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Trends in Translational Medicine and Drug Targeting and Delivery: New Insights on an Old Concept—Targeted Drug Delivery with Antibody-Drug Conjugates for Cancers

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Abstract

According to the JPS Drug Delivery Clinical Trials Database (jpharmscidatabase.org), 37,738, 14,104, and 8,060 clinical trials are registered to evaluate (1) drug delivery technology, (2) biomolecule platform, and (3) drug metabolism and PK-PD interactions. These numbers represent a 19–24% increase since 2012. Within biomolecules in clinical testing, antibodies constitute the majority and ~9% carry drug conjugates. Paul Ehrlich introduced the antibody-drug conjugate or “magic bullet” concept about a century ago. A monoclonal antibody-drug conjugate *Mylotarg* was licensed for treating cancer in 2000 and exhibits significant liver toxicity and immune hypersensitivity. Plasma drug instability and a bacterial derived drug may be partly to blame. Progress in antibody-drug conjugation chemistry, understanding how biologic systems respond to antibody-drug conjugates, and unwavering efforts of scientists have enabled successful development of highly potent and effective second-generation antibody-drug conjugates. With the approval of *Adcetris* for lymphoma in 2011 and *Kadcyla* in 2013, about a two- to fourfold gain in cancer response rate is attributed to drug conjugates. With a demonstrated higher safety profile, many more antibody-drug conjugates are in development. The clinical success of *Adcetris* and *Kadcyla* has raised hope that antibody-guided “drug bullets” may be truly “magical” in leading to a cure for cancer.

Over a century ago, Paul Ehrlich proposed, “if a *compound* could be made that selectively targeted to a disease-causing organism, then a *toxin* for that organism (in patients) could be delivered along with the agent of selectivity.”¹ In this *magische kugel* or “magic bullet” targeted drug delivery hypothesis, two critically important components—(1) a selective *compound* (or agent such as antibodies) for targeting and (2) a *toxin* (or drug)—are combined in one unit so that the toxin or drug will find its way only to disease-causing cells or pathogenic tissues. When fully realized, such a targeted drug delivery system would exhibit low or no toxicity to healthy tissues in the body. In light of recurring news on late-stage clinical trial failures of drug candidates citing lack of efficacy, toxicity, or both, there is renewed interest and resurgence in drug delivery and targeting research and development.

This century-old targeted drug delivery concept has been well-accepted as a great idea for integrating into drug development plans. Some have argued this could become a key

platform for delivering highly potent compounds that are otherwise too toxic and non-specific to cure incurable diseases. Many believe successful translation of this idea as a drug delivery platform could provide a much needed relief from late stage clinical failure due to lack of efficacy and concerns on safety. This tantalizing concept has been a core initiative of antibody-drug conjugates for many biopharmaceutical companies. While early attempts used polyclonal antibody-drug conjugates, the pharmaceutical exploration began in earnest with the introduction of monoclonal antibody technology by Milstein and Kohler² that allows for large-scale production of mono-specific antibody for therapeutic applications. With initial mouse monoclonal antibody technology in place and molecular biotechnologies enabling transition from mouse to human monoclonal antibody production, there are many therapeutic monoclonal antibody (mAb) products now licensed for human disease conditions. Due to the molecular flexibility in the design to recognize and bind to almost unlimited numbers of drug targets, and predictable pharmacokinetic and clearance mechanisms, mAb is one of the fastest growing drug delivery and targeting platforms for new drug development. A survey of the biologic drug market indicates that top-selling mAb therapeutics reaped over \$60 billion in annual sales in 2010.³ Currently, all clinical trials intended for product licensing are required by the FDA and other regulatory agencies to register with the ClinicalTrials database (ClinicalTrials.gov). According to this clinical trial registry, there are 6,000 clinical investigations related to mAb candidates. Compared to other drug delivery platforms we presented in the freely accessible J Pharmaceutical Sciences Drug Delivery Clinical Trials Database (jpharmscidatabase.org/), it is clear that the mAb platform continues to drive overall drug (inclusive of both small and bio-molecule) development. In our previous commentaries we have defined drug candidates in clinical trials according to (1) drug delivery technology system and device, (2) biomolecule platform and technology, and (3) drug metabolism and PK-PD interactions.⁴ As summarized accordingly in Table 1, there are currently about 37,738, 14,104, and 8,060 clinical trials registered for interventional studies in the above three categories. These numbers reflect an increase of 29, 19, and 24%, respectively, since our last data update and analysis.³ While clinical trials evaluating antibody drug candidates continue to dominate the majority of biomolecule platforms, about 9% ($673/7532 = 8.9\%$) of the antibody candidates under clinical evaluation are in the form of antibody-drug conjugates (Table 1). It is also interesting to note that many of the antibody-conjugates are in phase II and III studies with fewer number of trials listed as early phase I. Additional numerical distributions are presented in Table 1.

Even with maturation of mAb and molecular biotechnologies, development of effective and safe antibody-drug conjugates for antibody-dependent drug delivery has been challenging. Accumulated knowledge and maturation of science and technologies have enabled better defined limitations and implementation of creative approaches to overcome design and physiological challenges. Early designs of a number of antibody-drug conjugates used highly potent bacterial or plant toxins with enzymatic activity. These toxins such as diphtheria or pseudomonas toxin efficiently halt a cell's protein synthesis by enzymatic inactivation of ribosomal elongation factors. These antibody-toxins, often referred to as immunotoxins, have shown promise and have progressed to clinical trials. However, strong anti-toxin antibody-related human immune reactions have limited this approach. On the

other hand, antibody conjugated to a radionuclide that provides proximity killing of surrounding cells (with radiation energy) after docking to the antibody target (i.e., cancer cells) has proven to be successful but required specialized radionuclide labelling facilities to produce and deliver the product to clinic in time before radiolable decay. For example, the anti-CD20 antibody *Rituxan* for non-Hodgkin lymphoma is made more potent by conjugating to Y-90 radio-isotope in a product called *Zevalin* that provides an overall response rate improvement from 56% to 78–80% and a complete response rate from 16 to 30% in the two reported clinical trials submitted for product licensing.⁵ Another anti-CD20 antibody conjugated to I-131 radio-isotope (*Bexxar*) was also shown to produce enhanced overall and complete response rates in non-Hodgkin lymphoma patients.⁶ In addition to requiring specialized skilled pharmacists and containment facilities to produce radio-isotope-antibody conjugates, the bystander killing by radioisotope produces some non-specific toxicity and radio-decay also poses logistic challenges. For target cells capable of internalizing and taking up the antibody conjugates, an antibody-drug conjugate that is stable in blood and plasma but releases when bound and internalized by a target (e.g. tumor cells) could overcome the time, specialized facility, and on-site preparation requirements of antibody-nuclide conjugates.

Therefore, for the past two decades, a search has ensued for antibody-drug conjugates that overcome (1) the limitations of a toxin's immunogenicity and nuclide decay, (2) the time-sensitive and time-consuming labelling procedure, and (3) facility-intensive limitations. Initial drug choice focused on those with proven clinical efficacy in humans including vinblastine⁷ and doxorubicin (with effective cytotoxic concentrations EC_{50} in the 10^{-7} M range).⁸ After many years spent in clinical development and testing, low potency, conjugate instability,^{7,8} and to some extent conjugate immunogenicity⁷ as well as heterogeneous product characteristics were identified to limit efficacy and safety. An alternative approach is to make highly toxic antibiotic compounds such as calicheamicin ($EC_{50} \sim 10^{-9}$ – 10^{-10} M) (isolated from *Micromonospora echinospora clicheensis*) instead. Calicheamicin is made target selective by being chemically linked to the antibody gemtuzumab that recognizes tumor phenotype CD33. This antibody-drug conjugate, *Myotarg* (gemtuzumab ozogamicin), was tested in acute myeloid leukaemia (AML) patients expressing CD33. The initial encouraging clinical results with this antibody-calicheamicin ($EC_{50} \sim 10^{-9}$ – 10^{-10} M) conjugate led to accelerated approval over a decade ago in 2000. A follow-up phase III study was required after the accelerated approval. However, the study data showed that a significant number of patients experienced hepatotoxicity. Also severe immune related hypersensitivity reactions including anaphylaxis, infusion site reaction, and pulmonary events were noted. While infrequent, the adverse reactions could be fatal, thus requiring close clinical observation and a mitigation plan. With inability to demonstrate clinical benefits in a follow-up trial, there are concerns about *Myotarg* effectiveness and safety. Additional ongoing phase III studies, however, have hinted at a good to intermediate response in AML patients with cytogenetic risks; yet, the final results may determine the role of *Myotarg* in AML therapy.^{9,10} As calicheamicin in *Myotarg* is conjugated to anti-CD33 antibody gemtuzumab through lysine amino acid residues on mAb with a bi-functional linker and the final product carries a disulfide (S-S) bridge (see Figure 1A), the disulfide could be reduced (SH) both in plasma and inside the cell under certain conditions.

In mice, 50% of calicheamicin drug component was released from the antibody-drug conjugate *Mylotarg* within 48 hr.¹¹ This potent molecule design with potential to release calicheamicin prematurely and under reduced conditions may have contributed to the significant liver toxicity. In addition, the product exhibits molecular heterogeneity as only 50% of antibody molecules carry 3–4 molecules of calicheamicin while the remaining half of mAb in the dose lack drug toxin (*Mylotarg* product label). These experiences and the overall responses of the biologic systems have provided invaluable lessons and identified criteria for development of next generation antibody-drug conjugates with target selectivity, conjugate stability, and minimal or no immunogenic response. These lessons also provide a basis for setting appropriate specifications for selecting the most promising antibody-drug conjugates for clinical progression.

In addition, progress in molecular understanding of pathogenic cells at a molecular as well as at a human systems level has enabled refinement in drug target identification, selection, and delineation in humans or “at a systems level.” The systems level thinking is made possible by integrated knowledge across different disciplines including immunology, cell and molecular biology, chemistry, cancer cell biology, and physiology. It is now appreciated that many of the cancer markers or antigens are expressed in embryonic and cell developmental stages while some of the enzyme targets for infectious agents may have cross-reactive human host cell counterparts. The developments of antibody and other targeting moieties or molecules as well expansion of these to a pharmaceutical scale are made possible by advances in pharmaceutical biotechnologies fuelled by innovations in product development engineering as well as biomedical and pharmaceutical sciences.

Recent clinical success in development of the monoclonal antibody-drug conjugate brentuximab vedotin or *Adcetris*¹² has highlighted the maturation and the fruits of integrated or systems knowledge that spans across different disciplines in biomedical and pharmaceutical research and drug targeting research in particular. *Adcetris* is constructed with a mAb targeted to CD33 antigen that is expressed at high levels on lymphoma cells of patients diagnosed with Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (ALCL), but low levels in healthy cells in the tissues and cells in developmental stages. To enhance anti-CD33 monoclonal therapeutic potency, a highly potent mitotic small-molecule drug called monomethyl auristatin E, or MMAE, is conjugated to the anti-CD33 monoclonal antibody (Figure 1C). MMAE is highly potent ($EC_{50} \sim 10^{-9}$ – 10^{-11} M) but otherwise too toxic and non-specific to be considered as a drug (Figure 1C). It is a natural toxin (as opposed to calicheamicin isolated from *Micromonospora*) and thus has reduced immunogenic potential. To ensure release of the MMAE antimitotic drug from its antibody conjugate, scientists first modified the MMAE with a para-amino-benzyloxycarbonyl (PABC) group and added a protease responsive dipeptide, valine-citrulline (Val-Cit). The final *Adcetris*, *anti-CD33 mAb-Val-Cit-PABC-MMAE* antibody-drug conjugate binds to and is internalized by lymphoma cells expressing CD33 marker and releases MMAE after being subjected to intracellular lysosomal enzymes such as cathepsin B (Figure 1C). However, the antibody-drug conjugate is stable in plasma.¹³ The achievement in the conjugate chemistry, which provides blood and plasma stability of the highly potent toxic drug MMAE, and yet releases drug only inside target cells, is pivotal for successful clinical development. A

premature release of drug from conjugate would not only pose toxicity problems but would also render the antibody conjugate ineffective.

The path to the successful clinical development of *Adcetris* has taken over 20 years of hard work and creativity of many scientists and those associated with the sponsor, Seattle Genetics. With proven success of *Adcetris*, we now have a conjugation chemistry to design a plasma stable antibody-drug conjugate with high potency and chemical homogeneity. After early attempts in the 2000s with acid-sensitive antibody doxorubicin construct proved it to be unstable with insufficient potency^{7,8}, the team led by Peter Senter has redesigned the antibody conjugation chemistry to be built on the much more potent auristatin drug analogues MMAE and MMAF. After selecting CD30 as an antibody target for Hodgkin lymphoma and other lymphoid tumors, the preclinical development of anti-CD30 mAb-MMAE began in earnest in 2003 and the first clinical study was initiated in late 2006. Due to the promising clinical results, including 75% of patients exhibiting a drug response and 34% a complete response for 20.5 months (the time of publication), the FDA granted accelerated product approval in the third quarter of 2011 within 6 months of BLA submission. In recounting the successful development of *Adcetris*, Peter Senter attributed the success to their unwavering research focus on (1) target molecule selectivity for the target disease state, (i.e., lymphoma or specific cancers), (2) the drug-antibody linker, (3) conjugation technology that provided optimal homogeneity in function and molecular characteristics, and (4) evaluating the drug candidate in appropriate subject populations. Setting these detailed standards in the biologic systems context was the difference that set apart safety and efficacy of *Adcetris* compared to *Mylotarg*, which was approved some 11 years earlier. *Adcetris* appeared to be much safer and effective for respective disease indication and does not carry a Black-box warning in the product label as *Mylotarg* does for potential liver or severe immune related hypersensitivity (Table 2). Another antibody-drug conjugate targeted to erb-2 or HER2 antigen with a Herceptin antibody back bone (Figure 1B) with amino-linkage to maytansine has also proven to be stable in the plasma and susceptible to lysosomal peptidase.¹⁴ Maytansine is also reported to exhibit high cytotoxic potency ($EC_{50} \sim 10^{-11}$ – 10^{-12} M) (Figure 1B, Table 2). This antibody-drug conjugate called trastuzumab emtansine, or *Kadcyla*, developed jointly by ImmunoGen and Genentech, has gained marketing approval in early 2013. A brief comparison of molecular and pharmacokinetic characteristics as well as safety profiles for *Kadcyla*, *Adcetris*, and *Mylotarg* is presented in Table 2.

With the clinical success of the two new generation antibody-drug conjugates, one may ask, how much would one gain over that of native antibody molecules? This information has not been directly gathered in comparative or controlled clinical trials. However, one could compare the efficacy of parent trastuzumab (*Herceptin*) compared to that of trastuzumab emtansine (*Kadcyla* antibody-drug conjugate). A similar efficacy data comparison between cAC10, brentuximab, and brentuximab vedotin (*Adcetris*) are made and the results are summarized in Table 3. The parent cAC10 brentuximab mAb did not appear to be effective for Hodgkin lymphoma but the antibody-drug conjugate provided 75% response rate. In ALCL, the same antibody-drug conjugate increased the parent mAb response rate of 17% to 86%; a 69% enhancement. In metastatic breast cancer patients, trastuzumab-drug conjugate

extended the response rate of the parent mAb from 15–26% to 26–64%; 9–38% gain. Overall, with effective antibody-drug conjugate design, validated and appropriate drug target, potent drug and conjugation chemistry, the drug linked to antibody could significantly enhance the overall cancer response rate of the parent mAb. The real-world effectiveness and value of this new class of antibody-drug conjugates will unfold with time in clinical use.

The success story has clearly fuelled the resurgence in drug delivery and targeting research and development with a focus on strategic alliances and has resulted in a wave of antibody-drug conjugates entering clinical development. Table 4 summarizes some of the antibody-drug conjugates according to their respective target indications and the cytotoxic drugs linked to antibody. While the antigen targets for respective cancer may vary, the list of drugs clearly shows that all the antibody-drug conjugates entering clinical studies no longer use classical anticancer drugs with low potency such as doxorubicin and vinblastine. All the drugs on the list carry drugs that exhibit cytotoxicity in nM-pM range to enhance therapeutic potency of the antibody-drug candidates. However, even with the success and proven track record, due to a much longer development time required to optimize drug conjugation chemistry, not all antibody therapeutics will likely be converted into antibody-drug conjugates as a first generation pharmaceutical product. It is worth considering as a potential path for new mAb development where additional potency is necessary for therapeutic response. Although antibody-conjugates are more costly to produce, some may find a role in product and patent life-cycle extension for those facing patent expiration. Regardless, the role of antibody-conjugates with proven specificity, stability, and selective intracellular release of toxic drug, will likely grow as we search for a cure in cancers. Although it has taken more than a century to translate Ehrlich's dream of "magic bullet" into therapeutic reality, with the documented clinical success of antibody-drug conjugates, *Adcetris* and *Kadcyla*, perhaps these "drug bullets" targeted to cancer cells may turn out to be truly "magical" and eventually lead to a cure for patients with lymphoma and breast cancers.

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FIGURE 1.

Schematic representation of antibody-drug conjugate structures and free drug potency range. Panels A, B, and C represent the antibody, linker, and conjugated drug structure for *Mylotarg* (gemtuzumab-ozogamicin), *Kadcyla* (trastuzumab-emtansine), and *Adcetris* (brentuximab-vedotin), which are linked to Calicheamicin, Maytansine DM1, or Auristatin MMAE, respectively. The drug molecules for *Mylotarg* and *Kadcyla* are attached to monoclonal antibody (mAb) through lysine amino acid (-NH-) residues while drug for *Adcetris* is attached through a cysteine thioether (-S-) linkage. Please note that for *Mylotarg* there is a disulfide linkage susceptible to reduction in the plasma and extracellular space. The symbol n represents the number of drug molecules per mAb. For *Mylotarg*, about 50% of mAb exhibits $n = 2-3$ drug molecules and the remaining fraction exhibits no drug attachment. For details of free drug potency, see Table 2.

Summary of the number of clinical trials listed on ClinicalTrials.gov organized as the 3 major drug delivery categories (updated on September 10, 2013).*

Table 1

I. Drug Delivery Technology and System		All	Intervention	Phase I	Phase II	Phase III	Phase IV
Device		15,729	12,820	1,280	1,996	1,816	2,149
Dosage Form		13,614	12,896	3,629	4,288	2,590	1,536
Drug Delivery System		4,094	3,788	769	1,148	792	536
Formulation		3,446	3,339	1,522	828	672	305
Liposome		624	610	192	307	109	46
Transdermal		601	573	103	125	171	127
Formulation Comparison		1,470	1,440	681	272	321	140
Route		1,293	1,224	370	355	269	166
Sustained Release		375	358	63	90	124	56
Lipid Formulation		139	135	52	33	18	25
Nanoparticles		142	131	48	81	10	2
Aerosol and Inhalation		152	144	36	34	39	19
Prodrugs		129	123	53	53	15	10
Colloid		178	157	6	30	23	28
Drug Delivery Tech & System		Subtotal	37,738				

II. Biological Molecule Platform/ Technologies		All	Intervention	Phase I	Phase II	Phase III	Phase IV
Antibody		7,532	6,922	2,058	3,128	1,511	481
Biologics and Vaccines		4,048	3,927	1,410	1,411	932	410
Peptide		2,205	1,944	623	671	291	226
Recombinant Proteins		673	622	261	227	130	37
Antibody Conjugates		415	402	82	125	164	42
Antisense		119	116	67	59	13	0
Oligonucleotide		112	97	49	46	13	3
siRNA		72	53	19	18	17	5
Aptamer		22	21	10	9	4	1
Biological Molecule Platform		Subtotal	14,104				

III. PK/PD Interactions	All	Intervention	Phase I	Phase II	Phase III	Phase IV
Metabolic Inhibitor	2755	2547	403	546	735	637
Drug Transport Modulator	1910	1810	329	373	507	445
Drug Interactions	2790	2316	938	362	151	218
Metabolic Induction	906	755	98	154	108	123
Active Metabolite	658	632	320	163	45	47
PK/PD Interactions	Subtotal	8,060				

* All the clinical trial data filed with the ClinicalTrials.gov database were sorted according to the delivery platform listed under the three major categories. All clinical trials include observation and intervention studies.

Table 2

Comparison of molecular characteristics, pharmacokinetics, and safety profiles of antibody-drug conjugates *Mylotarg*, *Adcetris*, and *Kadcyla*.

	<i>Mylotarg</i> (Gemtuzumab- ozogamicin)	<i>Adcetris</i> (Brentuximab- vedotin)	<i>Kadcyla</i> (Trastuzumab- emtansine)
Drug toxin	Calicheamicin	Auristatin	Maytansine
Free Drug potency (EC ₅₀)	10 ⁻⁹ – 10 ⁻¹⁰ M	10 ⁻⁹ – 10 ⁻¹¹ M	10 ⁻¹¹ – 10 ⁻¹² M
Mechanism of drug actions	Topoisomerase II minor DNA groove binding	Tubulin depolymerization	Tubulin depolarization
Original source	Micromonospora echinospora clicheensis (bacteria)	Dolabella auricularia (sea hare); a synthetic derivative	Maytenus serrata (plant)
Ab-drug linker	Bi-functional hydrozone via lysine residues on mAb	Protease sensitive petide-thioether via lysine residues on mAb	Peptide-thioether via cysteine residues on mAb
Drug release mechanism	Low pH and disulphide reduction (serum unstable)	Peptidase and linker degradation (serum stable)	Peptidase and linker degradation (serum stable)
Drug-mAb ratio	Heterogeneous 50% = 2–3 50% = 0	More homogenous ~4	Less homogeneous ~3.5
Safety Warning	Hypersensitivity (severe) Hepatotoxicity	Progressive multifocal leukoencephalopathy (due to JC virus infection)	Heaptotoxicity, cardiotoxicity, Embryo-fetal toxicity
Pharmacokinetics			
Elimination t _{1/2}	6 d	4–6 d (single dose) 21 d (steady state)	4 d
V _{ss}	10 L	6–10 L	3.13 L

Table 3

Comparison of objective response rate for the monoclonal antibody-drug conjugated and their parent antibody counterpart

Cancer	Molecular Target	Native mAb	ORR [*] (%)	mAb-drug conjugate	ORR [*] (%)	Reference
Hodgkin lymphoma	CD30	cAC10 Brentuximab	0	Brentuximab vedotin	75	12,15
ALCL ^a	CD30	cAC10 Brentuximab	17	Brentuximab vedotin	86	15,16
Breast ^b	HER-2	Trastuzumab	15–26	Trastuzumab	26–64	17–21

^a ALCL, anaplastic large-cell lymphoma.

^b Metastatic breast cancer.

* ORR, Objective response rate for the respective cancer.

Table 4

A summary of antibody conjugate in clinical trials presented according to their progression in clinical development

Antibody-drug conjugate	Cancer Indication	Antibody Target	Cytotoxic drug conjugate
FDA Approved			
brentuximab vedotin (SGN-35)	HL, ALCL	CD30	Auristatin
gemtuzumab ozogamicin *	AML	CD33	Calicheamicin
trastuzumab emtansine	Metastatic Breast	HER2	Maytansine
Phase III			
inotuzumab ozogamicin	NHL, ALL	CD22	Calicheamicin
Phase II			
BT062	Multiple myeloma	CD138	Maytansine
CDX-011	Breast, melanoma	GPNMB	Auristatin
SGN-75	NHL, RCC	CD70	Auristatin
SAR3419	DLBCL, ALL	CD19	Maytansinoid
PSMA ADC	Prostate	PSMA	Auristatin
IMGN901	SCLC, Multiple myeloma	CD56	Maytansine
IMMU-130	Colorectal	CEACAM5	Camptothecin analog
Phase I			
AGS-16M8F	Renal CC	AGS-16	Auristatin
ASG-22ME	Solid tumors	nectin-4	Auristatin
ASG-5ME	Prostate, pancreatic	SLC44A4	Auristatin
BAY 94-9343	Solid tumors	Mesothelin	Maytansine
BIIB015	Solid tumors	Cripto	Maytansine
IMGN529	NHL, CLL	CD37	Maytansine
SAR566658	Solid tumors	CA6	Maytansine
SGN-CD33A	AML	CD33A	Auristatin
SGN-CD19A	AML, NHL	CD19A	Auristatin
MDX-1203	NHL, RCC	CD70	Alkylating agent (duocarmycin)
RG7593	Hematologic malignancies	CD22	Auristatin

* Approved by the FDA for marketing in 2000, but later withdrawn voluntarily from US market by the sponsor.

Abbreviations: ALCL; anaplastic large-cell lymphoma; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin lymphoma; MBC, metastatic breast cancer; NHL, non-Hodgkin lymphoma; Renal CC, renal cell carcinoma; SCLC, small-cell lung cancer.