Network Meta-Analysis to evaluate comparative efficacy, progression free survival and tolerability among Immune Checkpoint Inhibitor Therapies (CIT) in Melanoma patients

Tamara Ray, Madhav Channavazzala, Lakshmanan Jagannathan and Rukmini Kumar*

Vantage Research (www.vantage-research.net) Chennai

Introduction

- Induced upregulation of **immune checkpoints like PD1 and CTLA4** is one of the mechanism by which tumor cells evades host immune responses during the dynamic tumor immune interplay. **Checkpoint Inhibitor Therapies (CIT)** block these negative regulators and empower host immune response. Immunotherapies have brought about a paradigm shift in treatments in oncology due to their better clinical response. However, there is a need to explore combination therapies for improved efficacy. Fig 1.1 shows the current scenario of the evolving immuno-oncology space.
- In this rapidly growing space, **meta-analysis** (Fig 1.2) offers us a way to compare therapies by pooling multiple direct comparison trials. **Network Meta-Analysis (NMA)**, helps us in comparing more than two therapeutic interventions across same disease (Fig 1.3). This multiple treatment meta-analysis derives strength from both **direct and indirect effect estimates to improve accuracy** of treatments effects and also allows for **comparison of therapies that have not been investigated head to head in randomized clinical trials**
- **Vantage Research Immuno-Oncology Knowledge Base (IO-KB)** (Fig 1.4) is an in-house expertly curated database (from public literature) of about 70 clinical trials, conducted from 2010 to 2018, comprising of 21,000+ patient data with access to about 10 immunotherapies (mono and combination therapies) across various solid cancers. This database was used for identifying relevant publications for analysis.

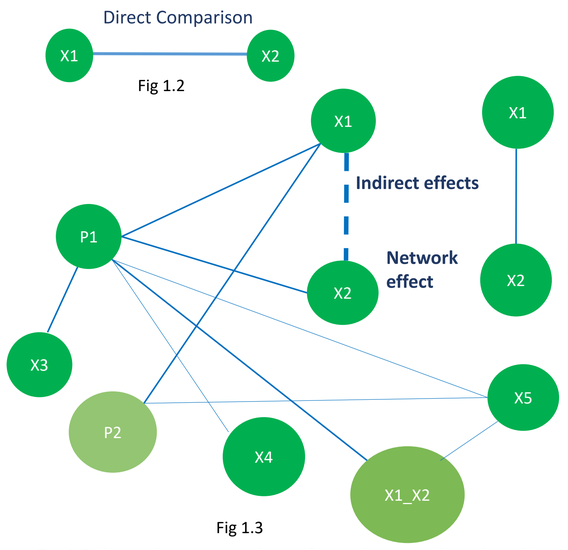
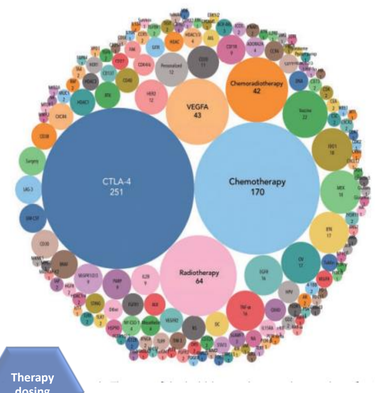


Fig 1.2 shows the meta-analysis of two therapies based on direct clinical evidence. Fig 1.3 shows a network for multiple treatment comparison

Figure 1.1 : Combination therapies with aPD-1/aPDL1 being explored in the immuno-oncology area.



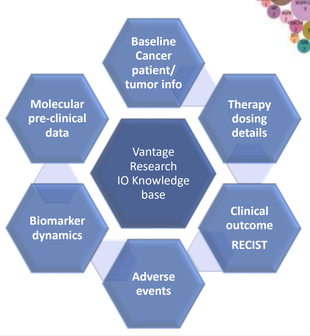


Figure 1.4 : Various modules of Vantage Research Immuno-oncology Knowledge base (Vantage Research IO-KB)

Methods-I: Research scope and Objective

- **Objective** is to Identify the best Immunotherapy for treating advanced non-resectable melanoma
- In this analysis, we have adhered to **PRISMA-NMA guidelines.**

P	Population	Stage III/IV Non-resectable Melanoma patients
I	Intervention	RCTs testing Checkpoint Inhibitors Therapies
C	Comparison	With standard of care-Chemotherapy
O	Outcome	Objective Response Rate (ORR) 6 months Progression free Survival (PFS) Occurrence of severe Adverse events (AE)

Fig 2.1 : PICO helps identify the scope of the analysis

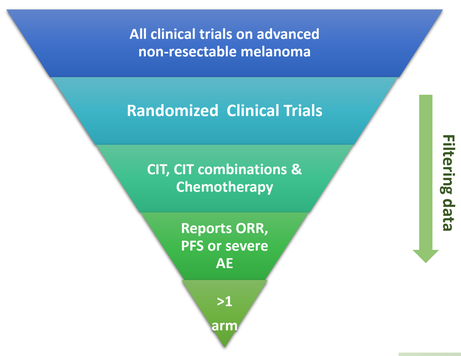
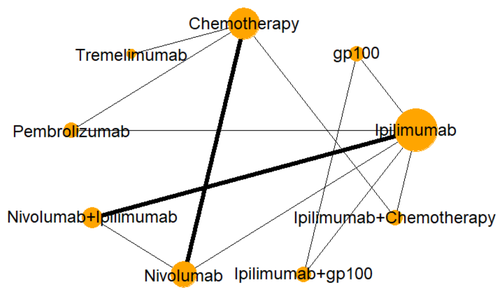
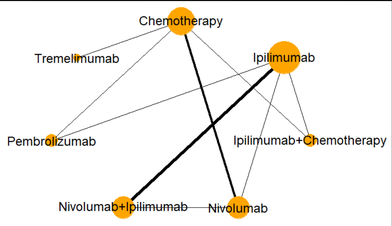


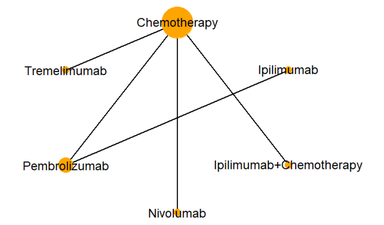
Fig 2.2 : Clinical trials studies were selected from Vantage Research IO-KB, filtered as per established scope of the analysis. **11 clinical trials were selected for this analysis**.
R programming language is used for the analysis using the **"gemtc"** package.



Outcome : Severe Adverse Events (Grade III and higher)



Outcome : Objective Response Rate (ORR)



Outcome : 6 month Progression Free Survival (PFS)

Fig 2.3 : Networks built from the selected clinical trials. Learning about Network structure is important for understanding accuracy and reliability of the results.

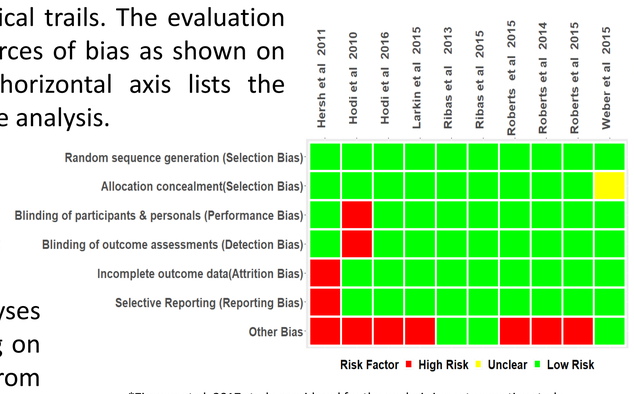
A star shaped network(bottom-right) as seen in the PFS network is a commonly observed structure

Methods-II: Examining Strength of Evidence

Cochrane Risk of Bias Scale was used to evaluate Risk of bias across all the selected clinical trails. The evaluation was done based on the six sources of bias as shown on vertical axis in Fig 3.1. The horizontal axis lists the selected clinical trials used in the analysis.

- **Transitivity checks**
- **Risk of Bias analysis**
- **Network Geometry Analysis**

These are qualitative analyses which help a reader in deciding on the reliability of the results from NMA.



*Zimmer et al, 2017 study considered for the analysis is a retrospective study

Figure 3.1 Risk of bias analysis evaluating the sources of risk (vertical axis) for each selected study (horizontal axis)

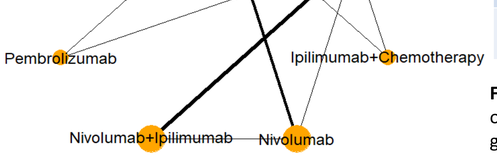


Figure 3.2

- 7 therapies are compared in this network built from 10 clinical trials and the total number of subjects involved are 4599.
- 9 of the 21 direct comparisons possible are known from trial data
- Strongest link Ipilimumab-Nivolumab+ipilimumab has 3 studies

Network or Global heterogeneity

Network	I^2
Objective Response Ratio (ORR)	65.23
Adverse Events (AE)	91.26

Figure 3.3 The I^2 values from the Q test tell us the extent of heterogeneity in the network. A higher I^2 implies a greater extent of heterogeneity

Pairwise or Local Inconsistency check

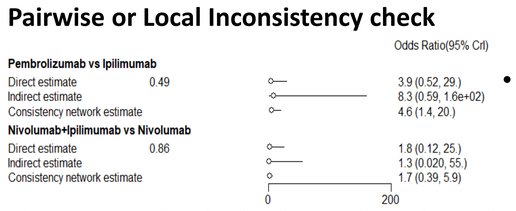


Figure 3.4 A snapshot of node splitting analysis is shown. The p-values indicate that there is no violation of consistency in the ORR and AE networks

- Heterogeneity in the network is modelled with a Random effects model. **Cochran's Q test** is used to check for heterogeneity in the network**.**
- Inconsistent networks cannot be relied with indirect comparisons. **Node-splitting analysis** is used to check the consistency property of the network by comparing direct and indirect estimates.
- Q test cannot be done on PFS network because every edge in the network is supported by single clinical evidence(**star shaped network**). Consistency checks cannot be done on a star shaped structure.

Results from the Analysis

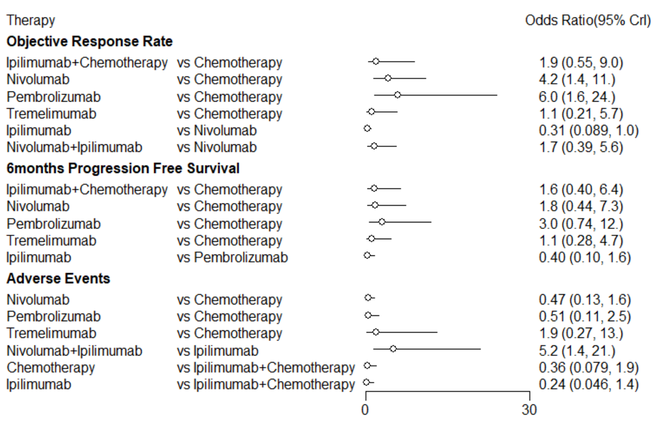
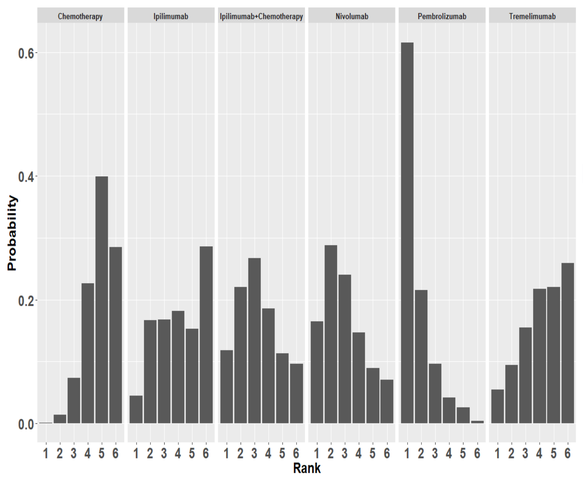


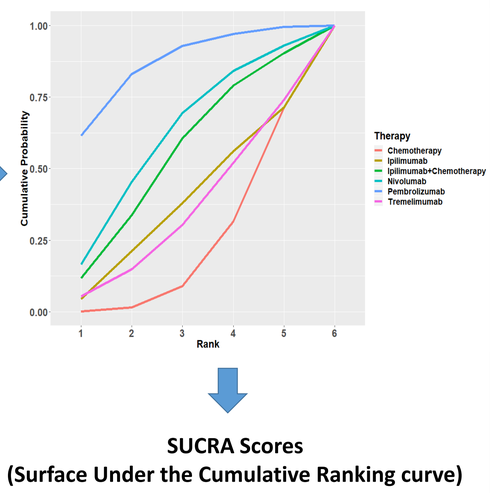
Fig 4.1 : Forest plot showing Odds Ratio(OR) with its mean and 95% credible interval(CrI) of therapies against a comparator from 3 networks. An efficacious treatment has high ORR, high PFS and low AE.

- Fig 4.1 shows the forest plot for the Odds Ratio (OR) from the 3 networks after the analysis. OR is the ratio of odds of success of two therapies.
- Success with respect to ORR means that a patient is either complete/partial responder(CR/PR). In the 6 months PFS network, a successful response is being progression free for at least 6 months. Odds ratio in the AE network is calculated as ratio of odds of experiencing adverse events of two therapies.
- **Rankogram**, is a probability mass function showing the probability of a therapy being the best (rank 1), 2nd best (rank 2) or likewise.
- Rankogram helps to compute the cumulative probability curves.
- Subsequently from the cumulative probability curve, **SUCRA scores** was derived. Better the response, higher the SUCRA score.

Rankograms



Cumulative probability curves



SUCRA Scores
(Surface Under the Cumulative Ranking curve)

Fig 4.2 : Rankograms (left) of 6 therapies are shown. In a rankogram, on the x-axis, rank of the therapies are plotted and on the y-axis, the probability that the therapy takes that rank. From this we can build the cumulative ranking curve(CDF, show in top right) which in turn is used to calculate SUCRA score

Conclusion and Future Directions

- **The SUCRA scores (Fig 5.1) are highest for aPD1 therapies amoung all the therapies compared.** aPD1 therapies affects the effector phase of T cells, predominantly in the **peripheral tissues** and **re-invigorate pre-existing cytotoxic CD8 T-cells** thereby empowering the host immunity. Hence aPD1 therapies are seen to be more efficacious. PD1 binding with its ligands decreases the magnitude of the immune response in T cells that are already engaged in an effector T-cell response. This results in a more restricted spectrum of T-cell activation compared with CTLA-4 blockade, which may explain the apparently lower incidence of immune-mediated adverse events (AEs) associated with PD-1 compared with a CTLA-4 blockade**.**
- Based on the 11 clinical trials we selected, Network Meta-Analysis across the three clinical outcomes shows that **Pembrolizumab ranks best for treating advanced non-resectable melanoma**.
- The networks built for the NMA are unique to each clinical outcome and are subject to change with the addition of new clinical publications and new therapies entering the space, hence these **analysis need to be updated on a regular basis.**
- In the future we aim to pool the data from multiple clinical outcomes into a single network and analyse a **multivariate network meta-analysis** and explore application of CIT in other relevant solid cancers like NSCLC (Non-small cell lung cancers), Urothelial cancers and other relevant solid cancers

SUCRA Score Table

		ORR network		AE network		PFS network	
	Therapies	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank
aPD1	Pembrolizumab	83	2	75	2	87	1
	Nivolumab	69	3	80	1	61	2
aCTLA4	Ipilimumab	27	5	65	3	38	4
aPD1+aCTLA4	Nivolumab+Ipilimumab	89	1	11	9	NA	
	Ipilimumab+Chemotherapy	46	4	17	8	55	3
	Tremelimumab	22	6	29	7	36	5
	Chemotherapy	14	7	47	6	23	6
	Ipilimumab+gp100	NA		63	4	NA	
	Vaccine	NA		62	5	NA	

Fig 5.1 : The table shows the SUCRA scores and the rank of the therapy in each network. The top table shows the 3 best therapies from the analysis by aggregating results from 3 clinical outcomes. The bottom table shows the remaining therapies in the study in no specific order.

References:

1. Mills et al, Demystifying trial networks and network meta-analysis, BMJ, 2013, 2. Hutton et al, The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions, Ann Intern Med. 2015
3. Tang et al, Comprehensive analysis of the clinical immuno-oncology landscape, Ann Oncol. 2018 4. Buchbinder El et al, CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition, Am J Clin Oncol. 2016