

Immunotherapy and The Clatterbridge Cancer Centre

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Oncological Immune
Inhibitors

Disinhibition of a person's immune system to utilise it in the management of malignancy



The impact of IO in melanoma



Very poor prognostic malignancy prior to the introduction of immunotherapy and (for some) targeted agents

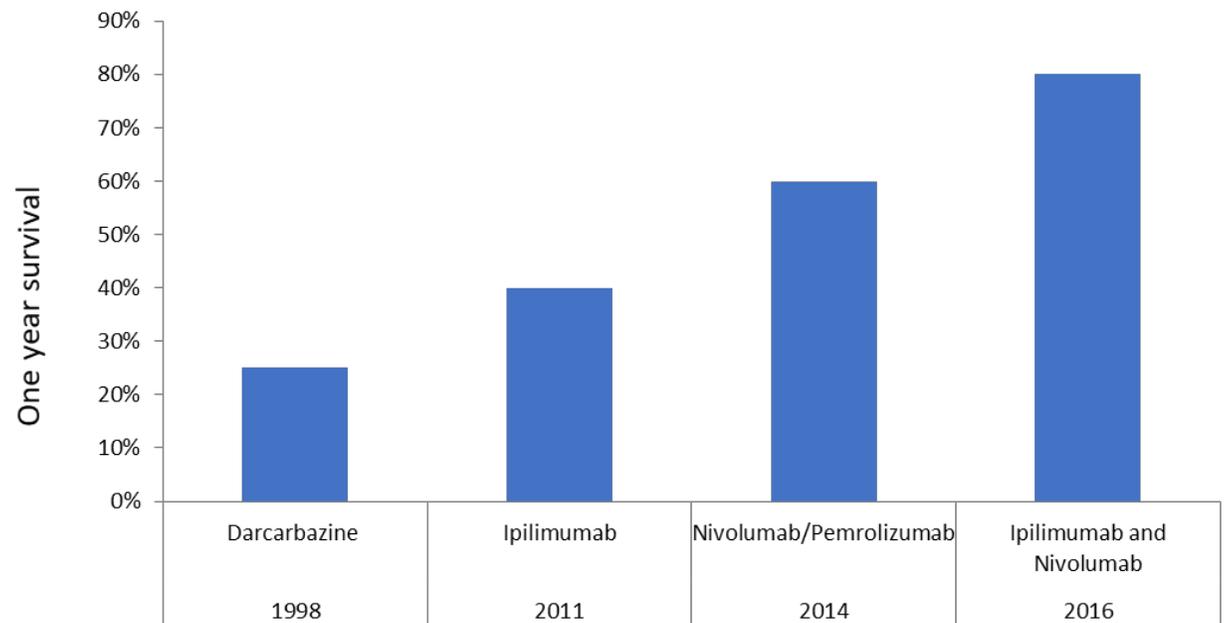
Median prognosis was 7 months from diagnosis to death up until the early 2000's

Chemotherapy had a limited role due to very limited efficacy (ORR 5%)

One year overall survival has increased from ~20% to ~80% with the introduction of checkpoint inhibitors

Early suggestions are a 2 year enduring response in ~50% of individuals

Response to immunotherapy continues after drug is stopped due to toxicity and often responses can be seen after initial progression



Carl's Story

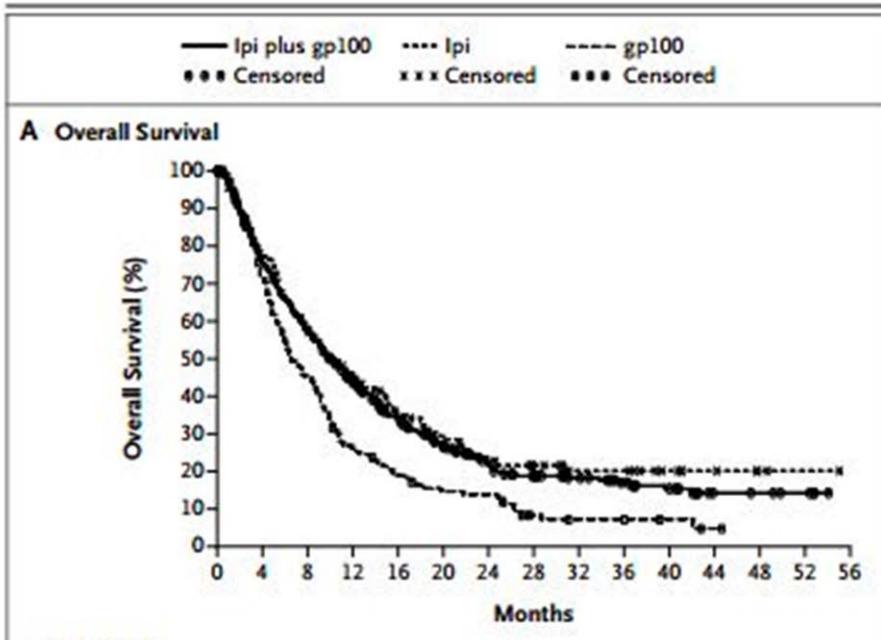


*patient has given permission for his picture to be used and contributed them to an article in the Huffington Post:

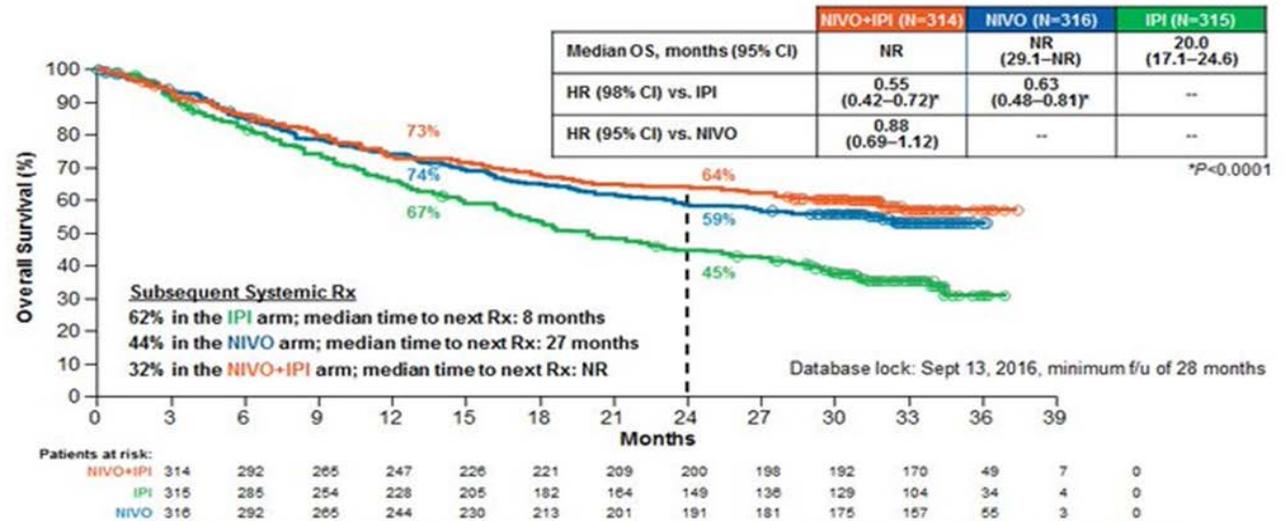
https://www.huffingtonpost.co.uk/entry/exclusive-i-thought-i-wouldnt-see-another-christmas-but-miraculous-treatment-has-cleared-my-tumours_uk_5c05729fe4b066b5cfa492a8?guccounter=1&guce_referrer_us=aHR0cHM6Ly93d3cuZ29vZ2xlLmNvbS8&guce_referrer_cs=PKQdEhpXNhtpeMAX-1XmtA

The Efficacy Triad

- Short Term Response
- Long Term Response
- Enduring Response

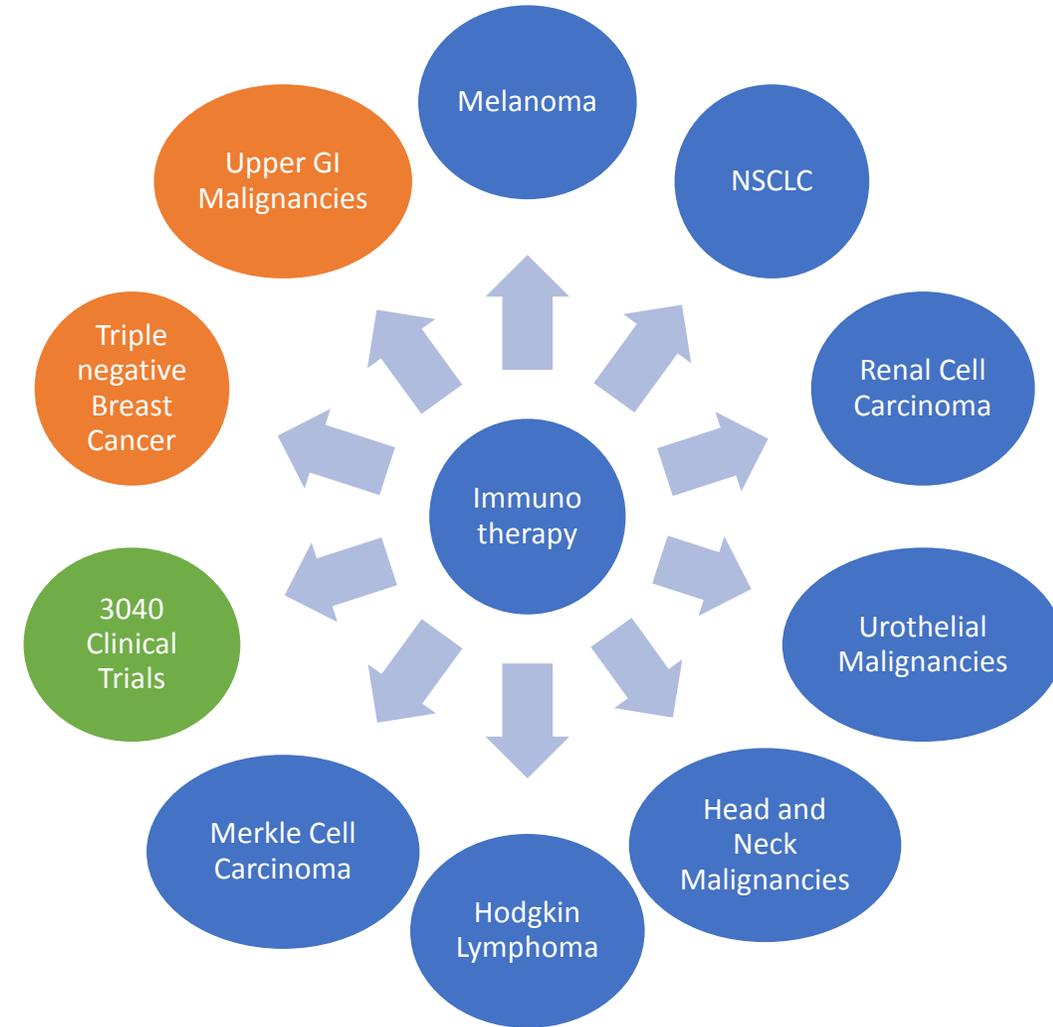
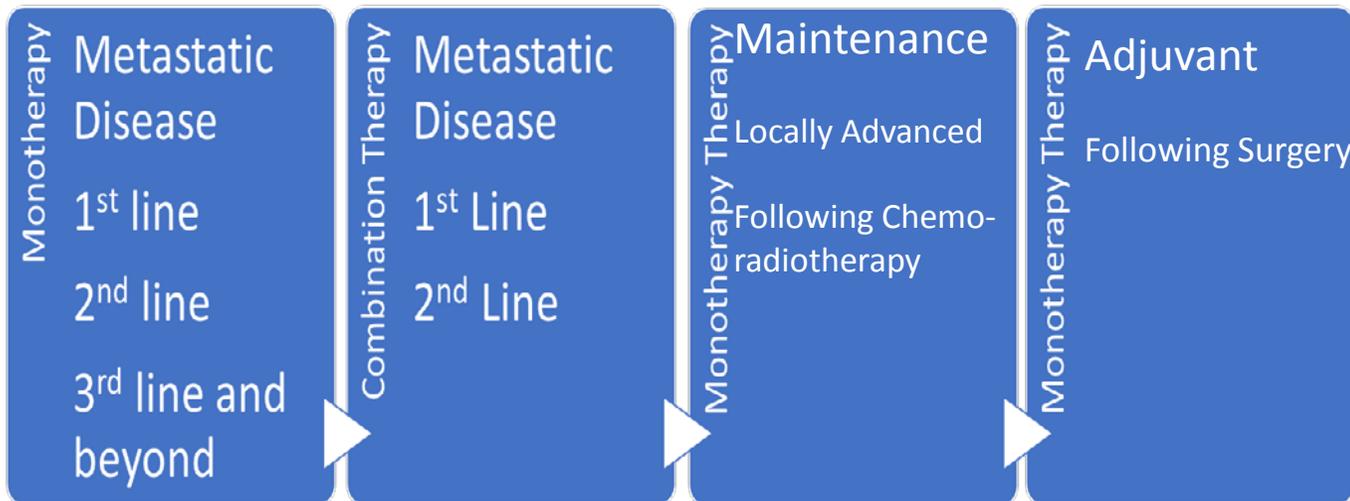
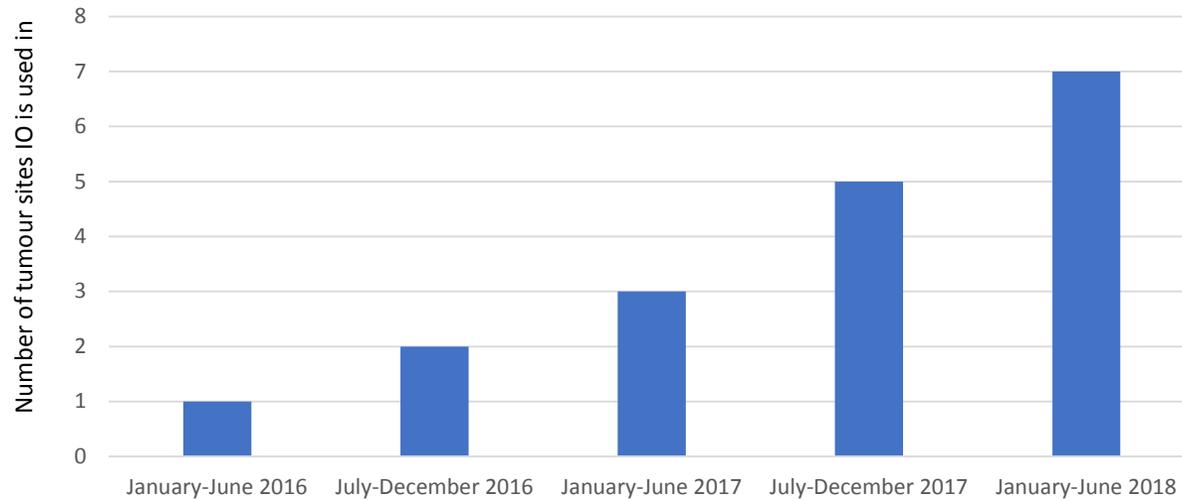


Overall Survival (Co-Primary Endpoint)

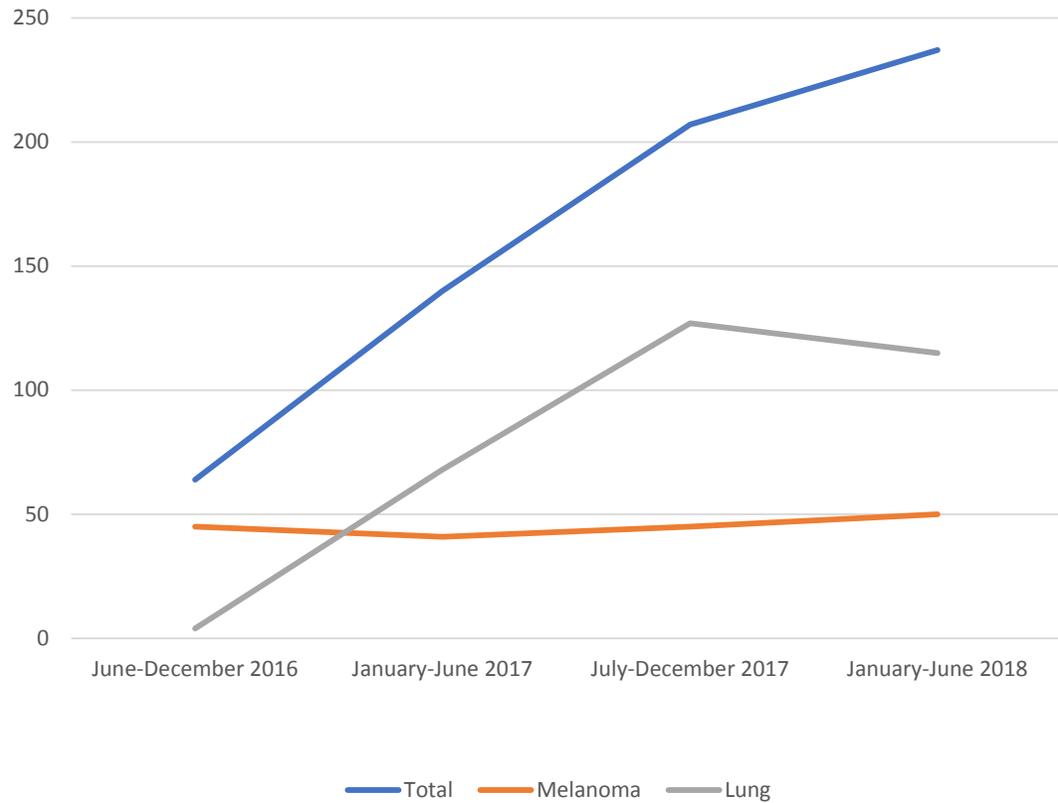


- 2-year OS rates were similar to results from the phase II CheckMate 069 trial of NIVO+IPI (64%)¹ and the phase CheckMate 066 trial of NIVO monotherapy (58%)²

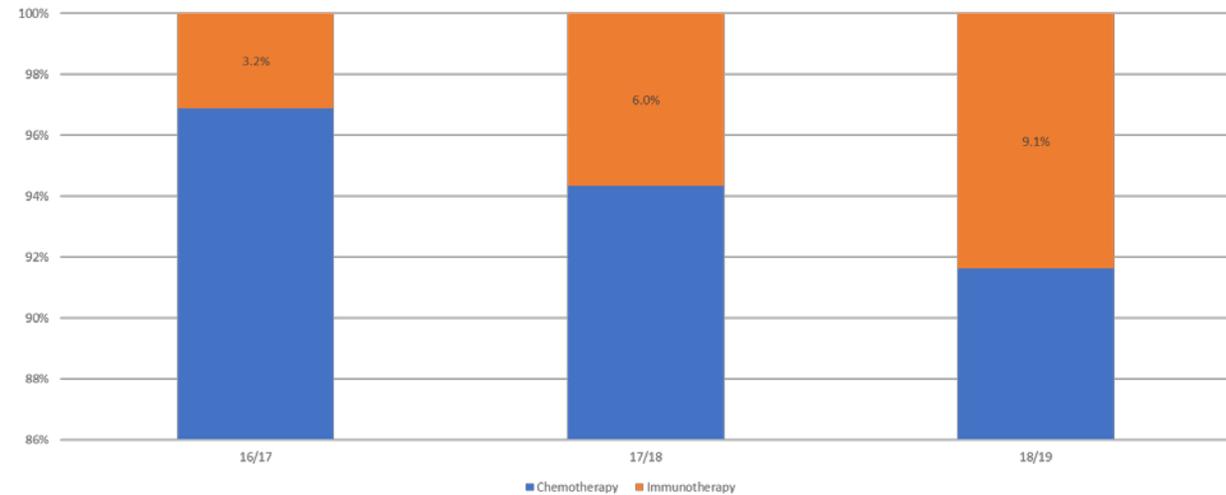
The evolving indications for IO therapy



The use of IO at Clatterbridge Cancer Centre



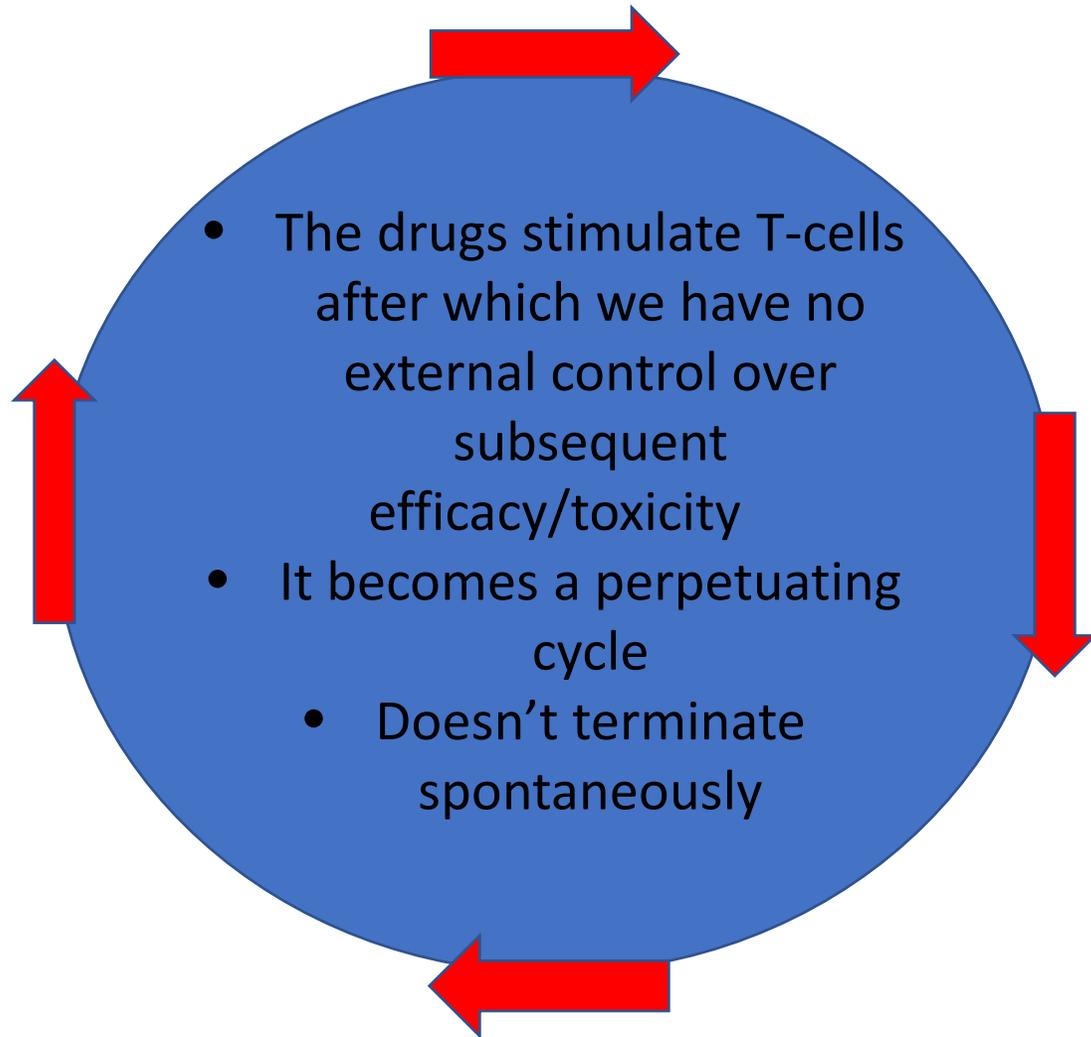
Time period	June-Dec 2016	2017	2018
Total number of new starters	64	347	452



The Patient Experience

- Generally well whilst receiving treatment
- Can often continue working
- Checkmate 024 – QoL and patient experience improved compared to TKI therapy
- Episodes of significant morbidity if a grade 3-4 toxicity is experienced
- Hospital stays do occur (particularly in combination therapy)
- Often prolonged courses of steroids
- Steroid doses are confusing and patients often find this challenging
- Often experience more than one toxicity over the course of treatment
- Find the reality of toxicity very challenging
- The impact of toxicity is very efficacy dependant!

Why/How is IO different from chemotherapy/SACT?

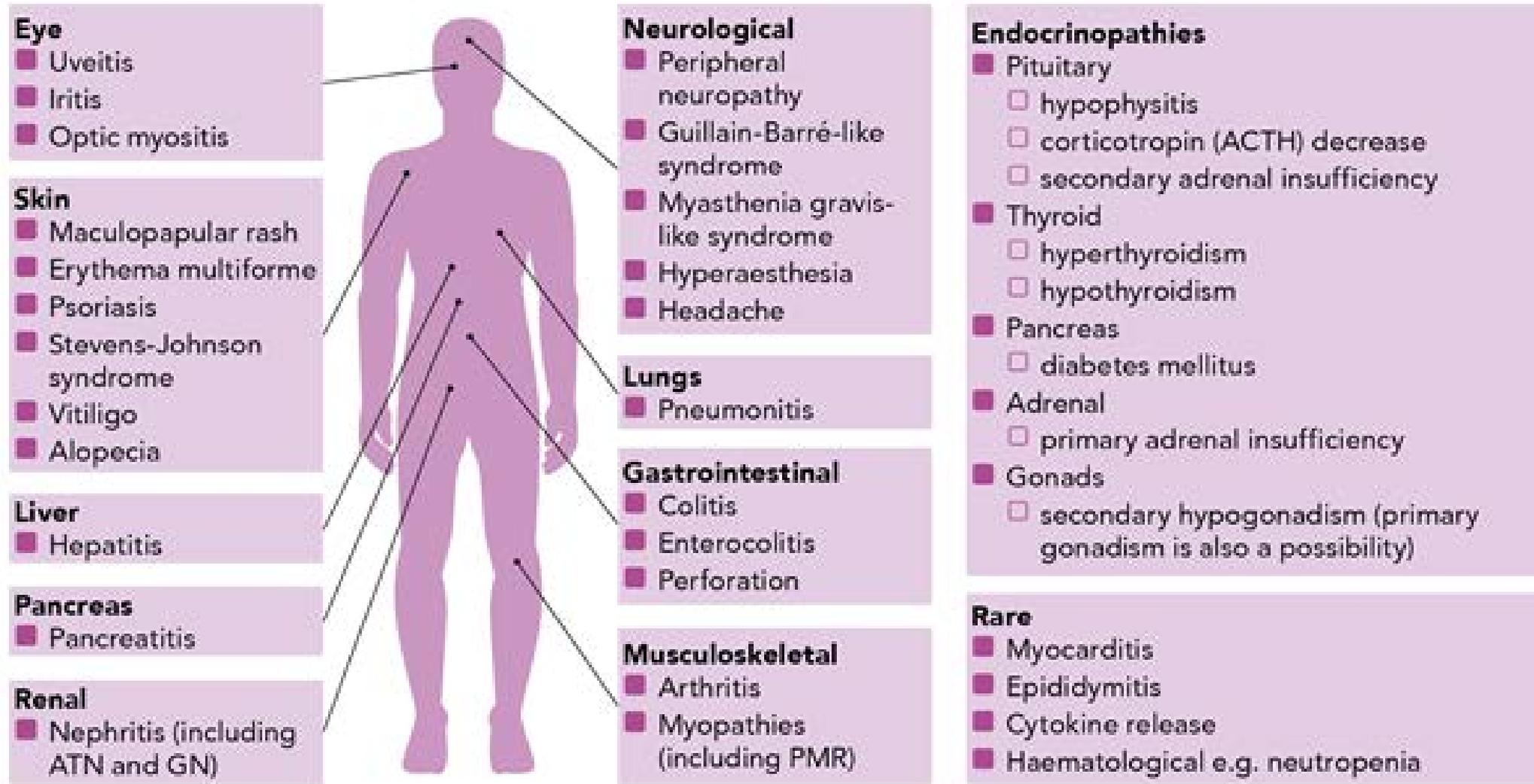


- Given every 3-4 weeks for up to 2 years (as opposed to 4-6 cycle courses) in the palliative setting
- Adjuvant therapy is given for a year
- Often have a delayed onset of effect (as it is the T-cells not the drug producing the effect)
- Withdrawal of the drug does not lead to cessation of efficacy or toxicity
- Very limited infusion issues
- **Different toxicities.....**

Established toxicity of cancer therapies

- Common chemotherapy side effects
 - Neutropenic Sepsis
 - Nausea and Vomiting
 - Hair loss
 - Bone marrow Suppression
 - Mucositis
 - Diarrhoea
 - Fatigue
 - Rash
 - Infusion related reactions

Immune-Related Adverse Events (irAEs)



Carl's Toxicity Journey



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https://www.huffingtonpost.co.uk/entry/exclusive-i-thought-i-wouldnt-see-another-christmas-but-miraculous-treatment-has-cleared-my-tumours_uk_5c05729fe4b066b5cfa492a8?guccounter=1&guce_referrer_us=aHR0cHM6Ly93d3cuZ29vZ2xlLmNvbS8&guce_referrer_cs=PKQdEhpXNhtpeMAX-1XmtA

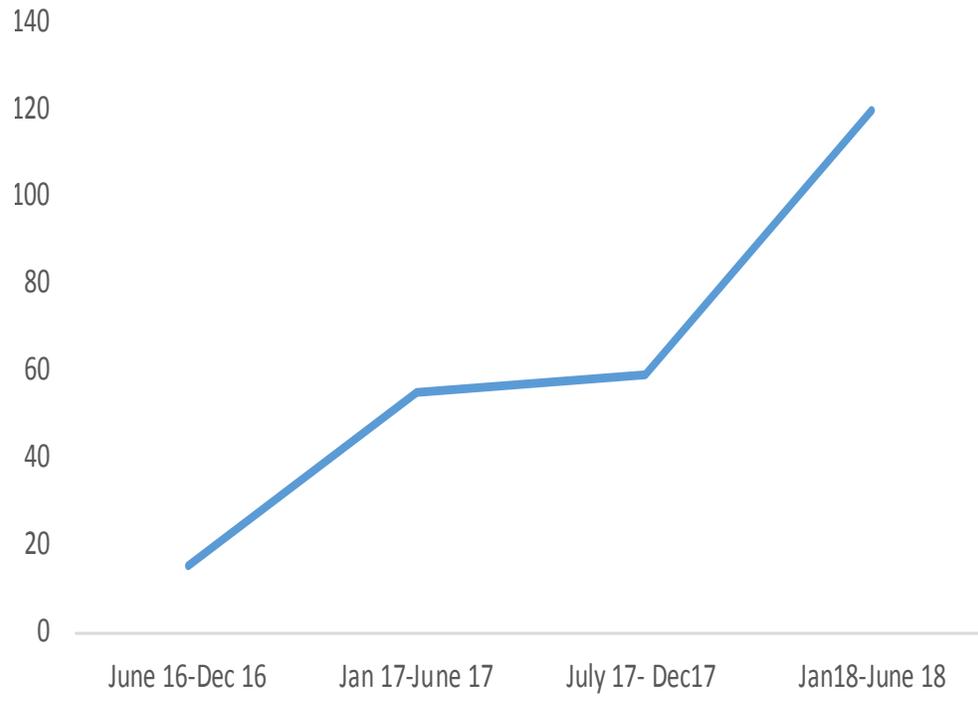
Chemo vs IO

- Two lines of treatment in the same patient with NSCLC

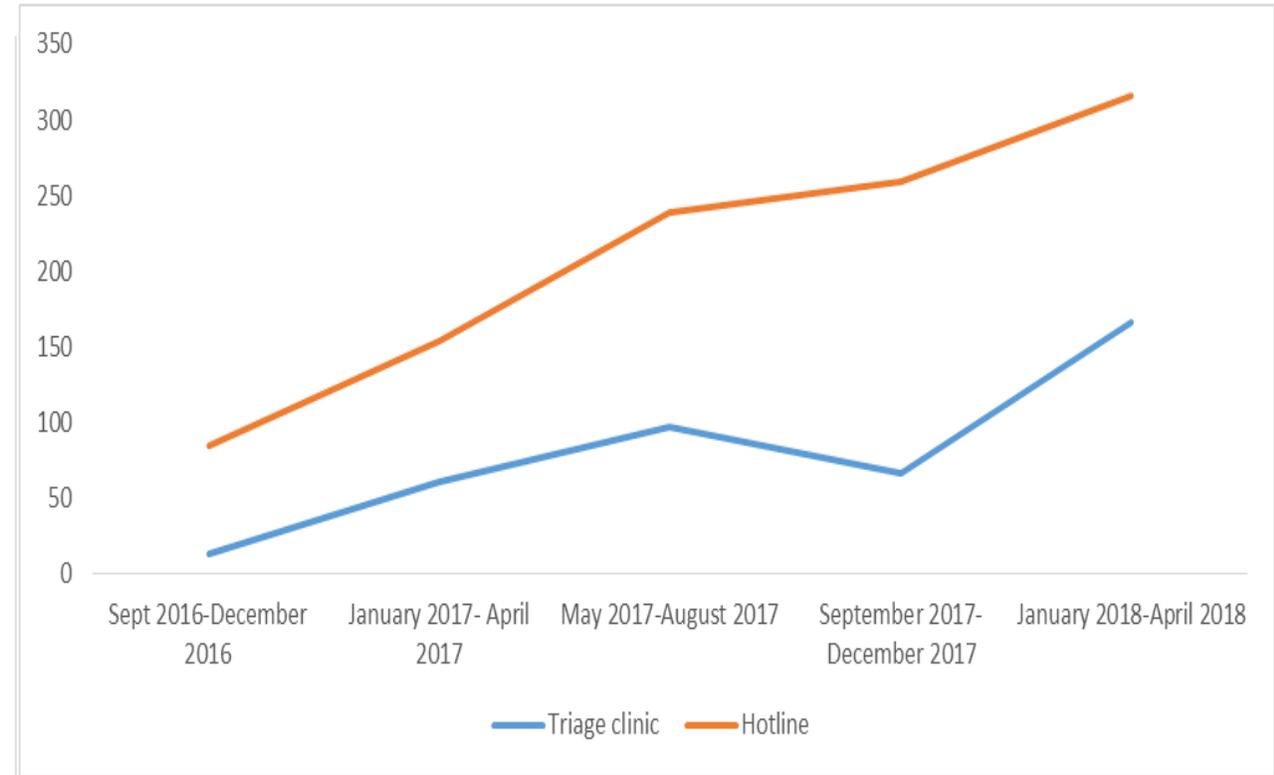
	No. of unplanned admission	Total length of stay of unplanned admission	Chemo clinic	CNS Tele clinic	Consultant clinic	Nurse led review clinic	Triage call	Triage Clinic	Trial nurse clinic
Chemo	0	0	5	0	3	0	0	0	0
IO	2	37	9	0	16	9	9	5	1

She progressed quickly on chemotherapy. She has had stable disease for 12 months on Immunotherapy despite only receiving 6 doses of treatment

Impact on acute medical services



The number of IO related admissions to CCC between June 2016 – June 2018



The number of patients receiving IO accessing hotline and triage clinic services between September 2016 – April 2018

The benefits we are seeing with IO are real and demonstrable in the real world as well as in trials

But it represents significant challenges to all

- Patients
- Relatives
- Clinical teams
- Management teams
- Commissioners

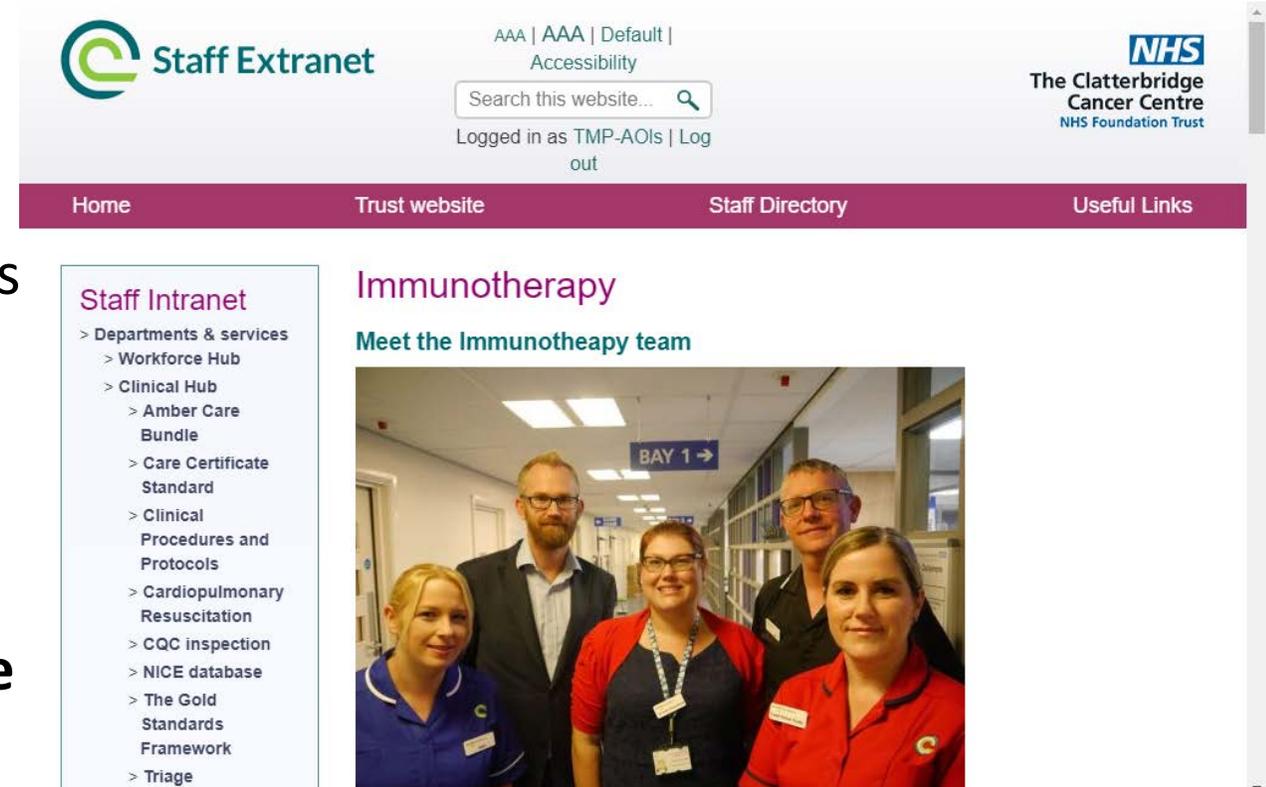
Challenges

- Understanding a rapidly moving field
- Ensuring a patient is treated with the most suitable therapy
- Capacity to deliver therapy with new indications ever increasing
- Flow through delivery services
- Patient toxicity management – initial presentation and follow up

IO at The Clatterbridge Cancer Centre

- Liverpool is one of the three most cancer stricken cities in England
- 26% of patients have a lung cancer diagnosis all of whom are now eligible to receive IO if considered fit enough
- High incidence of head and neck, upper GI and melanoma
- **Increasingly considered to be leaders in the clinical management of patients on checkpoint inhibitors**
- **Our protocols formed the backbone of the recently published UKONS national guidance**

<https://extranet.clatterbridgecc.nhs.uk/index.php/intranet/services/clinical-hub/immunotherapy>



Staff Extranet

AAA | AAA | Default | Accessibility

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Home Trust website Staff Directory Useful Links

Staff Intranet

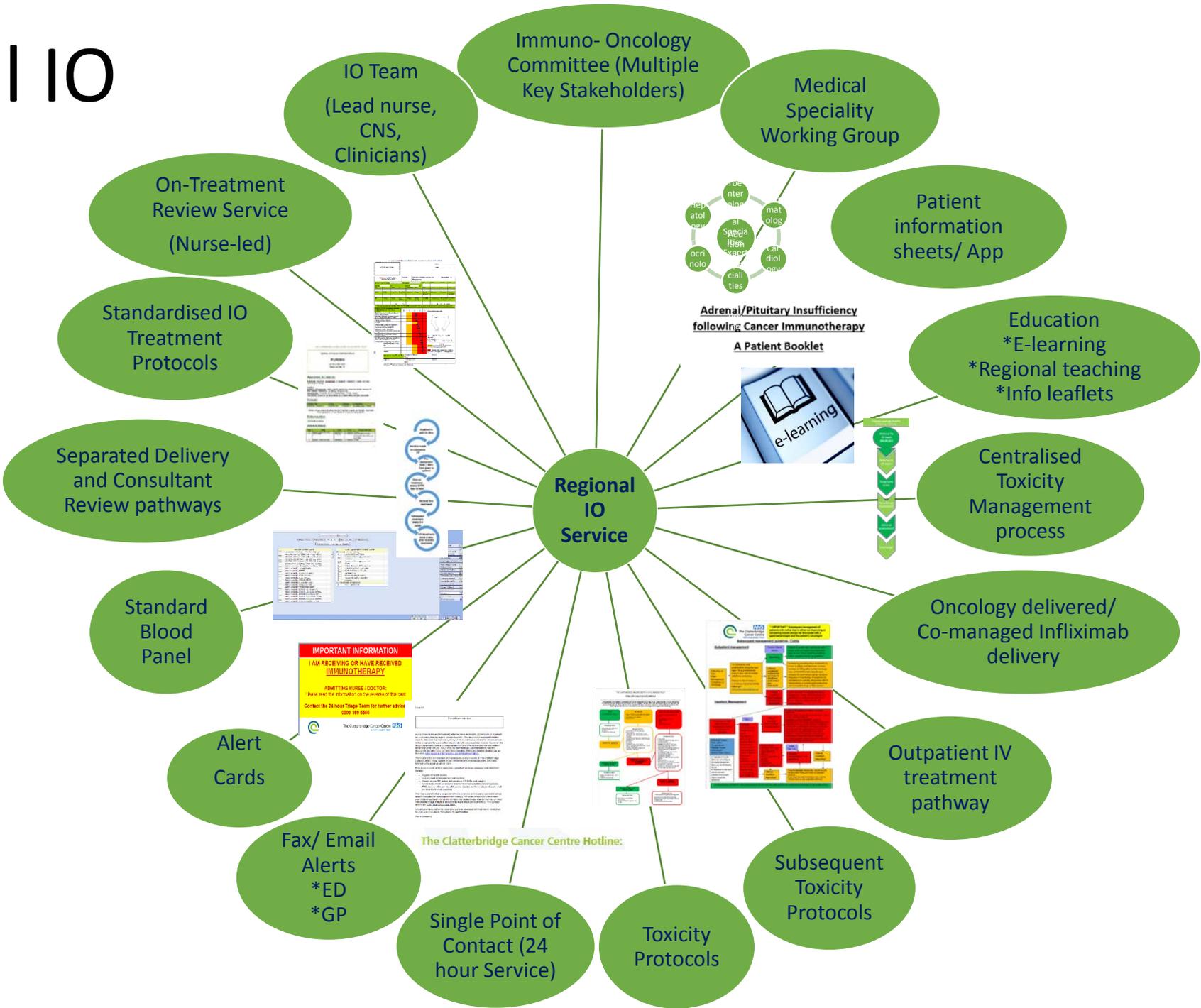
- > Departments & services
- > Workforce Hub
- > Clinical Hub
 - > Amber Care Bundle
 - > Care Certificate Standard
 - > Clinical Procedures and Protocols
 - > Cardiopulmonary Resuscitation
 - > CQC inspection
 - > NICE database
 - > The Gold Standards Framework
 - > Triage

Immunotherapy

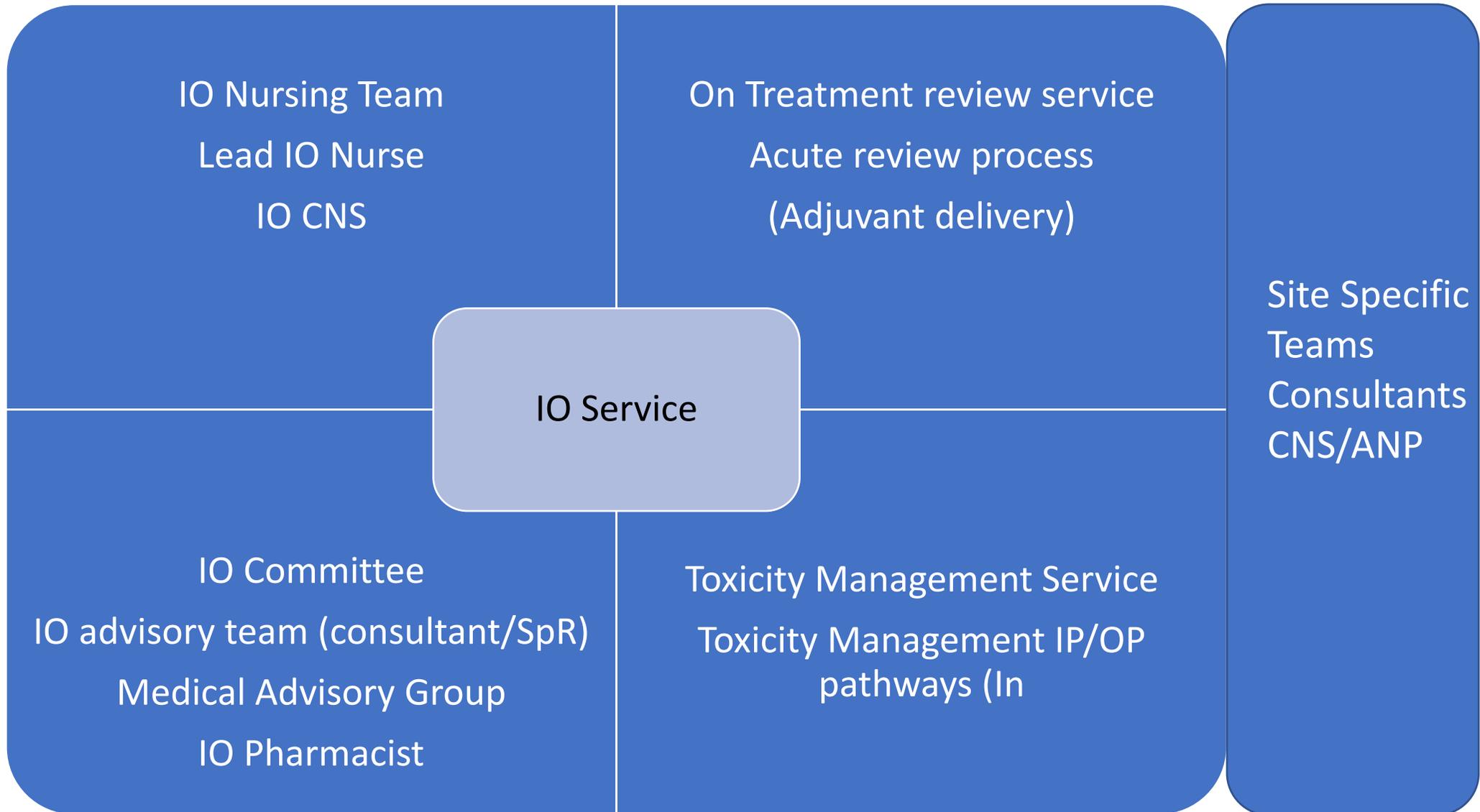
Meet the Immunotherapy team



Regional IO Service



I-O Lead Nurse and I-O Specialist Nurse	
On Treatment Review as Standard	
Acute Protocols – available regionally	
Alert Cards – IO card and Steroid Alert Card and development of IO specific information	
Inpatient Escalation Pathways	
<ul style="list-style-type: none"> IO expert group ; Established investigation pathways; Established medical specialty referral/ discussion pathways 	
Subsequent Management Pathways – two developed others in process	
Infliximab pathway for management of colitis at CCC	
Medical Specialties group – MDT/governance group/ pathways and specialist clinics	
Discharge/ Outpatient follow-up pathway and service	
Outpatient IV treatment pathway	
Immunotherapy Intranet Page	
Local Regional Education AND IO E-Learning module	
Hub working	Next steps
Patient information digital resources/ Self Management	Next steps
Expansion of IO team to meet ongoing needs	Next steps



IO Nursing Team
Lead IO Nurse
IO CNS

On Treatment review service
Acute review process
(Adjuvant delivery)

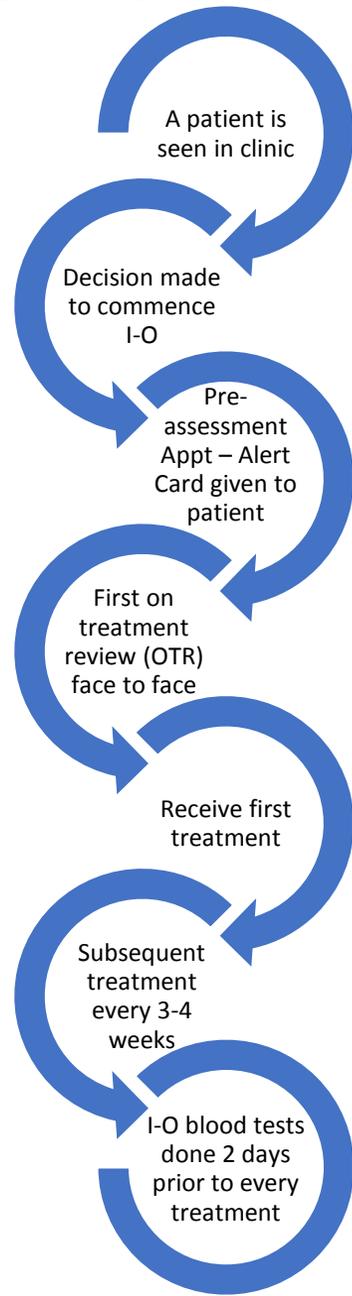
IO Service

IO Committee
IO advisory team (consultant/SpR)
Medical Advisory Group
IO Pharmacist

Toxicity Management Service
Toxicity Management IP/OP
pathways (In

Site Specific
Teams
Consultants
CNS/ANP

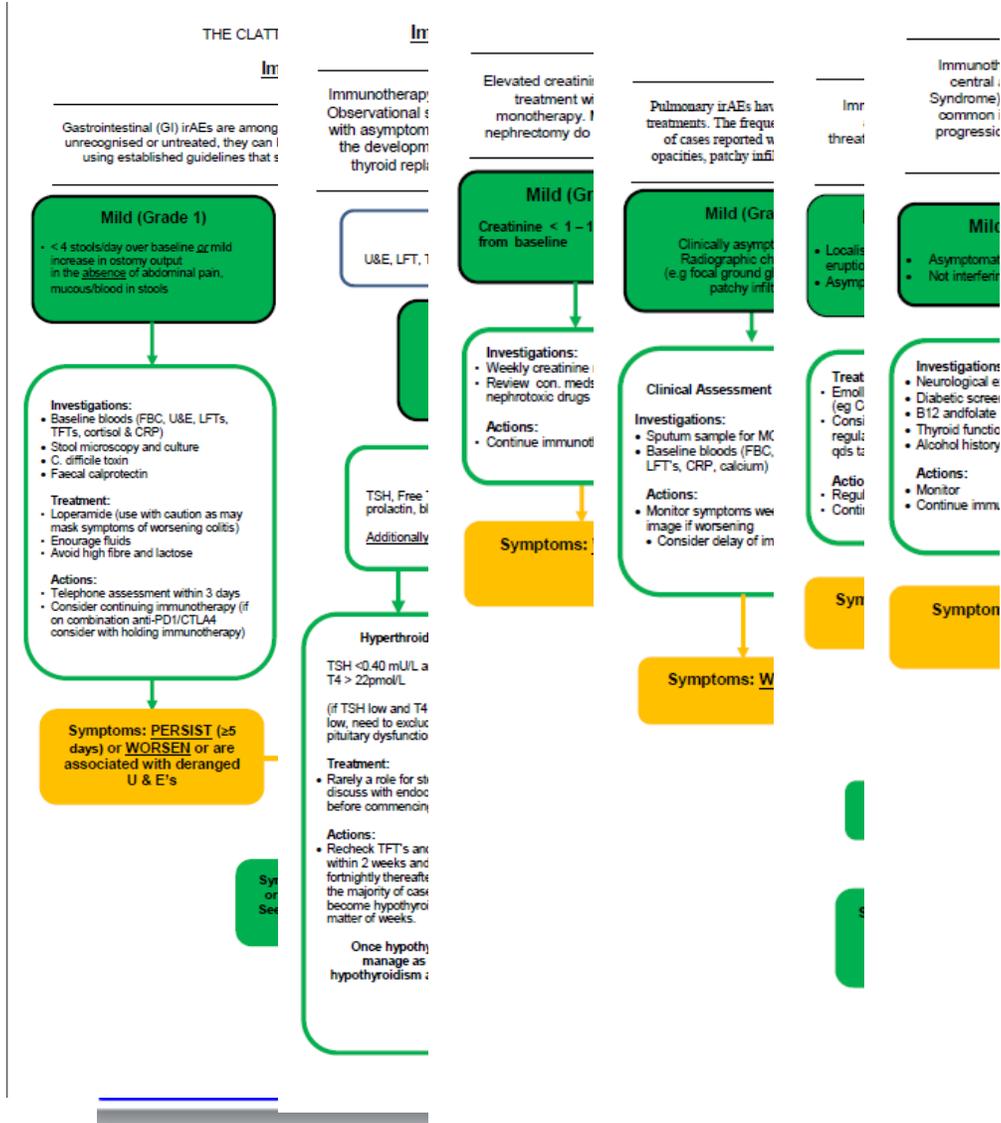
The Patient Pathway



- OTR either by phone or face-to-face by OTR team prior to each cycle of treatment
- Consultant review varies with some teams reviewing before each cycles and others reviewing every 8-12 weeks
- CT Scan every 8-12 weeks
- If patient develops symptoms of toxicity whilst on treatment then treatment is suspended and toxicity managed as per local guidelines
- If a patient is responding they potentially continue treatment for 2 years
- This is forward thinking compared to the rest of the country

IMPORTANT INFORMATION		
I AM RECEIVING OR HAVE RECEIVED IMMUNOTHERAPY		
ADMITTING NURSE / DOCTOR: Please read the information on the reverse of this card		
Contact the 24 hour Triage Team for further advice: 0800 169 5555		
Treatment Name: _____		
ADVICE TO HEALTH CARE PROFESSIONALS		
The patient is at risk of autoimmune side effects: Diarrhoea and colitis Hepatotoxicities Pneumonitis Addisonian crisis & other endocrinopathies Neuropathies Renal toxicities Skin rashes	Required blood tests: Full blood count Chemistry profile Liver function tests Random cortisol/ACTH Thyroid function tests Glucose	Immuno-Oncology guidelines: http://tinyurl.com/loalgorithms or scan QR Code: 
Steroids are frequently indicated in the management of side effects and DO NOT affect the efficacy of the immunotherapy Review the Immuno-Oncology Guidelines to see if steroid treatment is indicated		

Protocols



Steroid tapering guidance

Many patients will receive moderate- to high-dose steroid therapy for their immune-related toxicity for several weeks. Length of tapering is usually dictated by the severity of the irAE. Regular monitoring during tapering is strongly advised as there is an increased risk of irAE recurrence.

Oral steroid tapering:

- Initiate corticosteroid taper over 3-6 weeks
- Tapering guidance:**
- Monitor patient by telephone twice weekly during taper.
 - Reduce prednisolone dose by 10mg every 3 days (as toxicity allows) until dose is 10mg/day.
 - Once steroid dose is 10mg/day, reduce by 5mg every 5 days then stop.

Intravenous steroid tapering:

- Corticosteroid taper over at least 6 weeks
- Tapering guidance:**
- Continue IV methylprednisolone 2mg/kg/day for a total of 5 days then switch to oral methylprednisolone 1mg/kg/day x 3 days, then switch to oral prednisolone max. 60mg/day.
- Upon discharge:**
- Monitor patient by telephone twice weekly during taper.
 - Reduce prednisolone dose by 10mg every 7 days (as toxicity allows) until dose is 10mg/day.

Supportive measures:

Hyperglycaemia:

A baseline HbA1c should be requested at steroid initiation and random afternoon blood sugar monitoring (BM) should be undertaken whilst on treatment. If new hyperglycemia is detected, Endocrinology advice should be sought (many patients will require short term insulin in this setting). Pre-existing diabetes may require escalation in oral hypoglycaemic agents or insulin.

Insomnia:

This is the most common steroid-related side effect. Sleep hygiene counselling is important. Patients may require short-term use of zopiclone or benzodiazepines (with caution).

Osteoporosis:

Vitamin D and calcium levels should be taken at baseline and if low, replaced as appropriate. In patients on steroids for >3 months, or with pre-existing osteoporosis, alendronate or another bisphosphonate should be considered.

Infection:

In patients receiving the equivalent of prednisolone 25mg for ≥ 6 weeks we suggest PCP prophylaxis with co-trimoxazole (80/400mg Mon/Wed/Fri). The oropharynx should be monitored for candidiasis and may require topical therapy such as nystatin or oral fluconazole. If patients are on other immuno-modulatory agents eg Mycophenylate mofetil, consideration may be given to CMV prophylaxis with valgancyclovir, especially if CMV IgG negative and lymphopenic.

Immunotherapy Algorithms are available on the Northwest Coast Strategic Clinical Network website

Direct Tiny URL Link:

<http://tinyurl.com/foalgorithms>

QR Code:



Immuno-oncology Toxicity Follow-up Pathway

Referral to IO team (B8,B6,B2)

1. Patients discharged from CCC
2. CDU referrals
3. Identified and commenced on treatment in OPD
4. Patients identified via OTR
5. Patients in other trusts identified and referred by AO teams

Each group of patients outlined above will be introduced in phases over time with the service expanding over time to eventually cover outpatients with toxicity from all areas

Referral to IO team

- Referral email ccf-tr_otoxreferral@nhs.net using referral form (will sit on the immuno-oncology intranet page until a form can be built in meditech)
- Admin team book patient into telephone clinic
- Patient also booked into see the consultant in 3-4 weeks
- Patient placed on meditech patient list

Telephone clinic

- Patients assessed using patient assessment tool and documented on the SACT toxicity form
- Advice given based on the decision aid
- Steroid dosage confirmed for that week (as per steroid titration policy)
- If patient has endocrinopathy their hormone stability is assessed
- Blood tests taken alongside review as per pathway
- If the patient needs to be assessed but does not require A&E assessment they will be booked into CDU. Once ambulatory clinics in the hubs are established this will be devolved appropriately

Face-to-face review

If patients are identified using the decision aid to need review they will be booked in for assessment*

Penultimate assessment

- When patients on reducing courses of steroid reach 10mg prednisolone an email is sent to the patients treating team (Consultant/CNS/ANP)
- Admin team book the patient into the consultants clinic to consider restating immunotherapy
- If patient has an endocrinopathy and is stable this can occur after the first assessment. If there are issues with replacement etc then they would receive weekly f/u until resolved (as per decision aid)

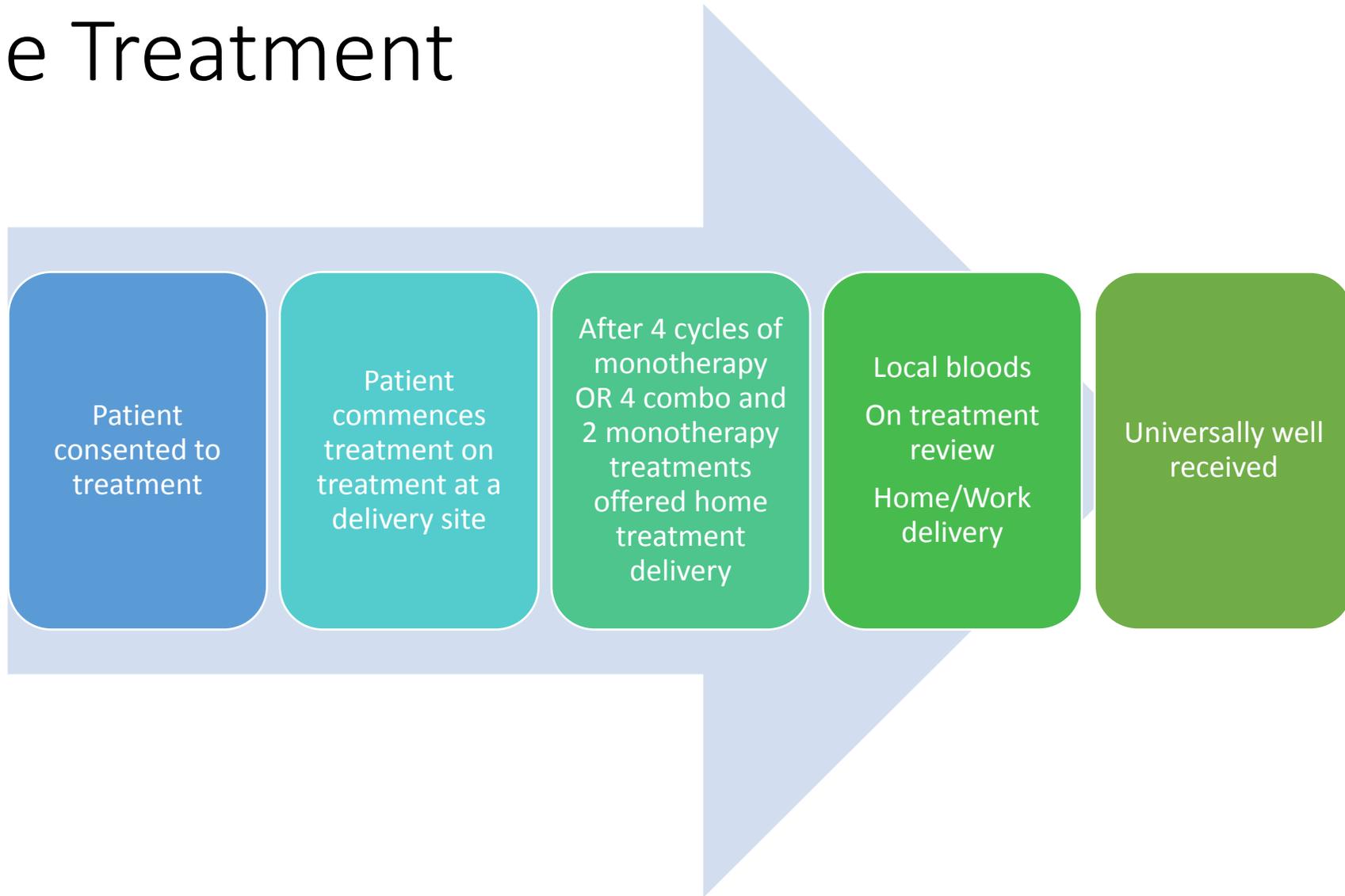
Adrenal assessment

- A week after a patient has completed steroid therapy they will have their adrenal function reviewed with a 9 am cortisol assessment
- If low managed as per adrenal failure protocol and patient to continue in telephone clinic

Discharge

- When off steroids and adrenal function has been assessed OR they have an managed endocrinopathy the patient will be discharged from the service
- Patients team emailed to inform them of completion
- Patient removed from meditech list

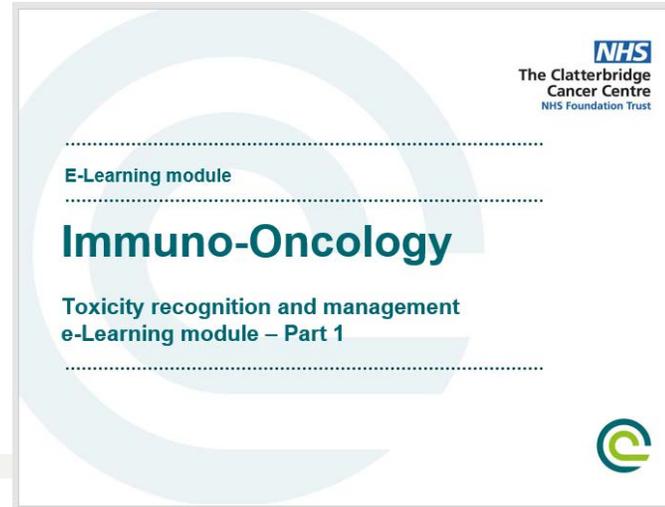
Home Treatment



Education, Education, Education

Crucial to the success of IO provision

- Mandatory E-learning module
- Recruitment of a Lead nurse for education with the trust
- IO update on nursing staff's training week
- Links with LHP to run national training days
- Multiple local training events
- Education to medical groups in the region including junior doctors, medical registrars, specialist groups, GPs and palliative care colleagues
- Acute oncology nurses delivering local teaching
- Contribution to national teaching



PRIMARY CARE UPDATE

Macmillan's GP Advisers, with the support of GPs and the wider Macmillan team



The Liverpool View: The future of training for oncology medics



Research Activities in CCC

Established in delivery of IO trials

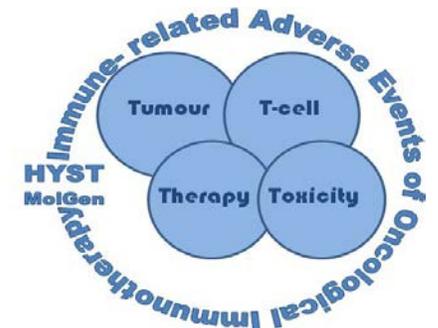
- Multiple drug companies
- Multiple tumour sites
- Checkpoint inhibitors, Tcell therapies, oncolytic viruses

Novel research ideas

- Committed to involvement in research to inform improved knowledge and management of toxicities
- Committed to collaborations to deliver this
- Committed to qualitative research in how to support patients, relative and healthcare professionals with the complexities of IO
- Grant applications have been made in these areas

Established research in collaboration with UofL

- Clinical fellows (CCC and MRC) researching in this area
- Established connections with ECMC
- National recruitment



Conclusions

- IO therapies have significantly altered the prognosis for numerous patients across numerous sites
- Due to the difference in mechanism patients on these therapies have different experiences and needs
- The delivery of these therapies requires a significant support system which is different and more time intense than traditional SACT
- CCC was ahead of the field in establishing protocols and pathways to support this and have an increasing reputation nationally for this
- We have established a IO team to support the trust and patients given the complexities and differences in requirement compared to other SACT
- There has been a lot done already, more to do and the landscape continues to evolve at a very rapid pace!