

# **Safety – Immune Related Adverse Events (irAE) Focus on NSCLC**

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# Overview

- Mechanisms driving ir-AE
- ir-AE reporting in clinical trials
- Variations in ir-AE profile
  - as per treatment
  - as per tumor type
- Impact on HRQOL

# Updated Systematic Review of Single Agent ICI Trials

| Agents                                 | Tumor Sites |            |          |           |                            |
|----------------------------------------|-------------|------------|----------|-----------|----------------------------|
|                                        | Melanoma    | NSCLC      | RCC      | Other     | Total no. of pts per agent |
| <b>Pembrolizumab</b>                   | 1220        | 495        |          | 71        | 1786 (26%)                 |
| <b>Nivolumab</b>                       | 828         | 535        | 573      | 355       | 2291 (33%)                 |
| <b>BMS-936559</b>                      |             |            |          | 207       | 207 (3%)                   |
| <b>MDPL3280A</b>                       |             |            |          | 68        | 68 (1%)                    |
| <b>Ipilimumab</b>                      | 1454        |            | 61       | 80        | 1595 (23%)                 |
| <b>Tremelimumab</b>                    | 782         |            |          | 143       | 925 (13%)                  |
| <b>Total no. of pts per tumor site</b> | 4284 (62%)  | 1020 (15%) | 634 (9%) | 924 (13%) | 6872                       |

# NSCLC PD-1 Trials: irAE

| irAE        | Pembrolizumab (n=495) |     | Nivolumab (n=535) |      |
|-------------|-----------------------|-----|-------------------|------|
|             | All Grades            | ≥G3 | All Grades        | ≥G3  |
| Fatigue     | 19%                   | <1% | 19%               | <1%  |
| Pruritus    | 11%                   | 0%  | 6%                | <1%  |
| Anorexia    | 11%                   | 1%  | 12%               | <1%  |
| Rash        | 9%                    | <1% | 8%                | <1%  |
| Arthralgia  | 9%                    | <1% | 4%                | 0%   |
| Pneumonitis | 4%                    | 2%  | 3%                | 1.5% |

# Mechanisms Driving ir-AE

Immune Checkpoints and Associations  
with Autoimmune Pulmonary Disease

# Immune Checkpoints

## CTLA-4

- Genome wide search identified linkages between asthma and 2q33 (region encoding *CTLA-4*) in hispanics<sup>1</sup>
- SNPs in *CTLA-4* gene associated with asthma, atopy and chronic bronchitis<sup>2,3</sup>
- *CTLA-4* polymorphisms are associated with COPD in Chinese patients<sup>4</sup>
- Murine models of acute lung injury have demonstrated CTLA-4 contribute to pulmonary inflammation<sup>5</sup>

<sup>1</sup> CSGA Nat Genet 1997, <sup>2</sup> Munthe-Kaas JACI 2004, <sup>3</sup> Zhu ERS 2009, <sup>4</sup> Liu Human Imm 2010, <sup>5</sup> Nakajima J Immunol 2010

## PD-1/PD-L1

- IHC revealed increased PD-L1 expression in sarcoidosis granulomas<sup>1</sup>
- In lupus susceptible mice, PD-L1 expression protects against fatal pneumonitis<sup>2</sup>
- T-helper cells from patients with granulomatosis with polyangiitis (Wegeners granulomatosis) had higher PD-1 expression<sup>3</sup>

<sup>1</sup> Braun Am J Respir Crit Care 2014, <sup>2</sup> Lucas J Immunol 2008, <sup>3</sup> Wilde Rheumatol 2011. ERS 2009

# ICI cause pulmonary ir-AE by:

- Affecting tissue infiltrating lymphocytes
- Changing cytokine profiles
- Modulating immune checkpoints associated with pulmonary autoimmune diseases

# Reporting of ir-AE in Clinical Trials

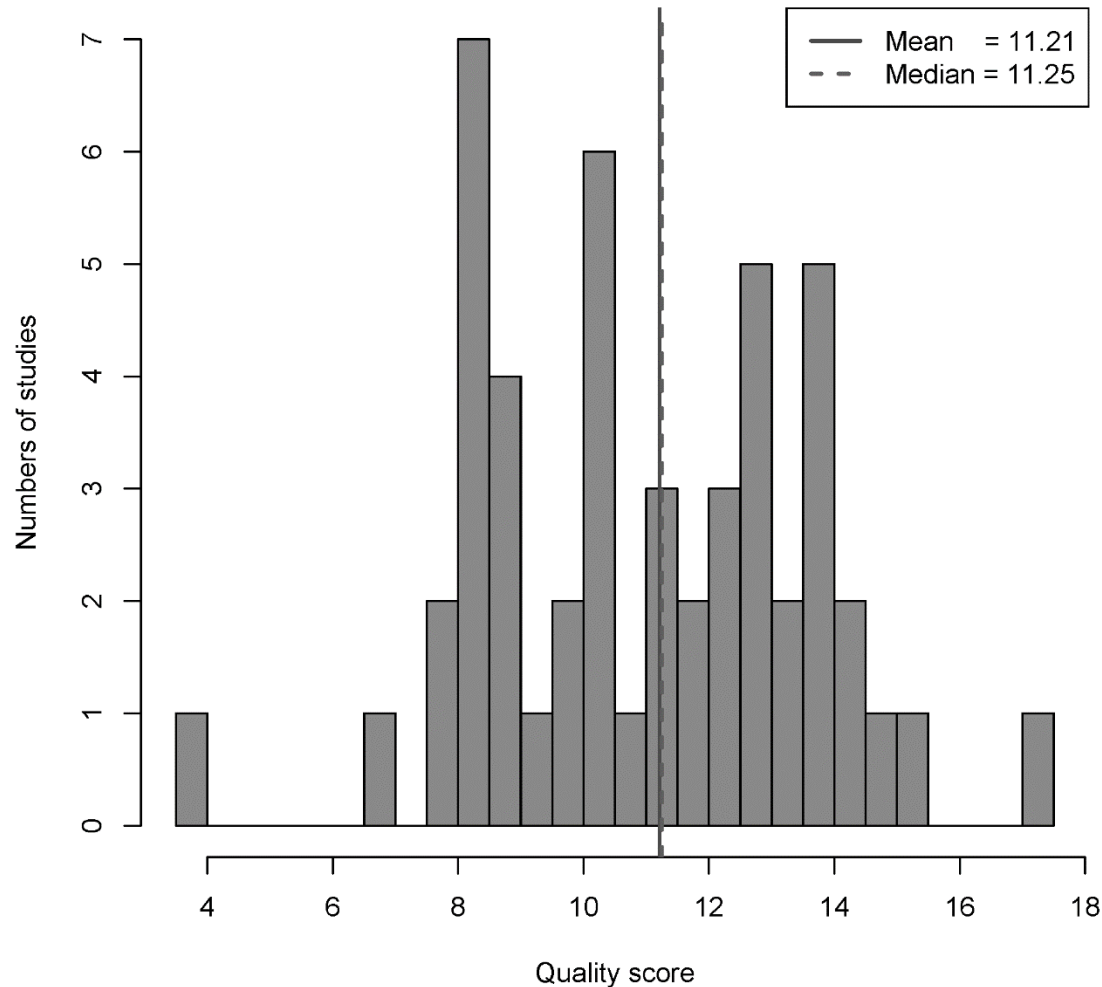
Reporting has improved over time but  
needs to be more comprehensive

# Components of the 21-point quality score and the scoring of each item

|                                                 |                                                                                 |                                                                                |                                                                                             |                                                                    |
|-------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|--------------------------------------------------------------------|
| Title/<br>abstract/<br>introduction<br>3 points | 16%                                                                             | 96%                                                                            | 82%                                                                                         |                                                                    |
|                                                 | Was irAE/harm/safety mentioned in the title                                     | Was irAE/harm/safety mentioned in the abstract                                 | Was irAE/harm/safety mentioned in the introduction                                          |                                                                    |
|                                                 |                                                                                 |                                                                                |                                                                                             | 1 point                                                            |
| Methods<br>6 points                             | 76%                                                                             | 18%                                                                            | 40%                                                                                         | 0.5 point                                                          |
|                                                 | Did the article use a validated instrument to report AEs                        | Did the article provide a definition for irAE                                  | Was the method for AE collection described                                                  |                                                                    |
|                                                 | 8%                                                                              | 22%                                                                            | 30%                                                                                         |                                                                    |
|                                                 | Was the method to decide study drug attribution provided                        | Were plans for presenting and analyzing the AEs reported                       | Was the follow-up interval for the AEs provided                                             |                                                                    |
|                                                 |                                                                                 |                                                                                |                                                                                             | 86%                                                                |
| Results<br>9 points                             | 52%                                                                             | 28%                                                                            | 100%                                                                                        | 60%                                                                |
|                                                 | Was the number of patients who discontinued treatment due to irAE/trAE reported | Was the number of patients who have a dose reduction due to irAE/trAE reported | Did the study provide denominators for analyses on AE                                       | Were irAEs separately reported                                     |
|                                                 | 78%                                                                             | 14%                                                                            | 8%                                                                                          | 6%                                                                 |
|                                                 | 18%                                                                             | 32%                                                                            | 70%                                                                                         | 68%                                                                |
|                                                 | Were all grades (1pt) or only ≥ Gr3 (0.5pt) AEs reported                        | Was the time to occurrence of all or at least one ≥ Gr3 irAE/trAE reported     | Was the management of all or at least one ≥ Gr3 irAE/trAE reported                          | Was the resolution of all or at least one ≥ Gr3 irAE/trAE reported |
|                                                 |                                                                                 |                                                                                |                                                                                             |                                                                    |
| Discussion<br>3 points                          | 94%                                                                             | 58% (29/50)                                                                    | 54% (29/50)                                                                                 | 58% (29/50)                                                        |
|                                                 | Did the authors interpret key AE(s) in the study                                | Was the number of patients who have a dose reduction due to irAE/trAE reported | Were AEs of the investigational drug interpreted as manageable or reversible in the article | Was the interpretation of AEs consistent with the presented data   |
|                                                 |                                                                                 |                                                                                |                                                                                             |                                                                    |
|                                                 |                                                                                 |                                                                                |                                                                                             |                                                                    |

(all reported" for 1 point, "at least one reported" for 0.5 point)

# Distribution of the Quality Scores for reporting of irAE



N=50 studies

**Table 1.** Univariate and multivariate regression analyses of factors associated with quality score

| Study characteristic                  | Quality score | Linear regression   |         |                       |         |
|---------------------------------------|---------------|---------------------|---------|-----------------------|---------|
|                                       |               | Univariate analysis |         | Multivariate analysis |         |
|                                       | Mean          | Coefficient         | P value | Coefficient           | P value |
| ICI target                            |               |                     |         |                       |         |
| CTLA-4                                | 11.22         | Ref                 |         | NA                    | NA      |
| PD-1/PD-L1                            | 11.63         | 0.40                | 0.78    |                       |         |
| Others                                | 10.50         | −0.65               | 0.66    |                       |         |
| Tumor type                            |               |                     |         |                       |         |
| Mixed                                 | 9.94          | Ref                 |         | Ref                   |         |
| Single                                | 11.49         | 1.54                | 0.11    | 1.13                  | 0.21    |
| Phase of study                        |               |                     |         |                       |         |
| Not phase I                           | 11.66         | Ref                 |         | NA                    | NA      |
| Phase I                               | 10.76         | −0.90               | 0.23    |                       |         |
| ICI agent regimen                     |               |                     |         |                       |         |
| Combination                           | 11.67         | Ref                 |         | NA                    | NA      |
| Single agent                          | 10.81         | −0.86               | 0.26    |                       |         |
| Randomized                            |               |                     |         |                       |         |
| No                                    | 11.02         | Ref                 |         | NA                    | NA      |
| Yes                                   | 11.95         | 0.93                | 0.33    |                       |         |
| Source of trial funding               |               |                     |         |                       |         |
| Nonindustry                           | 11.33         | Ref                 |         | NA                    | NA      |
| Industry                              | 11.19         | −0.14               | 0.91    |                       |         |
| Year of publication                   |               |                     |         |                       |         |
| 2003–2008                             | 9.09          | Ref                 |         | Ref                   |         |
| 2009–2013                             | 11.81         | 2.71                | 0.002   | 2.12                  | 0.01    |
| Journal impact factor                 |               |                     |         |                       |         |
| ≤15                                   | 10.27         | Ref                 |         | Ref                   |         |
| >15                                   | 12.63         | 2.36                | 0.001   | 2.20                  | 0.004   |
| Supplementary data                    |               |                     |         |                       |         |
| No                                    | 10.78         | Ref                 |         | NA                    | NA      |
| Yes                                   | 11.72         | 0.94                | 0.21    |                       |         |
| Region in which trials were conducted |               |                     |         |                       |         |
| Multinational                         | 12.05         | Ref                 |         | NA                    | NA      |
| North America                         | 10.98         | 0.80                | 0.57    |                       |         |
| Europe                                | 11.25         | −0.27               | 0.83    |                       |         |
| Other                                 | 10.00         | −1.25               | 0.67    |                       |         |
| Trial patient number                  |               |                     |         |                       |         |
| ≤45                                   | 10.60         | Ref                 |         | Ref                   |         |
| >45                                   | 11.82         | 1.22                | 0.10    | −0.14                 | 0.84    |

CTLA-4, cytotoxic T-lymphocyte antigen-4; ICI, immune checkpoint inhibitor; NA, not applicable; PD-1, programmed death-1; PD-L1, programmed death ligand 1; Ref: reference.

# **ir-AE from ICI of different classes**

**PD-1/PD-L1 inhibitors and CTLA-4  
inhibitors have different toxicity  
profiles**

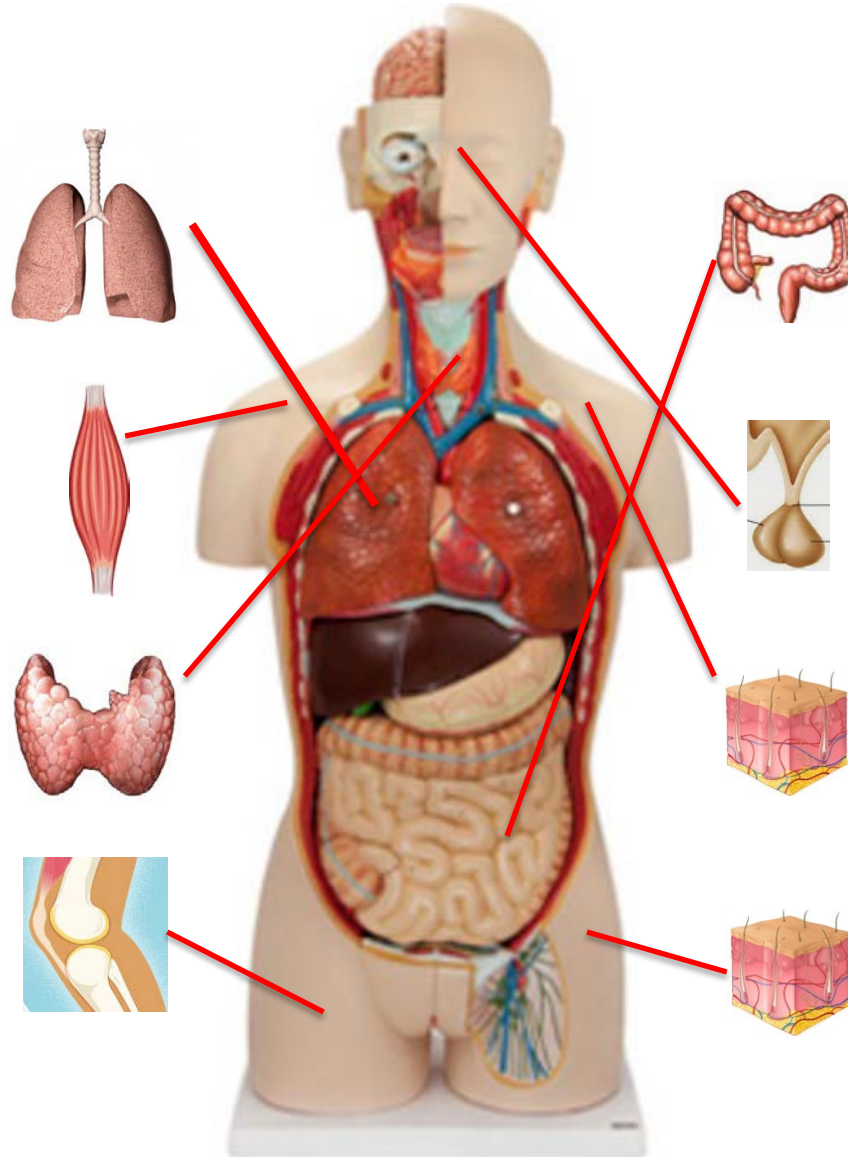
# PD-1/PD-L1 OR (95% CI)

Pneumonitis  
6.42 (3.24-12.74)

Myalgia  
4.99 (2.6-8.70)

Hypothyroidism  
4.29 (2.92-6.31)

Arthralgia  
3.54 (2.63-5.34)



# CTLA-4 OR (95% CI)

Colitis  
8.66 (5.83-12.89)

Hypophysitis  
6.54 (2.99-14.29)

Rash  
2.04 (1.78-2.32)

Pruritis  
1.82 (1.6-2.06)

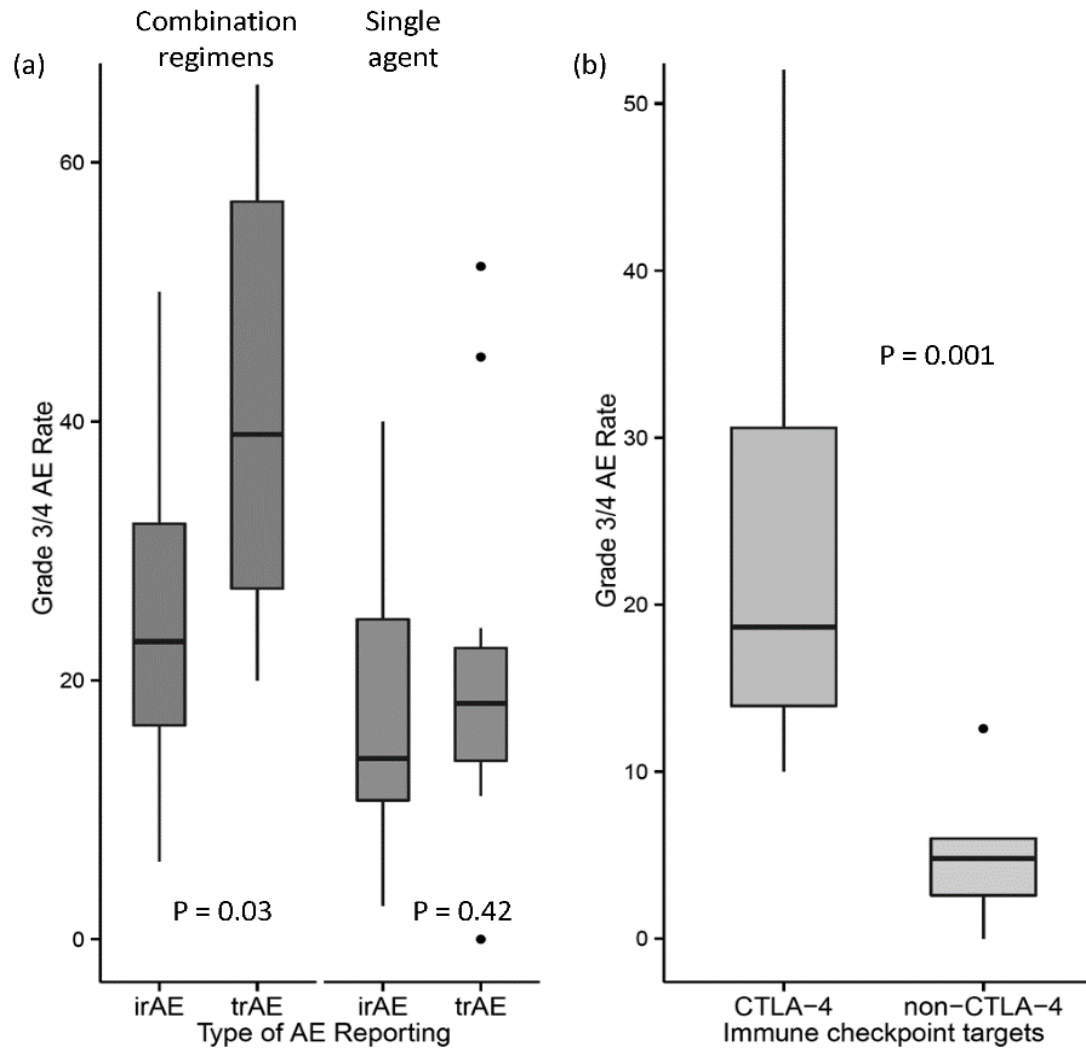
# ir-AE as per Tumor Type

ICI can have a histology-specific ir-AE profile

# PD-1 Clinical Trials

| irAE        | Melanoma vs NSCLC                                                                 |                                                                                   | Melanoma vs RCC                                                                     |                                                                                     |
|-------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
|             | OR, 95% CI                                                                        | p value                                                                           | OR (95% CI)                                                                         | p value                                                                             |
|             |  |  |  |  |
| Colitis     | 4.2, 1.3-14.0                                                                     | 0.01                                                                              | NA (No event for RCC)                                                               |                                                                                     |
| Diarrhea    | 1.9, 1.5-2.5                                                                      |                                                                                   | 1.3, 1.1-1.8                                                                        | 0.04                                                                                |
| Pruritus    | 2.4, 1.9-3.1                                                                      |                                                                                   | 1.5, 1.2-2.0                                                                        | 0.003                                                                               |
| Rash        | 1.8, 1.4-2.3                                                                      | <0.001                                                                            | 1.6, 1.2-2.1                                                                        | 0.002                                                                               |
| Pneumonitis | 0.4, 0.3-0.7                                                                      |                                                                                   | 0.3, 0.2-0.6                                                                        | <0.001                                                                              |

# Combination Regimens have higher irAE frequency



# Impact of ir-AE on QOL

Development and Validation of a  
Patient Reported Outcome tool to  
assess QOL from Immune Checkpoint  
Therapy

# Quality of Life (QoL)

- Impact of ICI on health related QoL is currently unknown
- Evaluation of QoL will be important to determining clinical benefit
- Generic tools to assess QoL are being incorporated into clinical trials of ICI e.g. EORTC QLQ-C30
- Need for a ICI specific QoL instrument

# FACT-ICM

## Development and Validation of Functional Assessment of Cancer Therapy – Immune Checkpoint Modulators

Princess Margaret Cancer Centre  
Tumor Immunotherapy Program

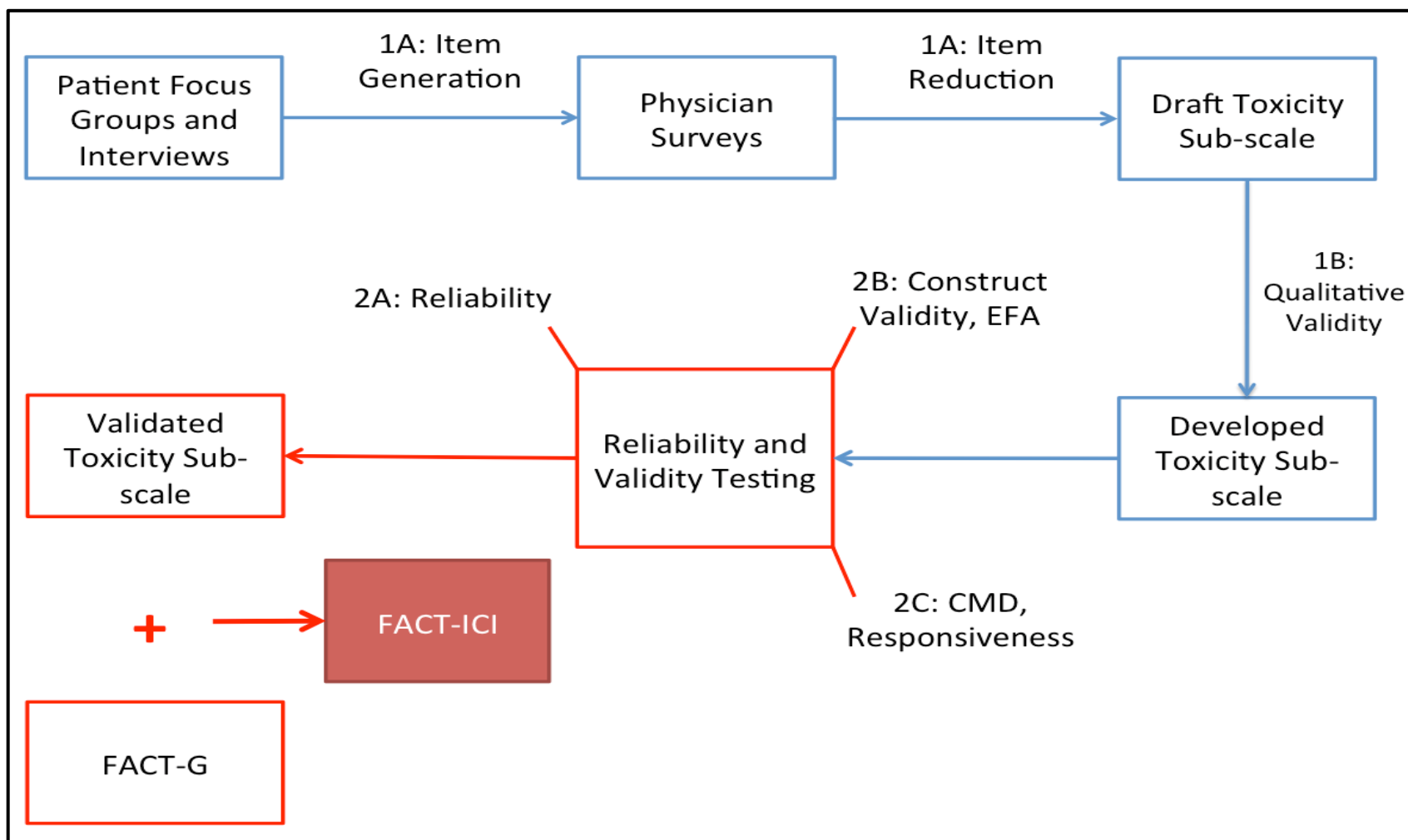


Odette Cancer Centre  
Sunnybrook Health Sciences Centre



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# Overall Study Design



# Regulators Perspective

## Drug Approval

- Given similar ORR with single agent ICI trials, toxicity is an important consideration
- To improve survival, combination ICI regimens are being tested [irAE must be appropriately reported]
- Frequency and severity of irAE is higher with combination regimens → ↓QoL
- New drug(s) approval will depend equally on survival outcomes and toxicity

# Questions

## Contact:

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# Management of ir-AEs

| Organ     | irAE                                                 | Management                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-----------|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Skin      | Pruritus, Rash, Vitiligo, Toxic Epidermal Necrosis   | <p>General Guidelines:</p> <ol style="list-style-type: none"> <li>1. Thorough Investigation to exclude other causes, for example: blood work, hormonal panels, cultures, CT scans, bronchoscopy, colonoscopy etc</li> <li>2. Initial symptom management: O2, oral or IV fluids, electrolyte replacement, anti-emetics, anti-diarrheals, anti-histamines, hormonal replacement</li> <li>3. For more severe toxicities consider oral or IV steroids till symptom resolution and then steroid taper</li> <li>4. Other immunosuppressants eg infliximab</li> <li>5. Surgery, ventilation, inotropes etc</li> </ol> <p>Remember protocol specific management guidelines for certain ir-AEs.</p> |
| GI        | Diarrhea, Colitis, Abdominal Pain, Bowel Perforation |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Liver     | ↑AST/ALT                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Lung      | Pneumonitis                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Endocrine | Thyroid, adrenal, hypothalamus abnormalities         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Nervous   | Neuropathy, Guillain-Barre, Myasthenia Gravis        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Eye       | Uveitis                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Kidney    | Nephritis                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |