Selecting a Rapid Point-of-Care Test Kit to Monitor Cytokine Levels in Patients Undergoing Dose Escalation in Immunotherapy

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ABSTRACT

A patient's immune system response to immunotherapy treatment can be so rapid as to present a risk of adverse events ranging from flu-like symptoms to even death as a result of Cytokine Release Syndrome (CRS).

To avoid CRS, clinicians conduct dose escalation studies and monitor cytokine levels in a patient's blood. If the samples are sent to central lab, getting back cytokine readings can take 12-24 hours. This is not fast enough to manage CRS. Rapid point-of-care test kits are needed to get results on site in less than 90 minutes.

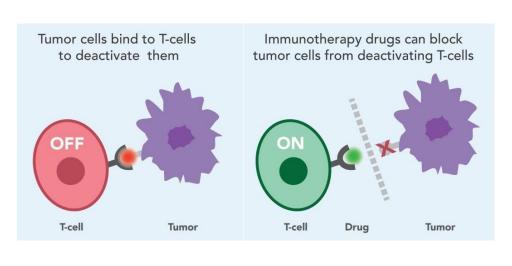
The goal of the project is to select a rapid point-of-care test kit from multiple suppliers already on the market so as to begin dose escalation studies by first Quarter 2020.

Among the many options considered, the Ella platform from Bio-Techne ranked highly according to the stakeholder's needs and is the best of the top 5 options analyzed.

BACKGROUND

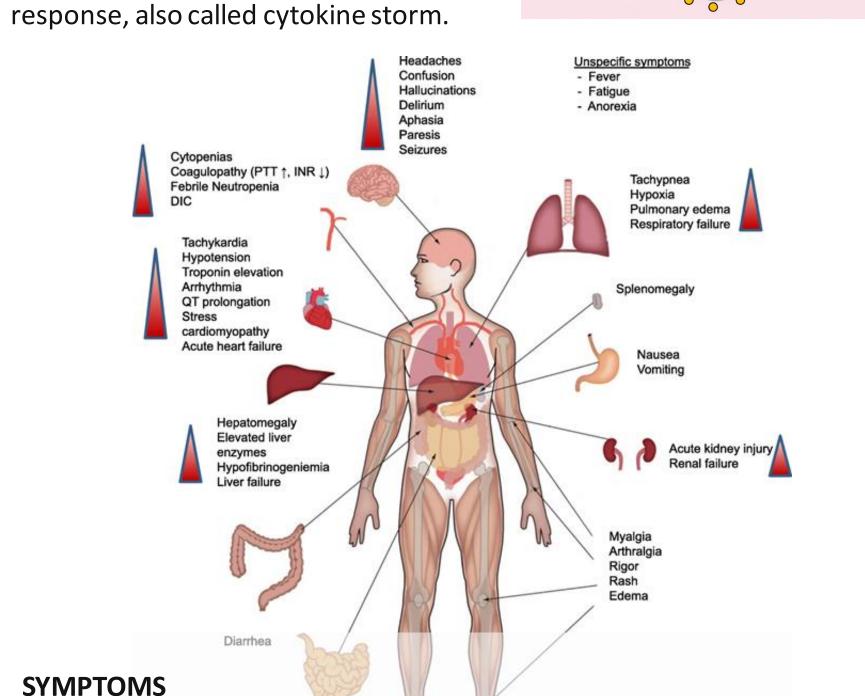
IMMUNO-ONCOLOGY

Cancer can survive unchecked because the immune system does not recognize it as an intruder, but immunotherapy (IO) can help the immune system detect the cancer and attack it.



CYTOKINE RELEASE SYNDROME

When a patient responds to IO, the response can be so rapid as to present a risk of adverse events if the dose is not carefully fine tuned to avoid Cytokine Release Syndrome. CRS is a runaway inflammatory



Symptoms include fever, fatigue, loss of appetite, muscle and joint pain, nausea, vomiting, diarrhea, rashes, fast breathing, rapid heartbeat, low blood pressure, seizures, headache, confusion, delirium, hallucinations, tremor, and loss of coordination.

CRS PREVENTION: DOSE ESCALATION STUDIES

Determine if dose range achieves both efficacy and safety requirements



TURN AROUND TIME



RAPID POINT-OF-CARE TEST KIT

To monitor cytokine levels at short intervals the clinician needs pointof-care kits that can be installed in a clinical setting and that is simple enough to be used by clinical staff.

CLINICAL BACKGROUND INFORMATION

The first patient is scheduled to be enrolled in a phase 1 dose escalation study by first quarter 2020. Patient failed to respond to standard of care therapy prior to being referred to immuno-oncology clinic.

This means that time is quickly running out to try cutting edge immunotherapy available at a limited number of treatment centers.

OBJECTIVE

AbbVie needs to select a point-of-care test kit to rapidly titrate a subset of cytokine biomarkers to monitor patients at risk of Cytokine Release Syndrome (CRS) at the onset of tumor treatment with immunotherapy during phase 1 dose escalation studies.

- Beginning with user needs and analytical product requirements, to comb through data sheets and websites from multiple suppliers to determine the closest matches to the desired test kit requirements.
- Using a Pugh Matrix, to reduce the number of vendor options.
- To analyze the top options to present the pros and cons to the stakeholders in order to help them make the final choice.

METHODS

USER/STAKEHOLDER NEEDS

SCORE ANALYTES **ASSAY TIME VALIDATED** DYNAMIC SENSITIVITY **AVAILIBILITY SPECIFICITY** RANGE (logs) (LLOD | pg/mL) (minutes) IL-6 & IFN-Y 1st Q 2020 < 60 medical no interaction 4-5 < 1 IL-6 only 60-90 scientific 1 - 2* > 90 * *not available* > 2 *no IL-6* no mention LIFECYCLE SCORE IMPRECISION SITE-TO-SITE COST (\$) **ACCURACY** (Dilution) PREDICATE (% CV) (% spike recovery) | LINEARITY(R2) | ASSAYS (R2) robustness & affordability 90 – 110% 90 – 110% ≥ 0.95 ruggedness large scale 80 - 120%0.90 - 0.95<u><</u> 20 80 - 120%70 – 130% 70 – 130% ≤ 0.90

MAIN INCLUSION CRITERIA • Analytes must have IL-6. IFN-Y is optional.

• Must be validated for at least research use.

• Assay time must be < 90 minutes.

• Availability: 6 clinics in the U.S. by first quarter 2020.

ASSESSMENTS Each attribute will be weighted according to importance and scored according to performance

on a scale of 1-5.

STATISTICAL METHODS UUU

For each attribute, the weight will be multiplied by the score and the cumulative sum for each product/vendor will be compared across the board. The top options will be compared with an in depth analysis on the pros and cons of each.

WEIGHTING FACTORS

7	ATTRIBUTE	WEIGHT	
	ANALYTES	5	
	ASSAY TIME		
	VALIDATED		HIGH IMPORTA
	AVAILIBILITY		
ı	SPECIFICITY		
	DYNAMIC RANGE		
	SENSITIVITY	3	
	IMPRECISION		
	ACCURACY		
	LINEARITY		
	PREDICATE ASSAYS	1	
	SITE-TO-SITE	0	LOW
	COST		IMPORTA
n	LIFECYCLE		

THE SELECTION PROCESS

the industry standard.

commercially in 2020.

the selection process.

1. Luminex was included because it is

as one of Ella's top competitors.

3. Proxim Diagnostics was included

because it has potential to meet

requirements for IL-6 once launched

More options will considered throughout

2. Meso Scale Diagnostics was included

RESULTS

TECHNOLOGY LANDSCAPE



30 OPTIONS \rightarrow < 10 OPTIONS

NO RELEVANT TECHNOLOGY

- Minifab
- Abreos Biosciences
- Microdermics

NO IL-6 OR IFN-Y

- Alere: AFINION
- Sekisui Diagnostics: FastPack
- True Diagnostics: TrueDX Assays Buhlmann: Quantum Blue CRP
- Abbott: i-STAT Handheld
- Abbott: Piccolo Xpress
- Nanomedical Diagnostics: Agile

ASSAY TIME > 90 MIN.

- Eve Technologies: Discovery & Multiplex Assays
- BioLegend: Legend MAX Kit
- Bio-Rad: Bio-Plex MAGPIX/200/3D ACD: RNAscope
- Novus Biological: IL-6 ELISA Kit
- R&D Systems: Quantikine ELISA Kit
- Quanterix: Simoa HD-1 Analyzer
- **Thermo Fisher Scientific: Luminex 200 & ProcartaPlex Simplex (industry standard)

NOT AVAILABLE BY 2020

- **Proxim Diagnostics: Handheld Analyzer (lifecycle)
- Bioporto: NGAL ELISA Kit Dakatari Diagnostics: Agile
- Zomedica Pharmaceuticals Corp: TRUFORMA
- Qorvo Biotechnologies: ZM-024 Milenia Biotech: QuickLine IL-6 ELISA
- **⊘**, EVALUATE.

ANALYZE.

COMPARE.

LIFECYCLE OPTIONS UNDER REVIEW

- **Protein Simple: Ella
- Protein Fluidics: PuMA (contact with supplier initiated)
- Vista Therapeutics: NanoBioSensor (contact initiated) Gyros Protein Technologies: Gyrolab xPlore (contact initiated)
- **Meso Scale Diagnostics: V-PLEX (assay time to be clarified)
- Singulex: Erena SMC Instrument (assay time to be clarified)
- Singulex: Clarity System (analytes to be clarified)

Xip Diagnostics: Molecular Counting: (analytes to be clarified)

PUGH MATRIX

RECOMMENDED

ATTRIBUTE	Thermo Fisher Scientific: Luminex 200 & ProcartaPlex Simplex		Meso Scale Diagnostics: MESO SECTOR S 600 & V-PLEX		Protein Simple: Ella		Proxim Diagnostics: Handheld Analyzer v2.1		Protein Fluidics: Pu•MA Vista Therapeutics: NanoBioSensor Gyros Protein Tech: Gyrolab xPlore		
ATTRIBUTE											
ANALYTES	IL-6 & IFN-Y	5	IL-6 & IFN-Y	5	IL-6 & IFN-Υ	5	IL-6 only	3	IL-6	3	
ASSAY TIME	run: 3-5 hrs read: ~45 min	1	turn around: <4.5 hrs smp prep: 2 hrs read: 1-3 min	1	assay prep: 10-15 min smp prep: 0-45 min read: 1 hr	5	smp-to-result: <15 min	5	< 90 min	3	
VALIDATED			RUO	3					RUO	3	
AVAILABILITY	available	5	available	5	available	5	unavailable	1	available	5	
SPECIFICITY	tested	5	tested	5	tested	5			These 3 technologie	gies	
DYNAMIC RANGE	3.6 logs	3	3.9 logs	3	4.0 logs	5	4.0 logs	5	satisfy the main inclusion criteria. Suppliers have been contacted for additional information on instrument performance.		
SENSITIVITY	0.038 pg/mL	5	0.06 pg/mL	5	0.26 pg/mL	5	1.5 pg/mL	3			
IMPRECISION	inter: 4.5% intra: 6.2%	5	inter: 7.3-5.2% intra: 4.5-3.6%	5	inter: 8.3-7.1% intra: 2.4-3.9%	5	< 10% CV	5			
ACCURACY	94-97%	5	87-92%	5	88-99%	5					
LINEARITY	102-115%	5	105-110%	5	110-120%	3					
PREDICATE ASSAYS	0.9733	5			> 0.9	3	0.953	5			
SITE-TO-SITE					7.5% CV						
*COST (does not represent large scale)	plate: \$200 - \$300 reader: \$62,500		plate: \$300 - \$400 reader: \$190,000		plate: \$750-\$1,200 reader: \$63,000		plate: \$1500 reader: \$1700				
EASE OF USE	CRO only		CRO only		POC + error mitigation		TBD		TBD		

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DISCLOSURES

All authors are employees of AbbVie. Didier Lefebvre may own AbbVie stock or options.

CONCLUSIONS

SCORE



The Ella platform satisfies all main inclusion criteria and a promising performance compared to the industry standard. It is the best option that we have the most information on currently.



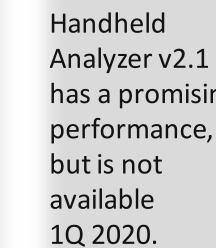
for all technical

long assay times.

attributes, but have

160







170

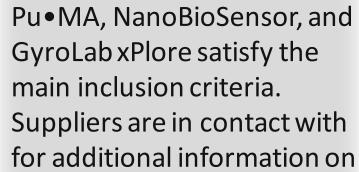


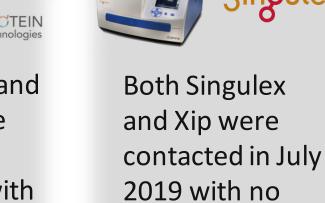


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