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Combined neoadjuvant chemo-immunotherapy therapy achieves superior downstaging of resectable non-small cell lung cancer as compared to chemotherapy, mono or dual immunotherapy

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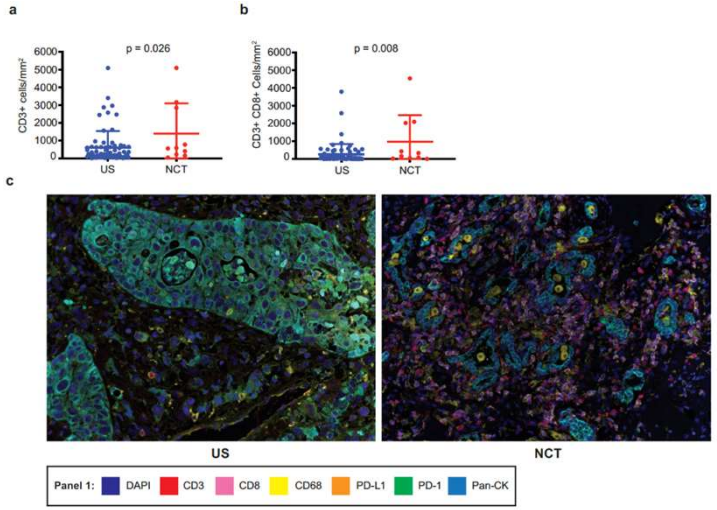
Background

- Tumor and nodal downstaging following neoadjuvant therapy has been associated with favorable prognosis [1, 2]
- Especially downstaging to ypN0 status results in significantly (3 times, 14 vs 44 months) improved disease-free survival [3]
- Nodal downstaging following chemotherapy alone ranges from 20-40% [1]
- Nodal downstaging following chemoradiation ranges from 40-65% [4,5]
- Most recently, chemoimmunotherapy regimen (NADIM trial) demonstrated downstaging rate of 90% [6]

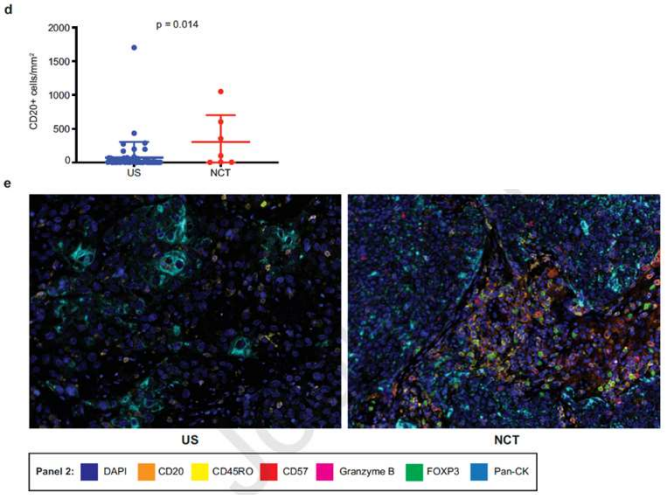
[1] Martin, Mehran, JTD 2017 [2] Kamel et al, ATS 2017 [3] Jaklish et al, JSO 2006, [4] Chino et al, Int J of Rad Onc and Biophysics 2009, [5] Decaluwe et al, EJCTS 2009, [6] Provencio et al, Lancet 2020

Background

Neoadjuvant Chemotherapy Increases Cytotoxic T cell, Tissue Resident Memory T cell and B Cell Infiltration in Resectable Non-Small Cell Lung Cancer Pierre-Olivier Gaudreau et al, JTO, 2020



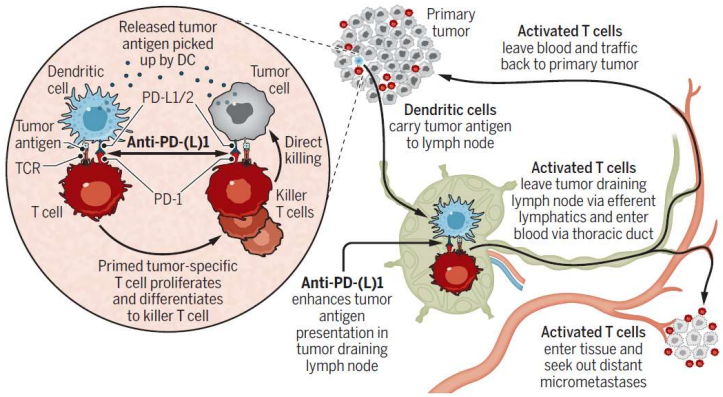
CD3+CD8+ cells

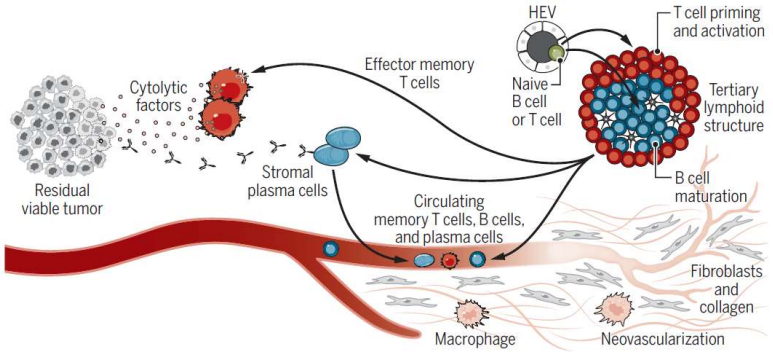


CD20+ cells

https://doi.org/10.1016/j.jtho.2020.09.027

Background





- the presence of intact tumor-draining lymph nodes at the time of checkpoint inhibitor treatment may allow for better neoantigen presentation to dendritic cells and the development of increased immunoreactive T cells

  Topalian et al, Science, 2020

- chemoimmunotherapy may increase immunogenic tumor specific peptides or released from the chemotherapy-induced cell death of the primary tumor
- This might lead to increases in primed neoantigen-specific T cells and B cells

Aim and Hypothesis

Aim:

- to evaluate the impact of four different systemic neoadjuvant therapies on tumor, nodal and overall pathological downstaging of surgically resectable I-IIIA NSCLC (AJCC 7th edition).

Hypothesis:

- Chemoimmunotherapy would achieve superior downstaging of both tumor and nodal status as compared to all other therapies

Methods

Chemotherapy only	N=302
Nivolumab	N=21*
Nivolumab + Ipilimumab	N=16*
Chemotherapy + Nivolumab	N=22*

NEOSTAR (NCT03158129)

* Represents resected patients only

Ethics approval: This study was approved by the University of Texas MD Anderson Institutional Review Board with a waiver of informed consent, protocol 2020-0337.

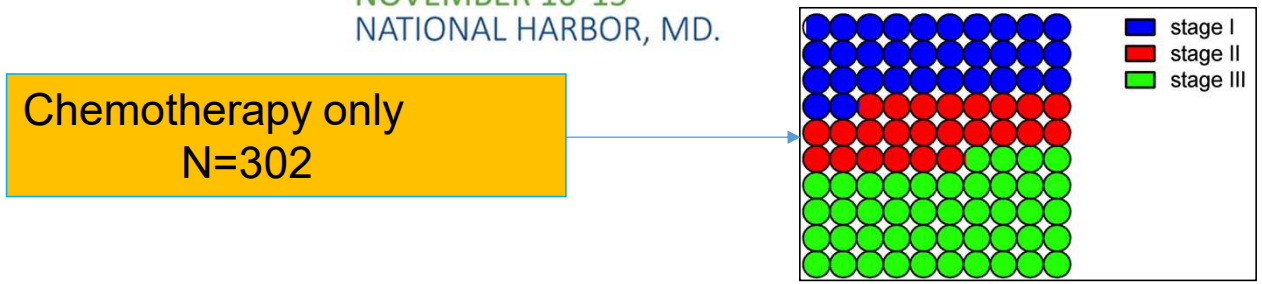
Clinical Staging (CT, PETCT, EBUS, mediastinoscopy)
cTumor
cNodes
cOverall stage

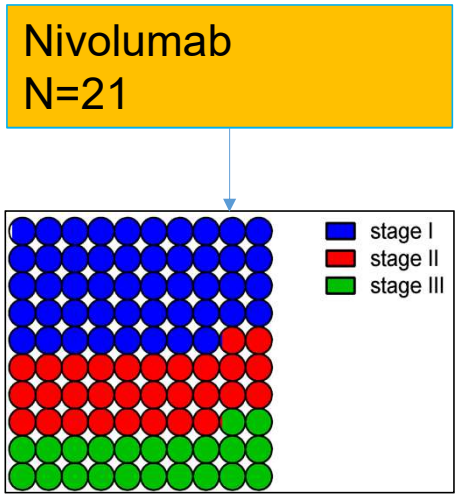
→

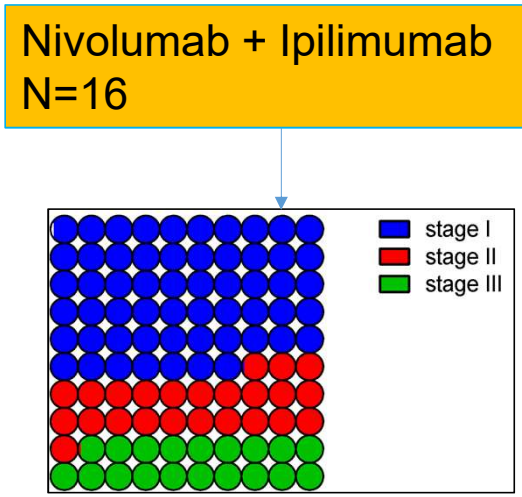
Pathological Staging (resected specimen)
ypTumor
ypNodes
ypOverall stage

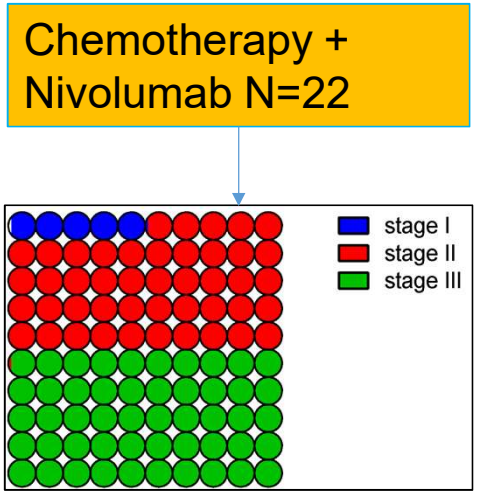
Fisher's exact test.

Methods (stage distribution)









Results

Tumor Downstaging

	Chemo N=302	Single ICI N=21	Dual ICI N=16	Chemo + ICI N=22	p
ypT **downstaged vs. stable/upstaged**	26% (79)	29% (6)	38% (6)	59% (13)	0.012

Nodal Downstaging

	Chemo N=302	Single ICI N=21	Dual ICI N=16	Chemo + ICI N=22	p
ypN **downstaged vs. stable/upstaged***	55% (96)	50% (3)	50% (2)	42% (5)	0.862

Overall Downstaging

	Chemo N=302	Single ICI N=21	Dual ICI N=16	Chemo + ICI N=22	p
Overall **yp downstaged vs. stable/upstaged**	38% (114)	38% (8)	38% (6)	68% (15)	0.048

Results

Tumor Upstaging

	Chemo N=302	Single ICI N=21	Dual ICI N=16	Chemo + ICI N=22	p
ypT upstaged vs. stable/downstaged	19% (N=58)	29% (N=6)	23% (N=3)	9% (N=2)	0.457

Nodal Upstaging

	Chemo N=302	Single ICI N=21	Dual ICI N=16	Chemo + ICI N=22	p
ypN upstaged vs. stable/downstaged*	29% (N=53)	29% (N=5)	33% (N=5)	12% (N=2)	0.479

Overall Upstaging

	Chemo N=302	Single ICI N=21	Dual ICI N=16	Chemo + ICI N=22	p
Overall yp upstaged vs. stable/downstaged	28% (N=85)	38% (N=8)	38% (n=6)	14% (N=3)	0.251

Conclusions

Chemotherapy + nivolumab achieved:

- the most robust tumor and overall pathological downstaging
- decreased probability of upstaging

- Whether the overall downstaging effect will result in improved overall survival will be determined with longer follow-up
- The results from ongoing phase III neoadjuvant chemo-immunotherapy trials will be crucial in potentially improving the standard-of-care for loco-regional NSCLC
- Cancers with driver mutations, or other biomarkers may demonstrate varied responses to these therapies

Limitations

- Unbalanced cohorts
- Small number of patients in immunotherapy groups
- Possibility of type 2 error
- Short follow up to comment on survival outcomes
- Inherent possibility in clinical staging errors
- Lack of data on mutations and other biomarkers

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