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Clinical Cancer Therapy in 2021: What you should not have missed in 2021

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Content of the talk

- Selected studies influencing the therapeutic guidelines in solid tumors
- New molecular therapies (including new immunotherapies)
- Innovations in rare tumors / histologies / molecular subgroups
- Emerging concepts in medical Oncology
- Selective negative studies
- Miscellaneous

ASCO/ESMO 2021 early setting studies influencing the current therapeutic guidelines

ICI efficacious even in earlier stages in the adjuvant setting

Study	Setting	Experimental drug	Results
KN 716	Melanoma stage II high risk	Pembro	↑ RFS ↓ Disease recurrence or death by 35%
IMP010	NSCLC stage IB-III adj	Atezolizumab	DFS ↑ (PDL1 ≥ 50%)

ASCO/ESMO 2021 metastatic setting studies influencing the current therapeutic guidelines (1)

More and extending role of ICI in the metastatic setting

Study	Setting	Experimental drug	Results
ORIENT-15	ESCC + GEJ	Sintilimab (PD1) vs placebo (+ chemo)	↑ OS, PFS and ORR of sintilimab + chemo
JUPITER - 02	Cavum, 1L metastatic	Toripalimab(PD1) + S0C Chemo.	↑OR, PFS, OS

ASCO/ESMO 2021 metastatic setting studies influencing the current therapeutic guidelines (2)

More and extending role of ICI in the metastatic setting

Study	Setting	Experimental drug	Results
CM743	Mesothelioma	Ipi/Nivo vs chemo	OS benefit (HR 0.75)
KN826	Cervix	Pembro + chemo ± beva	↑ PFS and OS
Relativity 047	Metastatic melanoma (untreated)	Nivo + relatimab(Lag3)	↑ PFS ↑ Time to initiate subsequent therapy

ESMO 2021 negative studies in other solid tumors failing to change the therapeutic guidelines

Tumor	Drugs/Approach	Setting	Results
CRC	Folfoxiri + beva ± Atezo	Metastatic disease	mPFS: 11.5 vs 13.1 (Δ: 1.6 mo) No ≠ in ORR (not clinically significant)
H&N	RT + CDDP (fit) or RT + cetuximab (unfit) vs RT + cetuximab + Avelumab	Locally advanced	Negative results

Selected Highlights in Breast Cancer (1)
Confirmation of the role of ADC in MBC

Study name (Drugs)	Patients characteristics	Key messages
Destiny – B03 (T-DXd vs T-DM1)	MBC, HER2+ Prior treatment with taxane +H	T-Deruxtecan > T-DM1 → T-DXd= 2nd line therapy
TULIP (T-duocarmazine vs TPC)	HER2 + mBC Prior therapy ++	Better PFS of T-duocarmazine
TROPION – Pan Tumoro1 Datopotamab - Deruxtecan	mTNBC (44 patients)	ORR 34% ORR (without Topo1ADC): 52%

Proposed Therapeutic Algorithm of HER2 amplified MBC in 2022 : An Evolving Field

- 1st L — Taxane + H + P
- 2nd L — T-deruxtecan
  - Active Brain mestastases : Tucatinib + H + Capecitabine
- 3rd L — Tucatinib or Neratinib
  - T-deruxtecan
  - Capecitabine-based
- 4th L — Chemo + Margetuximab ⇄ T-DM1
- > 4th L — Chemo + H ⇄ H + Lapatinib

HER2 mutated/HR+ MBC : Neratinib + Fulverstrant + Trastuzumab (SUMMIT trial)

Selected Highlights in Breast Cancer (2)

New combinations and duration of adjuvant ET

Study name (Drugs)	Patients characteristics	Key messages
FUTURE-C-Plus Famitinib (MTKI) Camrelizumab (PD1) + Nab-paclitaxel	mTNBC , 1L (48 patients)	ORR : 81% PFS (9mo) : 60%
GIM4 (5Y vs 7Y adj.ET)	High risk, Postmenopausal HR+/HER2-BC	7Y vs 5Y ET (↑DFS and OS!) ABCSG-16 (10Y was not sup. to 7Y) → 7-8Y = SOC

Selected Highlights in lung Cancers(1): Succesful new therapeutic strategies

Study name (Drugs)	Patients characteristics	Key messages
GEMSTONE-301 (Sugemalimab vs Placebo(P))	Unresectable St III NSCLC No PD after cCT/RT or sCT/RT consolidation	sugemalimab > P (PFS); well tolerated →2nd + study in the setting
Atalante -1 (OSE-2101 (vaccine targeting 5 antigens) vs docet or pemetrexed	mNSCLC HLA-A2 + EGFR/ALK – Failure on ICI and chemo (118 patients)	mOS : 11.1 vs 7.5 mo No ≠ in DCR mPFS : 2.7 vs 3.4 mo ORR : 8 vs 18%

Selected Highlights in lung Cancers(2) :

More on the efficacy of molecular oncology and ADC(1)

Study name (Drugs)	Patients characteristics	Key messages
Destiny – Lung 01 (T-deruxtecan)	HER2 mutated mNSCLC Refractory (91 patients) Asympt BM : 36%	ORR : 81% DCR : 92% mOS : 17.8 mo Pneumonitis 13% ; ILD 5.5%
ZENITH 20 Poziotinib	mNSCLC , HER2 exon 20 mutation (48 patients)	ORR : 43% DCR : 75% Discontinuation : 13% (rash, diarrhea & stomatitis)

Selected Highlights in lung Cancers :

More on the efficacy of molecular oncology and ADC(2)

Study name (Drugs)	Patients characteristics	Key messages
TROPION – Pan Tumor 01 (Datopotamab deruxtecan)	AGA mNSCLC (34 patients)	ORR : 35% mDOR 9.5mo
Patritumab – deruxtecan (HER3)	mNSCLC Post ITK (Prior osimertinib (86%)) (57 patients)	ORR : 39% DCR : 66% DOR : 7mo mPFS 8mo ILD : 7% of patients
Libertto-001 (Selpercatinib)	RET- fusion mNSCLC Prior platinum (49 patients) No platinum (39 patients)	Prior Plat : DCR 64% mDOR 17.5mo No Prior Plat : DCR 85% HTA

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Advanced NSCLC : Molecular Therapies in MET Positive Tumors

ABS n°	Target	Therapy	Outcome
1284P	cMET (EGFR mutated)	Capmatinib + Nazartinib (TKI)	ORR (pretreated MET+) : 43,5% ORR (MET –): 28% Peripheral oedema, nausea, diarrhea
1258O	EGFR–MET bispecific AbD + TKI	Amivantamab + Lazertinib	ORR (T. naive): 100% ORR (failed osimertinib): 36% Rash, IRR, paronychia
1283P 1286P	MET exon14 mutations	Tepotinib	ORR: 45% ORR (brain): 57%

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ESMO 2021 Negative Studies in NSCLC with clinical implication

Tumor	Drugs/Approach	Setting	Results
NSCLC	PORT	IIIA pN2 (resected)	No ≠ in DFS or OS
NSCLC	Docetaxel ± canakinumab (IL-1ß)	Metastatic disease	No ≠ in DFS or OS
EGFR-mut NSCLC	Osimert + beva	Metastic disease	Beva : no added value to osimertinib

Highlights in Digestive oncology :

ADC, an established therapeutic stragtegy

Study name (Drugs)	Patients characteristics	Key messages
Destiny Gastric 01 (T-DXd vs TPC)	HER2+ G or GE PD on Trastuzumab (125 vs 62 patients)	ORR : 51 vs 14% OS : 12.5 vs 8.4 mo, ILD : 10% (mostly gr 1 or 2)
Destiny- CRC01 (T-DXd)	HER2 + mCRC PD ≥ 2 lines	ORR : 45%
CHRONOS (Panitumumab Rechallenge)	mCRC RAS/RAF wt PD on anti-EGFR RAS/RAF/EGFR wt on tumor DNA after stopping anti-EGFR (27 patients)	ORR 30% DCR 63% mPFS 16 weeks

Highlights in GU Cancers:

New combinations based on ICI and targeted therapies

Study name (Drugs)	Patients characteristics	Key messages
PRINCE ^{177} Lu-PSMA-617 + Pembro (phase 1))	mCRPC + PSMA Expression (37 patients)	50% PSA response : 73% RECIST PR : 78% Ir AE : 27%
COSMIC – 021 (Caboz + Atezo)	mCRPC. Failure novel HT (132 patients)	PR : 15% Grade3+ TRAE : 55% of patients
NORSE (Erdafitinib (E) vs E + Cetrelimab (C) (PD1)	mUC. First-line FGFR + (53 patients)	<table><tr><th></th><th>ORR</th><th>DCR</th></tr><tr><td>E</td><td>33%</td><td>68%</td></tr><tr><td>E+C</td><td>100%</td><td>90%</td></tr></table> Toxicities : ↑ P, stomatitis & diarrhea
ESMO 21/Ab 656 Belzutifan (HIF-2α inh) + Cabozantinib	mCC RCC Prior ICI (52 patients)	ORR : 29% ; DCR : 92% Gr3 HTA : 23% of patients

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What is new in rare tumors/histologies

Rare tumors/ Histologies	Drug	Results
B3 Thynoma / Thymic Carcinoma	Nivo ± Ipi	ORR 12% PFSR6 35% mOS 21 mo mPFS : 6mo G3/4 AE : 57% DCR 63%
Pheochromocytoma and paraganglioma	Sunitinib vs placebo	PR 31% vs 8% (gSDHB mutation: PR 50%) mPFS 8.9 vs 3.6mo Sunitinib = SOC

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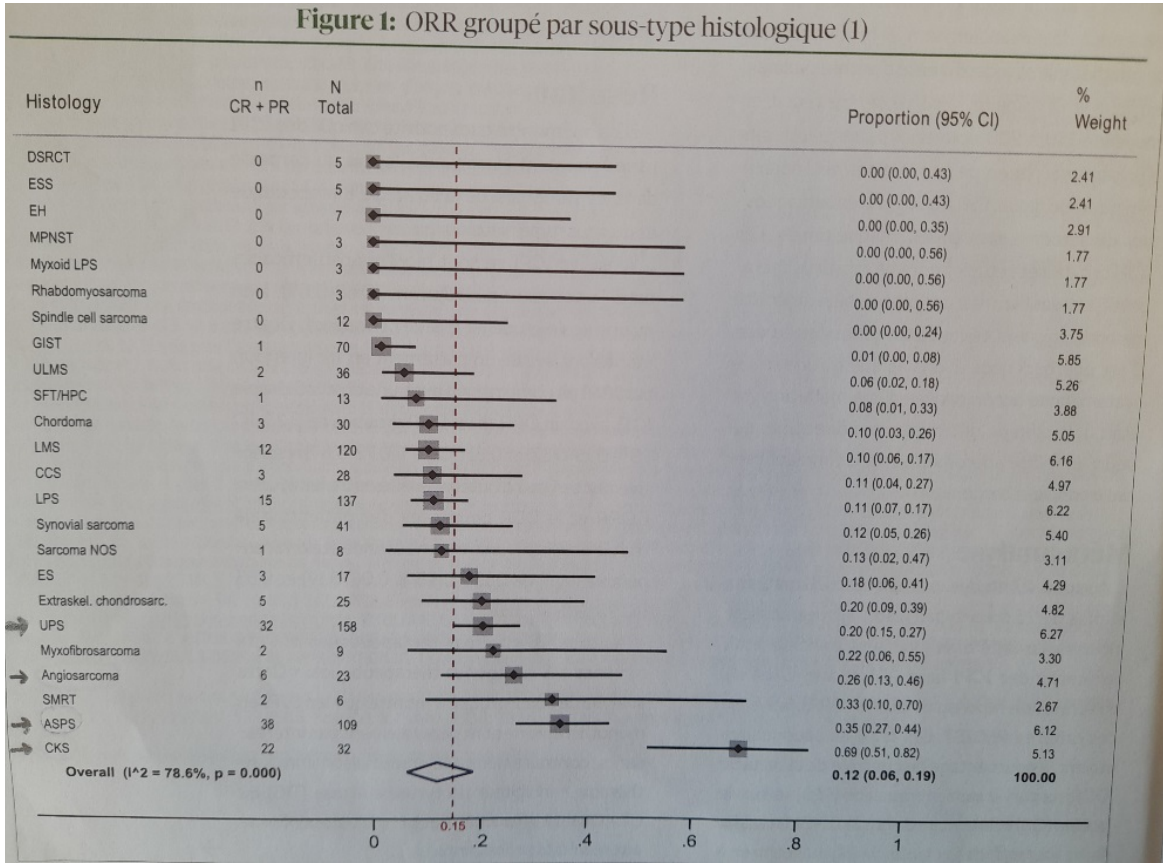
Immunotherapy (ICI) and Sarcomas in 2022 : Four histologies seem to benefit

- Kaposi sarcoma
- Angiosarcoma
- Undifferentiated pleomorphic sarcoma
- Alveola sarcoma



Saerens M et al EJC 152,165-182 2021

Other new molecular agents, approaches, combinations of interest for clinical practice

Important Targets, Selective agents and indications which need not te be missed

Target	Drug	Indication
NTRK Fusion genes	Larotrectinib Entrectinib	Solid adults and pediatric cancers harboring NTRK fusion genes
Transcription pathway	Lurbinectidine	mSCLC after PD on platinum (More efficacious in platinum sensitive disease)
ALK + NSCLC	Brigatinib	mNSCLC
FGFR2 fusion or other rearrangement	Pemigatinib	Metastatic cholangiocarcinoma
Epigenetic (EZH2)	Tazemetostat	Advanced epithelioid sarcoma
MSI-H or dMMR	Pembrolizumab and other ICIs	mCRC and other solid cancers
BRCA, HRD and other DNA repair genes	PARP Inhibitors	Ovarian, prostate, pancreatic, breast and other solid tumors

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Combination therapies (non ICI-based) remain an approach to tackle resistance

Agents (Target)	Setting	Results
Adagrasib (KRAS G12C) ± Cetuximab	mCRC	Adag mono : ORR 22% DCR 87% Adag + cetuximab: ORR 43% DCR 100%
Amivantamab (EGFR/MET) ± Lazertinib (TKI)	EGFR mut NSCLC resistant to osimertinib	Combo: ORR 36% mDOR 9.6mo Amivantamab mono: ORR 19% mDOR 5.9mo

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Combination therapy ICI-based in agnostic tumors e.g, Lenvatinib + Pembrozumab in Solid Tumors

ABS n°	Tumor	Outcome
LBA44	Melanoma (progressing on CPIs / 37% had BRAFV600)	ORR 21%
LBA41	Ovarian (4L) TNBC (2L/3L) CRC (3L) GBM (2L) BTC (2L) Gastric (2L)	ORR 32% ORR 29% ORR 22% ORR 16% ORR 9.7% ORR 9.7%

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New immunotherapy approaches in development beyond ICI

NIA (Target)	Setting	Results
Gavocabtagene autoleucel (T-CR fusion construct)	Mesothelin ⊕ tumors (mesothelioma, OV, cholang) (n=12 patients)	DCR 19% Median target lesion regression 24%
CLD 18-2 CAR-T cells	GC/GEJ/GI CLD18.2 ⊕ tumors	ORR (all) 48.6% ORR (GC) 57%
Bintrafusp Alpha (PDL1 + TGFß)	HPV⊕tumors (ICI naive:cevix,H&N,others)	ORR 28% mDOR 17mo mOS 21mo

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Emerging concepts/schemas of potential interest for clinical practice

- PARP inhib. maintenance retreatment (OReO/ENGOT ov-38 trial)
- mCRC (MSS, MGMT silenced/low) : TMZ → low dose Ipi/Nivo → increase TMB (ORR 42%!)
- Neoadjuvant Ipi/Nivo UC : Ipi3/Nivo1 > Ipi1/Nivo3 in terms of pCR
- Women receiving immuno may be at higher risk of AE than men !
- GETUG: Antiobiotics(60d before until 24d after) lead to worst PFS/OS in Nivo treated mRCC

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Neoadjuvant CPIs and locally advanced solid tumors with dMMR/MSI-H (CRC, pancreat, duod, other tumors…)

- pCR rate : 69% (after 3 cycles)
- RxR : 75%
- No surgery : 11%
- Luminal dMMR: 55% (CR)

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Biomarkers/liquid biopsy and implication for clinical practice (1)

- PD-L1 expression remain the best but not perfect predictive biomarker for PD1/PDL1 inhibitors
- BFAST: bTMB ≥ 16 is not useful to select mNSCLC who are candidate for atezolizumab (Q: what about the quantity and quality of neoantigens induced by these mutations ?!)
- New biomarkers for immuno : T cell receptor profile, moncyte subsets, plasma protein profiling… ?! → waiting validation

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Biomarkers/liquid biopsy and implication for clinical practice (2)

- Immuno-oncology score seems to predict response to atezo in TNBC (NeoTRIPa)
- Decrease in ct-DNA (regardless RECIST response) predicts OS on tebentafusp (T-CR-antiCD3 bispecific fusion prot) in uveal melanoma
- Preliminary data support ct-DNA multi-Omics (!WG methylation) for multi-cancer early detection

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Research priorities to accelerate progress against cancer (1)

1. Develop and intergrate artificial intelligence and deep learning in cancer research (Biospecimens analysis, imaging, clinical and molecular database to be shared,…)
2. Identify strategies that predict tumor response and mainly resistance to targeted therapies (blood and tissue-based biomarkers,…)
3. Optimize multimodality treatment for solid tumors. Escalation versus de-escalation strategies based on prognostic and predictive tools and valid biomarkers.

Research priorities to accelerate progress against cancer (2)

4. Increase and optimization of precision oncology (discovery of pathogenic gene alterations and selective therapies)

5. Discovery of selective tumor antigens to be targeted by antobody drugs conjugates

6. Optimize Care for older patients with cancer as well all supportive measures

7. Mangaement of oligometastatic disease in solid tumors

Thank you !

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