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# Context of Use? It's Just Exploratory!

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# Introduction

- Exploratory Endpoints
- F-star Context of Use Process
- Case Study 1: Interferon-γ
- Case Study 2: Interferon-α
- Conclusions

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# Exploratory Endpoints

- 'Exploratory Endpoint' is not a context of use
- Data can be used for a wide variety of reasons, especially in early trials
  - 'Fishing' for pharmacology
  - Investigating MoA
  - Looking for disease progression
  - Early PD endpoints
- In Phase I/II studies this is unlikely to be submitted to regulators, BUT
  - Data could be used for important commercial decisions
  - Data can be used to support significant analytical investment in later phases

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# F-star Context of Use Process

**Biomarker Strategy**

- Top level summary of biomarker strategy
- Concise plan of how biomarkers will progress through project
- Defines questions for biomarkers to answer

**Mid term Strategy (Phase)**

- More detailed strategy for each trial/phase
- Context of use is defined here

**Target Assay Profile (TAP)**

- Biomarker/trial dependent document
- Interprets assay requirements from CoU
- Can be shared with CRO partners

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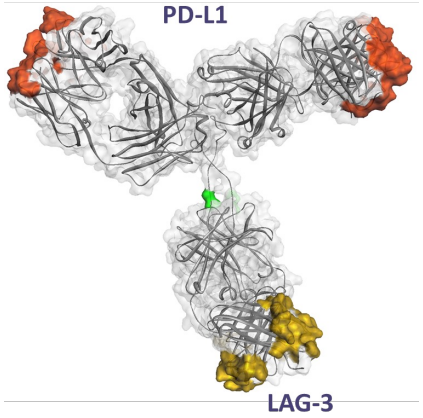
# Case Study 1: Interferon-γ

- FS118 bispecific LAG-3/PD-L1 antibody
- Dual antagonist of PD-L1 and LAG-3
- Prevents inhibition of T-cell proliferation
- T-cell proliferation and activation may involve increase in cytokines such as IFN- γ
- Assay to support Phase 1 study FS118-17101
- Cytokine assessment listed as exploratory endpoint

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## Case study 1: Questions and CoU

- Scientific Questions
  - Are serum cytokines such as Interferon-γ increased after administration of FS118
    - Do any increases correlate with FS118 exposure/dose
    - Do any increases correlate with potential immune cell proliferation?
- Commercial Decisions
  - Is investment in a more sensitive/precise method required for future trials
  - Data required quickly and under budgetary constraints
  - Insufficient internal resource- outsourcing compatible
- Context of Use:
  - *Information on qualitative/ semi-quantitative changes in cytokine levels is required to answer the initial question and potentially can help with the others.*
  - *If positive results are seen*
    - *Future method can be used to investigate further.*

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# Case study 1: Analytical Requirements (from TAP)

- Initial investigation only requires a qualitative change in Biomarker
  - High level of precision is not required
- Other Cytokines will be investigated at the same time
- Samples from broad range of different tumours
  - Disease specific data is not required at this stage
- Measure fold changes from baseline
  - Limited validation data required
  - Parallelism selectivity etc not required
- Options Available:
  - Multiplex assay (Luminex/ MSD etc)
  - High sensitivity singleplex (Quanterix/SMC/MSD-S-plex)
  - O-link panel (96 plex commercial panel)

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# Case Study 1: Conclusion

- Use MSD V-plex Pro-inflammatory panel 1
  - Already used by current CRO partners
    - Less contracting
    - Assay already in place - Performance already established
    - No additional validation required (at this stage)
  - Most cost efficient way of measuring cytokines of interest
  - Use single spiked Matrix QC in addition to Kit Controls for in-study validation
- Downsides
  - Will have to batch samples in profile
  - May not get baseline values (use LLoQ for fold changes)
- If primary question is answered, then focus budget on sensitive single-plex method for more in-depth investigation later.

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# Case study 2: Interferon-α

- SB 11285 STING agonist
- Activation of the STING (Stimulator of Interferon Genes) pathway induces both innate and adaptive immunity and subsequent activation of cytotoxic T cells and NK cells
- In preclinical studies using multiple tumour-derived cell lines, SB 11285 induced cytokines, such as IFN-α [1]
- Project and clinical trial inherited during merger of Spring Bank and F-star
- Assay required to support PhI/II study

[1] DOI: 10.1200/JCO.2020.38.15_suppl.TPS3162 *Journal of Clinical Oncology* 38, no. 15_suppl Published online May 25, 2020.

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# Case study 2: Questions and CoU

- Scientific Questions
  - Does SB 11285 treatment result in increase in IFN-α
  - Is magnitude similar to that seen in pre-clinical studies
  - Is IFN-α a suitable PD marker candidate for later studies
- Commercial Questions
  - Is investment into a robust PD assay required?
- Context of use:
  - *Information on quantitative changes in IFN-α is required to determine whether there are SB 11285 dependent increases in IFN-α and to support decisions on analytical investment and the use of IFN-α as a PD biomarker on future studies.*

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# Case Study 2: Analytical Requirements (from TAP)

- Sensitivity of less than 5 pg/mL (normal range 5.2-42 pg/mL)
- Precision needs to be able to see dose dependent increases in IFN-α (Pre-clinical changes not published)
- Disease specificity not required (Pan cancer trial)
- Parallelism should be determined to ensure results are quantitative.
- Must be outsourced - No capacity for clinical testing in house

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## Case Study 2 Conclusion

- An assay (MSD Singleplex) was already in place at a CRO, BUT:
  - Limited Qualification
    - No parallelism
    - Precision and stability based on recombinant controls in buffer
    - LoQ not tested- but Quoted LoD was 4pg/mL (2.5x background!)
  - Not suitable
- Other assays considered were MSD S-plex, SMC and Quanterix.

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# Case Study 2 Conclusion (cont.)

- Quanterix chosen because assay was in place at CRO with good analytical evaluation (validation) package
    - Demonstrated LoQ of 0.11 pg/mL
    - Limited parallelism
        - 1 Serum sample (to 1 in 2)
        - Multiple blood stimulation samples (to 1 in 4)
    - Precision was up to 16%
    - Stability package was good (3 months LT, 3FT and 24hr RT)
- Caveats
    - Samples to be analysed in profile
    - Clear data warnings to project team highlighting dangers of over interpretation

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## Conclusions

- Exploratory assays have wide ranging requirements - CoU is required
- Significant amount of validation is not required immediately:
  - Key parameters need to be established
  - Validate later once assay requirements are better understood
- CRO analytical evaluations (validations) are valuable, but must be reviewed against the CoU
- Stakeholder management is very important to prevent over interpretation of early data

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