Immunotherapy for Prostate Cancer (MSI-high Prostate Cancer, Combinations, CAR T, Bispecifics)

Julie N. Graff, MD
Professor of Medicine, Oregon Health & Science University
Section Chief Hematology/Oncology, VA Portland Health Care System
Director of Prostate cancer Analysis for Therapy CHoice

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Disclosures

- Institutional research funding from the following companies: Sanofi, Pfizer, Merck, Janssen
- I will be discussing non-FDA approved indications during my presentation.

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A. Begin with doublet or triplet therapy that includes androgen deprivation therapy plus next generation androgen receptor blocker.
B. Do A plus pembrolizumab
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A. BiTE is FDA approved for prostate cancer, and he does not need to be on the trial.
B. BiTE is an outpatient therapy.
C. BiTE shows promise as a treatment for prostate cancer.
D. BiTE shows promise as a treatment and nearly no one gets CRS.

Topics of the Talk

- State of Checkpoint Inhibition in Prostate Cancer in UNSELECTED patients
  - Opportunities are 3 in 100
- Immunosuppressive Environment of Prostate Cancer
- Chimeric Antigen T-Cell Receptor- CAR-T
- Bispecific T Cell Engagers

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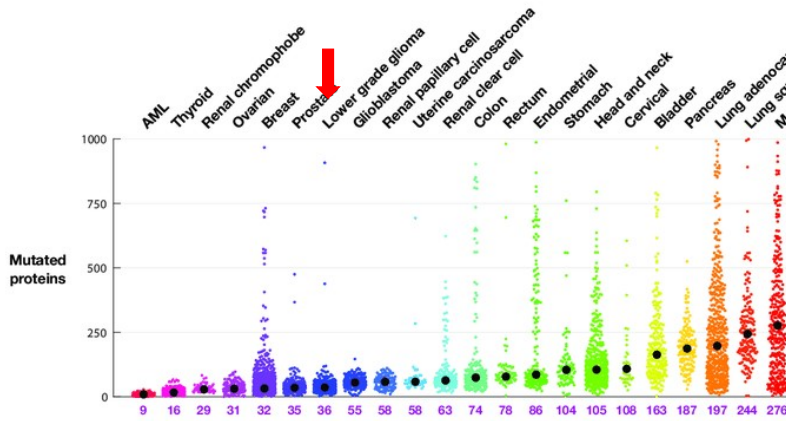
sitc Society for Immunotherapy of Cancer | ADVANCES IN Cancer IMMUNOTHERAPY 10TH ANNIVERSARY

Response to PD-1 Inhibition in MSI-H Prostate Cancer



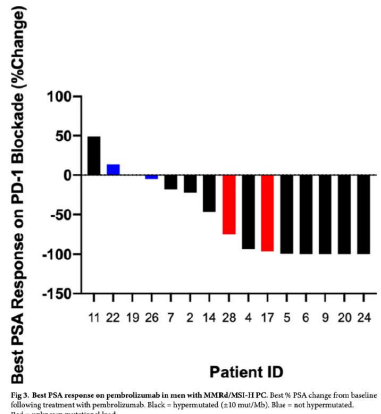


Fig 3. Best PSA response on pembrolizumab in men with MMRd/MSI-H PC. Best % PSA change from baseline following treatment with pembrolizumab. Black = hypermutated (≥10 mut/Mb). Blue = not hypermutated. Red = unknown mutational load.

https://doi.org/10.1371/journal.pone.0233260.g003

Frontiers in Immunology 10:1856; Aug 2019
DOI:10.3389/fimmu.2019.01856

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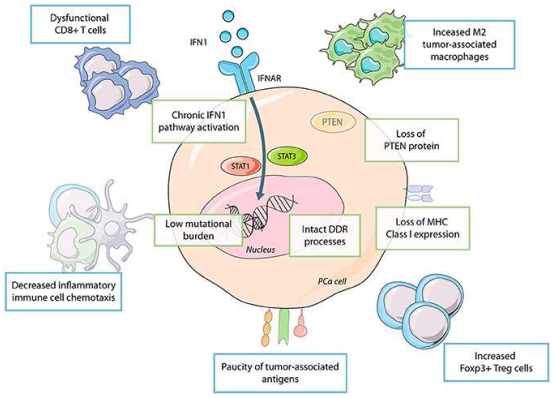
Checkpoint Inhibitors in Unselected Prostate Cancer Does not Work

- Phase 3 studies that have failed-
- CTLA-4 Inhibition
  - mCRPC setting- ADT + ipilimumab v. ADT alone in chemotherapy naïve and after chemotherapy for mCRPC
- PD-1 inhibition
  - Press Release from Merck: Enzalutamide + Pembrolizumab v. Enzalutamide + placebo- negative study
- PD-L1 inhibition
  - mCRPC setting- ADT + atezolizumab + enzalutamide v. ADT + placebo + enzalutamide

There's just something about prostate cancer….



Front. Immunol., 28 March 2019

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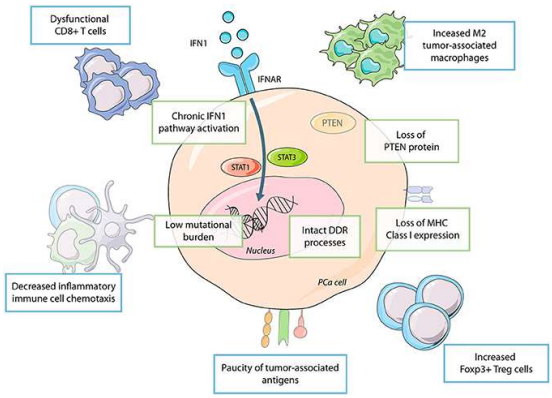
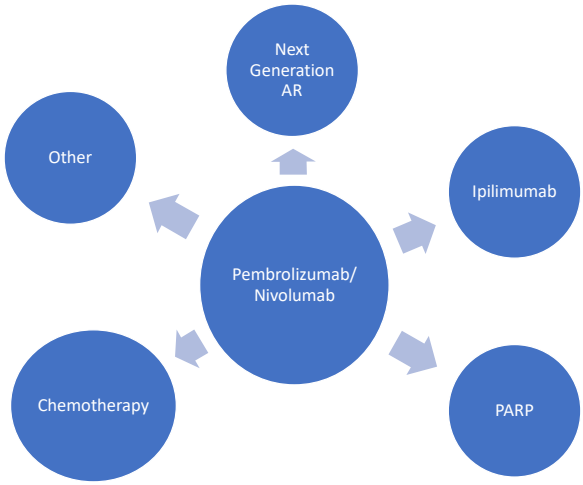


Front. Immunol., 28 March 2019

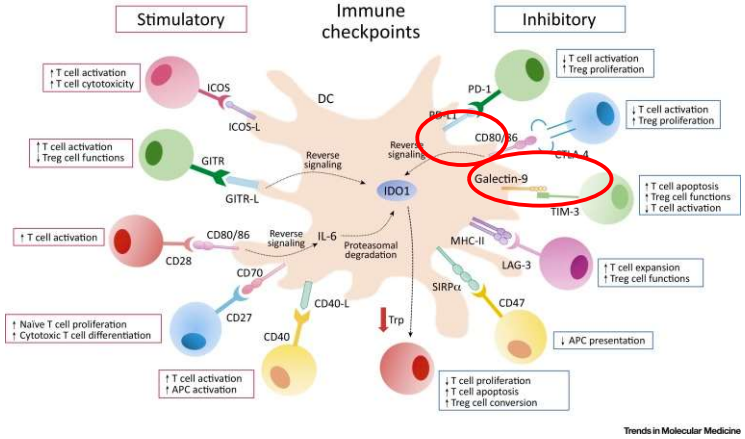
Combinations with PD-1 inhibition

<u>Goals of Combination Therapy</u>

- Create a "hotter tumor environment"
- Overcome known resistance mechanisms
- Influence antigen presentation



Immunotherapy + Immunotherapy



Trends In Molecular Medicine 2018. 24(11):931-941

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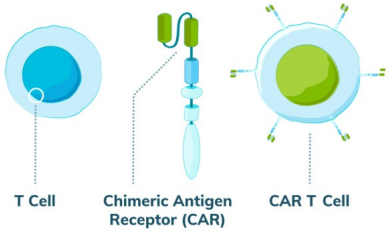
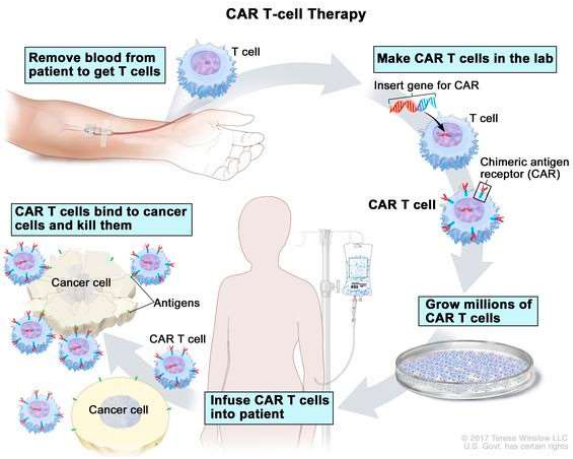
Chimeric Antigen T-Cell Receptor- CAR-T





https://www.mesothelioma.com/treatment/immunotherapy/car-t-cell-therapy/

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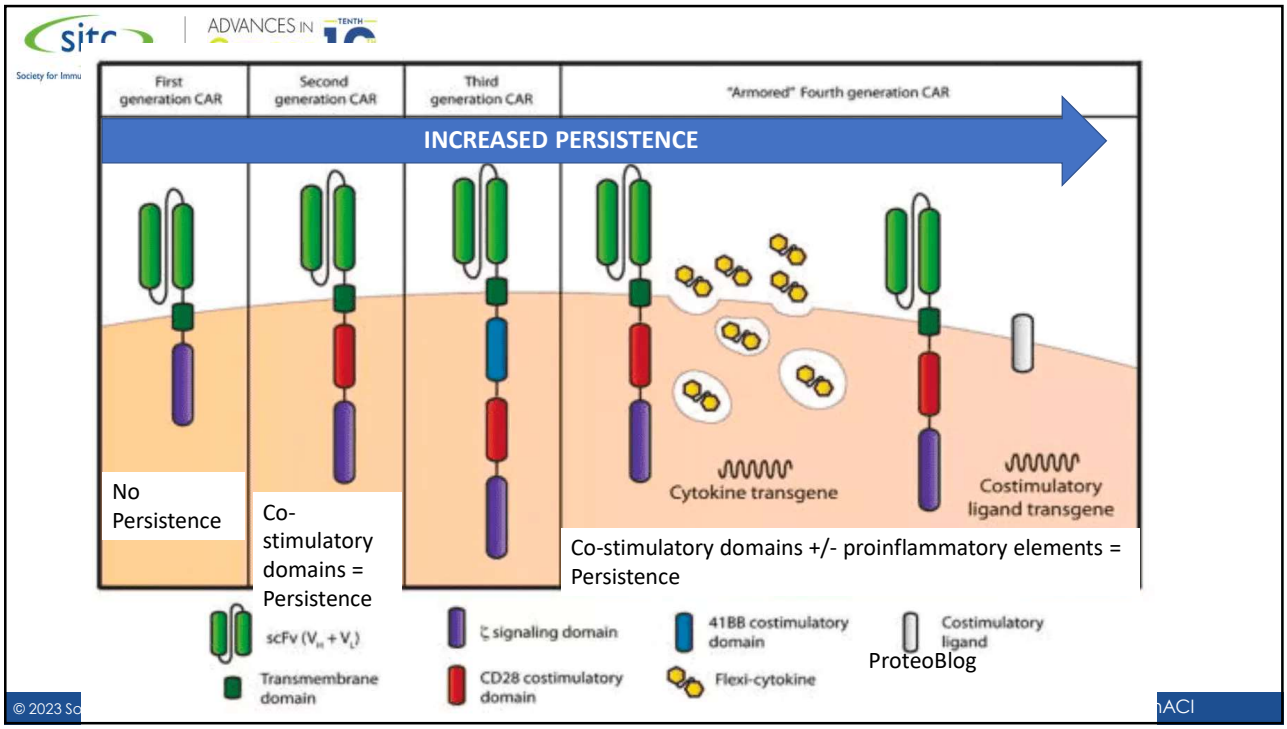

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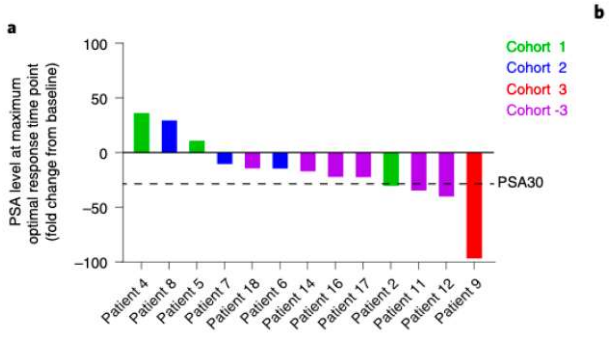
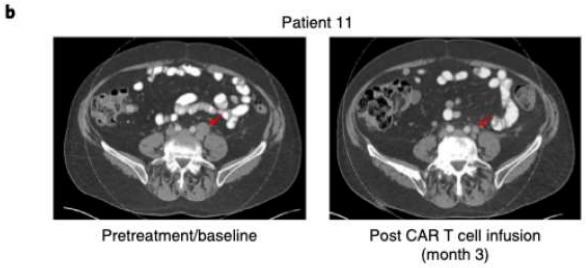
Early Trials of CAR-T in Prostate Cancer





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Process of T Cell Infusion

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Targets of Engineered T Cell Receptor

Target	Advantages	Disadvantages
Prostate Acid Phosphatase (PAP)	Secreted by malignant prostate cancer cells Stimulates cytotoxic T-lymphocytes in vivo Clinical success as immunotherapeutic target (Sipuleucel-T)	More highly expressed in well-differentiated cancers (Gleason 6/7) compared to higher grade cancer Expressed in other tissues such as kidneys/testes Secreted in large amounts systemically if prostate is damaged Not expressed on cell surface
Prostate Stem Cell Antigen (PSCA)	High expression in malignant cancer cells Positive correlation of expression to grade of disease Not released into blood circulation PSCA CAR-T cells have produced promising results in gastric and pancreatic cancers	A preclinical study suggested some tumours can 'escape' CAR-T cells by means of antigen heterogeneity
Epithelial cell adhesion molecule (EpCAM)	Positive correlation of expression to grade of disease EpCAM directed CAR-T therapy in breast cancer has produced promising results	A murine study suggested potential pulmonary toxicity due to EpCAM expression on basal respiratory epithelium

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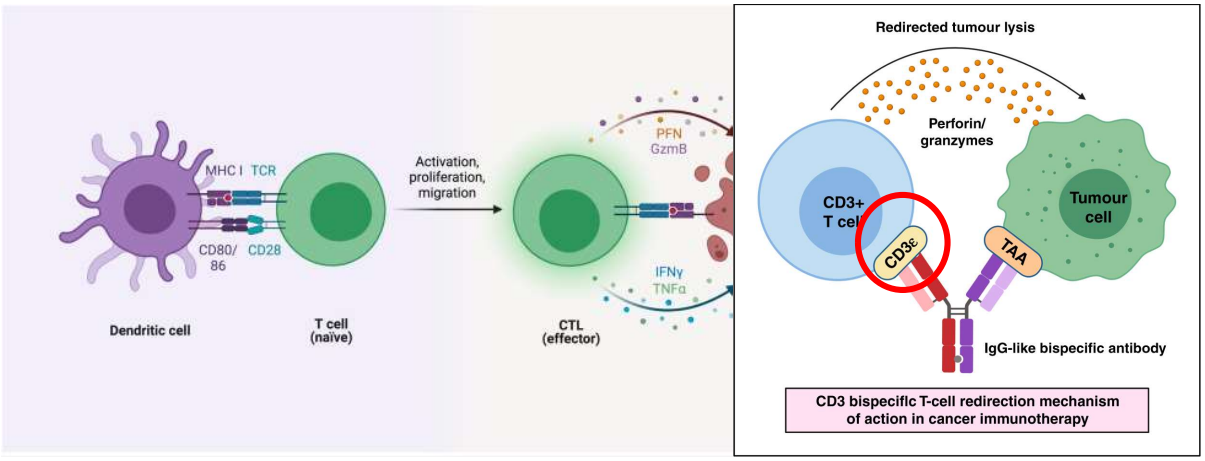
Targets of Engineered T Cell Receptor

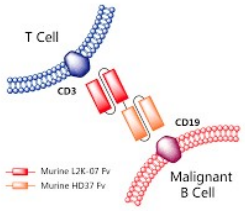
Target	Advantages	Disadvantages
Prostate-Specific Membrane Antigen (PSMA)	Positive correlation of expression to grade of disease Trafficking to tumour sites can be imaged High expression related to castration-resistant disease Targets neovasculature involved in metastatic disease	10–15% of prostate cancers do not express PSMA (de-differentiated neuroendocrine variants of prostate cancer express low or absent PSMA)
Prostate-Specific Antigen	Expressed specifically in prostate tissue Stimulates cytotoxic T-lymphocytes in vivo	Strongly expressed in benign prostatic tissue (i.e., benign prostatic hyperplasia)

Cancers (Basel). 2022 Feb; 14(3): 503

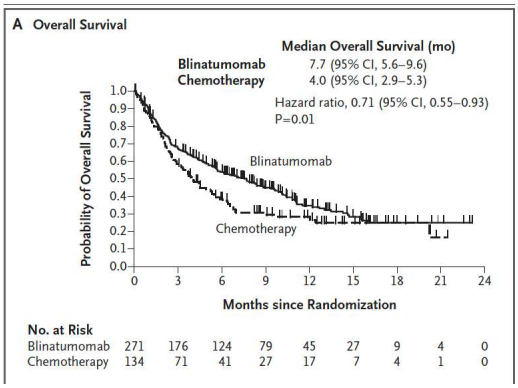
Bispecific T Cell Engagers = No Matchmaker Needed!



Model Bispecific T Cell Engager: Blinatumumab



FDA Approved for Advanced ALL



NEJM 2017; 376:836-47

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Clear Activity, But At What Cost?

Table 3. Adverse Events.*

Event	Blinatumomab Group (N=267)	Chemotherapy Group (N=109)
	no. of patients (%)	
Any adverse event	263 (98.5)	108 (99.1)
Event leading to premature discontinuation of trial treatment	33 (12.4)	9 (8.3)
Serious adverse event	165 (61.8)	49 (45.0)
Fatal serious adverse event	51 (19.1)	19 (17.4)
Any adverse event of grade ≥3	231 (86.5)	100 (91.7)
Grade ≥3 adverse event of interest reported in at least 3% of patients in either group		
Neutropenia	101 (37.8)	63 (57.8)
Infection	91 (34.1)	57 (52.3)
Elevated liver enzyme	34 (12.7)	16 (14.7)
Neurologic event	25 (9.4)	9 (8.3)
Cytokine release syndrome	13 (4.9)	0
Infusion reaction	9 (3.4)	1 (0.9)
Lymphopenia	4 (1.5)	4 (3.7)
Any decrease in platelet count	17 (6.4)	13 (11.9)
Any decrease in white-cell count	14 (5.2)	6 (5.5)

* Data are summarized for all patients who received at least one dose of trial treatment.

NEJM 2017; 376:836-47

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Classic Toxicities with BiTE Therapies

Cytokine Release Syndrome

- Uncontrolled systemic inflammatory response
- High IFN-gamma, IL-1, IL-6; result of T cell activation
- Less likely if step up in dose, lower volume of disease
- More likely at higher doses

Immune Effector-Cell-Mediated Neurotoxicity Syndrome (ICANS)

- Dizziness, tremor, confusion, encephalopathy
- Unclear Etiology, but appears T cells bind to endothelial cells in CNS
- Treated with dose interruption and corticosteroids
- Many questions remain

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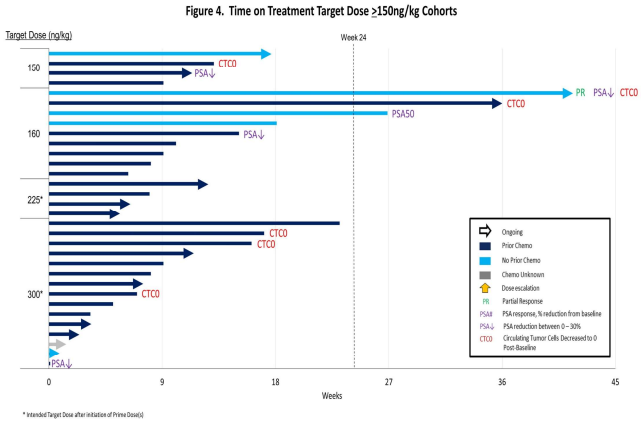
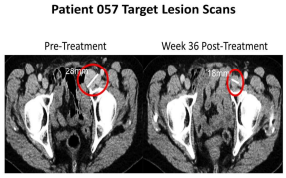
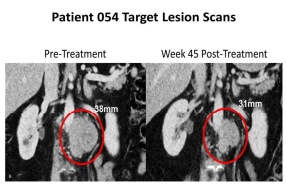
Anti-Tumor Activity

Treatment duration of >24 weeks in 20% of patients, Confirmed RECIST PR, PSA declines and CTC reductions observed across cohorts







J Clin Oncol 39, 2021 (suppl 15; abstr 5013)

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Adverse Events

CRS and transaminitis most common treatment-related AEs, occurred most often in Cycle 1

Table 3. Common Treatment Emergent Adverse Events (TEAEs) by Grade per CTCAE, V5.0

Event, n (%)	All Grades	Grade 3+
Cytokine-Related AEs[a]		
Cytokine Release Syndrome (CRS)[b]	61 (69%)	4 (4%)
Chills	60 (67%)	0 (0%)
Pyrexia	58 (65%)	2 (2%)
Hypotension	35 (39%)	6 (7%)
Infusion Related Reaction (IRR)	20 (22%)	0 (0%)
Flushing	13 (15%)	0 (0%)
Hypoxia	11 (12%)	4 (4%)
Liver Function Tests		
AST Increase	28 (31%)	19 (21%)
ALT Increase	26 (29%)	14 (16%)
Other Adverse Events		
Fatigue	45 (51%)	3 (3%)
Nausea	40 (45%)	1 (1%)
Vomiting	34 (38%)	1 (1%)
Anemia	28 (31%)	10 (11%)
Headache	24 (27%)	0 (0%)
Back Pain	21 (24%)	4 (4%)
Tachycardia	20 (22%)	1 (1%)
Constipation	20 (22%)	0 (0%)
Decreased Appetite	20 (22%)	0 (0%)

[a] Includes AEs that were reported as concurrent symptoms of the CRS events.
[b] CRS Grading according to ASTCT 2019 criteria.

- MTD not yet reached
- Most common DLTs: transaminitis G4 and CRS G3
  - Observed at doses ranging from 96 to 300 ng/kg
  - Occurred most often with first Target Dose
  - Majority of patients successfully rechallenged
- No Grade 4/5 CRS, no Grade 5 treatment-related AEs
- 2 of 89 (2%) pts discontinued treatment due to TRAEs

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C. Do A plus send for genetic counseling
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