Targeted Therapy Related Mouth Toxicities

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Supportive Care Makes Excellent Cancer Care Possible

And without it, cancer patients' suffering needlessly increases.

The aim is holistic patient care

Regimen-Related Toxicities

- Happen with all cancer treatments
- Range from mildly irritating to disability or death
- Impede optimum treatment
- Affect QoL during and after treatment
- Are expensive: and many costs are hidden

- Very rarely happen in isolation, so we shouldn't study them in isolation

Combining targeted therapies and immunotherapies across indications

2,756 Possible double combinations of all targeted therapies and immunotherapies

53 approved targeted and immunotherapy drugs in the US as of April 2015

240 Possible combinations of 1 immunotherapy and 1 targeted therapy

48 targeted drugs, 5 immunotherapy drugs

236 Possible combinations out of the above 240 that will involve drugs owned by separate pharmacos

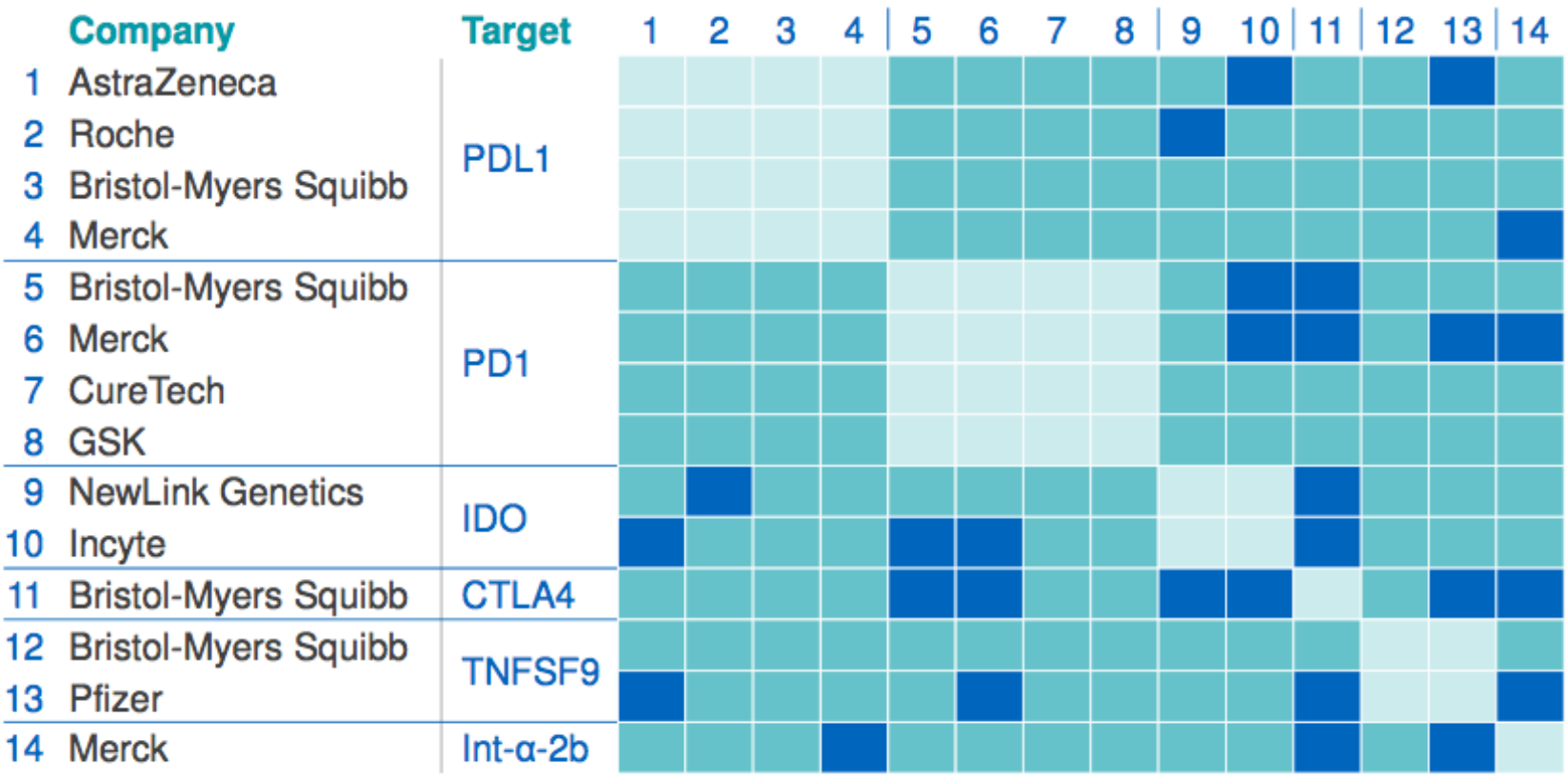
27 pharmacos own the 48 targeted therapies, 3 pharmacos own the 5 immunotherapy drugs

Only 1 pharmaco own at least 1 targeted therapy and 1 immunotherapy

PICKING THE RIGHT COMBINATIONS

High combinatorial complexity

MELANOMA IMMUNOTHERAPY EXAMPLE



What's next?

- Over 150 possible addressable combinations for immunotherapies only
- In melanoma, over 80% of such opportunities are not pursued today

SOURCE: McKinsey

The changing paradigm of supportive care in cancer patients

- Over the past 25 years
  - Reduction in severity of standard toxicities
    - Nausea/vomiting
    - Febrile neutropenia
    - Mucositis
    - Etc
  - We haven't abolished them, but Oncologists are getting better at managing them.

Emerging Therapies

- Treatment of cancer is changing fast
  - Targeted therapies
    - Monoclonal Antibodies
    - Small molecule TKIs
    - mTOR inhibitors
  - Immune therapy
- Pathobiology and therefore treatment of toxicities are changing too!

- Diarrhoea and skin toxicity are particularly common

Targeted Anti-Cancer Agents

- Huge increase in use over past 5-10 years
- Initially thought to be less toxic than traditional chemotherapy
  - But that turned out to be a myth – they are just differently toxic
  - We are scrambling to catch up with proper management
  - We are operating in a relatively “evidence-free” zone

Common Toxicities of Targeted Anti-Cancer Agents

- Skin toxicity
- Stomatitis and Diarrhoea
- Hepatotoxicity
- Cardiotoxicity
- Neurotoxicity
- Immunotoxicity

Lesson 1

- All drugs have targets, we just don't always know what they are when we start using the drugs
- Some targets are present on all cells
- Some are present only on some cells

Lesson 2

- One target isn't going to be enough in most diseases
  - So the silver bullet will fail!
  - Cells will find a way round a block

Lesson 3

- There is no such thing as a completely specific target
- Some of the best targeted agents also have receptors on
  - Heart
  - Oral mucosa
  - Blood vessels

  - And that is why we get toxicity

Lesson 4

- Oncologists are unable to resist combining drugs
- And combining drugs means combining toxicities

Combining Targeted Therapies

- Target two pathways or points on pathway instead of one
- Expect synergy of effect
- Ignore likelihood of synergy of toxicity
- End up with good effect but semi-lethal toxicity
- Everyone (except the supportive care experts) is surprised.

Lesson 5

- Toxicity specialists should be involved early in drug development

- “Supportive care enables excellent cancer care” (MASCC)

Lesson 6

- We fail to learn from history at our own peril, (and that of our patients)
- And we do still continue to fail…

Lesson 7

- There is no such thing as a drug with no toxicity

Importance of mechanism

- If we don't know the mechanism we cannot target it in treatment
- If we block the drug activity we may block its anti-tumour effect
- So side effect management is even more tricky than for normal chemotherapy
- Does toxicity clustering occur with targeted treatment?

Patient-Reported Outcomes

- Clinical staff always underestimate the incidence and severity of toxicity
- Complex reasons for patients to downplay
  - Fear of displeasing clinical staff
  - Fear of having treatment reduced/stopped
- Learned Helplessness
  - Discovering how bad toxicity is can be depressing for staff
- The patient is the one with the disease -and the symptom – and the knowledge of how bad it is!

Prevelence of oral lesions

- Pazopanib 4%
- Sorafenib 28%
- Sunitinib 38%
- Temsirolimus 41%
- Everolimus 44%

mTOR inhibitors

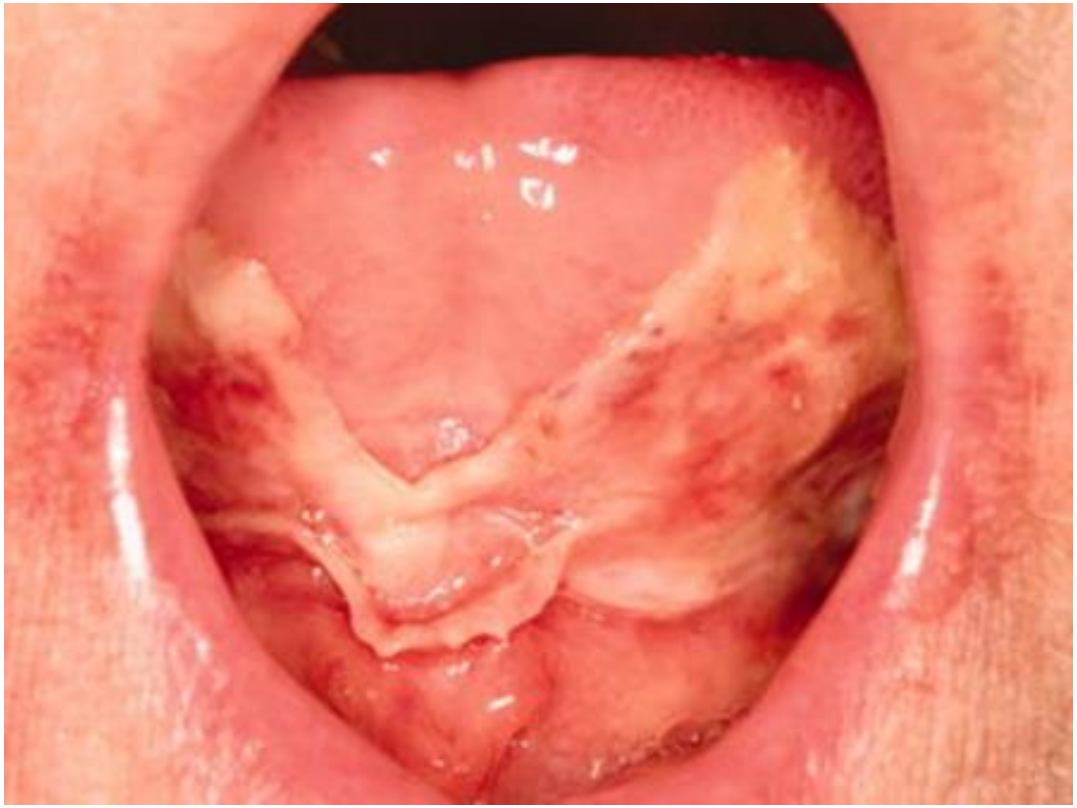
- Mammalian target of rapamycin kinase inhibitors
- Work well in renal cell Ca and others due to effect on HIF-1alpha gene expression and reduction of angiogenesis
- But …

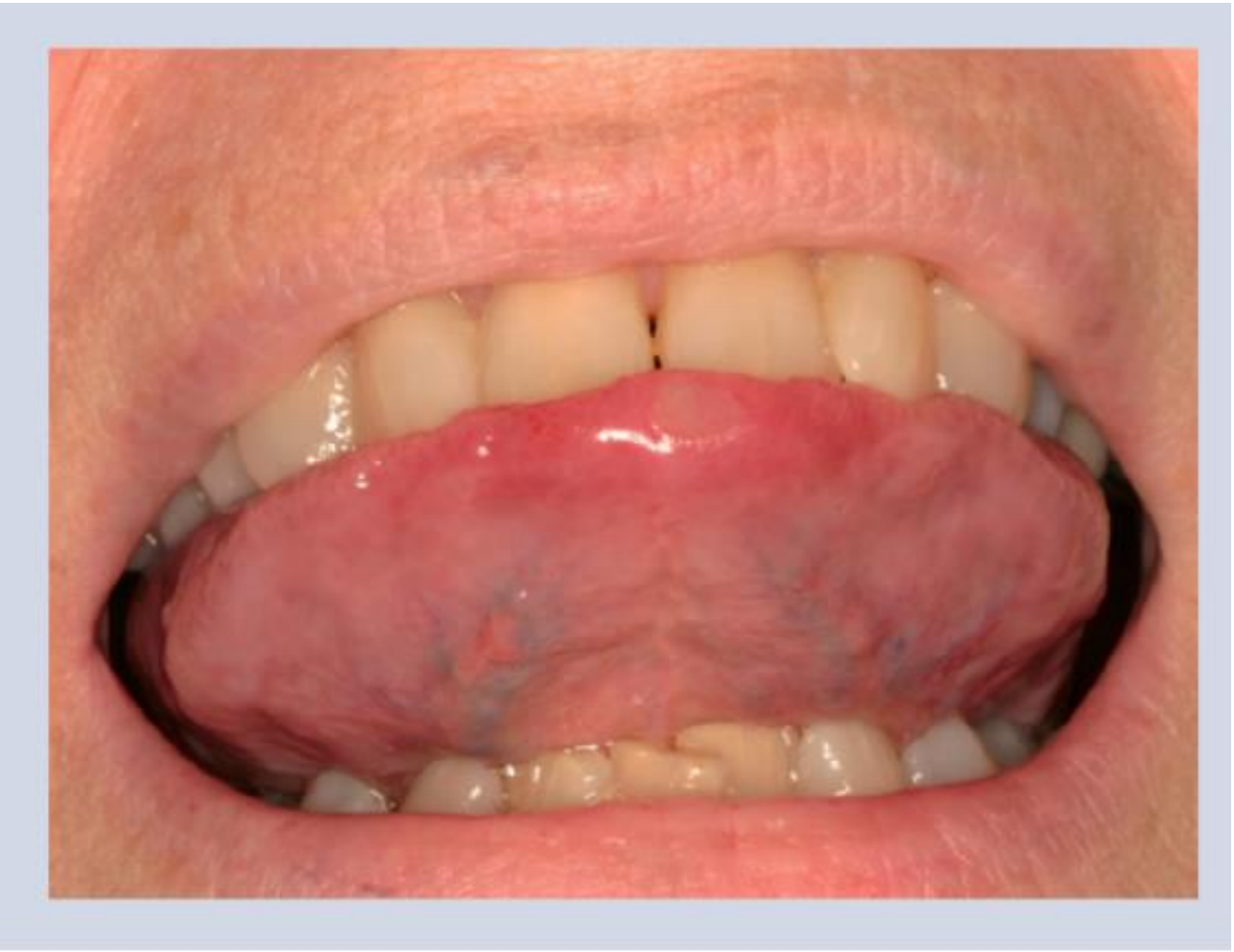
  This is a very complex pathway with lots of potential for error

Cohen JCO 2008 26 (3):348-9

Oral Mucositis from conventional chemotherapy

- Extensive, deep ulceration of the ventral tongue.
- Thick pseudo-membrane
- Typically, the architecture is not well defined.





- **Typical MiAS ulceration + erythematous halo resembling aphthous ulceration.**

MiAS (mTOR inhibitor associated stomatitis)

- Develops early and usually self-limiting
- Favours non-keratinised mucosa of
  - Lips
  - lateral tongue
  - buccal mucosa
  - Floor of mouth
  - Soft palate
- Resembles aphthous stomatitis
  - ? Immune (Antibody-dependent Cell-mediated immunity, and Immune complex formation)

Assessment Scale (Boers-Doets 2013)

Subjective component measuring pain

0 for no pain to 3 for a pain score of 6 or higher on a 0-10 scale.

Objective component measuring duration of lesions

0 for no visible lesion to 3 for lesion(s) persisting for more than 7 days.

Dose-modify only when both subjective and objective grades are 3

Ongoing validation clearly needed

Treatment

- Evidence is developing for steroid mouthwash

- Principles of basic oral care
  - patient education on oral hygiene measures and
  - avoiding hot, hard, spicy or acid foods

- Can be dose-limiting, but usually resolves on discontinuation (and/or continuation) of treatment

Other mTORi oral complications

- Oral pain
- Mucosal sensitivity,
- Xerostomia,
- Dysphagia,
- Altered or loss of taste
- Decreased oral intake

Sunitinib

- High prevelence of symptoms, but no correlation with objective ulceration

Table 2.

Prevalence and severity of OAEs

Table 2. Prevalence and severity of OAEs

Oral AE any grade (%)	Sunitinib for RCC	Sunitinib for GIST	Sorafenib for RCC	Sorafenib for HCC	Pazopanib	Temsirolimus	Eve
OM/S	38[b]	29[c]	28[a]	25[a]	4[e]	41[f]	44[g]
OM/S grade 3 or 4	0[b]	NR	NR	NR	0[e]	3[f]	5[g]
Oral pain	53[b]	6[c]	NR	NR	NR	NR	NR
(Aphthous like) ulcers	33[a]	43[a]	NR	NR	<1[e]	NR	NR
Dysphagia (difficulty swallowing)	7[b]	NR	NR	NR	NR	NR	4[g]
Difficulty oral intake	NR	NR	NR	NR	NR	NR	NR
Dry mouth	12[i]	6[d]	NR	NR	NR	NR	8[g]
Dysgeusia	63[b]	21[c]	NR	NR	16[e]	20[f]	10[g]
Other oral AE	Odynophagia 23[b]	Mucosal inflammation 12,[d] glossodynia 6[d]	NR	Hoarseness 6[b]	NR	NR	Muc infl 19[g]
Onset	1st–15th week;[a] Before 4th week in 81% of patients[a]		1st–8th week;[a] Before 4th week in 90% of patients[a]		NR	NR	NR
Dose interruption caused by oral AEs	9[a]		7[a]		NR	NR	NR
Dose reduction caused by oral AEs	26[a]		18[b]		NR	NR	NR

Time course

- Symptoms appear between 1 and 15 weeks after starting treatment
- 81% Sunitinib patients <4 weeks
- 90% Sorafenib

- Dose reduction:
  - 26% Sunitinib
  - 18% Sorafenib
- All able to continue/restart treatment

Table 4.

Selected tools and their potential to assess OAEs caused by TKIs and mTORIs

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Scale	NCI-CTCAEv3.0[a][51]	WHO Oral Toxicity Scale [16]	OMAS [16]	VHNSS
Developed for	Toxicities associated with conventional CT, RT, HSCT	OM following conventional CT, RT, and HSCT	OM caused by HSCT	Head an toxicitie chemo-I HNSCC
Scale description	Clinician rated, objective, subjective, and functional parameters; 0–5 point scale	Clinician rated, combined, objective, subjective, and functional parameters; 0–4 point scale	Clinician rated, objective tissue scale; 1 total score	PRO; su and func paramet includes scale for item
Main driver of scale	Severity of AE; impact on ADL	Ulceration and ability to eat and drink	Cumulative surface of ulcerations and severity of redness	PRO; se of toxici associat HNSCC treatmer function impact
Oral sites evaluated	Depends on toxicity; (nonkeratinized)	(Nonkeratinized) anatomical sites typically at	(Nonkeratinized) anatomical sites	Sympto associat

EGFRi oral toxicity

- Commonly seen with skin toxicity

MASCC EGFR Inhibitor Skin Toxicity Tool (MESTT)

Multinational Association of Supportive Care in Cancer ™

Skin Toxicity Scale (last updated July, 2009)

Organizing and Overall Meeting Chair:

Mario E. Lacouture, MD

AE Reporting

- The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v4.0 categorizes a broad collection of Aes experienced by cancer patients during treatment, and each event has a structured description and rating of severity.

- Scales such as the CTCAE v4.0 are often used in cancer-related Clinical Trials to report a broad range of AEs that can affect treatment (dosing/ therapy discontinuation), treatment outcome and health-related quality of life outcomes (HQOL).

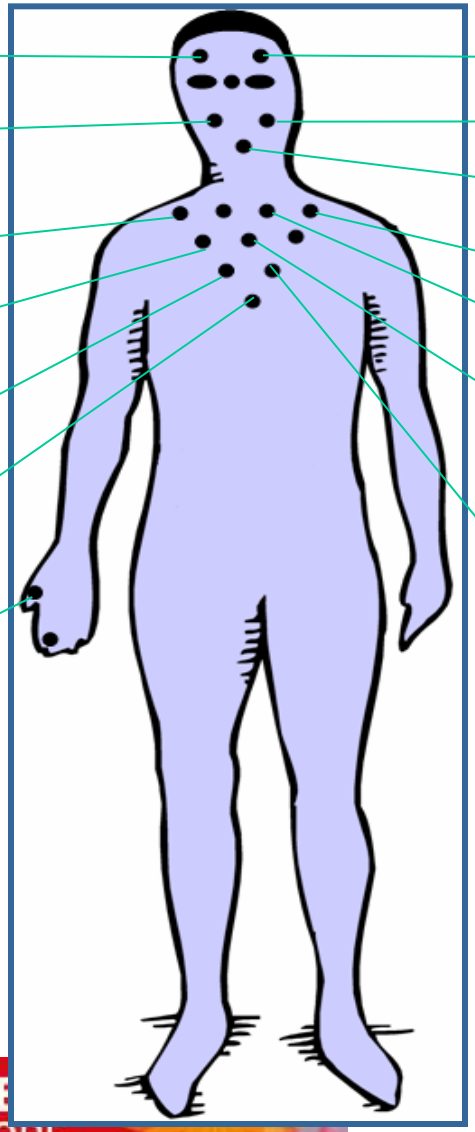
Need for a Comprehensive AE Scale

- The evolution of treatments often precede revisions to the CTCAE;

- The introduction of novel agents such as epidermal growth factor receptor inhibitors (EGFRIs) generate a constellation of AEs and associated clinicopathologic and scientific questions which are not characterized by the nosology of CTCAE v4.0.

- A comprehensive, standardized scale for the reporting of dermatologic AEs in EGFRI-treated patients should enable researchers to conduct more informative, controlled studies.

EFGRI Induced Dermatological Toxicities



Eye/ Eye Lash Changes

Mucositis 36%

Disruption of normal Hair growth (whole body)

Radiation dermatitis

Erythema

Flushing

Periungual / Nail Changes 58% and at 6-8 weeks

Hair Loss/ Hair Changes

Hyposalivation

Taste Changes

Telangiectasia

Papulopustular Rash (85%) in seborrheic areas

Hyperpigmentation

Xerosis/ pruritus

Mucositis, Hyposalivation and Taste Changes

- EGFRIs can result in a range of alterations in visible mucosal tissues, namely oral and perianal mucositis, in up to 36% of patients.
- Clinical severity varies from erythema to deep ulceration of the mucosa, with symptoms ranging from mild tenderness to pain and discomfort at rest and complete inability to tolerate food or fluids by mouth or bowel movements.
- Lip alterations include erythema or erosions of the outer lip and maceration in the angles.

Improvements for Mucositis, Hyposalivation and Taste Changes in the Scale

- The scale focuses on mucositis of the oral cavity and the anus specifically.
- Notable changes in PROs including the patient's level of pain, ability to eat and drink and recommendations to physicians for interventions to represent an increased focus on the patient's HQOL.
- Hyposalivation and taste changes are added to the scale in order to provide clinicians and researchers with a standardized way to measure these AEs.

MASCC EGFR Inhibitor Skin Toxicity Tool: Mucositis

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Mucositis **-Oral** **-Anal**	Mild erythema or edema, and asymptomatic	Symptomatic (mild pain, opiod not required): erythema or limited ulceration, can eat solid foods and take oral medication (Oral mucositis only)	Pain requiring opiod analgesic; erythema and ulceration, cannot eat solids, can swallow liquids (Oral mucositis only)	Erythema and ulceration, cannot tolerate PO intake; require tube feeding or hospitalization (Oral mucositis only)

Hyposalivation, Taste

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Hyposalivation	Can eat but requires liquids, no effect on speech	Moderate/thickened saliva: cannot eat dry foods, mild speech impairment (sticky tongue, lips, affecting speech)	No saliva, unable to speak without water, no oral intake without water	--
Taste	Altered or reduced taste; no impact on oral intake	Altered or reduced taste affecting interest and ability to eat no intervention required	Taste abnormalities, requires intervention	--

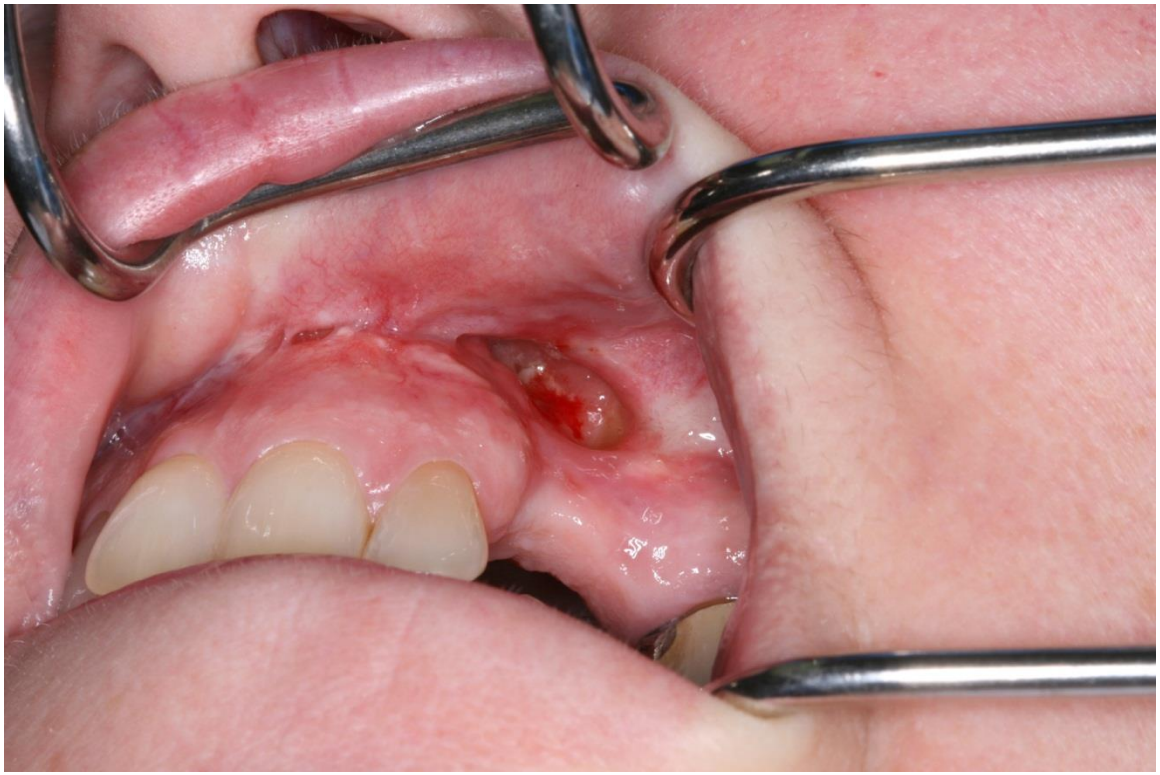
Rarer side effects

- Salivary gland function may be affected, with hyposalivation and qualitative salivary alterations
- mTORi's may cause periodontitis via immunosuppression and collagen synthesis effects
- Jaw osteonecrosis associated with Sunitinib and Bevacizumab has been reported

UK Government Health Warning

- Treatment with bevacizumab or sunitinib may be a risk factor for the development of ONJ
- Bisphosphanates may increase risk
- Dental examination and appropriate preventive dentistry should be considered before treatment with bevacizumab or sunitinib;
- Invasive dental procedures should be avoided in patients treated with bevacizumab or sunitinib who have previously received, or who are receiving, intravenous bisphosphonates
- Mechanism unknown but presumed through antiangiogenesis.

Osteonecrosis of Jaw



ONJ

- Incidence uncertain
  - Up to 11%
  - Usually associated with high dose use of bisphosphanates.
- Maxillo-facial area, usually tooth-bearing
- Spontaneous or associated with trauma
- Exposed alveolar bone visible

Treatment of ONJ

- Stage I
  - Antimicrobial rinses (ie, chlorhexidine 0.12%)
  - No surgical intervention
- Stage II
  - Antimicrobial rinses (ie, chlorhexidine 0.12%)
  - Systemic antibiotics or antifungals (infections may exacerbate BRONJ)
  - Analgesics
- Stage III
  - Antimicrobial rinses (ie, chlorhexidine 0.12%)
  - Systemic antibiotics or antifungals (infections may exacerbate BRONJ)
  - Analgesics
  - Surgical debridement or resection

Benign migratory glossitis (Geographical tongue)

- Bevacizumab, a monoclonal antibody targeting a vascular endothelial growth factor (VEGF) protein,
- Four patients with multifocal, erythematous circinate and serpiginous erosions on dorsal tongue surrounded by white hyperkeratotic rims & increased sensitivity to spicy food.
- Findings consistent with geographic tongue.
- Large prospective evaluations necessary to confirm potential relationship.

Gavrilovic 2012

Imatinib

- Tyrosine kinase inhibitor used to treat chronic myeloid leukemia (CML)
- Well tolerated
- Skin rashes and oral lesions are uncommon and appear to be dose-dependent
- Occasional reports of lichenoid lesions
- Occasional pigmented lesions
  - After 4 + years

Basso 2008

Pigmentation from Imatinib

- Three patients presented with painless, diffuse, grey-blue pigmentation of the mucosa of the hard palate.
- Histopathologically, deposition of fine, dark-brown, spherical granules within the connective tissue.
- No inflammation or hemorrhage,
- No melanosis or melanocytic hyperplasia in epithelium.
- Granules stained for Fontana-Masson and Prussian blue
- Similar to pigmentation caused by minocycline and anti-malarial medications, namely deposition of a drug metabolite containing melanin and iron.

Li 2012 Head Neck Pathology

Imatinib-related pigmentation

- Diagnosis depends on thorough medical history and characteristic clinical features.
- The hyperpigmented lesions are benign
- No treatment is required.

- Fortunately, the oral lesions occur on the hard palatal mucosa and are not of cosmetic concern.

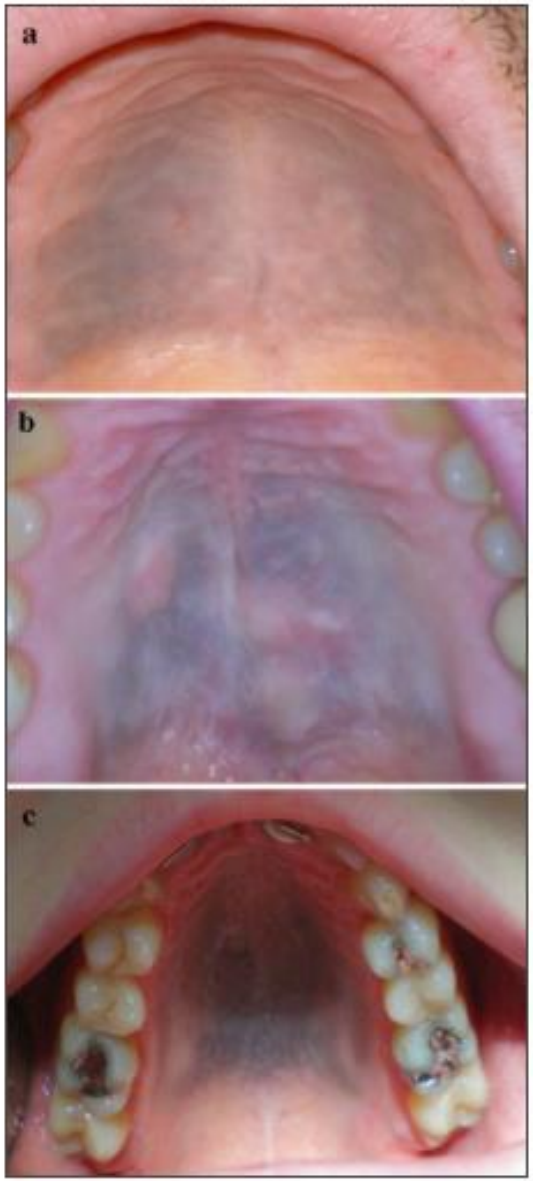


Fig. 1
Diffuse, grey-blue macular pigmentation on of the hard palatal mucosa in **a** Case 1, **b** Case 2, **c** Case 3

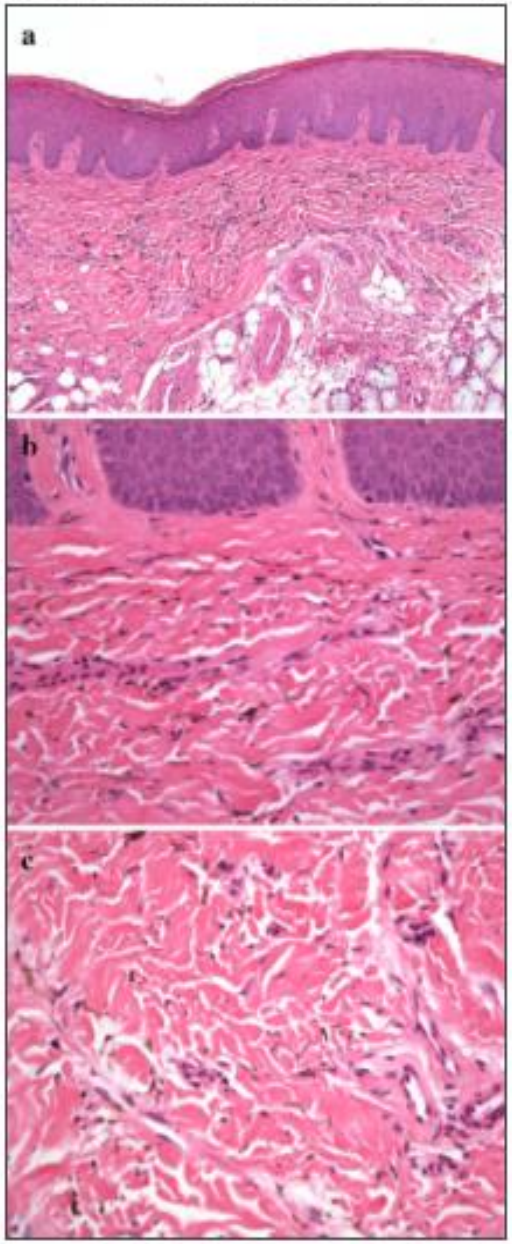


Fig. 2
Case 1: **a** Oral mucosa containing pigment within the lamina propria (H&E, ×40). **b** Fine spherical brown particles are exclusively within the lamina propria without melanocytic hyperplasia or melanosis of basal cells (H&E, × ...

Does immunotherapy count?

- Oral Mucositis and dry mouth more common with PD-1 receptor checkpoint inhibitors than with CTLA-4 blockade.
- 6.5% with Nivolumab (1 grade 3)
- Differential diagnosis includes candidiasis (particularly where oral steroids have been used)

- Some evidence for efficacy of oral steroid rinses and lignocaine

Postow 2015

Immune Checkpoint Inhibitors

- Use is rapidly increasing
- “guidelines” exist for management but based on little evidence
- Large numbers of very sick patients
- Oncologists are in denial

- Urgent, proper clinical research is needed

Incidence of Immune-Related Adverse Events associated with Ipilimumab and Pembrolizumab

	Ipilimumab (%)		Pembrolizumab	
Toxicity	All Grades	Grade 3-4	All Grades	Grade 3-4
GI (enterocolitis)	33	9	1	<1
Pneumonitis	<1	<1	2.9	<1
Hepatitis	2	1	<1	<1
Skin	45	3	11-30	0
Thyroiditis	2	<1	10	<1
Nephritis				

Differential Diagnosis

- Diagnosis of immune checkpoint–blockade toxicity is one of exclusion
  - Progression of underlying malignancy
  - Infection
  - Other possible causes must be ruled out prior to identifying a given toxicity as an irAE.
  - Withholding checkpoint-blockade therapy until the workup is complete.

Grading Toxicity

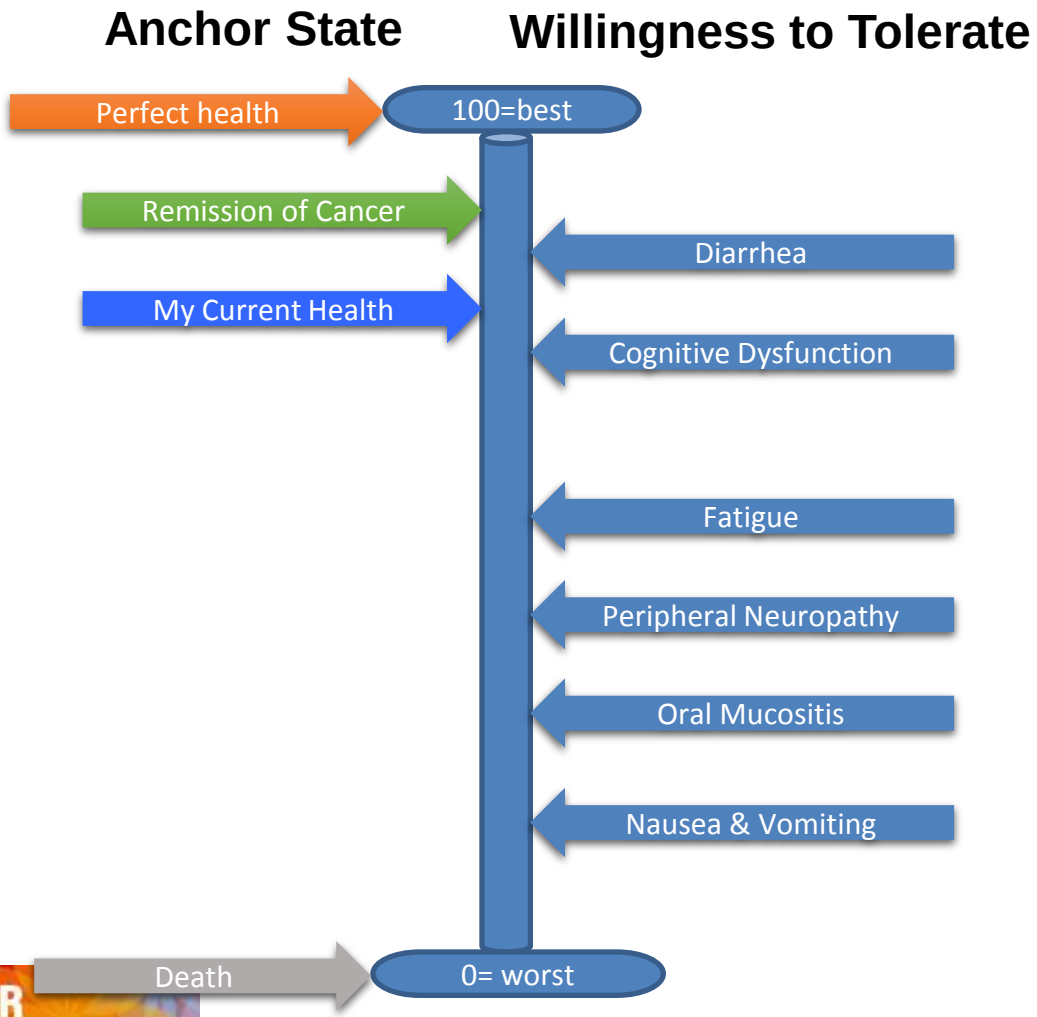
- Toxicities should be graded using the CTCAE
- Each toxicity is different and approaches need to be individualized.
  - grade 1 pneumonitis is a potentially life-threatening problem
    - So it needs to be reclassified as Grade 4!
  - grade 1 dermatitis generally does not require dose interruption.

Dose Adjustments: Pembrolizumab

- Withhold the drug for:
  - grade 2 pneumonitis, colitis, nephritis, or hepatitis
  - any grade 3 adverse reaction
  - any symptomatic hypophysitis.
- It can be restarted with improvement of these toxicities to grade ≤ 1.
- Permanent discontinuation for
  - life-threatening adverse events,
  - including grade 3 pneumonitis, nephritis, or hepatitis (- = Grade 4!)
  - any recurrent grade 3 adverse event;
  - or inability to reduce prednisone dosage to 10 mg daily after 12 weeks.
  - need for infliximab or alternative immunosuppression

Preference Assessment Inventory©

- Visual Analog Scale used by patient to quantify willingness to tolerate side effects
- Anchor State – helps frame analog scale methodology
- Rank-order tolerability assessed to enable informed consent and treatment decisions



Ref: Sun CC et al. *Support Care Cancer*. 2005 Apr;13(4):219-27

Hypothetical Case Study

- Mrs. Smith is a 75-year-old piano teacher, diagnosed with metastatic colon cancer
- There are a number of chemotherapy regimens that could be used to treat her—all have comparable therapeutic efficacy, but differ in side-effect profiles
- Appropriate choices of chemotherapy regimens include*:
  - FOLFOX +/- bevacizumab
  - FOLFIRI +/- bevacizumab
  - CAPEOX +/- bevacizumab
  - FOLFOXIRI +/- bevacizumab

Mrs. Smith's doctor:

1. Sends a saliva sample to lab for a genomic risk assessment
2. Asks Mrs. Smith to complete a Preference Assessment Inventory©

*NCCN: Colon Cancer Guidelines – Version 1.2014

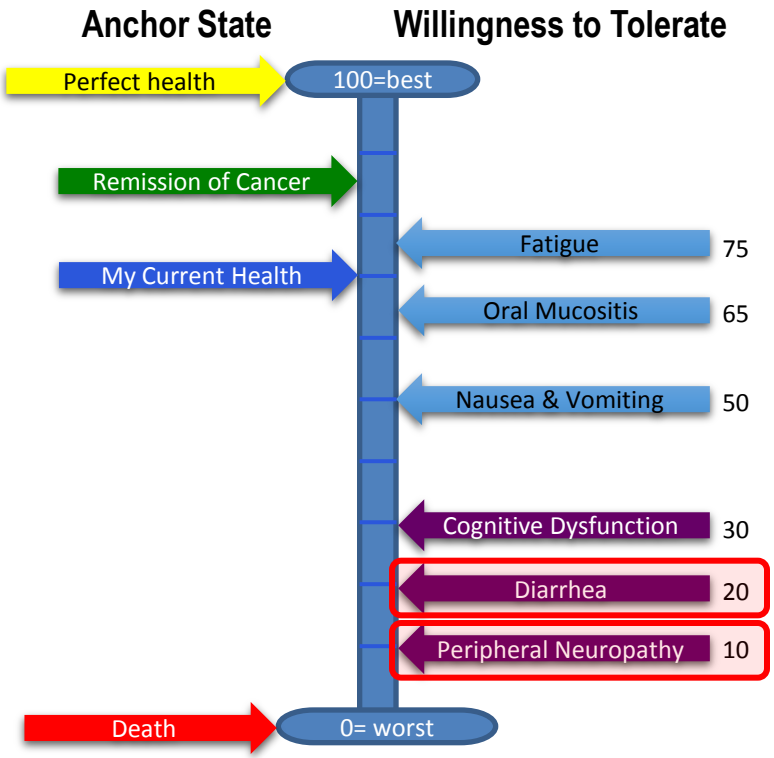
Results for Mrs. Smith

Mrs. Smith's Personalized Genomic Risk Profile

Chemotherapy regimens and risk assumptions of moderate-to-severe side effects (%)

Chemotherapy	CINV	OM	Diarrhea	CD	Fatigue	PN
FOLFOX +/- bevacizumab	30	<10	<10	<10	70	>90
FOLFIRI +/- bevacizumab	<10	<10	>90	<10	<10	<10
CapeOx +/ -bevacizumab	30	<10	>90	<10	70	>90
FOLFOXIRI +/- bevacizumab	30	<10	<10	<10	70	>90

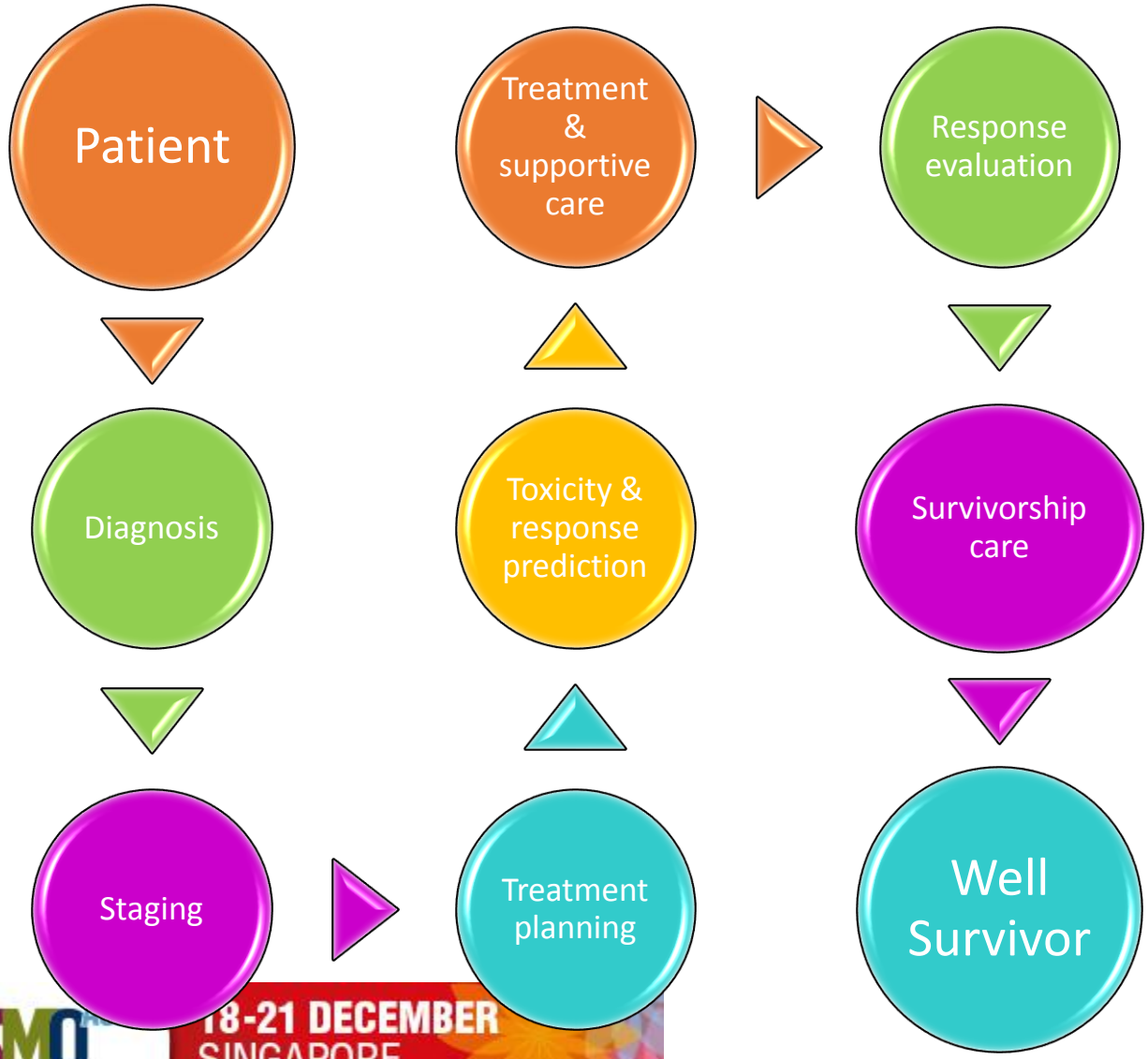
Mrs. Smith's Personal Preference Assessment Inventory



Actionable Outcome:

- Mrs. Smith is least willing to tolerate diarrhea & PN; yet she is at high risk for PN from several regimens & at high risk for diarrhea in 2 regimens
- Mrs. Smith and her doctor agree on a cancer care plan based on her genomic risk and preferences including prevention of diarrhea with loperamide & octreotide

Ideal Situation



Conclusion

- Oral toxicity of targeted agents is a real issue
  - We don't fully understand it
  - We don't have good evidence on how to manage it
- However, it is only one part of the picture
- We need to consider the whole patient
  - Therefore the links between the physical toxicities
  - The psychosocial toxicities
- Our track record so far is patchy
- We need to evolve in time with the science

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