Comparison of Phase I/II trials regarding antigen-specific versus non-specific anticancer immunotherapies

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Introduction

Antigen-specific immunotherapy targets particular tumour associated antigens in order to address and eradicate solely tumour-marker defined cancer cells. In contrast, non-specific agents generally stimulate the immune system by for example reversal of immune suppression, or activation of innate immunity for a better anti-cancer immune response. We investigated whether differences among these two classes are reflected in patient selection, objectives and results of Phase I/II studies.

Materials and Methods

A PubMed search for full length English articles published from 2010-2014 describing completed cancer immunotherapy phase I/II studies was conducted. Parameters were extracted and entered into a database to compile summary tables.

Results

The Pubmed search yielded 123 Phase I/II immune oncology articles. Table 1 provides an overview of the articles that were found for each year. Antigen-specific (79%) agents were investigated almost 4 times more than non-specific (21%) agents.

Table 1: Antigen-specific versus non-specific articles

Year	Articles N	Antigen-specific N (%)	Non-specific N (%)
2010	23	13 (11%)	10 (8%)
2011	27	24 (20%)	3 (2%)
2012	26	20 (16%)	6 (5%)
2013	24	21 (17%)	3 (2%)
2014	23	19 (15%)	4 (3%)
Total	**123**	**97 (79%)**	**26 (21%)**

Patient population

In total, 3518 patients were enrolled in the 123 phase I/II immune-oncology trials (Table 2). On average, a trial consisted of 29 patients. The median number of patients per trial was 18. Non-specific trials enrolled on average more patients (44 patients) than antigen-specific trials (25 patients).

Table 2: Distribution of patient population

	Antigen-specific N (%)	Non-specific	Total
Patients	2377 (68%)	1141 (32%)	**3518 (100%)**
Median (Q1:Q3)	17 (10:27)	27 (14:40)	**18 (11:30)**
Mean (range)	25 (5:187)	44 (6:296)	**29 (5:296)**

Most trials (95 [77%] of the 123) enrolled late-stage patients (Figure 1). Early-stage and disease-free patients were enrolled in only two (2%) and five (4%) trials, respectively.

Figure 1: Disease stages of participating patients

Single or mixed tumour types

As shown in Table 3, 73 (59%) of all trials used patients with a single tumour type. A significant difference was found between antigen-specific and non-specific trials, regarding the use of patients with single or mixed tumour types. According to this result, antigen-specific trials used more often a patient population with a single tumour type (68%) than non-specific trials (27%).

Table 3: Single or mixed tumour types

	Antigen-specific	Non-specific	Total
Tumour type	N (%)	N (%)	N (%)
Single*	66 (68%)	7 (27%)	73 (59%)
Mixed	31 (32%)	19 (73%)	50 (41%)
Total	**97 (100%)**	**26 (100%)**	**123 (100%)**

***P value: 0,0002 (chi-square test)**

Patient selection based on biomarkers and tumour type.

A significant difference was found between antigen-specific and non-specific trials, regarding patient selection based on biomarkers (Table 4). Antigen-specific trials selected patients significantly more often using biomarkers than non-specific trials.

Table 4: Patient selection with biomarkers

	Antigen-specific	Non-specific
Patient selection with bi-omarkers	**N (%)**	**N (%)**
Yes*	49 (51%)	4 (15%)
No	48 (49%)	22 (85%)
Total	**97 (100%)**	**26 (100%)**

***P value: 0,0013 (chi-square test)**

Route of administration

As shown in Table 5 the route of administration (RoA) for antigen-specific agents was mainly *SC* (39% vs 12%) and *ID* (37% vs 0%) compared to non-specific, whereas for non-specific agents it was mainly *IV* (46% vs 13%).

Table 5: Route of administration

RoA	Antigen specific %	Non-specific %	Δ Difference %
Not mentioned	2%	4%	-2%
Topical (TP)	0%	8%	-8%
Subcutaneous (SC)	39%	12%	28%
Per os ; by mouth (PO)	0%	8%	-8%
Post cibum; after meals (PC)	1%	0%	1%
intravesical (IVE)	0%	8%	-8%
intravenous (IV)	13%	46%	-33%
intratumorally (IT)	1%	8%	-7%
intraperitoneally; (IPT)	1%	0%	1%
intrapleural; (IP)	0%	4%	-4%
Intranasal (IN)	6%	0%	6%
Intramuscular (IM)	4%	0%	4%
intralesional; (IL)	0%	4%	-4%
Interadermal; (ID)	37%	0%	37%
intracutaneously; (IC)	2%	0%	2%

Study objective

In trials with antigen-specific agents the objectives “pharmacokinetics” (6% vs 54%) and the “maximum tolerated dose” (MTD, 10% vs 46%) were chosen less often compared to non-specific agents (Table 6).

Table 6: Objectives antigen vs non-specific immunotherapies

Objective	Antigen specific %	Non-specific %	Δ Difference %
Safety & Tolerability			
Safety	73%	73%	0%
Toxicity	18%	19%	2%
Tolerability	19%	27%	8%
MTD	10%	46%	36%
RP2D/RD/OD	4%	12%	7%
DLT	3%	19%	16%
Efficacy			
Efficacy	78%	96%	18%
PK			
PK	6%	54%	48%
PD			
PD	62%	54%	-8%
BOD	7%	4%	-3%
Biomarker evaluation	1%	8%	7%
Tumor expression	1%	4%	3%
Other			
Feasibility	11%	4%	-7%
Comparison drugs	1%	0%	-1%
Comparison patient population	2%	0%	-2%
Viral shedding	1%	0%	-1%
RoA	2%	0%	-2%

Tumour response evaluation

In total, 90 of the 123 trials (73%) evaluated tumour response (Figure 2). From these, 72 trials (80%) evaluated tumour response based on RECIST, whereas none used only irRC. Three of the 90 trials (just over 3%) evaluated tumour response based on both RECIST and irRC. Seven trials (8%) used other tumour response criteria (WHO criteria, modified RECIST, or MacDonald criteria).

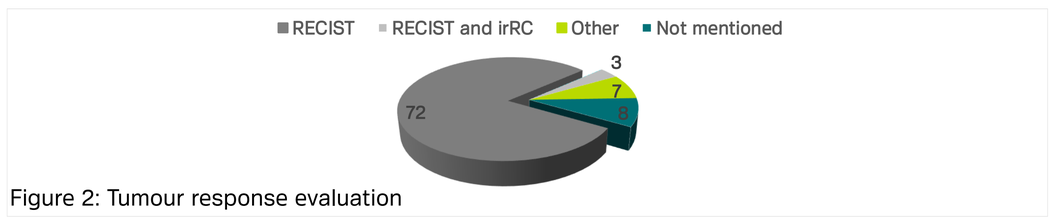

Figure 2: Tumour response evaluation

Optimal dose finding

Table 7 illustrates the amount of trials that made an optimal dose decision. This was defined as trials that recommended a dose for further investigation. Proportionally, more non-specific trials (46%) decided on an optimal dose than antigen-specific trials (23%).

Table 7: Optimal dose decision

Optimal dose decision:	Antigen-specific N trials (%)	Non-specific N trials (%)
Yes*	22 (23%)	12 (46%)
No	75 (77%)	14 (54%)
Total	**97 (100%)**	**26 (100%)**

***P value: 0,0175 (chi-square test)**

From the 34 trials that identified an optimal dose, 29 trials (85%) measured the MTD. However, the MTD was only reached in six (18%) of these trials: Five (19%) with non-specific and one (1%) with antigen-specific agents (Table 8).

Table 8: MTD in trials with optimal dose decision

MTD investigated	Antigen-specific N trials	Non-specific N trials	Total N trials
Yes	17 (77%)	12 (100%)	29 (85%)
If Yes, MTD reached in	1	5	6 (85%)
No	5 (23%)	0 (0%)	5 (15%)
Total	**22 (100%)**	**12 (100%)**	**34 (100%)**

Conclusion

There were differences in patient selection, objectives and results for studies with antigen-specific compared to non-specific agents. The main differences between both groups are:

- usage of single tumour indication (**68% vs 27%**),
- biomarker based patient selection (**51% vs 15%**),
- the route of administration (***SC*** & ***ID*** **vs** ***IV***),
- choice of objectives: pharmacokinetics (**6% vs 54%**) and MTD (**10% vs 46%**),
- decision on an optimal dose (**23% vs 46%**).

References

A list with references of the 123 articles can be provided upon request.