Computational Approaches to the Optimization of Dose and Schedule: 
Computational Science in Immuno-Oncology

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Disclosure

- Founder and CSO of AIQ Solutions
Inhibition of the PD-1 immune checkpoint protein (Hargadon et. al. 2018)

CHECKMATE-067 Trial 6.5 yr outcomes:
- Ipilimumab/Nivolumab vs Nivolumab vs Ipilimumab
- Median Overall Survival (Adverse Events):
  - Ipi/Nivo: 72.1 months (59%)
  - Nivo: 36.9 months (28%)
  - Ipi: 19.9 months (19%)
  - No ICI: ~6 months

Incredible success of immunotherapy – but it comes with the price!

- Immune checkpoint inhibitors (ICI) prevent cancer cells from suppressing immune response (Weber et al. 2010)
  - “Take the brakes off” the immune system
- ICI improve survival in multiple cancers... but also lead to significant adverse events

Metastatic melanoma

Wolchok et al, 2022, J Clin Oncol 40(2):127
Optimizing dose and schedule - “optimizing patient treatment journey”

OPTIMIZATION LOOP

Diagnosis, Staging

Treatment Selection

Response Assessment

Optimal stopping theory
Optimizing treatment schedules

- Treatment selection
- Response Assessment

Treatment A

Treatment B

Treatment C
Optimizing treatment schedules

<table>
<thead>
<tr>
<th>Treatment selection</th>
<th>Response Assessment</th>
</tr>
</thead>
</table>

**Treatment A**
- Treatment A
- Good response +Toxicity?
  - Continue treatment?
  - Switch treatment?
  - Pause & restart?
  - Stop & monitor?

**Treatment B**
- Treatment B
- Poor response +Toxicity?
  - Continue treatment?
  - Switch treatment?
  - Pause & restart?
  - Stop & monitor?

**Treatment C**
- Treatment C
- Toxicity
  - Continue treatment?
  - Switch treatment?
  - Pause & restart?
  - Stop & monitor?
Balancing risks and benefit

Treatment selection

Response Assessment

- Continue treatment?
- Switch treatment?
- Pause and restart?
- Discontinue?

Treatment A
Treatment B
Treatment C

The percentage of thematic references referring to specific themes.

- Patients
- Oncologists

- cost and financial toxicity
- treatment logistics and convenience
- personal and family responsibilities
- salience of cutting-edge treatment options
- attending important events and pursuing important goals
- treatment impact on engaging in daily activities
- emotional side effects of treatment
- cognitive side effects of treatment

(Rocque et. al., 2019)

Likelihood of benefit
Risk of toxicity
PRECISION MEDICINE

- The problem of response heterogeneity
- The problem of treatment resistance
Precision medicine aims for this...

Not all patients respond the same to any given therapy, therefore different treatments need to be chosen.
...but there is a big problem!

Just as not all patients respond the same to any given therapy, not all disease sites within a given patient respond the same.
...but there is a big problem!

Response heterogeneity poses significant challenge to optimizing treatments!

Just as not all patients respond the same to any given therapy, not all disease sites within a given patient respond the same.
Why heterogeneity?

**Spatial Heterogeneity**
Different disease sites have different responses to therapy at a given point in time.

**Temporal Heterogeneity**
The same disease site may respond differently at different points in time.

**First-line** → **Second-line** → **Third-line**
Treatment response heterogeneity

Spatial heterogeneity

Within each patient, fraction of lesions in each response category

Each bar represents an individual patient (n=1,100)

Cancers included: prostate, GU-bladder, renal, testicular, penile
H&N, NSCLC, GI-NET, melanoma, ACC

Courtesy of AIQ Solutions
Treatment response heterogeneity
Spatial heterogeneity

Within each patient, fraction of lesions in each response category

How can we assess response heterogeneity?
Only Quantitative Imaging Biomarkers can!

Each bar represents an individual patient (n=1,100)
Cancers included: prostate, GU-bladder, renal, testicular, penile H&N, NSCLC, GI-NET, melanoma, ACC

Courtesy of AIQ Solutions
Each bar represents an individual patient (n=250)

Treatment included: Immunotherapy or combination

75% of patients simultaneously have responding and progressing lesions

Within each patient, fraction of lesions in each response category

- New
- Increasing
- Stable
- Decreasing
- Disappeared

Melanoma/ICI (n=117)

- 65%

GU/Cabo+Nivo+/-Ipi (n=101)

- 87%

Prostate/Vaccine+/-ICI (n=32)

- 75%

Courtesy of AIQ Solutions
Sequential $^{68}$Ga-DOTATATE PET/CT imaging during Lutathera therapy
Treatment response heterogeneity
Temporal heterogeneity

Sequential $^{68}$Ga-DOTATATE PET/CT imaging during Lutathera therapy
Treatment response heterogeneity

Temporal heterogeneity

Proportion Favorable
- 0.33
- 0.58
- 0.55
- 0.50

Proportion Unfavorable
- 0.49
- 0.13
- 0.18
- 0.38
Treatment response heterogeneity
Temporal heterogeneity
The problem of treatment resistance

Although favorable response improves outcome, overall outcome is predominantly driven by resistance

The problem of treatment resistance

Although favorable response improves outcome, overall outcome is predominantly driven by resistance

How can we assess treatment resistance? Only Quantitative Imaging Biomarkers can!

Treatment response assessment - Current practice

Radiologists/nuc med physicians manually identify subset of lesions for treatment evaluation.

Manual and Qualitative Assessment

What information do we want to extract from imaging data?
- Number of lesions?
- Total disease burden?
- Inter-lesion heterogeneity?
- ……

How do you capture useful intelligence efficiently and objectively?
Treatment response assessment – State-of-the-art

Segment all lesions on baseline
Ohlendorf, F. (2020) QJNMMI

Segment 5 lesions
Batched longitudinal metrics
Urso, L. (2023) Diagnostics

Segment some lesions on baseline images
Werner, R. (2017) Oncotarget
Zwirtz, K. (2022) Pharmaceutics

This is needed!

Comprehensive
Measure every lesion

Longitudinal
Variations over time

Lesion-Level
Individual measurements

One lesion!
Why we need to assess every lesion?

Fernandes et al 2023, ESNM meeting
Why we need to assess EVERY lesion?

Assessment of ALL lesions

High risk group (N=29)
Low risk group (N=86)

P<<0.001

Assessment of FEW lesions

Recist

P=0.45

Percist

P=0.57

Liu et al 2022, ESMO Annual meeting
HOW CAN WE GET SUCH DATA?

- AI-based Treatment Response Assessment
Treatment response assessment – AI-based approach

Automatic and Quantitative Assessment

Our software automatically detects and classifies all lesions

US Patents 9603567, 10445878 Licensed to our spin-off: AIQ Solutions
Treatment response assessment – AI-based workflow

- Scanning
- Identification/Classification
- Localization/Quantification
- Matching/Response Assessment

Timepoint 1 Response Map Timepoint 2

11 9 10 7 2 11

New Lesions Progressing Lesions Stable Lesions Partially Responding Lesions Complete Responding Lesions

AI-driven lesion & organ segmentation

Channels: CT and PET images

Input Segment (Normal Resolution)

8 Convolutional Layers

2 Fully Connected Layers

Lymph Node Probability Map

DeepMedic Probability
Physician Contours

Convolutional Neural Network

Segment on CT

Quantify on PET

Blue: CNN bowel contour

Kamnitsas 2017
Treatment response assessment – AI-based approach

Automatic and Quantitative Assessment

Our software automatically detects and classifies all lesions

Responding to treatment

Resistant to treatment

Medium toxicity risk

High toxicity risk

US Patents 9603567, 10445878
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Associating data with clinical outcomes

Quantitative Imaging Biomarkers

Matching among images

Quantification of difference

Prognostication of outcomes

Surrogate Endpoints
(Predictive Biomarkers)
What to do with this intelligence?

- Change approach (29%)
  (different drug, palliative care, etc.)

- Treat resistance (43%)
  (localized ablation, etc.)

Serial imaging and other data

- Optimal (28%)
  - disease controlled
  - toxicity risk

- Suboptimal (72%)
  - limited resistance
  - widespread resistance

- Serial imaging and other data

- Continue therapy

- De-escalate therapy, monitor response
RISK-BENEFIT

- Population-based risk and benefit
- Patient-specific risk and benefit
Risk-benefit
Population-based

- Clinical trial-based data on probability of benefit and toxicity for each immunotherapy treatment
  - Risk-benefit ratio metric \( M = \frac{\text{probability of risk}}{\text{probability of benefit}} = \frac{p_R}{p_B} \)
  - Multiple possible definitions of benefit, based on clinical evaluation criteria (e.g., OS, PFS, RECIST evaluation)

<table>
<thead>
<tr>
<th>Definition of Benefit</th>
<th>Expression for ( p_B )</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Benefit</td>
<td>( p_{CR} + p_{PR} + p_{SD} )</td>
<td>RECIST-based</td>
</tr>
<tr>
<td>Objective Response</td>
<td>( p_{CR} + p_{PR} )</td>
<td>RECIST-based</td>
</tr>
<tr>
<td>PFS &gt; time ( T )</td>
<td>( 1 - p_{PFS,T} )</td>
<td>Outcome-based</td>
</tr>
<tr>
<td>OS &gt; time ( T )</td>
<td>( 1 - p_{OS,T} )</td>
<td>Outcome-based</td>
</tr>
</tbody>
</table>

CR – complete response
PR – partial response
SD – stable disease
OS – overall survival
PFS – progression free survival
## Risk-benefit

### Population-based

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab + nivolumab</th>
<th>Nivolumab</th>
<th>Ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>314</td>
<td>316</td>
<td>315</td>
</tr>
<tr>
<td><strong>Best overall response – N (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Response (CR)</td>
<td>61 (19)</td>
<td>52 (16)</td>
<td>16 (5)</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>122 (39)</td>
<td>88 (28)</td>
<td>43 (14)</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>38 (12)</td>
<td>31 (10)</td>
<td>69 (22)</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td>74 (24)</td>
<td>121 (38)</td>
<td>159 (50)</td>
</tr>
<tr>
<td>Unknown</td>
<td>19 (6)</td>
<td>24 (8)</td>
<td>28 (9)</td>
</tr>
<tr>
<td><strong>Toxicity – N (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-grade, any-toxicity</td>
<td>184 (59)</td>
<td>67 (21)</td>
<td>86 (28)</td>
</tr>
</tbody>
</table>

Wolchok et al, 2022, J Clin Oncol 40(2):127
Risk-benefit
Population-based

- Likelihood of risk and benefit of three ICI treatments:

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<th>Nivolumab</th>
<th>Ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p_B = p_{CR} + p_{PR} + p_{SD}$</td>
<td>0.70</td>
<td>0.54</td>
<td>0.41</td>
</tr>
<tr>
<td>$p_R = p_{AE,high-grade, any-toxicity}$</td>
<td>0.59</td>
<td>0.21</td>
<td>0.28</td>
</tr>
<tr>
<td>$M$</td>
<td>0.84</td>
<td>0.40</td>
<td>0.68</td>
</tr>
</tbody>
</table>

- The cost function $C$ is a function of patient risk tolerance:
  \[
  C = w_B (1 - p_B) + w_T p_T
  \]

- In spite of a higher $M$ a combination ipi+nivo is currently used as the first treatment option.
Risk-benefit space

Population-based risk-benefit

$p_B = 1 - p_{PD}$

$p_T = p_{g3-4,any organ}$
Risk-benefit
Individual patient imaging data (FDG PET)

TREATMENT RESPONSE

**Number of new lesions** (Anwar et al, 2018)
**Tumor shape** (Breki et al, 2016, Sana et al, 2019)
**Lymphoid cell-rich organs** (Nobashi et al, 2019, Prigent et al, 2021)

TOXICITY

**Pneumonitis** (Gandy et al, 2020)
**Colitis** (Lang et al, 2019, Vani et al, 2020, Lang et al, 2020, Sachpekidis et al, 2023)
**Thyroiditis** (Eshgi et al, 2018)
**Pancreatitis** (Alabed et al, 2015, Das et al, 2019)
**Endocrinopathies** (Shalit et al, 2023)
**Sarcoid reaction** (Cheshire et al, 2018)
**Hepatitis** (Prigent et al, 2020)
**Hypophysitis** (Caranci et al, 2020)
**Skeletal** (Moseley et al, 2018)
Predicting BENEFIT
Individual patient imaging data (FDG PET)

Melanoma/ICI (n=117)

GU/Cabo+Nivo+/-Ipi (n=101)

Prostate/Vaccine+/-ICI (n=32)

Courtesy of AIQ Solutions
Predicting RISKS
Individual patient imaging data (FDG PET)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Effected Organ</th>
<th>AUC</th>
<th>Sense</th>
<th>Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunotherapy</td>
<td>Kidneys</td>
<td>0.98</td>
<td>0.98</td>
<td>1.00</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>Pancreas</td>
<td>0.96</td>
<td>1.00</td>
<td>0.91</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>Bowel</td>
<td>0.95</td>
<td>1.00</td>
<td>0.80</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>Liver</td>
<td>0.93</td>
<td>0.90</td>
<td>1.00</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>Lungs</td>
<td>0.92</td>
<td>0.78</td>
<td>0.89</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>Adrenals</td>
<td>0.85</td>
<td>0.72</td>
<td>1.00</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>Thyroid</td>
<td>0.84</td>
<td>0.83</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Courtesy of AIQ Solutions
Example patient

MM patient starting on ipi+nivo

Benefit: PFS>6 mo.  Toxicity: colitis g3/4

Baseline response and toxicity from CHECKMATE-067 (Wolchok et al. 2017)

Risk-benefit space can be used to track disease response and toxicity risk at each imaging timepoint during treatment.
Risk-benefit space

Population-based risk-benefit

\[ p_B = 1 - p_{PD} \]

\[ p_R = p_{g3-4,any\ organ} \]

High risk tolerance picks combo tx
Low risk tolerance picks monotherapy

Patient-specific risk-benefit

Personalized r/b from patient imaging data
Summary

- **Optimizing cancer treatments** (schedule, dose) is complex:
  - Balancing risks and benefits of individual patients
  - Accounting for spatial and temporal (response) heterogeneity

- **Computationally complex AI-supported analytics** is needed:
  - Assessment of each individual lesion response (metastatic disease)
  - Modeling complex relationship to predict risks and benefits

- **Data-driven risk-benefit models** are needed:
  - Population-based risk-benefit models (large clinical trials)
  - Individual patient risk-benefit models (patient-specific data)
Thanks to:

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University of Ljubljana, Slovenia

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Thank you for your attention