# Introduction

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Precision oncology is quickly becoming mainstream in clinical practice and research, dedicated to high-technology diagnostics and innovative drug development. The identification of targetable molecular alterations and thus therapy adjustment enables treatment individualisation and increases efficacy.

The first Food and Drug Administration (FDA)-approved targeted therapy leading to clinical remissions was imatinib for the treatment of *BCR-ABL* rearrangement in chronic myeloid leukaemia in 2001. Today, the number of targeted therapies approved for use continues to grow.

Advances in precision oncology are usually implemented in highly specialised cancer research centres, which have access to clinical trials and advanced diagnostic technologies. To define molecular alterations and tailor therapy accordingly, a tissue sample is needed, which is delivered to a high-quality laboratory equipped with next-generation sequencing (NGS) technology. However, even smaller institutions without laboratories can take advantage of commercially available testing platforms to analyse paraffin-embedded tissue samples or plasma samples. Since

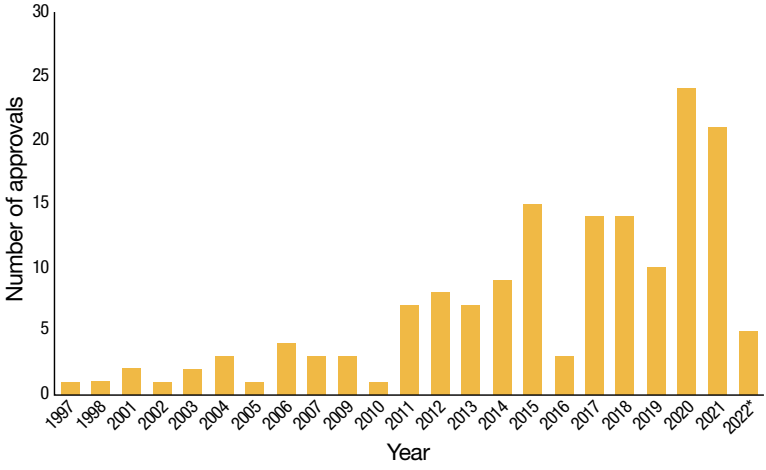


*Figure 1 FDA approvals of targeted therapies in oncology.*

*Approvals to end May 2022.
Abbreviation: FDA, Food and Drug Administration.

there is a risk of underutilisation of targeted therapies with confirmed benefits, or overutilisation when the drug-target combination has not yet been confirmed, appropriate identification of actionable mutations and assessment of available therapeutic options must be established by molecular tumour boards (MTBs). MTBs, comprised of a multidisciplinary team of specialists from the fields of molecular biology, pathology, oncology and research, enable interdisciplinary knowledge transfer in the highly complex field of cancer biology and research/clinical care. The MTBs need appropriate organisation (regular multidisciplinary meetings) and implementation of IT platforms capable of searching new scientific evidence in the context of available therapeutic options, as well as gathering real-world evidence. The emerging concept is to build a national/international network of MTBs to share knowledge about MTB recommendations as well as encouraging the active participation of healthcare professionals from peripheral hospitals, thereby providing access to precision oncology for all patients with cancer.

Non-small cell lung cancer (NSCLC) is recognised as a prototype disease for molecularly-driven targeted oncology. This approach is also now part of clinical practice in melanoma and colorectal cancer. As techniques evolve and become more cost effective, the use of molecular testing and molecularly guided drugs may be addressed to a larger number of patients. Therefore, the major implication for patients and healthcare systems is to build optimal therapeutic pathways based on pathological diagnosis, molecular testing, recommended therapies and access to clinical trials. The European Society for Medical Oncology (ESMO) Translational Research and Precision Medicine Working Group provides recommendations on precision oncology in daily practice, which are available here: https://oncologypro.esmo.org/oncology-in-practice/personalised-medicine/esmo-recommendations-in-precision-medicine.

Biomarker-driven therapies have an impact on clinical trial methodology and drug approval processes. Their novel designs enable the investigation of multiple hypotheses. The most widely used are protocols with multiple treatments (umbrella trials), multiple populations (basket trials) or those enabling the addition or removal of trial arms (platform trials). In recent years, the FDA and the European Medicines Agency (EMA) have approved an increasing number of precision oncology drugs targeting molecular biomarkers based on early-stage non-randomised clinical trials. This increase in the availability of novel treatments has contributed to a rise in global oncology spending: $185 billion in 2021 and predicted to exceed $300 billion by 2026[1]. From the perspective of patients and healthcare systems, monitoring the impact of new registrations on survival, quality of life and cost in the post-approval period is mandatory.

In conclusion, medical reality driven by precision oncology needs optimisation of resources used for patient diagnostics and care by applying the recommendations, gathering real-world evidence for research purposes and monitoring cost-effectiveness, and knowledge-sharing about the agnostic approach in research and clinical practices. With all these advances, it is critical to concentrate on community medical education to empower the implementation of precision oncology in clinical practice.

[1] IQVIA Institute. Global Oncology Trends 2022: Outlook to 2026. Published May 2022. https://www.iqvia.com/insights/the-iqvia-institute/reports/global-oncology-trends-2022 (date last accessed, 19 August 2022).

The idea behind the *ESMO Handbook of Targeted Therapies and Precision Oncology* was to provide comprehensive and practical information for clinicians, who should be familiar with the technology used to determine the types of genomic alterations, correctly interpret the molecular results and implement personalised management in cancer care.

*Table 1 FDA Approvals of Targeted Therapies in Oncology.*

| Year | Drug | Target(s) |
|---|---|---|
| 1997 | Rituximab | CD20 |
| 1998 | Trastuzumab | HER2 |
| 2001 | Imatinib<br>Alemtuzumab | BCR-ABL/PDGFR/KIT<br>CD52 |
| 2002 | Ibritumomab tiuxetan | CD20 |
| 2003 | Gefitinib<br>Bortezomib | EGFR<br>Proteasome |
| 2004 | Erlotinib<br>Cetuximab<br>Bevacizumab | EGFR<br>EGFR<br>VEGF |
| 2005 | Sorafenib | VEGFR/KIT/FLT3/PDGFR |
| 2006 | Sunitinib<br>Dasatinib<br>Vorinostat<br>Panitumumab | PDGFR/VEGFR/FLT3/KIT/RET<br>BCR-ABL/Src/KIT/LCK/PDGFR<br>HDAC<br>EGFR |
| 2007 | Nilotinib<br>Lapatinib<br>Temsirolimus | BCR-ABL<br>HER2/EGFR<br>mTOR |
| 2009 | Pazopanib<br>Everolimus<br>Ofatumumab | PDGFR/VEGFR/KIT/FGFR/ITK<br>mTOR<br>CD20 |
| 2010 | Romidepsin | HDAC |
| 2011 | Icotinib<br>Crizotinib<br>Vandetanib<br>Ruxolitinib<br>Vemurafenib<br>Ipilimumab<br>Brentuximab vedotin | EGFR<br>ALK/ROS/c-MET<br>EGFR/VEGFR/RET<br>JAK1/JAK2<br>RAF<br>CTLA-4<br>CD30 |
| 2012 | Axitinib<br>Radotinib<br>Bosutinib<br>Vismodegib<br>Carfilzomib<br>Regorafenib<br>Pertuzumab<br>Ado-trastuzumab emtansine | VEGFR<br>BCR-ABL<br>Abl1/Src<br>SMO<br>Proteasome<br>VEGFR/PDGFR/FGFR/RAF/RET/KIT<br>HER2<br>HER2 |

*Table 1 FDA Approvals of Targeted Therapies in Oncology.* (Continued)

| Year | Drug | Target(s) |
|---|---|---|
| 2013 | Cabozantinib | VEGFR/ROS/TIE2/MET/KIT/TRK2/RET |
| | Ponatinib | BCR-ABL/PDGFR/FGFR/Src/FLT3/KIT |
| | Afatinib | EGFR/HER2/HER4 |
| | Ibrutinib | BTK |
| | Trametinib | MEK1/MEK2 |
| | Dabrafenib | RAF |
| | Obinutuzumab | CD20 |
| 2014 | Ceritinib | ALK/ROS |
| | Apatinib | VEGFR2 |
| | Belinostat | HDAC |
| | Olaparib | PARP |
| | Idelalisib | PI3Kδ |
| | Ramucirumab | VEGFR2 |
| | Nivolumab | PD-1 |
| | Pembrolizumab | PD-1 |
| | Blinatumomab | CD19/CD3 |
| 2015 | Alectinib | ALK |
| | Cobimetinib | MEK1/2 |
| | Palbociclib | CDK4/CDK6 |
| | Osimertinib | EGFR |
| | Sonidegib | SMO |
| | Sirolimus | mTOR |
| | Panobinostat | HDAC |
| | Tucidinostat | HDAC |
| | Ixazomib | Proteasome |
| | Lenvatinib | PDGFR/VEGFR/FGFR/KIT/RET |
| | Nintedanib | VEGFR/PDGFR/FGFR/MDR1/BCRP |
| | Necitumumab | EGFR |
| | Dinutuximab | GD2 |
| | Daratumumab | CD38 |
| | Elotuzumab | SLAMF7 |
| 2016 | Venetoclax | BCL-2 |
| | Rucaparib | PARP |
| | Atezolizumab | PD-L1 |
| 2017 | Brigatinib | ALK/EGFR/IGFR1/FLT3/ROS |
| | Tivozanib | PDGFR/VEGFR/FGFR/KIT/RET |
| | Acalabrutinib | BTK |
| | Ribociclib | CDK4/CDK6 |
| | Abemaciclib | CDK4/CDK6 |
| | Neratinib | HER2/EGFR |
| | Midostaurin | FLT3/KIT |
| | Enasidenib | IDH2 |
| | Niraparib | PARP |
| | Copanlisib | PI3K |
| | Inotuzumab ozogamicin | CD22 |
| | Avelumab | PD-L1 |
| | Durvalumab | PD-L1 |
| | Gemtuzumab ozogamicin | CD33 |

*Table 1 FDA Approvals of Targeted Therapies in Oncology.* (Continued)

| Year | Drug | Target(s) |
|---|---|---|
| 2018 | Anlotinib | VEGFR/PDGFR/FGFR |
| | Lorlatinib | ALK |
| | Fruquintinib | VEGFR |
| | Binimetinib | MEK1/2 |
| | Encorafenib | RAF |
| | Dacomitinib | EGFR |
| | Gilteritinib | FLT3 |
| | Glasdegib | SMO |
| | Ivosidenib | IDH1 |
| | Larotrectinib | TRK |
| | Talazoparib | PARP |
| | Duvelisib | PI3Kδ/PI3Kγ |
| | Cemiplimab | PD-1 |
| | Moxetumomab pasudotox | CD22 |
| 2019 | Pexidartinib | CSF1R/KIT/FLT3 |
| | Zanubrutinib | BTK |
| | Entrectinib | TRK |
| | Erdafitinib | FGFR |
| | Quizartinib | FLT3 |
| | Fedratinib | JAK2 |
| | Alpelisib | PI3Kα |
| | Polatuzumab vedotin | CD79B |
| | Enfortumab vedotin | Nectin-4 |
| | Trastuzumab deruxtecan | HER2 |
| 2020 | Pemigatinib | FGFR |
| | Avapritinib | KIT/PDGFR |
| | Ripretinib | KIT/PDGFR |
| | Selumetinib | MEK 1/2 |
| | Capmatinib | MET |
| | Tepotinib | MET |
| | Tucatinib | HER2 |
| | Almonertinib | EGFR |
| | Tazemetostat | EZH2 |
| | Selpercatinib | RET |
| | Pralsetinib | RET |
| | Neratinib | HER2 |
| | Brexucabtagene autoleucel | CD19 |
| | Brigatinib | ALK |
| | Olaparib | HRR/BRCA |
| | Rucaparib | BRCA |
| | Erlotinib | EGFR |
| | Encorafenib | BRAF V600E |
| | Isatuximab | CD38 |
| | Belantamab mafodotin | BCMA |
| | Sacituzumab govitecan | TROP-2 |
| | Tafasitamab | CD19 |
| | Naxitamab | GD2 |
| | Margetuximab | HER2 |

*Table 1 FDA Approvals of Targeted Therapies in Oncology.* (Continued)

| Year | Drug | Target(s) |
|---|---|---|
| 2021 | Tivozanib | VEGFR1/2/3 |
| | Lorlatinib | ALK |
| | Umbralisib | PI3Kδ/CK1γ |
| | Tepotinib | MET |
| | Crizotinib | ALK/ROS 1 |
| | Carfilzomib | Proteasome |
| | Asciminib | ABL/BCR-ABL1 |
| | Abemaciclib | HER2 |
| | Ruxolitinib | JAK1/2 |
| | Cabozantinib | VEGFR/MET/KIT/RET/AXL/FLT3 |
| | Mobocertinib | EGFR exon 20 |
| | Zanubrutinib | BTK |
| | Ivosidenib | IDH1 |
| | Leventanib | VEGFR /FGFR /PDGFRA/RET/KIT |
| | Avapritinib | KIT/PDGFRA |
| | Infigratinib | FGFR2 |
| | Sotorasib | KRAS G12C |
| | Dostarlimab | PD-1 |
| | Amivantamab | EGFR/cMET |
| | Loncastuximab tesirine | CD19 |
| | Tisotumab vedotin | TF |
| 2022* | Alpelisib | PIK3CA |
| | Olaparib | PARP |
| | Pacritinib | JAK2/FLT3 |
| | Tebentafusp | gp100/CD3 |
| | Relatlimab | LAG-3 |

*Approvals to end May 2022.

A list of FDA-approved targeted therapies by tumour type is available here: https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/approved-drug-list (date last accessed, 19 August 2022).

Abbreviations: ALK, anaplastic lymphoma kinase; BCL-2, B-cell lymphoma 2; BCMA, B-cell maturation antigen; BCRP, breast cancer resistance protein; BTK, Bruton's tyrosine kinase; CDK 4/6, cyclin-dependent kinase 4/6; CTLA-4, cytotoxic T-lymphocyte associated antigen 4; EGFR, epidermal growth factor receptor; FDA, food and Drug Administration; FGFR, fibroblast growth factor receptor; FLT3, FMS-like tyrosine kinase 3; HDAC, histone deacetylase; HER2/4, human epidermal growth factor receptor 2/4; HRR, homologous recombination repair; IDH1/2, isocitrate dehydrogenase 1/2; IGFR1, insulin-like growth factor receptor 1; ITK, interleukin-2 receptor T-cell kinase; JAK1/2, Janus kinase 1/2; MDR1, multidrug resistance 1; mTOR, mammalian target of rapamycin; PARP, poly(ADP-ribose) polymerase; PD-1, programmed cell death protein 1; PDGFR, platelet-derived growth factor receptor; SMO, smoothened homologue; TF, tissue factor; TRK, tropomyosin receptor kinase; VEGFR, vascular endothelial growth factor receptor.

# Declaration of Interest:

Professor Lugowska has received personal honoraria for writing engagements from Roche, Novartis and BMS; institutional research grants from Roche and Agenus. She has received personal and institutional honoraria for her work as a Coordinating Principal Investigator from Roche, BMS, Janssen, Novartis, AstraZeneca, Incyte, Boehringer Ingelheim, Agenus, MacroGenics, Checkpoint Therapeutics, Pfizer, Lilly Oncology, MSD and Debiopharm.

Dr Misale has received personal consulting honoraria from Boehringer Ingelheim and institutional funding from Daiichi Sankyo and Boehringer Ingelheim.

Professor Califano has received personal advisory board honoraria from AstraZeneca, Bayer, Lilly Oncology, Roche, Pfizer, MSD, Takeda, Amgen, Janssen and Novartis, speaker honoraria from AstraZeneca, Lilly Oncology, Roche, Pfizer, MSD, Takeda, Amgen and Janssen; and personal speaker honoraria for educational activities from Medscape and PeerVoice. He has ownership interest in The Christie Private Care – LOC and has received institutional research funding for his work as a principal investigator from Roche, AstraZeneca, Pfizer, Clovis, Lilly Oncology, MSD, BMS, Abbvie, Takeda, Janssen and Novartis.

Professor Haanen has received personal honoraria for his role as a Scientific Advisory Board Member from Neogene Therapeutics and Scenic and institutional advisory board honoraria from Bristol Myers Squibb, Achilles Therapeutics, Ipsen, Merck Sharp & Dohme, Merck Serono, Pfizer, Molecular Partners, Roche, Sanofi, Third Rock Venture and Iovance Biotherapeutics. He has received institutional advisory board honoraria for his role as a Scientific Advisory Board member from BioNTech, Gadeta, Immunocore, Instil Bio, PokeAcel and T-Knife. He holds stocks/shares in Neogene Therapeutics and has received institutional research grants from Bristol Myers Squibb, BioNTech US, Merck Sharp & Dohme, Amgen, Novartis and Asher Bio.