

Determination of the Recommended Phase 2 Dose of birinapant in combination with pembrolizumab: Results from the dose escalation phase of BPT-201

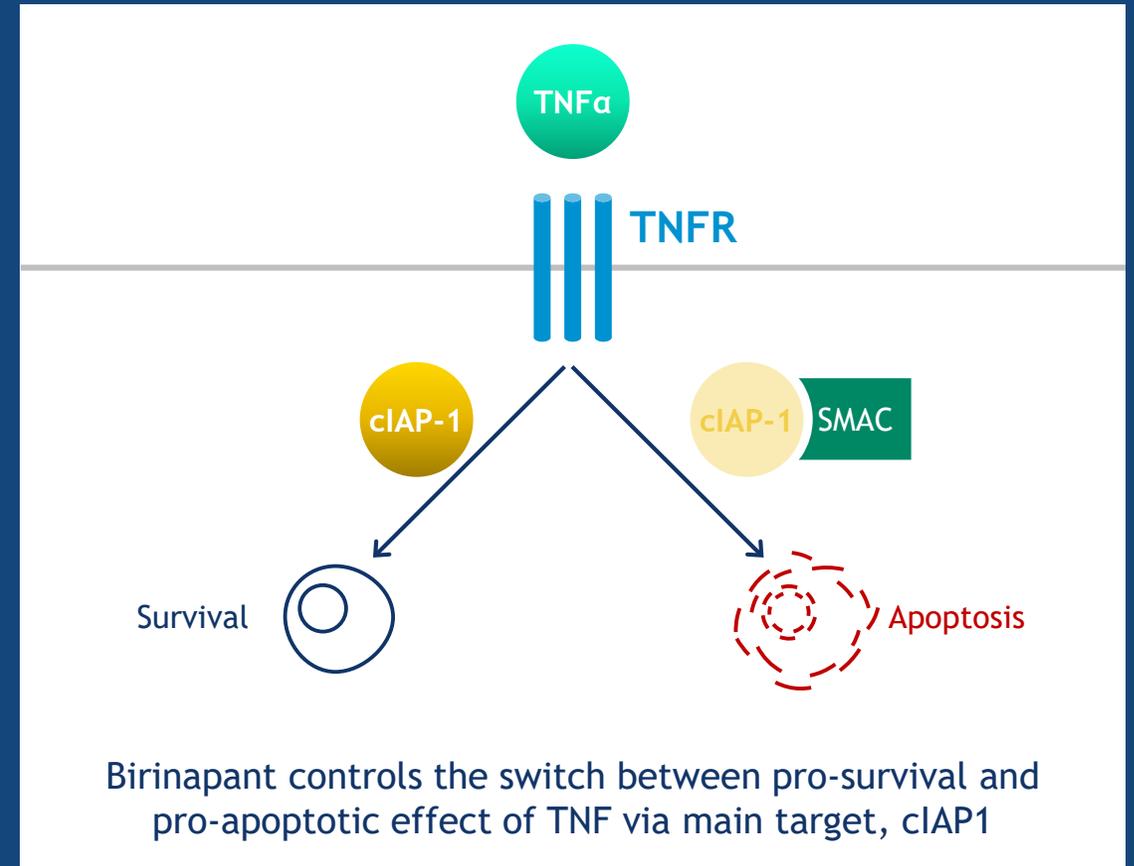
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SMAC mimetics exert anti-tumour activity by facilitating apoptotic cell death

- Inhibitor of Apoptosis proteins (IAPs) play a critical role in blocking apoptotic signals of the cell death pathways.
- IAP genes are frequently amplified in multiple cancers and may contribute to chemoresistance and treatment failure
- The activity of IAP is regulated by a second mitochondrial-derived activator of caspases (SMAC), a natural IAP antagonist
- Birinapant is a bivalent SMAC mimetic, potently targeting cellular(c) IAP1 for degradation, thereby promoting apoptotic cell death



Fulda, S. and Vucic, D. Targeting IAP proteins for therapeutic intervention in cancer. Nature Reviews Drug Discovery 2012; 11: 109

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Birinapant (BPT) is a potent bivalent SMAC mimetic

- Total of 460 patients have been treated with BPT; 84 as monotherapy and 376 in combination with other anti-cancer agents
- Birinapant monotherapy has predictable dose-dependent PK with a MTD of 47 mg/m²
- Pharmacodynamic effects are seen at doses well below MTD (75% reduction of cIAP at 5.6 mg/m²)
- In a study combining gemcitabine with BPT at doses of 11 - 22 mg/m² administered 2 of 3 weeks, the MTD was 22 mg/m²
- Greater efficacy and durable regressions are observed in a variety of preclinical tumor models when birinapant is combined with other apoptotic inducing agents. This was confirmed in clinical trials
- Birinapant has been generally well tolerated. Most adverse events were dose-related, transient and mild or moderate in severity
- Rare cases of following adverse events were reported
 - Bell's palsy, self-limited; no case at or below 22mg/m²
 - Asymptomatic and reversible grade 3 or 4 increases in amylase and lipase
 - Constellation of AEs including rash, fever, chills, hypotension, nausea, headache, hypophosphatemia without detectable increase in cytokines.

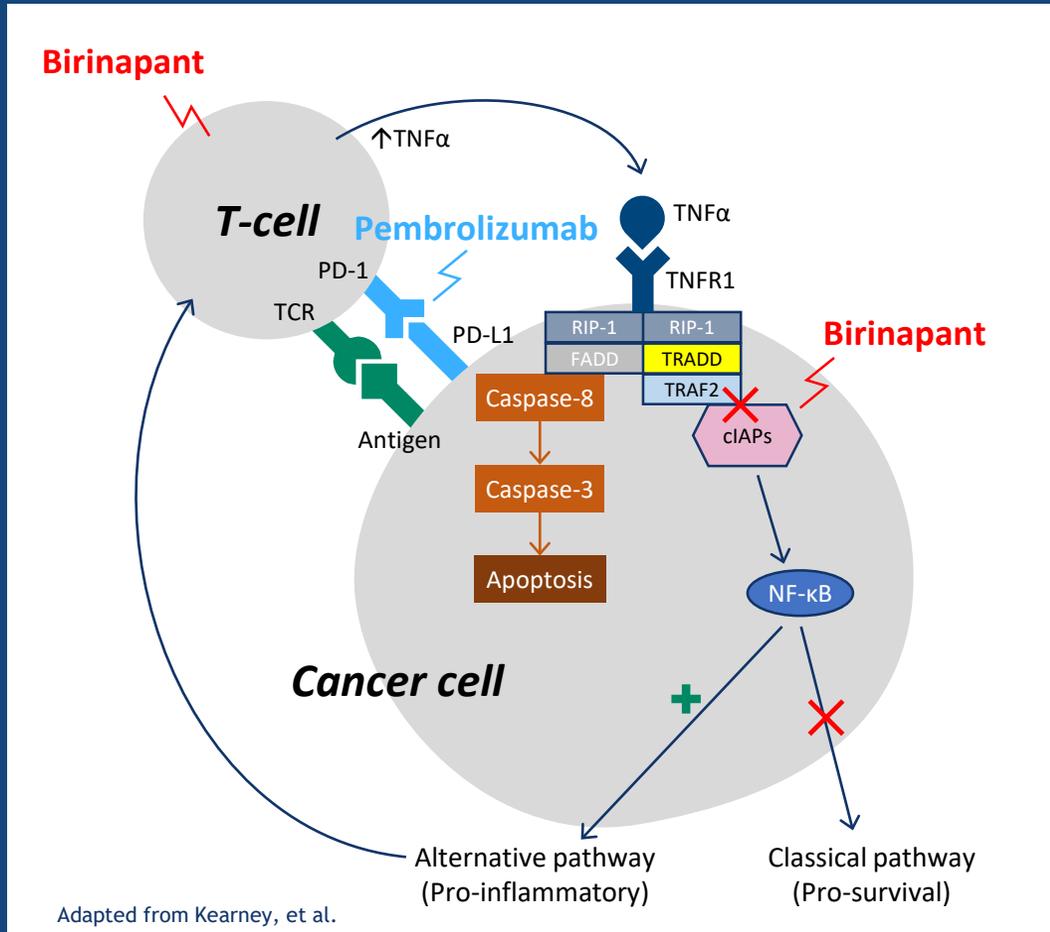
Benetatos CA et al. Birinapant (TL32711), a bivalent SMAC mimetic, targets TRAF2-associated cIAPs, abrogates TNF-induced NF-κB activation, and is active in patient-derived xenograft models. *Mol Cancer Ther*, 2014; 13(4): 867-79

Amaravadi RK et al. A phase 1 study of the SMAC-mimetic birinapant in adults with refractory solid tumors or lymphoma. *Mol Cancer Ther* 2015; 14(11): 2569-75

Noonan AM et al. Pharmacodynamic markers and clinical results from the phase II study of the SMAC-mimetic birinapant in women with relapsed platinum-resistant or refractory epithelial ovarian cancer. *Cancer* 2016; 122(4): 588-597

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Potential synergy between birinapant and pembrolizumab



- Birinapant controls the switch between the pro-survival and the pro-apoptotic effect of Tumor Necrosis Factor α (TNF α) via degradation of its main target, cIAP1
- Birinapant preferentially increases alternative NF- κ B signaling and can lead to activation of the immune system
- PD1 blockade further increases TNF α production which augments the pro-apoptotic signal of birinapant
- Synergistic effects of combining birinapant with immune checkpoint inhibitors have been demonstrated in preclinical models. Based on these observations, this clinical trial with birinapant and pembrolizumab was initiated (NCT02587962)

Chesi M et al. IAP antagonists induce anti-tumor immunity in multiple myeloma. Nature Medicine 2016; 22(12): 1411-1423

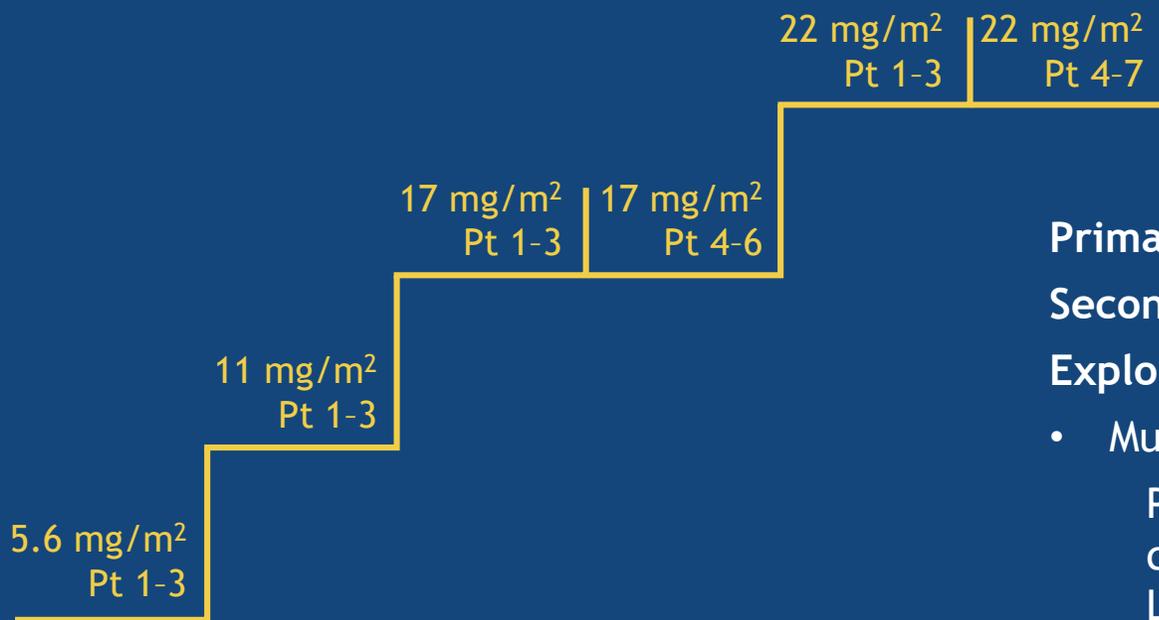
Beug ST et al. Smac mimetics synergize with immune checkpoint inhibitors to promote tumour immunity against glioblastoma. Nature Communications 2017; 8: 14278

Kaerney CJ et al. PD-L1 and IAPs co-operate to protect tumors from cytotoxic lymphocyte-derived TNF. Cell Death Differ 2017; 24(10): 1705-1716

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Phase 1/2, multicenter, single-arm, open-label, dose-escalation study of birinapant in combination with pembrolizumab in patients with relapsed or refractory solid tumors (NCT02587962)

3 +3 Dose escalation design



- 21-day cycle
- Birinapant (5.6 - 22 mg/m²) IV on days 1 and 8
- Pembrolizumab 200 mg IV on day 1

Primary Endpoint: Establishing Safety & Tolerability of a RP2D

Secondary Endpoints: Tumor response (RECIST 1.1)

Exploratory Endpoints:

- Multiple Biomarkers including:
 - PD-L1 and cIAP1 expression, IAP gene copy number, quantification and characterization of Tumor Infiltrating Lymphocytes (TILs) and serum cytokines
- iRECIST
- PK of birinapant

Key Inclusion Criteria

- ≥18 years with histologically confirmed solid malignancy that is metastatic or unresectable and for which standard curative or palliative measures do not exist
- Measurable disease by RECIST 1.1 criteria
- Life expectancy greater than 12 weeks
- Amylase and lipase values < ULN
- Adequate organ function
- Resolution of toxic effects from most recent chemotherapy, radiation therapy or surgery

Key Exclusion Criteria

- Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-CTLA4
- Prior use of anti-TNF therapies
- Immune deficiency or use of systemic steroids or immunosuppressive therapy
- Active autoimmune disease requiring systemic treatment
- Active non-infectious pneumonitis
- History of interstitial lung disease
- History of HIV or active hepatitis B or C
- Live virus vaccination within 30 days
- Use of blood products or G-CSF within 4 weeks

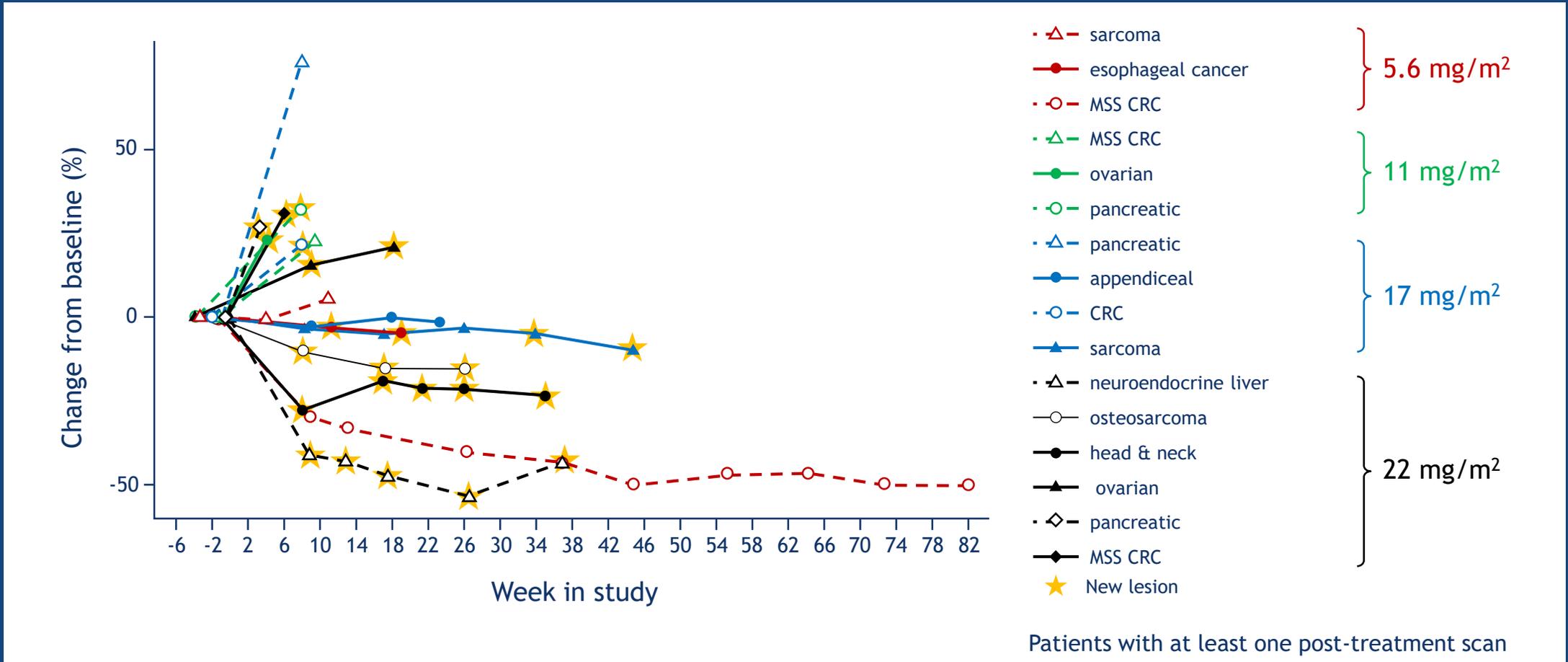
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Patient Demographics

	Diagnosis	Sex	Age (years)	Number of prior treatment lines	Birinapant + Pambrolizumab #Cycles	Reason for treatment discontinuation
Dose Level 1 5.6 mg/m ²	Sarcoma (spleen)	Female	39	4	3	Progression
	Esophageal adenocarcinoma	Female	71	3	6	Progression
	Colorectal adenocarcinoma (MSS)	Male	58	6	27	Active
Dose Level 2 11 mg/m ²	Rectal cancer (MSS)	Male	70	5	4	Progression
	Ovarian adenocarcinoma	Female	69	4	2	Progression
	Pancreatic adenocarcinoma	Female	75	2	3	Progression
Dose Level 3 17 mg/m ²	Pancreatic cancer	Female	64	6	4	Progression
	Appendiceal cancer	Female	68	3	8	Progression
	Colorectal (MSS/MSI status NA)	Female	64	2	3	Progression
	Sarcoma	Female	52	1	9	Withdrawal consent
	Fallopian tube	Female	58	10	2	Unrelated AE
	Pancreatic	Male	55	3	2	Progression
Dose Level 4 22 mg/m ²	Liver (neuroendocrine)	Female	72	0	11	Progression
	Osteosarcoma	Male	43	4	9	Active
	Head and Neck	Female	44	1	12	Progression
	Pancreatic	Female	66	2	1	Withdrawal consent
	Ovarian	Female	57	13	6	Progression
	Pancreatic	Male	68	5	1	Progression
	Colorectal (MSS)	Male	64	8	2	Progression
	Median (range)		64 (39-75)	4 (1-13)	3 (1-13)	

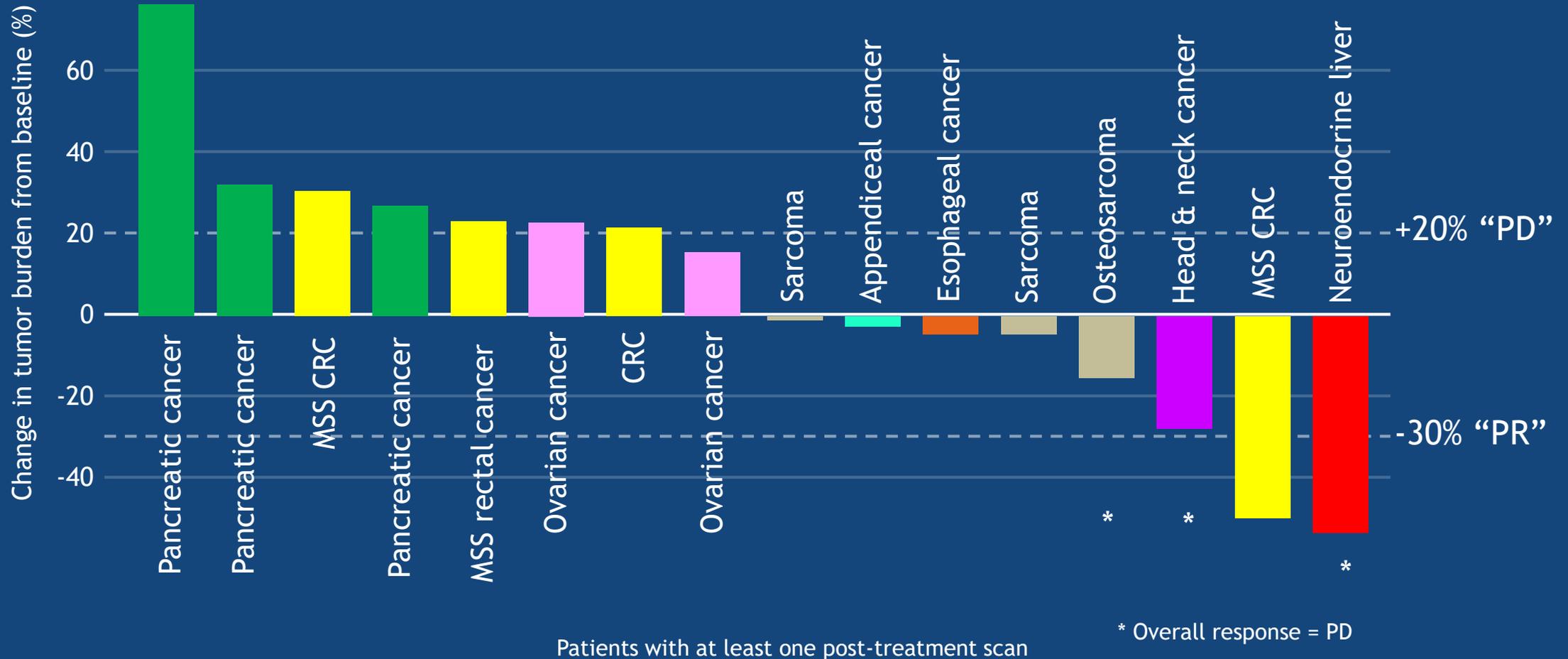
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Change in tumor burden (%) of target lesions by treatment duration according to RECIST 1.1 (independent Radiologist)



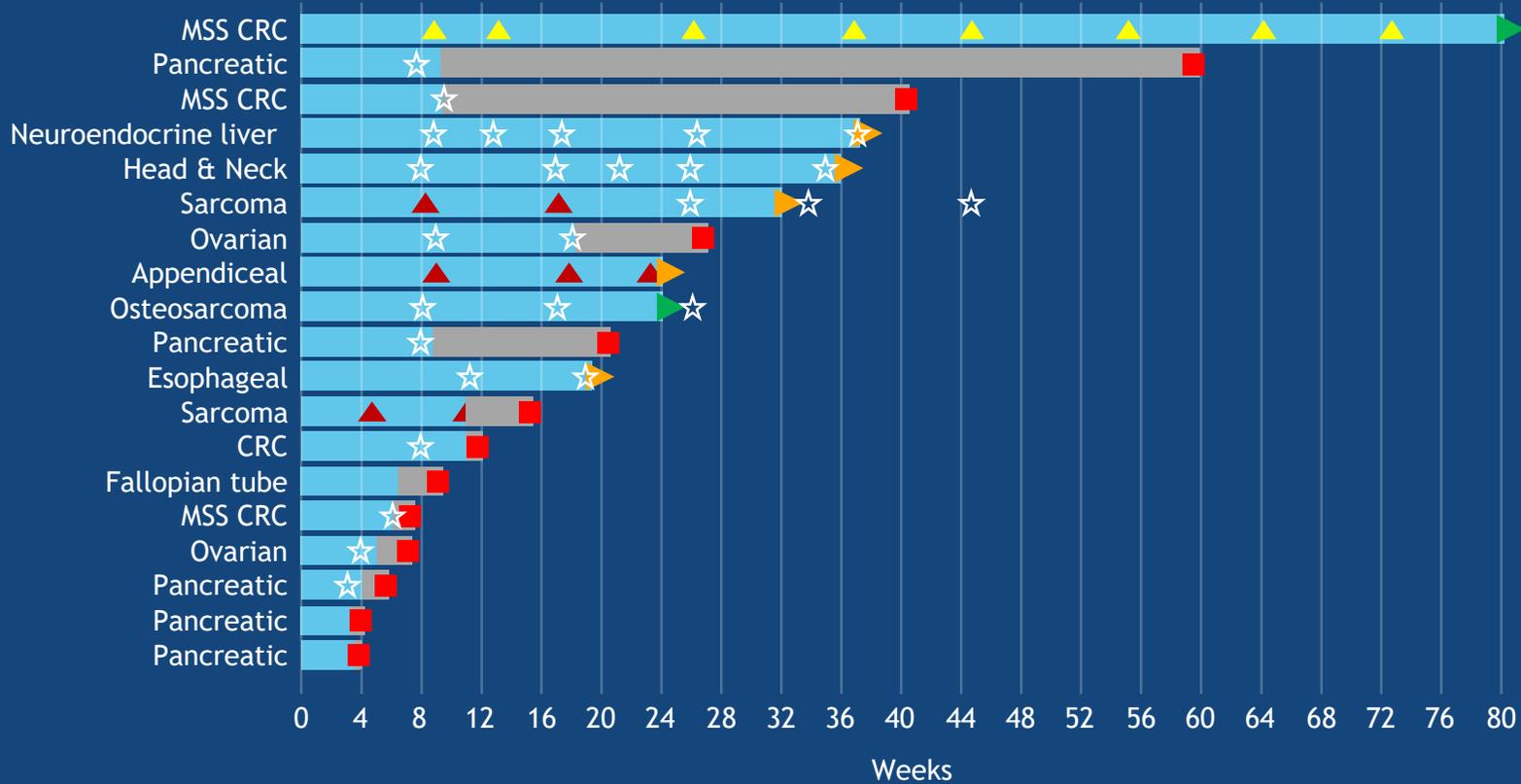
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Best change in tumor burden (%) of target lesions by RECIST 1.1 (independent radiologist)



One MSS-CRC patient responding with PR and still active after 27 cycles

Swimmers plot, RECIST 1.1 - independent radiological review (Efficacy data set)



ORR by RECIST 1.1:
5.3 % (1/19)

Patient with MSS-CRC
Remains on therapy 27+ cycles



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Combination of birinapant and pembrolizumab is well tolerated

On Treatment Related Gr 3 AEs and SAEs

Number of Patients	Level 1 5.6 mg (n=3)	Level 2 11 mg (n=3)	Level 3 17 mg (n=6)	Level 4 22 mg (n=7)
≥ grade 3 related AE	No events	Hypokalemia (1)	Maculopapular Rash (1) Diarrhea (1) Increased AST (1) Increased alkaline phosphatase (1) Increased bilirubin (1) Hyponatremia(1) Dehydration (1) Stomatitis (1)*	Elevated ALT (1)

* Related SAE

- Most common treatment related AE was grade 2/3 rash reported in 3 out of 19 patients
 - All Level 3 grade 3 AEs occurred in 3 of the 6 patients

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AEs Grade 3 or higher and dose modification or death

One DLT	Missed D8 dose due to grade 3 ALT increase in cycle 1 (22 mg/m ²)
AE's leading to birinapant dose reduction	Grade 3 maculo-papular rash (17 mg/m ²)
AE's Leading to treatment discontinuation	Grade 2 mucosal inflammation* (17 mg/m ²) Grade 3 back pain and dyspnea (17 mg/m ²) Grade 3 ascites, bacterial peritonitis, pleural effusion and portal hypertension (22 mg/m ²)
SAE in 30-day follow-up period	Death following hip fracture (unrelated) complicated by pneumonitis (multifactorial though possibly immune related) 20 days after receiving second cycle

* Treatment related

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AEs of Special Interest

Pembrolizumab:

No cases reported of immune-related AEs except for 1 case of pneumonitis considered possibly related

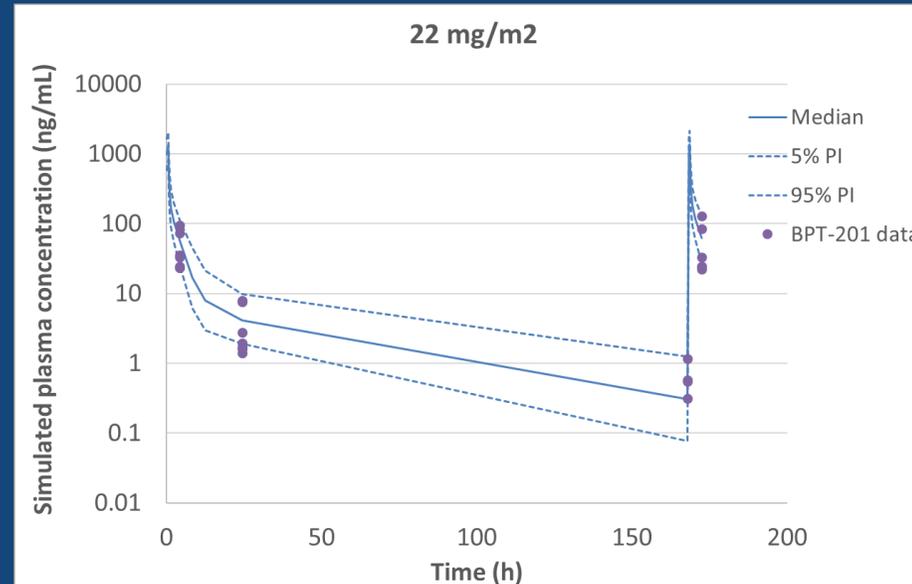
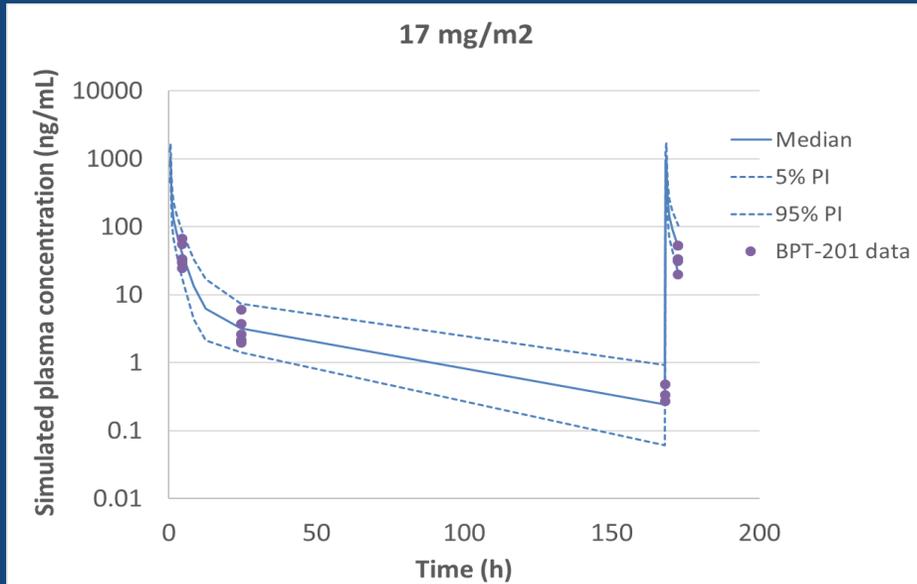
(No colitis, nephritis, hypothyroidism, hyperthyroidism, hypophysitis, hepatitis, pancreatitis, arthritis, type 1 diabetes, skin adverse reactions)

Birinapant:

- Two patients reported Grade ≥ 2 increased lipase (at 5.6 and 17 mg/m²)
- No cases of Bell's Palsy
- No cases of cytokine release syndrome

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Predicted plasma concentrations based on monotherapy population PK model and BPT-201 observations



- All patients were exposed to birinapant
- Birinapant exposure generally increased with dose in the range 5.6 to 22 mg/m²
- The vast majority of observations are within the 90% prediction interval based on monotherapy data

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Conclusions

- Combination of birinapant and pembrolizumab is safe and well tolerated
- Two patients are still on active combination treatment, one MSS CRC patient who achieved a PR and one osteosarcoma patient who had PD due to appearance of new lesions (as defined by RECIST 1.1 criteria) but had shrinking target lesions and, therefore, was allowed to stay on study treatment
- Two patients achieved a PR and seven patients achieved SD as defined by best target lesion response
- The recommended Phase 2 dose (RP2D) for birinapant is 22 mg/m² when given in combination with a fixed dose (200 mg) pembrolizumab
 - No major safety issues
 - No evidence of pembrolizumab effect on birinapant PK
- Ongoing dose-expansion at RP2D in MSS-CRC patients justified by:
 - Encouraging efficacy seen in MSS-CRC
 - Previous studies with birinapant showed evidence of clinical activity in CRC with reduction in cIAP*
- Translational data analysis is ongoing

* Amaravadi RK et al. A phase 1 study of the SMAC-mimetic birinapant in adults with refractory solid tumors or lymphoma. Mol Cancer Ther 2015; 14(11): 2569-75
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