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SPECIAL ARTICLE

Recommendations for the use of next-generation sequencing (NGS) for patients with advanced cancer in 2024: a report from the ESMO Precision Medicine Working Group

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Background: Advancements in the field of precision medicine have prompted the European Society for Medical Oncology (ESMO) Precision Medicine Working Group to update the recommendations for the use of tumour next-generation sequencing (NGS) for patients with advanced cancers in routine practice.

Methods: The group discussed the clinical impact of tumour NGS in guiding treatment decision using the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) considering cost-effectiveness and accessibility.

Results: As for 2020 recommendations, ESMO recommends running tumour NGS in advanced non-squamous non-small-cell lung cancer, prostate cancer, colorectal cancer, cholangiocarcinoma, and ovarian cancer. Moreover, it is recommended to carry out tumour NGS in clinical research centres and under specific circumstances discussed with patients. In this updated report, the consensus within the group has led to an expansion of the recommendations to encompass patients with advanced breast cancer and rare tumours such as gastrointestinal stromal tumours, sarcoma, thyroid cancer, and cancer of unknown primary. Finally, ESMO recommends carrying out tumour NGS to detect tumour-agnostic alterations in patients with metastatic cancers where access to matched therapies is available.

Conclusion: Tumour NGS is increasingly expanding its scope and application within oncology with the aim of enhancing the efficacy of precision medicine for patients with cancer.

Key words: next-generation sequencing (NGS), advanced cancer, precision medicine, ESCAT

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INTRODUCTION

Considering the evolving field of drug development and genomic data, the European Society for Medical Oncology (ESMO) Precision Medicine Working Group (PMWG) sought to update recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers published in 2020. After several discussions among the members of the group, a consensus was reached to adopt the same methodology as per the previous publication.¹ Moreover, the group made the decision to encompass rare cancers, including gastrointestinal stromal tumours (GISTs), sarcomas, thyroid cancers, and cancer of unknown primary (CUP). This expansion was motivated by increased understanding of the molecular landscape of these tumour types in recent years and the large patient population they represent. The PMWG concentrated its efforts on genomic alterations classified as ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) level I, since they are the key determinants for recommending the use of NGS for routine practice within specific cancer types. In addition, it was unanimously agreed to report ESCAT level II genomic alterations to facilitate patient enrolment in clinical trials and promote drug development. Updated alterations are highlighted in red in the respective tables. Notably, genomic alterations classified as ESCAT level III/IV were not reported in the manuscript since they should not be used for routine practice, and they frequently undergo updates and reclassification with limited impact on patient clinical outcomes (Supplementary Table S1, available at <https://doi.org/10.1016/j.annonc.2024.04.005>). Acknowledging the diverse technologies available for detecting fusions and the potential for incidental findings when employing NGS, the PMWG opted to include a dedicated chapter addressing specific considerations for medical oncologists when ordering NGS tests. The following recommendations are for routine practice only. In addition, as for 2020 recommendations, ESMO recommends that clinical research centres

carry out multigene sequencing for patients with metastatic cancers in order to accelerate clinical research. Finally, ESMO acknowledges that patients and their oncologists can order a multigene sequencing outside these recommendations if the patient is informed about the likelihood of benefit, if it does not generate substantial extra cost to the public health system, and if it does not lead to off-label use of drugs without sufficient evidence.

UPDATED RECOMMENDATIONS

Tumour-agnostic biomarkers

Table 1 provides a list of tumour-agnostic genomic alterations.

NTRK1,2,3 fusions, *RET* and *FGFR1/2/3* fusions/mutations, *BRFA*^{V600E} mutations, MSI-H, and tumour mutation burden-high (TMB-H) are designated as tumour-agnostic biomarkers, categorised as level IC. This classification is based on the clinical improvement of patient outcomes in basket trials.²⁻¹¹ Prospective randomised or open-label phase II studies have been carried out for certain tumours, enabling the categorisation of some of these biomarkers into level IA/IB in the respective section.

Summary of recommendations

ESMO recommends carrying out multigene NGS in patients with advanced cancers in countries where tumour-agnostic targeted therapies are accessible. Cost-effectiveness should be assessed at the local level and the decision to implement NGS should be taken accordingly. It is important for clinicians to ensure that fusions are integrated in the panel.

Genomic alterations according to ESCAT in advanced non-squamous non-small-cell lung cancer (NSCLC)

Table 2 provides a list of genomic alterations level I/II according to ESCAT in advanced non-squamous NSCLC.

Gene/Signature ^a	Alteration	Estimated prevalence (illustration of tumours with high prevalence of the alteration)	ESCAT score	Drug class matched	References
<i>NTRK1/2/3</i>	Fusions	80%-90% secretory breast cancer 15%-20% Spitzoid melanoma	IC	TRK inhibitors	Hong et al., <i>Lancet Oncol</i> 2020 ² Demetri et al., <i>Clin Can Res</i> 2022 ³
MSI-H/dMMR ^a	MSI-H/dMMR	15%-20% endometrial cancer 15%-20% gastric adenocarcinoma	IC	PD-1 checkpoint inhibitors	Marcus et al., <i>Clin Can Res</i> 2019 ⁴
<i>RET</i>	Fusions	7% thyroid papillary cancer 2% salivary gland cancer	IC	RET inhibitors	Subbiah et al., <i>Lancet Oncol</i> 2022 ⁵ Subbiah et al., <i>Nat Med</i> 2022 ⁵
<i>BRAF</i>	Mutations (p.V600E)	40%-45% melanoma 5%-6% small intestinal adenocarcinoma	IC	BRAF inhibitors + MEK inhibitors	Subbiah et al., <i>Cancer Discov</i> 2020 ⁷ Salama et al., <i>J Clin Oncol</i> 2020 ⁸
<i>FGFR1/2/3</i>	Fusions Mutations	20%-40% bladder cancer 3% glioblastoma multiforme 10%-20% urothelial carcinoma 10% endometrial cancer	IC	Pan-FGFR TKIs	Pant et al., <i>Lancet Oncol</i> 2023 ⁹
TMB-H ^a	TMB-H	40% small-cell lung cancer	IC	PD-1/PD-L1 checkpoint inhibitors	Valero et al., <i>JAMA Oncol</i> 2021 ¹⁰ Friedman et al., <i>Cancer Discov</i> 2022 ¹¹

dMMR, mismatch repair deficient; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FGFR, fibroblast growth factor receptor; MSI-H, microsatellite instability-high; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TKIs, tyrosine kinase inhibitors; TMB-H, tumor mutation burden-high; TRK, tropomyosin receptor kinase.
^aSignature; TKIs, tyrosine kinase inhibitors.

Table 2. List of genomic alterations level I/II according to ESCAT in advanced non-squamous non-small-cell lung cancer

Gene	Alteration	Estimated prevalence	ESCAT score	Drug class matched	References
EGFR	Common mutations (deletion exon 19, p.L858R)	15% Caucasian 50% Asian 30% LATAM	IA	First-, second- and third-generation EGFR TKIs EGFR-MET bispecific antibodies + third-generation EGFR TKIs	Midha et al., <i>Am J Can Res</i> 2015 ¹² Arrieta et al., <i>J Thorac Oncol</i> 2015 ¹³ Soria et al., <i>N Engl J Med</i> 2018 ¹⁴ Ramalingam et al., <i>N Engl J Med</i> 2020 ¹⁵ Cho et al., <i>Ann Oncol</i> 2023 ¹⁶ Passaro et al., <i>Ann Oncol</i> 2024 ¹⁷ Mok et al., <i>N Engl J Med</i> 2017 ¹⁸ Papadimitrakopoulou et al., <i>Ann Oncol</i> 2020 ¹⁹
	Acquired p.T790M mutation in exon 20	60% after first- or second-generation EGFR TKIs	IA	Third-generation EGFR TKIs	Park et al., <i>J Clin Oncol</i> 2021 ²⁰ Zhou et al., <i>N Engl J Med</i> 2023 ²¹ Cho et al., <i>J Clin Oncol</i> 2020 ²² Yang et al., <i>Front Oncol</i> 2022 ²³
	Exon 20 insertions	2%	IA	EGFR-MET bispecific antibodies or TKIs	
	Uncommon mutations (p.G719 variants in exon 18, p.L861Q in exon 21, p.S768I in exon 20)	10%	IB	Second- and third-generation EGFR TKIs	
ALK	Fusions	5%	IA	ALK TKIs	Mok et al., <i>Ann Oncol</i> 2020 ²⁴ Shaw et al., <i>N Engl J Med</i> 2020 ²⁵ Camidge et al., <i>J Thorac Oncol</i> 2021 ²⁶ Horn et al., <i>JAMA Oncol</i> 2021 ²⁷ Solomon et al., <i>Lancet Respir Med</i> 2023 ²⁸
KRAS	Mutations (p. G12C)	12%	IA	KRAS ^{G12C} TKIs	Jänne et al., <i>N Engl J Med</i> 2022 ²⁹ de Langen et al., <i>Lancet</i> 2023 ³⁰
RET	Fusions	1%-2%	IA	RET TKIs	Subbiah et al., <i>Clin Can Res</i> 2021 ³¹ Griesinger et al., <i>Ann Oncol</i> 2022 ³² Drilon et al., <i>J Clin Oncol</i> 2023 ³³ Zhou et al., <i>N Engl J Med</i> 2023 ³⁴
ROS1	Fusions	1%-2%	IB	ROS1 TKIs	Shaw et al., <i>Ann Oncol</i> 2019 ³⁵ Shaw et al., <i>Lancet Oncol</i> 2019 ³⁶ Drilon et al., <i>JTO Clin Res Rep</i> 2022 ³⁷
BRAF	Mutations (p. V600E)	2%	IB	BRAF TKIs + MEK TKIs	Planchard et al., <i>J Thorac Oncol</i> 2022 ³⁸ Riely et al., <i>J Clin Oncol</i> 2023 ³⁹
MET	Mutations exon 14 skipping	3%	IB	MET TKIs	Drilon et al., <i>Nat Med</i> 2020 ⁴⁰ Wolf et al., <i>J Clin Oncol</i> 2021 ⁴¹ Lu et al., <i>Lancet Respir</i> 2021 ⁴² Thomas et al., <i>J Thorac Oncol</i> 2022 ⁴³ Wolf et al., <i>Ann Oncol</i> 2022 ⁴⁴
	Focal amplifications	5% as primary 15% as mechanism of acquired resistance on EGFR TKIs	IIB	MET TKIs + third-generation EGFR TKIs EGFR-MET bispecific antibodies + third-generation EGFR TKIs	Yu et al., <i>Ann Oncol</i> 2021 ⁴⁵ Bauml et al., <i>J Clin Oncol</i> 2021 ⁴⁶ Shu et al., <i>J Clin Oncol</i> 2022 ⁴⁷ Marmarelis et al., <i>J Thorac Oncol</i> 2022 ⁴⁸ Hartmaier et al., <i>Cancer Discov</i> 2023 ⁴⁹ Tan et al., <i>J Clin Oncol</i> 2023 ⁵⁰
ERBB2	Hotspot mutations	3%	IIB	Pan-HER TKIs Anti-HER2 ADCs	Hyman et al., <i>Nature</i> 2018 ⁵¹ Li et al., <i>N Engl J Med</i> 2022 ⁵²
NRG1	Fusions	<1%	IIB	Anti-HER2/HER3 bispecific antibody	Schram et al., <i>JCO</i> 2022 ⁵³

ADC, antibody–drug conjugates; EGFR, epidermal growth factor receptor; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; HER, human epidermal growth factor receptor; LATAM, Latin America; PD, progressive disease; TKIs, tyrosine kinase inhibitors.

EGFR exon 20 insertions, labelled as level IIB in the previous recommendations, have now been reclassified as level IA. This is supported by the randomised phase III PAPILLON trial, which assessed amivantamab, a bispecific monoclonal antibody targeting both epidermal growth factor receptor (EGFR) and MET receptor, plus chemotherapy as compared to chemotherapy alone in patients with advanced NSCLC with EGFR exon 20 insertions. Progression-free survival (PFS) was longer in the amivantamab plus chemotherapy than in the chemotherapy arm [hazard ratio (HR) 0.40; 95% confidence interval (CI) 0.30-0.53; $P < 0.001$].²¹ In 2021, amivantamab has obtained an accelerated approval by the Food and Drug Administration (FDA). In 2023, a supplemental biological

license application has been submitted to the FDA and a type II extension of indication application to the European Medicines Agency (EMA), seeking expanded approval of amivantamab plus carboplatin/pemetrexed in the frontline treatment of this population. Another alteration that has been subject to reclassification is KRAS^{G12C} mutation, which has been reclassified as level IA. This decision was driven by the PFS improvement observed with sotorasib, a specific KRAS^{G12C} tyrosine kinase inhibitor (TKI), versus chemotherapy (HR 0.66; 95% CI 0.51-0.86; $P = 0.0017$) in patients with pre-treated advanced KRAS^{G12C}-mutated NSCLC in the randomised phase III study CodeBreak 200. No improvement in overall survival (OS) was observed (HR 1.01; 95% CI 0.77-1.33).³⁰ Accelerated approval was

granted by the FDA and conditional authorisation was provided by the EMA for sotorasib. Finally, *RET* fusions have been moved from level IC to IA in accordance with ESCAT, supported by findings from the phase III randomised LIBRETTO-431 trial. In this study, selpercatinib, a selective *RET* TKI, led to significantly longer PFS than platinum-based chemotherapy with or without pembrolizumab in the first line among patients with advanced *RET* fusion-positive NSCLC (HR 0.46; 95% CI 0.31-0.70; $P < 0.001$).³⁴ Selpercatinib has received regular approval from the FDA and EMA for this indication. It is noteworthy that the trials resulting in the upgrade of *EGFR* exon 20 insertions,²¹ *KRAS*^{G12C} mutations,³⁰ and *RET* fusions³⁴ have been reported after the ESMO Clinical Practice Guideline for diagnosis, treatment, and follow-up for patients with advanced NSCLC was published.⁵⁴ *NRG1* fusions are classified as level IIB based on the antitumour activity, overall response rate (ORR) 35% (95% CI 21-50), elicited by zenocutuzumab, an anti-human epidermal growth factor receptor 2 (HER2)/HER3 bispecific antibody, in patients with advanced *NRG1*-positive NSCLC.⁵³ Zenocutuzumab received the breakthrough therapy designation by the FDA for *NRG1* fusion-positive advanced NSCLC.

Summary of recommendations

No changes have been made to the indication of carrying out tumour NGS in patients with advanced non-squamous NSCLC in daily practice, as the working group has already recommended tumour NGS in these patients. However, with the inclusion of new genomic alterations categorised as ESCAT level I, it is crucial to carefully consider the optimal approach for tumour NGS implementation in the clinical management of patients with advanced non-squamous NSCLC.

Genomic alterations according to ESCAT in advanced breast cancer (ABC)

Table 3 provides a list of genomic alterations level I/II according to ESCAT in ABC.

ESR1 mutations have been upgraded to level IA based on the results of the EMERALD trial. In this randomised, phase III study, elacestrant, an oral selective oestrogen receptor degrader (SERD) demonstrated an improvement in PFS among patients with hormone receptor-positive/HER2-negative ABC (HR 0.70; 95% CI 0.55-0.88; $P = 0.02$), with a greater benefit observed in those with detectable *ESR1* mutations (HR 0.55; 95% CI 0.39-0.77; $P = 0.0005$).⁶⁴ It is important to emphasise that these data became available after the release of the ESMO Clinical Practice Guideline for the diagnosis, staging, and treatment of patients with metastatic breast cancer.⁷³ Several data recently reported high performance for tumour NGS in detecting germline *BRCA1/2* mutations; however, around 7% of these alterations were not identified. This suggests that patients presenting a high likelihood of harbouring germline *BRCA1/2* mutations and a negative tumour NGS should undergo dedicated germline testing.^{74,75} Capivasertib plus fulvestrant improved median PFS in patients with hormone receptor-positive/HER2-negative ABC (HR 0.60; 95% CI 0.51-0.71; $P < 0.001$), with a slightly greater benefit in patients exhibiting *AKT*-pathway alterations (HR 0.50; 95% CI 0.38-0.65; $P < 0.001$) in a randomised phase III study.⁷⁰ Based on these data, the FDA approved this combination for pre-treated patients with hormone receptor-positive/HER2-negative ABC with *PIK3CA/AKT1/PTEN* alterations. There is no consensus among experts regarding whether *AKT1/PTEN* mutations should be classified as level I or II in this patient population, given the low prevalence, and the observed

Table 3. List of genomic alterations level I/II according to ESCAT in advanced breast cancer

Gene	Alteration	Estimated prevalence	ESCAT score	Drug class matched	References
<i>ERBB2</i>	Amplifications	15%-20%	IA	Anti-HER2 monoclonal antibodies HER2 TKIs Anti-HER2 ADCs	Baselga et al., <i>N Engl J Med</i> 2012 ⁵⁵ Krop et al., <i>Lancet Oncol</i> 2014 ⁵⁶ Lin et al., <i>J Clin Oncol</i> 2020 ⁵⁷ Saura et al., <i>J Clin Oncol</i> 2020 ⁵⁸ Rugo et al., <i>JAMA Oncol</i> 2021 ⁵⁹
	Hotspot mutations	4%	IIB	Pan-HER TKIs Anti-HER2 ADCs	Hyman et al., <i>Nature</i> 2018 ⁵¹ Smyth et al., <i>Cancer Discov</i> 2020 ⁶⁰ Li et al., <i>Ann Oncol</i> 2023 ⁶¹
<i>PIK3CA</i>	Hotspot mutations	30%-40%	IA (ER-positive HER2-negative ABC)	α -specific PI3K inhibitors*	André et al., <i>N Engl J Med</i> 2019 ⁶² Rugo et al., <i>Lancet Oncol</i> 2021 ⁶³ Turner et al., <i>N Engl J Med</i> 2023 ⁷⁰
<i>ESR1</i>	Mutations	30%-40%	IA (ER-positive HER2-negative ABC resistant to AI)	SERDs	Bidard et al., <i>J Clin Oncol</i> 2022 ⁶⁴ Bardia et al., <i>Cancer Res</i> 2023 ⁶⁵
<i>BRCA1/2</i>	Germline pathogenic/likely pathogenic variants	4%	IA	PARP inhibitors	Litton et al., <i>N Engl J Med</i> 2018 ⁶⁶ Robson et al., <i>Eur J Cancer</i> 2023 ⁶⁷
	Somatic mutations	3%	IIB	PARP inhibitors	Tung et al., <i>J Clin Oncol</i> 2020 ⁶⁸
<i>PTEN</i>	Mutations/deletions	7%	I/II	AKT inhibitors	Schmid et al., <i>J Clin Oncol</i> 2020 ⁶⁹ Turner et al., <i>N Engl J Med</i> 2023 ⁷⁰
<i>AKT1</i>	Mutations (p. E17K)	5%	I/II	AKT inhibitors	Kalinsky et al., <i>JAMA Oncol</i> 2021 ⁷¹ Turner et al., <i>N Engl J Med</i> 2023 ⁷⁰
<i>PALB2</i>	Germline pathogenic/likely pathogenic variants	1%	IIB	PARP inhibitors	Tung et al., <i>J Clin Oncol</i> 2020 ⁶⁸ Gruber et al., <i>Nat Cancer</i> 2022 ⁷²

ABC, advanced breast cancer; ADCs, antibody–drug conjugates; AI, aromatase inhibitors; ER, oestrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; HER, human epidermal growth factor receptor; PARP, poly (ADP-ribose) polymerase; SERDs, selective oestrogen receptor degrader; TKIs, tyrosine kinase inhibitors.

*AKT inhibitors have shown efficacy in patients with *PIK3CA* mutated ER-positive HER2-negative ABC

benefit may predominantly arise from *PIK3CA* mutations. Nevertheless, as the determination of *AKT1/PTEN* alterations can provide drug access to these patients, the group recommends carrying out tumour NGS. Finally, poly (ADP-ribose) polymerase inhibitors (PARPi) showed antitumour activity in patients with ABC and either somatic *BRCA1/2* mutations (ORR 50%; 90% CI 28-72) or germline *PALB2* pathogenic/likely pathogenic variants (ORR 82%; 90% CI 53-96), leading to their reclassification as level IIB.⁶⁸

Summary of recommendations

Considering that tumour NGS can substitute germline *BRCA1/2* testing in most of the patients, along with the reclassification of *ESR1* mutations to level IA, it is recommended to carry out tumour NGS of a tumour (or plasma) sample from a patient with hormone receptor-positive/HER2-negative ABC as standard of care. The NGS testing should be done after resistance to endocrine therapy to optimise the likelihood of detecting *ESR1* mutations. Patients with high likelihood of harbouring germline *BRCA1/2* mutations should undergo clinical genetic testing even if these alterations were not detected by tumour NGS.

Genomic alterations according to ESCAT in advanced colorectal cancer (CRC)

Table 4 provides a list of genomic alterations level I/II according to ESCAT in advanced CRC.

In this version of the recommendations, we have integrated *KRAS*^{G12C} mutations in advanced CRC since they became level IA. This decision was grounded on the randomised phase III CodeBreak 300 trial. In this study, sotorasib plus anti-EGFR monoclonal antibody showed an improvement of PFS among patients with pre-treated *KRAS*^{G12C}-mutated advanced CRC (HR 0.49; 95% CI 0.30-0.80; *P* = 0.006).⁸⁰ Moreover, hotspot-inactivating missense mutations in the exonuclease domain of the polymerase epsilon (*POLE*) gene in mismatch repair (MMR)-proficient solid tumours were associated with TMB-H and predict high activity from anti-programmed cell death protein 1 (PD-1) therapy, warranting their classification at level IIB.⁸⁴ Finally,

we have accumulated data on *ERBB2* amplification actionability with novel agents such as trastuzumab plus tucatinib and trastuzumab deruxtecan, which have shown substantial antitumour activity, ORR 30%-40%, in non-randomised studies and are approved/recommended therapies according to different regulatory agencies.^{82,83}

Summary of recommendations

ESMO recommends carrying out multigene tumour NGS in daily practice for patients with advanced CRC, if the testing itself does not add extra cost as compared to standard procedures such as immunohistochemistry (IHC), polymerase chain reaction (PCR), or Sanger sequencing.

Genomic alterations according to ESCAT in advanced prostate cancer

Table 5 provides a list of genomic alterations level I/II according to ESCAT in advanced prostate cancer.

Since the prior recommendations, randomised phase III trials have demonstrated that treatment of advanced prostate cancer patients with *BRCA1/2* alterations with PARPi alone or in combination with androgen receptor signalling inhibitors results in prolonged OS, so the panel retained the IA classification for *BRCA1/2* alterations. Subgroup analyses of these studies suggest limited benefit for patients with *ATM* alterations, although these events have been associated with PARPi activity in phase II trials.^{85,87,89} Therefore, *ATM* alterations have been ranked as IIB instead of IIA. Additional evidence regarding the predictive value of *PALB2* alterations for PARP inhibition has been included in light of the previous recommendations. Nevertheless, due to their low prevalence, data on *PALB2* alterations mainly come from specific phase II trials, resulting in limited information on survival outcomes.^{95,96} Therefore, *PALB2* alterations are still categorised as level IIB. The randomised phase III trial IPATential 150 demonstrated improved radiographic PFS from the addition of ipatasertib to abiraterone in patients with metastatic castration-resistant prostate cancer with *PTEN* loss by NGS with no OS benefit.^{91,93} In consequence, the panel decided to retain

Table 4. List of genomic alterations level I/II according to ESCAT in advanced colorectal cancer					
Gene/Signature ^a	Alteration	Estimated prevalence	ESCAT score	Drug class matched	References
<i>KRAS, NRAS</i>	Mutations (exon 2, 3 and 4)	53%	NA ^b	Anti-EGFR monoclonal antibodies	Douillard et al., <i>N Engl J Med</i> 2013 ⁷⁶ Van Cutsem et al., <i>J Clin Oncol</i> 2015 ⁷⁷
<i>BRAF</i>	Mutations (p. V600E)	8.5%	IA	BRAF inhibitors + EGFR inhibitors	Kopetz et al., <i>N Eng J Med</i> 2019 ⁷⁸
MSI-H/dMMR ^a	MSI-H/dMMR	4.5%	IA	PD-1 checkpoint inhibitors	André et al., <i>N Engl J Med</i> 2020 ⁷⁹
<i>KRAS</i>	Mutations (p. G12C)	4%	IA	<i>KRAS</i> ^{G12C} TKIs + anti-EGFR monoclonal antibodies	Fakih et al., <i>N Engl J Med</i> 2023 ⁸⁰
<i>ERBB2</i>	Amplifications	2%	IIB	Anti-HER2 monoclonal antibodies ± anti-HER2 TKIs	Meric-Bernstam et al., <i>Lancet Oncol</i> 2019 ⁸¹ Siena et al., <i>Lancet Oncol</i> 2021 ⁸²
<i>POLE</i>	Mutations	<1%	IIB	Anti-HER2 ADCs	Strickler et al., <i>Lancet Oncol</i> 2023 ⁸³
				PD-1 checkpoint inhibitors	Rousseau et al., <i>Cancer Discov</i> 2022 ⁸⁴

ADCs, antibody–drug conjugates; dMMR, mismatch repair deficient; HER, human epidermal growth factor receptor; EGFR, epidermal growth factor receptor; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; MSI-H, microsatellite instability-high; NA, not applicable; PD-1, programmed cell death protein 1; TKIs, tyrosine kinase inhibitors.

^aSignature.

^bbiomarker of resistance.

Table 5. List of genomic alterations level I/II according to ESCAT in advanced prostate cancer

Gene	Alteration	Estimated prevalence	ESCAT score	Drug class matched	References
<i>BRCA1/2</i>	Germline and somatic mutations/deletions	9%-11%	IA	PARP inhibitors	de Bono et al., <i>N Engl J Med</i> 2020 ⁸⁵ Hussain et al., <i>N Engl J Med</i> 2020 ⁸⁶ Fizazi et al., <i>N Engl J Med</i> 2023 ⁸⁷ Chi et al., <i>Ann Oncol</i> 2023 ⁸⁸ Fizazi et al., <i>Nat Med</i> 2023 ⁸⁹
<i>PTEN</i>	Deletions/mutations	40%	IIA	AKT inhibitors	Abida et al., <i>Proc Natl Acad Sci</i> 2019 ⁹⁰ De Bono et al., <i>Clin Cancer Res</i> 2019 ⁹¹ Sweeney et al., <i>Lancet</i> 2021 ⁹² Sweeney et al., <i>J Clin Oncol</i> 2022 ⁹³
<i>ATM</i>	Mutations/deletions	6%	IIB	PARP inhibitors	De Bono et al., <i>N Engl J Med</i> 2020 ⁸⁵ Fizazi et al., <i>N Engl J Med</i> 2023 ⁸⁷ Fizazi et al., <i>Nat Med</i> 2024 ⁸⁹
<i>PALB2</i>	Mutations/deletions	1%	IIB	PARP inhibitors	Mateo et al., <i>N Engl J Med</i> 2015 ⁹⁴ de Bono et al., <i>N Engl J Med</i> 2020 ⁸⁵ Carreira et al., <i>Cancer Discov</i> 2021 ⁹⁵ Abida et al., <i>Eur Urol</i> 2023 ⁹⁶

ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; PARP, poly (ADP-ribose) polymerase.

the IIA classification for *PTEN* loss. Ongoing phase III trials are evaluating other AKT inhibitors in different scenarios of advanced prostate cancer.^{97,98}

Summary of recommendations

The earlier version of the manuscript had already recommended conducting tumour NGS in countries where PARPi are available for patients with advanced prostate cancer.

Genomic alterations according to ESCAT in advanced gastric cancer

The ESCAT classification of genomic alterations in advanced gastric cancer remains unmodified to recommendations provided in 2020 (Supplementary Table S2, available at <https://doi.org/10.1016/j.annonc.2024.04.005>).

Summary of recommendations

In line with its previous recommendations, ESMO does not recommend carrying out tumour NGS in patients with advanced gastric cancer as the standard of care, except in countries where tumour-agnostic targeted therapies are accessible. Cost-effectiveness should be assessed at the local level and the decision to implement NGS should be taken accordingly.

Genomic alterations according to ESCAT in advanced pancreatic ductal adenocarcinoma (PDAC)

Table 6 provides a list of genomic alterations level I/II according to ESCAT in advanced pancreatic ductal adenocarcinoma.

The panel considers *KRAS*^{G12C} mutations as level IB, based on the efficacy of sotorasib in patients with pre-treated advanced PDAC and *KRAS*^{G12C} mutation. In a prospective phase II single-arm study, sotorasib achieved an ORR of 21% (95% CI 10-37), a median PFS of 4.0 months (95% CI 2.8-5.6), and a median OS of 6.9 months (95% CI 5.0-9.1).¹⁰¹ In a phase II study among patients with platinum-sensitive advanced PDAC and harbouring pathogenic germline or somatic variants in *BRCA1/2* or *PALB2*, rucaparib demonstrated a median PFS of 14.5 months (95% CI 0.7-28.3) within the limited subgroup of patients carrying germline *PALB2* variants. These findings led to the categorisation of this alteration as level IIB. Additionally, significant antitumour activity was observed among patients with somatic *BRCA1/2* mutations, but sample size is too limited to rank them as level II.^{103,105}

It is worth mentioning that around 10% of patients with advanced PDAC present with *KRAS* wild-type disease. *KRAS* wild-type pancreatic cancer enriches for (tumour-agnostic) therapeutic targets such as *NRG1* fusions and alternative

Table 6. List of genomic alterations level I/II according to ESCAT in advanced pancreatic ductal adenocarcinoma

Gene	Alteration	Estimated prevalence	ESCAT score	Drug class matched	References
<i>BRCA1/2</i>	Germline pathogenic/likely pathogenic variants	4%-7%	IA	PARP inhibitors	Golan et al., <i>N Engl J Med</i> 2019 ⁹⁹ Kindler et al., <i>J Clin Oncol</i> 2022 ¹⁰⁰
<i>KRAS</i>	Mutations (p.G12C)	1%-2%	IB	<i>KRAS</i> ^{G12C} TKIs	Strickler et al., <i>N Engl J Med</i> 2023 ¹⁰¹ Bekaii-Saab et al., <i>J Clin Oncol</i> 2022 ¹⁰²
<i>PALB2</i>	Germline pathogenic/likely pathogenic variants	3%-4%	IIB	PARP inhibitors	Reiss et al., <i>J Clin Oncol</i> 2021 ¹⁰³
<i>NRG1</i>	Fusions	7%	IIB	Anti-HER2/HER3 bispecific antibody	Schram et al., <i>JCO</i> 2021 ¹⁰⁴

ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; HER, human epidermal growth factor receptor; PARP, poly (ADP-ribose) polymerase; TKIs, tyrosine kinase inhibitors.

MAPK drivers such as *BRAF*^{V600E} mutations.^{106,107} Zenocutuzumab, an anti-HER2/HER3 bispecific antibody, has been granted breakthrough therapy designation by the FDA for *NRG1* fusion-positive advanced PDAC and dabrafenib plus trametinib obtained the FDA approval for the treatment of *BRAF*^{V600E}-mutated cancers.¹⁰⁸ If multigene sequencing is not readily available, a suitable single-gene test to detect *KRAS* alterations (e.g. allele-specific PCR, PCR plus Sanger or Pyro Sequencing) could be applied to screen for *KRAS* wild-type pancreatic cancer, typically found in young patients. Due to the relevant number of therapeutic targets found in these patients, this specific group could qualify for tumour NGS.

Summary of recommendations

Considering that only germline *BRCA1/2* alterations are ranked ESCAT level I and that *KRAS*^{G12C} mutations can be detected by PCR, there is no evidence that tumour NGS could improve outcome of patients with advanced PDAC in routine practice. Nevertheless, considering the high unmet medical need and the number of alterations ranked ESCAT level II, ESMO recommends that patients get access to tumour NGS in the context of clinical genomics programmes to access PARP and *NRG1* inhibitors in clinical trials. Oncologists must verify that *NRG1* fusions are part of the NGS panel. In addition, ESMO recommends using tumour NGS in countries where tumour-agnostic targeted therapies are accessible. Cost-effectiveness should be assessed at the local level and the decision to implement NGS should be taken accordingly.

Genomic alterations according to ESCAT in advanced ovarian cancer

Table 7 provides a list of genomic alterations level I/II according to ESCAT in advanced ovarian cancer.

Considering the benefit of PARPi in patients with advanced ovarian cancer and *BRCA1/2* germline/somatic pathogenic/likely pathogenic variants or homologous recombination deficiency (HRD) signature,¹¹⁵⁻¹¹⁷ it is

recommended to carry out *BRCA1/2* and HRD testing using a validated assay in patients with advanced ovarian cancer. In a retrospective analysis of a randomised trial, it was reported that *KRAS* mutations could predict benefit of binimetinib in advanced ovarian cancer other than high-grade cancer.¹¹⁸ Since only one study has been reported so far, this alteration/drug match does not meet criteria of ESCAT level II.

Summary of recommendations

ESMO recommends running tumour NGS for patients with advanced high-grade ovarian cancer combined with an HRD signature. If DNA quality is suboptimal and/or in case of family history, patients who do not exhibit detectable tumour *BRCA1/2* mutations should undergo clinical genetic testing.

Genomic alterations according to ESCAT in advanced hepatocellular carcinoma

Alterations level I/II in advanced hepatocellular carcinoma are the tumour-agnostic biomarkers. Please refer to the section on [Tumour-agnostic biomarkers](#).

Summary of recommendations

It is not currently recommended to carry out tumour NGS in patients with advanced hepatocellular carcinoma in daily practice, except in countries where tumour-agnostic targeted therapies are accessible. Cost-effectiveness should be assessed at the local level and the decision to implement NGS should be taken accordingly. Moreover, it is important to emphasise that immunotherapy is indicated in advanced hepatocellular carcinoma regardless of genomic alterations.^{119,120}

Genomic alterations according to ESCAT in rare tumours

The most broadly accepted definition of rare cancer sets a threshold of an annual incidence of <6/100 000 people, which encompasses nearly 200 different entities, ~24% of all new cancer cases.¹²¹⁻¹²³ Large series have consistently

Gene/Signature ^a	Alteration	Estimated prevalence	ESCAT score	Drug class matched	References
<i>BRCA1/2</i>	Germline pathogenic/likely pathogenic variants Somatic pathogenic/likely pathogenic variants	15%-17% 5%-7%	IA	PARP inhibitors	Bell et al., <i>Nature</i> 2011 ¹⁰⁹ Mirza et al., <i>N Engl J Med</i> 2016 ¹¹⁰ Coleman et al., <i>Lancet</i> 2017 ¹¹¹ Pujade-Lauraine et al., <i>Lancet Oncol</i> 2017 ¹¹² Moore et al., <i>N Engl J Med</i> 2018 ¹¹³ González-Martin et al., <i>N Engl J Med</i> 2019 ¹¹⁴ Ray-Coquard et al., <i>N Engl J Med</i> 2019 ¹¹⁵ DiSilvestro et al., <i>J Clin Oncol</i> 2023 ¹¹⁶ González-Martin et al., <i>Ann Oncol</i> 2023 ¹¹⁷
HRD ^a	HRD	50% high-grade serous ovarian cancer	IA	PARP inhibitors	Mirza et al., <i>N Engl J Med</i> 2016 ¹¹⁰ Coleman et al., <i>Lancet</i> 2017 ¹¹¹ González-Martin et al., <i>N Engl J Med</i> 2019 ¹¹⁴ Ray-Coquard et al., <i>N Engl J Med</i> 2019 ¹¹⁵ González-Martin et al., <i>Ann Oncol</i> 2023 ¹¹⁷

ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; HRD, homologous recombination deficiency; PARP, poly (ADP-ribose) polymerase.

^aSignature.

demonstrated that rare cancers have impaired 5-year relative survival compared to common cancers.¹²³ Limited data on molecular profiles and the subsequent paucity of drug approvals are among the most critical leading causes. In addition, the rarity of each particular entity hampers proper drug development, and therefore most of the therapeutic indications for NGS in rare tumours fall on levels II or III. Given the heterogeneity and complexity of diseases and molecular backgrounds, the specific analysis of this subset of tumours is beyond the scope of these recommendations. Thus, a limited number of entities have been reviewed herein, and they were selected based on the recent approval of targeted therapies.

Genomic alterations according to ESCAT in advanced cholangiocarcinoma (CCA)

Table 8 provides a list of genomic alterations level I/II according to ESCAT in advanced CCA.

Trastuzumab plus pertuzumab demonstrated antitumour activity in patients with pre-treated advanced HER2-positive biliary tract cancer (BTC), yielding an ORR of 23% (95% CI 11-39) and a median PFS of 4 months (95% CI 1.8-5.7) in the MyPathway study.¹²⁹ This drug combination also displayed efficacy in advanced BTC with *ERBB2* mutations.¹³³ Additionally, the combination of FOLFOX and trastuzumab showed clinical efficacy in pre-treated HER2-positive BTC in a prospective phase II study.¹³⁷ Zanidatamab, a bispecific antibody targeting two distinct HER2 epitopes, achieved a median PFS of 5.5 months (95% CI 3.7-7.2), while median OS data were immature in HER2-positive advanced BTC.¹³¹ Tucatinib and trastuzumab were tested in patients with previously treated HER2-overexpressing or *ERBB2*-amplified BTC. The ORR was 46.7% (90% CI 30.8-63) and the median PFS was 5.5 months (90% CI 3.9-8.1).¹³² Furthermore, neratinib, an irreversible pan-HER TKI, was tested in patients with *ERBB2*-mutated BTC. Median PFS for the gallbladder cancer and CCA subsets were 3.7 months (95% CI 0.8-6.4) and 1.4 months (95% CI 0.5-9.1), respectively.¹³³ Based on these data, the panel assigned *ERBB2*

amplifications as level IB, while ranking *ERBB2* mutations as level IIB. At this point, the interplay between *ERBB2* mutations and HER2 overexpression in BTC cannot be assessed because of limited data availability. Accordingly, while some patients with *ERBB2*-mutated BTC and consecutive HER2 overexpression might benefit from HER2-directed therapies such as ADCs, the magnitude of clinical benefit cannot be measured at the moment. Dabrafenib plus trametinib improved clinical outcome in a multicohort trial involving pre-treated *BRAF*^{V600E}-mutated solid tumours, resulting in FDA accelerated approval in 2022 in this population.¹³⁶ In the subgroup of 53 patients with advanced BTC, the ORR was 53% (95% CI 37.7-68.6), the median PFS was 9 months (95% CI 5.5-9.4), and the median OS was 13.5 months (95% CI 10.4-17.6).¹³⁶ *BRAF*^{V600E} mutations are ranked as level IB. Finally, adagrasib, a selective irreversible *KRAS*^{G12C} inhibitor, demonstrated an ORR of 50% (95% CI 15.7-84.3), a median PFS of 11.3 months [95% CI 1.6-not reached (NR)], and a median OS of 15.1 months (95% CI 12.5-NR) in patients with *KRAS*^{G12C}-mutated CCA in the KRYSTAL-01 basket study, leading to the classification of these alterations as level IC.¹⁰²

Summary of recommendations

Based on the number of alterations classified as level I, it is recommended to carry out tumour NGS in patients with advanced CCA.

Genomic alterations according to ESCAT in advanced GIST

Table 9 provides a list of genomic alterations level I/II according to ESCAT in advanced GIST.

GISTs most often harbour oncogenic mutations in the receptor tyrosine kinases KIT or platelet-derived growth factor receptor A (PDGFRA),¹⁴³ and therefore GIST therapy is based on TKIs with KIT and PDGFRA inhibitory activity. Imatinib is the first-line treatment for advanced disease after achieving a milestone clinical benefit compared to historical records.¹³⁸ Subsequent placebo-controlled randomised clinical trials led to the regulatory approval of

Gene	Alteration	Estimated prevalence	ESCAT score	Drug class matched	References
<i>IDH1</i>	Mutations	8%-18% iCCA	IA	IDH1 inhibitors	Abou-Alfa et al., <i>Lancet Oncol</i> 2020 ¹²⁴
<i>FGFR2</i>	Fusions	5%-15% iCCA	IB	Pan-FGFR TKIs	Javle et al., <i>J Clin Oncol</i> 2018 ¹²⁵ Abou-Alfa et al., <i>Lancet Oncol</i> 2020 ¹²⁶ Pant et al., <i>J Clin Oncol</i> 2023 ¹²⁷ Goyal et al., <i>N Engl J Med</i> 2023 ¹²⁸
<i>ERBB2</i>	Amplifications	10%-20% dCCA, pCCA, GBC	IB	Anti-HER2 monoclonal antibodies Anti-HER2 ADCs	Javle et al., <i>Lancet Oncol</i> 2021 ¹²⁹ Merik-Bernstam et al., <i>JCO</i> 2023 ¹³⁰
	Mutations	3%-5%	IIB	Anti-HER2 bispecific antibodies HER2 TKIs Anti-HER2 monoclonal antibodies Pan-HER TKIs	Harding et al., <i>Lancet Oncol</i> 2023 ¹³¹ Nakamura et al., <i>J Clin Oncol</i> 2023 ¹³² Hyman et al., <i>Nature</i> 2018 ⁷¹ Cannon et al., <i>J Clin Oncol</i> 2023 ¹³³ Harding et al., <i>Nat Comm</i> 2023 ¹³⁴
<i>BRAF</i>	Mutations (p. V600E)	50%	IB	BRAF inhibitors + MEK inhibitors	Subbiah et al., <i>Lancet Oncol</i> 2020 ¹³⁵ Salama et al., <i>J Clin Oncol</i> 2020 ⁸ Subbiah et al., <i>Nature Med</i> 2023 ¹³⁶
<i>KRAS</i>	Mutations (p. G12C)	<1%	IC	<i>KRAS</i> ^{G12C} TKIs	Bekaii-Saab et al., <i>J Clin Oncol</i> 2022 ¹⁰²

ADCs, antibody–drug conjugates; dCCA, distal cholangiocarcinoma; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; GBC, gallbladder carcinoma; HER, human epidermal growth factor receptor; iCCA, intrahepatic cholangiocarcinoma; IDH1, isocitrate dehydrogenase 1; pCCA, perihilar cholangiocarcinoma; TKIs, tyrosine kinase inhibitors.

Table 9. List of genomic alterations level I/II according to ESCAT in advanced gastrointestinal stromal tumour

Gene	Alteration	Estimated prevalence	ESCAT score	Drug class matched	References
<i>KIT</i>	Mutations/insertions/deletions/indels	85%	IA	KIT/PDGFR TKIs	Demetri et al., <i>N Engl J Med</i> 2002 ¹³⁸ Demetri et al., <i>Lancet</i> 2006 ¹³⁹ Demetri et al., <i>Lancet</i> 2013 ¹⁴⁰ Blay et al., <i>Lancet Oncol</i> 2020 ¹⁴¹
<i>PDGFRA</i>	Mutations/insertions/deletions/indels	10%-15%	IA	KIT/PDGFR TKIs	Demetri et al., <i>N Engl J Med</i> 2002 ¹³⁸ Demetri et al., <i>Lancet</i> 2006 ¹³⁹ Demetri et al., <i>Lancet</i> 2013 ¹⁴⁰ Blay et al., <i>Lancet Oncol</i> 2020 ¹⁴¹
	Exon 18 D842V mutations	5%	IB	KIT/PDGFR TKIs	Heinrich et al., <i>Lancet Oncol</i> 2020 ¹⁴²

ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; PDGFR, platelet-derived growth factor receptor A; TKIs, tyrosine kinase inhibitors.

sunitinib, regorafenib, and ripretinib as the standard second-, third-, and fourth-line treatments,¹³⁹⁻¹⁴¹ displaying improvement of outcomes in patients with GIST and *KIT* or *PDGFRA* mutations. *KIT* and *PDGFRA* alterations are classified as level IA. The *PDGFRA* D842V primary mutation is present in ~5% of GISTs and leads to resistance to all known TKIs. A prospective non-randomised study showed clinical efficacy of avapritinib in patients with GIST and this specific alteration, but not in the general population.^{142,144} Based on this data, the FDA granted approval to avapritinib in this setting.

Summary of recommendations

Based on the number of alterations currently classified as level I, it is recommended to carry out tumour NGS in patients with advanced GIST.

Genomic alterations according to ESCAT in advanced soft-tissue sarcomas

Table 10 provides a list of genomic alterations level I/II according to ESCAT in advanced soft-tissue sarcomas.

Most actionable alterations in soft-tissue sarcomas are histology specific; thus, sarcoma experts recommend carrying out diagnostic procedures in referral institutions.¹⁵² However, as a significant proportion of these patients are not initially seen in such centres, NGS panels looking for actionable targets can aid to reclassify these entities, especially when carried out in the community.¹⁵³

Crizotinib demonstrated effectiveness (ORR 66.7%, 95% CI 34.9-90.1) and improved survival outcomes [median PFS 18

months (95% CI 4.0-not estimable); 3-year OS 83.3% (95% CI 48.2% to 95.6%)] in patients with advanced *ALK* fusion-positive inflammatory myofibroblastic tumours (IMTs),¹⁴⁶ leading to the classification of *ALK* fusions as level IB. Moreover, *COLIA1-PDGFB* fusions are ranked as level IB due to the clinical activity of imatinib in patients with dermatofibrosarcoma protuberans (DFSP) exhibiting these fusions. Imatinib has received regulatory approval for this indication.¹⁴⁸ *INI1/SMARCB1* alterations, frequently observed in epithelioid sarcoma, are categorised as level IB. This decision was based on the outcome improvement [median PFS 5.5 months (95% CI 3.4-5.9) and median OS 19 months (95% CI 11-not estimable)] of tazemetostat, an oral selective EZH2 inhibitor, in a cohort of 62 patients with advanced *INI1/SMARCB1*-altered epithelioid sarcoma from a basket trial.¹⁵⁰ In 2020, the FDA granted accelerated approval to tazemetostat in this subgroup of patients. Finally, mTOR inhibitors displayed antitumour activity in patients with advanced malignant perivascular epithelioid cell tumour (PEComa), achieving a confirmed response rate of 89% and 20% in patients harbouring *TSC2* or *TSC1* mutation, respectively.¹⁵¹ *TSC1/TSC2* alterations are ranked as level IIA.

Summary of recommendations

NGS is an essential tool for identifying the histological subtype of soft-tissue sarcomas and improving diagnosis. In addition, several alterations are classified as level I according to ESCAT in the metastatic setting, justifying the use of tumour NGS in this disease. Oncologists must ensure that the fusions they are seeking are included in the panel.

Table 10. List of genomic alterations level I/II according to ESCAT in advanced soft-tissue sarcomas

Gene	Alteration	Estimated prevalence	Sarcoma subtype	ESCAT score	Drug class matched	References
<i>ALK</i>	Fusions	66%	Inflammatory myofibroblastic tumour	IB	ALK TKIs	Schöffski et al., <i>Lancet Respir Med</i> 2018 ¹⁴⁵ Schöffski et al., <i>Eur J Cancer</i> 2021 ¹⁴⁶
<i>COLIA1-PDGFB</i>	Fusions	100%	Dermatofibrosarcoma protuberans	IB	KIT/PDGFR TKIs	Shimizu et al., <i>Cancer Res</i> 1999 ¹⁴⁷ Rutkowski et al., <i>J Clin Oncol</i> 2010 ¹⁴⁸
<i>INI1/SMARCB1</i>	Mutations/deletions	90%	Epithelioid sarcoma	IB	EZH2 inhibitors	Modena et al., <i>Cancer Res</i> 2005 ¹⁴⁹ Gounder et al., <i>Lancet Oncol</i> 2020 ¹⁵⁰
<i>TSC1/2</i>	Mutations/deletions	>80%	PEComa	IIA	mTOR inhibitors	Wagner et al., <i>J Clin Oncol</i> 2021 ¹⁵¹

ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; EZH2, enhancer of zeste homologue 2; mTOR, mammalian target of rapamycin; PEComa, perivascular epithelioid cell tumour; PDGFR, platelet-derived growth factor receptor; TKIs, tyrosine kinase inhibitors.

Table 11. List of genomic alterations level I/II according to ESCAT in advanced thyroid cancer

Gene	Alteration	Estimated prevalence	ESCAT score	Drug class matched	References
RET	Mutations	60% medullary thyroid cancer	IA	RET inhibitors	Ciampi et al., <i>iScience</i> 2019 ¹⁵⁴ Wirth et al., <i>N Engl J Med</i> 2020 ¹⁵⁵ Kim et al., <i>Clin Cancer Res</i> 2021 ¹⁵⁶ Mansfield et al., <i>J Clin Oncol</i> 2022 ¹⁵⁷ Hadoux et al., <i>N Engl J Med</i> 2023 ¹⁵⁸
	Fusions	7%	IB	RET inhibitors	Agrawal et al., <i>Cell</i> 2014 ¹⁵⁹ Wirth et al., <i>N Engl J Med</i> 2020 ¹⁵⁵ Kim et al., <i>Clin Cancer Res</i> 2021 ¹⁵⁶ Mansfield et al., <i>J Clin Oncol</i> 2022 ¹⁵⁷
BRAF	Mutations (p. V600E)	10%-50% anaplastic thyroid cancer	IB	BRAF inhibitors + MEK inhibitors BRAF inhibitors	Subbiah et al., <i>J Clin Oncol</i> 2018 ¹⁶⁰ Subbiah et al., <i>Ann Oncol</i> 2022 ¹⁶¹ Brose et al., <i>Lancet Oncol</i> 2016 ¹⁹⁴
		40%-50% papillary thyroid cancer	IIB		

ESCAT, ESMO Scale for Clinical Actionability of molecular Targets.

Genomic alterations according to ESCAT in advanced thyroid cancer

Table 11 provides a list of genomic alterations level I/II according to ESCAT in advanced thyroid cancer.

Selpercatinib as first-line therapy improved median PFS as compared to standard treatment in patients with *RET*-mutated medullary thyroid cancer (HR 0.28; 95% CI 0.16-0.48; $P < 0.001$) in a phase III randomised trial.¹⁵⁸ Consequently, *RET* mutations are classified as level IA. These data have been reported after the publication of the ESMO Clinical Practice Guideline for diagnosis, treatment, and follow-up of patients with advanced thyroid cancer.¹⁶² Furthermore, *RET* fusions are ranked as level IB based on the findings from the ARROW trial. In this prospective, phase II study, pralsetinib showed clinical benefit in patients with previously treated *RET* fusion-positive thyroid cancer, with an ORR of 86% (95% CI 64-97) and a median PFS of 19.4 months (95% CI 13.0-NR).¹⁵⁷ The FDA has granted accelerated approval and the EMA has issued a conditional marketing authorisation for selpercatinib in patients with advanced solid tumours displaying *RET* alterations.¹⁶³ Pralsetinib also received FDA accelerated approval for the same indication based on the results of the prospective multi-cohort ARROW trial.¹⁵⁶ Lastly, the panel designated *BRAF*^{V600E} mutations as level IB, considering the enhanced clinical outcomes observed in the cohort of pre-treated patients with advanced *BRAF*^{V600E}-mutated anaplastic thyroid cancer in the phase II ROAR basket study.¹⁶¹ In this trial, dabrafenib plus trametinib displayed a median PFS of

6.7 months (95% CI 4.7-13.8) and a median OS of 14.5 months (95% CI 6.8-23.2). The FDA has granted approval to dabrafenib plus trametinib in this population.

Summary of recommendations

Based on the number of alterations currently classified as level I, ESMO recommends carrying out tumour NGS in patients with advanced thyroid cancer.

Genomic alterations according to ESCAT in unfavourable CUP

Table 12 provides a list of genomic alterations level I/II according to ESCAT in unfavourable CUP.

The use of molecular targeted therapies in CUP is strongly recommended when the respective compound has received cancer type-agnostic approval (*NTRK* fusion-positive, MSI-high, and TMB-high cancers). Likewise, *BRAF*^{V600E} mutations and *RET* alterations can be considered as cancer type-agnostic targets. In addition, the CUPISCO study displayed an important improvement of PFS (HR 0.72; 95% CI 0.56-0.92; $P = 0.0079$) with molecular-guided therapy compared to chemotherapy as maintenance treatment for patients with unfavourable CUP and actionable genomic alterations. This underscores the crucial role of incorporating comprehensive genomic profiling into the routine practice for these patients.¹⁷¹ Targeted therapies are also strongly recommended in patients with tumours harbouring a genetic alteration suggestive of a putative primary in which molecular-guided therapies are licensed

Table 12. List of genomic alterations level I/II according to ESCAT in unfavourable cancer of unknown primary

Gene/signature ^a	Alteration	Estimated prevalence	ESCAT score	Drug class matched	References
TMB-H ^a	TMB-H	TMB > 10 (23%) TMB > 16 (12%) TMB > 20 (9%)	IB	PD-1 inhibitors + anti-CTLA4 inhibitors	Ross et al., <i>Oncologist</i> 2021 ¹⁶⁴ Tanizaki et al., <i>Ann Oncol</i> 2022 ¹⁶⁵ Pouyiourou et al., <i>Ann Oncol</i> 2022 ¹⁶⁶ Pouyiourou et al., <i>Nat Comm</i> 2023 ¹⁶⁷
ALK	Fusions	1%	IIB	ALK TKIs	Ross et al., <i>JAMA Oncol</i> 2015 ¹⁶⁸ Bochtler et al., <i>Int J Cancer</i> 2020 ¹⁶⁹ Ross et al., <i>Oncologist</i> 2021 ¹⁶⁴ Möhrmann et al., <i>Nat Commun</i> 2022 ¹⁷⁰

CTLA4, cytotoxic T-lymphocyte associated protein 4; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; PD-1, programmed cell death protein 1; TKIs, tyrosine kinase inhibitors; TMB-H, tumour mutation burden-high.

^aSignature.

and are the standard of care.¹⁷² In individual cases, NGS might clarify or provide clues regarding the putative primary, although in many cases some ambiguity might remain: NSCLC (*ALK* fusions, *ROS1* fusions), intrahepatic CCA (*FGFR2* fusions), salivary gland carcinoma (*ETV6-NTRK3*, *MYB*, *MYBL2*, *EWSR1-ATF1*, *MAML2*, *PLAG1*, and *HMG2* fusions, *PRKD1* mutations), NUT carcinoma (*NUTM1* fusions), prostate cancer (*TMPRSS2-ERG* fusions), sarcoma and other mesenchymal tumours (*EWSR1-FLI1*, *EWSR1-ERG*, *EWSR1-WT1*, *EWSR1-POU5F1*, *HEY1-NCOA2*, *COL1A1-PDGFB*, *ETV6-NTRK3*, *DDIT3*, *CREB3L2/CREB3L1*, *TFE3*, *NAB2-STAT6*, *SS18(SYT)* and *NR4A3* fusions, *SMARCB1* and *BCOR* alterations, *KIT* mutations), hepatocellular carcinoma (*PRKACA* fusions), renal cell carcinoma (*TFE3* fusions), and breast cancer (*ETV3* fusions). This list is not comprehensive and does not include haematological malignancies. In a prospective, phase II study nivolumab plus ipilimumab showed antitumour activity in patients with CUP relapsed after platinum-based chemotherapy. TMB-H was associated with a higher ORR of 60% (95% CI 15-25) compared to TMB-low, which had an ORR of 7.7% (95% CI 1-25). Moreover, TMB-H exhibited a superior median PFS (HR 0.32; 95% CI 0.09-1.10; $P = 0.056$), as well as a better OS (HR 0.32; 95% CI 0.09-1.09; $P = 0.056$).¹⁶⁷ TMB-H is ranked as level IB.

Summary of recommendations

Given the positive impact on patient outcomes observed with targeted therapy in this population and the capability of NGS to assist in identifying the primary tumour, it is recommended to carry out tumour NGS in patients with unfavourable CUP.

IMPORTANT CONSIDERATIONS WHEN ORDERING AN NGS

Technologies to detect fusion genes

Chromosomal rearrangements can create potent oncogenic fusion genes, which represent important therapeutic targets for precision oncology. Examples of gene fusions for which targeted drugs have been approved are those involving *ALK*, *ROS1*, *RET*, *FGFR1/2/3*, and *NTRK1/2/3*. In clinical practice, different technologies are employed for the identification of fusion genes. The advantages and limitations of these techniques are described in the following paragraphs. The main point is also to stress the fact that clinicians must assess whether the NGS panel includes the detection of the fusions recommended in a specific disease. NGS panels for gene fusions detection are based on DNA and/or RNA sequencing.¹⁷³ DNA sequencing has the advantage that DNA is more stable than RNA. However, DNA sequencing can only identify break points of translocations leading to gene fusions. These breaks may occur in large intronic regions, which may not be fully covered by a gene panel, or in regions comprising homopolymers/segmental duplication/repeated sequences, which can be challenging to sequence. Therefore, precise knowledge of the genomic architecture of a gene fusion of interest is critical, not only for the panel design but also for the interpretation of test results.¹⁷⁴ For example, a test that

does not detect a fusion might be false negative if the break point region is not fully covered by the gene panel employed for the diagnostic test. Several limitations of DNA-based fusion gene sequencing are overcome by RNA-based sequencing methods. RNA-based gene panels identify the transcript of the fusion gene resulting from a translocation, and provide data on the 'expression' of the fusion transcript, the fusion partner as well as the potential functionality (e.g. out-of-frame versus in-frame fusions).¹⁷⁵ In contrast to DNA-based assays, it does not provide information on break points. The sensitivity of NGS panels also depends on the technologies used for library preparation: hybrid capture based, amplicon based, or single primer extension (e.g. anchored multiplex PCR).¹⁷⁶ [Supplementary Table S3](https://doi.org/10.1016/j.annonc.2024.04.005), available at <https://doi.org/10.1016/j.annonc.2024.04.005>, summarises the pros and cons of the different NGS methods for fusion detection.

Technologies to detect homologous recombination deficiency (HRD)

HRD is indicative that a cell is unable to repair double-strand breaks using the homologous recombination DNA repair (HRR) pathway. To date, this has only been validated for a single clinical indication, namely the use of olaparib and bevacizumab as first-line maintenance in ovarian cancer.¹¹⁷ The prevalence in ovarian cancer is close to 50%.¹⁷⁷ The clinical utility of this signature as predictor of PARPi response has yet to be demonstrated in breast, prostate, and pancreatic cancers where the prevalence of HRD is comparably high, but under 15%.¹⁷⁸ [Supplementary Table S4](https://doi.org/10.1016/j.annonc.2024.04.005), available at <https://doi.org/10.1016/j.annonc.2024.04.005>, summarises the validated methods for detection of HRD.

Incidental results with NGS

The increase in sensitivity in NGS and the extension of the panel size with a large number of genes can expose incidental results from germline variants, secondary cancer, and haematological disease as clonal haematopoiesis.

Incidental germline variants. This question has been addressed by Kuzbari et al. in the ESMO PMWG recommendations.¹⁷⁹

Secondary cancers. The detection of secondary cancers on the tumour analysis represents the identification of a genetically distinct population of variant in the analysis from the initial solid tumour.¹⁸⁰ The use of large panels and especially on DNA from plasma exposed to the risk of discovering a second cancer ([Supplementary Table S5](https://doi.org/10.1016/j.annonc.2024.04.005), available at <https://doi.org/10.1016/j.annonc.2024.04.005>). This should be discussed for any divergence on the initial cancer variants and other dedicated variants to certain cancers. For those cases, a radiological investigation or a serum markers analysis should be proposed to exclude a secondary solid tumour.

Clonal haematopoiesis. Clonal haematopoiesis (CH) on the tumour analysis represents the presence of a genetically distinct population of blood cells in the absence of morphological evidence of haematological malignancies.¹⁸¹ High-risk CH can be found in patients with solid tumours especially on plasma cell-free DNA sequencing.¹⁸² To be referred as CH of indeterminate potential (CHIP), the somatic variants of haematological malignancy-associated genes should be with a variant allele fraction (VAF) $\geq 2\%$; however, it can be quite variable depending on the gene. [Supplementary Table S6](https://doi.org/10.1016/j.annonc.2024.04.005), available at <https://doi.org/10.1016/j.annonc.2024.04.005>, describes genes involved in CH.

The main driver of CHIP variants is clearly patient age, but other factors can be involved such as chemotherapy, radiation, or smoking.^{181,183} The main question is then the risk of transformation to acute myeloid leukaemia or myelodysplastic syndrome. This risk is not well determined except for certain genes as *JAK2*, *MPL*, and *MYD88*.¹⁸⁴ A high burden of variants on myeloid malignancy-associated genes should be followed up—any VAF $> 10\%$.

Health economics evidence

From the payer's point of view, since previous ESMO recommendations, advanced non-squamous NSCLC is the sole indication where the cost-effectiveness of a multigene panel sequencing approach compared with single-marker testing and sequential testing has been demonstrated at acceptable willingness-to-pay thresholds in Europe, Asia, and United States.¹⁸⁵⁻¹⁹¹ However, uncertainty remains regarding the optimal size of the NGS panel to be used in daily practice. For other indications, although the cost of NGS testing has decreased, relevant economic studies are needed to investigate the cost-effectiveness of a large-scale NGS testing strategy to guide cancer treatment decisions. Moreover, at the country level, the reimbursement/coverage of biomarker-driven therapies is a pre-requisite to the adoption of multigene panel sequencing approaches.

In addition, as shown by a recent survey carried out in Europe by ESMO,¹⁹² organisational and logistics obstacles (e.g. prescription process, access to therapies, molecular tumour board implementation, bioinformatics workflows, trained local personnel and laboratory infrastructures, regulatory and reimbursement environment, etc.) need to be tackled in order to increase the equity of access to biomolecular technologies across and within countries and to deliver results to clinicians in a timely manner.

Finally, the use of genomic scales such as ESCAT is essential to ensure that the adoption of NGS panels in daily practice will lead to an appropriate use of drugs where the level of evidence is high enough (ESCAT I/II). It is a major concern to limit the budget impact of the use of off-label targeted agents where the level of evidence is low and where no or only a small clinical benefit might be expected.¹⁹³

CONCLUSIONS

The ESMO PMWG recommends running tumour NGS in patients with advanced non-squamous NSCLC, breast,

colorectal, prostate, and ovarian cancer. In addition, for rare tumours, it is recommended to carry out tumour NGS in patients with advanced CCA, GIST, sarcoma, thyroid cancer, and unfavourable CUP. Finally, ESMO recommends to carry out tumour NGS to detect tumour-agnostic alterations in patients with advanced cancers, in countries where tumour-agnostic targeted therapies are accessible. This recommendation takes into consideration cost-effectiveness and ensures that the sought-after fusions are integrated in the panel.

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REFERENCES

- Mosele F, Remon J, Mateo J, et al. Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group. *Ann Oncol.* 2020;31:1491-1505.
- Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. *Lancet Oncol.* 2020;21:531-540.
- Demetri GD, De Braud F, Drilon A, et al. Updated integrated analysis of the efficacy and safety of entrectinib in patients with NTRK fusion-positive solid tumors. *Clin Cancer Res.* 2022;28:1302-1312.
- Marcus L, Lemery SJ, Keegan P, et al. FDA Approval Summary: pembrolizumab for the treatment of microsatellite instability-high solid tumors. *Clin Cancer Res.* 2019;25:3753-3758.
- Subbiah V, Wolf J, Konda B, et al. Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. *Lancet Oncol.* 2022;23:1261-1273.
- Subbiah V, Cassier PA, Siena S, et al. Pan-cancer efficacy of pralsetinib in patients with RET fusion-positive solid tumors from the phase 1/2 ARROW trial. *Nat Med.* 2022;28:1640-1645.
- Subbiah V, Puzanov I, Blay J-Y, et al. Pan-cancer efficacy of vemurafenib in BRAF V600-mutant non-melanoma cancers. *Cancer Discov.* 2020;10:657-663.
- Salama AKS, Li S, Macrae ER, et al. Dabrafenib and trametinib in patients with tumors with BRAFV600E mutations: results of the NCI-MATCH trial subprotocol H. *J Clin Oncol.* 2020;38:3895-3904.
- Pant S, Schuler M, Iyer G, et al. Erdafitinib in patients with advanced solid tumours with FGFR alterations (RAGNAR): an international, single-arm, phase 2 study. *Lancet Oncol.* 2023;24:925-935.
- Valero C, Lee M, Hoen D, et al. Response rates to anti-PD-1 immunotherapy in microsatellite-stable solid tumors with 10 or more mutations per megabase. *JAMA Oncol.* 2021;7:739-743.
- Friedman CF, Haisworth JD, Kurzrock R, et al. Atezolizumab treatment of tumors with high tumor mutational burden from mypathway, a multicenter, open-label, phase IIa multiple basket study. *Cancer Discov.* 2022;12:654-669.
- Midha A, Dearden S, McCormack R. EGFR mutation incidence in non-small-cell lung cancer of adenocarcinoma histology: a systematic review and global map by ethnicity (mutMapII). *Am J Cancer Res.* 2015;5:2892-2911.
- Arrieta O, Cardona AF, Martín C, et al. Updated frequency of EGFR and KRAS mutations in non-small-cell lung cancer in Latin America: the Latin-American Consortium for the Investigation of Lung Cancer (LICaP). *J Thorac Oncol.* 2015;10:838-843.
- Soria J-C, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med.* 2018;378:113-125.
- Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *N Engl J Med.* 2020;382:41-50.
- Cho BC, Felip E, Spira AI, et al. Amivantamab plus lazertinib vs osimertinib as first-line treatment in patients with EGFR-mutated, advanced non-small cell lung cancer: primary results from MAR-IPOSA, a phase III, global, randomized, controlled trial. *Ann Oncol.* 2023;34(suppl 2):S1254-S1335.
- Passaro A, Wang J, Wang Y, et al. Amivantamab plus chemotherapy with and without lazertinib in EGFR-mutant advanced NSCLC after disease progression on osimertinib: primary results from the phase III MARIPOSA-2 study. *Ann Oncol.* 2024;35:77-90.
- Mok TS, Wu Y-L, Ahn M-J, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med.* 2017;376:629-640.
- Papadimitrakopoulou VA, Mok TS, Han J-Y, et al. Osimertinib versus platinum-pemetrexed for patients with EGFR T790M advanced NSCLC and progression on a prior EGFR-tyrosine kinase inhibitor: AURA3 overall survival analysis. *Ann Oncol.* 2020;31:1536-1544.
- Park K, Haura EB, Leigh NB, et al. Amivantamab in EGFR Exon 20 insertion-mutated non-small-cell lung cancer progressing on platinum chemotherapy: initial results from the CHRYSALIS phase I study. *J Clin Oncol.* 2021;39:3391-3402.
- Zhou C, Tang K-J, Cho BC, et al. Amivantamab plus chemotherapy in NSCLC with EGFR exon 20 insertions. *N Engl J Med.* 2023;389:2039-2051.
- Cho JH, Lim SH, An HJ, et al. Osimertinib for patients with non-small-cell lung cancer harboring uncommon egfr mutations: a multicenter, open-label, phase II trial (KCSG-LU15-09). *J Clin Oncol.* 2020;38:488-495.
- Yang JC-H, Schuler M, Popat S, et al. Afatinib for the treatment of non-small cell lung cancer harboring uncommon EGFR mutations: an updated database of 1023 cases brief report. *Front Oncol.* 2022;12:834704.
- Mok T, Camidge DR, Gadgeel SM, et al. Updated overall survival and final progression-free survival data for patients with treatment-naïve advanced ALK-positive non-small-cell lung cancer in the ALEX study. *Ann Oncol.* 2020;31:1056-1064.
- Shaw AT, Bauer TM, de Marinis F, et al. First-line lorlatinib or crizotinib in advanced ALK-positive lung cancer. *N Engl J Med.* 2020;383:2018-2029.
- Camidge DR, Kim HR, Ahn M-J, et al. Brigatinib versus crizotinib in ALK inhibitor-naïve advanced ALK-positive NSCLC: final results of phase 3 ALTA-1L trial. *J Thorac Oncol.* 2021;16:2091-2108.
- Horn L, Wang Z, Wu G, et al. Ensartinib vs crizotinib for patients with anaplastic lymphoma kinase-positive non-small cell lung cancer: a randomized clinical trial. *JAMA Oncol.* 2021;7:1617-1625.
- Solomon BJ, Bauer TM, Mok TSK, et al. Efficacy and safety of first-line lorlatinib versus crizotinib in patients with advanced, ALK-positive non-small-cell lung cancer: updated analysis of data from the phase 3, randomised, open-label CROWN study. *Lancet Respir Med.* 2023;11:354-366.
- Jänne PA, Riely GJ, Gadgeel SM, et al. Adagrasib in non-small-cell lung cancer harboring a KRASG12C mutation. *N Engl J Med.* 2022;387:120-131.
- de Langen AJ, Johnson ML, Mazieres J, et al. Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with KRASG12C mutation: a randomised, open-label, phase 3 trial. *Lancet.* 2023;401:733-746.
- Subbiah V, Gainor JF, Oxnard GR, et al. Intracranial efficacy of selpercatinib in RET fusion-positive non-small cell lung cancers on the LIBRETTO-001 trial. *Clin Cancer Res.* 2021;27:4160-4167.
- Griesinger F, Curigliano G, Thomas M, et al. Safety and efficacy of pralsetinib in RET fusion-positive non-small-cell lung cancer including as first-line therapy: update from the ARROW trial. *Ann Oncol.* 2022;33:1168-1178.
- Drilon A, Subbiah V, Gautschi O, et al. Selpercatinib in patients with RET fusion-positive non-small-cell lung cancer: updated safety and

- efficacy from the registrational LIBRETTO-001 phase I/II trial. *J Clin Oncol.* 2023;41:385-394.
34. Zhou C, Solomon B, Loong HH, et al. First-line seliperatinib or chemotherapy and pembrolizumab in RET fusion-positive NSCLC. *N Engl J Med.* 2023;389:1839-1850.
 35. Shaw AT, Riely GJ, Bang Y-J, et al. Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001. *Ann Oncol.* 2019;30:1121-1126.
 36. Shaw AT, Solomon BJ, Chiari R, et al. Lorlatinib in advanced ROS1-positive non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 1-2 trial. *Lancet Oncol.* 2019;20:1691-1701.
 37. Drilon A, Chiu C-H, Fan Y, et al. Long-term efficacy and safety of entrectinib in ROS1 fusion-positive NSCLC. *JTO Clin Res Rep.* 2022;3:100332.
 38. Planchard D, Besse B, Groen HJM, et al. Phase 2 study of dabrafenib plus trametinib in patients with BRAF V600E-mutant metastatic NSCLC: updated 5-year survival rates and genomic analysis. *J Thorac Oncol.* 2022;17:103-115.
 39. Riely GJ, Smit EF, Ahn M-J, et al. Phase II, open-label study of encorafenib plus binimetinib in patients with BRAFV600-mutant metastatic non-small-cell lung cancer. *J Clin Oncol.* 2023;41:3700-3711.
 40. Drilon A, Clark JW, Weiss J, et al. Antitumor activity of crizotinib in lung cancers harboring a MET exon 14 alteration. *Nat Med.* 2020;26:47-51.
 41. Wolf J, Garon EB, Groen HJM, et al. Capmatinib in MET exon 14-mutated, advanced NSCLC: updated results from the GEOMETRY mono-1 study. *J Clin Oncol.* 2021;39:9020.
 42. Lu S, Fang J, Li X, et al. Once-daily savolitinib in Chinese patients with pulmonary sarcomatoid carcinomas and other non-small-cell lung cancers harbouring MET exon 14 skipping alterations: a multicentre, single-arm, open-label, phase 2 study. *Lancet Respir Med.* 2021;9:1154-1164.
 43. Thomas M, Garassino M, Felip E, et al. OA03.05 Tepotinib in patients with MET Exon 14 (METex14) skipping NSCLC: primary analysis of the confirmatory VISION cohort C. *J Thorac Oncol.* 2022;17:S9-S10.
 44. Wolf J, Garon EB, Groen HJM, et al. 26P Capmatinib in treatment (Tx)-naïve MET exon 14-mutated (METex14) advanced non-small cell lung Cancer (aNSCLC): updated results from GEOMETRY mono-1. *Ann Oncol.* 2022;33:S42.
 45. Yu HA, Ambrose H, Baik C, et al. 1239P ORCHARD osimertinib + savolitinib interim analysis: a biomarker-directed phase II platform study in patients (pts) with advanced non-small cell lung cancer (NSCLC) whose disease has progressed on first-line (1L) osimertinib. *Ann Oncol.* 2021;32:S978-S979.
 46. Bauml J, Cho BC, Park K, et al. Amivantamab in combination with lazertinib for the treatment of osimertinib-relapsed, chemotherapy-naïve EGFR mutant (EGFRm) non-small cell lung cancer (NSCLC) and potential biomarkers for response. *J Clin Oncol.* 2021;39:9006.
 47. Shu CA, Goto K, Ohe Y, et al. Amivantamab and lazertinib in patients with EGFR-mutant non-small cell lung (NSCLC) after progression on osimertinib and platinum-based chemotherapy: updated results from CHRYSALIS-2. *J Clin Oncol.* 2022;40:9006.
 48. Marmarelis ME, Lee S-H, Spira AI, et al. MA07.04 amivantamab and lazertinib in combination with platinum-based chemotherapy in relapsed/refractory EGFR-mutant NSCLC. *J Thorac Oncol.* 2022;17:S68.
 49. Hartmaier RJ, Markovets AA, Ahn MJ, et al. Osimertinib + savolitinib to overcome acquired MET-mediated resistance in epidermal growth factor receptor-mutated, MET-amplified non-small cell lung cancer: TATTON. *Cancer Discov.* 2023;13:98-113.
 50. Tan DS-W, Kim TM, Guarneri V, et al. Tepotinib + osimertinib for EGFR mutant (EGFRm) NSCLC with MET amplification (METamp) after first-line (1L) osimertinib. *J Clin Oncol.* 2023;41. 9021-9021.
 51. Hyman DM, Piha-Paul SA, Won H, et al. HER kinase inhibition in patients with HER2- and HER3-mutant cancers. *Nature.* 2018;554:189-194.
 52. Li BT, Smit EF, Goto Y, et al. Trastuzumab deruxtecan in HER2-mutant non-small-cell lung cancer. *N Engl J Med.* 2022;386:241-251.
 53. Schram AM, Goto K, Kim D-W, et al. Efficacy and safety of zenocutuzumab, a HER2 x HER3 bispecific antibody, across advanced NRG1 fusion (NRG1+) cancers. *J Clin Oncol.* 2022;40:105.
 54. Hendriks LE, Kerr KM, Menis J, et al. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol.* 2023;34:339-357.
 55. Baselga J, Cortés J, Kim S-B, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med.* 2012;366:109-119.
 56. Krop IE, Kim S-B, González-Martín A, et al. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2014;15:689-699.
 57. Lin NU, Borges V, Anders C, et al. Intracranial efficacy and survival with tucatinib plus trastuzumab and capecitabine for previously treated HER2-positive breast cancer with brain metastases in the HER2CLIMB trial. *J Clin Oncol.* 2020;38:2610-2619.
 58. Saura C, Oliveira M, Feng Y-H, et al. Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with ≥ 2 HER2-directed regimens: phase III NALA trial. *J Clin Oncol.* 2020;38:3138-3149.
 59. Rugo HS, Im S-A, Cardoso F, et al. Efficacy of margetuximab vs trastuzumab in patients with pretreated ERBB2-positive advanced breast cancer: a phase 3 randomized clinical trial. *JAMA Oncol.* 2021;7:573-584.
 60. Smyth LM, Piha-Paul SA, Won HH, et al. Efficacy and determinants of response to HER kinase inhibition in HER2-mutant metastatic breast cancer. *Cancer Discov.* 2020;10:198-213.
 61. Li BT, Meric-Bernstam F, Bardia A, et al. Efficacy and safety of trastuzumab deruxtecan (T-DXD) in patients (pts) with solid tumors harboring specific HER2-activating mutations (HER2m): primary results from the international phase 2 DESTINY-PanTumor01 (DPT-01) study. *Ann Oncol.* 2023;34(suppl 2):S458-S497.
 62. André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med.* 2019;380:1929-1940.
 63. Rugo HS, Lerebours F, Ciruelos E, et al. Alpelisib plus fulvestrant in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): one cohort of a phase 2, multicentre, open-label, non-comparative study. *Lancet Oncol.* 2021;22:489-498.
 64. Bidard F-C, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: results from the randomized phase III EMERALD trial. *J Clin Oncol.* 2022;40:3246-3256.
 65. Bardia A, Bidard F-C, Neven P, et al. Abstract GS3-01: GS3-01 EMERALD phase 3 trial of elacestrant versus standard of care endocrine therapy in patients with ER+/HER2- metastatic breast cancer: updated results by duration of prior CDK4/6i in metastatic setting. *Cancer Res.* 2023;83. GS3-01.
 66. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *N Engl J Med.* 2018;379:753-763.
 67. Robson ME, Im S-A, Senkus E, et al. OlympiAD extended follow-up for overall survival and safety: olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Eur J Cancer.* 2023;184:39-47.
 68. Tung NM, Robson ME, Ventz S, et al. TBCRC 048: phase II study of olaparib for metastatic breast cancer and mutations in homologous recombination-related genes. *J Clin Oncol.* 2020;38:4274-4282.
 69. Schmid P, Abraham J, Chan S, et al. Capiivasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer: the PAKT trial. *J Clin Oncol.* 2020;38:423-433.

70. Turner NC, Oliveira M, Howell SJ, et al. Capivasertib in hormone receptor–positive advanced breast cancer. *N Engl J Med*. 2023;388:2058-2070.
71. Kalinsky K, Hong F, McCourt CK, et al. Effect of capivasertib in patients with an AKT1 E17K-mutated tumor: NCI-MATCH subprotocol EAY131-Y nonrandomized trial. *JAMA Oncol*. 2021;7:271-278.
72. Gruber JJ, Afghahi A, Timms K, et al. A phase II study of talazoparib monotherapy in patients with wild-type BRCA1 and BRCA2 with a mutation in other homologous recombination genes. *Nat Cancer*. 2022;3:1181-1191.
73. Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol*. 2021;32:1475-1495.
74. Terraf P, Pareja F, Brown DN, et al. Comprehensive assessment of germline pathogenic variant detection in tumor-only sequencing. *Ann Oncol*. 2022;33:426-433.
75. Hodgson D, Lai Z, Dearden S, et al. Analysis of mutation status and homologous recombination deficiency in tumors of patients with germline BRCA1 or BRCA2 mutations and metastatic breast cancer: OlympiAD. *Ann Oncol*. 2021;32:1582-1589.
76. Douillard J-Y, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med*. 2013;369:1023-1034.
77. Van Cutsem E, Lenz H-J, Köhne C-H, et al. Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer. *J Clin Oncol*. 2015;33:692-700.
78. Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, binimetinib, and cetuximab in BRAF V600E-mutated colorectal cancer. *N Engl J Med*. 2019;381:1632-1643.
79. André T, Shiu K-K, Kim TW, et al. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. *N Engl J Med*. 2020;383:2207-2218.
80. Fakih MG, Salvatore L, Esaki T, et al. Sotorasib plus panitumumab in refractory colorectal cancer with mutated KRAS G12C. *N Engl J Med*. 2023;389:2125-2139.
81. Meric-Bernstam F, Hurwitz H, Raghav KPS, et al. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. *Lancet Oncol*. 2019;20:518-530.
82. Siena S, Di Bartolomeo M, Raghav K, et al. Trastuzumab deruxtecan (DS-8201) in patients with HER2-expressing metastatic colorectal cancer (DESTINY-CRC01): a multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2021;22:779-789.
83. Strickler JH, Cercek A, Siena S, et al. Tucatinib plus trastuzumab for chemotherapy-refractory, HER2-positive, RAS wild-type unresectable or metastatic colorectal cancer (MOUNTAINEER): a multicentre, open-label, phase 2 study. *Lancet Oncol*. 2023;24:496-508.
84. Rousseau B, Bieche I, Pasmant E, et al. PD-1 blockade in solid tumors with defects in polymerase epsilon. *Cancer Discov*. 2022;12:1435-1448.
85. de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2020;382:2091-2102.
86. Hussain M, Mateo J, Fizazi K, et al. Survival with olaparib in metastatic castration-resistant prostate cancer. *N Engl J Med*. 2020;383:2345-2357.
87. Fizazi K, Piulats JM, Reaume MN, et al. Rucaparib or physician's choice in metastatic prostate cancer. *N Engl J Med*. 2023;388:719-732.
88. Chi KN, Sandhu S, Smith MR, et al. Niraparib plus abiraterone acetate with prednisone in patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene alterations: second interim analysis of the randomized phase III MAGNITUDE trial. *Ann Oncol*. 2023;34:772-782.
89. Fizazi K, Azad AA, Matsubara N, et al. First-line talazoparib with enzalutamide in HRR-deficient metastatic castration-resistant prostate cancer: the phase 3 TALAPRO-2 trial. *Nat Med*. 2024;25:257-264.
90. Abida W, Cyrta J, Heller G, et al. Genomic correlates of clinical outcome in advanced prostate cancer. *Proc Natl Acad Sci U S A*. 2019;116:11428-11436.
91. de Bono JS, De Giorgi U, Rodrigues DN, et al. Randomized phase II study evaluating Akt blockade with ipatasertib, in combination with abiraterone, in patients with metastatic prostate cancer with and without PTEN loss. *Clin Cancer Res*. 2019;25:928-936.
92. Sweeney C, Bracarda S, Sternberg CN, et al. Ipatasertib plus abiraterone and prednisolone in metastatic castration-resistant prostate cancer (IPATential150): a multicentre, randomised, double-blind, phase 3 trial. *Lancet*. 2021;398:131-142.
93. Sweeney C, Chi KN, Bracarda S, et al. Activation of the AKT pathway and outcomes in patients (pts) treated with or without ipatasertib (ipat) in metastatic castration-resistant prostate cancer (mCRPC): next-generation sequencing (NGS) data from the phase III IPATential150 trial. *J Clin Oncol*. 2022;40:5056.
94. Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. *N Engl J Med*. 2015;373:1697-1708.
95. Carreira S, Porta N, Arce-Gallego S, et al. Biomarkers associating with PARP inhibitor benefit in prostate cancer in the TOPARP-B trial. *Cancer Discov*. 2021;11:2812-2827.
96. Abida W, Campbell D, Patnaik A, et al. Rucaparib for the treatment of metastatic castration-resistant prostate cancer associated with a DNA damage repair gene alteration: final results from the phase 2 TRITON2 study. *Eur Urol*. 2023;84:321-330.
97. Grönberg H. ProBio: an outcome-adaptive and randomized multi-arm biomarker driven study in patients with metastatic prostate cancer. 2024. Available at <https://clinicaltrials.gov/study/NCT03903835>. Accessed May 13, 2024.
98. AstraZeneca. A phase III double-blind, randomised, placebo-controlled study assessing the efficacy and safety of capivasertib+abiraterone versus placebo+abiraterone as treatment for patients with denovo metastatic hormone-sensitive prostate cancer characterised by PTEN deficiency. 2024. Available at <https://clinicaltrials.gov/study/NCT04493853>. Accessed May 13, 2024.
99. Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. *N Engl J Med*. 2019;381:317-327.
100. Kindler HL, Hammel P, Reni M, et al. Overall survival results from the POLO trial: a phase III study of active maintenance olaparib versus placebo for germline BRCA-mutated metastatic pancreatic cancer. *J Clin Oncol*. 2022;40:3929-3939.
101. Strickler JH, Satake H, George TJ, et al. Sotorasib in KRAS p.G12C-mutated advanced pancreatic cancer. *N Engl J Med*. 2023;388:33-43.
102. Bekaii-Saab TS, Spira AI, Yaeger R, et al. KRYSTAL-1: updated activity and safety of adagrasib (MRTX849) in patients (Pts) with unresectable or metastatic pancreatic cancer (PDAC) and other gastrointestinal (GI) tumors harboring a KRASG12C mutation. *J Clin Oncol*. 2022;40:519.
103. Reiss KA, Mick R, O'Hara MH, et al. Phase II study of maintenance rucaparib in patients with platinum-sensitive advanced pancreatic cancer and a pathogenic germline or somatic variant in BRCA1, BRCA2, or PALB2. *J Clin Oncol*. 2021;39:2497-2505.
104. Schram AM, O'Reilly EM, O'Kane GM, et al. Efficacy and safety of zenocutuzumab in advanced pancreas cancer and other solid tumors harboring NRG1 fusions. *J Clin Oncol*. 2021;39:3003.
105. Shroff RT, Hendifar A, McWilliams RR, et al. Rucaparib monotherapy in patients with pancreatic cancer and a known deleterious BRCA mutation. *JCO Precis Oncol*. 2018;2018:PO.17.00316.
106. Singhi AD, George B, Greenbowe JR, et al. Real-time targeted genome profile analysis of pancreatic ductal adenocarcinomas identifies genetic alterations that might be targeted with existing drugs or used as biomarkers. *Gastroenterology*. 2019;156:2242-2253.e4.
107. Singh H, Keller RB, Kapner KS, et al. Oncogenic drivers and therapeutic vulnerabilities in KRAS wild-type pancreatic cancer. *Clin Cancer Res*. 2023;29:4627-4643.
108. Schram AM, Odintsov I, Espinosa-Cotton M, et al. Zenocutuzumab, a HER2xHER3 bispecific antibody, is effective therapy for tumors driven by NRG1 gene rearrangements. *Cancer Discov*. 2022;12:1233-1247.
109. Cancer Genome Atlas Research NetworkBell D, Berchuck A, Birrer M, et al. Integrated genomic analyses of ovarian carcinoma. *Nature*. 2011;474:609-615.

110. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med*. 2016;375:2154-2164.
111. Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017;390:1949-1961.
112. Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2017;18:1274-1284.
113. Moore K, Colombo N, Scambia G, et al. Maintenance Olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*. 2018;379:2495-2505.
114. González-Martín A, Pothuri B, Vergote I, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*. 2019;381:2391-2402.
115. Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. *N Engl J Med*. 2019;381:2416-2428.
116. DiSilvestro P, Banerjee S, Colombo N, et al. Overall survival with maintenance olaparib at a 7-year follow-up in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation: the SOLO1/GOG 3004 trial. *J Clin Oncol*. 2023;41:609-617.
117. González-Martín A, Harter P, Leary A, et al. Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34:833-848.
118. Monk BJ, Grisham RN, Banerjee S, et al. MILO/ENGOT-ov11: binimetinib versus physician's choice chemotherapy in recurrent or persistent low-grade serous carcinomas of the ovary, fallopian tube, or primary peritoneum. *J Clin Oncol*. 2020;38:3753-3762.
119. Abou-Alfa GK, Chan SL, Kudo M, et al. Phase 3 randomized, open-label, multicenter study of tremelimumab (T) and durvalumab (D) as first-line therapy in patients (pts) with unresectable hepatocellular carcinoma (uHCC): HIMALAYA. *J Clin Oncol*. 2022;40: 379-379.
120. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382:1894-1905.
121. Gatta G, van der Zwan JM, Casali PG, et al. Rare cancers are not so rare: the rare cancer burden in Europe. *Eur J Cancer*. 2011;47:2493-2511.
122. Gatta G, Capocaccia R, Botta L, et al. Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study. *Lancet Oncol*. 2017;18:1022-1039.
123. DeSantis CE, Kramer JL, Jemal A. The burden of rare cancers in the United States. *CA Cancer J Clin*. 2017;67:261-272.
124. Abou-Alfa GK, Macarulla T, Javle MM, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol*. 2020;21:796-807.
125. Javle M, Lowery M, Shroff RT, et al. Phase II study of BGI398 in patients with FGFR-altered advanced cholangiocarcinoma. *J Clin Oncol*. 2018;36:276-282.
126. Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol*. 2020;21:671-684.
127. Pant S, Schuler MH, Iyer G, et al. Efficacy and safety of erdafitinib in adults with cholangiocarcinoma (CCA) with prespecified fibroblast growth factor receptor alterations (FGFRalt) in the phase 2 open-label, single-arm RAGNAR trial: expansion cohort results. *J Clin Oncol*. 2023;41:610.
128. Goyal L, Meric-Bernstam F, Hollebecque A, et al. Futibatinib for FGFR2-rearranged intrahepatic cholangiocarcinoma. *N Engl J Med*. 2023;388:228-239.
129. Javle M, Borad MJ, Azad NS, et al. Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway): a multicentre, open-label, phase 2a, multiple basket study. *Lancet Oncol*. 2021;22:1290-1300.
130. Meric-Bernstam F, Makker V, Oaknin A, et al. Efficacy and safety of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-expressing solid tumors: DESTINY-PanTumor02 (DP-02) interim results. *J Clin Oncol*. 2023;41:LBA3000.
131. Harding JJ, Fan J, Oh D-Y, et al. Zanidatamab for HER2-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, phase 2b study. *Lancet Oncol*. 2023;24:772-782.
132. Nakamura Y, Mizuno N, Sunakawa Y, et al. Tucatinib and trastuzumab for previously treated human epidermal growth factor receptor 2-positive metastatic biliary tract cancer (SGNTUC-019): a phase II basket study. *J Clin Oncol*. 2023;41:5569-5578.
133. Cannon TL, Rothe M, Mangat PK, et al. Pertuzumab plus trastuzumab (P+T) in patients (pts) with biliary tract cancer (BTC) with ERBB2/3 amplification (amp), overexpression (oe), or mutation (mut): results from the targeted agent and profiling utilization registry (TAPUR) study. *J Clin Oncol*. 2023;41: 546-546.
134. Harding JJ, Piha-Paul SA, Shah RH, et al. Antitumour activity of neratinib in patients with HER2-mutant advanced biliary tract cancers. *Nat Commun*. 2023;14:630.
135. Subbiah V, Lassen U, Élez E, et al. Dabrafenib plus trametinib in patients with BRAFV600E-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial. *Lancet Oncol*. 2020;21:1234-1243.
136. Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib plus trametinib in BRAFV600E-mutated rare cancers: the phase 2 ROAR trial. *Nat Med*. 2023;29:1103-1112.
137. Lee C-K, Chon HJ, Cheon J, et al. Trastuzumab plus FOLFOX for HER2-positive biliary tract cancer refractory to gemcitabine and cisplatin: a multi-institutional phase 2 trial of the Korean Cancer Study Group (KCSG-HB19-14). *Lancet Gastroenterol Hepatol*. 2023;8:56-65.
138. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med*. 2002;347:472-480.
139. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet*. 2006;368:1329-1338.
140. Demetri GD, Reichardt P, Kang Y-K, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381:295-302.
141. Blay J-Y, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2020;21:923-934.
142. Heinrich MC, Jones RL, von Mehren M, et al. Avapritinib in advanced PDGFRA D842V-mutant gastrointestinal stromal tumour (NAVIGATOR): a multicentre, open-label, phase 1 trial. *Lancet Oncol*. 2020;21:935-946.
143. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science*. 1998;279:577-580.
144. Kang Y-K, George S, Jones RL, et al. Avapritinib versus regorafenib in locally advanced unresectable or metastatic GI stromal tumor: a randomized, open-label phase III Study. *J Clin Oncol*. 2021;39:3128-3139.
145. Schöffski P, Sufliarsky J, Gelderblom H, et al. Crizotinib in patients with advanced, inoperable inflammatory myofibroblastic tumours with and without anaplastic lymphoma kinase gene alterations (European Organisation for Research and Treatment of Cancer 90101 CREATE): a multicentre, single-drug, prospective, non-randomised phase 2 trial. *Lancet Respir Med*. 2018;6:431-441.
146. Schöffski P, Kubickova M, Wozniak A, et al. Long-term efficacy update of crizotinib in patients with advanced, inoperable inflammatory myofibroblastic tumour from EORTC trial 90101 CREATE. *Eur J Cancer*. 2021;156:12-23.

147. Shimizu A, O'Brien KP, Sjöblom T, et al. The dermatofibrosarcoma protuberans-associated collagen type *1 α 1*/platelet-derived growth factor (PDGF) B-chain fusion gene generates a transforming protein that is processed to functional PDGF-BB1. *Cancer Res.* 1999;59:3719-3723.
148. Rutkowski P, Van Glabbeke M, Rankin CJ, et al. Imatinib mesylate in advanced dermatofibrosarcoma protuberans: pooled analysis of two phase II clinical trials. *J Clin Oncol.* 2010;28:1772-1779.
149. Modena P, Lualdi E, Facchinetti F, et al. SMARCB1/INI1 tumor suppressor gene is frequently inactivated in epithelioid sarcomas. *Cancer Res.* 2005;65:4012-4019.
150. Gounder M, Schöffski P, Jones RL, et al. Tazemetostat in advanced epithelioid sarcoma with loss of INI1/SMARCB1: an international, open-label, phase 2 basket study. *Lancet Oncol.* 2020;21:1423-1432.
151. Wagner AJ, Ravi V, Riedel RF, et al. *nab*-Sunitinib for patients with malignant perivascular epithelioid cell tumors. *J Clin Oncol.* 2021;39:3660-3670.
152. Gronchi A, Miah AB, Dei Tos AP, et al. Soft tissue and visceral sarcomas: ESMO—EURACAN—GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2021;32:1348-1365.
153. Gounder MM, Agaram NP, Trabucco SE, et al. Clinical genomic profiling in the management of patients with soft tissue and bone sarcoma. *Nat Commun.* 2022;13:3406.
154. Ciampi R, Romei C, Ramone T, et al. Genetic landscape of somatic mutations in a large cohort of sporadic medullary thyroid carcinomas studied by next-generation targeted sequencing. *iScience.* 2019;20:324-336.
155. Wirth LJ, Sherman E, Robinson B, et al. Efficacy of seliprecatinib in RET-altered thyroid cancers. *N Engl J Med.* 2020;383:825-835.
156. Kim J, Bradford D, Larkins E, et al. FDA approval summary: pralsetinib for the treatment of lung and thyroid cancers with RET gene mutations or fusions. *Clin Cancer Res.* 2021;27:5452-5456.
157. Mansfield AS, Subbiah V, Schuler MH, et al. Pralsetinib in patients (pts) with advanced or metastatic RET-altered thyroid cancer (TC): updated data from the ARROW trial. *J Clin Oncol.* 2022;40:6080.
158. Hadoux J, Elisei R, Brose MS, et al. Phase 3 trial of seliprecatinib in advanced RET-mutant medullary thyroid cancer. *N Engl J Med.* 2023;389:1851-1861.
159. Cancer Genome Atlas Research Network Agrawal N, Akbani R, Aksoy BA, et al. Integrated genomic characterization of papillary thyroid carcinoma. *Cell.* 2014;159:676-690.
160. Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib and trametinib treatment in patients with locally advanced or metastatic *BRAF* V600-mutant anaplastic thyroid cancer. *J Clin Oncol.* 2018;36:7-13.
161. Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib plus trametinib in patients with *BRAF* V600E-mutant anaplastic thyroid cancer: updated analysis from the phase II ROAR basket study. *Ann Oncol.* 2022;33:406-415.
162. Filetti S, Durante C, Hartl DM, et al. ESMO Clinical Practice Guideline update on the use of systemic therapy in advanced thyroid cancer. *Ann Oncol.* 2022;33:674-684.
163. Bradford D, Larkins E, Mushti SL, et al. FDA Approval summary: seliprecatinib for the treatment of lung and thyroid cancers with RET gene mutations or fusions. *Clin Cancer Res.* 2021;27:2130-2135.
164. Ross JS, Sokol ES, Moch H, et al. Comprehensive genomic profiling of carcinoma of unknown primary origin: retrospective molecular classification considering the CUPISCO study design. *Oncologist.* 2021;26:e394-e402.
165. Tanizaki J, Yonemori K, Akiyoshi K, et al. Open-label phase II study of the efficacy of nivolumab for cancer of unknown primary. *Ann Oncol.* 2022;33:216-226.
166. Pouyiourou M, Kraft B, Wohlfromm T, et al. 738P Combined ipilimumab and nivolumab in previously treated patients with cancer of unknown primary: results of the CheCUP trial. *Ann Oncol.* 2022;33:S881.
167. Pouyiourou M, Kraft BN, Wohlfromm T, et al. Nivolumab and ipilimumab in recurrent or refractory cancer of unknown primary: a phase II trial. *Nat Commun.* 2023;14:6761.
168. Ross JS, Wang K, Gay L, et al. Comprehensive genomic profiling of carcinoma of unknown primary site: new routes to targeted therapies. *JAMA Oncol.* 2015;1:40-49.
169. Bochtler T, Reiling A, Endris V, et al. Integrated clinicomolecular characterization identifies RAS activation and CDKN2A deletion as independent adverse prognostic factors in cancer of unknown primary. *Int J Cancer.* 2020;146:3053-3064.
170. Möhrmann L, Werner M, Oleś M, et al. Comprehensive genomic and epigenomic analysis in cancer of unknown primary guides molecularly-informed therapies despite heterogeneity. *Nat Commun.* 2022;13:4485.
171. Mileskhin L, Bochtler T, Pauli C, et al. Primary analysis of efficacy and safety in the CUPISCO trial: a randomised, global study of targeted therapy or cancer immunotherapy guided by comprehensive genomic profiling (CGP) vs platinum-based chemotherapy (CTX) in newly diagnosed, unfavourable cancer of unknown primary (CUP). *Ann Oncol.* 2023;34:S1254-S1255.
172. Krämer A, Bochtler T, Pauli C, et al. Cancer of unknown primary: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol.* 2023;34:228-246.
173. Kozal D, Hofman V, Christopoulos P, et al. Fusion-positive non-small cell lung carcinoma: biological principles, clinical practice, and diagnostic implications. *Genes Chromosomes Cancer.* 2022;61:244-260.
174. Neumann O, Burn TC, Allgäuer M, et al. Genomic architecture of FGFR2 fusions in cholangiocarcinoma and its implication for molecular testing. *Br J Cancer.* 2022;127:1540-1549.
175. Benayed R, Offin M, Mullaney K, et al. High yield of RNA sequencing for targetable kinase fusions in lung adenocarcinomas with no mitogenic driver alteration detected by DNA sequencing and low tumor mutation burden. *Clin Cancer Res.* 2019;25:4712-4722.
176. De Luca A, Esposito Abate R, Rachiglio AM, et al. FGFR fusions in cancer: from diagnostic approaches to therapeutic intervention. *Int J Mol Sci.* 2020;21:6856.
177. Konstantinopoulos PA, Ceccaldi R, Shapiro GI, et al. Homologous recombination deficiency: exploiting the fundamental vulnerability of ovarian cancer. *Cancer Discov.* 2015;5:1137-1154.
178. Nguyen L, Martens JWM, Van Hoeck A, et al. Pan-cancer landscape of homologous recombination deficiency. *Nat Commun.* 2020;11:5584.
179. Kuzbari Z, Bandlamudi C, Loveday C, et al. Germline-focused analysis of tumour-detected variants in 49,264 cancer patients: ESMO Precision Medicine Working Group recommendations. *Ann Oncol.* 2023;34:215-227.
180. Aldea M, Cerbone L, Bayle A, et al. Detection of additional occult malignancy through profiling of ctDNA in late-stage cancer patients. *Ann Oncol.* 2021;32:1642-1645.
181. Steensma DP, Bejar R, Jaiswal S, et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. *Blood.* 2015;126:9-16.
182. Marshall CH, Gondek LP, Luo J, et al. Clonal hematopoiesis of indeterminate potential in patients with solid tumor malignancies. *Cancer Res.* 2022;82:4107-4113.
183. Jaiswal S, Ebert BL. Clonal hematopoiesis in human aging and disease. *Science.* 2019;366:eaan4673.
184. Aldea M, Tagliamento M, Bayle A, et al. Liquid biopsies for circulating tumor DNA detection may reveal occult hematologic malignancies in patients with solid tumors. *JCO Precis Oncol.* 2023;7:e2200583.
185. Arriola E, Bernabé R, García Campelo R, et al. Cost-effectiveness of next-generation sequencing versus single-gene testing for the molecular diagnosis of patients with metastatic non-small-cell lung cancer from the perspective of Spanish reference centers. *JCO Precis Oncol.* 2023;7:e2200546.
186. de Alava E, Pareja MJ, Carcedo D, et al. Cost-effectiveness analysis of molecular diagnosis by next-generation sequencing versus sequential single testing in metastatic non-small cell lung cancer patients from a south Spanish hospital perspective. *Expert Rev Pharmacoecon Outcomes Res.* 2022;22:1033-1042.
187. Tan AC, Lai GGY, Tan GS, et al. Utility of incorporating next-generation sequencing (NGS) in an Asian non-small cell lung cancer (NSCLC)

- population: incremental yield of actionable alterations and cost-effectiveness analysis. *Lung Cancer*. 2020;139:207-215.
188. Wolff HB, Steeghs EMP, Mfumbilwa ZA, et al. Cost-effectiveness of parallel versus sequential testing of genetic aberrations for stage IV non-small-cell lung cancer in the Netherlands. *JCO Precis Oncol*. 2022;6:e2200201.
 189. Zou D, Ye W, Hess LM, et al. Diagnostic value and cost-effectiveness of next-generation sequencing-based testing for treatment of patients with advanced/metastatic non-squamous non-small-cell lung cancer in the United States. *J Mol Diagn*. 2022;24:901-914.
 190. Lemmon CA, Zhou J, Hobbs B, et al. Modeling costs and life-years gained by population-wide next-generation sequencing or single-gene testing in nonsquamous non-small-cell lung cancer in the United States. *JCO Precis Oncol*. 2023;7:e2200294.
 191. Zheng Y, Vioix H, Liu FX, et al. Diagnostic and economic value of biomarker testing for targetable mutations in non-small-cell lung cancer: a literature review. *Future Oncol*. 2022;18:505-518.
 192. Bayle A, Bonastre J, Chaltiel D, et al. ESMO study on the availability and accessibility of biomolecular technologies in oncology in Europe. *Ann Oncol*. 2023;34:934-945.
 193. Vashistha V, Katsoulakis E, Guo A, et al. Molecular-guided off-label targeted therapy in a large-scale precision oncology program. *JCO Precis Oncol*. 2023;7:e2200518.
 194. Brose MS, Cabanillas ME, Cohen EEW, et al. Vemurafenib in patients with BRAFV600E-positive metastatic or unresectable papillary thyroid cancer refractory to radioactive iodine: a non-randomised, multi-centre, open-label, phase 2 trial. *Lancet Oncol*. 2016;17:1272-1282.