Antibody–drug conjugates (ADCs) are a promising cancer treatment modality that enables the selective delivery of highly cytotoxic payloads to tumours.Upon reaching the tumour microenvironment (TME), either the masking moieties are removed or the antigen–binding sites change conformation in response to certain tumour–associated factors such as the abundance of proteases and acidic conditions, resulting in the localized restoration of the original target binding affinity of the antibody and payload release.Notable examples of homogeneous conjugation technologies include full alkylation of interchain disulfides (used in T–DXd and sacituzumab govitecan), THIOMAB80 (a conjugation method that involves genetically incorporated cysteine residues), incorporation of non–naturally occur– ring reactive amino acids81–83, cysteine rebridging84–89, Fc–affinity tags90 and site–specific conjugation using various enzymes (such as engineered glycosidases91–94, transglutaminases95–98, formylglycine–generating enzymes99,100 and sortases101–103) (Fig.By contrast, homogeneous ADCs with defined DARs are generated by full alkylation of interchain disulfides (as used in the manufacture of trastuzumab deruxtecan and sacituzumab govitecan) or site–specific conjugation through cysteine engineering techniques (such as THIOMAB), incorporation of reactive unnatural amino acids and following orthogonal coupling or enzymatic reactions.Subsequently, we highlight and discuss selected examples of novel ADC designs that are currently in the early stages of preclini– cal and clinical development as next–generation cancer therapeu– tics, including bispecific ADCs, probody–drug conjugates (PDCs), immune–stimulating antibody conjugates (ISACs), protein degrader– antibody conjugates (DACs) and dual–payload ADCs.To further enhance the tumour specificity of an ADC, antibodies capable of recog– nizing tumour–specific antigen variants with structural variations such as truncation, nicking (peptide bond cleavage caused by tumour–associated proteases) and other unique post–translational modifications have been explored (for example, EGFR variant III24,25, nicked TROP2 (refs.Resistance to ADCs is intricately linked to the tumour heterogeneity; aggressive ADC therapy can create selective pressures that favour small subpopulations of resistant clones that harbour specific traits, including alterations in drug metabolism, mutations in the target proteins or their downstream signalling pathways, activation of alternative signalling pathways and/or the presence of cancer stem–like cells8,9.Affinity– attenuated bispecific ADCs equipped with an MMAE payload showed a five– to sixfold greater therapeutic index than a cetuximab–MMAE ADC, based on differ– ences in in vitro cytotoxic potency against EGFR and MET–expressing tumour cells and nonmalignant keratinocytes.Certain ADCs involve antibodies of the IgG4 subclass (such as gemtuzumab ozogamicin and inotuzumab ozogamicin)11; nonetheless, IgG1 anti– bodies are now preferentially used because of their general stability in the systemic circulation (reflecting an elimination half–life of 14–21 days) and robust engagement of innate immune cells, such as natural killer (NK) cells and macrophages, through interactions with Fc?The pay– loads of current FDA–approved ADCs include anti–mitotic agents such as monomethyl auristatin E (MMAE), monomethyl auristatin F (MMAF) and the maytansine derivatives DM1 and DM4, DNA–damaging agents such as calicheamicins and pyrrolobenzodiazepine dimers (PBDs) and topoisomerase I inhibitors such as SN–38 and DXd.An interim analysis of the phase III MARIPOSA study (NCT04487080) supports the poten– tial of this approach; the combination of the EGFR–MET bispecific antibody amivantamab with the third–generation small–molecule EGFR inhibitor lazertinib resulted in a

median progression–free survival (PFS) of 23.7 months, compared with 16.6 months with osimertinib, another third–generation inhibitor, as monotherapy128. In this Review, we highlight advances in each ADC component (the monoclonal antibody, payload, linker and conjugation chemistry) and provide more–detailed discussions on selected examples of emerging novel ADCs of each format, enabled by engineering of one or more of these components.Several emerging ADC formats exist, including bispecific ADCs, conditionally active ADCs (also known as probody–drug conjugates), immune–stimulating ADCs, protein–degrader ADCs and dual–drug ADCs, and each offers unique capabilities for tackling these various challenges.Multiple factors might contribute to the lack of improvement in antitumour activity, although the authors speculated that monovalent binding did not effectively induce HER2 dimerization, a key process for HER2 endocytosis, thus offsetting any potential benefits from accelerated lysosomal trafficking.Aglycosylated antibodies can be vulnerable to structural distortion owing to thermal instability; nonetheless, data published in 2022 indicate that attaching small–molecule payloads to the CH2 domain of the Fc region can compensate for this instability15.ADCs with other payloads including tubulysins (anti–mitotics)35–39, duocarmycins (DNA alkylators)40, PNU–159682 (a topoisomerase II inhibitor)41–43 and amani– tin (an RNA polymerase II inhibitor)44–46 are currently being evaluated in preclinical and clinical studies.Research efforts from the past decade have focused on developing more–stable cleavable linkers, such as the GGFG tetrapeptide linker employed in T–DXd70, cathepsin–responsive trip– eptide linkers71–73, as well as linkers cleaved by ?–glucuronidase37,74,75, sulfatase76, phosphatase77 and legumain78,79.Second, if appropriate targets are chosen, bispe– cific ADCs might be capable of more tumour–specific binding owing to limited expression of both target antigens by nonmalignant cells and/or promoted payload uptake, thereby minimizing the risk of toxici– ties in nonmalignant tissues.Data from a preclinical study demonstrate superior internalization, lysosomal trafficking and improved thera– peutic activity in PDX models of NSCLC and oesophageal squamous cell carcinoma (ESCC) compared with monospecific bivalent .(ADCs.receptors (Fc?Rs)12.18), XMT–1522 (refs. 6). 10).29)).1 l2).115,118). 123). 133).141