post-asco update call

Core pipeline continues to advance

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Agenda

01 Pipeline highlights & strategy

02 Avelumab

03 TGF-ß trap / anti-PD-L1

04 Tepotinib

05 Upcoming catalysts

Pipeline highlights
Core pipeline continues to advance – select highlights

MS/ Immunology

Mavenclad
- Approved across Europe, Canada, Australia and additional countries
- US submission on track

Evobrutinib
- RMS: randomized controlled phase IIb trial positive – data at upcoming congress
- RA: signal finding positive; phase IIb ongoing
- SLE: phase IIb continues

Focus today

Oncology/ Immuno-Oncology

Avelumab
- Pivotal trials across six cancer types in seven indications ongoing
- ASCO 2018: 2-years landmark data in MCC – 36% survival at 2 years[1]
- 1L data published: ORR = 62%[2]

TGF-ß Trap/ Anti-PD-L1
- >670 patients safety database
- ASCO 2018: phase Ib data for two cohorts – NSCLC 2L; HPV-positive

Tepotinib
- Focus on c-met driven cancers
- ASCO 2018: NSCLC MET Exon 14 with ~50% response rates[3]
- Break-through designation for MET Exon 14 in Japan

(1) P. Nghiem et al, ASCO, Jun 2018 (abstract 9507) | (2) D'Angelo et al, JAMAOncology March 2018 (published online: 10.1001/jamaoncol.2018.0077) | (3) Felip E et al, ASCO 2018

Oncology strategy
Strategy anchored on five foundational pillars

1	**Targeted Oncology**	1. Erbitux: continued leadership in CRC and SCCHN 2. Tepotinib: c-met driven cancers	1. Numerous Erbitux ISTs incl. combination with Avelumab 2. Tepotinib in NSCLC, HCC
2	**Avelumab**	1. Monotherapy as a basis for combinations 2. Establish immunogenic priming in combination or sequence with CT/RT[1] 3. Novel combinations 4. Establish value of unique molecular characteristics (ADCC)	1. NSCLC 1L (high intensity) 2. Maintenance in UC 1L, gastric 1L, ovarian 1L 3. Avelumab + Inlyta (RCC 1L) 4. Unique combinations leveraging ADCC
3	**IO bi-functionals**	Engineer or access platforms where biology is best addressed by a bi-functional approach	• TGF-beta trap/anti-PD-L1 • Anti-LAG-3/anti-PD-L1 • NHS-IL 12
4	**DNA Damage Response inhibitors**	Establish leadership in DDR and leverage synergies across portfolio (immuno-oncology plus emerging platforms)	• DNA-PK-i • ATR-i • ATM-i
5	**Emerging Platforms**	Invest in complementary technologies within focus discovery areas	• Antibody-Drug-Conjugates (ADC, e.g. partnership with Mersana/Sutro)

[1] Acronyms: CT: Chemotherapy | RT: Radiotherapy | ATM: ataxia-telangiectasia mutated |ATR: ataxia telangiectasia and Rad3 | DNA-PK: DNA-dependent protein kinase | RCC: Renal Cell Carcinoma | MCC: Merkel Cell Carcinoma | NSCLC: non-small cell lung cancer | DLBCL: Diffuse Large B-cell Lymphoma | UC: Urothelial Cancer

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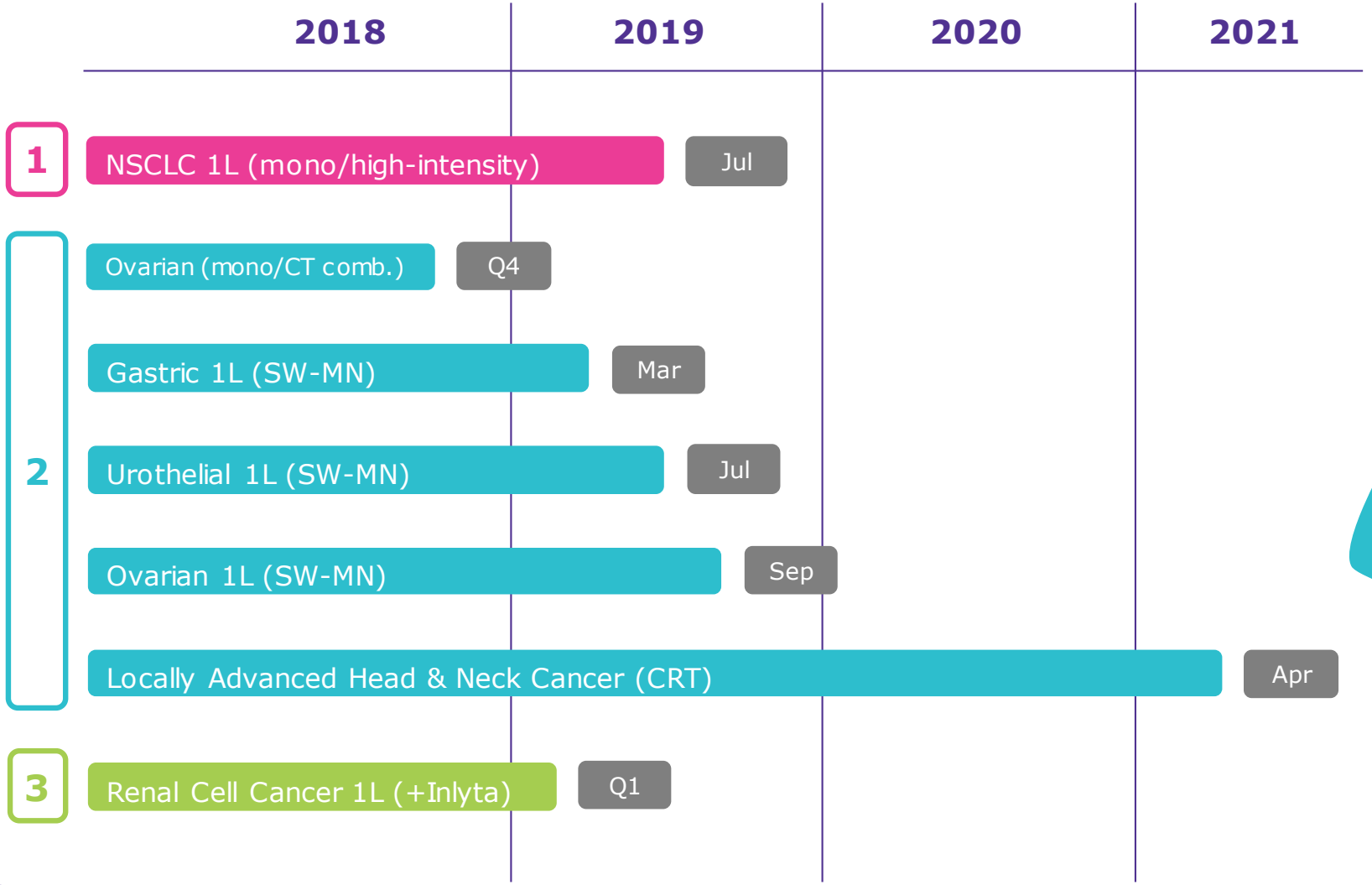
Avelumab:clinical program
Ongoing studies across six cancer types in seven indications



Monotherapy as basis for exploring combinations

Leverage potential of unique molecular characteristics (ADCC)

Establish potential of immunogenic priming (incl. combination and sequencing with CT/CRT)

Proprietary combinations

[1] Estimated primary completion date according to Clinicaltrials.gov as of June 7, 2018 | Acronyms: NSCLC: Non Small Cell Lung Cancer | CT: Chemotherapy | CRT: Chemoradiotherapy | Plat. Res./Ref.: Platinum Resistant/Refractory | MN: Maintenance | SW: Switch

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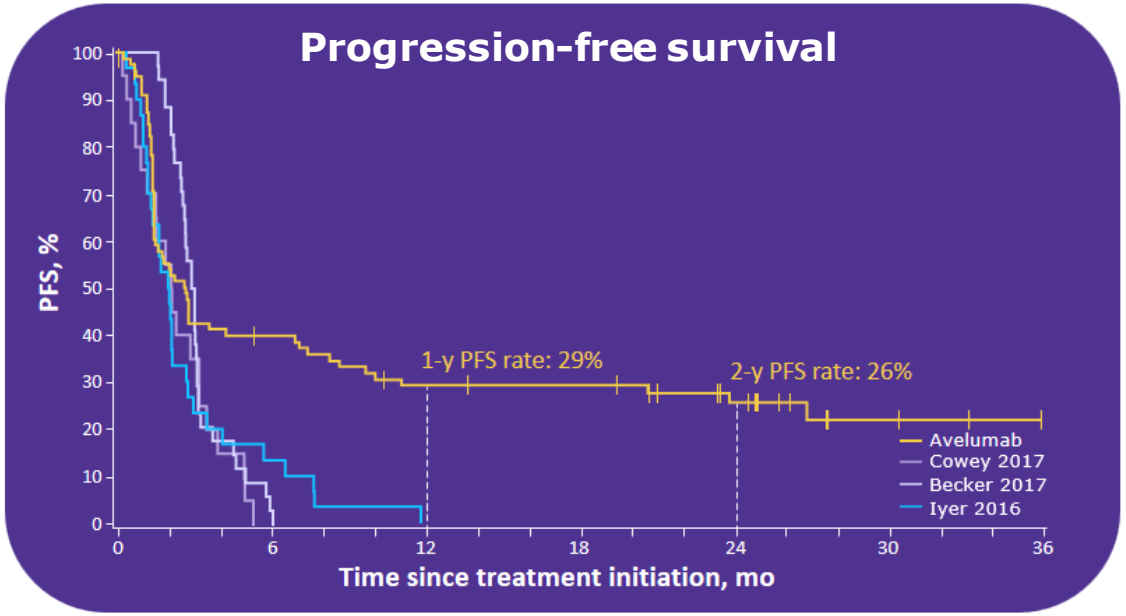
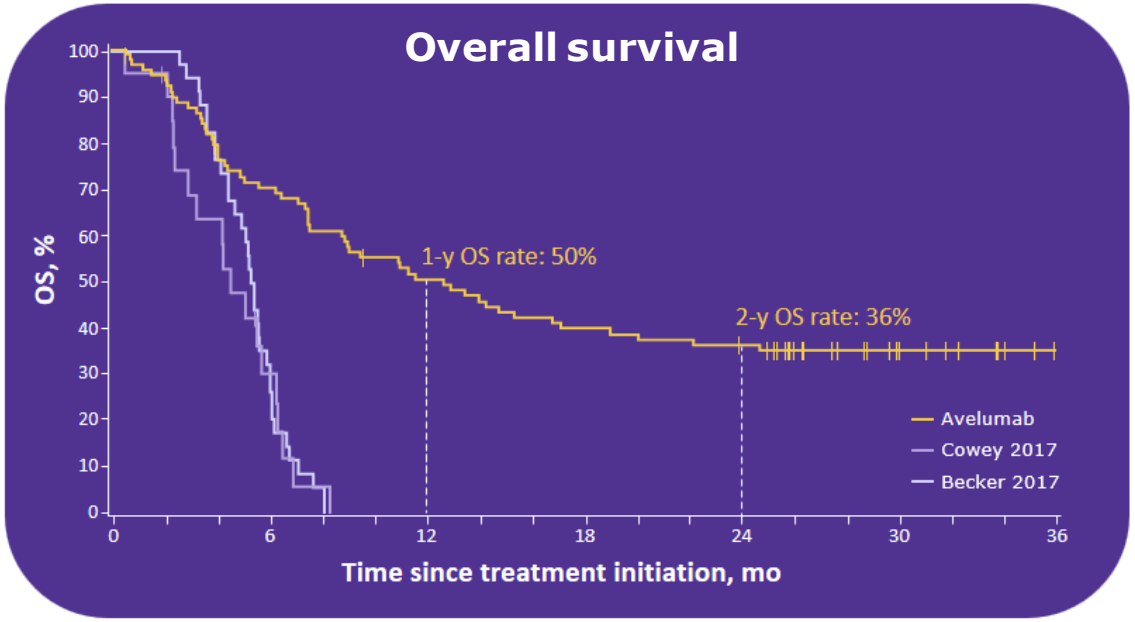
Avelumab: two year follow-up for Merkel Cell Carcinoma registrational study[1]
Changing the natural history of the disease





Merkel Cell Carcinoma

- **Chemo-sensitive disease** but responses seldom durable
- **Avelumab first approved therapy**
- 2 year follow-up confirmed **durable responses**
- **Survival rates: 36%** (2 years)

(1) P. Nghiem et al, ASCO, Jun 2018 (abstract 9507) | Figures for non-avelumab studies in upper two graphs are for illustrative purposes only and is not direct head-to-head comparison (retrospective data)

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Avelumab: latest publication (MCC)
Efficacy and safety established across 1L and 2L treatment

Independent Review (RECIST 1.1)[1]

Outcome	Patient Follow-up Group ≥3 mo	≥6 mo
Response[a]		
Confirmed ORR, % (95% CI)	62.1 (42.3-79.3)	71.4 (41.9-91.6)
Confirmed BOR, No. (%)		
Complete response	4 (13.8)	4 (28.6)
Partial response	14 (48.3)	6 (42.9)
Stable disease	3 (10.3)	1 (7.1)
Progressive disease	7 (24.1)	2 (14.3)
Nonevaluable[b]	1 (3.4)	1 (7.1)
Response durability[c]		
Median DOR (95% CI), mo	NE (4.0 to NE)	NE (4.0 to NE)
Proportion of responses with duration ≥3 mo, % (95% CI)	93 (61-99)	100 (NE)
Proportion of responses with duration ≥6 mo, % (95% CI)	83 (46-96)	89 (43-98)

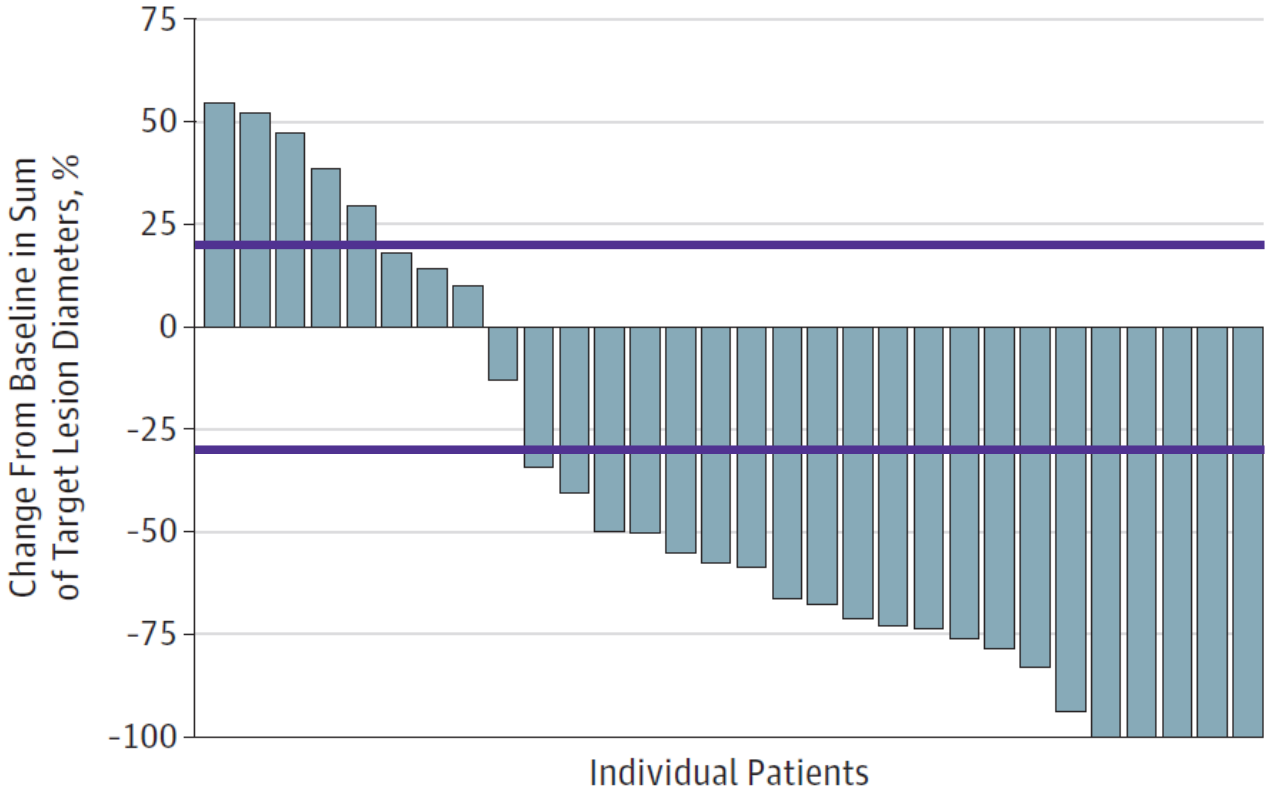
Abbreviations: BOR, best overall response; DOR, duration of response; NE, not estimable; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

[a] Includes 29 patients with at least 3 and 14 with at least 6 months of follow-up.

[b] Patient died before tumor assessment due to an adverse event unrelated to treatment with avelumab.

[c] Includes 18 patients with at least 3 and 10 with at least 6 months of follow-up.

Change in target lesion sum diameters[1]



(1) D'Angelo et al, JAMAOncology March 2018 (published online: 10.1001/jamaoncol.2018.0077)

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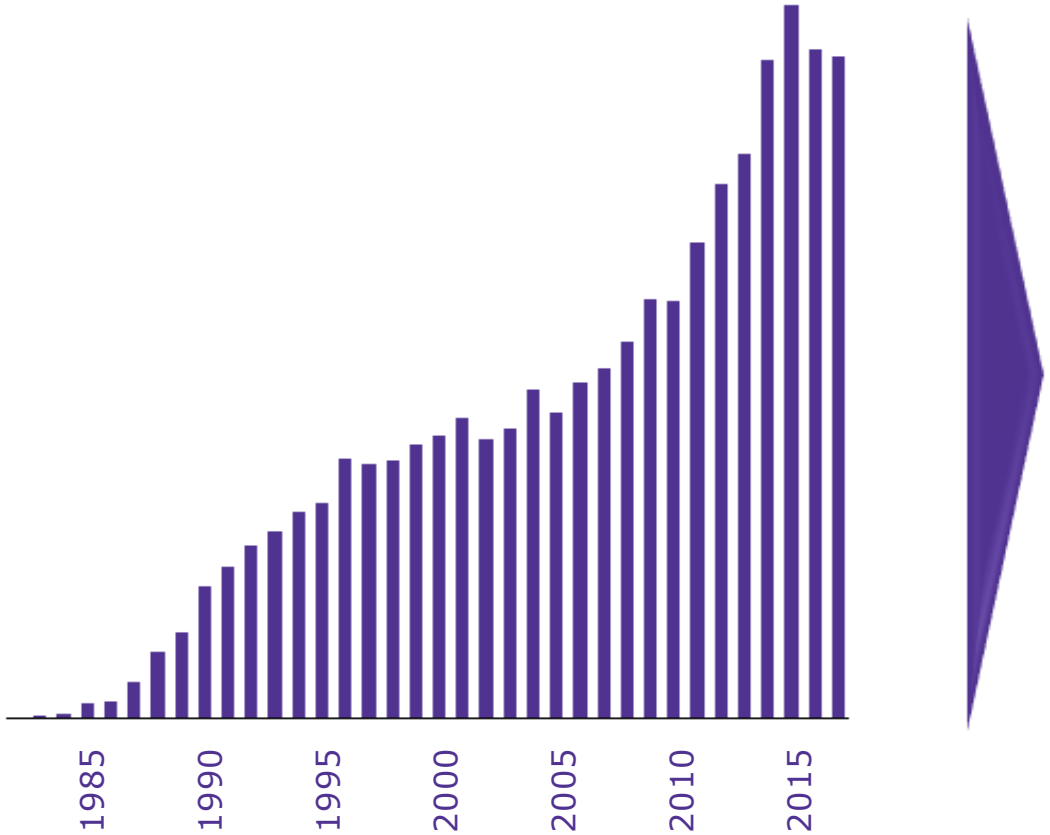
TGF-ß trap/anti-PD-L1: scientific background
TGF-β is a potential solution to improve IO outcome

TGF-β oncology publications



Key paper (2018)

Science Translational Medicine

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Enhanced preclinical antitumor activity of M7824, a bifunctional fusion protein simultaneously targeting PD-L1 and TGF-β

IRB BARCELONA

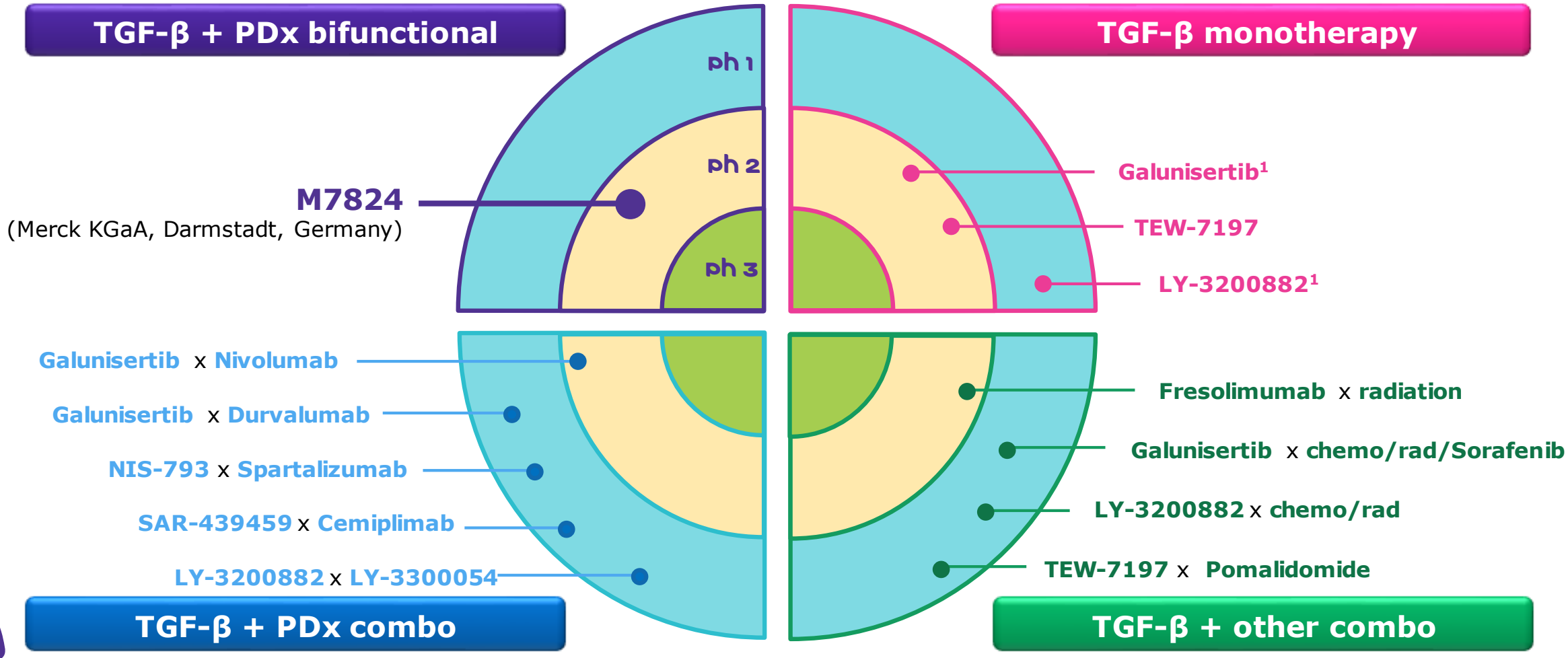
TGF drives immune evasion in genetically reconstituted colon cancer metastasis

nature
International journal of science

Genentech
A Member of the Roche Group

TGF-β attenuates immune response to PD-L1 blockade by contributing to exclusion of T cells

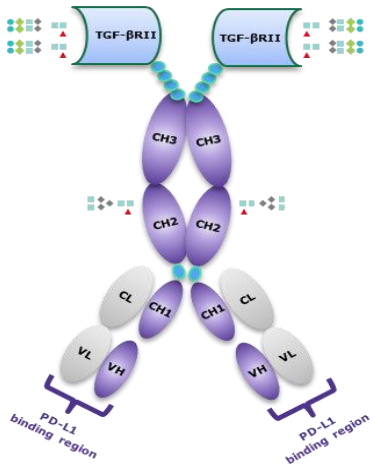
TGF-ß trap/anti-PD-L1: increasing investments in TGF-β therapy
Only bifunctional TGF-β trap/anti-PD-L1 in the clinic



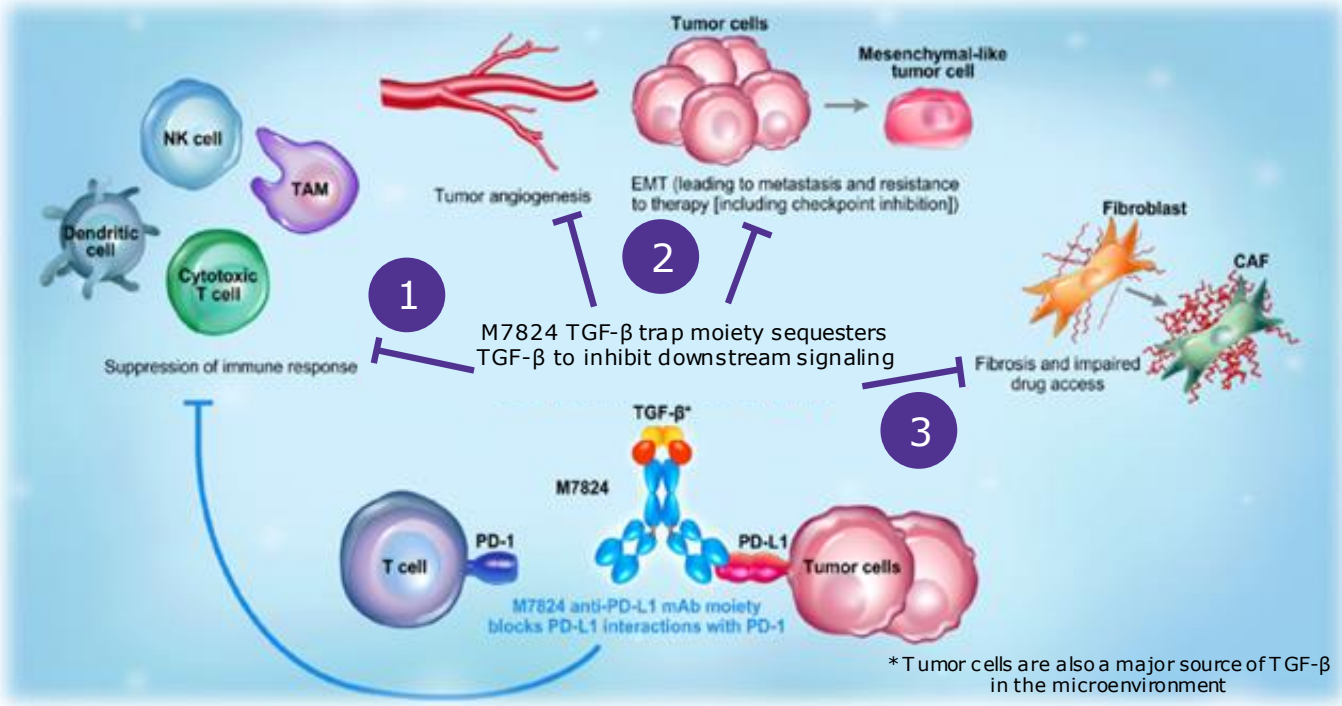
Source: clinicaltrials.gov (active trials only) | (1) small molecule

TGF-ß trap/anti-PD-L1: potential first-in-class bifunctional fusion protein
Trapping of TGF-β thought to target previously poorly addressable tumor biology

TGF-ß trap



Anti-PD-L1

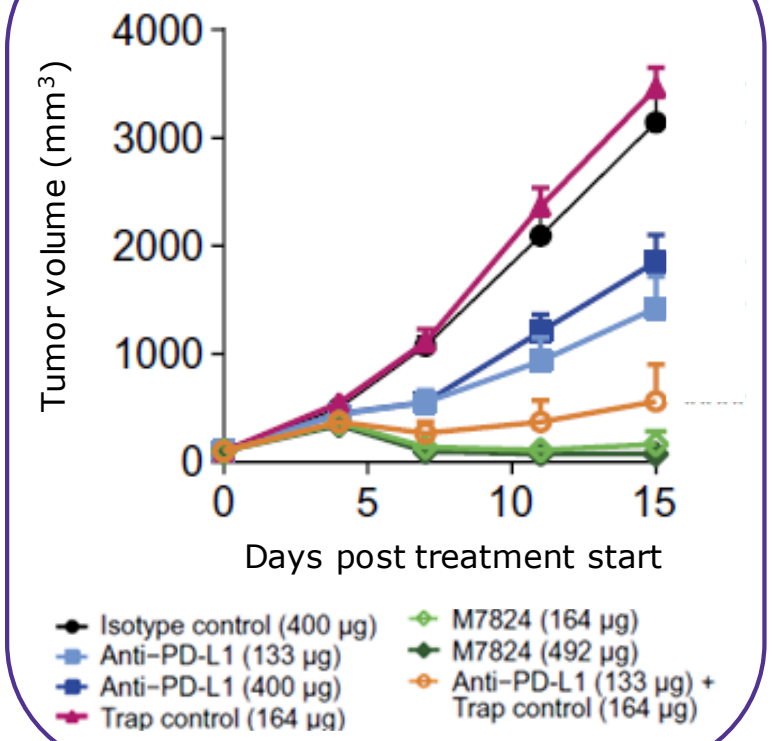


1. Differentiated **anti-immunosuppressive** effects: targeting immune-suppressed and/or fibrotic phenotypes
2. **Pre-empt metastases** in early disease: preventing epithelial to mesenchymal transformation (EMT)
3. Reduces fibrosis: **opening tumor to immune invasion** by removing protective wall (increasing CT/RT/IO efficacy)

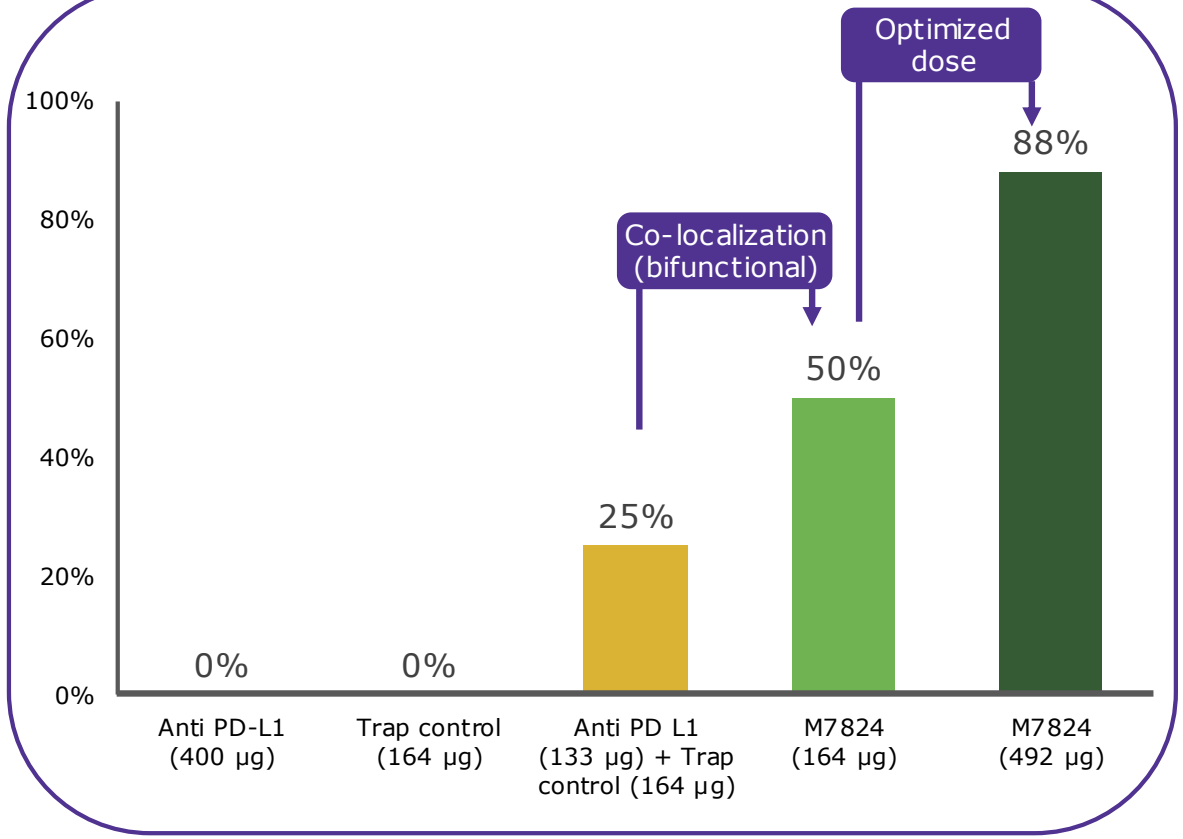
TGF-ß trap/anti-PD-L1: pre-clinical model

Bifunctional M7824 superior to co-administration of TGF-ß trap and anti-PD-L1[1]

MC38 Colorectal Cancer[1]



Complete Tumor Regression (%)[1]
(complete tumor regression after 171 days)



(1) Lan et al, Sci Transl Med, Jan 2018

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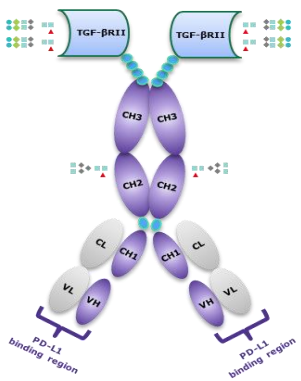
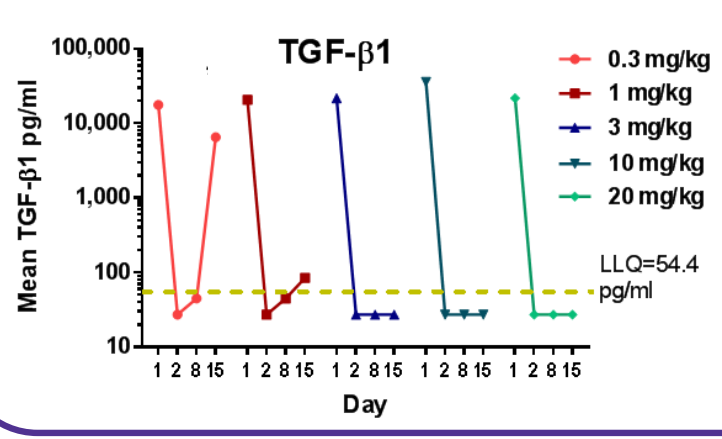
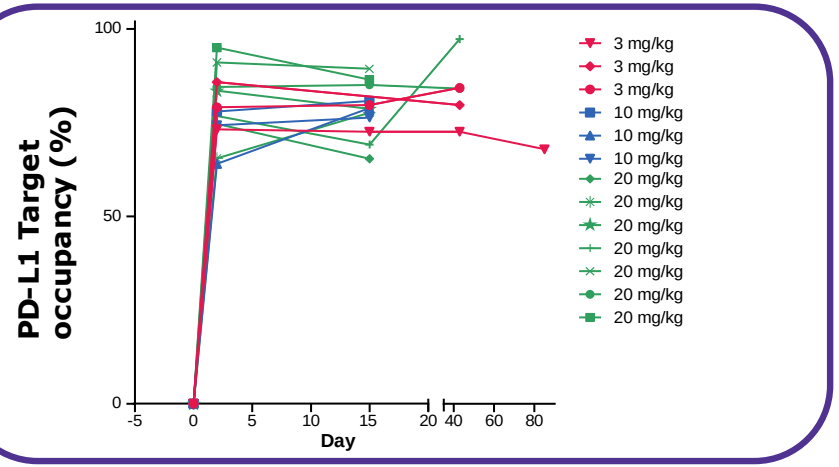
TGF-ß trap/anti-PD-L1: pharmacodynamic effects par design
M7824 traps TGF-β & occupies PD-L1[1] – 1200mg flat dose selected for ph II[2]

TGF-β sequestration[1]



PD-L1 occupancy[1]





- Through PD-L1 targeting, **M7824 accumulates at tumor site** (two independent synergistic mechanisms)
- **TGF-β effectively trapped** in tumor microenvironment (all isoforms TGF-ß1, ß2, ß3)[1]
- **Safety profile** similar to established PDx-inhibitors

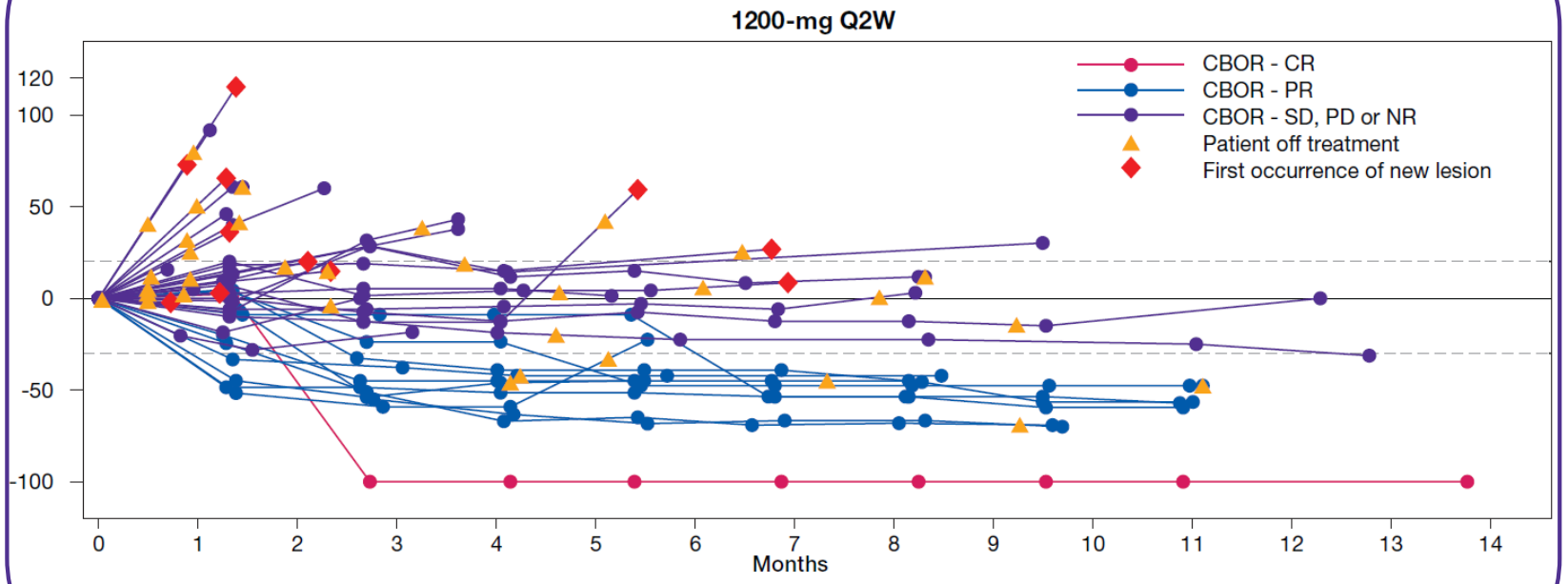
(1) Cao et al. AACR 2017 (abstract 3813); data only shown for TGF-β1 (similar for TGF-β2/3) | (2) Vugmeyster et al., ASCO 2018 (abstract 2566)

TGF-ß trap/anti-PD-L1: phase Ib results (PDx-naïve 2L NSCLC)

Encouraging durable responses seen across PD-L1 expression levels[1]

- **PD-L1 expression** of ≥80% **comparable** to TPS ≥50% (22C3)[1]
- Encouraging **efficacy comparing favorably** with established PDx-inhibitor monotherapy
  - **ORR = 27.5% (all-comer)** vs. ~18%[2]
  - **ORR = 40.7% (PD-L1+)** vs. ~18-27%[2]
  - **ORR = 71.4% (PD-L1 high)** vs. ~29-44%[2]
- **Manageable safety profile:** similar to established PDx-inhibitors (6% keratoacanthomas manageable; did not lead to discontinuation)

Change in sum of diameters (%)[1]



(1) L.G. Paz-Ares et al, ASCO, Jun 2018 (abstract 9017) – data cut-off: March 12, 2018 | (2) Herbst et al; Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial (www.thelancet.com Published online December 19, 2015 http://dx.doi.org/10.1016/S0140-6736(15)01281-7) and Garon et al; Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer (The NEW ENGLAND JOURNAL of MEDICINE) incl. Supplementary Appendix; table S7 (N Engl J Med 2015;372:2018-28. DOI: 10.1056/NEJMoa1501824)

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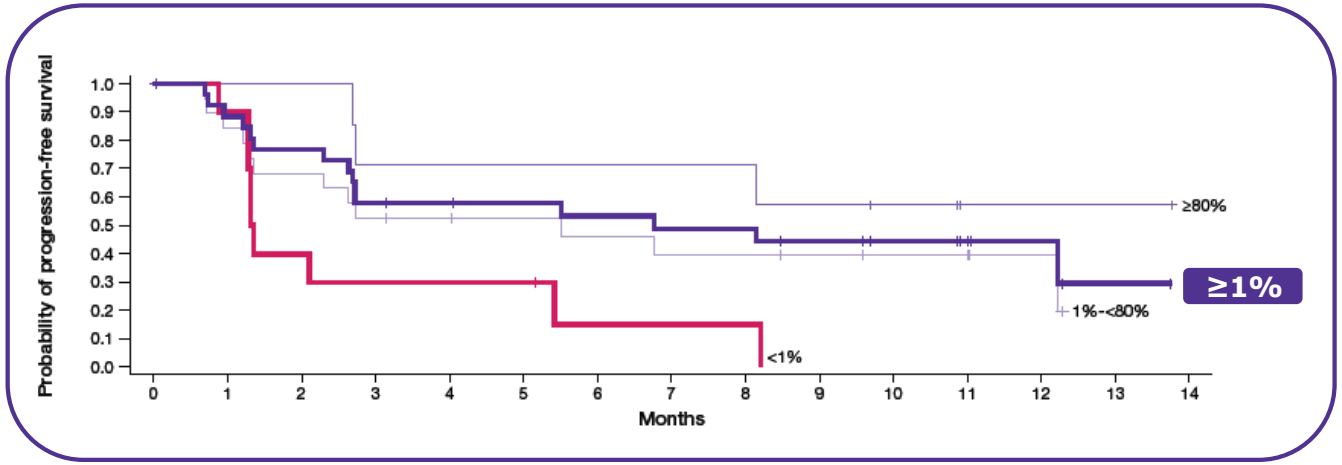
TGF-ß trap/anti-PD-L1: focus area NSCLC

Strong PFS signal in ph Ib – next step randomized ph II trial in NSCLC 1L

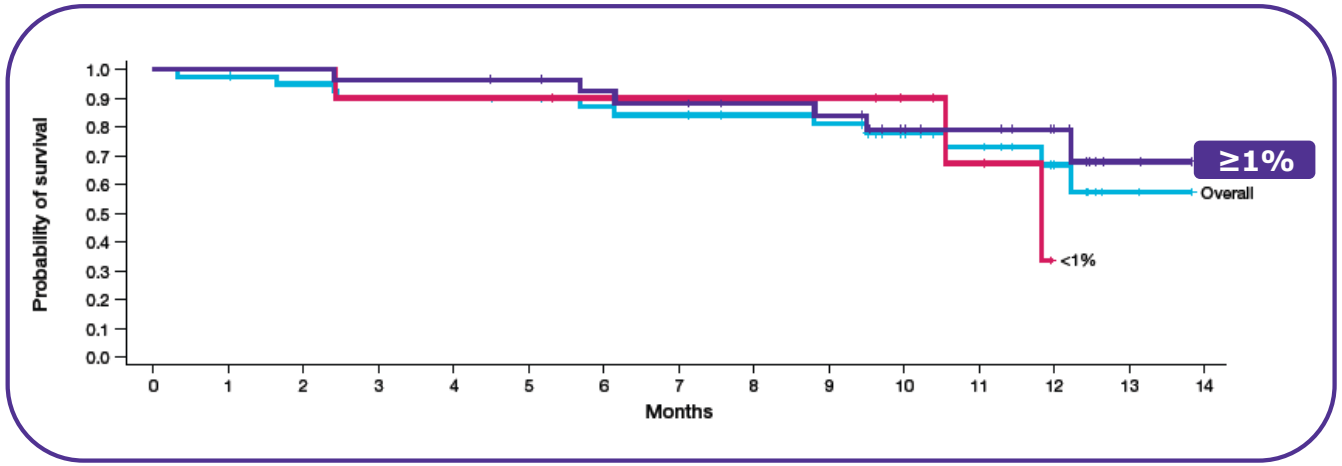
Progression free survival (PD-L1 ≥ 1%)

- M7824: **mPFS = 6.8 months**[1]
- Leading competitor: 4.0 months[2]



Overall Survival (PD-L1 ≥ 1%)

- M7824: **mOS not reached**[1]
- Leading competitor: 12.7 months[2]



(1) L.G. Paz-Ares et al, ASCO, Jun 2018 (abstract 9017); data shown for 1200mg Q2W dose | (2)Herbst et al; Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial (www.thelancet.com Published online December 19, 2015 http://dx.doi.org/10.1016/S0140-6736(15)01281-7)

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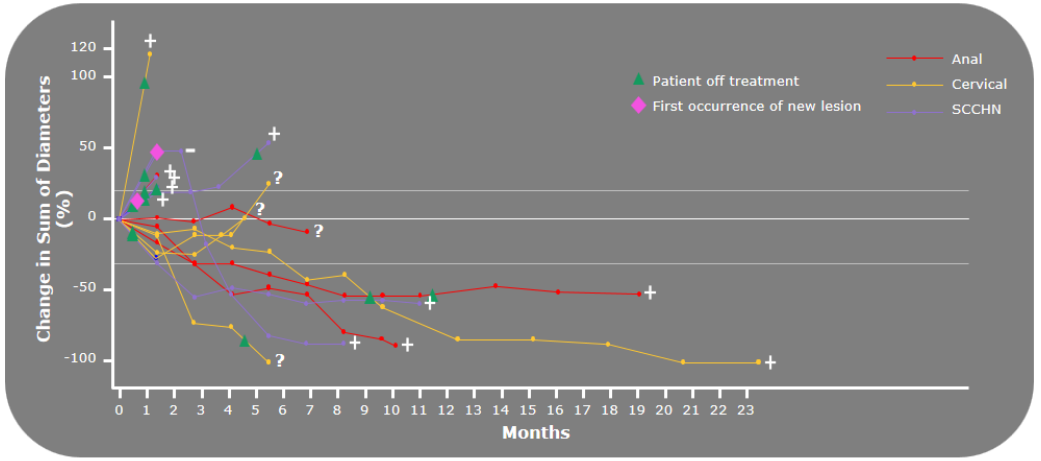
TGF-ß trap/anti-PD-L1: phase Ib results (HPV cohort at NCI)

HPV-assoc. cancers as potential pan-tumor therapy – prospective study ongoing at NCI

Patients with HPV-assoc. cancers

- Analyses of HPV+ cervical/SCCHN tumor samples from TCGA/Oncomine show frequent dysregulation of TGF-βR1 signaling – suggesting this **pathway plays a role in HPV-mediated carcinogenesis**
- **HPV associated** with almost all anal and cervical cancer, and some SCCHN[2-4]
- Retrospective subgroup analysis incl. 17 patients with HPV-associated cancers[1]:
  - Activity in all three tumor types
  - **Confirmed ORR = 41.7% (HPV+)[1]**
  - Clinical activity of anti-PD-1 monotherapies in **range of 17–26%**[5-8]
- **Phase II study by NCI** specifically accruing patients with HPV-associated malignancies

BOR as confirmed by independent radiologist[1]



BOR, n (%)	N=17 (all HPV associated tumors)	N-12 (all HPV-positive)
ORR	6 (35.3)[10]	5 (41.7)[10]
CR	2 (11.8)[9]	1 (8.3)
PR	4 (23.5)[10]	4 (33.3)[10]
SD	4 (23.5)	1 (8.3)
PD	7 (41.2)	6 (50.0)
DCR	10 (58.8)[10]	7 (50.0)[10]

(1) J.L. Gulley et al, ASCO, Jun 2018 (presentation) | (2) De Vuyst et al. Int J Cancer. 2009;124:1626–36 | (3) Ihloff et al. Oral Oncol. 2010;46:705–11 | (4) Mehanna et al. Head Neck. 2013;35:747–55 | (5) Bauml et al. J Clin Oncol. 2015;33 (suppl; abstr TPS3094) | (6) Ferris et al. N Engl J Med. 2016;375(19):1856 | (7) Frenel et al. J Clin Oncol. 2017;35(36):4035 | (8) Ott et al. Ann Oncol. 2017;28(5):1036 | (9) 1 patient had a confirmed BOR or PR and an unconfirmed BOR of CR (10) 1 PR did not meet the RECIST criteria

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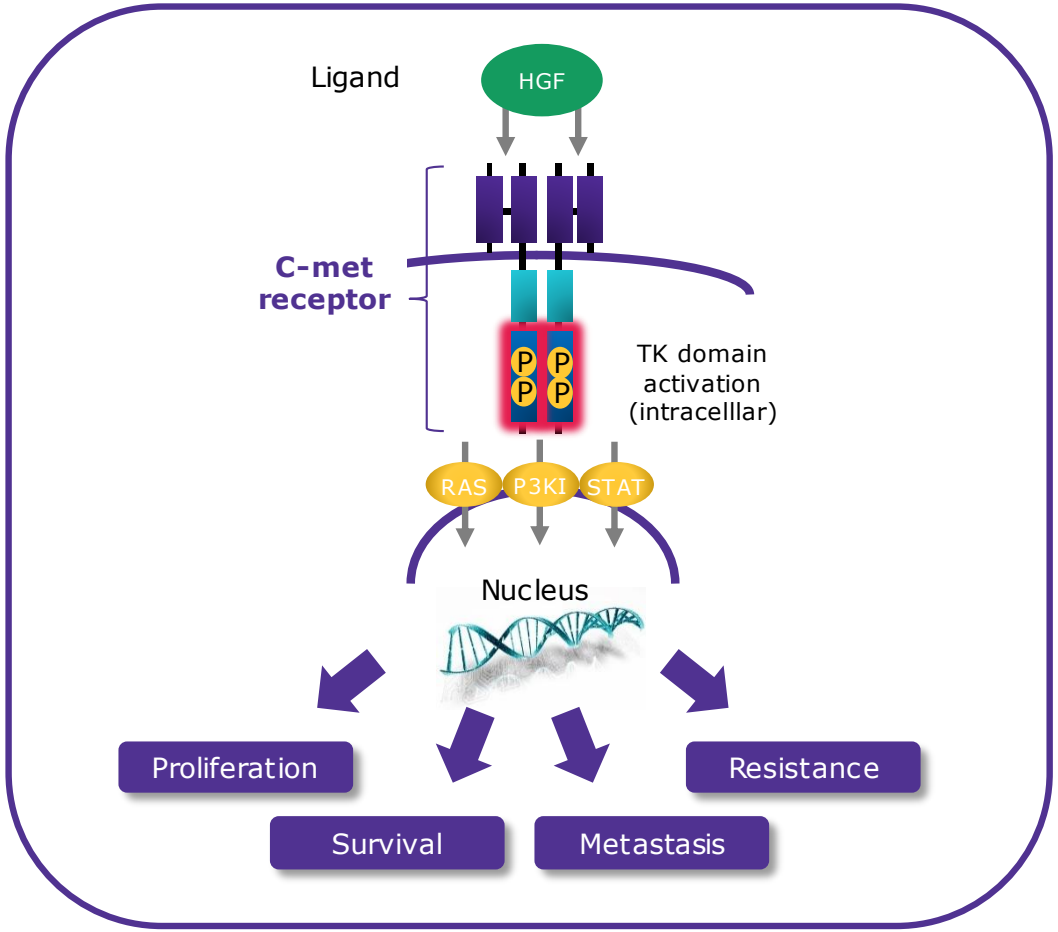
Tepotinib: proposed mode of action
Targeting c-met signaling pathway to disrupt tumor growth

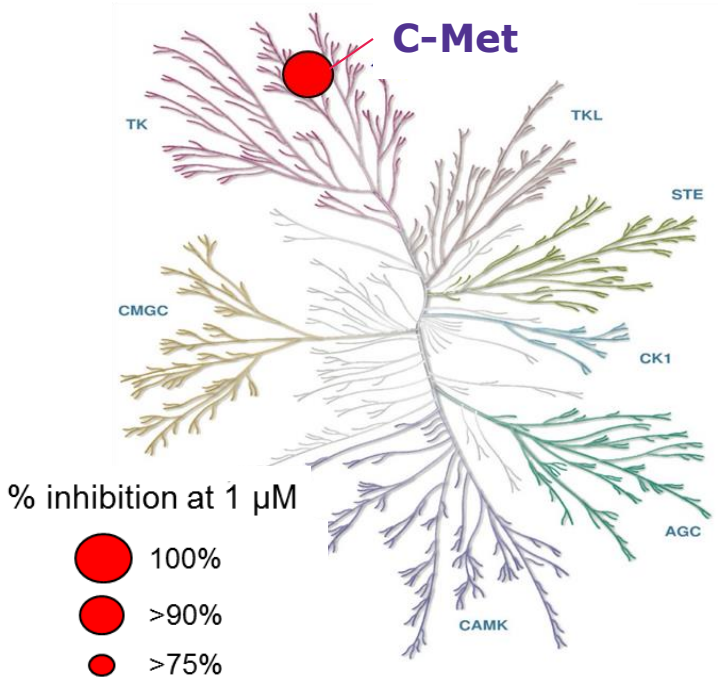


- c-Met (Mesenchymal-Epithelial Transition Factor) is a Receptor Tyrosine Kinase
- c-Met pathway frequently **deregulated in cancer**[1] acting as **oncogenic driver**[1-3]
- c-Met receptor can also mediate **resistance** to other cancer therapies [1-3]

(1) Ghiso, 2013 | (2) Maroun, 2014 | (3) Graveel, 2013 | ATP: adenosine triphosphate | TK: tyrosine kinase

Tepotinib: highly selective c-met inhibitor
Pre-clinical data indicated high target activity (>90% c-met inhibition)

Selectivity profile[1]



Tepotinib characteristics

- ATP competitive, **reversible small molecule** c-Met inhibitor[2]
- **Highly selective** according to preclinical benchmarking[1]
  - In panel of >240 kinases, only c-Met inhibited at 1 µM
  - >90% inhibition of phospho-c-Met levels (tumor biopsy)
- **Encouraging safety** profile: 147 patients treated up to 1,400 mg (MTD not reached). 37/60 (62%) patients on regimen 3 (QD) reported at least one treatment-related AE[3]
- RP2D: 500 mg QD (based on PK/PD modelling, PD, safety)
- Preliminary signs of **anti-tumor activity:** two confirmed PR; 12 had stable disease lasting for ≥ 6 weeks, including 1 unconfirmed PR[3]

(1) Merck KGaA, Darmstadt, Germany data on file | (2) Bladt et al, 2013 | (3) Falchook et al, ASCO 2015

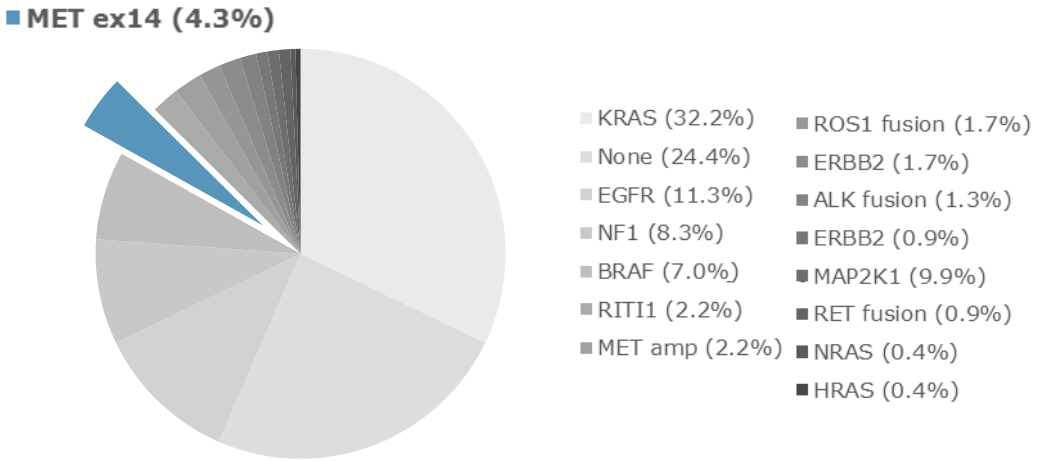
Tepotinib: precision medicine approach
Targeting biomarker enriched NSCLC population with critical medical need

Precision medicine

- Targeted therapies work in tumors that **critically depend on the target** for their growth or survival
- Target is often an **"oncogenic driver"** (tumor specific)
- **Prospective identification** of responders requires **predictive biomarkers**

Oncogenic drivers in lung adenocarcinoma[1]

- MET-mutations are clinically **unique molecular subtypes** of NSCLC
- MET exon 14 alteration confer oncogene addiction in **~3-4 % of NSCLC**
- **No approved therapy** specifically targeting METex14 and/or c-Met amplification

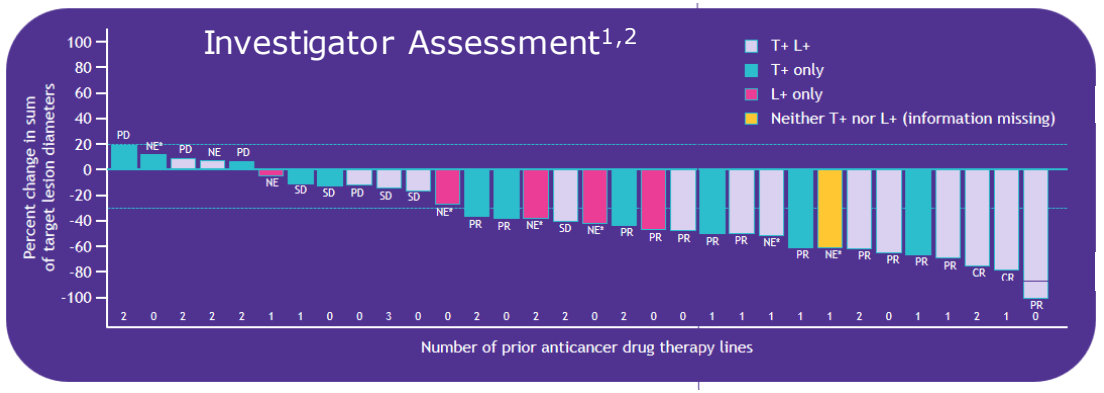


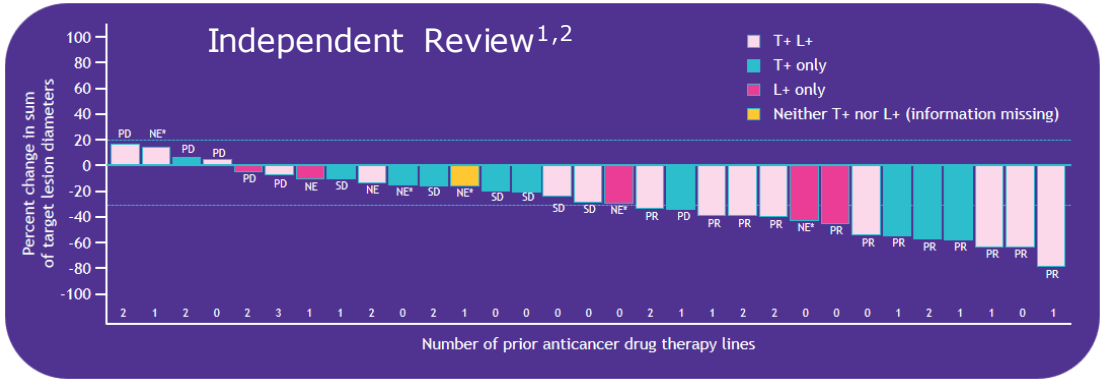
(1) Cancer Genome Atlas Nature 2014;511:543-50

Tepotinib: interim phase II results (NSCLC MET exon 14)
Encouraging efficacy with highly targeted approach

- **Encouraging signs of activity** in patients with advanced NSCLC harboring **MET exon 14-skipping mutations**
- ORR to date based on independent review **(42.9%)** and investigator assessment (**53.6% incl. two CR**)[1]
- Generally **well tolerated** (most common side effects: peripheral edema and diarrhea, both mild to moderate)
- Recruitment ongoing **(LBx and TBx)**[2]

Tepotinib 500 mg[1,3]	Investigator	Independent
Complete response	2 (7.1)	0 (0)
Partial response	13 (46.4)	12 (42.9)
Stable disease	5 (17.9)	6 (21.4)
Progressive disease	4 (14.3)	5 (17.9)
Non-evaluable	4 (14.3)	5 (17.9)
ORR n (%) [95% CI][4]	15 (53.6) [33.9, 72.5]	12 (42.9) [24.5, 62.8]
DCR: n (%) [95% CI][5]	20 (71.4) [51.3, 86.8]	18 (64.3) [44.1, 81.4]





(1) Felip E et al, ASCO 2018 | (2) L+, *MET*exon14-skipping mutation-positive in ctDNA (liquid biopsy = LBx); T+, *MET*exon14-skipping mutation-positive in tumor (tissue biopsy = TBx) | (3) Combined analysis (n=28); efficacy analysis includes only patients having at least 2 post-baseline assessments or who discontinued treatment for any reason (n=28) | (4) Confirmed complete response/partial response | (5) Confirmed complete response/partial response or stable disease lasting at least 12 weeks. | CI, confidence interval

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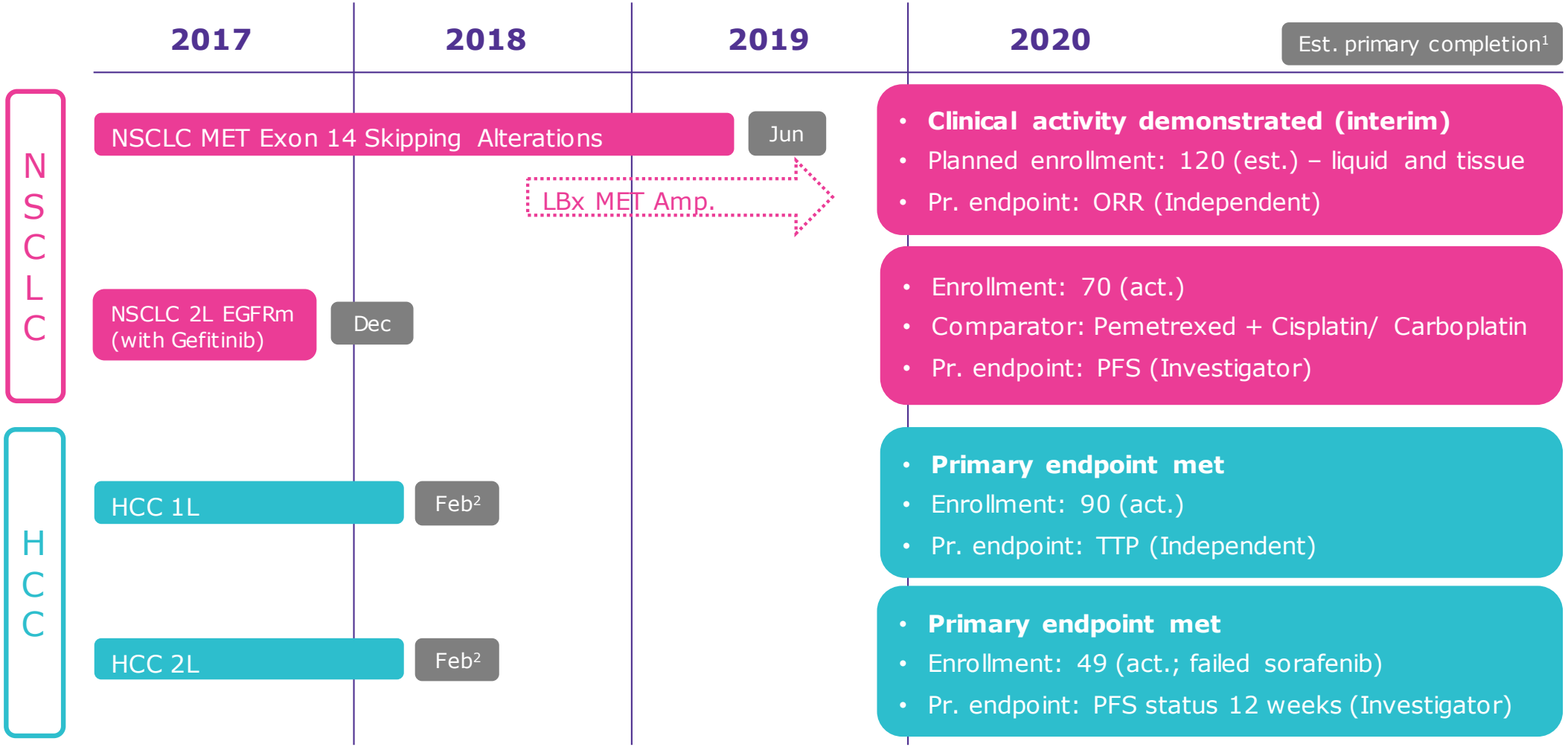
Tepotinib: program overview
Development will focus on biomarker enriched patient populations



(1) Estimated primary completion date acccording to Clinicaltrials.gov as of 24/05/18. | (2) Cut-off date for final analysis | Abbreviations: NSCLC – Non Small Cell Lung Cancer | HCC – Hepatocellular Carcinoma | EGFRm – Epidermal Growth Factor Receptor mutation | ORR – Objective Response Rate | DLT - Dose Limiting Toxicity | AE - Adverse Events | TTP - Time to Progression | PFS – Progression Free Survival | Est. – Estimated | Act. – Actual | Pr. – Primary | Amp. – Amplified

Agenda

01 Pipeline highlights & strategy

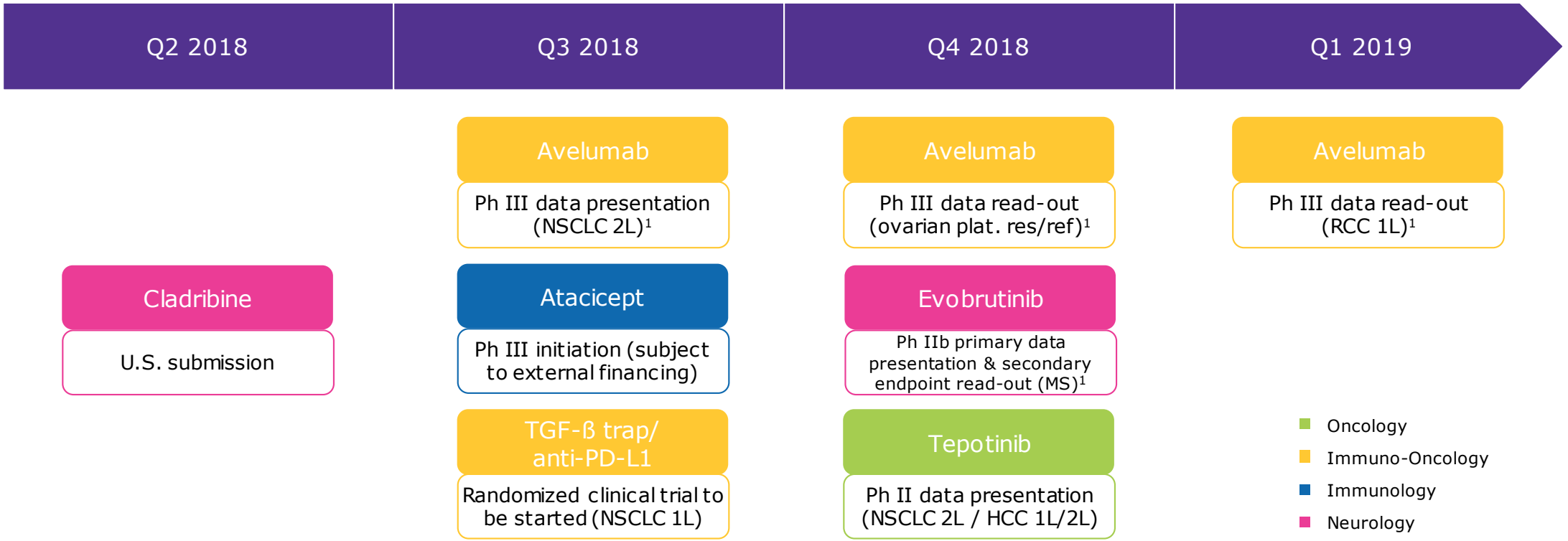
02 Avelumab

03 TGF-ß trap / anti-PD-L1

04 Tepotinib

05 upcoming catalysts

Upcoming catalysts
Major read-outs and ongoing pipeline development ahead



(1) Note: timelines are event-driven and may change.
Acronyms: NSCLC – Non small cell lung cancer | MS – Multiple Sclerosis | RCC – Renal Cell Carcinoma | HPV – Human papillomavirus | HCC – Hepatocellular Carcinoma | plat. res/ref – platinum resistant/refractory

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