

The range of non-surgical anti-cancer treatments

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Radiotherapy Half of all patients will receive radiotherapy during their - cancer journey . The mechanism of action of radiotherapy is that ionising radiation causes single- and double-stranded - DNA breaks. Cells most sensitive to radiotherapy are in mitosis or late G2 in the cell cycle. Damage may be caused - by the direct e f f e c t of the ionising radiation on the DNA. However, the predominant therapeutic e f f e c t is indirect, and is achieved by ionising radiation causing the creation of oxygen free radicals, which then damage the DNA. The fact that the or indirect damage is predominant explains why hypoxic cells - are relatively resistant to radiotherapy . In practice, adequate oxygenation of tissues is assisted by simple measures such as correcting anaemia prior to radiotherapy . Cancer types di f f e r greatly in their sensitivity to radiother apy . Similarly , higher doses of radiotherapy are needed to con trol bulky disease (~ 70 /uni00A0 Gy) than to eliminate residual tumour cells (~ 50 /uni00A0 Gy) or to palliate symptoms (~ 30 /uni00A0 Gy). Radiotherapy is mainly used as a localised treatment (Figure 12.7). The target area is defined by imaging, which will include anatomical imaging, such as CT and MRI, to identify the tumour mass, neighbouring structur es and landmarks for radiotherapy planning. Sometimes functional imaging, such as PET , is used to further define structures that should be included in the radiation field such as lymph nodes containing small volumes of tumour, whose metabolic signatur e is detected by PET . The planning and technical set-up of radiotherapy is a highly specialised subject. Planning can be extremely di f f i c u l t and time-consuming, e.g. in the treatment of head and neck cancer, where the treatment intent is curative but there are multiple vital and highly sensitive structures close to the target area. In general terms, the radiotherapy team will aim to pro vide a uniform therapeutic radiation dose to the target area, while sparing adjacent structures from significant damage. The most common form of treatment is external beam radiother apy in which x-rays are aimed at the tar get volume from an external source. Where necessary , modern radiotherapy can employ sophisticated computer programs and algorithms to sculpt the shape of the treatment volume. It is no w possible to irradiate irregularly shaped target volumes using techniques such as intensity-modulated radiation therapy (IMRT) and - image-guided radiation therapy (IGRT). The ability to give - high fractional doses in this way has led to the development of stereotactic ablative radiotherapy (SAbR), in which a small number of fractions can be used to treat primary tumours, or isolated metastases, to curative dose levels. Other ways of targeting the tumour volume include brachytherapy , in which the radiation source is brought ver y close to the tumour by insertion of radioactive seeds, and radionuclide therapy , in which a radioactive source is concen - trated at the tumour site. One of the main problems in determining the optimal schedule of radiation is that there is a dissociation between the acute e f f e c t s on normal tissues and the late damage. The acute reaction is not a reliable guide to the adverse consequences of treatment in the longer term. Since the late e f f e c t s following irradiation can take over 20 years to develop, this poses an

obvious difficulty: if a radiation schedule is changed it will be known within 2 or 3 years whether or not the new schedule - has improved tumour control; it may, however, be two decades before it is known, with any degree of certainty, whether or not the new technique is safe. - Anti-cancer drugs The classes of anti-cancer drugs, their modes of action and clinical indications are summarised in Table 12.6 .

upon for cure 70 with no 30 with residual cancer residual cancer 15 sensitive to 15 resistant to adjuvant therapy adjuvant therapy 5 relapse (inadequate 15 relapse despite therapy, toxicity, etc.) adjuvant therapy despite adjuvant therapy 10 patients whose residual disease was eradicated by adjuvant therapy Net benefit Futile therapy 20% 90% treated inappropriately Unnecessary therapy 70% Beneficial therapy 10% 10% treated appropriately No therapy 0% Figure 12.5 The concept of adjuvant chemotherapy. upon for cure Imperfect but clinically adequate test for residual disease 60 with no 40 with residual cancer, 'residual cancer', none are all are treated treated 15 sensitive to 10 with no 15 resistant to adjuvant therapy residual disease adjuvant therapy 5 relapse (inadequate 15 relapse despite therapy, toxicity, etc.) adjuvant therapy despite adjuvant therapy 10 patients whose residual disease was eradicated by Net benefit adjuvant therapy Futile therapy 20% 30% treated inappropriately Unnecessary therapy 10% Beneficial therapy 10% 70% treated appropriately No therapy 60% Figure 12.6 The concept of adjuvant chemotherapy and testing for minimal residual disease.

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Knowledge of Anatomy Patterns and probability of spread of disease Cross-sectional imaging CT, MRI Functional imaging Positron emission tomography (PET) Functional MRI Radiotherapy dose prescription Optimise the therapeutic ratio Choose that combination of total dose, number of treatments (fractions) and overall treatment time so that the damage to normal tissues is minimised and the effects on tumour are maximised Figure 12.7 The processes involved in clinical radiotherapy. CT, computed tomography; MRI, magnetic resonance imaging. TABLE 12.6 Examples of anti-cancer drugs currently in use. Class Examples Putative mode of action Drugs that interfere with formation of microtubules: 'spindle poisons' Vincristine Interfere with formation of microtubules: 'spindle poisons' Vinorelbine Stabilise microtubules Taxanes: paclitaxel docetaxel cabazitaxel 5-Fluorouracil Inhibition of thymidylate synthase, false substrate Drugs that interfere with DNA and RNA synthesis with DNA synthesis (antimetabolites) Methotrexate Inhibition of dihydrofolate reductase 6-Mercaptopurine Inhibit de novo synthesis of purines 6-Thioguanine Technical set-up Optimal use of radiation beams Simulate the 'beam's-eye view' of the target Diagnostic quality screening and imaging Images digitally reconstructed from CT planning images Three-dimensional planning Careful shaping of beams ('conformal therapy') Alter energy profile across the beam to sculpt the dose distribution to complex shapes ('intensity modulated radiation therapy' - IMRT) Optimal delivery of treatment Ensure day-to-day reproducibility of set up Online verification (portal imaging) Reference tattoos Immobilisation of patient (moulds, shells) Ensure that only the target is treated Eliminate effect of physiological movement (breathing, peristalsis): 'image-guided radiation therapy' - IGRT Quality control and cross-checking procedures throughout the whole process from target definition to follow-up Tumour types that may be sensitive to drug Lymphomas Leukaemias Brain tumours Sarcomas Breast cancer Non-small cell lung cancer Ovarian cancer Prostate cancer Head and neck cancer Breast cancer GI cancer Breast cancer Bladder cancer Lymphomas Cervical cancer purine synthesis Leukaemias Continued

Class Examples Putative mode of action Cytosine arabinoside False substrate in DNA synthesis
 Drugs that interfere with DNA synthesis (antimetabolites) Gemcitabine Inhibits ribonucleotide reductase – continued Mitomycin C DNA cross-linking, preferentially active at sites of Anal cancer
 Drugs that directly low oxygen tension (a bioreductive drug) damage DNA or interfere with its function Cisplatin Form adducts between DNA strands and interferes Germ cell tumours
 Carboplatin with replication Oxaliplatin Forms adducts between DNA strands and interferes Colorectal cancer with replication Doxorubicin Intercalates between DNA strands and interferes Breast cancer with replication Cyclophosphamide A prodrug converted via hepatic cytochrome p450 to phosphoramidate mustard. Causes DNA cross- links Ifosfamide Related to cyclophosphamide, causes DNA cross- Small cell lung cancer links Bleomycin DNA strand breakage via formation of metal Germ cell tumours complex Irinotecan Inhibits topoisomerase 1, prevents DNA from Colorectal cancer unwinding and repairing during replication Etoposide Inhibits topoisomerase 2, prevents DNA from Small cell lung cancer unwinding and repairing during replication Dacarbazine A nitrosourea that requires activation by hepatic cytochrome p450. Methylates guanine residues in DNA Temozolomide A nitrosourea but, unlike dacarbazine, does not require activation by hepatic cytochrome p450. Methylates guanine residues in DNA Actinomycin D Intercalation between DNA strands, DNA strand Rhabdomyosarcoma breaks Inhibit DNA repair by PARP , especially in DNA damage Olaparib mutated cancers response inhibitors Niraparib Rucaparib Hormones Tamoxifen Blocks oestrogen receptors Aromatase inhibitors that block postmenopausal Breast cancer Anastrozole (non-ovarian) oestrogen production Letrozole Exemestane Analogues of gonadotropin-releasing hormone, Leuprolide continued use produces downregulation of the Goserelin anterior pituitary with consequent fall in testosterone Buserelin levels Cabergoline Blocks prolactin release, a long-acting dopamine Prolactin-secreting pituitary tumours agonist Tumour types that may be sensitive to drug Leukaemias Lymphomas Non-small lung cancer Pancreatic cancer Bladder cancer Gastric cancer Head and neck cancer Rectal cancer Ovarian cancer Non-small cell lung cancer Head and neck cancer Oesophageal cancer Lymphomas Sarcomas Kaposi's sarcoma Breast cancer Lymphomas Sarcomas Sarcomas Lymphomas Germ cell tumours Lymphomas Brain tumours Sarcoma Glioblastoma multiforme Wilms' tumour BRCA

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directed to cell surface Cetuximab Antibody directed against EGFR antigens Bevacizumab Antibody directed against VEGFR Rituximab Antibody against CD20 antigen Alemtuzumab Antibody against CD52 antigen Antibody drug Trastuzumab Targets chemotherapy to conjugates deruxtecan Sacituzumab Targets chemotherapy to govitecan Enfortumab vedotin Targets chemotherapy to Inducers of Arsenic trioxide Induces apoptosis by caspase inhibition apoptosis Inhibition of nitric oxide Venetoclax BH3 mimetic Tumour types that may be sensitive to drug Pituitary tumours Prostate cancer Prostate cancer Non-small cell lung cancer Chronic myeloid leukaemia GISTs Non-small cell lung cancer Pancreatic cancer Renal cancer GIST refractory to Imatinib Colorectal cancer Thyroid cancer Breast cancer Renal cancer Breast cancer Multiple myeloma B from Acute promyelocytic leukaemia nesyl transferase and consequent Leukaemia ras -dependent signal transduction Acute leukaemia ras -dependent signal transduction Myelodysplastic syndrome Breast cancer Colorectal cancer Head and neck cancer Colorectal cancer Lymphomas Lymphomas Her2 expressing tumour Breast cancer Trop2 expressing tumour Breast cancer Nectin4 expressing tumour Urothelial cancer Acute promyelocytic leukaemia CML AML Lymphoma Continued

Cytotoxic chemotherapy Selective toxicity is the fundamental principle underlying cytotoxic chemotherapy . Tumour types vary greatly in their sensitivity to cytotoxic chemotherapy and their vulnerability to drugs with specific mechanisms of action. Treatments are often given for a limited number of treatment days during a cycle of treatment lasting typically 3–4 weeks. This allows the tumour to receive an effective dose while providing sufficient time for the patient to recover in time for the next cycle. Many treatment regimens give a limited number of cycles, typically three to six in total. Other regimens are maintenance treatments, in which an unlimited number of cycles are given. Hormonal treatments Several tumour types, notably breast cancer and prostate cancer, are stimulated by endogenous hormones. Removal of this stimulus from sensitive tumours will result in their shrinkage. An understanding of the relevant endocrine pathways has identified several points for therapeutic intervention, including interference with hormone receptors and with hormone production. Targeted treatments The explosion of knowledge about the molecular biology of cancer has identified multiple therapeutic targets. This has ushered in an era of highly specific treatments that aim to inhibit a target essential for tumour survival while leaving other tissues unaffected. At present, most targeted therapies are not absolutely specific for their primary target and therefore do have unwanted or 'off-target' side effects. In addition, successful inhibition of the target may have inevitable undesirable consequences in addition to the desired effect, so-called 'on-target' side effects. Many targeted treatments are given in continuous cycles and the dosing and toxicity management strategies are therefore of particular importance. These treatments will only work if a patient's tumour depends on a therapeutic target. The kinase inhibitor vemurafenib will only be effective in patients with melanoma whose

Class Examples Putative mode of action Immunological Ipilimumab Blocks CTLA-4 and thus releases the brakes on the mediators activation of T cells Block the PD-1 signalling on T lymphocytes and Pembrolizumab thereby prevents the inhibition of T-cell activation Nivolumab Atezolizumab Durvalumab Interferon alpha-2b Activates macrophages, increases the cytotoxicity of T lymphocytes, inhibits cell division (and viral replication) Thalidomide Anti-inflammatory, stimulates T cells, antiangiogenic HDAC inhibitors Panobinostat Acetylation of histones is associated with increased transcription of genes; inhibiting deacetylation can decrease expression of mutated or dysregulated genes Entinostat Acetylation of histones is associated with increased transcription of genes; inhibiting deacetylation can decrease expression of mutated or

dysregulated genes PI3K inhibitors Idelalisib Inhibits signalling via the PI3K/AKT/mTOR pathway and thereby switch off stimulus to cellular proliferation mTOR inhibitors Temsirolimus Inhibit mTOR, a key component in the PI3K/AKT/ Everolimus mTOR pathway MEK inhibitors Trametinib Inhibit the MAPK pathway Selumetinib RAF inhibitors Dabrafenib Inhibit the MAPK pathway Vemurafenib AML, acute myeloid leukaemia; ATP , adenosine triphosphate; CML, chronic myeloid leukaemia; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFR, epidermal growth factor receptor; FLT3, FMS-like tyrosine kinase; GI, gastrointestinal; GIST, gastrointestinal stromal tumour; HDAC, histone deacetylase; HER2, human epidermal growth factor receptor 2; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NF , nuclear factor; PARP , poly-ADP ribose polymerase; PD-1, programmed death receptor; PI3K, phosphoinositide 3-kinase; RAF , rapidly accelerated fibrosarcoma; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor. Tumour types that may be sensitive to drug Melanoma Lung cancer Renal cancer Melanoma Lung cancer Renal cancer Bladder cancer Hairy-cell leukaemia Myeloma Cutaneous T-cell lymphoma Melanoma B-cell lymphomas Renal cancer Neuroendocrine tumours Melanoma Neurofibroma Melanoma tyrosine kinase; mTOR, mammalian programmed cell death protein 1; PDGFR, platelet-derived

growth factor receptor tyrosine kinase; imatinib is particularly effective in patients with gastrointestinal stromal tumours who have mutations in exon 11 of the Kit gene – patients with mutations in exon 9 may still respond to imatinib but will require higher doses and patients without mutations in Kit are far less likely to respond to imatinib. Treatment choice therefore requires a molecular analysis of the patient's tumour. It is this determination of treatment at the individual level that has led to the concept of 'personalised medicine'. Although major advances have been made, important targets such as ras remain elusive at present, although several ras -targeted molecules are in development. Immunotherapy Treatments to activate the immune system against cancer have a long history , stimulated by the observation that up to half of the volume of certain tumours was known to be made up of immune cells, which appeared to be inactive or dead. There is now an appreciation that multiple malignancies activate mechanisms whose normal purpose is to down regulate the immune system after elimination of an infectious organism. These mechanisms are called T-cell checkpoints. Inhibition of these checkpoints can reactivate the immune cells and has had remarkable success in previously virtually untreatable diseases such as metastatic melanoma. This novel form of treatment is generally much better tolerated than cytotoxic chemotherapy but may result in side effects owing to the uncontrolled activation of the immune system. Side effects such as pneumonitis, colitis, adrenal failure and hypophysitis (pituitary inflammation) may be life-changing or life-threatening and are more common when using a combination of checkpoint inhibitors. Immunotherapy is a very active field of research and it is likely that vaccines and engineered immune cells will increasingly enter treatment protocols in the coming years. The range of non-surgical anti-cancer treatments

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adequate oxygenation of tissues is assisted by simple measures such as correcting anaemia prior to radiotherapy. Cancer types differ greatly in their sensitivity to radiotherapy. Similarly, higher doses of radiotherapy are needed to control bulky disease (~70 Gy) than to eliminate residual tumour cells (~50 Gy) or to palliate symptoms (~30 Gy). Radiotherapy is mainly used as a localised treatment (Figure 12.7). The target area is defined by imaging, which will include anatomical imaging, such as CT and MRI, to identify the tumour mass, neighbouring structures and landmarks for radiotherapy planning. Sometimes functional imaging, such as PET, is used to further define structures that should be included in the radiation field such as lymph nodes containing small volumes of tumour, whose metabolic signature is detected by PET. The planning and technical set-up of radiotherapy is a highly specialised subject. Planning can be extremely difficult and time-consuming, e.g. in the treatment of head and neck cancer, where the treatment intent is curative but there are multiple vital and highly sensitive structures close to the target area. In general terms, the radiotherapy team will aim to provide a uniform therapeutic radiation dose to the target area, while sparing adjacent structures from significant damage. The most common form of treatment is external beam radiotherapy in which x-rays are aimed at the target volume from an external source. Where necessary, modern radiotherapy can employ sophisticated computer programs and algorithms to sculpt the shape of the treatment volume. It is now possible to irradiate irregularly shaped target volumes using techniques such as intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT). The ability to give high fractional doses in this way has led to the development of stereotactic ablative radiotherapy (SABR), in which a small number of fractions can be used to treat primary tumours, or isolated metastases, to curative dose levels. Other ways of targeting the tumour volume include brachytherapy, in which the radiation source is brought very close to the tumour by insertion of radioactive seeds, and radionuclide therapy, in which a radioactive source is concentrated at the tumour site. One of the main problems in determining the optimal schedule of radiation is that there is a dissociation between the acute effects on normal tissues and the late damage. The acute reaction is not a reliable guide to the adverse consequences of treatment in the longer term. Since the late effects following irradiation can take over 20 years to develop, this poses an obvious difficulty: if a radiation schedule is changed it will be known within 2 or 3 years whether or not the new schedule has improved tumour control; it may, however, be two decades before it is known, with any degree of certainty, whether or not the new technique is safe. Anti-cancer drugs The classes of anti-cancer drugs, their modes of action and clinical indications are summarised in Table 12.6.

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damage Olaparib mutated cancers response inhibitors Niraparib Rucaparib Hormones Tamoxifen Blocks oestrogen receptors Aromatase inhibitors that block postmenopausal Breast cancer Anastrozole (non-ovarian) oestrogen production Letrozole Exemestane Analogues of gonadotropin-releasing hormone, Leuprolide continued use produces downregulation of the Goserelin anterior pituitary with consequent fall in testosterone Buserelin levels Cabergoline Blocks prolactin release, a long-acting dopamine Prolactin-secreting pituitary tumours agonist Tumour types that may be sensitive to drug Leukaemias Lymphomas Non-small lung cancer Pancreatic cancer Bladder cancer Gastric cancer Head and neck cancer Rectal cancer Ovarian cancer Non-small cell lung cancer Head and neck cancer Oesophageal cancer Lymphomas Sarcomas Kaposi's sarcoma Breast cancer Lymphomas Sarcomas Sarcomas Lymphomas Germ cell tumours Lymphomas Brain tumours Sarcoma Glioblastoma multiforme Wilms' tumour BRCA

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effective in patients with colorectal cancer who have wild-type (non-mutated) ras ; imatinib is particularly effective in patients with gastrointestinal stromal tumours who have mutations in exon 11 of the Kit gene – patients with mutations in exon 9 may still respond to imatinib but will require higher doses and patients without mutations in Kit are far less likely to respond to imatinib. Treatment choice therefore requires a molecular analysis of the patient's tumour. It is this determination of treatment at the individual level that has led to the concept of 'personalised medicine'. Although major advances have been made, important targets such as ras remain elusive at present, although several ras -targeted molecules are in development. Immunotherapy Treatments to activate the immune system against cancer have a long history , stimulated by the observation that up to half of the volume of certain tumours was known to be made up of immune cells, which appeared to be inactive or dead. There is now an appreciation that multiple malignancies activate mechanisms whose normal purpose is to down regulate the immune system after elimination of an infectious organism. These mechanisms are called T-cell checkpoints. Inhibition of these checkpoints can reactivate the immune cells and has had remarkable success in previously virtually untreatable diseases such as metastatic melanoma. This novel form of treatment is generally much better tolerated than cytotoxic chemotherapy but may result in side effects owing to the uncontrolled activation of the immune system. Side effects such as pneumonitis, colitis, adrenal failure and hypophysitis (pituitary inflammation) may be life-changing or life-threatening and are more common when using a combination of checkpoint inhibitors. Immunotherapy is a very active field of research and it is likely that vaccines and engineered immune cells will increasingly enter treatment protocols in the coming years. The range of non-surgical anti-cancer treatments

Radiotherapy Half of all patients will receive radiotherapy during their - cancer journey . The mechanism of action of radiotherapy is that ionising radiation causes single- and double-stranded - DNA breaks. Cells most sensitive to radiotherapy are in mitosis or late G2 in the cell cycle. Damage may be caused - by the direct effect of the ionising radiation on the DNA. However, the predominant therapeutic effect is indirect, and is achieved by ionising radiation causing the creation of oxygen free radicals, which then damage the DNA. The fact that the or indirect damage is predominant explains why hypoxic cells - are relatively resistant to radiotherapy . In practice, adequate oxygenation of tissues is assisted by simple measures such as correcting anaemia prior to radiotherapy . Cancer types differ greatly in their sensitivity to radiotherapy . Similarly , higher doses of radiotherapy are needed to control bulky disease (~70 /uni00A0 Gy) than to eliminate residual tumour cells (~50 /uni00A0 Gy) or to palliate symptoms (~30 /uni00A0 Gy). Radiotherapy is mainly used as a localised treatment (Figure 12.7). The target area is defined by imaging, which will include anatomical imaging, such as CT and MRI, to identify the tumour mass, neighbouring structures and landmarks for radiotherapy planning. Sometimes functional imaging, such as PET , is used to further define structures that should be included in the radiation field such as lymph nodes containing small volumes of tumour, whose metabolic signature is detected by PET . The planning and technical set-up of radiotherapy is a highly specialised subject. Planning can be extremely difficult and time-consuming, e.g. in the treatment of head and neck cancer, where the treatment intent is curative but there are multiple vital and highly sensitive structures close to the target area. In general terms, the radiotherapy team will aim to provide a uniform therapeutic radiation dose to the target area, while sparing adjacent structures from significant damage. The most common form of treatment is external beam radiotherapy in which x-rays are aimed at the target volume from an external source. Where necessary , modern radiotherapy can employ

Simulate the 'beam's-eye view' of the target Diagnostic quality screening and films Images digitally reconstructed from CT planning images Three-dimensional planning Careful shaping of beams ('conformal therapy') Alter energy profile across the beam to sculpt the dose distribution to complex shapes ('intensity modulated radiation therapy' – IMRT) Optimal delivery of treatment Ensure day-to-day reproducibility of set up Online verification (portal imaging) Reference tattoos Immobilisation of patient (moulds, shells) Ensure that only the target is treated Eliminate effect of physiological movement (breathing, peristalsis): 'image-guided radiation therapy' – IGRT Quality control and cross-checking procedures throughout the whole process from target definition to follow-up Tumour types that may be sensitive to drug Lymphomas Leukaemias Brain tumours Sarcomas Breast cancer Non-small cell lung cancer Ovarian cancer Prostate cancer Head and neck cancer Breast cancer GI cancer Breast cancer Bladder cancer Lymphomas Cervical cancer purine synthesis Leukaemias Continued

Class Examples Putative mode of action Cytosine arabinoside False substrate in DNA synthesis Drugs that interfere with DNA synthesis (antimetabolites) Gemcitabine Inhibits ribonucleotide reductase – continued Mitomycin C DNA cross-linking, preferentially active at sites of Anal cancer Drugs that directly low oxygen tension (a bioreductive drug) damage DNA or interfere with its function Cisplatin Form adducts between DNA strands and interferes Germ cell tumours Carboplatin with replication Oxaliplatin Forms adducts between DNA strands and interferes Colorectal cancer with replication Doxorubicin Intercalates between DNA strands and interferes Breast cancer with replication Cyclophosphamide A prodrug converted via hepatic cytochrome p450 to phosphoramidate mustard. Causes DNA cross- links Ifosfamide Related to cyclophosphamide, causes DNA cross- Small cell lung cancer links Bleomycin DNA strand breakage via formation of metal Germ cell tumours complex Irinotecan Inhibits topoisomerase 1, prevents DNA from Colorectal cancer unwinding and repairing during replication Etoposide Inhibits topoisomerase 2, prevents DNA from Small cell lung cancer unwinding and repairing during replication Dacarbazine A nitrosourea that requires activation by hepatic cytochrome p450. Methylates guanine residues in DNA Temozolomide A nitrosourea but, unlike dacarbazine, does not require activation by hepatic cytochrome p450. Methylates guanine residues in DNA Actinomycin D Intercalation between DNA strands, DNA strand Rhabdomyosarcoma breaks Inhibit DNA repair by PARP , especially in DNA damage Olaparib mutated cancers response inhibitors Niraparib Rucaparib Hormones Tamoxifen Blocks oestrogen receptors Aromatase inhibitors that block postmenopausal Breast cancer Anastrozole (non-ovarian) oestrogen production Letrozole Exemestane Analogues of gonadotropin-releasing hormone, Leuprolide continued use produces downregulation of the Goserelin anterior pituitary with consequent fall in testosterone Buserelin levels Cabergoline Blocks prolactin release, a long-acting dopamine Prolactin-secreting pituitary tumours agonist Tumour types that may be sensitive to drug Leukaemias Lymphomas Non-small lung cancer Pancreatic cancer Bladder cancer Gastric cancer Head and neck cancer Rectal cancer Ovarian cancer Non-small cell lung cancer Head and neck cancer Oesophageal cancer Lymphomas Sarcomas Kaposi's sarcoma Breast cancer Lymphomas Sarcomas Sarcomas Lymphomas Germ cell tumours Lymphomas Brain tumours Sarcoma Glioblastoma multiforme Wilms' tumour BRCA

- Ovarian cancer Breast cancer Prostate cancer Breast cancer Prostate cancer Continued

Class Examples Putative mode of action Hormones Bromocriptine Dopamine agonist, blocks stimulation of anterior – continued pituitary Block the effect of androgens Cyproterone acetate Flutamide Nilutamide Bicalutamide Abiraterone Block testosterone production Cyproterone acetate Inhibit EGFR tyrosine kinase Inhibitors of receptor Osimertinib tyrosine kinases Erlotinib Afatinib Gefitinib Imatinib Blocks ability of mutant BCR-ABL fusion protein to bind ATP Imatinib Inhibition of mutant c-KIT Erlotinib Inhibits EGFR tyrosine kinase Promiscuous tyrosine kinase inhibitors (PDGFR, Sunitinib VEGFR, KIT, FLT) Regorafenib Lenvatinib Lapatinib Inhibits tyrosine kinases associated with EGFR and HER2 Axitinib Inhibits tyrosine kinase associated with VEGFR Cyclin-dependent Palbociclib Inhibits growth signal kinase inhibitors Protease inhibitors Bortezomib Interferes with proteasomal degradation of regulatory proteins, in particular stops NF- preventing apoptosis Differentiating All- trans -retinoic acid Induces terminal differentiation agents Farnesyl transferase Lonafarnib Inhibition of farnesyl transferase and consequent inactivation of Tipifarnib Inhibition of farnesyl transferase and consequent inactivation of Trastuzumab Antibody directed against HER2 receptor Antibodies directed to cell surface Cetuximab Antibody directed against EGFR antigens Bevacizumab Antibody directed against VEGFR Rituximab Antibody against CD20 antigen Alemtuzumab Antibody against CD52 antigen Antibody drug Trastuzumab Targets chemotherapy to conjugates deruxtecan Sacituzumab Targets chemotherapy to govitecan Enfortumab vedotin Targets chemotherapy to Inducers of Arsenic trioxide Induces apoptosis by caspase inhibition apoptosis Inhibition of nitric oxide Venetoclax BH3 mimetic Tumour types that may be sensitive to drug Pituitary tumours Prostate cancer Prostate cancer Non-small cell lung cancer Chronic myeloid leukaemia GISTs Non-small cell lung cancer Pancreatic cancer Renal cancer GIST refractory to Imatinib Colorectal cancer Thyroid cancer Breast cancer Renal cancer Breast cancer Multiple myeloma B from Acute promyelocytic leukaemia farnesyl transferase and consequent Leukaemia ras -dependent signal transduction Acute leukaemia ras -dependent signal transduction Myelodysplastic syndrome Breast cancer Colorectal cancer Head and neck cancer Colorectal cancer Lymphomas Lymphomas Her2 expressing tumour Breast cancer Trop2 expressing tumour Breast cancer Nectin4 expressing tumour Urothelial cancer Acute promyelocytic leukaemia CML AML Lymphoma Continued

Cytotoxic chemotherapy Selective toxicity is the fundamental principle underlying cytotoxic chemotherapy . Tumour types vary greatly in their sensitivity to cytotoxic chemotherapy and their vulnerability to drugs with specific mechanisms of action. Treatments are often given for a limited number of treatment days during a cycle of treatment lasting typically 3–4 weeks. This allows the tumour to receive an effective dose while providing sufficient time for the patient to recover in time for the next cycle. Many treatment regimens give a limited number of cycles, typically three to six in total. Other regimens are maintenance treatments, in which an unlimited number of cycles are given. Hormonal treatments Several tumour types, notably breast cancer and prostate cancer, are stimulated by endogenous hormones. Removal of this stimulus from sensitive tumours will result in their shrinkage. An understanding of the relevant endocrine pathways has identified several points for therapeutic intervention, including interference with hormone receptors and with hormone production. Targeted treatments The explosion of knowledge about the molecular biology of cancer has identified multiple therapeutic targets. This has ushered in an era of highly specific treatments that aim to inhibit a target essential for tumour survival while leaving other tissues unaffected. At present, most targeted therapies are not absolutely specific for their primary target and therefore do - have unwanted or 'off-target' side effects. In addition, successful inhibition of the target may have inevitable undesirable consequences in addition to the desired effect, so-called 'on-target' side effects. Many targeted treatments are given in continuous cycles and the dosing

and toxicity management strategies are therefore of particular importance. These treatments will only work if a patient's tumour depends on a therapeutic target. The kinase inhibitor vemurafenib will only be effective in patients with melanoma whose

Class Examples
Putative mode of action
Immunological
Ipilimumab Blocks CTLA-4 and thus releases the brakes on the mediators activation of T cells
Block the PD-1 signalling on T lymphocytes and Pembrolizumab thereby prevents the inhibition of T-cell activation
Nivolumab Atezolizumab Durvalumab Interferon alpha-2b Activates macrophages, increases the cytotoxicity of T lymphocytes, inhibits cell division (and viral replication)
Thalidomide Anti-inflammatory, stimulates T cells, antiangiogenic
HDAC inhibitors Panobinostat Acetylation of histones is associated with increased transcription of genes; inhibiting deacetylation can decrease expression of mutated or dysregulated genes
Entinostat Acetylation of histones is associated with increased transcription of genes; inhibiting deacetylation can decrease expression of mutated or dysregulated genes
PI3K inhibitors Idelalisib Inhibits signalling via the PI3K/AKT/mTOR pathway and thereby switch off stimulus to cellular proliferation
mTOR inhibitors Temsirolimus Inhibit mTOR, a key component in the PI3K/AKT/mTOR pathway
Everolimus mTOR pathway MEK inhibitors Trametinib Inhibit the MAPK pathway
Selumetinib RAF inhibitors Dabrafenib Inhibit the MAPK pathway
Vemurafenib AML, acute myeloid leukaemia; ATP, adenosine triphosphate; CML, chronic myeloid leukaemia; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFR, epidermal growth factor receptor; FLT3, FMS-like tyrosine kinase; GI, gastrointestinal; GIST, gastrointestinal stromal tumour; HDAC, histone deacetylase; HER2, human epidermal growth factor receptor 2; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NF, nuclear factor; PARP, poly-ADP ribose polymerase; PD-1, programmed death receptor; PI3K, phosphoinositide 3-kinase; RAF, rapidly accelerated fibrosarcoma; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.
Tumour types that may be sensitive to drug
Melanoma Lung cancer Renal cancer Melanoma Lung cancer Renal cancer Bladder cancer Hairy-cell leukaemia Myeloma Cutaneous T-cell lymphoma Melanoma B-cell lymphomas Renal cancer Neuroendocrine tumours Melanoma Neurofibroma Melanoma tyrosine kinase; mTOR, mammalian target of rapamycin; PDGFR, platelet-derived

growth factor receptor; PI3K, phosphoinositide 3-kinase; RAF, rapidly accelerated fibrosarcoma; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor. Tumour types that may be sensitive to drug
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