Preclinical Mechanistic and Clinical Evaluation of the Corticosteroid Dexamethasone's Detrimental Effects on Immune Checkpoint Blockade in Glioblastoma Cancer

Bryan Iorgulescu, MD FCAP
Dana-Farber Cancer Institute
Brigham and Women's Hospital
Harvard Medical School

Disclosures

No conflicts of interest to disclose.

Background

- There is growing evidence that corticosteroids can exert detrimental effects on immunotherapy for cancer patients.
- Dexamethasone, a potent corticosteroid, is often administered to primary & metastatic brain tumor patients to reduce tumor- & treatment-associated edema.
- However, there are limited data on how dexamethasone (Dex) affects systemic & intratumoral immune activity in the setting of immunotherapy.

Arbour et al. *JCO*. 2018
Ricciuti et al. *JCO*. 2019

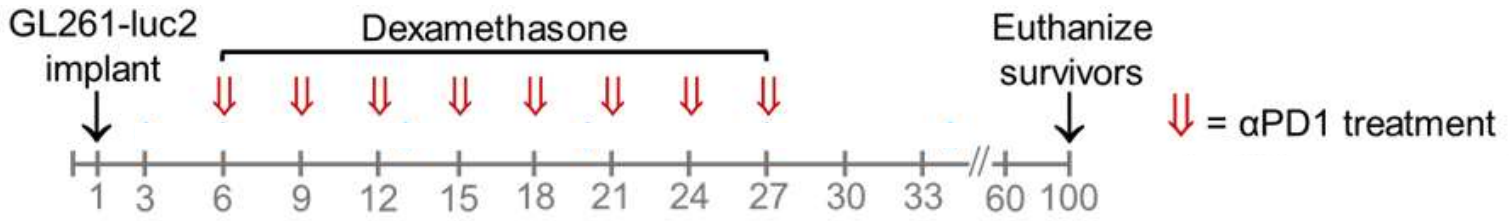
Background

- We were particularly interested in addressing this question in the context of PD-(L)1 inhibitors for glioblastoma (GBM)
  - given recent data from CheckMate-143 (a negative phase 3 study of nivolumab for recurrent GBM) suggesting that some patients who were not on dexamethasone may have benefited.

- So we investigated this question using 1) preclinical mouse GBM models & 2) our cohort of 181 GBM patients treated with PD-(L)1 inhibitors.

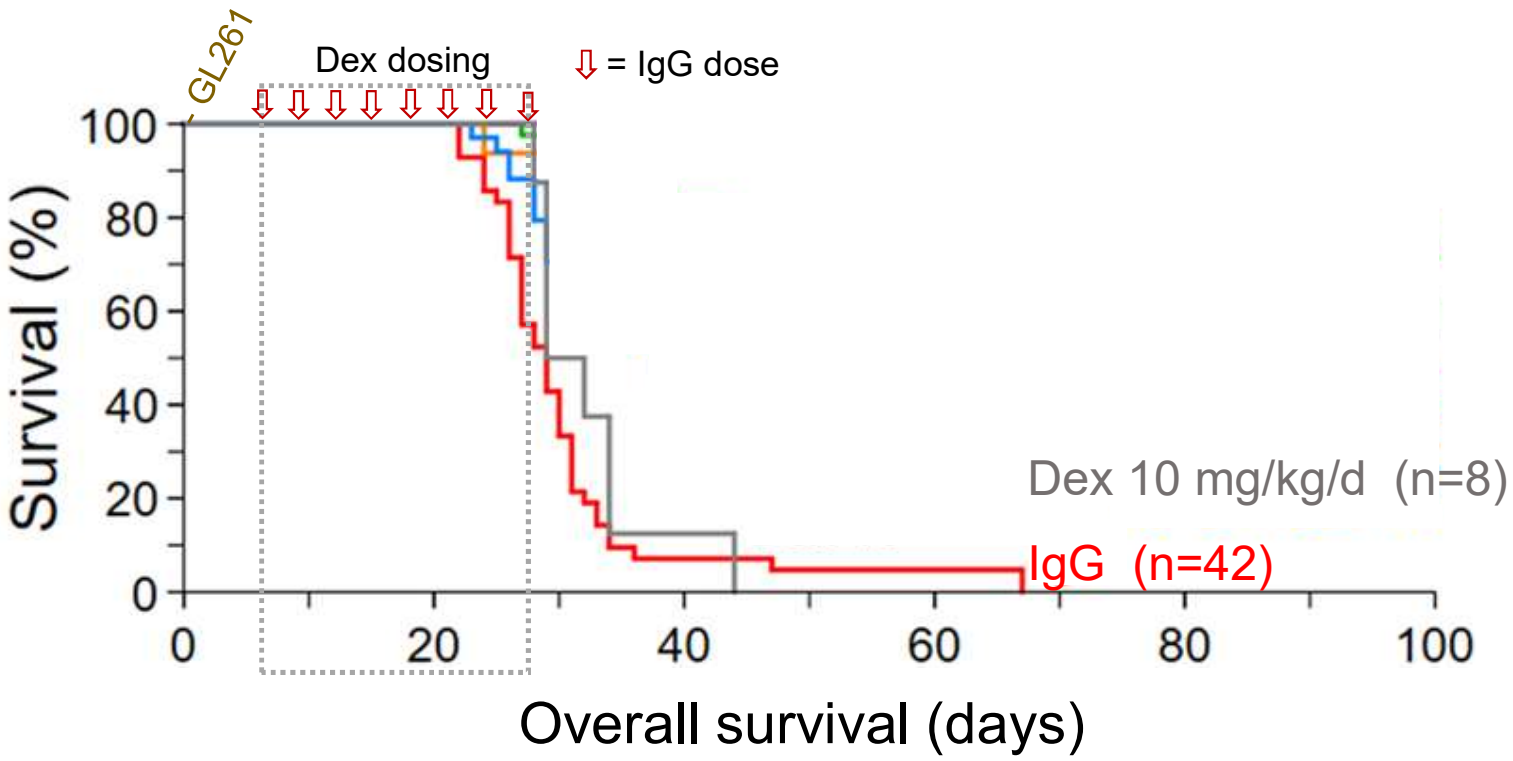
Reardon et al. *JAMA Oncol*. 2020

Preclinical Treatment Schema

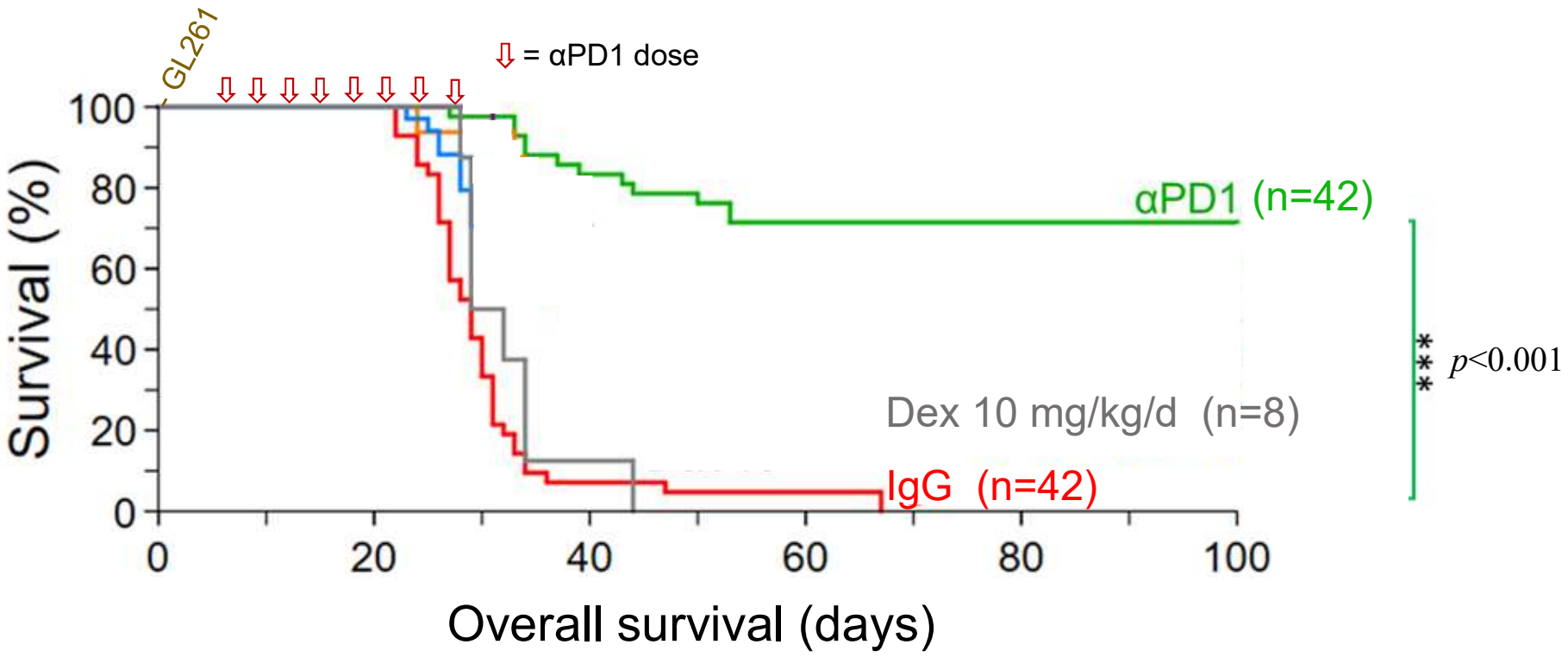


- Immuno-sensitive murine syngeneic GBM model (GL261)
- Dexamethasone dosed daily
- PD-1 antibody (8H3): loading dose (500µg) followed by 7x 250µg doses

Dexamethasone alone had no effect on survival

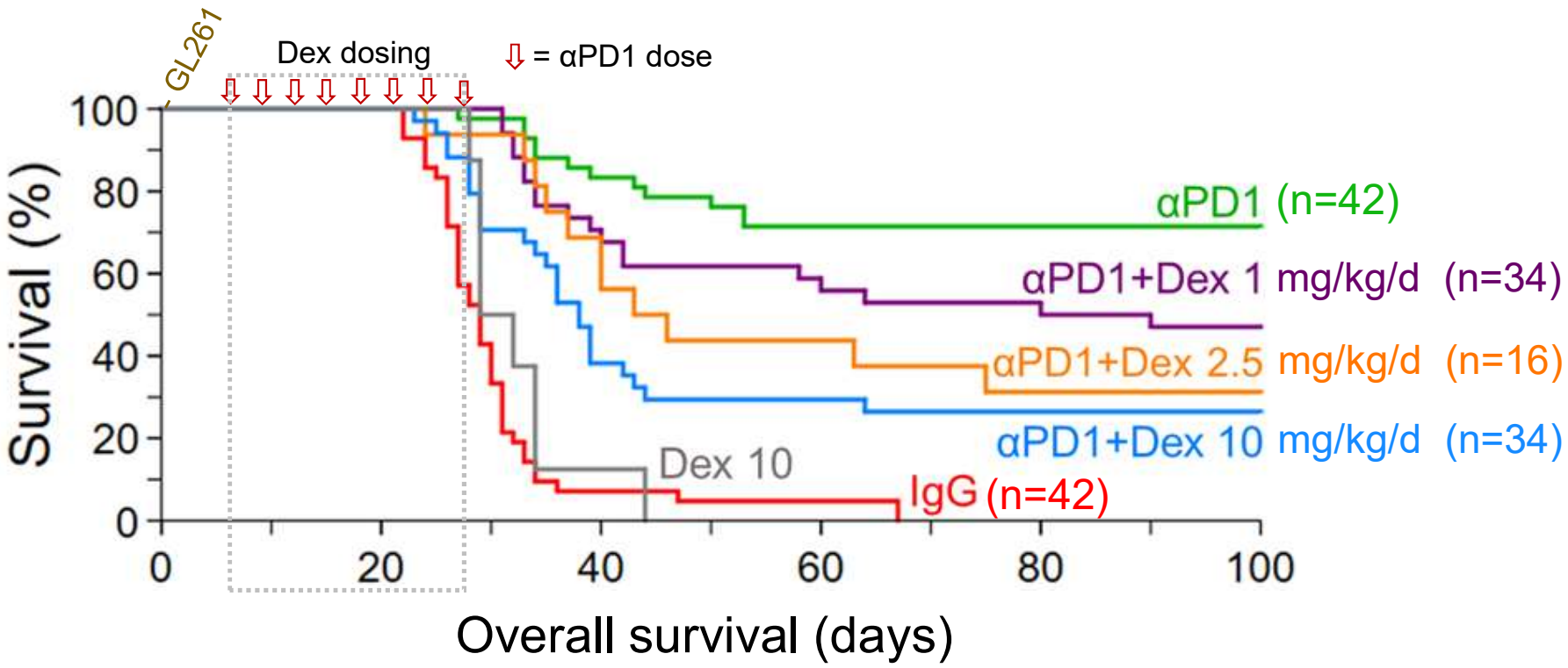


PD1 blockade cured a majority of GL261 mice

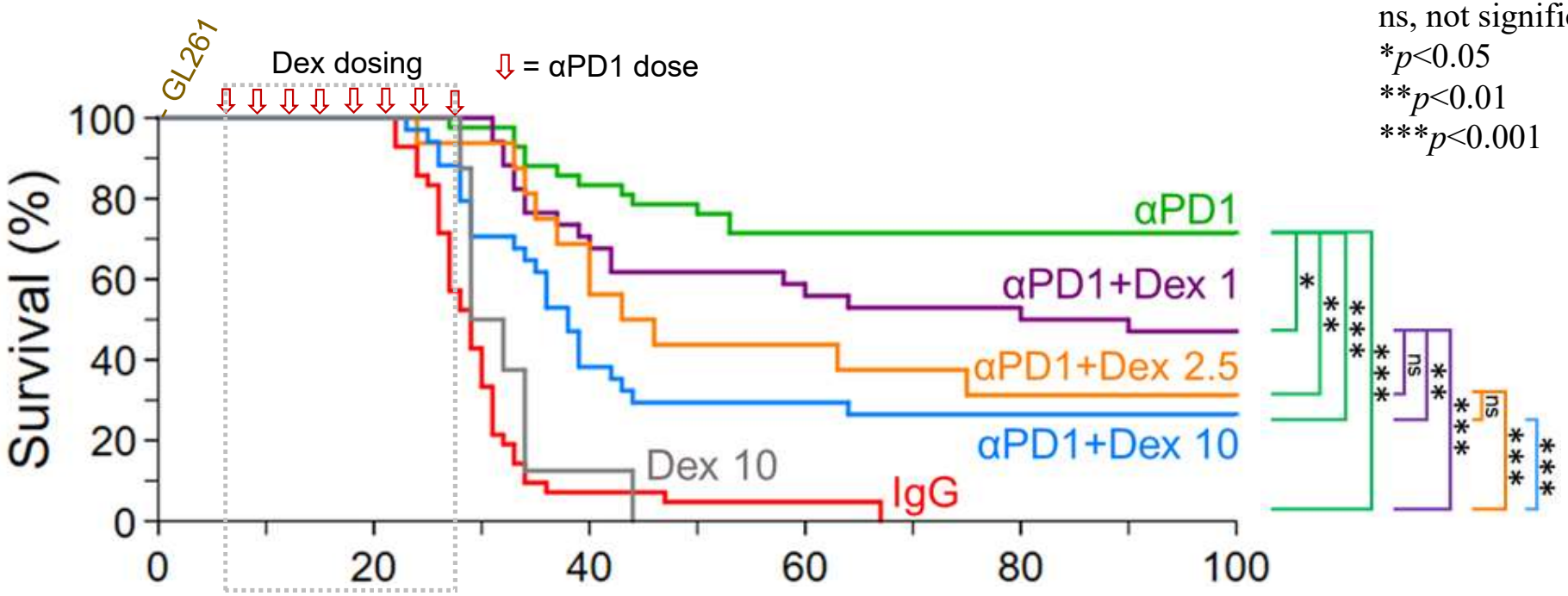


Reardon et al. *CIR*. 2016

Concurrent Dex reduced OS in a dose-dependent manner

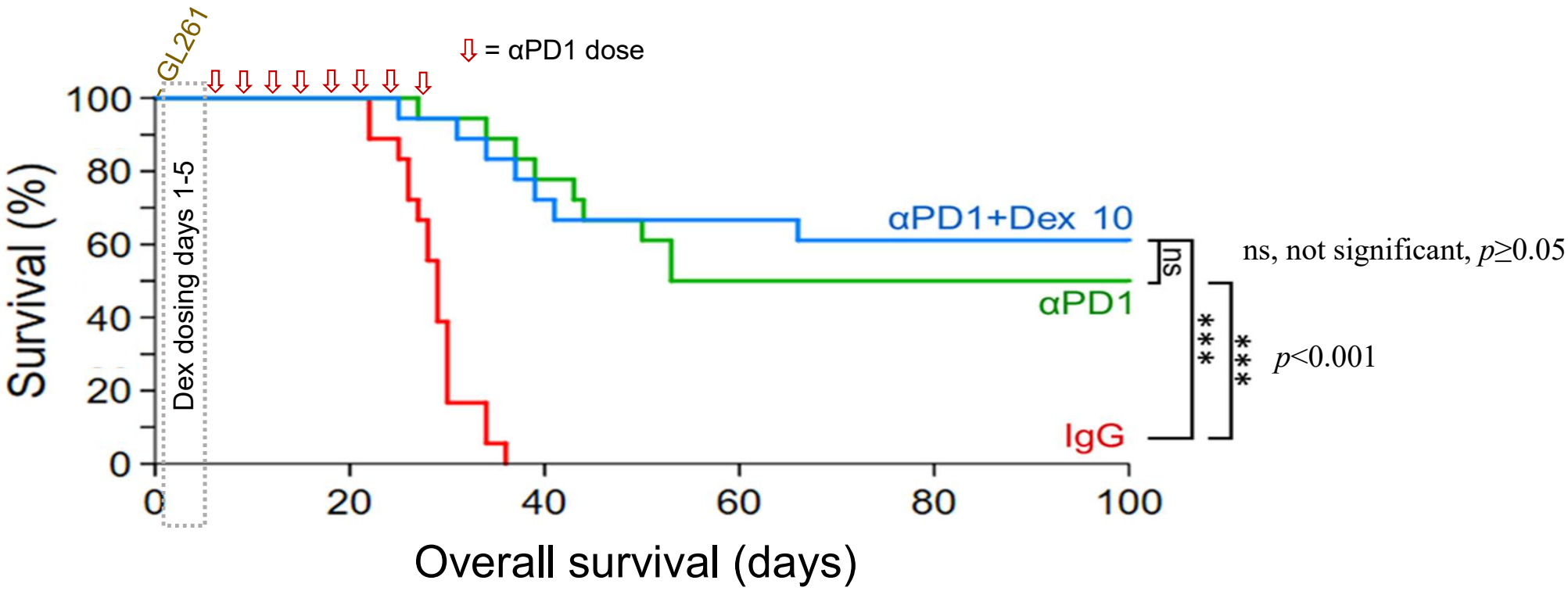


Concurrent Dex reduced OS in a dose-dependent manner



ns, not significant, $p \geq 0.05$
*$p<0.05$
**$p<0.01$
***$p<0.001$

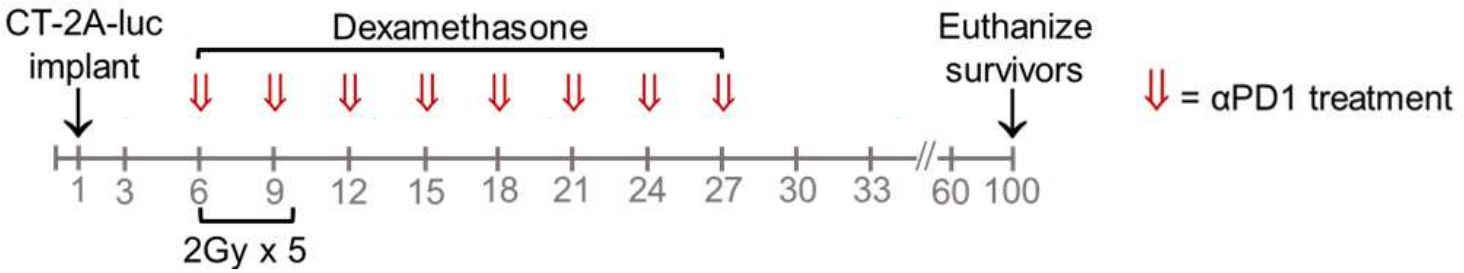
Dex had no effect on survival when given before αPD1



ns, not significant, $p \geq 0.05$

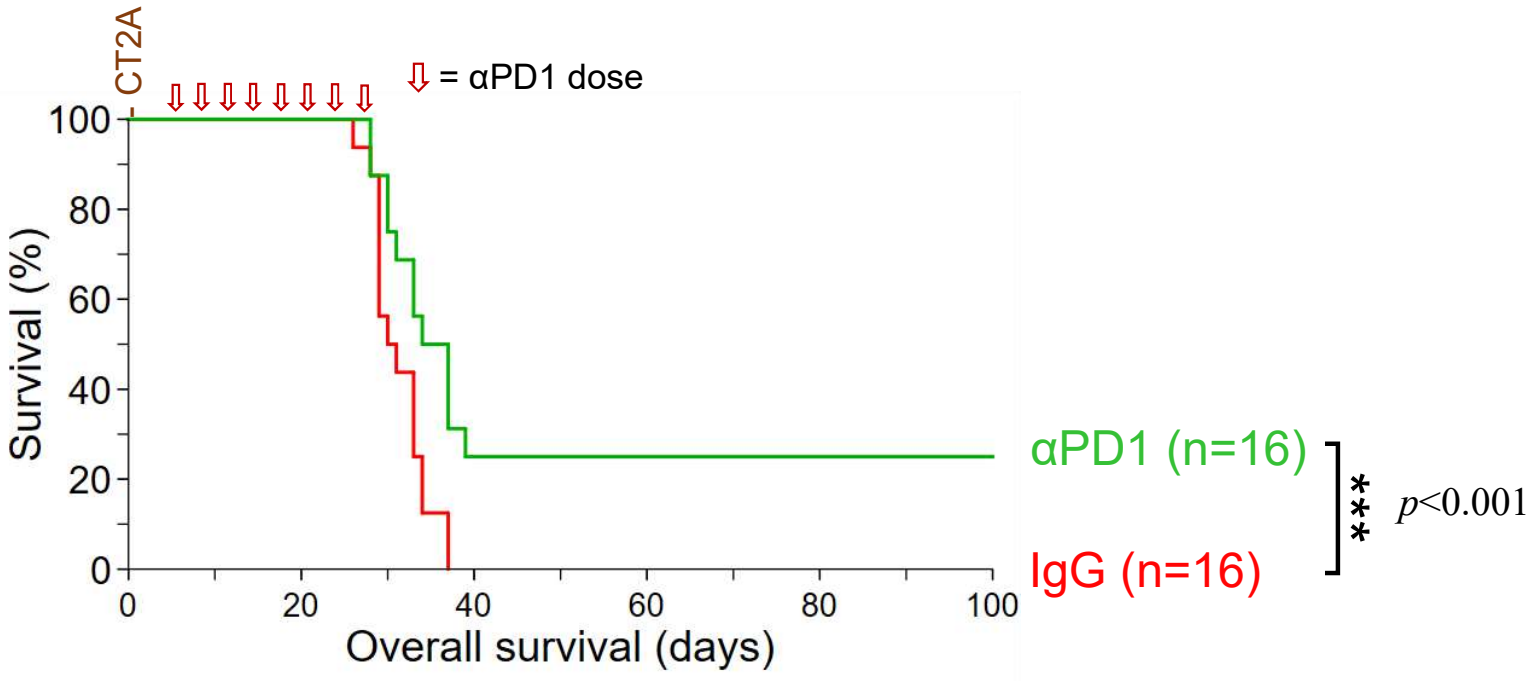
$p < 0.001$

How about in a more clinically-relevant context?

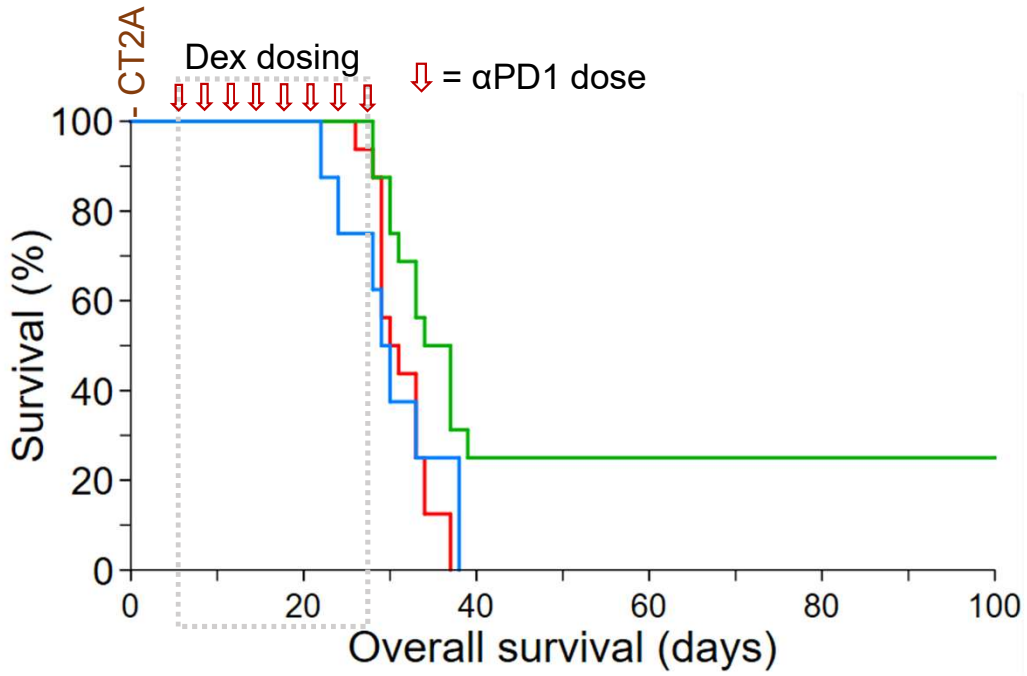


- Immuno-**resistant** murine syngeneic GBM model (**CT2A**)
- Dexamethasone dosed daily
- PD-1 antibody (8H3): loading dose (500µg) followed by 7x 250µg doses
- **Radiotherapy (2 Gy x 5)** - standard-of-care treatment in GBM patients

αPD1 modestly improved survival in CT2A mice



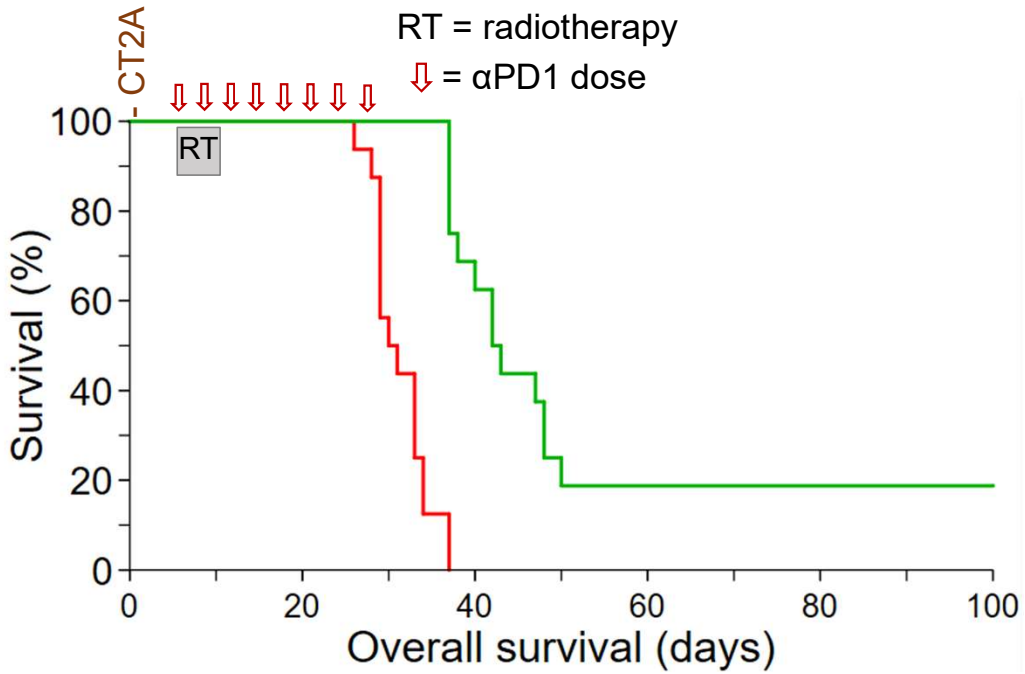
Concurrent Dex abrogated αPD1's survival benefit



αPD1 (n=16)
αPD1+ Dex10 (n=8)
IgG (n=16)

** $p<0.01$
ns

αPD1+RT modestly improved survival in CT2A mice

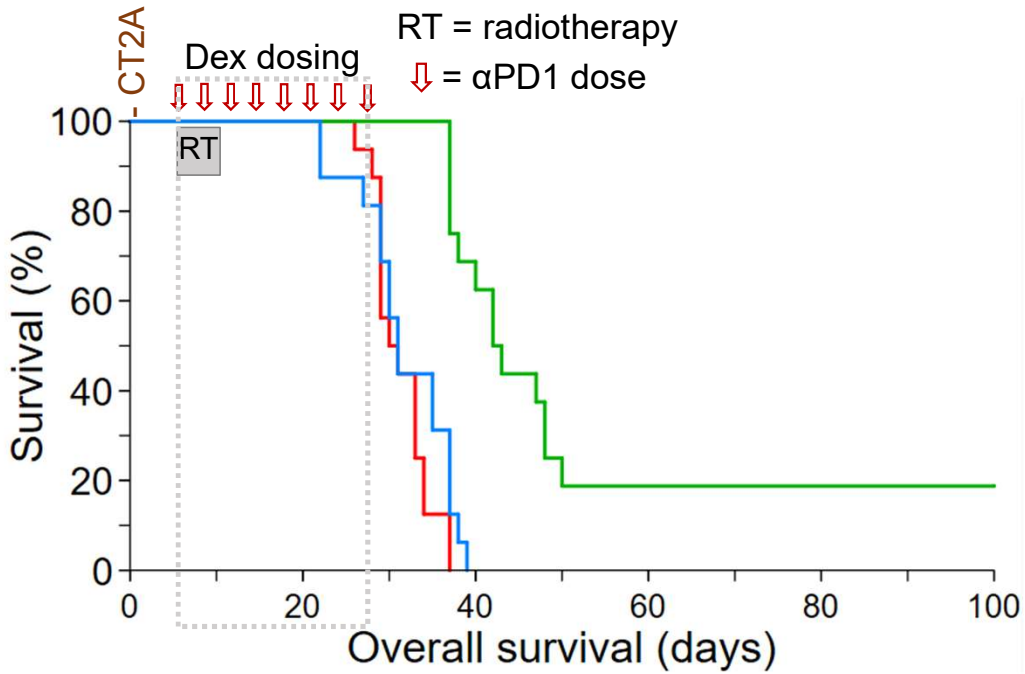


αPD1+RT (n=16)

IgG (n=16)

*** $p<0.001$

Concurrent Dex abrogated αPD1+RT's survival benefit



αPD1+RT (n=16)

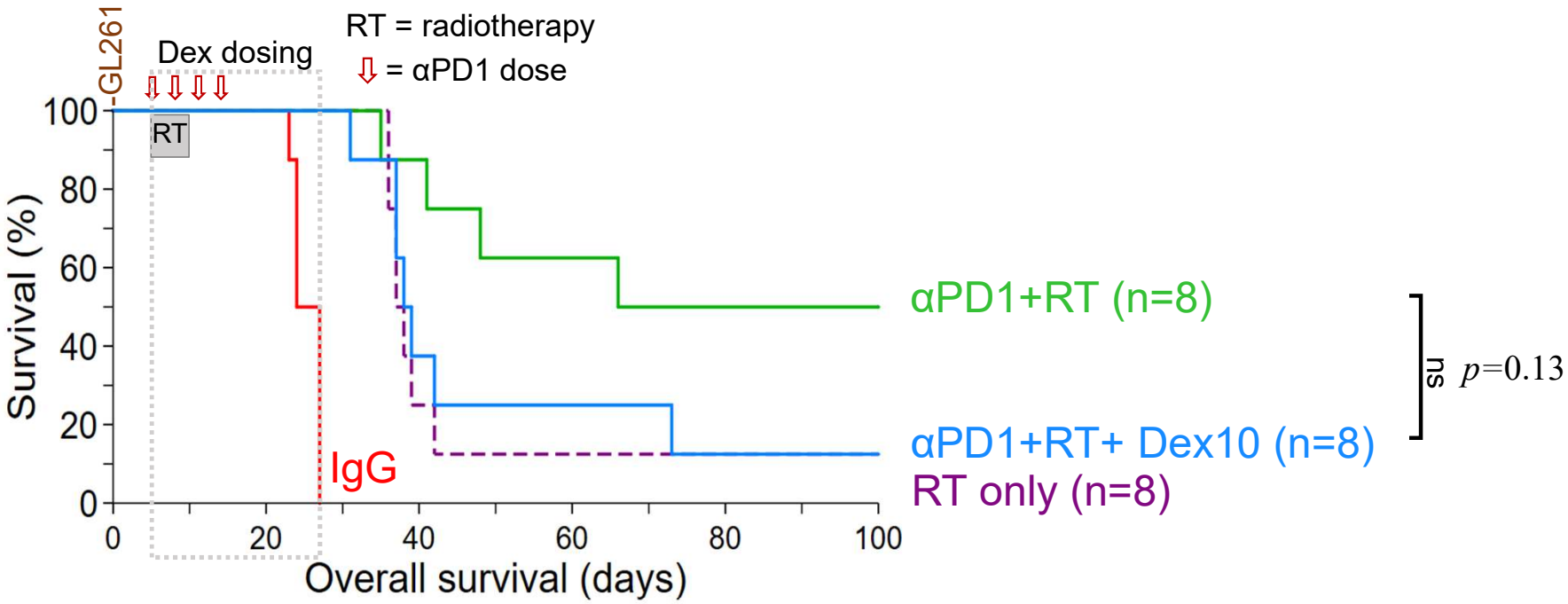
αPD1+RT+ Dex10 (n=16)

IgG (n=16)

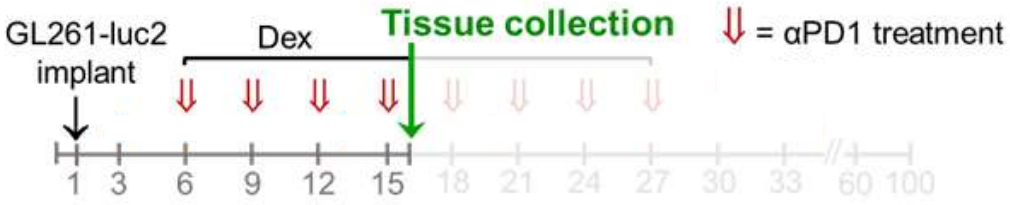
*** $p<0.001$

ns

Concurrent Dex abrogated αPD1+RT's survival benefit



Does concurrent Dex affect intratumoral & systemic immune cells?

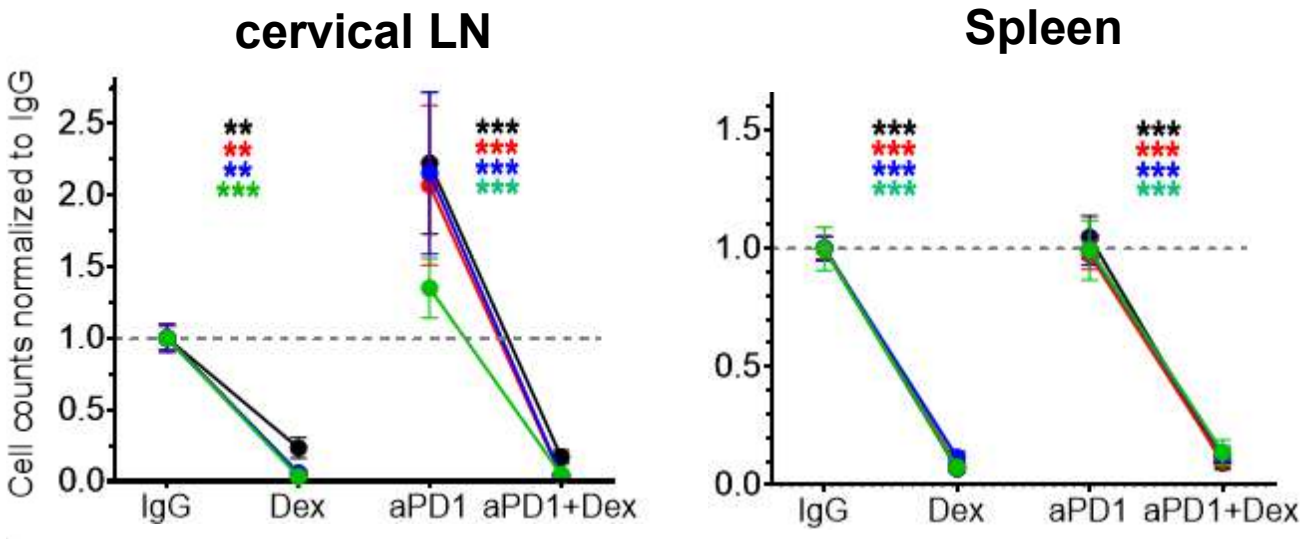


- GL261 GBM mouse models
- Tissues collected halfway though the αPD1 and Dexamethasone regimen
- Analyzed with multi-parameter flow cytometry

Dexamethasone decreased systemic lymphocytes

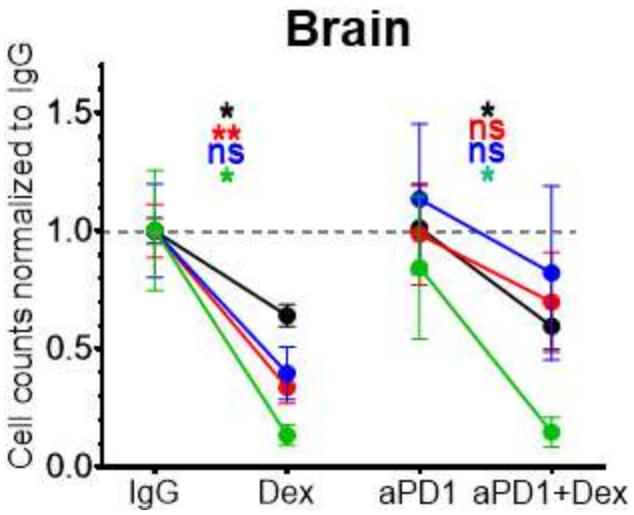
- CD45+
- CD3+
- CD8+
- CD4+

ns, not significant, $p \geq 0.05$
*$p<0.05$
**$p<0.01$
***$p<0.001$



Dex decreased intratumoral CD4+ lymphocytes

- CD45+
- CD3+
- CD8+
- CD4+



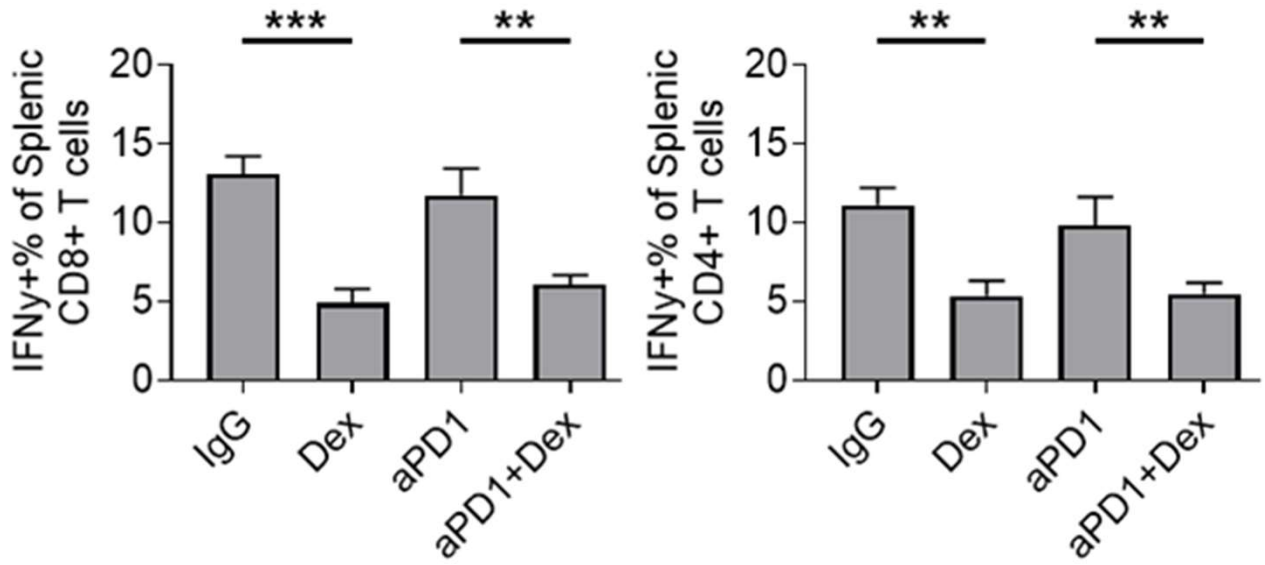
Dexamethasone decreased systemic lymphocytes

› Oncoimmunology. 2019 Jul 13;8(11):e1641390. doi: 10.1080/2162402X.2019.1641390. eCollection 2019.

Dexamethasone differentially depletes tumour and peripheral blood lymphocytes and can impact the efficacy of chemotherapy/checkpoint blockade combination treatment

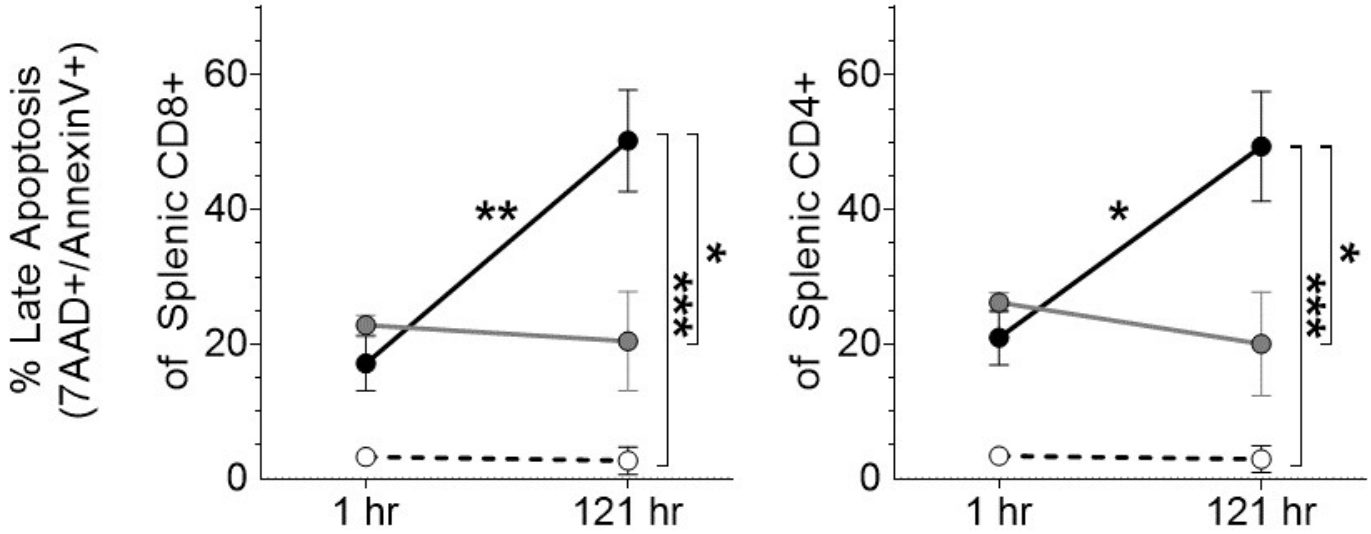
Wayne J Aston [1 2], Danika E Hope [1 3], Alistair M Cook [1 2], Louis Boon [4], Ian Dick [1 3], Anna K Nowak [1 2 5], Richard A Lake [1 3], W Joost Lesterhuis [1 3]

Dex reduced T cells' IFNγ production capability



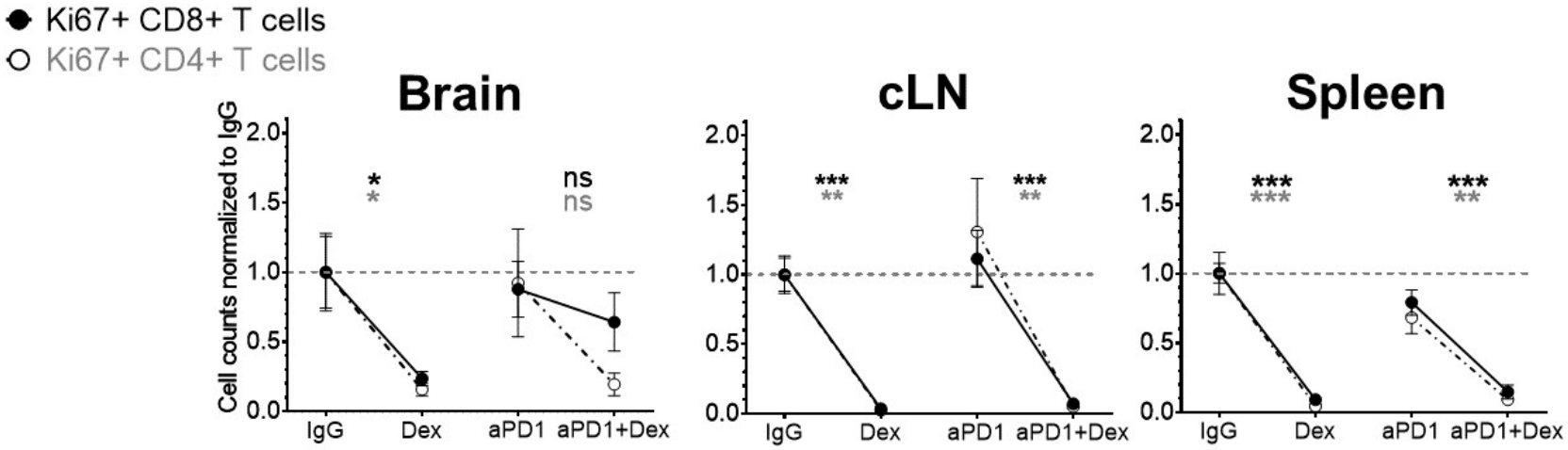
Dex induced late apoptosis of CD8 and CD4 T cells

- Saline control
- Dex 1 mg/kg/d
- Dex 10 mg/kg/d

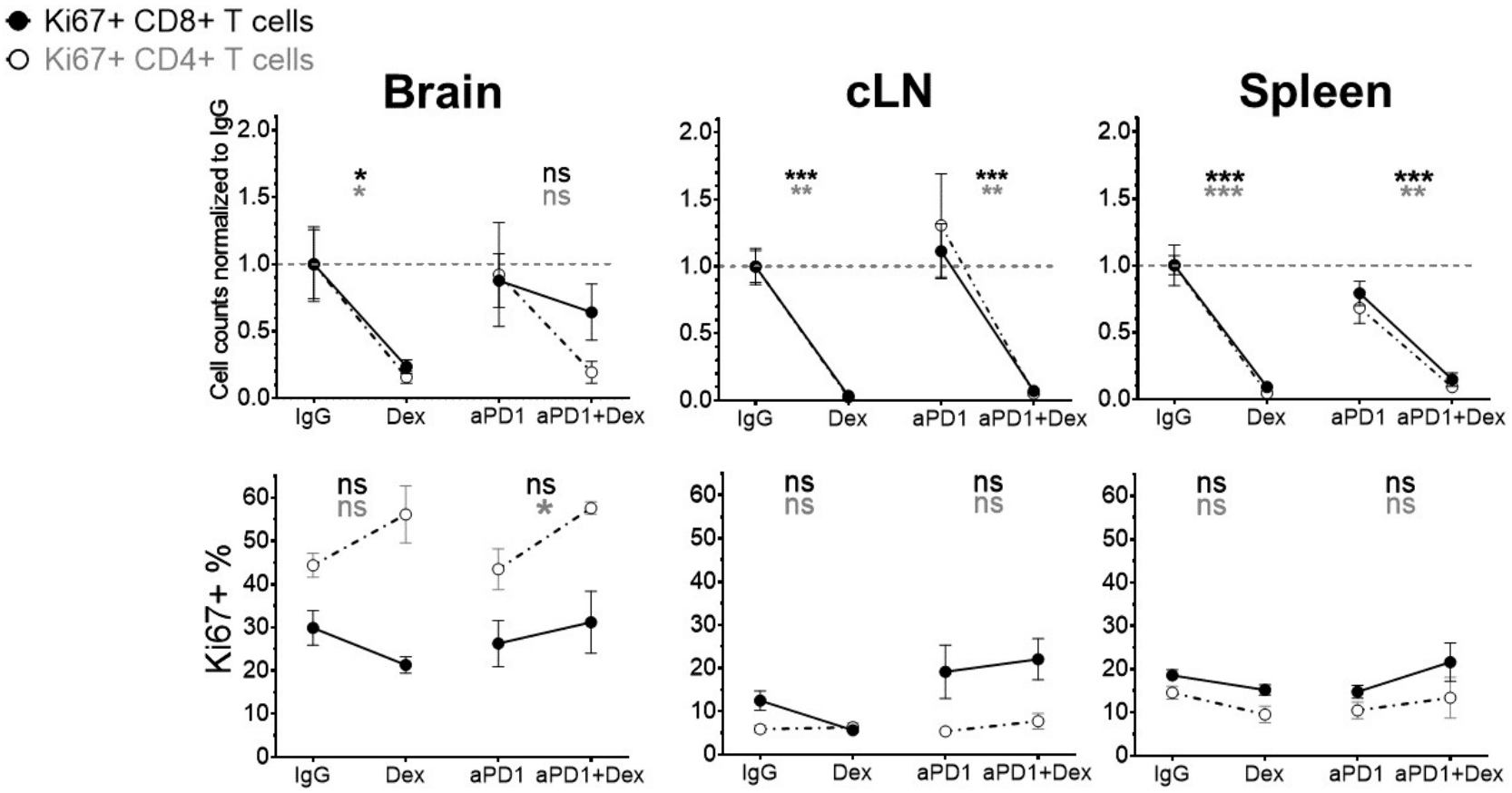


Time from start of Dex administration (daily doses)

Concurrent Dex reduced absolute numbers of proliferative T cells

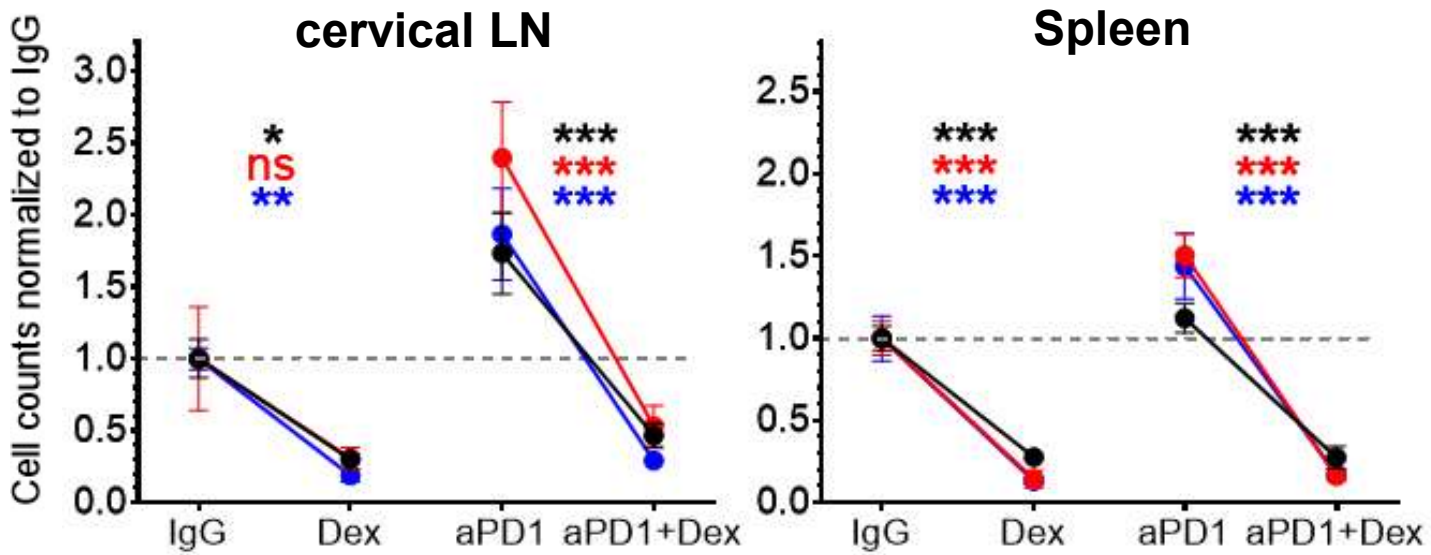


Concurrent Dex reduced absolute numbers of proliferative T cells



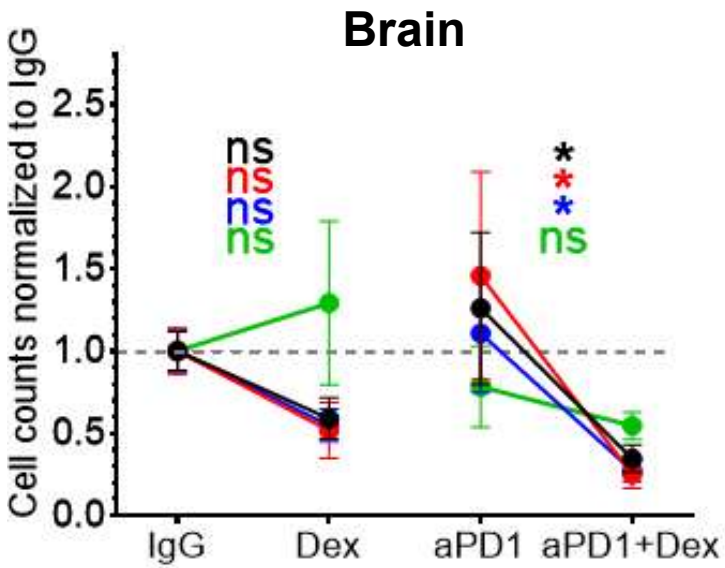
Concurrent Dex decreased systemic myeloid cells

- Myeloid cells (CD45^{hi} CD11b^{hi})
- Monocytes (Ly6C^{hi} Ly6G-)
- Macrophages (Ly6C$^{low\text{-}int}$ Ly6G-)

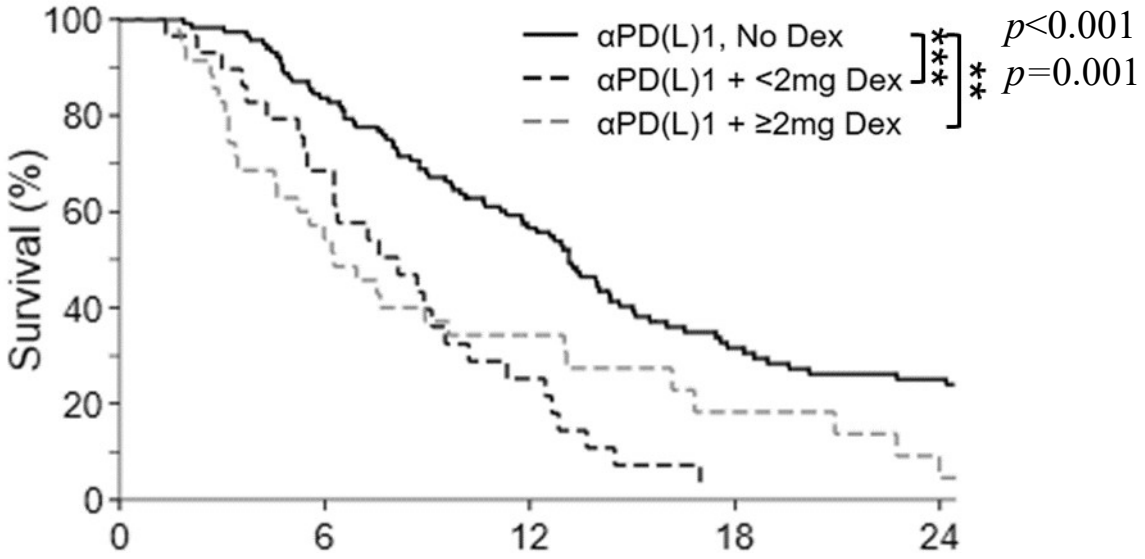


Concurrent Dex decreased intratumoral myeloid cells

- Myeloid cells (CD45^{hi} CD11b^{hi})
- Monocytes (Ly6C^{hi} Ly6G-)
- Macrophages (Ly6C$^{low\text{-}int}$ Ly6G-)
- Microglia (CD45^{lo} CD11b^{hi})



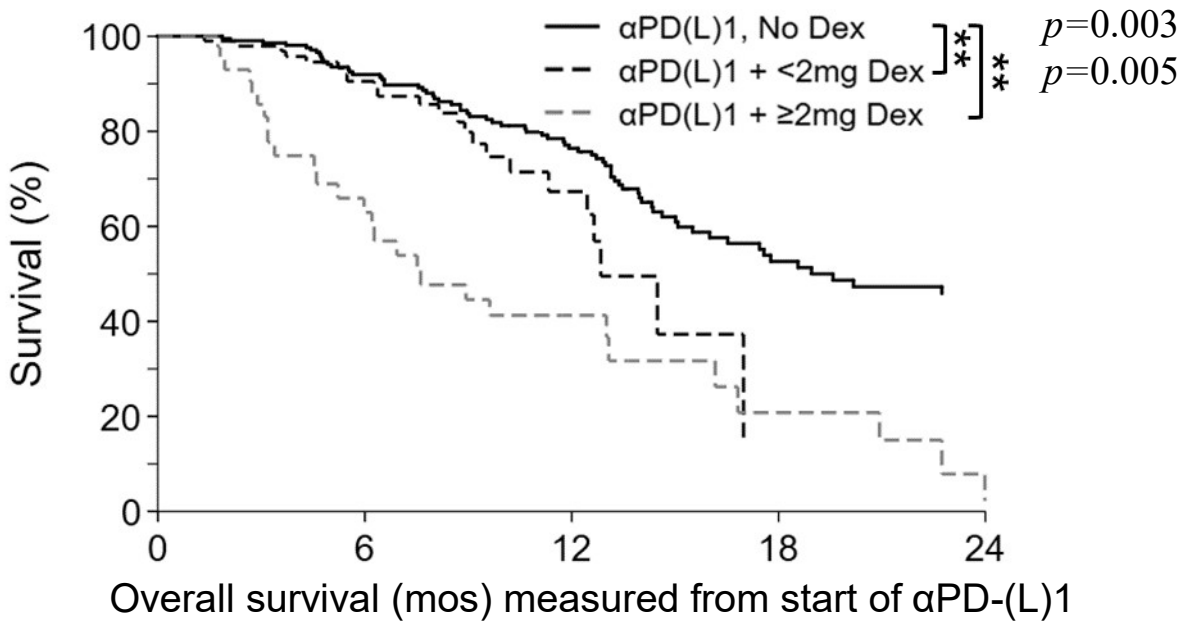
Dex reduced OS in 181 IDH-wt GBM patients treated with αPD(L)1



Overall survival (mos) measured from start of αPD-(L)1

Number at risk					
αPD(L)1, No Dex	117	97	64	29	23
αPD(L)1 + <2mg Dex	29	19	7	1	1
αPD(L)1 + ≥2mg Dex	35	19	11	4	1

Dex was the strongest independent risk factor for worse OS



Adjusted for:
Disease setting
Patient age
MGMT promoter methylation status
Patient performance status
Tumor volume
Extent of resection

Conclusions

- In both immuno-sensitive & resistant syngeneic mouse GBM models, concurrent Dex limited the survival benefit of anti-PD1 in a dose-dependent manner, suggesting that:

  1) alternatives to treat symptomatic cerebral edema should be considered (eg low-dose bevacizumab) when possible

  2) when Dex is required, the lowest possible dose of Dex should be used.

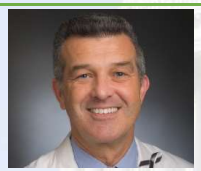
- Concurrent Dex reduced T cell counts – including intratumoral CD4 T cells – and the mechanism involved induction of apoptosis.

- Baseline Dex was independently associated with poor survival in IDH-wt GBM patients receiving PD-(L)1 inhibitors.

Conclusions

- Which together, reinforce that dexamethasone use should be minimized for brain tumor patients being considered for checkpoint inhibitors.

Thank you!



David Reardon
Clinical Director,
Center for Neuro-Oncology
Dana-Farber Cancer Institute

Prafulla Gokhale
Maria Speranza
Gordon Freeman
Arlene Sharpe
Paul Kirschmeier
Ana Anderson
E. Antonio Chiocca

Peter Sorger
Keith Ligon
MJ Lim-Fat
Benjamin Eschle
Michael Poitras
Margaret Wilkens
Kara Soroko
Chhayheng Chhoeu
Aine Knott
Yan Gao
Gregory Baker
Dennis Bonal
Quang-Dé Nguyen
Gareth Grant

Funding

- SITC 2020 Travel Award
- NIH NCI (K12, P01)
- Conquer Cancer Foundation/ASCO
- The Jennifer Oppenheimer Cancer Research Initiative
- The Ben & Catherine Ivy Foundation
- Hope It's A Beach Thing
- Pan Mass Challenge (Erica's Entourage and CRUS11TOUR)