NHS
Wessex
Cancer Alliance

Systemic Anti-Cancer Therapy (SACT)

Claire Marsh – Senior Programme Manager
(Treatments & Personalised Care)

Systemic Anti-Cancer Treatment

- No matter what the intention of SACT the experience/benefits must outweigh the problems associated with it.
- Chemotherapy is associated more with its widely known side effects than it is effectiveness in treating cancer.
- Chemotherapy kills fast-growing and fast-dividing cells, which includes cancer cells, but also includes healthy cells that have high rated of growth and division
- Immunotherapies (TKIs, Checkpoint inhibitors, MoABs) are targeted therapies or accelerate the effects of the bodies own immune system to fight cancer.

CYTOTOXIC CHEMOTHERAPY

Cyto-cell
Toxic-death

TARGETED DRUGS (personalised medicine):
Monoclonal Antibodies – "Mabs"
Immunotherapy - check point inhibitors
Protein Kinase Inhibitors – "ibs" (nibs, mibs, sibs & ribs)

Chemotherapy

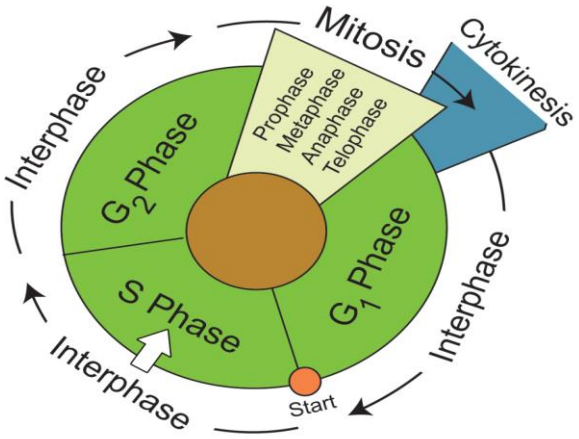
- Given Orally, IV, IM, SC, IT, intracavity
- Damage to normal tissue - cannot distinguish a normal cell from a cancer cell
- Single or in combination (regimen)
- Different drugs for different diseases/different doses
- Given over cycles
- Treatment intent – adjuvant, neoadjuvant, induction, palliative
- Total dose for some drugs

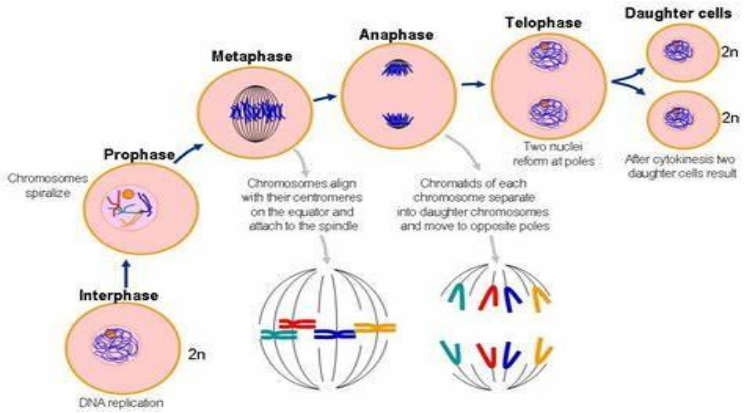
How does chemotherapy work?

At cellular level – cell cycle

- Carcinogenic/carcinogenicity
- Genotoxic/Reproductive toxicity
- Teratogenic/Teratogenicity or other developmental toxicity or organ toxicity at low doses

- G1 – this is a resting phase, where proteins are synthesised
- S - Synthesis of DNA (deoxyribonucleic acids)
- G2 - Resting phase, where RNA (ribonucleic acids) are synthesised
- M – Mitosis
- G0 - Resting phase with potential to divide (Cytokineses)





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Chemotherapy Agents

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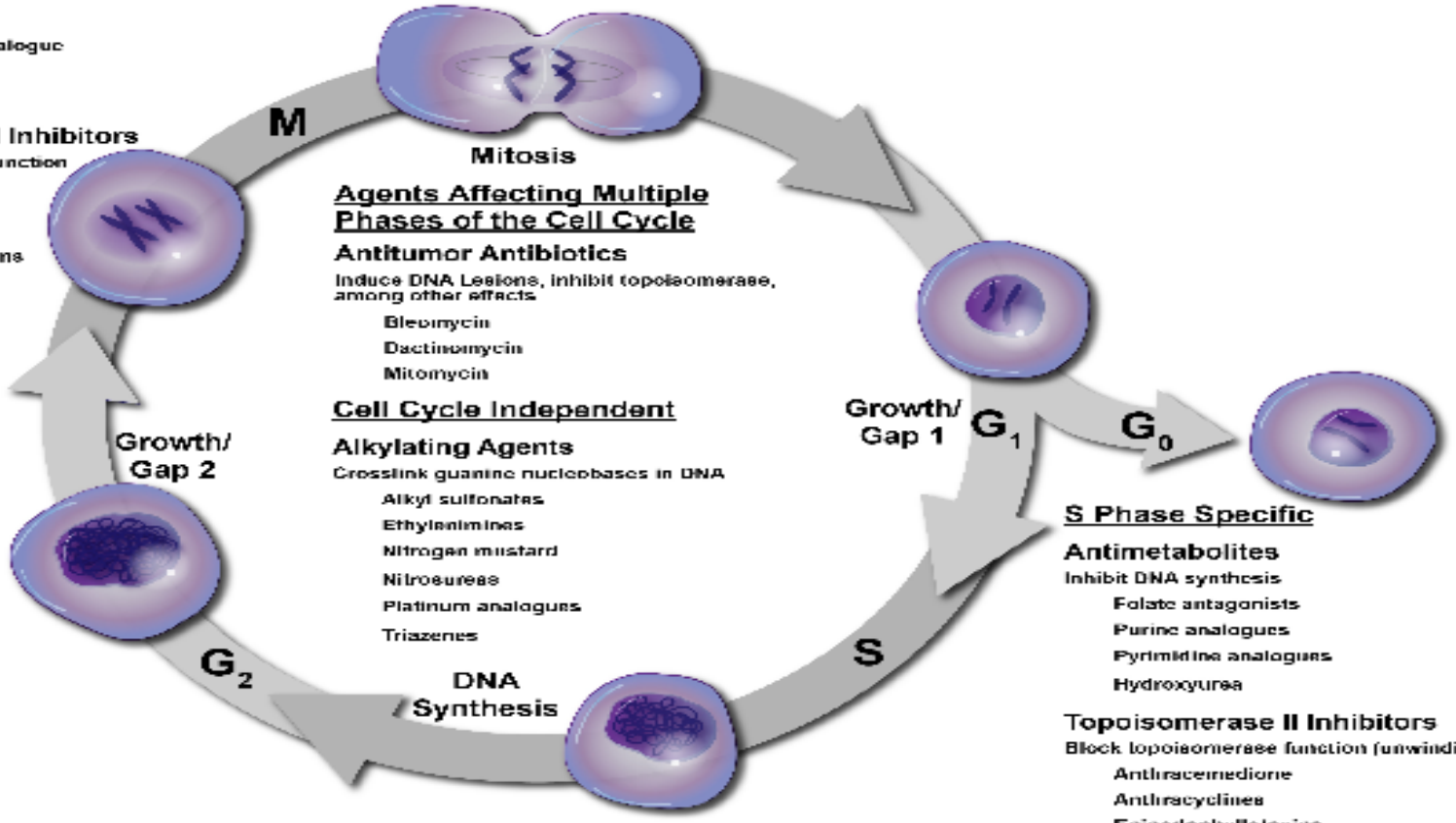
M Phase Specific

Antimicrotubule Agents
Inhibit function of microtubules
- Epothilones
- Halichondrin B analogue
- Taxanes
- Vinca alkaloids

Topoisomerase II Inhibitors
Block topoisomerase function (unwinding DNA)
- Anthracenedione
- Anthracyclines
- Epipodophyllotoxins



Agents Affecting Multiple Phases of the Cell Cycle

Antitumor Antibiotics
Induce DNA Lesions, inhibit topoisomerase, among other effects
- Bleomycin
- Dactinomycin
- Mitomycin

Cell Cycle Independent

Alkylating Agents
Crosslink guanine nucleobases in DNA
- Alkyl sulfonates
- Ethylenimines
- Nitrogen mustard
- Nitrosoureas
- Platinum analogues
- Triazenes

S Phase Specific

Antimetabolites
Inhibit DNA synthesis
- Folate antagonists
- Purine analogues
- Pyrimidine analogues
- Hydroxyurea

Topoisomerase II Inhibitors
Block topoisomerase function (unwinding
- Anthracenedione
- Anthracyclines
- Epipodophyllotoxins

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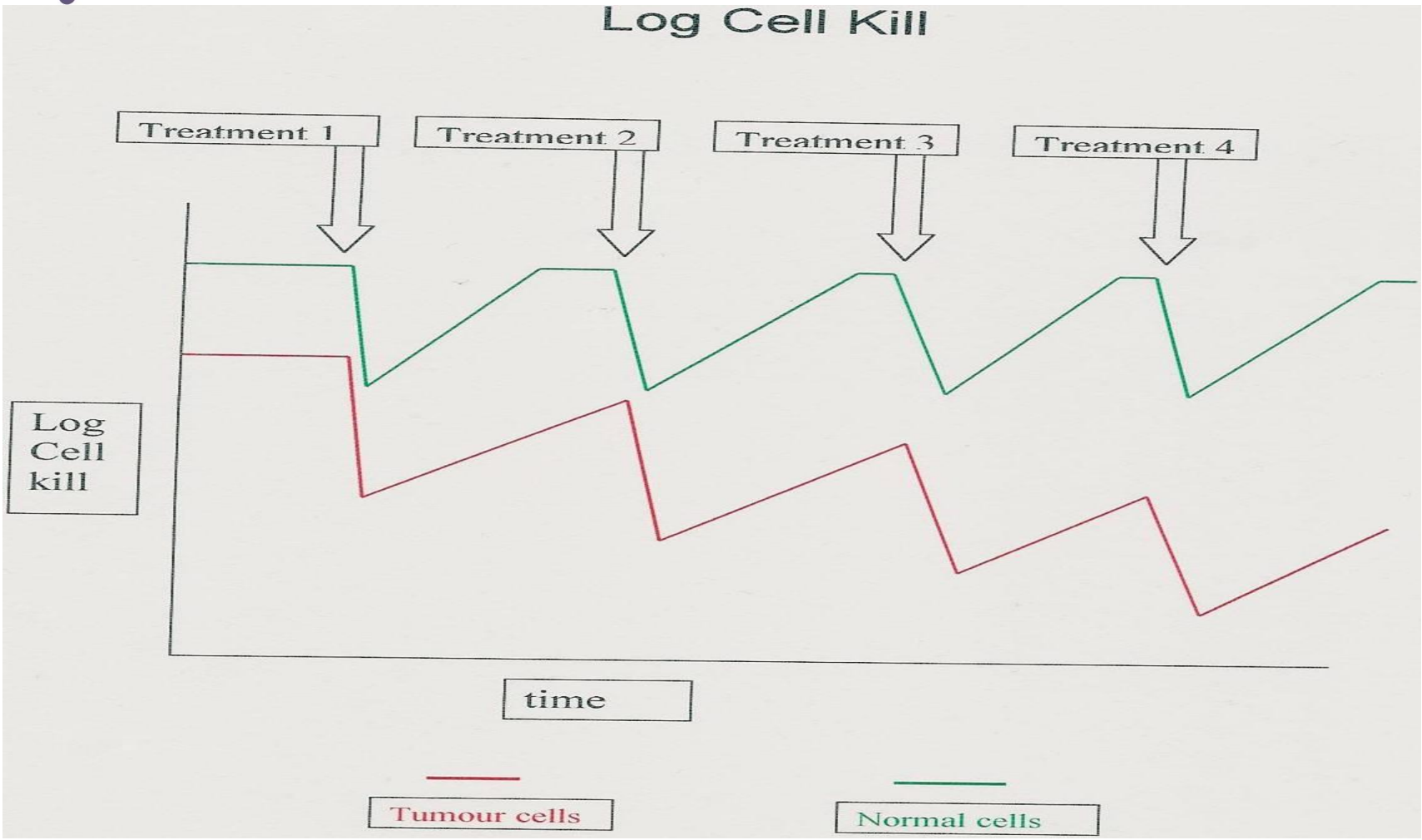
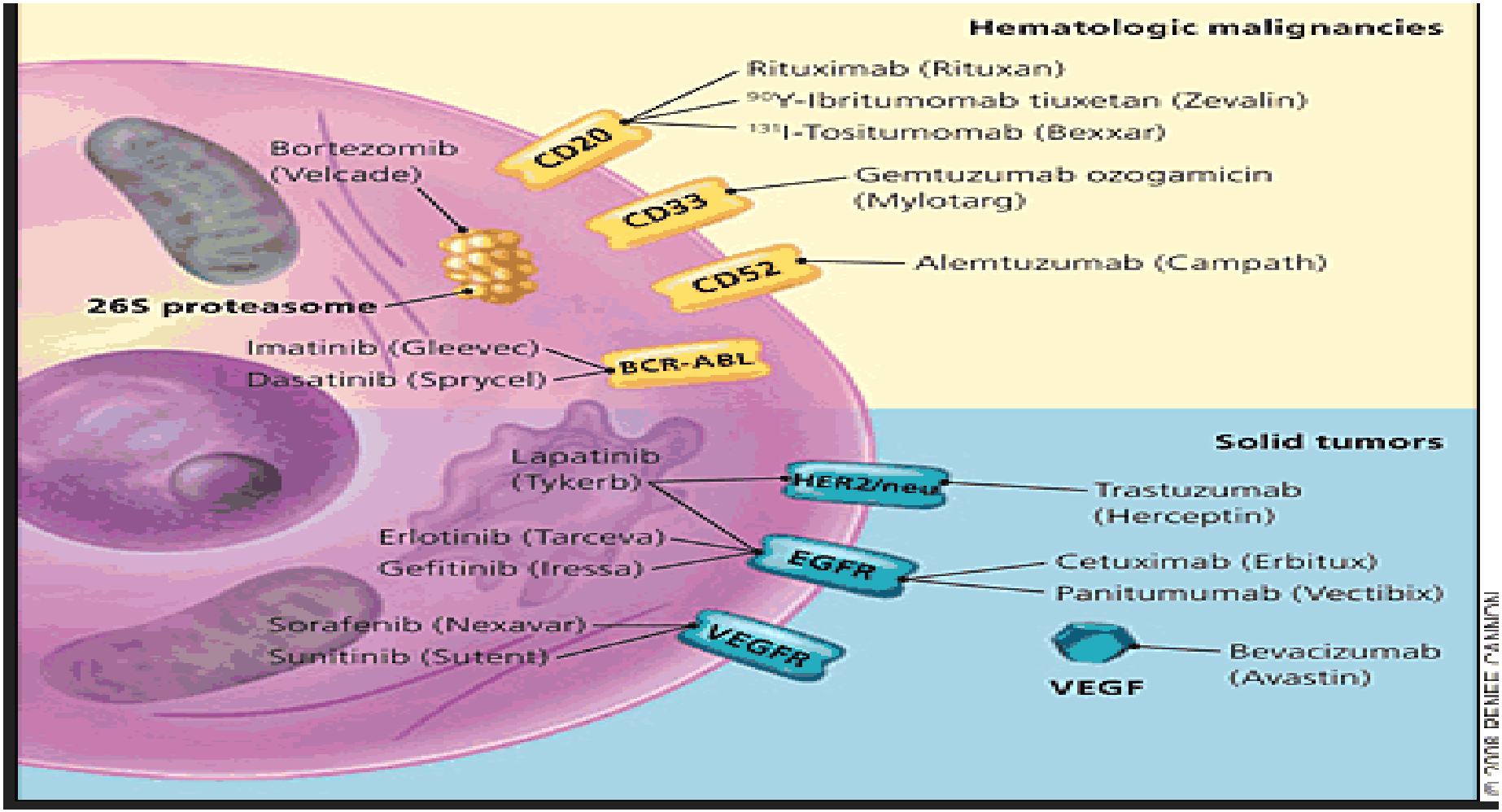

Log Cell Kill
Treatment 1
Treatment 2
Treatment 3
Treatment 4
Log Cell kill
time
Tumour cells
Normal cells

Targeted Treatments
(personalised medicine)

- **Monoclonal Antibodies "Mabs"** - block receptors on *outside* of cell (e.g.HER2, CD20)
- **Checkpoint Inhibitors –** bind to molecules involved in T-Cell regulation, remove inhibitory pathways that block a T-cell response (eg PD-1, PDL-1, CTLA-4)
- **Protein Kinase Inhibitors "ibs"** (nibs, mibs, sibs & ribs) - block enzyme signalling pathways *inside* the cell (e.g. TKIs, BRAF, proteasome inhibitors, mTOR/P13K, PARP inhibitors)
- **Hormone therapy -** block receptors

“Mabs” & “ibs”



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Checkpoint Inhibitors

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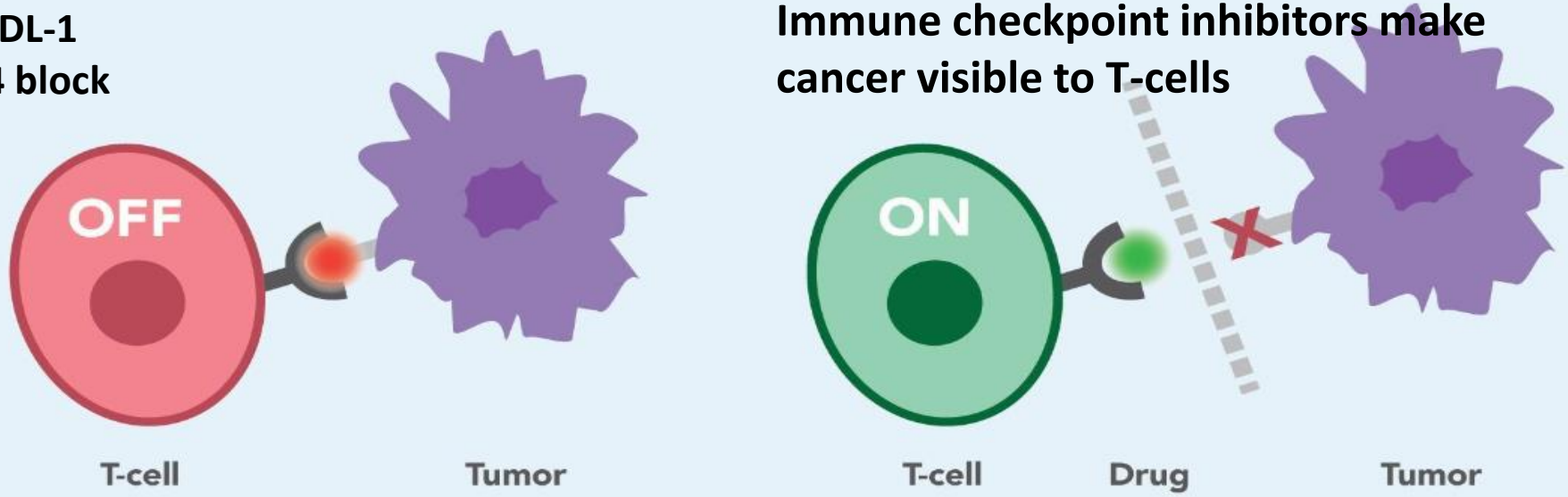
How Does Immunotherapy Work?

Tumor cells bind to T-cells to deactivate them

Immunotherapy drugs can block tumor cells from deactivating T-cells

PD1, PDL-1
CTLA-4 block
T cells

Immune checkpoint inhibitors make cancer visible to T-cells



Columbia University Medical Center

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With thanks for CR UK for allowing the use of this video.

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SACT Classification

Chemotherapy

- Anthracycline Antibiotics e.g. Epirubicin, Mitomycin
- Platinum Compounds e.g. Cisplatin, Carboplatin
- Taxane's e.g. Paclitaxel, Docetaxel
- Vinca Alkaloids e.g. Vincristine, Vinblastine
- Anti-metabolites e.g. Capecitabine, 5FU, Cytarabine
- Alkylating Agents e.g. Chlorambucil, Cyclophosphamide
- Topoisomerase 1 e.g. Irinotecan
- Topoisomerase 2 e.g. Etoposide
- Other e.g. Asparaginase, Arsenic

Immunotherapy

Tyrosine Kinase Inhibitors (TKIs)

- Proteasome Inhibitor e.g. Bortezomib (Velcade)
- Protein Kinase Inhibitor e.g. Afitinib,
- BRAF Kinase Inhibitor e.g. Dabrafenib
- Tyrosine Kinase Inhibitors e.g. Nilotinib, Imatinib
- mTor Protein Kinase Inhibitor e.g. Everolimus
- EGFR TKI e.g. Gefitinib

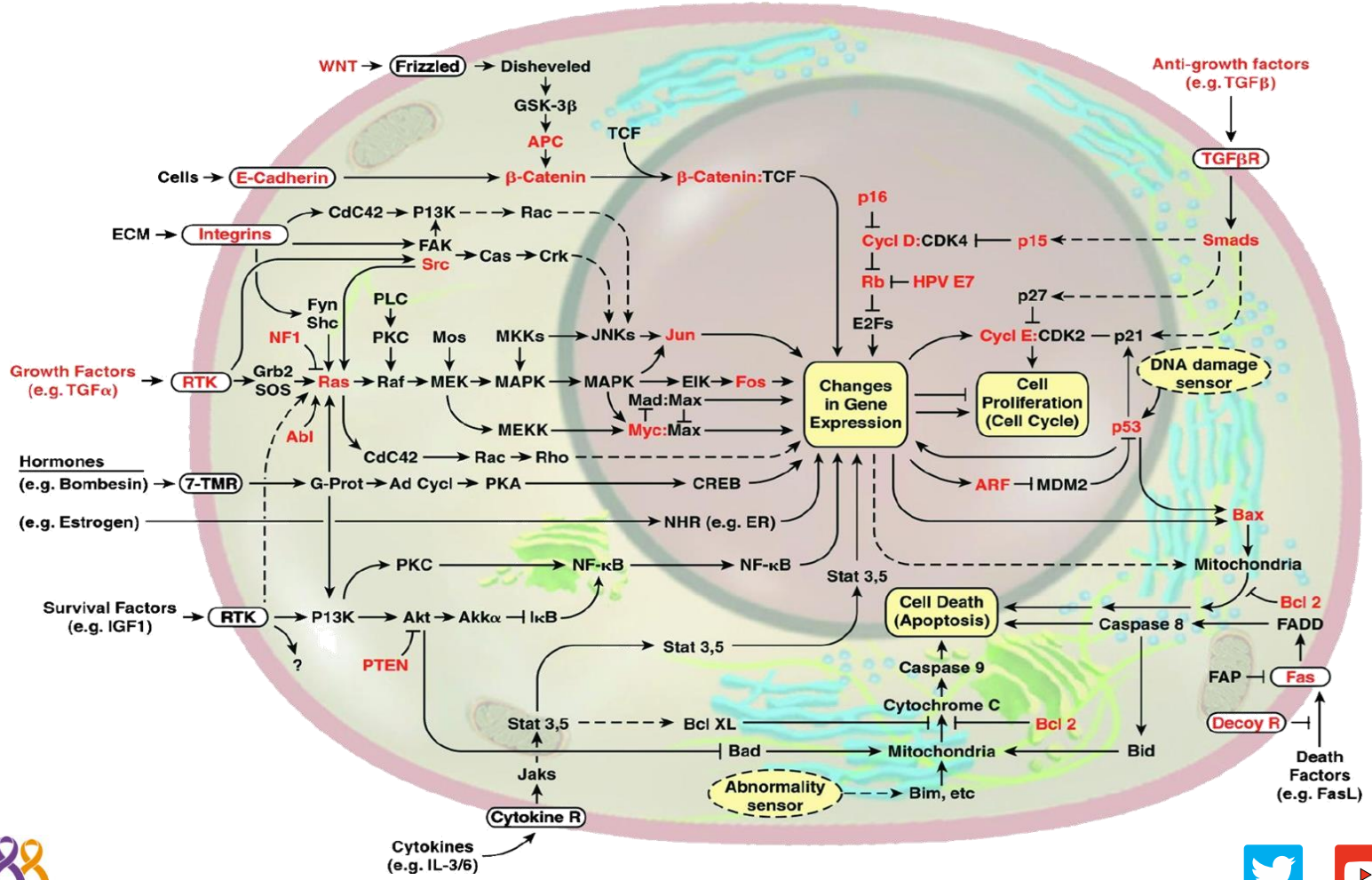
Monoclonal Antibodies

- CD20 e.g. Rituximab
- HER 2 e.g. Herceptin
- CD33 e.g. Mylotarg
- CD52 e.g. Campath
- EGFR e.g. Cetuximab
- VEGF e.g. Bevacizumab
- VEGFR e.g. Sorafenib

Checkpoint Inhibitors

- PD-1 & PDL-1 e.g. Pembrolizumab, Durvalumab, Nivolumab,
- CTLA-4 e.g. Ipilimumab

The Integrated Circuit of the Cell: Signal Transduction Pathways



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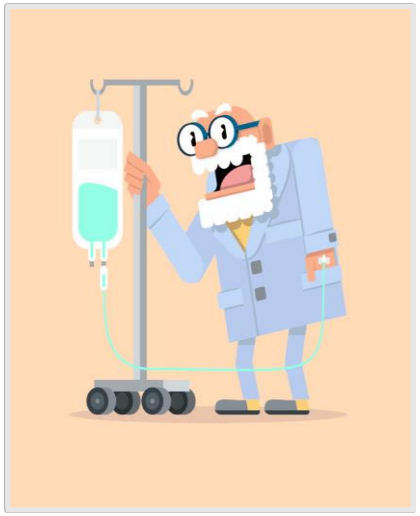
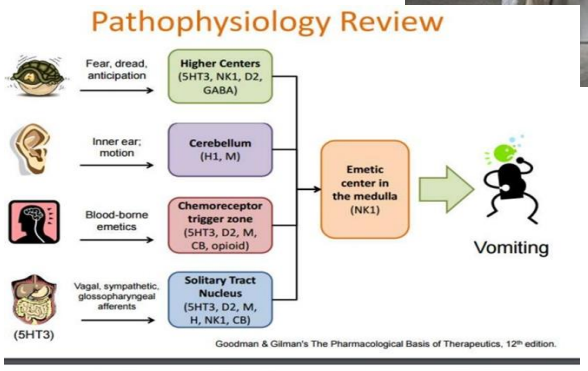
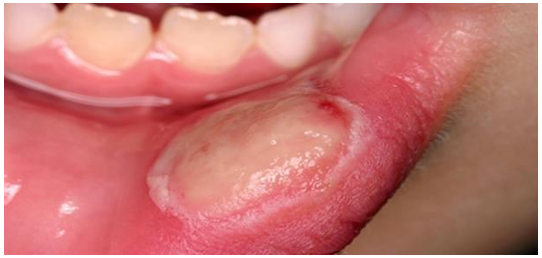
Common Side Effects - Chemotherapy

- Bone Marrow suppression
  - Anemia, Thrombocytopenia, Neutropenia
- Nausea & Vomiting
- Diarrhea
- Fatigue
- Oral Mucositis
- Hair Loss
- Skin toxicity – PPE







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Immunotherapy Toxicity

Immunotherapy activates the persons own immune system, taking the brakes off, to mount an exaggerated immune response allowing cancer cells to be destroyed.

Management

Early recognition

Early reporting

Early intervention/management

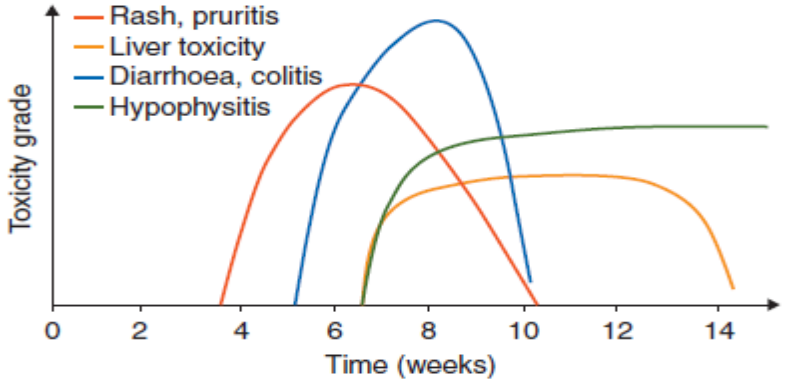

Figure 1. Timing of occurence of immune-related adverse events following ipilimumab treatment.
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Annals of Oncology 28 (Supplement 4): i119–i142, 2017
doi:10.1093/annonc/mdx225

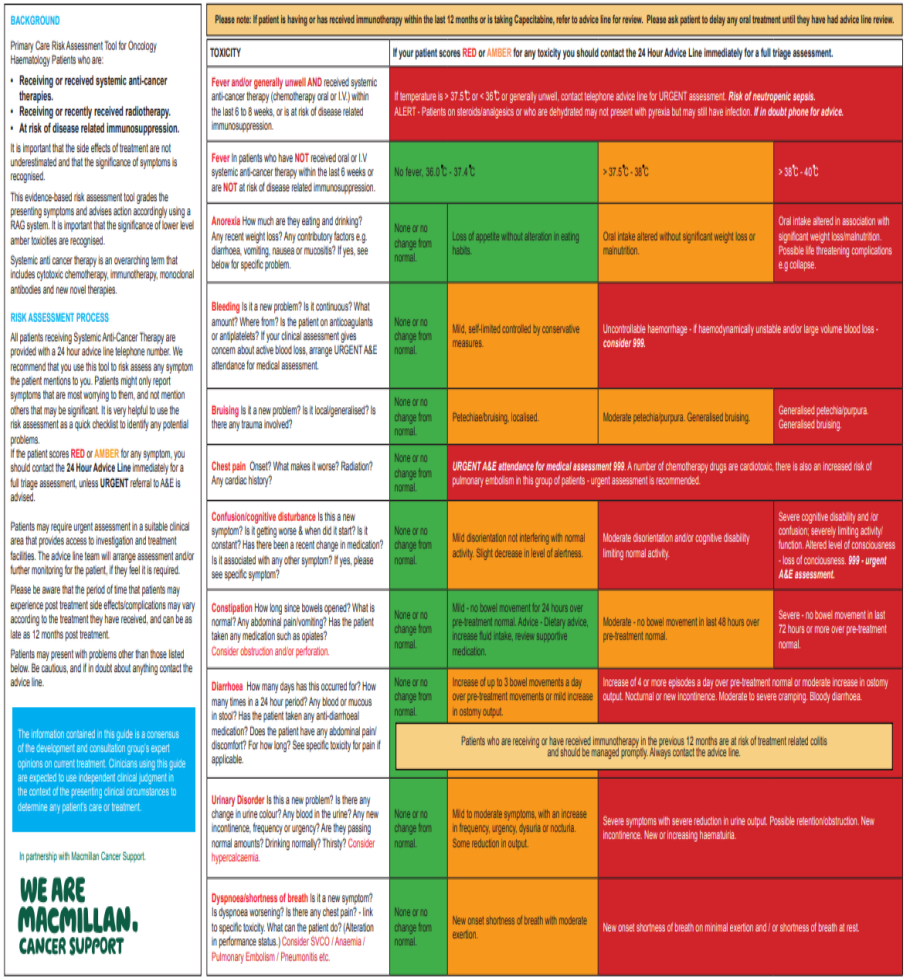
CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. B. A. G. Haanen[1], F. Carbonnel[2], C. Robert[3], K. M. Kerr[4], S. Peters[5], J. Larkin[6] & K. Jordan[7], on behalf of the ESMO Guidelines Committee*

UKONS/Macmillan Primary Care Risk Assessment Tool :: UK Acute Oncology Society

Wessex Cancer Alliance



BACKGROUND

Primary Care Risk Assessment Tool for Oncology Haematology Patients who are:

- **Receiving or received systemic anti-cancer therapies.**
- **Receiving or recently received radiotherapy.**
- **At risk of disease related immunosuppression.**

It is important that the side effects of treatment are not underestimated and that the significance of symptoms is recognised.

This evidence-based risk assessment tool grades the presenting symptoms and advises action accordingly using a RAG system. It is important that the significance of lower level amber toxicities are recognised.

Systemic anti cancer therapy is an overarching term that includes cytotoxic chemotherapy, immunotherapy, monoclonal antibodies and new novel therapies.

RISK ASSESSMENT PROCESS

All patients receiving Systemic Anti-Cancer Therapy are provided with a 24 hour advice line telephone number. We recommend that you use this tool to risk assess any symptom the patient mentions to you. Patients might only report symptoms that are most worrying to them, and not mention others that may be significant. It is very helpful to use the risk assessment as a quick checklist to identify any potential problems.

If the patient scores **RED** or **AMBER** for any symptom, you should contact the **24 Hour Advice Line** immediately for a full triage assessment, unless **URGENT** referral to A&E is advised.

Patients may require urgent assessment in a suitable clinical area that provides access to investigation and treatment facilities. The advice line team will arrange assessment and/or further monitoring for the patient, if they feel it is required.

Please be aware that the period of time that patients may experience post treatment side effects/complications may vary according to the treatment they have received, and can be as late as 12 months post treatment.

Patients may present with problems other than those listed below. Be cautious, and if in doubt about anything contact the advice line.

The information contained in this guide is a consensus of the development and consultation group's expert opinions on current treatment. Clinicians using this guide are expected to use independent clinical judgment in the context of the presenting clinical circumstances to determine any patient's care or treatment.

In partnership with Macmillan Cancer Support.

WE ARE MACMILLAN. CANCER SUPPORT

Please note: If patient is having or has received immunotherapy within the last 12 months or is taking Capecitabine, refer to advice line for review. Please ask patient to delay any oral treatment until they have had advice line review.

TOXICITY	If your patient scores RED or AMBER for any toxicity you should contact the 24 Hour Advice Line immediately for a full triage assessment.			
Fever and/or generally unwell AND received systemic anti-cancer therapy (chemotherapy oral or I.V.) within the last 6 to 8 weeks, or is at risk of disease related immunosuppression.	If temperature is > 37.5℃ or < 36℃ or generally unwell, contact telephone advice line for URGENT assessment. ***Risk of neutropenic sepsis.*** ALERT - Patients on steroids/analgesics or who are dehydrated may not present with pyrexia but may still have infection. ***If in doubt phone for advice.***			
Fever In patients who have **NOT** received oral or I.V systemic anti-cancer therapy within the last 6 weeks or are **NOT** at risk of disease related immunosuppression.	No fever, 36.0℃ - 37.4℃		> 37.5℃ - 38℃	> 38℃ - 40℃
Anorexia How much are they eating and drinking? Any recent weight loss? Any contributory factors e.g. diarrhoea, vomiting, nausea or mucositis? If yes, see below for specific problem.	None or no change from normal.	Loss of appetite without alteration in eating habits.	Oral intake altered without significant weight loss or malnutrition.	Oral intake altered in association with significant weight loss/malnutrition. Possible life threatening complications e.g collapse.
Bleeding Is it a new problem? Is it continuous? What amount? Where from? Is the patient on anticoagulants or antiplatelets? If your clinical assessment gives concern about active blood loss, arrange URGENT A&E attendance for medical assessment.	None or no change from normal.	Mild, self-limited controlled by conservative measures.	Uncontrollable haemorrhage - if haemodynamically unstable and/or large volume blood loss - ***consider 999.***	
Bruising Is it a new problem? Is it local/generalised? Is there any trauma involved?	None or no change from normal.	Petechiae/bruising, localised.	Moderate petechia/purpura. Generalised bruising.	Generalised petechia/purpura. Generalised bruising.
Chest pain Onset? What makes it worse? Radiation? Any cardiac history?	None or no change from normal.	***URGENT A&E attendance for medical assessment 999.*** A number of chemotherapy drugs are cardiotoxic, there is also an increased risk of pulmonary embolism in this group of patients - urgent assessment is recommended.		
Confusion/cognitive disturbance Is this a new symptom? Is it getting worse & when did it start? Is it constant? Has there been a recent change in medication? Is it associated with any other symptom? If yes, please see specific symptom?	None or no change from normal.	Mild disorientation not interfering with normal activity. Slight decrease in level of alertness.	Moderate disorientation and/or cognitive disability limiting normal activity.	Severe cognitive disability and /or confusion; severely limiting activity/ function. Altered level of consciousness - loss of concousness. ***999 - urgent A&E assessment.***
Constipation How long since bowels opened? What is normal? Any abdominal pain/vomiting? Has the patient taken any medication such as opiates? Consider obstruction and/or perforation.	None or no change from normal.	Mild - no bowel movement for 24 hours over pre-treatment normal. Advice - Dietary advice, increase fluid intake, review supportive medication.	Moderate - no bowel movement in last 48 hours over pre-treatment normal.	Severe - no bowel movement in last 72 hours or more over pre-treatment normal.
Diarrhoea How many days has this occurred for? How many times in a 24 hour period? Any blood or mucous in stool? Has the patient taken any anti-diarrhoeal medication? Does the patient have any abdominal pain/ discomfort? For how long? See specific toxicity for pain if applicable.	None or no change from normal.	Increase of up to 3 bowel movements a day over pre-treatment movements or mild increase in ostomy output.	Increase of 4 or more episodes a day over pre-treatment normal or moderate increase in ostomy output. Nocturnal or new incontinence. Moderate to severe cramping. Bloody diarrhoea.	
	Patients who are receiving or have received immunotherapy in the previous 12 months are at risk of treatment related colitis and should be managed promptly. Always contact the advice line.			
Urinary Disorder Is this a new problem? Is there any change in urine colour? Any blood in the urine? Any new incontinence, frequency or urgency? Are they passing normal amounts? Drinking normally? Thirsty? Consider hypercalcaemia.	None or no change from normal.	Mild to moderate symptoms, with an increase in frequency, urgency, dysuria or nocturia. Some reduction in output.	Severe symptoms with severe reduction in urine output. Possible retention/obstruction. New incontinence. New or increasing haematuria.	
Dyspnoea/shortness of breath Is it a new symptom? Is dyspnoea worsening? Is there any chest pain? - link to specific toxicity. What can the patient do? (Alteration in performance status.) Consider SVCO / Anaemia / Pulmonary Embolism / Pneumonitis etc.	None or no change from normal.	New onset shortness of breath with moderate exertion.	New onset shortness of breath on minimal exertion and / or shortness of breath at rest.	

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UKONS Oncology Nursing Society

ACUTE ONCOLOGY INITIAL MANAGEMENT GUIDELINES

Version 4.0
13.02.2023 (review date: 3 years or sooner if required due to new evidence)
Please check that you have the latest version.

Guidelines for the initial management of adult patients who have a cancer diagnosis, and present as an emergency or unplanned admission with a complication of their disease or cancer treatment.

The UK Acute Oncology Society have worked with UKONS on the review and development of these guidelines.

UKAOS UK Acute Oncology Society

The following professional bodies have reviewed the guidelines and support use in practice:

THE UK SACT BOARD Systemic Anti-Cancer Therapy

acp UKONS bopa

sam THE SOCIETY FOR ACUTE MEDICINE

'Inspiring Cancer Nursing' www.ukons.org

Management

- Most toxicities occur early within weeks to first 3 months of starting immunotherapy
- HOWEVER, first onset of toxicity has been documented as long as 1 year after discontinuation of treatment
- Steroids – PO or IV
- Steroid tapering – page 36

GUIDELINE 21.
Immune-Related Adverse Event: Diarrhoea & Colitis

Gastrointestinal (GI) irAEs are among the most common and although they are typically mild to moderate in severity, if they are left unrecognised or untreated, they can become life-threatening. These toxicities can be managed effectively in almost all patients by using established guidelines that stress vigilance and the use of corticosteroids and other immunosuppressive agents when necessary.

Mild (Grade 1)
- < 4 stools/day over baseline
- or mild increase in ostomy output in the absence of abdominal pain, mucous/blood in stools.

Investigations
- Baseline bloods (FBC, U&E, LFTs, TFTs, cortisol & CRP)
- Stool microscopy and culture
- C. difficile toxin
- Faecal calprotectin.

Treatment
- Encourage fluids
- Avoid high fibre and lactose.

Actions
- Regular monitoring
- Consider holding immunotherapy (if on combination anti-PD1/CTLA4 withhold immunotherapy).

Symptoms: PERSIST (≥5 days) or WORSEN or are associated with deranged U & E's

Moderate (Grade 2)
If any of the following symptoms are present:
- 4-6 stools/day over baseline or moderate increase in ostomy output
- Moderate abdominal pain/cramps/ discomfort (may represent enteritis/ gastritis in addition to colitis)
- Mucous in stool.

Clinical Assessment
As per mild (grade 1) +

Investigations
- CMV viral load + PCR (red top blood sample)
- Faeces CMV
- Faecal calprotectin
- Abdominal X-Ray (consider CT abdo/pelvis if AXR abnormal or in presence of abdominal pain)
- Consider Infliximab screen per Grade 3&4
- If recurrent, send for faecal elastase.

Treatment
- Prednisolone 60mg/day + gastric protection
- Fluid balance and replacement as appropriate (inc. diarolyte sachets).

Actions
- Omit next dose of immunotherapy
- Taper per steroid weaning guidance
- Telephone monitoring
- Endoscopy)
- Consider Gastroenterology advice/ review if not improving.

Assess response to treatment within 72 hours

Symptoms: Resolve or Improve to Mild. See steroid tapering guidance

PERSIST or WORSEN or RELAPSE

Severe or Life-Threatening (Grade 3 + 4)
If any of the following symptoms are present:
- ≥7 stools/day over baseline or significant increase in osotomy output
- Severe abdominal pain
- Fever
- Dehydration
- Blood in stool
- Incontinence
- Limiting ADL's.

As per moderate (grade2) +
Consider Admission of patient

Investigations on day 1
- Screen for Infliximab administration suitability on admission (to include- TB Quantiferon test, hepatitis screen, HIV, varicella zoster anti- bodies (IGG antibody), chest X-Ray (if chest CT not already performed)
- Refer for Upper and lower GI endoscopy with biopsies on day 1 of admission
- Daily bloods (FBC, U&E, LFTs & CRP)
- CT Abdomen/pelvis.

Treatment
- IV hydration and fluid balance
- IV Methylprednisolone 2 mg/kg/ day + gastric protection cover and continue for a minimum of 3 days
- Antibiotics are not required as standard
- **Use analgesia with CAUTION.**

Actions
- Daily stool chart
- Consider referral & potential transfer to gastroenterology
- Dietician review
- Consider discontinuation of immunotherapy
- Taper per steroid weaning guidance.

Review patient daily, if no improvement within 72 hours, consider infliximab treatment Consider local/national subsequent management guidelines

Interrupt SACT immunotherapy until discussed with Acute Oncology Team. Please contact on-call oncology/haematology team for advice. Ensure that the patient has monitoring/follow up planned with their oncology/immuno-oncology team.

Immunotherapy Late Effects Project - Welcome to Wessex Cancer Alliance

For GPs and Clinical Staff

Quick Reads

- Managing the side effects of immunotherapy- most common side effects and when to refer to their oncologist (Royal Marsden)
- 10 top tips cancer immunotherapy (Medscape UK)
- Immune related adverse events (A quick guideline sheet, with diagram from Cancer Research UK)
- Immunotherapy side effects- Key points for GPs & practice nurses seeing patients (A quick guideline sheet from CRUK)
- Addressing unmet patient needs through an immunotherapy late effects clinic (A poster presentation from European Society of Medical Oncology)
- Tackling the Adverse Effects of Immunotherapy (Oncology Live)

Webinars

- New Types of Cancer Treatments & Their Effects – a webinar from Gateway C

Medical Journal Articles

Endocrine complications of immunotherapies: a review – Royal College of Physicians

Not just skin deep: monoclonal therapies and pituitary endocrinopathy – The Endocrinologist

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update – Journal of Clinical Oncology – American Society of Clinical Oncology

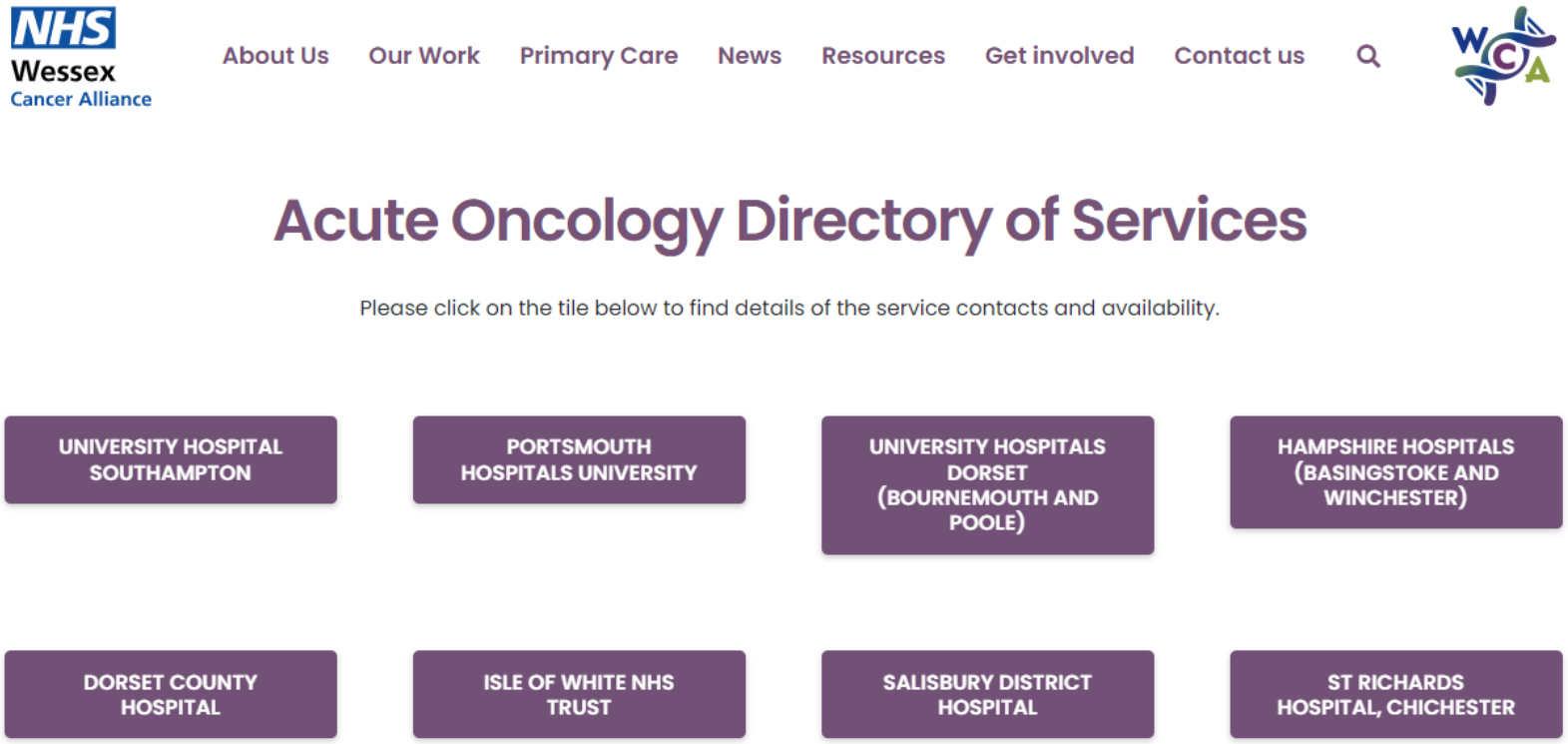
The side effects of immune checkpoint inhibitor therapy on the endocrine system – Indian Journal of Medical Research

Endocrine dysfunction induced by immune checkpoint inhibitors: Practical recommendations for diagnosis and clinical management – American Cancer Society Journal

Management of Immunotherapy-Related Toxicities, Version 1.2019, NCCN Clinical Practice Guidelines in Oncology – Journal of the National Comprehensive Cancer Network

Acute Oncology Services

[Acute Oncology Directory of Services - Welcome to Wessex Cancer Alliance]



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Questions

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