Pharmacological Reports (2025) 77:543–560
https://doi.org/10.1007/s43440-025-00715-8

REVIEW

Polypharmacology: new drugs in 2023–2024

Piotr Ryszkiewicz[1] · **Barbara Malinowska**[1] · **Eberhard Schlicker**[2]

Received: 6 February 2025 / Revised: 5 March 2025 / Accepted: 7 March 2025 / Published online: 17 March 2025

Abstract

Polypharmacology is an emerging approach to drug design and development that involves the use of multi-target-directed ligands (MTDLs), agents capable of interacting with multiple biological targets simultaneously. The effective treatment of chronic and multifactorial conditions, driven by the dysregulation of multiple interconnected pathways, such as cancer, autoimmune and metabolic disorders, cardiovascular and neurodegenerative diseases, is one of the most substantial challenges in contemporary pharmacology. 'Traditional' single-target-based treatment frequently shows limited effectiveness, as resistance to therapy develops or relapses occur. The rational use of MTDLs seems therefore a promising way to address the complexity of biological systems, feedback mechanisms, crosstalk, and molecular pathways. Many MTDLs have been successfully marketed to date. Moreover, plenty of them offer an additional benefit in comparison to 'traditional' treatment approaches. To assess whether the polypharmacological trend remains prevalent, we thoroughly analysed drugs approved in the years of 2023–2024 in Germany. Among 73 newly introduced substances, 18 are in line with the polypharmacology concept, including 10 antitumor agents, 5 drugs indicated for autoimmune disorders, 1 indicated for hand eczema, 1 antidiabetic (and anti-obesity) drug, and 1 modified corticosteroid.

Keywords Polypharmacology · Multi-target drugs · Multi-target-directed ligands · Targeted therapy · Cancer · Autoimmune disorders

Abbreviations

ACVR1	Activin A receptor, type 1
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
AI	Artificial intelligence
AKT1	RAC(Rho family)-alpha serine/threonine protein kinase
AT_1R	Angiotensin 1 receptor
BCMA	B-cell maturation antigen
BMI	Body mass index
C5(b), C6	Complement protein C5(b), C6
CAR T	Chimeric antigen receptor T-cell
CD3, 4, 8, 16, 19, 20, 38, 56	Cluster of differentiation 3, 4, 8, 16, 19, 20, 38, 56
CDCC	Complement-dependent cellular cytotoxicity
CDK4/6	Cyclin-dependent kinase 4/6
CRC	Colorectal cancer
CRS	Cytokine release syndrome
DL	Deep learning
DLBCL	Diffuse large B-cell lymphoma
DMD	Duchenne muscular dystrophy
EGFR	Endothelial growth factor receptor
EMA	European Medicines

✉ Piotr Ryszkiewicz
piotr.ryszkiewicz@umb.edu.pl

✉ Eberhard Schlicker
e.schlicker@uni-bonn.de

[1] Department of Experimental Physiology and Pathophysiology, Medical University of Białystok, Białystok 15-222, Poland

[2] Department of Pharmacology and Toxicology, University of Bonn, Venusberg Campus 1, 53127 Bonn, Germany

	Agency
ET_AR	Endothelin A receptor
EU	European Union
FDA	Food and Drug Administration
FGFR(-1, 2, 3, 4)	Fibroblast growth factor receptor (1, 2, 3, 4)
GCR	Glucocorticoid receptor
GIP	Glucose-dependent insulinotropic peptide
GLP1	Glucagon-like peptide 1
GM-CSF	Granulocyte-macrophage-colony-stimulating factor
GPRC5D	G protein-coupled receptor, class C, group 5, member D
HER2/neu	Receptor tyrosine kinase within the erb-b2 family
IBD	Inflammatory bowel disease
iCCA	Intrahepatic cholangiocarcinoma
IFN-α	Interferon alpha
IgAN	Immunoglobulin A nephropathy
IgG, A, M	Immunoglobulin G, A, M
IKK	Inhibitor of kappa-B kinase
IL-1, 2, 4, 6,7, 13, 15, 21, 23	Interleukin-1, 2, 4, 6,7, 13, 15, 21, 23
IRAK1	Interleukin-1 receptor-associated kinase 1
JAK 1/2/3	Janus kinase 1/2/3, receptor tyrosine kinase
$JAK2^{V617F}$	JAK2 receptor tyrosine kinase V617F mutant variant
MAC	Membrane attack complex
MCR	Mineralocorticoid receptor
MF	Myelofibrosis
MG	Myasthenia gravis
MHC	Major histocompatibility complex
ML	Machine learning
MM	Multiple myeloma
MTDL(s)	Multi-target-directed ligand(s)
mTOR	Mammalian target of rapamycin serine/threonine protein kinase
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
PBC	Primary biliary cholangitis
PBD	Pyrrolobenzodiazepine
PD-1	Programmed cell death protein 1
PI3K	Phosphatidylinositol-3-kinase
PIK3CA	Phosphatidylinositol-4,5-bisphosphate-3-kinase catalytic subunit alpha
PPARα, δ	Peroxisome proliferator-activated receptor alpha, delta
PTEN	Phosphatase and tensin homolog deleted on chromosome ten
S1P	Sphingosine-1-phosphate
S1P1, 2, 3, 4, 5	Sphingosine-1-phosphate receptor 1, 2, 3, 4, 5
SGB V	German Social Code, Book Five
STAT	Signal transducer and activator of transcription
TEC	Tyrosine kinase expressed in hepatocellular carcinoma
TYK2	Non-receptor tyrosine kinase 2
UC	Ulcerative colitis
UDCA	Ursodeoxycholic acid
VEGF(R)	Vascular endothelial growth factor (receptor)

Introduction

Polypharmacology is an innovative paradigm in drug discovery and therapeutic development that aims to develop drug candidates that modulate multiple molecular targets within a biological system. Unlike 'traditional' drug development, often focused on designing molecules that interact with a single specific target (a 'one drug, one target' approach) [1], polypharmacology aims to rationally use multi-target-directed ligands (MTDLs) to embrace the inherent complexity of biological systems, intrinsic feedback mechanisms, crosstalk, and molecular pathways [2]. This is of particular importance in the case of chronic and multifactorial conditions, such as cancer, metabolic disorders, neurodegenerative and cardiovascular diseases, driven by the dysregulation of multiple interconnected pathways [3–4].

Therapeutic strategies that address a single molecular target only might fail to achieve lasting efficacy, may be vulnerable to the emergence of resistance mechanisms or

adherence might not be adequate [1, 5]. By contrast, simultaneous modulation of multiple targets and disease pathways by MTDLs appears to be a solution to overcome these challenges [6]. MTDLs offer the chance to reduce the number of medications taken simultaneously and to simplify dosing schedules (multiple single-target drugs may require more frequent administration than e.g. once daily) which makes it easier for patients to follow their prescribed therapeutic regimen. This is particularly important in the context of chronic diseases or in elderly patients with multimorbidity. The convenience of using a single formulation instead of multiple ones is likely to improve treatment outcomes by increasing patient *adherence* [5]. Moreover, addressing multiple aspects of a disease simultaneously can result in better outcomes, which can further motivate patients to maintain their treatment [1, 5–6].

Small-molecule multi-targeting compounds are also likely to offer a more predictable pharmacokinetic profile. Moreover, due to complementary synergistic effects, a lower dose of a given multi-targeting drug may be required to achieve the desired outcome, which might diminish the risk of adverse drug effects. In some cases, due to the reduction of the need for simultaneous administration of multiple separate drugs, the risk of drug-drug interactions is reduced [5–6]. Furthermore, if one of the MTDL's domains is a specified antibody (as in the case of antibody-drug conjugates, i.e., dual-target-directed ligands, which belong to the most successful MTDLs), the chance for effective targeted therapy arises [2, 7].

On the other hand, MTDLs are *promiscuous* agents, i.e. their nature encompasses both therapeutic effects through interaction with the intended targets and potential adverse events and increased toxicity resulting from *off-target* interactions [8–10]. Thalidomide (originally developed in the 1950s as a sedative and anti-nausea medication which later appeared to cause teratogenic effects) is often used as a striking example of risks associated with drug promiscuity [5]. The complexity of the molecular design process of MTDLs and their *de novo* synthesis also deserves particular attention [2]. Firstly, choosing a proper target requires an intricate, comprehensive understanding of the interactions between multiple biological pathways at the molecular and cellular levels. Secondly, designing a molecule capable of interacting with all chosen targets and achieving the right balance between targeting multiple sites and concomitantly avoiding *off-target* effects can be very challenging. What is more, either due to the requirement of complicated resource-intensive technological processes or due to issues with the stability of molecules, synthesis of the designed molecule may be highly unprofitable or impossible [2].

Polypharmacology has always played a role in the drug development process and therapy, albeit unintentionally [1]. In the past, the multi-targeting properties of therapeutic compounds were discovered in most cases serendipitously [5, 10–11]. Nowadays, rapid advances in computational modeling, machine learning (ML) and deep learning (DL) techniques enable more efficient modeling of target protein structures and consequently a more predictable process of rational design of new compounds with *planned* multi-target activity [10–11]. The increasing use of artificial intelligence (AI) for identifying synergistic co-targets of a given MTDL and distinguishing them from anti-targets, which are responsible for causing harmful side effects, might give a chance to overcome many of the limitations of polypharmacology discussed earlier [11–12]. AI-supported docking simulations and compound interaction predictions are promising tools for anticipating the pharmacodynamics of compounds [11]. Moreover, AI-driven generative chemistry enables quick *de novo* creation of a plenitude of multi-targeted structures using a wide range of DL frameworks. However, those generative models often lack experimental verification, and the compounds they create are rarely novel and feasible for synthesis [11–12]. Nevertheless, the use of high-quality benchmark datasets and a *human-in-the-loop* framework with input from experts in the field of medicinal chemistry might help with refinement and enhancement of the practical application of such models. As the understanding of disease biology and drug-target interactions continues to evolve, the rational design of MTDLs as a core of polypharmacology will play an increasingly important role in the treatment of complex, multifactorial diseases and the future of personalized and precision medicine.

In our previous work, Ryszkiewicz et al. (2023) [5], we thoroughly discussed the concept of polypharmacology and compared the promises of clinical use of MTDLs to the benefits of traditional polytherapy, which is primarily based on the use of multiple selective compounds (for other reviews, see Manen-Freixa and Antolin (2024) [9]; Kabir and Muth (2022) [6] or Feldmann and Bajorath (2022) [10]). Moreover, we gave some remarkable examples of MTDLs already successfully used in pharmacotherapy of patients. Furthermore, we presented the full list of multi-target drugs marketed in Germany in 2022, highlighting their contribution to contemporary pharmacology. Noteworthy, those drugs underwent the central registration procedure by the European Medicines Agency (EMA) earlier. The present review updates the multi-target drugs marketed in the European Union (EU) for the years 2023 and 2024, with a specific focus on the German pharmaceutical market and local post-approval drug status.

Table 1 Eighteen new multi-target drugs authorized by the EMA and marketed in Germany in years 2023–2024

No.	INN (brand name) ATC code	Ap-pro-val[1]	Short description	Molecular mechanisms	Indication(s)[1]	References	Degree of innovation[2]	Additional benefit[3]
1.	Loncastuximab tesirine (Zynlonta®) *L01FX22*	2023	antibody-drug conjugate	antibody (b) CD19 SG3199 (tesirine) (b) DNA and forms cytotoxic crosslinks	relapsed or refractory diffuse large B-cell lymphoma and high-grade B-cell lymphoma in adult patients after two or more lines of systemic therapy	[19–20]	2	Ø
2.	Epcoritamab (Tepkinly®) *L01FX27*	2023	bispecific antibody	(b) CD20 on malignant B cells (b) CD3 on cytotoxic T cells	relapsed or refractory diffuse large B-cell lymphoma in adult patients after two or more lines of systemic therapy	[25, 29]	2	+ *nq*
3.	Glofitamab (Columvi®) *L01FX28*	2023	bispecific antibody	(b) CD20 on malignant B cells (b) CD3 on cytotoxic T cells	see epcoritamab	[26, 28]	2	+ *nq*
4.	Talquetamab (Talvey®) *L01FX29*	2023	bispecific antibody	(b) GPRC5D-expressing multiple myeloma cells (b) CD3 on cytotoxic T-cells	relapsed and refractory multiple myeloma in adult patients who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy	[36, 43]	3	+ *nq*
5.	Teclistamab (Tecvayli®) *L01FX24*	2023	bispecific antibody	(b) BCMA on malignant multiple myeloma B-lineage cells (b) CD3 on cytotoxic T cells	see talquetamab	[37, 44]	2	Ø
6.	Elranatamab (Elrexfio®) *not yet assigned*	2024	bispecific antibody	(b) BCMA on malignant multiple myeloma B-lineage cells (b) CD3 on cytotoxic T-cells	see talquetamab	[38, 45]	1	Ø
7.	Fruquintinib (Fruzaqla®) *L01EK04*	2024	small molecule, protein kinase inhibitor	(-) VEGFR-1 (-) VEGFR-2 (-) VEGFR-3	metastatic colorectal cancer in adult patients who have been previously treated with standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based protocols, anti-EGFR agents, and anti-VEGF agents, and who have progressed on or presented intolerance to treatment with either trifluridine / tipiracil or regorafenib	[52]	2	+
8.	Futibatinib (Lytgobi®) *L01EN04*	2024	small molecule, protein kinase inhibitor	(-) FGFR-1 (-) FGFR-2 (-) FGFR-3 (-) FGFR-4	locally advanced or metastatic cholangiocarcinoma in adult patients with a FGFR-2 fusion/rearrangement that have progressed after at least one prior line of systemic therapy	[57–58]	1	Ø
9.	Capivasertib (Truqap®) *L01EX27*	2024	small molecule, protein kinase inhibitor	(-) AKT1 (-) AKT2 (-) AKT3	estrogen receptor-positive, HER2/neu-negative locally advanced or metastatic breast cancer in adult patients with one or more PIK3CA/AKT1/PTEN-alterations following recurrence or progression on or after an endocrine-based regimen (in combination with fulvestrant)	[61–62]	3	*?*

Table 1 (continued)

No.	INN (brand name) ATC code	Ap-pro-val[1]	Short description	Molecular mechanisms	Indication(s)[1]	References	Degree of innovation[2]	Additional benefit[3]
10.	Momelotinib (Omjjara®) *not yet assigned*	2024	small molecule, protein kinase inhibitor	(-) JAK1/JAK2 (-) $JAK2^{V617F}$ (-) ACVR1 (-) other kinases from JAK family, e.g. IKK, IRAK1	disease-related splenomegaly or symptoms in adult patients with moderate to severe anemia who have primary myelofibrosis, post polycythemia vera myelofibrosis or post essential thrombocythemia myelofibrosis and who	[67–68]	2	
					• have been treated with ruxolitinib or			+
					• are JAK inhibitor naïve			+ *nq*
11.	Ritlecitinib (Litfulo™) *L04AF08*	2023	small molecule, protein kinase inhibitor	(-) JAK3 (-) TEC	severe alopecia areata in adults and adolescents aged 12 years and older	[74–75]	2	*life-style drug*[4]
12.	Etrasimod (Velsipity®) *L04AE05*	2024	small molecule, immuno-suppressant	(+) S1P1 (+) S1P4 (+) S1P5	moderately to severely active ulcerative colitis in patients aged≥16 years who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biological treatment	[78, 80]	2	Ø
13.	Zilucoplan (Zilbrysq®) *L04AJ06*	2024	peptide, immuno-suppressant	(b) C5 (-) C5b binding to C6	generalised myasthenia gravis in adult anti-acetylcholine receptor antibody positive patients as an add-on to standard therapy	[83–84]	2	Ø
14.	Elafibranor (Iqirvo®) *A05AX06*	2024	small molecule, PPAR agonist	(+) PPARα (+) PPARδ	primary biliary cholangitis in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in patients with an intolerance to UDCA	[90–91]	3	*?*
15.	Sparsentan (Filspari®) *C09XX01*	2024	small molecule, acting on the renin-angiotensin system	(-) ET_AR (-) AT_1R	primary immunoglobulin A nephropathy in adults with a urine protein excretion≥1.0 g/day (or urine protein-to-creatinine ratio≥0.75 g/g)	[93–94]	3	+
16.	Delgocitinib (Anzupgo®) *D11AH11*	2024	small molecule, protein kinase inhibitor	(-) JAK1 (-) JAK2 (-) JAK3 (-) TYK2	moderate to severe chronic hand eczema in adults for whom topical corticosteroids are inappropriate or inadequate	[101–102]	3	*?*

Table 1 (continued)

No.	INN (brand name) ATC code	Ap-pro-val[1]	Short description	Molecular mechanisms	Indication(s)[1]	References	Degree of innovation[2]	Additional benefit[3]
17.	Tirzepatide (Mounjaro®) *A10BX16*	2023	peptide, blood glucose lowering drug	(+) GLP1 (+) GIP	insufficiently controlled type 2 diabetes mellitus in adults (as an adjunct to diet and exercise): • as monotherapy if metformin is considered inappropriate due to contraindications or intolerance • in addition to other diabetes medication	[103–104]	3	+[5] *and Ø*
					chronic weight management in adults (as an adjunct to calorie-restricted diet and increased physical activity): • with BMI of ≥ 30 kg/m^2 or • ≥ 27 kg/m^2 and < 30 kg/m^2 with at least one weight-related condition		3	*life-style drug*[4]
18.	Vamorolone (Agamree®) *H02AB18*	2024	small molecule, modified corticosteroid	(+) GCR (-) MCR	Duchenne muscular dystrophy in patients aged 4 years or older	[111–112]	2	+ *nq*

[1]in countries in which other regulatory authorities are in charge (e.g., Food and Drug Administration (FDA) for the USA), drugs might have reached approval earlier or an additional indication might have been assigned

[2]degree of innovation according to the *Pharmazeutische Zeitung*: 1– me-too preparation; 2– step innovation; 3– disruptive innovation

[3]evaluation by the *Gemeinsamer Bundesausschuss*: additional benefit was minor (+), could not be quantified in terms of minor, considerable or major (+*nq*) or was absent (*Ø*); in some instances, the additional benefit assessment has not yet been completed (*?*)

[4]classification by the *Gemeinsamer Bundesausschuss* as life-style drug, i.e. costs will not be covered by the statutory health insurances

[5]only in patients without manifest cardiovascular disease that have not achieved adequate glycemic control with their previous insulin regime, in addition to diet and exercise

Abbreviations ACVR1, activin A receptor, type 1; AKT1, RAC(Rho family)-alpha serine/threonine protein kinase; AKT2, RAC-beta serine/threonine protein kinase; AKT3, RAC-gamma serine/threonine protein kinase; ATC, Anatomical Therapeutic Chemical classification system; AT_1R, angiotensin 1 receptor; BCMA, B-cell maturation antigen; BMI, body mass index; C5, C5b, C6, complement protein C5, C5b, C6; CD3, 19, 20, 38 cluster of differentiation 3, 19, 20, 38; EGFR, endothelial growth factor receptor; ET_AR, endothelin A receptor; FGFR-1, 2, 3, 4, fibroblast growth factor receptor 1, 2, 3, 4; GIP, glucose-dependent insulinotropic peptide; GCR, glucocorticoid receptor; GLP1, glucagon-like peptide 1; GPRC5D, G protein-coupled receptor, class C, group 5, member D; HER2/neu, receptor tyrosine kinase within the erb-b2 family; IKK, inhibitor of kappa-B kinase; INN, international non-proprietary name; IRAK1, interleukin-1 receptor-associated kinase 1; JAK 1/2/3, Janus kinase 1/2/3, receptor tyrosine kinase; $JAK2^{V617F}$, JAK2 receptor tyrosine kinase V617F mutant variant; MCR, mineralocorticoid receptor; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PPARα, δ, peroxisome proliferator-activated receptor α, δ; PTEN, phosphatase and tensin homolog deleted on chromosome ten; S1P1, 4, 5, sphingosine-1-phosphate receptor 1, 4, 5; TEC, tyrosine kinase expressed in hepatocellular carcinoma; TYK2, tyrosine kinase 2; UDCA, ursodeoxycholic acid; VEGF(R), vascular endothelial growth factor (receptor); (+), activates; (-), blocks; (b) binds to

New multi-target drugs in 2023–2024–arrangement of pharmacophores

In 2023 and 2024, 30 and 43 new drugs were authorized by the EMA, respectively, and consequently marketed in Germany (and also other EU countries) [13–14]. A closer look at the profile of the 73 newly introduced agents [15–16] showed that 18 of them can be categorized as having multi-targeting properties (seven in 2023, and eleven in 2024, Table 1). The drugs encompass small molecules, peptides, macromolecules (immunoglobulins, antibodies), and one conjugate of an antibody plus a small molecule. Before the 18 entities are described in terms of their pharmacological properties and indications (see next section), structural details of how the two pharmacophores are arranged in the molecule will be given for three examples, which represent three basic modes of spatial arrangement, previously reviewed in Ryszkiewicz et al. (2023) [5] and Kabir and Muth (2022) [6]. The pharmacophores can either be *linked* (i.e. combined using a spacer (linker), which can be enzyme-degradable in vivo), *fused* (i.e. directly attached to each other *via* covalent bonding with the omission of linker groups) or *merged* (integrated to form a single, unified entity, when two or more pharmacophores share a common structural core).

In the case of loncastuximab tesirine (#1 in Table 1), the antibody binding to CD19 (loncastuximab) is *linked* with the cytotoxic part of the molecule (tesirine) *via* a spacer (Fig. 1). In tirzepatide (#17 in Table 1), some amino acid residues specific for glucagon-like peptide 1 (GLP1) or for glucose-dependent insulinotropic peptide (GIP) are *fused*; on the other hand, other amino acid residues are shared by both peptides, i.e. pharmacophores are *merged* (Fig. 2 and further discussed in its legend). Sparsentan (#15 in Table 1) represents a pure example of *merged* pharmacophores, i.e., the parts of the molecule leading to blockade of ET_A and AT_1 receptors are overlapping (Fig. 3).

New multi-target drugs in 2023–2024–description

Ten of the 18 multi-target drugs are indicated for the treatment of cancer and cancer-related symptoms (#1-#10), another five for the treatment of autoimmune and/or inflammatory disorders (#11-#15), and one each for the treatment of eczema (#16), type II diabetes mellitus (and obesity) (#17), and Duchenne muscular dystrophy (#18).

The drugs used for managing malignant cancers can be divided into three groups. Drug #1 is an antibody-drug

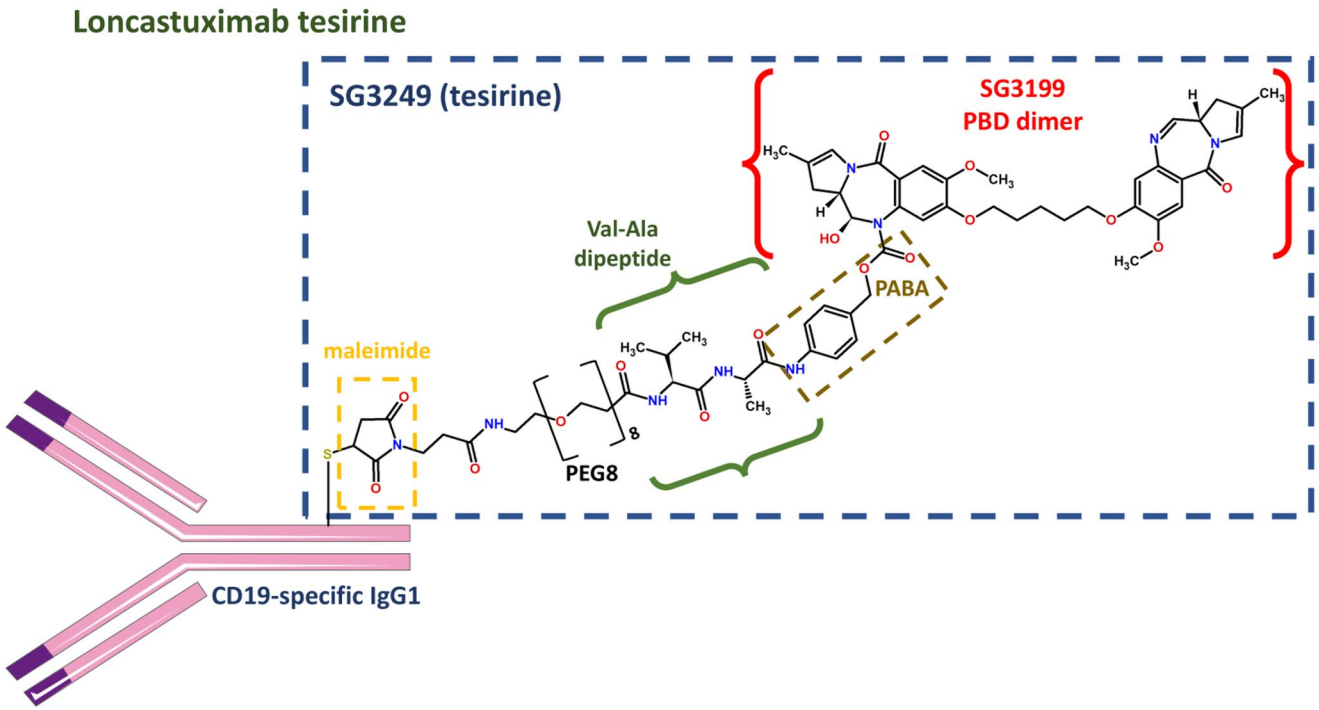

Fig. 1 Chemical structure and mechanism of action of **loncastuximab tesirine**, an antibody-drug conjugate with *linked* pharmacophores indicated for the treatment of B-cell lymphomas. Loncastuximab (a humanized IgG1 kappa monoclonal antibody) is bound to SG3249, also known as tesirine (blue rectangle, broken line), a cytotoxic alkylating agent. SG3249 (tesirine) consists of SG3199 (a pyrrolobenzodiazepine dimer, red parentheses), which is attached *via* a p-aminobenzoic acid moiety (brown box, broken line), to a protease-cleavable valine-alanine (Val-Ala) dipeptide linker (green parentheses), covalently bound *via* polyoxyethylene alkyl ether (PEG8) to a group containing a maleimide residue (orange box, broken line), which binds to the loncastuximab domain

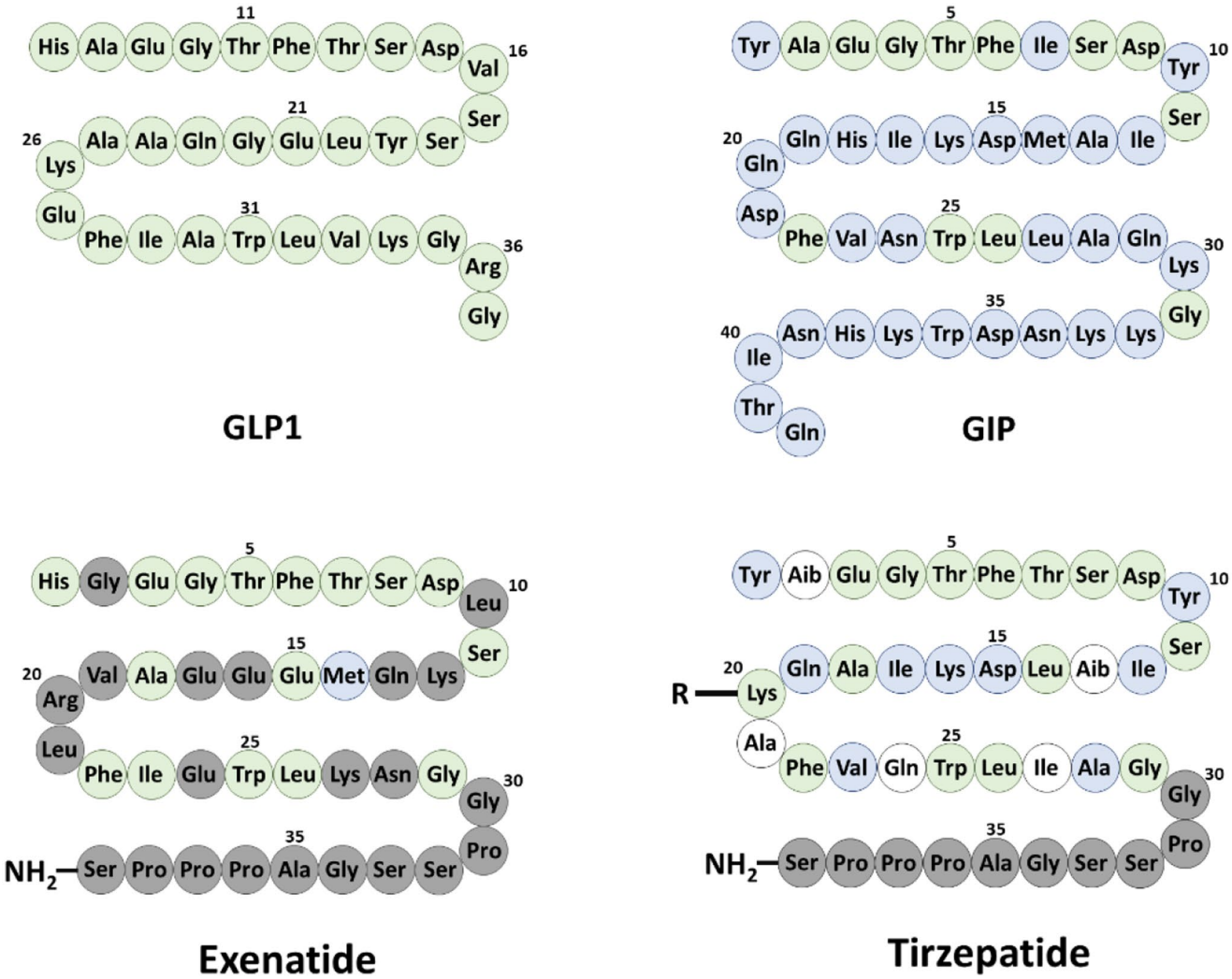

Fig. 2 Comparison of the chemical structures of **tirzepatide**, the first-in-class dual GLP1 and GIP analogue, of the native incretin molecules GLP1 and GIP, and of the GLP1 analogue exenatide. The origin of each amino acid residue is represented by a different colour: light green – deriving from GLP1, light blue – from GIP, grey – from exenatide. The tirzepatide molecule consists of a series of *fused* pharmacophores of GIP and GLP-1; some parts of the polypeptide chain are common to both GIP and GLP1 and might be considered *merged* pharmacophores. Note that 9 amino acids are specific for GIP, most of which increase the affinity for the GIP receptor. The non-canonical amino acid residue AiB^2 prevents degradation of tirzepatide in vivo by DPP-4. The C_{20} fatty diacid moiety attached to Lys^{20} extends the half-life of tirzepatide due to albumin-binding properties. There is some controversy as to whether the C-terminal amino acid residues deriving from exenatide are pharmacodynamically and/or pharmacokinetically important for the effect of tirzepatide [104, 119]. Re-drawn from [119]. AiB – α-aminoisobutyric acid; DPP-4 – dipeptidyl peptidase-4; GIP - glucose-dependent insulinotropic peptide; GLP1 – glucagon-like peptide 1

conjugate. The antibody domain provides selective delivery of an attached cytostatic molecule to cells expressing a given protein on their surface, thereby improving therapeutic effect, diminishing the risk of adverse drug reactions, and giving a chance to overcome the resistance of tumor cells to chemotherapy. Drugs #2-#6 are bispecific antibodies. *Via* simultaneous binding to cancer cells and T lymphocytes, they engage cytotoxic T-cells in a response against the tumor. Drugs #7-#10 are small organic compounds that inhibit protein kinases with different potency and selectivity. Due to the alteration of the dysregulated function of the affected target proteins, uncontrolled cell growth, survival, and division is blocked.

B-cell lymphomas represent a broad group of hematologic cancers with varying degrees of aggressiveness. Diffuse large B-cell lymphoma (DLBCL), a type of non-Hodgkin lymphoma, is one of the most common (and also the most aggressive) forms of this kind of neoplasm [17]. Despite the initial treatment, consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone, with the addition of rituximab (anti-CD20 monoclonal antibody) being effective in about 60–65% of patients, therapeutic options for

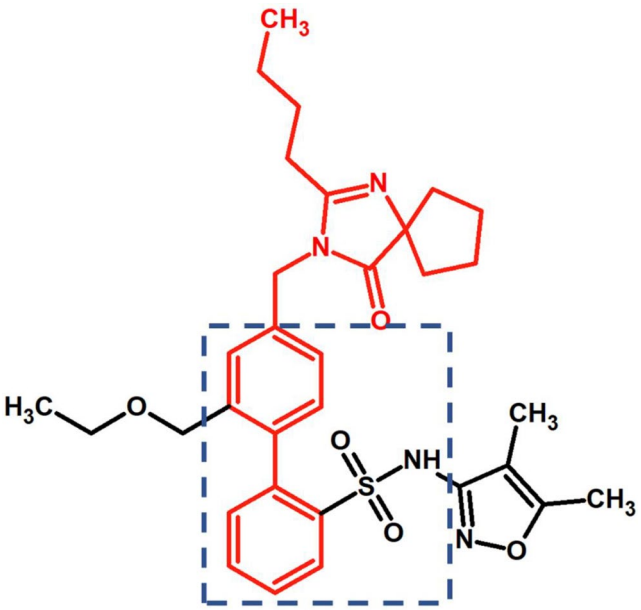

Fig. 3 Chemical structure of **sparsentan**, a first-in-class dual endothelin ET_A/angiotensin AT_1 receptor antagonist. Sparsentan molecule consists of structural elements of the AT_1 antagonist irbesartan (red colour) *merged* with a biphenylsulfonamide moiety, which acts as an ET_A receptor antagonist (blue box, broken line) [120–121]

the relapsed/refractory stage are very limited [7, 18]. Fortunately, three novel agents indicated for the treatment of this condition have reached the market in 2023 (Table 1). **Loncastuximab tesirine** (Zynlonta®; #1, Table 1; Fig. 1) is an antibody-drug conjugate, consisting of a CD19-directed humanised IgG1 kappa monoclonal antibody, attached through a protease-cleavable linker to SG3199, a pyrrolobenzodiazepine (PBD) dimer, which acts as an alkylating agent. SG3199 connected to its linker is also known as SG3249 or tesirine (Fig. 1) [19–20]. CD19 is expressed on B-type lymphocytes only. After the loncastuximab domain has bound to CD19, the whole antibody-cytotoxic drug conjugate is internalized, and then PBD dimers are released *via* proteolysis. Eventually, due to the binding of SG3199 to DNA, inter-strand crosslinks are formed, which results in the disruption of DNA replication, blocks cell division, and results in cell death [7, 18]. Interestingly, even if the expression of CD19 on malignant B lymphocytes is low or undetectable, the cytotoxic effect of loncastuximab tesirine is still manifested [21]. Zynlonta® was approved by the Food and Drug Administration (FDA) in the USA in 2021 [19]; in Europe, it was marketed two years later [18]. Loncastuximab tesirine has substantial antitumor activity in heavily pretreated Caucasian [22] and Chinese [23] patients with relapsed or refractory DLBCL, but both clinical trials have a single-arm design only (no placebo or active control). The most common adverse reactions are neutropenia, anemia, fatigue and increases in γ-glutamyltransferase activity [20].

Another two agents indicated for third-line DLBCL treatment, i.e. **epcoritamab** (Tepkinly®; #2, Table 1) and **glofitamab** (Columvi®; #3, Table 1), are IgG1 bispecific antibodies and share a similar mechanism of action [24]. Both epcoritamab and glofitamab are considered *conditional* agonists, which means that their activity is strictly dependent on simultaneous bonding to CD20 expressed on malignant B-cells, and CD3 expressed on T-cells. If the above condition is met, the formation of an *immunological synapse*, engaging both arms of a given bispecific antibody, will occur, resulting in T-cell activation, proliferation, secretion of cytokines, and subsequent depletion of CD20-expressing B-cells [25–26]. There are some characteristic differences between both antibodies [27–29]. Unlike epcoritamab, glofitamab binds bivalently to CD20. Moreover, the Fc region of epcoritamab is silenced to prevent target-independent immune response mechanisms. Therefore, the risk of undesirable antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cellular cytotoxicity (CDCC), and antibody-dependent cellular phagocytosis (ADCP) is vastly diminished [29].

Both medications have been studied in single-arm clinical trials and showed significant effectiveness with acceptable safety profiles [27]. There are now several new approaches for third-line DLBCL treatment but head-to-head comparisons have so far not been performed. An *indirect* comparison (inverse probability of treatment weighting) suggests that epcoritamab is equally effective as chimeric antigen receptor T-cell (CAR T) therapy but superior to chemoimmunotherapy, and polatuzumab- and tafasitamab-based regimens [30]. Note that the most common adverse effect associated with epcoritamab and glofitamab is cytokine release syndrome (CRS). It typically presents with symptoms such as fever (pyrexia), hypotension, tachycardia, and hypoxia [28–29].

Multiple myeloma (MM) is a bone marrow malignant neoplasm characterized by the clonal proliferation of plasma cells, which develop from activated B-lineage cells. This leads to the excessive production of monoclonal immunoglobulins or their light chains, which can accumulate and cause systemic damage [31–32]. The response to initial MM treatment (including the proteasome inhibitor bortezomib, the immunomodulator lenalidomide, and the glucocorticoid dexamethasone) is often inadequate. Relapses frequently occur at different stages of disease progression. Therefore, MM is still considered incurable [33–34]. **Talquetamab** (Talvey®; #4, Table 1), **Teclistamab** (Tecvayli®; #5, Table 1), and **Elranatamab** (Elrexfio®; #6, Table 1) are three novel fourth-line treatment options in patients with relapsed or refractory MM [35]. All three agents are considered bispecific antibodies; the first two (#4, and #5) are G4 proline, alanine, alanine immunoglobulins (IgG4 PAA)

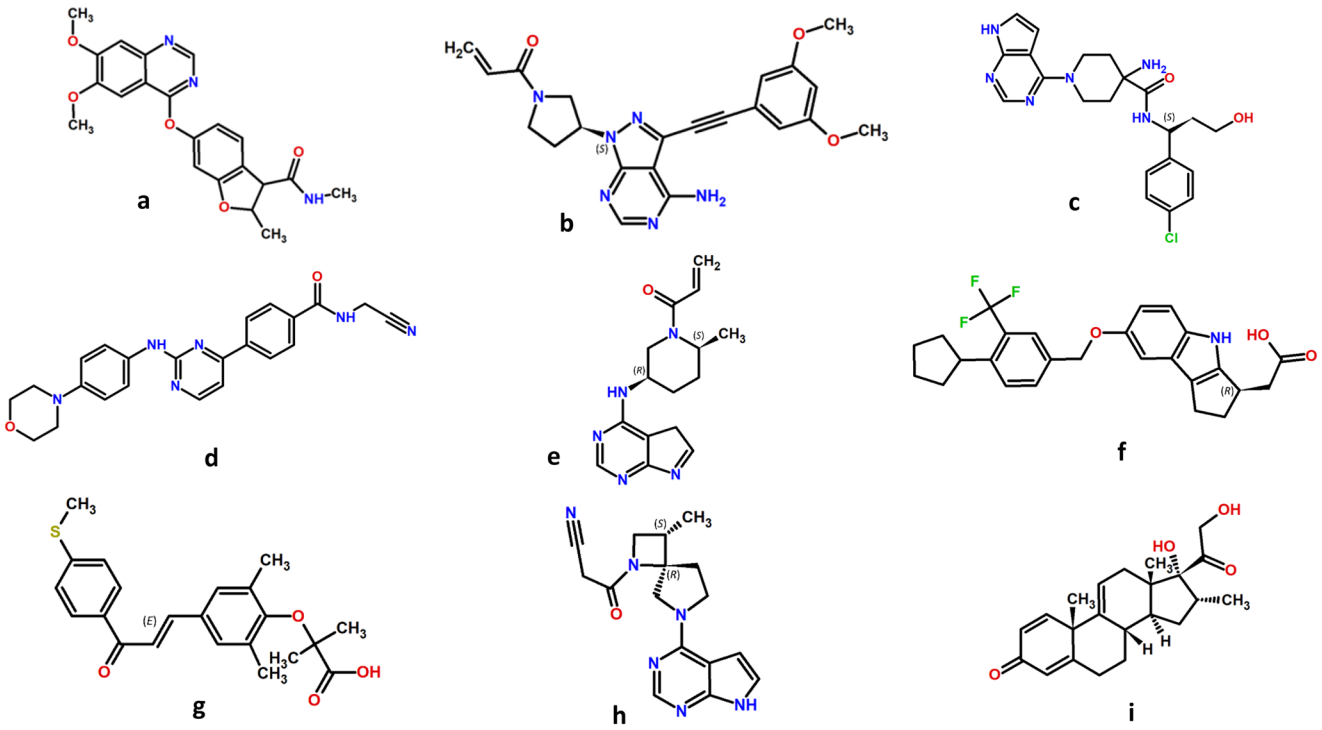

Fig. 4 Selected chemical structures of recently marketed multi-target-directed ligands (MTDLs), discussed in the text: **a** - fruquintinib; **b** - futibatinib; **c** - capivasertib; **d** - momelotinib; **e** - ritlecitinib; **f** - etrasimod; **g** - elafibranor; **h** - delgocitinib; **i** - vamorolone

[36–38]. Such a modification enhances the stability of the antibody in the serum [39]. All three drugs promote T-cell-mediated cytotoxicity *via* recruitment of CD3-expressing T-cells, as discussed earlier for epcoritamab and glofitamab. Talquetamab is directed against G protein-coupled receptor, family C, group 5, member D (GPRC5D), an orphan receptor expressed on malignant plasma cells [40–41]. Simultaneous binding of GPRC5D on MM cells and CD3 on cytotoxic T-cells results in T-cell activation, release of perforins and granzymes from secretory vesicles, and subsequent lysis of GPRC5D-expressing MM cells [42]. Noteworthy, the expression of GPRC5D in other tissues seems marginal, which limits the compound's toxicity [43]. Both teclistamab and elranatamab, besides targeting CD3+T-cells, are directed against B cell maturation antigen (BCMA), which is expressed on MM cells, but also on late-stage B-cells and plasma cells. Through drawing CD3-expressing T-cells in close proximity to BCMA+cells, activated cytotoxic T-cells evoke the lysis and death of BCMA-expressing cells. Noteworthy, this effect occurs regardless of native T-cell receptor specificity and does not involve major histocompatibility complex (MHC) class 1 molecules [44–45].

Each agent shows a relatively high response rate in monotherapy in patients with heavily pretreated MM [46]. However, there are no direct comparative clinical trials to date. In order to partially overcome this problem, indirect comparisons have been carried out. Using the inverse probability of treatment weighting (see above), both talquetamab [47] and teclistamab [48] are suggested to be superior to fourth-line treatment of MM, according to physicians' choice. Moreover, matching-adjusted indirect treatment comparisons of the respective single-arm clinical trials of teclistamab and elranatamab revealed that elranatamab is superior to teclistamab [49]. For each of the three antibodies, CRS is considered the most common adverse reaction [36–38].

Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths globally. Although the armamentarium of available therapies is gradually expanding, there are not many late-line treatment options, especially for heavily pretreated, metastatic CRC [50–51]. The vascular endothelial growth factor receptor (VEGFR) inhibitor **fruquintinib** (Fruzaqla®; #7, Table 1; Fig. 4a), a potent anti-angiogenic agent, fills this gap [50–52]. Unlike the representatives of earlier VEGFR inhibitor generations (such as regorafenib), fruquintinib is also suitable for combination therapy, as its pharmacokinetics seem more favourable and its *off-target* effects are vastly reduced [50]. In a double-blind, randomized clinical trial patients treated with placebo plus best supportive care showed a lower overall survival than patients treated with fruquintinib plus best supportive care [53]. Hypertension, anorexia, and proteinuria are the most frequent adverse reactions of fruquintinib [52].

Intrahepatic cholangiocarcinoma (iCCA) is a type of cancer that arises in the bile ducts, and accounts for 3% of

gastrointestinal tract cancers. The prognosis is very poor (5-year survival<20%) and treatment options for the late-stage disease are limited [54]. As fibroblast growth factor receptor 2 (FGFR-2) fusion or rearrangement occurs in 13-20% of iCCA patients, it has emerged as a promising drug target [55–56]. **Futibatinib** (Lytgobi®; #8, Table 1; Fig. 4b), unlike other representatives of FGFR inhibitors, covalently binds to all four FGFR isoforms, and therefore irreversibly inhibits constitutive FGFR signaling [57]. Thus, its efficacy is less likely to be limited by acquired drug resistance [55, 58]. A clinical benefit for iCCA patients was measurable; note that the drug had been studied in a single-arm clinical trial only [55]. Hyperphosphatemia is considered the most frequent side effect [57].

The serine/threonine kinase AKT is the key node in the phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR molecular pathway, which regulates a variety of cellular processes, including metabolism, gene transcription, migration, proliferation, cell cycle, and cellular survival. Activation of AKT in estrogen receptor-positive (ER+) breast cancer is associated with poor prognosis and resistance to endocrine therapy [59–60]. Mutations in the catalytic subunit of PI3K (PIK3CA), mutations in AKT1, upstream activation from other signaling pathways, and loss of phosphatase and tensin homolog (PTEN) function are the main causes of AKT activation in tumors [60–61]. **Capivasertib** (Truqap®; #9, Table 1; Fig. 4c) is a potent first-in-class inhibitor of the 3 isoforms of AKT (AKT1, AKT2, and AKT3). It inhibits the growth of cell lines from both hematological diseases and solid tumors, including breast cancer cells, regardless of the presence of PIK3CA or AKT1 mutations, or PTEN alterations [61–62]. In a randomized double-blind clinical trial, co-therapy of capivasertib and the estrogen receptor antagonist fulvestrant resulted in a longer progression-free survival than the administration of fulvestrant alone; this held true for patients with hormone receptor-positive advanced breast cancer when the disease had progressed during or after prior therapy with an aromatase inhibitor (e.g., letrozole), with or without a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor (e.g., palbociclib) [60, 63]. The most frequent adverse reaction is diarrhoea [61].

Anemia is a common manifestation of myelofibrosis (MF), a rare myeloproliferative cancer entity with a median survival of ~6 years after diagnosis [64–65]. **Momelotinib** (Omjjara®; #10, Table 1; Fig. 4d) is the first (and only) drug approved in Europe dedicated to patients with MF-related splenomegaly and anemia [66]. Momelotinib and its major metabolite (M21) are inhibitors of Janus kinases JAK1 and JAK2, and of the mutant variant $JAK2^{V617F}$, which contribute to the signaling of a number of cytokines and growth factors that are important for immune function and haematopoiesis. Moreover, due to antagonism at the activin A receptor type 1 (ACVR1), liver hepcidin expression is decreased, which results in improvement of iron availability and erythrocyte production [67]. Momelotinib and M21 also inhibit other kinases, including other JAK family members, the inhibitor of κB kinase (IKK) and the interleukin-1 receptor-associated kinase 1 (IRAK1) [66, 68]. Momelotinib is a useful treatment option across all levels of anemia severity, including cases with concurrent thrombocytopenia [64], which, in two head-to-head clinical trials was superior to danazol (parameter: total symptom score [69]) and noninferior to ruxolitinib (spleen volume [70]). The predominant drug-related side effect is diarrhoea [68].

The prevalence of autoimmune diseases and immune-mediated inflammatory disorders is worldwide and constantly increasing [71]. This has an impact on patients' quality of life, but also adds an additional economic burden to the healthcare system. Alopecia areata is an autoimmune disorder that causes hair loss, typically in small, round patches on the scalp or other body areas [72–73]. It affects 2% of the world population, and is linked to reduced life quality, and significant psychosocial challenges, often resulting in anxiety and depression. The progression of the condition is unpredictable, with periods of spontaneous improvement followed by relapses [73]. **Ritlecitinib** (Litfulo™; #11, Table 1; Fig. 4e) is an irreversible dual kinase inhibitor [74]. By blocking Janus kinase 3 (JAK3), it inhibits interleukin-derived (IL-2, IL-4, IL-7, IL-15, and IL-21) signaling in cellular settings. Additionally, simultaneous blockade of the tyrosine kinase expressed in the hepatocellular carcinoma (TEC) kinases family results in reduced cytolytic activity of CD8+T-cells and NK cells [74–75]. Although the involvement of JAK3 and TEC-mediated signaling pathways in the pathogenesis of alopecia areata seems evident, its complete pathophysiology is still not fully understood. Ritlecitinib treatment resulted in dose-dependent early decreases in absolute lymphocyte levels, subpopulations of CD3+, CD4+, and CD8+T-lymphocytes, and CD16/56+NK cells, with no changes in the CD19+B lymphocyte count, and immunoglobulin (IgG, IgA, IgM) levels [74]. Ritlecitinib≥30 mg per day for 24 weeks (with or without 200-mg loading dose during the initial 4 weeks) reduced scalp hair loss more markedly than placebo in a randomized, double-blind study [74]. Its main drug-related side effect is diarrhoea (~9% of patients) [75]. Ritlecitinib should not be used together with other JAK inhibitors, biologic immunomodulators, ciclosporin, or other strong immunosuppressants [74].

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) that causes long-lasting inflammation and ulcers in the inner lining of the colon and rectum. With an estimated prevalence of 5 million cases worldwide, UC is considered a significant global health concern [76].

Etrasimod (Velsipity®; #12, Table 1; Fig. 4f) is a sphingosine-1-phosphate (S1P) receptor modulator [77]. It selectively modulates three S1P receptor subtypes (S1P1, S1P4, and S1P5) with minimal affinity to S1P3, and no activity on S1P2, and is considered a balanced beta-arrestin and G-protein agonist at the S1P1 receptor [78–80]. Etrasimod reduces the lymphocyte count in peripheral blood, thereby reducing the quantity of activated lymphocytes in the tissue. The exact mechanism is unknown. Interestingly, the effect shows some degree of selectivity, as a greater reduction was observed in the case of cells associated with the adaptive immune response, which are known to play a role in driving UC pathology, compared to a minimal effect on cells involved in the innate immune response, important for immunosurveillance [80]. Etrasimod is recommended as a second-line treatment option, when previous conventional or biological therapies were inadequately tolerable, ineffective, or drug tolerance has developed [78–79]. Its efficacy was greater in patients naïve to biologics [79]. In a randomized double-blind clinical trial, etrasimod led to clinical remission more frequently than in placebo-treated controls, both when induction (after 12 weeks) and maintenance therapy (after 52 weeks) was considered [81]. Etrasimod has a shorter half-life in comparison to the S1P receptor modulator ozanimod and does not require dose titration. It also showed fewer interactions with other drugs and food. The most frequent side effects include lymphopenia and headache [80].

Immunosuppressants are also an important part of the treatment for myasthenia gravis (MG), an autoimmune disorder that leads to severe muscle weakness as a result of disrupted communication between nerves and muscles. Because autoantibodies against the nicotinic acetylcholine receptor are detected in about 80–90% of MG patients, acetylcholinesterase inhibitors (e.g., pyridostigmine) are frequently administered [82]. The synthetic macrocyclic peptide **zilucoplan** (Zilbrysq®; #13, Table 1) serves as a valuable add-on to such symptomatic treatment [83]. Zilucoplan appears to inhibit the activation of the terminal complement pathway *via* two distinct mechanisms: (i) By binding to C5 and blocking its conversion to C5a and C5b, the cytolytic activity of the membrane attack complex (MAC) is suppressed. (ii) It creates a steric hindrance that prevents C5b binding to C6, which blocks the MAC if any C5b is formed [83–84]. In a randomized double-blind clinical trial, zilucoplan improved motor skills like chewing, swallowing and breathing more markedly than placebo [85]. The most widespread side effects of zilucoplan consist of injection site reactions and pain, and upper respiratory tract infections [84].

Primary biliary cholangitis (PBC), the most common autoimmune liver disease, is marked by damage to interlobular bile ducts, resulting in cholestasis and the progression of liver fibrosis [86–87]. Treatment approaches are mainly focused on cholestatic consequences [88]. Unfortunately, nearly 40% of patients present an incomplete response to ursodeoxycholic acid (UDCA), the first-line drug in PBC [89]. Thus, other medications are needed as an adjuvant or replacement for UDCA. Activation of peroxisome proliferator-activated receptor (PPAR) α and δ by **elafibranor** (Iqirvo®; #14, Table 1; Fig. 4g), the first-in-class dual PPAR agonist, and its main active metabolite GFT1007, improves cholestasis, and decreases toxicity by modulating bile acid transporters, as well as the synthesis and detoxification of bile. The activation of PPARα and PPARδ also exerts anti-inflammatory effects [90–91]. In a randomized double-blind clinical trial in patients with PBC in whom UDCA was associated with inadequate response or unacceptable side effects, elafibranor improved biochemical indicators of cholestasis more markedly than placebo [87]. According to an expert opinion, the clinical efficacy of elafibranor is generally comparable to that of other second-line treatment options for PBC (such as the semi-synthetic bile acid analogue obeticholic acid, the lipid-lowering agent bezafibrate, and the PPARδ agonist seladelpar) [88]. Frequent drug-related side effects (more than 10% of patients) include non-serious, mild to moderate reactions, such as abdominal pain, diarrhoea, nausea, and vomiting [91].

Primary immunoglobulin A nephropathy (IgAN; sometimes also termed Berger´s disease), one of the most common forms of glomerulonephritis worldwide, is characterized by the deposition of circulating IgA-containing immune complexes in glomerular mesangial cells, which triggers subsequent glomerular and tubulointerstitial inflammation and fibrosis [92]. Endothelin 1 and angiotensin II contribute to IgAN progression by promoting hemodynamic changes, mesangial cell proliferation, enhanced expression and activity of proinflammatory and profibrotic factors, oxidative stress, and podocyte damage [93–94]. Persistent proteinuria and kidney failure are among the most common IgAN consequences. **Sparsentan** (Filspari®; #15, Table 1; Fig. 3) does not act *via* the immune system [95] but rather *via* antagonism against the two vasoconstrictive agents described above. In detail, it is the first-in-class dual endothelin ET_AR and angiotensin AT_1R receptor antagonist [94] and reduces proteinuria more effectively than angiotensin II receptor blockade alone [96–97]. The most frequent side effect of sparsentan is hypotonia [93].

Overactivation of the JAK-STAT pathway plays a role also in inflammatory conditions, including chronic hand eczema, a skin condition characterized by fluctuating symptoms, such as intense itching of hands and wrists, erythema, and swelling, often accompanied by pain. This can have a negative impact on the patients' quality of life, causing

considerable discomfort and emotional distress [98]. Topical corticosteroids are the first-line medications for alleviating these symptoms. However, their prolonged use can cause skin thinning, irritation, or the development of stretch marks [99–100]. Topical formulations with **delgocitinib** (Anzupgo®; #16, Table 1; Fig. 4h), a pan-JAK inhibitor, can therefore serve as a valuable alternative. Delgocitinib inhibits the activity of all JAK family members, i.e. JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). By doing so, it attenuates the signaling of pro-inflammatory cytokines, such as interleukin (IL)-2, IL-4, IL-6, IL-13, IL-21, IL-23, interferon (IFN)-α, and granulocyte-macrophagecolony-stimulating factor (GM-CSF) [101–102]. In a randomized double-blind clinical trial, delgocitinib cream demonstrated greater effectiveness compared to the cream vehicle [98]. The most frequent side effects are adverse reactions at the site of application [101].

Another first-in-class dual-targeting agent, **tirzepatide** (Mounjaro®; #17, Fig. 2; Table 1), is a long-acting glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP1) analogue, with high selectivity for human GIP and GLP1 receptors [103]. Both receptors are expressed on the α and β pancreatic endocrine cells, as well as in various other tissues including the heart, blood vessels, gastrointestinal system, immune cells (leukocytes), kidneys, and brain regions crucial for regulating appetite [104]. Long-term glycemic control in adults with type 2 diabetes mellitus is often difficult to achieve [105]. GLP1 agonists such as exenatide, liraglutide, and semaglutide currently serve as second-line therapy, following metformin [1]. However, adverse effects limit the ability to increase the dosage, thereby reducing the potential for higher therapeutic efficacy, particularly in terms of weight loss. To address this, combining GLP1 and GIP receptor agonism in a single drug was considered a potential solution, aided by the high molecular structure similarity between GLP1 and GIP (see Fig. 2) [1]. Tirzepatide reduces fasting and postprandial glucose levels. It also regulates appetite by increasing feelings of satiety and fullness while reducing hunger, leading to a decrease in food intake, body weight, and body fat percentage [106]. Consequently, tirzepatide was first approved by the EMA for diabetes treatment and half a year later for treatment of overweight (Table 1).

Tirzepatide resembles semaglutide (which is a GLP1 receptor agonist only) in its therapeutic profile. In terms of molecular structure, tirzepatide offers three key advancements over the first-generation GLP1 agonists: firstly, several residues in the peptide chain are modified to enhance GIP receptor-activating activity; secondly, the C-terminal is extended with a sequence from exenatide; thirdly, a fatty acid side chain is attached, similarly to semaglutide, to extend its half-life (see Fig. 2). In quantitative terms, tirzepatide was superior to semaglutide both in the treatment of diabetes (reduction of glycated hemoglobin) [107] and overweight [108]. The most common adverse reactions of tirzepatide include mild to moderate gastrointestinal disorders, e.g., nausea, diarrhea, and vomiting, which were more frequent during the dose escalation phase and decreased over time [104].

Duchenne muscular dystrophy (DMD) is a serious, progressive genetic disorder that leads to the gradual weakening of muscles, causing a rapid decline in mobility. DMD typically manifests between the ages of 2 and 5 years, and predominantly affects boys [109]. Glucocorticoids like prednisone and deflazacort are commonly used to treat DMD due to their strong anti-inflammatory effects. However, long-term use of these drugs can lead to serious side effects, such as growth suppression, weight gain, bone malformation, and an increased risk of infections [110]. To address this, **vamorolone** (Agamree®; #18, Table 1; Fig. 4i) was developed (i) as a novel dissociative corticosteroid, aiming to maintain effectiveness while reducing these harmful side effects [111]. Vamorolone binds to the glucocorticoid receptor, thereby triggering anti-inflammatory effects *via* inhibition of NF-κB mediated gene transcripts. (ii) Additionally, it prevents aldosterone from activating the mineralocorticoid receptor. (iii) Furthermore, due to its unique structure, vamorolone likely does not interact with 11ß-hydroxysteroid dehydrogenases, which reduces the potential for side effects that might arise from local increases in glucocorticoid activity [111–112]. The exact mechanism by which vamorolone provides therapeutic benefits for patients with DMD is not yet fully understood [112].

Two doses of vamorolone were tested against placebo and the standard glucocorticoid prednisone in double-blind, randomized clinical trials; the efficacy of vamorolone was higher than that of placebo and the efficacy of the higher dose of vamorolone was comparable to that of prednisone [113–115]. Typical adverse effects of vamorolone are cushingoid features, weight gain, insulin resistance, suppression of adrenal function, and irritability [112–114]. However, vamorolone, which was studied in boys aged from 4 to younger than 7 years, unlike prednisone did not affect growth nor did it affect bone turnover markers (which declined with prednisone) [114]. When boys treated with prednisone for 24 weeks were switched to vamorolone for another 24 weeks, growth significantly increased and bone turnover biomarkers showed a rapid reversal of their prednisone-induced decline [115].

New multi-target drugs in 2023–2024–evaluation

Newly introduced drugs are subject to at least two systems of evaluation after their introduction in Germany. The first evaluation system is described in the *Pharmazeutische Zeitung*, a weekly appearing journal for pharmacists, in which the degree of innovation is given in terms of me-too preparation, step innovation, and disruptive innovation (e.g., for epcoritamab (#2) and ritlecitinib (#11) in Gensthaler et al. (2023) [116]). The rating is listed for each of the 18 compounds in Table 1. Drugs were rated as step or disruptive innovations with two exceptions only.

The second type of evaluation is provided by the Joint Federal Committee (*Gemeinsamer Bundesausschuss*) consisting of representatives of physicians, dentists, hospitals, and health insurance providers. In accordance with the German Social Code, Book Five (SGB V), *section 35a*, they check after six months whether a newly introduced drug has an advantage over the standard therapy (this explains why the assessment for the very recently introduced drugs capivasertib, elafibranor, and delgocitinib is not yet available). When an additional benefit cannot be demonstrated, the annual treatment costs of the new drug must not exceed those of the appropriate comparator [117]. This procedure is stricter than that of the EMA, who postulates the therapeutic effect and safety of the new drug only. Table 1 shows that a minor or not quantifiable additional benefit could be shown for epcoritamab, glofitamab, talquetamab, fruquintinib, momelotinib, sparsentan, tirzepatide (for one group of diabetes patients only), and vamorolone.

The deeper sense of the activities of the *Gemeinsamer Bundesausschuss* is to dampen the steadily increasing costs of drugs. The assessment of the additional benefit of newly introduced drugs has already been discussed in the previous paragraph. To keep costs low, also SGB V, *Sect. 34*, is of interest, which contains a list of drugs that predominantly increase the quality of life, e.g. by reduction of body weight or stimulation of hair growth. Costs of such life-style drugs will not be covered by statutory health insurances with their 74 million policyholders. Recently, tirzepatide (treatment of overweight only) and ritlecitinib have been added to this list (Table 1) [118].

Conclusions

Polypharmacology, i.e. the design, synthesis, and clinical implementation of multi-targeting molecules, might offer favorable synergistic effects and could be a promising way, e.g., for overcoming drug resistance in malignant cancers or to provide a better alternative to poorly tolerated medications. Among the 73 substances introduced in Germany in 2023–2024, 18 were identified as multi-target-directed ligands (MTDLs), including small molecules, peptides, immunoglobulins (antibodies), and one antibody-drug conjugate. The number of polypharmacological drugs introduced remains relatively consistent year-to-year (11 substances approved in 2024, 7 in 2023, and 10 in 2022) [5]. Most of them are dedicated to cancer therapy. The chemical structures of three new MTDLs in which the pharmacophores are linked, fused or merged are described in more detail, respectively. The 18 new MTDLs comprise ten antitumor agents, including drugs indicated for B-cell lymphomas, multiple myeloma, colorectal cancer, cholangiocarcinoma, breast cancer, and myeloproliferative cancer-related splenomegaly. Another five drugs act against autoimmune disorders, like alopecia areata, ulcerative colitis, myasthenia gravis, primary biliary cholangitis, and IgA nephropathy. Another three drugs are indicated for the treatment of hand eczema, type II diabetes mellitus (and overweight) and Duchenne muscular dystrophy. All but two drugs were rated as step or disruptive innovations according to *Pharmazeutische Zeitung*, a German journal for pharmacists. Another rating in Germany, provided by a committee of physicians, dentists, hospitals, and health insurances (*Gemeinsamer Bundesausschuss*), revealed that eight of the 14 MTDLs evaluated so far show an additional benefit beyond that of the currently available standard therapy.

Author contributions P.R.: Conceptualization, Data curation, Funding Acquisition, Methodology, Project administration, Resources, Software, Visualization, Writing – original draft, Writing – review&editing. B.M.: Writing – review&editing. E.S.: Supervision, Writing – review&editing.

Funding The study was supported by the Medical University of Białystok, Poland, grant No. B.SUB.24.236.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

References

1. Rafehi M, Möller M, Ismail Al-Khalil W, Stefan SM. Medicinal polypharmacology in the clinic - translating the polypharmacolome into therapeutic benefit. Pharm Res. 2024;41(3):411–7. https://doi.org/10.1007/s11095-024-03656-8.
2. Lembo V, Bottegoni G. Systematic investigation of dual-target-directed ligands. J Med Chem. 2024;67(12):10374–85. https://doi.org/10.1021/acs.jmedchem.4c00838.
3. Doostmohammadi A, Jooya H, Ghorbanian K, Gohari S, Dadashpour M. Potentials and future perspectives of multi-target drugs in cancer treatment: the next generation anti-cancer agents. Cell Commun Signal. 2024;22(1):228. https://doi.org/10.1186/s12964-024-01607-9.
4. Rodrigues TC, de Sousa NF, Dos Santos AMF, Guimarães RD, Scotti MT, Scotti L. Challenges and discoveries in polypharmacology of neurodegenerative diseases. Curr Top Med Chem. 2023;23(5):349–70. https://doi.org/10.2174/1568026623666230126112628.
5. Ryszkiewicz P, Malinowska B, Schlicker E. Polypharmacology: promises and new drugs in 2022. Pharmacol Rep. 2023;75(4):755–70. https://doi.org/10.1007/s43440-023-00501-4.
6. Kabir A, Muth A. Polypharmacology: the science of multi-targeting molecules. Pharmacol Res. 2022;176:106055. https://doi.org/10.1016/j.phrs.2021.106055.
7. Tarantelli C, Wald D, Munz N, Spriano F, Bruscaggin A, Cannas E, et al. Targeting CD19-positive lymphomas with the antibody-drug conjugate loncastuximab tesirine: preclinical evidence of activity as a single agent and in combination therapy. Haematologica. 2024;109(10):3314–26. https://doi.org/10.3324/haematol.2023.284197.
8. Stefan SM, Rafehi M. Medicinal polypharmacology-a scientific glossary of terminology and concepts. Front Pharmacol. 2024;15:1419110. https://doi.org/10.3389/fphar.2024.1419110.
9. Manen-Freixa L, Antolin AA. Polypharmacology prediction: the long road toward comprehensively anticipating small-molecule selectivity to de-risk drug discovery. Expert Opin Drug Discov. 2024;19(9):1043–69. https://doi.org/10.1080/17460441.2024.2376643.
10. Feldmann C, Bajorath J. Advances in computational polypharmacology. Mol Inf. 2022;41(12):e2200190. https://doi.org/10.1002/minf.202200190.
11. Cichońska A, Ravikumar B, Rahman R. AI for targeted polypharmacology: the next frontier in drug discovery. Curr Opin Struct Biol. 2024;84:102771. https://doi.org/10.1016/j.sbi.2023.102771.
12. Munson BP, Chen M, Bogosian A, Kreisberg JF, Licon K, Abagyan R, et al. De novo generation of multi-target compounds using deep generative chemistry. Nat Commun. 2024;15(1):3636. https://doi.org/10.1038/s41467-024-47120-y.
13. vfa (Verband Forschender Arzneimittelhersteller). Innovationsbilanz 2023: Die neuen Medikamente und Anwendungsgebiete [Innovation balance 2023: The new drugs and areas of application]. https://www.vfa.de/de/arzneimittel-forschung/woran-wir-forschen/neue-medikamente-und-anwendungsgebiete-2023. Accessed 2 January 2025.
14. vfa (Verband Forschender Arzneimittelhersteller). Innovationsbilanz 2024 [Innovation balance sheet 2024]. https://www.vfa.de/de/arzneimittel-forschung/neuein-fuehrungen/innovationsbilanz-2024. Accessed 2 January 2025.
15. Pharmazeutische Zeitung, Arzneistoffe. Jahrgang 2023 [Drugs introduced in 2023] https://www.pharmazeutische-zeitung.de/arzneistoff-jahrgang/jahr/2023/. Accessed 2 January 2025.
16. Pharmazeutische Zeitung, Arzneistoffe. Jahrgang 2024 [Drugs introduced in 2024] https://www.pharmazeutische-zeitung.de/arzneistoff-jahrgang/jahr/2024/. Accessed 2 January 2025.
17. Kanas G, Ge W, Quek RGW, Keeven K, Nersesyan K, Jon E, Arnason. Epidemiology of diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) in the United States and Western Europe: population-level projections for 2020–2025. Leuk Lymphoma. 2022;63(1):54–63. https://doi.org/10.1080/10428194.2021.1975188.
18. Juárez-Salcedo LM, Nimkar S, Corazón AM, Dalia S. Loncastuximab tesirine in the treatment of relapsed or refractory diffuse large B-cell lymphoma. Int J Mol Sci. 2024;25(14):7580. https://doi.org/10.3390/ijms25147580.
19. Lee A. Loncastuximab tesirine: first approval. Drugs. 2021;81(10):1229–33. https://doi.org/10.1007/s40265-021-01550-w.
20. European Medicines Agency. Zynlonta® Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/zynlonta-epar-product-information_en.pdf. Accessed 3 January 2025.
21. Caimi PF, Hamadani M, Carlo-Stella C, Nickaeen M, Jordie E, Utsey K, et al. Understanding how CD19 expression levels impact the response to loncastuximab tesirine: a plain language summary. Future Oncol 2024 Nov 7:1–10. https://doi.org/10.1080/14796694.2024.2418751
22. Caimi PF, Ai W, Alderuccio JP, Ardeshna KM, Hamadani M, Hess B, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol. 2021;22(6):790–800. https://doi.org/10.1016/S1470-2045(21)00139-X.
23. Lin N, Sun X, Zhou H, Zou L, Zhou K, Liu L, et al. Loncastuximab tesirine in Chinese patients with relapsed or refractory diffuse large B-cell lymphoma: a multicenter, open-label, single-arm, phase II trial. Haematologica. 2025;110(3):683–92. https://doi.org/10.3324/haematol.2024.284973.
24. Radhakrishnan VS, Davies AJ. Bispecific antibodies in indolent B-cell lymphomas. Front Immunol. 2024;14:1295599. https://doi.org/10.3389/fimmu.2023.1295599.
25. Frampton JE. Epcoritamab: first approval. Drugs. 2023;83(14):1331–40. https://doi.org/10.1007/s40265-023-01930-4.
26. Shirley M. Glofitamab: first approval. Drugs. 2023;83(10):935–41. https://doi.org/10.1007/s40265-023-01894-5.
27. Davis JA, Granger K, Sakowski A, Goodwin S, Herbst A, Smith D, et al. Dual target dilemma: navigating epcoritamab vs. glofitamab in relapsed refractory diffuse large B-cell lymphoma. Expert Rev Hematol 2023 Jul-Dec;16(12):915–8. https://doi.org/10.1080/17474086.2023.2285978
28. European Medicines Agency. Columvi® Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/columvi-epar-product-information_en.pdf. Accessed 3 January 2025.
29. European Medicines Agency. Tepkinly® Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/tepkinly-epar-product-information_en.pdf. Accessed 3 January 2025.
30. Rosenthal A, Munoz J, Jun M, Wang T, Mutebi A, Wang A, et al. Comparisons of treatment outcomes of epcoritamab versus chemoimmunotherapy, polatuzumab-based regimens, tafasitamab-based regimens, or chimeric antigen receptor T-cell therapy, in third-line or later relapsed/refractory large B-cell lymphoma. J Hematol Oncol. 2024;17(1):69. https://doi.org/10.1186/s13045-024-01594-x.

31. Monteith BE, Sandhu I, Lee AS. Management of multiple myeloma: a review for general practitioners in oncology. Curr Oncol. 2023;30(5):4382–401. https://doi.org/10.3390/curroncol30050334.
32. Cowan AJ, Green DJ, Kwok M, Lee S, Coffey DG, Holmberg LA, et al. Diagnosis and management of multiple myeloma: a review. JAMA. 2022;327(5):464–77. https://doi.org/10.1001/jama.2022.0003.
33. Bhatt P, Kloock C, Comenzo R. Relapsed/refractory multiple myeloma: a review of available therapies and clinical scenarios encountered in myeloma relapse. Curr Oncol. 2023;30(2):2322–47. https://doi.org/10.3390/curroncol30020179.
34. Malard F, Neri P, Bahlis NJ, Terpos E, Moukalled N, Hungria VTM, et al. Multiple myeloma. Nat Rev Dis Primers. 2024;10(1):45. https://doi.org/10.1038/s41572-024-00529-7.
35. Waldschmidt JM, Rasche L, Kortüm KM, Einsele H. Comprehensive review of bispecific antibody constructs in multiple myeloma: affinities, dosing strategies and future perspectives. Clin Lymphoma Myeloma Leuk. 2024 Nov 22:S2152-2650(24)02423-6. https://doi.org/10.1016/j.clml.2024.11.012
36. European Medicines Agency. Talvey® Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/talvey-epar-product-information_en.pdf. Accessed 3 January 2025.
37. European Medicines Agency. Tecvayli® Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/tecvayli-epar-product-information_en.pdf. Accessed 3 January 2025.
38. European Medicines Agency. Elrexfio® Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/elrexfio-epar-product-information_en.pdf. Accessed 3 January 2025.
39. Tang Y, Cain P, Anguiano V, Shih JJ, Chai Q, Feng Y. Impact of IgG subclass on molecular properties of monoclonal antibodies. MAbs. 2021 Jan-Dec;13(1):1993768. https://doi.org/10.1080/19420862.2021.1993768.
40. Chari A, Minnema MC, Berdeja JG, Oriol A, van de Donk NWCJ, Rodríguez-Otero P, et al. Talquetamab, a T-cell-redirecting GPRC5D bispecific antibody for multiple myeloma. N Engl J Med. 2022;387(24):2232–44. https://doi.org/10.1056/NEJMoa2204591.
41. Liu L, Krishnan A. Talquetamab in multiple myeloma. Haematologica. 2024;109(3):718–24. https://doi.org/10.3324/haematol.2023.283931.
42. Zhou D, Wang Y, Chen C, Li Z, Xu K, Zhao K. Targeting GPRC5D for multiple myeloma therapy. J Hematol Oncol. 2024;17(1):88. https://doi.org/10.1186/s13045-024-01611-z.
43. Keam SJ. Talquetamab: first approval. Drugs. 2023;83(15):1439–45. https://doi.org/10.1007/s40265-023-01945-x.
44. Kang C. Teclistamab: first approval. Drugs. 2022;82(16):1613–9. https://doi.org/10.1007/s40265-022-01793-1.
45. Dhillon S. Elranatamab: first approval. Drugs. 2023;83(17):1621–7. https://doi.org/10.1007/s40265-023-01954-w.
46. Moore DC, Granger K, Hill H, Karabinos A, Davis JA. Elranatamab vs. teclistamab: battle of the BCMA bispecifics in relapsed/refractory multiple myeloma. Expert Rev Hematol. 2024;17(6):197–200. https://doi.org/10.1080/17474086.2024.2353751.
47. Einsele H, Moreau P, Bahlis N, Bhutani M, Vincent L, Karlin L, et al. Comparative efficacy of talquetamab vs. current treatments in the locommotion and momment studies in patients with triple-class-exposed relapsed/refractory multiple myeloma. Adv Ther. 2024;41(4):1576–93. https://doi.org/10.1007/s12325-024-02797-x.
48. Mateos MV, Chari A, Usmani SZ, Goldschmidt H, Weisel K, Qi K, et al. Comparative efficacy of teclistamab versus physician's choice of therapy in the long-term follow-up of APOLLO, POLLUX, CASTOR, and EQUULEUS clinical trials in patients with triple-class exposed relapsed or refractory multiple myeloma. Clin Lymphoma Myeloma Leuk. 2023;23(5):385–93. https://doi.org/10.1016/j.clml.2023.02.006.
49. Mol I, Hu Y, LeBlanc TW, Cappelleri JC, Chu H, Nador G, et al. A matching-adjusted indirect comparison of the efficacy of elranatamab versus teclistamab in patients with triple-class exposed/refractory multiple myeloma. Leuk Lymphoma. 2024;65(5):660–8. Epub 2024 Feb 12. PMID: 38347747.
50. Zhao S, Wang W, Li J, Li Z, Liu Z, Zhang S, et al. Clinical research progress of fruquintinib in the treatment of malignant tumors. Invest New Drugs. 2024;42(6):612–22. https://doi.org/10.1007/s10637-024-01476-6.
51. Stucchi E, Bartolini M, Airoldi M, Fazio R, Daprà V, Mondello G, et al. Fruquintinib as new treatment option in metastatic colorectal cancer patients: is there an optimal sequence? Expert Opin Pharmacother. 2024;25(4):371–82. https://doi.org/10.1080/14656566.2024.2336069.
52. European Medicines Agency. Fruzaqla® Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/fruzaqla-epar-product-information_en.pdf. Accessed 3 January 2025.
53. Dasari A, Lonardi S, Garcia-Carbonero R, Elez E, Yoshino T, Sobrero A, et al. Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): an international, multicentre, randomised, double-blind, phase 3 study. Lancet. 2023;402(10395):41–53. https://doi.org/10.1016/S0140-6736(23)00772-9.
54. Qurashi M, Vithayathil M, Khan SA. Epidemiology of cholangiocarcinoma. Eur J Surg Oncol. 2023 Sep;9:107064. https://doi.org/10.1016/j.ejso.2023.107064.
55. Goyal L, Meric-Bernstam F, Hollebecque A, Valle JW, Morizane C, Karasic TB, et al. Futibatinib for FGFR2-rearranged intrahepatic cholangiocarcinoma. N Engl J Med. 2023;388(3):228–39. https://doi.org/10.1056/NEJMoa2206834.
56. Guo J, Sun L, Chen Y, Ma J. Pemigatinib combined with immunotherapy and stereotactic body radiation therapy for FGFR2 fusion-positive advanced intrahepatic cholangiocarcinoma with brain metastasis: a case report. Front Pharmacol. 2024;15:1509891. https://doi.org/10.3389/fphar.2024.1509891.
57. European Medicines Agency. Lytgobi® Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/lytgobi-epar-product-information_en.pdf. Accessed 3 January 2025.
58. Javle M, King G, Spencer K, Borad MJ. Futibatinib, an irreversible FGFR1-4 inhibitor for the treatment of FGFR-aberrant tumors. Oncologist. 2023;28(11):928–43. https://doi.org/10.1093/oncolo/oyad149.
59. Alves CL, Ditzel HJ. Drugging the PI3K/AKT/mTOR pathway in ER + breast cancer. Int J Mol Sci. 2023;24(5):4522. https://doi.org/10.3390/ijms24054522.
60. Browne IM, André F, Chandarlapaty S, Carey LA, Turner NC. Optimal targeting of PI3K-AKT and mTOR in advanced oestrogen receptor-positive breast cancer. Lancet Oncol. 2024;25(4):e139–51. https://doi.org/10.1016/S1470-2045(23)00676-9.
61. European Medicines Agency. Truqap® Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/truqap-epar-product-information_en.pdf. Accessed 3 January 2025.
62. Luboff AJ, DeRemer DL. Capivasertib: a novel AKT inhibitor approved for hormone-receptor-positive, HER-2-negative metastatic breast cancer. Ann Pharmacother. 2024;58(12):1229–37. https://doi.org/10.1177/10600280241241531.
63. Turner NC, Oliveira M, Howell SJ, Dalenc F, Cortes J, Gomez Moreno HL, et al. Capivasertib in hormone receptor-positive

advanced breast cancer. N Engl J Med. 2023;388(22):2058–70. https://doi.org/10.1056/NEJMoa2214131.
64. Al-Ali HK, Kuykendall AT, Ellis CE, Sampath J, Mesa R. Anemia in myelofibrosis: a focus on proactive management and the role of momelotinib. Cancers (Basel). 2024;16(23):4064. https://doi.org/10.3390/cancers16234064.
65. Vlasakakis G, McCabe MT, Ho YL, Ferron-Brady G, Martin P, Bentley D, et al. Momelotinib: mechanism of action, clinical, and translational science. Clin Transl Sci. 2024;17(8):e70018. https://doi.org/10.1111/cts.70018.
66. Bruzzese A, Martino EA, Labanca C, Mendicino F, Lucia E, Olivito V, et al. Momelotinib in myelofibrosis. Expert Opin Pharmacother. 2024;25(5):521–8. https://doi.org/10.1080/14656566.2024.2343780.
67. Bose P. Momelotinib for the treatment of myelofibrosis. Blood. 2024;144(7):708–13. https://doi.org/10.1182/blood.2023023719.
68. European Medicines Agency. Omjjara® Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/omjjara-epar-product-information_en.pdf. Accessed 3 January 2025.
69. Verstovsek S, Gerds AT, Vannucchi AM, Al-Ali HK, Lavie D, Kuykendall AT, et al. Momelotinib versus danazol in symptomatic patients with anaemia and myelofibrosis (MOMENTUM): results from an international, double-blind, randomised, controlled, phase 3 study. Lancet. 2023;401(10373):269–80. https://doi.org/10.1016/S0140-6736(22)02036-0.
70. Mesa RA, Kiladjian JJ, Catalano JV, Devos T, Egyed M, Hellmann A, et al. SIMPLIFY-1: a phase III randomized trial of momelotinib versus ruxolitinib in Janus kinase inhibitor-naïve patients with myelofibrosis. J Clin Oncol. 2017;35(34):3844–50. https://doi.org/10.1200/JCO.2017.73.4418.
71. Miller FW. The increasing prevalence of autoimmunity and autoimmune diseases: an urgent call to action for improved understanding, diagnosis, treatment, and prevention. Curr Opin Immunol. 2023;80:102266. https://doi.org/10.1016/j.coi.2022.102266.
72. Dainichi T, Iwata M, Kaku Y. Alopecia areata: what's new in the epidemiology, comorbidities, and pathogenesis? J Dermatol Sci. 2023;112(3):120–7. https://doi.org/10.1016/j.jdermsci.2023.09.008.
73. Tosti A. Alopecia areata: the clinician and patient voice. J Drugs Dermatol. 2023;22(10):967–75. https://doi.org/10.36849/JDD.SF396143.
74. Blair HA, Ritlecitinib. First approval. Drugs. 2023;83(14):1315–21. https://doi.org/10.1007/s40265-023-01928-y.
75. European Medicines Agency. Litfulo® Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/litfulo-epar-product-information_en.pdf. Accessed 3 January 2025.
76. Le Berre C, Honap S, Peyrin-Biroulet L. Ulcerative colitis. Lancet. 2023;402(10401):571–84. https://doi.org/10.1016/S0140-6736(23)00966-2.
77. Wils P, Peyrin-Biroulet L. Etrasimod for the treatment of ulcerative colitis. Immunotherapy. 2023;15(5):311–21. https://doi.org/10.2217/imt-2022-0255.
78. Shirley M. Etrasimod: first approval. Drugs. 2024;84(2):247–54. https://doi.org/10.1007/s40265-024-01997-7.
79. Glassner K, Fan C, Irani M, Abraham BP. Therapeutic potential of etrasimod in the management of moderately-to-severely active ulcerative colitis: evidence to date. Clin Exp Gastroenterol. 2024;17:337–45. https://doi.org/10.2147/CEG.S391706.
80. European Medicines Agency. Velsipity® Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/velsipity-epar-product-information_en.pdf. Accessed 3 January 2025.
81. Sandborn WJ, Vermeire S, Peyrin-Biroulet L, Dubinsky MC, Panes J, Yarur A, et al. Etrasimod as induction and maintenance therapy for ulcerative colitis (ELEVATE): two randomised, double-blind, placebo-controlled, phase 3 studies. Lancet. 2023;401(10383):1159–71. https://doi.org/10.1016/S0140-6736(23)00061-2.
82. Crisafulli S, Boccanegra B, Carollo M, Bottani E, Mantuano P, Trifirò G, et al. Myasthenia gravis treatment: from old drugs to innovative therapies with a glimpse into the future. CNS Drugs. 2024;38(1):15–32. https://doi.org/10.1007/s40263-023-01059-8.
83. Shirley M, Zilucoplan. First approval. Drugs. 2024;84(1):99–104. https://doi.org/10.1007/s40265-023-01977-3.
84. European Medicines Agency. Zilbrysq® Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/zilbrysq-epar-product-information_en.pdf. Accessed 3 January 2025.
85. Howard JF Jr, Bresch S, Genge A, Hewamadduma C, Hinton J, Hussain Y, et al. Safety and efficacy of zilucoplan in patients with generalised myasthenia gravis (RAISE): a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Neurol. 2023;22(5):395–406. https://doi.org/10.1016/S1474-4422(23)00080-7.
86. Houri I, Hirschfield GM. Primary biliary cholangitis: pathophysiology. Clin Liver Dis. 2024;28(1):79–92. https://doi.org/10.1016/j.cld.2023.06.006.
87. Kowdley KV, Bowlus CL, Levy C, Akarca US, Alvares-da-Silva MR, Andreone P, et al. Efficacy and safety of elafibranor in primary biliary cholangitis. N Engl J Med. 2024;390(9):795–805. https://doi.org/10.1056/NEJMoa2306185.
88. Cumpian NA, Choi G, Saab S. Review of current and upcoming second-line treatments for primary biliary cholangitis. Dig Dis Sci. 2024 Dec 2. https://doi.org/10.1007/s10620-024-08742-w
89. Giannini EG, Pasta A, Calabrese F, Labanca S, Marenco S, Pieri G, et al. Second-line treatment for patients with primary biliary cholangitis: a systematic review with network meta-analysis. Liver Int. 2025;45(1):e16222. https://doi.org/10.1111/liv.16222.
90. Blair HA. Elafibranor: first approval. Drugs. 2024;84(9):1143–8. https://doi.org/10.1007/s40265-024-02075-8.
91. European Medicines Agency. Iqirvo® Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/iqirvo-epar-product-information_en.pdf. Accessed 3 January 2025.
92. El Karoui K, Fervenza FC, De Vriese AS. Treatment of IgA nephropathy: a rapidly evolving field. J Am Soc Nephrol. 2024;35(1):103–16. https://doi.org/10.1681/ASN.0000000000000242.
93. European Medicines Agency. Filspari® Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/filspari-epar-product-information_en.pdf. Accessed 3 January 2025.
94. Syed YY. Sparsentan: first approval. Drugs. 2023;83(6):563–8. https://doi.org/10.1007/s40265-023-01864-x.
95. Trachtman H, Komers R, Inrig J. Sparsentan: the first and only non-immunosuppressive therapy for the reduction of proteinuria in IgA nephropathy. Expert Rev Clin Immunol. 2024;20(6):571–6. https://doi.org/10.1080/1744666X.2024.2319132.
96. Nagasawa H, Suzuki H, Ueda S, Suzuki Y. Dual blockade of endothelin A and angiotensin II type 1 receptors with sparsentan as a novel treatment strategy to alleviate IgA nephropathy. Expert Opin Investig Drugs. 2024;33(11):1143–52. https://doi.org/10.1080/13543784.2024.2414902.
97. Chiu AW, Bredenkamp N. Sparsentan: a first-in-class dual endothelin and angiotensin II receptor antagonist. Ann Pharmacother. 2024;58(6):645–56. https://doi.org/10.1177/10600280231198925.

98. Bissonnette R, Warren RB, Pinter A, Agner T, Gooderham M, Schuttelaar MLA, et al. Efficacy and safety of delgocitinib cream in adults with moderate to severe chronic hand eczema (DELTA 1 and DELTA 2): results from multicentre, randomised, controlled, double-blind, phase 3 trials. Lancet. 2024;404(10451):461–73. https://doi.org/10.1016/S0140-6736(24)01027-4.
99. Saeki H, Kanda N. Treatment of chronic hand eczema with topical anti-inflammatory drugs other than topical corticosteroids. Med. 2024;5(10):1203–5. https://doi.org/10.1016/j.medj.2024.08.009.
100. Fardos MI, Singh R, Perche PO, Kelly KA, Feldman SR. Evaluating topical JAK inhibitors as a treatment option for atopic dermatitis. Expert Rev Clin Immunol. 2022;18(3):221–31. https://doi.org/10.1080/1744666X.2022.1993061.
101. European Medicines Agency. Anzupgo® Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/anzupgo-epar-product-information_en.pdf. Accessed 3 January 2025.
102. Dhillon S. Delgocitinib: first approval. Drugs. 2020;80(6):609–15. https://doi.org/10.1007/s40265-020-01291-2.
103. France NL, Syed YY. Tirzepatide: a review in type 2 diabetes. Drugs. 2024;84(2):227–38. https://doi.org/10.1007/s40265-023-01992-4.
104. European Medicines Agency. Mounjaro® Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/mounjaro-epar-product-information_en.pdf. Accessed 3 January 2025.
105. Anderson SL, Marrs JC. Tirzepatide for type 2 diabetes. Drugs Context. 2023;12:2023-6-1. https://doi.org/10.7573/dic.2023-6-1
106. Sinha R, Papamargaritis D, Sargeant JA, Davies MJ. Efficacy and safety of tirzepatide in type 2 diabetes and obesity management. J Obes Metab Syndr. 2023;32(1):25–45. https://doi.org/10.7570/jomes22067.
107. Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. N Engl J Med. 2021;385(6):503–15. https://doi.org/10.1056/NEJMoa2107519.
108. Rodriguez PJ, Goodwin Cartwright BM, Gratzl S, Brar R, Baker C, Gluckman TJ, Stucky NL. Semaglutide vs tirzepatide for weight loss in adults with overweight or obesity. JAMA Intern Med. 2024;184(9):1056–64. https://doi.org/10.1001/jamainternmed.2024.2525.
109. Chang M, Cai Y, Gao Z, Chen X, Liu B, Zhang C, et al. Duchenne muscular dystrophy: pathogenesis and promising therapies. J Neurol. 2023;270(8):3733–49. https://doi.org/10.1007/s00415-023-11796-x.
110. Grounds MD, Lloyd EM. Considering the promise of vamorolone for treating Duchenne muscular dystrophy. J Neuromuscul Dis. 2023;10(6):1013–30. https://doi.org/10.3233/JND-230161.
111. Keam SJ. Vamorolone: first approval. Drugs. 2024;84(1):111–7. https://doi.org/10.1007/s40265-023-01986-2.
112. European Medicines Agency. Agamree® Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/agamree-epar-product-information_en.pdf. Accessed 25 January 2025.
113. Ibrahim MS, Abdelwahab OA, Elawfi B, Ali FY, Amro S, Mohammed SF, et al. Meta-analysis of the efficacy and safety of vamorolone in Duchenne muscular dystrophy. Neurol Sci. 2024. https://doi.org/10.1007/s10072-024-07939-1.
114. Guglieri M, Clemens PR, Perlman SJ, Smith EC, Horrocks I, Finkel RS, et al. Efficacy and safety of vamorolone vs placebo and prednisone among boys with Duchenne muscular dystrophy: a randomized clinical trial. JAMA Neurol. 2022;79(10):1005–14. https://doi.org/10.1001/jamaneurol.2022.2480.
115. Dang UJ, Damsker JM, Guglieri M, Clemens PR, Perlman SJ, Smith EC, et al. Efficacy and safety of vamorolone over 48 weeks in boys with Duchenne muscular dystrophy: a randomized controlled trial. Neurology. 2024;102(5):e208112. https://doi.org/10.1212/WNL.0000000000208112.
116. Gensthaler BM, Gräfe KA, Rößler A, Siebenand S. Drei neulinge im Oktober [Three newly introduced drugs in October]. Pharm Ztg. 2023;168(44):3014–21.
117. Gemeinsamer Bundesausschuss. The benefit assessment of medicinal products in accordance with the German Social Code, Book Five. https://www.g-ba.de/english/benefitassessment/. Accessed 2 March 2025.
118. Gemeinsamer Bundesausschuss. Tirzepatid und Ritlecitinib als Lifestyle-Arzneimittel gelistet [Listing tirzepatide and ritlecitinb as life-style drugs]. https://www.g-ba.de/service/fachnews/150/. Accessed 17 January 2025.
119. Wang L. Designing a dual GLP-1R/GIPR agonist from tirzepatide: comparing residues between tirzepatide, GLP-1, and GIP. Drug Des Devel Ther. 2022;16:1547–59. https://doi.org/10.2147/DDDT.S358989.
120. Morphy R, Rankovic Z. Designed multiple ligands. An emerging drug discovery paradigm. J Med Chem. 2005;48(21):6523–43. https://doi.org/10.1021/jm058225d.
121. Murugesan N, Tellew JE, Gu Z, Kunst BL, Fadnis L, Cornelius LA, et al. Discovery of N-isoxazolyl biphenylsulfonamides as potent dual angiotensin II and endothelin A receptor antagonists. J Med Chem. 2002;45(18):3829–35. https://doi.org/10.1021/jm020138n.