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Program Update

ASCO, June 2, 2019

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Presentation Overview

1. **DCVax®-Direct**
   - Review of the technology and how it works
   - Follow up data from Phase I trial
   - New clinical trials

2. **DCVax®-L**
   - Progress on the road to unblinding
   - Follow up data on Information Arm

DCVax®-Direct for Inoperable Solid Tumors

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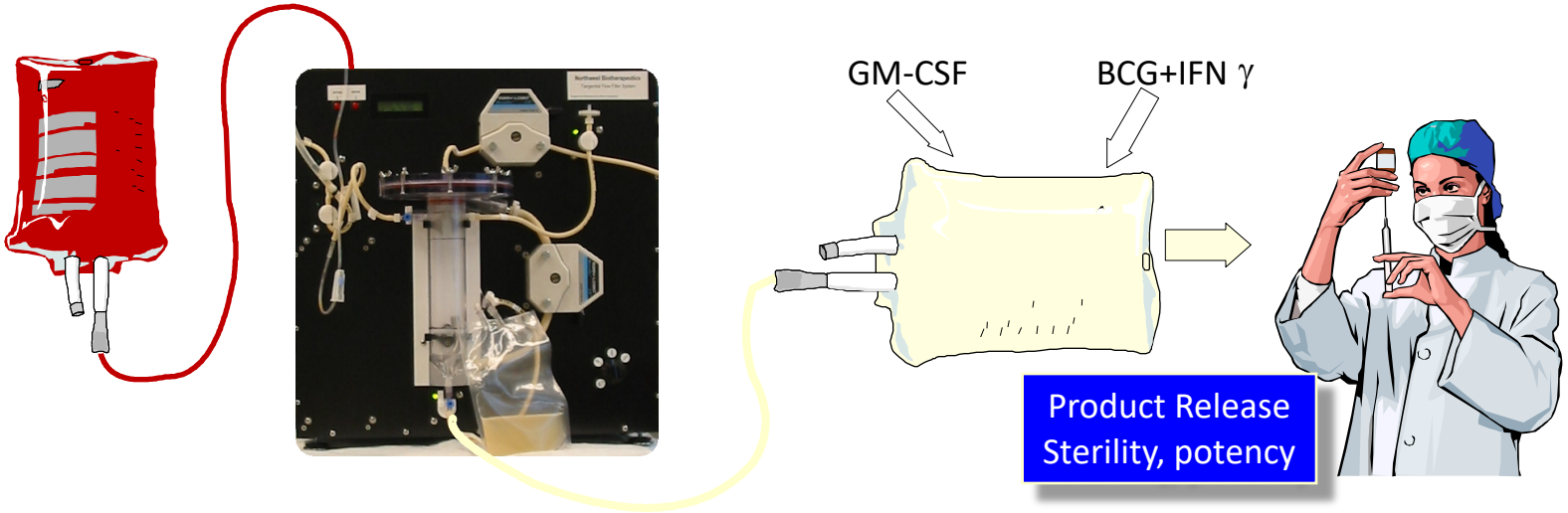
DCVax-Direct

- **DCVax-Direct is comprised of partially activated, autologous dendritic cells for intra-tumoral injection**
  - Partially activated DC retain the capability to take up antigen, and are irrevocably committed to full maturation
- **In preclinical work, optimally activated DC were meaningfully more effective in clearing established tumors than immature DC**
- **DCVax-Direct is manufactured using a proprietary, automated manufacturing system**

Key Points

- DCVax-Direct uses a unique and proprietary manufacturing approach that dramatically increases cytokine levels
- The amounts of cytokines produced (e.g. IL-8, Il-12, TNFα) correlate with survival in the Phase I trial
- DCVax-Direct may have multiple modes of action, and the produced cytokines may be directly or indirectly involved in some or all of these mechanisms
- DCVax-Direct induces mild fevers as the main adverse advent
- Survival Data from the Phase I trial strongly suggest a meaningful survival benefit from DCVax-Direct treatment
- First publication at *Subbiah et al., Clin Cancer Res, July 17 2018, DOI: 10.1158/1078-0432.CCR-17-2707*

DCVax-Direct – Automated Manufacturing



Leukapheresis | TFF purification | DC culture | Treatment

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Advantages of the DCVax-Direct System

- **The system initially produces fully immature DC**
  - **Consequentially, one has full control over the DC activation process**
  - **To produce DCVax-Direct, the cells are partially activated, retain antigen uptake capability, and progress irrevocably to fully mature DCs that induce an immune response**
- **The potency of the produced DC, e.g. measured by cytokine production, is significantly enhanced**
- **Automated manufacturing in a closed system reduces capital costs and labor requirements**

Growing Recognition of the Importance of Cytokines Roles in Cancer Therapy

3 key roles for cytokines in immune therapy

- Priming of the local tumor microenvironment for immune attack
- Stimulation of systemic immune cell function
- Direct killing of tumor cells

Renewed Attention to Cytokines for Cancer Therapy

- **Cytokine monotherapy for cancer (e.g. interferons, interleukin 2, interleukin 12) has been hampered by low efficacy and high toxicity**
- Cytokines are [now] being considered to better direct the nature of the T-cell infusion product, T-cell function and persistence in vivo, as well as to modulate the tumor microenvironment (*E. Petrozziello et al.; Immunotherapy 2015;7(5):573-84)*
- 'Armored' CAR T-cells are typically modified second generation CAR T-cells that have been further optimized to inducibly or constitutively secrete active cytokines or express ligands that further armor CAR T-cells to improve efficacy and persistence *(Yeku and Brentjens RJ; Biochem Soc Trans. 2016 Apr 15;44(2):412-8)*
- Cytokines are being investigated clinically with new engineered cytokine mutants (superkines), chimeric antibody-cytokine fusion proteins (immunokines), anticancer vaccines, CPIs, and cancer-directed monoclonal antibodies to increase their antibody-dependenT-cellular cytotoxicity or sustain cellular responses and anticancer efficacy *(Conlon, Miljkovic, Waldmann; J Interferon Cytokine Res. 2019 Jan;39(1):6-21*

DCVax-Direct and the Role of Cytokines

1. **DCVax-Direct DCs produce very large quantities of cytokines, such as TNF-α and interleukin 12**

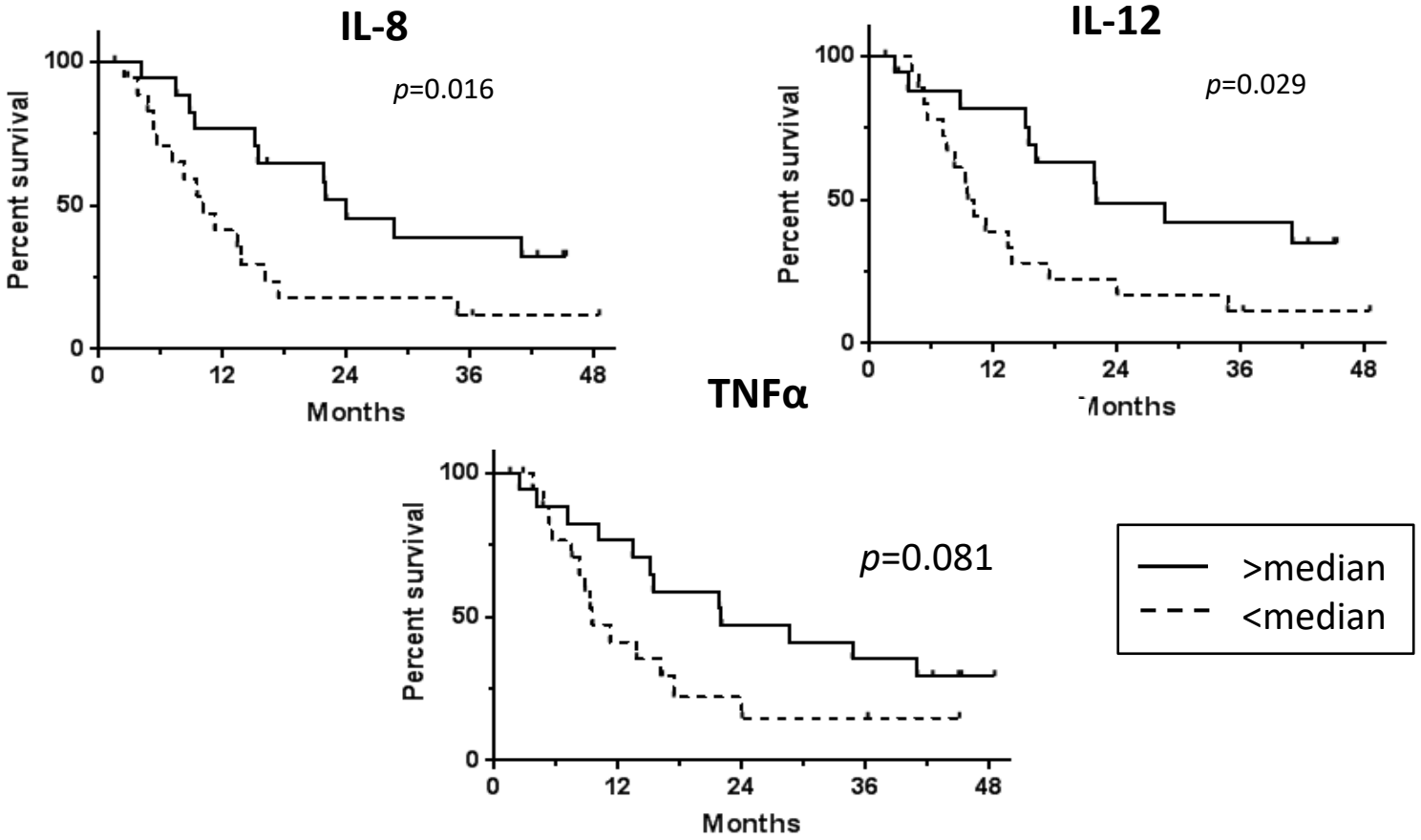
2. **These cytokines have 2 key functions:**
   - direct biological effects
   - indicators of potential effectiveness of DCs

3. **There are multiple observed major biological effects:**
   - DCVax-Direct causes rapid influx of T-cells into tumors
   - DCVax-Direct causes massive necrosis in injected tumors
   - DCVax-Direct mobilizes systemic anti-tumor T-cell responses

4. **The quantity of cytokines correlates with survival**

5. **The effects are produced without significant toxicity such as cytokine storms**

Cytokine Production and Survival



- **IL-8: mOS of 24 months vs 10 months**
- **IL-12: mOS of 22 months vs. 10 months**

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RMH and MDACC Scores

- **Patients in the DCVax-Direct Phase I trial had exhausted other treatment options**
- **For such patients, several methods can be used to predict survival**
  - Royal Marsden Hospital (RMH) Score
  - MD Anderson Cancer Center (MDACC) Score
- **The MDACC Score uses 5 risk factors to predict survival times*:**
  - High number of metastases (>2)
  - Gastrointestinal tumor (present)
  - Poor ECOG Performance status (≥1)
  - High lactate dehydrogenase (LDH) levels in blood (>618 IU/L)
  - Serum albumin levels <3.5 mg/dL

*Wheler J, Tsimberidou AM, Hong D, Naing A, Falchook G, Piha-Paul S, et al. Survival of 1,181 patients in a phase I clinic: the MD Anderson Clinical Center for targeted therapy experience. Clin Cancer Res. 2012;18(10):2922-9.

DCVax-Direct Phase I Trial: Actual vs. Predicted Survival

Using the MDACC Score, predicted survival was determined for all DCVax-Direct Phase I patients and compared to actual survival (the MDACC Score was calculated from patients treated with other experimental therapies)

Outcome: 76% of evaluable patients in the DCVax-Direct trial exceeded their predicted survival time, by an average of 14.3 months*

*Publication in preparation

DCVax-Direct Phase I Trial: Key Observations

- Activated DC can be safely administered to patients with unresectable solid tumors
- Early T-cell infiltration demonstrates modulation of the tumor microenvironment to allow influx of pre-existing anti-tumor T-cells
- T-cell infiltration, coupled with the emergence of shared TCR sequences between tumor and blood, demonstrates induction of a systemic anti-tumor immune response
- The expression of interferon gamma by infiltrating T-cells shows cytotoxic T-cell activity
- Induction of PD-L1 in tumor tissue in response to DCVax-Direct shows the potential for combination therapy with immune checkpoint inhibitors

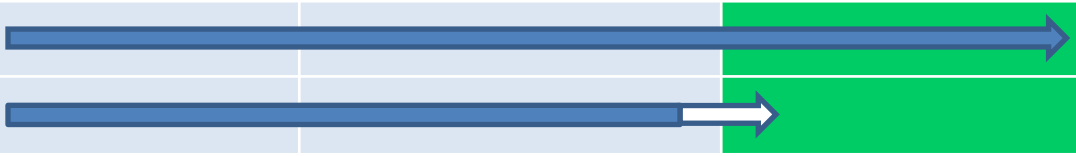
DCVax-Direct Phase I Trial: Key Observations (cont.)

- **DC quality, defined by the production of soluble cytokines, is predictive for survival**
- **The correlations between cytokine production and survival supports the mechanisms of action of DCVax-Direct:**
  - Direct killing of tumor cells
  - Making tumor micro-environment more permissive
  - Inducing anti-tumor T-cells to initiate tumor cell killing
- **DC-produced cytokines such as TNFα may be directly responsible for mediating tumor control in patients treated with DCVax-Direct**
- **Survival is longer than would be expected with other investigational therapies for the majority of patients**

DCVax-Direct – New Trials

- **Restart of DCVax-Direct manufacturing recently announced**
- **Multiple new clinical trials have been in preparation**
- **The first 2 of these new trials are anticipated to start in the coming months**
  - Brain metastases of lung- and breast cancers
  - Pediatric diffuse intrinsic pontine glioma (DIPG) and supratentorial high grade glioma (SHGG)

Indication	Design Phase	Submitted to FDA	Cleared by FDA
Brain metastases			
Pediatric DIPG/SHGG			



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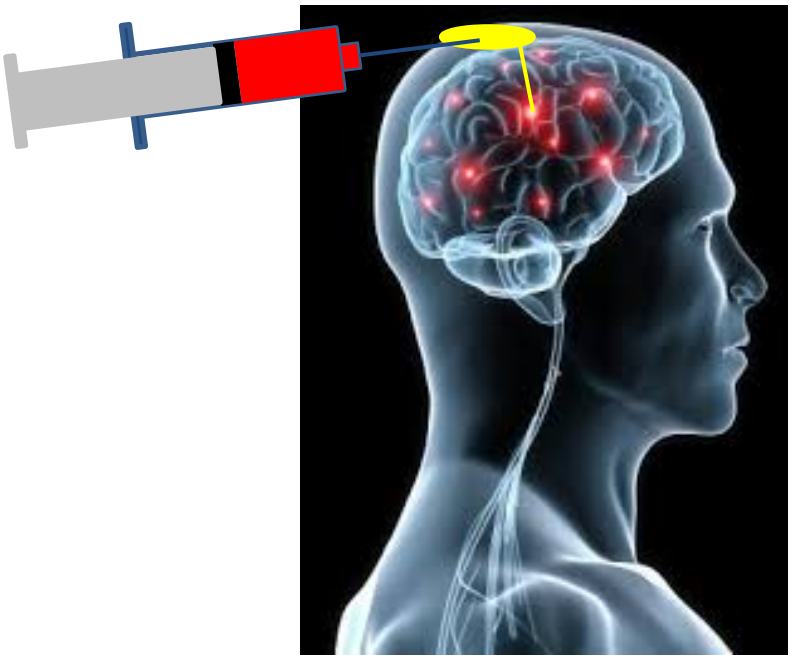
Brain Metastases – Severe Unmet Medical Need

- Brain metastases incidence in breast cancer patients, depending on subtype, ranges up to nearly 40%
- Patients with triple negative breast cancer (TNBC) or HER-2 positive subtypes have a significantly higher incidence of brain metastases; median survival in the metastatic TNBC population is around 7 months
- Survival is generally poor for patients with brain metastases who progress following radiation therapy

Brain Metastases Clinical Trial

- DCVax-Direct will be administered through a reservoir that is placed under the skin and which drains into the tumor



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Brain Metastases Trial Design

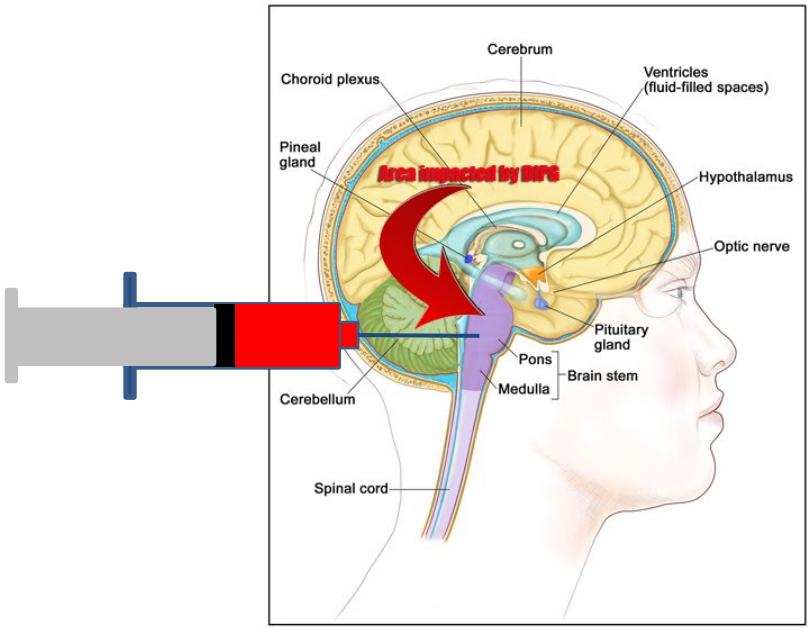
- The trial has been designed with and will be conducted at the Mayo Clinic
- Approximately 10 patients, expandable to 24 patients, 18-75 years of age
- Dose escalation design to identify the maximum tolerated dose
- 7 injections of DCVax-Direct administered over 10 weeks
- Injections are administered using an Ommaya reservoir, implanted under the skin
- Trial objectives include safety, tumor response, and survival

DIPG – Pediatric Severe Unmet Medical Need

- 90% of patients with DIPG die within 2 years
- The disease strikes early, typically at 6-9 years of age
- Radiation therapy provides some symptomatic improvement
- Numerous clinical trials with chemo or biologic therapy added to radiation have failed to improve outcome
- Surgery is not a feasible option
- Prognosis has not improved in the last 25 years
- Median survival time is 8-11 months, median time to progression is ~6 months
- DIPG is associated with a number of gene alterations, which can serve as neoantigens for DCVax-Direct therapy

DIPG and Pediatric SHGG Trial

DCVax-Direct will be administered directly into the tumor through stereotactic injections following biopsy of the tumor



Pediatric DIPG/SHGG Trial Design

- The trial is being designed together with several leading Cancer Centers
- Approximately 18 patients, 3 - 21 years of age
- Dose escalation design to identify the maximum tolerated dose
- 3 injections of DCVax-Direct, at Day 1, Day 7, and Day 22
- Injections are administered using stereotactic guidance
- Trial objectives include safety, tumor response, and survival

DCVax-Direct: Conclusions

- DCVax-Direct has activity in multiple different cancers
- High cytokine production is directly related to the magnitude of clinical benefit
- DCVax-Direct may extend life beyond what can be achieved with other experimental therapies
- Novel clinical trial designs using DCVax-Direct will be explored in severe unmet medical needs
- New manufacturing agreement with Cognate Bioservices allows for rapid initiation of these trials

DCVax®-L for Newly Diagnosed Glioblastoma Multiforme (GBM)

Status report on Phase III Trial

Key Elements Differentiating DCVax®-L

1. Uses the Master Cell of Immune System

- **Mobilizes the whole immune system (Many active agents rather than just 1 active agent)**

2. Fully personalized

- **Addresses complexity and heterogeneity; fits the patient's version of the cancer**

3. Uses ALL tumor antigens, not just 1 or a few

- **Minimizes tumor escape**

Summary of Phase III Trial

- **Patients with newly diagnosed GBM were considered for the trial**
- **331 patients were randomized to either DCVax-L or placebo, in a 2:1 ratio**
- **Randomization occurred after the 6 weeks of chemo-radiation that is part of standard treatment**
- **DCVax-L/placebo treatments are given on top of standard of care**
- **At the time of confirmed progression, patients were given the option to 'cross over' to DCVax-L without breaking the blind**
  - ~90% of patients have received DCVax-L treatment at some point
- **Last patient was enrolled in November of 2015**

The Road to Unblinding

- **Generation of the draft Statistical Analysis Plan (SAP)**
- **Presentation of the draft SAP to regulators**
  - Obtain feedback
  - Finalize the SAP taking the feedback into consideration

In parallel …

- **Checking and validation of the data by the CRO**
  - Review case report forms: hundreds of pages per patient, for 331 patients
  - 100% source document verification
  - Resolution of queries
- **Database lock (all data is held by an independent CRO)**
- **Unblind the trial data**

Statistical Analysis Plan (SAP)

- The SAP contains all of the planned analyses for the data that will emerge from the Phase III trial
- An effective SAP considers the original trial design, protocol, and subsequent scientific advances
- The SAP analyses, taken together, should provide the best insight into the effects of the treatment

SAP Update

- **We have worked for the past 5 months with 3 world class, independent statisticians to develop a draft SAP using state of the art statistical methods**
  - This stage required the most extensive work by the Company and its advisors
- **The draft SAP is nearly complete at this point**
- **Next stage will be to submit the SAP to regulators to get their comments, feedback, and buy-in**
  - The time frame for this stage is the most uncertain
- **Following finalization of the SAP we will proceed to unblind the trial and analyze the data**

Data Collection Update

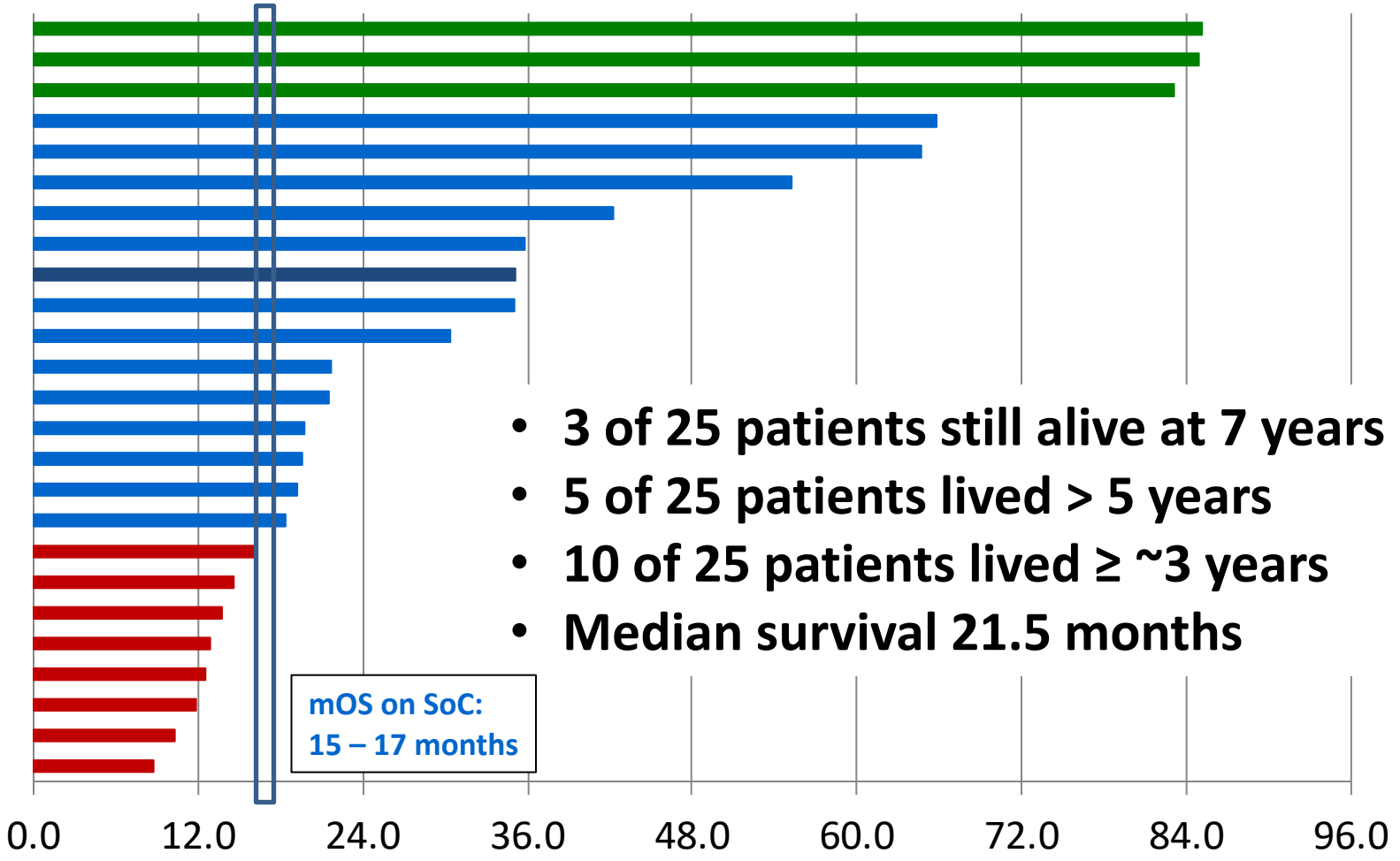
- Several thousands of queries were generated during the data collection process (as is typical for a large clinical trial)
- The independent CRO has been working intensively (while the Company has been working on the SAP) to source-verify the data and resolve queries
- At this point, only a few hundred queries remain to be resolved

Information Arm Summary

- **The Information Arm was an open label treatment setting for patients with radiographic evidence of disease progression post chemoradiation**
- **Patients were classified as 'confirmed rapid progressors' or 'indeterminate cases' based on follow-up scans**
- **The indeterminate group consists of actual or apparent rapid progressors that cannot be differentiated**

Updated survival data are encouraging and appear consistent with interim blinded data from the Phase III trial

Indeterminate Cases (PD/PsPD)



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DCVax-L: Conclusions

- DCVax-L is capable of inducing immune responses against glioblastoma tumors
- Early, blinded results from a Phase III trial suggest a survival advantage compared to current standard of care
- Final analysis of the Phase III data is upcoming

Acknowledgments

Patients and Families

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Cognate Bioservices

NWBio Scientific Advisory Board

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