WILSONS ADVISORY

Date 25 July 2024

Theme Company Update

Sector Healthcare

Company

Immutep Limited (IMM)

Next steps for Efti in HNSCC

We maintain our OVERWEIGHT rating with revised risked PT of $1.05/sh for Immutep. In the wash up following the topline data from Immutep's Phase IIb TACTI-003 trial in metastatic head and neck cancer (mHNSCC) we have seen the market react almost in opposition to the clinical and pharma community. Not to sugar coat things, we too were disappointed by the performance of the Efti combination in the low PD-L1 cohort (CPS 1-19) only in terms of where it stood vs a stellar performance by the control Keytruda arm (2x prior trial norms) which extinguished comparative benefit. Strong synergies in both the high PD-L1 (CPS≥20) and PD-L1 negative (CPS<1) cohorts however, demonstrating +68% and +689% respective response rate uplifts v comparator monotherapy, maintains our confidence in Efti's synergistic ability to boost and expand anti-PD-L1 blockbusters such as Keytruda. This remains core to our investment thesis. Whilst we await further explanation around the PD-L1 positive cohort data, we can be confident in the market opportunity in the hardest to tackle CPS<1 group. Putting our most conservative hat on, we slim the mHNSCC opportunity down to just these patients recognising that positive Overall Survival data from the study is critical to progressing this US$450M potential opportunity, which we should get within the next ~9 months. Leaps to trash Efti and its potential opportunity in NSCLC based on this data are outlandish with a ~20 month survival benefit hard to refute.

Recommendation	**OVERWEIGHT**
12-mth target price (AUD)	$1.05
Share price @ 24-Jul-24 (AUD)	$0.32
Forecast 12-mth capital return	225.6%
Forecast 12-mth dividend yield	0.0%
12-mth total shareholder return	**225.6%**

Market cap ($m)	468.5
Enterprise value ($m)	345.0
Shares on issue (m)	1,453
Sold short (%)	0.2
ASX All Ords weight (%)	0.0
Median turnover/day ($m)	1.2

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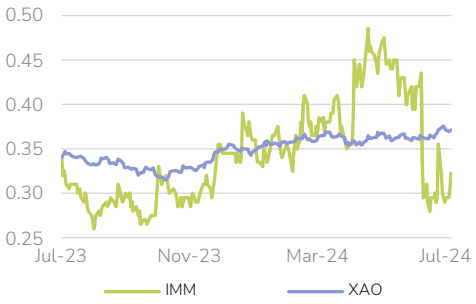
12-mth price performance ($)



	1-mth	6-mth	12-mth
Abs return (%)	(23.2)	(3.7)	(5.1)
Rel return (%)	(25.4)	(9.1)	(13.1)

Key Points

CPS<1 a key market opportunity. The PD-L1 negative cohort in 1L mHNSCC is nothing to scoff at. We can see US$450M sales opportunity that does not require displacement of existing SoC chemotherapy regimens, supported by the positive data, dearth of other options and strong safety profile of Efti + Keytruda combination. Accelerated Approval remains a maybe, but predicates indicate it's not unrealistic provided we see good translation of ORR benefit to OS early next year.

Setting the record straight. The view that this trial has shown Efti has failed is just false. Results demonstrate a robust uplift vs Keytruda monotherapy in all cohorts bar one – owing to a high control response. More data is needed to inform why this occurred but, in the meantime, comparison to an "expected" control response sees ~90% uplift with Efti addition – hardly a fail.

TACTI-004. The Phase III trial in mNSCLC has all final approvals to initiate site setup and begin recruitment having finalized regulatory discussions. IMM anticipate first patients 4Q24/1Q25, keeping them on track for end CY25 futility analysis, and end CY26 interim analysis.

Forecasts. No changes, until FY28e onwards - slimmed down mHNSCC opportunity focused on CPS<1 only. Peak sales reduce from US$850M to US$450M (outer years) reflecting the smaller population, however we maintain there remains upside to this conservative approach. R&D investment of $35M for Phase III HNSCC unchanged, as is AA as upside to our base case.

Valuation. Maintain O/W. SOTP valuation of $1.05/sh (-7%) reflecting removal of CPS≥1 patients from the mHNSCC opportunity for Efti. Risked PT $1.05/sh comprises: a) Efti 1L NSCLC ($0.75/sh); b) Efti in mBC ($0.21/share); and c) Efti in HNSCC ($0.09/sh). Unrisked $6.34/sh.

Financial summary (Y/E Jun, AUD)	FY22A	FY23A	FY24E	FY25E	FY26E
Sales ($m)	0.0	0.0	0.0	0.0	0.0
EBITDA norm ($m)	(34.7)	(40.8)	(43.1)	(51.9)	(45.0)
Consensus EBITDA ($m)			(46.5)	(53.0)	(60.4)
EPS norm (cents)	(4.3)	(4.7)	(3.6)	(4.5)	(2.8)

Key changes		1-Jul	After	Var %
EBITDA	FY24E	(43.1)	(43.1)	0%
norm	FY25E	(51.9)	(51.9)	0%
($m)	FY26E	(45.0)	(45.0)	0%
EPS	FY24E	(3.6)	(3.6)	0%
norm	FY25E	(4.5)	(4.5)	0%
(cents)	FY26E	(2.8)	(2.8)	0%
Price target		1.13	1.05	-7%
Rating		O/W	O/W	

Source: Company data, Wilsons Advisory estimate, Refinitiv, IRESS.
All amounts are in Australian Dollar (A$) unless otherwise stated.

Business Description

Immutep (IMM:ASX) is a clinical stage Australian biopharma operating in the immuno-oncology (IO) sector with their portfolio of LAG-3 directed biologics. Immutep have four assets under development, all with strong IP protection; two of which are out-licensed (LAG525 - Novartis, IMP731 - GSK) with attached milestone and royalty revenue optionality, with the remaining two (Efti and IMP761) being developed in-house for a range of oncology (incl. HNSCC, NSCLC, mBC) and autoimmune indications.

Catalysts

a) achievement of clinical trial endpoints; b) partnership opportunities; c) regulatory approvals (including IND approvals); d) corporate activity.

Investment Thesis

We maintain our OVERWEIGHT rating with revised risked PT of $1.05/sh. Our confidence remains in Efti's synergistic ability to boost and expand anti-PD-L1 blockbusters such as Keytruda. This remains core to our investment thesis. Whilst we await further explanation around the PD-L1 positive cohort data, we can be confident in US$450M market opportunity in the hardest to tackle CPS<1 group (at a minimum). Leaps to trash Efti in NSCLC based on this data are outlandish and ignore data.

Risks

a) adverse clinical trial outcomes; b) negative regulator interactions; c) competitive intensity of immuno-oncology field; d) available capital.

P&L ($m)	FY22A	FY23A	FY24E	FY25E	FY26E
Sales	0.0	0.0	0.0	0.0	0.0
EBITDA norm	(34.7)	(40.8)	(43.1)	(51.9)	(45.0)
EBIT norm	(36.8)	(42.9)	(45.1)	(54.1)	(47.5)
PBT norm	(36.7)	(42.0)	(42.6)	(53.4)	(47.2)
NPAT norm	(36.7)	(42.0)	(42.6)	(53.4)	(33.1)
NPAT reported	(36.7)	(42.0)	(42.6)	(53.4)	(33.1)
EPS norm (cents)	(4.3)	(4.7)	(3.6)	(4.5)	(2.8)
DPS (cents)	0.0	0.0	0.0	0.0	0.0

Growth (%)	FY22A	FY23A	FY24E	FY25E	FY26E
Sales	n/m	n/m	n/m	n/m	n/m
EBITDA norm	24.4	17.5	5.5	20.5	(13.3)
NPAT norm	22.6	14.4	1.5	25.4	(38.1)
EPS norm (cents)	(14.2)	9.0	(23.6)	25.4	(38.1)
DPS (cents)	n/m	n/m	n/m	n/m	n/m

Margins and returns (%)	FY22A	FY23A	FY24E	FY25E	FY26E

Interims ($m)	1H23A	2H23A	1H24A	2H24E	1H25E
Sales	0.0	0.0	0.0	0.0	0.0
EBITDA norm	(20.9)	(19.9)	(22.2)	(20.8)	(25.9)
EBIT norm	(21.8)	(21.0)	(23.2)	(21.9)	(27.0)
PBT norm	(21.6)	(20.4)	(21.2)	(21.4)	(26.6)
NPAT norm	(21.6)	(20.4)	(21.2)	(21.4)	(26.6)
NPAT reported	(21.6)	(20.4)	(21.2)	(21.4)	(26.6)
EPS norm (cents)	(2.5)	(2.3)	(1.8)	(1.8)	(2.2)
DPS (cents)	0.0	0.0	0.0	0.0	0.0

Stock specific	FY22A	FY23A	FY24E	FY25E	FY26E
R&D expense (m)	(31.3)	(36.3)	(40.4)	(50.0)	(25.0)
Licensing revenue (m)	0.2	0.0	0.0	0.0	0.0

Balance sheet ($m)	FY22A	FY23A	FY24E	FY25E	FY26E
Cash & equivalents	80.0	123.4	85.6	33.7	48.6
Current receivables	8.4	8.0	5.0	5.0	0.0
Current inventory	0.0	0.0	0.0	0.0	0.0
PPE	0.0	0.1	0.1	0.1	0.1
Intangibles	10.6	9.5	9.5	9.5	9.5
Other assets	3.2	6.5	4.9	5.7	3.4
Total assets	102.2	147.4	105.2	53.9	61.6
Current payables	5.8	9.0	8.2	9.9	6.6
Total debt	0.0	0.0	0.0	0.0	0.0
Other liabilities	2.2	1.8	2.1	2.1	2.6
Total liabilities	8.1	11.0	10.5	12.2	9.4
Minorities	0.0	0.0	0.0	0.0	0.0
Shareholders equity	94.1	136.5	94.7	41.8	52.2

Cash flow ($m)	FY22A	FY23A	FY24E	FY25E	FY26E
Operating cash flow	(30.2)	(35.4)	(36.4)	(51.7)	(31.8)
Maintenance capex	(0.0)	(0.1)	(0.0)	(0.0)	(0.0)
Free cash flow	(30.3)	(35.4)	(36.4)	(51.8)	(31.9)
Growth capex	0.0	0.0	0.0	0.0	0.0
Acquisitions/disposals	0.0	0.0	0.0	0.0	0.0
Dividends paid	0.0	0.0	0.0	0.0	0.0
Other cash flow	(3.3)	(1.2)	(1.3)	(0.2)	(3.2)
Cash flow pre-financing	(33.6)	(36.6)	(37.8)	(52.0)	(35.1)
Funded by equity	53.0	80.1	0.0	0.0	50.0
Funded by cash/debt	(72.4)	(123.5)	37.8	52.0	(64.9)

Liquidity	FY22A	FY23A	FY24E	FY25E	FY26E
Cash conversion (%)	87.4	88.9	90.4	101.1	102.8
Net debt ($m)	(80.0)	(123.4)	(85.6)	(33.7)	(48.6)
Net debt / EBITDA (x)	2.3	3.0	2.0	0.6	1.1
ND / ND + Equity (%)	(568.1)	(945.6)	(947.3)	(416.5)	n/m
EBIT / Interest expense (x)	n/m	46.7	18.0	74.0	n/m

Valuation	FY22A	FY23A	FY24E	FY25E	FY26E
EV / Sales (x)	n/m	n/m	n/m	n/m	n/m
EV / EBITDA (x)	n/m	n/m	n/m	n/m	n/m
EV / EBIT (x)	n/m	n/m	n/m	n/m	n/m
P / E (x)	n/m	n/m	n/m	n/m	n/m
P / BV (x)	2.9	2.8	4.0		
FCF yield (%)	(11.0)	(9.3)	(9.5)		
Dividend yield (%)	0.0	0.0	0.0	0.0	0.0
Payout ratio (%)	0.0	0.0	0.0	0.0	0.0
Weighted shares (m)	849.9	892.5	1,186	1,186	1,186

Source: Company data, Wilsons Advisory estimate, Refinitiv, IRESS.
All amounts are in Australian Dollar (A$) unless otherwise stated.

HNSCC data washup: implications and next steps

Where to from here? PD-L1 negative (CPS<1) cohort

CPS<1 cohort the key go-forward opportunity on an ROI basis. In the wake of the impressive Part B data from the TACTI-003 Phase IIb trial in PD-L1 negative (CPS<1) 1L mHNSCC patients we anticipate this to be the target cohort for IMM to pursue for Efti – purely on the basis of return-on-investment potential, with a) the most convincing data, b) the lack of competitors and c) the highest unmet need with potential for expedited development given the dearth of options for these patients. The overall response rate (ORR) of 35% achieved with the Efti + Keytruda combo compares favourably vs Keytruda (pembrolizumab) alone (5%) or chemotherapy-based current standard of care (SoC) (31 -39%). This result has demonstrated an ability to turn cold tumours hot – and hence ~7x the Keytruda response rate – and importantly match chemotherapy regimens albeit in the absence of material toxicity (Grade ≥3 AEs 15% vs 69-72%) (comparative data summary in **Figures 1 & 2**).

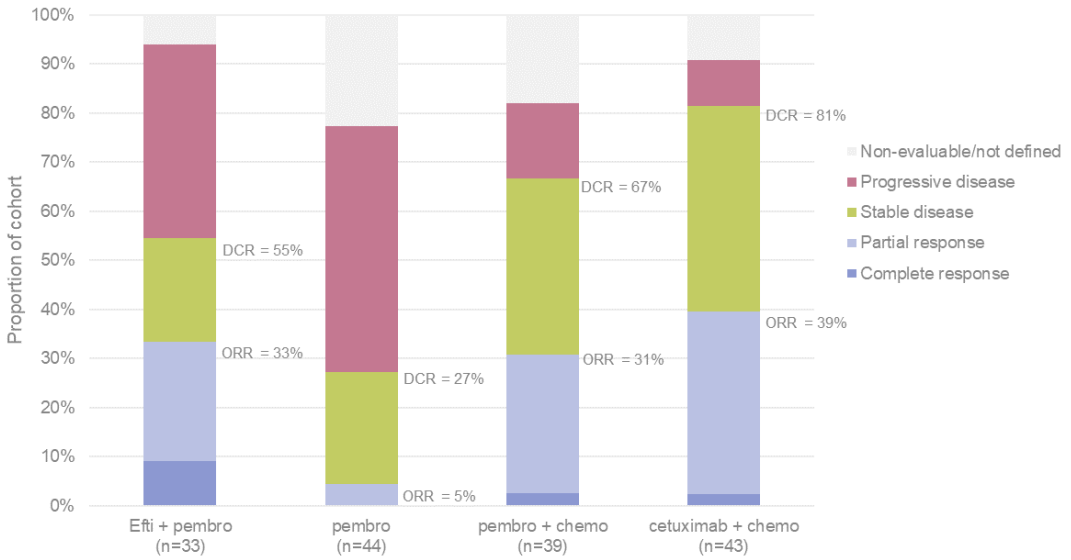
Complete response rate markedly better; can it translate to survival benefit? Notably, on a complete response basis, the Efti + Keytruda combo generated 3-4-fold more CRs that of SoC (9% vs 0-3%; **Figure 2 overleaf**), meaning more patients achieved optimal treatment (marked tumour reductions) with this combination. This data is still immature and therefore we have opportunity to potentially see further partial responses or stabilisations (impacting ORR/DCR) with time. Translation of this response benefit to elongation of overall survival (OS) is the next key readout we require confirming clinical benefit– which we would anticipate no earlier than 4Q'24 (likely ~1Q'25). Keeping in mind, a 2-3 month survival benefit on the basis of ~11.7months median OS for comparator regimens is the benchmark we seek (i.e. ~15month median OS aim for Efti + Keytruda).

Figure 1: Updated TACTI-003 data versus historical data, current SoC and competitor programs in 1L mHNSCC

Comparison of relevant trial programs in 1L mHNSCC							
	Efti + pembrolizumab	Efti + pembrolizumab	Pembrolizumab	Pembrolizumab	Pembro+ chemo	Cetuximab + chemo	Petosemtamab + pembro
	IO - IO	IO - IO	IO - IO	IO monotherapy (SOC only in 'hot' tumours)	IO - Chemo (now SOC)	2L SOC or for cold tumour patients	IO - EGFR/LGR5 bispecific
Checkpoint target	PD-1 + LAG-3	PD-1 + LAG-3	PD-1 + LAG-3	PD-1	PD-1	NA	NA
Study	TACTI-003 Part B	TACTI-003 Part A	TACTI-003 Part A	Keynote-048	Keynote-048	Keynote-048	NCT03526835
Phase	IIb	IIb	IIb	III	III	III	I/II
Therapy Line	1st	1st	1st	1st	1st	1st	1st
n	31	58	60	301	281	278	24
Demographics (% male)	74%	79%	70%	83%	80%	87%	78%
HPV status (% positive)	12.9%^	29%	65%	21%	21%	22%	57%
Current smoker	26%	22%	17%	*	*	*	NR
Median age	64	NR	NR	62	61	61	64
PD-L1 CPS <1	100%	0%	0%	15%	15%	15%	0%
CPS 1-19	0%	50%	55%	41%	40%	45%	42%
CPS ≥20		50%	45%	44%	45%	40%	56%
Median PFS	NR	NR	NR	2.3 months	4.9 months	5.2 months	NR
HR (for progression)	-	-	-	p>0.05	0.84 (p>0.05)	-	-
PF at 6 months	-	-	-	25%	45%	45%	-
Median OS	NR	NR	NR	11.6 months	13.0 months	10.7 months	NR
HR (for death)	-	-	-	0.83 (p=0.02)	0.77 (p=0.034)	-	-
Median Duration of response	>6 months	-	-	22.6 months	6.7 months	4.3 months	-
ORR (total)	35.5%	34.0%	26.7%	16.9%	36.0%	36.0%	67.0%
ORR CPS <1	35.5%	-	-	4.5%	30.8%	39.5%	-
ORR CPS ≥1	-	32.8%	26.7%	19%	36%	36%	67%
ORR CPS 1-19	-	34.5%	33.3%	14.5%	29.3%	33.6%	60%
ORR CPS ≥20	-	31.0%	18.5%	23%	38%	43%	71%
DCR (total)	58.1%	75.9%	59.3%	44%	64%	70%	87.5%
Response criteria	RECIST v1.1	RECIST v1.1	RECIST v1.1	RECIST v1.1	RECIST v1.1	RECIST v1.1	RECIST v1.1
Treatment-related Adverse Events (AEs)							
Discontinuation AEs	6%	6%	4%	0%	8%	9%	4%
Grade ≥3 AEs	15%	NR	NR	17%	72%	69%	40%
AEs leading to death	0%	NR	NR	1%	4%	3%	0%

^in patients with oropharyngeal tumours only. * only current + former smoker prevalence reported, not in a LFL manner with TACTI-003 reporting thus far. NR: Not reported. Petosemtamab included as a relevant competitor program from Merus therapeutics.
Source: Immutep, MSD, Merus Therapeutics, company data.

Figure 2: Response data comparison on CPS<1 cohorts only vs historical and SoC data



NOTE: This presents the Efti data on a LFL basis to KN-048 trial noting there were 31 of 33 patients evaluable, and hence the ORR/DCR are incrementally lower as a % of the total recruited cohort (ORR 35.5% reflects total evaluable cohort). This is to ensure apples for apples comparisons are being made.
Source: ESMO TACTI-003 presentation, Keynote-048 trial, company data.

Sizing the CPS<1 opportunity vs time/investment. The proportion of mHNSCC patients with PD-L1 absent tumours (CPS<1 group) is something that is poorly reported, with published ranges of 16-61% identified in our research[1,2,3]. We note Immutep have reported 20% of total mHNSCC as PD-L1 negative on the basis of MSD's KEYNOTE-048 study – noting of course this was not designed as a controlled incidence study and was convenience sampling. A meta-analysis of 23 trials conducted in HNSCC reports a ~41% proportion of CPS<1 patients[1], with another six study analysis suggesting PD-L1 negativity of tumours averaging 36% of patients across studies (21-61% range)[3]. Noting this, we align our modelling with Immutep's quoted 20% proportion to be conservative, however, appreciate that the sizing of this cohort could be ≥2x this size opportunity. Based on incidence levels of HNSCC across major markets, along with understood metastases rates, we continue to estimate an addressable population of 75,000 patients per year in 1L mHNSCC cohort across US/EU (with EU representing 2x market of US based on far higher incidence). Hence our CPS<1 addressable population estimate is 15,000 patients per year. In revised peak sales years, we assume treatment of ~5,000 CPS<1 patients. Applying a 30% incidence rate to CPS<1 lifts potential sales by 50%.

Further detail given later in this report, however, simply the return on investment required for the CPS≥1 cohorts is perhaps less evident from the current standpoint, with stronger SoC/competitive dynamics and less of an effect size uplift to support it. The CPS≥20 cohort of course demonstrating impressive ~doubling of ORR with Efti addition still demonstrates opportunity – albeit in a relatively less desperate patient cohort vs CPS<1.

Current SoC to displace in CPS<1. The current standard of care (SoC) for 1L mHNSCC with PD-L1 negative tumours is a chemotherapy-based regimen, either incorporating a combination with Keytruda (in US) or cetuximab (in EU). In each case it is understood that approximately 50% of these patients either refuse (~30%), or are ineligible for (~20%) chemotherapy, leaving them with very limited options – none efficacious. The opportunity for Efti in this patient group is to provide an efficacious alternative that is chemotherapy-free, and thus has a markedly reduced side effect/toxicity burden. Whilst we look to the Keytruda monotherapy historical data to see a 6-7x uplift with Efti addition, we more closely focus on that of the two commonly used chemotherapy regimens. Whilst their ORR levels are comparable to the Efti+Keytruda combo (31-39% vs 35%) the potential durability of the Efti combo (we are yet to see, premised on the differences seen with IO-IO vs IO-chemo combinations in the past), and its toxicity profile differs, offering a key point of differentiation that will drive market uptake. Notably, the initial target market we have modelled is of patients that are not currently receiving any chemotherapy-based regimen and hence there is limited to no competitive displacement required to achieve our market assumptions.

[1] Yang *et al*. 2018. The prognostic role of PD-L1 expression for survival in head and neck squamous cell carcinoma: A systematic review and meta-analysis. *Oral Oncology*. 86: 81-90.
[2] Lu et al. 2023. PD-L1 expression in recurrent or metastatic head and neck squamous cell carcinoma in China (EXCEED study): a multicentre retrospective study. *J Clinical Pathology*. doi: 10.1136/jcp-2023-209059
[3] Qiao et al. 2020. The evolving landscape of PD-1/PD-L1 Pathway in Head and Neck Cancer. *Frontiers in Immunology*. 11:1721.

Reminder on Accelerated Approval (AA) process. AA can be granted in situations where there is a high unmet need with existing data supporting positive efficacy and safety of a drug (typically on a surrogate endpoint), that is not generated from a pivotal/registrational late-stage trial (i.e. Phase III). AA have been seen in many oncology drugs and are particularly relevant for metastatic settings where patients have often low/non-existent cure rates and hence there is acceptance of a more 'liberal' approach to drug development.

The opportunity for AA in mHNSCC for an Efti + Keytruda combination has been raised for some time prior to TACTI-003 readout on the basis that strong efficacy signals could support such a filing with FDA. Importantly, this has never been our base case assumption and presented upside risk in our modelling of the mHNSCC opportunity for Efti. In any case, being granted AA does not dispel the requirement for a confirmatory Phase III trial – that is conducted in parallel to the drug being marketed (if AA granted). It is a regulatory requirement of AA that a Phase III program be planned and underway to receive AA (non-negotiable). In fact, a recent FDA change in 2022 can now require that a confirmatory trial to be enrolling patients at the time of an AA being granted as a precedent (to prevent lag time by companies on initiating the study – which has been a material problem over time).

Hence, we have continued to model a Phase III mHNSCC program with $35M R&D expense forecast for a small confirmatory study, and a further 2-3-year timeframe allowed to conduct the study prior to a standard approval (hence our FY28e first revenue assumption). It is our assessment some of the market has misunderstood this Phase III requirement in the event of AA, with this presenting further time/costs they did not anticipate. We would reiterate this has always been the premise of our forecasts.

Predicates for potential CPS<1 AA. Exact predicates are challenging to identify however we have found examples and guidelines supporting AA; a) for just a selected PD-L1 subgroup/s; b) based on single arm, non-randomised study data; c) on the basis of ORR endpoint, and d) with no approved treatment options[4,5].

FDA guidance for AA does not exclude the potential for single-arm trials with comparisons to historical data and note that ORR is the most typical endpoint used to support approvals when this nature of data is available[6]. Sample size may be small however must be able to adequately provide precision around the endpoint effect size (with the CPS<1 uplift at least robust vs controls) as well as inform duration of response and sufficiently describe the safety profile. In IMM's case they have data from a much larger HNSCC cohort (Part A) as well as TACTI-002 Part C data which included a further 12 CPS<1 patients. This is all supportive of a robust safety profile of the Efti + Keytruda combination to inform FDA decision-making. Importantly guidance reiterates the fact that AA is for cancers in which there are no alternative treatment options. We would argue that the CPS<1 cohort fits this requirement, at a minimum for the ≥20% of these patients that are unable to tolerate chemotherapy-regimens (and hence have no approved treatment options available to them).

Examples of accelerated approvals based on single-arm trials with ORR as the approvable endpoint include trastuzumab deruxtecan. AA was granted to AstraZeneca in 2022 for HER2-mutated NSCLC on the basis of ORR and duration of response (DoR) data[7]. GSK's dostarlimab-gxly is another such example[8] of AA (Aug 2021) granted on the basis of ORR and (DoR) data from a non-randomised, single arm Phase I/II study. These recent examples support the potential for CPS<1 accelerated approval, noting that we would only change this to our base case assumption following the availability of strong DoR data, as well as OS data that confirms a material survival response benefit over chemotherapy-based SoC regimens.

PFS not helpful here. It should be noted that progression-free survival (PFS) is as common surrogate endpoint used in AA. Notably, PFS has a very poor correlation with OS benefit in mHNSCC. For example, Keytruda monotherapy demonstrated median PFS of just 2.3 months in the pivotal KEYNOTE-048 trial vs 5 months for chemo-based regimens yet met or exceeded these on an OS basis (despite materially lower PFS). Clinical agreement is that PFS in this indication (and for immunotherapy) is not a good surrogate and hence ORR was the primary endpoint utilised, ahead of a confirmatory OS endpoint. Immutep should have PFS data from all TACTI-003 cohorts we expect in 2H CY24 however we question the relevance/importance of this data given what we know about its low readthrough value. OS likely in early CY25 is the informative endpoint of relevance.

[4] Gyawali B et al. 2023. The Accelerated Approval program for Cancer drugs – Finding the right balance. *New England Journal of Medicine*. 389 (11).
[5] Beaver J et al. 2021. "Dangling" Accelerated Approvals in Oncology. *New England Journal of Medicine*. 384 (18).
[6] Food and Drug Administration. Clinical trial considerations to support accelerated approval of oncology therapeutics: guidance for Industry. March 2023. Accessed online: https://www.fda.gov/media/166431/download
[7] https://www.astrazeneca.com/media-centre/press-releases/2022/enhertu-approved-in-us-for-her2-mutant-nsclc.html
[8] https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-dostarlimab-gxly-dmmr-advanced-solid-tumors

PD-L1 positive cohorts (CPS 1-19 and ≥20)

Exercise in hypotheticals: let's assume Keytruda "behaved" as it has in the past. If we look at the CPS≥1 population comprising both the CPS 1-19 and CPS≥20 cohorts and compare the ORR of Efti + Keytruda to what an expected Keytruda response rate was (i.e. substitute the CPS 1-19 ORR of 33.3% for the historical ORR value of 14.5%[9]) we see an ORR delta owing to Efti addition of +90% across CPS≥1 (32.8% combo vs ~17% control). This is of course more aligned with the expected uplift we had seen in 2L patients in TACTI-002. We appreciate this is not valid – an RCT trumps cross-trial comparisons, however we show this for illustrative purposes to identify that in fact we did not see the Efti combination "fail" but rather the control arm "excel". This is an important distinction some in the market are misinterpreting.

TACTI-003 Part A data: imbalances to blame? It is too soon to know why a clear correlation between ORR and CPS score was not seen across the Part A CPS cohorts, and notably why and how such a strong response rate (2x historical levels; ORR 33.3% vs KEYNOTE-048 14.5%) was observed with Keytruda monotherapy in the CPS 1-19 patient group. Immutep and their collaborator MSD are working to understand the data better with post-hoc analyses noting that this July data was preliminary topline data with much of the detail yet to be evaluated by the clinical team. Whilst a frustration for investors at present seeking answers, this is not an unrealistic situation given this was topline data and not a comprehensive final result with IMM still awaiting detailed data from clinical sites.

HPV positive patients generally have a better treatment prognosis in mHNSCC[10]. This is a generally accepted correlation, noting that there are studies supporting dose reductions in HPV-positive disease owing to this[11]. The estimated proportion of HNSCC cases that are HPV-positive is estimated at ~30% and rising (**Figure 3**). As a group, patients with HPV-positive HNSCC have improved clinical outcomes compared with patients with conventional, HPV-negative HNSCC when managed by similar modalities. This is even more evident in oropharynx located tumours.

We note that the Keytruda only arm in TACTI-003 had a 65% HPV-positive prevalence, compared to the Efti combo arm at 29% (**Figure 1**). KEYNOTE-048 as our key reference trial averaged 21% HPV-positive patients across all CPS cohorts. Notably, the Merus Therapeutics' Phase I/II petosemtamab data also shared a very high HPV positive rate (57%). We will await further data and analysis from IMM later this year but anticipate that HPV-status could have influenced Part A Keytruda response rates in a favourable manner given the material imbalance.

Figure 3: Differences between HPV-negative and HPV-positive HNSCC

Parameter	HPV-	HPV+
Gender	2-3 fold more common in men	4-5 fold more common in men
Age at diagnosis	Median age late 60s and 70s	Median age early 50s
Race		More common in Whites
Smoking	90% smoking history	50%-65% smoking history
Sexual behaviour	Not a significant risk factor	Number or oral and vaginal sex partners is an important risk factor
Site	Oral cavity and larynx most commonly	Oropharynx HPV+ <20% at other sites
Clinical picture	Varies	Early T stage, enlarged nodes
Incidence trends	Decreasing	Increasing
Survival rates	All sites: 65% 5-year survival Oropharynx: 25% 5-year survival	60%-80% 5-year survival

HPV-, Human papillomavirus negative; HPV+, human papillomavirus positive.

Source: ESMO[12]

The reality of stratification and recruitment. We appreciate IMM have indicated there are some imbalances between the two randomised groups in the Part A cohort, notably HPV-, smoking and site of primary tumour status. Having first-hand experience with recruitment of randomised and stratified clinical trials, the challenges of perfectly aligning groups across multiple international sites, with a small sample size (~60 per arm) is logistically challenging and a focus on perfect stratification by multi-factors would have significantly elongated recruitment of this trial – which was already behind initial estimates. The challenge of course with this study being recruitment of patients to a non-chemotherapy trial, from a cohort of clinicians that are used to chemotherapy-based regimens as SoC (always a tough displacement). We therefore do not see these imbalances as a failure of trial design or clinical management, but rather the realities of recruitment of a small trial such as this. We are yet to see a detailed breakdown of these baseline characteristics (HPV, smoker, sex, age) for each CPS cohort (CPS 1-19 and CPS ≥20) but can expect this detail at a conference in 2H '24.

[9] Burtness B et al. 2022. Pembrolizumab alone or with chemotherapy for recurrent/metastatic head and neck squamous cell carcinoma in KEYNOTE-048: Subgroup analysis by Programmed Death Ligand-1 Combined Positive Score. *Journal of Clinical Oncology*. 40 (21): 2321-2332.
[10] Johnson D et al. 2020. Head and Neck squamous cell carcinoma. *Nature Reviews Disease primers*. 6 (92).
[11] Yang M et al. 2022. Reduced-dose radiation in HPV-associated oropharyngeal carcinoma can improve outcome: a systematic review and meta-analysis.
[12] Economopoulou & Psyrri. 2017. ESMO Essentials for Clinicians: Head and Neck Cancers. Chapter 1; Epidemiology, risk factors and pathogenesis of squamous cell tumours. Accessed online

Recent competitive landscape changes. We had seen a dearth of actionable competition in mHNSCC until recently with Merus Therapeutics posting impressive (albeit early) Phase I/II data with petosemtamab, demonstrating ORRs of >60% across CPS 1-19 and CPS ≥20 cohorts when their asset was also combined with Keytruda (albeit in a non-randomised design; **Figure 1**). This data, whilst from a small cohort (n=24; PD-L1 positive only), is a promising early signal of potentially more to come from this asset, but is nevertheless from a small, non-randomised, immature program. This clearly has no impact on the CPS<1 landscape where there are no actionable programs in our assessment.

Upon further analysis of the baseline demographics, we can see that the Merus cohort carried a high level of HPV-positivity (57%; **Figure 1**) which as discussed above, is aligned with a more positive prognostic outcomes and has potentially 'aided' their high ORR results to date. Their drug is a bispecific antibody with a dual inhibitory mechanism of EGFR and LGR5. It seeks to inhibit EGFR signalling in two ways. Targeting EGFR is not a new approach of course in HNSCC, with a current SoC drug, cetuximab, an EGFR inhibitor. What is interesting perhaps for cetuximab, is that we have seen positive responses in HPV positive cases which have typically fared worse with cetuximab treatment. The data with petosemtamab is clearly early and we will keep a close eye on this program, tracking its potential in CPS≥1 HNSCC cohorts.

Relevance to TACTI-004 in 1L NSCLC?

Different starting points and different indications. HNSCC and NSCLC are chalk and cheese when we think about the backdrop for each indication. In the case of NSCLC, we see largely homogenous populations with a broad approval of IO-IO combinations already SoC (four currently). On the flip side, mHNSCC encompasses a broad range of cancers (oral cavity, oropharynx, larynx, sinonasal) with a large degree of heterogeneity in responses and a dearth of approved treatment options.

In fact, we have seen quite a pile of failed HNSCC programs, with Eisai and MSD's Phase III LEAP-010 study the most recent failure combining Keytruda with Lenvatinib (a tyrosine kinase inhibitor). Benefits in PFS and ORR were observed but did not translate to OS benefit over Keytruda alone. BMS' Phase III Checkmate-651 IO-IO combination study with nivolumab (anti-PD1) and ipilimumab (anti-CTLA4) another notable failure, failing to demonstrate OS superiority over cetuximab + chemotherapy) The failure to show superior OS benefit (despite their being a positive trend) was put down to a better than expected response in the comparator SOC arm versus historical expectations – ironically a familiar outcome in light of IMM's recent CPS1-19 experience. The failure of this ipi/nivo combination in mHNSCC, which has shown survival benefits in ≥5 other cancer types (incl. NSCLC, metastatic melanoma, advanced renal cell carcinoma) perhaps highlights the challenge associated with mHNSCC treatment, its resistance to IO approaches and its high mortality rate. This failure joins that of AstraZeneca also in a Phase III 1L mHNSCC program (EAGLE) also looking at an IO-IO anti-PD-1/anti-CTLA-4 combination, as well as GSK and their INDUCE-3 program also aiming to boost Keytruda response in HNSCC – this time by combination with feladilimab, a cytotoxic T cell promotor. In summary, there are a multitude of failed IO programs in mHNSCC, including many with Keytruda combinations. It is a challenging disease and far more so than mNSCLC where existing treatment options are more abundant, and broad in scope.

Phase II data quality at outset. The supportive data for both the TACTI-003 (HNSCC) and upcoming TACTI-004 (NSCLC) programs has been generated from TACTI-002 (as well as INSIGHT-003 in the case of NSCLC). The data generated in the Phase II TACTI-002 trial in HNSCC was from 2L patients (differ to 1L) and from a small sample size (n=39). In comparison, the NSCLC Phase II data from that same trial was generated in the same 1L cohort as being trialled in Phase III and was from a larger sample (n=114), with a more robust two-stage trial design. It would be fair to characterise the supporting Phase II data for NSCLC as more robust at outset supporting the planned TACTI-004.

Outlook

Changes to mHNSCC opportunity in risked valuation

Carve out CPS≥1 in mHNSCC. We take a conservative stance, noting the possibility of further supportive data later this year/next 12 months that could increase the opportunity for Part A cohorts in 1L mHNSCC for Efti, and restrict our go forward opportunity in this indication to CPS<1 cohorts only. This is supported by our view that the greatest ROI for Immutep lies in this cohort, and there is still potential for accelerated/limited further clinical development to progress Efti to market in this high unmet patient group based on the TACTI-003 Part B data.

Then:
In our prior modelling of Efti's opportunity in mHNSCC we looked at a PD-L1 positive approach (CPS≥1 cohorts) with first sales from FY28e (assuming no AA granted) across both US and EU major markets in a 1L adjunct setting. Our prior peak sales estimate in this indication, representing ~14% peak market share (FY37e) of all mHNSCC patients (assumes ~75,000 total patients seeking treatment per year) was ~US$850M (global sales). This opportunity was risked with 35% probability of success and contributed $0.17/share to our risked valuation and $0.59 to our unrisked valuation. We would reiterate again that our modelling has never included AA as a base case assumption, and that we continue to model a $35M R&D investment in relation to a follow on (Phase III) trial in mHNSCC to support any major market approval filings.

And now:
We maintain all our prior key assumptions regarding indication prevalence, R&D investment, approval/revenue timelines, risk weightings and pricing for Efti in 1L mHNSCC. Key changes include reduction of the addressable market (and share) to those with PD-L1 negative tumours (CPS<1), with associated lifts in peak potential market share of this highest unmet need cohort – on the premise of being able to provide the first chemo-free regimen to this cohort with no other competing programs in this PD-L1 negative cohort we are aware of. We continue to model FY28e as first revenues (per prior) with peak sales moderated to US$450M generated from ~35% of the CPS<1 cohort (representing 7% share of total mHNSCC cases across EU/US markets). Our risked probability of success remains unchanged at 35% for this program.

Risked PT of $1.05/sh reflects the reduction of the mHNSCC portion of risked valuation from $0.17/sh to $0.09/sh with CPS<1 only included (unrisked $0.59/sh to $0.32/sh of $6.34/sh total valuation). We make no other changes to our SOTP valuation (**Figure 4**), stressing that we view this as a conservative go forward approach and that our positive investment thesis continues to be centred around the 1L NSCLC opportunity for Efti based on a successful TACTI-004 interim readout in CY26.

Figure 4: Updated SOTP valuation for Immutep

Valuation (SOTP)		Risked valuation (A$m)	Comments / methodology	Un-risked valuation (A$m)
Efti mBC		337	Real options valuation for EU and US market	1,145
Efti HNSCC		137	Real options valuation for EU and US market	460
Efti NSCLC		1178	Real options valuation for EU and US market	8,345
IMP761		-	Phase I data 2H CY24 to determine addition to valuation	-
LAG525		-	Licensed to Novartis (milestones/royalty optionality)	-
Enterprise value ($M)		1652		9950
EV per share (A$) - PT	**$**	**1.05**	**Unrisked price per share (A$)**	**6.34**
SOI used for PT (M)		1569.4		
Current cash (A$M)		195	Current probability of success within risked valuation	17%
Equity value per share (A$)	$	1.18		

Source: Wilsons Advisory.

Funding adequacy. There is no change to funding adequacy or our capital requirements in our modelling. Post the June equity raise, IMM continue to be funded through to end CY26 (~$195M) – at which time we anticipate having passed the futility analysis (end CY25) for their Phase III NSCLC trial and have completed recruitment of that n=750 patient pivotal trial, with an interim analysis also achievable by CY26 end. The implications of our changes to the mHNSCC sales forecasts do not impact cash flow adequacy given timing (FY28e onwards), noting of course the R&D expense for the HNSCC program is unchanged at $35M (within our forecasts).

Catalysts and news flow

2H CY24: We expect further detail regarding the baseline characteristics and post-hoc analysis from the TACTI-003 Part A data. There is potential also for median progression free survival (PFS) data and duration of response (DoR) from both Part A/B cohorts also – noting that PFS in HNSCC has been a very poor indicator of overall survival benefit and thus this data we anticipate having limited materiality in the progression of the TACTI-003 trial (until OS data). Further data could help determine any underlying explanation of Keytruda's wow response in CPS 1-19 patients.

IMP761 Phase I safety data in healthy volunteers, as IMM's leading autoimmune-focused asset. This is not in the market's focus at all, nor in valuation at present.

AIPAC dosing data which will inform the Phase III NSCLC program – i.e. if 90mg dose vs 30mg to date.

Further INSIGHT-003 readouts from the triple combination in NSCLC will be key supportive data for TACTI-004 also.

1H CY25: We can expect OS data from TACTI-003 which is key, particularly for the Part B cohort to determine if the ORR uplift demonstrated by adding Efti translates to a meaningful survival benefit in those patients.

IMP761 Phase I efficacy signal data from a proxy assessment of immune response in stimulated patients. This could provide the first efficacy signal to support movement into a Phase II patient clinical trial.

2H CY25: TACTI-004 NSCLC futility analysis as a key go/no-go point for IMM's largest opportunity. This is a critical catalyst.

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