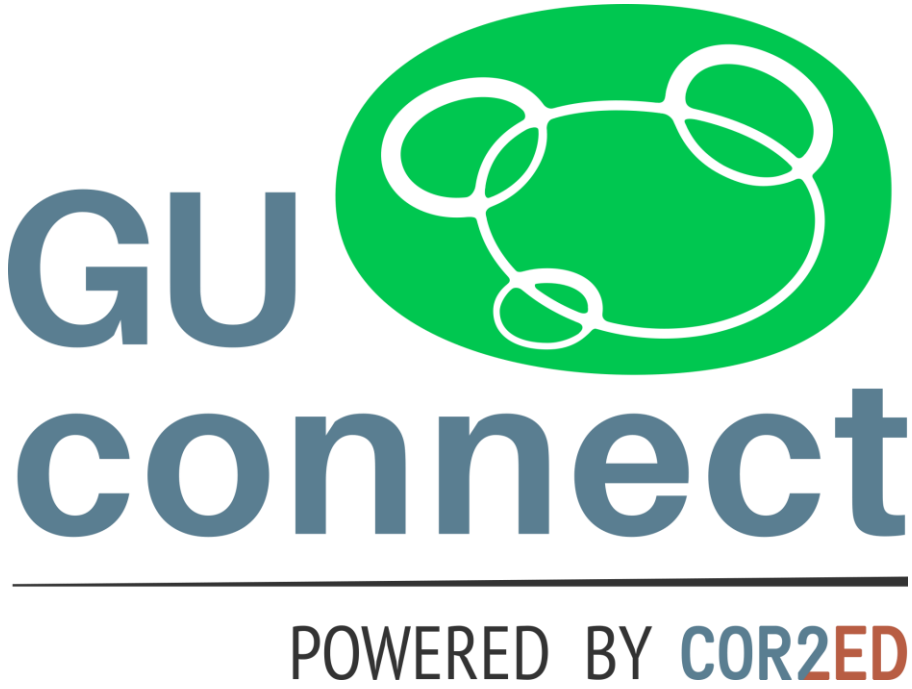
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HOW TO USE COMBINATION, SEQUENTIAL AND IMMUNO-ONCOLOGY THERAPIES IN mCRPC (METASTATIC CASTRATION-RESISTANT PROSTATE CANCER)?

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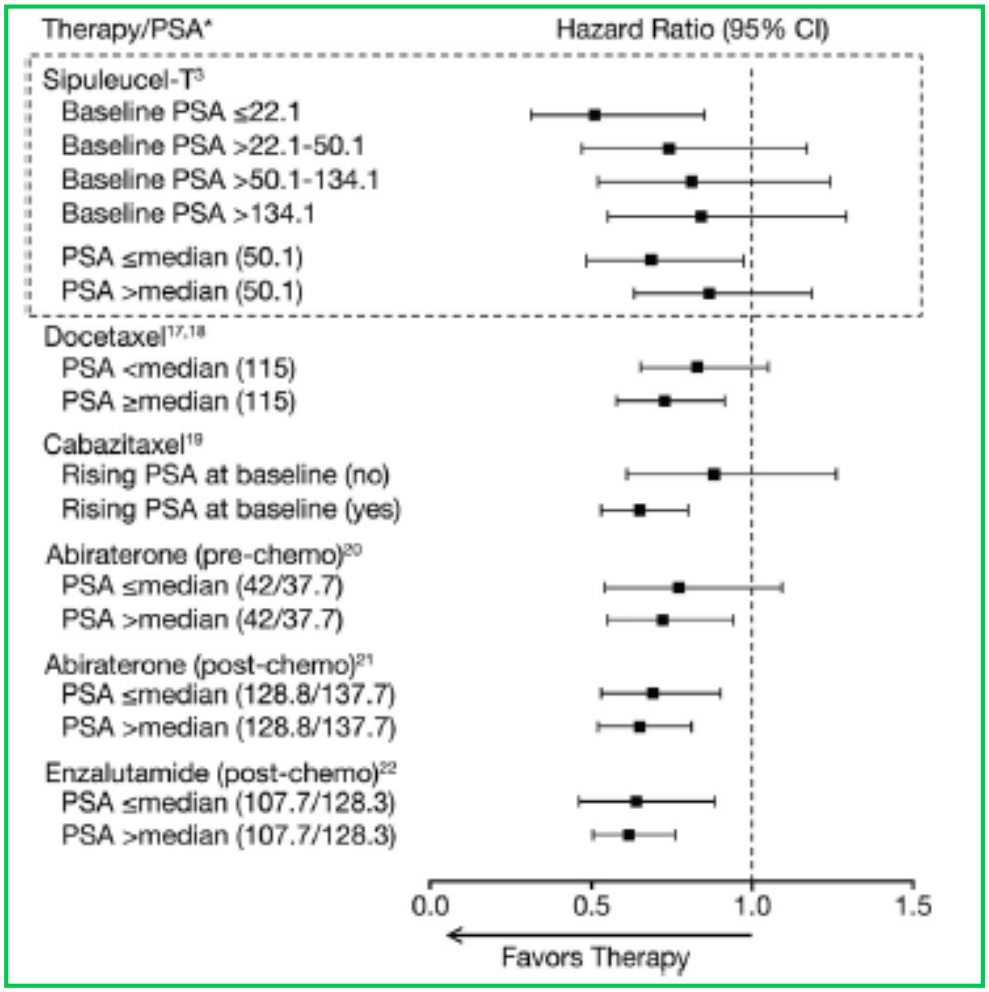
IMMUNOTHERAPY HAS ESTABLISHED VALUE IN mCRPC

- Summary of overall survival in metastatic castration-resistant prostate cancer (mCRPC) trials by baseline prostate-specific antigen (PSA).



CI, confidence interval. *PSA values are ng/mL.

Schellhammer PF, et al. Urology 2013; 81: 1297

PD-L1 IMMUNOHISTOCHEMISTRY IN PROSTATE CANCER

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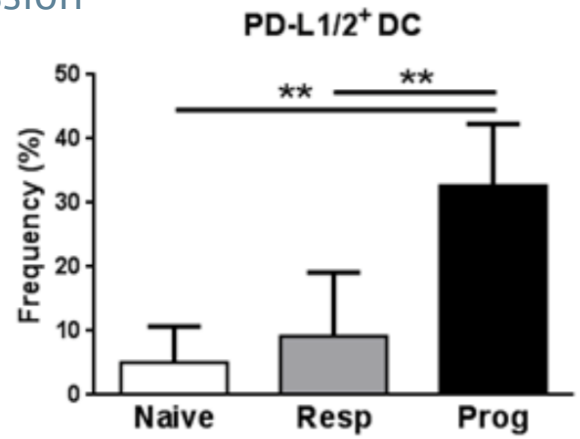
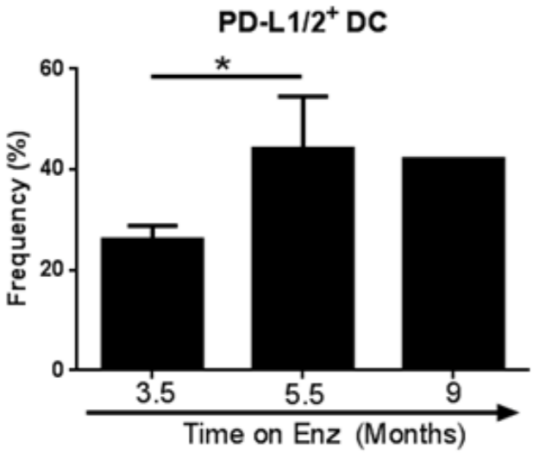
- Traditionally, PD-L1 staining by IHC in prostate cancer is rare
  - 3/20 (15%) primary prostate samples had focal PD-L1 positivity (>5%) and only 2 had plasma membrane staining on cancer cells[1]
- In aggressive localized prostate cancers, 52.2% of training cohort (n=209) cases and 61.7% of test cohort (n=611) cases expressed moderate to high (IHC2-3) PD-L1 levels[2]
  - Correlation with Ki-67, Gleason and AR expression
- PD-L1 expression upregulated by enzalutamide[3] with exposure and especially at progression

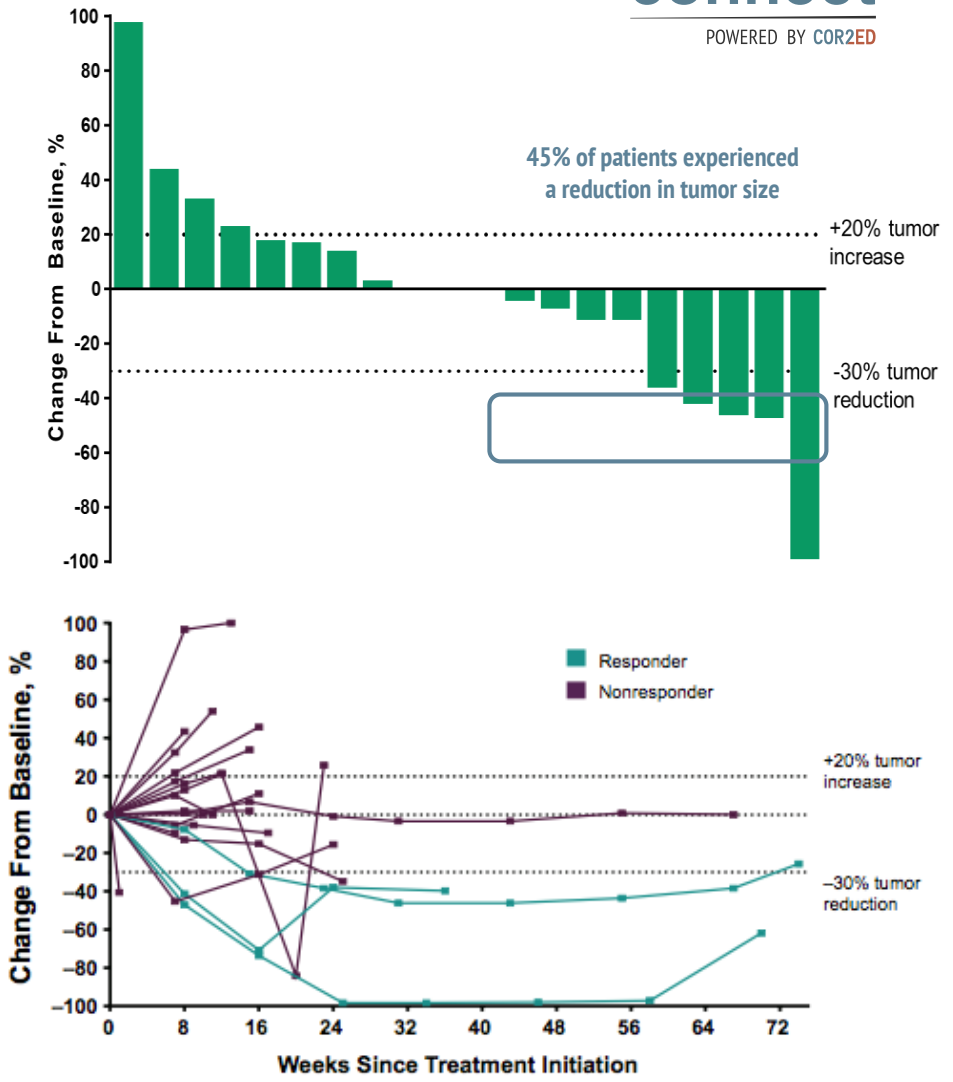




1. Martin AM, et al. Prostate Ca Prost Dis 2015; 18: 325–32; 2. Gevensleben H, et al. Clin Cancer Res 2015; Epub.
3. Bishop JL, et al. Oncotarget 2015; 6: 234–42

PEMBROLIZUMAB FOR PD-L1+ PROSTATE CANCER

- KEYNOTE-028 was a basket trial with a mCRPC cohort with RECIST 1.1 measurable disease and PD-L1+ (14.3% of screened patients)
- N=23 patients received pembrolizumab 10 mg/kg IV q2wk
- 5 patients (22%) experienced 6 immune-mediated AEs (thyroid, swelling, pneumonitis) but no discontinuations
- Primary endpoint ORR: 3 (13%) PR, 9 (39%) SD, 8 (35%) PD as best response



MUTATIONAL COMPLEXITY PREDICTS RESPONSE TO IMMUNE THERAPY IN SOLID TUMORS

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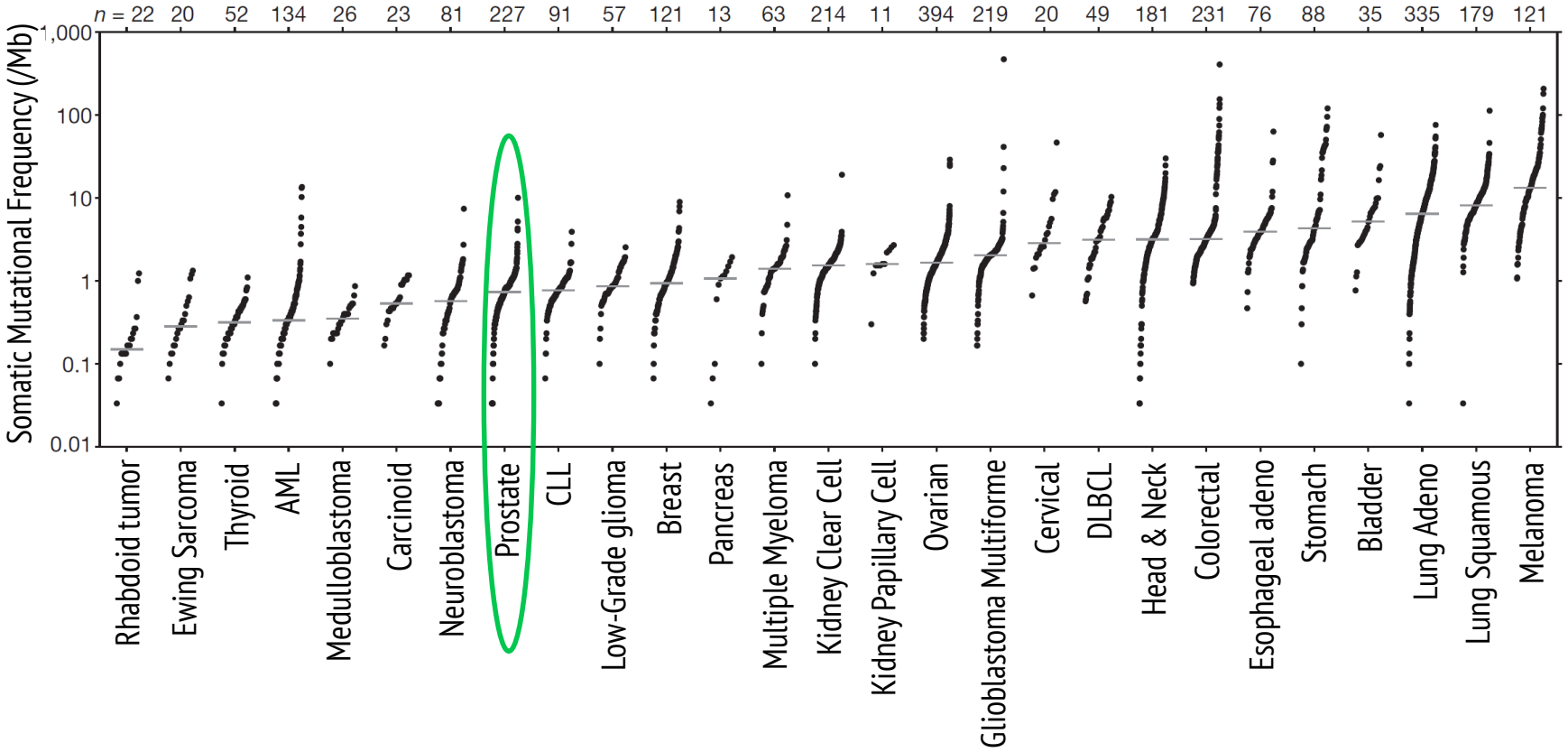

MUTATIONS ARE ASSOCIATED WITH NEOANTIGENS THAT CAN BE RECOGNIZED BY THE IMMUNE SYSTEM

Lawrence MS, et al. Nature 2013; 499: 214–8

MISMATCH REPAIR ALTERATIONS WITH MSI IN PROSTATE CANCER

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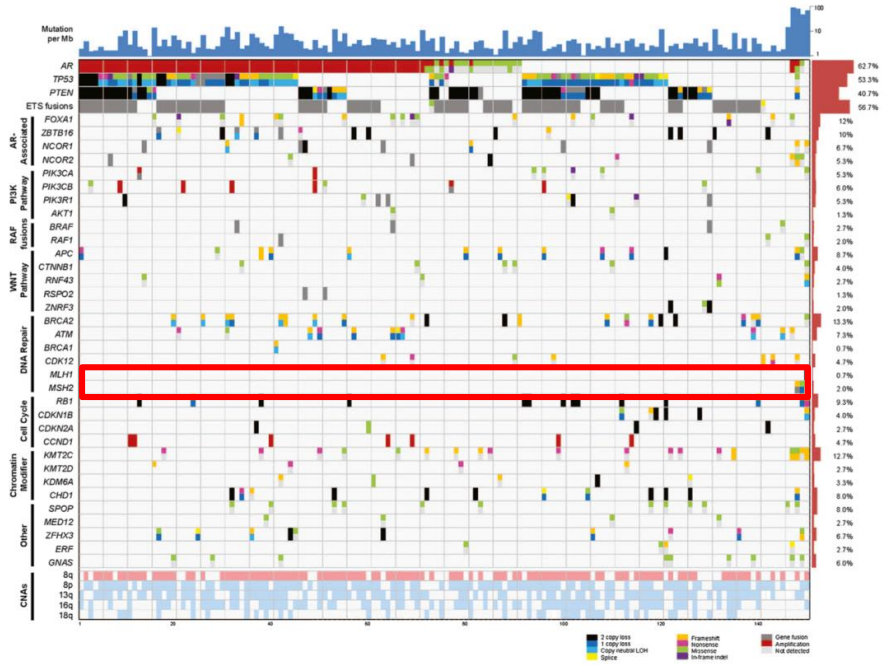
- 7/60 (11.7%) of advanced prostate cancers are hypermutated and all had mismatch repair gene mutations and MSI
- Hypermutation defined as >300 somatic protein altering mutations in metastatic tumors
- All mismatch repair alterations were in MSH2 or MSH6

SU2C mCRPC BIOPSIES

- 2.7% harbor MMR alterations in either MLH1 or MSH2, which are consistent with MSI



IN OTHER SOLID TUMORS MMR PREDICTS RESPONSE TO IMMUNE THERAPY

Pritchard CC, et al. Nat Commun 2014; 5: 4988

Robinson D, et al. Cell 2015; 161: 1215–28

DNA REPAIR GENE ALTERATIONS ARE COMMON IN METASTATIC PROSTATE CANCER

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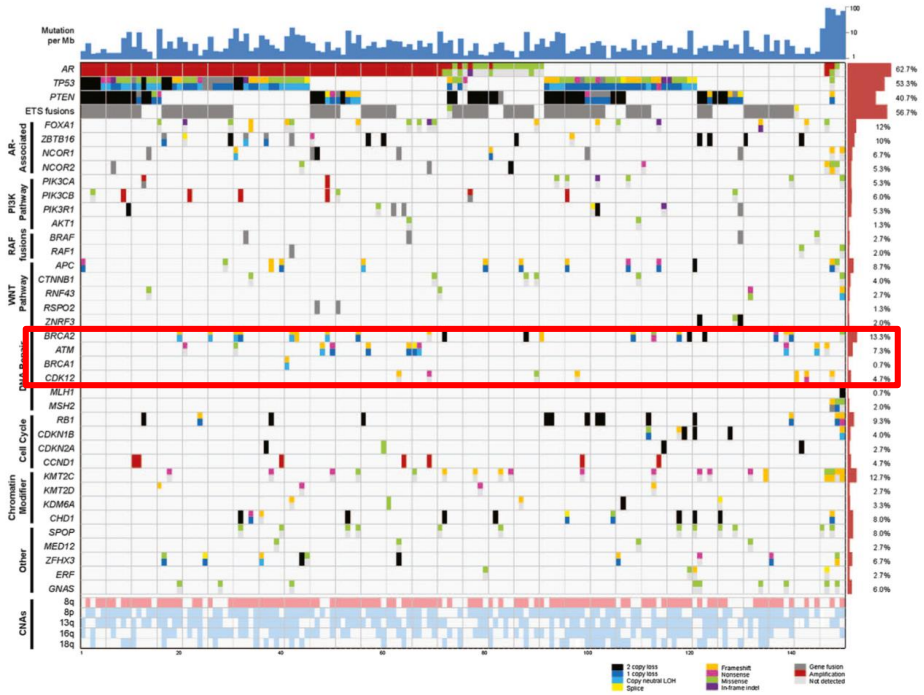

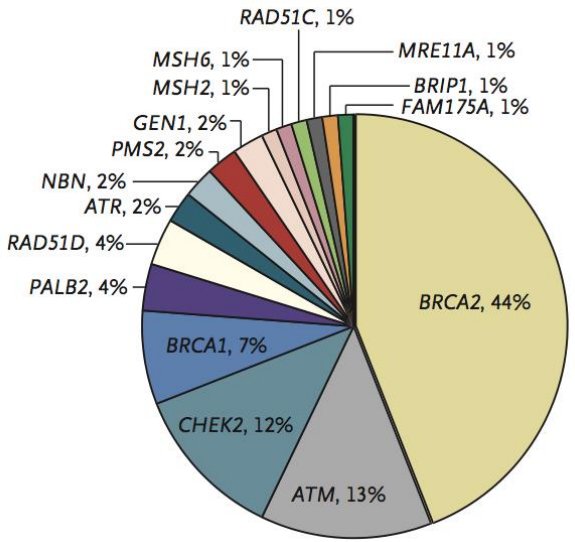

- 23% of metastatic castration-resistant prostate cancers harbor DNA repair alterations
- The frequency of DNA repair alterations increases with disease progression

- 11.8% of men with metastatic prostate cancer have a germline alteration in 16 DNA damage repair genes
- Age and family history did not affect mutation frequency

Robinson D, et al. Cell 2015; 161: 1215–28

Pritchard CC, et al. N Engl J Med 2016

KEYNOTE 365: PEMBROLIZUMAB COMBINATION THERAPIES IN mCRPC

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• mCRPC • Prior treatment with docetaxel (one other chemotherapy for mCRPC permitted, as well as up to two second generation hormonal manipulations)	**Cohort A:** Pembrolizumab + Olaparib (N=70)
• mCRPC • Prior treatment with abiraterone acetate or enzalutamide in the pre-chemotherapy mCRPC state	**Cohort B:** Pembrolizumab + Docetaxel (N=70)
• mCRPC • Prior treatment with abiraterone acetate in the pre-chemotherapy mCRPC state	**Cohort C:** Pembrolizumab + Enzalutamide (N=70)

ONGOING TRIALS IMMUNOTHERAPY IN mCRPC

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Trial	Agent(s)
Keynote 365 NCT02861573	Pembrolizumab + Docetaxel, Enzalutamide, or Olaparib
NCT02325557	Pembrolizumab + Listeria-PSA vaccine (ADXS31-142)
NCT02499835	Pembrolizumab + PAP DNA vaccine (MVI-816)
NCT03007732	Pembrolizumab, XRT, TLR9 agonist (SD-101)
NCT03024216	Atezolizumab + Sipuleucel-T
NCT02933255	Nivolumab + PROSTVAC and/or Ipilimumab
NCT01804465	Ipilimumab + Sipuleucel-T
NCT02463799	Sipuleucel-T + Radium223
NCT02814669	Atezolizumab + Radium223
NCT02985957	Nivolumab + Ipilimumab
NCT02933255	PROSTVAC + Nivolumab and/or Ipilimumab
NCT02788773	Durvalumab +/- Tremelimumab

HOW DO WE MAKE IMMUNOTHERAPY WORK BETTER FOR THE PROSTATE CANCER "NON-INFLAMED PHENOTYPE?"

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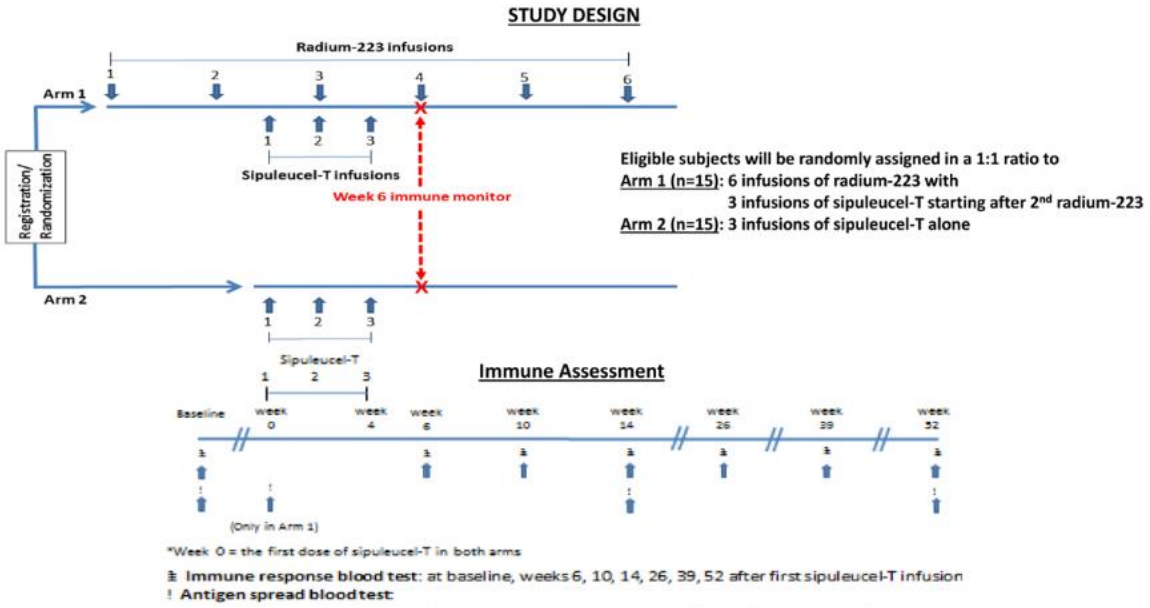
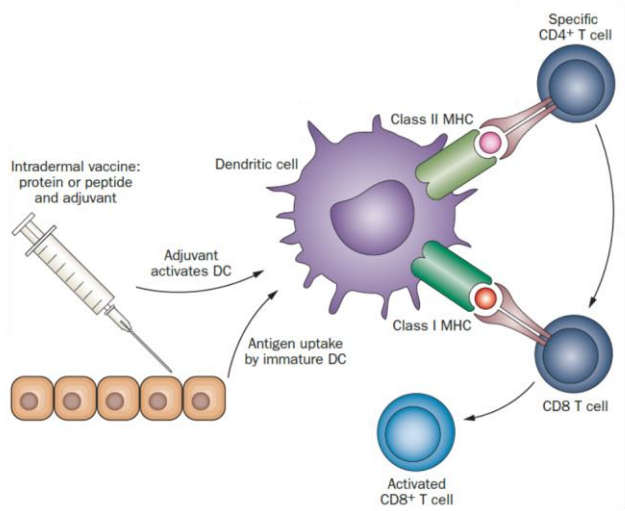
- Immune priming strategies may be necessary to generate tumor antigen specific T cells
  - Vaccine/ Listeria
  - Chemotherapy or radiation (release neoantigens)



INCREASING T CELL ACTIVATION BY "PRIMING" WITH A VACCINE



Park JC, et al. ASCO annual meeting 2015. abstr TPS

Drake CG, et al. J Nat Rev Clin Oncol 2014

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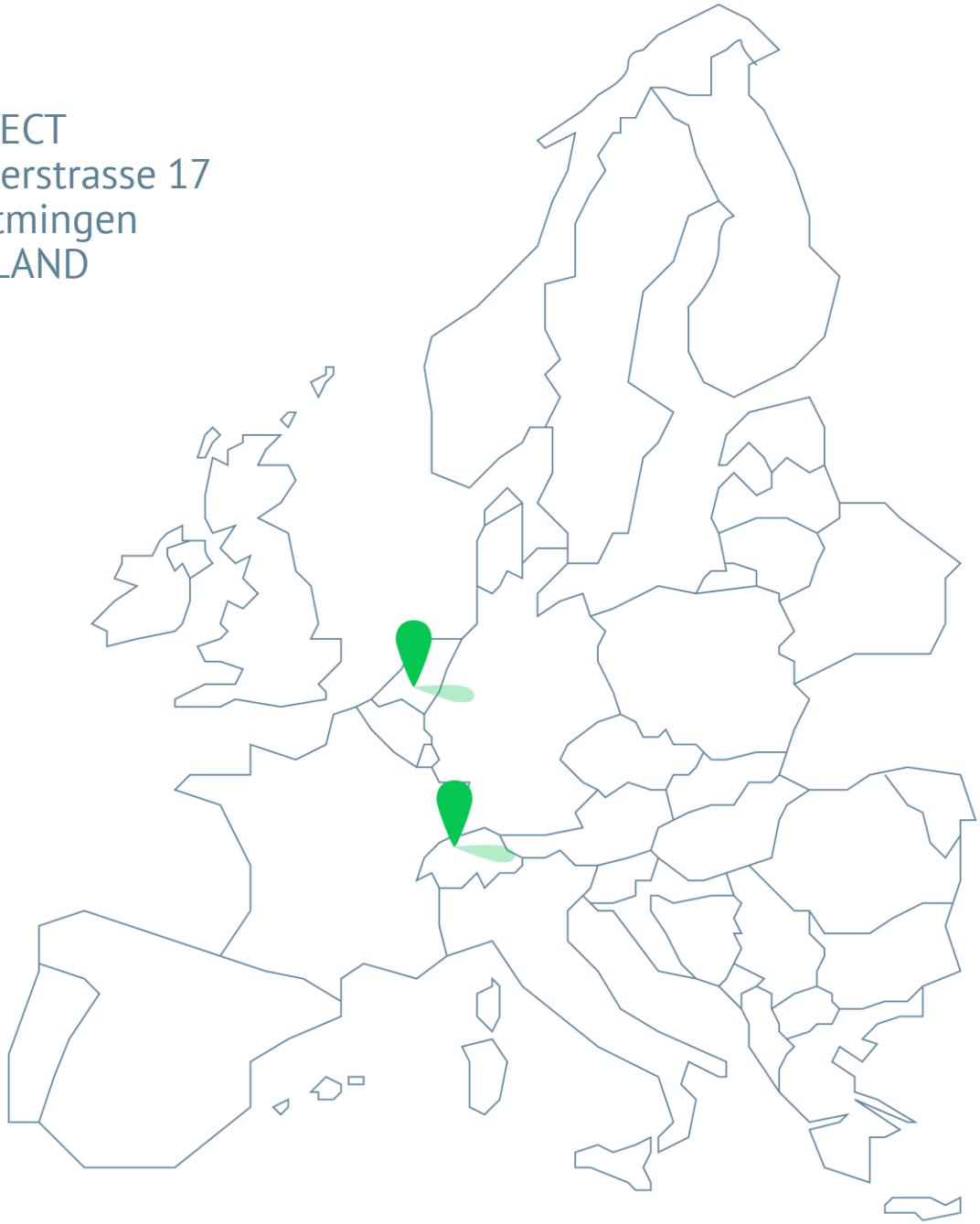

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