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The role of autophagy in resistance to targeted therapies

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ABSTRACT

Autophagy is a self-degradative cellular process, involved in stress response such as starvation, hypoxia, and oxidative stress. This mechanism balances macro-molecule recycling to regulate cell homeostasis. In cancer, autophagy play a role in the development and progression, while several studies describe it as one of the key processes in drug resistance. In the last years, in addition to standard anti-cancer treatments such as chemotherapies and irradiation, targeted therapy became one of the most adopted strategies in clinical practices, mainly due to high specificity and reduced side effects. However, similar to standard treatments, drug resistance is the main challenge in most patients. Here, we summarize recent studies that investigated the role of autophagy in drug resistance after targeted therapy in different types of cancers. We highlight positive results and limitations of pre-clinical and clinical studies in which autophagy inhibitors are used in combination with targeted therapies.

Introduction

Targeted therapies for cancer

Cancer is a multifactorial disease and one of the leading causes of death worldwide. Surgery, chemotherapy, and irradiation are the mainstream therapeutic approaches. Chemotherapeutic drugs act on rapidly dividing cells, but the main limitations are poor specificity and adverse effects. In the last years, a new generation of therapies have been developed to target cancer cells more specifically. Like conventional chemotherapy, targeted cancer therapies are based on compounds that inhibit cancer growth and metastasis [1]. However, they target specific cancer-associated pathways, reducing their impact on normal cells [2].

Targeted cancer therapies can be divided into 3 main groups: 1) monoclonal antibodies (mAbs), 2) small molecule inhibitors and 3) immunotoxins. Many of these approaches are already in different phases of pre-clinical and clinical trials.

According to the mechanism of action, MAbs can be divided into two classes: those that act independently of immune effector mechanisms, such as by induction of death signals mediated by cross-linking of surface receptor on the target cancer cell, or blocking an activation signal that is necessary for cancer cell growth; and those that require immune effector participation such as by antibody-dependent cellular cytotoxicity, complement mediated cytotoxicity and the ability of mAbs to alter the cytokine milieu or enhance development of an active anti-tumor immune response [3]. They are highly specific but can only interact with extracellular proteins as they cannot cross the plasma membrane. Over the past decade, multiple mAbs have gained approval by the U.S. Food and Drug Administration (FDA) to treat a wide range of cancers. Also, there are numerous pre-clinical and clinical trials involving mAbs for almost every type of cancer [1].

Small molecule inhibitors act by inhibiting proteins and blocking the activation of pathways that are dysregulated in cancer.

Tyrosine kinase (TK) inhibitors (TKIs) competitively bind to the active or inactive ATP binding site of a TK and are used to target proteins that are either downregulated or upregulated during cancer progression. When these molecules bind to their specific target, they block

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the tyrosine kinase domain and prevent the activation of downstream pathways. These drugs can be also used in conjunction with standard chemotherapy to improve therapeutic efficacy. To date inhibitors for over 20 different kinases have been developed and are in clinical trials [2]. Immunotoxins are basically modified mAbs or growth factors which have been conjugated to a toxin either by chemical bond or generated by recombinant DNA technology. The rationale is to deliver the toxin to a target expressed specifically by cancer cells.

Most of the pathways/targets of targeted therapy are also expressed by normal cells, thus targeted therapies are not free of adverse effects which limit their use. Most commonly reported adverse reactions are cutaneous rash, liver problem with haptic enzyme elevation, elevated blood pressure, coagulation defects up to rare gastrointestinal perforation. However, some mild side effects are associated with better outcome [4,5].

However, the main limitation of targeted therapy is the development of drug resistance [6]. Molecular characterization of resistant cell lines has revealed a diverse range of mechanisms, both genetic and non-genetic. Genetic mechanisms include mutation of the target, e.g. functional hyperactivation and mutation at the site of drug binding. Non-genetic mechanisms of resistance include oncogene switching, where a different protein substitutes the drug target, e.g. a growth factor receptor or kinase, or compensatory activation of other signaling pathways [7]. Also, autophagy has been shown to play an important role in resistance to targeted therapy in many different cancer types.

Autophagy

Autophagy is one of the most studied cellular processes through which intracellular components are delivered to lysosomes or other vacuoles for degradation [8]. Substrates of autophagy include aggregated proteins and damaged or excess organelles, e.g. mitochondria. The degradation products are recycled, which helps the cell to survive under different stress conditions (starvation and oxidative stress, etc.) [9]. Autophagy can be broadly classified into 3 sub-types: macroautophagy, microautophagy, and chaperone-mediated autophagy [10]. This review focuses on macroautophagy, which henceforth will be referred to as autophagy. Autophagy is characterized by the formation of autophagosomes: an isolation membrane (phagophore) encloses cytoplasmatic material or organelles forming the autophagosome, which then fuses with lysosomes.

Autophagosome formation is driven by autophagy-related proteins (ATGs), which form the autophagy activating kinase (ULK) complex, and regulatory proteins such as AMP-activated protein kinase (AMPK), mammalian target of rapamycin complex 1 (mTORC1), vacuolar protein sorting 34 (VPS34), p150, Beclin 1, B cell lymphoma 2 (BCL-2), and others [11]. It can be divided into four steps:

1) Initiation: Proteins needed to initiate the membrane formation are recruited [12].
2) Nucleation: Nucleation leads to the formation of the autophagosome membrane from the membrane source [13].
3) Expansion: This phase occurs until the complete formation of the autophagosome. The ATG12-ATG5- ATG16L1 complex mediates the lipidation of microtubule-associated protein 1A/1B-light chain 3 (LC3), which recruits the autophagy targets [14].
4) Degradation: Autophagosome-lysosome fusion is mediated by LAMP-2 and the small GTPase Rab7 [15].

In cancer, autophagy plays a crucial role in several processes including tumorigenesis, drug resistance, metastasis, microenvironment interactions [16]. Some studies have demonstrated that autophagy counteracts tumorigenesis, and mice deficient for various effectors of autophagy show an increase in spontaneous tumors [17,18]. Prolonged autophagy can also result in so-called “autophagic cell death” or “type II programmed cell death” [19,20]. On the other hand, autophagy is known to counteract different types of cellular stress (e.g. oxidative and endoplasmic reticulum stress) as induced by chemotherapy, radiotherapy and other types of cancer treatments [21–24]. Moreover, autophagy is involved in the recycling of some receptors resulting in reduced target therapy efficacy, thus and autophagy-deficient cells are more sensitive to target therapies [25].

Because of these biological effects, several autophagy inhibitors are being used in combination with different cancer treatments, including targeted therapies, to improve cytotoxic effects or revert drug resistance.

The most important autophagy inhibitors are:

Chloroquine (CQ) is widely known as a last stage inhibitor of autophagy as it interrupts the autophagosome-lysosome fusion step. CQ and its derivative hydroxychloroquine (HCQ) are the only FDA-approved drugs currently used in clinical trials, often combined with standard treatments [25].

Bafilomycin A1 (BafA1) also blocks the autophagosome-lysosome fusion by inhibiting V-ATPase, which prevents lysosome acidification [26].

3-Methyladenine (3-MA) blocks autophagy at an early stage, inhibiting class III phosphatidylinositol 3-kinase (PI3K). It is not considered a specific autophagy inhibitor, because it can also inhibit class I PI3Ks. Indeed, in some contexts, it can promote autophagy [27].

Specific and potent autophagy inhibitor-1 (Spautin-1) is an inhibitor of USP10 and USP13, that promotes the degradation of the PIK3C3/VSP34-Beclin 1 complex, thereby inhibiting autophagy [28].

Lys 05 is a CQ derivative that inhibits autophagy by accumulating in the lysosome [29].

Breast cancer

Endocrine therapy

Hormone receptor-positive breast cancer (BC) is the most common type of BC with approximately 70% of tumors expressing hormone receptors (estrogen receptor (ER) or progesterone receptor) [30]. The majority of these patients receive endocrine therapy such as selective estrogen receptor modulators (SERMs), most commonly tamoxifen (TAM); aromatase inhibitors (AIs) such as exemestane and letrozole, and selective ER degraders such as fulvestrant [31]. In the clinic, the efficacy of these treatments is often limited by intrinsic or acquired resistance [32,33] and several studies have shown that the aforementioned drugs induce autophagy, which is associated with resistance [30].

Initially, autophagy was interpreted as a tumor-suppressive mechanism as, non-viable ER + MCF-7 cells showed increased numbers of autophagosomes after 4-hydroxy-tamoxifen (4-OHT) treatment [34]. Samaddar et al. suggested that autophagy was activated as a survival mechanism following 4-OHT treatment but failed to rescue the cells [35]. Both Samaddar et al. and Qadir et al. showed that TAM/4-OHT combined with autophagy inhibition (3-MA, bafilomycin A1 or siRNAs targeting Beclin 1, ATG5 and ATG7) restored the sensitivity to TAM/4-OHT in resistant MCF-7 cells [32,35]. Accordingly, overexpression of Beclin 1 induced resistance to SERMs 4-OHT and raloxifene [36]. Also, TAM-resistant and both TAM- and fulvestrant-resistant cells could be re-sensitized by the autophagy inhibitor CQ [37]. Additionally, resistance to the AI exemestane could be reverted to some extent by 3-MA and Spautin-1 [38,39].

In this context, different players were identified to regulate autophagy and anti-estrogen resistance (Table 1). Prolylcarboxypeptidase, glucose-regulated protein 78 and the long non-coding RNA H19 mediated 4–OHT resistance by up-regulating autophagy [40–42] whereas microRNA (miR)-214 increased the TAM and fulvestrant sensitivity in antiestrogen-resistant MCF-7 cells by inhibiting authophagy [43].

Table 1
Summary of targeted therapies in which autophagy is involved in resistance.

	DRUG	CLASS	TARGET	CANCER SUBTYPE AND STAGE OF TREATMENT	EXPERIMENTAL MODEL	AUTOPHAGY MECHANISM/EFFECT	REF
LUNG	Bevacizumab	TKI	VEGF 1/2	*First-line therapy of unresectable, relapsed and/or metastatic NSCLC patients (also EGFR mutated)	TCGA data set analysis of LCs vs healthy patients LUAD-CLs A549, H1299, H1688, H446	The cytotoxic effect of Bevacizumab is improved by the UPSis Bortezomib/ MG132 induction of autophagy which culminates in the AGR2 degradation	[134]
	Erlotinib	TKI	EGFR	*First-line therapy of advanced and/or metastatic NSCLC patients EGFR mutated	NSCLC-CLs HCC827^{19del}, HCC4006^{19del}, H358^{wt}, and H1975$^{L858R/T790M}$	Addition of autophagy inhibitors enhances the erlotinib sensitivity to the cells	[106]
					LUAD-CLs A549, NCI-H1299, NCI-H292, NCI-H1650 and SK-MES-1	The EGFR inhibition of erlotinib induces impairment in PI3K/Akt/mTOR/p70S6K pathway activation which directly regulates autophagy flux	[107]
					Clinical phase I study on advanced NSCLC patients previously responded to EGFR inhibitor	The administration of CQ and HCQ in combination with erlotinib is safe and well-tolerated. No robust clinical effect has been reported, except for an EGFR-mutant patient.	[108]
	Afatinib	TKI	EGFR ErbB2-3–4	*Adult NSCLC patients locally advanced and/or metastatic EGFR mutated	LUAD-CLs H1975$^{L858R/T790M}$ and H1650^{del19} LC mouse models	Akt/mTOR and Erk pathways regulate the afatinib-induced autophagy, leading to inhibition of Caspase-3 partially mediated apoptosis in H1975 and H1650	[109]
	Crizotinib	ALKi	ALK HGFR c-Met ROS1	*First/second-line therapy for NSCLC patients ALK and/or ROS1 mutated	LUAD-CLs A549, H1299 H3122, and H3122CR-1 LC mouse models	The Crizotinib resistant H3122 CL showed a different regulation of PI3K/Akt/mTOR, strictly correlated to the autophagy activation	[115]
	Vismodegib	SHHi	SMO (smoothened)	**Phase II clinical trial in patients with extensive-stage SCLC	hLUAD-CLs A549 and NCI-H1975 LUAD xenograft mouse model	Vismodegib resistance is promoted by autophagy that inhibits apoptosis by ROS elimination and GLI2 pathway up-regulation	[135]
	Trametinib	MEKi	MEK1/2	*Adult NSCLC advanced patients BRAF V600 mutated	KRAS^{G12D}/TP53^{Null} mouse lung derived SC196 & SC274 Murine LC-CL SC274 $^{KRASG12D/TP53Nu}$	The MEK1/2 inhibition with Trametinib increased autophagy-mediated resistance to the drug, reverted by the use of CQ.	[111]
BREAST	Tamoxifen (TAM)	SERM	ER	*Postmenopausal patients with advanced HR + BC	MCF-7 and T-47D ER + BC cell lines	autophagy inhibition sensitized TAM/4-OHT- resistant cells to TAM/4-OHT	[35]
					MCF-7 ER + BC cell line	4-OHT resistannt in BC cells overexpressed PRCP which mediated resistance by up-regulating autophagy. Inhibition of PRCP blocked development of 4-OHT resistance and restored 4-OHT sensitivity in resistant cells.)	[41]
					MCF-7 (sensitive and TAM-resistant) ER + cell lines MCF-7- TAMR-Tet-shH19 xenograft mouse model BC patient- derived tissues	lncRNA H19 induced tamoxifen resistance in breast cancer by activating autophagy via the H19/SAHH/DNMT3B axis.	[41]
	Raloxifene (4-OHT)	SERM	ER	**Study of Tamoxifen and Raloxifene (STAR) in BC in postmenopausal women.	MCF-7 andBeclin 1-overexpressing MCF-7	Beclin-1 overexpression in BC cells, induced anti-estrogen resistance by sequestering ERα	[37]
	Fulvestrant (4-OHT)	Selective ER degrader	ER	*Postmenopausal advanced HR + BC patients	MCF-7 (sensitive and TAM-resistant), LCC9 and ZR-75–1 ER + BC cell lines MCF-7 and LCC9 xenograftmouse model	CQ increased anti-estrogen responsiveness of TAM- and/or Fulvestrant- in resistant cell lines and TAM + CQ treatment sensitized TAM-resistant xenografts	[37]
					MCF-7, (sensitive and TAM-resistant), MCF-7/LCC1 and MCF-7/LLC9 ER + BC cell lines LCC1 and LCC9 xenograft mouse model DMBA-induced BC rat model	Inhibition of GRP78 restored anti-estrogen sensitivity through the activation of TSC2/AMPK signaling leading to autophagy inhibition. Concurrent Beclin 1 and GRP78 knockdown synergistically reduced proliferation under Fulvestrant treatment	[40]
	Exemestane	AI	Aromatase	**Phase II clinical trial in advanced BC			

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Table 1 (*continued*)

	DRUG	CLASS	TARGET	CANCER SUBTYPE AND STAGE OF TREATMENT	EXPERIMENTAL MODEL	AUTOPHAGY MECHANISM/EFFECT	REF
					aromatase-overexpressing MCF-7, and LTEDaro ER + BC cell lines	Autophagy as a cytoprotective mechanism in acquired resistance to AIs, inhibition of autophagy and/or the PI3K pathway restored AI sensitivity	[38]
	Palbociclib	CDK4/6 inhibitor	CDK4/6	Locally advanced/metastatic HR+, HER2 negative BC	MCF-7, T-47D, ZR75-1, MDA-MB-231, HCC38, HCC1806, MDA-MB-157 MCF-7 xenograft mouse models BC PDX mouse models Data set analysis (TCGA)	BC cells activate autophagy after CDK4/6 inhibition as an escape mechanism from apoptosis. Palbociclib combined with autophagy inhibition decreased proliferation of cells *in vitro* and tumor growth *in vivo*	[45]
	Trastuzumab (lapatinib) (erlotinib) (gefitinib)	TKI	HER2	early stage or metastatic HER2 + BC, usually in combination with chemotherapyor alone after chemotherapy	SKBR-3 (sensitive and trastuzumab -resistant) HER2 + BC cell line	Autophagy is enhanced in trastuzumab-resistant cells and its inhibition sensitized cells to trastuzumab	[49]
					BT-474 and MCF-7 adherentHER2 + BC cells and spheroids	3D culture of BT-474 cells allowed formation of a protective microenvironment against trastuzumab, which could be overcome by the administration of autophagy inhibitors.	[136]
					JIMT-1 and SKBR-3 HER2 + BC cell lines JIMT-1 BCxenograft mouse model	Knockdown of ATG genes inhibited intrinsic resistance to trastuzumab,lapatinib, erlotinib and gefitinib.Treatment of JIMT-1 xenografts with trastuzumab + CQ and trastuzumab treatment of ATG12-silenced xenografts reduced tumor growth	[51,54]
					SKBR-3 and BT-474 HER2 + BC cell lines (both sensitive and trastuzumab-resistant) Patient clinical data and tissue samples	P130Cas protected HER2 from autophagic degradation by impairing its ubiquitination, thus conferring resistance to trastuzumab. P130Cas expression increased in tumor samples from patients who developed resistance to trastuzumab treatment.	[55]
					MCF-7 and MDA-MB-468 HER2 + BC cell lines	Inhibition of eEF-2 reduced pro-survival autophagy and increased response to trastuzumab, lapatinib and gefitinib.	[50]
	Lapatinib	TKI	EGFR HER2	In combination with capecitabine or trastuzumab in advanced/metastatic BC patients	MCF7, SKBR3, MDA-MB-361, and BT-474 HER2 + BC cell lines	Beclin-1 binds HER2 and promotes its phosphorylation. Lapatinib blocks this interaction, allowing the induction of autophagy by Beclin-1.	[137]
					BT-474 and AU-565 HER2 + BC cell lines	Autophagy inhibition enhances lapatinib sensitivity of lapatinib-resistant cells.	[53]
PROSTATE	Enzalutamide	Antiandrogen	Androgen receptor	Adult metastatic/no metastatic patients to a high level of risk CRPC	LNCaP Mice	Under enzalutamide treatment transmission electron microscopy induces an increase of autophagy vesicles (AVs) (induced by autophagy upregulation), confirming from the expression of the autophagy-proteins LC-3, ATG5 and Beclin 1 is increased while p62 is reduced.	[119]
	Abiraterone acetate (AA) (ZYTIGA)	Antiandrogen	CYP17 LHRH	Metastatic hormone			
				sensitive prostate cancer, mHSPC /metastatic castration resistant prostate cancer, mCRPC	LNCaP	AA increased autophagy in LNCaP cells demonstrated by the upregulation of ATG5 and LC3 and accumulation autophagosomes.	[123]
	Everolimus	mTORi	mTOR VEGF			Everolimus (EVS) used against (CRPC), there is a correlation between NPRL2 and EVS, NPRL2. NPRL2 overexpression induced tumor cell proliferation, resistance to EVS, whereas NPRL2 silencing inhibited proliferation. NPRL2 silencing promoted the activity enhanced mTOR signaling, and the decrease of autophagy	[118]

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Table 1 (*continued*)

	DRUG	CLASS	TARGET	CANCER SUBTYPE AND STAGE OF TREATMENT	EXPERIMENTAL MODEL	AUTOPHAGY MECHANISM/EFFECT	REF
						induced by NPRL2- silencing in EVS-treated CRPC cells was associated with the increase of apoptosis.	
COLON-RECTUM	Bevacizumab	TKI	VEGF		HT-29 Mice	Bevacizumab promoted autophagy, as evidenced by the appearance of autophagic vacuoles.	[61]
	Cetuximab	TKI	EGFR				
	Apatinib (YN968D1)	TKI	VEGFR-2		HT29 HCT116 MICE	Apatinib induced autophagy in colon cancer cells. inhibiting autophagy could stimulate ER stress associated CRC cell apoptosis both *in vitro* and *in vivo*, suggesting a protecting role of apatinib induced autophagy	[64,65]
	Cabozantinib (XL184)	TKI	MET VEGFR2		HCT116 HT29	The inhibition of multiple kinase pathways produces a change in metabolism from glycolysis to autophagy	
LIVER	Sorafenib	TKI	BRAF/CRAF VEGFR PDGFR FLT-3 FGFR-1	*Not responders HCC patients or not eligible for surgery	HCC	Autophagy is responsible for orchestrating adaptive responses to sorafenib in HCC. Inhibition of autophagy using either pharmacological inhibitors (chloroquine, 3-MA or bafilomycin A1) or essential autophagy gene (Beclin1 or Atg5) knockdown enhances the cytotoxicity of sorafenib against HCC cells, indicating that autophagy induced by sorafenib acts as a protective pathway	[99,102]
LEUKEMIA	Imatinib	TKI	BCR-Abl C-Kit PDGF	*First line in CML/ALL (Ph +) patients	Human CML K562 cell line	miRNA-30a induces apoptosis by inhibiting pro-autophagic genes expression (ATG-5 and Beclin-1)	[75]
	Dasatinib	TKI	BCR-Abl EPH C-Kit PDGFβ	*Second Line in CML/CLL patients	$p53^{wt}/p53^{del17}$ primary CLL Lymphocytes	Mutated p53 form inhibits autophagy resistance mechanism	[76]
	Ponatinib	TKI	BCR-abl RET c-KIT FGFR PDGFR VEGFR	*In LMC/$LLA^{Das/Nil-Res}$ (Ph +) or T315I mutated patients	Human $KCL22^{Pon-Res}$ PDX mouse models	Alternative mTOR target strategies sensitize TKI-resistant CML cells	[138]
	Perifosine	AKTi	AKT	**Clinical Trial Phase II on refractory/ relapsed LMC Patients	Human AML Kasumi-1, HL-60 Human CML K562	Perifosine-induced Autophagy due to up-regulation of ATG5	[77]
	Vorinostat	HDACi	HDAC	**Clinical Trial Phase II on AML/MDS patients	AML-CLs Kasumi-1 $^{t(8;21);}$ SKNO-1 $^{t(8;21)}$; HL60 Primary human AML-CL	Autophagy is activated by HDACi vorinostat in response to the accumulation of ubiquitinated proteins among which AML-ETO1.	[78]
LYMPHOMA	Bortezomib	UPSi	Proteasome 26S	*In MCL patients not eligible for ASCT	DLBCL derived ABC (su-DHL 8) and GCB (su-DHL 4) cell lines	The Bortezomib induced autophagy leads to a gained IκBα degradation with related up-regulation of NF-κB-regulated genes involved in the resistance	[81]
					D1/CDK4 aberrant MCL-CLs	The complex D1/CDK4 inhibits autophagy induced by Bortezomib, which in this way cannot lead to the NOXA degradation	[82]
					Primary effusion lymphoma cell line	Bortezomib induces a pro-survival autophagy activation, correlated with the expression/degradation of ER stress protein CHOP, BIP, and JNK	[83]
	Everolimus	mTORi	mTOR FKBP-12	**Clinical phase II trials on patients with w relapsed/refractory HL that has progressed after high-dose chemotherapy or ASCT	MCL-CL	Autophagy induced by drug promotes resistance by blocking the AKT-mTOR targeting	[84]
	Temsirolimus	mTORi	mTOR FKBP-12	*Adult MCL patients refractory/relapsed	BL-CL Namalwa, Raji, Daudi, Ramos, and DLBCL-CL	The co-administration of Tensirolimus with HDACi enhances the cytotoxic effect on tumor cells by the inhibition of autophagy	[85]
	Crizotinib	ALKi	ALK HGFR	**Clinical phase I/II trial on younger ALCL patients		Pharmacological or genetic autophagy inhibition potentiates the anti-tumoral activity of ALK inactivation.	[86]

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	DRUG	CLASS	TARGET	CANCER SUBTYPE AND STAGE OF TREATMENT	EXPERIMENTAL MODEL	AUTOPHAGY MECHANISM/EFFECT	REF
			c-Met ROS1		Karpas-299 $^{t(2;5)}$ and SU-DHL-1 $^{t(2;5)}$ ALK-positive ALCL-CLs and ALCL mouse models		
	Milatuzumab	mAb	CD74	**Clinical phase I/II trial on relapsed/ refractory B-cell NHL	Primary human MCL-CLand mouse models	Milutuzumab cytotoxicity is promoted by FTY720 which inhibits the autophagy-mediated degradation of CD74	[87]
MULTIPLE MYELOMA	Bortezomib	UPSi	Proteasome 26S	*Treated MM patients in progression, not eligible for ASCT or MM patients not eligible for any treatment.	Primary MM-CLs Bim^{-hi}/Bim-l^{ow}	Bim shows a dualistic role in Bortezomib resistant MM cells Bim^{-hi}/Bim^{-low}. The blockade of autophagy regulates alternatively the activation/inhibition of this apoptosis inducer	[89]
					MM-CLs	Bortezomib induces cytoprotective autophagy GRP78-mediated to increase the degradation of the accumulated unfolded protein.	[90]
	Carfilzomib	UPSi	Proteasome 20S	*Adult MM patients after first-line therapy	MM-CLs ANBL-6, INA-6, and JJN3	Carfilzomib induces permanently elevated levels of SQSTM1 protein involved in autophagosome formation and misfolded protein degradation.	[91]
	Sorafenib	TKI	BRAF/ CRAFVEGFR PDGFR FLT-3 FGFR-1	**Sorafenib in treating patients with relapsed or refractory MM	CD138 + hMM-CLs OPM-2, U-266, LP1, NCI-H929, Karpas 620, and RPMI-8226; 5T33MM-CL mouse models Clinical study on MM patients bone marrow samples	Sorafenib inhibits ERK activation but contemporary induces cytoprotective autophagy activation, with related up-regulation of anti-apoptotic Mcl-1 protein	[139]
PANCREAS	Trametinib	MEKi	MEK1/2	**Trametinib and HCQ in treating patients with pancreatic cancer	PDAC-CLs Mia-PaCa2, BxPC3 or PDX220$^{KRAS\ mut}$ PDA mouse models with KRAS$^{wt/\ mutated}$ cell lines	The combination of MEK1/2 inhibition plus autophagy inhibitor increases the regression of PDA-CLs RAS mutated.	[111]
	Binimetinib	MEKi	MEK1/2	**Binimetinib and HCQ in treating patients with KRAS mutant metastatic pancreatic cancer	hPDAC-CLs Pa01C, Pa02C, Pa04C, Pa14C and Pa16C Murine derived iKRAS cell line	Acute KRAS/ERK suppression increased autophagy by impairing metabolic processes	
MELANOMA	PLX4720 (Vemurafenib)	B-RAFi	B-RAF	Used in melanoma patients with mutation BRA-F V600E	A375 A375P SKMEL5, MEL1617 Mice	The blockade of BRAF combined with the pharmacological inhibition of Autophagy could be an important strategy to improve the efficacy of Vemurafenib on cells resistant to it, *in vitro* but also *in vivo*.	[114,115]
	Dabrafenib	B-RAFi	B-RAF	Used in melanoma patients with mutation BRA-F V600E, in clinical it is used with trametinib	A375 MEL624$^{B\text{-}RAFres}$	Autophagy is regulated by ER stress, they found a significantly PERK protein level reduction, after treatment with PERK siRNA in both A375 and MEL624 cells. The viability assay demonstrated that Dabrafenib group was more resistant to the treatment in comparison to the cotreatment group. These findings support the protective role of autophagy in melanoma cells to Dabrafenib treatment.	[116]

* http://www.ema.europa.eu.
** https://clinicaltrials.gov.

In vivo studies have shown that CQ and H19 knockdown restored the antiestrogen-sensitivity in TAM-resistant xenografts [37,42].

Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors including palbociclib have been approved for the treatment of advanced ER + human epidermal growth factor receptor 2 (HER2)-negative BC in combination with an AI or fulvestrant [44]. Vijayaraghavan et al. showed that palbociclib activated autophagy in MCF-7 cells *in vitro* and *in vivo*. Inhibition of autophagy (HCQ, CQ, Lys05, Spautin-1, bafilomycin A1 or Beclin 1 /ATG5 knockdown) sensitized the cells to CDK4/6 inhibitors including palbociclib [45] and combined treatment induced senescence *in vitro*. *In vivo*, the combination of palbociclib with HCQ or Lys05 led to a massive growth reduction of xenograft tumors. Based on these results a clinical trial is currently evaluating the efficacy of neoadjuvant letrozole and palbociclib with HCQ in ER + HER2- BC (ClinicalTrials.gov Identifier: NCT03774472).

HER2-targeted therapy

HER2-positive tumors comprise approx. 25% of BC cases and correlate with an aggressive phenotype and poor prognosis [46]. However, the development of HER2-targeted therapy represents a milestone in the treatment of this BC subtype and by now several agents targeting HER2 are available: the mABs trastuzumab and pertuzumab, mAb-drug conjugates like trastuzumab, and the TKIs lapatinib and neratinib [47,48]. HER2-targeted therapy is usually combined with chemotherapy, often in a neoadjuvant and adjuvant setting [31]. Unfortunately, 70% of patients develop resistance to trastuzumab treatment within a year [47].

Trastuzumab as well as lapatinib have been shown to induce autophagy *in vitro* [49,50], and cell lines with intrinsic or acquired resistance to trastuzumab [49,51,52] or lapatinib [53] exhibit increased basal autophagy.

Vazquez-Martin et al. observed that in trastuzumab-resistant HER2 + SKBR-3 cells the enhanced basal autophagy was further increased by trastuzumab treatment. Autophagy inhibition with 3-MA reduced viability and siRNA-mediated knockdown of LC3 decreased proliferation and re-sensitized the cells to trastuzumab [49]. Also HER2 + JIMT-1 cells intrinsically resistant to HER2-targeting drug, treatment with CQ or knockdown of ATG genes re-sensitized the cells to trastuzumab as well as lapatinib [54].

In a screen of more than 50 BC cell lines, Cufi et al. found that the autophagy protein ATG12 is commonly up-regulated in trastuzumab-resistant HER2-overexpressing cell lines. ATG12 silencing reduced the resistance of JIMT-1 cells to trastuzumab, lapatinib, erlotinib and gefitinib *in vitro*. *In vivo*, ATG12-silenced JIMT-1 xenografts exhibited markedly reduced tumor growth and trastuzumab treatment decreased tumor growth massively [51]. Also LC3 knockdown increased the sensitivity of JIMT-1 cells to trastuzumab, lapatinib, erlotinib, and gefitinib [52]. The combination of trastuzumab with CQ increased apoptosis and reduced cell viability and colony formation of JIMT-1 cells *in vitro* and decreased tumor volume by 90% *in vivo* [52]. In lapatinib-resistant BT-474 and AU-565 cell lines combination of CQ or 3-MA with lapatinib decreased cell proliferation and colony formation and enhanced apoptosis [53].

One of the mechanisms of action of trastuzumab involves the binding-mediated degradation of HER2. Bisaro et al. found that the p130Cas, a signaling protein involved in adhesion, migration and invasion, protects HER2 from being degraded by autophagy by preventing its ubiquitination. P130Cas is elevated in trastuzumab-resistant HER2 + BT-474 and SKBR-3 cell lines and histological samples of trastuzumab-unresponsive BC patients [55].

Taken together, all the described studies indicate that autophagy plays a major role in mediating resistance to targeted therapies for HER2-positive BC. This is supported by the observation that loss of the BECN1 gene encoding Beclin 1 correlates with an improved clinical response to trastuzumab [58]. Hence, autophagy inhibition in combination with targeted therapy for HER2-positive BCs is a promising path that should be evaluated in clinical trials. Nevertheless, caution should be taken as the role of autophagy in BC is controversial. There are also results showing that in lapatinib-sensitive BT-474 and AU-565 cells 3-MA treatment reduced the cytotoxic effect of lapatinib because in this case lapatinib-induced autophagy promoted apoptosis [56].

Colorectal cancer

Colorectal cancer (CRC) is one of the most diagnosed cancer worldwide being the fourth in United States. The incidence of CRC has declined in the last 40 years from 60.5 per 100.000 in 1976 to 40,7 in 2013, as well as the peak mortality has decreased from 28,6 in 1976 to 14.1 in 2014. Despite this, CRC represents a leading cause for cancer death worldwide [57].

The targeted therapies proven most effective in the treatment of CRC are targeting angiogenesis (e.g. bevacizumab, apatinib, cabozantinib) and the epidermal growth factor receptor (EGFR) (e.g. cetuximab) (Table 1) [58]. Bevacizumab is a recombinant humanized monoclonal antibody that binds to vascular endothelial growth factor A (VEGF-A) and blocking the VEGF-receptor 2 (VEGFR2) signaling [59,60]. Zhao et al. showed that bevacizumab induces autophagy in CRC cell lines, as evidenced by the appearance of autophagic vacuoles, punctate patterns of LC3 and the accumulation of Beclin 1. Inhibiting autophagy using CQ or RNA interference targeting Beclin 1 and ATG5 promotes bevacizumab-induced apoptosis and inhibits proliferation, suggesting that autophagy plays a protective role. The same results were obtained *in vivo*: inhibiting autophagy using CQ or small interfering RNA in combination with bevacizumab significantly inhibits tumor growth *in vivo* compared to bevacizumab alone. In the same study, bevacizumab increases hypoxia-inducible factor 1α (HIF-1α) expression. HIF-1α inhibition (YC-1) markedly reduced autophagy. These results suggest that hypoxia-induced autophagy in tumor cells may function as an adaptive response to hypoxia caused by anti-angiogenic therapy [61].

Apatinib (investigational compound YN968D1) is a TKI of the vascular endothelial growth factor receptor-2 (VEGFR2) [62]. It also inhibits other TKs such as c-Kit and c-SRC TKs, and reduces ABCB1 and ABCG2 transporters [63]. Lu et al. presented the first evidence that apatinib induces autophagy in colon cancer cells by inhibiting the AKT-mTOR signaling pathway [64]. Cheng et al. discovered that apatinib directly induces ER stress stimulating autophagy through the upregulation of the Inositol-requiring enzyme 1 (IRE1) signaling pathway. Meanwhile, inhibiting autophagy could stimulate ER stress-associated CRC cell apoptosis both *in vitro* and *in vivo*, suggesting a protective role of apatinib-induced autophagy. Blocking autophagy using CQ or a siRNA targeting ATG5 could significantly induce apoptosis in CRC cell lines *in vitro*. Additionally, the combination of CQ with apatinib has a greater suppressive effect in subcutaneous xenografts in nude mice compared with apatinib or CQ alone [65].

Cabozantinib (XL184) is an orally bioavailable inhibitor of multiple kinases involved in cell growth, angiogenesis and metabolism including VEGFR2/KDR, MET, AXL, RET, TIE2, and c-Kit. MET and VEGFR2 dual inhibition is central for cabozantinib effects [69]. Scott et al. observed a significant increase in autophagy following cabozantinib treatment in the HCT116 and HT29 CRC cell lines [66]. The inhibition of multiple kinase pathways produces a metabolic dysregulation, with a reduction of glycolysis leading to cell death. In this context autophagy act as a salvage mechanism promoting drug resistance. A combination of cabozantinib with autophagy inhibitors increases apoptosis in HCT116 and HT29 cell lines [66].

Cetuximab is a chimeric, anti-EGFR monoclonal IgG1 class antibody. It blocks EGFR signaling and modulates tumor cell growth by inhibiting proliferation, angiogenesis, and differentiation, and preventing metastasis [67,68]. Li et al. found that cetuximab induces

autophagy by two different mechanisms involving PI3K type I and type III. The EGFR/class-IPI3K/Akt/mTOR signaling pathway normally inhibits autophagy, and by disrupting this signal cetuximab activates autophagy. Moreover, cetuximab decreases BCL-2 thorough HIF-1 downregulation, this releases beclin 1 to form a complex with class III PI3K, which directedly induces autophagy [69]. PI3K–AKT–mTOR signaling pathway is one of the most dysregulated pathways in cancer as it regulates many cellular processes such as metabolism, motility and growth. For this reason, about 40 different inhibitors are being evaluated at different stages of clinical research [70]. Class III PI3K plays a fundamental role in autophagy, vesicular trafficking and phagocytosis, however, its role in cancer still remains elusive [70]. In the same direction, Guo et al. demonstrated that cetuximab induces autophagy in Caco-2 CRC cells [71].

Hematologic malignancies

Leukemia is cancer of the body's blood-forming tissues, including the bone marrow and the lymphatic system. There are different kinds of leukemia depending on the hematopoietic lineage and maturity of the aberrant cells. However, the most common kinds are acute myeloid leukemia (AML), acute lymphoid leukemia (ALL), chronic myeloid leukemia (CML) and chronic lymphoid leukemia (CLL) [72]. Typically, most forms of leukemia are treated with a standard multi-drug regimen for myelosuppression: anthracycline, alkylating agents (cyclophosphamide), corticosteroids and vinca alkaloids (vincristine). Targeted therapies are currently used mainly in CML, where the standard treatment includes imatinib, a TKI targeting BCR-ABL (Philadelphia Chromosome disease), c-Kit and platelet-derived growth factor (PDGF) receptors (Table 1) [73]. Recent studies highlight the role of autophagy in the resistance to this drug. Yu et al. demonstrated that imatinib inhibits the expression of miR-30a in CML patients primary cell lines [74]. miR-30a negatively regulates autophagy by directly targeting Beclin 1 and ATG5, thus its inhibition increases autophagy. Knockdown of Beclin 1 and ATG5 by miR30 or using shRNA reestablish imatinib cytotoxic effect [75]. Administration of other TKIs, such as dasatinib and ponatinib increases autophagy as a drug resistance mechanism. A study by Amrein et al. demonstrated that dasatinib induces autophagy in CLL primary lymphocytes and that CQ re-sensitize the cells [76]. Similarly, Mitchel et al. highlighted that ponatinib induces BCR-ABL-independent resistance in CML cells, through alternative activation of mTOR signaling. The pharmacological or genetic blockade of mTOR and autophagy enhanced the sensitivity of ponatinib-resistant CML cells to cell death *in vitro* and *in vivo* [80]. Similarly, Tong et al. showed that autophagy in inhibition can re-sensitize CML cells to perifosine, which targets PI3K/AKT/mTOR signaling pathway [77].

One more example in the context of AML is given by Torgersen et al. They showed that in AML1-ETO-positive AML cells, apoptosis induced by histone deacetylase (HDAC) inhibitors valproic acid and vorinostat is limited by the upstream activation of autophagy. Blocking autophagy results in enhanced caspase activity and apoptotic cell death [78].

Lymphoma is a heterogeneous group of chronic malignancies characterized by different etiopathogenesis, clinical behavior and response to treatment. Typically, the aberrant proliferation of precursor/mature lymphoid cells is restricted to lymphatic organs [79]. Lymphoma treatment depends on the tumor subtype and stage. Typically, for the more aggressive forms, the standard approach is CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOP-like combination chemotherapy, which can be combined with anti-CD20 mAb therapy (rituximab plus/or obinutuzumab) [80].

In the last decades, many molecular targeted therapies (mAbs or small molecule inhibitors) have been developed to treat lymphomas. For instance, bortezomib is a proteasome inhibitor that can kill cancer cells by blocking IκBα degradation, resulting in NF-κB inhibition, or by preventing the degradation of pro-apoptotic proteins. Recent studies on activated B-cells and germinal center B-cells derived from diffuse large B-cell lymphoma (DLBCL) (su-DHL 8 and su-DHL 4) demonstrated that bortezomib antagonizes the constitutive activation of NF-κB induced by TNF-α or TRAIL. Bortezomib resistance is mediated by the activation of the autophagy machinery, which is necessary for the degradation of many ubiquitinated proteins, including IκBα. Autophagy block using CQ reverted the resistance by preventing IκBα degradation and restored NF-κB activity [81]. Using the same approach, Heine et al. also explained that in D1/CDK4-aberrant mantle cell lymphoma (MCL) cell lines (Mino, Jeko-1, Rec-1, Jvm2, and Granta-519) exposed to bortezomib, the pro-apoptotic protein NOXA is efficiently expressed only when the D1/CDK4 complex inhibits autophagy, otherwise NOXA gets degraded [82]. Also, Granato et al. found that bortezomib induces the upregulation of proteins involved in ER stress and apoptosis (CHOP, BIP, and JNK) in primary effusion lymphoma cell lines. The pro-survival role of autophagy could be reversed by the administration of autophagy inhibitors or by the silencing of ATG genes [83].

The mTOR kinase inhibitors everolimus and temsirolimus have shown strong cytotoxicity in pre-clinical and clinical models of some hematological malignancies. Rosich et al. demonstrated that, in MCL cell lines, everolimus-induced autophagy promoted resistance by preventing AKT-mTOR targeting. This effect was reversed by genetic or pharmacological autophagy inhibition with CQ or ATG gene knockdown [84]. Moreover, Dong et al. showed that the HDAC inhibitor valproic acid (VPA) increased temsirolimus efficacy on Burkitt lymphoma (BL) cell lines (Namalwa and Raji) through autophagy and MYC inhibition. The authors confirmed the results also in pre-clinical mouse models of BL, reporting a significant decrease in tumor growth and contemporary MYC inhibition in the group receiving a combination of temsirolimus and an HDAC inhibitor [85].

Recent studies have shown that ALK-expressing anaplastic large cell lymphoma cells treated with ATP-competitive inhibitors targeting ALK and c-Met develop autophagy-mediated resistance. Mitou et al. demonstrated that crizotinib inactivated ALK, thereby increasing autophagy, which plays a pro-survival role and could be counteracted by the administration of autophagy inhibitors [86]. A very interesting study by Alinari et al. reported that FTY720 (fingolimod) and milatuzumab (anti-CD74 mAb) act synergistically on MCL cell line. FTY720 leads to increased expression of CD74 by blocking its autophagy-mediated degradation, thus increasing mAb efficacy [87].

Multiple Myeloma (MM) is a cancer originating from terminally differentiated plasma cells. The patients show bone marrow infiltration of clonal cells and the presence of monoclonal antibodies in the peripheral blood [88]. Standard treatments include a combination of bortezomib and lenalidomide which increased the five-year survival to 49% in the last years [88]. Chen et al have demonstrated that bortezomib-resistant cell display Bcl-2-like protein 11 (Bim) downregulation. HDACis and BH3 mimetics can revert the resistance by increasing Bim levels but this was correlated with Bim-associated autophagy regulation. Indeed, CQ was required to induce cell lethality [89]. Also, Jagannathan et al. have shown that bortezomib activates autophagy as a compensatory mechanism for the accumulation of unfolded proteins. Moreover, they have reported that the co-administration with metformin suppressed glucose-regulated protein 78 (GRP78), a key effector of bortezomib-induced autophagy, thus enhancing apoptosis [90]. Recent studies on MM demonstrated that carfilzomib, an irreversible proteasome inhibitor, induces overexpression of SQSTM1/p62, a cargo protein associated with autophagosomes. Co-administration with CQ sensitizes MM cells to the targeted therapy [91].

Liver cancer

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer [92]. Currently, surgical resection is recommended for very early stage and early stage HCC following chemo-/radiotherapy, but HCC is still prone to recurrence and metastasis after surgery and there is still no effective treatment for patients with advanced,

metastatic or drug-resistant HCC [93,94]. Therefore, it is essential to elucidate the mechanisms of tumorigenesis, metastasis, and drug resistance in HCC and to identify effective and safe therapeutic strategies and prognostic biomarkers [95]. In HCC, autophagy inhibition in combination with targeted therapy have shown a great potential in improving the efficacy on tumor cells while having a lesser effect on normal cells (Table 1) [96]. This provides the foundation for promising targeted therapy for HCC through autophagy inhibition.

Sorafenib (BAY 43–9006, Nexavar®), an oral multi-kinase inhibitor, remains the only FDA approved systemic drug for patients with advanced HCC [97,98]. Studies have shown that sorafenib treatment enhances autophagy in HCC cells, and is responsible for orchestrating adaptive responses to sorafenib. Inhibition of autophagy using either pharmacological inhibitors (CQ, 3-MA or bafilomycin A1) or knockdown of essential autophagy genes (Beclin 1 or ATG5) enhances the cytotoxicity of sorafenib in HCC cells, indicating that autophagy induced by sorafenib acts as a protective mechanism [99–102]. Shi et al. found that direct stimulation of ER stress by sorafenib in HCC cells induces autophagy via the upregulation of the IRE1 pathway and that inhibition of autophagy promotes ER stress-related apoptosis of HCC cells *in vitro* and *in vivo*. These results support the hypothesis that sorafenib-induced ER stress signals are critical for the induction of autophagy. Their data indicate that all the chemical and genetic autophagy inhibitors, 3-MA, CQ and ATG5 siRNA knockdown, potentiate sorafenib-induced cell death. They have also demonstrated that inhibition of autophagic degradation resulted in ER stress potentiation. Therefore, sorafenib-induced autophagy alleviated ER stress, diminishing the apoptotic signals and thus suppressing cell death [99].

Lung cancer

Lung cancer is the deadliest type of cancer worldwide with 1.7 million deaths each year [103]. It is classified into two groups: small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC), which make up 15% and 85% of lung cancer cases, respectively [104]. NSCLC is classified into squamous cell carcinoma (30%), large cell carcinoma (10%) and adenocarcinoma (40%) [105].

Standard treatment involves surgery followed by adjunct chemotherapy or radiation.

A large variety of drugs have been approved for targeted therapy in lung cancer: anti-angiogenic drugs, inhibitors targeting mutated proteins like EGFR, ALK, ROS1, and BRAF (Table 1).

Autophagy is well described as a mechanism of resistance to targeted therapy in lung cancer. The anti-angiogenic mAb bevacizumab synergizes with the proteasome inhibitors MG132 or bortezomib, which are also known to block autophagic flux, in lung cancer cells both *in vitro* and *in vivo*, suggesting a role in bevacizumab resistance. Studies [106,107] have shown that treatment with erlotinib, an EGFR TKI, induces autophagy in EGFR-mutated cell lines. In a non-sensitive EGFR wild type cell line, blocking autophagy with CQ decreases cell viability. Goldberg et al. [108] performed a phase 1 clinical trial treating NSCLC patients with HCQ with and without erlotinib and found that HCQ with or without erlotinib is safe and well-tolerated. Another clinically approved EGFR inhibitor, afatinib, was found to act synergistically in combination with CQ and 3-MA in EGFR-mutated NSCLC cell lines (H1975 and H1650) both *in vitro* and *in vivo* [109]. Crizotinib (PF02341066), an inhibitor of the ALK fusion oncoprotein, is clinically approved for the treatment of ALK-positive NSCLC patients. Its effectiveness is reduced after approximately a year of treatment due to the onset of resistance of the tumor. It was found that crizotinib-resistant cells downregulate ALK expression due to autophagy upregulation and the combination with CQ was able to overcome resistance [110]. Vismodegib, an inhibitor of the sonic hedgehog homolog pathway, is already used in lung adenocarcinoma (LUAD). A study has shown that vismodegib increases autophagy in LUAD cell lines and that the inhibition of autophagy with siRNAs targeting ATG5 or ATG7 increases its antiproliferative effect *in vitro*. Furthermore, its combination with CQ enhances anti-LUAD efficacy *in vivo*. The FDA has approved the BRAF inhibitor dabrafenib in combination with the MEK inhibitor trametinib for patients with $BRAF^{V600E}$ NSCLCs. Kinsey et al. found that in $BRAF^{V600E}$ cell lines (BxPC3) trametinib increases autophagic flux and its inhibition by CQ enhanced cytotoxicity [111]. Karsli-Uzunbas et al. conditionally deleted ATG7 in adult mice. Interestingly, acute autophagy ablation in mice with preexisting NSCLC blocked tumor growth, promoted tumor cell death, and inhibited more benign disease (oncocytomas) [112].

Melanoma

Melanoma is one of the main causes of cancer-related death worldwide, representing the most invasive and metastatic skin tumor type. Unfortunately, only a small proportion of patients with metastatic melanoma survive more than 10 years after the diagnosis of the disease. There are different types of targeted therapy approved by the FDA for melanoma with mutations in the BRAF gene, which result in the constitutive activation of the RAS/RAF/MEK/ERK pathway (Table 1). They include inhibitors targeting BRAF directly (vemurafenib, dabrafenib, encorafenib) or the MEK proteins (trametinib, cobimetinib, binimetinib) which act downstream of BRAF. In most cases, patients with a BRAF mutation receive both a BRAF and a MEK inhibitor, as combining these drugs often shows better response [113].

Recent studies have demonstrated the ability of BRAF inhibitors to induce autophagy as part of a transcriptional program that upregulates lysosome biogenesis/function, driven by the TFEB transcription factor. In $BRAF^{V600E}$-mutated xenografts, TFEB was inactivated independently from mTORC1, associated with high levels of TGF-β and more aggressive histopathological features [114]. BRAF inhibition activates JNK2/p38, which in turn phosphorylates ZKSCAN3, alleviating the repression of TFEB and increasing the production of lysosomal/autophagic factors. ZKSCAN3 (ZNF306) belongs to a family of zinc-finger transcription factors harboring KRAB and SCAN domains. It is a transcriptional repressor of the autophagy–lysosome network, and is regulated in conjunction with TFEB during starvation/lysosome activation. Inhibition of autophagy or the lysosomal pathway increases TGF-β levels, which leads to increased tumor aggressiveness. Treatment of the human melanoma cell line A375 expressing $BRAF^{V600E}$ with the BRAF inhibitor PLX4720, a progenitor of vemurafenib, leads to increased levels of the autophagy marker LC3 and degradation of p62 in a dose-dependent manner. The authors have highlighted that the $BRAF^{V600E}$-TFEB/ZKSCAN3-autophagy-lysosomal axis is a signaling pathway that works together with TGF-β and the EMT machinery, inducing tumor progression, metastasis and resistance to BRAF-targeted therapy in melanoma [114].

The evaluation of autophagic markers in different BRAF inhibitor sensitive (A375P, SKMEL5, MEL1617) and resistant (MEL1617R, WM983BR, MEL624) human melanoma cancer cell lines confirmed that after treatment with the BRAF inhibitor PLX4720, LC3-II/LC3-I ratio is significantly increased and p62 insignificantly reduced in all cell lines [120]. Ma et al. have demonstrated that treatment of these cell lines with vemurafenib induces binding of the mutant BRAF to the ER stress gatekeeper GRP78, which rapidly increases ER stress. Dissociation of GRP78 from the PKR-like ER-kinase promotes the PERK-dependent ER stress response which activates cytoprotective autophagy. In this system, combined BRAF and autophagy inhibition (HCQ) promotes tumor regression in BRAF inhibitor-resistant xenografts [115].

Treatment with the BRAF inhibitor dabrafenib induces a dose-dependent activation of autophagy in both sensitive (A375) or resistant (MEL624) human melanoma cell lines. In this context, dabrafenib activates ER stress-dependent autophagy, whereas PERK silencing attenuated autophagy. Autophagy inhibition (3-MA) increases the dabrafenib effect and restores sensitivity in resistant cell lines [116]. Xie et al. deleted ATG7 in $BRAF^{V600E}$-mutated melanoma cells [122] showing

that ATG7 deficiency in melanoma xenografts dramatically increases the survival of these mice. $BRAF^{V600E}$ inhibition results in larger tumor volume reduction in ATG7 null mice [117]. In conclusion, autophagy plays a key role in the resistance of BRAF mutant melanoma to BRAF inhibitors. Mutant BRAF can induce resistance to BRAF inhibitors through autophagy in multiple ways, including the subsequent increase in ATP synthesis, oxidative stress or ER stress. Therefore, autophagy can be considered a potential therapeutic target.

Prostate cancer

Prostate cancer (PC) is the most common cancer in men. While most types of prostate cancer grow slowly and may need minimal or even no treatment, other types are aggressive and can spread quickly.

The mTOR inhibitor everolimus is an important drug used in the treatment of prostate cancer, in particular for castration-resistant prostate cancer (CRPC) (Table 1). NPRL2 expression is upregulated in PC, particularly in CRPC where it induces tumor cell proliferation and resistance to everolimus. NPRL2 silencing inhibits proliferation, enhances mTOR signaling and decreased autophagy, which is associated with an increase in apoptosis [118].

Androgen deprivation or treatment with the anti-androgens enzalutamide or bicalutamide increased autophagic flux in PC cells *in vitro* and in PC models *in vivo* [119]. This effect is reduced by the knockdown of ATG5 and Beclin 1 or inhibition of the androgen-induced mTOR pathway [120]. Treatment with EPI-001 (EPI), an androgen receptor inhibitor, reduces cell growth and increases apoptosis in PC cells. Also, EPI-treated cells showed increased autophagosome formation [121]. The combination of EPI with autophagy inhibitors further reduces cell viability significantly. Therefore, this combination may offer a strategy to overcome resistance mechanisms in advanced PC [121].

Androgen deprivation therapy is a common therapy used in the clinic to treat PC, but in CRPC the remaining low levels of androgens are sufficient to activate androgen receptor signaling, which can be altered on several levels. Under enzalutamide treatment transmission electron microscopy has shown an increase in autophagy vesicles (AVs) (induced by autophagy upregulation), and increased expression of the autophagy-proteins LC3, ATG5 and Beclin 1 while p62 was reduced [122,123]. Interestingly, the combination of Abiraterone acetate (AA) and the autophagy inhibitor 3-MA greatly decreased the number of AVs. Inhibition of autophagy impaired cell viability, increased apoptosis, and induced G2/M cell cycle arrest [122,123].

(AA) increased autophagy in LNCaP cells as demonstrated by the upregulation of ATG5 and LC3 and the accumulation of autophagosomes [123]. Cells treated with the autophagy inhibitor 3-MA, or a combination of AA with 3-MA show lower expression of both ATG5 and Beclin 1, which is associated with a reduction of LC3-I and LC3-II [123]. Upregulation of autophagy induces resistance to AA and survival of LNCaP cells and AA treatment in combination with 3-MA increases apoptosis [123].

Limitations and perspectives

Several studies highlight that autophagy represents a pivotal process in cancer. Here, we have reported many studies in which autophagy is triggered by targeted therapy and results in drug resistance. Consequently, autophagy inhibitors, in most cases, revert the resistance and increase drugs effects *in vitro* and *in vivo*. However, it is questionable that different targeted therapy blocking different pathways in several cancer types will end up in the activation of a similar response to promote drug resistance. To address this issue, we have summarized the most relevant targeted therapies associated pathways in Fig. 1. It is to be noted that almost all targeted therapies interfere directedly or undirectedly with tyrosine kinases that have the MEK-ERK signaling pathway downstream. MEK-ERK pathway inhibition leads to the activation of LKB1 → AMPK → ULK1 signaling axis, a key regulator of autophagy [111,124]. In addition to this, autophagy can be triggered by several mechanisms associated with targeted therapy such as activation of Beclin 1 through class III PI3K, induction of oxidative and endoplasmic reticulum stress, alteration of AKT-mTOR pathway. Similarly, there are several mechanisms by which autophagy can contribute to drug resistance and survival. For instance, autophagy contributes to cell homeostasis by eliminating damaged organelles such as mitochondria and ER, and protein aggregates. Thanks to this action, autophagy can mitigate metabolic, oxidative and endoplasmic reticulum stresses [125,126]. Several studies report that these cellular stresses contribute to cell death following targeted therapies. For example, vemurafenib and bortezomib mediate cell death through ER stress in melanoma and pancreatic cancer [127,128] as well as apatinib in colorectal [65]. Similarly, erlotinib induces cell death through metabolic oxidative stress in head and neck squamous carcinoma [129]. In addition, autophagy can be involved in target recycling thus reducing the efficacy of targeted therapies [25]. Besides autophagy, many other resistance mechanisms have been identified and divided in three main categories: (1) alterations of the drug target, (2) alterations in upstream and downstream effectors resulting in pathway reactivation and (3) bypass mechanisms [130]. All these mechanisms require deep alteration at genetic or epigenetic level, which develop over time under selective pressure. On the contrary, autophagy is a generic response that is activated by a variety of cellular stress in a short time (within minutes to hours). Moreover, it does not require deep genetic or epigenetic alteration or selective pressure. Based on this, autophagy can be defined as an early and unique mechanism by which cancer cell counteracts the effect of targeted-therapy-induced stress. Indeed, drugs targeting autophagy are being tested in different clinical trials, in combination with standard chemotherapy or targeted therapy. However, there are limitations and concerns that need to be addressed. Autophagy has a dual role which is highly dependent on the specific context. Knockdown of autophagy-related genes increases the incidence of cancer in many tissues and, in certain conditions, it can contribute to cell death by a process named autosis. Moreover, autophagy is necessary for physiological processes in many cells such as immune system regulation, metabolism and senescence [131,132]. Indeed, autophagy inhibitors such as CQ and HCQ, which have been largely used to treat malaria and autoimmune disease, are not free of sides effects that range from skin rush to muscle weakness up to gastrointestinal and neurological disorders, and irreversible retinopathy. The severity of side effects becomes more important in long term treatments. In addition, CQ might exacerbate chemotherapy-related injuries in organs such as kidney, brain, heart and hematopoietic cells [133]. One additional important limitation concerns drugs specificity as both CQ and HCQ do not specifically inhibits autophagy. They rather accumulate into acidic cellular compartments and interfere with lysosomal function thus affecting autophagy as well as other cellular functions. For these reasons, it would be ideal to have a specific marker to identify those patients in which autophagy plays a major role and maximize treatments effect. Unfortunately, this marker is not available yet as monitoring autophagy *in vivo*, especially in humans, is particularly challenging.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

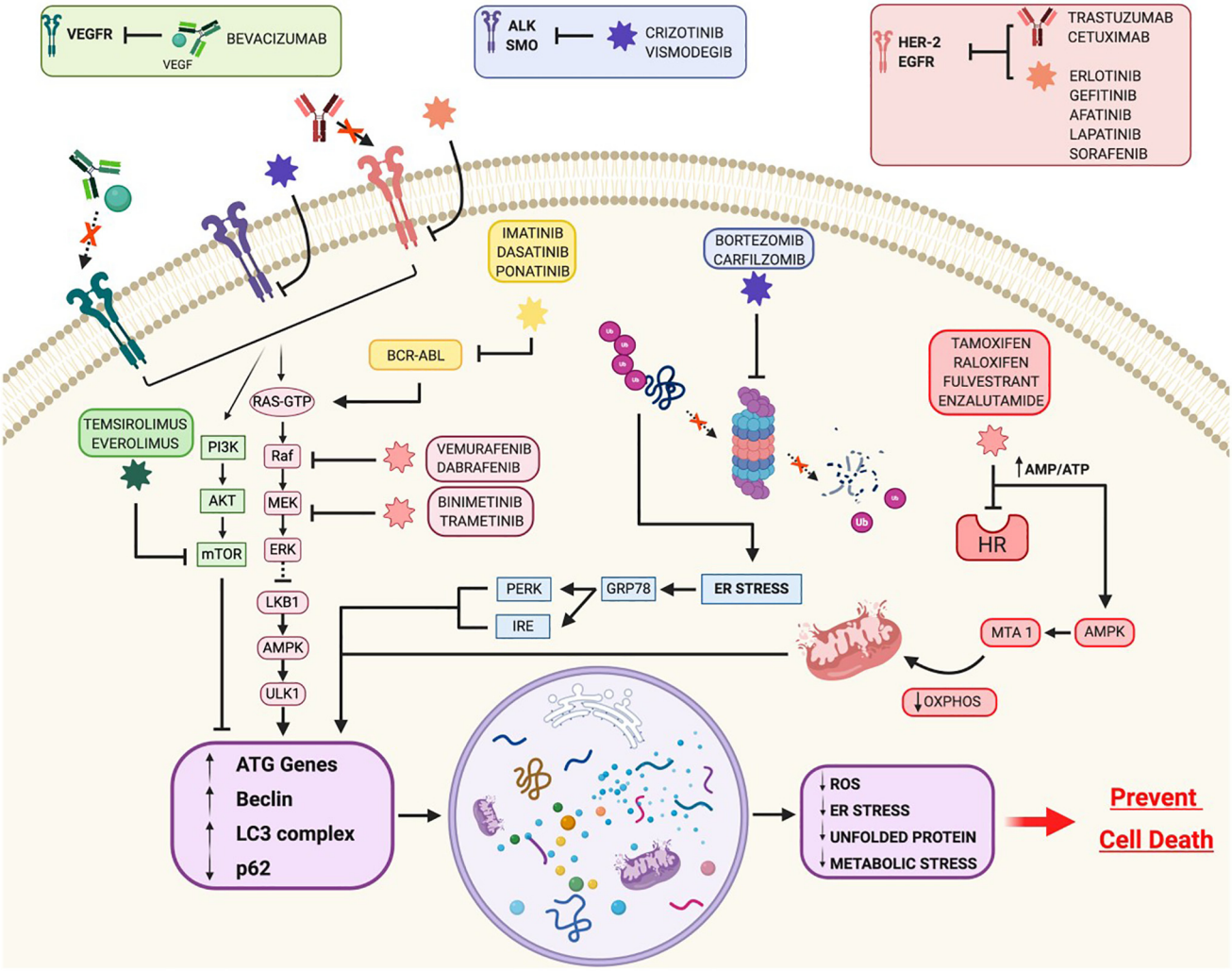

Fig. 1. Simplified schematic summary of the different mechanisms by which targeted therapies can induce autophagy. Several targeted therapy drugs impact, directedly or undirectedly, on the MEK-ERK signaling and induce autophagy by activating the LKB1 → AMPK → ULK1 signaling axis, a key regulator of autophagy. Many others impact on AKT-mTOR signaling which is the master autophagy regulator pathway. Proteasome inhibitors causes the accumulation of unfolded protein, which induce ER stress drive autophagy (ER-phagy). Hormones receptors blockade affect mitochondrial function, which induces mitochondria driven autophagy (mitophagy). Activation of autophagy machinery promote cell survival and drug resistance by mitigating cellular stress such as ER, oxidative and metabolic stresses. This must be considered a simplified schematic as many of this mechanisms can be activated contemporarily in different context, e.g. vemurafenib is a Raf inhibitor but it can also induce cell death through ER stress.

References

[1] Baudino TA. Targeted cancer therapy: the next generation of cancer treatment. Curr Drug Discov Technol 2015;12:3–20.

[2] Gerber DE. Targeted therapies: a new generation of cancer treatments. Am Fam Physician 2008;77:311–9.

[3] Torka P, Barth M, Ferdman R, Hernandez-Ilizaliturri FJ. Mechanisms of resistance to monoclonal antibodies (mAbs) in lymphoid malignancies. Curr Hematol Malig Rep 2019;14:426–38. https://doi.org/10.1007/s11899-019-00542-8.

[4] Cai J, Ma H, Huang F, Zhu D, Bi J, Ke Y, et al. Correlation of bevacizumab-induced hypertension and outcomes of metastatic colorectal cancer patients treated with bevacizumab: a systematic review and meta-analysis. World J Surg Oncol 2013;11:306. https://doi.org/10.1186/1477-7819-11-306.

[5] Petrelli F, Borgonovo K, Cabiddu M, Lonati V, Barni S. Relationship between skin rash and outcome in non-small-cell lung cancer patients treated with anti-EGFR tyrosine kinase inhibitors: a literature-based meta-analysis of 24 trials. Lung Cancer 2012;78:8–15. https://doi.org/10.1016/j.lungcan.2012.06.009.

[6] Longley D, Johnston P. Molecular mechanisms of drug resistance. J Pathol 2005;205:275–92. https://doi.org/10.1002/path.1706.

[7] Lackner MR, Wilson TR, Settleman J. Mechanisms of acquired resistance to targeted cancer therapies. Future Oncol 2012;8:999–1014. https://doi.org/10.2217/fon.12.86.

[8] Mizushima N. A brief history of autophagy from cell biology to physiology and disease. Nat Cell Biol 2018;20:521–7. https://doi.org/10.1038/s41556-018-0092-5.

[9] Li X, Zhou Y, Li Y, Yang L, Ma Y, Peng X, et al. Autophagy: a novel mechanism of chemoresistance in cancers. Biomed Pharmacother 2019;119:109415https://doi.org/10.1016/j.biopha.2019.109415.

[10] Mizushima N, Komatsu M. Autophagy: renovation of cells and tissues. Cell 2011;147:728–41. https://doi.org/10.1016/j.cell.2011.10.026.

[11] Lamb CA, Yoshimori T, Tooze SA. The autophagosome: origins unknown, biogenesis complex. Nat Rev Mol Cell Biol 2013;14:759–74. https://doi.org/10.1038/nrm3696.

[12] Alers S, Löffler AS, Wesselborg S, Stork B. Role of AMPK-mTOR-Ulk1/2 in the regulation of autophagy: cross talk, shortcuts, and feedbacks. Mol Cell Biol 2012;32:2–11. https://doi.org/10.1128/MCB.06159-11.

[13] Russell RC, Tian Y, Yuan H, Park HW, Chang Y-Y, Kim J, et al. ULK1 induces autophagy by phosphorylating Beclin-1 and activating VPS34 lipid kinase. Nat Cell Biol 2013;15:741–50. https://doi.org/10.1038/ncb2757.

[14] Mizushima N, Yoshimori T, Ohsumi Y. The role of Atg proteins in autophagosome formation. Annu Rev Cell Dev Biol 2011;27:107–32. https://doi.org/10.1146/annurev-cellbio-092910-154005.

[15] He C, Klionsky DJ. Regulation mechanisms and signaling pathways of autophagy. Annu Rev Genet 2009;43:67–93. https://doi.org/10.1146/annurev-genet-102808-114910.

[16] White E. Deconvoluting the context-dependent role for autophagy in cancer. Nat Rev Cancer 2012;12:401–10. https://doi.org/10.1038/nrc3262.

[17] Yue Z, Jin S, Yang C, Levine AJ, Heintz N. Beclin 1, an autophagy gene essential for early embryonic development, is a haploinsufficient tumor suppressor. Proc Natl Acad Sci U S A 2003;100:15077–82. https://doi.org/10.1073/pnas.2436255100.

[18] Choi AMK, Ryter SW, Levine B. Autophagy in human health and disease. N Engl J Med 2013;368:651–62. https://doi.org/10.1056/NEJMra1205406.

[19] Mathew R, Karantza-Wadsworth V, White E. Role of autophagy in cancer. Nat Rev Cancer 2007;7:961–7. https://doi.org/10.1038/nrc2254.

[20] Mele L, La Noce M, Paino F, Regad T, Wagner S, Liccardo D, et al. Glucose-6-phosphate dehydrogenase blockade potentiates tyrosine kinase inhibitor effect on breast cancer cells through autophagy perturbation. J Exp Clin Cancer Res 2019;38.. https://doi.org/10.1186/s13046-019-1164-5.

[21] Cave DD, Desiderio V, Mosca L, Ilisso CP, Mele L, Caraglia M, et al. S-Adenosylmethionine-mediated apoptosis is potentiated by autophagy inhibition induced by chloroquine in human breast cancer cells. J Cell Physiol 2018;233:1370–83. https://doi.org/10.1002/jcp.26015.

[22] Lamberti M, Porto S, Zappavigna S, Stiuso P, Tirino V, Desiderio V, et al. Levofolene modulates apoptosis induced by 5-fluorouracil through autophagy inhibition: Clinical and occupational implications. Int J Oncol 2015;46:1893–900. https://doi.org/10.3892/ijo.2015.2904.

[23] Jain K, Paranandi KS, Sridharan S, Basu A. Autophagy in breast cancer and its implications for therapy. Am J Cancer Res 2013;3:251–65.

[24] Mele L, Paino F, Papaccio F, Regad T, Boocock D, Stiuso P, et al. A new inhibitor of glucose-6-phosphate dehydrogenase blocks pentose phosphate pathway and suppresses malignant proliferation and metastasis in vivo. Cell Death Dis 2018;9. https://doi.org/10.1038/s41419-018-0635-5.

[25] Janser Félice A, Tschan Mario P, Rupert L. The role of autophagy in HER2-targeted therapy. Swiss Med Wkly 2019;149. https://doi.org/10.4414/smw.2019.20138.

[26] Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). - PubMed - NCBI 2016. doi.org/10.1080/15548627.2015.1100356.

[27] Wu YT, Tan HL, Shui G, Bauvy C, Huang Q, Wenk MR, et al. Dual role of 3-methyladenine in modulation of autophagy via different temporal patterns of inhibition on class I and III phosphoinositide 3-kinase. J Biol Chem 2010;285:10850–61. https://doi.org/10.1074/jbc.M109.080796.

[28] Liu J, Xia H, Kim M, Xu L, Li Y, Zhang L, et al. Beclin1 controls the levels of p53 by regulating the deubiquitination activity of USP10 and USP13. Cell 2011;147:223–34. https://doi.org/10.1016/j.cell.2011.08.037.

[29] McAfee Q, Zhang Z, Samanta A, Levi SM, Ma X-H, Piao S, et al. Autophagy inhibitor Lys05 has single-agent antitumor activity and reproduces the phenotype of a genetic autophagy deficiency. Proc Natl Acad Sci 2012;109:8253–8. https://doi.org/10.1073/pnas.1118193109.

[30] Waks AG, Winer EP. Breast Cancer Treatment: A Review. JAMA - J Am Med Assoc 2019;321:288–300. https://doi.org/10.1001/jama.2018.19323.

[31] Harbeck N, Gnant M. Breast cancer. Lancet 2017;389:1134–50. https://doi.org/10.1016/S0140-6736(16)31891-8.

[32] Qadir MA, Kwok B, Dragowska WH, To KH, Le D, Bally MB, et al. Macroautophagy inhibition sensitizes tamoxifen-resistant breast cancer cells and enhances mitochondrial depolarization. Breast Cancer Res Treat 2008;112:389–403. https://doi.org/10.1007/s10549-007-9873-4.

[33] Lui A, New J, Ogony J, Thomas S, Lewis-Wambi J. Everolimus downregulates estrogen receptor and induces autophagy in aromatase inhibitor-resistant breast cancer cells. BMC Cancer 2016;16:487. https://doi.org/10.1186/s12885-016-2490-z.

[34] Bursch W, Ellinger A, Kienzl H, Török L, Pandey S, Sikorska M, et al. Active cell death induced by the anti-estrogens tamoxifen and ICI 164 384 in human mammary carcinoma cells (MCF-7) in culture: the role of autophagy. Carcinogenesis 1996;17:1595–607. https://doi.org/10.1093/carcin/17.8.1595.

[35] Samaddar JS, Gaddy VT, Duplantier J, Thandavan SP, Shah M, Smith MJ, et al. A role for macroautophagy in protection against 4-hydroxytamoxifen-induced cell death and the development of antiestrogen resistance. Mol Cancer Ther 2008;7:2977–87. https://doi.org/10.1158/1535-7163.MCT-08-0447.

[36] John S, Nayvelt I, Hsu H-C, Yang P, Liu W, Das GM, et al. Regulation of estrogenic effects by beclin 1 in breast cancer cells. Cancer Res 2008;68:7855–63. https://doi.org/10.1158/0008-5472.CAN-07-5875.

[37] Cook KL, Wärri A, Soto-Pantoja DR, Clarke PA, Cruz MI, Zwart A, et al. Hydroxychloroquine inhibits autophagy to potentiate antiestrogen responsiveness in ER+ breast cancer. Clin Cancer Res 2014;20:3222–32. https://doi.org/10.1158/1078-0432.CCR-13-3227.

[38] Amaral C, Varela C, Azevedo M, da Silva ET, Roleira FMF, Chen S, et al. Effects of steroidal aromatase inhibitors on sensitive and resistant breast cancer cells: aromatase inhibition and autophagy. J Steroid Biochem Mol Biol 2013;135:51–9. https://doi.org/10.1016/j.jsbmb.2012.12.017.

[39] Amaral C, Augusto TV, Tavares-da-Silva E, Roleira FMF, Correia-da-Silva G, Teixeira N. Hormone-dependent breast cancer: Targeting autophagy and PI3K overcomes Exemestane-acquired resistance. J Steroid Biochem Mol Biol 2018;183:51–61. https://doi.org/10.1016/j.jsbmb.2018.05.006.

[40] Cook KL, Shajahan AN, Wärri A, Jin L, Hilakivi-Clarke LA, Clarke R. Glucose-regulated protein 78 controls cross-talk between apoptosis and autophagy to determine antiestrogen responsiveness. Cancer Res 2012;72:3337–49. https://doi.org/10.1158/0008-5472.CAN-12-0269.

[41] Duan L, Motchoulski N, Danzer B, Davidovich I, Shariat-Madar Z, Levenson VV. Prolylcarboxypeptidase regulates proliferation, autophagy, and resistance to 4-hydroxytamoxifen-induced cytotoxicity in estrogen receptor-positive breast cancer cells. J Biol Chem 2011;286:2864–76. https://doi.org/10.1074/jbc.M110.143271.

[42] Wang J, Xie S, Yang J, Xiong H, Jia Y, Zhou Y, et al. The long noncoding RNA H19 promotes tamoxifen resistance in breast cancer via autophagy. J Hematol Oncol 2019;12:81. https://doi.org/10.1186/s13045-019-0747-0.

[43] Yu X, Luo A, Liu Y, Wang S, Li Y, Shi W, et al. MiR-214 increases the sensitivity of breast cancer cells to tamoxifen and fulvestrant through inhibition of autophagy. Mol Cancer 2015;14:208. https://doi.org/10.1186/s12943-015-0480-4.

[44] Eggersmann TK, Degenhardt T, Gluz O, Wuerstlein R, Harbeck N. CDK4/6 Inhibitors expand the therapeutic options in breast cancer: palbociclib, ribociclib and abemaciclib. BioDrugs 2019;33:125–35. https://doi.org/10.1007/s40259-019-00337-6.

[45] Vijayaraghavan S, Karakas C, Doostan I, Chen X, Bui T, Yi M, et al. CDK4/6 and autophagy inhibitors synergistically induce senescence in Rb positive cytoplasmic cyclin E negative cancers. Nat Commun 2017;8:15916. https://doi.org/10.1038/ncomms15916.

[46] Seshadri R, Firgaira FA, Horsfall DJ, McCaul K, Setlur V, Kitchen P. Clinical significance of HER-2/neu oncogene amplification in primary breast cancer. J Clin Oncol 1993;11:1936–42. https://doi.org/10.1200/JCO.1993.11.10.1936.

[47] Zambrano J, Yeh ES. Autophagy and apoptotic crosstalk: mechanism of therapeutic resistance in HER2-positive breast cancer. Breast Cancer (Auckl) 2016;10:13–23. https://doi.org/10.4137/BCBCR.S32791.

[48] Booth L, Roberts JL, Avogadri-Connors F, Cutler RE, Lalani AS, Poklepovic A, et al. The irreversible ERBB1/2/4 inhibitor neratinib interacts with the BCL-2 inhibitor venetoclax to kill mammary cancer cells. Cancer Biol Ther 2018;19:239–47. https://doi.org/10.1080/15384047.2018.1423927.

[49] Vazquez-Martin A, Oliveras-Ferraros C, Menendez JA. Autophagy facilitates the development of breast cancer resistance to the anti-HER2 monoclonal antibody trastuzumab. PLoS ONE 2009;4:e6251https://doi.org/10.1371/journal.pone.0006251.

[50] Cheng Y, Li H, Ren X, Niu T, Hait WN, Yang J. Cytoprotective effect of the elongation factor-2 kinase-mediated autophagy in breast cancer cells subjected to growth factor inhibition. PLoS ONE 2010;5:e9715https://doi.org/10.1371/journal.pone.0009715.

[51] Cufí S, Vazquez-Martin A, Oliveras-Ferraros C, Corominas-Faja B, Urruticoechea A, Martin-Castillo B, et al. Autophagy-related gene 12 (ATG12) is a novel determinant of primary resistance to HER2-targeted therapies: utility of transcriptome analysis of the autophagy interactome to guide breast cancer treatment. Oncotarget 2012;3:1600–14. https://doi.org/10.18632/oncotarget.742.

[52] Cufí S, Vazquez-Martin A, Oliveras-Ferraros C, Corominas-Faja B, Cuyàs E, López-Bonet E, et al. The anti-malarial chloroquine overcomes primary resistance and restores sensitivity to trastuzumab in HER2-positive breast cancer. Sci Rep 2013;3:2469. https://doi.org/10.1038/srep02469.

[53] Chen S, Zhu X, Qiao H, Ye M, Lai X, Yu S, et al. Protective autophagy promotes the resistance of HER2-positive breast cancer cells to lapatinib. Tumour Biol 2016;37:2321–31. https://doi.org/10.1007/s13277-015-3800-9.

[54] Vazquez-Martin A, Cufí S, Oliveras-Ferraros C, Martin-Castillo B, Del Barco S, López-Bonet E, et al. Expression status of the autophagy-regulatory gene ATG6/BECN1 in ERBB2-positive breast carcinomas: bypassing ERBB2-induced oncogenic senescence to regulate the efficacy of ERBB2-targeted therapies. Genes Chromosomes Cancer 2011;50:284–90. https://doi.org/10.1002/gcc.20846.

[55] Bisaro B, Sciortino M, Colombo S, Camacho Leal MP, Costamagna A, Castellano I, et al. p130Cas scaffold protein regulates ErbB2 stability by altering breast cancer cell sensitivity to autophagy. Oncotarget 2016;7:4442–53. https://doi.org/10.18632/oncotarget.6710.

[56] Zhu X, Wu L, Qiao H, Han T, Chen S, Liu X, et al. Autophagy stimulates apoptosis in HER2-overexpressing breast cancers treated by lapatinib. J Cell Biochem 2013;114:2643–53. https://doi.org/10.1002/jcb.24611.

[57] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30. https://doi.org/10.3322/caac.21442.

[58] Peeters M, Price T. Biologic therapies in the metastatic colorectal cancer treatment continuum–applying current evidence to clinical practice. Cancer Treat Rev 2012;38:397–406. https://doi.org/10.1016/j.ctrv.2011.08.002.

[59] Presta LG, Chen H, O'Connor SJ, Chisholm V, Meng YG, Krummen L, et al. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res 1997;57:4593–9.

[60] Wood JM, Bold G, Buchdunger E, Cozens R, Ferrari S, Frei J, et al. PTK787/ZK 222584, a novel and potent inhibitor of vascular endothelial growth factor receptor tyrosine kinases, impairs vascular endothelial growth factor-induced responses and tumor growth after oral administration. Cancer Res 2000;60:2178–89.

[61] Zhao Z, Xia G, Li N, Su R, Chen X, Zhong L. Autophagy inhibition promotes bevacizumab-induced apoptosis and proliferation inhibition in colorectal cancer cells. J Cancer 2018;9:3407–16. https://doi.org/10.7150/jca.24201.

[62] Ivy SP, Wick JY, Kaufman BM. An overview of small-molecule inhibitors of VEGFR signaling. Nat Rev Clin Oncol 2009;6:569–79. https://doi.org/10.1038/nrclinonc.2009.130.

[63] Mi YJ, Liang YJ, Huang HB, Zhao HY, Wu CP, Wang F, et al. Apatinib (YN968D1) reverses multidrug resistance by inhibiting the efflux function of multiple ATP-binding cassette transporters. Cancer Res 2010;70:7981–91. https://doi.org/10.1158/0008-5472.CAN-10-0111.

[64] Lu W, Ke H, Qianshan D, Zhen W, Guoan X, Honggang Y. Apatinib has anti-tumor effects and induces autophagy in colon cancer cells. Iran J Basic Med Sci 2017;20:990–5. https://doi.org/10.22038/IJBMS.2017.9263.

[65] Cheng X, Feng H, Wu H, Jin Z, Shen X, Kuang J, et al. Targeting autophagy enhances apatinib-induced apoptosis via endoplasmic reticulum stress for human colorectal cancer. Cancer Lett 2018;431:105–14. https://doi.org/10.1016/j.canlet.2018.05.046.

[66] Scott AJ, Arcaroli JJ, Bagby SM, Yahn R, Huber KM, Serkova NJ, et al. Cabozantinib exhibits potent antitumor activity in colorectal cancer patient-derived tumor xenograft models via autophagy and signaling mechanisms. Mol Cancer Ther 2018;17:2112–22. https://doi.org/10.1158/1535-7163.MCT-17-0131.

[67] Kim ES, Khuri FR, Herbst RS. Epidermal growth factor receptor biology (IMC-C225). Curr Opin Oncol 2001;13:506–13. https://doi.org/10.1097/00001622-200111000-00014.

[68] Ciardiello F, Bianco R, Damiano V, Fontanini G, Caputo R, Pomatico G, et al.

Antiangiogenic and antitumor activity of anti-epidermal growth factor receptor C225 monoclonal antibody in combination with vascular endothelial growth factor antisense oligonucleotide in human GEO colon cancer cells. Clin Cancer Res 2000;6:3739–47.
[69] Li X, Fan Z. The epidermal growth factor receptor antibody cetuximab induces autophagy in cancer cells by downregulating HIF-1alpha and Bcl-2 and activating the beclin 1/hVps34 complex. Cancer Res 2010;70:5942–52. https://doi.org/10.1158/0008-5472.CAN-10-0157.
[70] Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: Divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer 2015;15:7–24. https://doi.org/10.1038/nrc3860.
[71] Guo G-F, Wang Y-X, Zhang Y-J, Chen X-X, Lu J-B, Wang H-H, et al. Predictive and prognostic implications of 4E-BP1, Beclin-1, and LC3 for cetuximab treatment combined with chemotherapy in advanced colorectal cancer with wild-type KRAS: analysis from real-world data. World J Gastroenterol 2019;25:1840–53. https://doi.org/10.3748/wjg.v25.i15.1840.
[72] Bertuccio P, Bosetti C, Malvezzi M, Levi F, Chatenoud L, Negri E, et al. Trends in mortality from leukemia in Europe: an update to 2009 and a projection to 2012. Int J Cancer 2013;132:427–36. https://doi.org/10.1002/ijc.27624.
[73] Nagar B, Bornmann WG, Pellicena P, Schindler T, Veach DR, Miller WT, et al. Crystal structures of the kinase domain of c-Abl in complex with the small molecule inhibitors PD173955 and imatinib (STI-571). Cancer Res 2002;62:4236–43. https://doi.org/10.2210/pdb1iep/pdb.
[74] San José-Enériz E, Román-Gómez J, Jiménez-Velasco A, Garate L, Martin V, Cordeu L, et al. MicroRNA expression profiling in Imatinib-resistant Chronic Myeloid Leukemia patients without clinically significant ABL1-mutations. Mol Cancer 2009;8:69. https://doi.org/10.1186/1476-4598-8-69.
[75] Yu Y, Yang L, Zhao M, Zhu S, Kang R, Vernon P, et al. Targeting microRNA-30a-mediated autophagy enhances imatinib activity against human chronic myeloid leukemia cells. Leukemia 2012;26:1752–60. https://doi.org/10.1038/leu.2012.65.
[76] Amrein L, Soulières D, Johnston JB, Aloyz R. p53 and autophagy contribute to dasatinib resistance in primary CLL lymphocytes. Leuk Res 2011;35:99–102. https://doi.org/10.1016/j.leukres.2010.05.029.
[77] Tong Y, Liu Y, You L, Qian W. Perifosine induces protective autophagy and up-regulation of ATG5 in human chronic myelogenous leukemia cells in vitro. Acta Pharmacol Sin 2012;33:542–50. https://doi.org/10.1038/aps.2011.192.
[78] Torgersen ML, Engedal N, Bøe S-O, Hokland P, Simonsen A. Targeting autophagy potentiates the apoptotic effect of histone deacetylase inhibitors in t(8;21) AML cells. Blood 2013;122:2467–76. https://doi.org/10.1182/blood-2013-05-500629.
[79] Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JWW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013;49:1374–403. https://doi.org/10.1016/j.ejca.2012.12.027.
[80] Ansell SM. Non-hodgkin lymphoma: diagnosis and treatment. Mayo Clin Proc 2015;90:1152–63. https://doi.org/10.1016/j.mayocp.2015.04.025.
[81] Jia L, Gopinathan G, Sukumar JT, Gribben JG. Blocking autophagy prevents bortezomib-induced NF-κB activation by reducing I-κBα degradation in lymphoma cells. PLoS ONE 2012;7:e32584https://doi.org/10.1371/journal.pone.0032584.
[82] Heine S, Kleih M, Giménez N, Böpple K, Ott G, Colomer D, et al. Cyclin D1-CDK4 activity drives sensitivity to bortezomib in mantle cell lymphoma by blocking autophagy-mediated proteolysis of NOXA. J Hematol Oncol 2018;11:112. https://doi.org/10.1186/s13045-018-0657-6.
[83] Granato M, Santarelli R, Lotti LV, Di Renzo L, Gonnella R, Garufi A, et al. JNK and macroautophagy activation by bortezomib has a pro-survival effect in primary effusion lymphoma cells. PLoS ONE 2013;8:e75965https://doi.org/10.1371/journal.pone.0075965.
[84] Rosich L, Colomer D, Roue G. Autophagy controls everolimus (RAD001) activity in mantle cell lymphoma. Autophagy 2013;9:115–7. https://doi.org/10.4161/auto.22483.
[85] Dong LH, Cheng S, Zheng Z, Wang L, Shen Y, Shen ZX, et al. Histone deacetylase inhibitor potentiated the ability of MTOR inhibitor to induce autophagic cell death in Burkitt leukemia/lymphoma. J Hematol Oncol 2013;6:53. https://doi.org/10.1186/1756-8722-6-53.
[86] Mitou G, Frentzel J, Desquesnes A, Le Gonidec S, AlSaati T, Beau I, et al. Targeting autophagy enhances the anti-tumoral action of crizotinib in ALK-positive anaplastic large cell lymphoma. Oncotarget 2015;6:30149–64. https://doi.org/10.18632/oncotarget.4999.
[87] Alinari L, Mahoney E, Patton J, Zhang X, Huynh L, Earl CT, et al. FTY720 increases CD74 expression and sensitizes mantle cell lymphoma cells to milatuzumab-mediated cell death. Blood 2011;118:6893–903. https://doi.org/10.1182/blood-2011-06-363879.
[88] San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 2008;359:906–17. https://doi.org/10.1056/NEJMoa0801479.
[89] Chen S, Zhang Y, Zhou L, Leng Y, Lin H, Kmieciak M, et al. A Bim-targeting strategy overcomes adaptive bortezomib resistance in myeloma through a novel link between autophagy and apoptosis. Blood 2014;124:2687–97. https://doi.org/10.1182/blood-2014-03-564534.
[90] Jagannathan S, Abdel-Malek MAY, Malek E, Vad N, Latif T, Anderson KC, et al. Pharmacologic screens reveal metformin that suppresses GRP78-dependent autophagy to enhance the anti-myeloma effect of bortezomib. Leukemia 2015;29:2184–91. https://doi.org/10.1038/leu.2015.157.
[91] Baranowska K, Misund K, Starheim KK, Holien T, Johansson I, Darvekar S, et al. Hydroxychloroquine potentiates carfilzomib toxicity towards myeloma cells. Oncotarget 2016;7:70845–56. https://doi.org/10.18632/oncotarget.12226.
[92] Liu L, Liao J-Z, He X-X, Li P-Y. The role of autophagy in hepatocellular carcinoma: friend or foe. Oncotarget 2017;8:57707–22. https://doi.org/10.18632/oncotarget.17202.
[93] He G, Lei W, Wang S, Xiao R, Guo K, Xia Y, et al. Overexpression of tumor suppressor TSLC1 by a survivin-regulated oncolytic adenovirus significantly inhibits hepatocellular carcinoma growth. J Cancer Res Clin Oncol 2012;138:657–70. https://doi.org/10.1007/s00432-011-1138-2.
[94] Sheng J, Qin H, Zhang K, Li B, Zhang X. Targeting autophagy in chemotherapy-resistant of hepatocellular carcinoma. Am J Cancer Res 2018;8:354–65.
[95] Huang F, Wang B-R, Wang Y-G. Role of autophagy in tumorigenesis, metastasis, targeted therapy and drug resistance of hepatocellular carcinoma. World J Gastroenterol 2018;24:4643–51. https://doi.org/10.3748/wjg.v24.i41.4643.
[96] Marinković M, Šprung M, Buljubašić M, Novak I. Autophagy modulation in cancer: current knowledge on action and therapy. Oxid Med Cell Longev 2018;2018:1–18. https://doi.org/10.1155/2018/8023821.
[97] Llovet JM, Hernandez-Gea V. Hepatocellular carcinoma: reasons for phase III failure and novel perspectives on trial design. Clin Cancer Res 2014;20:2072–9. https://doi.org/10.1158/1078-0432.CCR-13-0547.
[98] Colagrande S, Regini F, Taliani GG, Nardi C, Inghilesi AL. Advanced hepatocellular carcinoma and sorafenib: Diagnosis, indications, clinical and radiological follow-up. World J Hepatol 2015;7:1041–53. https://doi.org/10.4254/wjh.v7.i8.1041.
[99] Shi Y-H, Ding Z-B, Zhou J, Hui B, Shi G-M, Ke A-W, et al. Targeting autophagy enhances sorafenib lethality for hepatocellular carcinoma via ER stress-related apoptosis. Autophagy 2011;7:1159–72. https://doi.org/10.4161/auto.7.10.16818.
[100] Sun T, Liu H, Ming L. Multiple roles of autophagy in the sorafenib resistance of hepatocellular carcinoma. Cell Physiol Biochem 2017;44:716–27. https://doi.org/10.1159/000485285.
[101] Zhai B, Hu F, Jiang X, Xu J, Zhao D, Liu B, et al. Inhibition of Akt reverses the acquired resistance to sorafenib by switching protective autophagy to autophagic cell death in hepatocellular carcinoma. Mol Cancer Ther 2014;13:1589–98. https://doi.org/10.1158/1535-7163.MCT-13-1043.
[102] Shimizu S, Takehara T, Hikita H, Kodama T, Tsunematsu H, Miyagi T, et al. Inhibition of autophagy potentiates the antitumor effect of the multikinase inhibitor sorafenib in hepatocellular carcinoma. Int J Cancer 2012;131:548–57. https://doi.org/10.1002/ijc.26374.
[103] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424. https://doi.org/10.3322/caac.21492.
[104] Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. Nature 2018;553:446–54. https://doi.org/10.1038/nature25183.
[105] Inamura K. Lung cancer: understanding its molecular pathology and the 2015 WHO classification. Front Oncol 2017;7:193. https://doi.org/10.3389/fonc.2017.00193.
[106] Li Y-Y, Lam S-K, Mak JC-W, Zheng C-Y, Ho JC-M. Erlotinib-induced autophagy in epidermal growth factor receptor mutated non-small cell lung cancer. Lung Cancer 2013;81:354–61. https://doi.org/10.1016/j.lungcan.2013.05.012.
[107] Han W, Pan H, Chen Y, Sun J, Wang Y, Li J, et al. EGFR tyrosine kinase inhibitors activate autophagy as a cytoprotective response in human lung cancer cells. PLoS ONE 2011;6:e18691https://doi.org/10.1371/journal.pone.0018691.
[108] Goldberg SB, Supko JG, Neal JW, Muzikansky A, Digumarthy S, Fidias P, et al. A phase I study of erlotinib and hydroxychloroquine in advanced non-small-cell lung cancer. J Thorac Oncol 2012;7:1602–8. https://doi.org/10.1097/JTO.0b013e318262de4a.
[109] Hu X, Shi S, Wang H, Yu X, Wang Q, Jiang S, et al. Blocking autophagy improves the anti-tumor activity of afatinib in lung adenocarcinoma with activating EGFR mutations in vitro and in vivo. Sci Rep 2017;7:4559. https://doi.org/10.1038/s41598-017-04258-8.
[110] Ji C, Zhang L, Cheng Y, Patel R, Wu H, Zhang Y, et al. Induction of autophagy contributes to crizotinib resistance in ALK-positive lung cancer. Cancer Biol Ther 2014;15:570–7. https://doi.org/10.4161/cbt.28162.
[111] Kinsey CG, Camolotto SA, Boespflug AM, Guillen KP, Foth M, Truong A, et al. Protective autophagy elicited by RAF→MEK→ERK inhibition suggests a treatment strategy for RAS-driven cancers. Nat Med 2019;25:620–7. https://doi.org/10.1038/s41591-019-0367-9.
[112] Karsli-Uzunbas G, Guo JY, Price S, Teng X, Laddha SV, Khor S, et al. Autophagy is required for glucose homeostasis and lung tumor maintenance. Cancer Discov 2014;4:915–27. https://doi.org/10.1158/2159-8290.CD-14-0363.
[113] Domingues B, Lopes J, Soares P, Populo H. Melanoma treatment in review. ImmunoTargets Ther 2018;7:35–49. https://doi.org/10.2147/ITT.S134842.
[114] Li S, Song Y, Quach C, Guo H, Jang G-BB, Maazi H, et al. Transcriptional regulation of autophagy-lysosomal function in BRAF-driven melanoma progression and chemoresistance. Nat Commun 2019;10:1693. https://doi.org/10.1038/s41467-019-09634-8.
[115] Ma X-H, Piao S-F, Dey S, McAfee Q, Karakousis G, Villanueva J, et al. Targeting ER stress-induced autophagy overcomes BRAF inhibitor resistance in melanoma. J Clin Invest 2014;124:1406–17. https://doi.org/10.1172/JCI70454.
[116] Ji C, Zhang Z, Chen L, Zhou K, Li D, Wang P, et al. Endoplasmic reticulum stress-induced autophagy determines the susceptibility of melanoma cells to dabrafenib. Drug Des Devel Ther 2016;10:2491–8. https://doi.org/10.2147/DDDT.S112740.
[117] Xie X, Koh JY, Price S, White E, Mehnert JM. Atg7 overcomes senescence and promotes growth of BrafV600E-driven melanoma. Cancer Discov 2015;5:410–23. https://doi.org/10.1158/2159-8290.CD-14-1473.
[118] Chen Z, Jiang Q, Zhu P, Chen Y, Xie X, Du Z, et al. NPRL2 enhances autophagy and

the resistance to Everolimus in castration-resistant prostate cancer. Prostate 2019;79:44–53. https://doi.org/10.1002/pros.23709.
[119] Nguyen HG, Yang JC, Kung H-J, Shi X-B, Tilki D, Lara PN, et al. Targeting autophagy overcomes Enzalutamide resistance in castration-resistant prostate cancer cells and improves therapeutic response in a xenograft model. Oncogene 2014;33:4521–30. https://doi.org/10.1038/onc.2014.25.
[120] Boutin B, Tajeddine N, Vandersmissen P, Zanou N, Van Schoor M, Mondin L, et al. Androgen deprivation and androgen receptor competition by bicalutamide induce autophagy of hormone-resistant prostate cancer cells and confer resistance to apoptosis. Prostate 2013;73:1090–102. https://doi.org/10.1002/pros.22658.
[121] Kranzbühler B, Salemi S, Mortezavi A, Sulser T, Eberli D. Combined N-terminal androgen receptor and autophagy inhibition increases the antitumor effect in enzalutamide sensitive and enzalutamide resistant prostate cancer cells. Prostate 2019;79:206–14. https://doi.org/10.1002/pros.23725.
[122] Ma X, Zou L, Li X, Chen Z, Lin Z, Wu X. Inhibition of autophagy improves the efficacy of abiraterone for the treatment of prostate cancer. Cancer Biother Radiopharm 2019;34:181–8. https://doi.org/10.1089/cbr.2018.2559.
[123] Mortezavi A, Salemi S, Kranzbühler B, Gross O, Sulser T, Simon H-U, et al. Inhibition of autophagy significantly increases the antitumor effect of Abiraterone in prostate cancer. World J Urol 2019;37:351–8. https://doi.org/10.1007/s00345-018-2385-5.
[124] Sueda T, Sakai D, Kawamoto K, Konno M, Nishida N, Koseki J, et al. BRAFV600E inhibition stimulates AMP-activated protein kinase-mediated autophagy in colorectal cancer cells. Sci Rep 2016;6:18949. https://doi.org/10.1038/srep18949.
[125] Das G, Shravage BV, Baehrecke EH. Regulation and function of autophagy during cell survival and cell death. Cold Spring Harb Perspect Biol 2012;4:1–14. https://doi.org/10.1101/cshperspect.a008813.
[126] Vera-Ramirez L, Vodnala SK, Nini R, Hunter KW, Green JE. Autophagy promotes the survival of dormant breast cancer cells and metastatic tumour recurrence. Nat Commun 2018;9:1–12. https://doi.org/10.1038/s41467-018-04070-6.
[127] Beck D, Niessner H, Smalley KSM, Flaherty K, Paraiso KHT, Busch C, et al. Vemurafenib potently induces endoplasmic reticulum stress-mediated apoptosis in BRAFV600E melanoma cells. Sci Signal 2013;6. https://doi.org/10.1126/scisignal.2003057.
[128] Nawrocki ST, Carew JS, Dunner K, Boise LH, Chiao PJ, Huang P, et al. Bortezomib inhibits PKR-like endoplasmic reticulum (ER) kinase and induces apoptosis via ER stress in human pancreatic cancer cells. Cancer Res 2005;65:11510–9. https://doi.org/10.1158/0008-5472.CAN-05-2394.
[129] Orcutt KP, Parsons AD, Sibenaller ZA, Scarbrough PM, Zhu Y, Sobhakumari A, et al. Erlotinib-mediated inhibition of EGFR signaling induces metabolic oxidative stress through NOX4. Cancer Res 2011;71:3932–40. https://doi.org/10.1158/0008-5472.CAN-10-3425.
[130] Groenendijk FH, Bernards R. Drug resistance to targeted therapies: Déjà vu all over again. Mol Oncol 2014;8:1067–83. https://doi.org/10.1016/j.molonc.2014.05.004.
[131] Deretic V, Saitoh T, Akira S. Autophagy in infection, inflammation and immunity. Nat Rev Immunol 2013;13:722–37. https://doi.org/10.1038/nri3532.
[132] Kang C, Elledge SJ. How autophagy both activates and inhibits cellular senescence. Autophagy 2016;12:898–9. https://doi.org/10.1080/15548627.2015.1121361.
[133] Kimura T, Takabatake Y, Takahashi A, Isaka Y. Chloroquine in cancer therapy: a double-edged sword of autophagy. Cancer Res 2013;73:3–7. https://doi.org/10.1158/0008-5472.CAN-12-2464.
[134] Wang D, Xu Q, Yuan Q, Jia M, Niu H, Liu X, et al. Proteasome inhibition boosts autophagic degradation of ubiquitinated-AGR2 and enhances the antitumor efficiency of bevacizumab. Oncogene 2019;38:3458–74. https://doi.org/10.1038/s41388-019-0675-z.
[135] Fan J, Zhang X, Wang S, Chen W, Li Y, Zeng X, et al. Regulating autophagy facilitated therapeutic efficacy of the sonic Hedgehog pathway inhibition on lung adenocarcinoma through GLI2 suppression and ROS production. Cell Death Dis 2019;10:626. https://doi.org/10.1038/s41419-019-1840-6.
[136] Rodríguez CE, Reidel SI, de Kier Bal, Joffé ED, Jasnis MA, Fiszman GL. Autophagy protects from trastuzumab-induced cytotoxicity in HER2 overexpressing breast tumor spheroids. PLoS ONE 2015;10:e0137920https://doi.org/10.1371/journal.pone.0137920.
[137] Han J, Hou W, Lu C, Goldstein LA, Stolz DB, Watkins SC, et al. Interaction between Her2 and Beclin-1 proteins underlies a new mechanism of reciprocal regulation. J Biol Chem 2013;288:20315–25. https://doi.org/10.1074/jbc.M113.461350.
[138] Mitchell R, Hopcroft LEM, Baquero P, Allan EK, Hewit K, James D, et al. Targeting BCR-ABL-independent TKI resistance in chronic myeloid leukemia by mTOR and autophagy inhibition. JNCI J Natl Cancer Inst 2018;110:467–78. https://doi.org/10.1093/jnci/djx236.
[139] Kharaziha P, De Raeve H, Fristedt C, Li Q, Gruber A, Johnsson P, et al. Sorafenib has potent antitumor activity against multiple myeloma in vitro, ex vivo, and in vivo in the 5T33MM mouse model. Cancer Res 2012;72:5348–62. https://doi.org/10.1158/0008-5472.CAN-12-0658.