# Phase II trial of therapeutic vaccine consisting of autologous dendritic cells loaded with autologous tumor cell antigens from self-renewing cancer cells in patients with newly diagnosed glioblastoma

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# Disclosures

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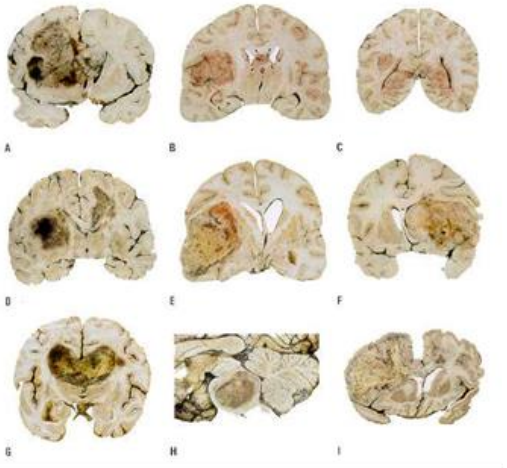
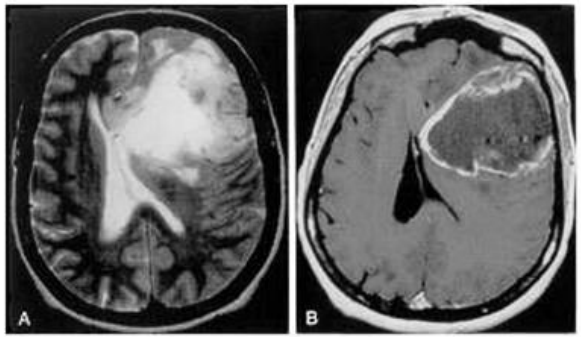
I am a consultant and/or a member of the speaker bureau for Novocure, ERC Belgium, Primimmune, Tocagen, and BTG International.

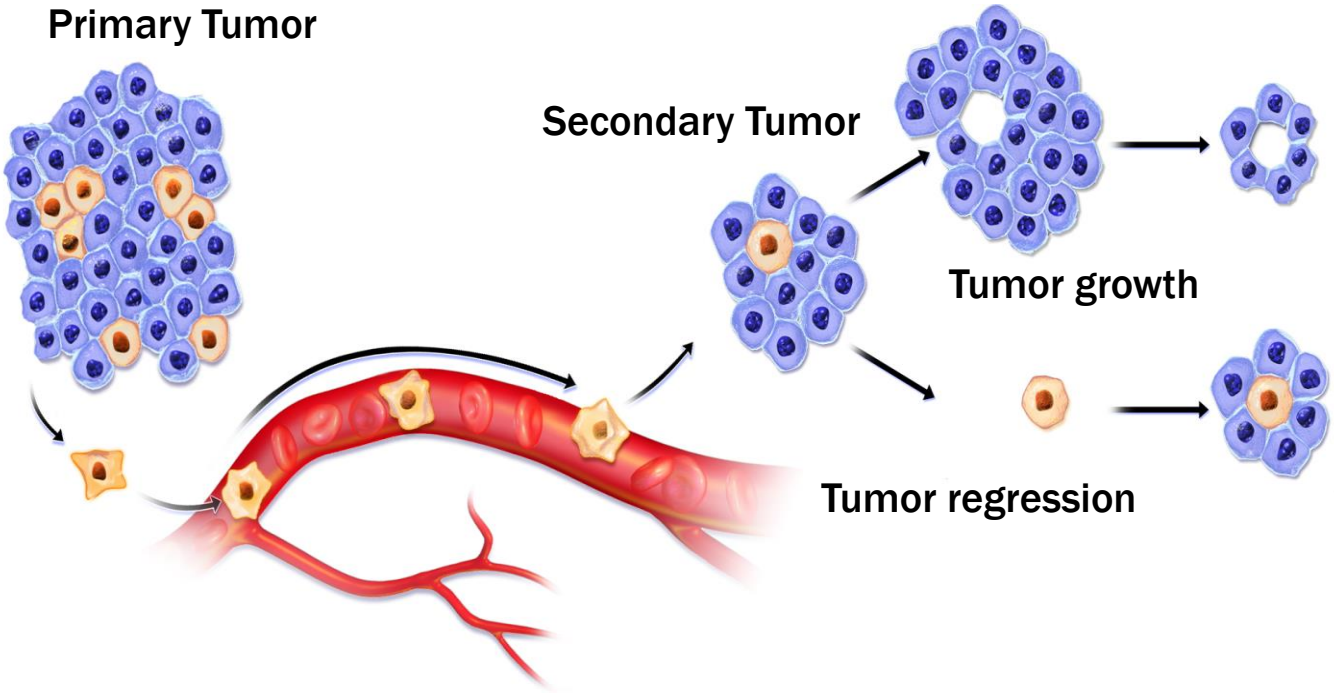
# Glioblastoma

- Most common and aggressive brain cancer (WHO grade IV astrocytoma)
- Incidence of 3.2 per 100,000 population
- Standard treatments are surgery, radiation, temozolomide, bevacizumab and alternating electrical fields
- Median Survival is 18-24 months





# Autologous Tumor Antigens from Tumor Initiating Cells




TIC specific therapy: delayed tumor regression, perhaps after measurable disease progression due to replication of terminally differentiated cells

Conventional cancer therapy: apparent near complete remission often followed by tumor relapse with progeny of TIC

Differentiated Tumor Cells

Tumor Initiating Cells (TIC)

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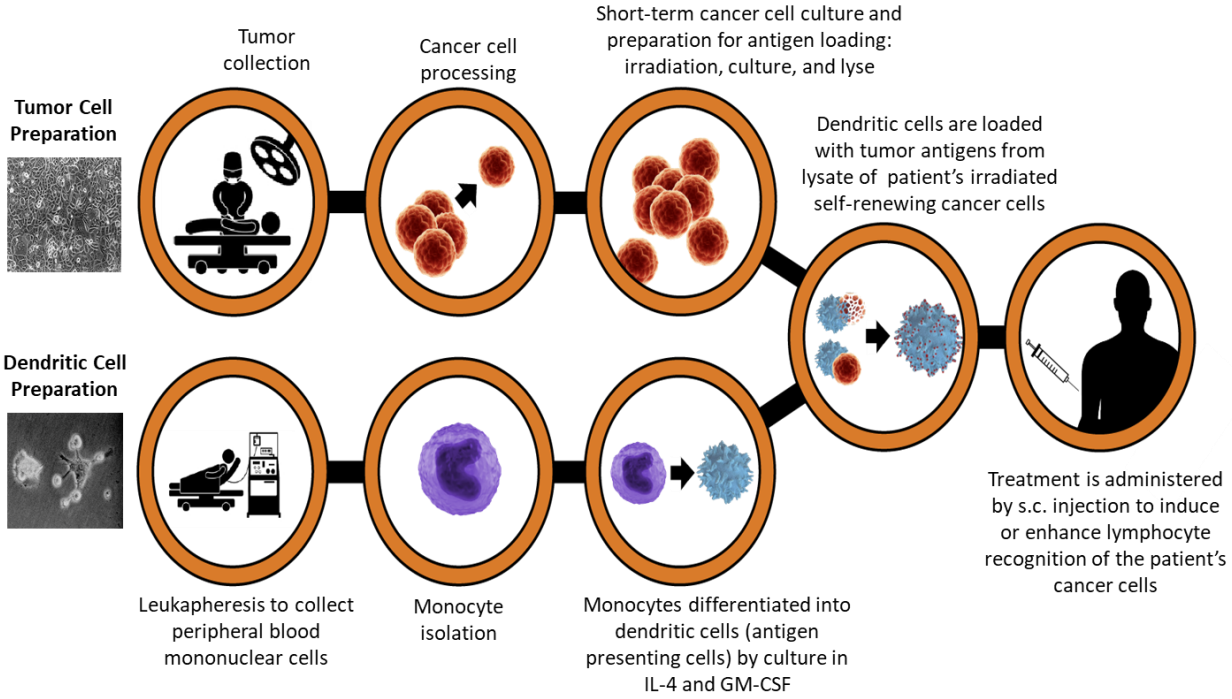
# Product and Rationale: DC-ATA

- Patient-Specific Autologous Dendritic Cells (DC) loaded with Autologous Tumor Antigens (ATA)
- ATA from lysate of irradiated autologous tumor cells that were self-renewing in a short-term cell culture (GSC)
- DC from peripheral blood mononuclear cells

# DC-ATA Manufacturing Process




4 weeks for TC, 1 week for DC-ATA, 3 weeks for QC/QA

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# DC-ATA Study Design

- ❑ Single arm, open label phase 2 trial (NCT03400917)
- ❑ N=55 evaluable patients
- ❑ Eligibility for tumor collection
  - Age $\leq$ 70 yrs
  - Imaging diagnosis of Glioblastoma
  - Amenable for tumor resection

# DC-ATA Intent to Treat

- GBM pathology confirmed
- Cell culture established
- Sufficient monocytes from leukapheresis
- Karnofsky Performance Status $\geq$ 70
- Tapering corticosteroids
- Plan to proceed with concurrent RT and temozolomide

# DC-ATA Treatment Scheme

- DCV s.c. weekly x 3, starting after recovery from chemoradiation
- Adjuvant TMZ or other standard therapy while giving monthly DCV injections (weeks 8, 12, 16, 20, and 24)
- Treatment continued through radiologic progression

# DC-ATA Outcomes

- Primary: Overall Survival: 50% decrease in death 15 months from enrollment
- Secondary: Progression-free survival 7 months from enrollment

# Study Progress to Date

- Manufacturing success rates:
  - 46/48 for tumor cell lines
  - 41/42 for leukapheresis products
    - 9 had to repeat the procedure
- Therapeutic phase
  - 37 eligible enrollees
  - 31 started treatment
  - 12 completed 8 doses
  - 5 stopped before 8 doses
  - 184 doses administered

Data available as of 16-OCT-2019

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# Patient Characteristics (n=33)

| | |
|---|---|
| Median Age | 58 (29 – 69) |
| Gender | |
| Male | 25 (76%) |
| Female | 8 (24%) |
| Race | |
| Hispanic | 7 (21%) |
| White | 26 (79%) |

| | |
|---|---|
| Median KPS | 80 (70 – 100) |
| IDH1 mutations | |
| Yes | 1 (3%) |
| No | 27 (82%) |
| Unknown | 5 (15%) |
| MGMT Methylated | |
| Yes | 9 (27%) |
| No: WT | 18 (55%) |
| Unknown | 6 (18%) |

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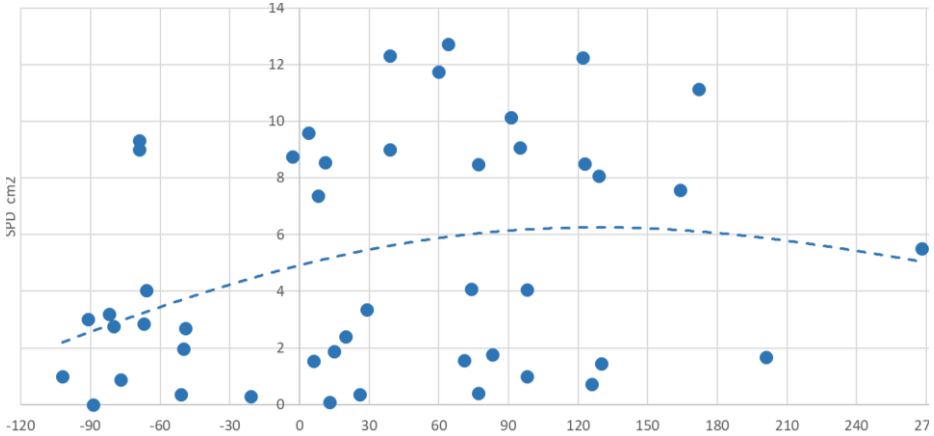
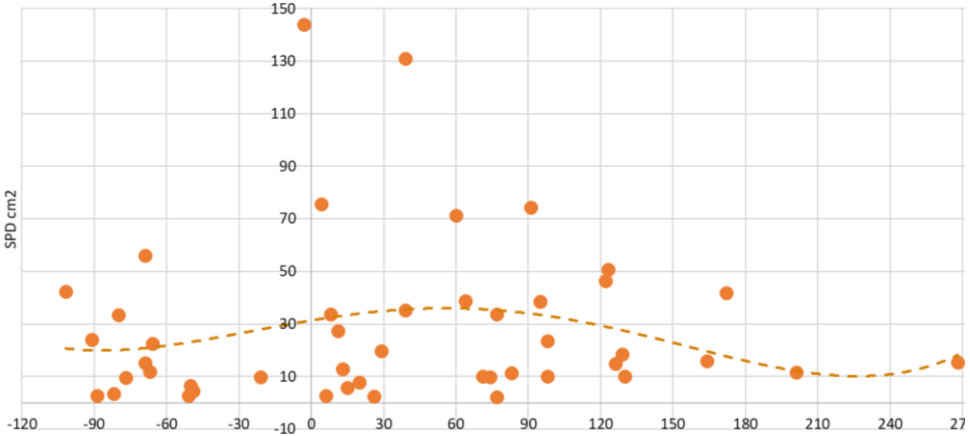
# Radiographic Responses ($cm^2$) versus Time (days)




T1 contrast enhancement




T2/FLAIR

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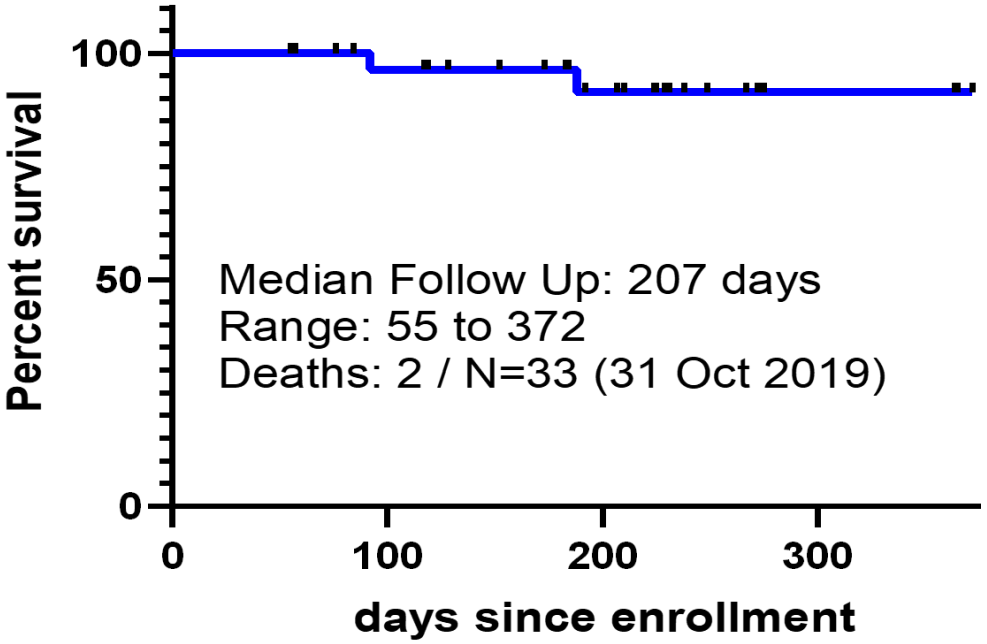
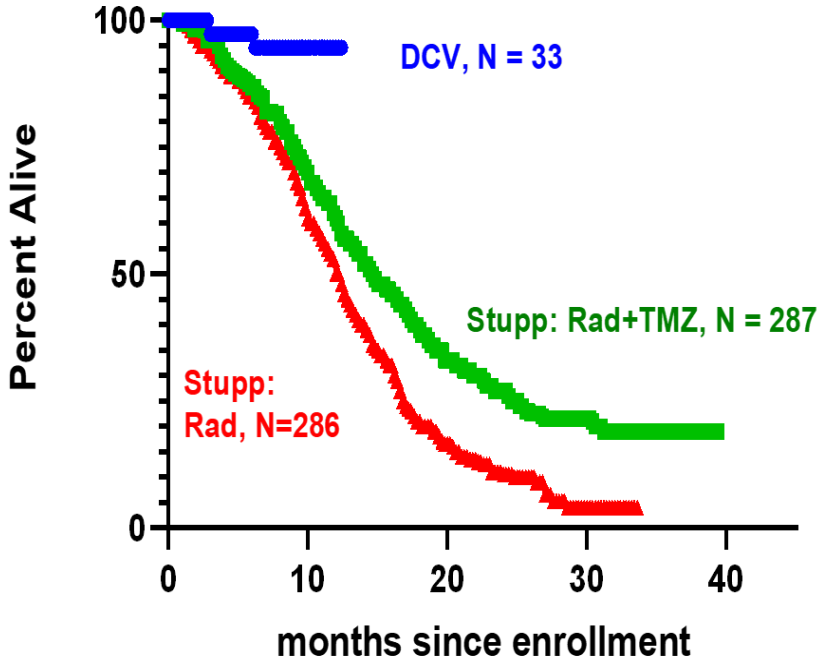
# Overall Survival to Date (n=33)

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# Serious Adverse Events

- 16/29 (55%) with 27 SAE
- All SAE involved hospitalization
- No SAE attributed to study treatment
- No SAE immediately following vaccination

| Between Doses | Number of SAE | Brief Description |
|---|---|---|
| 1 & 2 | 1 | chest pain, fever |
| 2 & 3 | 5 | seizure, fall, focal weakness, H/A |
| 3 & 4 | 5 | seizure, focal weakness, fall |
| 4 & 5 | 2 | fall, aphasia, general deterioration |
| 5 & 6 | 4 | seizure, visual change, focal weakness, pancreatitis |
| 6 & 7 | 4 | seizure, fall, focal weakness, aspiration pneumonia, cognitive decline, weakness left side |
| 7 & 8* | 4 | seizure, fall, abdominal pain, pancreatitis, pulmonary emboli |
| Beyond | 2 | hyponatremia, pancreatitis |

Data available as of 16-OCT-2019

# Immune Monitoring Methods

- 450 plasma biomarkers studied in 16 patients

  Assayed by RayBiotech, Inc (Waycross, GA)

- Specimen Collection: before vaccine dose at week 1,2, 3 and 8

- Looking at early response week 3 vs week 1 (after 2 doses) and late changes week 8 vs week 1 (after 3 doses)

# Pro-response inflammatory marker patterns are present in 60.7% of patients

| Marker | Responders (N) |
|---|---|
| IL12p40 | 10 |
| IL1b | 10 |
| IFNg | 9 |
| Granulysin | 9 |
| Eotaxin | 10 |
| Eotaxin-2 | 11 |
| Eotaxin-3 | 6 |
| IgE | 13 |
| IgG1 | 9 |
| IL10 | 9 |
| IL17B | 9 |
| IL17F | 10 |
| IL2 | 9 |
| IL5 | 11 |
| IL7 | 11 |
| TNFa | 9 |
| TNFb | 10 |

The response pattern include:

- Type II hypersensitivity – consistent in majority of the patients with significant increase of IgE, Eotaxins, IL5, IL17B, IL17F
- In some patients the Th1 response is blunted by corticosteroids reflected by lower values of IFNg/TNFa/Granulysis/IL1b
- Th2 response is consistent and include the increase of at least IgG1, IgE, IL12p40, IL10

# Conclusions

- The manufacturing process for DC-ATA has a low failure rate
- The DC-ATA treatment has good safety, with no treatment related SAE to date
- Preliminary OS data are reassuring
- Immune monitoring is in progress,  and it suggests that DC-ATA can induce inflammatory changes