Overview of immuno-oncology clinical trial conduct and design investigating combination therapies

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Abstract

Immunotherapies have been increasingly successful with their efficacy as monotherapy regimens now well established. The aim now is raising the response rate and show effects in a wider range of patients. For that, the focus shifted towards combination regimens, combining immunotherapies with other immunotherapies or standard therapies. The challenge is to identify which combination works, in what tumor indications and specifically in which population. **The aim of this research was to anticipate promising developments and to identify trends.** The amount of immuno-oncology combination trials has rapidly grown between 2014 and 2018. At this moment, 944 combination trials (85.5% of all) are ongoing/recruiting. Completed trials make up 2.6%. Our data shows that multiple ongoing trials are investigating the same category of immuno-oncology combination therapy, resulting in 1237 combinations containing 237 unique immuno-oncology combination therapies. We found that in 89.2% of trials, one combination is being tested, followed by 8.2% of trials testing two combination therapies. In 0.1% of trials, six combinations are being tested. Clearly visible is the increase of trials lasting less than 24 months, from 5.88% in 2014 to 29.76% in 2018. This may be due to a decline in long phase III trials. Only 1.6% of trials used biomarker driven patient inclusion in 2018 compared to 3.33% in 2014. The top 5 combination regimens are checkpoint inhibitor + chemotherapy (19.1%), checkpoint inhibitor combinations (11.9%), checkpoint inhibitor + radiation therapy (7.5%), checkpoint inhibitor + targeted therapy/tumor cell proliferation (4.9%), checkpoint inhibitor + chemotherapy + radiation therapy (3.9%). A separate analysis that excludes checkpoint inhibitors shows that tumor-targeting antibodies are the main combination partner, either with anti-angiogenesis- or chemo-therapy. The top 7 of most investigated tumor types together account for 50% of the trials. The remaining 50% of the combinations are studied in 26 tumor types. Lung cancer is the most investigated tumor type in 204 trials (18.6% of trials). Our analysis extended to identify trends in tumor type selection for specific combination therapies to distinguish guideline-driven combination from novel approaches. For the majority of combination trials, their efficacy results will be revealed within the next 2-4 years. Combining immuno-oncology agents increases the complexity and effects clinical trial design. Based on our analysis only a minority of current trials uses innovative designs (4.4%). The use of innovative clinical trial designs might provide an accelerated route of advancing the right combination therapies to the right patients. In summary, the field of immuno-oncology is rapidly developing and the next 2 years will potentially bring tailored cancer therapies into the clinics, requiring collaboration between sponsors to enable the investigation of multiple therapies within one trial.

Results

1. Increasing number of immuno-oncology combination trials

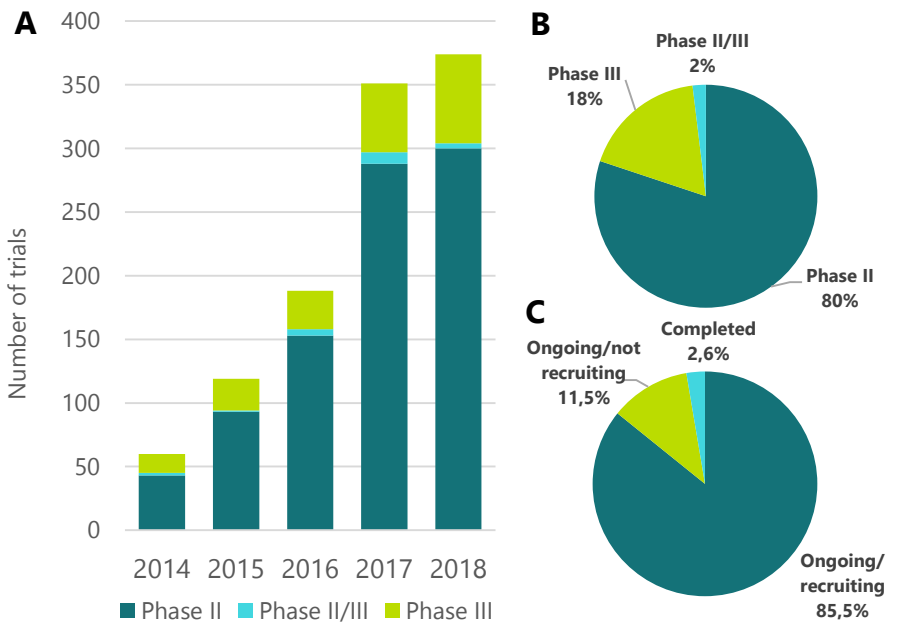


Figure 1 Number, Phase and Status of Trials: Immuno-oncology combination trials between 2014 and 2018 are shown by the number of trials per year (A), trial phase (B) and status (C).

2. Analysis of the number of combinations in IO trials

A

- **1096** trials
- **1237** combinations
- **237** unique IO regimens

B

No of combinations per trial	% of total
1	89,2
2	8,2
3	1,6
4	0,7
5	0,1
6	0,1

C

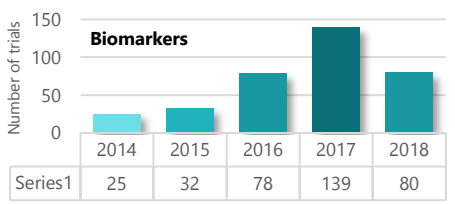


Figure 2 Analysis of combination trials: Number of trials and number of combinations 2014 – 2018 (A). Number of combinations per trial (B). The use of biomarker in combination trials (C).

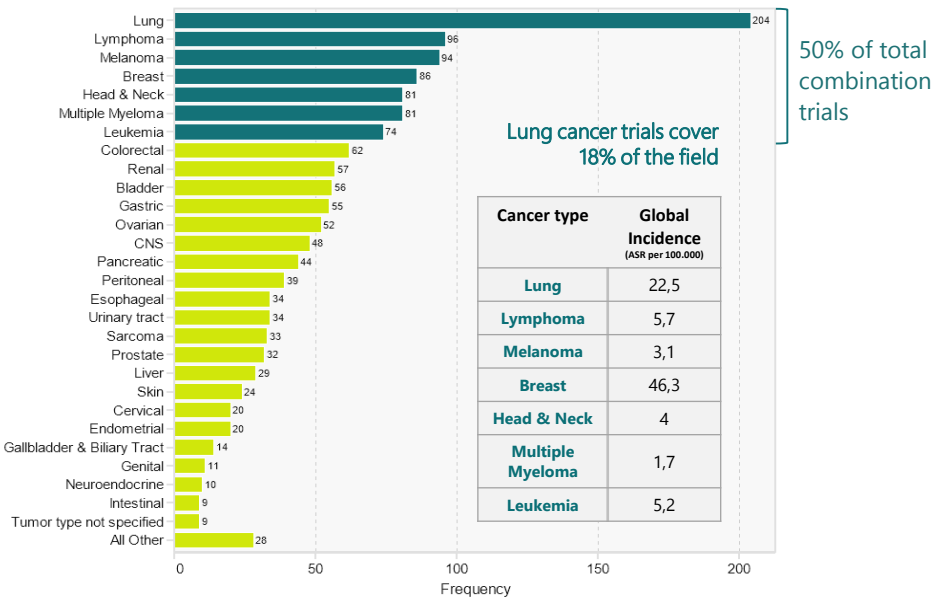
3. Top 5 IO combinations tested in trials

Figure 3 Top 5 investigated combination therapies: Displayed are the percentage of trials of total investigated therapies (n=1096). Together, the Top 5 account for almost 50 % of IO combination trials between 2014 – 2018.

Methods

External clinical trial search was performed using a global intelligence data platform and public clinical trial databases. Trials were selected on multiple criteria and the data export included **Phase II, II/III** and **Phase III** trials started between **01Jan2014** and **17Jan2019**. The total registry was sorted by the classification of immunotherapies and their combination partners. Analysis into the registry filtered out combinations that lacked immunotherapies. This immuno-oncology combination trial database was used to uncover trends and the results of the analysis are presented.

4. Tumor indications assessed in IO combination trials



Cancer type	Global Incidence (ASR per 100.000)
Lung	22,5
Lymphoma	5,7
Melanoma	3,1
Breast	46,3
Head & Neck	4
Multiple Myeloma	1,7
Leukemia	5,2

Figure 4 Overview of tumor indications: In total 34 tumor types are ranked based on the number of times each indication is investigated in IO combination trials.

5. Combination trials without immune checkpoint inhibitors

Tumor-targeting antibodies are most investigated, either with anti-angiogenesis- or chemo-therapy.

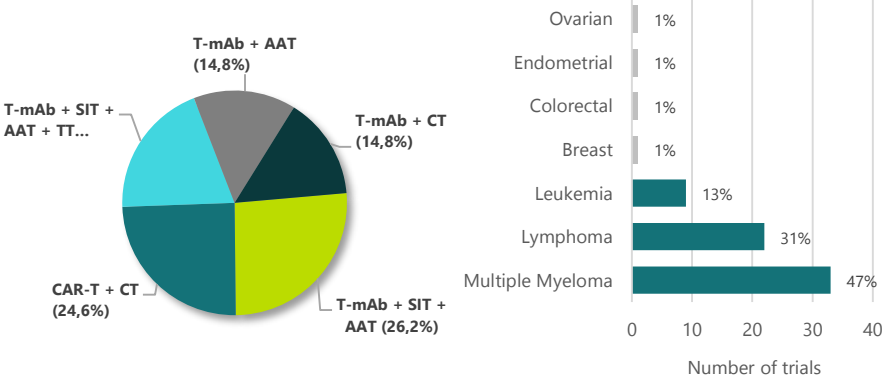


Figure 5 Top 5 investigated combination therapies excluding immune checkpoint inhibitors: Displayed are the percentage of trials and their combination therapies from a total of 1096 combination trials.

Conclusions

- Phase II – III trials in immuno-oncology are increasing with a minority being completed between 2014 - 2018
- The majority of combination trials evaluates one combination and overall there are 237 unique combinations being trialed
- Immune checkpoint inhibitors are dominating the combination therapies tested
- In the setting of IO combination trials lung cancer is the most assessed tumor type
- Excluding immune checkpoint inhibitors from the analysis reveals a different trial landscape in terms of tumor types and combination therapies