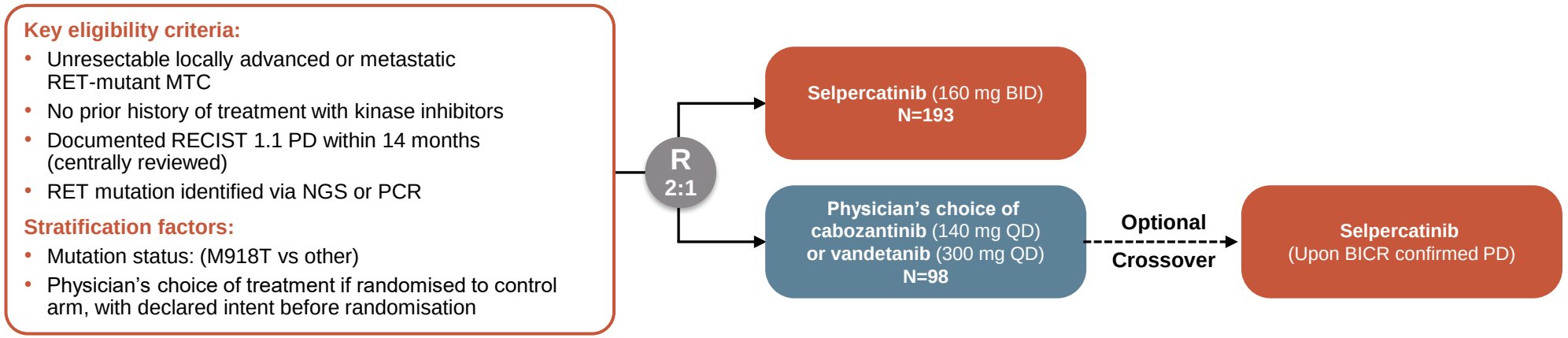
Li B, et al. Annals of Oncology 2023; 34: Suppl 2: S459–S460 (ESMO 2023 oral presentation)

RANDOMISED PHASE 3 STUDY OF SELPERCATINIB VERSUS CABOZANTINIB OR VANDETANIB IN ADVANCED, KINASE INHIBITOR-NAÏVE, RET-MUTANT MEDULLARY THYROID CANCER (LIBRETTO-531)

Hadoux J, et al. ESMO 2023. Abstract #LBA3

LIBRETTO-531: BACKGROUND AND STUDY DESIGN

- Selpercatinib is a highly selective and potent RET inhibitor approved for treatment of advanced RET-mutant MTC; it has not been directly compared with approved MKIs
- LIBRETTO-531 is a phase 3 open-label study designed to define the optimal first-line treatment for patients with advanced RET-mutant MTC



Primary objective: PFS per RECIST 1.1 by BICR

Secondary endpoints:

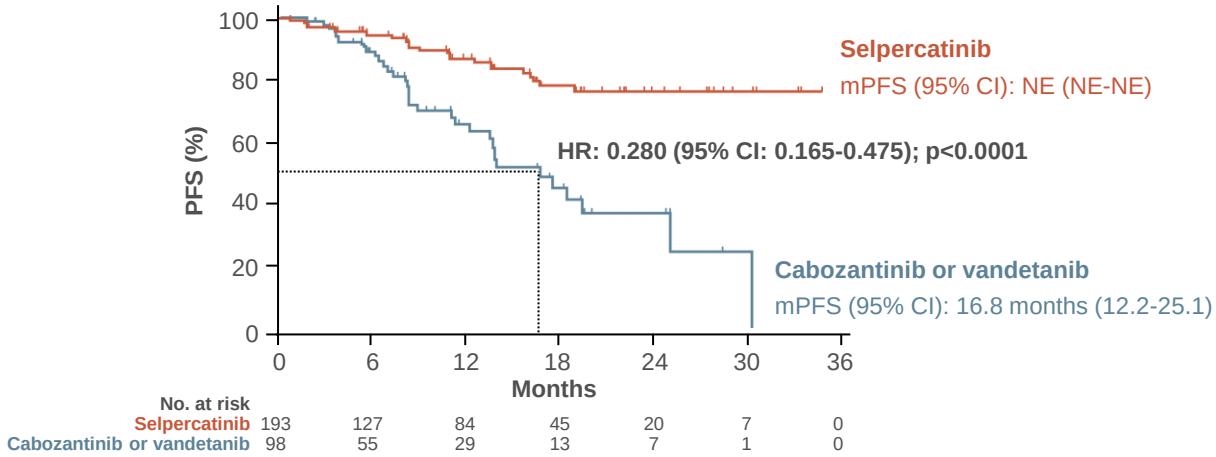
- **Efficacy** (TFFS by BICR and investigator, PFS by investigator, ORR by BICR and investigator, and OS)
- **Safety**

BICR, blinded independent central review; BID, twice daily; MKI, multikinase inhibitor; MTC, medullary thyroid carcinoma; NGS, next-generation sequencing; ORR, overall response rate; OS, overall survival; PD, progressive disease; PCR, polymerase chain reaction; PFS, progression-free survival; QD, once daily; R, randomisation; RECIST PD, Response Evaluation Criteria in Solid Tumours progression of disease; TFFS, treatment failure-free survival

Selpercatinib Prescribing Information; Hadoux J, et al. Ann Oncol. 2023;34 suppl 2:S1338 (ESMO 2023 oral presentation)

LIBRETTO-531: RESULTS

PFS (BICR)



- Median follow-up of 12 months
- Investigator-assessed PFS was similar with a hazard ratio (95% CI) of 0.187 (0.109-0.321); p<0.0001
- The study was considered positive for PFS if the two-sided p value was <0.0033; therefore, this trial met its primary endpoint for evidence of efficacy

EFFICACY RESULTS

	Selpercatinib (N=193)	Cabozantinib or vandetanib (N=98)
TFFS – median follow-up 12 months		
Median TFFS, months	NE	13.9
HR (95% CI) p value	0.254 (0.153-0.423) p<0.0001	
OS (ITT) – median follow-up 12 months		
HR (95% CI) p value	0.374 (0.147-0.949) p=0.0312	
ORR, % (95% CI)	69.4 (62.4-75.8)	38.8 (29.1-49.2)
Best overall response		
CR	23 (11.9)	4 (4.1)
PR	111 (57.5)	34 (34.7)
Median DOR, months (95% CI)	NE (NE-NE)	16.6 (10.4-NE)

SAFETY

- Dose reductions (38.9% vs 79.2% with cabozantinib and 72.0% with vandetanib) and permanent treatment discontinuations due to adverse events (4.7% vs 26.8%) were less common with selpercatinib than with MKIs
- Grade ≥3 TEAEs: selpercatinib 52.8% vs 76.3% with cabozantinib or vandetanib

BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; HR, hazard ratio; ITT, intention to treat; (m)PFS, (median) progression-free survival; NE, not evaluable; ORR, overall response rate; OS, overall survival; PR, partial response; TEAE, treatment-emergent adverse event; TFFS, treatment failure-free survival

Hadoux J, et al. Ann Oncol. 2023;34 suppl 2:S1338 (ESMO 2023 oral presentation)

LIBRETTO-531: SUMMARY

- LIBRETTO-531 trial met its interim analysis criteria for efficacy, with significantly improved outcomes with first-line selpercatinib, a highly selective and potent RET inhibitor, vs a MKI in patients with RET-mutated MTC
- Selpercatinib showed a favourable safety profile compared with MKIs
- LIBRETTO-531 highlights the importance of testing for RET mutations in patients with metastatic MTC

Clinical perspective

- **Selpercatinib should be considered the preferred first-line standard of care for patients with advanced RET-mutant MTC**
- **LIBRETTO-531 supports routine RET-mutation testing for all patients with advanced MTC, but further work is needed to identify predictive markers**

MKI, multikinase inhibitor; MTC, medullary thyroid cancer

Hadoux J, et al. Ann Oncol. 2023;34 suppl 2:S1338 (ESMO 2023 oral presentation)

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