Novel drugs approved by the EMA, the FDA and the MHRA in 2024: a year in review

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INVITED REVIEW

Novel drugs approved by the EMA, the FDA and the MHRA in 2024: A year in review

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Abstract

In the past year, the European Medicines Agency (EMA), the Food and Drug Administration (FDA) and the Medicines and Healthcare Products Regulatory Agency (MHRA) authorised 53 novel drugs. While the 2024 harvest is not as rich as in 2023, when 70 new chemical entities were approved, the number of 'orphan' drug authorisations in 2024 (21) is similar to that of 2023 (24), illustrating the dynamic development of therapeutics in areas of unmet need. The 2024 approvals of novel protein therapeutics (15) and advanced therapy medicinal products (ATMPs, 6) indicate a sustained trend also noticeable in the 2023 new drugs reviewed in this journal last year (16 and 11, respectively). Clearly, the most striking characteristic of the 2024 drug yield is the creative pharmacological design, which allows these medicines to employ a novel approach to target a disease. Some notable examples are the first drug successfully using a 'dock-and-block' mechanism of inhibition (zenocutuzumab), the first approved drug for schizophrenia designed as an agonist of M_1/M_4

Abbreviations: AAV, Adeno-associated virus; Ab, Antibody; ABR, Annualised bleeding rate; Acc, Accelerated approval; ADCC, Cell-mediated cytotoxicity; AKT, Protein kinase B; ALK, Anaplastic lymphoma kinase; ALL, Acute lymphoblastic leukaemia; AML, Acute myelogenous leukaemia; Apo, Apolipoprotein; ARIA, β-amyloid-related imaging abnormalities; ASO, Antisense oligonucleotide; ATMP, Advanced Therapy Medicinal Products; ATP, Adenosine triphosphate; Aβ, Amyloid β; BCG, Bacillus Calmette–Guérin vaccine; Br, Breakthrough; BRAF, Serine/threonine-protein kinase B-raf; CD, Cluster differentiation; CDC, Complement-dependent cytotoxicity; CFTR, Cystic fibrosis transmembrane conductance regulator; CHMP, Committee for Human Medicinal Products; CLDN, Claudin; COVID, Coronavirus disease; COPD, Chronic obstructive pulmonary disease; CR, Complete remission; CRF-1, Corticotropin releasing factor-1; CRF_1, CRF receptor 1; CSF-1, Colony-stimulating factor-1; CTLA-4, Cytotoxic T-lymphocyte-associated protein 4; DLL, Delta-like ligand 3; DMD, Duchenne muscular dystrophy; DOR, Duration of response; EMA, European Medicines Agency; $ET_{A/B}$, Endothelin-1 type A/B receptor; FDA, Food and Drug Administration; FIC, First-in-class; FLT, FMS-like tyrosine kinase; FCS, Familial chylomicronemia syndrome; HDI, Histone deacetylase inhibitor; FT, Fast-track; GVHD, Graft-versus-host disease; Hb, Haemoglobin; HER, erb-b2 receptor tyrosine kinase; HPCs, Haematopoietic progenitor cells; HSCs, Haematopoietic stem cells; ICI, Immune checkpoint inhibitors; IDH, Isocitrate dehydrogenase; IL, Interleukin; JAK, Janus kinase; MAb, Monoclonal antibody; MAGE, Melanoma antigen gene; MASH, Metabolic dysfunction-associated steatohepatitis; MEK, Mitogen-activated protein kinase kinase; MHRA, Medicines and Healthcare Products Regulatory Agency; NAI, Nogapendekin alfa inbakicept; NPC, Niemann–Pick type C; NSCLC, Non-small-cell lung cancer; NRG1, Neuregulin 1; ORR, Overall response rate; PBC, Primary biliary cholangitis; PBMC, Peripheral blood mononuclear cells; PD-1, Programmed cell death protein 1; PD-L1, Programmed death-ligand 1; PN, Prurigo nodularis; PNH, Paroxysmal nocturnal haemoglobinuria; PPAR, Peroxisome proliferator-activated receptors; RBC, Red blood cell; RSV, Respiratory syncytial virus; SARS-CoV2, Severe acute respiratory syndrome coronavirus 2; SCLC, Small-cell lung cancer; TCR, T-cell receptor; TFPI, Tissue factor pathway inhibitor; TG, Triglycerides; TIL, Tumour-infiltrating leukocytes; TR-β, Thyroid hormone receptor-β.

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muscarinic receptors (xanomeline), the first biparatopic antibody (zanidatamab), binding two distinct epitopes of the *same* molecule, the first haemophilia therapy that instead of relying on external supplementation of clotting factors, restores Factor Xa activity by inhibiting TFPI (marstacimab), or the first ever authorised direct telomerase inhibitor (imetelstat) that reprogrammes the oncogenic drive of tumour cells. In addition, an impressive percentage of novel drugs were first in class (28 out of 53 or 53% of the total) and a substantial number can be considered disease agnostic, indicating the possibility of future approved extensions of their use for additional indications. The 2024 harvest demonstrates the therapeutic potential of innovative pharmacological design, which allows the effective targeting of intractable disorders and addresses crucial, unmet therapeutic needs.

1 | INTRODUCTION

In this second yearly mini-review, the reader will find assembled all the novel drugs approved by the Food and Drug Administration (FDA), authorised by the European Medicines Agency (EMA) and licensed by the Medicines and Healthcare Products Regulatory Agency (MHRA) in 2024. We have employed the same inclusion/exclusion criteria as last year (Papapetropoulos et al., 2024), which we reiterate here as a reminder to those that accessed the previous mini-review, as well as for the benefit of new readers (Box 1):

BOX 1 Criteria used

Drug inclusion criteria:

1. The authorised drug is a new molecular entity or a new biological product, having never before received marketing approval by any of the three Agencies, and thus enters for the first time the market in either Europe or the United States.

2. If the product is a combination, it is either a novel combination of already approved drugs or at least one of its active ingredients is a novel compound that is approved for the first time.

Drug exclusion criteria:

1. The molecule is a new formulation of an already approved medicine.

2. It received authorisation in the past year for use in a new indication, whether in the same general field or in a different disease.

3. It is a generic or biosimilar version of a previously approved drug.

4. It is an updated version of an already approved vaccine (e.g. Flu and Covid-19).

Whereas in 2023, 70 novel drugs were licensed, the tally for 2024 is 53, a seemingly more modest outcome in comparison. However, because, to our knowledge, no other such review includes approvals by all three granting regulatory agencies (all reviews we are aware of rely solely on FDA approvals) and therefore the exclusion/inclusion criteria are different, we cannot make any judgement regarding longer-term trends in numbers of novel chemical entities approved. It is only logical to expect that there will be some significant year-to-year variation.

To compile the present review, we have relied on the official websites maintained by the three agencies, which are listed below:

For the FDA-approved drugs, including small molecules, proteins/biologicals, cellular/gene therapies and vaccines, we consulted the following constantly updated sites:

https://www.fda.gov/drugs/novel-drug-approvals-fda/novel-drug-approvals-2024; https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/2024-biological-license-application-approvals; and https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

For medicines authorised by the EMA, we accessed the monthly newsletters/highlights updates:

https://www.ema.europa.eu/en/news-and-events/publications/newsletters

The 2024 MHRA-licenced drug list was based on the official website of the UK MHRA, which lists all marketing authorisations for various products:

https://www.gov.uk/government/publications/marketing-authorisations-granted-in-2024

In addition, we also accessed 'The IUPHAR/BPS Guide to PHARMACOLOGY' (https://www.guidetopharmacology.org/), a website database with insightful, literature-based information pertaining to the pharmacological mechanism of action of molecules.

Pharmaceutical company choice in submitting the drug approval application can account for some of the difference in the number of new medicines approved by the EMA, the FDA and the MHRA. In addition, the regulatory processes by each of the three agencies differ

significantly (reviewed last year; Papapetropoulos et al., 2024) and can further contribute to this divergence. Occasionally, it is the opinions of a panel (committee) that determine whether or not an application receives an approval (FDA), marketing authorisation (EMA) or market licensing (MHRA). A striking example of this, which has raised many editorials and opinion articles, is the fate of the Alzheimer's disease **β-amyloid**-directed antibody **lecanemab** (Leqembi), which we briefly reviewed as a notable FDA approval last year (Papapetropoulos et al., 2024). This MAb was approved by the FDA in 2023 and by the MHRA in 2024, being the first therapy clinically proven to durably (albeit moderately) slow down the progressive decline in cognitive and functional capacities in early Alzheimer's disease patients, but EMA declined to authorise it. The major reason was the risk/benefit perception by the respective panels, mainly because of β-amyloid-related imaging abnormalities (ARIA), a side effect known to occur with the class of antibodies targeting β-amyloid (e.g. lecanemab and **donanemab**) and which is present in ~20–40% of the patients receiving the drug. ARIA includes temporary swelling and cerebral bleeds detected by imaging studies, which can occasionally cause serious and life-threatening brain oedema, seizures and other severe neurological symptoms, as well as fatal intracerebral haemorrhages. This risk necessitated the inclusion of a boxed warning in the prescribing information in the United States and also prompted the UK National Institute for Health and Care Excellence (NICE) to release a draft guidance indicating that '*it does not recommend lecanemab for use in the NHS*' (National Health System; https://brainsciences.scot/lecanemab-is-approved-by-mhra-in-great-britain/), despite its licence by the MHRA, a call that was re-iterated for donanemab. This cautious approach reflects the divergent estimate of benefit/risk regarding these two drugs by neurologists worldwide (Couzin-Frankel, 2024). A later (and perhaps not last) chapter in the saga was the reversal, by the EMA, of its initial negative opinion, in November 2024: '*On 14 November 2024, the Committee for Medicinal Products for Human Use (CHMP), following a re-examination procedure, adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Leqembi, intended for the treatment of early Alzheimer's disease in apolipoprotein E ε4 (ApoE ε4) non-carriers or heterozygotes*', paving the way for an authorisation in the EU.

Below, there are four tables that list the novel drugs approved by the three agencies, by the nature of the product: Small molecules (including small peptides; Table 1), Proteins/Antibodies (Table 2), Advanced Therapy Medicinal Products (ATMP; oligonucleotides and cellular/gene products; Table 3) and Vaccines (Table 4). This categorization is also shown in graphic mode in Figure 1. In our effort to facilitate a quick, at-a-glance comprehension of the drug's features and allow interested readers to easily explore more in-depth certain features of the drug, each table briefly lists clickable information, wherever available, on the disease indication, the pharmacological target/mode of action of each entity and the pivotal clinical trial(s) that enabled the approval.

Notwithstanding the lower yield of novel drugs in 2024 (53) compared to the previous year (70), the number of fist-in-class (FIC) entities is roughly equal (28, BOX 2) to last year (30). This inarguably reflects the fact that a high percentage (53%) of the 2024 drugs are the long-awaited outcome of insightful molecular targeting and ingenious initial design. We therefore offer below a condensed description of each of these 28 FICs, emphasising the pharmacological innovation that they offer, grouped by disease area. All approved drugs, grouped by disease area, are depicted in Figure 2.

2 | FIC DRUGS AUTHORISED IN 2024

2.1 | Oncology

2.1.1 | Afamitresgene autoleucel and Lifileucel

The prognosis of advanced, unresectable or metastatic melanoma is still bleak, despite the revolutionary progress made with the introduction of immune checkpoint inhibitors (ICI) and inhibitors targeting kinases **BRAF** (serine/threonine-protein kinase B-raf) and **MEK** (mitogen-activated protein kinase kinase). Primary resistance to ICI occurs in 40% to 65% of patients, about 30–40% develop acquired resistance, while poor responses and relapse characterise those cases under BRAF V^{600} mutation-directed therapy (Czarnecka et al., 2020; Gide et al., 2018; Long et al., 2017; Wolchok et al., 2017). To make things worse, ICIs are associated with serious, often life-threatening adverse effects. Cellular therapies outside solid tumours have been approved before, for example, for haematological malignancies (donislecel), sickle-cell anaemia or type I diabetes (for 2023 approvals, see Papapetropoulos et al., 2024). In 2024, two FIC T-cell therapies were authorised by the FDA, addressing intractable oncology indications. Lifileucel was the very first cell-based (T-cell-based) immunotherapy approved for solid tumours (Julve et al., 2024), followed a few months later by afamitresgene autoleucel (also briefly reviewed herein) and relies on the re-introduction in the patient of ex vivo-expanded autologous tumour-infiltrating lymphocytes (TILs), initially isolated from tumour biopsies (mostly from the lung) resected from the same patient. The trial that led to Lifileucel's approval (Chesney et al., 2022, a follow-up of Sarnaik et al., 2021) enrolled 153 patients who, despite prior treatment with a median of three treatments that included both anti-programmed cell death protein 1 (**PD-1**) and anti-cytotoxic lymphocyte-associated protein 4 (**CTLA-4**) antibodies (81.7% of patients) and MEK/BRAF inhibitors, had still a high tumour burden. Each patient underwent a non-myeloablative lymphodepletion regimen, followed by a single injection of autologous, expanded TILs ($>10^9$). The treatment also included up to six doses of high-dose **interleukin-2** to support in vivo expansion of the injected T-cells. The primary endpoint, Objective Response Rate (ORR), was 31.4%, with eight complete responses and 40 partial responses. Median duration of response (DOR) was not reached at the median study follow-up of 27.6 months, while 41.7% of the responses were maintained for over 18 months. At this timepoint, median overall survival was 13.9 months and progression-free survival was 4.1 months. The most common grade 3/4 treatment-related adverse events (in ≥30%) were thrombocytopenia (76.9%), anaemia (50.0%) and febrile neutropenia (41.7%). The durable, clinically significant responses and the overall favourable safety profile strongly argued in favour of the FDA's approval of this one-time TIL cell

TABLE 1 Small molecules.

Active ingredient/s	Proprietary name	Approved therapeutic use	Molecular target/ mode of action	Approving agency	Approval type	Pivotal clinical trial(s)	Link to GtoP
Acoramidis	Attruby	To treat cardiomyopathy of wild-type or variant transthyretin-mediated amyloidosis	Transthyretin (TTR) stabilisation and inhibition of TTR amyloid fibril formation	FDA		Gillmore et al., 2024	acoramidis | Ligand page | IUPHAR/ BPS Guide to PHARMACOLOGY
Aprocitentan	Tryvio /Jeraygo	Treatment of resistant hypertension	Dual endothelin receptor A and B (ET_A/ET_B) blocker	FDA, EMA		Xu et al., 2023; Schlaich et al., 2022	aprocitentan | Ligand page | IUPHAR/BPS Guide to PHARMACOLOGY
Arimoclomol	Miplyffa	Treatment of neurological symptoms of Niemann-Pick disease type C in combination with miglustat	Thought to co-induce heat-shock protein (HSP)	FDA	P, GT, Br, rare paediatric disease	Mengel et al., 2021	arimoclomol | Ligand page | IUPHAR/BPS Guide to PHARMACOLOGY
Berdazimer	Zelsuvmi	Topical treatment of *molluscum contagiosum*	Nitric oxide releasing agent, poorly understood mechanism	FDA		Sugarman et al., 2024; Pera Calvi et al., 2023; Browning et al., 2022	
Cefepime, enmetazobactam	Exblifep	To treat complicated urinary tract infections (cUTI), including pyelonephritis, hospital-acquired pneumonia or bacteremia	Cephalosporin + β-lactamase inhibitor antibacterial combination	FDA, EMA, MHRA		Keam, 2024; Maki, 2023	
Ceftobiprole medocaril	Zevtera	Treatment of a) *Staphylococcus aureus* bacteremia (SAB), b) bacterial skin and skin structure infections and c) community-acquired bacterial pneumonia	Cephalosporin prodrug, inhibits bacterial cell wall synthesis	FDA	P, FT, qualified infectious disease product	https://clinicaltrials.gov/study/NCT03138733; https://clinicaltrials.gov/study/NCT03137173; https://clinicaltrials.gov/study/NCT00326287	ceftobiprole | Ligand page | IUPHAR/BPS Guide to PHARMACOLOGY
Crinecerfont	Crenessity	To control androgen levels in classic congenital adrenal hyperplasia	Corticotropin releasing factor-1 (CRF-1) receptor antagonist	FDA	P, FT, Br	Auchus et al., 2024; Sarafoglou et al., 2024	
Danicopan	Voydeya	To treat extravascular haemolysis (EVH) in adults with paroxysmal nocturnal haemoglobinuria (PNH), in combination with ravulizumab or eculizumab	Complement factor D inhibition	FDA, EMA, MHRA		Lee et al., 2023; Nester et al., 2022	danicopan | Ligand page | IUPHAR/ BPS Guide to PHARMACOLOGY
Deuruxolitinib	Leqselvi	Treatment of severe alopecia areata	Janus kinase (JAK) inhibitor	FDA		King et al., 2024; King & Craiglow, 2023	
Elafibranor	Iqirvo	To treat primary biliary cholangitis in combination with ursodeoxycholic acid or as monotherapy	Selective PPAR α and δ agonist	FDA, EMA, MHRA	Acc	Arıvalo-Capas & Arıvalo-Serrano, 2024; Kowdley et al., 2024	elafibranor | Ligand page | IUPHAR/BPS Guide to PHARMACOLOGY
Ensartinib	Ensacove	To treat adult patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC)	Inhibits the oncogenic ALK kinase	FDA		Horn et al., 2021; Singhi and Horn, 2018	

TABLE 1 (Continued)

Active ingredient/s	Proprietary name	Approved therapeutic use	Molecular target/ mode of action	Approving agency	Approval type	Pivotal clinical trial(s)	Link to GtoP
Ensifentrine	Ohtuvayre	Maintenance treatment of chronic obstructive pulmonary disease (COPD)	Selective phosphodiesterase 3 (PDE3) and PDE4 inhibitor	FDA		Anzueto et al., 2023; Mahler et al., 2024	ensifentrine | Ligand page | IUPHAR/BPS Guide to PHARMACOLOGY
Flurpiridaz F 18	Flyrcado	A radioactive diagnostic drug to evaluate myocardial ischemia and infarction	Not having one	FDA		Maddahi et al., 2020; Maddahi et al., 2023	
Givinostat	Duvyzat	Treatment of Duchenne muscular dystrophy (DMD)	Histone deacetylase inhibition	FDA	P, FT, rare paediatric disease	Hoeper et al., 2023; Mercuri et al., 2024	givinostat | Ligand page | IUPHAR/BPS Guide to PHARMACOLOGY
Inavolisib	Itovebi	Combined with palbociclib and fulvestrant, to treat PIK3CA-mutated, hormone receptor+ (HR^+), $HER2^-$, locally advanced or metastatic breast cancer	Inhibitor of PI3Kα	FDA		Turner et al., 2024	inavolisib | Ligand page | IUPHAR/BPS Guide to PHARMACOLOGY
Iomeprol	Iomervu	Radiographic contrast agent	Not having one	FDA		Rengo et al., 2019	
Landiolol	Rapiblyk	Short-term reduction of ventricular rate in adults with supraventricular tachycardia including atrial fibrillation and atrial flutter	β1-adrenoceptor antagonist	FDA		Cafaro et al., 2023; Rehberg et al., 2024; Whitehouse et al., 2023	landiolol | Ligand page | IUPHAR/BPS Guide to PHARMACOLOGY
Lazertinib	Lazcluze	Treatment in combination with amivantamab of locally advanced or metastaticnon-small cell lung cancer (NSCLC) with epidermal growth factor receptor(EGFR) exon 19 deletions or exon 21 L858R substitution mutations	Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)	FDA	P	Cho et al., 2024	lazertinib | Ligand page | IUPHAR/BPS Guide to PHARMACOLOGY
Levacetylleucine	Agneursa	Treatment of neurological symptoms of Niemann–Pick disease type C	Thought to normalise energy metabolism, improving mitochondrial and lysosomal dysfunction	FDA	P, FT, rare Paediatric disease	Bremova-Ertl et al., 2022; Bremova-Ertl et al., 2024	
Mavorixafor	Xolremdi	Treatment of WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis)	CXC chemokine receptor 4 antagonist	FDA	P, FT, rare Paediatric disease	Badolato et al., 2024; Dale et al., 2020	mavorixafor | Ligand page | IUPHAR/BPS Guide to PHARMACOLOGY
Pegulicianine	Lumisight	Optical imaging agent for the detection of cancerous tissue	Peptide emitting fluorescence when cleaved	FDA	FT	Hwang et al., 2022; Smith et al., 2023	
Resmetirom	Rezdiffra	Treatment of noncirrhotic non-alcoholic steatohepatitis with moderate to advanced liver fibrosis	Selective agonist of thyroid hormone receptor-β (THR-β)	FDA	P, FT, Br	Suvarna et al., 2024; Younossi et al., 2024	resmetirom | Ligand page | IUPHAR/BPS Guide to PHARMACOLOGY
Revumenib	Revuforj			FDA	P, Br	Issa et al., 2023	

(Continues)

TABLE 1 (Continued)

Active ingredient/s	Proprietary name	Approved therapeutic use	Molecular target/ mode of action	Approving agency	Approval type	Pivotal clinical trial(s)	Link to GtoP
		Treatment of relapsed or refractory acute leukaemia with a lysine methyltransferase 2A gene (KMT2A) translocation	Binds to menin and prevents its interaction with KMT2A that drives malignancy				revumenib | Ligand page | IUPHAR/BPS Guide to
Seladelpar	Livdelzi	Treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA)	Selective agonist of peroxisome proliferator-activated receptor-delta (PPAR-δ)	FDA	Acc	Arıvalo-Capas and Arıvalo-Serrano, 2024; Caines et al., 2024; Hirschfield et al., 2024; Kowdley et al., 2024	seladelpar | Ligand page | IUPHAR/BPS Guide to PHARMACOLOGY
Sofpironium	Sofdra	Topical treatment of primary axillary hyperhidrosis	'Soft drug' competitive inhibitor of muscarinic acetylcholine receptors	FDA		Fujimoto et al., 2021; Yokozeki et al., 2021	sofpironium | Ligand page | IUPHAR/BPS Guide to PHARMACOLOGY
Sulopenem etzadroxil - probenecid	Orlynvah	To treat uncomplicated urinary tract infections	Inhibits bacterial cell wall synthesis (Sulopenem), reduces renal tubular excretion of Sulopenem (probenecid)	FDA	P, FT, qualified infectious disease product	Dunne et al., 2023	
Tovorafenib	Ojemda	To treat relapsed or refractory paediatric low-grade glioma harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation	Type II, pan-RAF kinase inhibition	FDA	P, Br, Acc	Kilburn et al., 2024; van Tilburg et al., 2024; NCT04775485;	tovorafenib | Ligand page | IUPHAR/BPS Guide to PHARMACOLOGY
Vanzacaftor, tezacaftor and deutivacaftor	Alyftrek	To treat cystic fibrosis	Vanzacaftor and tezacaftor improve processing and cell surface trafficking of CFTR (correctors), deutivacaftor increases CFTR activity (modulator)	FDA		Uluer et al., 2023	
Vorasidenib	Voranigo	Treatment of Grade 2 astrocytoma oroligodendroglioma with a susceptible IDH1 or IDH2 mutation	Dual inhibitor of isocitrate dehydrogenase-1 and −2 (IDH1 and IDH2)	FDA		Mellinghoff et al., 2023	vorasidenib | Ligand page | IUPHAR/BPS Guide to PHARMACOLOGY
Xanomeline - Trospium	Cobenfy	Treatment ofschizophrenia	Agonist of muscarinic acetylcholine receptors M1 and M4 (Xanomeline), peripheral-acting muscarinic antagonist (Trospium)	FDA		Kaul, Sawchak, Walling, et al., 2024; Kaul, Sawchak, Correll, et al., 2024	
FIC = first-in-class							

Note: P = Priority, Br = breakthrough, Acc = accelerated approval, FT = fast-track.

TABLE 2 Proteins and antibodies.

Active ingredient/s	Proprietary name	Approved therapeutic use	Molecular target/mode of action	Approving agency	Approval type	Pivotal clinical trial(s)
Axatilimab	Niktimvo	Treatment of chronic graft-versus-host disease (cGVHD)	Colony-stimulating factor-1 (CSF-1) receptor blockade	FDA	P	Wolff et al., 2024
Concizumab	Alhemo	For routine prophylaxis to prevent bleeding episodes in haemophilia A and B	TFPI inhibitory MAb	FDA	P	Matsushita et al., 2023
Cosibelimab	Unloxcyt	To treat unresectable metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC)	Programmed Death Ligand-1 (PD-L1) blockade	FDA		Clingan et al., 2023
Crovalimab	Plasky	Treatment of paroxysmal nocturnal haemoglobinuria (PNH)	Complement C5-targeting inhibitor	FDA, EMA, MHRA		Röth et al., 2024
Donanemab	Kisunla	Treatment of mild forms of Alzheimer's disease	Ab directed against aggregated forms of beta amyloid	FDA, MHRA	FT, P, Br	Heneka et al., 2024; Sims et al., 2023
Letibotulinumtoxin A	Letybo	Temporary improvement in the appearance of moderate to severe glabellar lines	Acetylcholine release inhibitor/neuromuscular blockade	FDA		NCT02677298; NCT02677805; NCT03985982
Marstacimab	Hympavzi	Reduce bleeding episodes in haemophilia A (congenital factor VIII deficiency) or haemophilia B (congenital factor IX deficiency) in patients without factor VIII or IX autoantibodies	TFPI targeting, resulting in factor Xa disinhibition	FDA		Mahlangu et al., 2023; NCT03363321, NCT03938793
Nemolizumab	Nemluvio	Treatment of prurigo nodularis	IL-31Rα antagonist	FDA	P, Br	Kwatra et al., 2023; Silverberg et al., 2024; Ständer et al., 2024
Nogapendekin alfa inbakicept	Anktiva	To treat BCG-unresponsive bladder cancer, together with *Bacillus* Calmette–Guerin (BCG)	IL-15/IL-15Rα-IgG fusion conjugate, 'superactivator' of the IL-15 receptor	FDA	Br	Chamie et al., 2023; Li et al., 2024; NCT0302285
Sotatercept	Winrevair	Treatment of pulmonary arterial hypertension (PAH, WHO group 1, functional class II to III)	Activin receptor type IIA (ActRIIA)-Fc fusion, inhibition of activin signalling	FDA, EMA		Hoeper et al., 2023; Pitre et al., 2024
Sugemalimab	Cejemly	Treatment of metastatic non-small cell lung cancer (NSCLC) in combination with platinum	PD-L1 blockade	EMA, MHRA		Li et al., 2023; Zhou et al., 2023
Tarlatamab	Imdelltra	Treatment of extensive stage small cell lung cancer with disease progression on or after platinum-based chemotherapy	Bispecific MAb / T-cell engager, targets delta-like ligand 3 and CD3	FDA	P, Br, Acc	Ahn et al., 2023; Paz-Ares et al., 2023; NCT05060016
Zanidatamab	Ziihera	To treat unresectable or metastatic HER2-positive (IHC 3+) biliary tract cancer	Bispecific, biparatopic HER2-targeting MAb	FDA	P, Br, Acc	Harding et al., 2023
Zenocutuzumab	Bizengri	To treat advanced, unresectable, or metastatic non-small cell lung cancer (NSCLC) or pancreatic adenocarcinoma harbouring a Neuregulin 1 (NRG1) gene fusion	Bispecific ab using dock (HER2 arm) and block (HER3 arm) mechanism to inhibit NRG1 fusion oncogenic signalling	FDA	P, Br, Acc	NCT02912949; Kim et al., 2024
Zolbetuximab	Vyloy	In combination with fluoropyrimidine and platinum, to treat CLDN18.2+, locally advanced	Targets the Claudin18.2 (CLDN18.2) tumour marker and elicits cytolysis	FDA, EMA, MHRA	P, FT	Shah et al., 2023; Shitara et al., 2023

(Continues)

TABLE 2 (Continued)

Active ingredient/s	Proprietary name	Approved therapeutic use	Molecular target/mode of action	Approving agency	Approval type	Pivotal clinical trial(s)
FIC = first-in-class		unresectable or metastatic HER2-gastric or gastroesophageal junction adenocarcinoma				

Note: P = Priority, Br = breakthrough, Acc = accelerated approval, FT = fast-track.

TABLE 3 Advanced therapy medicinal products (ATMP).

Active ingredient/s	Proprietary name	Approved therapeutic use	Molecular target/mode of action	Approving agency	Approval type	Pivotal clinical trial(s)
Afamitresgene autoleucel	Tecelra	Treatment of unresectable or metastatic synovial sarcoma	Autologous T-cells expressing a T-cell receptor (TCR) targeting tumour MAGE-A4 protein	FDA	P, Acc, regenerative medicine advanced therapy	D'Angelo et al., 2024; Hong et al., 2023
Fidanacogene elaparvovec	Beqvez	Treatment of moderate to severe haemophilia B (congenital factor IX deficiency)	Adeno-associated virus (AAV) gene-therapy vector for expression of a high-activity human factor IX variant (FIX-R338L/FIX-Padua)	FDA, EMA		Cuker et al., 2024; Pittman et al., 2024
Imetelstat	Rytelo	Treatment of anaemia in low- to intermediate-1 risk myelodysplastic syndromes	13-mer oligonucleotide, direct inhibitor of human telomerase RNA component	FDA		Platzbecker et al., 2024; NCT02598662
Lifileucel	Amtagvi	Treatment of unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 positive, a BRAF inhibitor with or without a MEK inhibitor	Tumour-derived autologous T-cell immunotherapy	FDA	P, FT, Acc, regenerative medicine advanced therapy	Chesney et al., 2022; Sarnaik et al., 2021; Schoenfeld et al., 2024
Obecabtagene autoleucel	Aucatzyl	To treat relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL)	CD19-directed genetically modified autologous CAR T-cells	FDA		Roddie et al., 2024
Olezarsen	Tryngolza	To treat familial chylomicronemia syndrome	Antisense oligonucleotide targeting apolipoprotein CIII (apoC3) mRNA	FDA	P, FT, Br	Stroes et al., 2024
FIC = first-in-class						

Note: P = Priority, Br = breakthrough, Acc = accelerated approval, FT = fast-track.

TABLE 4 Vaccines.

Active ingredient/s	Proprietary name	Approved therapeutic use	Molecular target/mode of action	Approving agency	Approval type	Pivotal clinical trial(s)
MRESVIA	MRESVIA	Respiratory syncytial virus mRNA-based vaccine	mRNA encoding the stabilised RSV prefusion F glycoprotein	FDA, EMA		Wilson et al., 2023
Pneumococcal 21-valent conjugate vaccine	Capvaxive	Active immunisation for the prevention of invasive disease caused by *Streptococcus pneumoniae*	Covers 21 *S. pneumoniae* serotypes	FDA	Acc	Kobayashi et al., 2024
FIC = first-in-class						

Note: P = Priority, Br = breakthrough, Acc = accelerated approval, FT = fast-track.

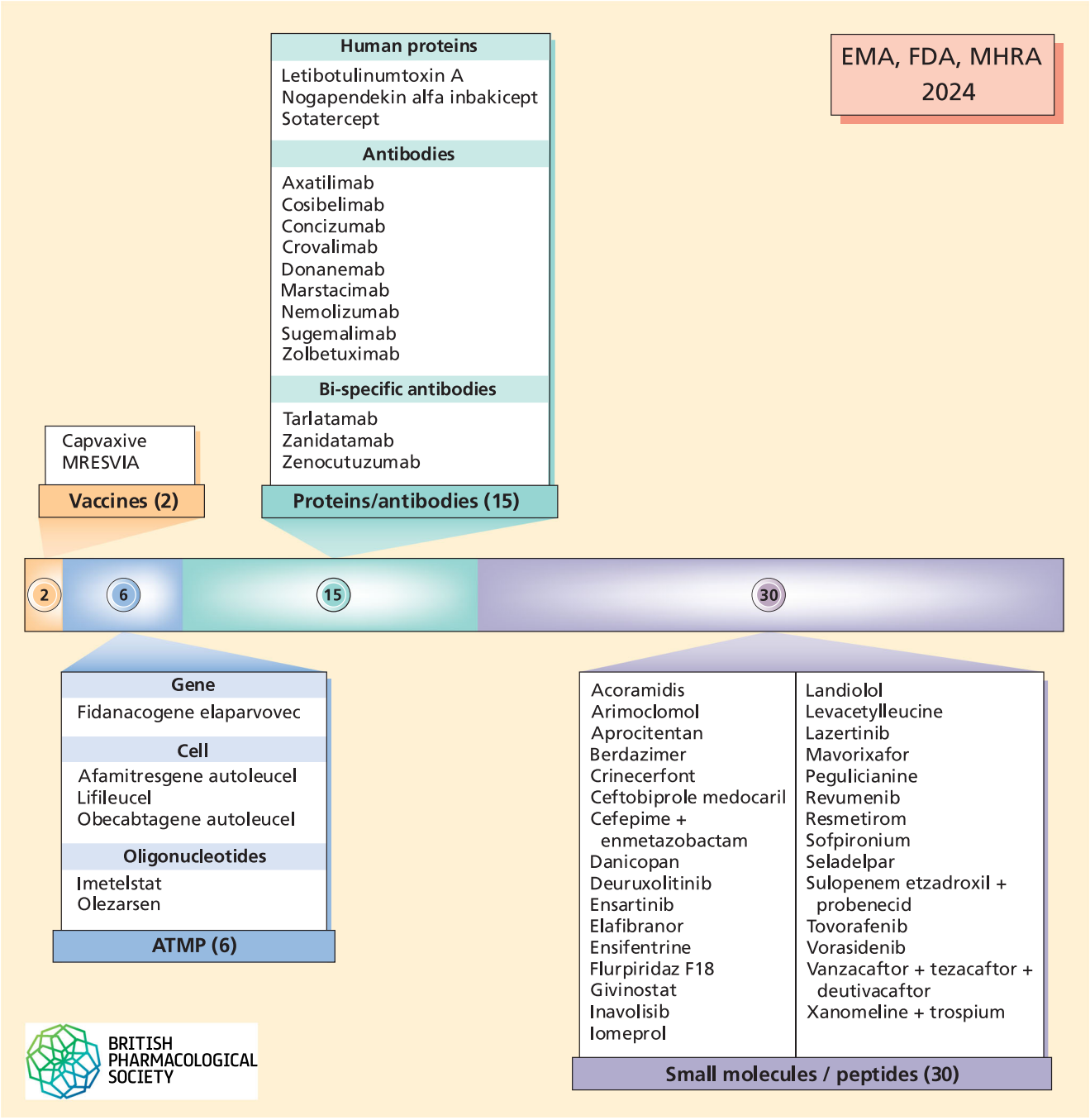

FIGURE 1 New drugs approved in 2024 by the EMA, FDA and MHRA categorised by chemical/biological category.

therapy in melanoma patients with progressive, ICI-refractory disease, characterised by very limited additional options. This is a fitting accomplishment for the ingenious cell-based approach to the immunotherapy of solid tumours initially pioneered for melanoma by Rosenberg and collaborators >30 years ago (Rosenberg et al., 1988).

Afamitresgene autoleucel (Tecelra), approved a few months after lifileucel (Amtagvi), became the second advanced cell therapy licensed for use in oncology indications outside haematology (for a roundup, please see https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products). Afamitresgene autoleucel differs from lifileucel in important aspects. For one, the former harvests peripheral blood mononuclear cells (PBMCs) from the patient and enriches them for T-cells, instead of isolating T-cells from the patient's tumour biopsies. In addition, afamitresgene autoleucel subsequently comprises an ex vivo cell-engineering step, by which T-cells are transduced with a replication-incompetent lentiviral vector containing the melanoma-associated antigen A4 (MAGE-A4) T-cell receptor (TCR) transgene. MAGE-A4 protein is overexpressed in multiple solid tumours, including synovial sarcoma. The transduced $CD4^+$ and $CD8^+$ T-cells expressing the affinity-optimised TCR are capable of enhanced potency against the MAGE-4A-expressing cancer cells. The promising efficacy and safety results

BOX 2 First-in-class (28)

Afamitresgene autoleucel	Arimoclomol
Axatilimab	Berdazimer
Crinecerfont	Danicopan
Elafibranor	Ensifentrine
Flurpiridaz F18	Imeltestat
Levacetylleucine	Lifileucel
Marstacimab	MRESVIA
Nogapendekin alfa inbakicept	Nemolizumab
Olezarsen	Resmetirom
Revumenib	Seladelpar
Sotatecerpt	Tarlatamab
Tovoracenib	Vorasidenib
Xanomeline-Trospium	Zanidatamab
Zenocutuzumab	Zolbetuximab

from a phase I clinical study (NCT03132922; Hong et al., 2023), were further confirmed in a multicentre, phase II, open-label, non-randomised trial (NCT04044768; SPEARHEAD-1; D'Angelo et al., 2024). This last trial was conducted in 52 patients with HLA-A*02 and confirmed cytogenetically metastatic or unresectable MAGE-A4^{+} synovial sarcoma ($n = 44$) or myxoid round cell liposarcoma ($n = 8$), which had been previously treated with at least one line of anthracycline or **ifosfamide** chemotherapy and a median of three lines of chemotherapy. The patients received a single dose of 10^{9}–10^{10} T-cells after lymphodepletion with **fludarabine** and **cyclophosphamide**. The primary endpoint was overall response rate (ORR) using Response Evaluation Criteria in Solid Tumours (version 1.1). ORR in this cohort was 37%: 39% for synovial sarcoma patients and 25% for myxoid round cell liposarcoma patients. The median DOR was 6 months; 45.6% had a DOR greater than or equal to 6 months, and 39.0% had a DOR greater than or equal to 12 months. Cytokine release syndrome occurred in 37 (71%) of the 52 patients, and cytopenias were the most common grade 3 or worse adverse events (lymphopenia in 50 [96%], neutropenia in 44 [85%], leukopenia in 42 [81%]). In this cohort, comprising patients who had received multiple chemotherapy treatments and with few, if any, remaining therapeutic options, the significant percentage of durable responses obtained by afamitresgene autoleucel is a milestone in this indication and demonstrates that affinity-optimised TCRs can enhance the anti-tumour efficacy of targeted, adoptive T-cell therapy, a strategy that can in the future be expanded to additional solid tumours.

2.1.2 | Imetelstat

Telomerase inhibitors have been in clinical trials for years, including **imetelstat**, which was first tested in 2015 in patients with essential thrombocythaemia, because of its ability to inhibit megakaryocytic proliferation in vitro (Baerlocher et al., 2015). Patients with myelodysplastic syndromes (MDS) require blood transfusions to treat anaemia; frequently, however, patients either fail to respond to standard anaemia drugs (e.g. **erythropoietin**) or are ineligible to receive them. Imetelstat is the first telomerase inhibitor ever approved and targets a novel mechanism in this disease. Previous in vitro and in vivo studies have shown that imetelstat can reduce the numbers of myelofibrosis (MF) cells but not normal cord blood CD34^{+} haematopoietic progenitor cells (HPCs, colony-forming unit–granulocyte/macrophage, burst-forming unit–erythroid, and colony-forming unit–granulocyte/erythroid/macrophage/megakaryocyte), irrespective of the patient's mutational status, as well as cause depletion of mutated HPCs from **JAK2** V617F^{+} MF patients (Wang et al., 2018). Imetelstat is a 13-mer oligonucleotide complementary to the template region of the telomerase RNA component, causing a direct, competitive inhibition of telomerase enzymatic activity (Marian et al., 2010). The efficacy of imetelstat, given *i.v.* every 4 weeks until either unacceptable toxicity or disease progression, was tested in the approximately 18 month-long clinical study (median stay in the trial, NCT02598661; Platzbecker et al., 2024), which evaluated the proportion of patients who achieved red blood cell transfusion independence (RBC-TI) for either longer than eight consecutive weeks and for longer than 24 consecutive weeks. The rate of the ≥8-week RBC-TI was 39.8% in the imetelstat group versus 15% in the placebo group, and the rates of ≥ 24-week RBC-TI were 28% and 3.3%, respectively. The observed adverse effects were mostly related to blood cell abnormalities and hepatic enzyme abnormalities (the latter present in ∼90% of the imetelstat group vs ∼47% of the placebo group). Imetelstat therefore constitutes a significant treatment progress for these patients who have exhausted currently available anaemia treatments and therefore addresses a critical unmet medical need. Because imetelstat and other telomerase inhibitors are currently under evaluation in diverse indications (https://clinicaltrials.gov/search?intr=telomerase%20inhibitor), it will be interesting to follow them up and compare the efficacy and long-term treatment effects of imetelstat. In addition, Imetelstat's preclinically-proven ability to induce ferroptosis and tumour cell oxidative stress that leads to the reduction of haematological cancer (AML) burden (Bruedigam et al., 2024) will need to be further evaluated and assessed as an additional mechanism contributing to its clinical efficacy in MDS.

2.1.3 | Nogapendekin alfa inbakicept (NAI)

The oldest approved cancer biotherapy/immunotherapy drug is the tuberculosis vaccine Bacillus Calmette–Guérin (BCG), which, by a still not completely elucidated mechanism, is effective in recruiting the immune system to suppress non-muscle-invasive bladder cancer (NMIBC) growth (Redelman-Sidi et al., 2014). For patients whose cancer does not respond to BCG, injection of a combination of the BCG vaccine with NAI (Anktiva) has been approved this year, making it the first-ever **IL-15**-related approved drug in any indication. NAI consists of a mutated 'super-agonist' form of human IL-15 (IL-15 N72D, 114 amino

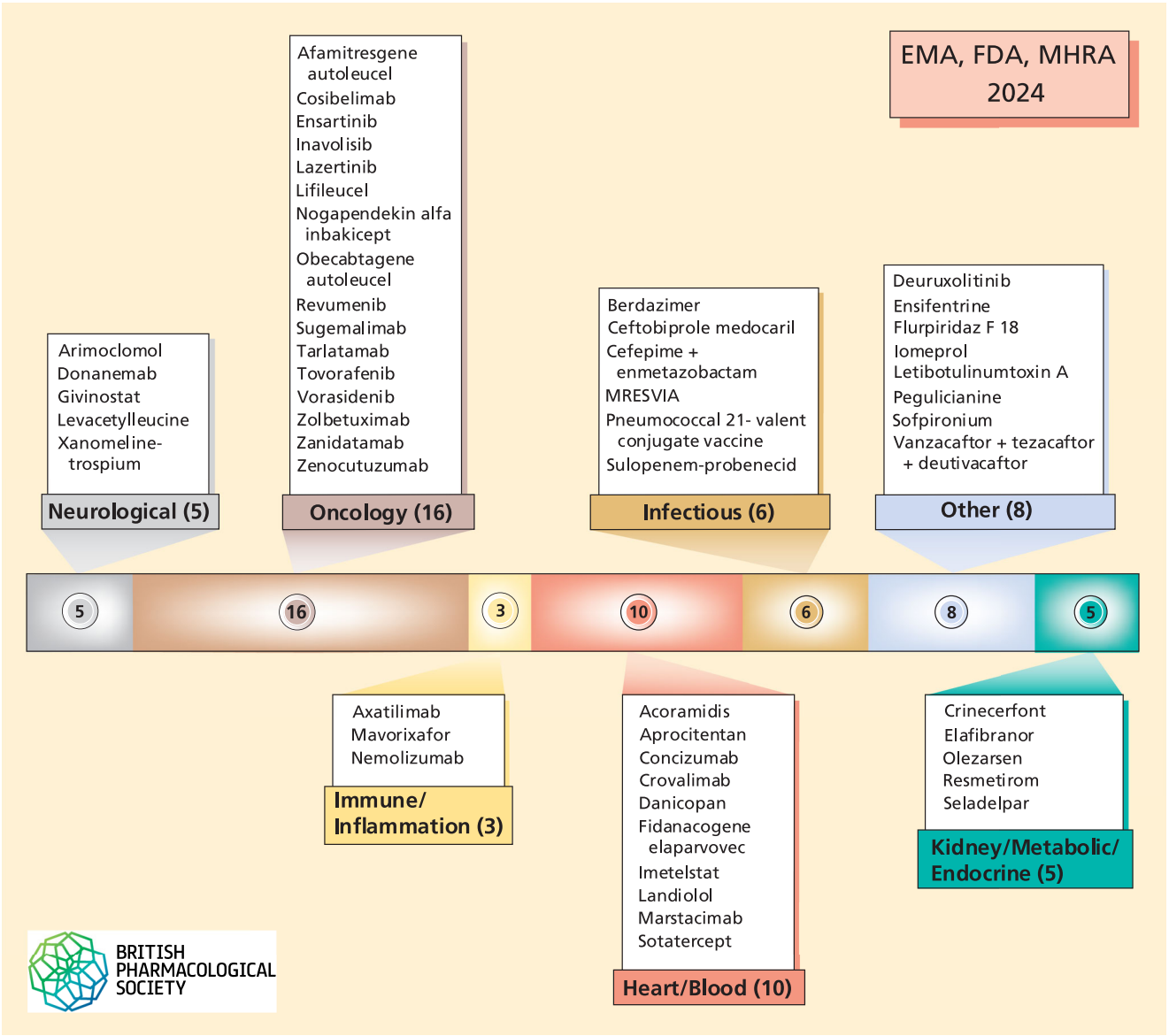

FIGURE 2 New drugs approved in 2024 by the EMA, FDA and MHRA by therapeutic area/category.

acid-long, 4–5-fold more bioactive than wild-type IL-15) linked to a dimeric IL-15Rα 'sushi' domain (65 amino acid-long) – IgG1 Fc fusion protein (232 amino acid-long; Chamie et al., 2023). This immunostimulatory complex allows IL-15 to be efficiently trans-presented by the **IL-15 receptor α** to the shared IL-2/IL-15 receptor (the **IL-2Rβ** and **IL-2Rγ** common subunits) on the surface of $CD4^+$ and $CD8^+$ T-cells and NK cells (Tamzalit et al., 2014), which can synergise with BCG to elicit antigen-presenting cancer cell cytotoxicity. The clinical trial was conducted with 77 adults with BCG-unresponsive, high-risk NMIBC with carcinoma in situ (CIS) with or without papillary (Ta/T1) disease after transurethral resection, and the endpoints were complete remission (CR) at evaluation during treatment and persistence of CR over time. Sixty-two percent of patients who received NAI with BCG showed CR at any time during the trial, and 58% of those patients displayed CR for over 1 year. Furthermore, 40% of patients with CR at any time during the trial of maintained CR for over 2 years (Li et al., 2024; Chamie et al., 2024). Importantly, no cancer-attributed deaths were noted in the NIA-treated population, nor cystectomy was deemed necessary. On the basis of these results, the drug was approved via the accelerated approval pathway, for the treatment of adult patients with BCG-unresponsive NMIBC with CIS with or without papillary tumours, under Breakthrough Therapy designation. Of note, multiple clinical trials using a combination of NAI with other immune modifiers are ongoing, and in the next couple of years it will be interesting to see whether and how this immunomodulator synergises with them.

2.1.4 | Revumenib

Most recently approved treatments for AML, such as **ivosidenib** and **midostaurin**, are directed at genetic mutations (in **IDH1** and **FLT-3**, respectively) found in only a minority of patients. A higher

percentage of AMLs harbour mutations in the nucleophosmin 1 (*NPM1*) gene and rearrangements in the lysine methyltransferase 2A (**KMT2A**) gene drive epigenetic changes instructing blood cells to dedifferentiate and assume a stem cell-like malignant phenotype. To induce this altered gene expression, the proteins produced by *KMT2A* (which was also previously called mixed-lineage leukaemia or MLL1) and by *NPM1* need to interact with a protein called menin, a step that enables them to form a transcriptional regulator complex and bind to DNA. The menin-binding motif is preserved in all KMT2A fusion proteins, and menin therefore is an essential oncogenic cofactor in this context. Rearrangements of *KMT2A* occur in 80% of infant acute lymphoblastic leukaemia (ALL) and in 5–15% of children and adults with acute leukaemia, whether myeloid, lymphoid or mixed phenotype, and their presence signals poor prognosis, with a 5-year overall survival of less than 25% and no specific targeted therapies available. Of note, *KMT2A* rearrangements occur in up to 10% of acute leukaemias, whereas *NPM1* mutations are found in up to 30% and thus the latter are the most common genetic alteration in acute myeloid leukaemia (Issa et al., 2023). **Revumenib** is a FIC small molecule that has been designed to bind to menin and prevent its interaction with MLL1, thus either reversing the cellular dedifferentiation process or inducing malignant cell death. Revumenib was tested in a one-arm, open-label, multicentre trial (AUGMENT-101; Issa et al., 2025) in 104 adult and paediatric patients with relapsed or refractory acute leukaemia with a *KMT2A* translocation and was administered until disease progression, unacceptable toxicity (most notably prolongation of the QT interval), failure to achieve morphological leukaemia-free state by four cycles of treatment or haematopoietic stem cell transplantation (HSCT).

The main efficacy measures were complete remission (CR) plus CR with partial haematologic recovery (CRh), the duration of CR + CRh, and finally conversion from transfusion dependence to independence. Revumenib treatment resulted in a 21.2% CR + CRh rate that lasted a median of 6.4 months. Among the 83 participants necessitating red blood cell (RBC) and/or platelet transfusions, 12 (14%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. Of the 21 patients independent of both RBC and platelet transfusions at baseline, 10 (48%) remained transfusion independent during any 56-day post-baseline period. These promising data show that targeting menin with revumenib can elicit significant remission and cancer burden clearance in refractory acute leukaemias characterised by *KMT2A* translocations. The authorisation of revumenib raises hopes that this and other menin inhibitors, currently in clinical trials, will succeed in improving the outcomes in the more numerous cases of acute leukaemia linked to the mutated *NPM1* protein (Candoni & Coppola, 2024).

2.1.5 | Tarlatamab

Small-cell lung cancer (SCLC) is characterised by high aggressiveness and a dire survival prognosis, despite the recent addition of check-point inhibitors (e.g. **atezolizumab** or **durvalumab**) to the standard of care therapy, **platinum** and **etoposide**; second line treatments (e.g. **topotecan**) are limited and there is no drug specifically authorised as a third line treatment when SCLC relapses. In SCLC, in contrast to healthy cells and tissues, the expression of the normally intracellularly located protein delta-like ligand 3 (**DLL3**) is aberrantly high and aberrantly trafficked to the cell surface. DLL3 therefore constitutes an attractive tumour-specific target for the design of new therapeutics (Paz-Ares et al., 2023). **Tarlatamab** goes a significant way to address this void. Of note, prior clinical trials with a DLL3-directed, toxin-linked MAb showed moderate therapeutic effectiveness and high frequency of serious or life-threatening adverse effects (Tendler & Rudin, 2023). Tarlatamab is a FIC bispecific MAb which has been designed to bind simultaneously to DLL3 and to **CD3**, thus enhancing the engagement of T-cells and enabling increased T-cell-mediated tumour-directed cytotoxicity. The study (NCT05060016; Ahn et al., 2023) that led to tartalamab's approval was conducted under Project Orbis, which consists of concurrent submission and review of oncology drugs among several counties (https://www.fda.gov/about-fda/oncology-center-excellence/project-orbis). The trial enrolled 99 adult patients with relapsed or refractory extensive stage-SCLC, who received prior treatment with platinum chemotherapy and at least one other therapy. At evaluation time, the 10-mg treatment group seemed to present more positive results than the 100-mg group. An objective response occurred in 40% of the patients in the 10-mg group, 59% of whom showed a DOR that was at least 6 months. At the temporary conclusion time of the study, 55% of these patients had an objective response, and their median progression-free survival was 4.9 months; estimated overall survival rate at 9 months was 68%. The most serious recurrent adverse event was cytokine release syndrome (CRS); however, all CRS cases were reversible and did not lead to discontinuation of tarlatamab. On the strength of these encouraging therapeutic and safety data, tarlatamab was granted accelerated approval, whereas definitive clinical approval will require conclusive verification of clinical benefit at the projected study end.

2.1.6 | Tovorafenib

Low-grade gliomas (LGG) are the most common brain tumour in children. While LGG are not as aggressive as glioblastoma, they can damage adjacent tissues and require several rounds of chemotherapy, frequently with multiple drugs, thus severely impacting the child's quality of life. A combination of **dabrafenib** and **trametinib**, approved very recently, targets specific mutant forms of the kinase BRAF; however, it is ineffective in the treatment of tumours with *BRAF* gene rearrangements or fusions, which are very common in paediatric LGG. **Tovorafenib** is a type II RAF kinase inhibitor that can target BRAF fusions and rearrangements, as well as specific BRAF mutations, such as $V^{600}E$, $V^{600}D$, wild-type BRAF and wild-type **CRAF** kinases (Tkacik et al., 2023), and does not induce paradoxical activation of the MAPK pathway seen with other inhibitors. In the 76-patient study that obtained accelerated approval, tovorafenib monotherapy was compared to standard-of-care treatment. The overall response rate

(complete or partial tumour response) was 51%, while the median DOR was 13.8 months (van et al., 2024; Kilburn et al., 2024). Tovorafenib, therefore, is the first type II (pan-)RAF kinase inhibitor to obtain authorisation and the first FDA approval of a systemic therapy for the treatment of patients with paediatric LGG with BRAF rearrangements, including fusions, justifying its FIC molecule designation. In addition, in contrast to current chemotherapy, it can be administered orally once a week at home, which is an important practical consideration with the paediatric population it targets.

2.1.7 | Vorasidenib

Mutations in the isocitrate dehydrogenase (*IDH*) genes have been described in a broad array of haematologic malignancies, including AML (acute myelogenous leukaemia), myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPNs), and also occur in solid tumours such as cholangiocarcinoma, chondrosarcoma and gliomas (Fruchtman et al., 2024). Several single inhibitors of mutant IDH1 or **IDH2** have been approved, for the treatment of haematological malignancies and peripheral tumours, including ivosidenib (IDH1 inhibitor) and **enasidenib** (IDH2 inhibitor) (Mellinghoff et al., 2023; Thol & Ganser, 2020). Gliomas are the most common primary brain malignancies in adults, and mutations in the *IDH1* or *IDH2* genes show in nearly all grade 2 diffuse gliomas in adults, resulting in the accumulation of the oncometabolite 2-hydroxyglutarate, which affects oncogenesis and tumour growth. Gliomas with mutations in either *IDH1* or *IDH2* and an unbalanced translocation between chromosomes 1 and 19 (1p/19q-codeleted) are classified as oligodendrogliomas, whereas those without 1p/19q codeletion (1p/19q–non-codeleted) as astrocytomas (Mellinghoff et al., 2023). **Vorasidenib** is a unique, FIC dual allosteric inhibitor of mutant IDH1 and IDH2, capable of crossing the brain. Vorasidenib was compared to placebo in the pivotal, double-blind, phase 3 trial (Mellinghoff et al., 2023; NCT04164901), conducted with 331 participating patients with residual or recurrent grade 2 IDH-mutant glioma, who had undergone no previous treatment other than surgery. The primary endpoint was imaging-based progression-free survival (27.7 months in the Vorasidenib group vs 11.1 months with placebo), and the secondary endpoint was the time to the next anticancer intervention, which was not reached at evaluation time for the Vorasidenib arm and was 17.8 months for the placebo arm. These results, combined with its mostly low-grade toxicity, led to the FDA approval of vorasidenib via Project Orbis review. Its continued evaluation in patients with higher grade (3 or 4) gliomas, as well as in those having received prior chemotherapy in addition to surgery, will reveal whether this drug can benefit additional subgroups in this very challenging disease indication.

2.1.8 | Zanidatamab

Therapeutic MAbs against cell-bound tumour antigens can elicit a maximal effect by simultaneously triggering multiple mechanisms, such as neutralisation of their target antigen's function, activation of cell-mediated cytotoxicity (ADCC) and engagement of complement-dependent cytotoxicity (CDC). The mitigated success of certain classical monoclonal or bi-specific approved antibodies, for example, the limited efficacy or **HER2**-targetting MAbs in additional HER2^{+} tumours besides breast and gastric cancer, is sometimes attributed to their sub-optimal target-binding mode, which does not allow them to fully engage all the above mechanisms. To do that, better avidity provided by multivalent binding is required for clustering, formation of higher order complexes (e.g. hexamers) and prolonged presence on the target (Oostindie et al., 2022). In contrast to monospecific or bispecific MAbs, biparatopic antibodies (bpAbs) bind distinct, non-overlapping epitopes on a *single* target, a feature that enables them to employ mechanisms of action not adequately triggered by monospecific and bispecific antibodies. **Zanidatamab** is a FIC biparatopic Ab, binding on two epitopes found on extracellular domains 2 and 4 of HER2 and engineered to enhance HER2 receptor crosslinking and clustering, HER2 internalisation, suppression of cell signalling and tumour growth. The formation by zanidatamab of HER2-Ab higher-order complexes, besides ADCC, also promotes C1q binding required for CDC and phagocytosis, enabling increased effector function (Weisser et al., 2023). Its efficacy was evaluated in HERIZON-BTC-01 (NCT04466891; Harding et al., 2023), an open-label, multicentre, single-arm trial in 62 patients with unresectable or metastatic HER2-positive (IHC3^{+}) biliary tract cancer (BTC), who had received at least one prior **gemcitabine**-containing regimen in the advanced disease setting, characterised by dire survival prognosis and few existing additional options. The major efficacy outcome measures were ORR and DOR. Zanidatamab treatment led to an ORR of 52% and a median DOR of 14.9 months, with manageable grade 3 adverse events in 18% of the patients. Zanidatamab's clinical success provides the first clinical proof-of-concept paradigm for biparatopic Abs, because it is the first such drug approved in any indication and offers a sorely-needed additional therapeutic option in BTC. Furthermore, HER2-amplified tumours, where previously authorised HER2-directed MAbs or small molecule therapies have not yet been successful in providing durable responses, also include colorectal cancer, pancreatic cancer and ovarian cancer, and for this reason, it will be interesting to see whether zanidatamab, providing a different HER2-targeting approach, will be effective in ongoing trials in these indications.

2.1.9 | Zenocutuzumab

Zenocutuzumab (Bizengri) is one more addition to tumour-agnostic treatments, which rely on common genomic and proteomic alterations across tumour types, identified by molecular profiling, to identify shared therapeutic targets. Such a biomarker-driven, disease-agnostic approach can therefore maximise the therapeutic benefit of such drugs. **Neuregulin 1** (NRG1) gene rearrangements are recurrent oncogenic drivers in multiple types of solid tumours and signal by binding mainly to the **HER3** and **HER4** members of the **ErbB RTK family** (that

includes **EGFR**, HER2, HER3 and HER4). The NRG1 ligand, especially NRG1 fusions with membrane partners that position it close to RTKs (Nagasaka & Ou, 2022), strongly triggers higher-order oligomerisation and signalling activation via HER2-HER3 multimers, considered the most oncogenic heterodimers of the ErbB family (Schram et al., 2022). Zenocutuzumab is a first-in-class (FIC) bi-specific humanised antibody employing an ingenious 'dock (HER2 arm) and block (HER3 arm)' approach: the HER2-targeting arm binds to HER2, which is more abundantly expressed on the tumour cell surface, favouring a high local concentration of the antibody, therefore enabling the HER3-targeting arm to prevent NRG1 binding to HER3. As a consequence, HER2-HER3 heterodimerisation and the ensuing potent downstream oncogenic (mitogenic) signalling is effectively blocked. Tarlatamab's effect is further improved by an engineered modification of the MAb's Fc domain, which increases its affinity for Fc receptors, resulting in enhanced antibody-dependent cellular cytotoxicity (ADCC). Zenocutuzumab was tested in the eNRGy study (NCT02912949; Kim et al., 2024) conducted in 64 patients with NRG1 fusion-positive malignancies, who had received at least two prior systemic therapies. Zenocutuzumab demonstrated a 33% overall response rate in NSCLC and 40% in pancreatic adenocarcinoma. The median response duration was 7.4 months in NSCLC and 3.7 to 16.6 months in pancreatic adenocarcinoma. Zenocutuzumab fills a poorly addressed need in oncology, that is, NRG1-fusion-positive cancers that have not shown adequate response to previous therapy and, being a disease-agnostic treatment, its use may expand to additional tumour types carrying the same biomarker. Last, its unique 'dock and block' design provides a proof-of-concept for the development of more drugs acting in a similar way in the near future.

2.1.10 | Zolbetuximab

Gastric cancer is the fifth most common cancer, and incidence of gastroesophageal junction adenocarcinomas has been increasing in the last few decades (Smyth et al., 2020). Because patients with early-stage disease are often asymptomatic, gastric or gastroesophageal junction (G/GEJ) adenocarcinomas are frequently diagnosed at an advanced or metastatic stage and treated with sequential lines of chemotherapy. The HER2 negative G/GEJ cancers have some of the highest unmet medical needs for additional targeted therapies (Kim et al., 2024; Shah et al., 2023). **Zolbetuximab** is a FIC monoclonal antibody against the tight-junction, cell surface molecule claudin18.2 (CLDN18.2), a pan-cancer marker, targeting splice variant 2 of **CLDN18**, a highly selective cell lineage marker of gastric mucosal cells which is retained on a significant proportion of malignant primary gastric cancers and their metastases. While in normal gastric mucosa CLDN18.2 is typically buried within tight junctions, loss of gastric mucosa cell polarity during malignant transformation may result in CLDN18.2 becoming more exposed and, thus, accessible to targeted therapies (Cao et al., 2022; Türeci, Sahin, et al., 2019). Zolbetuximab binds to the first extracellular N-terminal domain which is unique to the CLDN18.2 splice variant (Cao et al., 2022; Shah et al., 2023). Once the tumour cell CLDN18.2 is bound by zolbetuximab, several mechanisms are engaged that lead to eradication of the cells and shrinking of the tumour via ADCC and CDC, leading to cell lysis. In addition, blockade of CLDN18.2 by zolbetuximab is expected to modify cellular structural integrity, therefore also limiting cell replication and metastasis (Türeci, Mitnacht-Kraus, et al., 2019). Efficacy of zolbetuximab was evaluated in two randomised double-blind, multicentre trials: SPOTLIGHT (NCT03504397; Shitara et al., 2023) and GLOW (NCT03653507; Shah et al., 2023) in patients with CLDN18.2^{+}, advanced, unresectable or metastatic HER2- G/GEJ adenocarcinoma. The major efficacy outcome measure in both trials was progression-free survival (PFS); an additional measured outcome was Overall Survival (OS). In SPOTLIGHT, all patients received mFOLFOX6 (**folinic acid** plus **5-fluorouracil** and **oxaliplatin**) chemotherapy and were randomised to receive zolbetuximab or placebo. Median PFS was 10.6 months in the zolbetuximab/chemotherapy arm versus 8.7 months with placebo/chemotherapy, and median OS was 18.2 months and 15.5 months, respectively (NCT03504397; Shitara et al., 2023). Similar results were seen in GLOW, where all patients received CAPOX chemotherapy (**capecitabine** plus oxaliplatin) instead of FOLFOX and were again randomised to receive either zolbetuximab or placebo. Median PFS was 8.2 months in the zolbetuximab/chemotherapy arm versus 6.8 months with placebo/chemotherapy, and median OS was 14.4 months and 12.2 months, respectively (NCT03653507; Shah et al., 2023). These apparently modest, but in reality, very encouraging results in both major efficacy endpoints in the two trials led to the authorisation of zolbetuximab in this particularly intractable indication with a high unmet medical need. Furthermore, because CLDN18.2 is considered a pan-cancer marker (Sahin et al., 2008), it might be also targeted by zolbetuximab in additional CLDN18.2^{+} solid tumour indications, such as pancreatic cancer, possibly extending zolbetuximab's use in oncology as a tumour-agnostic agent.

2.2 | Immune/inflammatory diseases

2.2.1 | Axitilimab

Chronic graft-versus-host disease (cGVHD) is a serious complication of allogeneic stem-cell transplantation that reduces the survival of the graft and is seen in approximately 30% to 70% of patients who undergo this procedure. It is the major cause of complications and of non-relapse-associated death, and can severely affect the quality of life of the patients. About 50% of patients become refractory to immunosuppression by (first-line) glucocorticoids and face a poor outcome. Second- and third-line treatments of chronic GVHD vary substantially among centres and include, among others (reviewed in Kovalenko et al., 2023) **ibrutinib** (a **Bruton tyrosine kinase** inhibitor), **belumosudil** (an inhibitor of **Rho-associated coiled-coil kinase 2** (ROCK2)), **ruxolitinib** (a JAK1/2 inhibitor), **mycophenolate mofetil** and extracorporeal photopheresis. The colony-stimulating factor 1 (CSF-1)/**CSF-1 Receptor** (CSF-1R) signalling in monocytes and

macrophages contributes to the development and exacerbation of cGVHD, and therefore blocking the CSF-1R by a neutralising MAb is expected to modify the course of cGVHD. A phase II trial enrolled 241 patients that had not responded adequately to at least two systemic treatments (Wolff et al., 2024). The primary endpoint was the overall response, observed in 50–74% of the participants, depending on the dose. The success in achieving the secondary endpoint (reduction of more than five points on the modified Lee Symptom Scale) was reported in 41–60% of the participants, again depending on dose group. Of note, the cohort that received the 0.3-mg dose axitilimab scored better in both criteria than those receiving 1 or 3 mg, and the same was true for the presentation of adverse events leading to discontinuation of axatilimab. CSF-1R blockade by axalitimab (Niktimvo) treatment, therefore, led to a high incidence of response in patients with recurrent or refractory chronic GVHD, adding a valuable therapeutic tool to this very challenging indication. It is worth noting that a small molecule inhibitor of colony-stimulating factor 1 receptor, **pexidartinib**, was approved in 2019 to treat symptomatic tenosynovial giant cell tumour (TGCT), but in *clinicaltrials.gov*, there is no entry to show that it has been or is evaluated in cGVHD. Perhaps it will be repositioned and introduced in such an indication, based on the approval of this CSF-1R neutralising MAb.

2.2.2 | Nemolizumab

The cytokine **interleukin-31** (IL-31; Dillon et al., 2004) has been causally implicated in the pathophysiology of multiple atopic disorders such as atopic dermatitis (AD), allergic rhinitis and airway hyperreactivity, being one of the main drivers of its cardinal symptom, pruritus (Datsi et al., 2021). Atopic dermatitis does not include nodules, is eczematous and is a pre-disposing condition for prurigo nodularis (PN). PN is thought to be a consequence of neuro-immunologic dysregulation; it is characterised by firm nodular fibrotic skin lesions resulting from chronic scratching, is associated with the highest itch intensity scores among pruritic conditions which can become debilitating, and can severely affect patients' daily life and sleep. Current therapeutic options include **dupilumab**, a MAb directed against **interleukin-4 receptor alpha** (IL-4Rα) which blocks **IL-4** and **IL-13** signalling, while additional treatment options are considered inadequate. In this context, in 2024, the FDA approved **nemolizumab**, a FIC humanised MAb directed against the **IL-31 receptor alpha** (IL-31RA). Because IL-31RA is an obligate functional IL-31 receptor, forming a heterodimeric receptor complex with **oncostatin-M receptor beta chain** (OSMRB) (Dillon et al., 2004), nemolizumab effectively blocks the IL-31 cellular signalling and stems inflammation. In a first double-blind, multicentre, randomised trial (Kwatra et al., 2023), 274 adults with moderate-to-severe PN received placebo or nemolizumab monotherapy every 4 weeks for 16 weeks. The patients receiving nemolizumab showed a significant improvement in all criteria, including reduction of itch response (56.3% vs 20.9% with placebo) and a significant Investigator's Global Assessment (IGA) response (37.7% vs 11.0%, respectively). In parallel multicentre, international, similarly designed trials (OLYMPIA1 and 2) (Kwatra et al., 2023; Ständer et al., 2024), nemolizumab treatment similarly resulted in improvements in the primary endpoints, which were the proportion of patients with itch response (≥4-point improvement from baseline in weekly average; 58.4% responders to nemolizumab vs 16.7% vs with placebo) and the IGA response (26.3% vs 7.3%, respectively). These benefits persisted up to at least 24 weeks. Nemolizumab therefore fills an important therapeutic need in this patient population, and its use in the future may extend to additional atopic diseases, such as atopic dermatitis, where there are encouraging results (ARCADIA1 and 2; reported in Silverberg et al., 2024). Of note, nemolizumab has already received approval in Japan in 2022 for the treatment of atopic dermatitis.

2.3 | Heart/blood disorders

2.3.1 | Danicopan

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare haematologic disease characterised, among others, by chronic intravascular haemolysis. Somatic mutations of the phosphatidylinositol N-acetylglucosaminyltransferase subunit A (*PIG-A*) gene impairs biosynthesis of glycosylphosphatidylinositol (GPI) anchors. As a consequence, GPI-deficient erythrocytes lack GPI-linked complement regulators **CD55** and CD59 and become particularly vulnerable to complement activation. The recent emergence of treatments blocking complement factor B and C5 such as **iptacopan**, **eculizumab** or **ravulizumab** (briefly reviewed by us last year (Papapetropoulos et al., 2024)) has significantly improved long-term survival of these patients. However, more upstream, C3-mediated extravascular haemolysis can mitigate the clinical benefits of these therapies, and therefore, more upstream targeting could logically provide additional relief. During complement alternative pathway (AP) initiation, AP C3 convertase is generated via the cleavage of factor B by the serine protease complement factor D. This crucial step, where the complement cascade pathways merge, is inhibited by the FIC, small molecule factor D inhibitor, **danicopan**, which blocks the AP and thus the amplification of the terminal pathway (Risitano et al., 2021). Danicopan received FDA approval for the treatment of extravascular haemolysis (EVH) in adults with PNH, to be given as an add-on to C5-targeted approved antibodies such as eculizumab and ravulizumab (Lee et al., 2023; Nester et al., 2022). The patients still presenting significant extravascular haemolysis despite treatment for >6 months with eculizumab and ravulizumab (10–20% of the treated population) were assigned to receive daily oral danicopan or placebo. The primary endpoint at 12-weeks (interim evaluation) was a change in haemoglobin concentration from baseline: haemoglobin increased by 2·94 g/dl by danicopan versus 0·50 g/dl by placebo. The absence of serious adverse effects or new safety concerns argues in favour of an improved benefit/risk profile of danicopan in this patient population (Lee et al., 2023; Nester et al., 2022). Last

year, we predicted that complement-directed therapies are on the ascendant (Papapetropoulos et al., 2024), because they can potentially be used in various immune/inflammatory conditions where the complement system is over-activated. Danicopan, especially because it is an easily delivered, oral medication, can be combined with the above approved drugs in PNH and, perhaps in the future, with additional approved inhibitors, such as those aiming at the C3 component (pegcetacoplan) or the C1 component (**avacopan**), which have been approved for use in distinct disorders involving the complement (reviewed in West et al., 2024).

2.3.2 | Marstacimab

The patients who have genetic dysfunction or deficiency of **Factor VIII** (haemophilia A) or **Factor IX** (haemophilia B) are predisposed to uncontrolled external or internal (organ) bleeding, occasionally fatal, and require constant management with products supplementing these factors. A novel molecular target in the treatment of haemophilia is the serine protease inhibitor Tissue Factor Pathway Inhibitor (TFPI). All three isoforms of TFPI are serine proteases that contain 3 'Kunitz-type' (K) domains, of which the common K2 domain binds and inhibits **Factor Xa** (FXa) (Ahnström et al., 2024). **Marstacimab** targets the K2 domain of TFPI (Patel-Hett et al., 2019) and, as a consequence, increases haemostasis through the extrinsic pathway, by restoring Factor Xa activity, in essence taking out a 'break' in the cascade (TFPI-mediated inhibition). For this reason, it is the first treatment for haemophilia B that does not consist of external supplementation of clotting factors. Of note, the bispecific MAb **emicizumab**, previously approved to treat haemophilia A, is unsuitable for haemophilia B.

Marstacimab's approval was obtained by an open-label, multicentre trial (NCT03938792; BASIS) enrolling 116 patients with either severe haemophilia A or severe haemophilia B, both without inhibitors, which extended and confirmed the promising findings of an earlier phase I/II study (Mahlangu et al., 2023). For the first 6 months of the BASIS study, the patients received treatment with replacement factors either on-demand (33 patients) or prophylactically (83 patients), both in the form of i.v. infusions. Subsequently, the patients were given marstacimab prophylaxis (s.c) for 12 months. The primary measure of marstacimab's efficacy was the projected annualised bleeding rate (ABR) of treated bleeds. In the patients receiving on-demand factor replacement during the first 6 months of the study, the estimated ABR was 38, compared to the estimated ABR with marstacimab treatment of only 3.2 (reduction by 92%). Marstacimab also decreased ABR rates by 35% compared to prophylactic therapy. These results show that marstacimab is far superior to on-demand factor replacement and equivalent to or better than prophylactic therapy (NCT03938792). Marstacimab is the first subcutaneous option for haemophilia B, reducing the patients' dependence on frequent intravenous infusions (possibly several times a week), avoiding the concomitant damage on their veins and improving their quality of life. Marstacimab, successfully targeting a novel mechanism that regulates bleeding, is therefore a welcome addition to the current range of treatments available to haemophilia A and B patients, which comprise recombinant factors and gene therapy.

2.3.3 | Sotatercept

Sotatercept is a protein therapeutic consisting of the extracellular domain of the human **activin receptor type IIA** (ActRIIA) fused to the human IgG1 Fc domain. It acts as an inhibitor of activin signalling through the ActRIA, the signalling partner of the ActRIIA (which mediates binding), and is the first-ever drug to selectively target the ActRIIA cell receptor function (hence FIC). It is also the first treatment of pulmonary arterial hypertension (PAH) that works by redressing the observed imbalance between activin and bone morphogenetic protein (BMP) signalling in this disease, which is thought to cause both vascular cell proliferation and structural modulation, as well as increasing tissue inflammation (Joshi et al., 2022). Add-on sotatercept was given to patients receiving stable background therapy; it was delivered subcutaneously once every 3 weeks and was compared to other add-on approved therapies for its ability to significantly increase the 6-min walk distance (6MWD) at week 24 (primary endpoint). At evaluation time, the median change from baseline in this biomarker was 34.4 m in the sotatercept group versus 1.0 m in the placebo group (Hoeper et al., 2023; Pitre et al., 2024). In addition, significant positive changes were noted for 8 out of 11 secondary endpoints, such as change in pulmonary vascular resistance, change in N-terminal pro-**B-type natriuretic peptide** levels and improvement in WHO functional class, making sotatercept a promising, novel therapeutic option in hard-to-treat PAH.

2.4 | Kidney, metabolic and endocrine disorders

2.4.1 | Crinecerfont

The rare, autosomal recessive disease congenital adrenal hyperplasia (CAH) is caused by variants in genes encoding adrenal steroidogenic enzymes. The impaired synthesis of **cortisol** disrupts the negative feedback loop between the adrenal glands and the hypothalamus (which releases **corticotropin-releasing factor** [CRF]) and the anterior pituitary (which releases **corticotropin** (ACTH)). The resultant adrenal stimulation diverts the accumulated steroid precursors toward excessive synthesis of adrenal androgens (Mallappa & Merke, 2022). In both adults and paediatric patients, the usual treatment involves high, supraphysiological doses of cortisol, which has a cohort of side effects related, among others, to growth/skeletal and metabolic disorders such as insulin resistance, high blood pressure and mood changes (Sarafoglou et al., 2014). A substantial proportion of the CAH patients still have suboptimal androgen control (supraphysiological, elevated mean

androstenedione and 17-hydroxyprogesterone levels) even after using high glucocorticoid doses. The rationale and aim for the CRF_1 receptor antagonist development was to reduce the amount of exogenous hydrocortisone needed as close to normal physiological levels and to maintain an acceptable androgen level control. Crinecerfont is a selective, potent antagonist of CRF_1 receptor, with a pKi = 8.7 and is >1000 more potent in inhibiting the CRF_1 rather than CRF_2 receptor or for binding to CRF binding protein (Gully et al., 2002).

The approval of crinecerfont was based on the results of two separate, multinational, randomised clinical trials, in children and in adults, during which subjects received either crinecerfont or placebo (2:1 ratio). In the first trial (Sarafoglou et al., 2024), paediatric patients were treated for 28 weeks. The primary efficacy endpoint was the change in the androstenedione levels from baseline to week 4, which was 7.3 nmol/l in the crinecerfont group versus 19.0 nmol/l in the placebo group. A key secondary endpoint was the change in glucocorticoid dose from baseline to week 28 necessary to maintain androstenedione control; this dose had decreased by 18.0% in the crinecerfont-treated children, while it increased by 5.6% in those receiving placebo, demonstrating that crinecerfont reduced elevated androstenedione levels in paediatric participants with CAH and allowed for a decrease in the glucocorticoid dose from supraphysiologic to physiologic levels to maintain androstenedione control. In the second clinical trial conducted with adult CAH patients (Auchus et al., 2024), after an initial 4-week period with steady glucocorticoid dose to determine androgen levels, the participants randomly received (2:1) crinecerfont or placebo for 20 weeks, aiming at optimisation (maximal possible reduction) of the glucocorticoid dose that still allowed control of androstenedione levels. At the trial's conclusion, the change in the glucocorticoid dose that enabled androstenedione control was −27.3% in the crinecerfont group versus −10.3% in the placebo, reaching physiologic effective glucocorticoid dose in 63% of the patients in the crinecerfont group versus in only 18% in the placebo group. These results showed that also in adult patients with CAH, crinecerfont permitted a significantly greater reduction in the mean daily glucocorticoid dose compared to placebo, including a reduction of glucocorticoid dose compatible with normalisation of adrenal androgen levels. This FIC therapy, taken for the individual's lifetime, is therefore expected to have a significant effect in the overall health of this population by diminishing the need for deleterious glucocorticoid supplementation.

2.4.2 | Elafibranor and Seladelpar

Hepatic injury subsequent to autoimmune bile duct inflammation and damage results in primary biliary cholangitis (PBC), a chronic disease with few and inadequate therapeutic options (Barba Bernal et al., 2023; Schnabl, 2024). Ursodeoxycholic acid (UDCA) is the first-line 'gold standard' treatment, because it slows the biochemical processes that results in progression of PBC, but 30–40% of patients are non-responders. For these patients and those who have not tolerated UDCA therapy, the single second-line therapy approved is obeticholic acid (OCA), a bile-acid analogue. OCA, however, is not suitable for patients with decompensated cirrhosis or in those that develop portal hypertension and it can also cause pruritis. To fill this unmet medical need, two add-on drugs to treat PBC were approved in 2024. Elafibranor has a unique dual agonist profile, with effects deriving from its targeting mainly PPARα and PPARβ. It has been reported to also act on PPARγ, but without causing PPARγ tell-tale adverse effects, hence its designated PPARα/β functional selectivity. In contrast to elafibranor's PPARα/β dual action, seladelpar, also approved in 2024, selectively activates PPARβ, being >1000-fold less effective on PPARα or PPARγ. Both elafibranor's and seladelpar's pharmacological profiles therefore differ from thus far approved PPAR agonists such as fibrates (acting mainly on the PPARα receptor) and glitazones (stimulating essentially the PPARγ receptor), and for this reason they are both considered FIC drugs. Experimental evidence shows that PPARβ activation by seladelpar reduces synthesis of bile acids and involves induction of fibroblast growth factor 21 (FGF21; Kouno et al., 2022), and because elafibranor can also stimulate PPARβ, it is also thought to elicit similar activity. In addition, PPARα and PPARβ agonists display anti-inflammatory properties and this may be contributing to their efficacy in this indication, because PBC is an autoimmune disease. Elafibrinor and seladelpar were both compared to placebo control in patients that had not adequately responded to UCDA. After 52 weeks of treatment, surrogate endpoint biomarkers of liver injury were assessed: a reduction in alkaline phosphatase (ALP), normal total bilirubin, as well as reduction of pruritus intensity. With elafibranor, 55 of the 108 patients (51%) that received the drug showed reduced ALP, whereas only 2 out of 53 (4%) receiving the placebo responded by ALP decreases (Kowdley et al., 2024). The respective numbers for seladelpar were 61.7% and 20%, based on a trial with 191 participants (Hirschfield et al., 2024). In addition, 15% of elafibranor-treated patients showed normalised ALP levels (*vs.* none receiving placebo, Kowdley et al., 2024), with the respective numbers for seladelpar being 25% and 0%. Overall, the clinical biochemical biomarkers in both trials were similarly affected by the two drugs, and they can predict later endpoint outcomes (liver transplantation or death) in patients with PBC (Schnabl, 2024). Based on the above surrogate endpoint biomarkers of liver injury, both elafibranor and seladelpar received accelerated approval for the treatment of PBC in combination with UDCA in adults who have an inadequate response to UDCA (both drugs) or as monotherapy in patients unable to tolerate UDCA (elafibranor only). Given that there are quite important cross-pathogenic mechanisms operating in other chronic metabolic/inflammatory hepatic diseases such as metabolic dysfunction-associated steatotic liver disease (MASLD) and non-alcoholic fatty liver disease (NAFLD), it will be interesting to see the progress of these and other PPAR agonists, alone or in combination with approved therapies, in these additional indications; however, more definitive appreciation of their long-term effects will take years to develop.

2.4.3 | Olezarsen

Familial chylomicronaemia syndrome (FCS) is a rare (1 to 10 per 10^6 people) genetic disorder associated with greatly impaired degradation of triglycerides (TG) caused by mutations in the gene encoding LPL or in genes encoding factors controlling LPL function. This causes excessive TG accumulation and the presence of extremely high concentrations of circulating TG, well exceeding >1000 mg/dl, that is, 10- to 100-fold of normal (normal TG levels are <150 mg/dl; those above 500 mg/dl are considered 'severe hypertriglyceridaemia'). These high TG levels can cause severe abdominal pain, fatty deposits in the skin (xanthomas) and episodes of acute pancreatitis, which can be life-threatening and can appear as early as in infancy or much later in adulthood. Apolipoprotein CIII (apoC3) is a multifunctional protein that controls triglyceride (TG) levels through inhibition of LPL activity, mediated by apolipoprotein CII, and the resulting inhibition of lipolysis of triglyceride-rich-lipoproteins. In addition, apoC3 can also inhibit hepatic lipase activity-mediated hepatic clearance of remnants of triglyceride-rich lipoproteins (Gaudet et al., 2014; Ginsberg et al., 1986). Therapeutic options in FCS are extremely limited. Some time ago, the EMA authorised the LPL gene replacement product Glybera (alipogene tiparvovec expressing variant LPLS447X) whose licence, however, has not been renewed since 2017. Taking an altogether different tack, knocking down the levels of apoC3 protein is an approach expected to provide substantial benefit to FCS patients and has been in advanced testing for years (Gaudet et al., 2014). Olezarsen (Tryngolza) is a 13-mer antisense oligonucleotide (ASO)-GalNAc3 conjugate that selectively targets apoC3 mRNA, causing its degradation and a reduction of serum apoC3 protein. A once-a-month s.c. injection of this FIC ASO has been approved by the FDA in 2024 to reduce TG in adults with FCS, based on the efficacy and safety in a randomised, placebo-controlled, double-blind clinical trial (NCT04568434; Stroes et al., 2024). The participants were 66 FCS patients who, at baseline, presented with a mean TG level of 2630 mg/dl and a history of acute pancreatitis within the previous 10 years. The 80-mg dose of olezarsen (but not the 50-mg dose) reduced TG levels at 6 months by 43.5% with a concomitant apoC3 protein reduction of 73.7%. At the 1-year evaluation point, the olezarsen-treated patients presented a mean of only 1 episode of acute pancreatitis during this period, as compared to a mean of 11 episodes in the placebo group. In combination with the moderate severity adverse events associated with the drug, these results secured olezarsen's approval for the treatment of this very rare syndrome. It remains to be seen if olezarsen can be used in additional indications where a reduction of TGs is desirable. To this end, there are already some promising results in healthy volunteers (Karwatowska-Prokopczuk et al., 2024) and in individuals with moderate hypertriglyceridaemia (Bergmark et al., 2024), where monthly olezarsen treatment significantly caused a significant drop in TG levels and at the same time elicited favourable changes in VLDL-C, apoB and HDL-C levels. Based on the knowledge that apoC3 is causally associated with increased risk for atherosclerosis and cardiovascular disease and also promotes inflammatory responses in monocytes and endothelial cells and increases prothrombotic predisposition, it will be interesting to follow olezarsen's efficacy trials in reducing cardiovascular complications in individuals at risk with high TG levels.

2.4.4 | Resmetirom

The management of metabolic dysfunction-associated steatohepatitis (MASH), until now relied on lifestyle modification (in food intake and exercise) and use, in patient sub-populations, of vitamin E, **pioglitazone** or glucagon-like peptide-1 receptor (**GLP-1R**) agonists. In March 2024, the FDA approved **resmetirom**, a FIC selective agonist of the highly liver-expressed **thyroid hormone receptor-β** (THR-β), the first such drug approved by the FDA specifically for MASH with concurrent fibrosis (but not with cirrhosis). Following the activation of its cognate receptor, resmetirom reduces hepatic lipotoxicity by favouring THR-β-mediated lipid metabolism. The approval was based on biopsy-assessed, surrogate biomarkers at 12 months into the 54-month trial on nearly 1000 patients with biopsy-assessed MASH and who also followed a prescribed nutrition and exercise regime. At this early, mid-trial point, there was significant improvement in pathology markers such as fibrosis (25% with resmetirom vs 14% with placebo) as well as a higher resolution of MASH (respectively 28% vs 10%), although no clear positive changes in liver histology were yet observed; this last is no surprise given the slow response and regression of this disorder (Suvarna et al., 2024; Younossi et al., 2024). Resmetirom can be prescribed on the basis of non-invasive MASH-fibrosis diagnostic tests, while more definitive, long-term efficacy data will be available several years from now. However, given the high numbers in world population that present steatohepatitis which can progress to more severe disease (Diehl & Day, 2017), resmetirom is an important milestone addition to the existing treatments.

2.5 | Infectious diseases

2.5.1 | Berdazimer

Molluscum contagiosum is a common, contagious, persistent viral skin infection that accounts for ~1% of all dermatological conditions and which affects mainly children, teens and young adults, as well as sexually active individuals. The only FDA-approved, in-office treatment, up to now, was Ycanth, approved in 2023, a drug-device combination of GMP-produced **cantharidin** and gentian. Berdazimer (Zelsuvmi) is the first topical gel treatment for use at home. The molecule is a well-described **nitric oxide** (NO) donor with a broad anti-microbial and anti-viral spectrum, which is attributed to N-nitrosylation damage to viral proteins and reduction of the viral replication ability via release of oxygen species (Ward et al., 2023). However, the exact mechanism of action that enables lesion clearance is still not entirely understood. In the pivotal 12-week trial, berdazimer application caused a statistically significant complete clearance of skin lesions in 32.4% of patients (vs 19.7% in the vehicle group) and led to a > 90% clearance

in 43% of them versus 23.9% similar clearance in the vehicle group, with low frequency of mild application site adverse reactions such as erythema and pain (Browning et al., 2022; Sugarman et al., 2024).

2.5.2 | MRESVIA

Respiratory syncytial virus (RSV) can cause substantial morbidity and mortality in infants and among older adults. 2023 saw the authorisation by all three agencies of the first-ever long-awaited RSV vaccines (Abrysvo and Arexvy), which raised immunity via the administration of a recombinant RSV prefusion proteins F and which achieved 62% and 82% efficacy, respectively, in the >60-year old population (Papapetropoulos et al., 2024). MRESVIA is a FIC RSV vaccine approved in 2024 that is an mRNA-based vaccine. Its active ingredient is mRNA-1345, encoding the stabilised RSV prefusion F glycoprotein. It secured its approval on the strength of data from the double-blind, placebo-controlled ConquerRSV trial (Wilson et al., 2023; NCT05127434), conducted with about 37,000 adults over 60-years old. The primary endpoint was MRESVIA efficacy, defined as the prevention of the first episode of RSV-associated lower respiratory tract disease (RSV-LRTD) with at least two signs or symptoms, or with at least three signs or symptoms, from 14 days after vaccination through the next 12 months. At a median follow-up of 3.7 months, vaccine efficacy was calculated as 78.7% against RSV-LRTD with at least two signs or symptoms and 80.9% against RSV-LRTD with at least three signs or symptoms. Data analysis at the next median follow-up of 8.6 months showed vaccine efficacy of 62.5% against RSV-LRTD with at least two signs or symptoms and 61.1% against RSV-LRTD with at least three signs or symptoms, that is, efficacy comparable with the previous, conventional vaccines, while vaccine-attributed adverse reactions were mild to moderate and transient. Outside SARS-CoV2, this is the first clinically successful mRNA vaccine, further validating the mRNA vaccination approach. RSV vaccines experienced a rather problematic development, which is why last year's FIC approvals were heralded as milestones. It seems that immunisation with prefusion protein F can occasionally cause exacerbated respiratory tract disease in children, regardless of vaccine nature (i.e. classical, protein antigen-based vs mRNA-based vaccine), and intense scrutiny of RSV vaccine adverse effects is currently underway following signs of toxicity in clinical trials with MRESVIA in this population (Cohen, 2024).

2.6 | Respiratory diseases

2.6.1 | Ensifentrine

While single inhibitors of **PDE 3** or **PDE 4** have been approved previously for cardiovascular (PDE 3), dermal and respiratory (PDE 4) disorders, **ensifentrine** is the first dual PDE 3/4 inhibitor to receive approval, as treatment in moderate to severe COPD. In the context of lung obstructive diseases, such as asthma and COPD, PDE 4 inhibition is considered to provide mainly anti-inflammatory activity by targeting infiltrating leukocytes, whereas PDE 3 inhibition provides additional bronchodilatory action on the smooth muscle. Thus, in principle, ensifentrine combines the advantages of inhibiting the individual targets (Boswell-Smith et al., 2006; Matera et al., 2020). It is interesting to note that ensifentrine's pIC_{50} value for PDE 3A (9.4) is roughly 3.5 log units different than for PDE 4A (5.8). The FDA-approved ensifentrine (given by oral inhalation 2–3 times daily) on the basis of evidence from two placebo-controlled, randomised clinical trials (ENHANCE-1 and ENHANCE-2) that enrolled over 1500 adult patients with moderate to severe COPD (Anzueto et al., 2023; Mahler et al., 2024), and who were under concomitant treatment with long-acting **muscarinic receptor** antagonists or long-acting **β_2-adrenoceptor** agonists. Pulmonary function was evaluated after 12 weeks of treatment, with the main biomarker being change from baseline in the forced expiratory volume in 1 s (FEV_1) area under the concentration-time curve over 12 h. Ensifentrine significantly improved FEV_1 (>85% than placebo in both trials) and also improved other measures such as increased time to first exacerbation, with similar adverse effects to those of the placebo. Because PDE 4 inhibitors such as **roflumilast** have been in the clinical arena for some time, it will be interesting to see whether ensifentrine will provide better relief than the former, especially if combined with other COPD medications.

2.7 | Nervous system disorders

2.7.1 | Xanomeline and Trospium

Schizophrenia is present in ~1% of world population and manifests as delusions, hallucinations and disorganised speech, decreased motivation or social interactions and cognitive deficits, depending on the individual patient (Marder & Cannon, 2019). **Dopamine receptor** blockade is a characteristic feature, to a variable degree, of most of the approved medications and is characterised by frequent extrapyramidal effects and dyskinesias. The mode of action of most atypical (second generation) approved drugs is poorly understood and while it is attributed to activation or blockade of multiple receptors, including **serotonin receptors** (5-hydroxytryptamine (5-HT) receptors), these therapies also present a high frequency of adverse effects, especially metabolic syndrome-like disturbances (Marder & Cannon, 2019). Thus, novel mechanisms have been intensely targeted and explored, both to increase efficacy, because the response rate to current drugs is only ~70% and relapse is a dismal ~30%, as well as to mitigate the side effects of approved medications. The new, FIC anti-schizophrenia treatment, **xanomeline–trospium** combination, is heralded as a paradigm shift in how schizophrenia is targeted: it is the first anti-schizophrenia therapy in decades that does not rely on anti-dopaminergic effects of the active agent, but instead acts as a dual **M_1** / **M_4** muscarinic agonist to alleviate disease symptoms. Of note, xanomeline also can bind to other muscarinic subtypes with comparable affinity but preclinical experimentation in vivo suggests that the M_4 subtype and, to a lesser degree, the M_1 subtype mediate its therapeutic effects. In fact, xanomeline appears to associate both

ortho- and allosterically with the M_4 receptor (Burger et al., 2023). To mitigate xanomeline's effects via peripheral cholinergic receptor stimulation, an already approved, non-brain-penetrant non-selective muscarinic antagonist, trospium (Madersbacher & Rovner, 2006), was added. The combination's effectiveness for the treatment of schizophrenia in adults was evaluated in two identically designed studies (EMERGENT-2; Kaul, Sawchak, Correll, et al., 2024 and EMERGENT-3; Kaul, Sawchak, Walling, et al., 2024) at week 5 after treatment onset, using the change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score as the primary efficacy measure, a 30-item scale that measures symptoms of schizophrenia. In both studies, the participants who received xanomeline–trospium showed a significant reduction (in every criterion, twice the reduction obtained with placebo) in both negative and positive schizophrenia symptoms, in total PANSS and in the Global Impression-Severity scores, compared to the placebo group, and exhibited a mild safety profile, with fewer incidences of typical anti-schizophrenia side effects such as weight gain and extrapyramidal symptoms. Overall, xanomeline–trospium is an attractive and much-awaited alternative in this indication (Hall, 2024), inaugurating a new era for anti-schizophrenia therapies. Xanomeline has been in clinical evaluation for years for treating psychosis in Alzheimer's patients, showing signs of efficacy (not surprising, because it is known that $M_1/_4$ receptors are involved in the control of addiction, psychosis and cognition); however, its success was flustered by the peripheral effects of the drug. Xanomeline's 'resurrection' when combined with trospium may pave the way for its clinical testing in additional indications and may boost the development of other muscarinic agonists in CNS disorders.

2.8 | Rare/genetic diseases

2.8.1 | Arimoclomol and levacetylleucine

Niemann–Pick type C (NPC) is a rare genetic disease that results in progressive neurological symptoms and wide organ dysfunction, caused by mutations in either the ***NPC1*** or *NPC2* genes, affecting the lysosomal storage and transport of **cholesterol** and other lipids within a cell, resulting in the accumulation of multiple lipid species. NPC leads to severe systemic and central nervous system symptoms, such as loss of coordination, problems with 'saccadic' eye movements that can lead to impaired vision, delayed development, difficulty swallowing, decreased muscle tone, fits and learning difficulties, cognitive impairment, cerebellar ataxia, dysarthria, cataplexy and seizures. On average, the life expectancy of individuals affected by this devastating disease is only about 13 years. The two FIC drugs approved for this disease in 2024 work by a totally different mechanism. The first drug, **arimoclomol**, is given as a combination with **miglustat** and labelled as Miplyffa, which had been previously been authorised by EMA and the FDA for use in type 1 Caucher's disease and in late-onset Pompe disease (LOPD, **acid alpha-glucosidase** [GAA] deficiency) in combination with cipaglucosidase alfa replacement. In addition, miglustat has been previously authorised by EMA (in 2009) for use as a stand-alone therapy in NPC. These two substances offer a good example of approval divergence between the two agencies, together with lecanemab, analysed in Section 1. Now, the FDA approved the use in NPC of a new chemical entity, arimoclomol, in combination with miglustat. Miglustat functions as a competitive and reversible inhibitor of the enzyme **glucosylceramide synthase**, the initial enzyme in a series of reactions which results in the synthesis of most glycosphingolipids, and thus limits their generation. Arimoclomol, on the other hand, is a brain-penetrant hydroxylamine derivative that is thought to act as a heat-shock protein-70 (HSP70) co-inducer, in part by stabilising the interaction of Heat Shock Factor 1 (HSF1) with Heat Shock Elements (HSEs), which together transcriptionally regulate HSP production. HSP70 is a cellular defence mechanism against cellular or lysosomal stress, can stabilise lysosomal membranes and, as a consequence, can exert neuroprotective effects (Fernández et al., 2024; Kuta et al., 2020). The second drug to be approved in 2024 as a stand-alone treatment in NPC is levacetylleucine (L-acetylleucine; Acneursa) and acts by a totally different mechanism from arimoclomol. By participating in enzymatic pathways triggered by metabolic dysfunction, levacetylleucine normalises cellular energy metabolism through increases in **adenosine triphosphate** (ATP) energy production. This results in improved mitochondrial and lysosomal function and reduction in the storage of unesterified cholesterol and sphingolipids (Hall, 2024). Levacetylleucine also has been shown to normalise neuronal membrane potential, thereby improving, restoring and protecting neuronal circuits (Vibert & Vidal, 2001). However, it is unclear whether the above mechanisms mediate the therapeutic effect of levacetylleucine in the context of NPC.

Arimoclomol was evaluated in one placebo-controlled clinical trial (Mengel et al., 2021) of 50 patients with NPC, a subset of which were also given miglustat. The efficacy endpoint was the change from baseline in five-domain NPC Clinical Severity Scale (NPCCSS) score from baseline to 12 months, assessing ambulation, speech, swallowing and fine motor skills. Arimoclomol treatment resulted in a 65% reduction in annual disease progression compared to placebo, while in those also taking miglustat there was stabilisation of the disease up to the 12-month evaluation point, justifying FDA's recommendation of use as a combination therapy that provides a clinically meaningful benefit to the patients suffering from this ultra-rare disease.

Levacetylleucine's efficacy in NPC was tested (Bremova-Ertl et al., 2024) in a 24-week, double-blind, placebo-controlled, crossover trial (Bremova-Ertl et al., 2024; NCT05163288) with 60 participants. The primary endpoint was the total score on the Scale for the Assessment and Rating of Ataxia (SARA; range, 0 to 40, with lower scores indicating better neurologic status). Crossover data from the two 12-week periods in each group showed that the progress from baseline (~15.8 SARA) regressed by 1.97 points after 12 weeks of receiving levacetylleucine versus an increase of 0.60 points with placebo. The clearly better neurologic status of the patients given levacetylleucine led to the approval of the drug, although the relatively short trial period necessitates further evaluation of long-term efficacy and DOR in continuing trials.

It is no surprise, given the broad neuroprotective mechanisms by which the two drugs are thought to act, that they are being investigated in additional indications where neuronal cellular stress is considered pathogenic, such as amyotrophic lateral sclerosis (ALS) and inclusion body myositis (arimoclomol) and in ataxia-telangiectasia (levacetylleucine).

2.9 | Other indications

2.9.1 | Flurpiridaz F-18

Radiopharmaceuticals allow cardiologists to acquire a more accurate view of the condition of the ischaemic (or suspected ischaemic) heart and are instrumental in the interventional cardiology field. Flurpiridaz (Flyrcado) is the first new perfusion radiopharmaceutical approved by the FDA in almost three decades, the two most commonly-used tracers in the United States, rubidium-82 and N-13 ammonia, having been approved back in 1989 and 2000, respectively. Flurpiridaz consists of an analogue of pyridaben, a mitochondrial complex 1 (MC-1) inhibitor, linked to a fluorine 18 (F18) tracer, and it is expected to be manufactured offsite in specialised units, before being transferred to the cardiology clinic. What differentiates and offers an important advantage to this diagnostic drug is both its higher myocardial extraction and also a significantly longer half-life (~110 min) than all positron emission tomography (PET) perfusion radiopharmaceuticals that have been in use up to now. The efficacy and safety of flurpiridaz were evaluated in two prospective, multicentre, open-label clinical studies in adults with either suspected coronary artery disease (CAD) (Study 1: NCT03354273; Maddahi et al., 2023) or known or suspected CAD (Study 2: NCT01347710; Maddahi et al., 2020). In the latter study, flurpiridaz was compared to Tc-99 m-labelled single photon emission computed tomography (SPECT) and to invasive coronary angiography (ICA). Sensitivity of flurpiridaz PET (for detection of ≥50% stenosis by ICA) was 71.9% versus 53.7% with SPECT. Compared with SPECT, flurpiridaz also displayed higher receiver-operating characteristic curve analysis, showed superior discrimination of CAD and better ability for defect size, and had better image quality and diagnostic certainty. In addition, flurpiridaz PET proved safe and well tolerated. Flurpiridaz' improved diagnostic ability, especially in hard-to-image patients, such as those with high body mass index and women, for whom traditional imaging can be less accurate, is expected to lead to an increase in the number of patients that will be given access to myocardial perfusion imaging to evaluate the presence of myocardial ischemia or infarction when there is suspected or known coronary disease, and thus will significantly facilitate and optimise decision-making by cardiologists.

2.10 | Other notable approvals

Occasionally, there are novel drugs which are not categorised as FIC, that is, 'drugs that modulate an as-yet unprecedented drug target or biological pathway' (Eder et al., 2014) or have a unique pharmacological profile in modulating a known target. However, because they address unmet, important therapeutic needs, they deserve a special mention. In the following text, we summarise the pharmacology and therapeutic promise carried by two such non-FIC therapeutics approved in 2024.

2.10.1 | Aprocitentan

While **endothelin receptor** dual antagonists have been in use for the treatment of PAH for years, **aprocicentan** is now the first ET-1 antagonist to receive approval for resistant *systemic* hypertension. It has been designed and characterised as a dual endothelin receptor inhibitor, albeit with an IC_{50} value for **ET_A receptors** which is >200-fold lower than for **ET_B receptors**. In the PRECISION clinical trial (NCT03541174, Schlaich et al., 2022), the patients whose blood pressure had not previously responded adequately to standardised baseline therapy consisting of three antihypertensive drugs, among them a diuretic, received aprocitentan or placebo. The primary and key secondary endpoints were, respectively, changes in unattended office systolic blood pressure from baseline at week 4 and from withdrawal baseline by week 40. The trial also included monitoring 24-h ambulatory blood pressure changes. The least square mean change in office systolic blood pressure at 4 weeks achieved by aprocicentan was −15.3 mmHg versus −11.5 mmHg by placebo (i.e. a 3.8 mmHg difference), an effect that persisted up to week 40 (Schlaich et al., 2022) and was also seen in ambulatory systolic blood pressure (−4.2 mmHg less with aprocitentan than with placebo). Moderate oedema or fluid retention developed in 18% of patients receiving the highest aprocitentan dose (25 mg), requiring discontinuation in a small fraction (7 of the 730) of participants. Aprocitentan is the first dual endothelin inhibitor class drug authorised for the treatment of systemic hypertension when existing therapies are deemed inadequate, a condition linked to increased risk of cardiovascular complications and affecting roughly 10% of all hypertensive patients (Achelrod et al., 2015; Hunter et al., 2021). Aprocitentan constitutes therefore a valuable therapeutic addition to the antihypertension armamentarium.

2.10.2 | Givinostat

Until the 2024 approval of **givinostat**, several **histone deacetylase** inhibitors (HDI) have already been approved and have mostly been successful in treating haematological neoplasms, such as T-cell lymphomas and multiple myeloma (Pu et al., 2024). Givinostat is therefore the first orally administered HDI therapeutic approved in an indication outside oncology, as well as the first non-steroidal drug to treat patients with all genetic variants of Duchenne Muscular Dystrophy (DMD). Parenterally administered drugs such as **eteplirsen**, **golodirsen** and **ataluren** have been previously approved for DMD bearing specific dystrophin mutations (the authorisation of ataluren was recently not renewed by the EMA). For these reasons, givinostat constitutes a significant advance in the management of this devastating disease and

deserves a mention in this mini-review not only because it is the first HDI used in this new indication but also because within DMD it targets a novel molecular mechanism to modulate the disease. Givinostat was evaluated in a multicentre trial, on ambulant male paediatric patients with a genetic diagnosis of DMD. Its efficacy was assessed by multiple criteria related to improved movement ability, including as a primary endpoint the 4-stair climb assessment at 72 weeks after the onset of treatment. In this, the givinostat treatment group displayed a significantly favourable score compared to the placebo group (Mercuri et al., 2024; Muntoni et al., 2024), securing the authorisation of the drug. Of note, Elevidys (delandistrogene moxeparvovec), a one-shot gene therapy drug, delivering a short dystrophin form in an adenoviral vehicle, was approved in 2023 and has been reviewed briefly in Papapetropoulos et al. (2024). These developments reinforce the fact that orphan diseases and the unmet medical need they represent are actively targeted by a welcome group of newly licensed therapeutics (exemplified by the list of 'orphan' drugs approved in 2024 in Box 2).

3 | OVERALL CONCLUSIONS

Looking at the numbers, the 2024 roundup seems to present both similarities and differences compared to that of 2023. The most obvious difference is the total number of novel drugs which is lower (53) in 2024, compared with 70 new entities authorised in 2023. An additional obvious difference is the relatively few ATMPs, only six in 2024 (vs 11 in 2023). From a quick glance at the FDA's sites mentioned in Section 1, it appears that indeed 2023 was a peak year for ATMP approvals, unusual for this category of therapeutics. Proteins/antibodies accounted for 28% of the novel drugs authorised in 2024 (vs 23% in 2023), confirming the sustained focus of the pharmaceutical industry in the development of polypeptide therapeutics in recent years. The number and proportion of orphan drugs (BOX 3) also remained approximately the same: 21 (40%) in 2024 versus 24 (34%) in 2023, while just two novel vaccines were licensed in 2024 (vs six in the previous year). These are general observations on data from just two consecutive years and cannot provide a mid- or long-term trend.

The most striking difference from 2023, a fitting epilogue to 2024's roundup, is that the 2024 novel drug harvest is characterised by multiple innovative 'firsts', a select few of which are briefly listed below with their respective distinguishing pharmacological feature(s):

- First drug using a 'dock-and-block' mechanism of inhibition: zenocutuzumab is a bi-specific antibody employing an ingenious 'dock (HER2 arm) and block (HER3 arm)' approach, whereby it prevents HER2-HER3 heterodimerisation that is promoted by the NRG1 ligand's oncogenic mutants.
- First drug for schizophrenia in decades that targets an up-to-now unexplored, novel receptor in this disorder: the brain-penetrant M_1/M_4 muscarinic agonist xanomeline, given in combination with a peripheral muscarinic antagonist, trospium, to diminish peripheral side effects of the former.
- First drug, revumenib, which by binding to the protein menin, prevents its interaction with oncogenic MLL1 (the product of the *KMT2A* gene), thus leading to the disruption of the epigenetic changes elicited by this complex in cancer.
- First biparatopic antibody, zanidatamab, which, in contrast to bispecific MAbs, is engineered to bind on two distinct epitopes found on extracellular domains 2 and 4 of the *same* molecule, HER2. This mode of interaction enhances HER2 receptor crosslinking and clustering, HER2 internalisation, suppression of cell signalling, and fully and effectively engages both ADCC- and CDC-mediated cancer cell elimination, leading overall to reduction of tumour growth.
- First autologous T-cell therapies for solid tumours, lifileucel and afamitresgene autoleucel. Lifileucel consists of tumour-infiltrating T-cells from the melanoma patient's biopsy, which are expanded ex vivo and re-introduced in the recipient. Afamitresgene autoleucel comprises the introduction of a tumour antigen MAGE-A4-directed TCR transgene in the T-cells before infusion back into the sarcoma patient.
- First haemophilia B drug that differs radically from external supplementation of clotting factors or related products. Marstacimab targets TFPI and increases downstream haemostasis by restoring Factor Xa activity, in essence it operates by taking out a 'break' (TFPI-mediated inhibition).
- First telomerase inhibitor ever. Imetelstat is a 13-mer oligonucleotide complementary to the template region of the telomerase RNA component, directly inhibits telomerase enzymatic activity and suppresses myelofibrosis cell growth in patients with myelodysplastic syndromes, sparing normal haematopoietic progenitor cells (HPCs).
- First mRNA vaccine beyond SARS-CoV2. MRESVIA is an mRNA-based RSV vaccine approved for active immunisation of persons over 60 years old, introducing into the bloodstream mRNA-1345, which encodes the stabilised RSV prefusion F glycoprotein.

BOX 3 Orphan drugs (21)

Acoramidis	Afamitresgene autoleucel
Arimoclomol	Axatilimab
Concizumab	Crinecerfont
Danicopan	Fidanacogene elaparvovec
Givinostat	Imeltestat
Levacetylleucine	Lifileucel
Marstacimab	Mavorixafor
Olezarsen	Revumenib
Tarlatamab	Tovoracenib
Zanidatamab	Zenocutuzumab
Zolbetuximab	

The innovative design, the novel ('first-ever') approaches and the persistence to succeed in the face of occasional setbacks is a general characteristic of the novel drugs approved in 2024, just as it was also the case in 2023, and it is the embodiment of exciting, innovative pharmacology. It is undeniable that a significant proportion of them is going to benefit only a small number of patients, seen by the percentage (40%, 21/53) of the 2024 novel drugs approved for orphan diseases, whereas relatively few drugs are first-line treatments for more frequent disorders, for example, cardiovascular or infectious diseases. It is important to remember, however, that many of the orphan drugs employ strategies and approaches that are initially validated in diseases with a high unmet need, before they themselves or the general approach they are based on are extended and applied in adjacent or more remote indications. This promising feature of the 2024 novel drugs is exemplified by the quite substantial percentage of them that target mechanisms which are common in additional disorders and as such can be broadly considered disease agnostic. Examples just among the FICs are nogapendekin alfa inbakicept (NAI), imeltestat, tarlatamab, zenocutuzomab, vorasidenib, revumenib, zanidatamab, zolbetuximab, lifileucel and afamitresgene autoleucel (all suitable for clinical testing in other cancer indications); arimoclomol and levacetylleucine (CNS degenerative disorders); nevolizumab and danicopan (immune/inflammatory conditions); and finally olezarsen, elafibranor and seladelpar (dyslipidaemia, hepatic steatosis and related metabolic disorders).

3.1 | Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in https://www.guidetopharmacology.org/ and are *per*manently archived in the Concise Guide to PHARMACOLOGY 2021/2022 (Alexander et al., 2021).

AUTHOR CONTRIBUTIONS

A. Papapetropoulos and S. Topouzis wrote the original draft; the rest of the authors reviewed and edited the manuscript.

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CONFLICT OF INTEREST STATEMENT

PF is the founder and CEO of Pharmahungary Group, a group of R&D companies developing cardioprotective therapies and holding patents on cardioprotective molecules.

DATA AVAILABILITY STATEMENT

N/A Review.

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