The nuclear export protein XPO1 — from biology to targeted therapy

Asfar S. Azmi, Mohammed H. Uddin and Ramzi M. Mohammad✉

Abstract | Exportin 1 (XPO1), also known as chromosome region maintenance protein 1, plays a crucial role in maintaining cellular homeostasis via the regulated export of a range of cargoes, including proteins and several classes of RNAs, from the nucleus to the cytoplasm. Dysregulation of this protein plays a pivotal role in the development of various solid and haematological malignancies. Furthermore, XPO1 is associated with resistance to several standard-of-care therapies, including chemotherapies and targeted therapies, making it an attractive target of novel cancer therapies. Over the years, a number of selective inhibitors of nuclear export have been developed. However, only selinexor has been clinically validated. The novel mechanism of action of XPO1 inhibitors implies a different toxicity profile to that of other agents and has proved challenging in certain settings. Nonetheless, data from clinical trials have led to the approval of the XPO1 inhibitor selinexor (plus dexamethasone) as a fifth-line therapy for patients with multiple myeloma and as a monotherapy for patients with relapsed and/or refractory diffuse large B cell lymphoma. In this Review, we summarize the progress and challenges in the development of nuclear export inhibitors and discuss the potential of emerging combination therapies and biomarkers of response.

Progressive evolution has created highly complex eukaryotes with a number of subcellular compartments that perform specific functions[1,2]. Eukaryotic cells protect their chromosomes by limiting the access of different signalling proteins and transcription factors largely via the nuclear envelope. The nuclear pore complex (NPC), which has a multisubunit structure, is embedded in the nuclear envelope[3] and is capable of translocating hundreds of macromolecules per minute in both directions[4]. Smaller molecules (<40 kDa) can enter and exit the nucleus through the NPC by simple diffusion; however, larger proteins, RNAs and other biological moieties require energy-dependent active transport mediated by specialized carriers[5], with the help of the GTPase Ran (Ras-related nuclear protein, also known as RanGTP)[6]. A substantial majority of proteins with the specialized function of nuclear transport are members of the karyopherin family. Importins and exportins are two major subfamilies of karyopherin. Thus far, more than ten distinct importins and seven distinct exportins have been identified[7,8]. Four of these importins and one exportin (XPO1) function through the recognition of specific signals, comprising positively charged nuclear localization signals (NLSs) and a leucine-rich hydrophobic nuclear export signal (NES), respectively (Supplementary information)[3,7]. Among exportins, only XPO1 is responsible for the transportation of NES-containing nuclear proteins such as p53, RB1 and p27[5] (FIG. 1). XPO1 is overexpressed in patients with cancer, including in those with pancreatic, gastric, prostate and colorectal cancers, and such overexpression is associated with disease progression, treatment resistance, and inferior overall survival (OS) or progression-free survival (PFS)[9–12]. These observations indicate that XPO1 holds considerable value as a therapeutic target in patients with cancer (Supplementary Fig. 1). In this Review, we provide an overview of the mechanisms of nuclear export and how these relate to the clinical experience with XPO1 inhibitors in patients with cancer.

Nuclear import and export

Over the past few decades, research has generated a substantial body of information on the mechanisms of nuclear transport. Besides recognition of transport receptors and signals (NLS/NES), the characterization of the Ran energy gradient system (FIG. 2) has greatly improved our understanding of how signalling proteins are transported between the nucleus and the cytoplasm (termed nucleocytoplasmic shuttling). The NLS/NES signal of the transported protein binds to a specific karyopherin, which then binds to the NPC, a cylindrical ~125,000 kDa protein complex that consists of 500–1,000 molecules comprising 30 different types nucleoporins (Nups)[13–15]. At the end of the translocation

Karmanos Cancer Institute, Department of Oncology, Wayne State University School of Medicine, Detroit, MI, USA.

✉*e-mail: mohammad@karmanos.org*

https://doi.org/10.1038/s41571-020-00442-4

Key points

- The nuclear export protein exportin 1 (XPO1) is crucial for the maintenance of cellular homeostasis as it mediates the transport of >200 proteins, many of which are tumour suppressors, from the nucleus to the cytoplasm, making XPO1 a promising target for cancer therapy.
- Early XPO1 inhibitors achieved limited success owing to toxicities, although more selective inhibitors of XPO1 have been developed, with promising results. This advance has led to the FDA approval of selinexor as a fifth-line therapy for multiple myeloma and as a third-line therapy for diffuse large B cell lymphoma.
- Early signs of therapeutic activity of selinexor have been demonstrated in patients with lymphoma, glioblastoma and other solid tumours in which conventional therapies have been unsuccessful.
- No predictive biomarkers of a response to selinexor have been recognized thus far, which obstructs the further development of this agent and its related compounds.
- Clinical and preclinical investigations are assessing combinations of selinexor with standard-of-care therapies, including other targeted agents, in an attempt to overcome acquired resistance and to improve the therapeutic outcomes.

process, the karyopherin–cargo complex is dissociated in a Ran-dependent manner[16].

A total of seven exportins mediate the export of nuclear biomolecules (Supplementary information), of which XPO1 is the most widely characterized[17]. XPO1 belongs to the importin-β superfamily of karyopherins[18–20] and can export at least 221 NES-containing proteins plus a subset of nuclear RNAs into the cytoplasm[21,22]. The conserved hydrophobic NES present on the cargo molecules are recognized by XPO1[4,22,23] (Supplementary Fig. 2). Proteins containing a NES (such as cap-binding proteins 20 and 80) are capable of mediating XPO1-mediated export of mRNAs and small-nuclear RNA[24], although this process might also require other adapter proteins[23]. Once translocated, XPO1 facilitates the cytoplasmic localization of regulatory proteins, including the tumour suppressors p53, CDK1, adenomatous polyposis coli (APC), BRCA1 and BRCA2, survivin, nucleophosmin and members of the forkhead box family of transcription factors (FIG. 3)[25,26].

XPO1 as a therapeutic target

Nuclear import and export are strictly controlled by karyopherins, thus highlighting the importance of these proteins as therapeutic targets in various diseases, including cancer. Cancer cells are postulated to be more vulnerable to the inhibition of nuclear transport compared to their non-malignant counterparts owing largely to their higher rates of cellular proliferation and metabolism[27,28]. Hence, the inhibition of nuclear transport, alone or together with standard-of-care therapies, might be a promising approach for the treatment of patients with advanced-stage malignancies[29]. Despite the widespread use of nuclear import inhibitors, such as importazole, INI-43 and ivermectin, in the determination and targeting of nuclear cargo proteins in preclinical research, none of these agents has been introduced in clinical trials. The development of specific inhibitors of importins is challenging, and many attempts are still in their infancy[29]. By contrast, the development of exportin inhibitors has evolved at a rapid pace. The inhibition of nuclear export was originally investigated preclinically using antibiotics such as leptomycin B[30], anguinomycins[29,31] and ratjadones[32]. However, these agents were gradually superseded by small-molecule exportin inhibitors such as promiscuous natural agents, including goniothalamin, valtrate or curcumin[33–35], or agents of synthetic origin such as the selective XPO1 inhibitors selinexor, eltanexor, verdinexor and felezonexor[36–39]. A comprehensive summary of the pharmacology of nuclear export inhibitors has been provided elsewhere[29,40].

The first specific XPO1 inhibitor, leptomycin B, was discovered in the 1990s by Nishi et al.[30]. This antibiotic binds covalently to the cysteine 528 residue (Cys528) of XPO1 and is an irreversible inhibitor of the interactions between XPO1 and NES. Owing to its strong specificity for XPO1, leptomycin B was tested in phase I trials involving patients with treatment-refractory cancers; however, these trials were discontinued owing to the emergence of serious systemic toxicities, including nausea and vomiting, profound anorexia and malaise, even at low doses[41]. These toxicities were attributed to the presence of a long polyketide chain with an α,β-unsaturated lactone ring that binds to the Cys528 residue of the NES-binding domain of XPO1. During this interaction, three basic residues of XPO1 are able to mediate the hydrolysis of the lactone ring of leptomycin B, which prevents the de-conjugation of leptomycin B from Cys528 of XPO1, thus irreversibly blocking nuclear export both in malignant and non-malignant cells and resulting in severe toxicities[42]. Consequently, a number of leptomycin B analogues were developed, including leptomycin A, anguinomycin A/B/C/D and ratjadones A/C, although these have all thus far shown only limited therapeutic potential[29,43,44]. Felezonexor has been shown to inhibit nuclear export by covalently binding to Cys528 as well as by inducing the degradation of XPO1. The degradation of XPO1 is conferred by neddylation (a form of post-translational modification involving covalent labelling with the ubiquitin-like protein NEDD8) mediated by the cullin-RING ligase. Unlike leptomycin B, felezonexor is a reversible inhibitor of XPO1, and therefore fewer adverse events are anticipated. A phase I dose-escalation study involving this agent is currently ongoing (NCT02667873) and is expected to be completed in 2021 (REFS[29,45]).

After the early failures with leptomycin B and related compounds, researchers used consensus-induced fit docking (cIFD) structure-based drug development approaches to minimize the number of interaction points in the XPO1 binding pocket[46]. This strategy paved the way for the development of a newer class of small-molecule XPO1 inhibitors, known as selective inhibitor of nuclear export (SINE) compounds[47–49], including KPT-185, KPT-251, KPT-276, selinexor, eltanexor and verdinexor, all of which are orally bioavailable, highly selective XPO1 inhibitors[47,50–53]. Similar to leptomycin B, these inhibitors covalently interact with Cys528 in the NES-binding pocket of XPO1. However, hydrolysable enone groups of SINE compounds bind to regions located far from the basic residues of XPO1, making these agents slowly reversible inhibitors, which contributes to their better tolerance in vivo[42] (Supplementary Table 1). For example, 40–60%

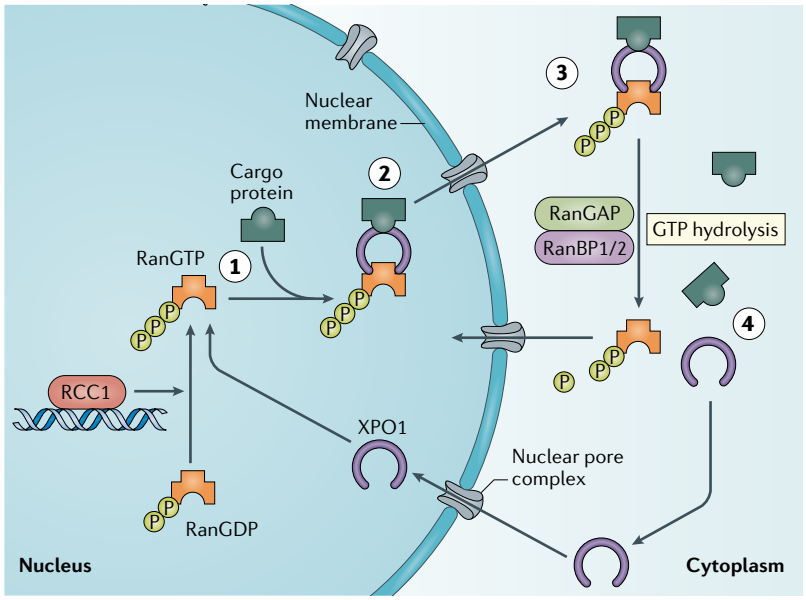

Fig. 1 | **Schematic representation of XPO1-mediated nuclear export.** In the nucleus, regulator of chromosome condensation 1 (RCC1; also known as Ran guanine exchange factor (RanGEF)) interacts with chromatin and the nucleotide exchange activity of this protein leads to increased levels of RanGTP, via conversion of RanGDP into RanGTP[15]. In the process of nuclear export: RanGTP binds to exportin 1 (XPO1) causing the opening of the nuclear export signal (NES) binding site through conformational changes (1). The leucine-rich NES domain of the cargo protein binds within the hydrophobic groove of XPO1, which contains the NES binding site. RanGTP and the cargo protein then bind to XPO1, thus forming a stable ternary complex, resulting in activation and subsequent conformational alterations (detailed in Supplementary Fig. 2). The activated complex then binds to a nucleoporin complex located at the nuclear pore complex[15] followed by export into the cytoplasm (2). Once outside the nucleus, the GTPase-activating protein RanGAP, in combination with co-stimulatory elements such as E3 SUMO-protein ligases 1/2 (also known as Ran-binding protein 1/2 (RanBP1/2))[15], interacts with the XPO1–cargo–RanGTP complex, causing structural alterations and the removal of RanGTP (3). RanGTP-unbound XPO1 then returns to its original autoinhibitory position followed by release of the cargo[169]. In the cytoplasm, RanGAP and RanBP1/2 are able to hydrolyse RanGTP into RanGDP[17], subsequently maintaining a high cytoplasmic concentration of RanGDP. Upon cargo release, XPO1 then shuttles back into the nucleus (4)[170].

of the inhibition and conjugation activity of KPT-185 is reversed after 24 hours[42]. Thus, SINE compounds bind to XPO1 for a sufficient length of time to induce cancer cell death while also permitting a level of nuclear export that enables the continued function or at least survival of non-malignant cells[54]. This approach, using selinexor, has received FDA approval for two malignancies — multiple myeloma (MM) and, more recently, diffuse large B-cell lymphoma (DLBCL) — based on data from several clinical trials[52,53] (TABLE 1).

Role of XPO1 in drug resistance

Drug resistance is a persistent problem in patients with cancer and is arguably the foremost obstacle to cure. In most patients, an initial response to one or more chemotherapies and/or targeted therapies typically fails within months to years owing to the development of resistance via several diverse mechanisms[55]. A number of mechanisms have been identified that are either partially or completely responsible for drug resistance. Findings from the past decade have demonstrated that XPO1 plays a key role in the development of anticancer drug resistance (FIG. 4). Research involving breast cancer cell lines demonstrates that XPO1 is intricately linked with the export of several drug targets, tumour suppressors and proteins with roles in cell-cycle regulation. For example, disproportionate XPO1-mediated export of BRCA1 has been shown to inhibit therapy induced apoptosis in these cells[56]. XPO1 has also been shown to export tumour suppressor proteins, such as APC and p53 in colon cancer and in other cancer types, and the oncogenic fusion protein BCR–ABL1 in chronic myelogenous leukaemia cells[57–60]. Thus, XPO1 inhibition is a mechanistically unique strategy that has the potential to overcome several forms of anticancer drug resistance, especially following the development of SINE compounds that have been evaluated in several clinical trials and lack the tolerability issues associated with leptomycin B and related compounds[61–64]. A more-specific approach, involving the use of antibodies designed to inhibit the interactions between NES and potential cargo proteins, also seems promising, although only limited investigations have been performed in this area thus far[60]. However, resistance can also develop against SINE compounds. Current evidence suggests that, in ovarian cancer, SINE resistance involves neuregulin 1 (NRG1) and HER3 (REF.[65]) and that resistance to these compounds might be cancer-type specific.

Protein mislocalization

Aberrant nuclear or cytoplasmic localization of specific proteins can affect tumour invasiveness, the propensity to form metastases, disease recurrence and therapy resistance, all of which can influence patient outcomes[66–71]. For example, the cytoplasmic localization of BRCA1 is independently associated with disease recurrence or lung metastasis in patients with sporadic low-grade, basal-like breast cancer who are >40 years of age and is associated with both survival duration and tumour grade[70,72]. Thus, patients with elevated cytosolic BRCA1 levels might have an increased risk of developing metastatic disease. Similarly, nuclear localization of HER2 has been demonstrated as a mechanism of trastuzumab resistance in breast cancer[73], and nuclear localization of the Hippo pathway effector protein Yes-associated protein (YAP) is implicated in the recurrence of cholangiocarcinoma[74]. Likewise, an abnormal source of nuclear glycogen synthase kinase 3b (GSK3b) has been shown to drive the growth of acute myeloid leukaemia (AML) cells as well as resistance to chemotherapy, in part owing to increased nuclear localization of the NF-κB subunit p65 (REF.[75]).

The mislocalization of tumour suppressor proteins might have tumour-promoting effects and is crucial for a response to certain therapies. For example, the cytoplasmic retention of cyclin-dependent kinase inhibitor 1B (CDKN1B, also known as $p27^{KIP1}$), which is usually located in the nucleus, is associated with tumorigenicity in various cancers. In a mechanistic study, mutant CDKN1B with loss of NLS function was found to accumulate in the cytosol, resulting in greater cancer cell motility, survival and tumorigenicity in MCF7 breast cancer cells owing to the downregulation of RhoA and activation of the AKT signalling pathway[71]. Similarly, the

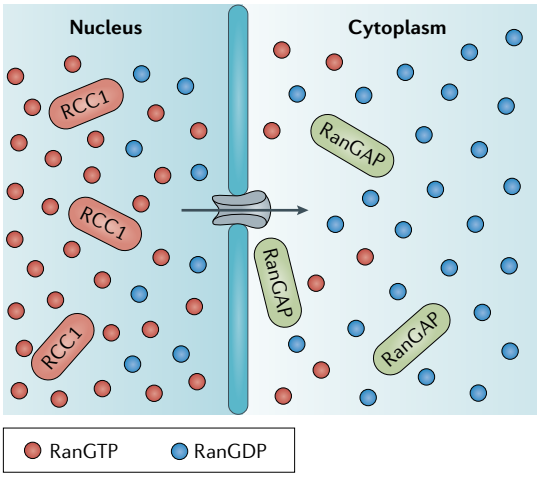

Fig. 2 | **Gradient of RanGTP across the nuclear membrane.** The GTP-binding nuclear protein Ran is a small G protein with an important role in determining the 3D conformation of exportin 1 (XPO1). Ran regulators (such as RanGAP) located in different subcellular compartments maintain a RanGTP–RanGDP gradient. Such a gradient is essential for the proper maintenance of the balance between the import and export of biomolecules, enabling the positioning of mitotic spindles and assembly of the nuclear envelope, among other processes[171]. The nucleus is enriched with RanGTP largely owing to the presence of regulator of chromosome condensation 1 (RCC1), which converts RanGDP to RanGTP by catalysing nucleotide exchange, whereas, in the cytoplasm, RanGAP converts RanGTP to RanGDP by promoting dephosphorylation of the bound GTP, resulting in the accumulation of RanGDP.

cytoplasmic expression of maspin (a tumour suppressor) is associated with an unfavourable prognosis in patients with soft-tissue sarcomas[68] and ovarian carcinoma[76] as well as with disease recurrence and metastasis in those with squamous cell carcinoma of the larynx[77,78].

p63, a member of the p53 family of tumour-suppressive transcription factors, is usually located in the nucleus, which is essential for the tumour-suppressive role of this protein. Aberrant cytoplasmic expression of p63 is associated with increased mortality in men with prostate cancer in both univariable and multivariable analyses[67]. p63 is strongly expressed in the nuclei of basal non-malignant prostate cancer cells, whereas cytoplasmic localization predominates following neoplastic transformation[67]. Similarly, cytoplasmic p63 immunoreactivity was associated with shorter OS durations in a cohort of 92 patients with lung adenocarcinomas[79].

The cytoplasmic expression of survivin, a member of the inhibitor of apoptosis family, is also associated with a poor prognosis in patients with pancreatic cancer[66] and in those with other forms of cancer[80]. The nuclear expression of survivin is associated with a favourable prognosis in patients with gastric[81] or transitional-cell carcinoma[82]; conversely, the overexpression of nuclear survivin is associated with a poor prognosis in patients with mantle-cell lymphoma (MCL)[83] or oesophageal squamous cell carcinoma[84]. Further investigations of the importance of the location of survivin and other tumour-suppressor proteins, with larger sample sizes and longer follow-up durations, are needed and should be requisite. Nonetheless, the available data indicate the potential utility of subcellular localization of tumour suppressors or other key proteins as biomarkers of prognosis and/or treatment outcome.

Overcoming drug resistance

Drug resistance in many cancers involves chemical inactivation via drug metabolism, altered DNA repair, activation of drug-efflux systems, modification of the drug target and/or targets, and intracellular mislocalization of either drug targets, tumour suppressors or proteins associated with cellular proliferation, among many other mechanisms[85]. Excessive nuclear export can contribute to the development of both cancer and treatment resistance[60]. In this section, we discuss data from the various studies in which SINE compounds were found to overcome drug resistance.

Bortezomib resistance. The proteasome inhibitor bortezomib, in combination with lenalidomide and dexamethasone, is an FDA-approved first-line therapy for MM. Acquired resistance to bortezomib is a common occurrence in patients with this malignancy. In an attempt to decipher the mechanism of resistance in patients with MM, investigators used isobaric tag-based and label-free quantitative proteomic approaches and identified a total of 112 differentially expressed proteins, including substantially increased expression of XPO1. Bioinformatics analyses revealed a strong cluster of differentially expressed proteins associated with XPO1, including structural maintenance of chromosomes 1A (SMC1A), regulator of chromosome condensation 2 (RCC2), chromosome segregation 1 (CSE1), nucleoporin 88 (NUP88), nucleoporin 50 (NUP50), translocated promoter region (TPR), heat shock protein family A member 14 (HSPA14), dynein light chain LC8-type 1 (DYNLL1), RAD21 cohesin complex component (RAD21) and Ran binding protein 2 (RanBP2)[86]. Further in vitro investigations of protein function confirmed the role of XPO1 overexpression in the emergence of bortezomib resistance[86]. SMC1A overexpression is associated with radioresistance in men with prostate cancer and can promote the emergence of a stemness phenotype[87]. The overexpression of RCC2 has been shown to block apoptosis and enhance drug resistance in cervical, breast and lung cancer cells in vitro[88]. The nucleoporin NUP88 recruits cytoplasmic XPO1 to the NPC and supports the recycling of XPO1 to the nucleus for the next round of export[89]. The depletion of TPR can negatively regulate XPO1-mediated nuclear export and can cause nuclear accumulation of p53, suggesting enhanced export of TSP or of other proteins when TPR is overexpressed[90]. Therefore, the inhibition of XPO1 is highly likely to affect the function of such proteins and might play a role in increasing drug sensitivity.

Hypoxia has been shown to promote tumour development and resistance to anticancer drugs, including resistance to bortezomib in MM. The inhibition of XPO1 with selinexor has been demonstrated to reduce cell survival, promote apoptosis and re-sensitize MM cells to bortezomib both in normoxic and hypoxic conditions

in experimental models[91]. Investigators in this study observed a delay in tumour development and progression as well as prolonged survival in mouse xenograft models of MM exposed to selinexor plus bortezomib compared with bortezomib alone, and to a lesser extent in mice that were exposed to selinexor alone relative to controls[91].

Anthracycline resistance. For several decades, head and neck squamous cell carcinoma (HNSCC) mortality has remained stable at ~40%[92,93], which can, at least in part, be attributed to the development of drug resistance[92,94]. Patients with HNSCC are mostly diagnosed with locoregionally advanced disease, and >50% have disease recurrence within 3 years following chemoradiotherapy and/or surgery[95]. Data published in 2018 indicate that >80% of patients with HNSCCs have cytoplasmic mislocalization of the transcription factor E2F7, which enables the transcription of proteins that confer resistance to anthracyclines[92]. These investigators confirmed that E2F7 is subject to XPO1-mediated nuclear export and demonstrated that mislocalization of E2F7 causes de-repression of sphingosine kinase 1 (*SPHK1*), leading to anthracycline resistance. Partial reversal of anthracycline resistance was demonstrated in HNSCC xenograft models exposed to selinexor plus doxorubicin[92].

MM is generally recognized as an incurable malignancy despite the availability of multiple advanced therapies, including proteasome inhibitors, immunomodulatory agents, histone deacetylase inhibitors and anti-CD38 antibodies[96]. Data from several studies[96,97] indicate that selinexor is able to overcome acquired resistance to doxorubicin in vitro, in mouse xenograft models and in biopsy material obtained from patients. In one study, the combination of selinexor plus liposomal doxorubicin inhibited the binding of topoisomerase 2A

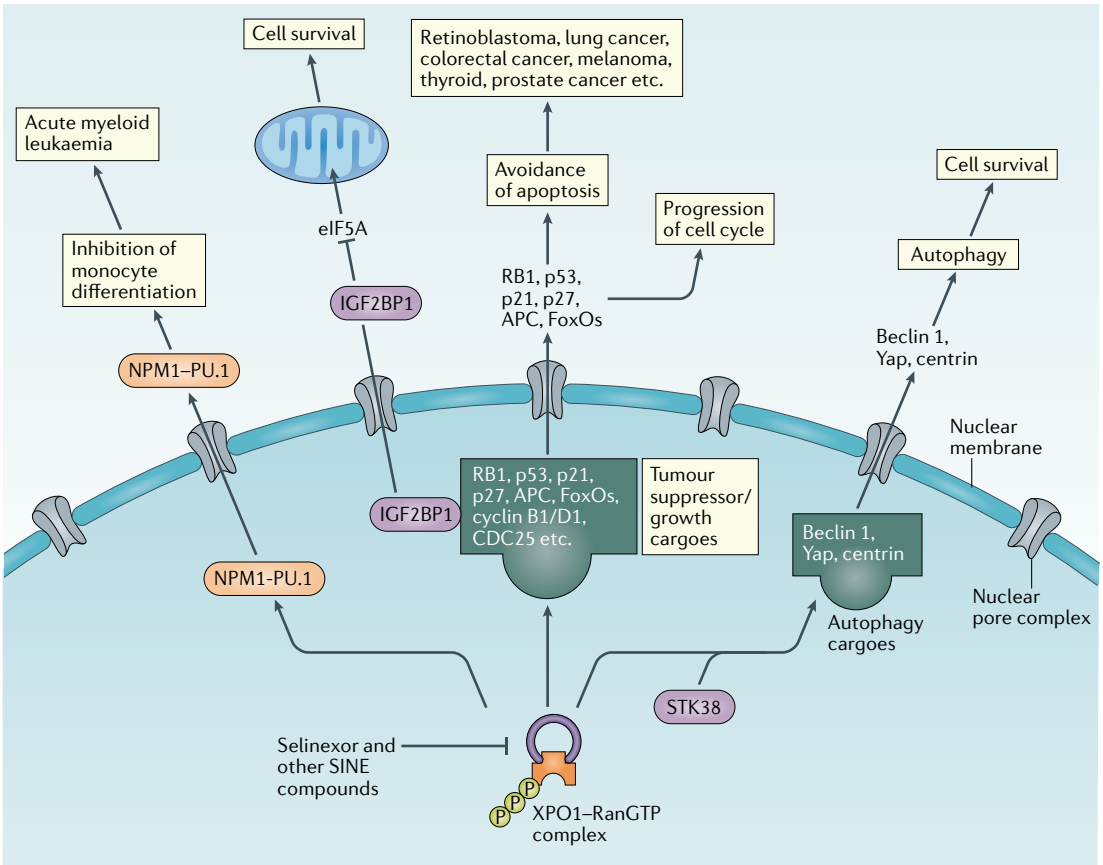

Fig. 3 | **XPO1 mediated nuclear export and mechanisms of oncogenesis.** The main physiological function of exportin 1 (XPO1) is the export of proteins and small nuclear RNAs from the nucleus to the cytoplasm. XPO1 overexpression leads to greater levels of export of several important cargoes. These cargoes include a number of proteins that are crucial for physiological cellular processes, including tumour-suppressor proteins (such as RB1, p53, adenomatous polyposis coli (APC), forkhead box proteins and others), growth regulators (such as p21, cyclin B1 or D1 and Ras-specific guanine nucleotide-releasing factor 1), anti-apoptotic proteins (such as nucleophosmin) and proteins involved in autophagy (such as beclin 1 and yes-associated protein 1 (YAP1))[23,24,40,203]. Tumour-suppressor proteins, such as RB1, p53, APC and others, induce oncogenesis by enabling the avoidance of apoptosis. In this scenario, the cell-cycle checkpoints typically remain active owing to the export of p21, p27 and other proteins. Insulin-like growth factor 2 mRNA-binding protein 1 export inhibits the mitochondrial accumulation of eIF5A and promotes cell survival[172]. XPO1-mediated export of the autophagy-related proteins beclin 1, YAP1 and centrin is aided by phosphorylated STK38, resulting in the promotion of cellular survival[203]. Nuclear export of nucleophosmin (NPM1) along with the interacting transcription factor PU.1 (NPM1–PU.1) inhibits monocyte differentiation, potentially resulting in the development of acute myeloid leukaemia[204]. SINE, selective inhibitor of nuclear export.

Table 1 | **Selected completed clinical trials involving selinexor in patients with haematological malignancies**

Study	Patient characteristics	Treatments	Outcomes	Treatment-related adverse events	Ref.
Multiple myeloma					
NCT01607892 Phase I	81 patients with R/R MM (median 6 prior lines of therapy)	Dose escalation: selinexor 3–60 mg/m^2; dose expansion: selinexor 45 mg/m^2 or 60 mg/m^2 plus 20 mg dexamethasone	ORR 4%, CBR 21% in patients receiving selinexor monotherapy; ORR 25%, CBR 33% in patients receiving selinexor plus dexamethasone	SAEs in 61% of patients receiving selinexor and in 39% receiving selinexor plus dexamethasone; 1 treatment-related death	140
NCT02199665 Phase I	21 patients with R/R MM (median 4 (2–10) prior lines of therapy)	Dose escalation: selinexor 30–60 mg/m^2 plus 20/27–20/36 mg/m^2 carfilzomib; dose expansion: selinexor 60 mg/m^2 plus carfilzomib 20/27 mg/m^2 plus 20 mg dexamethasone	ORR 38%, CBR 67% in patients after completion of cycle 1; median PFS 3.7 months; median OS 22.4 months	SAEs included upper-respiratory tract infections (14%), urinary tract infections (9%) and mastoid osteomyelitis (9%); treatment discontinued owing to toxicities in 2 patients	62
STORM I Phase II	79 patients with R/R MM (median 7 prior lines of therapy)	Selinexor 80 mg plus dexamethasone 20 mg twice weekly (6 doses) as part of a 28-day cycle; patients meeting laboratory criteria continued for up to 8 doses (no weeks off therapy)	ORR 21% (quad-refractory (21%), penta-refractory (20%)); median DOR 5 months; median PFS 2.3 months; median OS 9.3 months	19 patients had a total of 22 SAEs; common grade ≥3 adverse events included thrombocytopenia (59%), anaemia (28%), neutropenia (23%), hyponatraemia (22%), leukopenia (15%) and fatigue (15%); fatal intracranial bleeding in 1 patient	141
STORM II Phase II	122 patients with R/R MM (median 7 prior lines of therapy)	Selinexor 80 mg plus dexamethasone 20 mg twice weekly as part of a 28-day cycle	ORR 26%; median DOR 4.4 months; median PFS 3.7; median OS 8.8 months	SAEs in 63% of patients, including pneumonia (11%) and sepsis (9%); common grade ≥3 adverse events included thrombocytopenia (59%), anaemia (44%), hyponatraemia (22%) and neutropenia (21%); 2 treatment-related deaths reported	142
BOSTON Phase III	402 patients with R/R MM (1–3 prior lines of therapy)	Selinexor 100 mg once weekly plus 1.3 mg/m^2 bortezomib and 20 mg dexamethasone twice weekly (SVd) vs 1.3 mg/m^2 bortezomib and 20 mg dexamethasone twice weekly (Vd)	ORRs 76.4% vs 62.3%, $P=0.0012$; median PFS 13.9 vs 9.5 months, HR 0.70, $P=0.0066$; median OS not reached vs 25 months, $P=0.28$, in the SVd vs Vd groups, respectively	Common grade ≥3 adverse events included thrombocytopenia (35.9% vs 15.2%), fatigue (11.3% vs 0.5%) and nausea (7.7% vs 0%) in the SVd vs Vd groups, respectively	147
Diffuse large B cell lymphoma					
NCT01607892 Phase I	79 patients with R/R NHL, including 43 with R/R DLBCL (median 4 prior lines of therapy)	Dose escalation: 3–80 mg/m^2 selinexor; dose expansion: selinexor 35 mg/m^2 or 60 mg/m^2	ORR 31% (32% for DLBCL) and CBR 61% (51% for DLBCL) in patients receiving selinexor monotherapy	11 were potentially selinexor-related SAEs at doses between 30 and 70 mg/m^2; common grade ≥3 adverse events (in all patients) included thrombocytopenia (47%), neutropenia (32%) and anaemia (27%)	153
SADAL Phase II	127 patients with R/R DLBCL (2–5 prior lines of therapy)	Selinexor 60 mg twice weekly until disease progression	ORR 28% and DCR 37%, including CRs in 12% and PRs in 17%; median PFS 2.6 months; median OS 9.1 months; median DOR 23.0 months and 4.4 months for patients with CRs and PRs, respectively	48% of patients had SAEs including pyrexia (7.1%), pneumonia (4.7%), sepsis (4.7%), fatigue (3.9%), anaemia (3.1%), cardiac failure (3.1%), febrile neutropenia (3.1%); common grade 3–4 adverse events included thrombocytopenia (45.7%), neutropenia (24.4%) and anaemia (22.1%)	63
Acute myeloid leukaemia					
NCT01607892 Phase I	95 patients with R/R AML; ≥50% had received 3 or more prior therapies	Dose escalation: 3–70 mg/m^2 selinexor twice weekly as part of a 28-day cycle; dose expansion: selinexor 40 mg/m^2	ORR 14% and DCR 69%; median PFS 1.7 months; median OS 2.7 months; median PFS and OS 5.1 and 9.7 months among responders, respectively	15 SAEs were deemed possibly related to selinexor, of which 2 were fatal; grade 3–4 adverse events included thrombocytopenia (19%), anaemia (15%), fatigue (14%) and neutropenia (13%)	154

Table 1 (cont.) | **Selected completed clinical trials involving selinexor in patients with haematological malignancies**

Study	Patient characteristics	Treatments	Outcomes	Treatment-related adverse events	Ref.
Acute myeloid leukaemia (cont.)					
NCT02573363 Phase I	12 patients with newly diagnosed AML and 8 with R/R AML	Dose escalation: 60 mg (~35 mg/m^2) in 3 and 80 mg (~50 mg/m^2) in 17 patients; selinexor was administered with cytarabine (2–3 g/m^2) and mitoxantrone (20–30 mg/m^2)	ORR 70%, including CRs in 50%, projected 1-year survival 69%;recommended phase II dose 80 mg twice weekly	SAEs occurred in 30% of the patients, including 1 fatal event; common grade 3 adverse events included febrile neutropenia (70%), bacteraemia (25%) and pneumonia (20%)	61
NCT02530476 Phase Ib	14 patients with R/R AML harbouring *FLT3–ITD* or *FLT3–D835* mutations (median 3 prior lines of therapy)	Dose-escalation: sorafenib 400 mg twice daily plus selinexor 40 mg, 60 mg and 80 mg twice weekly	Incomplete CR in 29%; blast reduction (>50%) in 14%; 55% of patients with FLT3 inhibitor-refractory AML responded to treatment	NR	195
SELHEM Phase I	18 patients ≤24 years of age with R/R acute leukaemias (15 with AML)	Dose escalation: selinexor 30–70 mg/m^2 twice weekly as part of a 28-day cycle; fludarabine (30 mg/m^2) and cytarabine (2 g/m^2) were administered on days 15–19	47% of patients had a CR with or without blood count recovery	Common grade 3–4 adverse events included hyponatraemia (66.6%), hypokalaemia (55.6%) and febrile neutropenia (55.6%); 2 patients had treatment-related reversible cerebellar toxicities at 70 mg/m^2 selinexor	157
NCT02093403 Phase I	20 patients >60 years of age with R/R AML plus 5 with newly diagnosed AML; 30% had received ≥3 prior lines of therapy	Dose escalation: selinexor 23–55 mg/m^2 plus decitabine 20 mg/m^2 dose expansion: selinexor 60 mg/m^2 plus decitabine 20 mg/m^2	ORR 40% including CRs in 20%, incomplete CR in 4% and MLFS in 8%	SAEs observed in 84% including 1 selinexor- associated death; common grade ≥3 toxicities included asymptomatic hyponatraemia (68%), febrile neutropenia (44%), sepsis (44%), hypophosphatemia (36%) and pneumonia (28%)	196

AML, acute myeloid leukaemia; CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; DLBCL, diffuse large B cell lymphoma; DOR, duration of response; HR, hazard ratio; MLFS, morphologic leukaemia-free state; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; R/R, relapsed and/or refractory; SAEs, serious adverse events; SD, stable disease.

to XPO1, thus preventing nuclear export and resulting in apoptosis in CD138-positive and light chain-positive multidrug-resistant MM cells, without affecting CD138-negative and light chain-negative non-malignant bone marrow cells[96]. This combination also increased the extent of DNA damage in parental and therapy-resistant MM cells. These studies revealed a level of synergy between selinexor and liposomal doxorubicin[96] and with doxorubicin, bortezomib or carfilzomib[97] that warrants further clinical evaluation in patients with MM.

Ibrutinib resistance. The Bruton tyrosine kinase (BTK) inhibitor ibrutinib, which inhibits B cell receptor (BCR) signalling, is an FDA-approved, second-line therapy for patients with MCL; nonetheless, disease relapse is nearly universal in patients receiving this agent. The cytoplasmic localization of proteins with a role in NF-κB signalling is associated with ibrutinib resistance, which is reversed by selinexor in cell-line models of MCL[98] and cells derived from patients with chronic lymphocytic leukaemia (CLL)[99]. In an immunocytochemical analysis of MCL cell lines, selinexor was shown to mediate nuclear retention of IκB as well as of the NF-κB subunits p65 and p50 and to negatively regulate NF-κB activity, suggesting that selinexor could have antitumour activity in MCL[98]. This study further confirmed that cells with IκB retained within the nucleus have a greater degree of apoptosis. These findings are consistent with those of other studies in which selinexor causes nuclear retention of IκB in sarcoma and MM cell lines as well as in primary MM tumour cells[100,101]. Despite these findings, more research is needed to validate the activity of NF-κB signalling inhibition as the predominant mechanism of the antitumour activity of selinexor in MCL[98].

Gefitinib resistance. Despite most patients with *EGFR*-mutant non-small-cell lung cancer initially having a response to gefitinib, virtually all develop acquired resistance, with a median duration of response of 10–14 months[102,103]. A putative mechanism of resistance to gefitinib in patients with *EGFR*-mutant non-small-cell lung cancer involves the elevated expression of the DEAD box RNA helicase DDX17. This helicase disassociates E-cadherin/β-catenin complexes, causing nuclear translocation of β-catenin[104]. Consequently, β-catenin enhances the transcription of several target genes associated with resistance to EGFR inhibitors, including axin and cyclin D1. Interestingly, two NLS and four NES sequences have been identified in DDX17 (REF.[104]). The presence of NLS and NES in DDX17 enables nucleocytoplasmic shuttling; however, this protein is usually retained within the nucleus[105]. This RNA helicase is exported to the cytoplasm via an XPO1-dependent nuclear export mechanism, where it promotes dissociation of the E-cadherin/β-catenin complex, resulting in increased nuclear localization of β-catenin. These investigators confirmed the involvement of the NLS and NES regions by incorporating mutations at several

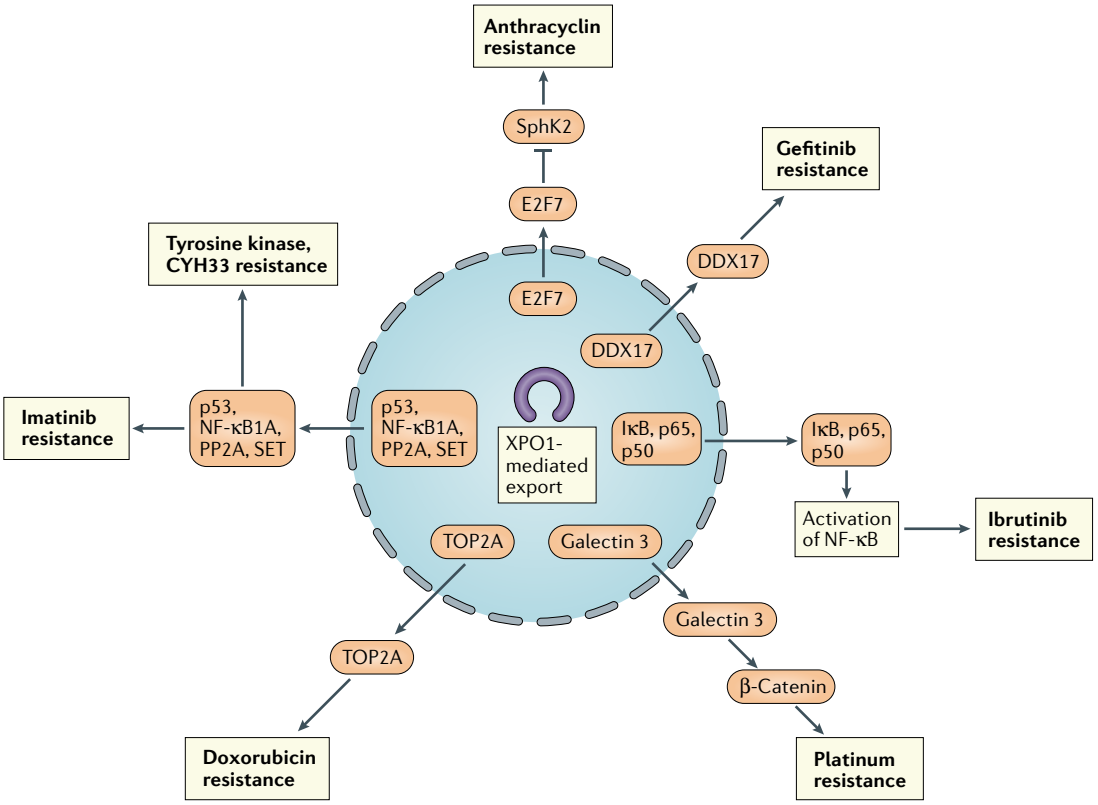

Fig. 4 | **The role of XPO1 in acquired drug resistance.** Excessive nuclear export is a factor in both the initiation and progression of cancer and is associated with resistance to chemotherapy. Enhanced exportin 1 (XPO1) activity results in the cytoplasmic retention of tumour-suppressor proteins (TSPs) such as p53. The mislocalization of such proteins leads to their functional inactivation and, consequently, to acquired therapy resistance. XPO1 overexpression can also promote export of the transcription elongation factor E2F7 in certain cancer types, such as head and neck squamous cell carcinoma, which can lead to anthracycline resistance owing to the inhibition of SphK2 in the cytoplasm[79]. Similarly, increased export of probable ATP-dependent RNA helicase DDX17 and topoisomerase 2α (TOP2A) can confer resistance to gefitinib or doxorubicin, respectively[83,89,90]. Nuclear export of important members of the NF-κB signalling pathway, such as inhibitors of NF-κB (IκB), p65 and p50, can activate this pathway and lead to the development of ibrutinib resistance[85]. Resistance to platinum compounds is also associated with nuclear export via XPO1. A mechanistic study showed that galectin 3 in the cytoplasm regulates β-catenin and induces resistance to platinum-based drugs. The export of nuclear galectin 3 to the cytoplasm enhances such regulation and subsequently promotes resistance to platinum-based compounds. [154,205,206]. Nuclear export of p53, protein phosphatase 2A (PP2A) and others are also associated with resistance to tyrosine-kinase inhibitors, especially to imatinib or the novel PI3K inhibitor CYH33 (REFS[88,89]).

locations in the NLS/NES sequences that interfere with importin and exportin binding. A reduction in gefitinib resistance was observed in both NLS/NES-mutated and *DDX17*-mutated PC9 cells compared with wild-type controls[104]. These results suggest that nuclear import and export could play a role in the regulation of sensitivity to gefitinib. Importin inhibitors are currently not clinically available; however, inhibition of the nuclear export of DDX17 and, potentially, of several other DEAD-box RNA helicases (DDX3, DDX25 and DDX48)[106] can be achieved using SINE compounds, providing an interesting avenue for the exploration of novel strategies designed to overcome gefitinib resistance. Although no data are currently available, this strategy could potentially also be applied to resistance to other EGFR TKIs.

Lenvatinib resistance. Lenvatinib, a TKI with multiple targets, is superior to placebo in patients with radioactive iodine (^{131}I)-refractory thyroid cancer (median PFS 18.3 versus 3.6 months). Despite most patients having an initial response (overall response rate (ORR) 64.8%), many become refractory to lenvatinib and have few effective treatment options following disease recurrence[107]. The inhibition of XPO1 with selinexor or eltanexor has been demonstrated to sensitize 8505C thyroid cancer cells (a lenvatinib-resistant cell line) to lenvatinib in vitro. Similar antitumour effects were observed with this combination in mouse xenograft models created using subcutaneous injections of this cell line. These results indicate an actionable therapeutic approach that has the potential to overcome lenvatinib resistance in patients with lenvatinib-refractory thyroid cancer[108].

Other TKIs. The development of acquired resistance to PI3Kα inhibitors limits the effectiveness of these agents in patients with *PIK3CA*-mutant hormone receptor-positive, HER2-negative metastatic breast cancer. Acquired resistance to the PI3Kα inhibitor alpelisib occurs owing to the loss of PTEN and activation of

mTOR, CDK4/6 or the kinase Pim1 (REFS[109–112]). Data from in vitro studies indicate that the inhibition of XPO1 can lead to nuclear localization of CCAAT-enhancer-binding protein-β, resulting in CDK4 degradation and cell-cycle arrest[113]. Another PI3Kα inhibitor, CyH33, has demonstrated a manageable safety profile, linear pharmacokinetics and some antitumour activity in a phase I clinical trial[114,115]; however, the effectiveness is likely to be limited by acquired resistance, albeit with different mechanisms to those of resistance to alpelisib[116]. CyH33 has been shown to maintain the activation of several oncogenic signalling pathways, including mTORC1, KRAS and E2F, independent of PI3K signalling in PI3K inhibitor-resistant MCF7R cells. Interestingly, the inhibition of XPO1 with selinexor overcomes such acquired resistance in CyH33-resistant breast cancer cell lines, principally by promoting the retention of p53 within the nucleus and leading to cell-cycle arrest[116].

Fusion of the genes encoding septin 9 and *ABL1* (*SEPT9–ABL1*) suppresses p53 expression, resulting in imatinib resistance in a small subset of several haematological malignancies, including chronic myeloid leukaemia (CML) and acute lymphocytic leukaemia. Data from several studies confirm that the combination of selinexor with imatinib effectively overcomes this resistance mechanism in mouse xenograft models[117,118]. This combination affects several key oncogenic signalling proteins, including nuclear retention of p53, NF-κB 1A (NF-κB1A), protein phosphatase 2A (PP2A) and the nuclear proto-oncogene SET[117].

Platinum resistance. Platinum-based chemotherapy remains in widespread clinical use. However, the development of platinum resistance is virtually inevitable and leads to disease recurrence in patients with several types of solid tumours. For example, women with platinum-resistant ovarian cancer typically have a median PFS duration of around 6 months and a median OS of approximately 16 months even with further treatment, following disease progression on platinum-based chemotherapy[119]. The increased expression of proteins with a role in DNA repair is one of the most important mechanisms of resistance to platinum-based chemotherapy[120]. SINE compounds can reduce the expression of many of these proteins in vitro, including CHEK1, MLH1, MSH2, RAD51 and PMS2 (REF.[121]). The underlying mechanism of this effect is currently unknown; however, binding of MYC to the *RAD51* and *CHEK1* promoters is substantially reduced by selinexor, and the effect might explain the reductions in the expression of proteins involved in DNA repair observed with selinexor[122]. *XPO1* overexpression is associated with platinum resistance and inferior outcomes in patients with ovarian cancer[123]. In this study, targeted inhibition of XPO1 with either selinexor or KPT-185 was shown to inhibit cellular proliferation and platinum resistance, both in platinum-resistant ovarian carcinoma cell lines and in mouse xenograft models. XPO1 inhibition was also found to induce the nuclear accumulation of ERK1/2, IκBα and p65 (NF-κB), thus resulting in the inhibition of NF-κB signalling and of tumour growth in these models. Clinically, among seven patients who received selinexor in this study, two of five evaluable patients had stable disease and one had a partial response; importantly, selinexor was well tolerated by all patients[123]. Common grade 1/2 adverse events included nausea (in all seven patients), fatigue (in six) and vomiting (in five). Grade 3 adverse events included thrombocytopenia, hyponatraemia and weight loss, all of which were observed in one patient only. No grade 4 adverse events were reported. These observations indicate that the inhibition of XPO1 is clinically feasible and might overcome platinum resistance. The β-galactosidase-binding protein galectin 3 has been linked with cisplatin resistance in BCR–ABL1-positive CML and acute lymphocytic leukaemia[124,125]. This protein regulates the β-catenin signalling pathway through GSK-3β phosphorylation[126] and is modulated by XPO1 (REF.[127]); accordingly, the inhibition of XPO1 can restore apoptotic cell death in cisplatin-resistant cells by retaining galectin 3 in the nucleus[60].

Gemcitabine resistance. Gemcitabine-based chemotherapy is a standard-of-care treatment for patients with pancreatic ductal adenocarcinoma (PDAC). Nevertheless, chemoresistance often limits the efficacy of this drug or regimen, and median OS outcomes typically remain at <1 year in cohorts of patients with metastatic disease[128–133]. Data from preclinical studies indicate that XPO1 inhibition might overcome gemcitabine resistance. The combination of selinexor plus gemcitabine has been shown to synergistically inhibit the growth of MIA PaCa-2 pancreatic and L3.6pl metastatic pancreatic cancer cell lines in vitro in both anchorage-dependent and anchorage-independent culture conditions[128]. Anchorage-independent growth is one of the defining characteristics of cancer stem cells (CSCs) and is associated with drug resistance[134]. PDACs have been shown to harbour such resistant CSC populations. Indeed, selinexor in combination with gemcitabine and nab-paclitaxel has been shown to disintegrate CSC spheroids in vitro and to inhibit tumour growth in patient-derived xenograft models[135]. Similar synergistic effects were achieved with selinexor plus gemcitabine in mouse orthotopic models of PDAC[128]. An analysis of the mechanisms of these effects confirms the well-recognized effects of selinexor, incldiung nuclear accumulation of $p27^{KIP1}$, depletion of the anti-apoptotic protein survivin, reduced accumulation of DNA repair proteins and the induction of apotosis[128]. In a phase Ib trial involving patients with metastatic PDAC, the combination of gemcitabine, nab-paclitaxel and selinexor led to stable disease in two of nine patients and to partial responses in a further two, one of which continued for 16 months[135]. Building on these findings, a phase II clinical trial is currently ongoing (NCT02178436).

XPO1 inhibitors in patients with cancer

Selinexor has shown promising antitumour activity in patients with heavily pre-treated haematological malignancies[52,53,100,136–139] (TABLE 1). Furthermore, the safety and efficacy of selinexor have been assessed in several clinical trials in a variety of settings, including early phase trials involving patients with advanced-stage

solid tumours (TABLE 2). A number of clinical trials with selinexor are currently ongoing (Supplementary Table 2).

Multiple myeloma

Standard-of-care therapeutic agents for patients with MM are categorized into three main classes, proteasome inhibitors (such as bortezomib and carfilzomib), immunomodulatory drugs (such as lenalidomide and pomalidomide) and CD38-targeting monoclonal antibodies (such as daratumumab). Almost all patients with MM will ultimately develop resistance to each of these agents. Thus, an urgent need exists for new MM therapeutics with a mechanism of action that is fundamentally different to that of the current

Table 2 | **Selected completed clinical trials involving selinexor in patients with solid tumours**

Study	Patient characteristics	Treatments	Outcomes	Treatment-related adverse events	Ref.
NCT01607905 Phase I	157 patients with advanced-stage solid tumours	Dose escalation: 3–85 mg/m^2 selinexor	PRs in 4% of patients, a further 17% had SD for ≥4 months; 1 patient had a CR; RP2D and MTD determined as 35 mg/m^2 and 65 mg/m^2 selinexor twice weekly, respectively	Most frequent grade 3–4 adverse events included thrombocytopenia (16%), fatigue (15%) and hyponatraemia (13%)	137
NCT01896505 Phase Ib	54 patients with advanced-stage refractory bone or soft-tissue sarcomas	Selinexor 30 mg/m^2 in 19 patients in cohort 1; or 50 mg/m^2 in 17 patients and 60 mg in 18 patients in cohort 2	ORR 0%; SD in 58% of patients (SD ≥4 months in 33%); food intake had no effect on most pharmacokinetic parameters	Drug-related SAEs reported in 9 patients; common grade ≥3 adverse events included fatigue (12.9%), anaemia (9.7%), lymphopenia (9.7%), leukopenia (9.7%) and thrombocytopenia (7.7%)	161
NCT02215161 Phase II	14 patients with metastatic CRPC refractory to abiraterone and/or enzalutamide	Selinexor 65 mg/m^2 or 60 mg twice weekly	64% of patients had a reduction in serum PSA levels; out of 8 patients with measurable disease, 2 had a PR and 4 had SD	SAEs were deemed unrelated to selinexor in 36%; grade 3–4 adverse events included anaemia (21.4%), nausea (14.3%) and vomiting (14.3%); this trial was terminated owing to an unacceptable risk to benefit ratio	197
NCT02402764 Phase II	10 patients with metastatic TNBC; (median 2 prior lines of chemotherapy)	Selinexor 60 mg twice weekly	No objective responses; CBR 30%; median PFS and OS 0.92 months and 6.0 months, respectively	One patient had possibly treatment-related encephalopathy; grade 3 adverse events included fatigue, platelet count reductions and dyspnoea (all in 1 patient); this trial was terminated owing to a failure to achieve the pre-planned response rate	198
SENTINEL trial Phase I	10 patients with metastatic CRC	Selinexor 20 mg or 40 mg plus mFOLFOX6	No clinical outcomes measured owing to limited treatment exposure	DLTs occurred in the first 4 patients receiving 40 mg selinexor, resulting in a reduction to the 20 mg dose; common adverse events included nausea (80%), diarrhoea (70%), vomiting (60%) and fatigue (60%)	199
NCT02025985 Phase II	114 patients with ovarian (66), endometrial (23) or cervical (25) cancer; (median of 6, 2 and 3 prior lines of therapy, respectively)	Selinexor at 35 or 50 mg/m^2 twice weekly or 50 mg/m^2 once weekly	DCR 30%, 35% and 24%, PRs in 8%, 9% and 4%, median PFS 2.6, 2.8 and 1.4 months, median OS 7.3, 7.0 and 5.0 months in patients with ovarian, endometrial and cervical cancers, respectively	20 treatment-associated SAEs, including nausea, vomiting or decreased appetite (7 events); hyponatraemia (2 events); anaemia, discomfort, blurred vision, cataract and cognitive disorder (all 1 event)	200
NCT02078349 Phase I	18 patients of Asian ethnicity with advanced-stage solid cancers	Dose escalation: 50 mg/m^2 selinexor once weekly, 40 mg/m^2 twice weekly and 20 mg/m^2 thrice weekly	Out of 13 evaluable patients, 2 had PRs, 8 had SD	No DLTs observed; however, the 40 mg/m^2 dosing schedule was discontinued owing to persistent grade ≥2 adverse events, including fatigue (50%), hyponatraemia (50%) and anorexia (17%)	201
NCT01986348 Phase II	76 patients with recurrent glioblastoma; (median of 2 prior lines of therapy)	Selinexor 50 mg/m^2 or 60 mg twice weekly, or 80 mg once weekly; patients eligible for surgery received up to 3 doses of selinexor before surgery	6-month PFS 9.7%, 11.4% and 15.1%, ORRs 8.3%, 7.1% and 10.0%, median OS 9.0, 8.4 and 9.5 months among patients in the 50 mg/m^2, 60 mg and 80 mg groups, respectively	Common adverse events included nausea (42–60%), leukopenia (7–43%), fatigue (43–71%), neutropenia (14–33%), decreased appetite (27–71%) and thrombocytopenia (23–67%)	202

CBR, clinical benefit rate; CR, complete responses; CRC, colorectal cancer; CRPC, castration-resistant prostate cancer; DCR, disease control rate; DLTs, dose-limiting toxicities; mFOLFOX6, 5-fluorouracil, leucovorin and oxaliplatin; MTD, maximum-tolerated dose; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial responses; PSA, prostate-specific antigen; RP2D, recommended phase II dose; SAEs, serious adverse events; SD, stable disease; TNBC, triple-negative breast cancer.

standard-of-care therapies. In this regard, targeting nuclear export with selinexor is considered a promising therapeutic approach. The safety and efficacy of selinexor monotherapy in patients with MM was initially evaluated in a phase I study[140]. As a single agent, efficacy was modest, with a 4% ORR and 21% clinical benefit rate. However, the administration of selinexor in combination with dexamethasone in a dose-expansion phase of this study greatly increased the ORR to 50%, with 46% of patients having a reduction in MM-related immunoglobulin levels. The most common grade 1–2 adverse events were non-haematological, including nausea (75%), fatigue (70%) and anorexia (64%), whereas grade 3–4 adverse events were predominantly haematological, including thrombocytopenia (45%)[140]. Data from the STORM trial confirmed the effectiveness of selinexor (80 mg) in combination with low-dose dexamethasone (20 mg). Among 79 eligible patients, 48 were deemed refractory to four previous treatments (including bortezomib, carfilzomib, lenalidomide and pomalidomide), and 31 were also refractory to anti-CD38 antibodies (such as daratumumab). The median PFS and OS durations were 2.3 and 9.3 months, respectively, and the ORR was 21%. Interestingly, the ORR among a subset of 17 patients with cytogenetically high-risk disease, including t(4;14), t(14;16) and del(17p), was 35%. The most frequent grade ≥3 adverse events included thrombocytopenia (59%), anaemia (28%), neutropenia (23%), hyponatraemia (22%), leukopenia (15%) and fatigue (15%)[141]. The second part of the STORM trial, which included 123 patients who received a median of seven prior line of therapies and with MM refractory to at least one immunomodulatory drug, one proteasome inhibitor, daratumumab, glucocorticoids and to their last treatment, revealed a partial response or better in 26% of patients. Moreover, a minimal or better response was achieved in 39% of patients, with median PFS and OS durations of 3.7 months and 8.6 months, respectively. Common haematological grade ≥3 adverse events included thrombocytopenia (57%), anaemia (44%) and neutropenia (21%). Common non-haematological adverse events of grade ≥3 included fatigue (25%) and hyponatraemia (22%). More than half of all patients had at least one clinically serious adverse event (63%), including pneumonia (in 11%) and sepsis (in 9%). These adverse events resulted in treatment discontinuation in 18% of patients. Two deaths were reported to be associated with either selinexor or dexamethasone. These high frequencies of adverse events and clinically serious adverse events partly reflect that the inclusion criteria for this study stipulated the enrolment of heavily pre-treated patients, including those with reduced renal function, thrombocytopenia and neutropenia[142]. In July 2019, selinexor plus low-dose dexamethasone was eventually granted accelerated FDA approval for patients with MM refractory to at least four prior lines of therapy based on these findings[141–143]. Furthermore, the EMA is currently considering selinexor plus low-dose dexamethasone as a candidate for accelerated assessment[143]. The accelerated approval of selinexor by the FDA was delayed owing to concerns regarding the single-arm, open-label study design of the STORM trial, which made determining the clinical activity of selinexor difficult in the context of the high risk of adverse events and a lack of robust single-agent activity[144]. The final decision to grant accelerated approval was based on a prespecified subgroup analysis of efficacy and safety in 83 patients whose disease was refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide and daratumumab[145].

Owing to the novel mechanism of action, considerable research interest exists in combining selinexor, and potentially other SINE compounds, with existing standard-of-care therapies. Among many other strategies, a phase I/II trial designed to determine a recommended phase II dose of selinexor in combination with liposomal doxorubicin and dexamethasone in patients with relapsed and/or refractory MM is currently ongoing (NCT02186834). Selinexor has also been tested in combination with carfilzomib and dexamethasone in a phase I trial (NCT02199665) involving patients with relapsed and/or refractory MM, revealing a recommended phase II dose of selinexor 60 mg, carfilzomib 20/27 mg/m^2 and dexamethasone 20 mg (REF.[62]). The most frequent treatment-associated grade ≥3 adverse events were thrombocytopenia (71%), anaemia (33%), lymphopenia (33%), neutropenia (33%) and infections (24%). The 21 patients in this cohort had a median PFS duration of 3.7 months and a median OS duration of 22.4 months[62]. However, a phase II trial (NCT02628704) involving this combination in the same setting has been withdrawn for reasons that are currently not specified. A similar combination is being tested in several trials, albeit with the irreversible proteasome inhibitor carfilzomib replaced with the reversible inhibitor bortezomib. Data from a phase Ib/II study demonstrate a median PFS duration of 9 months with an ORR of 63% in patients receiving selinexor plus low doses of bortezomib and dexamethasone[146]. Half of all patients had at least one grade ≥3 adverse event, including thrombocytopenia (50%), neutropenia (26%) and anaemia (19%). Non-haematological grade ≥3 adverse events included fatigue (14%), diarrhoea (7%) and nausea (5%)[146]. Preliminary data from an ongoing phase III study involving the same combination (NCT03110562) indicate that selinexor plus bortezomib and dexamethasone significantly improves median PFS duration (13.9 versus 9.5 months, HR 0.70; $P=0.0066$) and ORR (76.4% versus 62.3%; $P=0.0012$) compared with bortezomib plus dexamethasone. Grade 3–4 adverse events included thrombocytopenia (35.9% versus 15.2%), fatigue (11.3% versus 0.5%) and nausea (7.7% versus 0%)[147]. Patients with relapsed and/or refractory MM receiving pomalidomide plus low-dose dexamethasone had a reported ORR of 31% in a phase III trial[148]. In a separate, single-arm phase II trial involving patients with more heavily pre-treated disease, the addition of selinexor to this regimen resulted in an ORR of 58% with a similar haematological adverse event profile to other cohorts, including grade ≥3 neutropenia (54%), thrombocytopenia (33%), anaemia (29%) and leukopenia (15%), and fewer non-haematological grade ≥3 events, including fatigue (10%) and vomiting (2%)[149]. The adverse event profile of selinexor has now been established. Patients receiving this agent consistently have

reductions in platelet count (thrombocytopenia) and neutrophil count (neutropenia) over the first treatment cycle, and the severity of these adverse events typically peaks at between 28 and 42 days after starting treatment. The gastrointestinal adverse effects of selinexor, including nausea, vomiting and diarrhoea, also typically occur within 2 weeks of commencing treatment. Other common adverse effects include fatigue, decreased appetite, weight loss and hyponatraemia. These adverse effects are usually reversible with supportive care. A comprehensive description of the safety profile of selinexor in patients with MM is provided elsewhere[150].

Non-Hodgkin lymphoma

The improved outcomes observed with brentuximab vedotin and anti-PD-L1 antibodies in patients with Hodgkin lymphoma[151,152] have not been replicated in patients with non-Hodgkin lymphoma (NHL), thus highlighting a need for novel therapies. A phase I trial involving 70 patients with NHL of a range of subtypes, including 41 with DLBCL, revealed a disease control rate of 51% and an ORR of 32%. Encouragingly, three of the four patients with double-hit DLBCL featuring MYC–BCL2 translocations, which usually confer a worse prognosis, had objective responses, including one complete response[153]. Among all patients with NHL in this trial, the most frequent grade 3–4 haematological adverse events were thrombocytopenia (47%), neutropenia (32%) and anaemia (27%), which might be associated with baseline cytopenias prior to starting therapy in a subset of patients, including reduced platelet (15%) and neutrophil (13%) counts. Non-haematological grade 3 adverse events included fatigue (11%) and hyponatraemia (10%)[153].

Data from the phase IIb SADAL study demonstrated durable clinical benefit in patients with DLBCL who received selinexor monotherapy[63]. Among 127 patients with heavily pre-treated DLBCL (median of two prior lines of therapy), the ORR was 28%, including complete responses in 12%. At a median follow-up duration of 14.7 months, patients had a median PFS duration of 2.6 months and a median OS duration of 9.1 months. Patients with stable disease had a median OS duration of 18.3 months, and median OS was not reached in patients with a partial response or better. The most common grade 3–4 adverse events were thrombocytopenia (46%), neutropenia (24%), anaemia (22%), fatigue (11%), hyponatraemia (8%) and nausea (6%), and these were typically reversible with standard supportive care and/or dose modifications. The most common clinically serious adverse events were pyrexia (7%), pneumonia (5%) and sepsis (5%). No treatment-associated deaths were reported. Based on data from this single-arm study, in June 2020, the FDA granted accelerated approval of selinexor for adult patients with relapsed and/or refractory DLBCL who had previously received at least two lines of systemic therapy[63].

The efficacy and safety of selinexor in combination with rituximab and cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone chemotherapy (R-CHOP) is being assessed in a phase II trial that is currently recruiting patients (NCT03147885). Other combinations under ongoing evaluation in patients with DLBCL include rituximab plus gemcitabine, dexamethasone and cisplatin, with or without selinexor (NCT04442022), and selinexor plus venetoclax in patients with one of several high-risk haematological malignancies, including DLBCL (NCT03955783).

Acute myeloid leukaemia

The safety and tolerability of selinexor monotherapy was established in a phase I dose-escalation study involving 95 patients with relapsed and/or refractory AML (who had received a median of three prior lines of therapy)[154]. The ORR among 81 evaluable patients was 14%. At the molecular level, upregulation of p53 and downregulation of oncogenic fms-like tyrosine kinase 3 (FLT3) and KIT was observed[154]. Selinexor has also been tested in combination with existing standard-of-care therapies for AML in an attempt to achieve synergistic effects. The safety and efficacy of selinexor plus idarubicin and cytarabine was assessed in adult patients with relapsed and/or refractory AML in a phase II clinical trial. A lower cytarabine dose (100 mg/m^2 on days 1–7) was employed to enable better evaluations of the effect of selinexor[155,156]. Selinexor was administered at two different doses (40 mg/m^2 twice weekly for 4 weeks or 60 mg/m^2 twice weekly for 3 weeks) in cohorts 1 and 2, respectively. Out of 42 patients, a total of 20 across both cohorts had a complete response with or without complete blood count recovery. The ORRs in cohort 1 and 2 were 55.6% and 33.3%, respectively, with median OS durations of 12.6 months and 8.0 months. Common grade ≥3 adverse events observed in cohorts 1 and 2 included diarrhoea (55.6% and 40.0%), fatigue (14.8% and 13.3%), sepsis (25.9% and 20.0%), decreased platelet count (70.4% and 46.7%), decreased neutrophil count (44.4% and 40.0%), hyponatraemia (7.4% and 13.3%) and anaemia (70.4% and 33.3%). One treatment-related death occurred in cohort 2. Despite limitations in sample size, the addition of selinexor to chemotherapy at a flat dose of 60 mg twice-weekly for 3 weeks seems feasible in patients with AML[155,156]. The combination of selinexor with fludarabine and cytarabine has also been evaluated in a small-cohort, dose-escalation study involving patients ≤24 years of age with relapsed and/or refractory acute leukaemias (including 15 patients with AML). Patients received 30, 40, 55 and 70 mg/m^2 doses of selinexor twice weekly and were able to tolerate a dose of ≤55 mg/m^2. Two out of five patients had cerebellar toxicities at the 70 mg/m^2 dose of selinexor, in one patient without receiving fludarabine and cytarabine. This study demonstrated a favourable ORR (47% among 15 evaluable patients) in young patients with acute leukaemias[157]. The most common non-haematological grade 3 adverse events observed in these patients was asymptomatic hyponatraemia (in 12 patients)[157]. This study justifies further clinical evaluation of selinexor in young patients with acute leukaemias.

Interestingly, eltanexor, a second-generation SINE compound, has effects on tumour burden and survival similar to those of selinexor in mouse models of CML and AML, and is likely to be better tolerated owing to substantially reduced levels of central nervous system

penetration[122,158–160]. Eltanexor is currently being tested in patients with relapsed and/or refractory MM, colorectal cancer, castration-resistant prostate cancer or high-risk myelodysplastic syndrome (NCT02649790).

Solid tumours

Besides haematological malignancies, selinexor has also been tested in patients with solid tumours (TABLE 2). A phase Ib study involving patients with advanced-stage, treatment-refractory sarcoma revealed a recommended phase II dose of 60 mg (administered twice a week for 3 weeks followed by a 1-week break). No objective responses to selinexor were observed among 52 evaluable patients, although 23% had stable disease lasting ≥4 months[161]. The safety and preliminary efficacy of selinexor has also been assessed in a large-cohort phase I trial involving 189 patients with various advanced-stage solid tumours, including colorectal, prostate, pancreatic, ovarian, and lung cancers and melanoma. The investigators concluded that selinexor is safe and well tolerated at a recommended phase II dose of 35 mg/m^2 administered twice weekly. One patient out of 45 had dose-limiting nausea, vomiting and fatigue at this dose. The most frequent grade 3–4 adverse events at doses of ≥40 mg/m^2 were thrombocytopenia (17%), fatigue (15%) and hyponatraemia (13%). Among 157 patients evaluable for efficacy, one had a complete response, six had partial responses (ORR 4%) and a further 27 (17%) had stable disease lasting ≥4 months[137,162,163]. In general, selinexor monotherapy seems to be adequately tolerated in patients with solid tumours, although more conclusive data on efficacy are currently awaited[29,37,141,164,165].

Selinexor at 65 mg/m^2, twice weekly is the maximum tolerated dose in patients with solid tumours; however, the recommended phase II dose in patients with solid tumours is 35 mg/m^2 on the same schedule owing to tolerability issues[137]. The most frequent treatment-associated adverse events were grade 1–2 nausea, vomiting, anorexia and fatigue. Common grade 3–4 adverse events included thrombocytopenia (in 16% of patients), fatigue (in 15%) and hyponatraemia (in 13%). However, in patients with advanced-stage, soft-tissue or bone sarcomas, 60 mg selinexor administered on a 3-weeks-on, 1-week-off schedule was found to be well tolerated[161]. At least 10% of patients had treatment-related adverse events; common grade 3 adverse events included fatigue, diarrhoea, thrombocytopenia and neutropenia, whereas one patient had grade 4 anaemia. All adverse events were manageable with supportive care. Furthermore, data from this trial demonstrate that administration with food increases the peak plasma selinexor concentration by approximately 15–20%; however, this increase seemed to have no substantial effects on other pharmacokinetic parameters[161].

Novel biomarker strategies

XPO1 alterations

XPO1 expression is positively correlated with an unfavourable prognosis in patients with MM. Specifically, XPO1 overexpression seems to be linked with bortezomib resistance and shorter survival[166]. In addition, emerging evidence suggests that the *XPO1*^{E571K} mutation, resulting in missense substitution, has an important role in several oncogenic processes across various types of cancers[138,167]. The exact functional relevance of this mutation is incompletely understood, although mutations in this location might alter the hydrophobic NES-binding groove of XPO1. Such changes might affect the open–closed equilibrium, the shape of the groove and the binding affinity for NESs, resulting in alterations in the binding preferences of XPO1 for certain nuclear export cargoes[138]. In a mechanistic study, García-Santisteban et al. demonstrated that this mutation slightly increases the binding affinity of XPO1 for NESs with a more negatively charged C-terminal end, without affecting the export activity of XPO1 (REF.[168]). Nonetheless, data published in June 2020 revealed mitotic defects in homozygous E571K-mutant cell lines[169]. However, cells lines with or without this mutation have similar responses to SINE compounds, suggesting an unaltered sensitivity to XPO1 inhibitors[138].

XPO1^{E571K} has been detected in several different haematological malignancies, including primary mediastinal DLBCL, classical Hodgkin lymphoma, primary mediastinal B cell lymphoma, mediastinal grey-zone lymphoma and oesophageal squamous cell carcinoma[138,167]. Importantly, this alteration is detectable using molecular methods such as digital PCR and next-generation sequencing, either in tumour biopsy samples or in blood-derived, cell-free DNA, and can be used to determine the presence of minimal residual disease[158]. A retrospective study has revealed that *XPO1*^{E571K} can be detected in about 25% of patients with classical Hodgkin lymphoma. The presence of this variant in cell-free DNA at completion of therapy seems to be associated with a shorter PFS duration and has potential as a prognostic biomarker. However, prospective investigations involving large cohorts of patients are currently unavailable but will be essential in determining the clinical applicability of this approach in comparison with PET imaging[158,170]. *XPO1*^{E571K} might also be relevant to other forms of lymphoma. For example, primary bone marrow lymphoma has a distinct molecular signature with detectable *XPO1*^{E571} in about 50% of patients. Furthermore, this alteration is associated with a shorter PFS duration, suggesting a need for treatment escalation[138]. Similar prognostic associations of *XPO1*^{E571K} have been reported in patients with CLL, albeit in a much lower percentage of patients[158,171], and might also be applicable for other cancers.

Non-coding RNA regulation

miRNA biogenesis requires epigenetic processing, with one of the main steps being the export of nuclear pre-miRNAs[172]. Pre-miRNAs are known to be an XPO1 export cargo[173,174]. Specifically, the 5',7'-methylguanine-capped class of pre-miRNAs are recognized by the Cap binding complex, which guides the export of these pre-miRNAs via the phosphorylated adaptor for RNA export–XPO1 signalling pathway, rather than via XPO5 (REF.[173]). Whenever pre-miRNA complexes are present in the cytoplasm, RanGTP is converted into RanGDP, enabling exportins to release the pre-miRNA. The inhibition of nuclear export is thus speculated

to be an effective cancer treatment approach owing to the retention of pre-miRNAs within the nucleus. This effect might reduce the inhibitory miRNA-mediated regulation of several tumour suppressors (such as p53, $p27^{KIP1}$ and members of the forkhead box family of transcription factors), leading to the inhibition of cell growth, cell-cycle arrest and/or the initiation of apoptotic signalling pathways. miRNAs have an important physiological role in maintaining homeostasis in non-malignant cells; nonetheless, therapeutic targeting of their nuclear export (by XPO1/5 inhibitors), resulting in global retention of miRNAs, could be catastrophic for malignant cells. Genetic aberrations in malignant cells can lead to the aberrant expression of tumour suppressors such as p53, FOXO and p27, which are under the control of miRNAs, and can lead to excessive proliferation. Thus, the nuclear retention of pre-miRNAs using specific inhibitors can disrupt the control of tumour suppressors or other molecules with a role in cellular surveillance and might suppress tumorigenesis[175]. Interestingly, XPO1 expression has been shown to be under epigenetic control and is suppressed by miR-30, resulting in cell death that is reversed by methylation of this microRNA in preclinical models of PDAC[176].

Data published in 2017 indicate that the miRNAs miR-145, miR-34 and let-7 are mechanistically associated with XPO1 expression in PDAC cells[177]. This study confirmed that the upregulation of miR-145 by selinexor inhibits PDAC cell growth and migration. Mechanistically, selinexor downregulates several miR-145 target genes, including matrix metallopeptidase 1 (*MMP1*), membrane-type MMP (*MT-MMP*), *EGFR*, *MYC*, sex determining region Y-box 2 (*SOX2*) and p21 (RAC1) activated kinase 4 (*PAK4*), resulting an increase in miR-145 (REF.[177]). Moreover, XPO1-mediated upregulation of oncogenic miR-33b-3p has been observed in two gastric cancer cell lines[178]. XPO1 is also able to regulate the nucleocytoplasmic transport of primary miRNAs in quiescent primary human fibroblasts, in which XPO5 levels remain very low. The quiescence-induced primary miRNAs are modified with a 2,2,7-trimethylguanosine-cap, the proteins of which are then able to bind with XPO1 and have an essential role in miRNA biogenesis through nucleocytoplasmic transport[179]. Furthermore, the sequencing of non-coding RNAs has revealed that, besides miRNA, XPO1 is also involved in the regulation of piwi-interacting RNA[178]. Collectively, these studies demonstrate that the regulation of non-coding RNAs can be associated with XPO1 or XPO5 and that the genetic variants of these proteins, such as $XPO5^{M1115T}$, might be attractive prognostic markers in various cancer types[180] and should warrant further clinical investigation.

New and emerging combinations

Evidence is emerging on the synergistic effects of selinexor in patients with MM. Selinexor plus dexamethasone has received accelerated FDA approval as a fifth-line therapy for patients with MM. Furthermore, other combinations with platinum-based therapies (such as cisplatin and carboplatin) and taxanes (such as paclitaxel) are currently under clinical investigation (NCT04442022 and NCT02419495). In patients with AML, aberrant cytoplasmic localization of topoisomerase 2α (an established XPO1 cargo protein) is associated with resistance to topoisomerase inhibitors. Two topoisomerase 2α inhibitors — idarubicin and daunorubicin — have been demonstrated to synergistically inhibit the growth of AML cells and blasts in vitro and of mouse xenografts in vivo when applied in combination with selinexor[122]. Besides selinexor, another SINE compound (KPT-185) has been shown to synergize with the MDM2 inhibitor nutlin 3a in both p53-wild-type and p53-mutant cell lines and in primary cells derived from patients with AML[158,181]. In addition to ubiquitin ligase activity, hypermethylation owing to increased DNA methyltransferase activity is often also associated with AML, reflecting the silencing of tumour-suppressor genes. Decitabine, a hypomethylating agent, has been shown to promote the re-expression of genes that are silenced during myeloid differentiation and seems to be effective in some patients with AML[182]. In vitro investigations involving AML cell lines and primary blasts demonstrate that the in vitro effectiveness of decitabine is substantially enhanced when combined with selinexor[160]. The anti-leukaemia action of this combination has also been validated in vivo in a mouse model of AML[122,158]. Furthermore, genome-wide pooled CRISPR-based knockout screening identified XPO1 as a key target that might help to overcome resistance to FLT3 inhibitors in patients with AML. This study demonstrated synergy between selinexor and midostaurin or gilteritinib in AML cell lines and patient-derived cells[183].

The efficacy of ibrutinib is reduced substantially by the on-target mutation BTK^{C481S}. Selinexor has been shown to synergistically re-sensitize ibrutinib-resistant patient-derived primary CLL cells[99]. Similar synergistic effects were found in a mouse model where c57b cells were engrafted with $CD19^{+}CD5^{+}$ leukaemia derived from the ibrutinib-resistant Eμ-TCL1 murine model[99]. These preclinical data suggest that selinexor can bypass ibrutinib resistance caused by BTK^{C481S} (REFS[99,158]). NF-κB signalling has been shown to upregulate BTK expression. Thus, selinexor is able to indirectly reduce BTK expression through nuclear retention of IκB, leading to the inhibition of NF-κB[184]. Moreover, the C481S mutation does not entirely abolish the ability of ibrutinib to bind with BTK; rather, this alteration renders ibrutinib a reversible inhibitor[185]. Therefore, partial inhibition of BTK by ibrutinib in combination with the indirect downregulation of BTK expression by selinexor synergistically promotes tumour cell death[158].

Selinexor has also been shown to synergize with dexamethasone and everolimus in preclinical models of lymphoma. Mechanistically, this combination affects several cell survival signalling pathways, including NF-κB and mTOR signalling[139]. Selinexor and eltanexor have also been shown to synergize with the BCL-2 inhibitor venetoclax in double hit lymphoma cell lines and patient-derived xenografts harbouring *MYC* and *BCL2* alterations[186]. Similarly, the combination of selinexor with bortezomib is able to overcome resistance to proteasome inhibitors in cell line models, mouse models and in patient-derived cells owing to the synergistic inhibition

of IκBα and p65 phosphorylation[116]. Inhibiting phosphorylation protects IκBα from proteasomal degradation and enables anti-inflammatory activity against MM[100,158]. A similar mechanism is evident in the synergistic interactions between the XPO1 inhibitor S109 and irradiation observed in glioblastoma cell lines[187].

Selinexor has shown antitumour effects in experimental models of melanoma and colon cancer in combination with immune-checkpoint inhibitors[188]. Dual inhibition of XPO1 and PD-1 or its ligand (PD-L1) using selinexor and an immune-checkpoint inhibitor, respectively, was evaluated in syngeneic mouse models of melanoma and colon cancer. This combination not only showed the usefulness of this combination in terms of tumour suppression but also indicated substantial immunomodulatory functions, including changes in the types of immune cells of certain phenotypes such as natural killer cells and activated T cells. These observations merit further clinical investigation of the combination of XPO1 inhibition and anti-PD-1/PD-L1 antibodies[188]. Selinexor might also synergize with the Bcl-xL inhibitor A-1331852 and induces apoptotic cell death in several cancer cell lines, including A549, HeLa, U87, U118 and U251, through the impairment of ribosomal RNA processing and the resultant abnormal synthesis of MCL1 protein[189].

Conclusions

Owing to the central role of XPO1 in nuclear export, which is associated with the ability to modulate most of the hallmarks of cancer[43] and the unique characteristics of this protein relative to other cancer drug targets, several XPO1 inhibitors have been synthesized and tested in several clinical settings. The antitumour activity of selinexor has been demonstrated in patients with lymphoid malignancies, resulting in the FDA accelerated approval of this agent, in combination with dexamethasone, as a fifth-line therapy for patients with MM. In June 2020, a second accelerated approval was granted for the treatment of patients with refractory DLBCL following disease progression on two prior lines of therapy. Promising levels of antitumour activity have also been demonstrated in preclinical models of other haematological malignancies and solid tumours, thus affirming the need for further testing of these agents. Despite certain concerns regarding the balance between efficacy and safety, XPO1 inhibition is nonetheless a promising strategy and will likely be more effective in combination with various agents, including gemcitabine, anthracyclines, mTOR inhibitors, ibrutinib or immune-checkpoint inhibitors. SINE compounds in combination with other targeted therapies or cytotoxic agents can overcome several forms of acquired resistance to standard-of-care therapies. The potentiation of the antitumour activity of various agents by XPO1 inhibitors is evident in preclinical models and numerous trials are currently under way.

Some challenges to the further clinical implementation of XPO1 inhibitors continue to exist. XPO1 interacts physically with hundreds of proteins[190] and could export potentially thousands, as revealed by deep proteomic analysis[191] indicating that XPO1 plays a central role in a broad interaction network. In addition, the ability to export multiple classes of RNA makes XPO1 a hub protein for interactions between the proteome and transcriptome. Analysing such huge networks using traditional approaches is not feasible and requires the use of high-throughput computational approaches. Furthermore, to guide the design of future clinical trials intended to test synergistic effects in patients with drug-resistant cancers, high-throughput screening of potential combination therapies along with CRISPR-based, genome-wide library screening is an urgent necessity[192–194]. Furthermore, additional studies designed to identify possible biomarkers are desirable and could enable the identification of patients with tumours that are particularly sensitive to XPO1 inhibition. The role of several types of RNA, along with the emergence of *XPO1*^{E571K} and, potentially, other mutations in plasma cell-free DNA, offers important hints for future biomarker discovery.

Published online: 10 November 2020

1. Koonin, E. V. Darwinian evolution in the light of genomics. *Nucleic Acids Res.* **37**, 1011–1034 (2009).
2. Gabaldon, T. & Pittis, A. A. Origin and evolution of metabolic sub-cellular compartmentalization in eukaryotes. *Biochimie* **119**, 262–268 (2015).
3. Azmi, A. S. et al. Selective inhibitors of nuclear export for the treatment of non-Hodgkin's lymphomas. *Haematologica* **98**, 1098–1106 (2013).
4. Stade, K., Ford, C. S., Guthrie, C. & Weis, K. Exportin 1 (Crm1p) is an essential nuclear export factor. *Cell* **90**, 1041–1050 (1997).
5. Azmi, A. S. & Mohammad, R. M. Targeting cancer at the nuclear pore. *J. Clin. Oncol.* **34**, 4180–4182 (2016).
6. Azmi, A. S. The evolving role of nuclear transporters in cancer. *Semin. Cancer Biol.* **27**, 1–2 (2014).
7. Soniat, M. & Chook, Y. M. Nuclear localization signals for four distinct karyopherin-beta nuclear import systems. *Biochem. J.* **468**, 353–362 (2015).
8. Mahipal, A. & Malafa, M. Importins and exportins as therapeutic targets in cancer. *Pharmacol. Ther.* **164**, 135–143 (2016).
9. Saulino, D. M., Younes, P. S., Bailey, J. M. & Younes, M. CRM1/XPO1 expression in pancreatic adenocarcinoma correlates with survivin expression and the proliferative activity. *Oncotarget* **9**, 21289–21295 (2018).
10. Subhash, V. V. et al. Anti-tumor efficacy of Selinexor (KPT-330) in gastric cancer is dependent on nuclear accumulation of p53 tumor suppressor. *Sci. Rep.* **8**, 12248 (2018).
11. Gravina, G. L. et al. KPT-330, a potent and selective exportin-1 (XPO-1) inhibitor, shows antitumor effects modulating the expression of cyclin D1 and survivin [corrected] in prostate cancer models. *BMC Cancer* **15**, 941 (2015).
12. Aladhraei, M., Kassem Al-Thobhani, A., Poungvarin, N. & Suwannalert, P. Association of XPO1 overexpression with NF-kappaB and Ki67 in colorectal cancer. *Asian Pac. J. Cancer Prev.* **20**, 3747–3754 (2019).
13. Neumann, N., Lundin, D. & Poole, A. M. Comparative genomic evidence for a complete nuclear pore complex in the last eukaryotic common ancestor. *PLoS ONE* **5**, e13241 (2010).
14. Cautain, B., Hill, R., de Pedro, N. & Link, W. Components and regulation of nuclear transport processes. *FEBS J.* **282**, 445–462 (2015).
15. Hoelz, A., Debler, E. W. & Blobel, G. The structure of the nuclear pore complex. *Annu. Rev. Biochem.* **80**, 613–643 (2011).
16. Lange, A. et al. Classical nuclear localization signals: definition, function, and interaction with importin alpha. *J. Biol. Chem.* **282**, 5101–5105 (2007).
17. Dickmanns, A., Monecke, T. & Ficner, R. Structural basis of targeting the exportin CRM1 in cancer. *Cell* **4**, 538–568 (2015).
18. Fornerod, M., Ohno, M., Yoshida, M. & Mattaj, I. W. CRM1 is an export receptor for leucine-rich nuclear export signals. *Cell* **90**, 1051–1060 (1997).
19. Fukuda, M. et al. CRM1 is responsible for intracellular transport mediated by the nuclear export signal. *Nature* **390**, 308–311 (1997).
20. Ossareh-Nazari, B., Bachelerie, F. & Dargemont, C. Evidence for a role of CRM1 in signal-mediated nuclear protein export. *Science* **278**, 141–144 (1997).
21. Fu, S. C., Huang, H. C., Horton, P. & Juan, H. F. ValidNESs: a database of validated leucine-rich nuclear export signals. *Nucleic Acids Res.* **41**, D338–D343 (2013).
22. Okamura, M., Inose, H. & Masuda, S. RNA export through the NPC in eukaryotes. *Genes* **6**, 124–149 (2015).
23. Monecke, T., Dickmanns, A. & Ficner, R. Allosteric control of the exportin CRM1 unraveled by crystal structure analysis. *FEBS J.* **281**, 4179–4194 (2014).
24. Ullman, K. S., Powers, M. A. & Forbes, D. J. Nuclear export receptors: from importin to exportin. *Cell* **90**, 967–970 (1997).

25. Wang, A. Y. & Liu, H. The past, present, and future of CRM1/XPO1 inhibitors. *Stem Cell Investig.* **6**, 6 (2019).
26. Schmidt, J. et al. Genome-wide studies in multiple myeloma identify XPO1/CRM1 as a critical target validated using the selective nuclear export inhibitor KPT-276. *Leukemia* **27**, 2357–2365 (2013).
27. Angus, L., van der Watt, P. J. & Leaner, V. D. Inhibition of the nuclear transporter, Kpnbeta1, results in prolonged mitotic arrest and activation of the intrinsic apoptotic pathway in cervical cancer cells. *Carcinogenesis* **35**, 1121–1131 (2014).
28. Kuusisto, H. V. & Jans, D. A. Hyper-dependence of breast cancer cell types on the nuclear transporter Importin β1. *Biochim. Biophys. Acta* **1853**, 1870–1878 (2015).
29. Kosyna, F. K. & Depping, R. Controlling the gatekeeper: therapeutic targeting of nuclear transport. *Cells* **7**, 221 (2018).
30. Nishi, K. et al. Leptomycin B targets a regulatory cascade of crm1, a fission yeast nuclear protein, involved in control of higher order chromosome structure and gene expression. *J. Biol. Chem.* **269**, 6320–6324 (1994).
31. Bonazzi, S. et al. Anguinomycins and derivatives: total syntheses, modeling, and biological evaluation of the inhibition of nucleocytoplasmic transport. *J. Am. Chem. Soc.* **132**, 1432–1442 (2010).
32. Koster, M. et al. Ratjadones inhibit nuclear export by blocking CRM1/exportin 1. *Exp. Cell Res.* **286**, 321–331 (2003).
33. Wach, J. Y., Guttinger, S., Kutay, U. & Gademann, K. The cytotoxic styryl lactone goniothalamin is an inhibitor of nucleocytoplasmic transport. *Bioorg. Med. Chem. Lett.* **20**, 2843–2846 (2010).
34. Watanabe, K. et al. Anti-influenza viral effects of novel nuclear export inhibitors from Valerianae Radix and Alpinia galanga. *Drug Discov. Ther.* **5**, 26–31 (2011).
35. Niu, M., Wu, S., Mao, L. & Yang, Y. CRM1 is a cellular target of curcumin: new insights for the myriad of biological effects of an ancient spice. *Traffic* **14**, 1042–1052 (2013).
36. Azmi, A. S. et al. Selective inhibitors of nuclear export block pancreatic cancer cell proliferation and reduce tumor growth in mice. *Gastroenterology* **144**, 447–456 (2013).
37. Etchin, J. et al. KPT-8602, a second-generation inhibitor of XPO1-mediated nuclear export, is well tolerated and highly active against AML blasts and leukemia-initiating cells. *Leukemia* **31**, 143–150 (2017).
38. Grayton, J. E., Miller, T. & Wilson-Robles, H. In vitro evaluation of selective inhibitors of nuclear export (SINE) drugs KPT-185 and KPT-335 against canine mammary carcinoma and transitional cell carcinoma tumor initiating cells. *Vet. Comp. Oncol.* **15**, 1455–1467 (2017).
39. Sakakibara, K. et al. CBS9106 is a novel reversible oral CRM1 inhibitor with CRM1 degrading activity. *Blood* **118**, 3922–3931 (2011).
40. Azizian, N. G. & Li, Y. XPO1-dependent nuclear export as a target for cancer therapy. *J. Hematol. Oncol.* **13**, 61 (2020).
41. Newlands, E. S., Rustin, G. J. & Brampton, M. H. Phase I trial of elactocin. *Br. J. Cancer* **74**, 648–649 (1996).
42. Sun, Q. et al. Nuclear export inhibition through covalent conjugation and hydrolysis of leptomycin B by CRM1. *Proc. Natl Acad. Sci. USA* **110**, 1303–1308 (2013).
43. Sun, Q. et al. Inhibiting cancer cell hallmark features through nuclear export inhibition. *Signal Transduct. Target. Ther.* **1**, 16010 (2016).
44. Fleta-Soriano, E. et al. The myxobacterial metabolite ratjadone A inhibits HIV infection by blocking the Rev/CRM1-mediated nuclear export pathway. *Microb. Cell Fact.* **13**, 17 (2014).
45. Saito, N. et al. CBS9106-induced CRM1 degradation is mediated by cullin ring ligase activity and the neddylation pathway. *Mol. Cancer Ther.* **13**, 3013–3023 (2014).
46. Kalid, O., Toledo Warshaviak, D., Shechter, S., Sherman, W. & Shacham, S. Consensus induced fit docking (cIFD): methodology, validation, and application to the discovery of novel Crm1 inhibitors. *J. Comput. Aided Mol. Des.* **26**, 1217–1228 (2012).
47. Parikh, K., Cang, S., Sekhri, A. & Liu, D. Selective inhibitors of nuclear export (SINE)–a novel class of anti-cancer agents. *J. Hematol. Oncol.* **7**, 78 (2014).
48. Ranganathan, P. et al. Preclinical activity of a novel CRM1 inhibitor in acute myeloid leukemia. *Blood* **120**, 1765–1773 (2012).
49. Zhang, K. et al. Novel selective inhibitors of nuclear export CRM1 antagonists for therapy in mantle cell lymphoma. *Exp. Hematol.* **41**, 67–78.e4 (2013).
50. Walker, C. J. et al. Preclinical and clinical efficacy of XPO1/CRM1 inhibition by the karyopherin inhibitor KPT-330 in Ph+ leukemias. *Blood* **122**, 3034–3044 (2013).
51. London, C. A. et al. Preclinical evaluation of the novel, orally bioavailable selective inhibitor of nuclear export (SINE) KPT-335 in spontaneous canine cancer: results of a phase I study. *PLoS ONE* **9**, e87585 (2014).
52. Lapalombella, R. et al. Selective inhibitors of nuclear export show that CRM1/XPO1 is a target in chronic lymphocytic leukemia. *Blood* **120**, 4621–4634 (2012).
53. Etchin, J. et al. Antileukemic activity of nuclear export inhibitors that spare normal hematopoietic cells. *Leukemia* **27**, 66–74 (2013).
54. Fung, H. Y. & Chook, Y. M. Atomic basis of CRM1-cargo recognition, release and inhibition. *Semin. Cancer Biol.* **27**, 52–61 (2014).
55. Madden, E. C., Gorman, A. M., Logue, S. E. & Samali, A. Tumour cell secretome in chemoresistance and tumour recurrence. *Trends Cancer* **6**, 489–505 (2020).
56. Rodriguez, J. A., Schuchner, S., Au, W. W. Y., Fabbro, M. & Henderson, B. R. Nuclear-cytoplasmic shuttling of BARD1 contributes to its proapoptotic activity and is regulated by dimerization with BRCA1. *Oncogene* **23**, 1809–1820 (2004).
57. Kau, T. R., Way, J. C. & Silver, P. A. Nuclear transport and cancer: from mechanism to intervention. *Nat. Rev. Cancer* **4**, 106–117 (2004).
58. Vigneri, P. & Wang, J. Y. Induction of apoptosis in chronic myelogenous leukemia cells through nuclear entrapment of BCR-ABL tyrosine kinase. *Nat. Med.* **7**, 228–234 (2001).
59. O'Brate, A. & Giannakakou, P. The importance of p53 location: nuclear or cytoplasmic zip code? *Drug Resist. Updat.* **6**, 313–322 (2003).
60. El-Tanani, M., Dakir, E.-H., Raynor, B. & Morgan, R. Mechanisms of nuclear export in cancer and resistance to chemotherapy. *Cancers* **8**, 35 (2016).
61. Wang, A. Y. et al. A phase I study of selinexor in combination with high-dose cytarabine and mitoxantrone for remission induction in patients with acute myeloid leukemia. *J. Hematol. Oncol.* **11**, 4 (2018).
62. Jakubowiak, A. J. et al. Phase 1 study of selinexor plus carfilzomib and dexamethasone for the treatment of relapsed/refractory multiple myeloma. *Br. J. Haematol.* **186**, 549–560 (2019).
63. Kalakonda, N. et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial. *Lancet Haematol.* **7**, e511–e522 (2020).
64. Sadowski, A. R. et al. Phase II study of the oral selective inhibitor of nuclear export (SINE) KPT-335 (verdinexor) in dogs with lymphoma. *BMC Vet. Res.* **14**, 250 (2018).
65. Miyake, T. M. et al. NRG1/ERBB3 pathway activation induces acquired resistance to XPO1 inhibitors. *Mol. Cancer Ther.* **19**, 1727–1735 (2020).
66. Tonini, G. et al. Nuclear and cytoplasmic expression of survivin in 67 surgically resected pancreatic cancer patients. *Br. J. Cancer* **92**, 2225–2232 (2005).
67. Dhillon, P. K. et al. Aberrant cytoplasmic expression of p63 and prostate cancer mortality. *Cancer Epidemiol. Biomarkers Prev.* **18**, 595–600 (2009).
68. Takeda, C. et al. Cytoplasmic maspin expression predicts poor prognosis of patients with soft tissue sarcomas. *Diagn. Pathol.* **9**, 205 (2014).
69. Machowska, M., Wachowicz, K., Sopel, M. & Rzepecki, R. Nuclear location of tumor suppressor protein maspin inhibits proliferation of breast cancer cells without affecting proliferation of normal epithelial cells. *BMC Cancer* **14**, 142 (2014).
70. Santivasi, W. L. et al. Association between cytosolic expression of BRCA1 and metastatic risk in breast cancer. *Br. J. Cancer* **113**, 453–459 (2015).
71. Wu, F. Y. et al. Reduction of cytosolic p27(Kip1) inhibits cancer cell motility, survival, and tumorigenicity. *Cancer Res.* **66**, 2162–2172 (2006).
72. Rakha, E. A. et al. Expression of BRCA1 protein in breast cancer and its prognostic significance. *Hum. Pathol.* **39**, 857–865 (2008).
73. Cordo Russo, R. I. et al. Targeting ErbB-2 nuclear localization and function inhibits breast cancer growth and overcomes trastuzumab resistance. *Oncogene* **34**, 3413–3428 (2015).
74. Sugihara, T. et al. YAP tyrosine phosphorylation and nuclear localization in cholangiocarcinoma cells are regulated by LCK and independent of LATS activity. *Mol. Cancer Res.* **16**, 1556–1567 (2018).
75. Ignatz-Hoover, J. J. et al. Aberrant GSK3beta nuclear localization promotes AML growth and drug resistance. *Blood Adv.* **2**, 2890–2903 (2018).
76. Sood, A. K. et al. The paradoxical expression of maspin in ovarian carcinoma. *Clin. Cancer Res.* **8**, 2924–2932 (2002).
77. Marioni, G. et al. Nuclear expression of maspin is associated with a lower recurrence rate and a longer disease-free interval after surgery for squamous cell carcinoma of the larynx. *Histopathology* **46**, 576–582 (2005).
78. Goulet, B. et al. Nuclear localization of maspin is essential for its inhibition of tumor growth and metastasis. *Lab. Invest.* **91**, 1181–1187 (2011).
79. Narahashi, T. et al. Cytoplasmic localization of p63 is associated with poor patient survival in lung adenocarcinoma. *Histopathology* **49**, 349–357 (2006).
80. Altieri, D. C. & Marchisio, P. C. Survivin apoptosis: an interloper between cell death and cell proliferation in cancer. *Lab. Invest.* **79**, 1327–1333 (1999).
81. Okada, E. et al. Survivin expression in tumor cell nuclei is predictive of a favorable prognosis in gastric cancer patients. *Cancer Lett.* **163**, 109–116 (2001).
82. Lehner, R. et al. Immunohistochemical localization of the IAP protein survivin in bladder mucosa and transitional cell carcinoma. *Appl. Immunohistochem. Mol. Morphol.* **10**, 134–138 (2002).
83. Martinez, A. et al. Nuclear survivin expression in mantle cell lymphoma is associated with cell proliferation and survival. *Am. J. Pathol.* **164**, 501–510 (2004).
84. Grabowski, P. et al. Prognostic value of nuclear survivin expression in oesophageal squamous cell carcinoma. *Br. J. Cancer* **88**, 115–119 (2003).
85. Turner, J. G. & Sullivan, D. M. CRM1-mediated nuclear export of proteins and drug resistance in cancer. *Curr. Med. Chem.* **15**, 2648–2655 (2008).
86. Chanukuppa, V. et al. XPO1 is a critical player for bortezomib resistance in multiple myeloma: a quantitative proteomic approach. *J. Proteom.* **209**, 103504 (2019).
87. Yadav, S. et al. SMC1A is associated with radioresistance in prostate cancer and acts by regulating epithelial-mesenchymal transition and cancer stem-like properties. *Mol. Carcinog.* **58**, 113–125 (2019).
88. Wu, N. et al. RCC2 over-expression in tumor cells alters apoptosis and drug sensitivity by regulating Rac1 activation. *BMC Cancer* **18**, 67 (2018).
89. Kohler, A. & Hurt, E. Gene regulation by nucleoporins and links to cancer. *Mol. Cell* **38**, 6–15 (2010).
90. David-Watine, B. Silencing nuclear pore protein Tpr elicits a senescent-like phenotype in cancer cells. *PLoS ONE* **6**, e22423 (2011).
91. Muz, B., Azab, F., de la Puente, P., Landesman, Y. & Azab, A. K. Selinexor overcomes hypoxia-induced drug resistance in multiple myeloma. *Transl Oncol.* **10**, 632–640 (2017).
92. Saenz-Ponce, N. et al. Targeting the XPO1-dependent nuclear export of E2F7 reverses anthracycline resistance in head and neck squamous cell carcinomas. *Sci. Transl Med.* **10**, eaar7223 (2018).
93. Vigneswaran, N. & Williams, M. D. Epidemiologic trends in head and neck cancer and aids in diagnosis. *Oral Maxillofac. Surg. Clin. North Am.* **26**, 123–141 (2014).
94. Specenier, P. M. & Vermorken, J. B. Current concepts for the management of head and neck cancer: chemotherapy. *Oral Oncol.* **45**, 409–415 (2009).
95. Ferris, R. L. et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N. Engl. J. Med.* **375**, 1856–1867 (2016).
96. Turner, J. G. et al. Treatment of acquired drug resistance in multiple myeloma by combination therapy with XPO1 and topoisomerase II inhibitors. *J. Hematol. Oncol.* **9**, 73 (2016).
97. Turner, J. G. et al. CRM1 inhibition sensitizes drug resistant human myeloma cells to topoisomerase II and proteasome inhibitors both in vitro and ex vivo. *J. Cancer* **4**, 614–625 (2013).
98. Ming, M. et al. XPO1 inhibitor selinexor overcomes intrinsic ibrutinib resistance in mantle cell lymphoma via nuclear retention of IkappaB. *Mol. Cancer Ther.* **17**, 2564–2574 (2018).
99. Hing, Z. A. et al. Selinexor is effective in acquired resistance to ibrutinib and synergizes with ibrutinib in

chronic lymphocytic leukemia. *Blood* **125**, 3128–3132 (2015).
100. Kashyap, T. et al. Selinexor, a selective inhibitor of nuclear export (SINE) compound, acts through NF-κB deactivation and combines with proteasome inhibitors to synergistically induce tumor cell death. *Oncotarget* **7**, 78883–78895 (2016).
101. Turner, J. G. et al. XPO1 inhibitor combination therapy with bortezomib or carfilzomib induces nuclear localization of IκBα and overcomes acquired proteasome inhibitor resistance in human multiple myeloma. *Oncotarget* **7**, 78896–78909 (2016).
102. Shih, J. Y., Gow, C. H. & Yang, P. C. EGFR mutation conferring primary resistance to gefitinib in non-small-cell lung cancer. *N. Engl. J. Med.* **353**, 207–208 (2005).
103. Janne, P. A., Engelman, J. A. & Johnson, B. E. Epidermal growth factor receptor mutations in non-small-cell lung cancer: implications for treatment and tumor biology. *J. Clin. Oncol.* **23**, 3227–3234 (2005).
104. Li, K. et al. DDX17 nucleocytoplasmic shuttling promotes acquired gefitinib resistance in non-small cell lung cancer cells via activation of beta-catenin. *Cancer Lett.* **400**, 194–202 (2017).
105. Lamm, G. M., Nicol, S. M., Fuller-Pace, F. V. & Lamond, A. I. p72: a human nuclear DEAD box protein highly related to p68. *Nucleic Acids Res.* **24**, 3739–3747 (1996).
106. Yedavalli, V. S., Neuveut, C., Chi, Y. H., Kleiman, L. & Jeang, K. T. Requirement of DDX3 DEAD box RNA helicase for HIV-1 Rev-RRE export function. *Cell* **119**, 381–392 (2004).
107. Schlumberger, M. et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N. Engl. J. Med.* **372**, 621–630 (2015).
108. Khan, H. Y. et al. Targeting XPO1 and PAK4 in 8505C anaplastic thyroid cancer cells: putative implications for overcoming lenvatinib therapy resistance. *Int. J. Mol. Sci.* **21**, 237 (2019).
109. Juric, D. et al. Convergent loss of PTEN leads to clinical resistance to a PI(3)Kα inhibitor. *Nature* **518**, 240–244 (2015).
110. Elkabets, M. et al. AXL mediates resistance to PI3Kalpha inhibition by activating the EGFR/PKC/mTOR axis in head and neck and esophageal squamous cell carcinomas. *Cancer Cell* **27**, 533–546 (2015).
111. Vora, S. R. et al. CDK 4/6 inhibitors sensitize PIK3CA mutant breast cancer to PI3K inhibitors. *Cancer Cell* **26**, 136–149 (2014).
112. Le, X. et al. Systematic functional characterization of resistance to PI3K inhibition in breast cancer. *Cancer Discov.* **6**, 1134–1147 (2016).
113. Tan, M. et al. Novel inhibitors of nuclear transport cause cell cycle arrest and decrease cyst growth in ADPKD associated with decreased CDK4 levels. *Am. J. Physiol. Renal Physiol.* **307**, F1179–F1186 (2014).
114. Wei, X.-L. et al. A first-in-human phase I study of CYH33, a phosphatidylinositol 3-kinase (PI3K) α selective inhibitor, in patients with advanced solid tumors. *J. Clin. Oncol.* **38**, e15645 (2020).
115. Liu, X. L. et al. Decrease in phosphorylated ERK indicates the therapeutic efficacy of a clinical PI3Kalpha-selective inhibitor CYH33 in breast cancer. *Cancer Lett.* **433**, 273–282 (2018).
116. Liu, X. L. et al. Unbiased screening reveals that blocking exportin 1 overcomes resistance to PI3Kalpha inhibition in breast cancer. *Signal Transduct. Target. Ther.* **4**, 49 (2019).
117. Kawai, H. et al. Overcoming tyrosine kinase inhibitor resistance in transformed cell harboring SEPT9-ABL1 chimeric fusion protein. *Neoplasia* **21**, 788–801 (2019).
118. Nie, D. et al. KPT-330 inhibition of chromosome region maintenance 1 is cytotoxic and sensitizes chronic myeloid leukemia to imatinib. *Cell Death Discov.* **4**, 48 (2018).
119. Pujade-Lauraine, E., Banerjee, S. & Pignata, S. Management of platinum-resistant, relapsed epithelial ovarian cancer and new drug perspectives. *J. Clin. Oncol.* **37**, 2437–2448 (2019).
120. Stordal, B. & Davey, M. Understanding cisplatin resistance using cellular models. *IUBMB Life* **59**, 696–699 (2007).
121. Kashyap, T. et al. Selinexor reduces the expression of DNA damage repair proteins and sensitizes cancer cells to DNA damaging agents. *Oncotarget* **9**, 30773–30786 (2018).
122. Ranganathan, P. et al. XPO1 inhibition using selinexor synergizes with chemotherapy in acute myeloid leukemia by targeting DNA repair and restoring topoisomerase IIα to the nucleus. *Clin. Cancer Res.* **22**, 6142–6152 (2016).
123. Chen, Y. et al. Inhibition of the nuclear export receptor XPO1 as a therapeutic target for platinum-resistant ovarian cancer. *Clin. Cancer Res.* **23**, 1552–1563 (2017).
124. Yamamoto-Sugitani, M. et al. Galectin-3 (Gal-3) induced by leukemia microenvironment promotes drug resistance and bone marrow lodgment in chronic myelogenous leukemia. *Proc. Natl Acad. Sci. USA* **108**, 17468–17473 (2011).
125. Fei, F. et al. Galectin-3 in pre-B acute lymphoblastic leukemia. *Leukemia* **27**, 2385–2388 (2013).
126. Hu, K. et al. Galectin-3 mediates bone marrow microenvironment-induced drug resistance in acute leukemia cells via Wnt/beta-catenin signaling pathway. *J. Hematol. Oncol.* **8**, 1 (2015).
127. Haudek, K. C. et al. Dynamics of galectin-3 in the nucleus and cytoplasm. *Biochim. Biophys. Acta* **1800**, 181–189 (2010).
128. Kazim, S. et al. Selective nuclear export inhibitor KPT-330 enhances the antitumor activity of gemcitabine in human pancreatic cancer. *Mol. Cancer Ther.* **14**, 1570–1581 (2015).
129. Amrutkar, M. & Gladhaug, I. P. Pancreatic cancer chemoresistance to gemcitabine. *Cancers* **9**, 157 (2017).
130. Vickers, M. M. et al. Comorbidity, age and overall survival in patients with advanced pancreatic cancer - results from NCIC CTG PA.3: a phase III trial of gemcitabine plus erlotinib or placebo. *Eur. J. Cancer* **48**, 1434–1442 (2012).
131. Recht, A. & Harris, J. R. Selection of patients with early-stage breast cancer for conservative surgery and radiation. *Oncology* **4**, 23–30 (1990).
132. Corrie, P. G. et al. Scheduling nab-paclitaxel combined with gemcitabine as first-line treatment for metastatic pancreatic adenocarcinoma. *Br. J. Cancer* **122**, 1760–1768 (2020).
133. De Vita, F. et al. NAB-paclitaxel and gemcitabine in metastatic pancreatic ductal adenocarcinoma (PDAC): from clinical trials to clinical practice. *BMC Cancer* **16**, 709 (2016).
134. Phi, L. T. H. et al. Cancer stem cells (CSCs) in drug resistance and their therapeutic implications in cancer treatment. *Stem Cell Int.* **2018**, 5416923 (2018).
135. Azmi, A. S. et al. Preclinical assessment with clinical validation of selinexor with gemcitabine and nab-paclitaxel for the treatment of pancreatic ductal adenocarcinoma. *Clin. Cancer Res.* **26**, 1338–1348 (2020).
136. Jain, P. et al. Clinical and molecular characteristics of XPO1 mutations in patients with chronic lymphocytic leukemia. *Am. J. Hematol.* **91**, E478–E479 (2016).
137. Abdul Razak, A. R. et al. First-in-class, first-in-human phase I study of selinexor, a selective inhibitor of nuclear export, in patients with advanced solid tumors. *J. Clin. Oncol.* **34**, 4142–4150 (2016).
138. Jardin, F. et al. Recurrent mutations of the exportin 1 gene (XPO1) and their impact on selective inhibitor of nuclear export compounds sensitivity in primary mediastinal B-cell lymphoma. *Am. J. Hematol.* **91**, 923–930 (2016).
139. Muqbil, I. et al. Anti-tumor activity of selective inhibitor of nuclear export (SINE) compounds, is enhanced in non-Hodgkin lymphoma through combination with mTOR inhibitor and dexamethasone. *Cancer Lett.* **383**, 309–317 (2016).
140. Chen, C. et al. Safety and efficacy of selinexor in relapsed or refractory multiple myeloma and Waldenstrom macroglobulinemia. *Blood* **131**, 855–863 (2018).
141. Vogl, D. T. et al. Selective inhibition of nuclear export with oral selinexor for treatment of relapsed or refractory multiple myeloma. *J. Clin. Oncol.* **36**, 859–866 (2018).
142. Chari, A. et al. Oral selinexor-dexamethasone for triple-class refractory multiple myeloma. *N. Engl. J. Med.* **381**, 727–738 (2019).
143. Podar, K., Shah, J., Chari, A., Richardson, P. G. & Jagannath, S. Selinexor for the treatment of multiple myeloma. *Expert. Opin. Pharmacother.* **21**, 399–408 (2020).
144. ASH Clinical news. FDA Grants Selinexor Accelerated Approval Despite Concerns with Trial Data https://www.ashclinicalnews.org/online-exclusives/fda-grants-selinexor-accelerated-approval-despite-concerns-trial-data/#: ~ :text=The%20U.S.%20Food%20and%20Drug,treatment%20with%20two%20or%20mor (2019).
145. US Food & Drug Administration. FDA grants accelerated approval to selinexor for multiple myeloma. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-selinexor-multiple-myeloma (2019).
146. Bahlis, N. J. et al. Selinexor plus low-dose bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma. *Blood* **132**, 2546–2554 (2018).
147. Dimopoulos, M. Weekly selinexor, bortezomib, and dexamethasone (SVd) versus twice weekly bortezomib and dexamethasone (Vd) in patients with multiple myeloma (MM) after one to three prior therapies: initial results of the phase III BOSTON study. *J. Clin. Oncol.* **38**, 8501 (2020).
148. Miguel, J. S. et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. *Lancet Oncol.* **14**, 1055–1066 (2013).
149. Chen, C. I. et al. Selinexor, pomalidomide, and dexamethasone (SPd) in patients with relapsed or refractory multiple myeloma. *Blood* **134**, 141–141 (2019).
150. Gavriatopoulou, M. et al. Integrated safety profile of selinexor in multiple myeloma: experience from 437 patients enrolled in clinical trials. *Leukemia* **34**, 2430–2440 (2020).
151. Forero-Torres, A. et al. Phase 2 study of frontline brentuximab vedotin monotherapy in Hodgkin lymphoma patients aged 60 years and older. *Blood* **126**, 2798–2804 (2015).
152. Ansell, S. M. et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N. Engl. J. Med.* **372**, 311–319 (2015).
153. Kuruvilla, J. et al. Selective inhibition of nuclear export with selinexor in patients with non-Hodgkin lymphoma. *Blood* **129**, 3175–3183 (2017).
154. Garzon, R. et al. A phase 1 clinical trial of single-agent selinexor in acute myeloid leukemia. *Blood* **129**, 3165–3174 (2017).
155. Fiedler, W. et al. A phase II study of selinexor plus cytarabine and idarubicin in patients with relapsed/refractory acute myeloid leukaemia. *Br. J. Haematol.* **190**, e169–e173 (2020).
156. Fiedler, W. et al. Phase II results of ara-C and idarubicin in combination with the selective inhibitor of nuclear export (SINE) compound selinexor (KPT-330) in patients with relapsed or refractory AML. *Blood* **128**, 341 (2016).
157. Alexander, T. B. et al. Phase I study of selinexor, a selective inhibitor of nuclear export, in combination with fludarabine and cytarabine, in pediatric relapsed or refractory acute leukemia. *J. Clin. Oncol.* **34**, 4094–4101 (2016).
158. Camus, V., Miloudi, H., Taly, A., Sola, B. & Jardin, F. XPO1 in B cell hematological malignancies: from recurrent somatic mutations to targeted therapy. *J. Hematol. Oncol.* **10**, 47 (2017).
159. Hing, Z. A. et al. Next-generation XPO1 inhibitor shows improved efficacy and in vivo tolerability in hematological malignancies. *Leukemia* **30**, 2364–2372 (2016).
160. Ranganathan, P. et al. Decitabine priming enhances the antileukemic effects of exportin 1 (XPO1) selective inhibitor selinexor in acute myeloid leukemia. *Blood* **125**, 2689–2692 (2015).
161. Gounder, M. M. et al. Phase IB study of selinexor, a first-in-class inhibitor of nuclear export, in patients with advanced refractory bone or soft tissue sarcoma. *J. Clin. Oncol.* **34**, 3166–3174 (2016).
162. Gandhi, U. H. et al. Clinical implications of targeting XPO1-mediated nuclear export in multiple myeloma. *Clin. Lymphoma Myeloma Leuk.* **18**, 335–345 (2018).
163. Senapedis, W. T., Baloglu, E. & Landesman, Y. Clinical translation of nuclear export inhibitors in cancer. *Semin. Cancer Biol.* **27**, 74–86 (2014).
164. Sukari, A., Muqbil, I., Mohammad, R. M., Philip, P. A. & Azmi, A. S. F-BOX proteins in cancer cachexia and muscle wasting: emerging regulators and therapeutic opportunities. *Semin. Cancer Biol.* **36**, 95–104 (2016).
165. Hightower, R. M. et al. The SINE compound KPT-350 blocks dystrophic pathologies in DMD zebrafish and mice. *Mol. Ther.* **28**, 189–201 (2020).
166. Tai, Y. T. et al. CRM1 inhibition induces tumor cell cytotoxicity and impairs osteoclastogenesis in multiple myeloma: molecular mechanisms and therapeutic implications. *Leukemia* **28**, 155–165 (2014).
167. Maracaja, D. L. V. et al. EBV-positive primary large B-cell lymphoma: the role of immunohistochemistry and XPO1 in the diagnosis of mediastinal lymphomas.

Appl. Immunohistochem. Mol. Morphol. https://doi.org/10.1097/PAI.0000000000000820 (2019).
168. García-Santisteban, I. et al. A cellular reporter to evaluate CRM1 nuclear export activity: functional analysis of the cancer-related mutant E571K. *Cell Mol. Life Sci.* **73**, 4685–4699 (2016).
169. Baumhardt, J. M. et al. Recognition of nuclear export signals by CRM1 carrying the oncogenic E571K mutation. *Mol. Biol. Cell* **31**, 1871–1891 (2020).
170. Camus, V. et al. Detection and prognostic value of recurrent exportin 1 mutations in tumor and cell-free circulating DNA of patients with classical Hodgkin lymphoma. *Haematologica* **101**, 1094–1101 (2016).
171. Jeromin, S. et al. SF3B1 mutations correlated to cytogenetics and mutations in NOTCH1, FBXW7, MYD88, XPO1 and TP53 in 1160 untreated CLL patients. *Leukemia* **28**, 108–117 (2014).
172. Wu, K., He, J., Pu, W. & Peng, Y. The role of exportin-5 in microRNA biogenesis and cancer. *Genomics Proteom. Bioinforma.* **16**, 120–126 (2018).
173. Sheng, P. et al. Dicer cleaves 5′-extended microRNA precursors originating from RNA polymerase II transcription start sites. *Nucleic Acids Res.* **46**, 5737–5752 (2018).
174. Xie, M. et al. Mammalian 5′-capped microRNA precursors that generate a single microRNA. *Cell* **155**, 1568–1580 (2013).
175. Muqbil, I., Bao, B., Abou-Samra, A. B., Mohammad, R. M. & Azmi, A. S. Nuclear export mediated regulation of microRNAs: potential target for drug intervention. *Curr. Drug Targets* **14**, 1094–1100 (2013).
176. Azmi, A. S. et al. DNA-methylation-caused downregulation of miR-30 contributes to the high expression of XPO1 and the aggressive growth of tumors in pancreatic ductal adenocarcinoma. *Cancers* **11**, 1101 (2019).
177. Azmi, A. S. et al. Exportin 1 (XPO1) inhibition leads to restoration of tumor suppressor miR-145 and consequent suppression of pancreatic cancer cell proliferation and migration. *Oncotarget* **8**, 82144–82155 (2017).
178. Sexton, R. et al. Targeting nuclear exporter protein XPO1/CRM1 in gastric cancer. *Int. J. Mol. Sci.* **20**, 4826 (2019).
179. Martinez, I. et al. An exportin-1-dependent microRNA biogenesis pathway during human cell quiescence. *Proc. Natl Acad. Sci. USA* **114**, E4961–E4970 (2017).
180. Leaderer, D. et al. Genetic and epigenetic association studies suggest a role of microRNA biogenesis gene exportin-5 (XPO5) in breast tumorigenesis. *Int. J. Mol. Epidemiol. Genet.* **2**, 9–18 (2011).
181. Kojima, K. et al. Prognostic impact and targeting of CRM1 in acute myeloid leukemia. *Blood* **121**, 4166–4174 (2013).
182. Blum, W. et al. Clinical response and miR-29b predictive significance in older AML patients treated with a 10-day schedule of decitabine. *Proc. Natl Acad. Sci. USA* **107**, 7473–7478 (2010).
183. Brinton, L. T. et al. Cotargeting of XPO1 enhances the antileukemic activity of midostaurin and gilteritinib in acute myeloid leukemia. *Cancers* **12**, 1574 (2020).
184. Yu, L. et al. Proteasome-dependent autoregulation of Bruton tyrosine kinase (Btk) promoter via NF-κB. *Blood* **111**, 4617–4626 (2008).
185. Woyach, J. A. et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. *N. Engl. J. Med.* **370**, 2286–2294 (2014).
186. Liu, Y., Azizian, N. G., Dou, Y., Pham, L. V. & Li, Y. Simultaneous targeting of XPO1 and BCL2 as an effective treatment strategy for double-hit lymphoma. *J. Hematol. Oncol.* **12**, 119 (2019).
187. Liu, X. et al. Reversible inhibitor of CRM1 sensitizes glioblastoma cells to radiation by blocking the NF-κB signaling pathway. *Cancer Cell Int.* **20**, 97 (2020).
188. Farren, M. R. et al. Selinexor, a selective inhibitor of nuclear export (SINE), shows enhanced activity in combination with PD-1/PD-L1 blockade in syngeneic murine models of colon cancer and melanoma. *J. Immunother. Cancer* **3** (Suppl. 2), P355 (2015).
189. Zhu, Z. C., Liu, J. W., Yang, C., Zhao, M. & Xiong, Z. Q. XPO1 inhibitor KPT-330 synergizes with Bcl-xL inhibitor to induce cancer cell apoptosis by perturbing rRNA processing and Mcl-1 protein synthesis. *Cell Death Dis.* **10**, 395 (2019).
190. Martin, A. P. et al. STK38 kinase acts as XPO1 gatekeeper regulating the nuclear export of autophagy proteins and other cargoes. *EMBO Rep.* **20**, e48150 (2019).
191. Kirli, K. et al. A deep proteomics perspective on CRM1-mediated nuclear export and nucleocytoplasmic partitioning. *eLife* **4**, e11466 (2015).
192. Shalem, O. et al. Genome-scale CRISPR-Cas9 knockout screening in human cells. *Science* **343**, 84–87 (2014).
193. Mathews Griner, L. A. et al. High-throughput combinatorial screening identifies drugs that cooperate with ibrutinib to kill activated B-cell-like diffuse large B-cell lymphoma cells. *Proc. Natl Acad. Sci. USA* **111**, 2349–2354 (2014).
194. Doench, J. G. Am I ready for CRISPR? A user's guide to genetic screens. *Nat. Rev. Genet.* **19**, 67–80 (2018).
195. Zhang, W. et al. Combinatorial targeting of XPO1 and FLT3 exerts synergistic anti-leukemia effects through induction of differentiation and apoptosis in FLT3-mutated acute myeloid leukemias: from concept to clinical trial. *Haematologica* **103**, 1642–1653 (2018).
196. Bhatnagar, B. et al. Selinexor in combination with decitabine in patients with acute myeloid leukemia: results from a phase 1 study. *Leuk. Lymphoma* **61**, 387–396 (2020).
197. Wei, X. X. et al. A phase II trial of selinexor, an oral selective inhibitor of nuclear export compound, in abiraterone- and/or enzalutamide-refractory metastatic castration-resistant prostate cancer. *Oncologist* **23**, 656–e64 (2018).
198. Shafique, M. et al. A phase II trial of selinexor (KPT-330) for metastatic triple-negative breast cancer. *Oncologist* **24**, 887–e416 (2019).
199. Nilsson, S. et al. Selinexor (KPT-330), an oral selective inhibitor of nuclear export (SINE) compound, in combination with FOLFOX in patients with metastatic colorectal cancer (mCRC) - final results of the phase I trial SENTINEL. *Curr. Cancer Drug Targets* https://doi.org/10.2174/1568009620666200628105727 (2020).
200. Vergote, I. B. et al. Phase 2 study of the exportin 1 inhibitor selinexor in patients with recurrent gynecological malignancies. *Gynecol. Oncol.* **156**, 308–314 (2020).
201. Tan, D. S. P. et al. Phase I study of the safety and tolerability of the exportin 1 (XPO1) inhibitor selinexor (SXR) in Asian patients (pts) with advanced solid cancers. *J. Clin. Oncol.* **33**, 2542–2542 (2015).
202. Lassman, A. B. et al. Efficacy and safety of selinexor in recurrent glioblastoma. *J. Clin. Oncol.* **37**, 2005–2005 (2019).
203. Gu, X. et al. Leukemogenic nucleophosmin mutation disrupts the transcription factor hub that regulates granulomonocytic fates. *J. Clin. Invest.* **128**, 4260–4279 (2018).
204. Wahba, A., Rath, B. H., O'Neill, J. W., Camphausen, K. & Tofilon, P. J. The XPO1 inhibitor selinexor inhibits translation and enhances the radiosensitivity of glioblastoma cells grown in vitro and in vivo. *Mol. Cancer Ther.* **17**, 1717–1726 (2018).
205. Colevas, A. D. Chemotherapy options for patients with metastatic or recurrent squamous cell carcinoma of the head and neck. *J. Clin. Oncol.* **24**, 2644–2652 (2006).
206. Wang, T. F., Chu, S. C., Kao, R. H., Yao, C. Y. & Li, C. C. A phase II study of weekly paclitaxel and epirubicin in recurrent or refractory squamous cell carcinoma of the head and neck. *Jpn. J. Clin. Oncol.* **38**, 459–463 (2008).

Acknowledgements
Given the space limitations of this Review, the authors apologize for their inability to cite all relevant studies. Work in the lab of A.S.A. is supported by NIH R37CA215427.

Author contributions
A.S.A., M.H.U. and R.M.M. made substantial contributions to each stage of the preparation of this manuscript for publication.

Competing interests
A.S.A. has acted as a consultant of GLG Consulting and GuidePoint, has received research grants from EISAI Janssen and Rhizen and has been a speaker at an event organized by Karyopharm. The author's institution has received research funding (partially supporting the phase Ib/II studies NCT02178436 and NCT03147885) from Karyopharm. M.H.U. and R.M.M. declare no competing interests.

Publisher's note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Supplementary information
Supplementary information is available for this paper at https://doi.org/10.1038/s41571-020-00442-4.